ADF

05.-07.03.2026 FREIBURG

Abstractband zur 52. ADF-Tagung

05.–07. März 2026 · Messe Freiburg

Adaptive Immunity

Abstract-ID: 2

Altered B Cell Phenotype and Immunoglobulin Secretion in Chronic Spontaneous Urticaria

Hafsa Nagra[1,2], Martin Metz[1,2], Stefan Frischbutter[1,2]

[1]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany

[2]Institute of Allergology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

Introduction:
Chronic spontaneous urticaria (CSU) is a common skin disorder that is characterised by recurrent wheals, angioedema, or both, which comes with significant impact on patients' quality of life. The presence of IgE autoantibodies directed against endogenous proteins (e.g. thyroid peroxidase) or IgG autoantibodies, i.e. against the FceRI or IgE, are characteristic features of CSU. B cells play a crucial role in regulating immune responses and contribute to CSU pathogenesis by secretion of autoantibodies, promoting mast cell activation. However, detailed characterization of B cell subsets, phenotypes, and functional properties in CSU remains limited. Previously, we analysed peripheral B cell subpopulations in CSU patients versus healthy controls, identifying alterations in the B cell compartment. Building on these findings, the present study investigates functional changes, including immunoglobulin secretion to better understand B cell functions contributing to CSU pathogenesis and identify potential biomarkers or therapeutic targets.

Methods:

Peripheral blood mononuclear cells (PBMCs) were isolated from fresh EDTA blood samples of CSU patients and healthy controls. Circulating B cells were phenotypically characterised by flow cytometry to assess total B cells ($CD19^+$) and key subsets, including naive, switched, unswitched, and antibody-secreting cells. For functional studies, B cells were isolated from fresh whole blood of CSU patients and healthy controls, stained with a proliferation dye, and cultured for up to nine days. Supernatants were collected every other day to monitor proliferation and determine secreted antibody levels. A fraction of the B cells was stimulated with $F(ab')_2$ fragments of anti-IgM + IgG, CD40L, and IL-21 and/or IL-4 to stimulate immunoglobulin production.

Results:

Flow cytometric analysis revealed a significant increase in switched B cells in CSU patients compared to healthy controls ($P = 0.007$), indicating an activated B cell phenotype. Antibody-secreting cells (ASCs) were also significantly elevated ($P = 0.04$). No significant correlation was observed between serum IgE levels and total IgE expression on circulating B cells. Strong B cell proliferation was evident by day 5 of culture and, in some cases, by day 7. Supernatants were collected on day 3 for cytokine analysis and on day 5 for antibody quantification. Stimulation with combinations of BCR ($F(ab')_2$ Fragment Goat Anti-Human IgM + IgG), CD40L, and cytokines (IL-21 and/or IL-4) revealed distinct patterns of immunoglobulin production between CSU patients and healthy controls. Upon stimulation with BCR, CD40L, IL-21, and IL-4, B cells from CSU patients produced more than two times more IgE, IgG2, and IgG4 than healthy controls. In contrast, IgM production was higher in healthy controls at all stimulation conditions.

Discussion:
The increase in switched B cells and antibody-secreting cells indicates a systemic elevation of B cell activation in CSU patients, consistent with the higher production of IgE, IgG2, and IgG4 after stimulation. These results suggest enhanced class switching and plasma cell differentiation in CSU, reflecting B cell dysregulation with potential implications for disease pathogenesis and biomarker development.

Kategorie: Adaptive Immunity
Präsentationsart: Poster

Abstract-ID: 3

Novel peripherally active kappa-opioid receptor agonists with T cell specific anti-inflammatory and modulatory capacities

Hoffmann, K. [1]; Flämig, L. [2]; Wünsch, B. [2, 3]; Loser, K. [1]

1 University of Oldenburg, Institute of Immunology, Oldenburg, Germany

2 University of Münster, Institute of Pharmaceutical and Medical Chemistry, Münster, Germany

3 University of Münster, GRK 2515, Chemical biology of ion channels (Chembion), Münster, Germany

Chronic inflammatory and pruritic skin diseases, such as atopic dermatitis or psoriasis, involve complex interactions between the immune and the peripheral nervous systems, but also the activation of distinct T cell subsets. Kappa opioid receptor agonists (KORA) have been discussed as promising tools for the local treatment of these diseases, particularly because of their anti-inflammatory potential. However, many KORA are known to cross the blood-brain barrier (BBB) and to induce central side effects, which makes them poorly suitable for anti-inflammatory therapy and prompted us to develop new peripherally restricted KORA, chemically based on a perhydroquinoline scaffold.

In murine models, the new compounds attenuated Experimental Autoimmune Encephalomyelitis (EAE) and, on a molecular level, significantly down-regulated T cell activation and proliferation, accompanied by a reduced expression of key pro-inflammatory cytokines in PBMC from healthy human donors. Interestingly, this effect seemed to be specific to distinct T cell subsets. To better understand the cell type specific mode of action, we sorted and polarized primary murine CD4+ and CD8+ T cells towards Th1, Tc1, Th17 or Treg cells using established in vitro differentiation protocols and subsequently, stimulated them with the KORA.

In this context, we first observed that the new KORA had a high affinity for KOR and also a particular selectivity for this receptor, since stimulation of polarized T cells from KOR deficient (*Oprk1*-/-) mice with one of the compounds did not elicit any anti-inflammatory activity. This observation might potentially point to a minimized risk of side effects due to reduced cross-reactivity with other opioid receptors. It is worth mentioning that KOR expression was confirmed by histochemical staining in all polarized T cell subsets from wild-type (WT) but not *Oprk1*-/- mice. Since mitochondrial activity and changes in metabolism affect the energy production required for T cell polarization, proliferation, and cytokine secretion, we next performed metabolic analyses to investigate the impact of the new KORA on T cell bioenergetics. Interestingly, treatment with the compounds increased both, mitochondrial membrane potential and mitochondrial reactive oxygen species (mROS) generation in Th1, Tc1, Th17 and Treg cells from WT mice, whereas we observed no effects on mitochondrial activity when polarized *Oprk1*-/- T cells were stimulated with the newly developed KORA. However, BrdU incorporation assays revealed no significant impact of the compounds on cell division. Cytokine profiling studies using bead-based multiplex techniques showed no differences in cytokine expression between polarized T cells stimulated with one of the KORA and non-stimulated controls, suggesting that the peripherally restricted KORA may selectively influence murine T cell bioenergetics and mitochondrial function without broadly suppressing T cell activation or proliferation. To further analyze the molecular mechanisms underlying the different and T subset-specific effects of the new KORA, we performed RNA sequencing experiments which resulted in an over-representation of the GO terms related to T cell metabolism or immune signaling.

Together, these data suggest that the newly developed, peripherally restricted KORA were able to selectively and subset-specifically modify T cell energy metabolism and mitochondrial activity, which could make them promising candidates for future development towards personalized, tailored (and local) therapy options for inflammatory skin diseases.

Kategorie: Adaptive Immunity
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 4

Characterization of FcεRIα Autoantibodies in Type IIb Chronic Spontaneous Urticaria

Pashuk, M. [1,2,3]; Lerner, L. [1,2,3]; Steinert, C. [1,2,3]; Kolkhir, P. [1,2]; Bal, G. [1,2]; Metz, M. [1,2]; Scheffel, J. [1,2]

1. Institute of Allergology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

2. Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany

3. Department of Biology, Chemistry and Pharmacy, Freie Universität Berlin, Berlin, Germany

Introduction
Chronic spontaneous urticaria (CSU) presents with wheals, angioedema, or both for > 6 weeks without an identifiable external trigger. More than 50% of patients have autoallergic (type I) and/or autoimmune (type IIb) CSU characterized by mast cell (MC)/basophil-activating autoantibodies. Type IIb CSU is associated with functional IgG antibodies directed against the alpha subunit of the high-affinity IgE receptor (FcεRIα), and/or, less commonly, IgE itself. Clinically, type IIb CSU is more severe, characterized by higher UAS7 scores, reduced UCT scores, and a poorer response to both antihistamines and omalizumab when compared with type I CSU. Current knowledge of the underlying mechanisms in type II CSU remains limited. In this study, we investigated FcεRI-specific IgG autoantibodies to characterize their functional properties and better understand their role in disease pathogenesis.

Methods
Serum samples from 242 CSU patients were analyzed using IgG-anti-FcεRI ELISA and mast cell activation test (MAT). Type IIb CSU was defined by double positivity in ELISA and MAT. MAT-positive sera were preincubated with full-length recombinant FcεRIα protein to block autoantibody binding. Selected samples were further subjected to IgG purification using Protein G columns. IgG-depleted sera and purified IgG fractions were tested for their ability to activate MCs in MAT. Additionally, ELISA and MAT were repeated using original, IgG-depleted, FcεRI-blocked sera, and purified IgG fractions.

Results
Type IIb CSU was present in 5% of patients (MAT and ELISA positive), while 32%, 4% and 59% of samples were either single positive for MAT, single positive for ELISA or double negative, respectively. Preincubation of MAT-positive sera with recombinant FcεRIα protein reduced MC activation by up to 70 % in samples with higher autoantibody titers and by 10–20 % in low-titer samples, while MAT-positive sera lacking IgG-anti-FcεRI showed no inhibition. IgG depletion reduced MC activation in the tested samples to baseline levels observed in healthy controls. Purified IgG fractions still induced activation, although at approximately two- to three-fold lower levels than the original serum.

Discussion
In this study, the prevalence of type IIb CSU is in line with literature, whereas only a few patients have detectable but nonfunctional FcεRI autoantibodies. The reduction of mast cell activation after FcεRIα preincubation further supports the role of IgG-anti-FcεRI in disease pathogenesis, while the incomplete inhibition observed in some samples indicates additional IgG autoantibody targets. Approximately one-third of patients have mast cell-activating serum lacking IgG-anti-FcεRI. However, MC activation was reduced after IgG depletion, indicating an IgG-dependent mechanism mediated by other IgG autoantibodies. Together, these findings highlight the complexity of autoimmune mechanisms in CSU that requires further investigation.

Kategorie: Adaptive Immunity
Präsentationsart: Poster

Abstract-ID: 5

Peripheral tolerance shapes the T-cell repertoire against a tumor-associated self-antigen

Ann-Kristin Jochum[1,2*]; Mette-Triin Purde[1*]; Vincent Walter[3]; Bianca Broske[1]; Cheyenne Christin Collins[1]; Sandra S. Ring[1,4]; Oltin Tiberiu Pop[1]; Lukas Flatz[1,3,5]

1 Institute of Immunobiology, HOCH Kantonsspital St. Gallen, St. Gallen, Switzerland

2 Institute of Pathology, HOCH Kantonsspital St. Gallen, St. Gallen, Switzerland

3 Department of Dermatology, University Hospital Tübingen, Tübingen, Germany

4 TranslaTUM, Technical University of Munich, Munich, Germany

5 Department of Dermatology, HOCH Kantonsspital St. Gallen, St. Gallen, Switzerland

* These authors contributed equally to this work

Introduction: Mechanisms of central and peripheral immune tolerance prevent autoimmunity mediated by self-reactive T cells. However, tolerance to a tumor-associated self-antigen can also hamper the efficacy of tumor immunotherapies like cancer vaccines.

Methods: Here, we investigated the antigen-specific T-cell receptor (TCR) repertoire in mice who do and do not have immunological tolerance for the melanoma-associated antigen tyrosinase-related protein 2 (TRP2), before and after immunization. By utilizing TRP2 knockout mice and heterozygous littermate controls, we could study the same antigen as both a tumor-specific (TSA) and a tumor-associated antigen (TAA).

Results: We showed that while the TCR repertoires in untreated mice were comparably diverse, the TRP2-specific cells expanded significantly better after immunization in the TSA setting. The TRP2-specific TCR repertoires were similar in both genotypes, but the dominant T-cell clone only expanded strongly in the TSA setting. Knockout mice also showed complete rejection of established B16F10 melanomas after therapeutic immunization and their tumor-infiltrating T cells contained a significantly larger population with a naïve-like phenotype.

Conclusions: Peripheral T-cell tolerance is sufficient to prevent melanoma rejection after immunization despite not markedly altering the TCR repertoire composition. The model presented here is a useful tool to investigate the interaction between peripheral tolerance and antitumor immune responses, aiming to increase the efficacy of cancer vaccines targeting self-antigens.

Kategorie: Adaptive Immunity
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 6

Application of xenogeneic antigens induces bystander T cell responses that ameliorates pathogenesis in murine models of Epidermis bullosa acquisita

Noori, R[1]*; Bahreini, F[1]*; Bieber, K[2]; Dräger, S[2]; Ehlers, M[3]; Kalies, K[1]

1 Lübeck Institute of Anatomy, University of Lübeck, Lübeck, Germany

2 Lübeck Institute of Experimental Dermatology, University of Lübeck, Germany

3 Institute of Nutritional Medicine

*equal contribution

Introduction

Epidermolysis bullosa acquisita (EBA) is an autoimmune blistering disease caused by autoantibodies targeting type VII collagen, leading to dermal-epidermal separation. In experimental EBA models, disease development is associated with a Th1-skewed immune response.

Methods and Results

In the immunization-induced model, pretreatment with a xenogeneic antigen (ovalbumin in Alum and Titermax; OAT) completely prevented disease without affecting circulating and skin-bound mCol7c-specific IgG isotypes. Protection correlated with a reduced IFNγ/IL4 ratio in draining lymph nodes and an anti-inflammatory glycosylation pattern on non-specific IgGs, while glycosylation of mCol7c-specific IgGs remained unchanged. T cell receptor β-chain (TCRRβ) analysis revealed persistence of OAT-specific T follicular helper (Tfh) clonotypes during the autoimmune response, suggesting a protective bystander Tfh effect.

To extend these findings, we generated cell-derived nanoparticles (CDNPs) containing xenogeneic intracellular proteins and tested them in the antibody-transfer EBA model. CDNP treatment similarly reduced the IFNγ/IL4 ratio, accelerated wound healing, and increased TCRRβ diversity without inducing a proinflammatory response.

Discussion

These results indicate that xenogeneic protein exposure induces a protective bystander T cell response that modulates autoimmune inflammation. Ongoing studies aim to further define the mechanisms and therapeutic potential of CDNP-induced immune modulation in EBA.

Kategorie: Adaptive Immunity
Präsentationsart: Poster

Abstract-ID: 7

The Role of Anti-BP180 NC16A Autoantibodies in Placental Injury in Pemphigoid Gestationis

Preuß, Sophie L.; [1,2], Renshall, Lewis[3,4]; Bieber, Katja[2]; Gembicki, Michael[5]; Groß, Natalie[2]; Gocht, Andreas[6]; Vorobyev, Artem[1]; Gaffal, Evelyn[1]; Brownbill, Paul[3,4]; Ludwig, Ralf J.[1,2]

1 Department of Dermatology, University Medical Centre of the State of Schleswig-Holstein (UKSH), Campus Lübeck, Lübeck, Germany
2 Lübeck Institute of Experimental Dermatology, University of Lübeck, Lübeck, Germany
3 Maternal & Fetal Health Research Centre, Division of Developmental Biology & Medicine, School of Medical Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom
4 St Mary's Hospital, Manchester University Hospital NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom
5 Department of Gynaecology and Obstetrics, University Medical Centre of the State of Schleswig-Holstein (UKSH), Campus Lübeck, Lübeck, Germany
6 Institute of Pathology, University Medical Centre of the State of Schleswig-Holstein (UKSH), Campus Lübeck, Lübeck, Germany

Pemphigoid gestationis (PG) is a rare autoimmune blistering disease of pregnancy and the postpartum period, characterized by intense pruritus and blistering skin lesions. It results from a loss of immunotolerance against the hemidesmosomal antigen BP180, with pathogenic autoantibodies primarily directed against its NC16A domain. In addition to the skin, BP180 is expressed in amniotic epithelial cells and cytotrophoblasts of the villous epithelium. Consistent with this, autoantibodies from PG patients have been shown to bind placental tissue. While PG is associated with an increased risk of adverse pregnancy outcomes (APOs), the causal contribution of anti-BP180 NC16A autoantibodies remains largely unknown.

Direct and indirect immunofluorescence confirmed anti-BP180 NC16A IgG binding to the basement membrane zone (BMZ) of both amniotic epithelium and chorionic villi. Histopathological examination of a placenta from a PG patient revealed mild villitis and a reduced number of terminal villi. To further explore the pathogenic mechanisms, we established an ex vivo model of placental explant cultures. Preliminary findings indicate altered cytokine responses, with a trend toward increased IL-8 secretion in explants exposed to anti-BP180 IgG. No significant morphological changes were observed. Cryosection assays of placental tissue demonstrated split formation at the BMZ of chorionic villi following incubation with anti-BP180 NC16A antibodies compared to controls, indicating pathogenic activity of these antibodies on placental basement membranes.

Future studies will include culturing amniotic epithelial cells and cytotrophoblasts to assess the effects of anti-BP180 NC16A antibodies on release of inflammatory mediators and gene expression.

Collectively, these experiments provide novel insights into the potential mechanisms linking anti-BP180 NC16A autoantibodies to placental injury and APOs in PG. A better understanding of these pathways is urgently needed to improve maternal and fetal outcomes, not only in PG but also in other autoantibody-mediated pregnancy disorders.

Kategorie: Adaptive Immunity
Präsentationsart: Poster

Abstract-ID: 8

Improved anti-inflammatory function of *in vitro* expanded regulatory T -cells engineered to express membrane-bound CTLA-4

Heizmann, A.[1]; Wiesinger, M.[1]; May, M.[1]; März, J.[1]; Mark, C.[3]; Fabry, B.[3]; Voskens, C.[1,2]

1 Universitätsklinikum Erlangen, Department of Dermatology, Erlangen, Germany
2 Universitätsklinikum Erlangen, Deutsches Zentrum Immuntherapie (DZI), Erlangen, Germany
3 Friedrich-Alexander Universität Erlangen-Nürnberg, Department of Physics, Biophysics Group, Erlangen, Germany

CD4+CD25+CD127low regulatory T cells (Tregs) are essential for maintaining immune tolerance and suppressing inflammation. This project aims to engineer highly suppressive and motile Tregs to study their suppressive function and migration. Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is known as a driver of Treg mediated immune cell suppression by blocking the co-stimulatory molecules CD80/86 on antigen-presenting cells. In general, CTLA-4 is mainly intracellularly expressed and only short lived in its membrane-bound form. We hypothesized that the enhanced expression of membrane-bound CTLA-4 on the Tregs induced by Treg engineering would strengthen their function and improve their therapeutic efficacy.

Peripheral blood-derived Tregs were expanded using a GMP-compliant protocol and engineered via CTLA-4 mRNA electroporation. To evaluate their suppressive function, a dendritic cell stimulated proliferation assay was established. Differences in proliferation of CFSE labeled autologous CD4+ T cells in the presence or absence of engineered Tregs were monitored by flow cytometry. In addition, we investigated their migratory behavior in a 3-dimensional collagen gel mimicking the extracellular matrix of connective tissue. The number of motile Tregs, their speed and persistence were measured for a duration of 24 hours.

Engineered Tregs exhibited up to a 10-fold increase in membrane-bound CTLA-4 expression (MFI) while maintaining their Treg-like phenotype. Functionally the engineered Tregs showed a significant higher anti-inflammatory effect compared to non-engineered control Tregs. Blocking CTLA-4 with the clinically approved CTLA-4 blocking antibody Ipilimumab reversed that advantage, confirming the functional relevance of enhanced membrane-bound CTLA-4 expression to mediate suppression. Importantly, Treg engineering did not negatively affect Tregs migration.

These findings show that transient engineering of human-derived Tregs with CTLA-4 mRNA significantly improves their anti-inflammatory effect without impairing their migratory function in vitro, supporting their translation into a Treg based cell therapy to treat inflammatory skin disorders.

Kategorie: Adaptive Immunity
Präsentationsart: Poster

Abstract-ID: 9

Exploring novel genetic variants and the pathogenicity of autoantibodies in patients with pemphigus vulgaris and their first-degree relatives

Zarabadi, K [1]; Manz, R [2]; Emtenani, Sh [1]; Schmidt, E [1,3]

1 Lübeck Institute of Experimental Dermatology, University of Lübeck, Lübeck, Germany

2 Institute for Systemic Inflammation Research, University of Lübeck, Germany

3 Department of Dermatology, University-Hospital Schleswig-Holstein, Lübeck, Germany

Pemphigus vulgaris (PV) is a rare and severe autoimmune blistering disease, affecting the skin and surface-close mucous membranes. It is characterized by autoantibodies targeting two desmosomal proteins, desmoglein (Dsg) 1 and 3, leading to loss of keratinocyte adhesion and blister formation. Notably, a subset of first-degree relatives of PV patients exhibits circulating autoantibodies despite the absence clinical lesions. Genetic risk factors, particularly within the HLA locus and, to a lesser extent in non-HLA regions, contribute to PV risk. This study aims to identify novel susceptibility loci associated with the development of PV-related autoantibodies and clinical disease. For this purpose, blood and serum samples were collected from 34 PV patients and 89 first-degree relatives, including both seropositive and seronegative relatives, both without symptoms. Sera were analyzed for serum anti-desmosomal autoantibodies by indirect immunofluorescence on monkey esophagus and for anti-Dsg 3 IgG by ELISA, with detailed evaluation of IgG subclass profiles. Elevated anti-Dsg3 IgG1 and IgG4 autoantibodies were detected in 19.7% and 14% of first-degree relatives, respectively, based on ROC-derived cut-offs (0.092 for IgG1 and 0.177 for IgG4). Genomic DNA was extracted from blood samples and subjected to whole-exome (WES) and whole-genome sequencing (WGS), with data analyses currently ongoing. In the next phase, key genetic findings will be functionally validated using *in vitro* assays, including immunohistochemistry on PV skin samples and a dispase-based keratinocyte dissociation assay, the latter designed to assess the effects of transient gene silencing or overexpression on epidermal cell-cell adhesion.

Kategorie: Adaptive Immunity
Präsentationsart: Poster

Allergy and AD

Abstract-ID: 10

The role of T memory stem cells (T_{SCM} cells) in tolerance induction during allergen-specific immunotherapy

Albers, C.C.[1]; Uncuer, D.[1,2]; Westmeier, J.[1]; Neif, M.[1]; Steinbrink, K.[1]; Sulk, M.[1]; Becker, C.[1]; Raker, V.K. [1,2]

1 University of Münster, Department of Dermatology, Münster, Germany
2 University of Augsburg, Department of Dermatology, Augsburg, Germany

Background

Allergen-specific immunotherapy (AIT) remains the only causal treatment for IgE-mediated allergies. Despite its long-standing clinical use, AIT exhibits variable efficacy across allergens. T memory cells are crucial for the development and persistence of allergic diseases. A newly identified subgroup, the T memory stem cells (T_{SCM}), are central to long-term immune responses due to their capacity for self-renewal and their potential to differentiate into various memory and effector T cell subsets. Unlike terminally differentiated memory cells, T_{SCM} exhibit exceptional longevity and stability, potentially influencing the persistence or resolution of allergic responses. However, the specific role of T_{SCM} in tolerance induction during AIT remains largely unexplored. Understanding their modulation by AIT could provide new insights into mechanisms of immune tolerance and guide improvements in allergy treatment.

Methods

This project investigates changes in the frequency and phenotype of total and allergen-specific T_{SCM} in patients undergoing AIT for birch pollen allergy. Peripheral blood samples are collected at three time points (before AIT, during early treatment after 6 weeks, and after 6 months).

Total T_{SCM} populations are analyzed using multiparametric spectral flow cytometry, focusing on activation and differentiation markers. Allergen-specific T_{SCM} are identified with fluorescence-labeled **Bet v 1–HLA-DRB1*15:01 tetramers**, allowing detailed characterization of their frequency and immunophenotype.

Prior to longitudinal analyses extensive preparatory work was performed. Patients and non-allergic control subjects were genotyped for **HLA-DRB1*15:01** expression using PCR followed by confirmatory Sanger sequencing to identify individuals suitable for tetramer-based detection. **Flow cytometry protocols for tetramer-positive T cells and T_{SCM} populations** were optimized, verified against control **CLIP tetramers**, and validated in allergic and non-allergic donors to ensure staining specificity. Blood samples were processed and cryopreserved under standardized conditions to preserve functional integrity for downstream assays.

Results

31 patients have been recruited at the start of AIT in autumn 2025. The cohort has a mean age of **37 years** (range 20–64), with **71% female** participants. Most subjects are **polysensitized**, while five are monosensitized to birch pollen, based on specific IgE levels and skin prick testing. Approximately half of the cohort (**n=15**) initiated **subcutaneous AIT**, and the remainder started **sublingual AIT**.

To date at least **four patients** were confirmed to express **HLA-DRB1*15:01**, enabling the application of Bet v 1–specific tetramer staining for allergen-specific T_{SCM} identification. Both **tetramer and T_{SCM} staining protocols** were successfully established and verified, providing reliable detection of Bet v 1–specific $CD4^+$ T cells. The extensive sample collection and

validated analytical tools provide a strong basis for the upcoming longitudinal analyses of total and allergen-specific T_{SCM} during AIT.

Summary

This study investigates how AIT modulates T_{SCM} and promotes immune tolerance in birch pollen allergy. By characterizing total and allergen-specific T_{SCM} dynamics, the study aims to identify immune signatures linked to successful therapy. These findings may facilitate improved patient stratification, optimized treatment duration, and enhanced efficacy of AIT, contributing to the development of more precise and personalized allergy treatments.

Kategorie: Allergy and AD
Präsentationsart: Poster

Abstract-ID: 11

In vitro mast cells co-cultured with dermal fibroblasts for improved mast cell modelling

Miller, D.C.[1,2]; Luo, Y.[1,2]; Hu, M.[1,2]; Siebenhaar, F.[1,2]; Scheffel, J.[1,2]

1. Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology IA, Berlin, Germany
2. Institute of Allergology, Charité - Universitätsmedizin Berlin, Germany

Cultured primary human skin mast cells (hsMCs) are invaluable for studying skin-relevant allergens, antigens, and mast cell mediated-pathologies, as well as novel therapeutics to manage these. However, due to a lack of reliable availability and quantity, as well as inter-donor variability, studies utilising hsMCs are time and cost intensive, and sometimes produce variable results.

Peripheral blood stem cell-differentiated mast cells (PSCMCs) and human induced pluripotent stem cell-differentiated mast cells (hiPSC-MCs) are in vitro culture systems that can provide more readily available and reproducible MCs. However, since both of these systems require derivation in vitro, they may lack some specific functional qualities observable in freshly isolated primary hsMCs.

Therefore, we are establishing co-culture systems to improve the functional maturity of these in vitro MCs. Human dermal fibroblasts (HDFs) were mitotically inactivated and plated at a set density. PSCMCs or differentiating hiPSC-MCs were then added for several weeks, being replated onto fresh HDFs every 2-3 weeks as necessary.

MC response to stimulation was markedly altered following co-culture with HDFs. A consistent shift was observed across many classic MC cell surface markers, and the paracrine release profile of both co-cultured MCs as well as HDFs themselves was investigated.

Refinement of this co-culture approach is ongoing, and will identify optimal conditions and the role of specific exogenous and endogenous factors. This scalable and versatile system should greatly facilitate the availability of reproducible skin-relevant MCs, for bona fide disease modelling and compound testing in vitro.

Kategorie: Allergy and AD
Präsentationsart: Poster

Abstract-ID: 12

More than stress: Insights into self-reported triggers in chronic spontaneous urticaria: A CRUSE study

Witte-Haendel, E. Ramanauskaite, A. Lingnau, A. Britz, R. Sousa-Pinto, B. Gimenez-Arnau, A.M. Kocatuerk, E. Cherrez-Ojeda, I. Bousquet, J. Weller, K. 11. Magerl, M.

1 Institute of Allergology, Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany
2 Global Allergy and Asthma Excellence Network, ACARE\/UCARE coordinating office, Berlin, Germany
3 Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany
4 Information and Health Decision Sciences, Faculty of Medicine, University of Porto, Porto, Portugal 5 CINTESIS-Center for Health Technology and Services Research, University of Porto, Porto, Portugal 6 RISE-Health Research Network, University of Porto, Porto, Portugal
8 Department of Dermatology, Urticaria Center of Reference, and Excellence (UCARE), Hospital del Mar Medical Research Institute, Universitat Pompeu Fabra, Barcelona, Spain
9 Department of Dermatology, Urticaria Center of Reference, and Excellence (UCARE), Bahçeşehir University School of Medicine, Istanbul, Turkey
10 Universidad Espíritu Santo, Samborondón, Ecuador, Respiralab Research Center, Guayaquil, Ecuador
11 Respiralab, Respiralab Research Group, Guayaquil, Ecuador

Abstract:
Background. Besides its unpredictable nature, the existence of individually relevant and unspecific trigger factors such as NSAIDs, stress and infections may contribute to the burden of chronic spontaneous urticaria (CSU) as they have the potential to exacerbate CSU. Although the existence of CSU triggers is widely recognized, real-world evidence on their role in disease progression and outcomes remains limited.

Objective. This study aimed to explore self-reported CSU triggers and their relationship among various patient characteristics collected through the CRUSE mobile health (mHealth) application.

Methods. Self-reported data from CRUSE users in Germany between JUL 2022 and SEP 2025 were analyzed to assess associations between trigger factors and disease features.

Results. Data from 4,521 patients were analyzed, with a gender distribution of 24.4% male, 74.7% female, and 0.9% other and a mean age of 41.0 ± 13.1 years. Approximately 95% of patients reported wheals, either with (48.2%) or without (47.1%) angioedema, while only 4.6% experienced isolated angioedema. More than half of the patients (56.4%) reported the presence of CSU triggers, with a slight predominance in females (58.4% female vs. 52.3% male). The most commonly reported triggers were stress (27.0%), rubbing of the skin (22.5%), high temperatures (16.4%), and food (16.0%). Infection and medication accounted for 11.0% and 10.3%, respectively. Notably, females were more likely than males to report certain triggers, such as stress (27.9% vs. 25.1%), rubbing of the skin (24.4% vs. 17.4%), and infection (12.5% vs. 7.0%). Correlation analysis revealed a significant positive relationship between the presence and number of CSU triggers and disease duration (**p&lt0.01).

Conclusions. Our findings suggest that individually relevant and unspecific trigger factors may play a significant role in CSU. These real-world data underscore the importance of recognizing and managing triggers. Future analyses will aim to clarify these associations and their potential clinical implications.

Kategorie: Allergy and AD
Präsentationsart: Poster

Abstract-ID: 13

Assessment of IgE-dependent Mast Cell Degranulation in Chronic Inducible Urticaria Driven

Han Gao[1,2], Nana Shi[1,2], Zhenlan Wu[1,2], Pelle Rangsten[3], Markus Renlund[3], Hanna Bonnekoh[1,2], Jörg Scheffel[1,2]

1Institute of Allergology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

2 Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology IA, Berlin, Germany

3 Ascilion AB, Kista, Sweden

Introduction:
Chronic inducible urticaria (CIndU) is a form of chronic urticaria in which wheals and/or angioedema appear reproducibly upon physical or environmental stimuli, such as cold, pressure and others. Mast cell (MC) activation and degranulation drive the symptoms, yet the molecular pathways remain unclear. IgE-dependent MC activation via FcεR1 is well known in chronic spontaneous urticaria, its role in CIndU is less understood, and the variable response to omalizumab highlights this uncertainty. Moreover, potential (auto)antigens/allergens that are generated upon application of the respective trigger have not yet been identified, either in the blood or in the skin. Dermal interstitial fluid (dISF), a locally enriched source of skin mediators, represents a promising but under-utilized biofluid for biomarker discovery. Here we characterized the potential of dISF collected with a microneedle technology after skin provocation to induce IgE-dependent MC activation aiming to explore the relevance of skin derived auto-allergens in Cold Urticaria (ColdU) and Symptomatic Dermographism (SD).

Objective:
To explore the generation and relevance of skin derived auto-allergens upon provocation in ColdU and SD.

Methods:
dISF were collected from 3 healthy individuals 15min after cold- or scratching provocation. Sera from 30 ColdU patients (10 with low IgE (≤40kU/l), 10 with normal IgE (<100kU/l; >40kU/l), 10 with high IgE (≥100kU/l)) and 10 healthy controls were used to sensitize peripheral stem cell derived mast cells (PSCMCs) overnight in 37°C incubator in the presence or absence of Omalizumab. Sensitized cells were stimulated with dISF for 1h followed by FACS analysis of the surface expression of CD63. Collected sera from 30 SD patients (5 with low IgE (≤40kU/l), 12 with normal IgE (<100kU/l; >40 kU/l), 13 with high IgE (≥100kU/l)) and 10 healthy controls, then followed the protocol for ColdU.

Results:
FACS analysis of MC, stimulated with dISF after provocation, showed that in 20% of cases where cells were sensitized with serum of ColdU and 26.7% with serum of SD patients MC degranulation was induced, while dISF alone was not sufficient. The degree of mast cell activation i.e. CD63 positivity was heterogenous ranging from 2.89% to 61.87%. For both, ColdU and SD, we observed that a positive MC response was positively connected with total IgE levels. Patient Sera with elevated IgE levels >100kU/l more frequently showed MC activation (16.7%) than sere with normal 40kU/l-100kU/l (3.3%) and low IgE <40kU/l (0%).

Importantly, MC activation could be blocked by treatment of serum samples with omalizumab during sensitization of MCs. Interestingly, dISF collected from different donors showed a variable capacity to activate MCs.

Conclusion:

Our results indicate that IgE-dependent mast cell activation might be a relevant pathomechanisms in 20% ColdU and 26.7% of SD patients. Patients with high total IgE levels are more likely to exhibit IgE- dependent MC degranulation, while this is less relevant in patients with low total IgE. Soluble auto-allergens are produced upon provocation in the skin. The different responses to the individual dISF donors suggest that several antigens are produced which are common or specific to the individual skin. Our findings also suggest that MC in ColdU and SD are not solely IgE-dependent, and may also involve alternative pathways such as MRGPRX2-mediated signaling.

Kategorie: Allergy and AD
Präsentationsart: Poster

Abstract-ID: 14

Functional dichotomy of MRGPRX2 ligands in skin mast cell activation

Schneikert, J. [1,2*]; Tripathi, S. [1,2], Jin M. [1,2]; Ivanusic D. [1,2]; Zuberbier T. [1,2]; Babina M. [1,2]

1 Institute of Allergology, Charité—Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt Universität zu Berlin, Berlin, Germany

2 Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany

Background: MRGPRX2 (Mas-related G protein-coupled receptor member X2) is a receptor selectively expressed in (skin) mast cells (MCs) and suspected to play a major role in MC-associated diseases. MRGPRX2 mediates mast cell degranulation, leading to the release of prestored inflammatory mediators into surrounding tissues. This occurs through engagement of the receptor by various ligands, including drugs and peptides, the latter endogenous or exogenous. Endogenous ligands include as two major subfamilies neuropeptides like substance P and cortistatin-14, and host defense peptides (HDPs) such as cathelicidin (LL37). The relationship between neuropeptide- and HDP-triggered MRGPRX2 activation is poorly characterized in terms of signaling pathways and functional outputs.

Methods: Primary human MCs were isolated from foreskin tissue and used either ex vivo or after a 3-5-week-culture in the presence of SCF and IL-4. Cells were stimulated with either substance P, cortistatin-14 or LL37 and beta-hexosaminidase and tryptase were measured by enzyme activity tests. Histamine release was studied by an autoanalyzer or the HTRF assay. RNA interference was performed by transient transfection of small interfering RNA; Western blot and RT-qPCR served to assess knockdown efficiency.

Results: The compounds potently induced skin MC mediator release, though to different extents. LL37 was particularly efficient in releasing beta-hexosaminidase and histamine, but a poorer stimulator of tryptase secretion. Therefore, the ratios tryptase/beta-hexosaminidase and tryptase/histamine were lower for LL37 than neuropeptides. This observation was reproduced in different MC systems, i.e., precultured skin-derived MCs, ex vivo skin MCs and dermal cells containing MCs.

Based on our recent phosphoproteomics data showing global changes in phosphoproteins following MRGPRX2 stimulation, candidates pertinent to the degranulation machinery were selected, i.e., Rab27B, SWAP70, SYTL2 and SYTL3. Using RNA interference, we found that the synaptotagmin-like SYTL2, abundantly expressed in skin MCs, was required for degranulation stimulated by substance P or cortistatin-14. In contrast, LL37 promoted degranulation was unaffected by SYTL2 knockdown, insinuating that different machineries may assemble following MRGPRX2 ligation with neuropeptides versus HDPs.

Conclusions: We conclude that LL37 induced degranulation displays specific features that distinguishes it from other MRGPRX2 ligands, especially neuropeptides. The selective release of certain prefabricated mediators may have critical implications in MC-dependent diseases, that differ in signs and symptoms. For example, LL37 has been associated with rosacea, while SP has a role in urticaria and atopic dermatitis. It remains to be established whether LL37 is unique or the founding member of a subfamily of MRGPRX2 activators, that operate similarly.

Kategorie: Allergy and AD
Präsentationsart: Poster

Abstract-ID: 15

Dyspnea, joint pain, and recurrent fever are associated with CSU severity: Updated results of the UCARE Project "CSUplus"

Lueschow, J. [1]; Alperen Çevik, A. [27]; Bartosińska, J. [22,23]; Bavbek, S. [14]; Bidovec Stojkovic, U. [5]; Bizjak, M. [5,25,26]; Bouillet, L. [34]; Buranaporn, P. [17]; Cihanbeylerden, M. [19]; Conlon, N. [7]; Efe, O. [14]; Erdem, Y. [27]; Felipe Ensina, L. [6]; Fomina, D. [8,9,10]; Giménez-Arnau, A. M. [11]; Gülengül, M. [28]; Herzog, L. [1,2]; Karakaya, G. [19]; Koblowska, K. [12]; Kocatürk, E. [1,2,16]; Krasowska, D. [22]; Kulthanan, K. [17]; Li, J. [24]; Li, P. H. [3]; Makris, M. [18]; Mungan, D. [14]; Nasr, I. [21]; Nojarov, N. [1,2]; Özkaya, E. [27]; Papapostolou, N. [18]; Peng, C. [24]; Pesqué, D. [11]; Podder, I. [20]; Salameh, P. [1,2,29,30,31,32]; Singh Saini, S. [33]; Szczepanik-Kułak, P. [22]; Tomaszewska, K. [12]; Tosun, M. [8]; Tuchinda, P. [17]; Türk, M. [4]; Xiong, F. [24]; Zalewska-Janowska, A. [12]; Kolkhir, P. [1,2]; Siebenhaar, F. [1,2*] and Pyatilova, P. [1,2*]

[*] Contributed equally

1 Institute of Allergology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany.
2 Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin, Germany.
3 Division of Rheumatology and Clinical Immunology, Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong SAR, China.
4 Division of Immunology and Allergy, Department of Chest Diseases, Erciyes University Faculty of Medicine, Kayseri, Turkey.
5 Division of Allergy, University Clinic of Respiratory and Allergic Diseases Golnik, Golnik, Slovenia.
6 Division of Allergy, Clinical Immunology and Rheumatology, Department of Pediatrics, Federal University of São Paulo, CPAlpha Clinical Research Center, São Paulo, Brazil.
7 School of Medicine, Trinity College Dublin, St James's Hospital Dublin, Dublin, Ireland.
8 Department of Dermatology and Venereology, Sivas Cumhuriyet University, Sivas, Turkey.
9 Department of Clinical Immunology and Allergology, I.M., Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia.
10 Department of Pulmonology, Astana Medical University, Kazakhstan.
11 Department of Dermatology, Hospital del Mar and Research Institute, Barcelona, Universitat Pompeu Fabra, Barcelona, Spain.
12 Psychodermatology and Neuroimmunobiology of the Skin Department, Medical University of Lodz, Lodz, Poland.
13 Allergy Unit, 2nd Department of Dermatology and Venereology, University Hospital "Attikon", National and Kapodistrian University of Athens, Athens, Greece.
14 Division of Immunology and Allergy, Department of Chest Diseases, Ankara University Faculty of Medicine, Ankara, Turkey.
15 Allergy Research Center, Mashhad University of Medical Science, Mashhad, Iran.
16 Bahcesehir University School of Medicine, Department of Dermatology, Istanbul, Turkey.
17 Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.
18 Allergy Unit, 2nd Department of Dermatology and Venereology, National and Kapodistrian University of Athens, University General Hospital "Attikon", Athens, Greece.
19 Division of Allergy and Immunology, Department of Chest Diseases, Hacettepe University School of Medicine, Ankara, Turkey.

[20] Department of Dermatology, College of Medicine and Sagore Dutta Hospital, Kolkata, West Bengal, India.
[21] Immunology and Allergy Department, The Royal Hospital, Muscat, Oman.
[22] Department of Dermatology, Venereology and Pediatric Dermatology Medical Uniwersity of Lublin, Poland.
[23] Department of Cosmetology and Aesthetic Medicine Medical University of Lublin, Poland.
[24] Department of Dermatology, Xiangya Hospital, Central South University, Changsha, Hunan, China.
[25] Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia.
[26] Faculty of Medicine, University of Maribor, Maribor, Slovenia.
[27] Department of Dermatology and Venereology, Istanbul University, Istanbul Faculty of Medicine, Turkey.
[28] Gazi University Faculty of Medicine, Department of Dermatology, Turkey.
[29] School of Medicine, Lebanese American University, Byblos, Lebanon.
[30] Institut National de Santé Publique d'Épidémiologie Clinique et de Toxicologie-Liban (INSPECT-LB), Lebanon.
[31] Department of Primary Care and Population Health, University of Nicosia Medical School, 2417, Nicosia, Cyprus.
[32] Faculty of Pharmacy, Lebanese University, Hadat, Lebanon.
[33] Division of Allergy and Clinical Immunology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.
[34] National Reference Center for Angioedema (CREAK), Department of Internal Medicine/Clinical Immunology, Grenoble Alpes University Hospital, Grenoble, France.

Background: Additional non-defined signs and symptoms (ANDSiSys), referring to those not included in the current clinical definition of chronic spontaneous urticaria (CSU), are present in up to 66% of patients but remain poorly understood. This study aimed to determine how often, which and why ANDSiSys are present in CSU.

Methods: Patients were recruited from UCAREs. A patient-completed questionnaire included demographics, comorbidities, treatment response, intensity and onset of ANDSiSys, and validated patient-reported outcome measures (i.e., UCT, CU-Q_2oL and AECT).

Results: A total of 741 CSU patients from 13 countries were analyzed (mean age 43 years [range 18−85], median disease duration 24 months [IQR 10−60], 74.9% were female). Most reported wheals (58.2%) or wheals and angioedema (36.0%). The most common comorbidities were arterial hypertension (15.9%; n = 118), allergic rhino conjunctivitis (9.3%; n = 69), asthma (6.7%; n = 50), dyslipidemia (5.8%; n = 43) and Hashimoto thyroiditis (5.8%; n = 43). Every second patient (53.8%; n = 399) reported ≥1 ANDSiSys, most commonly joint pain (15.1%; n = 112), dyspnea („feeling unable to breathe in enough air/chest tightness", 14.4%; n = 107), flush (12.8%; n = 95), headache (12.7%; n = 94) and muscle pain (11.6%; n = 86). Dyspnea intensity was associated with poorer disease control and quality of life (UCT: β = -0.004, p = 0.001; CU-Q_2oL: β = 0.015, p <0.001), with stronger effects when dyspnea onset coincided with CSU (UCT: β = -0.186, p = 0.008; CU-Q2oL: β = 0.622, p <0.001). In patients without comorbidities, joint pain was also linked to poorer disease control (UCT: β = -0.003, p = 0.035). Among those with angioedema (with or without wheals), joint pain and recurrent fever were associated with poorer disease control (AECT: β = -0.004, p = 0.04; β = -0.008, p = 0.01).

Conclusions: Dyspnea was the most relevant ANDSiSys and was associated with poorer disease control and quality of life, particularly when it began concurrently with CSU. In patients with angioedema, joint pain and recurrent fever were linked to poorer disease control.

Kategorie: Allergy and AD
Präsentationsart: Poster

Abstract-ID: 16

Mrgprb2-induced anaphylaxis, but not IgE-mediated anaphylaxis, differs between KitD814V-mutant mastocytosis and control mice

Clauss, L.[1], Konantz, M.[1], Almeida Fonseca, T.[1], Ratti, E.[1], Makeeva, A.[1], Sheremeti, E.[1], Usart, M. [1], Stivala, S.[1], Hartmann, K.[1,2,3].

1 Department of Biomedicine, University Hospital Basel and University of Basel, Basel, Switzerland;

2 Division of Allergy, Department of Dermatology, University Hospital Basel and University of Basel, Basel, Switzerland;

3 Department of Clinical Research, University Hospital Basel and University of Basel, Basel, Switzerland

Introduction: Mastocytosis is characterized by the expansion and activation of mast cells (MC), particularly in the skin and bone marrow (BM), driven by a specific mutation in the KIT gene, KIT D816V, in over 90% of patients. The disease is associated with various symptoms of MC degranulation, including anaphylaxis, that can be life-threatening. Our lab utilizes a novel mouse model expressing the murine homologue of KIT D816V, Kit D814V, in all BM-derived hematopoietic stem cells (Scl-Cre;KitD814Vfl). Upon transgene induction, Scl-Cre;KitD814Vfl mice show increased numbers of mast cells, altered blood counts, extramedullary hematopoiesis and reduced survival, thus a phenotype that closely resembles human systemic mastocytosis. In the present study, we aimed to explore anaphylaxis in Scl-Cre;KitD814Vfl mice.

Methods: Anaphylaxis was induced by IgE-mediated (DNP-HSA or phospholipase A_2) and Mrgbrb2-mediated (ciprofloxacin) MC activation, and body temperature changes were recorded to assess the severity of the anaphylactic reaction. Serum samples were collected before and after anaphylaxis and cytokine release profiles were analyzed using the Olink Target 48 cytokine panel. For therapeutic intervention, mice were treated with the KIT-targeting tyrosine kinase inhibitor avapritinib for 16 consecutive days.

Results: KitD814V-mutant mice responded similarly to IgE-mediated anaphylaxis as their corresponding control littermates. However, significant differences in the decrease of body temperature between mutant mice and controls were observed following anaphylaxis induction with ciprofloxacin. Analyzing various serum cytokines before and after the anaphylactic reaction, we found a classic MC activation signature after anaphylaxis with “core” anaphylaxis cytokines, such as IL-10, IL-16 and CCL-12, among others, being elevated in both groups. Interestingly, certain cytokines were elevated in mastocytosis mice only, including IL-17f, IL-22 and Pdcd1lg2. Oral treatment of mice with avapritinib for 16 days reduced the severity of the anaphylactic reaction in mutant mice.

Discussion: In summary, using a novel transgenic mouse model of mastocytosis, we demonstrate that both the severity of anaphylaxis and the associated cytokine release profile differ between mutant and control mice. In particular, Mrgbrb2-mediated anaphylaxis was increased in Scl-Cre;KitD814Vfl mice. Treatment with avapritinib was able to effectively reduce the severity of anaphylaxis.

Kategorie: Allergy and AD
Präsentationsart: Poster

Abstract-ID: 17

The Role of Neutrophils in the Pathogenesis of Chronic Spontaneous Urticaria and Delayed Pressure Urticaria

Britz, M.[1]; Shankar, S.[1]; Wulfert, F.[1]; Steinert, M.[1]; Albers, C.[1]; Sulk, M.[1]; Erpenbeck, L.[1]

[1]Department of Dermatology, Venereology and Allergology, University Hospital Münster, Münster, Germany

Background: Urticaria has a lifetime prevalence of 20 % of the population and markedly impairs quality of life. For patients with chronic spontaneous urticaria (CSU) or delayed pressure urticaria (DPU) unresponsive to antihistamines treatment options are limited. A better understanding of underlying mechanisms is therefore essential.

Objective: We aim to shed light particularly on the pro-inflammatory role of neutrophils in chronic urticaria, including CSU and DPU, in order to identify novel therapeutic targets.

Methods: Skin biopsies from symptomatic CSU (n = 18–19), DPU (n = 10–14) and healthy controls (n = 5) were analyzed for neutrophil infiltration, NET formation and IL-17A-positive neutrophils by immunofluorescence. Peripheral blood neutrophils from CSU (n = 8) and DPU (n = 5) patients were examined by flow cytometry and neutrophil extracellular trap (NET) formation was evaluated, respectively. A proof-of-concept study with the IL-23 inhibitor Tildrakizumab was conducted in DPU (n = 4; injections at weeks 0, 4, 12). Disease activity (UCT) and quality of life (CU-Q2oL) were recorded longitudinally; in two patients, blood neutrophils were re-analyzed during therapy.

Results: Overall neutrophil infiltration was comparable between CSU and DPU but significantly higher in the deep dermis of DPU patients. NETosis occurred in both diseases, with a markedly increased rate in DPU. IL-23$^+$ cells were located in close spatial proximity to IL-17A$^+$ neutrophils. Peripheral blood analysis revealed enhanced neutrophil activation in both CSU and DPU compared to healthy controls, most pronounced in DPU, indicating a pro-inflammatory phenotype. Tildrakizumab treatment reduced peripheral neutrophil activation and improved symptoms, reflected by higher UCT and CU-Q2oL scores.

Conclusion: DPU shows stronger neutrophil activation and higher NETosis rates than CSU, both cutaneously and systemically, suggesting distinct activation patterns. The IL-23/IL-17 axis appears central in sustaining neutrophil activation and NET formation. Clinical improvement under Tildrakizumab highlights this pathway as a promising therapeutic target and underscores the key role of neutrophils in chronic urticaria.

Clinical Implications: Neutrophils play a pivotal role in CSU and DPU inflammation, particularly in DPU. Targeting neutrophil- and NET-associated cytokines such as IL-23 and IL-17 may offer new therapeutic options for patients refractory to standard treatment.

Kategorie: Allergy and AD
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 18

Epicutaneous sensitization followed by intradermal challenge of mice transgenic for the human TLR4 resembles a physiological model to study nickel contact dermatitis

Maximilian Heppel[1*], Marc Schmidt[2], Matthias Goebeler[2], Michael Peter Schön[1], Andrea Braun[1]

[1]Department of Dermatology, Venereology, and Allergology, University Medical Center Göttingen, Germany
[2]Department of Dermatology, Venereology, and Allergology, University Medical Center Würzburg, Germany

Nickel is one of the most frequent causes of allergic contact dermatitis (ACD). The underlying cellular mechanism of ACD is a type IV hypersensitivity reaction, mediated by dendritic cell sensitization and a T-cell dependent immune reaction. However, the exact interplay of immune cells that cause nickel allergy still needs further investigations.

To study ACD in mice, the classical contact hypersensitivity model (CHS) by epicutaneous allergen deposition is used since decades. However, as nickel is a weak sensitizer in mice, the state-of-the art mouse model for nickel sensitization uses the injection of nickel together with an adjuvant. This is due to the fact, that the murine TLR4 does not have the respective Ni^{2+} binding sites, and therefore mice expressing murine *Tlr4* usually lack binding and respective activation of the TLR4 pathway after nickel application. Our aim was therefore to establish a more physiological mouse model, which resembles the topical exposure routes found in humans using an epicutaneous sensitization treatment regime as it is used for classical CHS. To accomplish this, we utilized transgenic mice harboring the human TLR4 receptor (hTLR4), but lacking the murine counterpart.

In a first step, *hTLR4*-mice were epicutaneously treated by different concentrations of $NiCl_2$ in petrolatum (2.5-10%) during both, the sensitization and challenge phase. In this context, the number of sensitizations (1, 2 or 3) and the time until challenge (d5 and d14) was varied. However, no measurable increase in ear thickness as indicator of clinical severity could be induced in these mice.

Speculating that epicutaneous treatment is below threshold level, we assumed that the reaction might be triggered to induce clinical signs with a measurable increase in ear thickness by using an adjuvant. Since LPS is a known enhancer in the classical mouse models of nickel contact dermatitis, we next used the addition of LPS during sensitization or challenge phase together with the above mentioned epicutaneous $NiCl_2$ application (10%). Interestingly, none of these treatments were sufficient to induce a proper effector reaction.
However, when using topical sensitization (10% in petrolatum) together with intradermal (i.d.) injection of $NiCl_2$ during challenge, mice developed a robust ear swelling response indicating that epicutaneous nickel application is sufficient for sensitization. Moreover, this reaction could be further enhanced by application of LPS either during sensitization or challenge phase, irrespective of the route of application, since similar results were yieled when LPS was applied systemically (i.p.) or locally (s.c.).

Together, epicutaneous sensitization with $NiCl_2$ in petrolatum indeed leads to sufficient sensitization in hTLR4-transgenic mice. However, this treatment requires a challenge regime with a direct deposition of $NiCl_2$ in the skin via intradermal injection to induce a clinical reaction during effector phase. Thus, this model more closely resembles the sensitization path in humans and therefore allows to further dissect the immunological and molecular processes that take place during nickel contact dermatitis.

Kategorie: Allergy and AD
Präsentationsart: Poster

Abstract-ID: 19

A functional human iPSC-derived KIT D816V mast cell model for investigating BTK signaling in systemic mastocytosis

Hu, M.[1,2]; Miller, DC.[1,2]; Scheffel, J.[1,2]; Luo, Y.[1,2*]; Siebenhaar, F.[1,2*]

[1]Institute of Allergology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

[2]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany

*Contributed equally

Introduction

Systemic mastocytosis (SM), primarily driven by the gain-of-function KIT D816V mutation, leads to aberrant mast cell (MC) proliferation and activation. Clinical manifestations including pruritus, flushing, and anaphylaxis, result from excessive release of MC mediators. Bruton's tyrosine kinase (BTK) is a key downstream effector in FcεRI-dependent signaling pathways, which plays a central role in MC mediator release and activation. This study used recently established functional human induced pluripotent stem cell-derived mast cells carrying the KIT D816V mutation (hiPSC-MCs$^{KIT\ D816V}$) to investigate BTK signaling and evaluate their potential as a model for preclinical testing of BTK-targeted therapies in SM.

Methods

hiPSC-MCs$^{KIT\ D816V}$ and control cells were differentiated following established protocols and characterized by flow cytometry for MC-specific surface markers, such as CD117 and FCƐRI. MC activation was assessed by release of ß-hexosaminidase. Western blot was performed to show phosphorylation of KIT and its downstream signaling. Phosphorylation of BTK (pBTK) was assessed by intracellular flow cytometry (FACS) at baseline or following IgE sensitization and anti-IgE stimulation.

Results

hiPSC-MCs$^{KIT\ D816V}$ displayed typical MC phenotypes and robust IgE-mediated degranulation and upregulated phosphorylation of BTK. In contrast to control MCs, mutant MCs exhibited constitutive phosphorylation of KIT and certain downstream effectors. Notably, hiPSC-MCs$^{KIT\ D816V}$ showed an elevated basal pBTK level even in the absence of stimulation.

Discussion

We have established a functional hiPSC-derived MC model harboring the KIT D816V mutation that recapitulates the constitutive activation of KIT and the downstream signaling characteristics of systemic mastocytosis. This model suggests aberrant BTK activation as a potential effector of KIT D816V-driven mast cell hyperactivity. We are continuing development of this robust in vitro platform, for dissecting BTK-dependent mechanisms and for preclinical evaluation of BTK inhibitors as potential treatment strategies for SM patients.

Kategorie: Allergy and AD
Präsentationsart: Poster

Abstract-ID: 20

Cefuroxime-specific IgE analysis using an allergenic determinant of cefuroxime

Leonard George[1,2]; Timo Buhl[3]; Christian Möbs[1]; Wolfgang Pfützner[1,4]

[1]Clinical & Experimental Allergology, Department of Dermatology and Allergology, Philipps-Universität Marburg, Marburg, Germany; [2]Department of Trauma Surgery, Orthopedics and Sports Traumatology, Evangelisches Krankenhaus Oldenburg, Oldenburg, Germany; [3]Department of Dermatology, Venereology and Allergology, University Medical Center Göttingen, Göttingen, Germany; [4]Department of Dermatology and Allergology, Allergology Section, Allergy Center Hesse, University Hospital Marburg, Marburg, Germany

Cefuroxime is a second-generation cephalosporin antibiotic that is frequently used in surgical disciplines as perioperative prophylaxis. Immediate skin reactions to cephalosporins have been reported with a frequency of 1 to approximately 3%, and systemic reactions are considered a very rare event, occurring at a frequency of 1 in 1,000 to 100,000 applications. However, cefuroxime is one of the most common triggers of drug anaphylaxis in Germany, and therefore diagnostic skin tests with cefuroxime always bear a certain risk of anaphylactic reactions. Consequently, there is a high need for reliable test systems detecting cefuroxime-specific IgE antibodies in patient serum as a safe alternative.

To test whether an allergenic determinant of cefuroxime improves identification of patients with cefuroxime sensitization in comparison to other established diagnostic methods, we included 409 patients with a history of IgE-mediated immediate-type allergy to betalactam antibiotics (BLA) in this study. Patients with suspected BLA allergy were further characterized by skin tests, basophil activation tests and/or oral provocation tests (OPT), and by serum analysis of total IgE and allergen-specific IgE to set of commercially available BLA (i.e. penicilloyl G/V, amoxicillin, ampicillin, cefaclor) and the cefuroxime-determinant. Based on these results, patients were divided into subgroups for calculating the sensitivity and specificity of the specific IgE test utilizing the allergenic determinant of cefuroxime. Comparison of patients with only a history of an immediate-type allergy to cefuroxime (n=83) and patients with, in addition, a confirmed hypersensitivity to cefuroxime by skin test, BAT and/or OPT (n=21) revealed positive IgE test results for the cefuroxime-determinant in 14.5% and 9.5%, as well as in 26.5% and 23.8% of the patients using a cut-off of 0.35 kUA/l and 0.1 kUA/l, respectively. Accordingly, the determinant-based analysis of cefuroxime-specific IgE showed a lower sensitivity for the diagnosis of patients with suspected cefuroxime allergy compared to skin tests, but a high specificity. Thus, component-based IgE testing represents an added value with regard to the exclusion of cefuroxime sensitization, but it is not suitable for determining the causative allergen in suspected BLA/cefuroxime-associated anaphylaxis.

Kategorie: Allergy and AD
Präsentationsart: Poster

Abstract-ID: 21

Deciphering the Immune Events Underlying Percutaneously Acquired Wheat Allergy

Ercan, N[1]; Kandage, S[1]; Kiani, C[1]; Kaesler, S[1]; Biedermann, T[1]; Brockow, K[1]

1 Technical University Munich, Department of Dermatology and Allergy Biederstein, Munich, Germany

Introduction: Food allergy (FA) is an acquired pathological defense reaction to non-self but harmless food components. It is a complex, multifactorial disease influenced by genetic, environmental and immunological factors but the exact pathomechanism remains unclear. Recent research has shown that percutaneous sensitization is an important mechanism for the development of food allergy. The dual allergen exposure hypothesis proposes that the initial route of allergen exposure can determine the immune outcome which could be either developing tolerance via oral exposure or allergic sensitization and subsequent food allergy via exposure through a compromised skin barrier. This hypothesis explains the significantly higher risk of food allergies in children with atopic dermatitis (AD) which is characterized by an impaired skin barrier.

Wheat allergy is one of the most common one with a prevalence of 0.2% to 1%. In adults, the most common form is wheat-dependent exercise-induced anaphylaxis (WDEIA), an IgE-mediated wheat allergy requiring cofactors like exercise, alcohol or specific drugs to trigger an allergic reaction after eating wheat products. Sensitization leading to wheat allergy can occur via the skin as evidenced by an outbreak of WDEIA in Japan in >1000 people who have used the same facial soap containing the hydrolyzed wheat protein (HWP). Our project focuses on identifying the mechanisms underlying the susceptibility for percutaneous initiation of wheat allergy. Therefore, we aimed to establish a mouse model to characterize and functionally prove involved networks driving the percutaneous wheat sensitization and subsequent wheat allergy.

Methods: A **proof-of-principle experiment was conducted** to validate the feasibility of our sensitization model. Gliadin was applied to mice via two different sensitization routes such as epicutaneous and intraperitoneal injection. The epicutaneously sensitized groups received tape stripping (or SDS) to mimic the skin barrier disruption along with gliadin application. After gliadin exposure process, mice received both local and systemic challenges to observe the clinical symptoms and allergic reaction.

Results: The efficiency of sensitization was validated by the increased production of gliadin-specific IgE and IgG1 antibodies. These mice sensitized to gliadin developed systemic anaphylaxis upon challenge.

Discussion: This preliminary study demonstrated that epicutaneous exposure to gliadin, particularly in the context of skin barrier disruption, can elicit systemic allergic responses upon re-exposure to the allergen.

Kategorie: Allergy and AD
Präsentationsart: Poster

Abstract-ID: 22

The role of inflammaging in contact hypersensitivity

Forssmann, Lennard (1); Rühl-Muth, Ann-Catherine (1); Martin, Stefan F. (1); Esser, Philipp R. (1)

(1) Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg,

Department of Dermatology and Venereology, Freiburg, Germany

Allergic contact dermatitis is a classical T cell mediated type IV reaction. This sterile inflammatory skin disease occurs with a prevalence of 5-10% in the general European population and is caused by repeated exposure to one of the ~4000 known chemical sensitizers. The role of the innate immune response not only for the sensitization but also the elicitation phase of ACD (and in the murine model contact hypersensitivity (CHS)) is becoming increasingly clear - without complete activation and maturation of dendritic cells (DCs), activation and proliferation of antigen-specific T cells does not occur. The Toll-like receptor (TLR) family, particularly TLRs -2 and -4, plays a key role in the innate immune response. It is known that mice lacking TLR2+4 or TLR4+interleukin-12 receptor β2 (IL12Rβ2) are resistant to the development of CHS – a state that can be overcome by heterologous activation of the innate immune system, e.g., by injection of the synthetic oligonucleotide CpG, thereby activating TLR9. Recently, we realized that while TLR2/4 deficient mice are resistant to CHS responses as long as they are young (up to 12 weeks old), they do show allergic responses to TNCB at older age despite the genetic knockout being still present. Therefore, we speculate that ageing associated inflammation itself might mimic the heterologous innate immune stimulation and might be responsible for the restoration of CHS susceptibility. Especially the occurrence of senescent cells in the aged organism with their massive production of the senescent associated secretory phenotype (SASP) including the release of several pro-inflammatory cytokines could promote the CHS reactions. In an attempt to mimic the aged situation in the TLR2/4 deficient mice, which show a significant increase in body weight, we performed high fat diet (HFD) feeding and observed that even at a young and in general CHS-resistant age, the mice were responsive to TNCB treatment. As HFD is known to result in chronic inflammation by the induction of a senescent cellular phenotype, this was another indicator that ageing might contribute to CHS potency. To check that aged TLR2/4 mice do not simply become susceptible to CHS due to a reduced skin barrier function, we performed lucifer yellow penetration studies and were able to show that the skin barrier remains intact, even for mice > 400 days of age. Most importantly, when we treated aged TLR2/4 deficient mice with the senomorphic rapamycin effectively downmodulating the SASP secretion by following a protocol with a sneak-out time to avoid unintentional side-effects on mTOR signalling, we observed a reversion of the susceptibility to TNCB-induced CHS responses to the `young´, resistant phenotype even in old (53 weeks) mice. This reversion was correlated to a change in gene marker expressions such as p21, ERCC1 and Nrf2 which were differentially expressed between young and old mice and were reverted to the young situation when comparing rapamycin treated with solvent treated old mice. To further assess the functionality of the lymph node cells, we performed an ex vivo stimulation with PMA/ionomycin comparing solvent and rapamycin treated mice and observed no difference in the T cell response as measured by IFN-gamma secretion. These results provide first indications that ageing itself might promote the susceptibility to sensitizers due to the generation of a chronic proinflammatory skin micromilieu and that senomodulation, especially when applied local and topically, might provide a strategy to aid current treatment options.

Kategorie: Allergy and AD
Präsentationsart: Poster

Abstract-ID: 23

Single cell analysis reveals dynamic changes of distinct cell populations in human nickel allergy

Schmidt, M.[1], Knorz, A.[1], Meder, K.[1], Goller, S.[1], Imdahl, F.[2], Rocca, Y.[1], Goebeler M.[1], Khoueiry, P.[2]

1 Department of Dermatology, University Hospital Würzburg, Würzburg, Germany

2 Single Cell Center Würzburg, Helmholtz Institute for RNA-based Infection Research (HIRI), Würzburg, Germany

Introduction:
Metal allergies are prime examples of delayed-type hypersensitivity divided into two phases: In the sensitization phase, initial contact with an allergen leads to activation of skin-resident cells and formation of metal-reactive T cells. During elicitation, these T cells mount an immune response resulting in clinically apparent eczema within 72h after exposure. Two main mechanisms have been implicated in the initiation of metal hypersensitivity: Direct or indirect activation of innate immune receptors such as Toll-like receptor 4, and conditional innate immune activation via the NLRP3 inflammasome. Yet, the responsible cell type(s) mediating these responses are unknown. Moreover, it is unclear whether the elicitation phase is mainly dominated by infiltration of circulating metal-responsive T cells or if tissue-resident T cells contribute.

Methods:
Here, we analyzed the relevance of different cell types in human nickel hypersensitivity by single-cell RNA sequencing and immunofluorescence analysis of skin samples of nickel-sensitized donors epicutaneously exposed to diluent and nickel for 8 or 72h.

Results and Discussion:
Nickel specifically activated distinct populations of endothelial cells, suprabasal keratinocytes, fibroblasts, and CCR7$^+$ dendritic cells, co-expressing the TLR4-interacting proteogylcan DCN and CCR7 ligand CCL21 within 8 h. Skin-resident T cells were not involved in the early hypersensitivity response, as their gene expression remained unaltered 8h after nickel exposure. However, substantial changes in the cutaneous T cell compartments occurred after 72h, with massive infiltration of KLF2$^+$ central memory T cells being a recurrent feature of both nickel-sensitized patients and individuals allergic to the glucocorticoid contact allergen budesonide.

Kategorie: Allergy and AD
Präsentationsart: Poster

Abstract-ID: 24

Regulation of the AhR signaling pathway during allergic contact dermatitis

Santiago Valle Torres[1], Irmgard Förster[1] and Heike Weighardt[1]

[1]Immunology and Environment - Life and Medical Sciences Institute, Bonn, Germany

The aryl hydrocarbon receptor (AhR) has a well-known role in regulating skin barrier function and allergic reactions. Its activity is regulated by the AhR repressor (AhRR) and three cytochrome P450 (CYP) enzymes, CYP1A1, CYP1A2 and CYP1B1, that metabolize AhR ligands. We have recently shown that the AhRR is highly expressed in immune cells but not epidermal keratinocytes suggesting a different regulatory mechanism for AhR in non-immune skin cells. Therefore, the molecular mechanisms and beneficial or adverse consequences of AhR activation in the skin are not entirely understood. Here we show how deletion of AhR regulatory pathways, such as AhRR and CYP enzyme deficiency, affect onset and pathology of allergy models, such as contact hypersensitivity (CHS) and atopic dermatitis (AD). Mice lacking AhRR and CYP enzymes display different symptoms during CHS despite both being negative regulators of AhR activity. This is potentially caused by differences in the immune response as well as the aforementioned divergent AhRR expression in different cell populations. Thus, our findings will help to understand the mechanism of regulation of AhR activation by AhRR and CYP enzymes in the skin allowing future development of therapeutic agents for cutaneous disorders that target the AhR signaling pathway in the skin.

Kategorie: Allergy and AD
Präsentationsart: Poster

Abstract-ID: 25

Distinct Immunomodulatory Signatures of Nickel Sulfate and Lyral in a Human Immune-Competent Full-Thickness Skin Model

Marvin Nüsken, Moritz M. Hollstein, Prasad Dasari, Michael P. Schön, Timo Buhl
Department of Dermatology, Venereology and Allergology, University Medical Center Göttingen, Germany

Background:
Contact allergens such as nickel sulfate ($NiSO_4$) and the fragrance compound Lyral (HICC) elicit distinct immune polarization patterns, with metals typically inducing Th1/Th17-type and fragrances Th2-type inflammation.

Methods:
To delineate these mechanisms, both allergens were applied to a primary human full-thickness skin model composed of autologous fibroblasts, keratinocytes, and integrated immune cells, enabling analysis under near-physiological conditions. Models were exposed to 0.5% $NiSO_4$ (in PBS or petrolatum) for 24–48 h or to Lyral (in petrolatum) for 24 h. Dinitrochlorobenzene (DNCB) served as positive control. Morphology, cytokine secretion, immune cell activation, and gene expression were assessed by immunohistochemistry, flow cytometry, qPCR, and multiplex cytokine assays.

Results:
Both allergens preserved tissue integrity but induced distinct immune activation profiles. $NiSO_4$ triggered marked upregulation of IL1B, IL12A/B, and IL23A mRNA in epidermal and dermal compartments, accompanied by increased IL17A and IL5 expression and enhanced secretion of IL-10. Expression of the co-stimulatory molecules CD80 and CD86 was differentially regulated, with CD86 upregulated and prolonged exposure reducing CD80 expression. In contrast, Lyral exposure strongly induced MHC-I and CXCL8 mRNA together with secretion of IL-18 and IFN-γ, but without IL12 induction, consistent with a Th2-skewed cytokine milieu.

Conclusion:
$NiSO_4$ elicited a mixed Th1/Th17-type response, whereas Lyral favored Th2-like activation. These findings reproduce key immunological hallmarks of metal- and fragrance-induced contact dermatitis and highlight the potential of immune-competent human skin models for mechanistic allergen profiling and preclinical sensitizer testing.

Kategorie: Allergy and AD
Präsentationsart: Poster

Abstract-ID: 26

Capicua (CIC): A Key Regulator of Mast Cell Homeostasis and Proliferation

Manqiu Jin[1,2]; Daniel Ivanusic[1,2]; Jean Schneikert[1,2]; Alejandra Flores-Gómez[3,4]; Shiva Raj Tripathi[1,2]; Mariano Barbacid[5,6]; Torsten Zuberbier[1,2]; Matthias Drosten[3,4,5]; and Magda Babina[1,2]

1 Institute of Allergology, Charité-Universitätsmedizin Berlin, Freie Universität Berlin and Humboldt Universität Zu Berlin, Berlin, Germany

2 Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany.

3 Molecular Mechanisms of Cancer Program, Centro de Investigación del Cáncer (CIC), Salamanca, Spain

4 Instituto de Biología Molecular y Celular del Cáncer (IBMCC), CSIC-USAL, Salamanca, Spain

5 Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Instituto de Salud Carlos III, Madrid, Spain

6 Tumor Biology Program, Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain

Background: Capicua (CIC) is a highly conserved transcriptional repressor whose inactivation downstream of receptor tyrosine kinases contributes to cell cycle entry. Plausibly, CIC acts as a tumor suppressor that is frequently inactivated in cancers. Our previous work demonstrated that CIC is highly expressed in human skin mast cells (MCs) and dynamically regulated by the SCF/KIT axis to undergo ERK-dependent degradation. *Vice versa*, CIC negatively regulates KIT sensitivity to SCF. Given its role in growth control, CIC dysregulation may predestine to MC hyperproliferation. The aim of this study was to investigate the consequences of CIC loss on numerical changes in human and murine MCs.

Methods: Primary MCs were isolated from human foreskin tissue and expanded in the presence of SCF and IL-4. Knockdown of CIC was achieved using self-delivering siRNA with efficiency confirmation by RT-PCR and Western blot. SCF-dependent proliferation was assessed by monitoring cell counts (Casy Cell Counter and Analyzer), metabolic activity (MTT and ATP assays) and DNA content. The expression of CIC and CIC-repressed genes was compared between primary skin MCs and the MC leukemia line HMC-1. For in vivo studies, conditional Cic deletion was induced in adult mice (UBC-Cre/ERT2 × floxed Cic) by tamoxifen, enabling systemic Cic deletion. Skin samples were sectioned and stained with acidic toluidine blue to visualize and quantify MCs.

Results: CIC silencing could be effectively achieved in purified skin MCs and prompted increased proliferation, as evidenced by numerical changes, cell-associated DNA content, and metabolic activity. The silencing of CIC also upregulated ETV1 and ETV5, key CIC-repressed genes. CIC expression was markedly lower in leukemia-derived HMC-1 cells compared to skin MCs, while expression of ETV1, ETV4 and ETV5 was substantially higher in the cell line. Analyses in mice revealed that the elimination of Cic led to sizeable MC hyperplasia in all skin sites assessed (ear, tail, and back) at three- and eight-months post-inactivation.

Conclusion: Loss or reduction of CIC on its own promotes MC expansion in both human and murine systems, indicating that CIC safeguards MC homeostasis by keeping proliferation at

bay. Selective CIC stabilization may provide new therapeutic avenues for MC-proliferative diseases like mastocytosis.

Kategorie: Allergy and AD
Präsentationsart: Poster

Abstract-ID: 27

Investigation of potential cross-reactivity between house dust mite single allergens and human homologues in atopic dermatitis

Baumann, P. C.[1]; Knape, S.[2]; Jappe, U.[2]; Werfel, T.[1,3]; Roesner, L. M.[1,3]; Traidl, S.[1,3]

[1]Department of Dermatology and Allergy, Hannover Medical School, Hannover, Germany
[2]Division of Clinical and Molecular Allergology, Research Center Borstel, Borstel, Germany
[3]Cluster of Excellence RESIST (EXC 2155), Hannover Medical School, Hannover, Germany

The majority of atopic dermatitis (AD) patients are sensitised to airborne allergens, especially *Dermatophagoides pteronyssinus*, the European house dust mite (HDM). HDMs are one of the most prominent sources of allergens worldwide, with 35 HDM allergens recognised by the WHO/IUIS. While many minor allergens are clinically relevant, their immunological relevance remains poorly understood. Distinct sensitisation patterns have been detected in atopic patients, revealing Der p 20 to be frequently present in AD patients. However, little is known about its allergenic properties and associated T cell responses. Interestingly, Der p 20 shares sequence homologies with the human creatine kinase-B (CK-BB), which is also expressed in the skin. Similarly, Der p 10, an HDM tropomyosin, shares sequence homologies with the human tropomyosin (TPM3). Since it is known that T cells and IgE antibodies can cross-react with tropomyosins from different species and autoreactivity is a known phenomenon in AD, the question arises whether cross-reactivity can occur between these HDM single allergens and their human homologues.

To investigate potential cross-reactivity with self-antigens, allergen-specific T cell responses and their cytokine profiles were assessed. PBMC of HDM-sensitised AD patients were stimulated with either recombinant HDM allergens or the corresponding homologous human proteins. The resulting T cell lines (TCLs) were then co-cultured with irradiated autologous PBMC for antigen presentation and restimulated with the respective HDM allergens and homologous human proteins. Afterwards, T cell proliferation and their released cytokines were measured to assess functional responses and potential cross-reactivity. In addition, serum samples from these patients were analysed using semi-quantitative anti-IgE dot blots and a blocking approach to detect IgE reactivity to HDM allergens and their human homologues.

Specific T cell proliferation could be observed not only for the HDM extract, but also for the HDM single allergens Der p 20 and Der p 10, as well as for their respective human homologues CK-BB and the human tropomyosin. Tropomyosin-specific TCLs could be restimulated with their homologue in individual patients, meaning that Der p 10-specific TCLs were also reactive to the human tropomyosin and vice versa. On the IgE level, anti-Der p 20, anti-CK-BB, anti-Der p 10, and anti-TPM3 specific IgE were detectable via dot blot in the sera of HDM-sensitised AD patients, as a first step indicating cross-reactivity on the IgE level. Additionally, pre-incubation with the respective homologue partially blocked the detection of the specific IgE, confirming the observed results.

These findings suggest that IgE and T cell cross-reactivity can occur in individual patients between HDM allergens and human proteins, supporting the hypothesis that HDM exposure may contribute to the exacerbation of AD not only through classical allergenic pathways but also by promoting autoreactivity. Furthermore, targeted identification of sensitisation to minor allergens could allow for more personalised and precise therapy in the long term.

Kategorie: Allergy and AD
Präsentationsart: Poster

Abstract-ID: 28

Unraveling the Sweet Side of IgE: Glycosylation Modulates Disease Severity in Peanut Allergy

Carolin Steinert[1,2,3]; Johannes Stadlmann[4]; Sabine Altrichter[1,2,5,6,7]; Jörg Scheffel[1,2]

1 Institute of Allergology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

2 Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany

3 Department of Biology, Chemistry and Pharmacy, Freie Universität Berlin, Berlin, Germany

4 Institute of Biochemistry, Department of Chemistry, University of Natural Resources and Life Sciences (BOKU), Vienna, Austria

5 Department of Dermatology and Venerology, Kepler University Hospital, Linz, Austria

6 Center for medical research, Johannes Kepler University, Linz, Austria

7 Clinical Research Institute for Inflammation Medicine, Medical Faculty, Johannes Kepler University, Linz, Austria

Introduction:

Immunoglobulin E (IgE) plays a central role in allergic diseases, mediating hypersensitivity reactions through interactions with the Fc epsilon RI on mast cells and basophils. Emerging evidence suggests that glycosylation modifications, particularly sialylation, significantly influence IgE's functional properties. This study aims to explore the role of IgE glycosylation in peanut allergy, with focus on disease-associated glycosylation patterns and the immunomodulatory impact of IgE sialylation.

Methods:

Ara h 2/6 specific IgE antibody derived from immortalized B cells of a peanut allergic patient was enzymatically modulated to alter terminal sialylation levels. The resulting IgE variants with high and low sialic acid content were checked for glycosylation status via *Sambucus nigra* lectin blot and used to evaluate IgE- Fc epsilon RI -mediated mast cell activation and IgE-mast cell binding by flow cytometry. Further, plasma samples from well characterized peanut allergic patients (n=30) were assessed for their IgE glycome. Based on oral food challenge threshold levels, patients were stratified into low threshold responders (LTR) and high threshold responders (HTR). Total IgE was purified from plasma using an anti-IgE pulldown approach followed by SDS-Page. Subsequently glycan profiling was performed by liquid chromatography-electrospray ionization tandem mass spectrometry (MS).

Results:

Treatment of Ara h 2/6 specific IgE with β-1,4-galactosyltransferase and α-2,6-sialyltransferase resulted in a high sialic acid content (high sial. IgE), while IgE treated with Sialidase A resulted in undetectable sialic acid (low sial. IgE). Mast cells sensitized with high sial. IgE showed significantly less activation after stimulation with anti-IgE and Ara h 6 compared to cells sensitized with low sial. IgE. However, no differences in IgE binding to mast cells were detected between the two IgE variants.

Using MS on IgE purified from patient samples, all six glycosylation sites could be analyzed, showing a preference of high mannose type carbohydrates at N275 while all other sites were predominantly occupied by complex type N-glycans. Samples revealed an individual

heterogeneity regarding their carbohydrate composition. Reduced terminal galactose ($p = 0.0078$) but increased terminal N-acetylglucosaminylation ($p = 0.0404$) were detected in IgE from LTR patients, as compared to HTR ones. Also, side-specific differences at N173 and N219 were observed between both patient groups with LTR having less sialic acid, galactose and core fucose but more N-acetylglucosamine (GlcNAc) and mannose residues.

Discussion:

Mainly galactose, GlcNAc and sialic acid content was different between low and high threshold peanut allergic patients. Further studies involving larger cohorts will be necessary to verify these results. In addition, unspecific or specific IgE to other allergens may obscure specific allergy associated glycosylation patterns, requiring the enrichment of specific IgE instead of total IgE for analysis.

Kategorie: Allergy and AD
Präsentationsart: Poster

Cellular biology

Abstract-ID: 29

Unveiling PTX3: a novel biomarker in the pathogenesis of bullous pemphigoid

Urban, L. S.[1]; Hoffmann, M. H.[2]; Ludwig, R. J.[1,3]; Schmidt, E.[1,4]; Emtenani, S.[1]

1 Lübeck Institute of Experimental Dermatology, University of Lübeck, Lübeck, Germany

2 Institute for Systemic Inflammation Research, University of Lübeck, Germany

3 Institute and Comprehensive Center for Inflammation Medicine, University-Hospital Schleswig-Holstein, Lübeck, Germany

4 Department of Dermatology, University-Hospital Schleswig-Holstein, Lübeck, Germany

Bullous pemphigoid (BP), the most common autoimmune blistering disease, is characterized by autoantibodies targeting type XVII collagen (BP180), leading to complement activation and leucocyte-mediated tissue injury. This study investigated the role of pentraxin 3 (PTX3), an acute-phase protein regulating innate immunity, inflammation, and complement activation, in BP pathogenesis. Serum and plasma levels of PTX3 were significantly elevated in BP patients compared with healthy controls. Immunohistochemical analysis demonstrated pronounced PTX3 upregulation in early BP skin lesions, predominantly in keratinocytes and innate immune cells, including neutrophils, mast cells, dendritic cells, and macrophages, relative to matched controls. *In vitro*, stimulation of HaCaT keratinocytes with anti-BP180 NC16A IgG induced BP180 internalization and elevated IL-8 secretion; however, PTX3 expression remained unchanged. Pharmacological modulation of the upstream NF-κB/PTX3 axis using Y-27632 (a ROCK1/2 inhibitor) and GGTI298 (a RhoA/Rac inhibitor) markedly reduced dermal-epidermal separation in *ex vivo* human skin model. Notably, GGTI298, but not Y-27632, significantly attenuated reactive oxygen species (ROS) production in immune complex-activated neutrophils. Collectively, these findings establish PTX3 as a key contributor to BP pathogenesis and suggest that targeting the NF-κB/PTX3 pathways could mitigate neutrophil-driven tissue damage. Thus, PTX3 may serve as a future diagnostic biomarker and therapeutic target for early-stage BP management, a hypothesis that we are currently exploring *in vivo*.

Kategorie: Cellular biology
Präsentationsart: Poster

Abstract-ID: 30

Defining the Relevance of BP230-Specific Autoantibodies in Bullous Pemphigoid Pathogenesis

Johannisson, S.[1]; Schittek, B.[2]; Sauer, B.[2]; Fehrenbacher, B.[2]; Enk, A.[1]; Hadaschik, E.[1]

1 Heidelberg University Hospital, Department of Dermatology, Heidelberg, Germany
2 Tübingen University Hospital, Department of Dermatology, Tübingen, Germany

Introduction
Bullous pemphigoid (BP) is an autoimmune blistering disease characterized by the presence of circulating autoantibodies directed against BP180 and BP230, both essential structural components of the hemidesmosomal complex. While the pathogenic relevance of BP180-specific autoantibodies is well established, the contribution of BP230-specific autoantibodies - particularly those recognizing epitopes within the N-terminal domain - remains unclear due to the intracellular localization of BP230.

Methods
To investigate the immunogenic potential of N-terminal BP230 autoantibodies in an active BP mouse model, K5-Cre:BP230 knock-out (KO) mice were immunized with BP230 fragments. Given the pivotal role of $CD4^+$ T cells in BP pathogenesis, FACS-sorted $CD4^+$ T cells from spleens of immunized K5-Cre:BP230 KO mice were transferred to nude mice lacking mature T cells but display a normal B cell compartment. A pathogenic murine monoclonal IgG1 antibody isolated from Treg-deficient scurfy mice which targets the SR9 domain of the N-terminal domain of BP230 is 20B12. Focusing on the pathogenic mechanism, a blister-inducing capacity in vivo after injecting 20B12 into neonatal C57BL/6 (WT) mice as well as in Fc-gamma-receptor KO mice have already been demonstrated but not in complement factor 3 (C3) KO mice and in a human skin model.

Results
Immunization of K5-Cre:BP230 KO mice with human/murine BP230 resulted in the induction of BP230-specific autoantibody production. FACS-sorted $CD4^+$ T cells showed a similar activation status among all experimental groups. In serum of nude mice adoptively transferred with BP230-reactive T cells circulating skin-specific antibodies could be detected as early as two weeks after start of transfer in some individuals. Despite displaying autoantibodies nude mice transferred with BP230-reactive $CD4^+$ T cells did not develop clinical skin symptoms independent from the BP230 epitope used for immunization and showed no health-related loss in body weight. Injection of murine 20B12 in C3 KO mice did not abolish the formation of microscopic subepidermal blisters in the skin 48 hours post injection. These results indicate a pathogenic mechanism of 20B12 independent of complement (C3) activation. Cross-reactivity of murine 20B12 targeting also human BP230 the pathogenicity of 20B12 was evaluated in an ex vivo human skin model. In two independent experiments using foreskin of two different healthy donors, separation of dermis-epidermis was observed in H&E-stained paraffin sections. To resolve the intracellular presence of 20B12 in basal keratinocytes confocal laser scanning microscopy was used.

Discussion
The absence of immune cells in the skin biopsy suggests the pathogenicity of 20B12 may be mediated through steric hindrance or an alternative non-inflammatory pathway. The adoptive transfer experiment may elucidate the role of BP230-reactive $CD4^+$ T cell populations as contributor to the BP disease and may help to understand the pathogenic relevance of BP230-specific autoantibodies, particularly those targeting N-terminal epitopes, in the immunopathogenesis of human BP.

Kategorie: Cellular biology
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 31

Fibroblast Activation and Therapeutic Modulation by Janus Kinase Inhibitors in Mucous Membrane Pemphigoid

Liu, J.[1]; Prasad Sah, S.[1]; Patzelt, S.[1]; Schmidt, E.[1,2]

1 Lübeck Institute of Experimental Dermatology, University of Lübeck, Lübeck, Germany

2 Department of Dermatology, University of Lübeck, Lübeck, Germany

Background Mucous membrane pemphigoid (MMP) is a rare, chronic autoimmune blistering disorder predominantly affecting mucosal surfaces such as the oral cavity, eyes, nose, and genitalia. The disease is characterized by autoantibodies targeting basement membrane zone (BMZ) components, primarily BP180 (type XVII collagen) and laminin 332. In MMP, autoantibody-mediated chronic inflammation leads to subepithelial blistering, erosions, and fibrosis that can cause irreversible functional impairment. Current standard therapies rely on systemic immunosuppressants/ immunomodulants including high-dose long term corticosteroids, dapsone, azathioprine, and mycophenolate mofetil, with refractory cases managed by rituximab, high-dose IVIG, or cyclophosphamide. However, these regimens have limited efficacy and substantial adverse effects, highlighting the urgent need for safer, targeted treatments. Janus kinase (JAK) inhibitors have recently emerged as promising modulators of autoimmune inflammation. JAK signaling regulates multiple cytokine-mediated immune and stromal pathways, suggesting potential relevance in MMP pathogenesis.

Methods and Results In our study, we investigated fibroblast-mediated mechanisms in MMP, focusing on their responses to anti-murine laminin alpha3 (mLAMA3) autoantibodies and the modulatory potential of JAK inhibition. Using murine L929 fibroblasts, we confirmed mLAMA3 expression and specific binding of pathogenic anti-mLAMA3 IgG by immunofluorescence, localizing mLAMA3 to the membrane and extracellular matrix. Fibroblast activation was evidenced by increased vimentin expression in vitro and experimental MMP skin sections. Functional assays demonstrated that anti-mLAMA3 IgG-induced CXCL2 secretion by fibroblasts triggered immune complex–mediated reactive oxygen species (ROS) release from normal human monocytes. Treatment with JAK inhibitors, particularly the JAK1 inhibitor upadacitinib and JAK3 inhibitor ritlecitinib, effectively suppressed CXCL2 production and oxidative responses while preserving fibroblast viability at 50 nM concentrations. Cytokine proteome profiling further identified antibody-driven upregulation of M-CSF and PAI-1, which was attenuated by JAK inhibition, whereas several mediators exhibited JAK-independent regulation. Transcriptomic analysis by RNA sequencing revealed broad alterations in fibroblast gene expression upon anti-mLAMA3 IgG exposure, including activation of inflammatory, oxidative stress, and extracellular matrix remodeling pathways. These transcriptional changes were largely reversed by JAK inhibitor treatment, confirming that JAK signaling contributes to fibroblast-driven inflammation and tissue remodeling in MMP.

Discussion Together, these findings position fibroblasts as active regulators of MMP pathogenesis and identify JAK inhibition as a mechanistically targeted therapeutic strategy for modulating both immune and stromal disease components. Building upon these results, upcoming studies will evaluate the therapeutic efficacy of multiple JAK inhibitors targeting JAK1, JAK2, JAK3, and TYK2 in MMP mouse models under preventive and therapeutic conditions, benchmarking against standard immunosuppressive regimens. Collectively, this translational framework aims to provide mechanistic insight into JAK-dependent signaling in MMP and establish the rationale for precision JAK inhibition as a novel therapeutic avenue for this debilitating autoimmune disease.

Kategorie: Cellular biology
Präsentationsart: Poster

Abstract-ID: 32

DPP4 and its inhibition have no impact on the antibody-mediated tissue destruction in a bullous pemphigoid-like mouse model

S. Patzelt[1*], J. Im[1*], H.O. Dikmen[1], S. Emtenani[1], K. Boch[1], C. Sadik[2], E. Schmidt[1,2]

[1]*Lübeck Institute of Experimental Dermatology, University of Lübeck, Lübeck, Germany*

[2]*Department of Dermatology,* University-*Hospital Schleswig-Holstein, Lübeck, Germany*

*** Equal contribution**

Dipeptidyl peptidase 4 inhibitors (DPP4i, gliptins) are oral anti-diabetic drugs that are discussed to trigger bullous pemphigoid (BP), the autoimmune blistering skin disease. BP is characterized by tense blisters, erythematous plaques, and autoantibodies against BP180 (type XVII collagen, Col17) and BP230, structural proteins of the dermal–epidermal junction. We investigated the impact of DPP4 inhibition on clinical presentation and antibody levels in a BP-like mouse model of epidermolysis bullosa acquisita (EBA) using genetic and pharmacological approaches. In the genetic approach, BP-like EBA was induced in DPP4-deficient and wild-type C57BL/6J mice (n=15 per group) by subcutaneous injections of anti-mCol7 IgG (5 mg/mL) every other day until day 12. In the pharmacological approach, C57BL/6J mice were fed vildagliptin or sitagliptin (6 mg/mL) for six weeks prior to disease induction, with vehicle-fed mice as controls (n=8 per group). Disease severity was monitored by measuring affected body surface area every four days until day 16. No significant differences in disease severity or body weight were observed between DPP4-deficient and wild-type mice, or between vildagliptin-, sitagliptin-, and vehicle-treated mice. These findings suggest that DPP4 inhibition does not interfere with the effector phase of the disease, *i.e.,* the antibody-mediated tissue destruction in this model. The data imply that DPP4i-induced BP may rather be related to pre-existing disease states, such as diabetes or genetic predisposition. Additionally, sera from 45 patients with BP were analyzed. Patients were grouped as (n = 15 each) BP with diabetes but without gliptin treatment, BP without diabetes or gliptin treatment, and BP with both diabetes and gliptin treatment. The results showed an elevation of soluble DPP4 levels in BP patients with diabetes when compared to BP patients without diabetes. However, membrane-bound DPP4 levels were similar across groups. Moreover, immunofluorescence staining of BP peri-lesional skin biopsies revealed DPP4 expression on mast cells, neutrophils, and macrophages. Ongoing studies will address the impact of DPP4i on tolerance breakdown using an immunization-induced mouse model of BP-like EBA. Susceptible mice will be treated with DPP4i or vehicle before immunization with Col7, and DPP4-deficient mice backcrossed onto a BP-like EBA-susceptible background will be compared to DPP4-sufficient littermates.

Kategorie: Cellular biology
Präsentationsart: Poster

Abstract-ID: 33

Skin sebaceous glands are an iron metabolic hub

Fries, A. [1]; Keidel, S. [1]; Hansmann, F. [2]; Thalheim, T. [3]; Siwczak, F. [1]; Pfannkuche, H. [1]; Schneider, M. [1]

1 Institute of Veterinary Physiology, Veterinary Faculty, University of Leipzig, Leipzig, Germany

2 Institute of Veterinary Pathology, Veterinary Faculty, University of Leipzig, Leipzig, Germany

3 Deutsches Biomasseforschungszentrum, Leipzig, Germany

Sebaceous glands (SG) are exocrine glands usually found in association with hair follicles. They comprise specialized gland cells, known as sebocytes, which undergo a continuous differentiation process from the periphery of the gland towards its center, culminating in sebum secretion via a holocrine mechanism. Sebum reaches the skin surface via the hair follicle canal and contributes to the protective function of the skin barrier. In the last years, several studies highlighted metabolic processes in the SG and their potential systemic implications.

To reveal processes and pathways particularly important for sebum production, we re-assessed available skin single-cell RNA sequencing data. Our analysis revealed iron metabolism to be a particularly important feature of sebocytes in comparison to other skin cell types. Specifically, we detected significant higher expression of transcripts within the gene ontology terms “SG iron ion binding”, “SG iron−sulfur cluster binding”, and “SG cellular iron ion homeostasis”, including transcripts as Scd1, Fa2h, Aco1, Cisd1, and numerous transcripts encoding cytochrome p450 family members.

To further support a role for iron metabolism in SGs, we pursued detection of the transferrin receptor (TFRC), the initial component in cellular iron uptake and metabolism, by immunofluorescence. Skin samples from various locations on humans, mice, horses and cattle were fixed in paraformaldehyde and tissue sections were cut. For immunofluorescence staining, sections were preincubated with 5% goat serum followed by incubation with the primary rabbit anti-TFRC antibody and the secondary goat anti-rabbit-Cy3 antibody. Images were captured with a monochrome camera connected to a wide-field fluorescence microscope with Apotome. In all samples, a positive immunofluorescent signal could be detected within the SG but hardly in the surrounding dermal tissue.

Thus, the transcriptome analysis was supported by immunofluorescence-based detection of TFRC in sebocytes. Further investigations are necessary to characterize iron metabolism in SGs in detail and to assess the potential of harnessing iron metabolism to modulate sebum secretion.

Kategorie: Cellular biology
Präsentationsart: Poster

Abstract-ID: 34

Synergistic inhibition of melanoma by cold atmospheric plasma and SM837—molecular insights from single-cell RNA sequencing

Anna Staffeld[1], Lea Dauernheim[1], Philipp Ficht[1], Martin Hein[2], Peter Langer[2], Steffen Emmert[1], Lars Boeckmann[1]

1 Clinic and Policlinic for Dermatology, Venereology, and Allergology, University Medical Center Rostock, Rostock, Germany

2 Institute of Chemistry, Rostock University, Rostock, Germany

Despite major advances in melanoma treatment through targeted and immune checkpoint therapies, resistance and relapse remain major clinical challenges. This underscores the need for novel therapeutic strategies that target melanoma through alternative mechanisms and rational combinations. Cold atmospheric plasma (CAP) represents an emerging approach in oncology, exerting anticancer effects through reactive oxygen and nitrogen species (RONS) and electromagnetic fields. In parallel, the chromone derivative SM837 has recently been identified as a promising small molecule with synergistic anti-melanoma activity when combined with CAP.

To explore the contribution of different CAP components for the synergistic effects, A375 melanoma cells were exposed to either direct CAP, indirect CAP (CAP treated medium), or CAP induced electromagnetic fields in the presence or absence of SM837. Both direct and indirect CAP treatment showed a synergistic reduction in metabolic activity in combination with SM837. However, longer CAP treatment times where required for the indirect treatment compared to direct treatment, suggesting that not only long lived RONS but also electromagnetic components contribute the synergistic efficacy.

To further dissect the molecular basis of this synergy and the role of different CAP components in this process, single-cell RNA sequencing (scRNA-seq) was performed 48 h post-treatment using the BD Rhapsody system. UMAP clustering of the gene expression data revealed highly similar transcriptomic profiles for A375 melanoma cells treated directly and indirectly with CAP. Cells treated with CAP induced electromagnetic fields (no RONS), however, showed transcriptomic profiles barely different from untreated controls. In contrast, SM837 treatment induced a pronounced transcriptional shift, dominating the cellular response. Additional exposure to direct or indirect CAP only marginally modified the SM837-driven gene expression pattern. Differential expression analysis indicated upregulation of stress- and apoptotic response genes (VMP1, SQSTM1) and downregulation of proliferation- and cell-cycle-associated genes (GNAS, FST) for cells treated with SM837. Whereas in CAP treated cells indications for activation of oxidative stress response, DNA damage, and p53-mediated senescence pathways could be seen, consistent with enhanced cellular stress and growth arrest under treatment.

These findings demonstrate that, under the tested conditions, SM837 elicits stronger transcriptional reprogramming than CAP alone, while direct and indirect plasma treatments exert largely overlapping molecular effects. Our data suggest that different CAP components contribute to stress-related signaling, and that SM837 remains the primary driver of the observed transcriptomic alterations in melanoma cells.

Kategorie: Cellular biology
Präsentationsart: Poster

Abstract-ID: 35

Unravelling the role of the E3 Ligase TRIM32 as a member of the Protein Quality Control machinery and its potential link to Aging

Mari D. [1,2,3], Hartmann M. [3], Cao Z. [3], Scharffetter-Kochanek K. [3], Iben S.[3], Michaelidis T. M. [1,2]

[1] Department of Biological Applications & Technologies, School of Health Sciences, University of Ioannina, Ioannina, Greece
[2] Biomedical Research Institute, Foundation for Research and Technology-Hellas, Ioannina, Greece.
[3] Department of Dermatology and Allergic Diseases, Ulm University, Ulm, Germany

Proteostasis, the dynamic regulation of the structural and functional integrity of the proteome, has garnered vast scientific interest since its disruption has been linked to the development and progression of a wide range of pathologies, including aging. Thus, the scientific community is increasingly exploring the mechanisms that safeguard protein homeostasis, such as the Protein Quality Control (PQC) system. One of the major components of PQC is the Ubiquitin-Proteasome-System (UPS). The UPS is responsible for diverse modifications of target proteins through a complex "ubiquitin code" that regulates multiple aspects of eukaryotic cell biology. Its action relies on the activity of E3-ligases, a class of proteins that determine the targets of the UPS and thus play a decisive role in the system's selectivity. These exceptional enzymes not only determine proper degradation, but also the proper regulation, localization, and function of proteins, thus regulating cell homeostasis overall. A prominent subfamily of E3-ligases includes the RBCC/TRIM (RING finger, B-box, coiled-coil/tripartite motif) proteins, which are critical regulators of many cellular processes such as cell cycle regulation, differentiation, and apoptosis, also involved in antiviral responses. Therefore, any disruption of their efficient functioning can lead to severe and diverse pathological conditions. We aim to understand the role of E3 ligase TRIM32, an important member of this family, in maintaining cellular homeostasis. In addition, we focus on the TRIM32(P130S) mutation located in the B-box domain of the protein that leads to the Bardet–Biedl syndrome, a pleiotropic, autosomal recessive disorder that has not been extensively studied under the scope of proteinopathy. Our results indicate that TRIM32 can impact cellular proliferation and neuronal differentiation, in agreement with earlier findings showing that this E3 ligase is a critical cell fate determinant during development. Moreover, preliminary data show that in skin fibroblasts, there is a negative correlation of TRIM32 levels with *in vivo* aging and a positive correlation with *in vitro* aging (replicative aging), indicating a possible role of this ligase in molecular aging processes. We also found that the TRIM32(P130S) mutant can activate the UPR under physiological conditions, possibly causing a state of chronic proteotoxic stress and cell “fatigue”, which could contribute to the development/progression of Bardet-Biedl syndrome, thus opening new perspectives for studying the pathogenic mechanisms of this disease.

Kategorie: Cellular biology
Präsentationsart: Poster

Abstract-ID: 37

Human memory CD4$^+$T cells induce hyperresponsiveness in mast cells

He, J.[1,2,3]; Metz, M.[1,2]; Frischbutter, S.[1,2]

1 Institute of Allergology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

2 Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany

3 Department of Dermatology, The Affiliated Hospital of Southwest Medical University, Luzhou, 646000, China

Introduction: CD4 helper T cells (T cells) infiltrate and localize in proximity to mast cells (MC) in inflammatory environments, such as the skin in chronic spontaneous urticaria and psoriasis. Emerging evidence indicates that T cells can influence the phenotypic and functional features of MCs via both soluble mediators and receptor-ligand mechanisms. Therefore, T cells have the potential to regulate MC activities and may be involved in chronic MC-mediated disorders. The functional outcomes of MC-T cell interactions, particularly involving human primary skin MCs (hMC) and pathogenic memory CD4$^+$T cells (Tm), have, however, not yet been studied in detail.

Objective: This study aims to assess how primary Tm influence the phenotype and function of primary hMC.

Methods: IgE-sensitized hMC were either co-cultured with activated Tm (act-Tm) or their supernatants (Tm-sup) for 18 hours. Anti-IgE induced hMC degranulation was assessed by flow cytometry and cytokines in the Tm-supernatant were measured by a multiplex assay. To assess the contribution of T cell-derived cytokines in hMC activation, hMC were primed overnight with recombinant cytokines or Tm-sup in the absence or presence of respective cytokine neutralizing antibodies. The cytokine profile of primed hMC was analyzed by multiplex assay. In parallel, short-term stimulations under identical conditions were performed to investigate intracellular signalling pathways.

Results: act-Tm ($p = 0.0011$) and Tm-sup ($p = 0.0056$) significantly enhanced FcεRI-dependent hMC degranulation, even in sub-degranulating anti-IgE concentrations. Recombinant IFN-γ and IL-4 increased degranulation of FcεRI-activated hMC, from 43% to 58%, while blocking of IFN-γ reduced Tm-sup-induced degranulation by 32%. Simultaneous neutralisation of both IL-4 and IFN-γ reduced release of GM-CSF by 40%, IL-13 by 108%, and TNF by 90%. Furthermore, Tm-sup increased phosphorylated STAT1 and PLCγ1 levels in hMC, which were both reduced following neutralisation of IFN-γ.

Conclusion: Tm cells and their cytokine IFN-γ promote a hyperresponsive MC phenotype, characterized by increased degranulation and cytokine secretion. Targeting interactions between MCs and T cells or blocking T cell-derived IFN-γ, could offer a selective strategy to reduce MC activation in chronic MC-driven diseases.

Kategorie: Cellular biology
Präsentationsart: Poster

Abstract-ID: 38

Development of Intervention Strategies to Target Ribosomal Accuracy

Gruber, J.[1]; Cao, Z.[1]; Hartmann, M.[1]; Schug, A.[1]; Lingenfelder, C; Scharffetter-Kochanek, K.[1]; Iben, S.[1]

1 Ulm University, Department for Dermatology and Allergic Diseases, Ulm, Germany

Ribosomal translation is the most error prone process of gene expression. Whereas during transcription of mRNA by RNA polymerase II 10^{-6} errors are made, protein synthesis at the ribosome makes 10^{-4} to 10^{-3} errors.

Our group is trying to elucidate if ribosomal errors change throughout human lifetime and aging and if ribosomal error rate contributes to human diseases.

We were able to show in recent projects that ribosomal error rate is regulated during human aging where the accuracy of protein synthesis is increased but overall translation is reduced. In premature aging diseases like Cockayne Syndrome ribosomal biogenesis is disturbed, leading to an increased error rate in translation thus resulting in impaired protein homeostasis (proteostasis).

In further projects we aim to understand if the regulation of ribosomal error rate is disturbed in human diseases, especially in aging associated neurodegeneration. These diseases are characterized by a loss of proteostasis that might be influenced by ribosomal error rate.

In this project we aim to improve the quality of translation without reducing total protein synthesis. This parameter was tested by investigating known pharmaceuticals like cycloheximide which inhibits the translation in the 60S subunit of ribosomes and is an established antibiotic enabling studies on the proteome and protein synthesis of eukaryotic cells. Our aim is to identify novel biologicals and possible therapeutic strategies to improve the quality of protein synthesis. This treatment could foster healthy aging.

Kategorie: Cellular biology
Präsentationsart: Poster

Abstract-ID: 39

Medical Gas Plasma as a Novel Therapeutic Approach for Actinic Keratosis: Mechanistic Insights into Selective Cytotoxicity

McKeever, L. [1]; Singer, D. [1]; Bekeschus, S. [1,2]

1 ZIK plasmatis, Leibniz Institute for Plasma Science and Technology (INP), Felix-Hausdorff-Str. 2, 17489 Greifswald, Germany

2 Department of Dermatology, Venerology, and Allergology, Rostock University Medical Center (UMR), Strempelstr. 13, 18057 Rostock, Germany

Actinic keratosis (AK) is one of the most prevalent precancerous skin conditions, driven by chronic ultraviolet (UV) exposure and the accumulation of DNA and oxidative damage in keratinocytes. These lesions represent an early stage of cutaneous squamous cell carcinoma (cSCC) development, and carry a variable but significant risk of malignant progression. Given the growing incidence of AK in aging and fair-skinned populations, it represents both a clinical and socioeconomic burden on dermatological care. Current treatment options, such as cryotherapy, photodynamic therapy, and topical drugs, can be painful, cosmetically unfavourable, and non-selective, often leading to incomplete clearance and recurrence. This underscores the need for new, tissue-preserving, and patient-friendly treatment modalities.

Medical gas plasma, a partially ionized gas that produces a rich mixture of reactive oxygen and nitrogen species (RONS), has shown promising efficacy in wound healing and oncology. Its ability to locally modulate redox balance, oxidative signaling, and immune activity offers a unique therapeutic mechanism to selectively target dysplastic keratinocytes while sparing healthy skin. However, the molecular determinants of this selectivity and the downstream signaling events driving its efficacy remain insufficiently defined.

In this study, we investigated the biological effects of controlled plasma exposure on a panel of human keratinocyte cell lines representing healthy (HaCaT), pre-malignant (HT-297.T), and malignant (A431) stages of transformation. Optimised plasma treatment parameters were applied to evaluate dose-dependent responses using high-content fluorescence imaging, flow cytometry, and phosphokinase arrays. Cell viability, oxidative stress, and modes of cell death were characterised, alongside the secretion of growth factors, cytokines, and chemokines relevant to inflammation and immune activation in the skin microenvironment.

Preliminary results indicate that plasma treatment induces selective cytotoxicity in AK- and SCC-derived cells, accompanied by stress kinase activation (p38, ERK1/2, GSK3-alpha/beta) and increased expression of immunogenic cell death markers, including PD-L1/2 and HMGB1. In contrast, normal keratinocytes display resilience and maintain redox homeostasis, suggesting a differential oxidative stress tolerance that underlies plasma's selectivity. Furthermore, plasma exposure altered the secretion of pro-inflammatory and wound-healing mediators such as GM-CSF, TGF-alpha, and VEGF, pointing to immune-modulatory and regenerative responses that may enhance lesion clearance and post-treatment repair.

Together, these findings highlight medical gas plasma as a promising, non-invasive dermatological therapy capable of selectively targeting dysplastic keratinocytes through redox-mediated signaling and immunogenic modulation. This work establishes foundational insight into the biological selectivity of plasma treatment in keratinocyte models and supports its further translational development as a complementary strategy for actinic keratosis management and early cSCC prevention.

Kategorie: Cellular biology
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 40

With aging, you cannot afford errors anymore- how ER-stress signaling shapes protein synthesis in aging human skin fibroblasts

Hartmann, M. [1]; Cao, Z. [1]; Wagner, M. [2]; Schug, A. [1]; Scharffetter-Kochanek, K. [1]; Iben, S.[1]

1 Ulm University Hospital, Department of Dermatology and Allergic Diseases, Ulm, Germany

2 Ulm University Hospital, Department for Neurology, Ulm, Germany

We identified disturbed ribosomal biogenesis in premature-aging diseases such as Cockayne syndrome. This pathomechanism might contribute to neurodegeneration. Disturbed ribosomal biogenesis leads to increased translational infidelity, resulting in a loss of protein homeostasis (Alupei et al. 2018). A loss of protoestasis is characteristic of most neurodegenerative diseases (Wagner et al. 2024).

Comparing skin fibroblasts from healthy young and old donors, we find improved protein synthesis (lower ribosomal error rate) with aging. To gain mechanistic insights, we could identify endoplasmic reticulum (ER) stress as the primary regulator of translational fidelity. In cells from old donors, protein kinase R-like endoplasmic reticulum kinase (PERK) expression is increased. The PERK repressor GRP78 is reduced, leading to increased phosphorylation of eIF2alpha, the primary translation regulator. Phosphorylation of eIF2alpha increases the accuracy of protein translation at the cost of inhibiting protein synthesis. Counteracting ER stress, especially by blocking PERK, increases translation errors. Using nanopore sequencing, we compared the transcriptomes of young and old donors and of young donors after ER stress induction. Gene analysis revealed that 75% of genes responding to ER stress induction are differently expressed in old compared to young fibroblasts. This indicates that translation regulation in aging is closely connected to ER stress.

We hypothesize that healthy aging depends on sustained protein synthesis accuracy. Cellular compensation mechanisms that balance the proteome are declining with aging; a misregulated translational error rate might disrupt the homeostasis of cells and organs.

Kategorie: Cellular biology
Präsentationsart: Poster

Abstract-ID: 41

A STAT1/OXPHOS/GBP1 axis represents a potential therapeutic target for non-communicable granulomatous skin disease

Huerta Arana, M Klapproth, H Stanczak, M.A Bopp, L Witschurke, K Seitz, R Lopéz Martinez, M Zamek, J Henschke, S Rana, N 11O'Sullivan, D, Max, Lackmann, J, Damsky, W, von Stebut, E, Sanin, D.E, Zigrino, P

Planck Institute for Immunobiology and Epigenetics Freiburg, Germany.
Malaghan Institute of Medical Research Wellington, New Zealand.
Excellence Cluster on Cellular Stress Responses in Aging Associated Diseases (CECAD) Cologne, Germany.

Abstract:
Granuloma annulare (GA) and cutaneous sarcoidosis (cSAR) represent non-communicable granulomatous skin conditions. They share an overlapping immunopathology in which the aberrant activation of macrophages by IFN-g constitutes a central disease mechanism. Nevertheless, our understanding of the molecular events occurring in pathologically activated GA and cSAR macrophages remains limited. Here, we utilized published single-cell RNA sequencing datasets from GA and cSAR lesions and performed experiments with primary human cells, including a recently established in-vitro granuloma model. In-vitro cultures were investigated by flow cytometry, Seahorse measurements, SCENITH, proteomics and transcriptomics. Furthermore, we analyzed human GA and cSAR lesions by means of immunofluorescence microscopy and flow cytometry. In both diseases, IFN-g triggered Janus Kinase (JAK)/Signal Transducer and Activator of Transcription 1 (STAT1) signaling in macrophages, confirming IFN-g as a central pathology-driving factor. Comparative transcriptomics showed that oxidative phosphorylation (OXPHOS) dominates in IFN-g–activated lesional macrophages, and, using primary human macrophages, we showed IFN-g directly increases OXPHOS. Moreover, OXPHOS was required for the IFN-g-dependent induction of immune effector functions in human macrophages. Integration of single-cell data with in-vitro data identified an IFN-g-induced, OXPHOS-sensitive response network centered on guanylate-binding protein 1 (GBP1). Through GBP1 siRNA-mediated knockdown and pharmacological inhibition in primary human macrophages, we show that IFN-g-driven expression of CXCL10 and other immune effectors was GBP1-dependent. Together, these data outline a linear axis, STAT1-OXPHOS-GBP1-CXCL10, linking signaling, metabolism and macrophage effector programs. In the in-vitro human granuloma model, pharmacologic inhibition at multiple nodes, JAK-STAT1 blockade, OXPHOS suppression, or GBP1 inhibition, all reduced granuloma formation. Given reported variable responses to clinical JAK inhibition, our findings propose OXPHOS and GBP1 as additional, druggable targets for cutaneous granulomatous diseases and provide a rationale for combinational targeting.

Kategorie: Cellular biology
Präsentationsart: Poster

Abstract-ID: 42

Brown algae extract restored expression of filaggrin and suppressed inflammation in a 3D AD skin model

Heinemann, N. [1]; Rademacher, F. [1]; Gläser, R. [1]; Piker, L. [2]; Harder, J.[1]

1 University Hospital Schleswig-Holstein, Department of Dermatology, 24105 Kiel, Germany

2 oceanBASIS GmbH, 24159 Kiel, Germany

Atopic dermatitis (AD) is a highly prevalent chronic skin disease resulting in dry skin and itchy eczema. While the underlying mechanisms are not fully understood, it is known that skin barrier defects and T-helper (Th) type 2 -driven inflammation play a crucial role in AD. Current topical treatment often involves corticosteroids, which effectively reduce inflammation, but do not address the barrier dysfunction and may even weaken the skin barrier over long-term use.

Therefore, there is a need for innovative topical agents that not only exert anti-inflammatory effects but also promote skin barrier restoration in order to relieve the patient's symptoms. Brown algae may represent a promising source for such an agent, as they contain a broad variety of unique bioactive compounds, exhibiting anti-inflammatory and antioxidant effects.

The aim of this study was to evaluate potential beneficial effects of a brown algae extract in an organotypic 3D AD skin model. To this end, an organotypic 3D skin model was stimulated with an AD-typical cytokine mixture consisting of interleukin (IL)-4, IL-13, IL-22 and tumor necrosis factor (TNF) alpha. This resulted in a reduced gene expression of the barrier molecule filaggrin (FLG) and an induced expression of inflammatory markers such as C-C motif chemokine ligand 26 (CCL26) and thymic stromal lymphopoietin (TSLP-L, the pro-inflammatory form of TSLP), thus reflecting the gene expression signature typical of AD.

Adding the brown algae extract to the AD model for 24 h restored the FLG expression to normal levels and significantly suppressed the expression of different inflammatory markers. Furthermore, the extract induced a strong cytochrome P450 family 1 subfamily A member 1 (CYP1A1) expression, an aryl hydrocarbon receptor (AhR) specific responsive gene. The AhR is a ligand depending transcription factor playing an important role for the induction of skin barrier molecules. Thus, the CYP1A1 induction by the extract may indicate a potential involvement of the AhR in the observed induction of FLG.

In summary, this study demonstrated anti-inflammatory and skin barrier strengthening effects of a brown algae extract in a 3D AD skin model. Additional studies are needed to further define the bioactive components involved and their mode of action. By targeting both the inflammation and the dysregulated skin barrier, the brown algae extract may offer a promising addition to the current topical treatment options for AD.

Kategorie: Cellular biology
Präsentationsart: Poster

Abstract-ID: 43

An Improved Human 3D Skin Model for Aging Research

Huth, Sebastian [1,#]; Marquardt, Yvonne [1]; Huth, Laura [1]; Singh, Karmveer [2,3]; Scharffetter-Kochanek, Karin [2,3,#]; Baron Jens Malte [1]; Maity, Pallab [2,3]

[1]Dep. Dermatology & Allergology, Medical Faculty RWTH Aachen University, Aachen, Germany;
[2]Dep. Dermatology & Allergic Diseases, Ulm University Medical Center, Ulm, Germany;
[3]Aging Research Center, Ulm University, Ulm, Germany
[#] Corresponding authors

Background: Skin aging research has traditionally relied on in vivo animal models, ex vivo human skin, and in vitro 2D monolayer cultures. While these systems have advanced our understanding, they present significant limitations, including ethical and regulatory concerns, high costs, time constraints, and poor translational relevance. In line with the 3R principle, there is a growing demand for alternative models that more faithfully recapitulate human skin aging. In vitro 3D skin equivalents have emerged as promising tools, yet most current models rely on replicative or stress-induced senescent fibroblasts, which only partially mimic intrinsic aging and show limited overlap with the proteomic and transcriptomic profiles of chronologically aged skin.

Methods: To address this gap, we developed a novel full-thickness 3D human skin model incorporating primary dermal fibroblasts and epidermal keratinocytes derived from elderly donors (average age 80 years) referred to as „old model“ as opposed to “young” 3D models (average age 20 years) over 7, 14, and 21 days of culture.

Results: At day 7, both young and old 3D models displayed comparable epidermal and dermal differentiation. However, by days 14 and 21, the old models exhibited key features of aged skin. Among the marked changes are structural changes with reduced epidermal thickness, impaired differentiation (decreased K1-positive cells), thinning of the stratum corneum, and persistent dermal atrophy at all time points. In addition, old 3D models showed alterations of the extracellular matrix, such as diminished collagen I and hyaluronan. Reduced numbers of Ki67-positive proliferative cells in both epidermis and dermis, alongside increased numbers of fibroblasts and keratinocytes expressing senescence markers (p21, p16) highlight cellular senescence. Furthermore, IGF-1 expression was reduced in dermal fibadf 2026roblasts and induction of AP1/JunB in both fibroblasts and keratinocytes, known drivers of chronological aging. Transcriptome profiling revealed profound differences between young and old 3D models. Pathway enrichment analyses highlighted ECM remodelling, metalloproteinase activation, cytokine-chemokine signalling, IGF-1 binding, and cellular senescence as overrepresented processes. Gene set enrichment further identified IL6 signalling, p53-mediated transcriptional regulation, and collagen degradation as enriched, while antimicrobial defence, keratinization, and lysosomal pathways were underrepresented. These molecular signatures mirror functional impairments of aged skin, including barrier disruption and increased infection susceptibility. Of note, comparative analyses demonstrated that the transcriptomic and proteomic profiles of the old 3D model substantially overlap with published datasets of aged human skin, with 25–35% similarity at the gene level and 50–60% similarity at the pathway level. The modest gene-level overlap reflects the absence of immune and endothelial cell contributions in the in vitro system, yet the pathway-level concordance underscores its translational relevance.

Conclusion: This novel human full-thickness 3D skin model faithfully recapitulates multiple hallmarks of chronological skin aging. By closely mirroring intrinsic aging processes, it represents a significant advancement over existing models and provides a robust platform for mechanistic studies and preclinical testing of anti-aging interventions, including senolytic and senomorphic agents.

Kategorie: Cellular biology
Präsentationsart: Poster

Abstract-ID: 44

UV-induced Toxicity of Titanium Dioxide Nanoparticles in Barrier-impaired Skin

P.-K. Ficht[1]; P. Bockelmann[1]; A. Staffeld[1]; M. E. Katsanou[2]; M.-L. Sellin[3]; A. Jonitz-Heincke[3]; W. Friedrich-Maus[2]; S. Emmert[1]; L. Wegewitz[2]; L. Boeckmann[1]

1 Clinic and Policlinic for Dermatology, Venereology and Allergology, University Medical Center Rostock, Rostock

2 Department for Energy Research and Physical Technologies, Technical University Clausthal, Clausthal-Zellerfeld

3 Department of Orthopaedics, Rostock University Medical Center, Rostock

Titanium dioxide nanoparticles (TiO_2-NPs) are widely used as physical UV blockers in commercial sunscreens and have long been considered safe for application. However, following their ban as a food additive by the European Union in 2022 due to potential carcinogenicity after ingestion and inhalation, concerns have also emerged regarding their dermal safety. Upon exposure to highly energetic radiation such as UV light, TiO_2-NPs can act as photocatalysts generating reactive oxygen species (ROS), which may induce oxidative DNA damage such as 8-oxoguanine formation. While most studies report that TiO_2-NPs remain confined to the stratum corneum, these findings are based on intact skin and may not apply to compromised barriers in conditions such as atopic dermatitis (AD) or psoriasis. Therefore, the safety of TiO_2-NPs was evaluated with focus on dermal penetration depth depending on skin barrier function as well as molecular responses to particles and UV light.

Preliminary experiments confirmed the photocatalytic activity of coated and uncoated TiO_2-NPs using methylene blue degradation for quantification. UV-A was identified as a suitable irradiation source, since UV-B caused high cytotoxicity in XTT assays even in the absence of nanoparticles. The UV-A-mediated cytotoxicity in HaCaT cells depended on UV-A dose, nanoparticle concentration, coating type (SiO_2, SiO_2–Al_2O_3), and incubation time prior to irradiation. Time-dependent cellular uptake was visualized by hyperspectral enhanced darkfield microscopy (HEDFM), while ROS generation was detected via H_2DCFDA assay and immunofluorescent staining of 8-oxoguanine. Raman spectroscopy revealed a loss of amide I bands, indicating severe protein damage only in the combined TiO_2-NP and UV-A treatment group. Significant formation of micronuclei as a sign of chromosome damage was detected for sub-lethal doses of TiO_2-NPs (10 µM) even without UV-A irradiation in case of SiO_2-Al_2O_3-coated particles.

To investigate penetration and biological effects in more physiological models, 3D skin equivalents and human ex vivo skin were used. An AD-like phenotype was induced by cytokine treatment (IL-4, IL-13, IL-31), resulting in reduced filaggrin and loricrin expression and characteristic spongiosis. Reduced skin barrier function was quantified by diffusion of FITC-dextran. Diffusion profiles of TiO_2-NPs were analyzed by total reflection X-ray fluorescence (TXRF) and HEDFM, revealing nanoparticle penetration up to the dermal layer (<100 µm) in both healthy and AD skin which is deeper than previously reported. These findings highlight the necessity of re-evaluating TiO_2-based sunscreen safety under barrier-impaired conditions using advanced analytical technologies.

Kategorie: Cellular biology
Präsentationsart: Poster

Abstract-ID: 45

Mast cells drive eosinophil activation via GM-CSF-dependent and independent pathways

Tang, Q.[1,2,4]; Metz, M.[1,2]; Levi-Schaffer, F.[1,2,3]; Frischbutter, S.[1,2]

1 Institute of Allergology, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

2 Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany
3 Pharmacology and Experimental Therapeutics Unit, School of Pharmacy, Institute for Drug Research, Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel

4 Department of Dermatology, North Sichuan Medical College, Nanchong, People's Republic of China

Introduction

Mast cells (MCs) and eosinophils (Eos) co-exist in the inflamed tissue during the late and chronic phases of allergic reactions, forming the "Allergic Effector Unit" (AEU). The AEU operates through an array of soluble mediators and ligand-receptor interactions that mutually enhance the pro-inflammatory functions of both cell types. While this cellular cross-talk is recognized as a cornerstone of allergic inflammation, the intracellular mechanisms that activate Eos as result of contact with MC-derived factors, particularly following IgE-dependent stimulation, remains incompletely understood. Previously, we identified MC-derived GM-CSF as crucial mediator in MC-Eos crosstalk. Here, we assessed intracellular signaling processes in Eos induced by supernatant of anti-IgE stimulated MCs to dissect key activating factors that govern Eos activation within the AEU context.

Methods

MCs were isolated from healthy human skin, and Eos were obtained from the peripheral blood of healthy donors or patients with chronic spontaneous urticaria (CSU). MCs were sensitized with IgE overnight and activated by 1µg/ml anti-IgE followed by flow cytometry to detect degranulation via CD63. To identify MC-derived mediators driving Eos activation, Eos were incubated with supernatants from anti-IgE-activated MCs with or without neutralizing antibodies against key cytokines such as GM-CSF. Eos activation was measured by surface CD69 level using flow cytometry. Intracellular signaling was analysed by Western blot to detect phosphorylation of STAT5, Erk1/2, p65, p38, and AKT. The functional role of these pathways was further examined using pathway-specific inhibitors.

Results

Supernatants from MCs induced phosphorylation of STAT5, ERK1/2, JAK2, AKT, and p65 in eosinophils, with comparable responses in cells from CSU patients and healthy controls. GM-CSF neutralization demonstrated that phosphorylation of STAT5 and ERK1/2 was specifically dependent on mast-cell-derived GM-CSF, whereas JAK2 and AKT activation persisted, indicating triggering of GM-CSF-independent signaling. In contrast, pharmacological inhibition showed that CD69 upregulation on eosinophils was mediated by ERK1/2 and JAK2, but not STAT5. Finally, inhibition of chymase as an alternative MC mediator did not affect eosinophil activation, suggesting that mast-cell-derived chymase is not involved in eosinophil activation in this context.

Conclusion
These data demonstrate that MC signals, particularly GM-CSF, are critical drivers of eosinophil activation, but additional MC-dependent mechanisms act in parallel to sustain eosinophil responses and need to be identified.

Kategorie: Cellular biology
Präsentationsart: Poster

Abstract-ID: 46

Tracking the Consequences of LRIG1 Overexpression in Melanocytes for Skin Homeostasis and Melanoma Development

Hommel, T.[1]; Wagner, B.[1]; Högler, S.[2]; Dahlhoff, M.[1]

1 University of Veterinary Medicine Vienna, Institute of *in vivo* and *in vitro* Models, Vienna, Austria

2 University of Veterinary Medicine Vienna, Laboratory Animal Pathology, Vienna, Austria

Melanoma is the most aggressive form of skin cancer, known for its poor prognosis and a strong metastatic potential. It is driven by multiple somatic mutations, which are often caused by environmental insults, and lead to a highly heterogenous patient group. The development of novel therapeutic strategies has already improved the survival rate, but the rapid emergence of therapy resistance underlines the necessity to further investigate potential oncogenic drivers.
In this context, the role of leucine rich repeats and immunoglobulin like domains 1 (LRIG1) is controversially discussed. LRIG1 functions as an essential regulator of receptor tyrosine kinases, especially the four ERBB receptors, which are crucial for maintaining homeostatic processes such as cell proliferation, differentiation, apoptosis and migration. LRIG1 and the ERBBs play a pivotal role in balancing stem cell quiescence and activation. ERBB3 is known for suppressing maturation and promoting a proliferative and migratory cell character, particularly in melanocytes and their precursor cells. In line with this, increased expression and mutations of the epidermal growth factor receptor (EGFR, ERBB1) and ERBB3 are associated with a higher metastatic risk in melanoma patients. LRIG1 usually acts as a tumor suppressor by negative regulation of ERBBs and the downstream RAS-RAF-MEK-ERK signaling pathway. Expression of LRIG1 can not only affect the cell itself, but also surrounding tissue, as proteolytic shedding releases ectodomain fragments of different lengths, which mediate paracrine effects. Treatment with one of these soluble LRIG1 ectodomains was already shown to inhibit melanoma cell proliferation *in vitro*. However, our results suggest that the effect of LRIG1 overexpression is dependent on individual mutation profiles. This is consistent with literature, which reports that the tumor-suppressive effects of LRIG1 are limited to melanomas with triple wild-type genes (*BRAF*, *NRAS*, *NF1*) and tumors with increased EGFR expression. In fact, previous studies from our group even showed that keratinocyte-specific LRIG1 overexpression led to the formation of heavily pigmented naevi with markedly increased MLANA expression in a two-stage skin carcinogenesis model.
To better understand the characteristics and dynamics of LRIG1 overexpression in melanocytes during skin homeostasis and melanoma initiation and progression, we established a novel mouse model. In this model a tetracycline trans-activator is expressed under the control of the endogenous tyrosinase promoter (*Tyr*-tTA), allowing conditional overexpression of the target gene *Lrig1* (pTRE-*Lrig1*) specifically in melanocytes. Interestingly, we could only detect an increase in a shed form of LRIG1, but not the full-length protein in the skin of these mice. Despite that, we found focal melanin accumulation in granuloma-like structures in the dermis, suggesting potential melanocyte degradation. To further study this phenotype, we generated double-transgenic mice with additional melanocyte-specific GFP expression (*Tyr*-tTA; pTRE-*Lrig1*; pTRE-*H2BGFP*). This approach now allows both, *in vivo* tracking of LRIG1 overexpressing melanocytes by GFP labeling as well as a functional analysis in a physiologically relevant context.

Kategorie: Cellular biology
Präsentationsart: Poster

Abstract-ID: 47

Spatial Transcriptomics and Self-Organizing Maps Unveil Molecular Signatures of the Gland of Moll

Konecny, T. [1,2]; Binder, H. [1,2]; Hampel, U. [3]; Hansmann F. [4]; Pfannkuche H.[5]; Schneider, M.R.[5]

1 Interdisciplinary Centre for Bioinformatics (IZBI), University of Leipzig, Leipzig, Germany
2 Armenian Bioinformatics Institute (ABI), Yerevan, Armenia
3 Department of Ophthalmology, University Hospital Leipzig, Germany
4 Institute of Veterinary Pathology, Veterinary Faculty, University of Leipzig, Leipzig, Germany
5 Institute of Veterinary Physiology, Veterinary Faculty, University of Leipzig, Leipzig, Germany

Introduction
The glands of Moll are specialized apocrine glands of the human eyelid whose precise physiological function remains poorly understood. Previous studies have characterized a few cellular components and secretion products, which suggest a potential role in local immune defense. Here, we hypothesize that combining spatial transcriptomics (ST) with unsupervised machine learning can provide a comprehensive molecular blueprint of these elusive structures. This study demonstrates that ST, enhanced by Self-Organizing Maps (SOM), can effectively characterize rare cell populations and address the existing knowledge gap.

Results
We applied the Leiden clustering algorithm to ST data from human eyelid tissue (Binder et al. 2025) to delineate the gland of Moll. We defined 63 ST-based Moll gland-associated markers (ST markers) and ranked them by specificity to the Moll gland. Gene Ontology (GO) enrichment analysis revealed significant enrichment for extracellular exosomes (GO:0070062) and 4-phosphate/phosphoenolpyruvate-family amino acid metabolism (GO:1902221). Concurrently, a SOM-derived set of 28 co-regulated genes, containing 10 genes shared with the ST markers, was enriched for apocrine sweat gland (BTO:0001458) and tyrosine metabolism pathways (GO:0006570). Expression of GLYATL2, encoded by one of the genes in the latter group, was confirmed by immunofluorescent staining in Moll glands, thus supporting the validity of our approach.

Conclusions
Our study provides the first comprehensive molecular characterization of the human gland of Moll. The findings demonstrate that integrating ST (even in low-resolution) with SOM is a powerful strategy for the functional analysis of rare cell types within complex tissues. The identified gene signatures establish a new molecular foundation for understanding Moll gland biology and suggest a specialized role in tyrosine metabolism and exosome-related secretory processes that extends beyond its previously assumed immune function.

References
Binder H, Hampel U, Loeffler-Wirth H, Hansmann F, Pfannkuche H, Schmidt M, Schneider MR. Spatial transcriptome analysis of the human eyelid depicts meibomian gland cell differentiation: A pilot study. Physiological Reports. 2025 Sep;13(18):e70571.

Kategorie: Cellular biology
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 48

Hepatoprotective herbal drugs modulate Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)-like spheroids, psoriasis-like keratinocytes and their interaction

Wölfle, U.[1], Haarhaus, B.[1], Ditengou, F.A.[2], Weiskirchen, R.[3], Rusignuolo, G.[4], Boettler, T.[4], Schempp, C.[1]

[1]Research group skintegral, Department of Dermatology and Venerology, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany, [2]Institute for Disease Modeling and Targeted Medicine (IMITATE), Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany, [3]Institute of Molecular Pathobiochemistry, Experimental Gene Therapy and Clinical Chemistry (IFMPEGKC), RWTH Aachen University, Aachen, Germany, [4]Department of Internal Medicine II, Medical Center, Faculty of Medicine, University of Freiburg, Germany

Introduction Metabolic dysfunction-associated steatotic liver disease (MASLD) is a common comorbidity of psoriasis, a chronic non-communicable inflammatory skin disease. This research project aimed to investigate the interaction of traditional herbal hepatoprotective drugs and silymarin on chronic inflammation in cellular models of MASLD and psoriasis, and how both can be influenced by these components. **Methods:** Three-dimensional (3D) liver spheroids were generated from HepG2/LX-2 cells, along with 3D multicellular liver spheroids containing human primary hepatocytes, Kupffer cells and liver endothelial cells. The spheroids were induced to become steatotic and inflamed MASLD-like spheroids through treatment with free fatty acids, fructose and LPS. These MASLD- like spheroids were then exposed to two well-characterized herbal drugs (Hepar SL™ and Iberogast™), the hepatoprotective flavonolignan silymarin, the monoclonal anti-IL-17A antibody ixekizumab, and the acetyl-CoA carboxylase inhibitor firsocostat. The degree of steatosis and release of pro-inflammatory cytokines were assessed in the MASLD-like spheroids. Additionally, *in vitro* generated psoriasis-like keratinocytes were either treated with the compounds or exposed to conditioned media (CM) from MASLD-like spheroids. **Results:** The herbal compounds demonstrated various anti-inflammatory effects in both MASLD- like spheroids and psoriatic keratinocytes. However, only silymarin exhibited an anti-steatotic effect in MASLD-like spheroids. In psoriatic keratinocytes, some herbal compounds reduced the psoriatic phenotype and inflammation markers, as did CM from MASLD- like spheroids treated with herbal compounds.
Conclusion: These findings suggest that herbal hepatoprotective drugs could add beneficial effects to the conventional treatment of patients with psoriasis and MASLD.

Kategorie: Cellular biology
Präsentationsart: Poster

Abstract-ID: 49

Establishment of a melanocyte-specific conditional *Ahr* deletion mouse model and a UVB-induced skin inflammation model

Li, W.[1]; Gellert, S.[1]; Knauth, K.[1]; Celebi, M.[1]; Bonifatius, S.[1]; von Wricz Rekowski, M.[1]; Buzzai, A.[1]; Mengoni, M.[2]; Braun, A.[1]; Tüting, T.[1]

1 Otto-von-Guericke-University, Department of Dermatology, Magdeburg, Germany

2 University of Lübeck, Department of Dermatology, Allergy and Venerology, Lübeck, Germany

The aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor that plays roles in detoxification, regulation of cell growth and differentiation, and inflammatory responses. UVB exposure photoconverts tryptophan into 6-formylindolo(3,2-b)carbazole (FICZ), an endogenous AHR ligand that activates AHR signaling. Prior studies have implicated AHR in orchestrating protective responses of melanocytes following UVB irradiation, whereas in melanoma contexts, AHR has been associated with tumorigenesis and metastasis. However, how AHR modulates responses of melanocytes to UVB irradiation and how it affects melanomagenesis remains unclear. To address this knowledge gap, we decided to establish appropriate genetically engineered mouse models where the *Ahr* gene can be specifically deleted in melanocytes and melanoma cells. In initial work, we crossed mice carrying the Cre^{ERT2} under the control of the tyrosinase promotor ($TyrCre^{ERT2}$ mice) with mice carrying a LoxP-flanked *Ahr* gene ($Ahr^{fl/fl}$ mice) and mice carrying a LoxP-flanked tdTomato reporter gene in the ROSA26 locus (Ai9 mice). In these $TyrCre^{ERT2}$-$Ahr^{fl/fl}$-Ai9 mice treatment with 4-hydroxytamoxifen (4-OHT) deletes the *Ahr* gene and induces expression of tdTomato specifically in melanocytes. For identification and isolation of viable mouse melanocytes from the epidermis, we established a flow cytometry-based strategy. Live ($7\text{-}AAD^-$) melanocytes were gated as $CD117^+$, $CD45^-$, where CD117 serves as a characteristic surface marker for both melanocytes and mast cells. Mast cells were subsequently excluded by gating out $CD45^+$ cells. Our results confirmed that live melanocytes constitute approximately 3-5% of cells isolated from mouse epidermal sheets. Using this approach, we could verify the expression of tdTomato in approximately 50% of melanocytes isolated from back skin of 4-OHT treated $TyrCre^{ERT2}$-$Ahr^{fl/fl}$-Ai9 mice. We are currently validating the deletion of the *Ahr* gene following 4-OHT treatment and are investigating how different protocols for 4-OHT application impact on the frequency of genetic deletion. To assess how AHR affects the responses of melanocytes to UVB, we established an *in vivo* UVB inflammation model where we treated wild type mice with or without UVB exposure at sunburn-dose level (4.5 KJ/m^2 per exposure) on days 0 and 3 using a UVB irradiation chamber. On day 4, the back skin of mice was harvested, sectioned and stained with H&E, which showed UVB-induced epidermal thickening. The increased immune cell infiltration relative to non-irradiated controls was confirmed by CD45 immunohistochemistry (IHC). Next, we will investigate how *Ahr* deletion impacts on melanocyte responses to UVB inflammation. In the future, we will also introduce the conditional deletion of the *Ahr* gene into our genetically engineered $Hgf\text{-}Cdk4^{R24C}$ mouse melanoma model, where transgenic overexpression of the hepatocyte growth factor (HGF) promotes cell survival and proliferation through activation of Ras signal pathways and an oncogenic mutation in the cyclin-dependent kinase 4 ($Cdk4^{R24C}$) abrogates binding of the tumor suppressor p16INK4a and continuously drives cell proliferation.

Kategorie: Cellular biology
Präsentationsart: Poster

Abstract-ID: 50

A Novel hiPSC-Derived Endothelial Cell Model with Kallikrein Activity for Inflammatory Disease Research

Yanyan Luo;[1,2] Alexis Bocquet;[3,4] Jörg Scheffel;[1,2] Valeria Fernandez Vallone;[5] Gürkan Bal;[1,2]Carolina Elisa Vera Ayala;[1,2] Harald Stachelscheid[5]; Thomas Buttgereit.[1,2*]

1 Institute of Allergology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany
2 Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany
3 National reference center for angioedema (CREAK), Internal medicine department, CHU Grenoble Alpes, Grenoble, France
4 Univ. Grenoble Alpes, CNRS, CHU Grenoble Alpes, Grenoble INP, TIMC, Grenoble, France
5 Berlin Institute of Health at Charité – Universitätsmedizin Berlin, Core Unit pluripotent Stem Cells and Organoids (CUSCO), Berlin, Germany

Introduction: Endothelial dysfunction is a critical driver in the pathogenesis of numerous inflammatory diseases. The lack of predictive human cell models that faithfully recapitulate complex inflammatory pathways, such as the Kallikrein-Kinin System (KKS), hinders mechanistic studies and drug development. Human induced pluripotent stem cells (hiPSCs) offer a renewable source for generating physiologically relevant cell types. We aimed to develop and characterize a robust hiPSC-derived endothelial cell (hiPSC-EC) model suitable for investigating endothelium-related inflammatory pathologies.

Methods: We established a protocol to differentiate human induced pluripotent stem cells (hiPSCs) into a pure population of endothelial cells (hiPSC-ECs). The resulting cells were characterized by using flow cytometry, immunofluorescence (IF), and functional enzymatic assays.

Results: The differentiation protocol consistently yielded a highly pure population of cells exhibiting classic cobblestone endothelial morphology. Characterization confirmed that the hiPSC-EC model expresses canonical endothelial markers, including CD31, CD144 (VE-Cadherin), and VEGFR2 (KDR), indicating a mature endothelial phenotype. IF staining revealed correct localization of VE-Cadherin at cell-cell junctions. Furthermore, the model demonstrated significant expression of the bradykinin receptors B1R and B2R, key components of the KKS. Critically, functional analysis confirmed that the hiPSC-EC model possesses measurable kallikrein activity.

Conclusions: We have successfully established and characterized a hiPSC-derived endothelial cell model. This model not only displays the requisite endothelial markers and morphology but also uniquely expresses key functional components of the Kallikrein-Kinin System including B1R and B2R. Furthermore, cells displayed kallikrein activity, leading to the generation of bradykinin when incubated with high molecular weight kininogen. This human-relevant, potential patient-specific model provides a valuable new platform for dissecting the complex pathological mechanisms of endothelium-related inflammatory diseases (such as hereditary angioedema) and serves as a robust tool for preclinical drug screening and development.

Kategorie: Cellular biology
Präsentationsart: Poster

Abstract-ID: 51

Endothelial Cell Apoptosis and Fibroblast Senescence in Diabetic Angiopathy - Implications for a Novel Therapeutic Approach

Wang, Yongfang[1,2]; Koroma, Albert Kallon[1,2]; Singh, Karmveer[1,2]; Scharffetter-Kochanek, Karin[1,2]*; Maity, Pallab[1,2*] (*contributed equally)

1 Department of Dermatology & Allergology, Ulm University, Ulm, Germany,

2 Aging Research Center ARC, Ulm University, Germany

Background: The incidence of obesity and diabetes mellitus is increasing worldwide causing heavy socioeconomic and clinical burden. Impaired wound healing, a frequent complication in patients with diabetes and obesity, remains an urgent, unmet clinical challenge. Impaired angiogenesis constitutes a major cause of non-healing wounds under diabetic conditions. However, the underlying mechanisms are poorly understood.

Methods: To gain further insight in the pathogenic role of fatty acids such as palmitate and oleate – both increased in obesity and type 2 diabetes (T2DM) – we explored diabetic angiopathy by a multipronged in vitro and in vivo approach.

Results: Interestingly, fatty acids (both palmitate and oleate) profoundly impaired angiogenesis in a concentration-dependent manner in the in vitro tube formation assay. This assay requires the interaction of endothelial cells and stromal fibroblasts, the latter providing the scaffold and secretory factors for differentiation of endothelial cells for vessel formation. Single-cell transcriptomic profiling of endothelial-fibroblast co-cultures revealed an enrichment of apoptosis related genes in endothelial cells, while enrichment of senescence related genes in fibroblasts, when subjected to fatty acids. Fatty acid-induced senescent fibroblasts showed upregulation of key genes coding for senescence-associated secretory phenotype (SASP), including IL6 and IL8, alongside increased expression of the cell cycle inhibitor p21, suggesting a robust pro-inflammatory and growth-arrested state. This was further supported by immunostaining, which showed following fatty acid exposure, an increased number of fibroblasts positive for the senescence markers p21 and p27. These fibroblasts also exhibited increased senescence-associated β-galactosidase activity, accompanied by a reduced number of Ki67-positive proliferating cells. Employing specific ELISAs, fatty acid-induced senescent fibroblasts were shown to release pro-inflammatory molecules such as IL-6 and IL-8 fostering inflammation and disturbing angiogenesis. Using cytometry and western blot analysis, we confirmed fatty acids enhanced endothelial cells death through caspase-9, caspase-3 dependent apoptosis. Endothelial apoptosis was associated with redox imbalance, including a significant drop in the GSH/GSSG ratio, increased reactive oxygen species, and higher levels of lipid peroxidation. We next validated our in vitro data using a full thickness wound model in diabetic mice (db/db), which show higher fatty acid levels. Histologically, a severe reduction of vessels in the uninjured and wounded skin of db/db mice was observed. Immunostaining of sections from uninjured and wounded skin of db/db mice showed an increase in TUNEL and active caspase-3 positive endothelial cells, with less Ki67 positive and an increased number of p27, p21 positive senescent fibroblasts. Strikingly, co-treatment of senolytic compounds and pan-caspase inhibitors rescued the fatty acid-induced impairment of tube (vessel) formation, highlighting the therapeutic potential of targeting both senescence and apoptosis.

Conclusion: Our findings suggest that T2DM related fatty acids induce endothelial cell apoptosis and fibroblast senescence which suppress proliferation, migration, sprouting of endothelial cells and, hence, new vessel formation. Our findings hold promise for developing new strategies for advanced treatment of difficult-to-treat diabetic wounds.

Kategorie: Cellular biology
Präsentationsart: Poster

Abstract-ID: 52

Proteomic Profiling Reveals Cell-Type-Specific Death Pathways in Plasma-Treated Actinic Keratosis Models

Wang, Z[1,2]; Mckeever, L[1,2]; * Bekeschus, S[1,2]; * Wende, K[1]

1 Leibniz Institute for Plasma Science and Technology (INP), 17489 Greifswald, Germany

2 Department of Dermatology, Venerology, and Allergoly, Rostock University Medical Center, 18057 Rostock, Germany

Introduction: Actinic keratoses (AK) is a widespread carcinoma in situ caused by chronic ultraviolet (UV) exposure and having a high risk of progressing to squamous cell carcinomas. Due to its cumulative nature, the prevalence of AK increases with age. Accordingly, therapeutic interventions such as imiquimod or photodynamic therapy (PDT) aim to normalize cell proliferation and immune response. Similar to PDT, gas plasma technology provides a local and tunable mix of reactive species that can target cancerous cells. First case studies suggest the effectiveness of gas plasma in AK [1,2], yet the biomedical mechanisms need further clarification.

Methods: This study investigated the molecular mechanisms of gas plasma treatment using a disease-relevant cell model, including an AK cell line (HT297.T), a malignant SCC cell line (A431), and normal keratinocytes (HaCaT), through untargeted proteomic profiling and bioinformatic analysis.

Results: The results showed that Plasma treatment induced a general depression of the cell cycle across all three cell lines, accompanied by down-regulation of TP53. Notably, the same plasma treatment time elicited distinct cell death patterns: caspase-4-mediated pyroptosis was characteristic of the AK cells (HT297.T), while IRE1α-activated unfolded protein response (UPR), indicative of potential apoptosis, was a feature of the malignant SCC cells (A431). In contrast, programmed cell death pathways were deactivated in normal keratinocytes. The normal keratinocytes instead exhibited a robust activation of the cellular stress response, including the KEAP1-NRF2 pathway, without UPR activation, to counteract oxidative stress. These mechanisms will be further validated in an AK mouse model to guide the optimization of gas plasma therapy for actinic keratosis.

This work is part of the plasmACT MSCA Doctoral Network on Plasma Medicine Against Actinic Keratosis.

Kategorie: Cellular biology
Präsentationsart: Poster

Abstract-ID: 53

Manipulations of Alzheimer proteins result in altered translational error rate of the ribosomes

Zhouli Cao[1], Max Hartmann[1], Danhui Zhang[1], Amy Lee Schug[1], Karin Scharffetter-Kochanek[1] and Sebastian Iben[1]

1 Department of Dermatology and Allergic Diseases, Ulm University Hospital, 89081 Ulm, Germany

In previous studies, our lab identified disturbed ribosomal biogenesis and function in the premature aging diseases Cockayne syndrome and trichothiodystrophy. The subsequent loss of protein homeostasis (proteostasis) might be the driving force of the severe neurodegeneration characterizing these diseases. Loss of proteostasis is caused by an elevated error rate of ribosomal protein synthesis (translational infidelity) and results in an increased endoplasmic reticulum (ER) stress (Alupei et al. 2018, Phan et al. 2021, Khalid et al. 2023). Given the fact that a loss of proteostasis characterizes most neurodegenerative diseases of the aging body, we are asking the question where the misfolded proteins come from. Does the error rate of protein synthesis affect aging-associated diseases, such as Alzheimer's disease (AD)? We employed both CRISPR-Cas9 and short hairpin RNA (shRNA) technologies to knock down PSEN1 and amyloid beta precursor protein (APP) expression in human fibroblasts, creating a cellular model of AD. Surprisingly, knocking down PSEN1 significantly increased the error rate of protein translation whilst knocking down APP reduced translational errors of the ribosome. In line with these results, we find an increased protein aggregation in fibroblasts with PSEN1 deficiency and less protein aggregation in cells with reduced APP levels. Interestingly, manipulations of the Alzheimer proteins themselves led to altered ER stress signaling, a hallmark of Alzheimer`s disease. Future work will show if the loss of proteostasis in AD is causally related to ribosomal dysfunction.

Kategorie: Cellular biology
Präsentationsart: Poster

Abstract-ID: 54

CCL17- and CCL22-specific aptamers provide therapeutical potential in dermatological diseases

Gottschalk, M. [1]; Jonczyk, A. [2]; Bahr, L. [1,3]; Renzl, C. [2,4]; Weighardt, H. [1]; Mayer, G. [2,4]; Förster, I. [1]

1 Immunology and Environment, Life and Medical Sciences (LIMES) Institute, University of Bonn, Germany

2 Chemical Biology and Chemical Genetics, Life and Medical Sciences (LIMES) Institute, University of Bonn, Germany

3 Department of Microbiology and Immunology, The Peter Doherty Institute for Infection and Immunity, University of Melbourne, Australia

4 Centre of Aptamer Research and Development, University of Bonn, Germany

Around 20 % of the world's population suffer from allergic contact dermatitis (ACT). The chemokines CCL17/CCL22 and their receptor CCR4 are notably involved in allergies. We could already demonstrate that CCL22- and CCL17-deficient mice develop significantly reduced symptoms in contact hypersensitivity (CHS), a mouse model for ACT. Short, single stranded DNA- or RNA-molecules, so-called aptamers, specifically bind target molecules and should thus be suitable for a therapeutic inhibition of chemokines. To validate this hypothesis, we first generated aptamers specific for murine (m) CCL22 and CCL17.

In an in-vitro transwell system, the mCCL22-inhibiting aptamer AJ102.29m, as well as the mCCL17-binding aptamers MF11.46.m and MF35.47.m significantly reduced the chemokine-dependent T-cell migration. When applied intraperitoneally, these aptamers ameliorated the CHS-reactions in wildtype-mice, in line with the results observed in CCL22- and CCL17-deficient mice in vivo. After topical application of AJ102.29m in creme according to the german drug codex (DAC), we microscopically observed the penetration of the aptamers into the murine dermis. In addition, treatment of ear skin with the aptamer reduced the ear-swelling reaction in the CHS-model in vivo. To evaluate the effectiveness of aptamers in human, we generated aptamers against human (h) CCL17. Hereof, eight candidates showed specific binding to hCCL17. First results indicate, that selected aptamers inhibit the transwell migration of human Mac-1 and Hut78 cells towards hCCL17 in vitro.

Our results show that the non-invasive, topical application form of aptamers provide a promising option in the therapy of allergic skin diseases and other chemokine-driven disorders, e.g. cutaneous lymphomas. Future experiments will focus on the penetration of these aptamers into the human skin after topical application ex-vivo.

Kategorie: Cellular biology
Präsentationsart: Poster

Abstract-ID: 55

Functional Evaluation of a Conditioned Human Secretome for Skin Repair Applications

Flütter, L. [1,2]; Zöphel, S.[1,3]; Köder, N.[1]; Klose, P.[1]; Scherer, J.[1,2]; Schinke, M.[4]; Groeber-Becker, F.[1,5]; Lachmann, N.[4,6] and Groneberg, D.[1]

1 Translational Center for Regenerative Therapies TLZ-RT, Fraunhofer-Institute for Silicate Research ISC, Würzburg, Germany
2 Institute of Medicine and Biology, Julius-Maximilians-University, Würzburg, Germany
3 Interdisciplinary Center for Clinical Research IZKF, University Hospital Würzburg, Würzburg, Germany
4 Fraunhofer Institute for Toxicology and Experimental Medicine ITEM, Hannover Germany
5 Department of Ophthalmology, University Hospital Düsseldorf, Heinrich-Heine-University, Germany
6 REBIRTH Research Center for translational and regenerative medicine, Hannover, Germany

Chronic and impaired wound healing remains a significant clinical challenge, affecting approximately one million patients on an annual basis in Germany. Current therapeutic approaches, including topical wound dressings and surgical debridement, primarily provide symptomatic relief, often resulting in only partial or temporary improvement. The underlying causes of this condition, including persistent inflammation and delayed re-epithelialization due to dysregulated crosstalk between immune and skin cells, remain largely unaddressed. It is essential to target these fundamental mechanisms in pursuit of restoring skin homeostasis and achieving durable wound regeneration.

We present a novel *in vitro* approach using a co-culture system of organoid-based human skin models with hiPSC-derived macrophages to produce bioactive media for skin regeneration. The resulting conditioned medium comprises a complex mixture of bioactive factors secreted under physiologically relevant conditions. The co-culture model was further characterized by immunofluorescence staining and qPCR analysis using CD86 and CD163 as markers to evaluate macrophage polarization status and confirm structural integrity of the skin model.

Preliminary functional assays employing primary human dermal fibroblasts, epidermal keratinocytes, and reconstructed human epidermis (RHE) indicated a trend toward enhanced proliferation and improved tissue organization subsequent to treatment with the immune-conditioned medium. These preliminary observations were supported by real-time impedance monitoring (xCELLigence) and WST viability assays, suggesting a potential pro-regenerative effect. Further investigations in full-thickness human skin equivalents (FTSE) and detailed molecular characterization of the secretome are currently underway.

This study explores a novel cell-free regenerative strategy that harnesses bioactive factors based on the paracrine signaling profile of human co-culture models. Such an approach may provide the basis for future development of next-generation wound healing therapeutics or advanced medical skin care formulations. In later stages, defined fractions of the secretome will be isolated and characterized to identify specific components responsible for the observed regenerative effects and to enable targeted applications.

Kategorie: Cellular biology
Präsentationsart: Poster

Abstract-ID: 56

Linking CTCL cell biology with response to mogamulizumab for therapy optimization and identification of resistance mechanisms

Tengler, L.[1,3]; Melchers, S.[1,2,3]; Beltzig, P.L.[1,3]; Mößinger, K.[4]; Gschnell, M.[5]; Klespe, K.[6]; Livingstone, E.[7]; Wobser, M.[8]; Nicolay, J.P.[1,2,3,9]

1 Department of Dermatology, Venereology and Allergology, University Medical Center Mannheim/ University of Heidelberg, Mannheim, Germany.

2 Skin Cancer Unit, German Cancer Research Center (DKFZ), Heidelberg, Germany.

3 Section of Clinical and Experimental Dermatology, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany.

4 Core Facility Next Generation Sequencing, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

5 Department of Dermatology and Allergology, University Hospital of Marburg, Philipps University Marburg, Marburg, Germany.

6 Skin Cancer Center Hannover, Department of Dermatology and Allergy, Hannover Medical School, Hannover, Germany.

7 Department of Dermatology, University Hospital, Essen, Germany.

8 Department of Dermatology, University Hospital Würzburg, Würzburg, Germany.

9 DKFZ-Hector Cancer Institute at the University Medical Center Mannheim, Mannheim, Germany.

Introduction

Mycosis fungoides and Sézary syndrome belong to the heterogeneous group of primary cutaneous T cell lymphomas (CTCL). In 2018, the anti-CCR4 monoclonal antibody mogamulizumab (Moga) was approved for CTCL treatment. Currently, there is growing evidence on both primary and secondary therapy resistance. However, it has not yet been conclusively clarified which factors influence therapy response or may promote therapy resistance.

Materials and Methods

33 CTCL patients were included from five German dermatology centers belonging to the ADO lymphoma network. PBMCs and FFPE skin samples were collected at different time points: prior Moga-initiation, during Moga-therapy and at disease progression, as well as on the onset of Moga-associated rash (MAR). PBMC populations were analyzed by flow cytometry, while plasma proteins were examined via bead-based flow cytometric immunoassays. Alterations in the cellular signaling pathways implied in CTCL pathogenesis were analyzed with intracellular stainings. Furthermore, single-cell RNA sequencing was performed from 4 patients. This study was financially supported by Kyowa Kirin.

Results

Analysis of the PBMC frequency showed a significant reduction in CCR4+CD4+ T helper cells as well as a modest decrease in FoxP3+CD4+ regulatory T cells during Moga-therapy. In contrast, CD4+CD26- Sézary cells only slightly decreased and often increased at disease progression. Besides, during Moga-therapy, a significant downregulation of the NF-κB signaling pathway was detected. The analysis of the cytokine and chemokine milieu revealed alterations of IL-4, IFN-γ and IL-22 levels. Preliminary data from the single-cell RNA sequencing indicate a loss of $CCR4^+$ T cells and an increased expression of Bcl-2 at the time of resistance.

Conclusions

This study aims to better characterize the biology of malignant CTCL cells and their skin microenvironment to identify predictors of Moga-therapy response and resistance. The observed upregulation of Bcl-2 might hint toward a possible combination therapy with venetoclax to overcome resistance mechanisms.

Kategorie: Cellular biology
Präsentationsart: Poster

Hidden Gems

Abstract-ID: 57

Impact of alpha-melanocyte-stimulating hormone on mitochondrial function in human dermal fibroblasts

Flis, D.[1]; Stegemann A.[2]; Borkowska, A.[1]; Ziolkowski, W. [1]; Böhm, M.[2]

1 Dept. of Pharmaceutical Pathophysiology, Gdanski Uniwersytet Medyczny, Gdansk, Pomeranian Voivodeship, Poland

2 Dept. of Dermatology, University of Münster, Münster, Germany

Alpha-Melanocyte-stimulating hormone (alpha-MSH) is a tridecapeptide that controls the tanning response of human skin by promoting eumelanogenesis. It also protects against UV-mediated genotoxic stress. The actions of alpha-MSH are elicited via melanocortin receptors (MCRs), among which MC1R is most abundantly expressed in melanocytes. However, other cell types such as fibroblastic cells also express MC1R. We recently speculated on a direct link between alpha-MSH-MC1R signaling in dermal fibroblasts and photoaging (Böhm et al. Endocr. Rev. 2025) as individuals with loss-of-function MC1R mutations were reported to show increased photoaging. As a first approach to study the impact of alpha-MSH on mitochondria, key organelles controlling metabolism, aging and senescence, we used the substrate-uncoupler-inhibitor titration protocol (high-resolution respirometer, Oroboros) in MC1R wild-type human dermal fibroblasts (MC1R-wt-HDFs) and MC1R loss-of-function HDFs (MC1R-LOF-HDFs). Our data indicated that MC1R-LOF-HDFs had significantly lower OXPHOS coupling efficiency than MC1R-wt-HDFs stimulated for 24 h with alpha-MSH ($p=0.0193$ vs MC1R-LOF-HDFs; $p=0.0108$ vs MC1R-LOF-HDFs-alpha-MSH). This was related to the significantly lower respiration of MC1R-LOF-HDF cells' mitochondria after being treated with NADH-related substrates ($p=0.0420$). Also, the ratio of oxygen consumption rate in CI and CII conditions of cells without alpha-MSH versus treated with alpha-MSH was significantly different in both groups ($p=0.0140$ for both CI and CII). Additionally, the electron transport through the electron transfer system after FCCP stimulation showed that after alpha-MSH stimulation, MC1R-wt-HDFs represent significantly higher oxygen consumption than MC1R-LOF-HDFs ($p=0.0151$). Functional studies with pharmacological inducers of canonical cAMP signaling such as forskolin are currently underway to examine whether and how mitochondrial function is modulated in HDFs by this important pathway.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 58

Alpha-MSH-MC1R signalling and the impact of UVA in adult human dermal fibroblasts

Böhm, M.[1]; Stegemann, A.[1]; Wolnicka-Głubisz, A.[2]; Schäfer, N.[3]; Niland, S.[4]; Eble, J.[4]; Raker, V.[1]; Steinbrink, K.[1]; Grässel, S.[3]; Larue, L.[5]

1 Dept. of Dermatology, University of Münster, Münster, Germany

2 Dept of Biophysics and Cancer Biology, Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, Krakow, Poland

3 Dept. of Orthopedic Surgery ZMB im Biopark, University Hospital of Regensburg, Regensburg, Germany

4 Dept. of Physiological Chemistry and Pathobiochemistry, University of Münster, Münster, Germany

5 Institut Curie, Centre Universitaire, Orsay Cedex, France

Alpha-melanocyte-stimulating hormone (alpha-MSH) is a key endocrine mediator of photoprotection in the ultraviolet B (UVB)-light induced skin response. Its effects are mediated by the melanocortin-1 (MC1R) receptor and include direct cytoprotective mechanisms as well as increased eumelanin synthesis. Previous studies have shown that individuals with the red hair and fair skin phenotype, carrying loss-of-function *MC1R* alleles, exhibited accelerated dermal photoaging, though the underlying mechanism remain poorly known. To investigate the role of the alpha-MSH-MC1R-cAMP signalling axis in mediating UVA-induced stress responses in cutaneous cells implicated in dermal photoaging. Primary human dermal fibroblasts from adult donors were genotyped for common *MC1R* variants and analysed in both 2D monolayer and 3D spheroid culture models. UVA-induced oxidative stress and DNA damage response were assessed by flow cytometric analysis, real-time PCR, and Western immunoblotting for growth arrest and genes such as heme oxygenase (HO)-1, Sirtuin 1, and senescence-associated secretory phenotype (SASP). Functional MC1R signalling was evaluated by cAMP assays, with receptor expression confirmed by RT-PCR and Western immunoblotting. UVA exposure induced reactive oxygen species (ROS), and upregulation of p21, HO-1, Sirtuin 1, Interleukin-6 and -8. Although MC1R expression and functional cAMP signalling was confirmed, alpha-MSH treatment did not attenuate these UVA-induced stress responses. Likewise, pharmacological activation of canonical cAMP signalling failed to mitigate UVA-driven oxidative and inflammatory changes. These findings do not support a direct UVA-photoprotective role for the alpha.MSH-MC1R axis in adult dermal fibroblasts. They further suggest that canonical cAMP signalling is unlikely to represent an effective therapeutic target for preventing UVA-induced cellular alterations contributing to dermal photoaging.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 59

Melatonin-Driven Mitochondrial Regulation Accelerates Cutaneous Wound Healing

Kleszczyński, K.[1]; Okabe, K.[2]; Okura, M.[2]; Takaya, K.[2]; Ishii, T.[2]; Kishi, K.[2]

1 Department of Dermatology, University of Münster, Münster, Germany

2 Department of Plastic and Reconstructive Surgery, Keio University School of Medicine, Tokyo, Japan

Efficient wound healing depends on the coordinated regulation of keratinocyte proliferation, migration, and differentiation—processes tightly governed by mitochondrial activity and redox balance. Melatonin, a pleiotropic indoleamine with potent antioxidant and mitochondrial-stabilizing properties, has emerged as a key regulator of tissue regeneration. Here, we investigate the role of melatonin in modulating mitochondrial function and promoting skin repair during cutaneous wound healing. In vitro studies using human epidermal keratinocytes and dermal fibroblasts demonstrated that melatonin enhanced mitochondrial membrane potential ($\Delta\Psi m$) and stimulated cell proliferation, as assessed by fluorescence imaging and MTT viability assays, respectively. Scratch assays further revealed that melatonin increased cell migratory capacity even in the presence of mitomycin C.

In vivo, daily topical application of melatonin to 8 mm excisional wounds in C57BL/6 mice markedly accelerated re-epithelialization compared with vehicle controls. Melatonin-treated wounds showed reduced inflammation and earlier tissue contraction by days 3–6, followed by near-complete closure and minimal scabbing by days 9–12. Quantitative analysis confirmed significantly enhanced wound closure kinetics at days 6, 9, and 12 ($p < 0.01$, $p < 0.001$). Histological markers indicated increased proliferation (Ki-67) and vascularization (CD31) in melatonin-treated skin.

Collectively, these findings demonstrate that melatonin accelerates cutaneous wound healing by preserving mitochondrial function and orchestrating the temporal expression of keratinocyte differentiation markers. This dual action highlights its therapeutic potential for enhancing epidermal regeneration and restoring skin integrity following injury.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 60

Melatonin as a Mitochondrial Guardian in Cutaneous Anti-Aging

Okabe, K.[1]; Okura, M[1]; Takaya, K.[1]; Ishii, T.[1]; Kishi, K[1]; Kleszczyński, K.[2]

1 Department of Plastic and Reconstructive Surgery, Keio University School of Medicine, Tokyo, Japan
2 Department of Dermatology, University of Münster, Münster, Germany

Cellular senescence is an irreversible growth arrest that occurs as a result of different damaging intrinsic and extrinsic stimuli, including DNA damage, telomere shortening and dysfunction or oncogenic stress. Human skin, the largest organ of the body, provides a physical barrier against harmful microbes, toxins, and protects from ultraviolet radiation (UVR). Increasing evidence suggests that senescent cells accumulate in chronologically aged and photoaged skin; and may contribute to age-related skin changes and pathologies. Skin health is considered one of the principal factors representing overall “well-being” in humans. Thus, there is an imperative to consider melatonin’s regulatory activity on cellular senescence of the skin.

Melatonin, an evolutionarily ancient derivative of serotonin with hormonal properties, is the main neuroendocrine secretory product of the pineal gland. It regulates circadian rhythmicity and exerts anti-oxidative, anti-inflammatory, immunomodulatory, and anti-tumor capacities.

Herein, in vitro studies using human epidermal keratinocytes exposed to UVB (50 mJ/cm^2), we noticed that melatonin attenuates altered cell survival ratio, and affects expression of senescence markers (p53, p16, γH2AX, IL-6). Moreover, melatonin ameliorates UVB-induced oxidative stress and depolarization of mitochondrial transmembrane potential (mtΔΨ) indicating the mitochondrial dysfunction-associated senescence (MiDAS). In vivo studies have been performed using C57BL/6 mice treated subcutaneously biennially with melatonin (10 mg/kg) and changes in skin aging has been substantially ameliorated followed by melatonin-treated mice compared to control ones. These data enclose changes within skin aging and the impact of the melatoninergic anti-oxidative system controlled by melatonin, targeting the prevention or reversal of skin senescence.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 61

Unfolding the Kunitz Domain: Molecular Consequences of COL7A1 Missense Variants in Recessive Dystrophic Epidermolysis Bullosa

El Mabrouk, H.1,2, Sayar, B.1 , H´mida, D.2 , Nystrom, A.1 , Has, C.1

1 Department of Dermatology, Medical Center, University of Freiburg, Freiburg, Germany

2 Laboratory of Human Cytogenetics, Molecular Genetics and Reproductive Biology, Department of Genetics, Farhat Hached University Hospital, University of Sousse, Sousse, Tunisia

Dystrophic epidermolysis bullosa (DEB) results from mutations in *COL7A1*, encoding type VII collagen (C7), the main structural component of anchoring fibrils at the dermo-epidermal junction. The C-terminal non-collagenous 2 (NC2) domain is essential for initiating C7 dimerization and anchoring fibril assembly. Within it lies the BPTI/Kunitz domain (KD), considered dispensable for C7 maturation, although its structural conservation across species suggests an overlooked functional role. Objectives: To re-evaluate the contribution of the Kunitz domain by characterizing two *COL7A1* missense variants located within this region, linking structural disruption to molecular pathology.

Genetic and in silico analyses were performed for two patients with recessive DEB. Structural modeling predicted conformational consequences of the KD variants. Functional investigations, including proliferation, adhesion, protein stability, and transcriptomic profiling, were performed on patient-derived keratinocytes. Chaperone rescue assays evaluated the reversibility of ER stress.

Both variants disrupted conserved cysteines essential for intradomain disulfide bonding, leading to predicted domain destabilization. In patient keratinocytes, the KD variant caused marked C7 reduction, intracellular retention, and increased protein turnover consistent with ER-associated degradation. Transcriptomic analysis indicated ER stress and secondary activation of inflammatory and matrix-remodeling pathways. Immunofluorescence of skin sections showed severe loss of anchoring fibrils. Notably, treatment with chemical chaperones partially restored C7 expression and alleviated stress markers, supporting a reversible folding defect.

This study suggests a structural contribution of the Kunitz domain to C7 stability rather than a merely vestigial role. While functional assays were limited to a single patient-derived model, the findings illustrate how disruption of this conserved region perturbs protein homeostasis and anchoring fibril organization. Further structural and biochemical investigations are required to clarify the precise role of the KD and its therapeutic relevance in DEB.

Kategorie: Hidden Gems
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 62

Immunological markers and Cancer Testis Antigens (CTAs) in patients with advanced cutaneous squamous cell carcinoma (cSCC) receiving anti-PD-1 therapy

Cheng, J.[1]; Geier, M.[1]; Müller-Hermelink, E.[1]; Ghoreschi, F.[1]; Moritz, R.[1]; Leoni, Z.[2]; Dobos, G.[1]; Sinnberg, T.[1]; Eigentler, T.[1]

1 Charité – Universitätsmedizin Berlin, Department of Dermatology, Venereology and Allergology, Berlin, Germany.

2 Charité – Universitätsmedizin Berlin, Institute of Pathology, Berlin, Germany.

Background
Cutaneous squamous cell carcinoma (cSCC) is the second most common malignant skin tumor with a rapidly rising incidence, primarily affecting elderly Caucasian males. While primary cSCC generally has a favorable prognosis, advanced stages show aggressive behavior and poor outcomes. Cemiplimab remains the only approved anti-PD-1 therapy for advanced cSCC in Europe; however, reliable predictive biomarkers for treatment response are lacking. This study aimed to identify potential immunological and cancer testis antigen (CTA) biomarkers associated with anti-PD-1 response.

Methods
Candidate CTAs were selected from the CT database (http://www.cta.lncc.br) and analyzed in publicly available cSCC transcriptomic datasets (GSE125285) using Galaxy and R2 platforms to determine significantly deregulated CTAs. Primer pairs were designed for six CTAs (MAGEA3, MAGEA4, PBK, KNL1, CEP55, ROPN1) and 19 genes related to anti-PD-1 response (e.g., CD8A, PDCD1, CD274) or cSCC biology (e.g., MMP1, MMP3, MMP13). RNA isolation, cDNA synthesis, pre-amplification, and qPCR were performed on four cSCC cell lines (SCC-12, SCC-13, SCL-I, SCL-II) and healthy keratinocytes, followed by validation in FFPE tissue samples stratified by disease control. Immunohistochemistry (IHC) was performed to assess MAGEA protein expression (H-Score), while tumor-infiltrating lymphocyte density (eTIL%) and spatial distribution were quantified digitally using QuPath. Neutrophil-to-lymphocyte ratios (NLR) from peripheral blood were analyzed pre- and post-therapy.

Results
qPCR screening revealed no significant differences in expression between disease control (DC; n=20) and non-disease control (NDC; n=24) subgroups, although CTLA4 expression showed a downward trend in DC patients. A significantly higher STAT1/CTLA4 expression ratio (>124) was observed in the DC group and correlated with prolonged progression-free survival, suggesting enhanced baseline immune activation. IHC demonstrated MAGEA protein expression in more than half of advanced cSCC cases, with a strong correlation between MAGEA4 mRNA and its H-score. Patients in the DC collective showed a weak trend toward higher MAGEA H-Scores, which correlated with lower eTIL%, indicative of an immune-excluded (“cold”) phenotype. NDC patients exhibited a trend toward higher eTIL% and brisk infiltration patterns, consistent with an immunosuppressive tumor microenvironment. Furthermore, post-treatment NLR was significantly higher in the NDC group, whereas most NDC patients displayed decreasing NLR (ΔNLR), reflecting immune normalization.

Conclusion
DC patients treated with anti-PD-1 therapy in advanced cSCC exhibited a more functionally active immune system, characterized by high STAT1/CTLA4 ratios and lower NLR values, whereas NDC patients displayed an exhausted, immunosuppressive tumor milieu. Elevated MAGEA expression, though associated with low eTILs, may still coexist with effective immune responses in certain patients in the DC collective. A composite biomarker model integrating a STAT1/CTLA4 ratio >124, a low baseline NLR (<10; to be validated), and MAGEA H-Score

could serve as a predictive algorithm for favorable therapeutic outcomes in advanced cSCC. Ongoing analyses include IHC-based evaluation of FOXP3, CTLA4, and CD4 to further elucidate immune-suppression mechanisms that distinguish DC from NDC patients.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 63

Characterizing ribosomal biogenesis and function in XP/CS

Wang, S.[1]; Scharffetter-Kochanek K.[1]; Iben, S.[1]

1 Ulm University, Department of Dermatology and Allergic Diseases, Ulm, Germany

Xeroderma pigmentosum (XP) and Cockayne syndrome (CS) are both autosomal recessive disorders linked to the failure of nucleotide excision repair, yet their clinical symptoms differ largely. Specific mutations in XPB or XPD can cause a combined phenotype of XP/CS, which combines CS features, such as growth retardation and neurodegeneration, with the UV-induced skin cancer susceptibility of XP. Our previous research has shown that loss of proteostasis and impaired ribosome biogenesis are key pathomechanisms in CSA and CSB mutant cells, but it remains unclear whether this is a universal feature of all CS cells or can also be found in XP cells.

To address this, we analyze a series of patient-derived lymphoblastoid cell lines carrying XPB/CS, XPD/CS, XPB/XP, and XPD/XP genotypes. We then systematically evaluate key cellular processes, including translation fidelity, ribosome stability and composition, proteome stability, rRNA transcription and modification, ER stress, and the unfolded protein response (UPR). This work aims to identify whether disrupted proteostasis and ribosome biogenesis are a general hallmark across CS mutations, that can distinguish CS from XP, thereby elucidating the molecular basis of the XP/CS complex.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 64

Deciphering the molecular impact of aging on the development of autoimmunity and autoimmune diseases

Solmaz Alizadehmoghaddam Katja Bieber Kathrin Kalies Sören Dräger

Institute of Experimental Dermatology (LIED), University of Lübeck, Germany,
Institute of Anatomy, University of Lübeck, Germany

Abstract
Background and Aims Aging is a major risk factor for autoimmune diseases, but the molecular mechanisms connecting immunosenescence to autoimmunity remain unclear. Kinases regulate signaling networks involved in immune tolerance, inflammation, and cellular aging. This study investigates age- and sex-related differences in kinase activity and their potential roles in pre-autoimmune states.

Methods
Wild-type C57BL/6J mice of different ages (1, 3, and 18 months) were housed under specific pathogen-free conditions. Liver and pancreas samples were analyzed for histopathology, immune cell infiltration, and autoantibody presence. Kinase activity profiling was performed using PamGene™ arrays to identify altered signaling pathways. Hepatocyte senescence was modeled in vitro using AML-12 cells exposed to 50 nM doxorubicin for 4 days. Senescence-associated β-galactosidase staining and secretion of SASP factors were assessed.

Results
Aged mice showed signs of chronic inflammation and immune infiltration, accompanied by increased antinuclear antibody titers and autoimmune-like lesions. Kinome analysis revealed age- and sex-dependent changes in pathways related to immune activation and metabolic regulation, including mTOR, PKC, and ZAP70. Doxorubicin-induced AML-12 senescent cells displayed increased SASP factor secretion, supporting a link between kinase dysregulation and inflammatory signaling.

Conclusions
Age- and sex-dependent kinase alterations contribute to immune imbalance and tissue inflammation in aging mice. Understanding these changes may help identify early molecular signatures of autoimmunity and potential kinase targets for therapeutic modulation.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 65

Impact of filaggrin gene variants on treatment outcomes in atopic dermatitis in a Swedish register

Tayefi, M[1,2 ††]; Jonsson, P[1,2††]; Svedbom, A[1,2]; Ivert, L. U[1,2]; Wahlgren C.F[2]; Tapia-Paez, I[1]; Johansson E. K[1,2]; Maria Bradley[1,2]

1 Dermatology and Venereology Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden,

2 Department of Dermatology, Karolinska University Hospital, Stockholm, Sweden.

†† P.J. and M.T. contributed equally to this work

Background: Atopic dermatitis (AD), characterized by relapsing inflamed and pruritic skin lesions and quality of life impairment, is one of the most common chronic inflammatory skin diseases, with a prevalence estimated at 15-25% in children and 3-7% in adults. The filaggrin (FLG) protein is vital to the structural integrity and function of the skin barrier and pathogenic FLG gene variants, found in up to 50% percent of AD patients with Northern European ancestry, are the strongest known genetic risk factor for development of AD as well as a known negative modifier of the disease course.

Objectives: To describe the impact of *FLG* loss of function (LoF) mutations on patient characteristics, systemic treatment outcomes and drug survival in AD.

Methods: The presence of *FLG* mutations 2282del4, R501X or R2447X in patients in the Swedish multicenter prospective SwedAD register was determined. Clinical characteristics as well as outcome measures (Eczema Area and Severity Index, Itch Numeric Rating Scale, Dermatology Quality of Life Index, and Patient-Oriented Eczema Measure) were assessed at baseline, and at 6, 12 and 24 months for patients on systemic treatment. Differences at baseline and follow up between patients with wild type (+/+) versus those with homo- (-/-) or heterozygous (+/-) *FLG* mutations were examined. The joint drug survival of all systemic treatments with at least 10 individual treatment episodes, as well as those of dupilumab (DUP) and methotrexate (MTX) separately, was determined using Kaplan-Meier survival curves and Cox regression models, comparing the discontinuation rates between patients with wild type versus those with homo- or heterozygous *FLG* mutations.

Results: Genetic testing of 448 patients showed homozygous *FLG* mutations in 9 (2.0%), heterozygous mutations in 87 (19.4%), and wild-type alleles in 352 patients (78.6%). Patients with *FLG* mutations (-/- or +/-) had a higher prevalence of asthma and allergy compared to patients with wild type alleles, however no other clinically relevant differences in disease severity could be detected at baseline. Analysis of 433 treatment episodes in 330 patients (269 DUP, 78 MTX, 38 upadacitinib, 14 cyclosporine A, 13 abrocitinib, 11 tralokinumab, and 10 baricitinib episodes, respectively) showed few statistically significant differences regarding treatment outcomes, and none deemed clinically relevant, as patients responded similarly to systemic therapy regardless of FLG mutation status. No differences in drug survival between patients with or without *FLG* mutations were detected, regardless of systemic agent.

Discussion: Our findings are in line with recent data from the Dutch BioDay registry of 285 adult AD patients evaluated at week 16 and 52 of DUP treatment, where equal levels of EASI score reduction and improvement of patient reported outcomes in the FLG mutation and WT groups were reported. A key limitation in the present study is the lack of information on systemic treatment received before inclusion into the registry, as well as a relatively low number of treatment episodes with agents other than DUP or MTX.

Conclusions: In this nationwide real-word cohort, *FLG* loss of function mutations were not associated with clinically meaningful differences in the outcome of systemic treatments or drug survival in adults with moderate-to-severe atopic dermatitis. These findings suggest a limited utility of in the use of FLG gene mutations as a predictive biomarker in AD.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 66

Distinct trajectories of childhood atopic dermatitis are associated with differences in long-term inflammatory and cardiometabolic disease risks

Florian Thaqi[1], Philip Curman[1-4], Katja Bieber[1], Henning Olbrich[5], Diamant Thaçi[6], Ralf J. Ludwig[1,5,6]

1. Lübeck Institute of Experimental Dermatology, University of Lübeck, Lübeck, Germany

2. Dermato-Venereology Clinic, Karolinska University Hospital, Stockholm, Sweden

3. Division of Dermatology and Venereology, Department of Medicine (Solna), Karolinska Institutet, Stockholm, Sweden

4. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

5. Department of Dermatology, University-Hospital Schleswig-Holstein (UKSH), Lübeck, Germany

6. Institute and Comprehensive Center for Inflammation Medicine, University of Lübeck, Lübeck, Germany

Atopic dermatitis (AD) is a common inflammatory skin disease of early childhood that is frequently linked to later type 2 inflammatory diseases (T2IDs) and other systemic comorbidities. The long-term health impact of different AD trajectories, however, remains uncertain, as few studies have directly compared distinct disease courses. This study evaluated how childhood AD trajectories (persistent, transient, or none) relate to long-term risks of T2IDs, autoimmune diseases, and cardiometabolic disorders. Using the U.S. TriNetX network, a multicenter, population-based database of electronic health records from diverse healthcare organizations, we performed a retrospective cohort analysis including propensity-score matching, sensitivity tests, and stratified analyses by sex and ancestry. Children with AD onset before two years of age were categorized according to disease trajectory (persistent or transient) and compared with matched non-AD controls. Outcomes included incident T2IDs, autoimmune diseases, cardiovascular risk factors, venous thromboembolism (VTE), and major adverse cardiovascular events (MACE), expressed as hazard ratios (HRs). Persistent AD was associated with significantly increased long-term risks of T2IDs (HR 2.11, 95% CI 2.01–2.21), autoimmune diseases (HR 1.68, 1.60–1.76), and cardiovascular risk factors (HR 1.38, 1.22–1.56), but not VTE or MACE. Compared with transient AD, the persistent trajectory conferred higher risk across most outcomes. The risk of eosinophilic esophagitis was particularly elevated among females and children with Black or African American ancestry, whereas other sex- or race-specific differences were limited. These findings indicate that persistent childhood AD is associated with a substantial long-term inflammatory and cardiometabolic burden, while transient AD confers only minimal excess risk. The results highlight the prognostic importance of disease trajectory and underscore the need for early, disease-activity-adapted management strategies to mitigate future systemic complications in affected children.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 67

Dupilumab treatment is not associated with changes in lymphoma risk in atopic dermatitis and other type 2 inflammatory diseases: Data from a large-scale retrospective cohort study

Khalaf Kridin[1-3], Katja Bieber[1], Henning Olbrich[4], Dagmar von Bubnoff[4], Gema Hernandez[5,6], Henner Zirpel[7], Nikolas von Bubnoff[8], Diamant Thaçi[7], Ralf J Ludwig[1,4,7]

1. Lübeck Institute of Experimental Dermatology, University of Lübeck, Lübeck, Germany

2. Unit of Dermatology and Skin Research Laboratory, Galilee Medical Center, Nahariya, Israel

3. Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel

4. Department of Dermatology, University Clinic Schleswig-Holstein (UKSH), Lübeck, Germany

5. TriNetX, LLC, Cambridge, MA, United States

6. Biomedical Informatics Group, Artificial Intelligence Department, E.T.S.I. Informáticos, Universidad Politécnica de Madrid, Madrid, Spain

7. Institute and Comprehensive Centre for Inflammation Medicine, University-Hospital Schleswig-Holstein, Lübeck, Germany

8. Department of Hematology and Oncology, University Medical Center Schleswig-Holstein and University Cancer Center Schleswig-Holstein (UCCSH), University of Lübeck, Lübeck, Germany

The association between atopic dermatitis (AD) and lymphoma risk remains uncertain. Dupilumab, approved for moderate to severe AD, has been suspected to increase lymphoma risk, raising safety concerns. This study aimed to clarify the association between AD and lymphoma and to extend this analysis to non-dermatological type 2 inflammatory diseases (T2IDs). Furthermore, it evaluated whether dupilumab treatment modifies lymphoma risk in patients with AD or other T2IDs. A retrospective cohort analysis was conducted using the U.S. TriNetX network, comprising real-world electronic health records from multiple healthcare organizations. Propensity-score matching was used to ensure comparability between cases and controls, and sensitivity analyses confirmed robustness. Among 801,508 matched individuals, AD was associated with a higher risk of lymphoma, including cutaneous T-cell lymphoma (CTCL) and non-Hodgkin lymphoma (NHL). In an extended analysis of more than 14.4 million cases and controls, non-dermatological T2IDs also showed significantly increased lymphoma risks. In patients with AD treated with dupilumab compared with other systemic therapies (n=7,840 per group), dupilumab exposure did not increase lymphoma risk and instead tended to be associated with lower risks. A similar pattern was observed for non-dermatological T2IDs (n=16,908 per group), where dupilumab use was linked to a more pronounced risk reduction. All results remained consistent across all sensitivity analyses. The main limitations include the retrospective design, variable data quality, and possible miscoding of diagnoses. In summary, AD and other T2IDs are associated with a significantly increased risk of lymphoma, affecting both CTCL and NHL. However, treatment with dupilumab appears not to elevate this risk and may even mitigate it, particularly for NHL. These findings suggest that the inflammatory milieu of T2IDs, rather than dupilumab exposure, underlies the observed lymphoma associations.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 68

Global Burden of Skin Diseases 1990–2021: Insights from the GBD Study

Zou, Y[1]; Buhl, T[1]

1.Department of Dermatology, Venereology and Allergology, University Medical Center Göttingen, Göttingen, Germany.

Background:
Dermatological diseases can be broadly classified into inflammatory, infectious, neoplastic, and other common skin disorders. Although most are not life threatening, they can substantially impair daily life and overall well-being.

Methods:
Using data from the Global Burden of Disease (GBD) Study 2021, we estimated prevalence, incidence, mortality, and burden of skin diseases, measured as years of life lost, years lived with disability, and disability-adjusted life years. To explore trends and differences across countries and regions, we applied statistical and forecasting models, inequality assessments and regression analyses, focusing in particular on China, the United States of America, and Europe.

Results:
Between 1990 and 2021, global age-standardized trends increased for several skin conditions significantly, including pyoderma (EAPC 0.68), bacterial skin diseases (0.64), acne vulgaris (0.43), and other skin and subcutaneous diseases (0.46). Moderate increases were observed for pruritus (0.35) and psoriasis (0.23). Several conditions, including seborrheic dermatitis, fungal skin diseases, contact dermatitis, urticaria, and cellulitis, showed only minor increases. In contrast, declines were observed for alopecia areata (–0.14) and atopic dermatitis (–0.20), while scabies, viral skin diseases, and decubitus ulcer showed minor decreases.

Conclusion:
Between 1990 and 2021, the global burden of skin diseases rose, mainly driven by bacterial infections, inflammatory conditions, and chronic dermatological disorders. The most pronounced increases were seen in pyoderma, bacterial skin diseases, and acne vulgaris, underscoring the growing public health relevance of skin infections and inflammation. In contrast, declines in alopecia areata, atopic dermatitis, scabies, and viral skin diseases may reflect progress in treatment, hygiene, and prevention. Sustained monitoring and targeted interventions are essential to address the changing burden of skin diseases.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 69

Analysis of the Molecular Etiology of Polyautoimmunity in Alopecia Areata Patients

Brand, F. [1]; Abdolozahdeh, H. [2]; Betz, R. [2]; Basmanav, B. [2]

[1] Universität Bonn, Universitätsklinikum Bonn, Klinik für Dermatologie und Allergologie

[2] Universität Bonn, Universitätsklinikum Bonn, Institut für Humangenetik

Alopecia Areata (AA) is an autoimmune disorder and a common cause of hair loss in the population with an estimated lifetime risk of 2.1%. Typically, AA is considered as a polygenic disease, with genome-wide association studies providing evidence of 14 common risk variants that are associated with AA, many of which are implicated with immune responses or immune phenotypes. However, AA can also be considered as a manifestation of inborn errors of immunity or Polyautoimmunity. In this way, AA manifests through mono- or oligogenic etiologies by deleterious mutations in immune genes (e.g. AIRE, CTLA4, FOXP3), in conjunction with autoimmune comorbidities such as Hashimotos disease or Vitiligo.

To analyze the molecular etiology of AA patients, we recruited and whole genome sequenced (WGS) a cohort of 400 AA patients with at least one autoimmune comorbidity (e.g. Hashimotos disease, Systemic Lupus Erythematosus). For each patient, we track their status for a total 32 potential autoimmune comorbidities and 61 atopic comorbidities in addition to AA specific metadata (e.g. age of onset, severity), allowing us to assess comorbidity profiles of polyautoimmunity with AA and to associate any genomic variant with the observed phenotypes.

We use standardized pipelines to process WGS data from all AA cases and 262 technology-matched controls. This dataset allows us to perform whole genome screening tests, gene-based burden tests, region-based burden tests and to compute polygenic risk scores for our case collective, providing evidence for novel gene to phenotype links in cases of AA with autoimmune comorbidities. Furthermore, we select pathogenic and likely pathogenic, as well as rare deleterious variants in our dataset in order to investigate individual cases for a mono- or oligogenic etiology of their polyautoimmunity phenotypes.

The whole genome screening yields new associations between AA and potential disease genes causing polyautoimmunity phenotypes and many genomic loci. Most of the loci fall into lncRNA regions, providing potential targets for follow-up analyses regarding the contribution of these regions to the overall phenotype, given that the effect-size of individual variants is expected to be low. Secondly, the pathogenic variant analysis shows that known genes that are associated with AA (e.g. KRT82, ULBP3) are enriched for pathogenic mutations in our cohorts, as are genes that are associated with comorbidities such as FLG (atopic dermatitis) and FCN3 (Systemic Lupus Erythematosus).

This first large-scale WGS-based assessment of polyautoimmunity in AA patients shows that a fraction of AA cases with autoimmune comorbidities are caused by one or very few deleterious mutations in known genes, constituting a mono- or oligogenic etiology of AA in these cases. However, in other cases AA is driven by a complex interaction of multiple genetic variants and environmental factors.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 70

Genetic and Molecular Similarities of Autoimmune Diseases

Isha Barve[1], Marius Möller[1], Inke König[2], Hauke Busch[1]

[1]Lübeck Institute for Experimental Dermatology (LIED) University of Lübeck, Germany

[2]Institute of Medical Biometry and Statistics (IMBS), University of Lübeck, Germany

Autoimmune diseases are genetically heterogeneous, yet many share overlapping molecular pathways and genetic risk factors. While genome-wide association studies (GWAS) have identified common variant associations with PV, the role of rare genetic variants and their pathogenesis remains poorly understood. In this project, we aim to explore and functionally classify genetic and pathway similarities across autoimmune diseases, with a particular emphasis on the contribution of rare variants. As a first step, we analyzed Pemphigus vulgaris (PV), a rare autoimmune blistering disorder characterized by autoantibodies targeting desmoglein 3 (Dsg3) and, in some cases, desmoglein 1 (Dsg1), leading to the loss of keratinocyte adhesion. Previous work suggests that autoantibody binding alone is insufficient to initiate disease; instead, mechanical stress and cell detachment activate key inflammatory pathways such as NF-κB, MAPK, and JAK-STAT.

To explore the impact of rare variants in PV, we performed rare variant burden testing on whole-genome sequencing (WGS) data from the UK Biobank. Burden testing identified 31 statistically significant genes that were subsequently filtered for tissue-specific gene expression in skin and mucosal tissues. The resulting gene set was linked to cell adhesion, inflammation, and tissue remodeling. Among them, JAG2, part of the Notch signaling pathway, emerged as a major burdened gene. SND1 and PTPRK which participate in NF-κB signaling and cell–cell adhesion, respectively, were also found to carry deleterious variants. Thus, rare variants in these novel players might affect inflammation and cell-cell adhesion and predispose the skin to detachment. A burden testing on 140 Bullous pemphigoid (BP) samples identified 250 statistically significant genes out which 108 were common across skin and mucosal tissue types. These significantly expressed genes were found to be linked to bio-processes crucial for maintaining skin integrity such as Golgi organization, vesicle transport, autophagosome regulation, and integrin-mediated signaling. 4 genes involved in epithelial cell polarity, actin binding and cell adhesion, carried deleterious variants and were consistently expressed across skin and mucosal tissues after GTEx integration. Thus, we found rare variants that were different from PV and closely related to the locus of split formation, destabilizing the skin's basement membrane and resulting in cell–matrix separation leading to blistering in BP. Further studies will include testing the robustness of these findings and extending the analysis to other autoimmune diseases such as Psoriasis and Systemic Lupus Erythematosus to explore shared genetic and molecular mechanisms

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 71

Ribosomal biogenesis and function in ALS: The role of FUS depletion and mutation

Y.Li, M.Hartmann, D.Zhang, Z.Cao, K.scharffetter-Kochanek, S.Iben

Department of Dermatology and Allergic Diseases, Ulm, Germany

In skin cells of progeroid children suffering from Cockayne syndrome and Trichothiodystrophy, we could identify disturbances in ribosomal biogenesis and function followed by a loss of proteostasis. As loss of proteostasis, characterizes aging-associated neurodegeneration, we are now investigating if disturbances in ribosomal biogenesis and function contribute to the development of neurodegenerative diseases of the aging body. ALS(Amyotrophic Lateral Sclerosis) is a lethal progressive neurodegenerative disease associated with aging, characterized by loss of motor neuron cells and muscle atrophy. FUS(fused in sarcoma) accounts for about 4% of fALS (familial ALS) mutations and 1% of sALS (sporatic ALS) mutations. FUS is involved in many aspects of RNA metabolism, including transcription, splicing and translation.

In our work, using SH-SY5Y cells and HEK 293T cells with FUS knockout and ALS mutations, we investigate ribosomal biogenesis under physiological and stress conditions. We can show that FUS depletion and FUS mutation significantly increase translational error rates and repress protein synthesis and ribosomal biogenesis. Besides, ER stress and proteome stability, as well as ribosomal assembly are also affected by FUS depletion/mutation. Interestingly, results in the neuroblastoma SH-SY5Y cells were not reflected in the HEK 293T cells, indicating a cell type specificity of FUS function.

These results suggest that the ribosome biogenesis defects previously described in CS and TTD patient skin cells also found in FUS-related ALS pathology. We are now planning to further investigate this mechanism in ALS patient-derived skin cells in the future.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 72

LRIG3 in skin biology: from homeostasis to tumorigenesis

Ghorbanalipoor, S.[1]; Posch, C.[2,3]; Meisel, P. F.[1]; Simroth, A. T.[1]; Hommel, T.[1]; Dahlhoff, M.[1]

[1]Institute of *in vivo* and *in vitro* Models, University of Veterinary Medicine Vienna, Vienna, Austria

[2]Department for Dermatology, Klinik Hietzing, Vienna Healthcare Group, Vienna, Austria

[3]Faculty of Medicine, Sigmund Freud University Vienna, Vienna, Austria

Introduction: The leucine-rich repeats and immunoglobulin-like domains (LRIG) protein family, comprising LRIG1, LRIG2, and LRIG3, regulates growth factor receptors and plays a pivotal role in tissue development and homeostasis. Due to their crucial function in modulating growth factor receptor signaling, they have gained increasing attention as potential regulators of tumorigenesis. The function of LRIGs in maintaining skin homeostasis is primarily understood due to the most extensively studied member, LRIG1. It is expressed in the interfollicular epidermis and hair follicles (HFs) and promotes stem cell (SC) quiescence, and its overexpression in murine skin leads to alopecia and hyperkeratosis. While LRIG2 overexpression has no obvious impact on skin homeostasis, it increases inflammation, angiogenesis, and an early onset of cutaneous squamous cell carcinoma.

Methods and Results: Here, we provide the first insights into how overexpression of LRIG3, the last member of the LRIG protein family, influences cutaneous homeostasis in the mouse using the Tet-Off system. Visible hair loss was the most prominent effect on the skin of double transgenic (*Lrig3*-TG) mice. Using western blot analyses, we revealed extensive changes in the skin protein profile, such as lower expression of keratin 1 and loricrin and, conversely, higher expression of involucrin, filaggrin, transglutaminase-1, beta-tubulin, vinculin, beta-actin, E-cadherin, and P63 in *Lrig3*-TG mice when compared with controls. Moreover, deviated expression levels of proteins linked to the HFSC, including B lymphocyte-induced maturation protein 1, leucine-rich repeat-containing G-protein-coupled receptor 6, and LRIG1, were detected in the skin of *Lrig3*-TG versus control mice. Additionally, in relation to control mice, an activation of ERBB and NOTCH signaling cascades accompanied by stimulated PI3K/AKT pathway was observed in the skin of *Lrig3*-TG mice. Furthermore, to investigate the potential contribution of LRIG3 to skin carcinogenesis, we first evaluated the expression level of LRIG3 in human skin cancer and found higher expression of LRIG3 in the malignant melanoma patient-derived skin sections as well as the A375 cell line. Next, we induced a two-stage chemical carcinogenesis in an *Lrig3*-knockout (KO) mouse line and the wild-type littermates. We observed a reduced tumor burden in the *Lrig3*-KO mice in comparison with controls.

Discussion: Taken together, our study suggests that LRIG3 may uphold the balance of skin function and, more specifically, HF through an ERBB-mediated signaling pathway. These findings support the potential of the *Lrig3*-TG mouse line as a model for studying HF biology and could provide new insights into therapeutic intervention in hair loss conditions. In addition, our results imply LRIG3 as an oncogenic contributor to skin cancer and might be a targetable driver for skin cancer treatment.

Kategorie: Hidden Gems
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 73

Generation of Second-hit Mutated Keratinocyte Cell Line Models and Identification of Novel Therapeutic Targets for Porokeratosis

Wang, W. Li, D. Has, C.
Department of Dermatology, Medical Center, University of Freiburg, Freiburg, Germany

Porokeratosis (PK) is a group of epidermal differentiation disorders and one of the most common genodermatoses associated with an increased risk of malignant transformation into skin carcinoma and melanoma. Current treatment for PK is primarily focused on lesion destruction or reducing scaling and inflammation associated with these lesions. However, the patients need lifelong treatment and the outcome is often unsatisfactory, especially in patients with porokeratosis of Mibelli (PM) and linear porokeratosis (LP) with larger skin lesions and higher malignant transformation rates. Recent evidence shows that abnormalities in the mevalonate pathway via Knudson's "two-hit" mutation hypothesis are responsible for the pathogenesis of PK and up to date more than 200 pathogenic germline and somatic variants in the mevalonate pathway genes are associated with PK. The phenotypes of PK reflect both the deficiency of metabolic pathway end products and the accumulation of toxic metabolite synthesized proximally in the pathway, therefore it is rational to identify common therapy targets with human keratinocyte cell line models carrying pathogenic mutations. To date, there are no PK cell line models and only two mouse models with *MVD* deficiency have been published, however, both mouse skin lesions differed from the typical lesional skin from patients.

We have performed transcriptome analysis of primary lesional skin samples from a LP patient and discovered targeted anti-IL-17A therapy for PK. Improvement was observed after several weeks, and persisted over the entire treatment period without side effects or therapeutic response reduction. To further develop a therapy to cure the disease and improve the life quality of patients without lifelong treatment, we have generated immortalized cell line models of second-hit disease-causing keratinocytes carrying a PMVK pathogenic mutation. These cell line models in 2D culture recapitulated several key phenotypes of primary PK lesional skins including selective growth advantage, abnormal differentiation, elevated IL-17 pathway, deregulated cellular cholesterol level and positive response to lovastatin treatment. Transcriptome analysis revealed distinct gene expression patterns and multiple potential therapeutic targets of second-hit mutated keratinocytes. Treatment with several drugs against selected therapeutic targets in these keratinocytes showed amended cell morphologies, improved cell differentiation as well as normalized gene expression, therefore providing preclinical rational to employ these drugs in the off-label treatment of PK.

In summary, we have generated the first PK second-hit mutated cell line models and provide a robust platform to investigate disease mechanisms and discover new therapies for PK.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 74

Investigation of stress induced metabolic changes in the progeroid Cockayne syndrome (CS) shows metabolic dysfunctions in CS cells

Teodora Svilenska[1], Chiara Cimmaruta[2], Claudia Bogner[3], Vincent Laugel[4], Wolfram Gronwald[3], Miria Ricchetti[2], Y. Kamenisch[1]* and M. Berneburg[1]*

[1]Department of Dermatology, University Hospital Regensburg, 93042 Regensburg, Germany, Tel.: 0941 944-9601,

[2]U5 Molecular Mechanisms of Pathological and Physiological Ageing, Institut Pasteur, 25, rue du Dr. Roux, 75724 Paris Cedex 15, France

[3]Institute of Functional Genomics, Department Functional Genomics, Am BioPark 9, 93053 Regensburg, Germany, Tel.: 0941 943 5015

[4]University Hospital of Strasbourg, Neuromuscular Centre at Hautepierre Hospital, Hautepierre Hospital, Avenue Molière, 67000 Strasbourg, France

*: corresponding authors

Cockayne syndrome (CS) is a rare genetic disease with progeroid symptoms, like, progressive severe neurological defects and UV sensitivity with no treatment up to now. The investigation of metabolic changes, which are associated with aging processes or stressors, can increase the knowledge of the complex processes leading to aging of cells and organisms.

Previous results have shown that exposure of human skin cells to stressors like UVA irradiation or reactive oxygen species (ROS) leads to significant changes in the cell metabolism, especially in the glucose metabolism. The high levels of UVA induced glucose and pyruvate consumption could be involved in the ROS detoxification strategies of these ROS treated cells. Furthermore, it has been shown, that CS cells can exhibit higher levels of cellular ROS damage than WT cells.

In this study, we investigated the impact of stressors (ROS) on the metabolism and oxygen consumption in primary human skin fibroblasts derived from CS patients with the premature aging syndrome or from healthy individuals (WT). These cells were exposed to repetitive low dose UVA irradiation (inducing ROS) with subsequent measurement of cellular oxygen consumption using a Clark type electrode and metabolic changes in the supernatant of the cells, using nuclear magnetic resonance spectroscopy (NMR).

UVA irradiation induced significant changes in many metabolites (glucose, lactate, pyruvate, glutamine, glutamate, choline, alanine, betaine, acetate) in the cellular supernatant. Similar to WT cells, CS cells showed UVA induced higher glucose and pyruvate consumption, as well as higher lactate and alanine secretion. Interestingly, metabolic differences between WT and CS cells are already present without external stressors (UVA irradiation) and many of these differences increase upon UVA treatment. Concerning cellular respiration, differences in the oxygen consumption rate, between CS and WT cells were visible without external stressors. These results show differences in metabolism between CS cells of patients with premature aging symptoms and WT cells. It is known, that, under specific conditions, processes of cellular respiration can generate high levels of ROS. Therefore, it can be speculated, that CS cells try to exploit metabolic ROS detoxification strategies associated to glycolysis (higher glucose and pyruvate consumption than WT cells) and reduce ROS production during respiration (lower respiration rate than WT cells).

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 75

Development and Functional Characterization of CD3- and CD16a-Directed Bispecific Engagers Targeting Melanoma-Associated Antigens

Sanchez-Diaz, Mercedes[1]; Atilla Aydin, Serra[1]; Levagina, Polina[1]; Primke, Kimberly[1]; Eigentler, Thomas[1]; Sinnberg, Tobias[1]

[1]Department of Dermatology, Charité – Universitätsmedizin Berlin, Germany

Introduction: Melanoma is the most aggressive skin cancer, and its incidence continues to rise. Despite advances with immune checkpoint inhibitors, many patients develop resistance or relapse. Bispecific engagers can redirect immune effector cells toward tumor cells by simultaneously binding a tumor-associated antigen and an immune receptor. While CD3-directed bispecific T-cell engagers (BiTEs) have shown success in hematologic malignancies, their efficacy in solid tumors remains limited, partly due to low T-cell infiltration. Engaging FcγRIIIa (CD16a) on NK cells and macrophages may overcome this limitation. We developed CD3- and CD16a-directed bispecific antibody constructs (BiTEs and BiKEs) targeting the melanoma-associated surface antigens MCAM/CD146, CSPG4, and CD228/melanotransferrin to enhance immune-mediated melanoma cell killing.

Methods: Single-chain variable fragments (scFvs) specific for MCAM, CSPG4, or CD228 were cloned into bispecific constructs of two formats: (i) BiTEs (anti-CD3) and (ii) BiKEs (anti-CD16a). Constructs were transiently transfected and expressed in HEK293 cells, and supernatants were collected 72 h post-transfection. Specific binding to melanoma cell lines (A2058, A375, UACC257, HT144, G361) and immune effector cells (NK-92/CD16a, RAW264.7/CD16a, and PBMCs) were quantified by flow cytometry. T-cell activation was assessed using a Jurkat-NFAT Gaussia luciferase reporter assay following co-culture with melanoma targets and BiTE supernatants, with luminescence measured at 6, 18, and 24 h. Phagocytosis and melanoma cell death were quantified by flow cytometry as $CFSE^{+}CD11b^{+}$ macrophages and $CFSE^{+}$Zombie $Violet^{+}$ melanoma cells, respectively, after 3 h co-culture with BiKE constructs. Real-time cytotoxicity was evaluated using the xCELLigence SP platform, where melanoma cells were seeded on E-Plates and subsequently co-cultured with PBMCs ± bispecific constructs at defined effector-to-target ratios.

Results: Agarose gel electrophoresis confirmed the expected plasmid sizes of our BiTE/BiKE constructs of approximately 8.9–9 kb. HEK293 transfection efficiency, based on GFP-positivity, ranged from 25–67%: CD19/CD3 (67%), CD19/CD16 (51%), MCAM/CD3 (52%), MCAM/CD16a (30%), CD228/CD3 (45%), CD228/CD16a (46%), and CSPG4/CD16a (25%). Binding of CD228/CD16 and MCAM/CD16 was demonstrated for our five melanoma cell lines. In the Jurkat-NFAT Gaussia reporter assay, co-culture with MCAM/CD3 and CD228/CD3 BiTEs yielded significantly higher luciferase activity compared to co-culture without BiTE, and co-culture with control-BiTEs (CD19/CD3 and CD19/CD16). Phagocytosis assays using three melanoma lines (A375, A2058, HT144) revealed higher percentages of $CFSE^{+}CD11b^{+}$. Real-time impedance analysis (xCELLigence) with A2058 targets showed a marked reduction in cell index values after treatment with MCAM/CD3 and CD228/CD3 compared with co-culture with PBMCs alone.

Conclusions: We designed and expressed bispecific CD3- and CD16a-engaging antibodies targeting three melanoma-associated antigens. These constructs demonstrated specific binding and functional activity in activating immune cells toward melanoma cells. These findings support the potential of bispecific antibody platforms engaging NK cells and macrophages as novel therapeutic strategies for melanoma immunotherapy.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 76

High-Throughput Identification and Preclinical Validation of Fimepinostat and Adavosertib as Promising Therapeutic Candidates for Cutaneous T-Cell Lymphoma

Deniz Özistanbullu,[1,2] Karola Bahrami,[1] Monika Doll,[1] Gabi Reichenbach,[1] Martina Sarah Pöschl[1], Raphael Wilhelm,[2] Nadja Zöller,[1] Anke König,[1] Pascal Spahn,[3] Manuel Jäger,[3] Sven R Quist,[4,5] Lars Winkler,[6] Jan P Nicolay,[7] Bastian Schilling,[1] Roland Kaufmann,[1] Markus Meissner,[1] Johannes Kleemann[1], Jindrich Cinarl Jr[8] and Stefan Kippenberger [1#]

[1]Department of Dermatology, Venereology and Allergology, University Hospital Frankfurt, Goethe University, 60596 Frankfurt, Germany
[2]Department of Dermatology, University Medical Center of the Johannes Gutenberg University, 55131 Mainz, Germany
[3]Department of Dermatology, Städtisches Klinikum Karlsruhe, 76133 Karlsruhe, Germany
[4]Clinic of Dermatology, Helix Medical Excellence Center Mainz, 55128 Mainz, Germany
[5]Department of Dermatology, Otto-von-Guericke Universität Magdeburg, 39120 Magdeburg, Gernany
[6]Experimental Pharmacology & Oncology Berlin-Buch GmbH, 13125 Berlin, Germany
[7]Department of Dermatology, Venereology and Allergology, University Medical Center Mannheim, University of Heidelberg, 68167 Mannheim, Germany
[8]Interdisciplinary Laboratory for Paediatric Tumour and Virus Research, Dr. Petra Joh Research Institute, 60529 Frankfurt am Main, Germany.

Cutaneous T-cell lymphomas (CTCL) are rare non-Hodgkin lymphomas with increasing incidence and limited curative options, particularly in advanced disease where currently available therapies often induce only partial and short-lived responses. This therapeutic gap underscores the need for novel agents with improved efficacy and selectivity. To address this, we screened approximately 2,200 compounds using an MTS-based high-throughput approach aimed at identifying substances with robust activity in CTCL models.

From this unbiased screen, the dual PI3K/HDAC inhibitor fimepinostat and the Wee1 inhibitor adavosertib—both currently being evaluated in Phase-II clinical trials—were identified as promising candidates for follow-up and were selected for comprehensive mechanistic evaluation. In vitro, both compounds significantly reduced cell viability in several CTCL cell lines (HuT78, SeAx, MyLa, HH) in a dose-dependent manner and induced apoptosis, as reflected by increased caspase-3/7 activity; adavosertib additionally caused a characteristic G_2/M cell-cycle arrest. Phospho-antibody array profiling revealed broad treatment-induced alterations across numerous signaling pathways, including a reduction in DNA damage response–related kinase activity and suppression of stress-regulated signaling nodes. These observations were supported by Western blot analyses, which demonstrated activation of DNA damage responses, including γH2A.X induction and p53 stabilization, together with attenuation of central pro-survival signaling mechanisms. In vivo, oral administration of fimepinostat and adavosertib significantly reduced tumor growth in a MyLa xenograft mouse model, with treated animals displaying markedly smaller tumor volumes compared to controls.

Collectively, these findings identify fimepinostat and adavosertib—discovered via systematic high-throughput screening and both in mid-stage clinical development—as promising therapeutic candidates for CTCL. Their potent and selective antitumor activity across mechanistically distinct pathways provides a strong rationale for further preclinical studies and supports future clinical evaluation in patients with CTCL.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 77

Pharmacological inhibition of Focal Adhesion Kinase (FAK) exerts compound-dependent effects on cancer-associated fibroblasts (CAF) and cutaneous squamous cell carcinoma (cSCC) cells

Amschler, K.[1]; Thoms, K.M.[1]; Kareem, A.[1]; Bußmann, J.[1]; Dösereck, T.E.[1]; Hofemeier, A.[2]; Lubern, M.[3]; Lutz, S.[2]; Schön, M.P.[1]; Lorenz, V.N.[1]

1 University Medical Center Göttingen, Department of Dermatology, Venereology, and Allergology, Göttingen, Germany

2 Institute of Pharmacology and Toxicology, University Medical Center Göttingen, Göttingen, Germany

3 Third Institute of Physics – Biophysics, Georg August University Göttingen, Göttingen, Germany

Cancer-associated fibroblasts (CAFs) are a predominant cellular component of the tumor stroma and play a pivotal role in the pathogenesis of cutaneous squamous cell carcinoma (cSCC) by orchestrating the synthesis and dynamic remodeling of the extracellular tumor matrix. Through their multifaceted functional activities and reciprocal signaling with tumor cells, CAFs can modulate therapeutic penetrance and foster resistance mechanisms frequently observed during PDL1 checkpoint immunotherapy or alternative epidermal growth factor receptor (EGFR) inhibitor treatments. Focal adhesions (FAs) constitute principal sites of extracellular matrix (ECM)–cell attachment, where the focal adhesion kinase (FAK) orchestrates downstream signaling pathways governing actin cytoskeletal remodeling, cellular migration, and proliferation. Previously, we identified an increased abundance of FAs and increased collagen contraction forces within cSCC-derived CAFs. Building on these findings, we investigated the effects of FAK inhibition in cSCC-derived CAFs as well as in cSCC tumor cell lines, individually and in an organotypic model to mimic the tumor microenvironment. For targeting FAK pharmacologically, a degrading proteolysis-targeting chimera (PROTAC) and the small-molecule inhibitor defactinib were applied to cSCC-derived CAFs and to TGF-β pre-stimulated normal dermal fibroblasts (NDFs) resulting in a CAF-resembling phenotype. While PROTAC treatment induced robust FAK protein degradation at nanomolar concentrations, defactinib attenuated phosphorylated, active FAK levels in CAFs and NDFs at micromolar concentrations. Subsequent experiments using subtoxic concentrations maintained cell viability but resulted in significant functional impairments, particularly following PROTAC-induced FAK degradation. In three-dimensional contraction assays with CAF and NDF-populated collagen strands, cell contractility was diminished following PROTAC treatment. In addition, immunofluorescence analyses revealed cytoskeletal disorganization and a decrease in FAs following PROTAC treatment. By contrast, defactinib treatment did not affect any of the aforementioned functions in CAFs and NDFs. Compared to CAFs/NDFs, the tumor keratinocyte lines A431 and HSC-1 demonstrated higher FAK and pFAK levels. Treatment with defactinib - but not PROTAC – resulted in a significant reduction in tumor cell viability at micromolar concentrations. In the organotypic tumor model, defactinib further suppressed tumor cell invasion into the CAF-enriched tumor-resembling matrix at similar concentration ranges. Collectively, these observations suggest that both FAK inhibitors exert distinct, potentially mechanism-dependent effects, that also vary depending on the respective target cell type. Ongoing investigations aim to uncover whether FAK inhibition in CAFs can modulate tumor matrix permissiveness, how this affects the organotypic interaction with tumor keratinocytes, and if combination therapies with clinically approved drugs may amplify the inhibitory effects observed.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 78

Itching, stress, and negative emotions in atopic dermatitis and psoriasis: Interactions in everyday life and relevance for quality of life

Thiem, A[1]; Reimer, N[2]; Kampel, T[1]; Emmert, S[1]; Spitzer C[2]

1 Clinic and Policlinic for Dermatology, Venereology and Allergology, University Medical Center Rostock, Rostock, Germany

2 Clinic and Policlinic for Psychosomatic Medicine and Psychotherapy, University Medical Center Rostock, Rostock, Germany

Background:
The chronic inflammatory skin diseases atopic dermatitis (AD) and psoriasis (PSO) are associated with reduced quality of life and impaired mental health. Chronic pruritus (itching) could play a key mediating role in this context, as it is modulated by environmental influences, physiological factors, and psychosocial factors such as negative affects and stress.

Objectives:
With the help of Ecological Momentary Assessment (EMA), the interactions between pruritus, negative affects, and stress, as well as modulating biopsychosocial factors in the everyday environment of those affected, are to be understood

Methods:
In this longitudinal study, patients with AD (N=60) and PSO (N=60) were asked to record the variables itching, stress, and negative affectivity five times a day via a smartphone app over a 15-day period. In addition, the participants kept a standardized digital diary every evening to record their skin condition and stress factors.
In an initial examination, sociodemographic data, information on physical and mental health, quality of life, and psychosocial factors were collected using standardized self-assessment instruments; disease severity was assessed by the treating dermatologist. A follow-up was conducted after the EMA phase.

Results:
AD sufferers reported significantly more itching and a significantly lower quality of life than patients with PSO. In AD patients, itching was most strongly explained by disgust (d= 0.44), stress (d= 0.20), and shame (d= 0.16). Stress was mainly influenced by anger (d=0.60), anxiety (d= 0.55), helplessness (d= 0.55) and itching (d= 0.25).

Discussion:
The preliminary results show differential correlations between itching, stress, and negative affectivity in the everyday lives of those affected. Taking these into account could potentially improve the holistic treatment of chronic skin diseases. App-based diagnostics and interventions or digital diaries could be used to support this.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 79

Integrated Transcriptomic and Proteomic Profiling Reveals Mechanotransductive Pathways in Chronic Pruritus

Authors: E. Teitge[1]; H. Renkert[1]; C. Zeidler[1]; S. König[2] S. Ständer[1]; H. Wiegmann[1]; K. Agelopoulos[1]

[1] University Hospital Münster, Section for Pruritus Medicine, Department of Dermatology and Center for Chronic Pruritus, Münster, Germany

[2] University of Münster, IZKF Core Unit Proteomics, Münster, Germany

Introduction

Chronic nodular prurigo (CNPG) is a chronic inflammatory skin disease characterized by intensely pruritic nodules and a self-perpetuating itch-scratch cycle. Repetitive scratching not only exacerbates skin barrier disruption but also imposes continuous mechanical stress on resident skin cells. This mechanotransductive stimulation is increasingly recognized as a critical yet mechanistically not fully understood driver of disease pathogenesis and progression.

Methods

To investigate the molecular impact of repeated mechanical stress, primary human keratinocytes derived from CNPG patients were subjected to cyclic stretch for six hours using the Cytostretcher platform (Curi Bio). This in vitro model mimics biomechanical forces exerted during chronic scratching and enables the controlled assessment of mechanotransductive responses. Cells were subsequently analyzed by integrated transcriptomic (RNA-seq) and proteomic (mass spectrometry) profiling to comprehensively characterize the stress-induced molecular landscape.

Results

The multi-omics approach revealed a broad deregulation of genes and proteins, reflecting profound cellular reprogramming. Particularly, mechanical stress induced an enrichment of pathways associated with type 2 inflammation, including components in cytokine-signaling pathways, along with genes involved in neuroinflammation, axonal guidance, cutaneous innervation, and neuronal projection. Furthermore, alterations in components regulating chromatin organization, transcription, and RNA processing were identified, suggesting long-term epigenetic and transcriptional remodeling in response to mechanical stimuli.

Discussion

Collectively, these data demonstrate that mechanical stress alone is sufficient to induce substantial molecular changes in keratinocytes, deregulating pathways linked to inflammation, neuroimmune interaction, and pruritus. These results emphasize the pivotal contribution of biomechanical stress in the pathophysiology of CNPG and reveal mechanistic insights into how chronic scratching perpetuates disease progression through cellular reprogramming, potentially extending to other dermatological conditions involving persistent scratching.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 80

Neuroanatomy and Central Sensitization in Chronic Prurigo under Dupilumab Treatment

Felix Witte[1]; Claudia Zeidler[1]; Henning Wiegmann[1]; Lea-Sophie Stahl[1]; Anna Brenske[1]; Svenja Royeck[1]; Konstantin Agelopoulos[1]; Sonja Ständer[1]

[1]Department of Dermatology, Section Pruritus Medicine and Center for chronic pruritus, University Hospital Münster, Münster, Germany

Background and Objectives

Itch is the predominant and most distressing symptom experienced by patients with chronic prurigo (CPG/prurigo nodularis). Dupilumab, an interleukin-4 receptor alpha antagonist, is approved for the treatment of moderate to severe CPG, showing beneficial effects on both pruritic skin lesions and itch intensity. However, the underlying cutaneous neuronal changes contributing to itch in CPG, as well as their development during treatment, remain insufficiently understood. Existing evidence indicates a decreased intraepidermal nerve fibre density (IENFD) in CPG lesions compared to healthy skin.[1] Findings in atopic dermatitis suggest that dupilumab may improve IENFD and neuronal sensitization processes.[2] The aim of this study was to investigate cutaneous neuronal alterations in CPG patients undergoing treatment with dupilumab.

Materials and Methods

Adult patients with moderate to severe CPG received dupilumab 300mg subcutaneously every two weeks for 16 weeks. Skin biopsies were analysed at initial assessment (IA) and at follow-up (FU, week 16) for IENFD, next to alloknesis and hyperknesis assessment and clinical outcome parameters. This study is still active regarding FU visits, the cohort size is n = 50.

Results

Preliminary data reveal a significant improvement of itch intensity (WI-NRS/24h, $p < 0.001$, $n = 36$) and quality of life (DLQI, $p < 0.001$, $n = 34$) after 16 weeks of dupilumab treatment. Clinical improvement was paralleled by a significant increase in IENFD ($n = 35$) from BL pruritic lesional (PL) skin to FU former pruritic lesional (FPL) skin ($p < 0.001$). Further, IENFD was higher in BL non-pruritic non-lesional (NPNL) skin than in BL PL skin ($p < 0.001$, $n = 46$). Alloknesis was observed significantly more often ($p = 0.008$) and more intense ($p = 0.003$) in BL PL skin than in BL NPNL skin. Hyperknesis was detected more often ($p = 0.014$) and more intense ($p = 0.017$) in BL PL skin than in FU FPL skin.

Discussion and Conclusion

The analysis of cutaneous neuronal alterations in inflammatory skin diseases is an emerging field, with CPG representing a less studied disease in this respect. In our study, we found under biologic treatment with dupilumab a recovery of the IENFD at FU back to levels observed in non-lesional skin at BL. Interestingly, signs of neuronal sensitisation[3], as induced by Th2 interleukins in pruritic nodules at baseline and reflected by elevated alloknesis and hyperknesis, also improved during therapy. This restoration of intraepidermal nerve fibre structure and function parallels the reduction of itch in our cohort, thereby deepening our understanding of the neuronal response underlying effective itch control observed with biologic treatment in CPG.

References

[1] Pogatzki-Zahn et al., J Invest Dermatol. 2020
[2] Wiegmann, Witte et al., J Invest Dermatol. 2025
[3] Agelopoulos et al., Dermatologie (Heidelb), 2022

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 81

Investigating the Impact of Aryl Hydrocarbon Receptor Activation on Skin Homeostasis and Pruritus

Renkert, H.[1], Teitge, E.[1], Ständer, S.[1], Agelopoulos, K.[1], Wiegmann, H.

1. Section Pruritus Medicine and Center for chronic pruritus, Department of Dermatology, University Hospital Münster, Münster, Germany

The aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor that plays a pivotal role in regulating cellular responses to xenobiotic compounds. Recent evidence suggests that AHR is a key mediator of cutaneous homeostasis, influencing epidermal barrier function, keratinocyte differentiation, and immune modulation. This study aimed to elucidate the role of AHR in modulating cutaneous inflammation and neurocutaneous communication, with a focus on its impact on keratinocyte biology and neuroepidermal interactions. Primary human keratinocytes were treated with a panel of AHR agonists, including phytochemicals with established AHR activity and the prototypical ligand benzo[a]pyrene. Subsequent analysis of keratinocyte behavior employed standardized wound healing assays to assess alterations in cellular proliferation and migration. Quantitative reverse transcription polymerase chain reaction (RT-qPCR) was used to examine transcriptomic changes in genes involved in inflammatory signaling pathways, pruritus, and neuroepidermal communication, including IL-4, IL-13, IL-31, and their corresponding receptors, as well as Cyp1a1 and neurotrophic factors such as Sema3a and NGF. To investigate the functional consequences of AHR activation in a neurocutaneous context, keratinocytes were co-cultured with F11 neuronal cells and exposed to AHR agonists, enabling assessment of intercellular communication and ligand-dependent modulation of neuroepidermal signaling. Our data demonstrate that AHR ligands significantly modulate keratinocyte gene expression profiles, with notable effects on inflammatory response genes, pruritogenic mediators, and neuroepidermal interaction molecules. Moreover, ligand treatment altered the dynamics of cell-cell communication between keratinocytes and F11 cells, suggesting a regulatory role for AHR in neurocutaneous cross-talk. These findings collectively underscore the integral role of AHR in orchestrating inflammatory responses and neuroepidermal interactions, highlighting its significance in the pathogenesis of inflammatory skin disorders and pruritic conditions. The results of this study provide novel insights into the molecular mechanisms underlying AHR-mediated regulation of cutaneous homeostasis and neurocutaneous communication, with implications for the development of therapeutic strategies targeting AHR in dermatological disorders.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 82

Topical application of a non-covalent keratine-delta-9-tetrahydrocannabinol-conjugate as a treatment for atopic dermatitis

J. Herrmann[1]; J. Wohlrab[1]

1 Department of Dermatology und Venereology, Martin-Luther-Universität Halle-Wittenberg, Halle (Saale)

Introduction

The utilization of hemp (Sativa, Indica) as a medicinal plant has been a practice spanning over two millennia. The effects of phytocannabinoids are utilized, particularly the psychotropic effect of delta-9-tetrahydrocannabinol (THC) and the antioxidant, anti-inflammatory, and antiemetic effects of cannabidiol (CBD). The observed effects are facilitated by the endocannabinoid system, specifically via its receptors and ion channels (namely CB1, CB2, TRPA, and TRPV1). The effects of THC on cannabinoid receptors have been the subject of much research. It has been demonstrated that THC acts as a partial agonist on peripheral and central CB1 receptors and on CB2 receptors on immune cells by inhibiting adenylate cyclase, thereby lowering the concentration of intracellular cyclic adenosine monophosphate (cAMP). In a series of studies, researchers have observed the antipruritic and anti-inflammatory properties of cannabinoids, such as delta-9-tetrahydrocannabinol (THC), particularly in the context of topical therapy for atopic dermatitis.

Atopic dermatitis (AD) is a chronic, recurrent inflammatory skin disease caused by a complex interaction of genetic, immunological, and environmental factors. The pathogenesis of the condition under investigation is centered on a disrupted epidermal barrier function, accompanied by a pathomicrobiome and a dysregulated immune response. Treatment options are rather limited; glucocorticoids, calcineurin inhibitors, and phosphodiesterase-4 inhibitors are available for topical application.

Methods

A topical THC formulation was developed that fulfills the special physicochemical properties of the substance and ensures sufficient cutaneous bioavailability. An investigation was conducted into the expression pattern of cannabinoid receptor types and the cytotoxic properties of THC on relevant cutaneous cell types in a dose-dependent manner. The HET-CAM test was used to validate the preclinical tolerability of a formulation specially developed for the application of THC. In order to optimize cutaneous bioavailability, a protein-drug conjugate (PDC) of beta-keratin and THC was developed, and the non-covalent interactions were characterized using capillary electrophoresis (CE). The concentration-time profile of diffusion in the Franz cell was finally determined on freshly excised ex vivo human skin, thereby establishing the necessary foundation for clinical validation.

Results & Discussion

CB1R and CB2R were detected in all skin cell types analyzed. The No Observed Adverse Effect Level (NOAEL) for proliferative activity and viability for the investigated skin cell types was determined to be greater than 25 µmol/L. The developed formulation demonstrated organoleptic, microbiological, and chemical stability for a period of up to six months. Furthermore, the formulation exhibited no evidence of aberration in the HET-CAM test. The results of the diffusion tests demonstrated that the developed PDC enhances the cutaneous bioavailability of THC in comparison with THC administered in isolation.

Outlook

A clinical proof-of-concept (PoC) study in humans is currently being prepared to demonstrate the antipruritic and anti-inflammatory effects of the developed preparation when applied

topically. It will also be investigated whether a toxicological relevant systematic bioavailability can be excluded after topical application. We have succeeded in developing a stable THC-containing formulation for topical application that can be clinically tested for its antipruritic and anti-inflammatory effect in chronic inflammatory dermatoses.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 83

Systemic immunotherapy restores audio-visual induced itch perception in the brain in patients with atopic dermatitis

Gaffal, E.[1,2)]; Liebe, T. [1)]; Tempelmann, C. [3)]; Scheermann, D. [3)]; Bonifatius, S. [2)]; Tueting T. [2)]

[1)] University Hospital Schleswig-Holstein, Dept. of Dermatology, Lübeck, Germany

[2)] University Hospital Magdeburg, Dept. of Dermatology, Magdeburg, Germany

[3)] University Hospital Magdeburg, Neurology, Magdeburg, Germany

Introduction: Itch is one of the most distressing symptoms experienced by patients with atopic dermatitis (AD), often dominating their daily lives and significantly impairing sleep, concentration, and emotional well-being. Visual triggers of pruritus, specifically the phenomenon known as "contagious itch," are well documented in patients with AD. Exposure to visual cues such as videos or images of others scratching can induce or intensify itch and scratching behavior in these patients, with a greater effect than in healthy controls. These phenomena highlight that sensory and cognitive inputs interact with central itch-processing pathways. Systemic treatment of patients with monoclonal antibodies targeting the IL4/IL-13 cytokine signaling axis lead to a massive improvement of cutaneous symptoms but also to an attenuation of itch and itch related comorbidities. Whether systemic immunotherapy also affects the mechanisms how the brain processes visually triggered sensations of itch and scratching behavior is not known.

Methods: We enrolled 23 AD patients and 19 age- and sex-matched healthy controls (HC) into our study and exposed them to neutral and itch-inducing audio-visual stimuli (two short videos). We assessed the subjective sensation of itch on a numeric rating scale and counted the number of scratching movements. One week later, we performed functional MRI (fMRI) scans while participants watched neutral and itch-inducing visual stimuli (two series of pictures and words) to assess the neural correlates of visually induced itch sensations. AD patients were investigated again after 3 months of dupilumab therapy that inhibits IL4/IL-13 cytokine signaling.

Results: When compared to HC, AD patients reported increased sensations of itch and showed increased scratching movements when exposed to itch-inducing audio-visual stimuli. That directly correlated with increased functional connectivity between visual, temporal and prefrontal cortical areas measured in fMRI. These observations indicate altered brain processing of itch-inducing audio-visual stimuli in AD patients. Importantly, we found that 3 months of dupilumab therapy was able to normalize the altered brain networks that drive visually induced pathologic itch-scratch cycles in AD patients. Based on our observations we aim to further understand the treatment effects of IL4/IL-13 cytokine signaling on central itch-processing pathways.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 84

Metabolic orchestration of epidermal skin barrier development

Knuever, J.[1]; Boix, J.[2]; Niehoff, N.[2]; Sen, A.[2]; Pla-Martin, D.[2]; Wiesner, R.J.[2]

1 Centre for Skin Diseases, Department of Dermatology and Allergy, University Hospital Bonn, Germany

2 Center for Physiology and Pathophysiology, Institute of Systems Physiology, University of Cologne, Germany

Epidermis is one of the most rapidly proliferating tissues in the body with high demands for energy and necessity of metabolic fine tuning. We showed that to meet these requirements, keratinocytes constitutively express hypoxia-inducible factor 1 alpha (HIF-1α), even in the presence of oxygen levels sufficient for HIF-1α hydroxylation.

Previously, we reported that mice with severe epidermal mitochondrial dysfunction due to a mutated Twinkle Helicase which is mainly responsible for mitochondrial DNA replication, actually showed a hyperproliferative epidermis but rapidly died of systemic lactic acidosis and hypoglycemia, indicating excessive glycolysis (Twinkle epidermal mutation).

Now, we interrogated HIF-1α function in glycolysis by its epidermal ablation (HIF-1a knock-out) combined with mitochondrial dysfunction (Twinkle HIF-KO double transgenic mutants), which resulted in decreased proliferation but even earlier lethality due to a severe barrier defect.

We could demonstrate that HIF-1α is indispensable for maintaining a high aerobic glycolytic flux necessary for supplying energy but also for synthetizing cellular building blocks such as lipids, which are both essential for proliferation as well as barrier formation. HIF-1α is stabilized in keratinocytes in the presence of oxygen by high levels of HIF-1α transcripts, low levels of prolyl-4-hydroxylases (PHD2 and PHD3), and a low cellular a-ketoglutarate/lactate ratio, likely inhibiting prolyl-4-hydroxylase activity.

Our data suggest a key role for constitutive HIF-1α expression allowing a Warburg-like metabolism in healthy, highly proliferative keratinocytes, similar to that in tumor cells.

Furthermore, by evaluating all genotypes in the mice individually (controls, HIF epidermal knock-out, Twinkle epidermal mutation, double transgenic mutants) we could compare the cellular consequences of the distinct metabolic disturbances. Here, we pinpointed a crucial role of mitochondrial oxidative phosphorylation for keratinocyte differentiation and of glycolysis for epidermal proliferation.

When both cellular mechanisms are lacking, the development of a functional epidermal barrier is completely disturbed, leading to direct postnatal death of the mice due to massive transepidermal water loss (inside-out barrier dysfunction) and outside-in disruption leading to a cytokine storm, respectively.

When epidermal differentiation is impaired in the Twinkle mutated mice, a compensatory hyperproliferation and inflammation is observed, resembling a psoriatic phenotype. Interferring with epidermal proliferation only (HIF epidermal knock-out) shows a rather mild phenotype with a thinner epidermis and loss of polar lipids.

Taken together, these findings can now be translated into the clinics by investigating metabolic kinetics inflammatory or genetic skin diseases where proliferation and/or differentiation are altered.

Kategorie: Hidden Gems
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 85

RNase 7 and LL-37 restrict keratinocyte infection with HSV-1 strains resistant to antiviral compounds

Liu, Z. [1]; Klug, I. [1]; Traidl, S. [1,4]; Chopra, S. [1]; Rademacher, F. [2]; Hinrichs, H. [2]; Villalvazo Guerrero, J. C. [3,5]; Sodeik, B. [3,4,5]; Harder, J. [2]; Werfel, T. [1,4]; Döhner, K. [1,4]

1 Department of Dermatology, Hannover Medical School, Hannover, Germany

2 Department of Dermatology, Quincke Research Center, Kiel University, Kiel, Germany

3 Institute of Virology, Hannover, Medical School, Hannover, Germany

4 Cluster of Excellence RESIST (EXC 2155), Hannover, Germany

5 DZIF – German Centre for Infection Research, Partner site Hannover-Braunschweig, Germany

Atopic dermatitis (AD) is a chronic inflammatory skin disorder characterized by a compromised skin barrier, immune dysregulation, and an imbalanced skin microbiome. These factors increase susceptibility to infectious diseases, such as eczema herpeticum (EH), which is primarily caused by herpes simplex virus type 1 (HSV-1). Drug-resistant HSV-1 strains are a growing health issue, especially in immunocompromised individuals.

Ribonuclease 7 (RNase 7, R7) is an antimicrobial protein (AMP) produced by keratinocytes that exhibits broad-spectrum antibacterial and immunomodulatory activities. We have shown that R7, in the presence of low amounts of self-DNA, promotes an immune response that protects keratinocytes from HSV-1 infection. Moreover, at higher, but still physiological concentrations, R7 inhibits HSV-1 infection even without the addition of self-DNA and independently of interferon-stimulated gene induction.

To assess whether R7 and other AMPs reduce HSV-1 gene expression and viral release following infection with drug-resistant strains, human primary keratinocytes were infected with parental and drug-resistant HSV-1 reporter virus strains. Supernatants containing released virus were diluted and used to infect indicator Vero cells, and viral gene expression was quantified by automated microscopy. The AMP LL-37, and the antiviral drugs acyclovir (ACV), pritelivir, and amenamevir reduced HSV-1 parental strain gene expression and viral release from keratinocytes. Moreover, LL-37 and R7 suppressed HSV-1 gene expression of a pritelivir-resistant strain in keratinocytes.

We collected skin rinses from AD patients with ($ADEH^+$) or without ($ADEH^-$) a history of EH, as well as from healthy donors, and quantified AMP levels by ELISA. Consistent with transcript data from AD skin, R7, psoriasin, and human β-defensin-2 (hBD-2) concentrations were higher in AD lesions than in non-lesional AD or healthy control skin. $ADEH^+$ lesions also exhibited higher levels of these AMPs than non-lesional AD or healthy skin. Herpetic lesions from $ADEH^+$ patients tended to secrete more R7 than AD lesions or healthy skin. The local SCORAD of AD lesions correlated significantly with hBD-2 concentrations, but not with R7 or psoriasin levels.

We have previously shown that high amounts of self-DNA and RNase inhibitor (RI) attenuate the antibacterial activity of AMPs. Similarly, RI also interfered with the antiviral activity of R7. Detecting RI in skin rinses required sample concentration prior to Western blot analysis, and RI abundance in AD lesions varied among individuals. In $ADEH^-$ samples, self-DNA levels were significantly higher in lesional skin than in non-lesional skin. Similar results were observed in $ADEH^+$ samples, with herpetic lesions showing the highest self-DNA levels.

In conclusion, R7 contributes to the antiviral defense even against drug-resistant strains by enhancing keratinocyte immunity and directly inhibiting HSV-1 infection and viral release. However, individual differences in RI and self-DNA levels may modulate this activity. Future studies will clarify how R7 impacts viral release and interacts with RI in AD skin.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 86

Stage-Specific Transcriptomic Responses of *Staphylococcus epidermidis* During Host Colonization and Infection

Li, P.[1]; Bongarts, P.[2]; Brakert, L.[2]; Huang, J.[2]; Both, A.[2]; Lausmann, C.[3]; Gehrke, T.[3]; Yazdi, A.S.[1]; Rohde, H.[2]; Burian, M.[1]

1 Department of Dermatology and Allergology, RWTH University Hospital Aachen, Aachen, Germany

2 Institute for Medical Microbiology, Virology and Hygiene, University Hospital Hamburg-Eppendorf, Hamburg, Germany

3 Helios Endo Klinik, Hamburg, Germany

Staphylococcus epidermidis is a ubiquitous skin commensal that can transition from a benign colonizer to an opportunistic pathogen, frequently implicated in prosthetic joint infections (PJIs). The molecular mechanisms driving this commensal-to-pathogen shift remain poorly defined. To investigate this transition, we performed ex vivo transcriptional profiling of *S. epidermidis* isolates obtained from patient-matched nasal swabs and synovial fluid samples from individuals with PJIs. Comparative quantitative real-time PCR (qRT-PCR) analyses were conducted to assess differential gene expression between the commensal (nasal) and invasive (synovial fluid; SF) niches, focusing on genes associated with virulence, adhesion, immune evasion, and metabolism.

The analysis revealed environment-specific transcriptional programs underlying the commensal-to-pathogen transition. Three distinct gene expression patterns were identified: (i) Consistently expressed genes, including immune evasion factors (*cap*C, *dlt*A, and *fmt*C) and adhesins (*sdr*G), which exhibited stable expression across both niches, reflecting essential survival functions; (ii) Lifestyle-specific adaptation factors, differentially expressed between infection and colonization, e.g. significant upregulation of *sdr*H and the major autolysin *atl*E in SF compared to nasal colonization; and (iii) Heterogeneously expressed genes, suggestive of strain- or patient-specific adaptive trajectories. Notably, central metabolic genes (*fum*C, *glt*A, *icd*) and the histidine kinase *agr*C of the Agr quorum sensing system as well as its downstream target gene *psm*β1 showed pronounced downregulation in SF, indicating sufficient exogenous nutrient supply and supporting the notion that the bacterium favors a persistence-oriented strategy.

The study provides direct *ex vivo* evidence of stage-specific gene expression patterns that enable *S. epidermidis* to transition between commensal and pathogenic lifestyles. These findings contribute to the general concept of *S. epidermidis* pathogenicity related to genome-encoded virulence determinants, advancing the understanding of context-dependent gene activation that fosters adaptation to distinct host niches.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 87

Dermal dissemination and vascular interaction of Borrelia burgdorferi in human skin

Sophie Weninger[1], Michael Frömmel[1], Lisa Kleissl[1,3], Bärbel Reininger[1], Michiel Wijnveld[2], Luisa Thebault[1], Anna Gabriel[1,3], Hannes Stockinger[2], Georg Stary[1,3*], Johanna Strobl[1,3*]

1 Department of Dermatology, Medical University of Vienna; Vienna, 1090, Austria.

2 Institute for Hygiene and Applied Immunology, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna; Vienna, 1090, Austria.

3 CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences; 1090 Vienna, Austria.

* equal contribution

Introduction: Erythema migrans (EM), the earliest and most common manifestation of Lyme disease, is a target-shaped rash caused by infection with the tick-borne spirochete *Borrelia burgdorferi*. The mechanisms driving *B. burgdorferi* migration through skin and its interactions with cutaneous structures, such as dermal vessels, remain poorly understood.

Methods and Results: To mimic dermal migration of *B. burgdorferi* after tick bites, we used an ex vivo human skin infection model by injecting live *B. burgdorferi* (2×10^6 spirochetes) subepidermally into healthy skin. Analysis by qPCR targeting the flagellin gene revealed presence of *B. burgdorferi* at the injection site, corresponding to approximately 10^6 spirochetes. Two hours post-injection, no bacteria were detected at distant sites. After 24 hours, *B. burgdorferi* DNA was consistently found up to 1 cm from the inoculation site, and in some samples, up to 5 cm. Quantitatively, the qPCR signal at 1 cm corresponded to roughly 10^2–10^3 spirochetes, as determined by standard titration. Based on these data, migration kinetics were modeled using a diffusive random walk approach, yielding a diffusion coefficient of 0.64 $\mu m^2/s$ after 24 hours. Immunofluorescence staining of EM skin samples revealed higher *B. burgdorferi* loads at tick bite sites compared to the rash border in line with the ex vivo model. Spirochetes localized predominantly around lymph and blood vessels, while intervascular regions showed lower bacterial loads. Endothelial-bound von Willebrand factor (vWF), used as a marker for vascular integrity was reduced in EM tissue compared to healthy skin, indicating vascular dysfunction.

Discussion: Collectively, the data demonstrates that *B. burgdorferi* migrate short distances in human skin within 24 hours and from the site of the tick bite to the periphery of the EM rash, consistent with its characteristic outward expansion. Furthermore, we suggest potential systemic translocation via lymph/blood vessels with associated endothelial damage. Together, these findings indicate that *B. burgdorferi* spread within the skin and along dermal vessels may facilitate early systemic dissemination in Lyme disease.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 88

In Vitro Analysis of Optimal Effective Concentration Combinations and Synergistic Effects in binary Antimicrobial Formulations

Greger L.M. [1, 3], Greger C. [2], Hiller K.-A. [1, 3, †, *], Maisch T. [3, †, *]

[1] Department of Conservative Dentistry and Periodontology, University Hospital Regensburg, 93053 Regensburg, Germany
[2] University of Regensburg, 93053 Regensburg, Germany
[3] Department of Dermatology, University Hospital Regensburg, 93053 Regensburg, Germany
[†] These authors share senior authorship

Introduction

This study presents a comparative evaluation of Optimal Effective Concentration Combinations (OPECCs) and synergy assessments based on the Loewe additivity and Bliss independence models for binary antimicrobial formulations *in vitro*. The objective was to explore how these analytical strategies can inform the assessment of antimicrobial combinations relevant to dermatological applications, such as topical antiseptics and antibiotics. By highlighting methodological differences, this work aims to enhance understanding of how antimicrobial interactions can be optimized for effective dermatologic therapeutic regimens, particularly in the context of increasing antimicrobial resistance among cutaneous pathogens.

Methods

Binary combinations of Benzalkonium chloride, Chlorhexidine, Cetylpyridinium chloride, and Ciprofloxacin—agents commonly utilized in dermatologic and wound care—were evaluated against *Escherichia coli* and *Staphylococcus aureus*. OPECCs and synergy scores were determined from optical density (OD) measurements after 3 hours of aerobic incubation at 37 °C in Mueller–Hinton medium.

Results

OPECCs were successfully established for all tested binary antimicrobial pairs. For each single component, the OPECC concentrations were consistently below their respective minimum effective concentrations when used individually, indicating potential dose-sparing effects. Synergy scores derived from the Loewe and Bliss models ranged from −13.4 (antagonistic) to 11.2 (synergistic), with the Bliss model generally yielding higher synergy indices. However, the concentration pairs associated with maximal synergy did not consistently align with the optimal effective antibacterial outcomes. No consistent relationship was observed between OPECC-derived concentrations, synergy model predictions, or antibacterial efficacy. Notably, a high synergy score did not necessarily correlate with effective antimicrobial performance.

Conclusion

This comparative analysis revealed that model-based assumptions of “additivity” or “independence” may lead to identification of concentration pairs that exhibit theoretical synergy but practically were not relevant. In contrast, the model-independent OPECC approach directly identifies effective concentration combinations from empirical 2-dimensional OD data, reflecting the true biological response without being dependent from theoretical interaction models. By more accurately mapping effective antimicrobial interactions, the OPECC method offers a promising complementary tool for the development and optimization of topical antimicrobial combinations in dermatology. Such an approach could improve formulation strategies for managing skin infections, enhancing therapeutic efficacy while mitigating the progression of antimicrobial resistance.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 89

Raising the voice of urticaria: Ten Years of UCARE (Urticaria Centers of Reference and Excellence) - A decade of progress and innovation in urticaria management, research and education

Witte-Haendel, E. Witte, K. Bednareck, S. Britz, R. Ciupka, K. Dufour-Feronce, A. Giussi, B. Locke, R. Lingnau, A. Neisinger, S. 11. Ramanauskaite, A. , Giménez-Arnau, A., Cherrez-Ojeda, I., Ensina, L.F.
Kocatuerk, E.. Kolkhir, P. Kulthanan, K.,. Bonnekoh, H. 2,3. Buttgereit, T. 2 ,3 Hackler, Y. 2 ,3 Siebenhaar, F. 2,3, Magerl, M. 2,3, Metz, M. 2, 3. Zuberbier, T.

1 Global Allergy and Asthma Excellence Network, ACARE\/UCARE coordinating office, Berlin, Germany
2 Institute of Allergology, Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany
3 Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany
4 Department of Dermatology, Urticaria Center of Reference, and Excellence (UCARE), Hospital del Mar Medical Research Institute, Universitat Pompeu Fabra, Barcelona, Spain
5 Universidad Espíritu Santo, Samborondón, Ecuador 6 Respiralab Research Group, Guayaquil, Ecuador
7 Division of Allergy, Clinical Immunology and Rheumatology, Department of Pediatrics, Federal University of São Paulo, São Paulo, Brazil
8 Department of Dermatology, Urticaria Center of Reference, and Excellence (UCARE), Bahçeşehir University School of Medicine, Istanbul, Turkey
9 Urticaria Center of Reference and Excellence (UCARE), Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Abstract:
Ten years after its launch, the UCARE network has gained a key role in empowering patients and establishing excellence in urticaria care. In view of the major challenges involved in treating urticaria, UCARE was launched in 2016 as the first disease-specific initiative of the Global Allergy and Asthma Excellence Network, with the aim of developing strategies to address the unmet needs and thus reduce the worldwide burden of patients. Significantly, the UCARE network has grown to become the largest and most active consortium of urticaria experts with a global reach, expanding to 207 centers across 52 countries as of October 2025. It has initiated a variety of educational programs for physicians and patients, global research efforts culminating in >30 collaborative research projects and related publications, a digital health program, global urticaria registries (CURE, CARE), and guideline activities. Moreover, UCARE is hosting regular conferences and events and promotes patient organisation collaboration approaches. Here we describe the journey of UCARE over the past ten years, from the vision to its establishment until now and highlight the key program elements, activities and achievements. Furthermore, we give an outlook into the future of UCARE.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 90

Diseased and vitiligo-induced ex vivo organ culture models as preclinical research platforms

Thomas Rouille[1]; Joana Viola-Söhnlein[1]; Claudia Janoschka[1]; Sabrina Altendorf[1]; Karin Pappelbaum[1]; Markus Fehrholz[1]; Ilaria Piccini[1]; Janin Edelkamp[1]; Marta Bertolini[1]

1. QIMA Life Sciences, QIMA Monasterium GmbH, Münster, Germany

Vitiligo is a multifactorial disorder with limited treatment options. Here, we assessed the effects of the FDA-approved drug ruxolitinib on ex vivo (peri-)lesional vitiligo skin. Fresh-frozen (peri-)lesional samples from two patients (male, 47 y; female, 48 y) displayed significantly reduced melanin content and fewer $SOX10^+$ and $GP100^+$ melanocytes compared with non-lesional skin, alongside increased pathogenic $CD3^+NKG2D^+$ T cells and memory $CD3^+CD69^+CD103^-/CD103^+$ T-cell subsets, confirming that the selected biopsy sites reproduced hallmark vitiligo pathology. For model validation, ruxolitinib was applied to (peri-)lesional skin from two or three patients (1 male, 2 females, 28–59 y). RNA-seq after 24 h revealed downregulation of type I interferon–associated and chemokine/cytokine genes, with concurrent upregulation of melanocyte-related transcripts. After 96 h, quantitative histochemistry and immunofluorescence demonstrated that ruxolitinib treatment increased epidermal melanin content, elevated $MITF^+$ melanocyte numbers, and reduced apoptotic $MITF^+$/caspase-3^+ cells. In addition, it decreased $CD3^+CD69^+$ T cells without affecting total epidermal $CD3^+$ counts in (peri-)lesional skin. To broaden experimental capabilities, we developed a vitiligo-like skin model using biopsies from one to three healthy donors. Exposure for 48 h to a proprietary, disease-inducing cocktail reproduced key disease features, including melanin loss, reduced $MITF^+$ melanocytes, increased epidermal $CD3^+$ and activated $CD3^+CD69^+$ T cells, and enhanced release of apoptotic mediators FASL and FAS. In summary, ruxolitinib ameliorated multiple pathological hallmarks of vitiligo in (peri-)lesional skin ex vivo, whereas its impact on the induced vitiligo-like model remains to be determined. These data support the utility of our patient-derived and experimentally induced organ culture systems as robust platforms for mechanistic studies and therapeutic testing in vitiligo.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 91

Helichrysum Italicum Essential Oil Facilitates Hair Growth Through IGF-1 Signaling in healthy human hair follicles ex vivo

Géraldine Lemaire[1]; Cecilia Colombero[2]; Karin Pappelbaum[2]; Marta Bertolini[2]; Janin Edelkamp[2]; Valérie Cenizo[1]

1. Laboratoires M&L SA-Groupe L'Occitane, Manosque, France;
2. QIMA Life Sciences, QIMA Monasterium GmbH, Münster, Germany

The *Helichrysum Italicum* essential oil (IEO) is recognized for its anti-inflammatory, antibacterial and antioxidant properties and we have previously reported that IEO has benefits on epidermal keratinocyte differentiation and barrier formation. Given this re-epithelization effect and the fact that HM keratinocytes proliferation in the HF epithelium is necessary for hair growth, we here investigated the effect of IEO on hair growth promotion in healthy human hair follicles (HFs) *ex vivo*. Healthy human amputated HFs were microdissected from two donors and cultured for 7 days with 0.0005%, IEO or vehicle control (DMSO 0.5%). Quantitative (immuno)histomorphometry revealed that treatment with IEO significantly increased hair shaft production in anagen and anagen + catagen HFs and prolonged the anagen phase accompanied by a reduced hair cycle score and significantly increased hair matrix keratinocyte proliferation in anagen and catagen HFs, with a similar trend observed for anagen-only HFs. Next, we investigated the protein expression of IGF-1, an anagen-maintaining growth factor, in the dermal papilla (DP) and outer root sheath (ORS). Treatment with IEO resulted in a strong tendency towards increased IGF-1 expression in the DP, but not ORS, of anagen and anagen + catagen HFs. Our initial results suggest that IEO supports hair growth by sustaining the anagen phase, possibly through IGF-1 activity, and underscore its promise as a potential natural hair growth enhancing approach.

Kategorie: Hidden Gems
Präsentationsart: Poster

Abstract-ID: 92

IGFL2 as a potential novel marker for early therapeutic response in psoriasis

Sebastian Huth[1]; Yvonne Marquardt[1]; Laura Huth[1]; Jens Malte Baron[1]

[1]Department of Dermatology and Allergology, Uniklinik RWTH Aachen, Aachen, Germany

Psoriasis vulgaris is one of the most common chronic inflammatory skin diseases, affecting approximately 2% of the global population. Despite extensive research, its underlying pathogenic mechanisms remain incompletely understood. We recently developed an IL-17A–induced long-term three-dimensional (3D) skin model exhibiting a psoriasis-like phenotype. Gene expression analysis revealed a significant downregulation of Insulin Growth Factor-Like 2 (IGFL2) after five days of IL-17A stimulation, whereas an eleven-day treatment with the anti–IL-17A antibody Secukinumab induced a marked upregulation. Interestingly, five to ten days after discontinuation of Secukinumab, concurrent IL-17A stimulation again reduced IGFL2 expression, suggesting a potential link between IGFL2 levels and therapeutic response. Since the biological function of IGFL2 and its gene family remains poorly understood, we further investigated its role in skin biology by generating a stable IGFL2 knockout in the immortalized keratinocyte cell line HaCaT using CRISPR/Cas9, alongside a transient siRNA-mediated knockdown in primary keratinocytes. In human 3D full-skin models established with these cells, both IGFL2 knockout and knockdown resulted in increased epidermal thickness and enhanced Ki67 expression, indicating elevated keratinocyte proliferation.
Overall, our findings suggest that IGFL2 plays an important role in the pathogenesis of psoriasis and could serve as a potential early marker for predicting response to at least IL-17A-targeted therapies.

Kategorie: Hidden Gems
Präsentationsart: Oral Presentation & Poster

Innate Immunity

Abstract-ID: 94

The role of macrophages in *Staphylococcus aureus* skin colonisation in inflammatory skin diseases

Keib, A.; Schittek, B.

University Hospital Tübingen, Department of Dermatology, 72076 Tübingen, Germany

Introduction: Atopic dermatitis and psoriasis are inflammatory skin diseases with specific pathological T cell immune responses with a predominance of TH2 or TH1 polarized T cells, respectively. It is thought that this T cell imbalance influences the higher predisposition to *Staphylococcus aureus* (*S. aureus)* skin colonization in atopic dermatitis patients compared to psoriasis patients. However, it is well known that tissue-resident macrophages are important for tissue homeostasis and remodeling and are key players in the inflammatory immune response of the skin and in the primary defense against pathogens. We hypothesize that differentially polarized macrophages orchestrate the decision toward type 1 or type 2 immune cell responses in psoriasis and atopic dermatitis patients, respectively, thereby modulating susceptibility to *S. aureus* skin colonization. The aim of this work was to analyse the influence of differentially polarized monocyte-derived macrophages (MDMs) on *S. aureus* colonization in different skin models (e.g. primary human keratinocytes (PHKs), 3D human psoriasis and atopic dermatitis models).

Methods: MDMs were polarised to M0 (MCSF), M1-like macrophages [M(IFN gamma + LPS)] or M2-like macrophages [M(IL-4 + IL-13)]. Polarisation state was confirmed by Flow Cytometry. PHKs were cultured alone or with MDM in a paracrine setting (0.4 micrometre transwell inserts). After twenty-four hours of conditioning, PHK monolayers were challenged with *S. aureus* at MOI 30 for ninety minutes; colony-forming units (CFU) per well were enumerated. Bacterial burden was confirmed by GFP microscopy. Barrier signatures (tight-junction and antimicrobial markers) are being evaluated by quantitative polymerase chain reaction (qPCR), enzyme-linked immunosorbent assay (ELISA) and immunocytochemistry and will be correlated with CFU outcomes.

Results: Across three biological replicates with independent PHK and MDM donors, MDM co-culture with PHKs reproducibly influenced *S. aureus* skin colonization in a polarisation-dependent manner: M1 and M2 polarized macrophages increased *S. aureus* skin colonization with the greatest effect of M2 polarized ones. Polarisation quality control by flow cytometry showed the expected M1-like and M2-like marker patterns before challenge and remained stable throughout conditioning. Paracrine signalling via transwell inserts was sufficient to modify keratinocyte susceptibility, indicating the involvement of soluble mediators. Barrier-signature assays are underway to link changes in CFU with epithelial programmes.

Conclusion: Preliminary data support a model in which differentially polarized macrophages influence keratinocyte susceptibility to *S. aureus* colonization predominantly through paracrine cues.

Kategorie: Innate Immunity
Präsentationsart: Poster

Abstract-ID: 95

Immunoregulatory role of IRE1 in neutrophil homeostasis

Paulina Hegyiova[1], Yizhu Tian[1,] Florian C. Kurschus[1]

[1] Department of Dermatology, Heidelberg University Hospital. Heidelberg, Germany

Psoriasis is an autoimmune disease triggered by an overactivated immune system in the absence of ongoing infection or other causes. The typical symptoms, such as red, scaly, raised plaques and lesions, arise from abnormal keratinocyte differentiation and simultaneous leukocyte infiltration into the epidermis. Once arrived in peripheral tissue, leukocytes such as neutrophils, dendritic cells and T cells cause local inflammation through the expression of inflammatory cytokines and factors that in turn activate other immunoregulatory cells. The development of the disease and its amplification result from an intricate interplay between skin tissue cells and the cross-regulatory effects of the involved immunocytes. Simultaneously, the involvement of various arms of the unfolded protein response, the ER-mediated regulatory pathway activated by cellular stress and dysregulated protein synthesis, is shown to play a role in the development of psoriasis. The UPR is not only involved in keratinocyte differentiation but also regulates inflammation by activating various downstream pathways, which in turn promote pro-inflammatory cytokine production. This includes IRE1 and its target XBP1. The IRE1-mediated ER stress response ultimately supports immunocyte activation, including neutrophils. Activated neutrophils, in turn, further promote inflammation in the infiltrated tissue by releasing neutrophil extracellular traps (NETs), composed of decondensed chromatin and antimicrobial proteins. Originally, NETosis serves to protect the host from extracellular pathogens and aids in the degradation of such. However, if this process becomes dysregulated, for example, during chronic inflammation, it quickly results in extensive immune activation, tissue damage and disease development. This in turn contributes to a self-reinforcing cycle of inflammation and ER stress.

Research on other autoinflammatory skin diseases indicates a significant role of neutrophils in endothelial damage and inflammation. In addition to this, dermal γδ T cells have been shown to play a significant role in the pathogenesis of psoriasis, producing pathogenic cytokines and activating other immune cells, including neutrophils. Previous work done in our lab points to a connection between γδ T cells and neutrophils in the development of psoriasis. Therefore, the role of neutrophils in the context of psoriasis requires further investigation. This project focuses on the involvement of the IRE1 pathway in neutrophil homeostasis as well as on the interplay between γδ T cells and neutrophils in a psoriatic mouse model. The effects of IRE1 inhibitors on neutrophils and NETosis are studied in vitro by flow cytometry and immunofluorescence microscopy. Further, targeting IRE1 in neutrophil-depleted mice in an IMQ-induced psoriatic model in vivo elucidates the role of this arm of the UPR in disease development and γδ T cell-expansion.

Kategorie: Innate Immunity
Präsentationsart: Poster

Abstract-ID: 96

A noncanonical role for neutrophil-derived Ki-67 in systemic lupus erythematosus

Shankar, S[1+]; Holsapple, JS[1+]; Andrés-Sanchez, N[2]; Schevchuk, O[3]; Linard Matos. AL[4]; Steinert, M[1]; Krasinska, L[2]; Soehnlein, O[4]; Kruss, S[5]; Fisher, D[2*]; Erpenbeck, L[1*]

[1] Department of Dermatology, University Hospital Münster, Münster, Germany

[2] Institut de Génétique Moléculaire de Montpellier, CNRS, University of Montpellier, INSERM, Montpellier, France

[3] Proteomic facility, University of Essen, Essen, Germany

[4] Institute for Experimental Pathology (ExPat), Centre for Molecular Biology of Inflammation (ZMBE), University of Münster, Münster, Germany

[5] Department of Chemistry and Biochemistry, Ruhr University Bochum, Bochum, Germany

Neutrophils combat invading pathogens through multiple effector mechanisms, including the formation of neutrophil extracellular traps (NETs)—chromatin fibers decorated with antimicrobial proteins that capture and neutralize pathogens. NETosis critically depends on the enzyme peptidyl arginine deiminase 4 (PAD4), which citrullinates histones and drives chromatin decondensation. Excessive NET formation is known to contribute to autoimmune pathology, notably in systemic lupus erythematosus (SLE).

Interestingly, neutrophils, although terminally differentiated, can re-express components of the cell cycle machinery, including the proliferation marker Ki-67. Although Ki-67 has been extensively studied for its role in chromatin organization and mitosis in proliferating cells, its role remains entirely enigmatic in the context of NETosis. Here, we identify nuclear accumulation of Ki-67 in neutrophils undergoing NET formation. Using siRNA-mediated knockdown in human neutrophils and Ki-67–deficient mice, we demonstrate that loss of Ki-67 markedly enhances NETosis. Mechanistically, Ki-67 interacts with PAD4, as shown by proximity ligation assays, and limits PAD4's access to histones, thereby reducing histone citrullination and delaying chromatin decondensation.

Importantly, neutrophils from patients with systemic—but not cutaneous—lupus show reduced Ki-67 expression, consistent with enhanced chromatin decondensation and an increased propensity for NETosis. Our findings identify a previously unrecognized role of neutrophil-derived Ki-67 as a negative regulator of NET formation, acting through PAD4 modulation, and suggest that loss of Ki-67 contributes to accelerated NETosis in SLE.

Kategorie: Innate Immunity
Präsentationsart: Poster

Abstract-ID: 97

Inherited loss-of-function mutation in the adaptor protein STING is associated with elevated infection rates

Sarah Rösing[1,2]; Tabea Kaiser[3]; Benjamin Klein[4]; Nick Zimmermann[2]; Regina Treudler[5]; Carina Baer de Oliveira Mann[3]; Claudia Günther[1,2]; 1) Department of Dermatology, University of Tübingen, Tübingen, Germany; 2) Department of Dermatology, Faculty of Medicine Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany; 3) Department of Bioscience, TUM School of Natural Sciences, Technical University of Munich, Garching 85748, Germany; 4) Department of Dermatology, Venerology and Allergology, University of Leipzig Medical Center, Leipzig, Germany; 5) Institute of Allergology, Charite Universitätsmedizin Berlin, Corporate, Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

STING (stimulator of interferon genes) serves as a central adaptor in the innate immune response and is activated by cyclic GMP-AMP synthesized by the cyclic GMP-AMP synthase (cGAS) after sensing double stranded DNA in the cell. This triggers the production of type I interferons (IFNs) and various cytokines through the nuclear factor kappa B (NF-κB) pathway, both of which are essential for an effective antiviral immune response.
A female 60-year-old patient presented with a history of recurrent infections in childhood, that ultimately required a tonsillectomy at age 10. Since adolescence, she experienced hearing impairment, persistent, severe bowel symptoms as well as intermittent arthralgia and developed urticarial skin lesions. Her son suffered from more than five infectious episodes annually until age five, including severe pneumonia at the age of ten months and subsequent pulmonary atelectasis, which manifested as shortness of breath at three years old. By five years of age, he required continuous positive airway pressure therapy. In adulthood, his infection frequency normalized to two to three episodes per year.
Because a hereditary disease was suspected, exome sequencing was performed, which identified a heterozygous STING stop mutation in both individuals. Patient fibroblast sequencing confirmed the mutation, and Western blot analysis revealed markedly reduced STING protein levels, indicating mutation-induced STING loss. To test whether the mutation results in a loss of STING, the cytoplasmic domain with and without the mutation, was expressed in bacteria and subsequently purified. Unlike the wild-type form, the mutant STING protein was not detected, suggesting that the mutation impairs proper synthesis of the protein. This effect was validated by transfecting mutant STING and cGAS in naturally STING-deficient HEK293T and STING-depleted THP1 cells. Using a dual luciferase assay, it was shown that both cell lines failed to induce type I IFN or NF-κB signaling pathways after stimulation with double stranded DNA. To reproduce the heterozygous state found in patients, both mutant and wild-type forms of STING were co-expressed with cGAS in the respective cell lines. Under these conditions, Type I IFN and NF-κB signaling were induced but remained weaker than in wild-type STING–expressing cells. Thus, the heterozygous condition harbors a reduced responsiveness to immune stimulation. Functional analysis further demonstrated that, upon stimulation with the cGAS agonist G3-YSD, patient fibroblasts exhibited attenuated expression of interferon-stimulated genes, corroborating a weakened innate immune response in these patients.
In summary, we identified a STING loss-of-function mutation that abolishes proper protein synthesis, offering mechanistic insight into the molecular cause of the patients' infection susceptibility.

Kategorie: Innate Immunity
Präsentationsart: Poster

Abstract-ID: 98

The Role of Neutrophil-driven Thrombopoeisis in Intermittent Hypoxia and Obstructive Sleep Apnea

Shaza El Nemr[1,2,4,7], Zhe Zhang[1,4], Pontus Mertsch[3,6], Evangelos Maroulis[1], Michael Spannagl[5], Markus Sperandio[2,4], Verena Raker[7,8], Steffen Massberg,[1,2,4], Tobias Petzold[1,2,4]

[1] Medizinische Klinik und Poliklinik I, Klinikum der Universität München, Ludwig-Maximilians-University Munich, Munich, Germany

[2] DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany

[3] Comprehensive Pneumology Center (CPC-M), Member of the German Center for Lung Research (DZL), Munich, Germany

[4] Institute of Surgical Research at the Walter-Brendel-Centre of Experimental Medicine, University Hospital, LMU Munich

[5] Anesthesiology and Transfusion Medicine, Cell Therapeutics and Hemostaseology, Ludwig-Maximilians-University Munich, Germany

[6]Medizinische Klinik und Poliklinik V, Klinikum der Universität München, Ludwig-Maximilians-University Munich, Munich, Germany

[7]University Hospital Augsburg, Dermatology, Augsburg, Germany

[8]University Hospital of Muenster, Department of Dermatology, Germany.

There is growing evidence that intermittent hypoxia (IH) plays a crucial role in the development of cardiovascular risk in obstructive sleep apnea (OSA), a prevalent sleep disorder, through the activation of inflammatory pathways [1]. The development of translational IH models in mice has allowed investigation of its role in the activation of inflammatory mechanisms and promotion of cardiovascular disease in OSA [2]. In OSA patients and mice exposed to intermittent hypoxia, bone marrow thrombopoiesis is excessive resulting in increased numbers of young immature reticulated platelets and enhanced thrombus formation. Within the bone marrow, megakaryocytes reside in a close milieu to different hematopoietic and immune cells, particularly neutrophils. Yet, little is known about the specific mechanisms behind the increase of thromboembolism in OSA and how platelets entailed blood hypercoagulability.

Accordingly, we recruited OSA patients (i.e. AHI: Apnea-Hypopnea-Index value more than 5 events/h) undergoing polysomnography and we observed that they have elevated platelet production and increased production of ROS and CXCR4 which are both neutrophil derived.

We further detected increased mean platelet volume and platelet distribution width in patients with severe OSA (AHI ≥ 30 events/h) suggesting increased platelet production. Importantly, we also found a positive correlation of reticulated platelet counts with AHI in OSA patients. Blood obtained from OSA patients showed increased ex-vivo thrombus formation under the flow on collagen compared to healthy controls. Recruitment of RNA rich (i.e. TO high) reticulated platelets to collagen surface was significantly enhanced in OSA compared to control blood. Our data demonstrate that inhibition of immune-thrombopoiesis e.g. by LFA-1 blockade or genetic ablation of CXCR4 in neutrophils, efficiently reduced reticulated platelet counts in hypoxic mice. Moreover, the platelet activation markers mostly P-selectin, PAC-1/active αIIBβIII, CD63 and GPVI were highly expressed on resting platelets; indicating that OSA platelets exhibited stronger thrombotic profile with elevated expression of adhesion and signaling molecules.

We conclude that excessive mature and immature platelets production and reactivity expose OSA patients to increased thrombotic risk and that CXCR4 mediated neutrophil-MK interactions drive thrombopoiesis in intermittent hypoxia. Hence, targeting reticulated platelets and neutrophils can be a promising approach to correct platelet homeostasis and prevent thrombotic complications in OSA and potentially other inflammatory complications.

References:

[1] Senaratna, C.V.; Perret, J.L.; Lodge, C.J.; Lowe, A.J.; Campbell, B.E.; Matheson, M.C.; Hamilton, G.S.; Dharmage, S.C. Prevalence of Obstructive Sleep Apnea in the General Population: A Systematic Review. Sleep Med. Rev. 2017, 34, 70–81.

[2] Luciano F. Drager, Vsevolod Y. Polotsky, Christopher P. O'Donnell, Sergio L. Cravo, Geraldo Lorenzi-Filho, and Benedito H. Machado. Translational approaches to understanding metabolic dysfunction and cardiovascular consequences of obstructive sleep apnea. Am J Physiol Heart Circ Physiol. 2015, 309: H1101–H1111.

[3] Spicuzza L, Caruso D, Di Maria G. Obstructive sleep apnoea syndrome and its management. Ther Adv Chronic Dis. 2015 Sep;6(5):273-85. doi: 10.1177/2040622315590318. PMID: 26336596; PMCID: PMC4549693.

Kategorie: Innate Immunity
Präsentationsart: Poster

Abstract-ID: 99

Mechanism of dermal T cells expansion in inflammation

Stenzaly, E.1 Ibberson, D.2 Tian, Y.1 Kurschus, F.1

1 Department of Dermatology, Heidelberg University Hospital, 69120 Heidelberg, Germany

2 Institute Deep Sequencing Facility, Core Facility Heidelberg University, 69120 Heidelberg, Germany

Interleukin-17 plays a crucial role in orchestrating immune responses at epithelial barriers. Among the various immune cell types capable of producing IL-17, dermal γδ T cells represent a particularly rapid and potent source during early inflammatory responses. Despite their importance of IL-17 in inflammatory skin diseases such as psoriasis, the mechanisms underlying the expansion, activation and migration of IL-17 producing γδ T cells remain incompletely understood.

Using single-cell RNA sequencing (scRNA-seq), we identify transcriptional signatures and V-region similarities within the γδ T cell receptor repertoire, providing insights into lineage relationships and potential clonal expansion of IL-17 producing subsets. Using scRNA-seq and high-parametric flow cytometry, we aim to track the dynamics of γδ T cells migration between skin and skin-draining lymph nodes following topical imiquimod treatment, a well-established model for IL-17 driven skin inflammation.

This project aims to characterize distinct γδ T cells responses and to clarify whether IL-17-producing γδ T cellsproliferate locally within the skin before migrating to clonal lymph nodes, or whether expansion mainly occurs in local lymph nodes. Second, we want to understand whether specific clones expand as opposed to classes of different γδ T cell subsets. These insights will advance the understanding of IL-17 driven immune regulation and the tissue-specific dynamics of γδ T cells in inflammatory context

Kategorie: Innate Immunity
Präsentationsart: Poster

Psoriasis & Inflammatory skin diseases

Abstract-ID: 100

An immunocompetent skin model with patient-derived Th2 cells incorporating sensory neurons to mimic neurocutaneous inflammation in atopic dermatitis

Hahn, K. K.[1]; Addy, D.[1]; Liao, K.[1]; Schön, M. P.[1], Dasari, P.[1]; Buhl, T.[1]

1 University Medical Center Göttingen, Department of Dermatology, Venereology and Allergology, Göttingen, Germany

Atopic dermatitis (AD) is characterized by chronic inflammation, epidermal barrier dysfunction, and severe pruritus, largely driven by T helper 2 (Th2) cells and their cytokines IL-4 and IL-13. These type 2 cytokines can directly activate sensory neurons and thus contribute to the (itch) sensation. Although neuropeptides secreted by activated sensory neurons are known to enhance neurocutaneous inflammation, the precise immunological interplay between Th2 cells, sensory neurons, and keratinocytes remains elusive. Suitable animal or *in vitro* models to study neurocutaneous inflammation in AD are lacking. We have established a primary cell-based, Th2-immunocompetent full-thickness skin model of AD incorporating sensory neurons to investigate therapy-relevant signaling pathways.

The commercially available Phenion full-thickness skin model is based on primary human keratinocytes seeded onto a fibroblast collagen matrix, with epidermis formation occurring during a 10-day differentiation period at the air-liquid interface.

To mimic immune responses in this model, primary human $CD4^+$ T cells were isolated from peripheral blood mononuclear cells and polarized towards Th2 cells *in vitro*, verified by flow cytometric analysis of lineage-specific transcription factor expression, ELISA-based quantification of IL-13 secretion, and qPCR analysis of cytokine gene expression. Successful integration of Th2 cells into the skin model was confirmed by immunohistochemistry (IHC) and flow cytometric detection of $CD3^+$ cells, as well as by the presence of IL-13 in the culture supernatant. Integration of Th2 cells, similar to IL-4/IL-13 stimulation, led to a trend towards reduced expression of epidermal barrier markers *filaggrin*, *involucrin*, and *loricrin*, confirmed by IHC staining.

Furthermore, polarized Th2 cells from AD patients were successfully integrated into the skin model. Again, we detected a downregulation of barrier marker expression in gene analysis. As expected, treatment with the IL-4Rα-directed monoclonal antibody dupilumab reversed this effect, supporting the feasibility of the model for drug testing. Interestingly, ELISA analysis revealed decreased secretion of proinflammatory mediators MCP-1, IL-6, and IL-8 in untreated models, which increased upon dupilumab treatment, indicating complex regulatory effects.

Human induced pluripotent stem cells (hiPSC) were differentiated into sensory neurons *in vitro* according to a published protocol by Muller et al. (*Acta biomaterialia*, 2018), and their integration into the skin model was demonstrated by IHC staining for β3-tubulin.

Taken together, we propose a novel testing platform to study the effects of Th2 cells and sensory neurons on neurocutaneous inflammation in AD.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 101

mTOR inhibition reveals activated fibroblasts as drivers of granulomatous inflammation in humans

Brazdilova K.[1,2]; Kopf A. [1,2]; Gabriel A. [1,2]; Thebault L. [1]; Kleissl L. [1,2]; Krausgruber T. [2,3]; Weichhart T. [4]; Bock C. [2,3]; Stary G. [1,2]

1 Medical University of Vienna, Department of Dermatology, Vienna, Austria

2 CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria

3 Medical University of Vienna, Institute of Artificial Intelligence, Center for Medical Data Science, Vienna, Austria

4 Medical University of Vienna, Institute of Medical Genetics, Center for Pathobiochemistry and Genetics, Vienna, Austria

Introduction

In a recent clinical trial, systemic inhibition of mTORC1 (mechanistic target of rapamycin complex 1) resulted in a long-lasting remission in a subset of patients with cutaneous sarcoidosis, a prototypic granulomatous inflammatory disease. To uncover the cellular and molecular mechanisms underlying granuloma resolution and to functionally explore key interactions driving disease persistence, we applied single-cell RNA sequencing to longitudinal skin biopsies from trial participants.

Methods

Lesional and non-lesional skin biopsies were digested, processed and sequenced using the 10X Genomics Chromium protocol. After quality control, single cells were integrated using an scVI model, clustered, and annotated based on canonical marker genes. Differential expression analysis between timepoints was performed using limma on pseudobulked counts. Primary human dermal fibroblasts were isolated from skin of healthy individuals or sarcoidosis patients and exposed to sarcoidosis-related cytokines in vitro, followed by transcriptomic profiling using the SmartSeq2 platform.

Results

In the single-cell RNAseq dataset, all major cutaneous cell populations were recovered, alongside distinct granuloma-specific cell subsets. Following mTOR inhibition, macrophages, helper T cells and fibroblasts exhibited marked transcriptional remodeling, particularly in pathways associated with granulomatous inflammation. These shifts resulted in a transcriptional profile resembling healthy skin and correlated with clinical improvement. Notably, granuloma-associated cell subset proportions decreased dramatically after treatment, indicating their elimination as a key factor in the observed transcriptional shift. Fibroblast activation through T cell-derived cytokines emerged as driver of granuloma maintenance and immune cell recruitment to granulomas via chemerin, a process we successfully recapitulated in vitro. Cytokine stimulation of fibroblasts in vitro reproduced transcriptional phenotypes observed in patient-derived fibroblasts, and was reversed by mTOR inhibition, paralleling the in vivo response.

Conclusions

Our findings define a pathogenic circuit involving T cells, fibroblasts, and macrophages that sustains granulomatous inflammation. mTORC1 blockade disrupts this loop, leading to a loss of granuloma-associated cell states, disrupting the granuloma architecture by directly targeting fibroblasts as structural cells, and ultimately leading to resoration of tissue homeostasis.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 102

Acute spontaneous Urticaria: A systematic scoping review of the current knowledge on clinical course, associated factors, etiology, and potential biomarkers with a focus on characteristics associated with transition to chronic urticaria

Lena Marie Böhm[1,2], Yi Rui Tricia Chong[3], Christopher Rüger[1,2], Pavel Kolkhir[1,2], Martin Metz[1,2], Thomas Buttgereit[1,2], Hanna Bonnekoh[1,2]

1 Urticaria Center of Reference and Excellence (UCARE), Institute of Allergology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

2 Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany

3 National Skin Centre, Singapore

Introduction: Acute spontaneous urticaria (ASU), manifesting by transient itchy wheals and/or angioedema (≤6 weeks), is a common mast cell–mediated skin condition. While usually self-limiting, ASU can progress to chronic spontaneous urticaria (CSU). The mechanisms underlying this transition remain yet unknown.

Objective: To systematically scope the existing evidence on demographics, clinical presentation, duration, associated factors and biomarkers of ASU, with a specific focus on identifying characteristics linked to progression to CSU.

Methods: Systematic search of MEDLINE, EMBASE, Web of Science, CINAHL and CENTRAL was conducted, using the keywords "acute urticaria", "acute spontaneous urticaria" and "acute hives" without restriction on publication dates and languages. Studies selected include experimental or observational research with ASU patients according to the current international guideline. Two investigators independently reviewed titles and abstracts to identify relevant articles and resolved discrepancies by discussion and consultation of a third reviewer.

Findings: We identified 77 eligible studies, published between 1980 - 2024, including 19 case-control, 35 cohort and 23 cross-sectional studies encompassing a total of 17.997 ASU patients. The mean age was 32.5 years, 62% were female. ASU presented with wheals and angioedema in 126/975 and isolated wheals in 675/975 patients. If pruritus was reported (6 studies) it affected all patients. Infectious symptoms (12 studies), particularly fever (9 studies) and gastrointestinal complaints (6 studies), were extracutaneous features. Mean ASU duration was 8.7 days, with recurrence rates of 13%. CRP (14 studies) and total IgE (16 studies) emerged as the most consistently studied biomarkers. Patients progressing to CSU (12%, pooled proportion across 9 studies) were younger (mean 24.4 years), had a similar gender distribution and showed positive anti-TPO antibodies (2 studies).

Conclusion: Evidence on ASU remains fragmented and is mostly based on single-study findings. Larger, prospective studies are needed to validate biomarkers, identify reliable predictors of progression, and improve clinical management of ASU.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 103

Efficacy of a Newly Generated rhTSG-6 in Modulating Inflammatory Pathways Involved in Skin Repair

Mina Yamani[1], Subha Karthikeyan[2], Albert Kallon Koroma[1], Philipp Haas[1], Yongfang Wang[1], Tianhui Yang[1], Adelheid Hainzl[1], Linda Krug[1], Susanne Schatz[1], Pallab Maity[1], Meinhard Wlaschek[1], Karmveer Singh[1], Stefan Kochanek[2] and Karin Scharffetter-Kochanek[1]

[1]Department of Dermatology & Allergic Diseases and [2]Department of Gene Therapy, Ulm University, Ulm, Germany

Introduction

Chronic wounds are characterized by persistent, dysregulated inflammation mainly caused by unrestrained M1 macrophage activation with enhanced NF-κB–dependent cytokine release. Tumor Necrosis Factor-Stimulated Gene-6 (TSG-6) is a multifunctional immunomodulatory glycoprotein secreted by human mesenchymal stem cells (hMSCs) in response to inflammatory stimuli. TSG-6 inhibits NF-κB signaling, reduces pro-inflammatory cytokine production, and promotes a pro-regenerative microenvironment, thereby resolving inflammation and enhancing tissue repair. Despite its therapeutic potential, the clinical use of recombinant human TSG-6 (rhTSG-6) is limited by issues with current recombinant forms, which are often produced in murine cells and include affinity tags that may alter protein structure, activity, and translational relevance, as well as by difficulties in scalable production, challenges in purification, and poor stability. This study investigated the anti-inflammatory effects of a newly engineered, tag-free rhTSG-6 produced in CHO cells, which introduces post-translational modifications similar to those found in humans. We here compare its activity with that of a commercial rhTSG-6 and evaluate its efficacy in macrophage-mediated inflammation *in vitro*.

Methods

We first pre-treated human monocyte–derived macrophages with rhTSG-6 before stimulation with lipopolysaccharide (LPS) and differentiation into an M1 phenotype. NF-κB activation and nuclear translocation were quantified by immunofluorescence microscopy. Transcriptional responses were assessed by qPCR for TNF-α, IL-1β, and IL-6. Protein expression of TNF-α and IRF-1 (Interferon Regulatory Factor), a member of the family of macrophage transcription factors, was evaluated by Western blot analysis, and cytokine secretion was quantified using ELISA. Four treatment groups were analyzed: (i) a negative control using phosphate-buffered saline (PBS), (ii) LPS stimulation alone as a positive control, (iii) pretreatment with various concentrations of rhTSG-6 (500 ng/ml, 100 ng/ml, and 10 ng/ml) for 24 hours, followed by LPS stimulation for three hours, and (iv) treatment with rhTSG-6 alone for 24 hours.

Results

Our *in vitro* studies showed that rhTSG-6 strongly suppresses LPS-induced inflammatory responses in M1 macrophages. LPS stimulation induced strong NF-κB nuclear translocation, which was significantly reduced by pre-treatment with rhTSG-6, resulting in fewer NF-κB–positive nuclei. qPCR analysis revealed strong inhibition of key pro-inflammatory cytokine genes, with TNF-α, IL-1β, and IL-6 significantly downregulated at the transcriptional level. Western blotting confirmed decreased TNF-α and IRF-1 expression, indicating broad suppression of M1 inflammatory signalling. ELISA revealed lower secretion of these cytokines, further supporting the gene expression profile on the protein level.

Discussion

In conclusion, our results show that the newly engineered and commercially available rhTSG-6 exhibited similar efficacy in reducing inflammatory responses in M1 macrophages. Nevertheless, the tag-free CHO cell–derived rhTSG-6 represents a more suitable candidate

for further therapeutic development due to its clinically compatible production system. Future studies will characterize the anti-inflammatory and regenerative functions of the newly designed rhTSG-6 and associated cell-based therapies *in vitro* and *in vivo*, with particular emphasis on its ability to modulate macrophage activation, support endogenous stem cell niches, and enhance tissue regeneration in skin and bone repair.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 104

Comparison of Four Assays for Anti-Laminin 332 Antibodies in Mucous Membrane Pemphigoid

Goletz, S.[1*]; Ishii, N.[2*]; Kiehne, C.[3]; Diercks, G. F. H.[4]; Koga, H.[2´]; Li, X.[5]; Qian, H.[5]; Tsuruta, D.[6]; Tateishi, C.[6]; Mine, M.[6]; Hashimoto, T.[6*]; Schmidt, E.[1,3*]; and Bremer, J.[4*]

1 Lübeck Institute of Experimental Dermatology, University of Lübeck, Lübeck, Germany
2 Department of Dermatology, Kurume University School of Medicine, Kurume, Japan
3 Department of Dermatology, University of Lübeck, Lübeck, Germany
4 University of Groningen, University Medical Center Groningen, Department of Dermatology, UMCG Center of Expertise for Blistering Diseases, Groningen, The Netherlands
5 Daqing Oilfield General Hospital, Daqing, China
6 Department of Dermatology, Graduate School of Medicine, Osaka Metropolitan University, Osaka, Japan

*equal contribution

Anti-laminin 332 mucous membrane pemphigoid (MMP) is a rare autoimmune subepidermal blistering disease characterized by predominant mucosal involvement and circulating IgG autoantibodies against the basement membrane protein laminin 332. Accurate serological detection of anti-laminin 332 IgG is essential due to its diagnostic and prognostic relevance, particularly regarding its association with malignancy. In this prospective multicenter blinded study, we compared the diagnostic performance of four assays for anti-laminin 332 serum IgG. Sera from patients with anti-laminin 332 MMP (n = 23), bullous pemphigoid (n = 29), pemphigus vulgaris (n = 19), and healthy blood donors (n = 27) were analysed using (i) the laminin 332 Biochip® employing HEK293 cells expressing recombinant laminin 332, (ii) the keratinocyte footprint assay (KFA) presenting native laminin 332, and (iii–iv) two immunoblots based on recombinant and native laminin 332, respectively. The KFA detected all 23 anti-laminin 332 MMP sera (sensitivity 100%, specificity 100%), while both immunoblots identified 18/23 sera (sensitivity 84%) but also showed reactivity in control sera (specificity 84–85%). The Biochip® detected 16/23 sera (sensitivity 70%) with 100% specificity. The superior diagnostic accuracy of the KFA may reflect the preservation of native conformational epitopes within the keratinocyte matrix. The laminin 332 Biochip®, although slightly less sensitive compared to the three other assays, achieved optimal specificity and provides a standardized, CE-certified, and widely available alternative suitable for routine diagnostics. These findings support the inclusion of laminin 332 testing in the diagnostic algorithm of MMP to improve diagnostic accuracy and guide malignancy screening that is recommended to employ in all MMP patients with anti-laminin 332 reactivity.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 105

A novel humanized pemphigus mouse model is driven by disease characteristic Type 17 / Type 2 T cell and desmoglein-3 specific B cell polarization

Riaz, S. [1]; Hertl, M. [1]; Hudemann, C. [1]

1 Department of Dermatology and Allergology, Philipps-University Marburg, Germany

Introduction: Pemphigus vulgaris (PV) is an autoimmune blistering disease in which IgG autoantibodies against Desmoglein (Dsg)3 and Dsg1 disrupt intercellular adhesion, ultimately causing acantholysis and suprabasal bullae. The hallmark of PV immunopathogenesis is the formation of anti-Dsg3 specific IgG via antigen-specific B and T cell interaction.

Objective: The aim of this study is to establish and characterize a novel hDsg3-driven active PV mouse model with an associated antigen-specific lymphocyte formation. For this purpose, a humanized active transgenic PV mouse model was established.

Methods: Splenic tissues and serum were analyzed at d21 and d35 post immunization to capture the dynamic progression from early activation to peak adaptive (antigen-specific) immune response. Multicolor flow cytometry was used to phenotypically profile B and T cell subsets in murine spleen and assess the cytokine profiles in the murine serum.

Results: Immunization with the PV associated hDsg3 protein resulted in an overall Th2 /Th17 polarization with a significant proliferation of follicular helper Tfh2 /Tfh17 compartment compared to control mice. Multiplex cytokine assay from immunized mouse sera displayed increased levels of Th2 (IL-4 and IL-13) and Th17 related cytokines (IL-17A). While the increase in general plasma cells and plasmablasts was more discrete, hDsg3-specific plasmablasts showed a robust expansion until d35, and hDsg3-specific plasma cells stabilize from d21 to d35 after initial expansion. Functional analysis of splenic hDsg3-specific plasma cells using ex-vivo co-culture in combination with CD44+ memory T cells revealed the capacity to secreting pathogenic hDsg3-specific IgG after polycloncal or antigen-specific stimulation.

Discussion: Our active mouse model recapitulates multiple features of PV, from the T cell Th2/Th17 skewing accompanied by elevated levels of associated cytokines IL-4, IL-13, and IL-17A, ultimately culminating in hDsg3-specific IgG production by hDsg3-specific CD138+ B cells. It represents a novel tool for in-depth mechanistic studies of PV, as well as for advancing therapeutic development and strategies for inducing immunological tolerance.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 106

Association of airborne pollen levels with *Staphylococcus aureus* abundance on skin of Atopic Dermatitis patients

Reiter, A [1]; Plaza, M [1,2]; Maintz, L [3]; Rauer, L [1,2]; Reiger, M [1]; CK-CARE, study group [4]; Traidl-Hoffmann, C [1,2,4]; Hülpüsch, C [1,4]; Neumann, AU [1,2]

1 University Hospital Augsburg, Institute of Environmental Medicine and Integrative Health, Augsburg, Germany

2 Helmholtz Munich, Institute of Environmental Medicine, Augsburg, Germany

3 University Hospital Bonn, Department of Dermatology and Allergy, Bonn, Germany

4 Christine Kühne – Center for Allergy Research and Education (CK-Care), Davos, Switzerland

Background: Atopic Dermatitis (AD) is a chronic inflammatory skin disease associated with skin barrier disruption, immune imbalance and microbial dysbiosis due to increased *Staphylococcus aureus* abundance in lesional skin. Pollen has been shown to cause AD exacerbation, and exposure to pollen was reported to increase AD severity. However, it is unknown if pollen also affects *S. aureus* on skin of AD patients. Here, we used the data from the large ProRaD cohort of AD patients to test whether there is an association between airborne pollen levels and *S. aureus* abundance on skin of AD patients.

Methods: Lesional and non-lesional skin swabs were sampled cross-sectionally from 355 adult patients with mild to severe AD in Augsburg and Bonn. Microbiome relative abundance was estimated using next-generation sequencing (16S V1-V3). Pollen airborne levels were measured daily using the POMO automated counter and the Burkard trap.

Results: Patients with moderate AD present in general with significantly lower *S. aureus* relative abundance in lesional skin as compared to severe AD patients. However, 17.3% of moderate AD patients are moderate-high-outliers, having high *S. aureus* relative abundance in lesional skin. Interestingly, 96% of the moderate-high-outliers are observed in the months of February-August, corresponding to the pollen season, and only 4% in the period of September-January ($p<0.003$). This is confirmed in both centers, Augsburg and Bonn, and for all 3 years of recruitment. Moreover, in moderate AD patients, a higher lesional skin relative abundance of *S. aureus* is associated ($p<0.004$) with a higher maximum level of airborne pollen during the 5 days prior to the sampling visit. This association is not observed for mild or severe AD patients.

Conclusions: These findings show for the first time that higher airborne pollen levels are associated with higher *Staphylococcus aureus* abundance in skin of AD patients. Further studies are needed to better understand why this is observed only for moderate AD patients, and whether the pollen effect is by direct interaction with *Staphylococcus aureus* or indirectly through its effect on the skin barrier or the immune microenvironment.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 107

Longitudinal Analysis of Skin Barrier and Microbiome Responses to Topical Corticosteroids and pH-Lowering Emollients in Atopic Dermatitis

Berk, B. [1,2]; Rohayem, R. [1]; Reiger, M. [1,3]; Klepper, L. [1,3]; Ranieri. C. [1]; Gülzow, C. [1,2]; Seide, C. [4]; Worthmann, A. C. [4]; Schölermann, A. M. [4]; Rippke, F. [4]; Traidl-Hoffmann, C. * [1,2,3]; Hülpüsch, C. * [1,2]; Neumann, A. U. * [1,3]

1 Institute of Environmental Medicine and Integrative Health, Faculty of Medicine, University of Augsburg, Augsburg, Germany

2 Christine Kühne Center for Allergy Research and Education (CK-CARE), Davos, Switzerland

3 Institute of Environmental Medicine, Helmholtz Munich, Augsburg, Germany

4 Beiersdorf AG, Hamburg, Germany

Introduction: Atopic dermatitis (AD) is a chronic inflammatory skin disease marked by disrupted epidermal barrier, increased skin pH and enhanced *Staphylococcus aureus* colonization. The complex relationship between the cutaneous microenvironment and the skin microbiome in AD remains only partly understood. This study aimed to explore how topical corticosteroids (TCS) and pH-lowering emollients affect skin physiology and microbiome composition under real-life clinical conditions.

Methods: In a double-blind, placebo-controlled study, 29 patients with mild-to-moderate AD were enrolled. Participants received TCS treatment for two weeks, followed by six weeks of application of pH-lowering verum and placebo emollients on contralateral body sites. Clinical scoring, skin physiology measurements and microbiome sampling were performed every 2–4 weeks. Microbiome composition was assessed using 16S rRNA sequencing, while absolute *S. aureus* counts were quantified via standardized qPCR.

Results: TCS therapy led to a significant reduction in SCORAD scores across all participants and was associated with a marked decrease in transepidermal water loss (TEWL), particularly in individuals with high baseline TEWL. Skin pH and hydration remained unaffected by TCS. In patients with high initial *S. aureus* colonization, both relative and absolute abundances of S. aureus declined significantly following TCS treatment. The verum emollient caused a clear reduction in skin pH compared to placebo, while both emollients comparably increased skin hydration. However, *S. aureus* abundance rebounded to baseline levels during both verum and placebo application, regardless of pH reduction.

Conclusions: This study provides longitudinal insights into treatment effects and microbiome dynamics in AD under real-life conditions. TCS improved skin barrier function and reduced *S. aureus* colonization without altering skin pH. Although pH-lowering emollients effectively reduced skin pH, they did not influence *S. aureus* levels, indicating that pH modulation alone may be insufficient to restore the AD-associated microbiome. Future studies should confirm these findings in cohorts with more severe AD.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 108

Staphylococcus aureus colonization of the nasal cavity of patients with atopic dermatitis is frequently observed under dupilumab treatment

Bouheraoua, S. [1#]; Stavrou, F. [1#]; Weisel, L-M. [1]; Pham, C. [1]; Nishanth, G. [2]; Schlüter, D. [2,3]; Werfel, T. [1,3]; Roesner, L.M. [1,3]

[#]equal contribution

1 Hannover Medical School (MHH), Department of Dermatology and Allergy, Hannover, Germany

2 Hannover Medical School (MHH), Institute of Medical Microbiology and Hospital Epidemiology, Hannover, Germany

3 Hannover Medical School (MHH), Cluster of Excellence RESIST (EXC 2155), Hannover, Germany

Patients with atopic dermatitis (AD) exhibit a dysbiosis within the skin microbiome, often characterized by an excessive overgrowth of *Staphylococcus aureus.* Its importance as a driver of disease symptoms has been extensively studied and it is meanwhile accepted that colonization is associated with more severe clinical symptoms. Treatment with the IL-4 receptor alpha chain blocking antibody dupilumab has been shown to ameliorate the skin dysbiosis while improving the disease symptoms. Further on it is known that *S. aureus* colonizes the anterior nares of approximately 30% of the general population.

This study aimed to investigate the presence of *S. aureus* in the nose and on the skin in a clinical cohort of 91 adult AD patients with regard to treatment and clinical severity. Skin swabs from the nose and the lesional AD skin were tested for presence of *S. aureus*. The severity of AD was assessed by SCORAD as well as the local SCORAD of the lesion which was investigated.

Our study confirms previous studies reporting that presence of *S. aureus* on the skin, but not nasal colonization, is associated with higher SCORAD. This was also reflected by the local SCORAD of the target lesion. The most common systemic therapy was dupilumab, which was associated with lower *S. aureus* burden in general and specifically the lowest number of *S. aureus* skin positive patients. Nasal carriage was unexpectedly frequent, and detectable in 57% of dupilumab treated patients. Noteworthy, the duration of dupilumab treatment had no effect on the nasal carriage of *S. aureus*.

In conclusion, our study confirms that dupilumab reduces the *S. aureus* burden on the skin of AD patients, but suggests that its effect on *S. aureus* in the nasal cavity is weaker. Although nasal carriage does not appear to be associated with more severe AD, it still merits attention, as it presumably acts as a reservoir for the pathogen.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 109

Identification of mucosal tissue bound Th2 / Th17 T and B cells in a novel humanized mouse model of pemphigus vulgaris

Förster, K.[1]; Riaz, S.[1]; Berg, B.[1]; Hudemann, C.[1]

[1]*Department of Dermatology and Allergology, Philipps-University Marburg, Germany*

Introduction: Pemphigus vulgaris (PV) is a severe autoimmune blistering disease affecting skin and mucosa, mainly caused by IgG autoantibodies against desmoglein1 (Dsg1) and 3 (Dsg3). Loss of adhesion between Dsg molecules leads to characteristic suprabasal acantholysis. Multiple studies have indicated that both B and T cells play a significant role in PV, as their interaction leads to production of Dsg-specific autoantibodies. While other passive and active preclinical mouse models are used for cellular target analysis in PV, primarily humanized mice expressing HLA alleles associated with PV susceptibility were employed to study T and B cell interactions and to analyse immunological therapies. However, histological PV characteristics such as acantholysis due to failure of epithelial hDsg3-specific IgG binding in the epidermis have not yet been successfully reproduced in these models.

Methods: Current *ex vivo* data revealed a Th2/Th17 polarisation as well as the development of Dsg3-specific B plasma cells producing hDsg3-specific IgG in the novel active PV mouse model. However, the presence and functionality of lymphocytes in mucosal tissue have not yet been investigated. We therefore aim to quantify Th2/Th17 T and B cell populations in mucosal tissues (cheek, tongue, palate and oesophagus tissue) in a preclinical humanized mouse model of PV. Here, a novel hDsg3-tg mouse was subjected to hDsg3-antigen immunization, followed by analysis at day 35. Mucosal tissues were collected and fixated for subsequent microscopic analysis revealing B cell (CD20) as well as Th2 (CD3+ GATA3+) and Th17 (CD3+ IL-17A/RORγt) infiltration.

Results: Compared to non-treated control, we found a profound infiltration of Th2 and Th17 T cells as well as B cells co-localizing with membrane-bound anti-Dsg3 IgG in the buccal mucosa as well as in the palate and tongue. Thus, we were able to link the presence of lymphatic Th2 / Th17 T cell polarization to the mucosa as the primary organ of clinical PV symptoms.

Discussion: Inflammatory infiltration is a hallmark of PV and therefore imperative for a representative mouse model. In this sense, the characterization of the cellular population infiltrating targeted organs is the first step into asserting our hDsg3 mouse model. Furthermore, such animal models are crucial for the investigation of new therapeutical approaches and to provide insights into cellular immunomechanisms that encompass PV disease development.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 110

Immune profiling of desmoglein 3 (Dsg3)-reactive T helper cells in pemphigus vulgaris

Barbara B. Berg[1]; Julia Hinterseher[1]; Jonas Kornfeld[1]; Christian Möbs[1]; Michael Hertl[1]; Karolin Vollkman[1]

1 - Department of Dermatology and Allergology, Marburg University, Marburg, Germany

Introduction: Pemphigus vulgaris (PV) is a rare autoimmune blistering disease of the skin and mucous membranes, caused by IgG autoantibodies directed against desmoglein 1 (Dsg1) and 3 (Dsg3), desmosomal cadherins essential for epidermal cell adhesion. T helper (Th) cells play a critical role in disease development and progression by secreting cytokines and supporting B cell mediated autoantibody production.

Methods This study aimed to detect and characterize disease-promoting Dsg3-reactive T helper cells from PV patients using an ex vivo CFSE-based proliferation assay. Dsg3 immunodominant peptides were used for stimulation of CFSE-stained PBMCs from PV patients and healthy controls (HC). Additionally, PV patients were stratified into acute, chronic, and remittent stages. The relative frequency of peptide-specific Th cells was determined by CFSE dye dilution, and cytokine secretion was quantified in culture supernatants using cytometric bead arrays and ELISA.

Results and discussion: PV patients displayed heterogeneous Dsg3-specific Th cell responses. In acute and remittent PV, Dsg3-reactive Th cells exhibited a Th2/Th17-dominant cytokine pattern, whereas Th2 polarization predominated during chronic disease. PBMCs from HC displayed low-level proliferative responses to Dsg3 peptides. Collectively, this combined detection and functional characterization approach for Dsg3-reactive T helper cells enables the identification of autoreactive T cells with distinct cytokine signatures across disease stages.

Conclusion This novel assay, which for the first time allows ex vivo detection of Dsg3-reactive T cells with defined functional profiles, establishes a foundation for monitoring autoreactive T cell responses and developing individually tailored immunotherapies for PV patients.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 111

Stromal regulation of inflammation in pemphigoid diseases

Sbaraglia A.M.[1], Robrahn L.[1], Friščić J.[1], Androšević I.[1], Macias L.[2], Fähnrich A.[3], Ludwig R.[4], Hoffmann M.[1]

[1.] University of Lübeck, Institute for Systemic Inflammation Research, Lübeck, Germany;

[2.] University of Lübeck, Institute of Medical Biometrics and Statistics, Lübeck, Germany;

[3.] Lübeck Institute for Experimental Dermatology/ Medical Systems Biology University of Lübeck;

[4.] Lübeck Institute for Experimental Dermatology, Lübeck, Germany;

Pemphigoid diseases (PDs) are autoimmune skin disorders characterized by linear deposition of autoantibodies at the dermal–epidermal junction with subepidermal blister formation. Clinically, PDs exhibit a relapsing–remitting course with differential affection of different body parts. In a retrospective study we also observed that flares of bullous pemphigoid predominantly target sites previously affected by inflammation, suggesting an involvement of tissue resident cells priming the tissue for recurrent inflammatory attacks. Although dermal fibroblasts (DFv s) are increasingly recognized as local immunomodulatory cells, their role in PD pathogenesis remains largely unexplored.
In a local mouse model of epidermolysis bullosa acquisita (EBA) repeated injection of anti-collagen (Col) 7 immunoglobulin G resulted in exacerbated inflammation, confirming the occurrence of inflammatory tissue priming. Increased inflammation during flares was also observed in *Rag2*$^{-/-}$ mice, indicating that tissue priming occurs independently of the adaptive immune system. DFs isolated from primed sites displayed metabolic activation and pathogenic transcriptional changes compared to naïve or single-injection groups. Adoptive transfer of primed DFs conferred enhanced inflammatory susceptibility to recipient mice, confirming the ability of DFs to directly prime the skin. Notably, primed DFs exhibited a transcriptional activation of Interferon-gamma-JAK/STAT pathways, Furthermore, tissue priming was absent in *Ifngr1*$^{-/-}$ mice and was reversed by Ruxolitinib treatment, a JAK1/2 inhibitor, implicating IFN-gamma–JAK/STAT signalling playing a role in mediating inflammatory tissue priming in the passive EBA model. Our findings identify DFs as key mediators of local inflammatory priming in PDs. Targeting therapy, e.g. by Ruxolitinib, is a promising strategy to unprime previously affected skin tissue and -promote sustained drug-free remission in PDs.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 112

Reduction of IL-17+ T cells under guselkumab (anti-IL23) therapy in oral lichen planus: results from a phase 2 trial

Barbara B. Berg[1]; Alexander Reuss[2]; Nelli Ens-Jäger[2]; Laura G. Kostenis[1]; Antonio M. Santos[1]; Julie Fischer[1]; Matthias Hahn[3]; Kerstin Steinbrink[4]; Franziska Schauer[5]; Amir Yazdi[6]; Julia Hinterseher[1]; Dario Didona[1]; Michael Hertl[1]

1 - Department of Dermatology and Allergology, Marburg University, Marburg, Germany
2 - Coordinating Centre for Clinical Trials (KKS), Marburg University, Marburg, Germany
3- Department of Dermatology, - University of Tübingen, Tübingen, Germany
4 - Department of Dermatology, University of Münster, Münster, Germany
5 -Department of Dermatology, University of Freiburg, Freiburg, Germany
6 - Department of Dermatology, RWTH Aachen, Aachen, Germany

Introduction: Oral lichen planus (OLP) is a chronic inflammatory disease of the oral mucosa characterized by white reticular lesions, erythema, and erosions, predominantly affecting the buccal mucosa, tongue, and gingiva. It affects about 1% of the population, with a prevalence in women >40 years. Erosive OLP markedly impairs quality of life and is potentially precancerous. Although current therapies alleviate symptoms, they are not curative. Increasing evidence suggests dysregulation of the IL-23/IL-17 axis as a central mechanism in OLP pathogenesis. In this context, guselkumab, a monoclonal antibody targeting the IL-23 p19 subunit and blocking downstream IL-17 production represents a potential therapy for OLP.

Methods: We here conducted an open-label, randomized, multicenter phase II trial coordinated by the Department of Dermatology and Allergology at Marburg. Forty-five patients with moderate-to-severe OLP were randomized into two groups at a 2:1 ratio: the immediate-treatment group (Arm A) received guselkumab 100 mg subcutaneously at weeks 0, 4, 12, and 20; and the waiting-control group (Arm B) that received guselkumab regimen with a 12-week delay. Baseline therapy consisted of triamcinolone acetonide 0.1%, or an equivalent topical steroid applied twice daily over the study.

Results and discussion: The primary endpoint of this study was response, defined as a $\geq$ 50% reduction in the relative numbers of IL-17A+/IL-17F+ CD4+ or CD8+ T cells, identified in histological sections of oral mucosa by immunofluorescence 12 weeks after randomization. The secondary endpoint included *ex vivo* characterization of T cells isolated from mucosal lesions by flow cytometry. We next compared both arms for IL-17A+/IL-17F+ CD4+ and CD8+ T cell frequencies and cross-tabulated responder status between histological and flow-cytometric assessments. Biopsies of buccal mucosa were obtained at baseline, week 12, and week 24.

At baseline, no differences were found between both groups by either method regarding the number of IL-17+ T cells in mucosal lesions. In Arm A, immunofluorescence revealed median reductions from baseline to week 12 by 79% for CD4+IL-17A+, 52% for CD4+IL-17F+, 99% for CD8+IL-17A+, and 100% for CD8+IL-17F+ T cells. At week 24, reductions remained pronounced, i.e., 85%, 40%, 96%, and 88%, respectively. In Arm B, there was a median reduction from baseline to week 12 by 73% for CD4+IL-17A+, an increase of 121% for CD4+IL-17F+, reductions of 72% for CD8+IL-17A+, and 96% for CD8+IL-17F+ cells. A median reduction from baseline to week 24 (i.e. 12 weeks after start of guselkumab in Arm B) of 93% was observed for CD4+IL-17A+, 80% for CD4+IL-17F+, 99% for CD8+IL-17A+, and 94% for CD8+IL-17F+ cells. Furthermore, altogether, in Arm A, 52% of the patients showed a response after 12 weeks compared to 29% in Arm B.

Flow cytometry analysis showed a 100% median reduction of CD4+IL-17A+ T cells after 12 weeks of guselkumab in Arm A and 49% median reduction of CD4+IL-17A+ T cells at week 12 in Arm B. Response at 12 weeks was 33% in Arm A and 36% in Arm B.

Regarding clinical outcomes, over baseline, week 12 and week 24, mean Escudier disease activity score decreased from 16.8 to 13.8 to 10.3 in Arm A and from 18.0 to 14.5 to 13.1 in Arm B. Mean pain score declined from 6.3 to 5.1 to 3.5 in Arm A and from 5.6 to 5.1 to 5.1 in Arm B. Similar results were seen with ABSIS mucosa score: over baseline, week 12 and week 24, mean ABSIS mucosa decreased from 5.7 to 4.9 to 3.8 in Arm A and from 5.6 to 4.8 to 4.7 in Arm B. The mean ABSIS mucosa functional score developed from 18.1 to 14.9 to 12.5 in Arm A and from 18.3 to 19.8 to 15.8 in Arm B.

Conclusion: Guselkumab markedly reduced numbers of IL-17A+/IL-17F+ CD4+ and CD8+ T cells in OLP lesions, suggesting that IL-23 blockade effectively down-regulated IL-17+ mucosal T cells. This effect was confirmed by clinical improvement measured by Escudier and ABSIS scores.The waiting-control group (Arm B) showed some decrease in disease activity, but this improvement was less pronounced compared to Arm A. Overall, these favorable findings warrant further studies aimed at therapeutic targeting of the IL-23/IL-17 axis in OLP.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 113

Impact of nanoplastics on barrier function and Th2 driven inflammatory signaling on Atopic Dermatitis

KADRI, E.K. [1]; Aydin, G. [1]; Kaesler, S. [1]; Evers, B. [1]; Biedermann, T. [1]

1 Technical University Munich, Department of Dermatology and Allergy Biederstein, Munich, Germany

Introduction

Micro- and nanoplastics (NP) are emerging environmental pollutants that are ubiquitously present in air, food, and cosmetics. Growing evidence suggests that they can interact with epithelial and immune cells, potentially disturbing tissue homeostasis and promoting inflammation. However, their specific effects on the skin, particularly under atopic dermatitis (AD)-like conditions, remain poorly understood. This project aims to investigate how NPs affect inflammatory and barrier-related pathways in both human and mouse skin models using in-vivo, ex vivo, and in vitro approaches.

Methods

To explore the effects of NP in the context of AD in mice, we used Balb/C mice to replicate AD like conditions. Tape stripping has been performed on the back skin of the mice, then S. aureus (SA) and/or NP on day 0 and day 3 have been applied on the lesion, trans-epidermal-water-loss (TEWL) has been measured on both day 0 and day 3. Flow cytometry on cells isolated from the lesional skin and lymph nodes has been performed to observe different populations focusing mainly on Th2 cytokine expressing cells. The expression of Th2 cytokines, alarmins, barrier-related genes, and other inflammation markers's genes was analysed by qPCR. Protein analysis has been performed by LEGENDplex analysis.

To explore the effects of NP on inflammation and barrier function in human skin, Healthy human skin punch biopsies were cultured ex vivo under air–liquid interface conditions. Mechanical barrier disruption was induced by tape stripping, and Th2 cytokine stimulation was achieved by preincubation with IL-4/IL-13. Skin biopsies were subsequently exposed to 20 nm polystyrene NP for 6 h or 24 h. Gene expression of epithelial alarmins, Th2-associated chemokines, inflammatory mediators, and barrier-related markers was assessed by quantitative PCR. In parallel, primary human keratinocytes were exposed to increasing concentrations of NP under conditions with or without Th2 cytokine stimulation. Further analyses, including immunohistochemistry for filaggrin and claudin-1 to assess barrier integrity, are planned.

Results

First in-vivo measurements showed an increase in TEWL values across the treated groups with a significant increase in the groups that received NP, indicating barrier permeabilization. qPCR data show a remarkable downregulation of barrier proteins after application of NP, and trends and significant upregulations in alarmins and Th2 transcription factors, the effect is even more exacerbated upon application of SA and NP on the lesions combined. This indicates the induction/enhancement of a Th2 response by NP, along with the disruption of the skin barrier upon contact with NP. Protein analysis shows a higher concentration of certain cytokines upon exposure to NP. These data, provide valuable cues on the mechanism of Th2 polarization upon NP exposure.

NP exposure induced a distinct epithelial activation pattern in ex vivo human skin. In the absence of mechanical barrier disruption or Th2 cytokine stimulation, NP exposure resulted in a significant induction of epithelial alarmin pathways and Th2-associated chemokine responses. Following mechanical barrier disruption, NP exposure was still associated with increased epithelial alarmins and Th2-associated responses. In contrast, under Th2 polarization induced by IL-4/IL-13, NP exposure did not result in a consistent additional epithelial response.

In primary human keratinocytes, NP exposure induced upregulation of epithelial stress and Th2-associated pathways together with downregulation of barrier-associated gene expression. These effects were observed under both baseline conditions and following IL-4/IL-13 preincubation in a concentration-dependent manner. These keratinocyte data are preliminary and derived from a single donor (n = 1).

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 114

Local inflammatory tissue priming in Pyoderma gangraenosum

Friscic, Jasna Murthy, Sripriya Schilf, Paul Hoffmann, Markus

ISEF, Lüebeck. Germany
Dermatology Clinic, Luebeck, Germany

Abstract:
Numerous chronic inflammatory diseases are heralded by recurrence of acute inflammatory bouts at specific sites which have previously already been affected by inflammation or injury. Numerous chronic inflammatory diseases, such as rheumatoid and gouty arthritis, are heralded by recurrence of acute inflammatory bouts at specific sites which have previously already been affected by inflammation or injury. In context of local tissue priming in chronic inflammatory diseases of the skin, the phenomenon of pathergy takes an important place. One of the prototypic disorders characterized by pathergy is Pyoderma gangraenosum (PG). With the premise that pathergy is conveyed by the local stromal tissue sensitization through inflammatory priming, we performed repeated in vitro treatment of human dermal fibroblasts with IL-1b, the most prominent hallmark of secretory dysregulation in PG. Upon repeated challenge, dermal fibroblasts were able to convey the priming effect, with strong invigoration of their functional phenotype. Upon re-stimulation, they increased their adhesion, proliferation and migration capacity. Treatment of neutrophils with conditioned media induced ROS production as well as NET formation. Regardless of the strong pathergy effect, available data on the role of stromal tissue and local inflammatory priming still remain scarce. This research intends to give more insight in the role of dermal fibroblasts in the inflammation conveyance and disease development.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 115

Restoring Well-Being in Atopic Dermatitis: Superior WHO-5 Improvement Under Biologic Therapy Compared to JAK-Inhibitors

Kroß, K., Gerdes, S.

University Hospital Schleswig-Holstein, Campus Kiel, Center for Inflammatory Skin Diseases at the Department of Dermatology, Venereology and Allergology, Kiel, Germany

Atopic dermatitis (AD) is a chronic inflammatory skin disease that substantially affects patient well-being and quality of life. Modern systemic therapies, including Biologics and Janus Kinase Inhibitors (JAK-Inhibitors), have improved disease control, yet data on their effects on subjective well-being remain limited. The World Health Organization–Five Well-Being Index (WHO-5) is a brief, validated questionnaire for assessing psychological well-being and allows comparison with normative population values, but it has rarely been applied in dermatology. This retrospective study evaluated changes in well-being, measured by the WHO-5, in patients with moderate-to-severe AD treated with Biologics or JAK-Inhibitors. All patients were managed at our Center for Inflammatory Skin Diseases, where the WHO-5, the Dermatology Life Quality Index (DLQI), and the Eczema Area and Severity Index (EASI) are routinely collected. Patients initiating therapy with a Biologic (dupilumab, tralokinumab) or a JAK-Inhibitor (baricitinib, abrocitinib, upadacitinib) completed both questionnaires at baseline (T1, prior to therapy initiation), after 6–12 weeks (T2, end of induction phase), and at the last follow-up under ongoing therapy (T3, ranging from 6 months to 3.5 years). In total, 224 patients were analyzed (151 Biologic-treated, 73 JAK-Inhibitor–treated). Baseline WHO-5 scores were markedly reduced compared to the German general population (mean 65.7): 38.5 in the Biologic group and 37.1 in the JAK-Inhibitor group. At T2, WHO-5 increased to 61.1 and 54.2, respectively; at T3, to 57.5 and 50.5. Differences between treatment groups were statistically significant at both follow-up time points T2 (p=0,032) and T3 (p=0,040). Despite the broad follow-up range, sustained WHO-5 improvements at T3 indicate long-term stability of treatment benefit. WHO-5 correlated positively with improvements in DLQI and EASI, linking subjective well-being to both dermatological quality of life and objective disease severity. These findings demonstrate that the WHO-5 is a sensitive, patient-centered, and easily applicable outcome measure in AD. Biologics appear to restore well-being more effectively than JAK-Inhibitors, supporting the inclusion of the WHO-5 as a meaningful patient-reported outcome in clinical research and routine practice.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 116

An Abrocitinib surrogate molecule alleviates disease severity, reduces flare-ups and increases skin barrier integrity in a humanized mouse model of atopic dermatitis

Sofoklis Koudounas1; Markus Fehrholz1; Ralf J Ludwig1,2; Kristian Reich3; Melissa Watkins4; Amos Gilhar5; Ilaria Piccini1; Marta Bertolini1

1. QIMA Life Sciences, QIMA Monasterium GmbH, Münster, Germany;
2. University of Schleswig-Holstein, Lübeck, Germany;
3. University Medical Center Hamburg-Eppendorf, Hamburg, Germany;
4. Pfizer Inc, New York, NY, USA;
5. Technion – Israel Institute of Technology, Haifa, Israel;

Atopic dermatitis (AD) is a chronic inflammatory skin disease marked by immune cell activation, skin barrier dysfunction, and recurrent flare-ups. Recurrence of AD is thought to be driven, at least in part, by memory T cells. The Janus kinase 1 (JAK1) inhibitor abrocitinib has shown clinical efficacy in AD and modulates signaling induced by multiple cytokines and type I/II interferons. Thus, JAK1 inhibition offers a broad immunomodulatory scope, and its therapeutic benefits in AD may extend beyond currently reported clinical outcomes. Here, we aimed at investigating the mechanisms whereby Abro reduces AD disease recurrence using a humanized AD mouse model in which disease relapses can be observed following exposure to sonic stress. Human abdominal skin from three donors was grafted onto SCID mice and subsequently injected intradermally with autologous Th2-polarized peripheral blood mononuclear cells (PBMCs). Animals were then treated once daily by oral gavage with PF-06667291, an abrocitinib surrogate molecule (ASM), or vehicle control for 14 consecutive days. Following treatment cessation, sonic stress was applied to provoke disease flare-ups. Skin samples were collected two weeks later and evaluated using macroscopic imaging, histological staining, quantitative (immuno-)histomorphometry, and RNA sequencing (RNA-Seq). Treatment of AD xenografts with ASM led to a significant reduction in epidermal thickness, while the expression levels of keratin 1 and involucrin were unchanged. In addition, following flare-up induction, ASM treatment tended to increase filaggrin expression and significantly upregulated claudin-1, indicating a beneficial effect on skin barrier integrity. After two weeks of ASM treatment, epidermal $CD3^+$ T-cell numbers were reduced. Following sonic stress induction, T-cell counts were decreased in both the epidermis and dermis. Dermal skin-resident $CD3^+CD45RO^+$ T cells showed a tendency to be reduced by ASM treatment, whereas no change was observed in the epidermis. In contrast, epidermal and dermal skin-homing $CD3^+CD45RO^+CLA^+$ T-cell numbers were decreased after two weeks of treatment, with reductions also observed in the dermis following sonic stress induction. RNA-Seq analysis of xenografts following lesion recurrence after sonic stress treatment revealed that ASM treatment was associated with increased expression of skin barrier–related genes (*IVL, HRNR, CLDN8*) and decreased expression of inflammatory genes linked to Th1 (*CXCL9, CXCL10*), Th2 (*CCL13, CCL17, CCL18, CCL22*), and Th17 (*CXCL1, DEFB2*) pathways, as well as alarmins (*S100A7, S100A8*). These results suggest that abrocitinib may also act directly on keratinocytes, thereby contributing to flare prevention, potentially through reinforcement of the epidermal barrier alongside its targeted anti-inflammatory effects.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 117

The effect of hiPSC-derived sensory neurons on Th2-cells in 3D full-thickniss skin model

Mahmoud Alrifai , Katharina Hahn1, Darryl Addy1, Christin Korb1, Prasad Dasari1, Timo Buhl1

[1]*Department of Dermatology, Venereology and Allergology, University Medical Center Göttingen*

Atopic dermatitis is an immune-mediated chronic inflammatory skin disease characterized by intense pruritus, eczematous lesions and dry skin, particularly mediated by proinflammatory T helper 2 (Th2) cells. The type 2 cytokines IL-4 and IL-13 directly activate sensory neurons (SNs) and thereby contribute to itch. However, the mechanism of how neuropeptides secreted from activated SNs can modulate the function of Th2 remains enigmatic. To determine whether SNs affect the function of Th2 cells, human induced pluripotent stem cells (hiPSCs)-derived SNs were co-cultured with human *in vitro* differentiated Th2 cells in trans-wells. The expression of Th2 derives cytokines such as IL-4, IL-5 and IL-13 was determined by qRT-PCR and ELISA. SNs completely abolished the expression of IL-4, IL-5 and IL-13 from Th2 cells. Furthermore, SNs increased Th2 cell apoptosis. Treatment IL-4/ IL-13R blocking antibody Dupilumab partially restored the expression Th2 cytokines. To determine whether Th2 cytokines modulate the function of SNs, the expression of various neuropeptides was quantified by qRT-PCR. Th2 cytokines induced the expression of PACAP, CGRP, TAC1, NMU, NPY and decreased the expression of BNP and Somatostatin. To investigate whether calcitonin gene- related peptide (CGRP) secreted by SNs modulates Th2 cell function, SNs and Th2 co-cultures were treated with humanized CGRP-blocking antibody fremanezumab. CGRP antibody treatment significantly restored the expression Th2 cytokines. Thus, SNs and Th2 cells modulate the function of each other cell.

Finally, we will integrate SNs into immunocompetent full-thickness 3D skin models to study the function of SNs in full-thickness skin models. We will build an epidermis on top of the 3D skin models using keratinocytes and integrate SNs and Th2 CD4+ T cells. We will also analyze epidermal thickness and keratinocyte cell proliferation in the skin models. In addition, we will study the cytokines and neuropeptides released by T cells and SNs, as well as their receptors. Together, these findings suggest a bidirectional crosstalk between sensory neurons and Th2 cells that critically regulates inflammatory and neuroimmune responses in atopic dermatitis. Integrating both cell types into a 3D full-thickness skin model will provide a powerful platform to dissect their interactions under physiologic conditions and identify novel therapeutic targets for neuroimmune modulation in allergic skin inflammation.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 118

Oak Processionary Moth Setae Induce Monocyte-Driven Skin Inflammation

Prasad Dasari[1], Antonia Gellermann[1], Anna Moog[1], Susann Forkel[1], Michael P. Schön[1,2], Timo Buhl[1,2]

[1]Department of Dermatology, Venereology and Allergology, University Medical Center Göttingen, Germany.
[2]Lower Saxony Institute of Occupational Dermatology, University Medical Center Göttingen, Germany.

Thaumetopoea processionea (Oak Processionary Moth, OPM) is a lepidopteran species widespread across Europe. OPM larvae produce urticating hairs (setae), posing a major health hazards to humans and animals. Cutaneous contact induces intense dermatitis ("caterpillar dermatitis"), while inhalation can cause respiratory inflammation, potentially precipitating allergic asthma or anaphylaxis. Climate change-driven range expansion has caused exponential increases in OPM-related health problems throughout Germany, particularly among forest workers, hunters, farmers, and hikers, resulting in substantial socioeconomic burdens. Despite clinical significance, pathophysiological mechanisms underlying setae-induced cutaneous and systemic immune responses remain poorly understood. Monocytes are early responders in toxin- or particle-induced dermatitis, bridging innate and adaptive immune activation. To elucidate mechanistic bases of setae-induced inflammation, we employed a murine ear sensitization model. Topical setae application induced rapid vasodilation and significant ear swelling (mean +/- SD: setae 0.068 ± 0.021 mm; PBS 0.022 ± 0.007 mm; n=4 per group). Inflammation progressively intensified over four days before resolving slowly. Histological analysis revealed dense immune cell infiltration with pronounced epidermal hyperplasia. Flow cytometry identified predominant monocyte infiltration within 24 hours post-exposure, followed by differentiation into activated macrophages and dendritic cells, sustaining the inflammatory cascade. Morphometric analysis confirmed marked epidermal thickening, and repeated topical exposure elevated peripheral blood eosinophil counts, indicating systemic immune activation. This study provides first mechanistic evidence that OPM setae trigger severe skin inflammation via monocyte recruitment and activation, driving macrophage- and dendritic cells-driven immune repsonse. These findings clarify the pathogenesis of processionary moth-induced dermatitis and may guide targeted therapeutic strategies for lepidopterism or preventive strategies for occupational and environmental exposure to processionary moth setae.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 119

Interferon autoantibodies in atopic dermatitis patients with a history of eczema herpeticum

Stephan Traidl[1,2]; Petra Kienlin[1]; Gabriele Begemann[1]; Ilona Klug[1]; Katinka Döhner[1,2]; Eva Moennig[1,2]; Lennart M. Roesner[1,2]; Thomas Werfel[1,2]

[1]Department of Dermatology and Allergy, Hannover Medical School, Hannover, Germany

[2]Hannover Medical School, Cluster of Excellence RESIST (EXC 2155), Hannover, Germany.

A subgroup of patients with atopic dermatitis (AD) has impaired viral clearance and skin barrier capabilities, which can lead to severe herpes simplex virus (HSV) complications, referred to as eczema herpeticum (EH). Although autoantibodies against interferons have been associated with increased viral susceptibility, their presence has not yet been confirmed in EH patients.

In this study, we assessed the prevalence and functionality of interferon (IFN) autoantibodies in patients with a history of EH (ADEH+) compared to those without (ADEH-). We used a bead-based immunoassay to detect autoantibodies against interferons (IFN-α2, IFN-ω, and IFN-γ) in serum samples from ADEH+ and ADEH− patients. Functional effects of IFN-γ autoantibodies were assessed by measuring STAT1 phosphorylation in peripheral blood mononuclear cells and TLR3 gene expression in primary keratinocytes following IFN-γ stimulation. Serum cytokine concentrations were quantified using a cytokine multiplex assay.

Significant more ADEH+ patients had anti IFN-γ autoantibodies compared to ADEH- and VZV patients. Patients´ sera containing IFN-γ autoantibodies impaired IFN-γ–induced STAT1 phosphorylation and TLR3 upregulation in IFN-γ stimulated keratinocytes *in vitro*, confirming functional activity. Serum IFN-γ levels measured by comparable between ADEH+ and ADEH− patients.

Our findings reveal functional IFN-□ autoantibodies in serum of ADEH+ patients, highlighting a potentially critical mechanism of immune dysregulation in this subgroup. These autoantibodies may contribute to the impaired antiviral response seen in ADEH+ patients. Further research is needed to explore the diagnostic and therapeutic implications of autoantibodies in ADEH+ patients.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 120

TYMP: A Novel Biomarker in Psoriasis Regulated by IL-17 Signaling via NF-κB1-Mediated Transcriptional Activation

Zou, Y[1], Wang, J[2]

1. Department of Dermatology, Venereology and Allergology, University Medical Center Göttingen, Göttingen, Germany.

2. Department of Dermatology, The First People's Hospital of Jiangxia District, Wuhan City (Union Jiangnan Hospital Huazhong University of Science and Technology), Wuhan 430200 Hubei, PR China

Background:

Psoriasis is a common chronic and relapsing immune-mediated inflammatory skin disease with a substantial global burden. Identifying novel molecular biomarkers involved in disease pathogenesis is essential for improving diagnosis and developing targeted therapeutic strategies.

Methods:

Integrated analyses of single-cell RNA sequencing and bulk RNA sequencing datasets were performed to identify differentially expressed genes (DEGs) in psoriatic skin. In vitro psoriatic inflammation–like conditions were established by stimulating HaCaT keratinocytes with a cytokine cocktail (M5). An imiquimod (IMQ)-induced mouse model was used to validate findings in vivo. Gene expression was further examined using multiplex immunohistochemistry (mIHC) and conventional immunohistochemistry (IHC) in clinical samples. Mechanistic regulation of TYMP expression was investigated focusing on IL-17 signaling and NF-κB1-mediated transcriptional activation.

Results:

Single-cell transcriptomic analysis revealed distinct DEG profiles in basal, cycling, granular, and spinous keratinocyte subtypes when comparing normal and psoriatic skin. Across all four keratinocyte populations, 2,027 genes were consistently upregulated and 622 genes were downregulated ($p < 0.05$). Among these, TYMP emerged as the most significantly upregulated gene in all keratinocyte subtypes, with no prior functional characterization in psoriasis. Bulk RNA-seq analysis of an independent psoriasis cohort identified 3,741 upregulated and 3,991 downregulated genes ($p < 0.05$), consistently confirming TYMP as one of the top upregulated candidates. mIHC and IHC analyses of clinical samples demonstrated marked overexpression of TYMP in psoriatic keratinocytes. Functional validation using in vitro and in vivo models showed that TYMP expression was induced by inflammatory stimuli mediated through the IL-17 signaling pathway. Further mechanistic analyses revealed that TYMP is transcriptionally activated by NF-κB1 in keratinocytes.

Conclusions:

Our study identifies TYMP as a previously unrecognized keratinocyte-associated biomarker in psoriasis, regulated by IL-17–NF-κB1 signaling. These findings provide new insights into keratinocyte-driven inflammatory responses in psoriasis and suggest TYMP as a potential diagnostic marker and therapeutic target.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 121

Limited satisfaction of patients with Hidradenitis suppurativa and their treating dermatologists with medical care: Data from a multi-center study

Kerstin Wolk;[1] Giorgia Cugno;[1;2;3] Georgios Kokolakis;[1] Sylke Schneider-Burrus;[1;4] Dagmar Wilsmann-Theis;[5] Katharina Assaf;[5] Rotraut Moessner;[6] Christian Kromer;[6] Falk G. Bechara;[7] Nessr Abu Rached;[7] Wiebke K. Peitsch;[3] Lisa C. Schneider;[3] Andreas Happ;[8] Valentina Siddi;[9] Diana Kubitzki;[10] Durdana Groß;[11] Markus Friedrich;[2] Staffan Vandersee;[12] Khusru Asadullah;[13] Robert Sabat[1]

[1] Translational Skin Inflammation Research and former Psoriasis Research and Treatment Center, Department of Dermatology, Venereology and Allergology, Charité – Universitätsmedizin Berlin, Berlin, Germany

[2] Dermatology practice Dr. Friedrich / Dr. Philipp, Oranienburg, Germany

[3] Department of Dermatology and Phlebology, Vivantes Klinikum im Friedrichshain, Berlin

[4] Centre for Dermatosurgery, Havelklinik, Berlin, Germany

[5] Centre of skin diseases, University Hospital Bonn, Bonn, Germany

[6] Department of Dermatology, Venereology, and Allergology, University Medical Center Göttingen, Göttingen, Germany

[7] ICH - International Center for Hidradenitis suppurativa / Acne inversa, Department of Dermatology, Venereology and Allergology, Ruhr-University Bochum, Bochum, Germany

[8] Department of Dermatology, Klinikum Frankfurt (Oder), Germany

[9] Dermatology practice Siddi & Bachmann, Berlin, Germany

[10] MVZ Lobetal gGmbH, Bernau bei Berlin, Germany

[11] Dermatology practice Dr. Gross, Potsdam, Germany

[12] Department of Dermatology, Bundeswehr Hospital, Berlin, Germany

[13] Dermatology Potsdam MVZ, Potsdam, Germany

Background: Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease characterized by deep-seated painful inflammatory nodules, suppurating abscesses, and fistulas in intertriginous areas, imposing a substantial physical burden on those affected [Sabat et al., *Lancet*, 2025;405(10476):420–438]. Beyond somatic symptoms, many patients experience embarrassment, depression, sexual difficulties, social withdrawal, and limitations in their professional lives. Traditional treatments—often supported by limited evidence—are only moderately effective and frequently associated with adverse effects. While HS long suffered from low awareness—even within advanced healthcare systems—substantial advances have emerged in recent years, including awareness campaigns, insights into pathogenesis, registry development, validated scoring instruments, guideline developments, and approval of biologic therapies. Whether these advances have measurably improved real-world care, however, remains uncertain.

Research question and study design: To address this question, we conducted a prospective, questionnaire-based, multicenter study in Germany to assess satisfaction with current HS care from the perspectives of both patients and their treating dermatologists (DRKS00031572). For context, we collected complementary data on psoriasis care. The study encompassed multiple types of dermatology care facilities and included both residents and board-certified dermatologists. In addition to investigating satisfaction across settings, we used multivariable regression to identify factors associated with satisfaction and to highlight priority areas for improving HS care.

Results and Conclusion: A total of 124 HS patients and 133 psoriasis patients answered the questionnaires. Moreover, 40 and 36 questionnaires completed by dermatologists treating HS patients and psoriasis patients, respectively, were received.

The data demonstrate limited satisfaction of both patients and dermatologists with current medical care for HS and suggests that improvement can be achieved through the use of effective therapies and regular consultations at dermatologists who take sufficient time and effort to inform patients about HS.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 122

Serration pattern analysis in the diagnosis of pemphigoid diseases

Sequeira Santos, A.M.,1 Berg, B.,1 Didona, D.,1 Hertl, M.,1

Department of Dermatology and Allergology, Philipps University Marburg, Marburg, Germany

Abstract:
The pemphigoid diseases (PD), including bullous pemphigoid (BP) and epidermolysis bullosa acquisita (EBA), are autoimmune blistering disorders that primarily affect elderly patients and associated with significant morbidity and mortality. Accurate immunoserological classification is crucial to guide appropriate treatment for the distinct clinical variants.
Direct immunofluorescence (DIF) microscopy of perilesional skin is a sensitive method, used for differentiating BP from EBA that enables the detection of characteristic serration patterns of tissue-bound IgG and C3 deposits along the basement membrane zone: n-serrated pattern is indicative of BP, whereas a u-serrated pattern characterizes EBA. Moreover, recent studies have shown that, with adequate training, serration pattern recognition can be effectively incorporated into routine diagnostics.
The aim of this study was to evaluate the feasibility of serration pattern analysis in routine diagnostics of BP and EBA. In a retrospective analysis, we re-examined DIF samples from patients with PD (n = 45). Following optimization of our protocol, serration patterns of tissue-bound IgG and C3 were analysed using confocal microscopy.
Our findings indicate that serration pattern analysis can enhance diagnostic accuracy in distinguishing BP from EBA. However, successful implementation required substantial modifications to the conventional DIF staining protocol and access to confocal microscopy, which may limit its routine use in standard diagnostic settings.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 123

Virulence genes landscape of *S. aureus* strains and their associations with disease factors in a cohort of atopic dermatitis patients

Bouheraoua S. [1]; Stavrou F. [1]; Pham, C. [1]; Vital, M.[2]; Nishanth, G. [2]; Schlüter, D. [2,3]; Werfel, T. [1,3]; Roesner, L.M. [1,3]

1 Hannover Medical School (MHH), Department of Dermatology and Allergy, Hannover, Germany

2 Hannover Medical School (MHH), Institute of Medical Microbiology and Hospital Epidemiology, Hannover, Germany

3 Hannover Medical School (MHH), Cluster of Excellence RESIST (EXC 2155), Hannover, Germany

The skin microbiome of patients with atopic dermatitis (AD) has been shown to be less diverse and less even compared to that of healthy skin, and hallmarked by a dominance of the pathogen *Staphylococcus aureus.* This gram-positive bacterium has been shown to be capable of worsening the AD symptoms by releasing antigens, proteases and toxins, of which some act as superantigens, to disrupt the skin barrier, promote immune dysregulation and support the skin inflammation. Consequently, *S. aureus* skin colonization is associated with a more severe clinical AD phenotype. Earlier studies identified clonotypes frequently observed in AD patients, while describing a high degree of strain diversity of *S. aureus* within AD. Recent findings indicate the presence of on-person evolution suggesting that adaptation to the host may serve as an important mechanism of AD skin colonization.

This study aimed to analyze AD clinical isolates of *S. aureus* by genome sequencing and to investigate associations with clinical severity.

110 *S. aureus* strains derived from the nose and the lesional skin of a cross-sectional clinical cohort of 91 adult AD patients were analyzed. The severity of AD was assessed by SCORAD as well as the local SCORAD of the sampled site. 31 *S. aureus* strains isolated from the nose and skin infections or abscesses of 24 individuals without AD were analyzed for means of comparison.

In our hands, AD *S. aureus* strain genomes clustered phylogenetically based on patient ID and clonal types, but not on the sampling site. The strains belonged to several clonal types, however, clonal types previously reported to be significantly associated with skin infections or with increased cell adhesion were detected in this cohort. Subsequently, we focused on the virulence factors and observed that the presence of virulence genes associated with immunomodulatory and proteolytic functions showed a positive association with AD strains vs non-AD strains. Interestingly, these were more likely to be negatively associated with disease severity, particularly the local SCORAD.

In conclusion, our study provides an overview of *S. aureus* strains in a cohort of adult AD patients and draws a landscape of the virulence genes. In line with the idea of a long-term co-evolution with the host´s immune system, the skin-colonizing strains of adult AD patients predominantly harbor immunomodulatory and proteolytic virulence factors.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 124

In vitro cytotoxicity of lenalidomide, thalidomide, iberdomide, hydroxychloroquine, and mepacrine on cutaneous cell types

C. Berry[1]; J. Wohlrab[1]

1 University Hospital, Martin-Luther-University Halle-Wittenberg, Department of Dermatology and Venereology, Halle (Saale), Germany

Introduction
Thalidomide and it´s derivatives including lenalidomide show anti-inflammatory and antiangiogenic properties. Systemic administration of thalidomide and lenalidomide has demonstrated encouraging therapeutic effects in CD8+ T cell-mediated autoimmune diseases, particularly in cutaneous lupus erythematosus (CLE). However, their potential for severe side effects (i.e., thromboembolic events, peripheral neuropathy, and teratogenicity) limits their use. These medications are classified as immunomodulatory imide drugs (IMiDs), which cause their effect through binding to CRL4A-CRBN E3 ubiquitin ligase. This promotes the ubiquitination of IKZF1/3 (Ikaros/Aiolos) and inhibits ubiquitination of AMPKa1, leading to a lower concentration of NF-kappaB, fewer CD8+-T cells, more iNK-T cells as wells as a shift to a Th2 cell mediated response in the skin. As a result, the concentration of pro-inflammatory cytokines like TNF-alpha, IL-1, IL-6, IL-8, and IL-12 decreases, while the concentration of anti-inflammatory cytokines like IL-10 increases. Lenalidomide has a stronger inhibitory effect on the TNF-alpha production, while showing a reduced potential for side effects compared to thalidomide.

Methods
This project aims to establish the preclinical requirements for the formulation of a topical application of lenalidomide. To that end, the cytotoxic effects of lenalidomide, thalidomide, iberdomide, hydroxychloroquine, and mepacrine on cutaneous cell types will be characterized using cell viability, proliferation, and cell migration as parameters. The cells were subjected to concentrations ranging from 0 to 1000 µmol/L. Cell viability was assessed with the CellTiter-Glo® Luminiscent Viability Assay. The Cell Proliferation ELISA, BrdU (colorimetric) was used to test for cell proliferation. Cell migration was measured in a scratch assay using HaCaT cells und fibroblasts.

Results
Currently, lenalidomide shows no cytotoxic effects up to at least 100 µmol/L. Cells treated with thalidomide and iberdomide exhibit similar results to lenalidomide treatment. However, iberrdomide can show cytotoxic effects at lower concentrations especially in keratinocytes. Hydroxychloroquin and mepacrine can induce cytotoxic effects starting at 100 µmol/L and 5 µmol/L respectively.

Discussion
The results available to date provide a solid toxicological basis for the development of a topical treatment strategy using lenalidomide.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 125

Does anti-cytokine treatment truly restore skin homeostasis? A multimodal analysis of healed and treatment-resistant psoriatic skin

Villalba Bosque, A. [1]; Baldyga, A. [1]; Lee, H.J. [1]; Deland, A. [1]; Meier, K. [1]; Leson, S. [1]; Ghoreschi, K. [1]; Hilke, F.J. [1]

1 Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and HumboldtUniversität zu Berlin, Department of Dermatology, Venereology and Allergology, Berlin, Germany

Introduction
Biologic therapies targeting IL-17, IL-23 and TNF-α have revolutionized psoriasis management and achieve remarkable clinical clearance. Yet, it remains unclear whether clinically "healed" skin under therapy is immunologically and functionally equivalent to healthy skin. Distinguishing suppression from true restoration is critical for defining remission and optimizing treatment duration.

Objectives
To determine whether biologic therapy restores structural and immunological homeostasis in psoriatic skin, and to identify molecular differences between *healed* and *treatment-resistant* plaques within the same patient.

Methods
Fourteen psoriasis patients under ongoing biologic therapy (anti-TNF-α, anti-IL-17A, anti-IL-23, or anti-IL-12/23) were enrolled; paired 4 mm biopsies were collected post-therapy from clinically healed skin adjacent to a resistant plaque (n = 12 evaluable pairs). Healthy control skin was obtained from 14 individuals without inflammatory disease.

Formalin-fixed, paraffin-embedded sections were analyzed by:

1. Histology and immunohistochemistry (IHC): keratinocyte proliferation (Ki67), differentiation (KRT16), barrier proteins (filaggrin = FLG, loricrin = LOR), and immune infiltrates (CD3, CD4, CD8, MPO).
2. qRT-PCR: inflammatory (IL-1β, IL-6, IL-36γ, TNF-α, IL-17A, IL-23R) and regulatory mediators (IL-10, FOXP3, TGFβ1, CTLA-4).
3. Label-free LC-MS proteomics: differential protein abundance and pathway enrichment (limma, Reactome).

Results
Healed and resistant plaques displayed distinct morphological and molecular signatures despite being from the same patient. Resistant plaques showed marked keratinocyte hyperproliferation (↑ Ki67, $p < 0.01$) and aberrant differentiation (↑ KRT16), with elevated IL-36γ, IL-17A, IL-23R and TNF-α expression—indicating sustained IL-23/IL-17 axis activation. Healed plaques, although clinically normal, still exhibited residual epidermal hyperproliferation compared to healthy skin, yet showed enhanced FLG expression and increased IL-10 and FOXP3 levels, suggesting compensatory barrier remodeling and regulatory activation. Proteomic profiling (> 6,000 quantified proteins) revealed clear clustering: resistant plaques were enriched for keratinocyte activation and innate immunity markers (SERPINB4, KRT16/17, S100A8/9), whereas healed plaques clustered closer to healthy controls and showed enrichment for matrix and adhesion proteins (LUM, FHL1, SORBS1). Hierarchical clustering positioned healed samples intermediately between resistant and healthy skin, illustrating a continuum from inflammation to partial homeostasis.

Conclusion

Anti-cytokine therapy induces morphological and partial molecular restoration of psoriatic skin but does not fully re-establish homeostasis. Clinically healed plaques maintain low-grade proliferative and immunological activity—particularly residual IL-36- and IL-23/IL-17-axis signaling—suggesting a state of controlled suppression rather than complete resolution. Future work should focus on therapy-specific molecular signatures, spatially resolved immune profiling, and longitudinal sampling to define biomarkers of molecular remission. Integrating these parameters could guide individualized therapy duration and prevent relapse.

Discussion
This paired post-therapy analysis provides a high-resolution snapshot of psoriatic skin under biologic control. It emphasizes that clinical healing ≠ immunological health and supports a future precision-medicine approach combining cytokine blockade with barrier- and innate-targeted strategies.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 126

Cutaneous microbiota transfer from atopic dermatitis skin to human 3D skin models decreases expression of barrier molecules

Klutke, K.; Rademacher, F.; Heinemann, N.; Gerdes, S.; Gläser, R.; Harder, J.

University Hospital Schleswig-Holstein, Campus Kiel, Department of Dermatology and Allergy, Kiel, Germany

The chronic inflammatory skin disease atopic dermatitis (AD) is characterized in part by a disrupted skin barrier. This is also associated with an impaired expression or mutation of skin barrier molecules such as filaggrin, keratins and involucrin. Another hallmark of AD is the underlying type 2 inflammation and a dysbiosis of the cutaneous microbiota that is typically reflected by a decreased microbial diversity. It is still a matter of debate to which extent cutaneous microbiota alterations in AD trigger inflammation and promote disruption of the skin barrier.
To gain more insight into the functional role of the skin microbiota in AD, we transferred microbiota derived from adult AD skin to a human 3D skin model. Microbiota of lesional and non-lesional AD skin was harvested by swabbing and subsequent differential centrifugation. Age-, gender-, and localization-matched microbiota samples of healthy individuals served as controls. The recovered microbiota was applied to the surface of 3D skin models and incubated for 24 h. Stimulation was done in the presence or absence of the AD-associated type 2 cytokines interleukin (IL)-4 and IL-13. After incubation, real-time PCR was performed to analyze gene expression of various skin barrier molecules and differentiation markers: filaggrin, involucrin and keratin 1. Filaggrin expression was also analyzed by immunostaining.
As a result, filaggrin expression was significantly downregulated by the lesional AD microbiota and to a lesser extent by microbiota of non-lesional AD skin. Exposure with IL-4 and IL-13 led to a significant decrease in filaggrin levels. Co-exposure of IL-4 and IL-13 with any kind of microbiota further exacerbated the suppression of filaggrin expression. Analysis of keratin 1 expression revealed similar results as seen for filaggrin. In contrast, no type of microbiota caused a reduction in involucrin expression. IL-4 and IL-13 significantly downregulated involucrin expression. IL-4 and IL-13 together with microbiota of lesional or non-lesional AD skin further decreased involucrin expression.
In summary, our data highlight the capacity of AD-derived cutaneous microbiota to downregulate expression of barrier molecules, especially in combination with type 2 cytokines. These findings may be of great impact for targeted therapies in AD.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 127

Secreted factors of skin commensals protect healthy but not barrier-compromised skin from *S. aureus* colonization

Johanna Jakob[1]; Jule Focken[1]; Birgit Schittek[1]

1 University Hospital Tübingen, Department of Dermatology, Tübingen, Germany

Staphylococcus aureus is the most common cause of bacterial skin infections worldwide. While about 20-30% of healthy individuals are colonized in the nose by *S. aureus*, prevalence in atopic dermatitis (AD) patients is markedly increased (70-90%). There, it is commonly found in lesions where it exacerbates chronic skin inflammation [1]. Our previous work showed that in healthy skin presence of skin commensals such as *Staphylococcus epidermidis* or *S. lugdunensis* protects against *S. aureus* colonization. This effect can even be mediated by secreted factors of the bacteria in the absence of viable commensal bacteria e.g. bacteria conditioned medium (BCM). However, upon loss of barrier integrity, this protective effect is lost [2,3].

We now aimed to elucidate potential microbial ligands, the corresponding cellular receptors and mechanisms behind this protective effect. Additionally, we aimed to investigate the role of inflammation and loss of barrier integrity in the conversion of the protective effect in skin (lesions) of AD patients. To do so, we stimulated primary human keratinocytes (PHKs), human skin explants and 3D human skin reconstructs with BCM as well as different microbiome-derived ligands and analyzed the adhesion and invasion of *S. aureus.* Furthermore, we assessed the immune response by a range of techniques including LEGENDplex analysis, RT2 Profiler PCR array and ELISA. To model barrier impairment as in AD and elucidate the effects of microbiome derived ligands and BCM on damaged or inflamed skin, we used tape-stripping on human skin explants.

We could show that BCM of commensal bacteria in healthy skin induces an anti-inflammatory and protective immune response and upregulation of barrier genes. This was mediated at least in part by the aryl hydrocarbon receptor (AHR) signaling pathway as inhibitor studies showed. Additionally, various genes involved in innate pattern recognition receptor (PRRs) signaling were differentially regulated in PHKs upon BCM stimulation, hinting at a potential second mechanism involving PRRs. In inflamed or barrier-compromised skin, however, treatment with microbial factors in the BCM exacerbates skin inflammation and induced the secretion of danger-associated molecular patterns (DAMPs) likely favoring *S. aureus* colonization.

[1] Wang Z. et al. Understanding the role of *Staphylococcus aureus* in atopic dermatitis: strain diversity, microevolution, and prophage influences. *Front. Med*. 2024 Nov 18 11:1480257

[2] Burian M. et al. The Protective Effect of Microbiota on *S. aureus* Skin Colonization Depends on the Integrity of the Epithelial Barrier. J Invest Dermatol. 2017 Apr;137(4):976-979

[3] Bitschar K et al. Lugdunin amplifies innate immune responses in the skin in synergy with host- and microbiota-derived factors. Nat Commun. 2019 Jun 21;10(1):2730

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 128

Severe cutaneous adverse drug reactions (SCARs)

Deciphering the role of innate immunity signaling cascade in AGEP pathogenesis

Julia Laube[1]; Mark Mellett[1]; Ines Lederbogen[1]; Mirjam Nägeli[1]; Maja Mockenhaupt[2]; Alexander Navarini[3]; Lars E French[4]; Emmanuel Contassot[3]; Barbara Meier-Schiesser[1]

1 Dermatologic clinic, University Hospital Zurich, Switzerland

2 Clinic for dermatology and venerology, University Hospital Freiburg, Germany

3 Department of biomedicine, University of Basel, Switzerland

4 Clinic and Policlinic for dermatology and allergology, Ludwig-Maximilians-University München, Germany

Acute generalized exanthematous pustulosis (AGEP) and maculopapular exanthema (MPE) are cutaneous drug reactions belonging to the spectrum of type IV hypersensitivity. While a certain drug may elicit only a mild skin eruption in MPE, it can trigger a severe, rapid onset pustular eruption with systemic symptoms in AGEP. Currently, no reliable predisposing markers for AGEP are known, rendering prevention impossible. Although previous studies have emphasized the involvement of the adaptive immune system in AGEP pathogenesis, the role of the innate immunity remains poorly understood. The rapid onset upon drug intake and the characteristic neutrophilic pustules suggest a pivotal role of innate immune mechanisms in AGEP initiation and progression.

In this study, we aimed to elucidate mechanistic differences in innate immune signaling between AGEP, MPE and healthy controls at the molecular level. Bulk RNA sequencing of lesional skin revealed a pronounced upregulation of innate immune markers in AGEP compared with MPE and healthy skin, which was confirmed at the protein level for selected innate cytokines. Furthermore, whole-exome sequencing of peripheral blood samples from AGEP, MPE and healthy individuals demonstrated an enrichment of single nucleotide polymorphisms in genes related to myeloid leucocyte activation and Toll-like receptor signaling in AGEP patients. In line with that, *in vitro* assays demonstrated that peripheral blood mononuclear cells from AGEP patients exhibit dysregulated Toll-like receptor signaling, resulting in a faster and stronger response to pathogen-associated molecular patterns (PAMPs), even in the absence of culprit drugs.

These findings highlight a crucial role of innate immune receptor signaling in AGEP onset and pathogenesis and may pave the way toward identifying potential biomarkers for the prediction and prevention of AGEP and other severe cutaneous adverse reactions.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 129

Comparative Effects of Baricitinib and Upadacitinib on Innate and Adaptive Immunity in Atopic Dermatitis

Liao, K.[1]; Dasari, P.[1]; Buhl, T.[1]

1 University Medical Center Göttingen, Department of Dermatology, Venereology and Allergology, Göttingen, Germany

Atopic dermatitis (AD) is a chronic, relapsing, pruritic inflammatory skin disorder, characterized by recurrent eczematous lesions and intense itching, driven by complex neuro-immune interactions. Innate drivers include macrophages, dendritic cells, mast cells, eosinophils, and type 2 innate lymphoid cells (ILC2); adaptive responses are dominated by T helper 2 cells (Th2) in acute lesions with contributions from T helper 1 cells (Th1) and T helper 17 cells (Th17) in chronic phases. Targeted therapies now include IL-4Rα/IL-13 biologics and oral JAK inhibitors such as baricitinib (JAK1/2) and upadacitinib (JAK1-selective). Although both drugs show high clinical efficacy, their precise cellular mechanism and the differential effects in AD remain unclear. To investigate these mechanisms, human monocyte-derived macrophages (M1/M2), dendritic cells (MoDCs), and naïve $CD4^+$ T cells were differentiated *in vitro* and treated with baricitinib or upadacitinib (0.0625-1 µM). Both inhibitors reduced the apoptosis of M1 macrophages and downregulated expression of CD80/CD86 and decreased production of IL-6, IL-12 and TNF-alpha in a concentration-dependent manner (RT-qPCR, flow cytometry, ELISA) on M1 macrophages. In M2 macrophages, CD200R and CD206 expression was also suppressed. On MoDCs, expression of CD80, CD83, and CD86 and the secretion of pro-inflammatory cytokines (IL-12, IL-6, TNF-α) were markedly reduced. Naïve CD4+T cells were successfully differentiated into Th1, Th2 and Th17 subsets, and both inhibitors suppressed proliferation and lineage-specific cytokine production (IFN-γ from Th1, IL-4/IL-5/IL-13 from Th2, and IL-17A from Th17 cells). In conclusion, these findings indicate that JAK inhibition modulates both the innate and adaptive immune pathways relevant to AD, providing a mechanistic basis for the clinical efficacy of these JAK inhibitors. Baricitinib and upadacitinib showed largely comparable immunomodulatory profiles despite their different JAK selectivity.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 130

Topical application of CDK4/6 inhibitors as a novel therapeutic strategy for psoriasis

Kolb A. [1], Focaccia E. [1], Kulis-Mandic A.-M. [1], Fischer B. [1], Klein M. [2], Kübelbeck T. [1], Wegner J.[1], Wittmann M.[1], Kramer D. [1]

1 University Medical Center of the Johannes Gutenberg University Mainz, Department of Dermatology, Mainz, Germany

2 University Medical Center of the Johannes Gutenberg University Mainz, Institute for Immunology, Mainz, Germany

Psoriasis is a common autoinflammatory skin disease characterized by hyperkeratosis and massive infiltration of neutrophils, macrophages, and IL-17A-expressing T cells. We previously identified the transcriptional regulator IkappaBzeta, encoded by *NFKBIZ*, as a key mediator of IL-17A- and IL-36-driven skin inflammation in psoriasis. Furthermore, we demonstrated that CDK4/6 inhibitors potently suppress psoriasis-associated inflammation by specifically repressing IkappaBzeta expression in keratinocytes, thereby abrogating psoriasis-related proinflammatory gene expression in both, cell culture experiments and psoriasis mouse models. Building on these findings, we developed a topical CDK4/6 inhibitor-containing ointment, which effectively inhibited psoriasis-associated skin inflammation in a chronic psoriasis mouse model driven by keratinocyte-specific IL-17A overexpression, and in ex-vivo treated human skin biopsies derived from treatment naïve psoriasis patients. Importantly, topical application of CDK4/6 inhibitors showed no detectable off-target effects in mouse skin, aside from a robust suppression of IL-17A-dependent pro-inflammatory gene expression. These data suggest that topical treatment with CDK4/6 inhibitors represents a specific, effective, and safe therapeutic strategy for psoriasis.

Moreover, autoinflammatory diseases such as psoriasis often get “imprinted” into the skin, thereby contributing to the chronification of the disease. Consequently, as current anti-psoriatic drugs only inhibit the symptoms but do not cure, termination of the therapy leads to a rapid relapse of the disease at the same sites which have been affected before therapy start. Therefore, we further investigated whether topically applied CDK4/6 inhibitors are also able to reverse long-lasting changes of the skin after experimentally induced psoriasis in mice. Remarkably, topical CDK4/6 inhibition not only suppressed acute psoriatic inflammation but also prevented the persistence of proinflammatory imprinting that renders the skin hypersensitive to future inflammatory stimuli.

In conclusion, our results identify topical treatment with CDK4/6 inhibitors as a promising and innovative approach to treat psoriasis, with the potential to both suppress active inflammation and prevent epigenetic imprinting and chronification of the disease.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 131

Promotion of psoriasis-associated inflammation in TH17 cells and keratinocytes by the epigenetic modulator H2A.J

Kübelbeck, T.[1], Stastny, A.[1], Beumer, N.[2], Kolb, A.[1], Klein, M.[2], Deppermann, C.[3], Wittmann, M.[1], Kramer, D.[1]

1 Department of Dermatology, University Medical Center of the Johannes Gutenberg-University Mainz, Germany

2 Institute of Immunology, University Medical Center of the Johannes Gutenberg-University Mainz, Germany

3 Center for Thrombosis and Hemostasis, University Medical Center of the Johannes Gutenberg University Mainz, Germany

Epigenetic changes in the skin are increasingly recognized to contribute to the onset and chronification of psoriasis, but which epigenetic changes contribute to the skin hypersensitivity of psoriasis patients has been less investigated so far. Histone variants constitute a poorly studied class of epigenetic modulators that can replace classical histones at distinct promoter and enhancer regions, thereby altering their accessibility and thus overall gene expression.

By investigating human psoriasis and a psoriasis-like mouse model, we revealed a link between the histone variant H2A.J (gene H2afj) and psoriasis. We detected increased mRNA and protein expression of H2A.J in lesional and non-lesional samples from psoriasis patients. Furthermore, single cell sequencing of human psoriatic lesions showed increased H2AFJ expression especially in basal and differentiated keratinocytes, dendritic cells and T-cells. In line with these findings, global H2afj knockout (KO) mice were partially protected from experimentally-induced psoriasis-like inflammation. This was evident by reduced hyperkeratosis, less ear swelling, and significantly lower levels of psoriasis-associated systemic inflammation. This phenotype could partially be explained by the diminished expression of psoriasis-associated signalling molecules such as CXCL1, CXCL5, and IL-17A in the psoriatic skin of H2A.J KO mice, along with a reduced skin infiltration of neutrophils, monocytes, and IL-17A-expressing T-cells. On the cellular level, we identified H2A.J as a key regulator of IL-17A-responsive genes in keratinocytes, and effector molecules, such as Il17a and Il17f, in TH17 cells, thereby potentially explaining the observed phenotype in mice. On the molecular level, H2A.J-dependent gene expression regulation was likely due to its ability to localize to specific gene promoters, subsequently increasing promoter accessibility and transcription factor binding at distinct promoter regions. Importantly, increased H2A.J expression in keratinocytes also induced long lasting changes in the transcriptome of keratinocytes, thereby inducing a hyperresponsiveness of keratinocytes towards re-occurring IL-17A stimulation. Consequently, we suggest, that this phenomenon of H2A.J-mediated imprinting of IL-17 responses in keratinocytes might potentially also contribute to the chronification of psoriasis in human patients, rendering keratinocytes hypersensitivity to normally harmless insults.

In summary, our data on human psoriasis patients and a murine psoriasis model imply that H2A.J is an epigenetic regulator of IL-17-associated inflammation and thus contributes to the acute and chronic activation of TH17 cells and keratinocytes in psoriasis.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 132

Testing established MAP kinase inhibitors in a different approach of the human skin organ culture model for pemphigus vulgaris

Lennart Gooß[1], Veronika Hartmann[1], Christoph M. Hammers2,3 , Reza Akbarzadeh[6], Walter Raasch[5], Jennifer E. Hundt[1,4]

[1] Lübeck Institute of Experimental Dermatology, University of Lübeck, 23562 Lübeck, Germany

[2] Department of Dermatology, Venerology and Allergology, University of Regensburg, 93040 Regensburg, Germany

[3] Department of Dermatology, Allergy, and Venerology, University of Lübeck, 23562 Lübeck, Germany

[4] Center for Research on Inflammation of the skin, University of Lübeck, 23562 Lübeck, Germany

[5] Institut for Experimental Pharmacology and Toxicology, University of Lübeck, 23562 Lübeck, Germany

[6] Department of Rheumatology and Clinical Immunology, University of Lübeck, 23562 Lübeck, Germany

Introduction

Pemphigus vulgaris is an autoimmune blistering disease of the skin and mucous membranes. It involves IgG-autoantibodies directed against desmoglein 1 (DSG1) and/or DSG3, which are part of the protein complex for desmosomal adhesion. The presence of the autoantibodies can lead to the disruption of adhesion, resulting in intraepidermal blistering.

Methods

The human skin organ culture (HSOC) model for pemphigus vulgaris was previously established to better understand the pathomechanism of PV. The single chain variable fragrment (scFv) PX43 directed against DSG1 and DSG 3 induces the split formation in healthy donor skin, mimicking the effects of the autoantibodies in patients with PV.

Two hours prior and simultaneous to the scFv inhibitors are injected to take further influence on the skin and potentially change the amount of split formation observed in the skin. The antimetabolite 5-Fluorouracil, the tyrosinekinase inhibitor Lapatinib, the WNT-pathway modulators BIO and IWR-1 and the RNA-2-polimerase inhibitor alpha-Amanitin are the five substances tested in separate experiments. These substances previously showed significant results in a 2D-Model – the keratinocyte dissociation assay – and were now tested in the 3D HSOC model. After 24 hours of incubation hematoxylin and eosin (H&E) sections were prepared for quantitative evaluation of the split formation. Additionally immunofluorescence stainings for qualitative control of the PX43 binding sites and the distribution of DSG1/3 throughout the skin were prepared and samples were collected for possible RNA sequencing later.

Results and discussion

The data shows that none of the substances above have significant effects on the amount of split formation observed in the HSOC model. This suggests, that these signaling pathways do not play crucial roles in the pathogenesis of pemphigus vulgaris.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 133

Methylprednisolone blocks complement deposition in an ex vivo model of pemphigoid diseases

Marvin Tigges[1]; Ilaria Piccini[1]; Leon F. Schmidt-Jiménez[2]; Janin Edelkamp[1]; Katja Bieber[2]; Andreas Recke[2]; Ralf J. Ludwig[1,2]; Marta Bertolini[1]

[1]Qima Life Sciences, Qima Monasterium, Münster, Germany;
[2]Lübeck Institute of Experimental Dermatology, University of Lübeck, Lübeck, Germany

Pemphigoid diseases (PD) are characterized and caused by autoantibodies (Aab) targeting structural components of the dermal-epidermal junction (DEJ) in the skin and/or mucous membranes, with Aab mediated subepidermal blistering being a common clinical feature. Deposition of complement at the DEJ, specifically C3, is a hallmark of PD, and is used for its' diagnosis. Systemic or topical corticosteroids are the mainstay of PD treatment. In many cases, prolonged corticosteroid treatment is needed to induce or maintain remission, contributing to the high morbidity and increased mortality rate of corticosteroid treated PD patients. Hence, elucidating their mode of action could point the way to novel treatments suppressing inflammation with a reduced risk of adverse events. We evaluated the impact of the corticosteroid methylprednisolone (MP) on PD pathogenesis by recapitulating MPs' inhibitory action on immune complex-activated neutrophils, another factor in disease pathogenesis. Evaluating the impact of MP on C3 deposition in human skin cryosections, incubated with PD-antibodies and a complement source, we found a pronounced and dose-dependent inhibition of C3 deposition along the DEJ in MP-incubated sections. Hence, MP may block the proteolytic cleavage of complement compounds upstream of C3. Additional investigations are ongoing to understand whether this effect is unique to MP, or if it is class-specific, and to determine the concentration of C-cleavage products, i.e. C5a, Bb and C4d in the supernatant to pinpoint where MP affects complement activation. Our findings provide a mechanistic link between the clinical efficacy of corticosteroids and the molecular pathogenesis of PD, highlighting complement as a valuable therapeutic target.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 134

Platelet-Monocyte interactions via FXa and GPIbα promote systemic fibrosis

Neif, M[1]; Braun, I[1]; Tiemann, J[1]; Klein, M[2] ; Ruf, W[3]; Jurk, K[3] ; Raker, VK[1,4]

1. Dermatology, University Hospital Muenster, 48159 Muenster, Germany
2. University Medical Center Mainz, Research Institute for Immunotherapy, 55131 Mainz, Germany
3. Center for Thrombosis and Haemostasis, University Medical Center Mainz, 55131 Mainz, Germany
4. Department of Dermatology and Allergology, University Hospital Augsburg, 86179 Augsburg

Once viewed solely as mediators of hemostasis, platelets are now recognized as key regulators of immune and inflammatory responses, secreting cytokines such as TGF-β and activating circulating monocytes. We investigated coagulation-related gene expression in the skin of systemic sclerosis (SSc) patients and in murine models, focusing on the functional contribution of platelets and coagulation proteases in SSc.

RNA bulk sequencing analysis of healthy and SSc skin revealed that $CD45^+$ cells overexpress coagulation-associated genes, including F13A1 (F13), F2R(PAR-1), and platelet-derived growth factors (PDGFs), promoting cellular proliferation and infiltration. Notably, $CD45^-$ populations, including fibroblasts and keratinocytes, also showed marked F13A1 expression, consistent with chronic tissue remodelling.

To functionally assess coagulation in fibrosis, we employed Fos-related antigen-2 transgenic (Fra-2tg) mice, which overexpress the Fra-2 transcription factor, a member of the AP-1 family that regulates genes involved in cell proliferation, inflammation, and extracellular matrix production. Fra-2tg mice spontaneously develop vasculopathy and multiorgan fibrosis, making them a preclinical model for systemic sclerosis. These mice exhibited increased inflammatory monocytes ($CD11b^+Ly6C^+MHC^+$), a shift from $iNOS^+$ to $CD301b^+$ tissue phagocytes as well as an elevated number of platelet–monocyte clusters (PMCs; $CD11b^+CD41^+$), correlating with fibrosis severity. Platelet depletion (weeks 5–12) reduced $CD301b^+$ cell polarization, dermal α-SMA^+ cell counts, and skin thickness, indicating a functional role in fibrosis progression.

Mechanistically, platelet GPIbα directly interacts with the myeloid integrin CD11b/Mac-1, facilitating the formation of platelet–monocyte clusters and driving the activation of monocytes toward a pre-fibrotic, pro-inflammatory phenotype. This interaction promotes the polarization of tissue phagocytes toward a $CD301b^+$ reparative/fibrotic state, which is closely associated with extracellular matrix deposition and fibroblast activation. Consistent with this mechanism, IL-4R/GPIbα-transgenic mice, which lack the extracellular GPIbα domain and thus have impaired platelet–myeloid interactions, exhibited markedly reduced collagen deposition and attenuated skin thickening following hypochlorous acid–induced fibrosis, highlighting the critical role of platelet–monocyte crosstalk in fibrogenesis.

Given the overexpression of F2R in human SSc skin, we targeted the PAR-1–activating coagulation protease FXa, a key mediator upregulated in SSc skin, using both pharmacologic inhibition with rivaroxaban and a myeloid-specific FXa knockout in fibrotic mice. Both interventions effectively reduced fibrosis, demonstrating that coagulation proteases act not only in hemostasis but also as potent drivers of fibrotic responses.

Collectively, these findings identify platelet-derived coagulation mediators—particularly GPIbα and FXa—as potential drivers of fibrosis and promising therapeutic targets in systemic sclerosis and related fibroinflammatory diseases.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 135

Testing ion channel inhibitors in the human skin organ culture model for pemphigus vulgaris

Marie Jaboreck[1]; Axel Künstner[1]; Tanja Lange[2]; Christoph M. Hammers[1,3]; Veronika Hartmann[1]; Jennifer E. Hundt[1]

[1] Lübeck Institute of Experimental Dermatology, University of Lübeck, 23562 Lübeck, Germany

[2] Department of Rheumatology and Clinical Immunology, University of Lübeck, 23562 Lübeck, Germany

[3] Department of Dermatology, University of Lübeck, 23562 Lübeck, Germany

Introduction

Pemphigus vulgaris (PV) is an autoimmune blistering disease caused by IgG autoantibodies targeting desmoglein 1 and 3 (DSG1/3), leading to acantholysis and intraepidermal blister formation. Clinically, PV is characterized by flaccid blisters and painful, partially crusted erosions. Current treatments focus primarily on immunosuppression.

To investigate the role of specific ion channel inhibitors in PV pathogenesis, four substances amlodipine (calcium channel inhibitor), capsazepine (TRPV 1 inhibitor), dooku 1 (Piezo 1 inhibitor) and dyclonine (TRPV 3 inhibitor) were tested in the keratinocyte dissociation assay (KDA) by Zillikens and Rahimi. All four reduced keratinocyte monolayer fragmentation significantly, suggesting a potential protective effect.

Methods

Based on these findings, the inhibitors were further tested in a **human skin organ culture (HSOC) model** for PV developed in the Hundt lab. In this model, skin splits in healthy doner skin are induced by intradermal injection of the single-chain variable fragment (scFv) PX43, which targets DSG1 and DSG3. To ensure that the inhibitors bind to their designated targets, the inhibitors were prior injected to the skin for a 2-hour preincubation. After that preincubation the inhibitors were injected together with the scFv followed by a 24-hour incubation time to investigate the influence of the inhibitors on split formation. After the incubation period, the skin was harvested.

Results and discussion

Analysis included hematoxylin-eosin staining to measure split formation and immunofluorescence stainings for quality controls. Results showed that none of the inhibitors significantly reduced split formation in the HSOC, suggesting that these inhibitors do not play a crucial role in the pathogenesis of PV.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 136

Testing the effect of kinase inhibitors on the human skin organ culture model for pemphigus foliaceus

Namazi, D.[1], Hartmann, V.[1], Kalies, K.[2], Braun, R.[3], Hammers, C.[1], Hundt, J.[1]

[1] Lübeck Institute for Experimental Dermatology (LIED), University of Lübeck, Germany
[2] Institute for Anatomy, University of Lübeck, Germany
[3] Clinic for Surgery, UKSH Campus Lübeck, Germany

Pemphigus foliaceus (PF) is an autoimmune blistering disease characterized by autoantibodies targeting desmoglein 1 (DSG1), leading to acantholysis and superficial blister formation within the epidermis. Previous studies demonstrated that inhibition of certain kinases reduced split formation in the human skin organ culture (HSOC) model for pemphigus vulgaris (PV). This study investigates whether those kinase inhibitors can inhibit the epidermal split formation in the HSOC model for PF.
In the HSOC model for PF skin samples were injected intracutaneously with selected kinase inhibitors (PF-573228 [FAK1/2], PP2 [Lck/Fyn], PRT062607 [Syk], Saracatinib [Src Pan], KX2-391 [Src], RK 24466 [Lck], SU 6656 [Fyn/Lck/Yes]) followed by a two hour incubation and subsequent injection of the anti-DSG1 single-chain variable fragment (scFv) PF1-8-15 together with the same inhibitor. After 24 hours of incubation at 37 °C and 5 % CO_2, samples were then processed for hematoxylin-eosin (H&E) staining, direct immunofluorescence (DIF) staining, desmoglein 1/3 immunostaining, and quantitative histometric analysis.
Quantitative evaluation of seven HSOC experiments (n = 7) revealed no statistically significant reduction in split formation with any of the tested kinase inhibitors under current conditions.
The injection of the anti-DSG1 scFv PF1-8-15 induced PF-like intraepidermal split formation. H&E and DIF staining consistently showed suprabasal splits and intercellular IgG deposition characteristic of PF.
The HSOC model for PF successfully reproduces disease-typical split formation.
In contrast to the HSOC model for PV, kinase inhibition of Src, FAK, Syk, and Lck/Fyn pathways did not significantly reduce epidermal split formation in PF.
Future work includes transcriptomic analyses and extended kinase profiling to identify additional therapeutic targets.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 137

Early Epidemiologic and Immune Predictors of Atopic Dermatitis: Reduced Cord Blood Regulatory B10 Cells in the Munich Atopy Prediction Study (MAPS)

Short Title: Reduced B10 Cells Linked to Future Atopic Dermatitis

S. Preis[1,2], S. Kaesler[1], M. Köberle[1], M. Hils[1], B. Evers[1], R. L. Silva[1], Y. Skabytska[1,3], L. Schellenberger[1], H. Hufnagel[1], M. Schielein[1], B. Kuschel[1,4], Y. Amar[1], A. Zink[1], T. Biedermann[1]*, Z. Kurgyis[1]

[1]Technical University of Munich, School of Medicine, Department of Dermatology and Allergy

[2]Institute for Medical Information Processing, Biometry, and Epidemiology, Pettenkofer School of Public Health LMU Munich, Munich, Germany

[3]Department for BioMedical Research DBMR, University of Bern, Switzerland

[4]Technical University of Munich, School of Medicine, Department of Gynaecology, University Hospital rechts der Isar, Munich

Background: A complex interaction between environmental and lifestyle factors, immune dysregulation, and skin barrier integrity is believed to contribute to the development of atopic dermatitis (AD). However, the precise mechanisms underlying disease onset in infants remain largely unclear.

Methods: The 'Munich Atopic Prediction Study' (MAPS) is a comprehensive clinical and biological investigation of a prospective birth cohort from Munich, Germany. Information on pregnancy, child development, environmental influences, parental exposure to potential allergens, as well as illnesses affecting both children and parents is gathered through questionnaires. This is complemented by thorough clinical examinations conducted by trained dermatologists, with a particular focus on allergies and skin health. Biomarker analyses were performed e.g. on cord blood immune cells using flow cytometry (FACS analysis).

Results: Maternal AD (aOR = 3.06, p = 0.020) and affected siblings (aOR = 4.80, p = 0.039) are associated with an increased risk of AD, whereas cold-remedy intake showed a protective association (aOR = 0.11, p = 0.047). Infants later diagnosed with AD (total 74 infants, AD n = 27, healthy n = 47) are characterized by reduced frequencies of $CD4^+$ T cells (p = 0.0247) and increased B cell counts (p = 0.0067). Moreover, for the first time, we could identify a significant reduction in regulatory B (Breg) cell frequencies in these infants (p = 0.0015). Furthermore, our findings suggest that maternal allergen-specific immunotherapy may have a beneficial effect on the development and frequency of Breg cells (p = 0.0497).

Conclusion: Our study identifies early immune alterations, particularly a reduction in cord blood Breg cells, as potential contributors to AD pathogenesis. Incorporating Breg cell measurements into neonatal immune panels, along with key perinatal and familial risk factors, may enhance early risk stratification and enable more personalized prevention of atopic diseases.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 138

HIF-1α mediates Th17-dependent inflammatory responses in psoriasis

Magassa, S. [1]; Mahapatra, KD.[1]; Jargosh, M.[2]; Langreder, N.[1]; Bourhani, H.[1]; Eyerich S.[1]; Garzorz-Stark, N.[1]

1 University Medical Center Freiburg, Department of Dermatologyand Allergy, Freiburg, Germany

2 Technical University Munich, Department of Dermatology and Allergy Biederstein, Munich, Germany

Psoriasis is one of the most prevalent chronic, non-communicable inflammatory skin disorders, affecting approximately 2–3% of the global population. This condition is characterized by aberrant interactions between immune cells and keratinocytes, resulting in epidermal hyperplasia and abnormal differentiation. Its pathogenesis is multifactorial, involving genetic predispositions, environmental triggers, and autoantigens. In this study we investigated the centrality of hypoxia-inducible factor 1 alpha (HIF-1-alpha) in psoriasis using integrated transcriptomic, cellular, and functional approaches. Whole transcriptome analysis of human psoriatic skin biopsies revealed significant upregulation of HIF-1-alpha and its downstream transcriptional targets, indicating an active hypoxic program in lesional epidermis. Spatial transcriptomic and immunofluorescence analyses demonstrated that HIF-1-alpha is predominantly induced in the suprabasal layers of psoriatic epidermis. Functional cytokine stimulation studies of primary keratinocytes showed that Th17 cytokines, specifically IL-17A and IL-22, robustly induce HIF-1-alpha expression in the epidermis. Genetic depletion of HIF-1- alpha in epidermal cells markedly abated Th17 cytokine-induced epithelial dysregulation, indicated by reduced proliferation, differentiation abnormalities, and suppression of proinflammatory gene expression. Mechanistic assays confirmed HIF-1-alpha as a modulator of the epidermal inflammatory response, including enhanced neutrophil chemoattraction and regulation of multiple epidermis-derived pro-angiogenic factors. Importantly, loss of HIF-1-alpha significantly impaired the glycolytic capacity of keratinocytes, particularly under Th17 inflammatory conditions. Notably, the epidermal HIF-1- alpha regulated gene signature demonstrated potential to stratify therapy response in psoriasis, suggesting clinical biomarker utility. In summary, these results position HIF-1 alpha as a central molecular checkpoint integrating Th17-driven inflammation, metabolic adaptation, and tissue remodeling in psoriasis, and highlight its value as a therapeutic target and biomarker for precision medicine applications in psoriatic disease.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 139

Inherited p62 Dysfunction Promotes Chronic Interferon Signaling in Autoimmune Disease

Shrutika Kavali [1]; Sarah Roesing [1,2]; Nisarg Dobaria [1]; A. Pichlmair [3]; M. Lee-Kirsch [4]; Claudia Guenther [1,2]

[1] Department of Dermatology, Faculty of Medicine Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany

[2] Department of Dermatology, University of Tübingen, Tübingen, Germany

[3] Institute of Virology, TU Munich, Germany,

[4] Department of Pediatrics, University Hospital, TU Dresden, Germany

A multigenerational family comprising eight affected individuals across four generations presented with a distinct autoinflammatory phenotype. Affected members exhibited autoimmune manifestations, including Chilblain lupus and Dermatomyositis. Whole-exome sequencing identified a heterozygous stop mutation in SQSTM1, encoding the multifunctional adaptor protein p62 (also known as sequestosome 1). p62 functions as a selective autophagy receptor that mediates degradation of ubiquitinated cargo and regulates diverse cellular stress and inflammatory signaling pathways. The identified stop variant lies within the PB1 domain, crucial for p62 homodimerization, heterodimerization, and assembly of signaling complexes essential for its biological activity.

Previously, SQSTM1 mutations have been implicated in amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration (FTLD), and as a common cause of Paget's disease of bone. Additionally, biallelic mutations causing functional loss of p62 have been associated with disrupted selective autophagy and early-onset neurodegenerative diseases.

To investigate how this heterozygous mutation manifests in our family's phenotype, we performed functional protein and transcriptional analyses. Western blot analysis of patient-derived fibroblasts revealed markedly reduced total p62 protein levels in all affected individuals, suggesting that the mutant allele leads to p62 haploinsufficiency. To determine whether the mutant transcript produces a truncated protein or undergoes degradation via nonsense-mediated mRNA decay (NMD), quantitative PCR was performed using primers spanning exonic regions both upstream and downstream of the premature stop codon. The data showed a significant reduction in SQSTM1 transcript abundance on both sides of the mutation, indicating that the mutant mRNA is degraded by NMD. Consistently, Western blot analysis did not detect any truncated p62 fragments in patient fibroblasts compared to healthy controls, confirming that the mutant allele does not produce a stable truncated protein.

These results demonstrate that the SQSTM1 stop mutation of the PB1 domain causes haploinsufficiency through transcript degradation, resulting in loss of p62. Ongoing investigations aim to elucidate how this p62 haploinsufficiency contributes to the diverse autoimmune phenotypes observed in this family.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 140

Establishment and Clinical Application of a Transdermal Drug Delivery Sustained-Release System Based on a Nano-Microneedle

Wang, S.[1]; Qiao, X.[2]; Chen J.[2]; Zhang R.[1]

1 The Second Affiliated Hospital of Nanjing Medical University, Department of Dermatology, Nanjing, China

2 Nanjing University of Chinese Medicine, College of Pharmacy, Nanjing, China

Background

Transdermal drug delivery enables localized or systemic therapy while avoiding first-pass metabolism, however the stratum corneum severely limits drug penetration. For chronic dermatoses such as atopic dermatitis (AD), sustained-release strategies are required to maintain therapeutic efficacy and improve patient compliance.

Objective

To develop and evaluate a nano-microneedle–mediated transdermal sustained-release system that enhances percutaneous drug delivery and provides a minimally invasive therapeutic approach for AD.

Methods

Transdermal permeation of compound betamethasone injection was measured using Franz diffusion cells and High Performance Liquid Chromatography (HPLC). In vivo fluorescein sodium imaging assessed penetration depth, and H&E staining evaluated skin safety. Therapeutic efficacy was investigated in a DNCB-induced AD mouse model using modified SCORAD scoring, histopathology, mast cell analysis, and ELISA measurement of IgE, IL-4, and IL-13. A self-controlled clinical study in patients with mild-to-moderate AD compared nano-microneedle–assisted delivery of compound betamethasone with saline, with clinical severity, pruritus, and adverse events assessed after 7 days.

Results

Nano-microneedle treatment increased 24-hour cumulative permeation of betamethasone dipropionate and betamethasone sodium phosphate by 3.29-fold and 4.66-fold, respectively. In AD mice, treatment resulted in significant reductions in lesion severity, epidermal thickness, mast cell infiltration, as well as serum IgE and IL-13 levels (all $p < 0.0001$). Clinically, 27 patients completed follow-up, with the treatment side showing greater improvement in SCORAD feature scores ($p < 0.05$) and pruritus reduction ($p < 0.001$). No serious adverse events were observed.

Conclusion

This nano-microneedle–mediated transdermal sustained-release system effectively overcomes the skin barrier, enhances compound betamethasone delivery, and alleviates both local inflammation and systemic immune responses. Its minimally invasive and long-acting properties support its potential as a therapeutic platform for chronic inflammatory skin diseases such as AD.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 141

Inhibition of RIPK1 prevents keratinocyte cell death and reduces skin inflammation in type 1 mediated chronic inflammatory skin diseases

Sophia Wasserer[1,5]; Manja Jargosch[1,2]; Danping Ding-Pfennigdorff [3]; Theresa Raunegger[1,5]; Jessica Eigemann[1,2,5]; Eckart Bartnik[3]; Carsten B. Schmidt-Weber[2]; Tilo Biedermann[1]; Stefanie Eyerich[2,6,7]; Kilian Eyerich[6]; Peter Florian[3,4]; Matthias Herrmann[3]; Joachim Saas[3] and Felix Lauffer[1,5]

[1] Department of Dermatology and Allergy, Technical University of Munich, Munich, Germany

[2] Center of Allergy and Environment (ZAUM), Technical University of Munich and Helmholtzzentrum Munich, Munich and Neuherberg, Germany, Member of the German Center of Lung Research (DZL)

[3]Sanofi R&D, Immunology and Inflammation Therapeutic Area, Type 1/17 Immunology Cluster, Industriepark Hoechst, 65926 Frankfurt am Main, Germany

[4]Boehringer Ingelheim Vetmedica GmbH, Global AH Research, Ingelheim, Germany

[5]LMU Hospital, Department of Dermatology and Allergy, Munich, Germany
[6] Department of Dermatology and Venereology, Medical Center, University of Freiburg, Freiburg, Germany

[7] Institute for Immunodeficiency, Center for Chronic Immunodeficiency, Medical Center-University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

Introduction: Chronic inflammatory skin diseases driven by type 1 immune responses primarily affect the skin, hair, nails, and mucosa, with a substantial impact on patients' quality of life. Lichen planus (LP) and cutaneous lupus erythematosus (CLE) are two representative diseases characterized by a type 1-dominant immune response that induces keratinocyte cell death, resulting in the histopathological pattern known as interface dermatitis (ID). Despite recent advances in understanding their pathogenesis, no targeted therapies have yet been approved for these diseases.

Methods: In this study, we investigated the role of RIPK1-dependent necroptosis in type 1-driven inflammatory skin disease (ISD) using eclitasertib, a novel small-molecule kinase inhibitor of RIPK1, in human keratinocyte models of type 1 ISD and a murine model of TNF-α–driven systemic inflammation.

Results: First, we demonstrated that markers of necroptosis (RIPK1, RIPK3, MLKL) are specifically upregulated in LP and CLE and correlate with the severity of ID.

To assess the potential of targeting necroptosis, we tested the effects of eclitasertib on cell death, inflammation, and hypothermia. In a murine model of TNF-α–induced systemic inflammatory response syndrome, RIPK1 inhibition by eclitasertib restored body temperature when orally administered 15 minutes after TNF-α injection. In human models of type 1 ISD, RIPK1 inhibition prevented keratinocyte cell death and normalized epidermal architecture in three-dimensional skin equivalents upon stimulation with LP/CLE T-cell supernatant. Furthermore, RIPK1 inhibition resulted in decreased release of IL-1α, IL-1β, TNF-α, IL-8, and CCL20 from keratinocytes and three-dimensional skin equivalents. Finally, treating LP skin biopsies with the RIPK1 inhibitor ex vivo markedly reduced IFN-γ, TNF, CCL3, CXCL8, CXCL9, CXCL10, and CXCL11 gene expression and downregulated pathways associated with inflammation.

Conclusion: Thus, RIPK1 inhibition targets two central pathogenic mechanisms in LP and CLE: epidermal cell death and type 1–mediated skin inflammation.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 142

AI-Based Classification of Neutrophilic Dermatoses Using Serum Cytokine Profiles

Fischer, S.[1], Bonnekoh, H.[2,3], Gebala, J.[2,3], Butze, M.[2,3], Vera Ayala, C.[2,3], Kappelmann-Fenzl, M[1], Krause, K.[2,3], Frischbutter, S.[2,3]

1 Deggendorf Institute of Computer Science, Deggendorf, Germany

2 Institute for Allergology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

3 Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany

Introduction:
Neutrophilic dermatoses (NDs) are a heterogenous group of inflammatory skin diseases characterized by the accumulation of neutrophils in the skin in the absence of clinical infection. In most cases, neutrophilic dermatoses are associated with systemic disorders including hematological, autoimmune or autoinflammatory diseases. Patients present with polymorphic skin lesions including wheals, plaques, papules, nodules, pustules, abscesses, bullae and ulcers. Despite overlapping clinical and histopathological features, patient stratification and accurate diagnosis remain challenging due to the lack of reliable biomarkers and distinct diagnostic criteria.

Objective:
Development of an AI-based diagnostic model for improvement of disease classification and patient stratification in NDs based on serum cytokine profiles.

Methods:
Patients with the following NDs were included: pustular psoriasis (n=21), hidradenitis suppurativa (n=21), nodulocystic acne (n=12), pyoderma gangraenosum (n=13), Behcet's disease (n=8), adult onset Still's disease (n=15), Schnitzler syndrome (n=12) and healthy controls (n=22). Sera were obtained and a multiplex assay including 45 secreted mediators was performed. The mediators were categorized into Th1/Th2, Th9/Th17/Th22/Treg cytokines, inflammatory cytokines, chemokines, and growth factors. Data were evaluated using a supervised machine learning approach based on Random Forest algorithms to classify disease categories and determine cytokine feature importance.

Results:
Distinct cytokine expression patterns were observed across disease groups, reflecting disease-specific inflammatory signatures. The Random Forest model trained on cytokine expression data achieved a classification accuracy representing a threefold improvement over random prediction. In comparison, physician-based classification using 297 clinical diagnostic parameters reached 100% accuracy, confirming the internal consistency of the dataset and the feasibility of the AI approach. Feature importance analysis revealed disease-specific cytokine associations: IL-1β absence was most predictive for healthy controls, while its presence strongly contributed to classification of pustular psoriasis and acne. VEGF-A was a major discriminator for hidradenitis suppurativa and Schnitzler syndrome, whereas IL-1RA, IL-21, IL-2, MCP-1, and IFN-α expression was linked to other entities. These findings indicate that selected cytokines contribute differentially to disease classification and may serve as candidate biomarkers for future diagnostic refinement.

Conclusion:

This study demonstrates the potential of AI-assisted cytokine profiling to improve the classification and stratification of NDs. Although cytokine-based Random Forest models currently show moderate accuracy, integration with clinical and histopathological parameters may substantially enhance diagnostic precision. The identification of key cytokines with high discriminatory value provides a basis for future biomarker-driven diagnostic tools and supports the development of precision medicine approaches in NDs.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 143

Early Life Multi-Omics Analysis: Prenatal Enhanced Immunological Experience Protects Against Atopic Dermatitis

Amar, Y. [1]; Schellenberger, L. [1]; Kleigrewe, K. [2]; Schloter, M. [3]; Zink, A. [1]; Köberle, M. [1]; Kaesler, S. [1]; Biedermann, T. [1]

1 Technical University Munich, Department of Dermatology and Allergy Biederstein, Munich, Germany.

2 Technical University Munich, Bavarian Center for Biomolecular Mass Spectrometry, Munich, Germany.

3 Helmholtz Center Munich, Research Unit Comparative Microbiome Analysis, Munich, Germany.

Atopic dermatitis (AD) is a chronic inflammatory skin disorder affecting up to 20% of children and 5% of adults in industrialized countries. Characterized by a defective skin barrier and a Th2-biased immune response, AD frequently manifests in early infancy. Although its pathogenesis is increasingly understood, the precise factors driving AD development remain largely unknown. To address this gap, we established the Munich Atopy Prediction Study (MAPS), a prospective birth cohort including 407 mother/infant dyads. Within this sub-cohort, we aimed to identify early immune molecular signatures associated with AD development and elucidate key maternal factors influencing the foetal immune environment.

Infants' cord blood (CB) was collected at birth and peripheral blood (PB) was harvested at 3 years of age. Our multi-omics analysis involved investigating over 30 cytokines and chemokines, alongside in-depth metabolomics. We specifically focused on short chain fatty acids (SCFAs), well-documented for their immunomodulatory properties, assessing their levels in both CB of AD and healthy infants, and in the stool of their respective mothers. Additionally, we performed functional assays on infants' peripheral blood mononuclear cells (PBMCs), exposing them to various microbial stimuli (TLR2/6 ligands, *Staphylococcus aureus* from AD patients, and skin commensals) to assess differential responsiveness to potential dysbiotic triggers.

Counterintuitively, we observed an upregulation of the inflammatory response in CB samples of healthy infants compared to those who developed AD. This signature comprised a mixed Th2/Th1 response, notably involving the upregulation of IL-13, TNF-a, IFN-g, CXCL9, CXCL10, and CXCL11. In contrast, the cytokine and chemokine profiles of AD infants' PB at 3 years exhibited the canonical AD profile, characterized by an upregulation of Type 2 related signatures, including IL-5, IL-13, IL-22, CCL17, CCL22, along with CCL4 and CCL20. Consistent with the CB findings, the exposure of control infants' PBMCs to microbial triggers revealed a strong Th2/Th1 mixed response. Furthermore, although maternal gut microbiome composition was similar, its SCFAs functional profile differed and was traceable to the infants' CB, suggesting a potential influence on foetal programming. Our findings provide valuable insight into the early immune molecular markers associated with AD initiation. Specifically, they suggest that a prenatal enhanced immunological experience may protect against AD development, offering a crucial foundation for preventive strategies and biomarker identification.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 144

Modulation of Cutaneous Microbiota by Systemic Antibiotics and TNF-a/IL-17 Blockade in Hidradenitis Suppurativa Patients

Amar, Y. [1]; Regert, V. [1]; Niedermeier, S. [1]; Silva, RL. [1]; Foesel, BU. [2]; Kublik, S. [2]; Schloter, M. [2]; Köberle, M. [1]; Biedermann, T. [1]; Volz, T. [1]

1 Technical University Munich, Department of Dermatology and Allergy Biederstein, Munich, Germany
2 Helmholtz Center Munich, Research Unit Comparative Microbiome Analysis, Munich, Germany.

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease characterized by deep-seated painful nodules, abscesses, sinus tracts, and scarring. Although the exact pathogenesis has not yet been conclusively uncovered, a multifactorial genesis involving genetic predispositions, lifestyle factors, and the microbiome is hypothesized. This study investigated the cutaneous microbiome dysbiosis in HS patients and evaluated for the first time the effects of three often-prescribed therapeutics on its composition. The treatments consisted of a combination of two antibiotics (ATB) (Clindamycin/Rifampicin), and two biologics: Adalimumab (Ada) targeting TNF-a, and Secukinumab (Sec) targeting IL-17A. Skin swabs were collected on the lesional (L) and non-lesional (NL) skin from 52 HS patients at baseline and 12 weeks following therapy. Additionally, 26 age- and gender-matched healthy subjects were sampled on the same skin areas, and the collected swabs were analyzed using 16S rRNA sequencing.

We found that HS patients have a significantly altered skin microbiota, characterized by increased relative abundances of anaerobic bacteria such as *Finegoldia magna*, *Peptoniphilus grossensis*, and *Fenollaria massiliensis*. Commensal bacteria such as *Cutibacterium acnes*, *Staphylococcus hominis*, and *Staphylococcus epidermidis* were significantly reduced. Notably, *Campylobacter urealyticus*, an animal gut-associated microbe, was also detected on lesional HS skin. The investigated treatments, particularly the antibiotic combination and Secukinumab, led to noticeable changes in the lesional skin microbial composition without affecting non-lesional HS skin. Consistent with this, they slightly increased the microbial richness on both L and NL skin. The ATB combination noticeably decreased the proportions of the pathogens *C. urealyticus*, *F. massiliensis*, *L. clevelandensis* but had no impact on key skin commensals including *S. hominis*, *C. acnes* and *S. epidermidis*. Furthermore, the ATB treatment resulted in a significant increase in the proportions of the skin commensal *C. tuberculostearicum*.

In contrast, Ada and Sec were unable to reduce the pathogen proportions and even led to a slight decrease in *S. epidermidis* and *S. hominis* abundances. We report that systemic antibiotic therapy is the most effective approach among the investigated treatments for correcting HS dysbiosis by significantly reducing pathogens load while preserving key commensals. This highlights the essential, albeit temporary, role of anti-microbial components in HS treatment. Future studies should focus on the functional consequences of this dysbiosis to develop durable, personalized therapeutic strategies that precisely modulate the HS microbiome. Validation in a larger cohort is necessary.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 145

Regulation of the interaction between innate and adaptive immunity by ATF3

Knoll, M.[1]; Heneka, Y.M.[1]; Holstein, J.[1]; Reinknecht, S.[1]; Brueck, J.[2]; Yazdi, A.S.[3]; Roecken, M.[1]

1 Eberhard Karls University Tuebingen, Department of Dermatology, Tuebingen, Germany

2 University Medical Center Mainz, Department of Nuclear Medicine, Mainz, Germany

3 RWTH Aachen, Department of Dermatology and Allergology, Aachen, Germany

During the fast response of innate immunity, immature Antigen Presenting Cells (APC) are stimulated by innate signals into a mature state, in which they are able to prime naïve T cells initiating an adaptive immune response. These innate signals include cytokines like IL-1, IL-6 and TNF activating and shaping the adaptive immune response. A strong or even harmful innate immune response during autoinflammation, for example, is normally not resulting in a response of the adaptive immune system. Yet, the regulatory mechanisms controlling the induction of innate signals and the decision of inducing or preventing adaptive immunity are still poorly understood and remain elusive. The Activating Transcription Factor 3 (ATF3) is among the first molecules being activated in response to innate stimuli, thereby suppressing key innate molecules and cytokines preventing an excessive inflammatory reaction. We have previously shown that the loss of ATF3 results in an aberrant sensitivity towards innate signals, prompting us to study the effects of ATF3 on the persistence of innate and of T cell-mediated immune responses *in vivo*.

Using a model of Contact Hypersensitivity Reactions (CHSR), we deeply characterized the regulatory function of ATF3 on the expression of key cytokines during the sensitization and elicitation phases, representing the initiation of the innate immunity and the transition to the adaptive immune response. Using TNCB, *Atf3*$^{-/-}$ or wt mice were sensitized at the abdomen and subsequently challenged at the ear. Following TNCB sensitization, mRNA levels of *Il1b*, *Il6* and *Il12a* increased during the first 24 hours significantly faster and stronger in the abdominal skin of *Atf3*$^{-/-}$ mice compared to wt mice. While *Il1b* and *Il6* expression levels decreased already after 6 hours, elevated levels of *Il12a* mRNA persisted up to 24 hours in *Atf3*$^{-/-}$ mice. *Tnf* expression was highest after 24 hours. In sharp contrast, during the TNCB challenge the T cell-associated cytokine *Ifnγ* and the IFNγ-induced chemokines *Cxcl10* and *Cxcl9* were strongly reduced in ear tissue of *Atf3*$^{-/-}$ mice as compared to wt mice. To determine whether ATF3 affected directly the activation of the adaptive immunity, we analysed CD4^{+} T cells isolated from the ear draining lymph nodes. CD4^{+} T cells from wt mice expressed *Il2*, *Ifnγ* and the IFNγ-induced chemokines *Cxcl10* and *Cxcl9*, while they were strongly reduced in CD4^{+} T cells from draining lymph nodes of *Atf3*$^{-/-}$ mice.

In vitro, we investigated the role of ATF3 in antigen presentation and CD4^{+} T cell activation. Cultures of LPS-stimulated and OVA-loaded *Atf3*$^{-/-}$ or wt DCs together with OTII-CD4^{+} T cells revealed lower levels of *Il2*, *Ifnγ* and *Il4* cytokines upon co-culture with *Atf3*$^{-/-}$ DCs. To determine the cause for the reduced capacity of ATF3-deficient DCs to stimulate CD4^{+} T cells, we analysed the effect of ATF3 during LPS-mediated DC maturation. Indeed, *Atf3*$^{-/-}$ DCs showed an aberrant morphology with an irregular shape, underdeveloped dendrites and disturbed actin distribution.

In summary, these data suggest that ATF3 regulates the interplay of innate and adaptive immunity. Whild attenuating innate immune responses, expression of ATF3 seems to be necessary to allow activated APCs to prime naïve T cells for adaptive T_H1 immune responses. These and other data thus show that absence of ATF3 promotes a state of autoinflammation with attenuated T cell activation.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 146

TDRKH-mediated piRNA regulation sustains pro-inflammatory M1 macrophage polarization in psoriasis

Zou, Y[1,2]

1.Department of Dermatology, Venereology and Allergology, University Medical Center Göttingen, Göttingen, Germany.

2.Department of Dermatology, Renmin Hospital, Hubei University of Medicine, Shiyan, P.R.China

Background
Psoriasis is a chronic inflammatory skin disease with a strong genetic component, yet how susceptibility genes translate into cell-specific inflammatory programs remains incompletely understood.

Methods
To identify causal genes and downstream regulatory mechanisms, we integrated transcriptome-wide association analysis and summary-data-based Mendelian randomization. Long-read sequencing was used to characterize alternative splicing and alternative polyadenylation (APA) of candidate genes. Single-cell RNA sequencing was applied to resolve cell-type–specific expression patterns in psoriatic lesions. Functional validation was performed using in vitro M1 macrophage models focusing on piRNA-mediated regulation.

Results
Genetic analyses identified TDRKH as a robust psoriasis susceptibility gene across multiple tissue contexts. Long-read sequencing revealed pronounced APA changes of TDRKH, characterized by 3′UTR lengthening associated with increased mRNA stability in patients. Single-cell analysis demonstrated marked infiltration of pro-inflammatory M1 macrophages in psoriatic lesions, with high TDRKH expression in this subset and activation of the IL-23/IL-17 inflammatory axis. Functional experiments showed that TDRKH knockdown reshaped the piRNA landscape in M1 macrophages, leading to reduced expression of specific piRNAs targeting anti-inflammatory regulators, including STAT6 and PPARγ, thereby attenuating the pro-inflammatory phenotype.

Conclusions
Our study identifies TDRKH as a genetically driven regulator linking alternative polyadenylation to piRNA-mediated post-transcriptional control of macrophage polarization in psoriasis. These findings provide a mechanistic framework connecting genetic susceptibility to sustained inflammation and highlight the TDRKH–piRNA axis as a potential translational target in psoriasis.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 147

The role of liquid biopsy and circulating cell-free DNA as a potential biomarker for disease severity and treatment response in psoriasis

Agata Baldyga[1]; Kathrina Meier[1]; Nawa Arif[1]; Christoph Zeyen[1]; Maria Kinberger[1]; Sonja Molin[1]; Sonja Leson[1]; Kamran Ghoreschi[1]; Franz Joachim Hilke[1]
[1]Department of Dermatology, Venereology and Allergology, Charite – Universitaetsmedizin Berlin, Germany

Introduction
Psoriasis is a chronic inflammatory disorder of the skin and joints, characterized by immune dysregulation, keratinocyte hyperproliferation, and persistent inflammation. Increasing evidence indicates that this cutaneous process is accompanied by systemic inflammatory activity, reflected by elevated circulating cell-free DNA (cfDNA) levels that correlate with disease severity and treatment response. cfDNA consists of short, non-encapsulated DNA fragments (~166 bp) released upon cell death and serves as a surrogate marker of tissue damage and immune activation. In psoriasis, cfDNA is thought to originate mainly from keratinocytes and neutrophil extracellular traps, linking epidermal turnover and systemic inflammation. These properties make cfDNA an attractive liquid biopsy target, offering a minimally invasive means to quantify inflammatory burden, monitor therapeutic response, and explore cell-of-origin through methylation signatures.

Methods
This study aimed to quantify circulating cfDNA levels in a German psoriasis cohort and assess their relation to disease severity (PASI), subtype, duration, and treatment response. Psoriasis-related cfDNA fragments carrying TNFα, KRT14, and KRT6A sequences, as well as keratinocyte-derived methylation signatures, were explored using the tissue-specific methylation atlas of Loyfer et al. A total of 91 psoriasis patients (56 vulgaris, 32 arthritis, 3 pustulosis) and 12 healthy controls were included. cfDNA was isolated from plasma (QIAamp MinElute ccfDNA Midi Kit) and quantified by Qubit fluorometry; target detection was performed via digital droplet PCR (ddPCR). Nanopore sequencing was initiated to characterize tissue-specific methylation and enable cell-of-origin analysis. Patients were followed longitudinally (baseline–week 36) according to therapeutic regimen (topical, systemic, biologic).

Results
cfDNA concentrations were significantly elevated in psoriasis patients compared to controls, with a trend toward higher values in psoriatic arthritis, independent of cutaneous involvement. Levels were also higher in patients with a positive family history. cfDNA correlated with PASI, subtype, and disease duration. Across follow-up, cfDNA displayed a reproducible biphasic pattern: levels rose during the first four weeks of therapy, declined toward week 16 but remained above baseline, and increased again by weeks 24–36. This pattern was observed across subtypes and independent of baseline severity. Targeted ddPCR confirmed TNFα, KRT14, and KRT6A cfDNA fragments, with KRT14 most abundant and showing a trend toward higher copy numbers in more severe baseline disease. Nanopore-based methylation profiling revealed distinct cfDNA cell-of-origin patterns in psoriasis, characterized by higher macrophage and NK cell contributions.

Discussion
These findings highlight cfDNA-based liquid biopsy as a sensitive, non-invasive biomarker for psoriasis disease activity. Integrating quantitative, targeted, and epigenetic cfDNA profiling may enhance disease stratification and longitudinal monitoring, paving the way for personalized disease management.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Abstract-ID: 148

Integrated Proteomic and Transcriptomic Profiling Reveals Site-Specific Inflammatory and Barrier Pathways in Psoriasis

Hyun Joon Lee[1]; Katharina Meier[1]; Kamran Ghoreschi[1]; Franz Joachim Hilke[1]
[1] Department of Dermatology, Venereology and Allergology, Charité – Universitätsmedizin Berlin, Germany

Background
Psoriasis vulgaris manifests in distinct anatomical regions that differ in morphology and therapeutic responsiveness. Although modern biologic therapies have markedly improved overall disease control, lesions in specific sites, such as the scalp, inverse, and palmoplantar areas, frequently show delayed or incomplete resolution compared to classical plaque sites. The biological basis of this regional heterogeneity remains insufficiently understood, and the concept of “hard-to-treat” psoriasis continues to reflect clinically observed treatment challenges rather than an intrinsic resistance to therapy.

Objective
To delineate shared and site-specific molecular programs underlying regional heterogeneity in psoriasis through integrated proteomic and transcriptomic analyses of classical and clinically difficult-to-treat lesions.

Methods
Formalin-fixed, paraffin-embedded skin biopsies were collected from 12 classical plaques, 12 difficult-to-treat plaques (scalp, inverse, palmoplantar; n = 4 each), and 14 healthy controls. Proteomic profiling was performed by label-free liquid chromatography–mass spectrometry (LC–MS), and data were analyzed with DIA-Analyst, followed by pathway enrichment (GO, KEGG, Reactome) to define protein-level alterations. In parallel, whole-transcriptome sequencing (Illumina 150-bp paired-end) was used to quantify differential gene expression (edgeR; FDR < 0.05; $|\log_2 FC| > 1$) and assess transcriptional pathway activity. Integrative concordance analyses were conducted to identify site-associated molecular signatures shared across both datasets.

Results
Quantitative proteomic profiling identified 5,174 proteins, and RNA sequencing revealed 4,032 differentially expressed genes (DEGs) between psoriatic and healthy skin. Principal component analysis clearly separated psoriatic from healthy samples, while classical and difficult-to-treat plaques clustered closely, consistent with a conserved inflammatory core characterized by keratinocyte hyperproliferation, cornified envelope formation, and innate immune activation. Comparative analyses revealed additional, site-specific molecular adaptations in difficult-to-treat regions, including upregulation of keratinocyte activation markers (KRT14, KRT17), inflammatory mediators (SERPINB2), interferon-inducible effectors (TAP2, DDX60), an oxidative stress regulator (CYGB), and barrier-associated proteins (KLK11, GBA2, MPZL2). Concordant upregulation of KRT14, DDX60, and MPZL2 across both datasets indicates coordinated dysregulation of keratinocyte, interferon, and barrier pathways—particularly involving altered lipid metabolism and proteolytic activity. By contrast, classical plaques showed concordant upregulation of LDHAL6B.

Conclusion
Psoriasis lesions across anatomical sites share a fundamental inflammatory architecture but exhibit region-specific molecular adaptations shaped by local microenvironmental pressures. Difficult-to-treat regions display enhanced interferon signaling, oxidative stress responses, and epidermal barrier remodeling, which may contribute to their reduced therapeutic responsiveness. Ongoing spatial proteomic analyses aim to map cell-type–specific protein localization and refine the mechanistic understanding of regional psoriasis heterogeneity.

Kategorie: Psoriasis & Inflammatory skin diseases
Präsentationsart: Poster

Skin biology and tissue remodelling

Abstract-ID: 149

Influence of extracellular adenosine on growth and differentiation of dermal fibroblasts and on leukocyte-fibroblast-cocultures.

Arnold V.[1]; Ring S.[1]; Alabdullah M.[1]; Enk A.[1]; Mahnke K.[1]

1 Heidelberg University Hospital, Department of Dermatology, Heidelberg, Germany

Adenosine plays a key role in modulating inflammation and tissue repair in the skin. It is generated by conversion of extracellular adenosine-5'-monophosphate (AMP) by CD73 (ecto-5'-nucleotidase). Dermal fibroblasts actively contribute to innate immunity and skin homeostasis through cytokine release and interaction with immune cells. It is still unclear, how the signaling via Adenosine 2A receptors (A2AR) in fibroblasts influences inflammatory responses, extracellular matrix remodeling, and wound healing processes.
To investigate this, primary dermal $CD140a^+CD90.2^+Vimentin^+$ fibroblasts were isolated from C57BL/6N (WT), $CD73^{-/-}$ and $A2AR^{-/-}$ mouse ears. *In vitro* cultured fibroblasts were stimulated with 100ng/mL lipopolysaccharide (LPS) to mimic inflammation and 1mM AMP was added. Under these conditions WT and $A2AR^{-/-}$ fibroblasts produced equal amounts of adenosine, while $CD73^{-/-}$ fibroblasts did not produce any.
All fibroblast lineages produced IL-6 and CXCL-1 in response to LPS. However, $A2AR^{-/-}$ fibroblasts grew faster and produced more IL-6, Collagen I and CXCL-1, suggesting an exaggerated response to inflammation leading to fibrosis. To investigate functional effects, leukocyte recruitment was explored in Boyden chambers. Recruitment of $Ly6G^+Ly6C^+$ cells as well as of $CD3^+$ T cells was higher in fibroblast cultures than in medium controls throughout all conditions, but differences were apparent between individual fibroblast lines. $A2AR^{-/-}$ fibroblasts recruited the most $CD45^+$ cells followed by WT and $CD73^{-/-}$ fibroblasts. Under stimulatory conditions, AMP supplemented WT fibroblast cultures recruited less $CD45^+$ cells as compared to controls without AMP supplementation. Thus, these data indicate that triggering of the A2AR by CD73-produced adenosine suppresses leukocyte recruitment. Interestingly, there were no differences between the fibroblast lineages in the activation of $Ly6G^+Ly6C^+$ isolated from bone marrow, but all displayed increased activation compared to the controls, showing the importance of fibroblasts for recruiting immune cells in general. Furthermore, all fibroblast lines were tested for their capacity to suppress T cell proliferation in vitro. Here, WT fibroblasts suppressed the activation of $CD8^+$ cells when stimulated with LPS in the presence of AMP. However, this doesn't seem to be a direct effect of adenosine on $CD8^+$ T cells, as $CD73^{-/-}$ fibroblasts suppressed T cells activation equal to WT fibroblasts. Nevertheless, as $A2AR^{-/-}$ fibroblasts failed to suppress T cell activation, we concluded that triggering its own adenosine receptor is necessary to convey T cell suppressive effects in fibroblasts.
In conclusion, dermal fibroblasts play a major role in the immune system and recruit and activate leukocytes via cytokines and chemokines. Fibroblasts that are unable to sense adenosine, due to lack of the A2A receptors, show excessive pro-inflammatory actions. Since leukocytes come in close contact to fibroblasts on their way to dermal injury and inflammation, fibroblasts and their AMP-to-adenosine turnover could be a potential target in wound healing or immune system related skin diseases.

Kategorie: Skin biology and tissue remodelling
Präsentationsart: Poster

Abstract-ID: 150

The dermal extracellular matrix protein cochlin establishes a skin-autonomous antibacterial defense axis via c-MET

Bao, X.[1,2]; Nyström, A.[1]

1 Medical Center - University of Freiburg, Department of of Dermatology, Freiburg, Germany

2 University of Freiburg, Faculty of Biology, Freiburg, Germany

The extracellular matrix protein cochlin, through its N-terminal LCCL domain, activates innate immunity in the inner ear and at infection sites via an unclear mechanism. We previously linked elevated LCCL domain levels to reduced bacterial burden in the skin.

Here, we investigated its mechanism of action in skin. Epidermal keratinocytes, but not macrophages or fibroblasts, were identified as the primary Cochin LCCL domain-responding cells. Mechanistically, the LCCL domain bound to c-MET, triggering EGFR signaling through activation of the protease ADAM17. This cascade led to the production of antimicrobial peptides and cytokines, followed by immune cell recruitment.

Signaling induced by the cochlin LCCL domain was distinct from that of HGF, accounting for functional differences observed between HGF and the LCCL domain upon c-MET activation. Inhibition of the c-MET–ADAM17–EGFR axis abolished the broad antibacterial activity of the LCCL domain in skin, as demonstrated by 16S rDNA amplicon sequencing.

Importantly, the spatial separation we identify between cochlin – expressed by papillary dermal fibroblasts and fibroblasts associated with hair follicles – and c-MET – expressed by basal epidermal keratinocytes – establishes an antibacterial axis that becomes active only upon injury or barrier disruption.

Collectively, our findings identify a novel, skin-autonomous, and therapeutically exploitable antibacterial system.

Kategorie: Skin biology and tissue remodelling
Präsentationsart: Poster

Abstract-ID: 151

Assessing the Regenerative Potential of Recombinant Leukemia-Inhibiting Factor (LIF) on Wound Healing in 3D in vitro Skin Models

Hoeppel, A.[1] Ramadani, A.[2] Stueve, P.[2] Ritter, U.[2] Feuerer, M.2 Szepanowski, L.-P.[3] Groeber-Becker, F.[1+3] Groneberg, D.[1]

1Fraunhofer-Institute for Silicate Research ISC, Würzburg, Germany
2Leibniz Institute for Immunotherapy, Regensburg, Germany
3University Hospital Düsseldorf, Heinrich-Heine-University, Department of Ophthalmology, Düsseldorf, Germany

Abstract:
Impaired cutaneous wound healing remains a significant clinical challenge, necessitating novel therapeutics that can accelerate re-epithelialization and restore the skin's barrier function. Successful repair requires coordinated cell migration, proliferation and differentiation. Therefore, advanced in vitro platforms, including three-dimensional (3D) skin models are essential for screening and validating potential treatments.

In this context, the leukemia inhibitory factor (LIF) is a pleiotropic cytokine belonging to the IL-6 family. During injury and inflammation, LIF is induced in multiple cell types, including keratinocytes, fibroblasts, endothelial cells, monocytes\/macrophages and T cells. It modulates inflammatory responses while supporting epithelial cell survival, migration and proliferation, thereby contributing to tissue homeostasis and repair.

The Translational Center for Regenerative Therapies at the Fraunhofer Institute for Silicate Research (ISC) (TLC-RT) has developed various 3D skin equivalents, including reconstructed human epidermis (RHE), full-thickness skin equivalents (ftSE), and hiPSC-derived skin organoids. A key advantage of these models is their ability to form a fully stratified epidermis, a functional barrier, and an induced basal lamina, thus closely mimicking human skin architecture.

To address wound healing, fully differentiated 3D skin models were mechanically wounded using a defined biopsy punch to create a standardised defect. To investigate its therapeutic potential, recombinant LIF was administered systemically at defined concentrations. We compared two distinct application kinetics: (1) continuous exposure and (2) a pulsatile regimen. The pulsatile approach was designed to mimic the transient, dynamic signalling characteristic of endogenous cytokine release during natural healing. Wound closure and tissue regeneration were monitored over 14 days using a multi-parametric approach. Functional barrier recovery was quantified using impedance spectroscopy (TEER). Structural healing and re-epithelialization were monitored non-invasively by optical coherence tomography (OCT). Cytotoxicity and metabolic viability were assessed using LDH and MTT assays, respectively. Finally, terminal histological analysis (H&E staining) was used to confirm tissue architecture, stratification and wound closure.

This study aimed to determine the optimal concentration of recombinant LIF and, critically, its application kinetics (pulse versus continuous) for promoting cutaneous wound healing. By correlating functional data (TEER) with structural analysis (OCT and H&E staining) and cell health (LDH and MTT assays), this work seeks to validate LIF as a potent, non-cytotoxic candidate for advanced regenerative therapies.

Kategorie: Skin biology and tissue remodelling
Präsentationsart: Poster

Abstract-ID: 152

Dynamic, disease-progression dependent pro-fibrotic response of dermal fibroblasts in RDEB – Insights to pathomechanisms and treatments

Bing Hang[1], Alexander Nyström[1]

1 University of Freiburg, Department of Dermatology, Freiburg, Germany

Recessive dystrophic epidermolysis bullosa (RDEB) is a rare disease caused by pathogenic variants of the *COL7A1* gene encoding type VII collagen (COL7). In RDEB COL7 deficiency leads to a decrease in dermal cohesion strength, resulting in increased skin fragility and secondary damage. The clinical features for RDEB include congenital skin and mucosal blisters and subsequent formation of mutilating deformities in which fingers and toes are wrapped in scars. Previous studies showed that progressive dermal fibrosis is driven by injury and inflammation and that this process appears to be mediated by the dermal fibroblasts. Our project aims to investigate potential, dynamic changes in activity and function of fibroblast at different stage of RDEB.

To investigate fibroblast phenotypic transitions in RDEB, we analyzed dermal fibroblasts derived from young and adult donors. Western blot analysis revealed that adult-donor RDEB fibroblasts exhibited higher expression of tenascin-C (TnC), a marker of dermal fibrosis, but lower levels of α-smooth muscle actin (αSMA), a marker of contractive activity, compared to young fibroblasts. Consistently, immunofluorescence staining of skin samples from RDEB donors and fibrotic sites in RDEB model mice showed stronger αSMA expression in young tissues than in adult tissues. Collagen-gel contraction assays further demonstrated that young RDEB fibroblasts possessed greater contractile capacity than adult fibroblasts.

To explore the molecular mechanisms underlying these differences, we performed receptor cytokine and tyrosine kinase (RTK) array analyses. Through these, we identified an intrinsically increased synthesis of selected inflammatory factors, including IL8, and an increased abundance of EGFR in adult RDEB fibroblasts. Notably, however, EGFR activation was not enhanced compared with young donors, which was also consistent with higher CXCL10 levels – a chemokine normally suppressed by EGFR activity. Subsequent stimulation and inhibition experiments using the canonical EGFR ligand EGF and the EGFR inhibitor AG1478 revealed a direct link between EGFR signaling and increased αSMA expression, while inhibition of EGFR reduced αSMA but upregulated TnC and fibronectin.

These findings indicate that EGFR-related signaling plays a key role in regulating fibroblast activation and phenotypic switching during RDEB progression. This study highlights EGFR as a potential therapeutic target for modulating fibroblast function and improving tissue remodeling in RDEB.

Kategorie: Skin biology and tissue remodelling
Präsentationsart: Poster

Abstract-ID: 153

COL23A1 may regulate keratinocyte differentiation and extracellular matrix remodelling: a bulk transcriptomic perspective

Chopra, S.[1]; Traidl, S.[1,2]; Roesner, L. M.[1,2]; Döhner, K.[1,2]; Werfel, T.[1,2]

1 Department of Dermatology and Allergy, Hannover Medical School, Hannover, Germany

2 Cluster of Excellence RESIST (EXC 2155), Hannover Medical School, Hannover, Germany.

Collagen XXIII alpha 1 chain (COL23A1) is a type II transmembrane protein predominantly expressed on keratinocytes within the basal layer of the epidermis. It is also produced by fibroblasts in the adjacent papillary dermis, positioning COL23A1 at the epidermal-dermal interface. In the epidermis, integrin α2β1 serves as a receptor for COL23A1, mediating key processes such as cell adhesion, migration, and extracellular matrix (ECM) interactions that are essential for maintaining epidermal homeostasis and overall skin architecture.

Elevated COL23A1 expression is associated with a higher risk of several cancers, where it promotes metastasis by enhancing anchorage-independent growth and reinforcing cell-cell and cell-matrix adhesions. Recently, we identified a novel role for COL23A1 in eczema herpeticum (EH), a severe viral skin infection that typically occurs in individuals with pre-existing inflammatory skin conditions such as atopic dermatitis (AD). We demonstrated that increased COL23A1 expression enhances keratinocyte susceptibility to herpes simplex virus type 1 (HSV-1) infection by upregulating cell surface viral entry factors while suppressing antiviral defenses. Since the differentiation state of keratinocytes influences HSV-1 infection as well, with undifferentiated cells being more permissive, we explored whether COL23A1 overexpression affects keratinocyte differentiation along with ECM composition.

We reanalyzed our previously published bulk RNA-sequencing data (GSE278244) from *COL23A1* overexpressing HaCaT cells and controls. *COL23A1* overexpression was associated with transcriptional upregulation of basal and early differentiation keratins, including *KRT14* and *KRT15*, suggesting a shift toward a basal-like phenotype. Notably, *RNASE7* expression was downregulated, consistent with its higher expression in differentiating compared to proliferating keratinocytes. Reduced *RNASE7* levels could therefore contribute to weakened antimicrobial and antiviral defenses in *COL23A1* overexpressing cells.

ECM-associated genes such as *COL6A1*, which supports cell adhesion and basement membrane integrity, and *GJB2* (Connexin-26), which mediates intercellular communication in basal and suprabasal layers, were also upregulated. In addition, the *MMP1* and *KLK11* genes, encoding a matrix metalloproteinase that regulates ECM turnover and a kallikrein family member involved in epidermal proteolysis and barrier maintenance, respectively, were elevated, indicating active ECM remodelling dynamics. Interestingly, *TFPI* and *TFPI2* genes, which encode protease inhibitors, were downregulated, suggesting a potential loss of feedback control during tissue remodelling.

In summary, our findings indicate that elevated *COL23A1* expression may reprogram keratinocytes toward a transcriptional state defined by basal-like phenotype and enhanced ECM activity. This basal-like shift along with reduced *RNASE7* expression could further explain why *COL23A1* overexpressing keratinocytes are more easily infected with HSV-1. However, experimental confirmation is required and further validation in 3D skin models will be essential to clarify the functional impact of COL23A1 on epidermal differentiation and tissue remodelling. These studies may also help elucidate how elevated COL23A1 expression, which we could show earlier in a subgroup of AD patients, further contributes to EH susceptibility in AD patients.

Kategorie: Skin biology and tissue remodelling
Präsentationsart: Poster

Abstract-ID: 154

Mechanotransduction-driven epidermal barrier defects in skin chronic inflammatory diseases

Dianyu Cao[1,2], Svenja Kleiser[1,2], Ramin Omidvar[2], Christine Gretzmeier[1], Winfried Römer[2], David Ranzinger[1], Dimitra Kiritisi[1,3], Alexander Nyström[1]

[1]Medical Center – University of Freiburg, Department of Dermatology, Freiburg, Germany

[2]Facuty of Biology, University of Freiburg, Freiburg, Germany

[3] First Department of Dermatology, *Aristotle University of Thessaloniki, Thessaloniki, Greece*

Fibrotic reactions and ensuing skin stiffening occur in a wide range of chronic injury-induced and inflammatory skin diseases. In such conditions, epidermal changes including hyper- or parakeratosis, dysregulated epidermal differentiation, and barrier dysfunction occur. These changes have frequently been attributed to inflammation, while the contribution of keratinocyte-intrinsic responses to the biochemically and mechanically altered microenvironment has been less explored. The aim of this work was to address how injury- and inflammation-induced chemo-biomechanical alterations sensed by keratinocytes contribute to epidermal dysfunction.

Toward this end, we first established the genetic disease *dystrophic epidermolysis bullosa* (DEB) as a model with predictable and directional stiffening of the epidermal basement membrane zone. Using atomic force microscopy in combination with immunohistological and lipidomic analyses on DEB model mice across disease progression, we determined that mechanical stiffening precedes dysregulated epidermal activation, eventually leading to barrier disruption. The findings were validated in human DEB and, importantly, in eczema samples, including atopic dermatitis. Along with basement membrane zone stiffening, deposition of injury- and inflammation-associated fibronectin occurred in both DEB and eczema.

Based on this, we devised a reductionist model replicating disease progression using collagen hydrogels of defined stiffnesses (1.5 kPa to 4.2 kPa) coated with fibronectin, representing homeostatic and disease-advancing stiffnesses, respectively. Epidermal development by human healthy donor keratinocytes seeded on such hydrogels and airlifted replicated the observed changes in human skin, with impaired barrier formation occurring on the stiffer hydrogels. Signaling analyses identified integrin α5β1–epidermal growth factor receptor–YAP-mediated activation of c-Jun N-terminal kinase (JNK) and subsequent STAT1 activation in basal keratinocytes sensing fibronectin on increasing stiffness. This activation was associated with dysregulated epidermal activity and improper barrier formation *in vitro*. Inhibition of the identified pathway using CC90001 and upadacitinib, targeting JNK and JAK1–STAT1 respectively, restored epidermal barrier formation on stiff hydrogels. Lastly, repurposing upadacitinib improved epidermal appearance in the context of dermal stiffening occurring in morphea.

Collectively, we identified that keratinocyte-intrinsic responses to epidermal basement zone stiffening occurring in an injured environment contribute to epidermal barrier defects, which can be restored by targeting the cellular stiffness response.

Kategorie: Skin biology and tissue remodelling
Präsentationsart: Poster

Abstract-ID: 155

Mimicking human skin in REAL: realistic, ethical, automated and layered

Amelie Reigl[1,2,3] Saskia Zöphel[1,4] Nina Köder [1,3] Pauline Klose,[1,3], Lynn Flütter[1,3], Johanna Scherer[1,3,5], Shanice Gundel[1], Anna-Sophie Hauser[1,3], Anika Höppel[1,3], Tobias Weigel[1], Maximilian Schinke, Nico Lachmann[6], Florian Groeber-Becker[1,2,3,7] and Dieter Groneberg, [1,2,3]

1 Translational Center for Regenerative Therapies, Fraunhofer-Institute for Silicate Research ISC, Würzburg, Germany

2Fraunhofer Project Center for Stem Cell Process Engineering, Würzburg, Germany

3 TigerShark Science, Project Group at Fraunhofer ISC, TLZ-RT, Würzburg, Germany

4 Interdisciplinary Center for Clinical Research IZKF, University Hospital Würzburg, Würzburg, Germany

5Institute of Anatomy and Cell Biology, Julius-Maximilians University Würzburg, Germany

6 Fraunhofer Institute for Toxicology and Experimental Medicine ITEM, Hannover Germany

7 Department of Ophthalmology, University Hospital Düsseldorf, Heinrich-Heine-University, Germany

Human induced pluripotent stem cell (hiPSC)-derived skin organoids represent a major advancement for modelling skin biology and disease in vitro. These organoids reproduce the complexity of native human skin, including appendages such as hair follicles and sebaceous glands, providing a physiologically relevant environment compared to conventional 2D or traditional models.

Our work aims to overcome current limitations of organoid systems, such as inside-out orientation, absence of vasculature, and lack of immune components by developing an automated and standardized differentiation and cultivation process to generate functional, correctly oriented skin organoids. We established an semi-automated differentiation workflow and long-term cultivation in a bioreactor, producing skinorganoids with all important cell types (keratinocytes, melanocytes, fibroblasts, adipocytes) and structures like hair follicles with reduced hands-on time. Furthermore, we developed a static air–liquid interface (ALI) culture on porous nanofibers to mimic the physiological environment and induce correct tissue orientation. After 28 days at the ALI, organoids displayed a mature epidermal barrier with marker expression of CK5 and CK1 for basal and differentiated keratinocytes, as well as loricrin and ZO-1 for barrier integrity. Hair follicle formation was confirmed by Ki67, CK17, and E-cadherin staining.

Our research demonstrates that automation, bioreactor-based cultivation, and ALI culture on specialized nanofibers significantly enhance the reproducibility and functionality of in *vitro skin* organoids. These advances enable their application across diverse research contexts, including disease modelling, skin fibrosis, wound healing, melanoma studies, innervation research, and skin-on-chip systems.

Kategorie: Skin biology and tissue remodelling
Präsentationsart: Poster

Abstract-ID: 156

Modeling skin innervation in advanced human 3D *in vitro* skin models

Scherer; J.[1,2,3]; Zöphel, S.[1,4]; Reigl A.[1,2]; Köder, N.[1,2]; Klose, P.[1,2]; Höppel, A. [1,2]; Flütter, L.[1,2,3]; Groeber-Becker, F.[1,5]; Groneberg, D.[1,2] and Wörsdörfer, P.[6]

1 Translational Center for Regenerative Therapies TLZ-RT, Fraunhofer-Institute for Silicate Research ISC, Würzburg, Germany
2 TigerShark Science, Project Group at Fraunhofer ISC, TLZ-RT, Würzburg, Germany
3 Institute of Medicine and Biology, Julius-Maximilians-University, Würzburg, Germany
4 Interdisciplinary Center for Clinical Research IZKF, University Hospital Würzburg, Würzburg, Germany
5 Department of Ophthalmology, University Hospital Düsseldorf, Heinrich-Heine-University, Germany
6 Institute for anatomy and cell biology, Julius-Maximilians-University Würzburg

The interaction between the nervous system and the skin plays a crucial role in maintaining cutaneous homeostasis and modulating inflammation, wound healing, and sensory perception. However, conventional in vitro skin models often lack innervation, limiting their ability to accurately mimic physiological and pathological processes involving neurocutaneous communication.

In our work, we were able to build a full-thickness skin equivalent from human primary fibroblasts and keratinocytes with integrated neural organoids containing both peripheral and central nervous system components. Using immunofluorescence analysis, we confirmed that the neural organoids were successfully integrated into the dermis of the full-thickness skin equivalent, with outgrowing nerve fibers in the dermis. Furthermore, immunofluorescence staining revealed nerve fibers near the epidermis that showed improved differentiation.

In addition to full-thickness skin models, we generated three-dimensional skin organoids from human induced pluripotent stem cells (hiPSCs) that more accurately replicate native skin architecture. Within these hiPSC-derived skin organoids, we characterized a spectrum of skin-specific cell types, including keratinocytes (CK5), dermal cells (vimentin), and adipocytes (Nile Red), but lacking skin innervation. With the addition of neural organoids, we achieved innervation of the skin organoids, with nerve fibers penetrating the epidermis and mimicking free nerve endings. This was demonstrated by light sheet microscopy and immunofluorescence staining. Additionally, nerve fibers in the dermis were accompanied by Schwann cells and even showed the beginning of myelination, analyzed by transmission electron microscopy and immunofluorescence staining. Furthermore, the differentiation protocol for the skin organoids was refined, thereby enabling innervation of the skin organoids without the necessity for neural organoids. In the subsequent phase of the study, the functionality of the nerve fibers will be assessed in both innervated skin models.

In this project, we established innervated human skin models of different complexity that replicate native architecture and neurocutaneous interactions, offering advanced in vitro platforms for studying sensory function and evaluating diverse compounds.

Kategorie: Skin biology and tissue remodelling
Präsentationsart: Poster

Abstract-ID: 157

Understanding confined functions of neutrophils and platelets in the pathophysiology of diabetic wound healing

Jonathan Kessler[1], Ainur Kakpenova[1], Sandra Franz[1]

1 Department of Dermatology, Venereology and Allergology, Medical Faculty, University Leipzig

Neutrophils are among the first immune cells recruited to injury sites, where they eliminate pathogens by phagocytosis, degranulation, and formation of neutrophil extracellular traps (NETs), and promote inflammation and tissue repair through cytokine and growth factor release. Sustained neutrophil activation is linked to chronic inflammation and impaired wound healing, as observed in diabetic ulcers. However, how neutrophil behavior is altered in diabetic wound healing remains insufficiently understood.

We investigated the spatiotemporal distribution of neutrophils in full-thickness wounds in wildtype and diabetic mice. In wildtype wounds, neutrophils infiltrated from the wound bed and migrated toward the upper wound layers, where they accumulated in the eschar. In contrast, diabetic wounds showed delayed and prolonged neutrophil infiltration, with cells remaining predominantly in deeper tissue layers and exhibiting increased NET formation. Consistently, human diabetic wounds contained more neutrophils and NETs in the wound bed, whereas in acute wounds neutrophils were mainly localized in the eschar.

To explore mechanisms underlying altered neutrophil distribution and function, we analyzed peripheral blood neutrophils from healthy and diabetic donors using multicolor flow cytometry. Neutrophils from diabetic individuals displayed significant changes in surface marker expression, including reduced levels of the maturation marker CD10 and increased expression of CXCR2, indicating altered maturation states.

We further focused on low-density neutrophils (LDNs), a subset reported to be increased in inflammatory diseases and associated with enhanced NET formation. LDNs were distinguished from normal-density neutrophils (NDNs) by density gradient separation and we further subdivided them based on CD16 expression into immature $CD16^{low}$ and mature $CD16^{high}$ subsets. While both subsets were detected in healthy and diabetic donors, the proportion of $CD16^{high}$ LDNs was significantly increased in diabetes. This subset exhibited a platelet-activated surface marker profile and its abundance positively correlated with patients' HbA1c levels, suggesting a link to metabolic disease severity.

Given that platelets are frequently present in a pre-activated state in diabetes and that LDNs are enriched under chronic inflammatory conditions, we hypothesized that LDNs represent a population of platelet-activated neutrophils in circulation. To test this, we stimulated neutrophils in vitro with platelet releasates, which induced a surface marker profile closely resembling that of LDNs, supporting a mechanistic link between platelet-derived signals and the LDN phenotype.

Together, these data indicate that diabetes is associated with systemic neutrophil alterations and increased platelet–neutrophil interactions, which may contribute to abnormal neutrophil localization, excessive NET formation, and impaired wound healing in diabetic ulcers.

Kategorie: Skin biology and tissue remodelling
Präsentationsart: Poster

Abstract-ID: 158

Hoxc13 regulates pigmentation of skin appendages in clawed frogs

Julia Steinbinder[1]; Attila Placido Sachslehner[1]; Corina Dörner[1]; Kris Vleminckx[2]; Leopold Eckhart[1]
1. Department of Dermatology, Medical University of Vienna, Vienna, Austria.
2. Department of Biomedical Molecular Biology, Ghent University, Ghent, Belgium.

Introduction
Human hair and nails depend on the transcription factor Hoxc13. In a recent study, we disrupted the hoxc13 gene in clawed frogs (Xenopus tropicalis) to demonstrate that the role of Hoxc13 in skin appendages, and specifically in the upregulation of hair keratin genes, has evolved in a common ancestor of tetrapods. Here, we investigated which other skin appendage-associated genes are regulated by Hoxc13.
Results
We identified a previously uncharacterized member of the tyrosinase gene family, which is phylogenetically distinct from the genes encoding tyrosinase (TYR), tyrosinase-related protein 1 (TYRP1) and dopachrome tautomerase (DCT). However, the amino acid residues implicated in catalytic activity of tyrosinases are conserved in the TYR-like protein of the frog. Accordingly, upon expression in recombinant form, the TYR-like protein displayed tyrosinase activity. RNA-seq analysis and mRNA in situ hybridization revealed expression of the TYR-like gene specifically in the claw-bearing toes of Xenopus tropicalis. CRISPR-Cas9-mediated disruption of hoxc13 suppressed the expression of the TYR-like gene and abolished the pigment formation on the toe tips. By contrast, mutations in canonical pigmentation genes, manifesting in an albino phenotype, do not abrogate the pigmentation of Xenopus claws.
Conclusion
We conclude that a unique mechanism of pigmentation involving a non-conventional tyrosinase is controlled by Hoxc13 in amphibians.

Kategorie: Skin biology and tissue remodelling
Präsentationsart: Poster

Abstract-ID: 159

Modelling intercellular communication driving matrix formation in healthy and fibrotic skin conditions

Salek M. [1]; Weiss T.[2]; Pfisterer K.[1]; Vorstandlechner V.[2]; Kühtreiber H.[1]; Auer L.[3]; Bucekova M.[1]; Ankersmit H. J.[3,4]; Mildner M. [1]

[1]Department of Dermatology, Medical University of Vienna

[2]Department of Plastic and Reconstructive and Aesthetic Surgery, Medical University of Vienna

[3]Department of Thoracic Surgery, Medical University of Vienna

[4]Aposcience AG, Vienna

Recent studies highlight the crucial role of Schwann cell - M2 macrophage interactions in driving the initiation and progression of keloids, which are fibrotic skin lesions characterized by abnormal and excessive extracellular matrix (ECM) accumulation.

To investigate this process, we established a novel three-dimensional in vitro model utilizing the self-secreted matrix of dermal cells derived from keloid or healthy skin. Subsequently, we incorporated monocytes and differentially polarized macrophages from blood into the in vitro models to assess their effects on skin fibroblasts and Schwann cells derived from large nerves, as well as the reciprocal influence of Schwann cells on macrophages.

Models generated from keloid-derived dermal cells showed enhanced ECM production and a higher degree of collagen fibre alignment compared to those derived from healthy skin cells. Schwann cells from large nerves and fibroblasts derived from healthy skin exerted minimal effects on macrophage phenotype. In contrast, macrophages markedly influenced Schwann cell gene expression in a phenotype-dependent manner, as revealed by RNA sequencing. Co-culture of Schwann cells with monocytes induced only minor transcriptional changes in Schwann cells. However, co-culture of monocytes with fibroblasts increased collagen fibre alignment. Exposure to M1 macrophages promoted a pro-inflammatory phenotype in Schwann cells with upregulation of genes involved in antigen presentation, whereas M2 macrophages enhanced the expression of ECM components and factors associated with TGF beta signalling.

Overall, our in vitro model recapitulates key features of keloid pathology observed in vivo, providing a valuable platform for mechanistic studies and the evaluation of potential therapeutic strategies. The crosstalk between Schwann cells and M2 macrophages in keloids may represent a critical mechanism driving excessive matrix deposition, thereby contributing to the persistent and uncontrolled growth characteristic of these fibrotic lesions.

Kategorie: Skin biology and tissue remodelling
Präsentationsart: Poster

Abstract-ID: 160

Evaluation of hydroxylated Tropoelastin as an extracellular matrix in wound healing

Kibria, N.[1]; Seifert, F.[2]; Knape J.P.[2]; Pietzsch, M.[2]; Wohlrab, J.[1]

1 University Hospital, Department Dermatology und Venereology, Martin-Luther-University, Halle (Saale), Germany

2 Institute of Pharmacy, Department Downstream Processing, Martin-Luther-University, Halle (Saale), Germany

Introduction

According to new statistics, approximately one million individuals in Germany are afflicted from chronic wounds. Widespread pathological phenomena are leg ulcers in general and diabetic foot syndrome. The prevalence increases with age. The management of chronic wounds necessitates specialized care and attention to facilitate healing. This phenomenon is particularly pronounced in elderly patients, as alterations and changes at the cellular and systemic levels can impede wound healing. In addition to addressing diseases that directly compromise wound healing potential, local wound care holds significant practical importance. The German market offers a wide variety of over 2,500 different wound dressings, most of which have only limited therapeutic evidence.
Elastin, an essential proteinogenic compound of the extracellular matrix, plays a critical role in maintaining the elasticity and robustness of the tissues that envelop it, including the skin. It occurs in the extra cellular space of elastogenic cells in a process that involves a sophisticated series of reactions of the soluble precursor tropoelastin (TE). In mammalian species, tropoelastin is hydroxylated to a certain percentage at its proline residues, which presumably allows adaptation of the properties of elastin according to its functionality. Human skin elastin shows a hydroxylation degree of app. 10 %.
Several publications deal with the use of elastin and tropoelastin in acute wound settings. A recent publication indicates that, in addition to local effects, there are also systemic effects of recombinant human TE in polymer blends improving wound healing. This systemic effect could be of interest for chronic wound treatment as well.

Methods

In this project recombinant hydroxylated TE (TE-Hyp) shall be investigated in a comparable context of prohealing effect. The project is focused on the characterization of novel TE-Hyp formulations for chronic wounds and the local effect of TE-Hyp.
Tropoelastin and proline-hydroxylated derivatives (TE-Hyp) were examined for their cytotoxic potential. Futhermore, their influence on the proliferation behavior of the dermal cell lines involved in wound healing was evaluated. The tested healthy dermal cell-lines included: fibroblasts, keratinocytes, mesenchymal stemcells and endothelial cells, which were incubated with different concentrations of TE and TE-Hyp (0,001; 0,01; 0,1; 0,5; 1,0 mg/mL) for 24, 48 and 72 hours. A luciferin-based assay (Cell-Titer-Glo) was used to assess vitality. A BrdU-based enzyme-linked immunosorbent assay (ELISA) was used to evaluate proliferation.

Results

The results of this study suggest that TE and TE-Hyp do not exhibit significant cytotoxic potential up to a concentration of 0.5 mg/ml. The proliferation behavior of the tested cells remained unchanged up to a concentration of 1.0 mg/ml (TE) or 0.5 mg/ml (TE-Hyp). Subsequent studies will assess the efficacy of TE-Hyp in specialized wound treatment methodologies, such as the scratch and HET-CAM assays. Additionally, the preclinical foundation for its clinical implementation will be established.

Kategorie: Skin biology and tissue remodelling
Präsentationsart: Poster

Abstract-ID: 161

Skin organoids-on-chip: enhancing *in vitro* skin models through automation and perfusion

Nina Köder[1,2], Amelie Reigl[2], Saskia Zöphel[2,3], Adrian Weghofer[4,5], Florian Groeber-Becker[2], Dieter Groneberg[2], and Peter Loskill[4,5,6]

1 Institute of Biomedical Engineering, Dept. for Medical Technologies and Regenerative Medicine, Eberhard Karls University Tübingen, Tübingen, Germany

2 Translational Center for Regenerative Therapies, Fraunhofer-Institute for Silicate Research ISC, Würzburg, Germany

3 Interdisciplinary Center for Clinical Research (IZKF), University Hospital Würzburg, Würzburg, Germany

4 Department for Microphysiological Systems, Institute of Biomedical Engineering, Eberhard-Karls-University Tübingen, Tübingen, Germany

5 NMI Natural and Medical Sciences Institute at the University of Tübingen, Tübingen, Germany

6 3R-Center for in vitro Models and Alternatives to Animal Testing, Eberhard-Karls-University Tübingen, Tübingen, Germany

Skin organoids derived from induced human pluripotent stem cells (hiPSC) hold immense promise as *in vitro* models for studying skin biology and disease. They faithfully mimic the complexity of native skin, including the presence of hair follicles and sebaceous glands, providing a more physiologically relevant environment for research [1]. Despite these benefits, current methods for their differentiation present significant challenges, as well as their inside-out orientation and lack of vasculature.

To address these challenges, this project proposes the automation of the skin organoid differentiation process. By utilizing a commercially available liquid handler, we seek to streamline workflows, reduce labor costs, and enhance consistency in differentiation outcomes. Initial results demonstrate successful differentiation yielding all requisite cell types and structures, albeit with some manual steps remaining despite a notable reduction in hands-on time.

Addressing the absence of vasculature, we integrated skin organoids cultured at the air-liquid interface into an Organ-on-a-Chip system [2]. This dynamic perfusion system replicates the *in vivo* vascular environment, facilitating the study of complex interactions between skin and perfusion. Integration into a chip with precise orientation enhances the viability of organoids within the system, enabling studies of at least 14 days. Co-culture with endothelial cells in the microfluidic channels replicates native skin conditions, as evidenced by cell survival and alignment.

The advancements achieved in this project significantly enhance the physiological relevance of skin organoid-on-chip systems, with broad implications for biomedical research and translational applications. Future improvements should focus on the integration of immune cells to enable the modeling of inflammatory skin diseases and immune responses. This would further expand the platform's potential for drug testing, including the assessment of side effects and interactions in multi-organ contexts.

[1] J. Lee, W. van der Valk, S. Serdy et al. (2022). *Nature protocols vol. 17(5),* 1266-1305. doi: 10.1038/s41596-022-00681-y

[2] E. Kromidas, A. Geier, A. Weghofer et al. (2023). *Advanced healthcare materials 13*, 2302714. doi:10.1002/adhm.202302714

Kategorie: Skin biology and tissue remodelling
Präsentationsart: Poster

Abstract-ID: 162

Development and optimization of an *in vitro* reconstructed human epidermis (RHE) based on hiPSC-derived skin organoids

Klose, P. [1]; Zöphel, S. [1,3]; Reigl, A. [1]; Köder, N. [1]; Höppel, A. [1]; Scherer, J. [1,3,4]; Flütter, L. [1,3]; Groeber-Becker, F. [1,5]; Groneberg, D. [1]

1 Translational Center for Regenerative Therapies TLZ-RT, Fraunhofer-Institute for Silicate Research ISC, Würzburg, Germany

2 Interdisciplinary Center for Clinical Research IZKF, University Hospital Würzburg, Würzburg, Germany

3 Institute of Medicine and Biology, Julius-Maximilians-University, Würzburg, Germany

4 Institute of Anatomy and Cell Biology, Julius-Maximilians University Würzburg, Germany

5 Department of Ophthalmology, University Hospital Düsseldorf, Heinrich-Heine-University, Germany

Background: The Reconstructed Human Epidermis (RHE) provides a physiologically relevant alternative to animal testing and is widely used in in vitro dermatological, toxicological, and pharmacological research. However, current RHE models typically rely on primary human epidermal keratinocytes (HEK), whose availability and reproducibility are limited due to restricted expansion capacities and donor variability. Human induced pluripotent stem cells (hiPSC) offer a renewable and well-defined alternative. However, generating functional RHEs from hiPSC-derived HEK remains challenging. In this study, hiPSC-derived skin organoids (SKO) were investigated as a novel and sustainable HEK source for RHE generation.

Objective: This study aimed to establish a functional hiPSC-derived RHE and optimize culture conditions to promote physiological differentiation and barrier function. Additionally, functional assays, including ET50 viability testing and quantitative PCR (qPCR) for barrier-associated markers, were conducted to validate the model.

Methods: Keratinocytes were isolated from hiPSC-derived skin organoids using a dispase-based isolation protocol and expanded on collagen I-coated culture surfaces. For RHE generation, cells were cultured at the air-liquid interface for 14 days under optimized culture conditions. The resulting models were analyzed by histology and optical coherence tomography (OCT) to evaluate tissue stratification and stratum corneum formation. The model's barrier integrity was assessed via impedance spectroscopy (TEER1000Hz), and ET50 determination using the MTT viability assay. Gene expression of differentiation and barrier markers (FLG, LOR, IVL, CDH1) was quantified by qPCR.

Conclusion: Keratinocytes isolated from hiPSC-derived skin organoids expressed basal markers CK5 and CK14 and successfully formed multilayered epidermal equivalents with physiological stratification and marker expression comparable to primary RHEs. Optimization of culture conditions through collagen I-coated inserts and lowering of glucose content in the culture medium resulted in improved epidermal differentiation and barrier integrity. ET50 and qPCR analyses further confirmed functional barrier properties and upregulation of late differentiation markers under optimized conditions. Together, these results demonstrate a

clear proof of concept for generating a functional RHE based on hiPSC-derived keratinocytes from skin organoids. This approach aims for improved scalability and reproducibility of human-relevant skin models, supporting the replacement of primary cell-based systems, and advancing the 3R principles in preclinical dermatological research.

Kategorie: Skin biology and tissue remodelling
Präsentationsart: Poster

Abstract-ID: 163

Immune cell priming with LPS enhances tissue repair in aging skin

Philipp Haas[1#], Yongfang Wang[1#], Albert Kallon Koroma[1#], Jinnan Cheng[1], Mahyar Aghapour[1], Adelheid Hainzl[1], Linda Krug[1], Susanne Schatz[1], Meinhard Wlaschek[1], Pallab Maity[1,2,#], Karin Scharffetter-Kochanek[1,2,#] and Karmveer Singh[1,2,#]

[1]Department of Dermatology and Allergic Diseases, Ulm University, Ulm, Germany.
[#] Contributed equally
[2]Corresponding authors

Aging is characterized by the functional decline and loss of structural integrity of all organs across species. In mammals, aging is accompanied by reduced tissue regeneration and persistent inflammation. Worldwide, chronic wounds in elderly present a major challenge to the medical and socioeconomic infrastructure of societies. A comprehensive understanding of how the aging process impacts wound homeostasis is lacking. We here studied wound healing in mice which closely reflect tissue repair in humans and occurs in overlapping yet highly synchronized phases that includes blood clotting, inflammation, re-epithelialization and a long-lasting tissue remodeling phase. In recent years, the emerging concept of immune memory that were originally thought to be limited to adaptive immune system, was established also for innate immune cells such as macrophages, monocytes, natural killer cells and for non-immune cells such as hematopoietic stem cells and epithelial cells as well. To explore the role of immune priming on wound repair during aging, four 6mm full excisional thickness punch biopsies including epidermis and dermis were created on the back of young and old C57BL/6J mice. Employing histology, immunostaining and flow cytometry techniques, we found that immune priming by the bacterial cell wall component lipopolysaccharide (LPS) restore disrupted wound repair in aged mice skin. We found that a short pulse of toll-like receptor 4 activator LPS before wounding markedly accelerate wound healing in aged mice which – if non-primed – exhibit a defective epidermal wound closure as quantitatively assessed. LPS priming facilitates early barrier formation, keratinocyte responsiveness and their differentiation towards a newly reconstituted wound epithelium. Previously unreported, we found that the formation of a protective epidermal barrier following LPS priming partly depends on innate immune cells. Using immunostaining of wound sections, we found that structural elements such as neutrophil expulsed traps (NET) including DNA and membrane protrusions originating from LPS-activated neutrophils and arginase-1 positive regenerative macrophages, reinforce physical skin barrier in aged wounds. Collectively, this not only prevents the invasion of pathogens into the restoring skin tissue after injury, but also avert the persistence of low-grade inflammation associated with aged wounds. The number of innate immune cells and the inflammation associated marker STAT3 declined in LPS primed healed wounds of aged mice. These findings underscore the benefit of immune priming in reconstituting crosstalk between innate immune cells and epithelial cells that consequently accelerate skin barrier and suppress chronic inflammation. Our study provide an intriguing insights into potential therapeutic interventions with immune disorders and compromised barriers, including for obesity, diabetes and aging-related wound healing disorders.

Kategorie: Skin biology and tissue remodelling
Präsentationsart: Poster

Abstract-ID: 164

Assessment of Penetration and Biological Response of Cold Atmospheric Plasma in Intact and Barrier-Defective Human Skin

W. Peschke[1]; P.-K. Ficht[1]; A. Staffeld[1]; S. Emmert[1]; L. Boeckmann[1]

[1]Clinic and Policlinic for Dermatology, Venereology, and Allergology, University Medical Center Rostock, Germany

Cold Atmospheric Plasma (CAP) has attracted increasing interest in dermatology for its antimicrobial and wound-healing promoting effects. Although much progress has been made in understanding the mechanisms of action, the impact of CAP on epidermal cell dynamics and the penetration depth are not fully understood.
Against this background, this study investigates CAP-induced effects on proliferation, apoptosis, and gene expression profiles of cells in human ex vivo skin tissues as well as in reconstructed 3D skin models. The goal is to assess the penetration depth of CAP-induced effects and the role of an intact skin barrier in this process.
Human ex vivo skin samples (donor age >80 years) were treated repeatedly with CAP (plasma-jet) for five minutes at defined intervals and kept in tissue culture medium for two days. Control samples from the same donor were treated with argon gas (no CAP). Cryosections were prepared and analyzed via immunohistochemistry for Ki67 (proliferation) and TUNEL (apoptosis). Microscopic analyses and quantification of Ki67 and TUNEL positive cells revealed no significant differences between CAP treated and gas treated tissues with intact skin barrier. However, an unusual swelling of epidermal cells was observed in all samples. This may be due to the prolonged incubation of the tissues in cell culture medium.
In ongoing experiments, we are investigating the effect of CAP on barrier defective skin using human skin samples as well as in vitro skin models with atopic-like inflammation induced by IL-4, IL-13 an IL-31 treatment. Furthermore, we will perform spatial transcriptomic analyses and measure cytochrome C release into the culture medium as an additional apoptosis indicator.
So far, our findings show limited or no plasma penetration through an intact skin barrier. Hence, CAP appears to exert negligible biological effects on intact human skin, possibly due to insufficient penetration through the stratum corneum. The use of 3D skin models and defined barrier disruption approaches will provide further insights into the penetration depth of CAP in barrier-defective skin and its effects on epidermal cell dynamics, thereby enabling a deeper understanding of CAP's biological impact and its potential therapeutic applications in barrier-impaired skin conditions.

Kategorie: Skin biology and tissue remodelling
Präsentationsart: Poster

Abstract-ID: 165

In Vitro Assessment of the Biocompatibility and Antimicrobial Properties of Silver-Containing Wound Dressings

Wieland Milz[1]; Sabine Illner[2]; Ann Charloth Kufahl[3]; Anneke Lemken[1]; Aenne Foth[1]; Philipp-Kjell Ficht[1]; Selina Schultz[2]; Thomas Eickner[2]; Niels Grabow[2]; Tomas Fiedler[3]; Steffen Emmert[1]; Lars Boeckmann[1]

[1] Clinic and Policlinic for Dermatology, Venereology and Allergology; University Medical Center Rostock
[2] Institute for Biomedical Engineering; University Medical Center Rostock
[3] Institute for Medical Microbiology, Virology and Hygiene; University Medical Center Rostock

Chronic wounds prone to infection pose significant clinical challenges for patients and the healthcare system. In order to prevent and treat microbial infections and hence to foster the healing process, silver-coated wound dressings are commonly used. However, besides the antimicrobial properties, silver may also exert detrimental effects on human cells. Against this background, the present study aims to evaluate the biocompatibility and antimicrobial efficacy of commercial silver-containing wound dressings, as well as novel electrospun poly-p-dioxanone (PPDO)-nanofiber nonwovens. Two-dimensional cell culture experiments were conducted on a human fibroblast cell line (GM637) and a human keratinocyte cell line (HaCaT). They were treated with extracts from different wound dressings and placed in direct contact with punches. A significant decrease in metabolic activity was observed, which indicates a cytotoxic effect of these silver-containing wound dressings. In order to investigate the role of reactive oxygen species (ROS) and the mutagenicity of the extracts, inhibitory concentrations were approximated using diluted extracts. The antimicrobial potential of the wound dressings was tested on four potential wound-associated bacterial strains: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, and *Pseudomonas aeruginosa*. Ongoing investigations are focusing on the suitability of PPDO as a basic material for silver-containing wound dressings as well as on modifications of the silver-containing nanofiber nonwovens in order to reduce cytotoxicity while maintaining antimicrobial properties.

Kategorie: Skin biology and tissue remodelling
Präsentationsart: Poster

Translational Research

Abstract-ID: 166

Tirzepatide and GLP-1RAs reduce risk for systemic autoimmune rheumatic diseases in obesity, unlike surgery or other weight loss treatments

Fatemeh Gorzin[1]*, Henning Olbrich[2]*, Jens Y Humrich[3], Diamant Thaci[4], Jens U Marquardt[5-7], Gabriela Riemekasten[3], Walter Raasch[6,8,9], Svenja Meyhöfer[5-7], Ralf J. Ludwig[1,4]

[1] Lübeck Institute of Experimental Dermatology, University of Lübeck, Lübeck, Germany

[2] Department of Dermatology, University-Hospital Schleswig-Holstein (UKSH), Lübeck, Germany

[3] Department of Rheumatology and Clinical Immunology, University of Lübeck, Lübeck, Germany

[4] Institute and Comprehensive Center for Inflammation Medicine, University of Lübeck, Lübeck, Germany

[5] Medical Clinic I, University of Lübeck, Lübeck, Germany.

[6] Center of Brain, Behavior and Metabolism, University of Lübeck, Lübeck, Germany.

[7] German Center for Diabetes Research (DZD), Munich, Germany

[8] Institute for Experimental and Clinical Pharmacology and Toxicology, University of Lübeck, Germany

[9] DZHK (German Centre for Cardiovascular Research), partner site Hamburg/Kiel/Lübeck, Germany

*equal contribution

Introduction: Globally, obesity is rapidly increasing and it is known as an important risk factor for multiple chronic inflammatory diseases including systemic rheumatologic diseases (SRDs). It has been shown that GLP-1RAs (glucagon like peptide 1 receptor agonists) may contribute to better outcomes such as improving mortality in psoriasis. These medications enhance insulin secretion and suppress appetite. Nevertheless, the role of weight loss intervention strategies among obese or overweigh people is not fully understood. We aim to compare the impact of different weight loss interventions on the subsequent risk of developing systemic rheumatologic diseases in overweight and obese individuals.

Methods and Results: We conducted retrospective cohort analysis using the TriNetX global research network to compare four weight loss intervention strategies: GLP-1RAs, tirzepatide , a dual GLP-1 and GIP (glucose-dependent insulinotropic polypeptide) receptor agonist, bariatric surgery, and other pharmacological weight loss drugs. Incidence of systemic rheumatologic disease was compared across cohorts defined by standardized inclusion criteria, adjusting for age, sex, and comorbidities.

We demonstrated that compared with other pharmacological medications, incretin-based drugs, i.e., GLP-1RAs and tirzepatide associated with lower risk of subsequent development of SRDs. While compared to bariatric surgery, the results showed a tendency to lower the risk though the findings were not consistent across all analysis.

Discussion: incretin- based treatments are associated with a lower risk of developing systemic rheumatologic diseases compared with other weight-loss interventions. These findings should be interpreted within the limitations of the observational study design. Nonetheless, GLP1RA and tirzepatide may represent preferred therapeutic options for the treatment of obesity.

Kategorie: Translational Research
Präsentationsart: Poster

Abstract-ID: 167

The Hamburg Sentinel Lymph Node Liquid Biopsy Cohort – SLN(L)B

Felicitas Höfermann[1,2,*]; Julian Kött[1,2,*]; Noah Zimmermann[1,2]; Tim Zell[1,2]; Isabel Heidrich[1,2,3]; Glenn Geidel[1,2]; Stefan W. Schneider[1,2]; Daniel J. Smit[2,3]; Christoffer Gebhardt[1,2]

1 Department of Dermatology and Venereology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
2 Fleur Hiege Center for Skin Cancer Research, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
3 Institute of Tumor Biology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Introduction
Patients with AJCC stage IIB/C melanoma and negative sentinel lymph node biopsy (SLNB) show considerably worse relapse-free (RFS) and overall survival (OS) compared to patients with stage IIIA melanoma and positive SLNB. With the expansion of adjuvant systemic therapies to stage IIB there is an increasing need for additional methods to identify high risk patients in order to enable individualized treatment decisions. Blood-based 'liquid biopsy' approaches offer a minimally invasive alternative to tissue-based diagnostics, e.g. through analysis of promising biomarkers including circulating tumor DNA (ctDNA). Moreover, a biomarker-guided selection of patients and management of therapy duration would be preferable in a neoadjuvant setting.

Objective
This study investigates the prognostic value of perioperative liquid biopsy in melanoma patients who receive SLNB.

Materials and Methods
This monocentric prospective, observational study enrolls patients who receive SLNB at the University Skin Cancer Center in Hamburg since January 2024. SLNB is performed in patients with tumor thickness of ≥1mm or in those with thinner primary tumors with additional risk factors. The sentinel lymphnode is considered positive if metastatic melanoma cells are detected histologically within the node. Serum, EDTA plasma and citrate plasma are collected preoperatively and on the first postoperative day after SLNB, as well as longitudinally during therapy. Tissue samples from primary tumors and sentinel lymph nodes were collected from all available patients in the cohort up to February 2025. For future analyses, ctDNA will be measured from EDTA plasma among other biomarkers.

Results
From January 2024 to September 2025 blood was collected from 211 patients aged 30 to 90 years (mean age 62.9; 50.2% women) before SLNB, and from 62.6% of these patients also postoperatively. In 13.3% of patients, the SLNB result was positive.
After SLNB, the patients were staged according to the 8th edition of the AJCC classification into stage IA (26.5%), IB (30.8%), IIA (13.7%), IIB (8.5%), IIC (5.2%), IIIA (3.8%), IIIB (2.4%) and IIIC (9%). Tumor thickness was distributed as following: ≤1 mm (26.5%), >1–2 mm (41.2%), >2–3mm (11.8%), >3–4 mm (7.1%) und >4 mm (13.3%). 41 patients received adjuvant or palliative systemic therapy with pembrolizumab (n=29), dabrafenib + trametinib (n=5), pembrolizumab + V940/placebo (n=6) or ipilimumab + nivolumab (n=1). The remaining patients did not receive systemic therapy after SLNB.

Summary

This prospective Hamburg SLNB Liquid Biopsy cohort (SLN(L)B) enables investigation of prognostic biomarkers in melanoma patients before and after SLNB and could contribute to a reduction of SLNBs and individualisation of therapy.
Kategorie: Translational Research
Präsentationsart: Poster

Abstract-ID: 168

Molecular Tumor Boards in Malignant Melanoma: Uncovering Challenges and Opportunities in a Bicenter Real-World Analysis

Geidel, G. [1,2,3]; Lowinus, T. [4]; Metzger, P. [5]; Czurda, R. [1]; Schipperges, V. [5]; Paul, U. [6]; Rünger, A. [1,2,3]; Kött, J. [1,2,3]; Heidrich, I. [1,2,3,7]; Lehr, S. [8], Kühn; J. [4], Becker, H. [4,9,10]; Miething, C. [4]; Werner, M. [9,10,11]; Laßmann, S. [9,10,11]; Duyster, J. [4,9,10]; Brummer, T. [9,10,12]; Simon, R. [6]; Alsdorf, W. [3,13,14]; Christopeit, M. [3,9,13,14]; Bokemeyer, C. [3,9,13,14]; Eyerich, K. [8]; Schneider, S.W. [1,2]; Rafei, D. [8]; Börries, M. [5,9,10]; Meiss, F. [8]; Gebhardt, C. [1,2,3]

[1] Department of Dermatology and Venereology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[2] Fleur Hiege Center for Skin Cancer Research, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[3] University Cancer Center Hamburg, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[4] Department of Medicine I, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany
[5] Institute of Medical Bioinformatics and Systems Medicine, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany
[6] Institute of Pathology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[7] Institute of Tumor Biology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[8] Department of Dermatology and Venereology, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany
[9] German Cancer Consortium (DKTK), partner site Freiburg; and German Cancer Research Center (DKFZ), Heidelberg, Germany
[10] Comprehensive Cancer Center Freiburg, Medical Center—University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany
[11] Institute for Surgical Pathology, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany
[12] Institute of Molecular Medicine and Cell Research Centre of Biochemistry and Molecular Cell Research (ZMBZ), University of Freiburg, Freiburg, Germany
[13] Department of Oncology, Hematology and Bone Marrow Transplantation With Section Pneumonology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[14] Center for Personalized Medicine – Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Background and objectives: Malignant melanoma is an aggressive cancer with early metastasis. Despite therapeutic advancements, approximately 50% of patients succumb to metastatic disease. Molecular tumor boards aim to identify targetable molecular alterations to guide individualized treatment strategies. Yet, real-world data on patient selection, referral timing, recommendation rates, implementation, and clinical impact remain limited.

Methods: In this exploratory retrospective bicenter analysis, we evaluated 80 patients with advanced melanoma who presented at institutional molecular tumor boards of two comprehensive cancer centers. Clinical and molecular tumor data were analyzed using bioinformatic tools to characterize mutation profiles, treatment recommendations, and their real-world implementation.

Results: Most patients (88.3%) had stage IV melanoma at the time of molecular tumor board presentation and had received a median of three prior systemic treatment lines. Actionable treatment recommendations were formulated in 77.9% of eligible cases, yet only 33.7% of these recommendations were implemented. Non-implementation was most commonly

attributable to early patient death or regulatory barriers. Importantly, when molecular tumor board-guided therapies were applied, patients experienced significantly improved progression-free survival (7.85 vs. 4.34 months; PFS ratio 1.8) and overall survival (10.64 vs. 5.06 months) compared with patients in whom recommended treatments were not implemented.

Conclusions: These findings indicate that molecular tumor boards frequently generate clinically actionable recommendations for metastatic melanoma, but late-stage referral substantially limits their real-world implementation. When applied, molecularly guided treatment strategies may confer meaningful clinical benefit, underscoring the importance of earlier integration of molecular tumor boards into melanoma care pathways.

Kategorie: Translational Research
Präsentationsart: Poster

Abstract-ID: 169

Lanadelumab treatment is effective and safe in patients with Factor XII associated cold-induced autoinflammatory syndrome: results from an open-label proof-of-concept study

Hanna Bonnekoh[1,2]; Carolina Vera Ayala[1,2]; Felix Aulenbacher[1,2]; Benjamin Grimmer[1,2]; Monique Butze[1,2]; Jörg Scheffel[1,2]; Stefan Frischbutter[1,2]; Karoline Krause[1,2]

1. Institute of Allergology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

2. Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany

Introduction
Factor XII associated cold-induced autoinflammatory syndrome (FACAS) is a rare hereditary autoinflammatory disease characterized by cold-induced urticarial rash, chills, arthralgia, headache and fatigue with autosomal-dominant inheritance. In FACAS, a substitution mutation in gene *F12* (T859A, p.W268R) results in activation of the FXII-kallikrein-kinin pathway with signs of increased bradykinin production and local upregulation of interleukin-1β (IL-1β). Treatments with bradykinin-B2-antagonist icatibant and IL-1-antagonist anakinra were effective in reducing disease activity but could not be maintained due to its short half-life or side effects.

Objective
To investigate the effects and safety of the kallikrein inhibitor lanadelumab in FACAS patients.

Methods
We performed a phase II, exploratory, proof-of-concept, single-center, open-label, single arm interventional trial in patients with active FACAS. The study comprised a run-in baseline period of 4 weeks followed by a 28-week open-label treatment phase with subcutaneous injections (lanadelumab 300 mg) every 2 weeks and an 8-week period of follow-up. Efficacy was assessed by changes in disease activity (patient-reported disease activity, PR-DA total score, 0-50; PR-DA subscores for urticarial rash, fatigue, chills/fever, headache, arthralgia each 0-10), inflammatory markers (C-reactive protein [CRP], serum amyloid A [SAA], erythrocyte sedimentation rate [ESR], S100A8/9) and quality of life (Dermatology Life Quality Index, DLQI; SF-36).

Results
4 patients were included in the study. During treatment with lanadelumab, the clinical signs and symptoms assessed by the PR-DA total score of FACAS patients declined from a mean value of 15.47 (SD = 5.92) at baseline (weeks 4 to 1), to a mean value of 3.60 (SD = 7.16) at weeks 9 to 12 and a mean value of 1.65 (SD = 3.30) at weeks 25 to 28. Also, all subscores (i.e. urticarial rash, fatigue, chills/fever, headache, and arthralgia) reduced from baseline to week 9 to 12 and week 25 to 28 during treatment. The quality of life of FACAS patients improved during lanadelumab treatment, as the DLQI total score declined from a mean value of 9.00 (SD = 5.77) at week 0 (Visit 2, Baseline), to a mean value of 0.00 (SD = 0.00) at week 12, and to a mean value of 0.25 (SD = 0.50) at week 28. SF-36 mental and physical component scores increased from baseline over time during the study. Mean serum CRP, ESR and S100A8/9 were normal at baseline and remained normal at week 12 and week 28. Mean serum SAA levels demonstrated only marginal changes (7.38 mg/L (SD 6.66), reference 6.4 mg/L at baseline to 5.97 mg/L (SD = 3.24) at week 12 and 7.30 mg/L (SD = 4.98) at week 28). A total of 9 adverse events (AEs) were documented, none of which were serious (SAEs). One of the

AEs was “possibly related”, all other AEs were “unlikely” or “not related”. All 4 patients completed the study.

Conclusion
In this open-label trial, lanadelumab treatment provided continuous symptom control and improvement of quality of life in all four FACAS patients. Lanadelumab showed a good safety profile and may be considered a therapeutic option for FACAS patients.

Kategorie: Translational Research
Präsentationsart: Poster

Abstract-ID: 170

Baseline serum KDR and FGF2 increased in patients with immune checkpoint blockade-induced colitis

J. Böhl[1], R. Bonkaß[1], A. Bhatnagar[1], L. Mahdi[1], A. Mousa[1], J. Hassel[1,2], R. Reschke[1,2,3]

1 Heidelberg University, Medical Faculty Heidelberg, Department of Dermatology and National Center for Tumor Diseases (NCT), NCT Heidelberg, a partnership between DKFZ and University Hospital Heidelberg, Heidelberg, Germany.

2 German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ) Core Center Heidelberg, Heidelberg, Germany.

3 Clinical Cooperation Unit Applied Tumor Immunity, German Cancer Research Center, Heidelberg, Germany.

Objective:

Immune checkpoint inhibitors (ICIs) have transformed cancer treatment but often induce immune-related adverse events (irAEs), whose underlying mechanisms remain poorly understood. This study aims to explore systemic immune alterations associated with irAEs by analyzing 48 immune-related proteins using the OLINK® Proximity Extension Assay (PEA). Our goal is to uncover biomarkers that could enable safer, more targeted immunotherapies.

Methods:

Serum samples from 40 patients were analyzed using the Olink Target 48 Immune Surveillance panel, which quantifies immune-related proteins. Baseline serum was collected from patients before starting ICI therapy. Patients were stratified into three groups based on the subsequent development of irAEs: 9 without side effects, 16 with colitis, and 15 with cutaneous irAEs.

Results:

We found that patients who developed colitis exhibited significantly higher serum levels of FGF2 (Fibroblast Growth Factor 2) and KDR which is also known as VEGFR-2 (Vascular Endothelial Growth Factor Receptor 2) when compared to those with cutaneous irAEs. Both proteins are linked to vascular angiogenesis and endothelial activation. No other protein levels in the panel showed significant differences between patients with cutaneous side effects, colitis, or no side effects.

Conclusion:

Higher serum concentrations of KDR and FGF2 may predict a greater likelihood of developing colitis as an irAE following ICI treatment. These findings warrant further validation with a larger sample size and longitudinal studies to track protein levels during treatment. The role of KDR and FGF2 in serum samples at the time of irAE onset, as well as in affected tissues, should be further explored, particularly in colitis patients.

Kategorie: Translational Research
Präsentationsart: Poster

Abstract-ID: 171

Patient-Perceived Stress in Occupational Dermatology: Insights from a Qualitative Interview Study

Maurice Waitek; Karoline Lukaschek; Elke Weisshaar
Division of Occupational Dermatology, Department of Dermatology, Ruprecht-Karls University Heidelberg, Heidelberg, Germany

Introduction
Stress remains an under-explored and under-researched factor in occupational dermatology. Although psychological factors and comorbidities are well established in dermatology, research on stress in occupational skin diseases (OSD) remains limited. Previous studies have largely reported elevated stress levels among patients with chronic hand eczema (CHE) but have not investigated the specific contexts or subjective experiences of stress. Given the clinical observation of increasing psychosocial strain and demand for psychological counselling among this patient group, this study aimed to explore stress from the patient perspective through qualitative interviews.

Methods
From June 2024 to July 2025, patients with severe CHE presenting to the division of occupational dermatology were invited to participate in a structured qualitative interview, following the Standards for Reporting Qualitative Research (SRQR)- criteria. The study aimed to achieve an unbiased and open presentation of patients' views on stressors in their daily lives. Inclusion criteria comprised a confirmed CHE diagnosis, sufficient German language skills, and informed verbal consent. In total, 62 interviews were conducted (25 females, 40.3%; 37 males, 59.7%), with participants aged between 21 and 63 years (mean = 49.1 years, SD = 12.0).

Results
Semi-structured interviews comprising both structured and open-ended questions lasted between 20 and 45 minutes. The interview guide, consisting of 17 open-ended questions, was developed based on clinical experience and preliminary interviews with three CHE patients. Participants described stress primarily in the context of work, citing time pressure, interpersonal conflicts (e.g., with supervisors), and excessive workload as key stressors. Commonly reported stress symptoms included irritability, nervousness, rushing at work, and physical tension.

Discussion
The findings indicate that stress plays a substantial role in the experience and management of OSD. Stress appears to be multifaceted and highly relevant for patients with occupational CHE, as it may impair work performance, exacerbate disease severity, and hinder treatment outcomes. Moreover, many patients seemed unaware of their stress levels and underestimated the role of stress as a contributing factor in disease progression and as a potential risk factor for conditions such as depression and anxiety. This study was conducted to develop and establish a qualitative interview approach that can be applied in future research to systematically assess stress in patients with OSD.

Kategorie: Translational Research
Präsentationsart: Poster

Abstract-ID: 172

Influence of the intestinal microbiome on the development of immune-related adverse events (irAE) in patients with melanoma

Polensky, L.[1,2*]; Kött, J.[1,2*]; Kempski, J.[3]; Tang, Y.[3]; Kocheise, L.[3]; Blomen, C.[1,2]; Zell, T.[1,2];

Zimmermann, N.[1,2]; Geidel, G.[1,2]; Smit, D.[2,4]; Pantel, K.[2,4]; Schneider, S.[1,2]; Huber, S.[3]; Gebhardt, C.[1,2]

1 University Medical Center Hamburg-Eppendorf (UKE), Department of Dermatology and Venereology, Hamburg, Germany

2 University Medical Center Hamburg-Eppendorf (UKE), Fleur Hiege Center for Skin Cancer Research, Hamburg, Germany

3 University Medical Center Hamburg-Eppendorf (UKE), I. Department of Medicine (Gastroenterology and Hepatology), Hamburg, Germany

4 University Medical Center Hamburg-Eppendorf (UKE), Institute of Tumor Biology, Hamburg, Germany

Introduction

Immune checkpoint inhibition (ICI) therapy has revolutionized the treatment of melanoma. However, not all patients respond to ICI. Furthermore, ICI treatment can trigger immune-related adverse events (irAE), including immune-mediated colitis (IMC), which can lead to discontinuation of treatment despite oncological response. IMC is one of the most common and serious side effects, affecting up to 40% of patients receiving Ipilimumab plus Nivolumab. To date, it is not yet sufficiently understood why some patients develop side effects while others do not. However, the impact of the gut microbiome has already been shown. It can influence immunological and inflammatory processes locally and systemically through soluble factors such as cytokines. Nevertheless, little is known which bacterial strains exactly promote or inhibit the effect of ICI, which composition of the microbiome leads to irAE and which lifestyle-related factors have an impact.

Methods

The primary endpoint of our study is the occurrence of immune-related adverse events (irAE ≥ CTCAE grade 3) under CTLA-4-, PD-1- or combined CTLA-4- and PD-1-inhibitor therapy. Stool and blood samples have been collected from melanoma patients (AJCC v8 stage II/III/IV) before their first four ICI infusions and additionally when irAE occur. Stool samples have been analyzed using 16S rRNA sequencing. We will also examine the cytokine and peripheral blood mononuclear cell (PBMC) composition using cytometric bead array (CBA) and fluorescence-activated cell sorting (FACS) and the PBMCs will be isolated from EDTA plasma. The results will be statistically associated with the microbiome, ICI response and the occurrence of irAE. Dietary habits and medication intake have been recorded using a questionnaire of the German Nutrition Society and clinical data have been obtained from the patient's medical record.

Results

130 patients have already been enrolled in the study and stool samples from 37 patients have been sequenced so far. 32 of these developed an irAE, of which 5 developed an irAE ≥ CTCAE grade 3. 9 patients of the 37 patients experienced an IMC, of which 1 developed an IMC ≥ CTCAE grade 3. In the preliminary analysis, we observed no difference in microbiome diversity

when comparing the stool microbiome of patients who experienced irAE and those who did not experienced irAE. However, a significantly different microbial composition was identified in patients with IMC compared to patients who did not experienced IMC. In the IMC-group the proportion of Firmicutes was lower. These bacteria are protective by producing short-chain fatty acids and having a lactate and butyrate metabolism. This is important, as butyrate stabilizes the intestinal barrier and acts as an anti-inflammatory signaling substance. At the same time, in patients with IMC, the proportion of pro-inflammatory bacteria of the phylum Bacteroidetes was higher. We also observed similar findings in patients who experienced irAE ≥ CTCAE grade 3. In this case, the abundance of Ruminococcus-species, a genus also belonging to the protective Firmicutes filum, was lower, while the proportion of potentially pathogenic bacteria of the genus Dorea was higher.

Discussion

So far, the results indicate a correlation between the occurrence of irAE and the composition of the gut microbiome. Data from further analyses, particularly regarding treatment response and therapy effectiveness, are expected shortly and will be presented at the congress.

Kategorie: Translational Research
Präsentationsart: Poster

Abstract-ID: 173

C5aR expressing neutrophils are increased in the skin of chronic spontaneous urticaria patients

Huang L. [1,2]*; Metz M.*[1,2]*; Muñoz M.*[1,2]

[1]Institute of Allergology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin, Germany
[2]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany

Introduction
Mast cells (MCs) are considered to be key in the pathogenesis of chronic spontaneous urticaria (CSU); however, emerging evidence suggests that complement activation and neutrophil recruitment also play a central role promoting urticarial symptoms. Mechanisms underlying complement activation, C5a and neutrophil activation as important drivers or amplifiers of MC responses in patient lesions have not been investigated.

Methods
We assessed the numbers of neutrophils and MCs in lesional skin of CSU patients and healthy controls by the immunohistochemical stainings of myeloperoxidase (MPO) and tryptase respectively. In addition, C5aR co-stainings in the skin were performed as well as correlations between the patient clinical data, laboratory parameters including levels of C5 and C5a in plasma and number of neutrophils and MCs in the skin of CSU patients.

Results
High numbers of MPO^+ cells were found in lesional skin of CSU patients whereas no MPO staining was observed in the skin of healthy controls. However, the number of $tryptase^+$ cells was similar in both groups. Interestingly, C5aR expression was only found in MPO^+ cells and in close contact with MCs in lesional skin of CSU patients. Higher levels of C5 were also found in the plasma of CSU patients compared to controls. Furthermore, we found significant correlations between MPO^+ cell numbers and disease activity assessed by the UAS7 scores as well as with IgG anti-TPO levels ($r=0.52$, p-value: 0.04 and $r=0.84$, p-value < 0.0001, respectively).

Discussion: Increased numbers of MPO- and C5aR-expressing cells and their close contact with MCs in the skin of CSU patients suggest an important role of neutrophils and complement activation in the development of urticarial symptoms. An oral anti-C5aR inhibitor is currently being investigated in a phase II clinical trial with CSU patients. Our results highlight the potential role of an anti-C5aR therapy as novel and alternative treatment for CSU.

Kategorie: Translational Research
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 174

Ocular adverse events during Dupilumab and Tralokinumab Therapy: Data from the TREATgermany Registry

Nele Manjah1*; Susanne Abraham1,2*; Barbara Kind1; Luise Heinrich1; René Sachse3; Pauline Sander1; Annice Heratizadeh4; Thomas Werfel4#; Stephan Weidinger5#; Jochen Schmitt1# and the TREATgermany Study Group

1 Center of Evidence-based Healthcare, University Hospital and Medical Faculty Carl Gustav Carus, TU Dresden
2 University Allergy Center, Medical Faculty Carl Gustav Carus, TU Dresden
3 Dr. René Sachse, Daten-Praxis, Freisinger Str. 9, 86567 Hilgertshausen-Tandern
4 Division of Immunodermatology and Allergy Research, Department of Dermatology and Allergy, Hannover Medical School, Hannover, Germany
5 Center for Inflammatory Skin Diseases, Department of Dermatology and Allergy, University Hospital Schleswig-Holstein, Kiel, Germany

Background
Ocular adverse events (oAEs) during therapy with dupilumab and tralokinumab in atopic dermatitis (AD) are a known side effect, often referred to as dupilumab-related ocular surface disease (DROSD) when occurring under dupilumab treatment. The aim of this study was to characterize the frequency, course, and risk factors of oAEs under biologic therapy in the German AD registry TREATgermany in order to derive predictive risk profiles for clinical practice.

Methods
This registry-based analysis included 1,849 patients (data cut 07/2023) with AD documented in TREATgermany. Quality-assured real-world data from routine clinical practice were analyzed, including systemic therapies and physician-reported oAEs, which were actively assessed at each visit. Logistic regression analyses with stepwise selection were performed to identify independent risk factors and to calculate odds ratios (OR).

Results
Under dupilumab therapy, 305 of 1,176 patients (25.9%) developed oAEs, of whom 41 paused or discontinued treatment. Under tralokinumab, oAEs were reported in 14 of 151 patients (9.3%), leading to treatment discontinuation in five cases. The most frequently reported event was conjunctivitis (including synonyms), followed by ocular dryness, itching, and blepharitis. Median time to onset of oAEs was 101 days for dupilumab and 90 days for tralokinumab. Symptom duration varied considerably, ranging from spontaneous resolution within weeks to persistence for more than one year. Therapy-independent risk factors included AD involvement of the face at registry entry (OR 1.45; p=0.011), comorbid asthma (OR 1.51; p=0.0053), prior systemic corticosteroid use (OR 1.95; p<0.001), and use of topical class-3 corticosteroids within 12 months prior to registry entry (OR 1.52; p=0.0039).

Conclusion
Ocular adverse events are a common, mostly mild to moderate complication during treatment with dupilumab and tralokinumab. Facial AD involvement, comorbid asthma, and previous systemic or potent topical corticosteroid therapy define an increased risk for oAEs. These findings support close ophthalmologic monitoring, early recognition, and timely management to promote treatment continuation and optimize patient outcomes.

Kategorie: Translational Research
Präsentationsart: Poster

Abstract-ID: 175

Gene-expression based differentiation between psoriasis and eczema – Putting methodical advances in dermatological diagnostics into practice

Bentz, P.[1]; Eyerich, K.[2]; Weisshaar, E.[1]

1 Division of Occupational Dermatology, Department for Dermatology, Heidelberg University Hospital, Ruprecht-Karls-University, Heidelberg, Germany
2 Clinic for Dermatology and Venerology, University Hospital Freiburg, Freiburg, Germany

The diagnosis of psoriasis and eczema poses major challenges, both clinically and dermatohistopathologically. Overlapping forms resulting in eczematoid psoriasis or psoriasiform eczemas can make a diagnosis especially difficult. Dermatology is at the brink overcoming historical disease classification taxonomies based on morphology. Classification based on molecular expressions in lesional skin can open new paths towards reliable diagnostics. CCL27 and NOS2 have been proven to be robust markers for the differentiation of both diseases, which are especially present in occupational dermatology. With the ongoing launch of highly disease specific (systemic) drugs, clear diagnoses are of great importance for successful treatment and reduction of healthcare costs.

In 2021, a cohort of 287 occupational dermatology patients has been diagnosed via molecular diagnostics (Mdx) and followed over 3 years, collecting data on i.a. disease progression, severity, treatment and patient-reported outcomes. 46.73% (n=133) of the participants are women ($Ø_{age}$: 50.4±12.2 years). Dermatoses persisted for an average of 7 years. The initial clinical diagnosis of these cases was unclear in 38.9%. Mdx resolved these cases in over 95%. Overall, only 36.3% of the cases had a consistent clinical and molecular diagnosis. After 3 years (n=160), treatment with topical and systemic glucocorticosteroids reduced strongly (topical: -25.5%; systemic: -16.4%). Meanwhile, use of disease-specific, systemic drugs increased (e.g. dupilumab, adalimumab) by 5%, as well as the overall amount of patients receiving systemic therapies (+15.5%). From initial 71.4% of the cases only 41.4% reported a continuous disease course, whereas 30.6% had a chronically and 18.5% an occasionally relapsing disease course. 9.6% no longer had any or only a single relapse within the preceding 12 months. This decrease is statistically significant with moderate effect size (V=2314.5, $p < .005$, CI: .5 - 1.5, r= .414). Accordingly, disease severity decreased significantly over the study course (V=739.5, $p < .005$, CI: .5-1.5, r= .483). Severe to very severe courses reduced by 40%; 7.7% had healed. Health-related quality of life measured by DLQI (Dermatology Life Quality Index) significantly increased, too (V=23956, p<.005, r=.240, 95%-CI =.130 - .350).

To further investigate clinical long-term courses and to for the first time apply Mdx in a longitudinal setting, a follow-up research project started in 01/2025. Patients of this cohort are contacted again and asked for taking part in a second Mdx. Afterwards they are again followed up over 3 years, using the same outcome measures and investigating the persistence or change in molecular signatures. While the initial process asked for 4 mm punch biopsies of lesional skin, now the Mdx can be performed with a superficial shave just until the dermoepidermal junction. This procedure reduces burden and risk for patients and improves applicability, as it is performable by trained, non-medical staff. To date, 53 people have already be included and the minimum amount of necessary patients was reached.

We see promising results for Mdx use in distinguishing eczema from psoriasis in a real world setting, accompanied by improvement of clinical and patient-reported outcomes. Methodical advances now provide improved practicability and ease of use. A follow-up study will investigate development of both diseases on a molecular level, as well as practical outcomes.

Kategorie: Translational Research
Präsentationsart: Poster

Abstract-ID: 176

Clitocine for Translational Read-through in Junctional Epidermolysis bullosa

Zhang, R.[1], Has, C.[1], Sayar, SB[1].
1 Department of Dermatology, Medical Center – University of Freiburg, Germany

Most patients with junctional epidermolysis bullosa (JEB) carry disease-causing pathogenic variants in *LAMB3*, the gene coding for the laminin b3-chain. The *LAMB3* nonsense mutation c.1903C>T (p.R635*) is recurrent across different populations. In a biallelic state it leads to lack of laminin-332 (LAM332) and severe skin and mucosal fragility, and impaired wound healing. Gene and stem cell therapy were effective in JEB-*LAMB3*, but not available in the clinical setting. Translational read-through (TRID) therapy is a relevant approach for JEB-LAM332. In this study, we evaluate read-through activity of nine TRIDs in JEB-LAMB3 and identify clitocine to induce superior read-through than aminoglycosides.

Kategorie: Translational Research
Präsentationsart: Poster

Abstract-ID: 177

MoleVision: AI-Supported Classification of Real-World Imaging Data in Borderline Melanocytic Lesions

Fietz, S.[1]; Lorenz C.[1]; Bolouli Mi.[2]; Mammadova, F.[3]; Knof, M.[1]; Vladimirova, G.[4]; Giuliani, M.[4]; Sirokay, J.[1]; de Vos-Hillebrand, L.[1]; Obermaisser, R.[3]; Hoff, N.[4]; Bohlouli Ma.[2]; Landsberg, J.[1]

[1] Center for Skin Diseases, University Hospital Bonn, Bonn, Germany
[2] Petanux GmbH, Bonn, Germany
[3] Chair of Embedded System, University of Siegen, Siegen, Germany
[4] Department of Dermatology, University Hospital Düsseldorf, Düsseldorf, Germany

Background: Numerous studies have demonstrated the potential of artificial intelligence (AI) in distinguishing between benign and malignant melanocytic lesions. However, most published datasets lack real-world and histologically confirmed “borderline” cases such as dysplastic nevi, and thin (< 1mm) melanomas, limiting model performance in real-world scenarios. In addition, current approaches often rely on single-dimensional data and lack the multidimensional integration needed to improve diagnostic accuracy and robustness. *MoleVision* aims to develop and validate a neural network trained on a multidimensional, histopathologically confirmed real-world dataset to reliably distinguish benign from malignant melanocytic lesions. Secondary goals include integrating radar technology and explainable AI within an embedded system.

Materials & Methods: *MoleVision* integrates high-quality macroscopic and dermoscopic images with detailed clinical data as the foundation of its learning algorithms. A special focus is placed on real-world “borderline” melanocytic lesions, such as dysplastic nevi in situ melanomas, and melanomas with a tumor thickness of < 1mm. Patients are prospectively enrolled at two skin cancer centers (UKB and UKD), with ambiguous cases undergoing standard excision and histopathological review. The neural network will be trained and validated on two independent datasets (UKB and UKD), while the potential of radar sensor technology is explored to further enhance diagnostic performance.

Results: By now, we have collected and annotated multidimensional image and clinical data from a total of *N* = 1,119 melanocytic lesions, including 703 cases from 433 patients at the University Hospital Bonn. 472/703 lesions were confirmed histologically. At this site, image data is currently available for 288 invasive melanomas (IM) and 30 in situ melanomas (NIM), while multidimensional image and clinical data have been acquired for 43 IM and 17 NIM. Both subcohorts include a particularly high proportion of thin (tumor thickness < 1mm) melanomas. Comprehensive radar data has been collected from a subcohort of *N* = 23 skin lesions. Preliminary hierarchical clustering after dimensional reduction enabled an accurate distinction between benign and malignant melanocytic lesions.

Outlook: Recent studies (Brinker et al., Nature Communications, 2025) have shown that even experienced dermatopathologists often arrive at divergent diagnoses when assessing “borderline” melanocytic lesions. To enhance diagnostic accuracy and consistency, > 400 histopathological diagnoses (UKB cohorts) will therefore be re-evaluated by an expert panel of 5–8 dermatopathologists. Subsequently, our pre-developed AI will be trained and validated on the newly generated multidimensional real-world data.

Kategorie: Translational Research
Präsentationsart: Poster

Abstract-ID: 178

Improving Outpatient Workflows through Structured History Collection with Large Language Models

Steinbuch, S. C. [1,2,3]; de Vos-Hillebrand, L. [2]; O'Neill-Dee, C. [4]; Wu, I. [5,6]; Steinbuch, H. [7]; Kulcsár, Z. [2,3]; Ranjan, A. [8]; Verma, A. [4]; Landsberg, J. [2]; Dietrich, D. [3]; Hardin, C. C. [6]; Jain, R. K. [1]; Subudhi, S. [1]

1 Edwin L. Steele Laboratories, Department of Radiation Oncology, Massachusetts General Hospital, Boston, United States
2 University of Bonn, University Hospital Bonn, Clinic for Dermatology-Oncology and Phlebology, Bonn, Germany
3 University of Bonn, University Hospital Bonn, Clinic and Polyclinic for Ear, Nose and Throat Medicine, Bonn, Germany
4 Department of Medicine (Nephrology), Boston University Chobanian & Avedisian School of Medicine, Boston, United States
5 Harvard-MIT Health Sciences and Technology Program, Harvard Medical School, Boston, United States
6 Medicine-Pulmonary and Critical Care Medicine, Massachusetts General Hospital, Boston, United States
7 Department of Internal Medicine, University Hospital of Zürich, Switzerland
8 Adobe, Boston, United States

Introduction: Comprehensive and accurate history taking is a cornerstone of high-quality patient care. However, this process is often constrained by limited time and documentation burden. We hypothesize that Large Language Models (LLMs), when provided with appropriate guiding prompts, will be able to effectively and efficiently collect histories.

Methods: We developed a structured prompting framework that performs quality checks based on the patient's responses and then assesses the completeness of the sections in the medical history. If an adequate history has not been collected, it asks relevant question within the same section; otherwise, it proceeds to the next section, ensuring full coverage of the required components. We applied this framework to build an interactive application. To evaluate the performance, we applied the application to 52 New England Journal of Medicine (NEJM) case reports and 20 constructed clinical scenarios. In each case, a simulated patient interacted with the chatbot application. To run the framework, we used one of the three LLMs (GPT-4o, Gemini-2.5-lite, or Grok-3). Upon completion of the interaction with the simulated patient, the chatbot generated a structured, EHR-ready clinical summary that included suggested differential diagnoses and initial investigations. This output was then made available through the physician's interface.

Results: Across all cases, the structured prompting chatbot captured relevant histories with more than 85% accuracy. The suggested investigations closely aligned with those used to establish the final diagnosis. Regarding the diagnostic performance, the chatbot provided the correct diagnosis in approximately 50% of the NEJM cases using history alone, and over 90% in the constructed cases, respectively.

Discussion: These findings demonstrate that LLM-guided, agentic chatbots can reliably elicit comprehensive and clinically meaningful histories in standardized scenarios. Further validation in outpatient clinical settings is warranted to assess usability, workflow integration, and impact on efficiency. Concluding, this application has the potential to reduce documentation burden, standardize data quality, and improve the quality of patient care.

Kategorie: Translational Research
Präsentationsart: Poster

Abstract-ID: 179

Molecular therapies for junctional epidermolysis bullosa with *COL17A1* nonsense mutation

Tan, Y.[1], El Mabrouk, H.[1], Zhang, R.[1], Has, C.[1], Sayar, SB.[1]

1 Department of Dermatology, Medical Center, University of Freiburg, Freiburg, Germany.

Junctional Epidermolysis Bullosa (JEB) is a rare, genetically heterogeneous mechanobullous disorder. Its primary clinical manifestation is skin blistering, which leads to wounds that may become chronic. Many patients with JEB due to collagen XVII (C17) deficiency (JEB-C17) have a normal life span but develop chronic wounds that are difficult to treat and may progress to squamous cell carcinoma. Although gene therapy approved by the FDA and EMA exists for dystrophic EB, no such treatments are currently available or developed for JEB. Because JEB is ultra-rare, there is limited interest from pharmaceutical companies. In this study, we designed the therapeutic strategy for JEB-C17. We developed TRID(s) cocktail containing different TRIDs with nonsense mediated decay inhibitors and anti-oxidants. We observed that different TRIDs cocktails showed selective read-through activity in overcoming certain nonsense mutations. This suggests that TRID cocktail based personalized therapy needs to be developed for JEB-C17.

Kategorie: Translational Research
Präsentationsart: Poster

Tumor biology

Abstract-ID: 180

An *in silico* scoring-based framework for tumor antigen discovery

Glaser, H. 1; Purde, M. 1; Flatz, L. 1,2

1 Kantonsspital St. Gallen, Institute of Immunobiology, St. Gallen, Switzerland
2 Department of Dermatology, University Hospital Tuebingen, Tuebingen, Germany

As targets of the immune system, tumor antigens play a central role in the development of effective cancer immunotherapies. Specifically, tumor-associated antigens are common targets, as they can be shared across patients and cancer types. Especially tumor entities lacking established target antigens highlight the need for discovering novel cancer antigens that can be targeted individually or in combination.

Here, we developed a computational pipeline to score and rank tumor antigens using publicly available transcriptomic data. Instead of filtering antigens using strict arbitrary thresholds, this method scores them by integrating criteria such as magnitude of expression in tumor, prevalence across patients and tumor specificity, avoiding the removal of potentially relevant candidates. For each antigen, two scores are calculated: one identifies universal antigens, which are broadly expressed across patients, and the other captures niche antigens highly expressed in a subset of patients. Due to its adaptable architecture, the method is applicable across cancer types, providing a systematic approach for tumor-associated antigen discovery.

Applied to melanoma as a proof of concept, the pipeline successfully ranked well-established melanoma-associated antigens as top candidates and revealed potential novel targets for immunotherapy.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 181

Linking deficiency of lymphoid collagen VII and autoimmunity

Panagiota Moraiti[1,2], Dimitra Kiritsi[1,3], Gregor Conradt[1,2], John Atanga[1], Alexander Nyström[1]

[1]Department of Dermatology, Medical Faculty, Medical Center, University of Freiburg, Germany

[2]Faculty of Biology, University of Freiburg, Germany

[3]First Department of Dermatology, School of Medicine, Aristotle University, Thessaloniki, Greece

Dystrophic Epidermolysis Bullosa (DEB) is a rare genetic disorder characterized by chronic skin fragility and blistering, caused by pathogenic variants in the *COL7A1* gene encoding collagen VII. DEB not only results in skin blistering, but also progressive fibrosis and multi-organ failure with features of autoimmunity. Previous studies indicated that collagen VII deficiency might predispose to autoimmunity in DEB. Here, we aimed to explore the relationship between loss of lymphoid collagen VII and autoimmunity. Mice with generalized collagen VII deficiency displayed evidence of progressive immune-driven disease, with increasing tissue deposition of antibodies. To exclude contribution of injury from tissue fragility to the phenotype, we employed K14-driven collagen VII knockout mice. In these mice, collagen VII is absent in medullary thymic epithelial cells (mTECs) within the thymus, while skin integrity remains intact due to collagen VII expression by fibroblasts in dermis. Although these mice appeared phenotypically healthy at birth and as young adults, a subset developed a progressive inflammatory disease, which presented as hyperkeratotic, inflamed skin lesions and enlarged lymphoid organs. Sera from these mice contained elevated levels of autoreactive antibodies with wide reactivity including antinuclear antibodies. The specific localization of collagen VII within the thymus and its absence in mTECs in our mouse model highlights its crucial role in maintaining immune tolerance. Our study indicates that the collagen VII dysregulation in lymphoid organs might be linked to an increased risk of autoimmunity.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 182

EORTC CLTG study to collect cases of patients with primary cutaneous T-cell lymphoma and a secondary hematologic neoplasm

Melchers, S.[1] Funke, N.[2] Bernard, P.[3] Booken, N.[4] Cowan, R.[5] Dummer, R.[6] Guenova, E.[7] Hansen-Abeck, I.[8] Hartmann, A.[9] Hatzakis, A.[10] Jonak, C.[11], King-Stokes, N.[12], Kreuter, A.[13], Mitsunaga, K.[14], Moritz, R. K. C.[15], Nikolaou, V.[16] Obeid, M.[17], Ottevanger, R.[18], Ortiz-Romero, P.[19], Papadavid, E.[20], Porkert, S.[21], Quaglino, P.[22], Roccuzzo, G.[23], Roggo, A.[24], Scarisbrick, J. J.[25], Vermeer, M.[26], Wehry, U.[27], Wobser, M.28, Ziemer, M.[29], Weiss, C.[30], Nicolay, J. P.[31]

1 Department of Dermatology, Venereology and Allergology, University Medical Center Mannheim\/ University of Heidelberg, Mannheim, Germany Skin Cancer Unit, German Cancer Research Center (DKFZ), Heidelberg, Germany Section of Clinical and Experimental Dermatology, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany.
2 Department of Dermatology, Venereology and Allergology, University Medical Center Mannheim\/ University of Heidelberg, Mannheim, Germany.
3 Department of Dermatology, University Hospital of Lausanne and Faculty of Biology and Medicine, University of Lausanne, Lausanne, Switzerland.
4 Department of Dermatology and Venereology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
5 Department of Clinical Oncology, The Christie NHS Foundation Trust, and University of Manchester, Manchester, UK.
6 Department of Dermatology, University Hospital Zurich, Zurich, Switzerland.
7 Department of Dermatology, University Hospital of Lausanne and Faculty of Biology and Medicine, University of Lausanne, Lausanne, Switzerland.
8 Department of Dermatology and Venereology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.
9 Department of Dermatology, University Hospital Erlangen, Erlangen, Germany.
10 Department of Dermatology, University Hospital Birmingham, Birmingham, UK.
12 Department of Dermatology, University Hospital Birmingham, Birmingham, UK.
13 Department of Dermatology, Venereology and Allergology, HELIOS St. Elisabeth Klinik Oberhausen, University Witten-Herdecke, Oberhausen, Germany.
14 Department of Dermatology, Hospital Universitario 12 de Octubre, Institute i+12, CIBERONC, Medical School, University Complutense, Madrid, Spain.
15 Department of Dermatology, Venereology and Allergology, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany.
16 National and Kapodistrian University of Athens, 2nd Department of Dermatology and Venereology, Attikon General Hospital, University of Athens, Chaidari, Greece.
17 Department of Clinical Oncology, The Christie NHS Foundation Trust, and University of Manchester, Manchester, UK.
18 Department of Dermatology Leiden University Medical Center Leiden Netherlands.
19 Department of Dermatology, Hospital Universitario 12 de Octubre, Institute i+12, CIBERONC, Medical School, University Complutense, Madrid, Spain.
20National and Kapodistrian University of Athens, 2nd Department of Dermatology and Venereology, Attikon General Hospital, University of Athens, Chaidari, Greece.
21 Department of Dermatology, Medical University of Vienna, Vienna, Austria.
22 Department of Medical Sciences, Section of Dermatology, University of Turin, Turin, Italy.
23 Department of Medical Sciences, Section of Dermatology, University of Turin, Turin, Italy.
24 Department of Dermatology, University Hospital Zurich, Zurich, Switzerland.
25 Department of Dermatology, University Hospital Birmingham, Birmingham, UK.
26 Department of Dermatology Leiden University Medical Center Leiden Netherlands.
27 Department of Dermatology, Venereology and Allergology, HELIOS St. Elisabeth Klinik

Oberhausen, University Witten-Herdecke, Oberhausen, Germany.
28 Department of Dermatology, Venereology and Allergology, University Hospital Würzburg, Würzburg, Germany.
29 Department of Dermatology, Venereology and Allergology, University Medical Center, Leipzig, Germany.
30 Department of Medical Statistics and Biomathematics, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany.
31 Department of Dermatology, Venereology and Allergology, University Medical Center Mannheim/ University of Heidelberg, Mannheim, Germany, Skin Cancer Unit, German Cancer Research Center (DKFZ), Heidelberg, Germany, Section of Clinical and Experimental Dermatology, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany, DKFZ-Hector Cancer Institute at the University Medical Center Mannheim, Mannheim, Germany.

Abstract:
Introduction
Primary cutaneous lymphomas are rare lymphoproliferative diseases that primarily affect the skin but can also spread to lymph nodes, blood, and viscera. For primary cutaneous T-cell lymphomas (CTCL), it is postulated that affected patients have an increased risk of other hematologic neoplasm such as M. Hodgkin or chronic lymphocytic leukemia (CLL). However, studies that systematically record the frequency of secondary hematologic neoplasms are still lacking. The aim of this study is to quantify secondary hematologic neoplasm diagnoses in CTCL patients, to collect clinical characteristics and to identify possible predictors of disease progression.

Materials and Methods A total of 204 patients collected from 17 Departments of Dermatology in 9 countries were included in this multinational, multicenter study. Cases were collected via the EORTC Cutaneous Lymphoma Tumor Group (CLTG) and the ADO Cutaneous Lymphoma Working group.

Results
A total of 204 patients diagnosed with CTCL and an additional hematologic neoplasm were included. Over 30 secondary hematologic neoplasm diagnoses were observed. The most frequent secondary hematologic neoplasms included M. Hodgkin (18.63%), CLL (14.71%), and lymphomatoid papulosis (11.27%). The secondary hematologic neoplasms primarily manifested in the peripheral blood (30.49%) the lymph nodes (19.51%), and the skin (8.45%). Regarding the CTCL, 87.19% of the patients were diagnosed with MF and MF variants, and 5.42% with Sézary Syndrome. The majority of CTCL patients had early stage disease (72.38% stage I). Strikingly, although suffering from early stage disease, 65% of the patients received systemic first line therapy for their CTCL, pointing towards more persistent symptoms. Surprisingly, the assessment of the temporal relationship between the CTCL and the secondary hematologic neoplasm revealed, that in the majority of cases (61.19%), the secondary hematologic neoplasm preceded the CTCL diagnosis. Further information on the course of treatment, adverse drug reactions, remission status, as well as laboratory chemical parameters such as differential blood count, lactate dehydrogenase, and blood involvement by flow cytometry were assessed.

Conclusions
Patients with CTCL may develop a variety of secondary hematologic neoplasm. The most common secondary hematologic malignancies in our study cohort were M. Hodgkin, CLL, and lymphomatoid papulosis. In our study population, secondary hematologic neoplasms tended to precede the CTCL diagnosis. A further statistical analysis of the collected data is currently conducted at the Institute for Biostatistics of the Medical Faculty Mannheim of the University of Heidelberg. The final data will be presented at the ADF Meeting 2026 in Freiburg.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 183

Novel Potential Targets for CAR T-Cell Therapy of Merkel Cell Carcinoma

Feuchter, N. [1]; Bremm, F. [1]; Juraschek, K. F. [1]; Güse, E. [1]; Hof, M. M. C. [1]; Berking, C. [1]; Vera, J. [1]; Schaft, N. [1]; Dörrie, J. [1]

1 Department of Dermatology, Friedrich-Alexander-Universität (FAU) Erlangen-Nürnberg, Uniklinikum Erlangen, Comprehensive Cancer Center Erlangen European Metropolitan Area of Nuremberg (CCC ER-EMN), CCC WERA, Deutsches Zentrum Immuntherapie (DZI), Bavarian Cancer Research Center (BZKF), Erlangen, Germany (*Schaft, N. and Dörrie, J. share senior authorship*)

Merkel cell carcinoma (MCC) is a rare but highly aggressive neuroendocrine skin cancer, often associated with a life-threatening prognosis due to its strong metastatic potential. The occurrence of MCC is mainly associated with the expression of a truncated version of the large T antigen (truncLT) originating from the Merkel cell polyomavirus (MCPyV). This viral oncoprotein is assumed to drive carcinogenesis by dysregulating multiple cellular regulatory processes like cell cycle progression and immune response. Although antibody-mediated immune checkpoint inhibition targeting PD-1 or PD-L1 has emerged as a major advancement in MCC treatment, clinical observations still report a substantial proportion of patients with limited response and compromised long-term survival.

Given the proven clinical success of CAR T-cell therapy in hematological cancers and its emerging efficacy against solid tumors, we aimed to identify new CAR T-cell targets on MCC tumor cells to expand the present treatment panel. Therefore, we generated and analyzed bulk RNA-sequencing data from the established MCC cell lines MKL-1, MKL-2, and WaGa to identify suitable surface and/or transmembrane proteins. Besides confirmed protein surface expression of promising antigen candidates on MCC cells, target selection was further refined based on low antigen expression on healthy tissue and pre-existing data in the context of other tumors. Finally, the transmembrane transporter protein SLC1A5 and the receptor tyrosine kinase ErbB3 were identified, for which CAR constructs were available from other projects. The corresponding CARs consisted of respective scFvs in established backbones containing a CD28 transmembrane element and an intracellular CD3zeta signaling domain.

CAR expression was induced in over 80 % of primary human $CD8^+$ T cells isolated from the whole blood of healthy donors via transient mRNA electroporation which was verified for a minimum of 22 h by flow cytometry for both constructs. Furthermore, antigen-specific lysis of the MCC cell lines MKL-1, MKL-2, and WaGa was achieved by anti-SLC1A5-CAR-equipped cytotoxic T cells in an effector cell dose-dependent manner after 20-22 h *in vitro* co-incubation. Potential antigen-independent off-target activity was simultaneously excluded by monitoring the viability of autologous lymphocytes as targets in the same co-cultures. Relative rates of CAR-dependent lysis of MCC cells reached up to 60 % for MKL-1 and MKL-2 cells at a 5:1 CAR T-cell to target cell ratio, while WaGa cell lysis exhibited considerable, but lower, efficacy with an average of 15 % at the same effector:target cell ratio. Anti-ErbB3-CAR-expressing T cells, however, did not induce comparable MCC tumor cell lysis.

Taken together, we successfully identified SLC1A5 as a novel CAR target on MCC cells based on RNA-sequencing data. T cells expressing the anti-SLC1A5-CAR mediated antigen-specific tumor cell killing and demonstrated strong potential for future application in CAR T-cell therapy.

Kategorie: Tumor biology
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 184

Disrupting Epigenetically Regulated BIRC5 Expression as a Therapeutic Strategy in BRAFi-Resistant Melanoma

Gerloff, D.[1]; Cynis, H.[2] ;Gul, S.[3] Uebel, A.[1] ;Hiemer, S.[1,4]; Sunderkötter C[1]

1 Department of Dermatology and Venereology, University Hospital, Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany

2 Department of Drug Design and Target Validation, Fraunhofer Institute for Cell Therapy and Immunology, Halle(Saale), Germany

3 Innovation Area Drug Screening & Compound RepurposingFraunhofer Institute for Translational Medicine and Pharmacology ITMP, Hamburg, Germany

4 Krukenberg Cancer Center Halle, University Hospital Halle, Martin Luther University Halle-Wittenberg, Halle, Germany

Introduction: BRAF mutations have been observed in approximately 50–60% of malignant melanomas. Despite the fact that tumours with these mutations initially respond to BRAF-targeted therapies (BRAFi), acquired resistance frequently emerges and limits treatment effectiveness. As demonstrated in our previous research, the presence of BRAFi resistance has been observed to be associated with epigenetic modifiers, such as EZH2 and HDACs. These modifiers have been shown to regulate gene expression by altering the structure of chromatin. Despite the evidence that these regulators drive cancer progression, their precise role in the development of BRAFi resistance remains poorly understood.

Aim: The objective of this study was to investigate if the inhibition of HDACs could target melanoma cells resistant to BRAFi and to elucidate the underlying molecular mechanisms.

Results: In a compound screening of 80 different HDAC inhibitors, four candidates were identified that demonstrated robust effects in various BRAFi-resistant cell lines, in addition to exhibiting synergistic interactions with BRAFi in the context of melanoma cells. It was observed that cells with a BRAF mutation exhibited heightened sensitivity to these HDAC inhibitors in comparison to BRAF wild-type cell lines and normal healthy cells. Utilising next-generation sequencing on resistant melanoma cells treated with various inhibitor combinations, we identified downstream signalling pathways and various deregulated gene expressions mediated by HDACs. One of the genes that was identified as being deregulated was BIRC5, a gene which has been previously characterised as an anti-apoptotic oncogene in a variety of cancers. Inhibition of BIRC5 by the inhibitor YM155 or by siRNA resulted in a significant reduction in cell viability in both BRAFi-sensitive and resistant melanoma cells. The analysis of data sets indicates that BIRC5 expression is elevated in melanoma cells, particularly in those with a BRAF mutation, in comparison with normal melanocytes. In addition, elevated BIRC5 expression has been demonstrated to be associated with poorer survival outcomes in melanoma patients with BRAF mutations.

Conclusion: In conclusion, our data reveal that BIRC5 (Survivin) expression is epigenetically maintained by HDAC activity in BRAFi-resistant melanoma cells, allowing continued proliferation and survival despite BRAFi treatment. Pharmacological inhibition of HDACs or direct targeting of BIRC5 downregulates its expression and restores apoptotic sensitivity and cell cycle arrest, providing a novel therapeutic strategy to overcome resistance in BRAF-mutant melanoma.

Kategorie: Tumor biology
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 185

Soluble Immune Profiling Reveals Distinct Systemic Immune Signatures in Melanoma Progression and in Response to Immunotherapy.

Alessandra Rünger[1,2]; Merle Reetz[3]; Sarina Heinemann[3]; Katharina Kolbe[3]; Jessica Stanik[3]; Glenn Geidel[1,2]; Julian Kött[1,2]; Stefan W. Schneider[1,2]; Katrin Lamszus[3]; Malte Mohme[3]; Cecile Maire[3]; Christoffer Gebhardt[1,2]

[1]Department of Dermatology and Venerology, University Medical Center Hamburg-Eppendorf (UKE), Hamburg, Germany

[2]Fleur Hiege Center for Skin Cancer Research, University Medical Center Hamburg-Eppendorf (UKE), Hamburg, Germany

[3]Department of Neurosurgery, University Medical Center Hamburg-Eppendorf (UKE), Hamburg, Germany

Introduction:
Despite advances in the treatment of advanced melanoma, some patients, particularly those with melanoma brain metastases (MBMs), remain a therapeutic challenge. We hypothesize that melanoma progression is accompanied by systemic immune alterations, that these are further amplified in patients with MBMs, and that these correlate with clinical outcomes. By profiling soluble immune mediators in healthy donors and melanoma across disease stages, we aimed to identify circulating immune signatures associated with disease progression and treatment response.

Methods:
Forty-six soluble immune mediators, including cytokines, chemokines, growth factors, angiogenic and immune checkpoint molecules, were profiled in patient plasma using LEGENDplex™ multiplex bead-based immunoassays. 97 plasma samples were analyzed from healthy donors (HD, *n*=19) and melanoma patients across three stages: stage II/III disease (*n*=18), distant extracranial (*n*=8) and brain metastases (*n*=13). For all patient groups, paired samples were collected from the same individuals at two timepoints, prior to and during immune checkpoint inhibitor therapy. Data were analyzed to assess systemic immune alterations linked to melanoma progression and treatment response.

Results:
In metastatic melanoma, multiple soluble immune mediators were altered compared with non-metastatic disease. Markers of T-cell activation and immune checkpoint engagement (sCD25, PD-L2, LAG-3, and Galectin-9) were markedly elevated in metastasis, with sCD25 increasing nearly twofold and Galectin-9 rising by over 60% in brain metastatic patients compared to lower-grade disease. Chemotactic and myeloid-associated mediators (CCL2 and sTREM-2) and the neurotrophic factor BDNF were also increased, with BDNF approximately 1.5-fold higher in brain metastases than in low-grade tumors, indicating enhanced myeloid and neuroimmune activity.

Pro-angiogenic and inflammatory cytokines were upregulated, with VEGF roughly doubling in brain metastases **and both sCD25 and IL-6 showing pronounced increases under immunotherapy, consistent with immune activation.** The soluble decoy receptor sRAGE declined with disease progression, suggesting loss of counter-regulation. Growth and tissue-repair factors (PDGF-BB, IL-7, CCL11, and EGF) were higher in metastatic patients. Notably,

PDGF-BB increased approximately 1.5- to 2-fold in brain metastases relative to non-metastatic disease. Components of the TNF and IL-6 signaling pathways (sTNF-RI, sTNF-RIII, and sCD130) were also increased, indicating systemic inflammatory activation. In contrast, innate and platelet-derived mediators (PAL-1, PTX3, and sCD40L) varied without a consistent trend. **Several immune alterations correlated with clinical parameters, suggesting links to treatment response**

Conclusion:
In metastatic melanoma, particularly with brain metastases, we observed a distinct systemic immune and cytokine profile characterized by checkpoint activation, myeloid and neuroinflammatory signaling, and enhanced angiogenic and growth-factor activity. While immunotherapy amplified several of these immune pathways, considerable heterogeneity within patient groups suggests that individual clinical factors, including treatment response, further shape the soluble immune landscape beyond disease progression alone.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 186

Biological Safety Assessment of Novel Helium Multijet Cold Atmospheric Plasma Technology in Actinic Keratosis – from In Vitro to In Vivo.

Ossowska, A.[1.], Zende, R.[2.], Staffeld, A.[1.], Bekeschus, S.[1,3.], Stancampiano, A.[2.], Robert, E.[2.], Emmert, S[1.], Boeckmann, L.[1.]

1 University Medical Center Rostock, Clinic and Polyclinic for Dermatology and Venereology, Rostock, Germany

2 CNRS/University of Orleans, GREMI, Orleans, France

3 Leibniz Institute for Plasma Science and Technology, Greifswald, Germany

Actinic Keratosis (AK) is among the most frequently treated skin conditions, impacting millions across Europe, the U.S., and Australia, with incidence rates rising in ageing populations. Although only a small percentage of these lesions progress to cutaneous squamous cell carcinoma (cSCC), AK presents a considerable treatment challenge and economic burden due to its widespread occurrence. Existing chemical and physical treatments often have limitations, including significant side effects, restricted treatment coverage, or low patient compliance. Cold atmospheric pressure plasma (CAP) therapy has emerged as a promising alternative, offering high efficacy with minimal side effects. However, most of the supporting evidence remains experimental. Furthermore, currently available CAP devices are limited in their ability to uniformly treat non-flat, lesion-covered areas or have a small application area, resulting in prolonged treatment times.

This project is part of the PlasmACT Marie Skłodowska-Curie Actions doctoral network, which seeks to advance AK treatment through the development and optimization of a novel multijet helium plasma device. The study is performed in accordance with European medical device standards (DIN EN ISO 10993-5), facilitating its translation into clinical practice and the European market. The primary objective of this project is to validate the safety and efficacy of helium plasma multijet therapy for AK, promoting its integration into routine dermato-oncology and supporting the broader implementation of plasma-based medical technologies in oncology.

The in vitro genotoxicity testing using the OECD approved micronucleus assay showed that treatment with the novel plasma device does not induce chromosomal damage in the healthy keratinocyte cell line (HaCaT). Furthermore, prolonged continuous exposure in confluent cell cultures caused minimal cytotoxicity in HaCaT keratinocytes, as assessed by the OECD-approved XTT assay, suggesting good tolerance of the treatment up to three minutes at the 70% cytotoxicity threshold.

Additional evaluation of dermatological safety has been assessed physically via *ex vivo,* contact-less temperature measurement which showed that continuous, manual treatment does not cause the surface temperature of porcine skin to increase beyond 40˚C. Electrical characterisation shows power delivery to target surface is influenced by the applicator-to-surface distance, the material properties of the treated substrate, input voltage, and grounding configuration.

Comprehensive in vivo safety and efficacy assessments are ongoing in SKH-1 hairless mice with UV-induced AK. The safety and tolerability of helium plasma treatment are being examined at molecular and histological levels in uncompromised skin, while therapeutic efficacy and long-term outcomes are evaluated based on the rate and success of AK lesion clearance in this murine model.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 187

Neutrophil extracellular traps (NETs) as potential biomarkers of immunotherapy in melanoma

A. Zeinal Abedini [1,2]; J. Kött [1,2] A. T. Bauer [1]; J. Gerwers [3]; D. J. Smit [2,4]; I. Heidrich [1,2,4]; G. Geidel [1,2]; A. Rünger [1,2]; T. Zell [1,2]; N. Zimmermann [1,2]; K. Pantel [2,4]; T. Renné [3]; S.W. Schneider [1,2]; C. Gebhardt [1,2]

1 University Medical Center Hamburg-Eppendorf, Department of Dermatology and Venereology, Hamburg, Germany

2 University Medical Center Hamburg-Eppendorf, Fleur Hiege Center for Skin Cancer Research, Hamburg, Germany

3 University Medical Center Hamburg-Eppendorf, Clinical Chemistry and Laboratory Medicine, Hamburg, Germany

4 University Medical Center Hamburg-Eppendorf, Institute of Tumor Biology, Hamburg, Germany

Introduction:

Neutrophil granulocytes, the first defense against infections, are able to influence tumor growth and release web-like DNA structures called neutrophil extracellular traps (NETs), which are coated with enzymes and proteins to trap pathogens. NETs, known for their procoagulant properties, have become a focus of research particularly for their potential as biomarkers in melanoma patients undergoing immune checkpoint inhibitor (ICI) therapy, which we aimed to investigate.

Methods:

The study cohort consisted of 40 advanced melanoma patients with varying responses to ICI therapy, sourced from our melanoma biobank. Patients were categorized into three groups based on clinical characteristics: ICI responders (sustained response), primary non-responders (radiologically confirmed progression within 6 months), and secondary non-responders (progression after more than 6 months). Blood samples were collected at baseline, 1 month, 3 months into therapy, and if applicable at the time of disease progression. Initially, isolated neutrophils were co-incubated with plasma from different patient groups, including healthy donors, control patients, patients with progressive disease (PD), and patients in complete remission. NET quantification in serum was conducted using the ELK Biotechnology Citrullinated Histone H3 (CitH3) ELISA Kit. Furthermore, MMP8 levels were measured using the Sigma-Aldrich ELISA Kit to assess neutrophil activation and degranulation, as MMP8 serves as a marker of neutrophil-derived enzymatic activity. In parallel, DNase I activity in patient serum was assessed by Single Radial Enzyme-Diffusion Assay, and SYBR Safe fluorescence was measured using the Biorad ChemiDoc MP system. Additionally, tumor tissue sections were stained with DAPI, CitH3, and CD15 to evaluate neutrophil infiltration in primary tumors, metastases, and lymph nodes. Lastly, platelet activation was evaluated by flow cytometry using the PAC-1 monoclonal antibody and by a platelet factor 4 (PF4) ELISA. Platelet–leukocyte aggregates (PLAs) were also quantified by flow cytometry using the PAC-1 antibody in combination with leukocyte-specific markers.

Results:

Current evaluation of tissue staining and MMP8 levels is ongoing.

Analysis of neutrophil-related markers revealed distinct patterns associated with clinical response to ICI therapy. Regarding NET quantification, a significant difference can be observed within the responder group when comparing samples collected at baseline and at 1 month into ICI therapy. DNase I activity, responsible for NET degradation, remained stable across all cohorts.

Evaluation of MMP8 levels demonstrated a significant difference when comparing ICI responders to the combined non-responder cohort (comprising both primary and secondary resistance). Furthermore, a notable trend can be observed between responders and primary non-responders at baseline.

Additionally, immuno-resistant melanoma patients exhibited higher platelet activation prior to ICI therapy, while lower levels of PLAs were observed in patients undergoing ICI treatment.

Conclusion / Outlooks:

This study is currently being expanded through ongoing experimental investigations to broaden the initial findings. Our findings reveal that neutrophil and platelet dynamics are closely linked to ICI outcomes: responders exhibit significant early NET shifts and distinct MMP8 profiles compared to non-responders, the latter of whom are characterized by higher baseline platelet activation and reduced circulating PLAs during treatment. This research has great potential to improve melanoma therapy and enable early detection of resistance.

Kategorie: Tumor biology
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 188

Cytokeratins as tumor associated antigens in oropharyngeal and cutaneous squamous cell carcinoma

Balciunaite, B.[1]; Walter, V.[1]; Kilic, M.[1]; Wacker, M.[7,8,9,10]; Jochum, A. K.[2,3]; Abdou, M. T.[2]; Pop, O. T.[2]; Purde, M.[2]; Walz, J.[7,8,9,10]; Flatz, L.[1,2,4,5,6]

1 Department of Dermatology, Eberhard Karls University Hospital Tübingen, Tübingen, Germany

2 Institute of Immunobiology, Kantonsspital St. Gallen, St. Gallen, Switzerland

3 Institute of Pathology, Kantonsspital St. Gallen, St. Gallen, Switzerland

4 Department of Dermatology, Dermatology and Venerology, Kantonsspital St. Gallen, St. Gallen, Switzerland

5 Department of Dermatology, University Hospital Zürich, University of Zürich, Zürich, Switzerland

6 Department of Oncology and Haematology, Kantonsspital St. Gallen, St. Gallen, Switzerland

7 Department of Peptide-based Immunotherapy, University of Tübingen, Tübingen, Germany

8 Institute of Cell Biology, Department of Immunology, University of Tübingen, Tübingen, Germany

9 German Cancer Consortium (DKTK) and German Cancer Research Center (DKFZ), partner site Tübingen, Tübingen, Germany

10 Cluster of Excellence iFIT (EXC 2180) 'Image-Guided and Functionally Instructed Tumor Therapies', University of Tübingen, Tübingen, Germany

Background: Keratinocyte differentiation antigens (KDAs) have been identified as tumor-associated antigens and correlate with improved survival in non-small cell lung cancer patients undergoing checkpoint blockade. KDA-specific T cell clonotypes have been detected in tumors and in checkpoint blockade–induced lichenoid rashes. Histologically, these rashes in squamous cell carcinoma (SCC) patients show epidermal T cell infiltration, in contrast to the dermal infiltration observed in adenocarcinomas, suggesting that SCC patients develop keratin-reactive T cells.

Objective: To investigate whether squamous cell carcinomas of different origins harbor keratin-reactive T cells.

Methods: Cutaneous SCC (cSCC) samples underwent HLA-I and HLA-II mass spectrometry analysis. The publicly available PCI-DB database by *Lemke et.al.* was used to characterize the immunopeptidome of oropharyngeal SCC (OPSCC). T cell stimulations were performed using keratin peptide pools. Single-cell RNA sequencing (scRNA-seq) was used to identify keratin-specific T cell receptors (TCRs) in peripheral blood. DNA from cSCC tumor samples was analyzed for TCR CDR3 regions using the Cellecta DriverMap AIR TCR-BCR Profiling Kit.

Results: Immunopeptidomic analysis confirmed the presentation of keratin-derived peptides on MHC-I molecules in both OPSCC and cSCC tissues. T cell stimulations demonstrated the presence of cytokeratin-reactive T cells in both patient groups, with responses in cSCC primarily directed against keratin 14, and in OPSCC against keratins 5 and 14. Although keratin-derived peptides were also detected in healthy skin, keratin-reactive $CD8^+$ T cells were

absent from the peripheral blood of healthy individuals. HLA typing revealed an association between keratin 14–reactive T cells and the HLA-B*07 allele (Fisher's exact test, $p = 2.0 \times 10^{-5}$). Keratin 5 and 14–reactive $CD8^+CD69^+CD137^+$ T cells were isolated for scRNA-seq and V(D)J analysis, identifying keratin-specific TCR clonotypes. CDR3β sequencing confirmed that keratin 14–specific TCRs infiltrate cSCC tumors.

Conclusions: Our findings demonstrate that oropharyngeal and cutaneous SCC patients develop autoreactive T cells specific for keratinocyte differentiation antigens, which are presented on HLA-I molecules within tumors. These results establish KDAs as relevant tumor-associated antigens in squamous cell carcinoma.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 189

Genomic and transcriptomic analysis of response to anti-PD1 therapy in advanced cutaneous squamous cell carcinoma

Lorenz, C.[1] Helbig, D.[2] Mitra, S.[3] Abedpour, N.[3] Schwarz, R.[5] Bucaciuc-Mracica, T.[5] Cartolano, M.[3] Bröckelmann, P.[5] Persa, OD.[6] Dengler, S.[7] 11Kreuter, A.[8], Laimer, M.[9], Fröhlich A.[1], Landsberg, J.[1], Scheel, C.[10], Mauch, C.[10], Brägelmann, J.[2]

1 University Hospital Bonn, Center for Skin Diseases, Bonn, Germany
2 University Hospital Cologne, Department of
3 University of Cologne, Department of Translational Genomics, Cologne, Germany
5 University Hospital Cologne, Department I of Internal Medicine, Cologne, Germany
6 Technical University Munich, Department of Dermatology and Allergy Biederstein, Munich, Germany
7 Dortmund Hospital, Department of Dermatology, Dortmund, Germany
8 Helios St. Elisabeth Hospital Oberhausen, Department of Dermatology, Venereology and Allergology, Oberhausen, Germany
9 University Hospital of the Paracelsus Medical University Salzburg, Department of Dermatology and Allergology, Salzburg, Austria
10 St. Josef Hospital, Department of Dermatology, Venereology and Allergology, Bochum, Germany

Abstract:
Cutaneous squamous cell carcinoma (cSCC) is the second most common human malignancy worldwide and increasing incidence rates have been described worldwide. Although, excision is often curative, up to 5% of cSCCs develop metastases and approx. 1.5% of patients succumb to the disease. Traditionally, therapeutic options for patients with advanced or metastatic cSCC had been very limited. Recently, immune checkpoint blockade (ICB) with anti-programmed cell death 1 (PD-1) antibodies such as cemiplimab have been approved due to promising single-agent activity in patients with advanced or metastatic cSCC. Compared to other entities, cSCC patients have high response rates, however at least 50% of patients do not respond to anti-PD1 antibodies or develop resistant disease. Currently, it is not well understood, which factors underlie this differential responsiveness.

Here we combine genomic, transcriptomic, and spatially resolved proteomic profiling of 56 cSCC tumour samples prior to ICB therapy to identify molecular markers indicative of response to therapy. While genomic profiling revealed a significant association between features such as tumour mutational burden or neoantigen load and clinical outcome, transcriptomic profiling identified a highly immunogenic and immune infiltrated phenotype with enhanced response to anti-PD1 therapy. These findings not only shed light on the molecular characteristics of cSCC tumours that drive differential responses to ICB, but also provide potential biomarkers which could be used for clinical risk stratification in patients with cSCC for whom ICB is being considered.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 190

The Influence of melanoma extracellular vesicles on the vascular endothelium in the context of metastasis and clinical progression.

Carlos van Werde[1,2,*]; Julian Kött[1,2,*]; Alexander T. Bauer[1]; Yuanyuan Wang[1]; Jannis Akrivakis[1]; Daniel J. Smit[2,3]; Isabel Heidrich[1,2,3]; Glenn Geidel[1,2]; Alessandra Rünger[1,2]; Noah Zimmermann[1,2]; Tim Zell[1,2]; Klaus Pantel[2,3]; Stefan W. Schneider[1,2]; Christoffer Gebhardt[1,2]; Christian Gorzelanny[1]

1 Department of Dermatology and Venerology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

2 Fleur Hiege Center for Skin Cancer Research, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

3 Institute of Tumor Biology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Melanoma cells release extracellular vesicles (EVs) into the tumor microenvironment and systemic circulation. Previous studies suggest that tumor-derived EVs modulate the vascular endothelium in distant organs to promote hematogenous metastasis. This project aims to understand EV-induced changes in endothelial cells and their impact on tumor progression. We hypothesize that melanoma EVs induce a proadhesive, procoagulatory, and barrier-disruptive activation of endothelial cells, facilitating vascular escape of circulating melanoma cells. We further expect to identify similarities in the vascular endothelial growth factor (VEGF) signalling in proteomic EV analysis for patients with metastatic melanoma.

EVs were isolated from culture supernatants of metastatic melanoma cell lines MV3 and B16F10 via differential ultracentrifugation and ultrafiltration. Size and concentration of isolated EVs were analysed by nanoparticle tracking. Human umbilical vein endothelial cells (HUVECs) were incubated with 100–10,000 EVs per cell for 24 hours. RNA from melanoma EV-treated HUVECs was analysed by RNA sequencing. Barrier integrity was assessed by electrical cell substrate impedance sensing (ECIS), and adherens junctions were visualized by CD31 immunostaining. EV uptake was confirmed by fluorescence microscopy. A murine melanoma model (n=13) using C57BL/6 mice was used to evaluate the impact of EVs on lung metastases formation. The experimental group received 2.5×10^{10} EVs prior to B16F10 melanoma cell injection, while controls received melanoma cells only. After 14 days, lungs were dissected and the metastatic surface area was quantified. Additionally, a cohort of 40 patients with metastatic melanoma (20 with primary progress and 20 with progression-free survival $\geq$ 12 months, both under immune checkpoint inhibition) was selected, and blood samples were collected. In the coming weeks, EVs will be isolated from melanoma patients' plasma and analysed using liquid chromatography coupled mass spectrometry.

RNA sequencing revealed significant enrichment of pathways associated with vascular development, angiogenesis, and endothelial barrier function. Key regulated genes in HUVECs following EV treatment included an upregulation of Aquaporin 1 (AQP1) ($\log_2$FC = 2.68; padj = 0.004), and a downregulation of Kruppel-like factors KLF2/4 ($\log_2$FC = -1.1; padj = 0.01). ECIS revealed a 12% reduction in resistance in EV-treated HUVECs ($p < 0.01$), indicating impaired barrier function. CD31 immunostaining confirmed intercellular gaps and disrupted adherens junctions. In vivo, EV pre-treatment of mice showed a 12% increase in lung

metastases. The results for the proteomic profiling of our patient cohort are expected to be finished by February 2026.

These findings suggest that melanoma EVs promote hematogenous metastasis through direct effects on endothelial integrity. The involvement of AQP1 and KLF2/4 aligns with literature implicating them in endothelial dysfunction during metastatic progression. In next steps we will aim to identify a specific signalling profile in the EVs of our progression cohort, to draw more detailed mechanistic conclusions. In the future, targeting endothelial responses to tumor-derived EVs may offer a novel therapeutic strategy to limit metastatic spread.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 191

From Nevus to Metastasis: tRNAs as drivers of melanoma development and progression

Schultz, C.[1]; Valdivia Martinez, D. I.[2]; Gnauck, J.[3]; Mörl, M.[3]; Stadler, P.F.[2]; Kunz M.[1]

1 University of Leipzig Medical Center, Department of Dermatology, Venereology and Allergology, 04103 Leipzig, Germany

2 University of Leipzig, Department of Computer Science, Bioinformatics, 04107 Leipzig, Germany

3 University of Leipzig, Institute of Biochemistry, 04103 Leipzig, Germany

Altered gene translation of tumor-specific mRNAs is a well-recognized hallmark of cancer. In this study, we investigate melanoma biology from a novel translational perspective by focusing on transfer RNAs (tRNAs) as key adaptors in protein synthesis. Our aim is to uncover coordinated expression patterns of specific tRNAs and mRNAs as a molecular basis for malignant transformation and metastasis in melanoma. Moreover, we explore how targeted modulation of the tRNA pool – through overexpression or knockdown of individual tRNAs – affects melanocyte and melanoma cell behavior.

mRNA and tRNA were isolated from tissue samples of 30 patients, using LOTTE-seq (Long Hairpin Oligonucleotide-based tRNA High-Throughput Sequencing) for precise quantification of tRNA. Approximately 100 tRNA isodecoders (gene cluster) showed differential expression during melanoma development and progression, with the majority upregulated in melanoma and metastasis compared to benign nevi. The transition from nevus to metastasis was particularly striking, showing the most pronounced changes in tRNA expression. On the anticodon level, around 20 tRNA isoacceptors were differentially expressed, and we identified both positive and negative correlations between specific tRNA anticodons and mRNA codon demand. These findings point toward the existence of melanoma-specific, or potentially cancer-specific, tRNAs. In functional studies, overexpressed tRNAs were knocked down in melanoma cell lines using siRNAs. Live-cell-Imaging revealed a reduction in proliferation upon tRNA depletion. Future experiments aim to establish more stable knockdowns via shRNA, extend the analyses to additional tRNAs, and include melanocyte controls.

Overall, our results indicate that the composition of the tRNA pool plays an important role in melanoma development. The ability to modulate tRNA expression opens exciting prospects for novel therapeutic approaches targeting translational regulation in skin cancer.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 192

Oncogenic *HRAS*-driven immune escape in cutaneous squamous cell carcinoma

Radicchi, D.[1,2]; Gretzmeier, C.[2]; Kiritsi, D.[2]; Nyström, A.[2]

1 Faculty of Biology, University of Freiburg – Freiburg, Germany

2 Department of Dermatology, Medical Faculty, University of Freiburg Medical Center – Freiburg, Germany

RAS mutations are recurrent in skin malignancies, and *HRAS* mutations can be found in 10 - 25% of cutaneous squamous cell carcinomas (cSCCs), the second most common non-melanoma skin cancer. Even though RAS activity in various cancer hallmarks is well known, the role of oncogenic *HRAS* in creating a tumor-promoting microenvironment is less studied. Previous research indicates that oncogenic *HRAS* causes dose-dependent epidermal activation and inflammation. Emerging evidence suggests that *HRAS* mutations not only drive tumor cell-intrinsic changes but also modulate the tumor microenvironment (TME) to favor immune evasion in cSCCs.

To understand the microenvironmental consequences of oncogenic *HRAS* signaling in skin, we modelled acute oncogenic HRAS activation by transiently introducing $HRAS^{Q61}$ and $HRAS^{G12V}$ in healthy human keratinocytes. In addition, we have created human keratinocytes cell lines that stably express $HRAS^{G12V}$, modelling chronic oncogenic HRAS activation.

We observed both common and disparate effects of these activating mutations, with contextual effects on immunity. While both oncogenic variants induced a strong pro-inflammatory response, they also upregulated the expression of genes associated with the generation of immunosuppressive metabolites and their subsequent production. Notably, oncogenic *HRAS* signaling increased extracellular adenosine, a metabolite with potent immunosuppressive properties, through modulation of CD39 and CD73 via distinct signaling pathways.

To further explore these effects, we examined chronic oncogenic HRAS activation in vivo using mouse models bearing $Hras^{Q61}$- and $Hras^{G12V}$-mutated skin tumors. We intriguingly observed differential immune infiltration patterns. Consistent with the inflammatory response predicted by our in vitro models, neutrophils constituted a major component of the immune infiltrate in both mouse models. Macrophage recruitment occurred exclusively in G12V-mutated tumors, suggesting oncogenic variant-specific immune interactions within the TME. Importantly, we could disclose that oncogenic *HRAS* induces neutrophil extracellular trap (NET) formation, or NETosis, contributing to further inflammation and immune evasion within the TME.

Understanding the interplay between oncogenic *HRAS* signaling and immune escape provides insight into potential therapeutic strategies that can be translated into improved and personalized treatments. Targeting HRAS-associated immunosuppressive pathways, such as adenosine production or NETosis, may represent promising strategies to enhance anti-tumor immunity and improve outcomes in *HRAS*-mutated cSCCs.

Kategorie: Tumor biology
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 193

Aryl hydrocarbon receptor-driven metabolic reprogramming uncovers novel vulnerabilities in metastatic melanoma

Feyza Cansiz [1,2]; Luiza MN Melo [1,2]; Gabriele Allies [1,2]; Jonas Rösler [1,2,3]; Constantin Krempe [1,2,3]; Swagata Goswami [4]; Nina Lapa [1,2]; Ahmed Sadik [5]; Sven W Meckelmann [3]; Christiane Opitz [5]; Omer H. Yilmaz [4]; Dirk Schadendorf [1]; Alpaslan Tasdogan [1,2]

1 University Hospital Essen, Department of Dermatology, 45147 Essen, Germany

2 German Cancer Consortium (DKTK), partner site Duisburg-Essen, a partnership between DKFZ and University Hospital Essen, Germany

3 Applied Analytical Chemistry, University of Duisburg-Essen, Essen, Germany

4 Department of Biology, The David H. Koch Institute for Integrative Cancer Research at MIT, Massachusetts Institute of Technology, Cambridge, MA, USA.

5 DKTK Brain Cancer Metabolism Group, German Cancer Research Center (DKFZ), 69120 Heidelberg, Germany

The aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor that exhibits considerable ligand and cell-type-specific effects. The AHR regulates several biological processes, including tissue homeostasis, the development of pathological conditions, and plays an important role in the context of cancer. Thus far, studies have revealed a more tumor-suppressive role of AHR in the case of melanoma. However, the precise AHR-induced mechanisms during melanoma progression and metastasis formation remain unknown, forming the basis of our investigation.

We investigated the role of AHR in a human melanoma PDX model. Non-metastasizing PDX samples exhibited higher AHR protein levels, accompanied by pronounced changes in AHR target-gene expression and signaling in primary tumors. In parallel, we examined CRISPR/Cas9-mediated AHR knockout in human melanoma cell lines with distinct BRAF mutational backgrounds. Using global metabolomics, isotope tracing with labeled glucose and glutamine, and integrated transcriptomic and proteomic analyses, we delineated how altered AHR signaling reshapes metabolic and signaling pathways in a mutation-dependent manner.

Our findings suggest that the loss of AHR leads to phenotypic alterations, including heterogeneous metabolic shifts, changes in proliferation, and enhanced invasive and migratory behavior differentially in our panel of melanoma cell lines. With this, our study demonstrates that AHR plays an essential role in melanoma tumor initiation and metastatic progression. Herein, these results provide a foundation for future research aimed at identifying vulnerabilities in the AHR pathway to improve therapies for patients with advanced-stage melanoma.

Kategorie: Tumor biology
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 194

Combining PI3K and MEK inhibitors: a novel avenue for melanoma therapy.

H. Niessner [1], L. Fröhlich [1], T. Wagner [2, 1], S. Mane [1], C. Garbe [1], L. Flatz [1, 3], T. Sinnberg [1, 4]

[1] University of Tuebingen, Department of Dermatology, Tuebingen, Germany
[2] University of Tübingen, NMI Natural and Medical Sciences Institute, Reutlingen, Germany
[3] Kantonsspital St. Gallen, Department of Dermatology, Venereology and Allergology, St. Gallen, Switzerland
[4] Charité-Universitätsmedizin, Department of Dermatology, Venereology and Allergology, Berlin, Germany

Introduction: Despite substantial progress through immune checkpoint blockade and MAPK-targeted therapies, treatment resistance remains a major limitation in advanced melanoma. Aberrant activation of the PI3K/AKT signaling cascade occurs in approximately 70% of melanomas and contributes to tumor progression and adaptive resistance mechanisms. Co-targeting the PI3K and MAPK pathways therefore represents a rational therapeutic strategy to enhance efficacy in NRAS- and BRAF-mutant melanoma.

Methods: The therapeutic impact of combined PI3K and MEK inhibition was investigated in NRAS- and BRAF-mutant melanoma cell lines. Cell viability, apoptosis (cleaved Caspase-3, cleaved PARP), and cell cycle dynamics were assessed following treatment with alpelisib and trametinib, alone or in combination. In vivo efficacy was evaluated in NSG mice bearing subcutaneous melanoma xenografts treated orally with alpelisib (30 mg/kg), trametinib (0.3 mg/kg), or both agents daily for four weeks. Tumor growth, body weight, and histopathological markers (phospho-ERK and cleaved PARP) were analyzed to assess treatment efficacy and tolerability.

Results: Alpelisib monotherapy exerted limited antitumor activity, whereas combined PI3K and MEK inhibition produced synergistic suppression of tumor growth and robust induction of apoptosis across both NRAS- and BRAF-mutant models. In vivo, the combination markedly reduced tumor burden and prolonged overall survival compared with either monotherapy, with the strongest antitumor effects observed in NRAS-mutant melanoma. No significant systemic toxicity was detected.

Conclusion: Dual inhibition of PI3K and MEK demonstrates potent antitumor synergy and may represent a promising therapeutic approach for melanoma harboring NRAS or BRAF mutations, particularly in NRAS-mutant tumors where current treatment options remain limited.

Kategorie: Tumor biology
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 195

Functional Characterization of the Protein Biomarkers CCN1, PRAME, and GP100 in Circulating Tumor Cells of Uveal Melanoma: Cellular Mechanisms and Diagnostic Potential

Isabel Heidrich[1,2,3], Hanna Freiberg[2], , Daniel Smit[1,3], Christoffer Gebhardt[2,3,] Klaus Pantel[1,3]

[1] Institute of Tumor Biology, University Medical Center Hamburg-Eppendorf, Martinistraße 52, 20246 Hamburg, Germany.

[2] Department of Dermatology and Venereology, University Medical Center Hamburg-Eppendorf, Martinistraße 52, 20246 Hamburg, Germany.

[3] Fleur Hiege Center for Skin Cancer Research, University Medical Center Hamburg-Eppendorf, Martinistraße 52, 20246 Hamburg, Germany

Background
Uveal Melanoma (UM) remains a significant medical challenge despite considerable therapeutic advances in oncology. UM, the most common primary intraocular malignancy in adults, shows high metastatic potential and poor prognosis once dissemination occurs. Even with modern therapies, effective biomarkers for early detection and monitoring are limited. Circulating tumor cells (CTCs) represent a promising minimally invasive source for molecular characterization and real-time disease surveillance. Beyond established markers such as chromosome 3 status and LDH, novel candidates including Cellular Communication Network Factor 1 (CCN1/Cyr61), Preferentially Expressed Antigen in Melanoma (PRAME), and Glycoprotein 100 (gp100) have emerged as potential regulators of tumor cell behavior and may serve as CTC-associated biomarkers in UM.

Objectives
To investigate the expression and functional relevance of CCN1, PRAME, and gp100 in CTCs of patients with uveal melanoma and evaluate their diagnostic and prognostic potential as circulating biomarkers.

Methods
Peripheral blood samples from 40 UM patients (30 stage IV, 10 stage II/III) are analyzed. CTCs are isolated using density gradient enrichment and microfluidic separation with the Parsortix system. An optimized antibody panel targeting PRAME, GP100, and CCN1 ensures high sensitivity and specificity in fluorescence-based detection. The marker panel is applied systematically to patient samples to assess CTC prevalence, morphology, and protein expression profiles, particularly under immunotherapy. Depending on preliminary findings, individual CTCs are isolated by micromanipulation for downstream molecular analysis. The molecular findings will be systematically correlated with clinical outcomes to evaluate their prognostic and therapeutic relevance.

Results
Preliminary data reveal significant molecular differences between CTCs from early-stage and metastatic UM. CCN1 expression is notably higher in advanced disease, suggesting a potential role in CTC survival and vascular interaction. PRAME shows heterogeneous yet distinct expression patterns that may indicate immune escape during active therapy, while gp100 remains a dependable marker of melanocytic origin. Ongoing correlation studies suggest that these signatures could forecast metastatic progression and treatment response, providing new insights into UM disease dynamics. Further analyses and complete results will be available and presented at the ADF meeting.

Conclusion
CCN1, PRAME, and gp100 appear to be key determinants of CTC biology in uveal melanoma. Their combined assessment may enhance early detection of metastasis and support biomarker-guided, minimally invasive monitoring. This study integrates molecular diagnostics with patient-derived analyses to uncover mechanisms of UM progression and pave the way for personalized surveillance and therapy strategies in ocular oncology.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 196

Prognostic Value of Circulating Tumor DNA Detection and Quantification in Metastatic Uveal Melanoma

Kött, J. [2,3*]; Ramelyte, E. [1*]; Lawless, A. R. [4]; Ciernik, A. [1]; Heidrich, I. [2,3,5]; Zellweger, C. [6]; Montazeri, K. [3]; Mangana, J. [1]; Smit, D. J. [3,5]; Geidel, G. [2,3]; Freiberger, S. N. [7]; Orjuela S. [7]; Dummer, R. [1]; Sullivan, R. J. [4]; Levesque, M. P. [1#]; Gebhardt C. [2,3#]

1 Dermatology Department, University Hospital Zürich and Faculty of Medicine, University of Zürich, Zürich, Switzerland

2 Department of Dermatology and Venereology University Medical Center Hamburg-Eppendorf, Hamburg, Germany

3 Fleur Hiege Center for Skin Cancer Research, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

4 Mass General Cancer Center, Harvard Medical School, Boston, MA, USA

5 Institute of Tumor Biology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

6 Institute for Diagnostic and Interventional Radiology, University Hospital Zürich, Zürich, Switzerland

7 Oncobit AG, Schlieren, Switzerland

* Contributed equally

# Contributed equally

Background
Tumor-derived DNA fragments circulating in the bloodstream (ctDNA) offer a minimally invasive approach for dynamic disease surveillance. Although ctDNA has demonstrated prognostic utility for overall survival (OS) in patients with metastatic uveal melanoma (mUM) receiving tebentafusp, its predictive capacity across different therapeutic regimens and monitoring timepoints requires further characterization. This study evaluates the prognostic significance of ctDNA detectability and mutant allele fraction (MAF) quantification at treatment initiation and throughout therapy.

Methods
To evaluate ctDNA surveillance as a prognostic instrument for assessing therapeutic response and clinical outcomes in patients with mUM, utilizing a tumor-agnostic IVDR-certified digital PCR platform detecting GNAQ Q209P/L and GNA11 Q209P/L mutations.

Results
Analysis of 655 samples from 75 mUM patients revealed that undetectable ctDNA at baseline before first-line treatment is associated with superior OS (HR = 0.13, 95% CI: 0.02-1.02, p = 0.02) and progression-free survival (PFS) (HR = 0.31, 95% CI: 0.09-1.13, p = 0.008). Comparable correlations emerged across all treatment lines (OS: HR = 0.19, 95% CI: 0.04-0.86, p = 0.002; PFS: HR = 0.27, 95% CI: 0.08-0.89, p = 0.02). Persistently detectable ctDNA within 3 months post-treatment initiation independently predicted inferior outcomes, regardless of baseline status. Additionally, elevated MAF (>5%) at baseline or during treatment indicated substantially worse prognosis versus lower MAF levels (median OS 4 vs 21 months, p < 0.001;

median PFS 2.5 vs 3.6 months, p = 0.004), underscoring the importance of quantitative ctDNA assessment.

Conclusion
Both ctDNA presence and MAF value at baseline constitute robust adverse prognostic indicators in mUM. These results validate ctDNA monitoring as a clinically valuable non-invasive biomarker for disease surveillance. This tumor agnostic approach with an easy and time-saving workflow has a strong prognostic value without the limitation of tumor informed assays.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 197

Spatio-temporal characterization of the melanoma microenvironment in conjunction with peripheral tumor associated sensory neurons

Sirokay J[1], Brand, F[1]., Turner C. [1], Landsberg J. [1], Sirokay J. [1]

University of Bonn, Centre for Skin Diseases, Department for Dermatooncology, Bonn, Germany

Recently, peripheral nociceptive nerves were identified as modulators of T-cell mediated anti-tumor responses in the microenvironment of melanomas. However, it remains unclear how peripheral neurons are recruited into the melanoma microenvironment and what effects they exert on tumor cell differentiation and inflammatory infiltrates. Most of our knowledge of neurogenesis in peripheral tissues comes from embryonal development and regenerative processes in wound healing. It is hypothesized that cancer cells recapitulate developmental mechanisms and “hijack“ regenerative pathways for progression and metastatic spread.

To further our understanding of the interplay between tumor microenvironment, peripheral neurons and melanoma cells permitting invasive growth and metastases we performed a targeted Xenium analysis of two melanomas and the corresponding lymph node metastases, totaling 2.8M cells. In addition, we are analyzing immunohistochemically stained whole-slide images to complement the Xenium data with information regarding regions of interest, such as nerve endings in relation to melanoma cells and their microenvironment. So far, our analysis comprises cell segmentation and cell type identification in both types of tissues, using supervised and unsupervised algorithms. In our preliminary analysis, we have found two distinct clusters of melanoma cells, whose spatial locations could elucidate novel mechanisms contributing to the spread of melanoma and its metastasis. Our next steps will be to perform k-Nearest Neighbors and other analyses to locate spatial niches of cell types of particular interest in order to assess the spatial micro-environments of these tumor clusters.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 198

Predictive Role of Autoantibodies in Immune Checkpoint Inhibitor Therapy using Liquid Biopsies

Julian Steininger[1]; Björk Klein[2]; Dana Westphal[2]; Friedegund Meier[2]; Claudia Günther[1,2]

1 Department of Dermatology, University Hospital Tübingen, 72076 Tübingen, Germany
2 Department of Dermatology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität (TU) Dresden, 01307 Dresden, Germany

Introduction
Immune checkpoint inhibitors (ICIs) have transformed cancer treatment, particularly in malignant melanoma (MM), yielding remarkable therapeutic outcomes. However, despite their effectiveness, ICIs can cause severe immune-related adverse events (irAEs). The underlying mechanisms driving these diverse immune outcomes remain poorly understood, and currently, there is no reliable method to predict an individual patient's response or risk of immune-related toxicity. Consequently, there is a critical need for diagnostic approaches to stratify patients according to their likelihood of achieving effective therapy while minimizing irAEs.

Methods
From March 2020 to March 2023 a total of 100 patients (30 women, 70 men, median age 72) receiving ICI therapy for advanced skin cancer (94% MM, 6% NMSC) were included at the University Hospital Dresden. Blood samples were collected before, during, and after ICI therapy. 35 autoantibodies (AABs), each associated with specific autoimmune diseases, were selected to establish a customized detection panel. A log fold change greater than 1.5 during therapy was defined as positive. Tumor responses (complete response [CR], partial response [PR], or progressive disease [PD]) were analyzed separately based on ongoing staging assessments.

Results
The observed responses were as follows: CR in 35%, PR in 25%, and PD in 28% of patients. During the observation period, 109 AEs were reported, most frequently gastrointestinal (n=26), dermatologic (n=19), endocrine (n=15), and hepatologic (n=14) in nature. The AEs affected 63 patients in total: 32 patients experienced 1 irAE, 19 had 2 irAEs, 10 had 3 irAEs, and 2 had 4 irAEs. There was no correlation between development of any (Fisher: 0.2585) or severe (Fisher: 0.7720) irAEs and gender. Preliminary analyses identified 64 patients with elevated AAB levels; 43 exhibited a single elevated AAB, while 21 had multiple elevations (up to 4). Organ-specific irAEs showed no clear association with specific AABs. Multinomial regression models (group 1: no AABs; group 2: 1 AAB; group 3: multiple AABs) demonstrated no difference in therapy responses between group 1 and group 2, whereas a significant difference was observed between group 1 and group 3. Consequently, groups 1 and 2 were combined and compared with group 3 using a binomial regression model. In this analysis, patients with PD exhibited a markedly lower likelihood of having AABs ≥ 2 (OR ≈ 0.14, $p = 0.03$) compared with those with CR, whereas gender and the presence of irAEs were not significantly associated.

Discussion
In our model, we were unable to establish a clear association between specific AABs and the development of irAEs. However, we observed that the presence of at least 2 AABs was significantly associated with improved therapeutic response. This finding is biologically plausible, as it may reflect a more active immune system, which in turn could enhance antitumor efficacy.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 199

Senescent Fibroblasts Drive Melanoma Progression Through GCP-2 Induced CREB Phosphorylation Enhancing Glycolysis

Abhijit Basu [1 2], Vida Farsam [1], Karmveer Singh [1 2], Diana Crisan [1], Nicolai Treiber [1 2], Lars Alexander Schneider [1], Margit Huber [1], Jennifer I Engelmeyer [3], Björn Schumacher [3], Pallab Maity [1 2], Daniel Brandt [4], Martin Jastroch [4 5], Cornelia Mauch [6 7], Hartmut Geiger [2 8], Dimitris Kletsas [9], Karin Scharffetter-Kochanek [1 2]

[1]Department of Dermatology and Allergic Diseases, University of Ulm, Ulm, Germany.

[2]Aging Research Center (ARC), University of Ulm, Ulm, Germany. [3]Institute for Genome Stability in Ageing and Disease, Medical Faculty and Cologne Excellence Cluster for Cellular Stress Responses in Ageing-Associated Diseases (CECAD) Research, University of Cologne, Cologne, Germany. [4]Helmholtz Diabetes Center & German Diabetes Center (DZD), Helmholtz Zentrum München, Division of Metabolic Diseases, Technische Universität München, Neuherberg, Germany. [5]Department of Molecular Biosciences, The Wenner-Gren Institute, Stockholm University, Stockholm, Sweden. [6]Department of Dermatology and Venereology, University of Cologne, Cologne, Germany.[7]Department of Dermatology, Ruhr University Bochum, Bochum, Germany. [8]Institute of Molecular Medicine and Stem Cell Aging, University of Ulm, Ulm, Germany. [9]Laboratory of Cell Proliferation & Ageing, Institute of Biosciences and Applications, NCSR "Demokritos", Athens, Greece.

Aging constitutes the largest risk factor for melanoma progression. While a contribution of factors secreted from senescent skin fibroblasts to the progression of melanoma has been proposed, the nature of such factors and subsequent underlying mechanisms remains elusive. Here we show that the chemokine GCP-2 is excessively released by senescent fibroblasts in vitro and the skin of old melanoma patients. GCP-2 regulates, via phosphorylation of the transcription factor CREB at serine 133, defense-, cell cycle control-, and glycolysis-enhancing genes in melanoma cell lines. GCP-2 promotes oncogenic properties in vitro and in vivo in murine melanoma models. Inhibition of CREB phosphorylation in melanoma cells represses glycolytic target genes and induces a switch from glycolysis to oxidative phosphorylation that translates into a significant decline in tumor size in vivo in murine melanoma models. This study identifies a senescent fibroblast to chemokine to CREB to metabolic axis that drives melanoma progression. Targeting this axis may hold promise for novel therapeutic approaches in difficult-to-treat melanoma in older adults.

Kategorie: Tumor biology
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 200

Gene Expression Analysis of Cutaneous Squamous Cell Carcinoma and Its Association with Response to Anti-PD-1 Therapy

Schaper-Gerhardt K.[1], DeTemple V.K.[1], Beikirch M.[1], Ulama A.[1], Schacht V.[2], Sachse M.[3], Mohr P.[4], Gambichler T.[5], Gutzmer R.[1]

1 Department of Dermatology, Johannes Wesling Medical Center, Ruhr-University Bochum, Campus Minden, Minden, Germany
2 Department of Dermatology, Allergy and Venerology, Hannover Medical School, Hannover, Germany
3 Department of Dermatology, Klinikum Bremerhaven, Bremerhaven, Germany.
4 Elbe Kliniken Buxtehude, Buxtehude, Germany
5 Department of Dermatology, St. Josef-Hospital Bochum, Ruhr-University Bochum, Bochum, Germany

Introduction: Anti–PD-1 therapy has markedly improved outcomes for patients with advanced cutaneous squamous cell carcinoma (cSCC). Nevertheless, nearly half of treated patients fail to derive clinical benefit. To investigate the molecular determinants of therapeutic response and to identify potential predictive biomarkers, we conducted whole-transcriptome profiling using HTG EdgeSeq on 26 tumor samples from 20 patients with advanced cSCC who subsequently received anti–PD-1 therapy.

Methods: Baseline clinical characteristics and treatment outcomes were documented, and differentially expressed genes (DEGs) were analyzed in relation to treatment response. Patients were classified as responders or non-responders based on best overall response and further stratified into early progressors and long-term responders, using a progression-free survival (PFS) cut-off of >1 year.

Results: Consistent with previous reports, immune-related gene signatures, including interferon-gamma (IFN-γ) signaling and cytolytic activity scores, were enriched in patients with durable responses, supporting their association with a pre-existing inflamed tumor microenvironment. In addition to these established signatures, we identified several novel DEGs that significantly distinguished patients according to best overall response and early progression. Elevated expression of SLC7A5, TJP1 and ANKS4B was associated with reduced response rates and early disease progression, suggesting that metabolic and structural pathways may contribute to resistance to PD-1 blockade. ROC characteristic and Kaplan–Meier analyses demonstrated that high expression of these genes was linked to significantly shorter PFS compared with low expression, underscoring their potential prognostic relevance.

Discussion: This transcriptomic study identifies both known and previously unrecognized molecular features associated with response to anti–PD-1 therapy in advanced cSCC. Despite the need for validation in larger independent cohorts, this study yields hypothesis-generating evidence on key biological processes associated with response to immunotherapy in cSCC.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 201

Sensitizing IkappaB-zeta-expressing melanoma to immunotherapy'

Kulis-Mandic, A. [1], Kolb, A. [1], Klein M. [2], Kramer D. [1]

1 University Medical Center of the Johannes Gutenberg University Mainz, Department of Dermatology, Mainz, Germany

2 University Medical Center of the Johannes Gutenberg University Mainz, Institute for Immunology, Mainz, Germany

IkappaB-zeta, encoded by the NFKBIZ gene, is a poorly characterized transcriptional co-regulator of NF-kappaB that is known to activate or repress a subset of NF-kappaB-dependent cytokines and chemokines. Whereas it's normally only inducibly expressed upon stimulation with certain pro-inflammatory cytokines (e.g., IL-1β) or Toll-like receptor (TLR) ligands (e.g., LPS), we recently identified constitutive IkappaB-zeta expression in around 30% of all melanomas. Functional analyses revealed that melanoma-derived IkappaB-zeta enhances tumor growth and confers resistance to immune checkpoint blockade. This was due to an IkappaB-zeta-dependent induction of pro-tumorigenic cytokines, like IL-1β and IL-6, while simultaneously repressing T-cell chemoattractants (CXCL9, CXCL10, CCL5), subsequently fostering an immunosuppressive tumor microenvironment (TME).

Given the clinical relevance of CDK4/6 inhibitors in oncology, we now investigated their potential to modulate IkappaB-zeta function in melanoma, especially as CDK4/6 inhibitors are known to be able to modulate IkappaB-zeta expression, at least in keratinocytes. Surprisingly, CDK4/6 inhibitor treatment did not diminish IkappaB-zeta expression in melanoma, but rather induced an interferon response, which completely depended on the presence of IkappaB-zeta. Strikingly, these effects were absent in IkappaB-zeta-negative lines, implicating IkappaB-zeta as a critical mediator of CDK4/6 inhibitor-induced immunogenicity. In vivo studies using the B16-F10 melanoma model demonstrated that abemaciclib (CDK4/6 inhibitor) synergized with anti-PD-1 therapy. However, synergistic tumor cell death was only detectable IkappaB-zeta-positive melanomas, whereas tumors lacking IkappaB-zeta even showed antagonistic effects upon combination therapy. In agreement with this observation, the combination therapy using abemaciclib and anti-PD1 therapy restored chemokine expression (Cxcl9, Cxcl10, Ccl5) and cytotoxic cell infiltration into the TME, but only in the presence of melanoma-derived IkappaB-zeta expression.

Thus, our data establish tumor-intrinsic IkappaB-zeta as a predictive biomarker for stratifying melanoma patients who are likely to benefit from a combination therapy, using CDK4/6 inhibitors as sensitizers to immune checkpoint blockade. Prospective clinical validation of IkappaB-zeta as a biomarker could refine patient stratification and enable precision immunotherapy regimens.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 202

Role of non-canonical G protein signaling in therapy resistance and DNA repair in melanoma

Roveri,L. [1]; Schittek,B. [1]

1 University Hospital Tübingen, Department of Dermatology, Tübingen, Germany

Melanoma progression is characterized by the acquisition of multiple sequential driver mutations resulting in the activation of oncogenic pathways such as MAPK, PI3K/ AKT and G protein signaling. Targeted therapies with MAPK inhibitors result in an initial good response in the majority of melanoma patients; however, most patients rapidly develop therapy resistance. Acquired resistance is mainly achieved by overexpression of RTKs as well as by activation of PI3K/ AKT and Wnt/ β-catenin signaling and reactivation of MAPK signaling.

Girdin and Daple are guanine nucleotide exchange modulators (GEMs) that transmit signals from diverse receptors including RTKs and can modulate MAPK, PI3K/ AKT and Wnt/ β-catenin signaling pathways. Overexpression of Girdin and Daple has a negative prognostic impact in patients with melanoma and colorectal cancer; however, the underlying mechanisms including detailed expression pattern and mode of action in tumor progression and in therapy resistance are unknown.

In this study we analyzed Girdin and Daple expression during melanoma progression and after development of acquired resistance towards MAPK inhibitors. We found that both GEMs are increasingly expressed during melanoma progression. Furthermore, most melanoma cell lines with acquired resistance towards MAPK inhibitors showed decreased expression of Girdin and Daple. We found that the MAPK signaling pathway is involved in the regulation of Girdin and Daple expression as expression was altered in melanoma cells using BRAF and MEK inhibitor treatment. Girdin and Daple expression was also altered after treatment with poly(ADP-ribose)-polymerase (PARP) inhibitors indicating the involvement of Girdin and Daple in DNA damage repair.

These data suggest that Girdin and Daple are involved in melanoma progression and DNA repair and might be potential targets to overcome therapy resistance in melanoma.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 203

PlasmACT: Advancing Gas Plasma Therapy as a Novel Treatment for Actinic Keratosis through Interdisciplinary Research and Training

McKeever, L.[1]; Wang, Z.[1]; Boeckmann, L.[2]; Emmert, S.[2]; Wende, K.[1]; Bekeschus, S.[1,2]

1 ZIK plasmatis, Leibniz Institute for Plasma Science and Technology (INP), Greifswald, Germany

2 Department of Dermatology, Venerology, and Allergology, Rostock University Medical Center (UMR), Rostock, Germany

Actinic keratosis (AK) is one of the most common precancerous skin lesions, affecting millions of individuals worldwide, particularly in fair-skinned populations with chronic UV exposure. As AK represents an early stage in the development of cutaneous squamous cell carcinoma, its effective management is critical for skin cancer prevention. However, current treatment options, including topical chemotherapeutics, cryotherapy, and photodynamic therapy, often suffer from limitations such as prolonged recovery time, local irritation, and high recurrence rates. There is a clear need for new therapeutic approaches that are both efficacious and well-tolerated.

PlasmACT, a European doctoral network funded by the Marie Skłodowska-Curie Actions (MSCA), addresses this challenge by investigating cold atmospheric plasma as a novel, non-invasive therapeutic modality for AK. The consortium brings together academic institutions from Germany, Belgium, the Netherlands, and France, alongside eight industrial partners, combining expertise in dermatology, plasma physics, chemistry, molecular biology, and medical device engineering.

The overarching goal of PlasmACT is to establish the scientific foundations and translational framework for plasma-based dermatological therapies. The network's eight doctoral candidates are pursuing complementary projects that collectively investigate the biochemical, cellular, and biophysical effects of CAP, focusing on mechanisms such as redox modulation, stress signalling, and immune activation in skin cells and tissues. Parallel efforts in device optimization, dosimetry, and computational modelling ensure that biological findings are tightly linked to technological and physical parameters.

Through an integrated program of research, training, and academic–industrial collaboration, PlasmACT not only advances understanding of plasma–skin interactions but also nurtures the next generation of plasma medicine specialists. The consortium's activities include thematic training schools, secondments, and joint workshops designed to foster cross-sector innovation and harmonize experimental approaches across Europe.

By bridging fundamental plasma science with applied dermatological research, PlasmACT aims to pave the way for safe, effective, and accessible plasma-based treatments for AK and potentially other inflammatory or neoplastic skin disorders. The project exemplifies how interdisciplinary and international collaboration can accelerate innovation in dermatology and contribute to the future of precision, minimally invasive skin care.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 204

Integrative single-cell transcriptomic analysis identifies early diagnostic signatures in Mycosis fungoides

Lopes, L.O. [1]; Bergmann, E.[1]; Sinnberg, T.[1]; Gabor, D.[1], Moritz, R.[1]

1 Department of Dermatology, Venereology, and Allergology, Charité-Universitätsmedizin Berlin, Berlin, Germany

Introduction: Mycosis fungoides (MF), the most common subtype of cutaneous T-cell lymphoma, frequently presents in early stages with clinical and histopathological features indistinguishable from benign inflammatory dermatoses, including parapsoriasis (PP). This diagnostic ambiguity reflects a limited understanding of the cellular and molecular programs defining early MF.

Methods: Here, we integrated publicly available single-cell RNA sequencing datasets from early-stage MF, PP (large and small-plaque), benign inflammatory dermatoses, and healthy skin to construct a unified single-cell atlas of human skin. Using probabilistic batch correction and unsupervised clustering, we resolved conserved epithelial, stromal, vascular, and immune compartments across conditions and performed cell-type-resolved transcriptional analyses.

Results: Within the T cell compartment, early MF and large-plaque PP shared a core inflammatory transcriptional program enriched for cytokine-related biological processes, while each condition also displayed distinct disease-specific gene expression signatures. These findings indicate that PP does not transcriptionally overlap completely with either benign inflammation or MF but instead occupies an intermediate molecular state. Exploratory T-cell receptor sequencing from FFPE skin biopsies further revealed substantial inter-sample heterogeneity in clonal architecture, ranging from diverse repertoires to pronounced clonal dominance, underscoring the limited discriminatory value of clonality alone in early disease.

Discussion: Together, this study provides a cell-resolved framework for distinguishing early MF from inflammatory mimics and establishes a reference atlas to support future diagnostic marker discovery and patient stratification.

Keywords: Mycosis fungoides; Single-cell RNA sequencing; Parapsoriasis

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 205

Immunological profiling of basal cell carcinoma under PD-1 inhibition, Hedgehog inhibition, no systemic therapy

L. Mahdi[1], R. Bonkaß[1], J. Böhl[1], A. Bhatnagar[1], A. Mousa[1], A. Kryeziu[1], M. Bortolomeazzi[3], J-P. Mallm[3], P. Sant[3], L. Schütze[3], S. Mughal[4], B. Brors[4], J. Hassel[12], R. Reschke[125]

[1] Department of Dermatology and National Center for Tumor Diseases (NCT), Medical Faculty Heidelberg, Heidelberg University, NCT Heidelberg, a partnership between DKFZ and University Hospital Heidelberg, 69117 Heidelberg, Germany
[2] German Cancer Consortium (DKTK), DKFZ, Core Center Heidelberg, 69120 Heidelberg, Germany
[3] German Cancer Research Center (DKFZ), Single Cell Open Lab, Heidelberg, Germany
[4] German Cancer Research Center (DKFZ), Division of Applied Bioinformatics, Heidelberg, Germany
[5] German Cancer Research Center (DKFZ), Applied Tumor Immunity, Heidelberg, Germany

Background

Basal cell carcinoma (BCC) is the most common skin cancer in humans. For locally advanced or metastatic disease, systemic treatment with Hedgehog inhibitors (HHIs) is needed, while refractory cases can be treated with anti-PD-1 therapy. Both treatments improve outcomes but remodel the tumor immune microenvironment (TME) in certain ways that are not fully understood. In addition, BCCs associated with Gorlin-Goltz syndrome may exhibit a distinct immune phenotype, warranting comparative analysis.

Methods

BCC samples from patients treated with cemiplimab (PD-1 blockade), HHIs, or without systemic therapy (naive) were analyzed using multiplex immunofluorescence (COMET platform) quantifying 13 immune and stromal markers (CD3, CD4, CD8, FOXP3, PD-L1, PD-1, Ki-67, CD68, CD11c, CD20, CD45, CD56, αSMA). Marker frequencies were normalized to total cell counts. Representative cases additionally underwent spatial transcriptomic profiling (Xenium, 10× Genomics).

Results

Preliminary protein immunofluorescence analyses revealed distinct immunological profiles. Gorlin-associated BCCs displayed a $CD8^+$ $PD\text{-}1^+$-dominant T-cell signature with reduced $CD4^+$ $FOXP3^-$ effector T cells compared to sporadic BCCs ($p = 0.05$).
Tumours receiving systemic treatment showed a significantly higher abundance of macrophages ($CD68^+$) compared with naive BCCs, with both cemiplimab-treated and HHI-treated tumours exhibiting increased macrophage fractions relative to untreated cases. HHI-treated tumours further displayed increased fractions of $CD3^+$, $CD4^+$, $CD8^+$ T cells and dendritic cells ($CD11c^+$) compared to both naive and cemiplimab-treated groups. Initial Xenium analyses demonstrated that Gorlin-Goltz-associated tumours upregulated proliferation- and epithelial-related genes (CCND1, KIT, EPCAM), whereas sporadic BCCs showed higher expression of B-cell differentiation and plasma-cell–related transcripts (CD27, CD38, IGHM, MZB1).

Conclusion

In this exploratory cohort of 14 BCCs, distinct treatment-associated tumor and immune signatures were identified. Systemically treated tumours were macrophage-rich compared with naive BCCs, while HHI therapy was associated with enhanced adaptive immune infiltration. Gorlin-associated BCCs displayed a $CD8^+$-dominant immune phenotype. These findings suggest that HHI-induced TME activation may prime tumors for subsequent PD-1 blockade and support biomarker-guided immunomodulatory strategies in advanced BCC. Integration of protein- and RNA-level spatial data is ongoing.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 206

Targeting Melanoma with *de novo* Proteins: Design, development and investigation of ErbB3 *de novo* binder

MA. Lingner Chango[1,2]; C. Wüst[2]; C. Schulz[1]; M. Kunz[1]; CT. Schoeder[2]

[1]Department of Dermatology Venerology and Allergology, University of Leipzig Medical Center Leipzig, Germany

[2]Institute for Drug Discovery, University of Leipzig Medical Center, Leipzig, Germany

The Erb-B2 receptor tyrosine kinase 3 (ERBB3) is recognized as a driver of tumor progression and therapy resistance in melanoma and other cancers. In melanoma, ERBB3 overexpression correlates with poor prognosis and has been implicated in metastasis formation and drug resistance. Single-cell RNA sequencing data generated in our group revealed a high expression of ERBB3 in a substantial subset of melanoma cells across 10 patient samples, underscoring its potential as a therapeutic target.

Following our analysis, ERBB3 was chosen as a target, to generate a *de novo* designed protein binder, with potential applications in targeted therapy and other therapeutic strategies such as CAR T cell approaches. While monoclonal antibodies against ERBB3 (e.g., patritumab) already exist, *de novo* binders offer several advantages, including rapid design cycles, increased thermal stability, and improved biodistribution, making them an attractive alternative.

Using two independent computational design pipelines, RFdiffusion and BindCraft, we generated multiple candidate binder scaffolds and selected 2 rounds of 56 top designs for experimental evaluation. These binders were expressed in HEK293 cells using a human Fc-tag for purification and detection. In a low-throughput ELISA format, unpurified supernatants were tested for binding to recombinant human ERBB3, alongside controls for BSA, and human EGFR, and ERBB2 to assess specificity. The most promising candidates were subsequently purified and characterized via biolayer interferometry (BLI) to determine binding kinetics. Flow cytometry experiments were conducted to investigate cell-surface binding on three ERBB3-positive melanoma cell lines and one ERBB3-negative line (MaMel56). Patritumab served as a positive control in all assays.

From the 56 designs, we identified 6 minibinders that bind with moderate affinity but high specificity to ERBB3, without relevant cross-reactivity to EGFR, ERBB2, or BSA. Importantly, FACS analysis confirmed binding of the minibinder to ERBB3-positive melanoma cells, comparable to patritumab, while no binding was observed for the ERBB3-negative control line.

These results demonstrate the successful translation of computational protein design into a functional, cell-surface targeting ERBB3 minibinder and represent an important step toward the development of modular, *de novo* binders for targeted melanoma therapies.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 207

AP-1 factors induce phenotype switching in melanoma by enhancer binding

Zubeir El Ahmad[1,2]; Alexander Oliver Matthies[1]; Anja Katrin Boßerhoff[1]; Melanie Kappelmann-Fenzl[1,2]

1 Institute of Biochemistry, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Erlangen, Germany
2 Faculty of Computer Science, Deggendorf Institute of Technology, Deggendorf, Germany

Malignant melanoma, the most aggressive type of skin cancer, evolves from the transformation of pigment-producing melanocytes. Its development and stepwise progression to a metastatic cell state are characterized by specific mutations, dynamic transcriptional changes, and major alterations in the epigenome. An interplay of these characteristics contributes to the high plasticity for which melanoma cells are known and can lead to the emergence of a therapy-resistant subpopulation, ultimately causing disease relapse. This cellular plasticity usually involves a cellular switch from a melanocytic to a mesenchymal-like state, and the underlying reprogramming is fundamentally mediated by tumor-related transcription factors (TFs), such as members of the AP-1 family. The AP-1 family is a versatile group of TFs known to play an important role in melanoma by regulating the gene expression of specific target genes, thereby favoring the mesenchymal-like state by facilitating processes like invasiveness and angiogenesis. However, an in-depth understanding of changes in the regulatory landscape of melanoma driven by AP-1 binding to distal cis-regulatory elements and its implications on gene expression influencing tumor plasticity remains elusive.

This study aims to elucidate epigenetically modified regulatory features of the DNA with an impact on tumor-associated gene expression changes affecting cellular behavior. Therefore, ChIP-Seq experiments were performed using 4 different melanoma cell lines (Sbcl-2, WM3211, WM1366, WM1158) and normal human epidermal melanocytes (NHEMs) with an H3K27ac-specific antibody to precipitate transcriptionally active regions. Further, we performed ChIP-sequencing with c-Jun and Fra-1 antibodies, respectively, to gain more insight into the role of AP-1 members in the regulatory landscape and combined the sequencing results with transcriptomic data. The results clearly revealed AP-1 binding to distal enhancers, which could be verified by publicly available data of enhancer (H3K4me1)- and promoter (H3K4me3) -defining histone marks from another melanoma cell line (SKmel147) and melanocytes (NHM). The determination of cell-type-specific regulatory regions led to the identification of around 18,000 active melanoma-gained enhancers, whose target gene expression demonstrated a significant upregulation compared to NHEMs. On average, half of these regions are potentially regulated by c-Jun and Fra-1 via direct DNA binding, considering a high AP-1 binding motif rate (~80%) and chromatin accessibility. Functionally, these enhancer-regulated AP-1 targets comprise key players in invasive-specific processes such as cell migration and EMT.

Overall, our data suggest that AP-1 is a major regulator of the enhancer landscape in melanoma, resulting in transcriptional changes that promote mesenchymal-associated traits.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 208

Inflammatory conditions promote sustained AHR activation in melanoma and squamous carcinoma cell lines

Metehan Celebi[1], Hatice Genç[3], Susan Gellert[1], Susanne Bonifatius[1], Maxi Wricz Rekowski[1], Anthony Buzzai[1], Thomas Haarmann-Stemman[3], Andreas Dominik Braun[1], Miriam Mengoni[2], Thomas Tüting[1]

[1]Laboratory of Experimental Dermatology, Department of Dermatology, Otto-von-Guericke-University, 39120 Magdeburg, Germany

[2]Department of Dermatology, Allergy and Venerology, University of Lübeck, 23538 Lübeck, Germany

[3]IUF - Leibniz Research Institute for Environmental Medicine, 40225 Düsseldorf, Germany

The aryl hydrocarbon receptor (AHR) is a ligand-binding transcription factor belonging to the basic helix-loop-helix Per-Arnt-Sim (bHLH-PAS) superfamily. Historically, AHR is best known for mediating the toxicity and tumor-promoting effects of the carcinogen 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Physiologically, AHR is required for tanning responses, thereby providing protection against UV irradiation. In recent years, it has become clear that AHR activation by dietary compounds and endogenous molecules can also promote the expression of genes implicated in several stages of tumorigenesis across different cancer types.

In the current project, we hypothesize that chronic AHR signaling is a hallmark of melanoma cells and promotes the malignant transformation of melanocytes. To address this hypothesis, we assessed the duration of AHR signaling by qRT-PCR of the AHR target gene CYP1A1 in a selected panel of mouse and human melanoma cell lines (HCmel12, B16-F10, YUMM 5.2, RIM-3, MaMel65, MZ7). In these cell lines, we stimulated AHR activation using the Ultraviolet B-derived endogenous AHR agonist Formylindolo[3,2-b]carbazole (FICZ) which is normally degraded by healthy cells via the CYP1A1 enzyme. We observed that exposure of melanoma cells to FICZ led to sustained AHR signaling for up to 72 hours. In contrast, the immortalized melanocyte cell line Melan-A showed only a small and transient CYP1A1 induction that returned to baseline after 24 hours. This supports our hypothesis that melanoma cells but not melanocytes show a chronic activation of AHR signaling after stimulation with the endogenous ligand FICZ.

To compare the dynamics of AHR signaling between UV-promoted skin cancer types, we performed bulk RNA-seq on human melanoma (MZ7, MaMel65) and squamous carcinoma (A431, SCL1) cell lines after stimulation with the AHR ligands FICZ for 6h, 24h and 72h. Similar to our observations in melanoma cells, CYP1A1 expression was highly expressed at all time points by A431 cells but not SCL1 cells, indicating chronic AHR signaling in a subset of squamous cell carcinoma cell lines. Because we observed a modulation of inflammatory responses by AHR signaling in our previous work, we performed bulk RNA sequencing of our human melanoma and squamous cell carcinoma cell line panel after treatment with TNF-a in addition to AHR activation with FICZ. In accordance with our previous findings, AHR enhanced TNF-a induced dedifferentiation of melanoma cells in MZ7 cells.

Our findings support our hypothesis that chronic AHR activation might be a hallmark of a subset of malignant skin cancer cells. Furthermore, our results provide a basis to study how activation of AHR shapes inflammatory responses in melanoma and squamous cell carcinoma cells.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 209

Improving the response of melanoma patients to PARP inhibitors by identifying predictive biomarkers

Tausche, P; Schittek, B

Experimental Oncology, Dermatology at the University Clinic Tübingen, 72076 Tübingen

Up to 90% of cutaneous melanomas exhibit hyperactivation of the mitogen-activated protein kinase (MAPK) signaling pathway. Although the development of targeted therapies to inhibit MAPK signaling improved the prognosis of metastatic melanoma patients, the majority of patients experience disease progression after MAPK inhibitor (MAPKi) therapy due to resistance development. The molecular mechanisms leading to resistance towards MAPK inhibition have been extensively investigated. However, so far, no clinical breakthrough has been achieved to overcome resistance towards targeted therapy. Thus, novel molecular approaches to target therapy resistance in melanoma are urgently needed.

In our previous work we found that MAPKi resistant melanoma cells are particularly sensitive to treatment with Poly(ADP-ribose) polymerase inhibitors (PARPi) due to a lower basal expression of the DNA damage sensor ataxia–telangiectasia-mutated (ATM) [1]. Consequently, MAPKi resistant melanoma cells demonstrate diminished homologous recombination repair (HRR) activity, resulting in reduced repair of double strand breaks (DSB) caused by the PARPi. Furthermore, we found that MAPKi suppresses the expression of HRR genes and together with PARPi act synthetic lethal in melanoma cells.

In this work we identified promising predictive biomarkers for treatment response towards PARPi and the combination of PARPi and MAPKi in MAPKi sensitive and resistant melanoma cells. Database as well as synthetic lethality screening revealed a list of candidate kinases genes implicated in DNA damage sensing, base excision repair and nucleotide excision repair which are involved in increasing sensitivity towards PARPi in melanoma cells. We focused on those genes which are downregulated in MAPKi resistant melanoma cells compared to their sensitive parental cells. Downregulation of some of these genes in MAPKi sensitive melanoma cells confirmed that this increased sensitivity towards PARPi. Our study provides further evidence that PARPi treatment of MAPKi resistant melanoma patients might be a new treatment option and that the genes we identified in our study might be potential biomarkers for the treatment response.

Reference:

1. Fröhlich, L. M. *et al.* PARP Inhibitors Effectively Reduce MAPK Inhibitor Resistant Melanoma Cell Growth and Synergize with MAPK Inhibitors through a Synthetic Lethal Interaction In Vitro and In Vivo. *Cancer Research Communications* **3**, 1743–1755 (2023).

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 210

MEK5/ERK5 inhibition sensitizes *NRAS*-mutant melanoma to MAPK-targeted therapy by preventing Cyclin D/CDK4-mediated G1/S progression

Paudel, R.[1]; Goller, S.[1]; Gillitzer, A.[1]; Meder, K.[1]; Knorz, A.[1]; Schrama, D.[1]; Goebeler, M.[1]; Schmidt, M. [1]

1 Department of Dermatology, Venereology and Allergology, University Hospital Würzburg, Würzburg, Germany

Introduction:

Despite the advent of immune-oncological therapies, patients with advanced NRAS-mutant melanoma still have a significantly worse prognosis than their BRAF-mutant counterparts. This is mainly due to a high propensity for resistance to available therapies targeting the RAS/RAF/MEK/ERK mitogen-activated protein kinase (MAPK) pathway (MAPKi). Preclinical studies and mouse models have implicated the stress-activated MEK5/ERK5 MAPK cascade as a major resistance pathway activated by MAPKi-based targeted therapy in *NRAS*-mutant melanoma. Accordingly, MAPKi/ERK5i co-inhibition was capable of triggering a sustained cell cycle arrest in *NRAS*-mutant melanoma cells, but the key mediator(s) of its vigorous anti-proliferative effect remain elusive.

Methods:

Using siRNA mediated gene knockdown and CRISPR/*Cas9* mediated gene knockout of MEK5 and combining with therapeutic MEKi inhibtion (MEKi), we investigated the mechanism of MAPKi/ERK5i-induced cell cycle arrest in *NRAS*-mutant melanoma cells. Specific ERK5i were employed to validate data generated with genetic tools.

Results and Discussion:

Transcriptome analysis of human *NRAS*-mutant melanoma cells established that MAPKi/ERK5i-induced a near-complete shutdown of the mitotic machinery as consequence of a sustained G1 cell cycle arrest. This arrest was not only observed in diverse treatment-naïve melanoma cells but could also be induced in cells that already had developed resistance to MEKi and was accompanied by suppression of Cyclin D1 and E2F-mediated gene expression. Forced expression of Cyclin D1 and its effector kinase CDK4 restored cell cycle progression and mitotic gene expression in *NRAS*-mutant melanoma cells exposed to MEKi/ERK5i, implying Cyclin D/CDK4 activity as major target of combined MEKi/ERK5i. These findings suggest Cyclin D/CDK4 dependency as a major vulnerability of *NRAS*-mutant melanoma that could effectively be targeted by combined MAPKi/ERK5i.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 211

DIRAS1: Upregulated and Under Investigation
Exploring its potential role in cutaneous squamous cell carcinoma

Meisel, P.F.[1]; Kolbe, T.[1,2]; Posch, C.[3,4]; Dahlhoff, M.[1]

[1]Institute of *in vivo* and *in vitro* Models, University of Veterinary Medicine Vienna, Vienna, Austria
[2]Department of Agricultural Sciences, University of Natural Resources and Life Sciences, Tulln, Austria
[3]*Department for Dermatology, Klinik Hietzing, Vienna Healthcare Group, Vienna, Austria*
[4]Faculty of Medicine, Sigmund Freud University Vienna, Vienna, Austria

Cutaneous squamous cell carcinoma (cSCC) is the second most common type of skin cancer worldwide. Although it accounts for the majority of NMSC-related deaths, targeted therapies for metastatic cSCC remain limited, highlighting the need to identify novel therapeutic strategies.

While cSCC exhibits a heterogeneous mutational landscape, oncogenic *HRAS* mutations appear to occur predominantly in locally advanced or metastatic tumors, suggesting a role for aberrant RAS signaling in disease progression. The DIRAS protein family consists of three RAS-related small GTPases (DIRAS1-3) which have been proposed to antagonize RAS signaling. DIRAS1 has been reported to act as tumor suppressor in various types of cancer, including glioblastoma, colorectal cancer, and cervical carcinoma. To investigate its role in context of NMSC we analyzed publicly available transcriptomics data and found DIRAS1 expression upregulated in cSCC patient samples.

To study the function of DIRAS1 *in vivo* we generated a transgenic mouse line by overexpressing *Diras1* under the control of the ubiquitous *chicken beta actin* promoter (*Diras1*-TG). To explore the role of DIRAS1 in NMSC, we employed an inducible two-stage chemical carcinogenesis model using 7,12-dimethylbenz[a]anthracene (DMBA) and 12-O-tetradecanoylphorbol-13-acetate (TPA). *Diras1*-TG mice showed a delayed onset of papilloma development and significantly reduced papilloma burden compared to control littermates. We showed a significant reduction of RAS activation in papilloma of *Diras1*-TG mice. Analysis of downstream targets of RAS revealed a reduced phosphorylation of ERK1/2, suggesting that DIRAS1 overexpression inhibits the MAP kinase signaling pathway *in vivo*. Additionally, we observed increased expression of the tumor suppressor protein PTEN as well as reduced inactivation of PTEN in *Diras1*-TG mice.

To further elucidate the role of DIRAS1 in skin carcinogenesis we conducted additional *in vivo* experiments. We could observe less profound TPA induced epidermal hyperplasia in *Diras1*-TG mice compared to control littermates. Furthermore, we aim to analyze the effect of UVB radiation on *Diras1*-TG mice to explore the potential role of DIRAS1 in apoptotic cell death.

So far, our findings show that overexpressing DIRAS1 suppresses oncogenic RAS signaling *in vivo*, indicating an important role in skin carcinogenesis.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 212

Physiologically Relevant Modeling of Melanoma-Skin Interactions Using Full-Thickness and Organoid Systems

Zöphel, S.[1,2]; Köder, N.[1]; Wußmann, M.[1]; Groeber-Becker F.[1,3]; Schrama, D.[4]; Groneberg, D.[1]

1 University Hospital Wuerzburg, Interdisciplinary Centre for Clinical Research, Würzburg, Germany

2 Fraunhofer-Institute for Silicate Research ISC, Translational Center for Regenerative Therapies TLZ-RT, Würzburg, Germany

3 University Hospital Duesseldorf, Heinrich-Heine-University, Department of Ophthalmology, Düsseldorf, Germany

4 University Hospital Würzburg, Department of Dermatology, Venereology and Allergology, Würzburg, Germany

Malignant melanoma poses a significant clinical challenge as the most aggressive and therapy-resistant form of skin cancer. Despite advances in targeted treatment strategies, preclinical translation remains a significant barrier, as conventional 2D cultures and animal models replicate the architecture and complexity of human skin and its tumour microenvironment. In order to overcome this limitation, we have established physiologically relevant in vitro models of melanoma-skin interaction using two human-based systems: skin organoid (SO) derived from human induced pluripotent stem cells, and a full-thickness skin equivalents (FTSE) derived from primary skin cells.

The hiPSC-based skin organoids demonstrate a highly organised structure comprising a stratified epidermis, dermal fibroblast layers, melanocytes, and appendage-like structures such as hair follicles, sweat, and sebaceous glands, thereby providing a physiologically relevant basis for studying melanoma progression. Through co-culture of fluorescently labelled melanoma cells, we are developing an integrated platform that captures the nuances of the tumour microenvironment and enables the study of melanoma invasion and tumour-stroma interactions.

Concurrently, the FTSE model was developed to provide a structurally controlled, engineered tissue system. Within this model, cancer-associated fibroblasts (CAFs) were incorporated to reproduce the tumour-associated stroma and to assess their influence on melanoma behaviour and microenvironmental remodelling. It is evident that both models facilitate the establishment of melanoma-skin co-cultures within a tissue-like context, thus offering complementary platforms for future studies with the objective of elucidating tumour-stroma dynamics and the mechanisms underlying melanoma progression.

In conclusion, these advanced in vitro systems provide physiologically relevant, human-specific platforms for investigating melanoma–skin interactions. The utilisation of hair-bearing skin organoids facilitates the capture of the inherent complexity and architectural characteristics of human skin, while full-thickness skin equivalents offer a superior level of architectural precision and stromal versatility. Collectively, these elements overcome the key limitations of conventional models and deliver greater translational value for preclinical research and drug testing, thus supporting the development of more effective and targeted melanoma therapies.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 213

MelanoDetect: Circulating Tumor Cells Across Melanoma Stages and Therapies

Atilla Aydin, S.[1]; Geier, M.[1]; Primke, K.[1]; Schlaak, M.[1]; Eigentler, T.[1]; Sinnberg, T.[1]

1 Charité - Universitätsmedizin Berlin, Skin Tumor Centre, Department of Dermatology, Venereology, and Allergology, Berlin, Germany

Objectives: Despite significant advancement in treatment, melanoma remains one of the deadliest cancers due to high relapse rates, treatment resistance and a lack of predictive biomarkers to guide therapeutic decisions. Circulating melanoma cells (CMCs) show potential as a minimally invasive, real-time readout of tumor burden and biology, but adoption is limited by low-yield capture of heterogeneous cells from blood. We aimed to establish a clinically deployable CMC workflow using self-produced single chain variable fragments (scFvs) for multimarker immunomagnetic enrichment, followed by imaging based single cell isolation and downstream integrated single cell RNA and DNA sequencing.

Methods: Target melanoma antigens were selected by in silico analysis of TCGA and published single-cell RNA-seq datasets. scFvs were engineered by joining variable heavy and light chains of antibodies with preclinical use, appended with tags for purification and site-specific biotinylation. The constructs were cloned into pET-scFv-T plasmid and scFvs were expressed in E.coli. 3D structures of scFvs were predicted by Alphafold3; biotinylation/size were tested by streptavidin western blotting. Binding efficiency and specificity of scFvs were assessed by flow cytometry on melanoma cell lines and PBMCs, using streptavidin for detection and commercial antibodies as benchmarks. CMC enrichment workflow using scFvs and streptavidin magnetic beads was established on the CellMag magnet, which is the manual counterpart of the CELLSEARCH® and was optimized by repeated spike-in experiments in whole blood and PBMC suspensions, evaluating different bead sizes and incubation conditions. Enriched cells are further characterized by staining for melanoma markers and CD45 and CD34 as exclusion markers and morphologically verified CMCs are isolated as single cells from the DEPArray platform. Patient derived CMCs will be processed with ResolveOME (BioSkryb Biosciences) for single cell genomic and transcriptomic library preparation.

Results: In silico expression analysis resulted in six candidate antigens and demonstrated broad coverage of heterogeneous melanoma populations: MCAM, CSPG4, GD2, CD228, PMEL, TYRP1. 3D structure predictions confirmed correct protein folding and western blot analyses confirmed the size and biotinylation of scFvs. scFvs showed robust and specific binding comparable to commercial antibodies for MCAM, CSPG4, GD2, and CD228 in flow cytometry analyses for melanoma cells with no non-specific binding to PBMCs. PMEL and TYRP1 showed limited or inconsistent surface availability and were excluded from the antigen panel. In spike-in enrichment experiments, direct enrichment from whole blood with smaller anti-biotin magnetic beads (130 nm vs 4 µm) yielded the best performance with ~80% capture efficiency.

Conclusion: This workflow combines cost efficient in-house scFv production and a robust enrichment protocol for clinical application. In a prospective cohort of 130 AJCC stage II–IV patients, we will validate the assay and assess the prognostic and predictive value of CMCs

by serially quantifying baseline and on-treatment CMC counts and profiling isolated CMCs with integrated single-cell genomics and transcriptomics. Quantifying CMCs may provide a non-invasive predictive biomarker, while integrated single-cell multi-omics of CMCs can delineate how genetic alterations and dynamic transcriptional states cooperate to drive metastasis and therapy resistance.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 214

Repetitive hepatic passaging drives proliferative reprogramming in liver metastases of NRAS-mutant melanoma

Vormehr, S. [1]; Dietsch. B. [1]; de la Torre; C. [2], Dong, H. [3]; Rambow, F. [3]; Wohlfeil. S [1,4,5]; Géraud, C. [1,4,6]

1 Section of Clinical and Molecular Dermatology, University Medical Center and Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

2 Core Facility Platform Mannheim, Medical Faculty Mannheim, NGS Core Facility, Heidelberg University, Mannheim, Germany

3 Department of Applied Computational Cancer Research, IKIM, University Hospital Essen, Essen, Germany

4 DKFZ Hector Cancer Institute at the University Medical Center Mannheim, Heidelberg, Germany

5 Skin Cancer Unit, German Cancer Research Center (DKFZ), Heidelberg, Germany

6 European Center for Angioscience (ECAS), University Medical Center and Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

Background: Cutaneous melanoma (CM) is an aggressive melanocytic malignancy with high metastatic potential. Despite the approval of immune checkpoint inhibitors for melanoma, treatment outcomes remain heterogeneous. *BRAF*-mutant melanomas respond well to targeted therapies but often develop resistance within a few months, whereas treatment options for *NRAS*-mutant tumors remain limited. This is particularly critical for hepatic metastases, which frequently occur in advanced CM and are associated with therapy resistance and poor prognosis. *NRAS*-mutant melanomas also display an intrinsically higher proliferative capacity, suggesting distinct molecular programs that enable adaptation and growth in the hepatic niche.

Methods: To investigate the mechanisms of hepatic adaptation, we used an immunocompetent in vivo model and Wt31 melanoma cells with a NRAS Q61K mutation. Liver colonization was modeled by repeated intrasplenic injections, followed by isolation, expansion and reinjection of the tumor cells for five times, resulting in a liver-adapted subclone. Tumor growth and morphology were analyzed histologically. Transcriptomic profiling (bulk and single-cell RNA sequencing) followed by immunofluorescence and in situ hybridization were applied to identify and validate transcriptional and phenotypic changes associated with hepatic adaptation.

Results: After spleen injection the liver-passaged subclone showed significantly larger hepatic metastases as compared to the parental subline, while the number of metastatic lesions was similar. Analyses with routine histology stainings or immunofluorescences confirmed the increased size of hepatic metastases of the passaged subclone, while no alterations were found for the morphology of the hepatic metastases, growth pattern or vascularization. The cell proliferation of the liver metastases, which was assessed by Ki67 stainings, was significantly increased in the passaged-subline as compared to the parental line. Transcriptomic analyses also confirmed an enhanced proliferative signaling and revealed changes of oxidative phosphorylation. Interestingly, the phenotype of enhanced metastatic proliferation was also observed in lung metastases after intravenous injection of the passaged subline in comparison to the parental line. Therefore, we conclude that the serial hepatic passaging induced tumor-intrinsic transcriptional reprogramming towards a hyperproliferative state without generating a hepatotropic subline.

Conclusion: Our findings suggest that hepatic selection may promote proliferative adaptation in NRAS-mutant melanoma. Ongoing functional studies targeting candidate genes identified in transcriptomic analyses will help validate their potential role in hepatic colonization. Ultimately, this work may help identify tumor-intrinsic targets to overcome therapy resistance and improve treatment outcomes for patients with NRAS-mutant melanoma, particularly those with liver metastases.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 215

Neural crest–like phenotype in melanoma revealed by methylomic profiling under anti–PD-1 therapy

Fietz, S.[1]; Brand, F.[1,3]; Lorenz, C.[1]; Petersen, M.[4]; de Vos-Hillebrand, L.[1]; Dietrich, D.[2]; Landsberg, J.[1]

1 Center for Skin Diseases, University Hospital Bonn, Bonn, Germany
2 Center for Otolaryngology, Head and Neck Surgery, University Hospital Bonn, Bonn, Germany
3 Institute for Genomic Statistics and Bioinformatics (IGSB), University Bonn, Bonn, Germany
4 High Performance Computing and Analytics Lab (HPC/A-Lab), University Bonn, Bonn, Germany

Introduction: Most patients with metastatic melanoma develop primary or secondary resistance to therapy, reducing the effectiveness of systemic treatments. In this context, epigenetic regulatory mechanisms can drive dedifferentiation and contribute to tumor plasticity. This project aims to uncover epigenetically regulated patterns, genes, and signaling pathways involved in (de)differentiation, plasticity, and immune cell interactions in melanoma to identify potential biomarker candidates and clinically relevant targets to overcome therapy resistance

Methods: Tumor samples from *N* = 48 patients with metastatic melanoma collected prior to anti-PD-1 immunotherapy were stratified into clear responders and non-responders, forming a case-control-like study cohort. Genome-wide DNA methylation and transcriptome profiling were performed using the Illumina EPIC (850k) array and 3′-RNA sequencing.

Results: The UKBonn cohort was characterized by mutational status, tissue origin, survival, and therapy response. Differential methylation analysis between responders and non-responders identified distinct CpG sites. The top 1,000 were used for gene annotation and enrichment analysis, revealing pathways related to neural differentiation. Basic methylation analysis, including quality control, preprocessing, filtering, and differential methylation resulted in 10 of 143 CpG sites that remained significant after false discovery rate correction. These CpG sites were localized to eight genes linked to neuronal and developmental pathways, consistent with the neural crest origin of melanoma, as well as epithelial and immune-associated signatures.

Outlook: Further analyses will focus on highly variable CpG sites in the TCGA SKCM cohort and on relative methylation differences as additional filtering criteria. Validation of these findings in independent published cohorts is planned.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 216

Risk factors for hyperprogression in melanoma patients treated with immune checkpoint inhibition

Tim Zell[1,2], Noah Zimmermann[1,2], Glenn Geidel[1,2], Stefan W. Schneider[1,2], Julian Kött[1,2], Christoffer Gebhardt[1,2]

[1] Department of Dermatology and Venereology University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[2] Fleur Hiege Center for Skin Cancer Research, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Background:
Hyperprogression under immune checkpoint inhibition (ICI) represents a dramatic and clinically critical pattern of disease acceleration. However, the underlying risk factors in melanoma remain poorly understood. This study aimed to identify clinical and molecular characteristics associated with hyperprogression in comparison to patients with primary resistance to ICB.

Methods:
To identify patients with hyperprogression, we focused on a cohort of 244 patients from the multicenter skin cancer registry ADOReg treated with ICB for metastatic melanoma who had normal LDH and ECOG 0 or 1 at baseline and primary resistance to ICB, defined by a progression within 6 months of treatment start (according to SITC criteria). Hyperprogression was defined as progression within three months, accompanied by a transition to an ECOG performance status of 3 or 4, or an increase in serum LDH levels, or both. Associations between progression category and potential risk factors, including age, gender, metastatic sites (brain, lung, liver, bone, skin), molecular markers (BRAF, NRAS), and treatment regimen (monotherapy vs. combination therapy) were assessed. Chi-square or Fisher's exact tests were applied for categorical variables, and age was analyzed as a continuous variable using Student's t-test and the Mann–Whitney U test.

Results:
Hyperprogression was observed in 102 patients (41,8% of patients with primary resistance to ICB) and significantly associated with younger patient age (mean 59.3 vs. 65.5 years, $p = 0.0012$), the presence of bone metastases before treatment start ($p = 0.0028$), and combination therapy ($p = 0.019$). No significant associations were observed for gender, other metastatic sites, or BRAF/NRAS mutation status.

Conclusion:
Younger age, bone metastases, and combination therapy were identified as potential risk factors for hyperprogression in melanoma. These findings may help to stratify risk and refine treatment decisions. Prospective validation in larger cohorts is warranted.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 217

The influence of YB-1 on DNA Repair Pathways and Sensitivity towards PARP inhibitors in Melanoma

Heintze, T.[1]; Brethauer, W.[1]; Schittek, B[1]

1 University of Tübingen, Department of Dermatology, Division of Dermatooncology, Germany

Melanoma cells frequently exhibit hyperactivation of the MAPK signaling pathway, making this pathway an attractive therapeutic target. However, the efficacy of targeted therapy using MAPK inhibitors (MAPKi) is limited by the rapid development of drug resistance in melanoma patients, emphasizing the need for new therapeutic approaches.

Y-box binding protein-1 (YB-1) is overexpressed during melanoma progression and expression level correlates to poor prognosis in melanoma patients as well as invasive potential of melanoma cells. Previous studies suggested that YB-1 is a stimulator of poly(ADP-ribose) polymerase-1 (PARP1) activity, indicating a possible role of YB-1 in the DNA damage response and in the sensitivity towards PARP inhibitors.

In this study we explored the role of YB-1 in the DNA damage response. In A375 melanoma cells with a CRISPR/Cas9 mediated knockout of YB-1 we observed a marked reduction in the expression of several DNA repair genes and a decreased sensitivity to PARP1 inhibition. This is in line with a severe decrease in cell proliferation. Collectively, our data provide new insights into the role of YB-1 in regulating the DNA damage response.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 218

Effect of PI3K-gamma/delta inhibition, alone and in combination with KIT Inhibition, on the phenotype of mastocytosis in a novel KitD814V-mutant mouse model

Almeida Fonseca, T.[1], Konantz, M.[1], Ratti, E.[1], Sheremeti E.[1], Makeeva, A. [1], Clauss, L.[1], Usart, M. [1], Stivala, S.[1], Hartmann, K. [1,2,3]

1 Department of Biomedicine, University Hospital Basel and University of Basel Basel, Switzerland.
2 Division of Allergy, Department of Dermatology, University Hospital Basel and University of Basel Basel, Switzerland.
3 Department of Clinical Research, University Hospital Basel and University of Basel Basel, Switzerland.

Background:
Systemic mastocytosis refers to a myeloid neoplasm characterized by clonal proliferation of mast cells (MC), predominantely driven by the KIT D816V mutation. This in turn leads to downstream activation of the PI3K/AKT and STAT5 signaling pathways amongst others, resulting in increased MC proliferation and cytokine release. Despite the recent success in treatment by the selective KIT tyrosine kinase inhibitor avapritinib, resistance or incomplete responses still remain major challenges. The PI3K inhibitor duvelisib, approved in chonic lymphocytic leukemia, acts through dual targeting of the PI3K gamma/delta pathway. In the present study, we aimed to investigate the individual and combined effects of duvelisib and avapritinib in a novel mouse model of systemic mastocytosis (Scl-Cre;KitD814Vfl), generated by CRISPR-Cas9 in our lab.

Methods:
Mutant KitD814V expression was induced in adult Scl-Cre;KitD814Vfl mice by tamoxifen. Two weeks after induction, bone marrow cells from CD45.2 mutant mice were isolated, mixed at a 1:1 ratio and transplanted into lethally irradiated CD45.1 recipient mice. Six weeks after transplantation, animals were treated by daily oral gavage for 16 consecutive days with duvelisib, avapritinib, their combination, and vehicle. Body weight, peripheral blood counts (measured using an automated hematology analyzer), and chimerism (through flow cytometry) were monitored at baseline and at termination. At day 16, spleen and liver weights, bone marrow and peripheral blood viable cell counts, and serum mast cell protease 1 (Mcpt1) levels were measured (through ELISA) to assess disease burden.

Results:
All treatments were tolerated without critical weight loss or overt toxicity. Blood analyses revealed a strong decline in white cell and reticulocyte counts under avapritinib and combination treatment, while duvelisib showed a moderate reduction. Neutrophils and lymphocytes returned to near-physiologic levels with avapritinib treatment. Chimerism analysis showed an increase in $CD45.1^+$ donor-derived cells and a reduction of mutant $CD45.2^+$ cells in the avapritinib and combination groups, indicating restoration of normal hematopoiesis. Terminal readouts demonstrated significant reductions in spleen and liver weight ($p < 0.001$) and bone marrow cell burden after avapritinib or combination therapy. Serum Mcpt1, a marker of MC infiltrates, was significantly decreased in all treated cohorts, with the strongest suppression in the combination treatment group.

Conclusions:
Our results show that avapritinib significantly reduces myeloproliferation and MC burden in recipient mice, while blocking the PI3K gamma/delta pathway with duvelisib only gives partial hematologic improvement. The combination is more effective with regard to cellular and biochemical parameters than either treatment alone, suggesting that both treatments

synergistically inhibit the PI3K pathway. Ongoing histopathologic analyses will clarify the mechanisms underlying these responses and shed further light on whether combined targeting of KIT and PI3K signaling may offer an improved rationale for patients with systemic mastocytosis.

Kategorie: Tumor biology
Präsentationsart: Poster

Abstract-ID: 219

Predictive biomarkers for advanced basal cell carcinoma under systemic treatment

DeTemple, V.K.[1];Chung, S.[1]; Busche, T.[2]; Beikirch, M.[1]; Rückert, C.[2]; Alter, M.[1]; Angela, Y.[1]; Stadler, R.[1];Bredemeier, S.[1]; Hassel, J.[3]; Hübbe, H.[3]; Sachse, M.M.[4]; von Wasielewski, I.[5]; Schacht, V.[5]; Leiter, U.[6]; Gebhardt, C.[7]; Huyhn, J.[8]; Pföhler, C.[9]; Livingstone, E.[10]; Ohletz, J.[11]; Stege, H.[12]; Glutsch, V.[13]; Persa, O.D.[14]; Mengoni, M.[15]; Gutzmer, R.[1]; Schaper-Gerhardt, K.[1]

1 Johannes Wesling Hospital Minden, Department for Dermatology, University Hospital, Ruhr-University Bochum, Minden, Germany
2 University Bielefeld, Medical Faculty OVLW & Centre for Biotechnology (CeBiTec), Bielefeld, Germany
3 University Hospital Heidelberg, Department for Dermatology, Heidelberg, Germany
4 Hospital Bremerhaven, Department for Dermatology, Bremerhaven, Germany
5 Hannover Medical School, Department for Dermatology, Hannover, Germany
6 University Hospital Tübigen, Department for Dermatology, Tübingen, Germany
7 University Hospital Hamburg Eppendorf, Department for Dermatology, Hamburg, Germany
8 Charité, University Hospital Berlin, Department for Dermatology, Berlin, Germany
9 University Hospital Saarland, Department for Dermatology, Homburg, Germany
10 University Hospital Essen, Department for Dermatology, Essen, Germany
11 Vivantes MVZ GmbH, Department for Dermatology, Berlin, Germany
12 University Hospital Mainz, Department for Dermatology, Mainz, Germany
13 University Hospital Würzburg, Department for Dermatology, Würzburg, Germany
14 Klinikum rechts der Isar, technical university of Munich, Department for Dermatology, München, Germany
15 University Hospital Schleswig-Holstein, Department for Dermatology, Lübeck, Germany

Introduction: Basal cell carcinoma (BCC) is the most frequent skin tumor woldwide. The majority of cases can be cured via surgical excision, however, patients with locally advanced or metastasized disease (advBCC) are in need of systemic treatment. Here, hedgehog inhibitors (HHI) are approved as first-line regimen with response rates of approximately 60%; as second-line treatment the checkpoint inhibitor (PD1i) cemiplimab reaches response rates of about 30%. Due to aging populations and increase in BCC incidences, advanced cases gain rising clinical relevance. To date, no clinically validated biomarkers exist to predict treatment response. In this project, we aim to identify predictive biomarkers for HHI and PD1i treatment for advBCC using bulk RNA sequencing and immunohistochemistry.

Methods: We analysed a total of 95 histologically confirmed BCC samples (formalin fixed, paraffin embedded) from 55 patients collected from 12 skin cancer centers in Germany. Patients either received only HHI (49 samples, 26 patients), subsequent PD1i as second-line treament (16 samples, 11 patients), or were reinduced with HHI as a third-line regimen (30 samples, 18 patients). For bulk RNA sequencing two methods were used: (i) 34 samples from 27 patients were included for whole transcriptome analyses (HTG EdgeSeq), (ii) an extended cohort of 71 samples from 50 patients was subsequently analysed in a focused gene panel using nCounter technology. Differential gene expression was evaluated with DESeq2 using R Studio. Samples were grouped by PFS (short versus long PFS, cut-off at median) per treatment regimen (HHI or PD1i). Following further statistical (GraphPadPrism) and survival analysis (R Studio), five significantly differentially expressed genes were chosen for functional evaluation via immunohistochemistry (85 samples, 49 patients). Staining features were scored using a predefined matrix of histological parameters.

Results: In Kaplan-Meier regressions, longer PFS in second-line PD1i treatment correlated with low expressions of T helper cell marker CD4 ($p=0.021$) and macrophage marker CD68 ($p<0.0001$). Longer PFS was also associated with high expressions of basal differentiation

marker KRT14 (p=0.00032) and of oncogene GRM1 (p=0.0098). In multivariate analysis for the PD1i subcohort - also including clinical parameters - only KRT14 was able to predict progression as an independent factor (HR 0.629). For HHI treatment regimens, no gene succeeded as predictive marker in survival analysis.

Discussion: In contrast to previous studies, our data did not show a relevance of CD8 or PD-L1 expression, often positively correlated with response to PD1i. Instead, a reduced expression of CD4 and CD68 was associated with longer PFS under PD1i. Additionally, the most promising potential biomarker in our study, KRT14, suggests that divergence from the physiological follicular differentiation programme may lead to early progression of BCCs under PD1i. Correlations with immunhistochemical stainings are pending to detect the local distribution of immune cells and KRT14 within the BCC and its tumor microenvironment. For further clinical validation larger patient cohorts are needed.

Kategorie: Tumor biology
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 220

Molecular effects of cryotherapy and combined aftercare treatment in a human 3D model of actinic keratosis

Yvonne Marquardt, Sebastian Huth, Laura Huth, Jens Malte Baron

Department of Dermatology and Allergology, Uniklinik RWTH Aachen, Aachen, Germany

Actinic keratosis (AK) is a localized epidermal lesion. Left untreated, some AKs may progress to cutaneous squamous cell carcinoma. Early, solitary lesions are commonly treated with brief applications of liquid nitrogen spray. Although this approach is effective, it often causes transient irritation of the surrounding skin and leads to the formation of superficial wounds.

In this *in vitro* study, we utilized a three-dimensional, full-thickness human skin model of AK using SCC12 cells. This model is employed to investigate the molecular effects of cryotherapy and the impact of subsequent topical aftercare treatment with dexpanthenol-containing ointment.

Histological analysis revealed pronounced ablative lesions in the epidermal compartment of the 3D skin models, evident immediately after cryotherapy and persisting at day 5. In this context, the models treated topically with the dexpanthenol-containing ointment exhibited an accelerated epidermal wound healing response at day 5 after cryotherapy. Molecular profiling was performed five days after treatment using next-generation sequencing (NGS).

Gene set enrichment analysis (GSEA) revealed an inflammatory response in 3D skin models 5 days after cryotherapy, characterized by upregulation of cytokines and chemokines, including CXCL6, IL1RL1, and CXCL5, compared with untreated controls. Matrix metalloproteinases, such as MMP9 and MMP2, were also elevated. In contrast, epidermal differentiation markers of the late cornified envelope (LCE) family and genes critical for skin barrier maintenance, including AQP3, were downregulated.

Interestingly, in our second approach, topical aftercare with dexpanthenol-containing ointment resulted in significant upregulation of epidermal differentiation markers, including LCEs, filaggrin, and loricrin, as well as genes critical for skin barrier maintenance, such as AQP3. These molecular changes were consistent with the histological observation of accelerated wound healing. Furthermore, dexpanthenol aftercare treatment appeared to modulate the inflammatory response, as evidenced by downregulation of cytokines such as CCL5.

This newly established in vitro skin model based on SCC12 cells closely replicates the histological features of actinic keratosis observed *in vivo*. It represents a valuable platform for studying molecular mechanisms and evaluating therapeutic interventions. Furthermore, it contributes to the reduction of animal experimentation in accordance with the 3Rs principle (Replacement, Reduction, and Refinement).

Kategorie: Tumor biology
Präsentationsart: Poster

Tumor Immunology

Abstract-ID: 221

Therapy-associated immune landscape changes in Cutaneous T-Cell Lymphoma (CTCL)

A. Bhatnagar[1]; M. Bortolomeazzi[3]; P. Sant[3]; L. Schütze [3]; A. Kryeziu[1]; R. Bonkaß[1]; L. Mahdi[1]; J. Böhl[1]; A. Mousa[1]; J-P.Mallm[3]; S. Mughal[4]; B. Brors[4]; J. Hassel[1,2]; R. Reschke[1,2,5]

1 Department of Dermatology and National Center for Tumor Diseases (NCT), Medical Faculty Heidelberg, Heidelberg University, NCT Heidelberg, a partnership between DKFZ and University Hospital Heidelberg, 69117 Heidelberg, Germany

2 German Cancer Consortium (DKTK), DKFZ, Core Center Heidelberg, 69120 Heidelberg, Germany

3 German Cancer Research Center (DKFZ), Single Cell Open Lab, Heidelberg, Germany.

4 German Cancer Research Center (DKFZ), Division of Applied Bioinformatics, Heidelberg, Germany

5 German Cancer Research Center (DKFZ), Applied Tumor Immunity, Heidelberg, Germany

BACKGROUND
Cutaneous T-cell lymphoma (CTCL), including mycosis fungoides (MF) and Sézary syndrome (SS), represents a rare clonal malignancy of skin-homing T cells. Several systemic therapies are available for advanced CTCL, including mogamulizumab (anti-CCR4 antibody) and brentuximab vedotin.

Brentuximab vedotin is an antibody drug conjugate targeting CD30-expressing cells, delivering the cytotoxic agent monomethyl auristatin E (MMAE) to induce apoptosis.

Previous studies have shown that CTCL is driven by heterogeneous genetic programs encompassing both activation- and proliferation-associated transcriptional signatures. The marked heterogeneity of CTCL lesions and their variable responses to systemic therapy underscore the need for deeper molecular characterization to identify therapeutic targets and biomarkers of disease progression.

METHODS
We characterized the spatial proteomic and transcriptomic landscape of CTCL using complementary spatial omics technologies applied to matched patient samples. First, COMET multiplex immunofluorescence was performed using the SPYRE panel comprising 13 markers (CD3, CD4, CD8, FOXP3, PD-L1, PD-1, Ki-67, CD68, CD11c, CD20, CD45, CD56, and αSMA) to map immune and stromal cell subsets. Second, 10x Genomics Xenium in situ spatial transcriptomics was employed using the Immuno Oncology panel (targeting 380 genes) for high resolution RNA profiling.

We compared advanced stage MF patients receiving systemic therapy (mogamulizumab or brentuximab vedotin) with treatment naïve patients to investigate how the tumor microenvironment (TME) evolves across disease stages and in response to distinct therapeutic modalities.

RESULTS
Preliminary immunofluorescence analyses revealed treatment associated remodeling of T-cell subsets within the TME. Treatment naïve samples exhibited a significantly higher proportion of total T cells (Mann-Whitney-Wilcoxon test, $p < 0.05$) compared with samples from patients undergoing systemic therapy, suggesting therapeutic reduction of malignant and reactive T-cell populations.

Notably, $CD4^+FOXP3^+$ regulatory T cells (Tregs) were more abundant in treatment-naïve patients, indicating a more immunosuppressive microenvironment prior to therapy. Conversely, biopsies obtained during systemic treatment showed a trend toward increased $CD8^+$ T-cell infiltration, suggesting a shift in the CD4/CD8 ratio.

CONCLUSION
In our exploratory cohort of 13 CTCL samples, we observed a reduction in total T-cell infiltration in patients receiving systemic therapy, consistent with therapeutic efficacy in mycosis fungoides and Sézary syndrome. The higher frequency of Tregs in treatment naïve samples supports the concept of a suppressive TME, whereas the relative enrichment of $CD8^+$ T cells in the systemic therapy group points toward immune reactivation. These findings highlight the potential of spatially resolved proteogenomic profiling to elucidate mechanisms of treatment response and resistance in CTCL.

Integration of multiplex protein imaging with spatial transcriptomic data is ongoing to refine cellular interaction networks and identify predictive markers of therapeutic outcome.

Kategorie: Tumor Immunology
Präsentationsart: Poster

Abstract-ID: 222

Spatial profiling identifies chemokine-enriched immune-stromal interfaces linked to PD-1 blockade response in cutaneous squamous cell carcinoma

Mousa, A.M.[1,5,8]; Bonkaß, R.[1,5]; Mahdi, L.[1]; Böhl, J.[1]; Kryeziu, A.[1]; Bhatnagar, A.[1]; Richter, J.[1]; Westhoven, C.[5]; Bortolomeazzi, M.[3]; Mallm, J.P.[3]; Sant, P.[3]; Mughal, S.[2,5]; Brors, B.[2,5,6,7]; Hassel, J.[1,2]; Reschke, R.[1,2,4]

[1] Department of Dermatology and National Center for Tumor Diseases (NCT), Medical Faculty Heidelberg, Heidelberg University, NCT Heidelberg (a partnership between DKFZ and University Hospital Heidelberg), 69117 Heidelberg, Germany; [2] German Cancer Consortium (DKTK), DKFZ, Core Center Heidelberg, 69120 Heidelberg, Germany; [3] German Cancer Research Center (DKFZ), Single Cell Open Lab, Heidelberg, Germany; [4] Applied Tumor Immunity, German Cancer Research Center (DKFZ), Heidelberg, Germany; [5] Division of Applied Bioinformatics, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 280, 69120 Heidelberg, Germany; [6] Medical Faculty and Faculty of Biosciences, Heidelberg University, 69120 Heidelberg, Germany; [7] National Center for Tumor Diseases (NCT), Im Neuenheimer Feld 410, 69120 Heidelberg, Germany; [8] Faculty of Biosciences, Pharmacy Division, Heidelberg University, 69120 Heidelberg, Germany

Background

Durable clinical benefit from PD-1 blockade in cutaneous squamous cell carcinoma (cSCC) is limited to a subset of patients. The molecular and spatial determinants of effective baseline antitumor immunity remain poorly understood.

Methods

Baseline FFPE biopsies from clinically annotated responders and non-responders to cemiplimab were profiled using Visium HD, Xenium and MERSCOPE spatial transcriptomics. Matched serum samples (n=45) were analyzed using Olink Reveal and Immuno-Oncology panels. Tumor and stromal compartments were segmented, and neighborhood and proximity analyses were applied to map immune-stromal interactions. Differential gene-expression and protein analyses identified spatial and systemic correlates of response.

Results

Responders showed organized immune-stromal architectures at the tumor margin enriched for chemokines (CXCL13, CCL14, CCL15) and myeloid/dendritic-cell transcripts (LAMP3, FCER1A). Neighborhood enrichment revealed significant colocalization of T cells and myeloid cells in these chemokine-rich zones. Serum proteomics corroborated this pattern with higher inflammatory and antigen-presentation proteins (CXCL9, CXCL10, CCL19) in responders. IFN-gamma levels were significantly increased in on-treatment responder serum, consistent with enhanced T-cell activity. In contrast, non-responders lacked structured margins and displayed diffuse immune infiltration within repair-oriented stroma.

Conclusions Integrated spatial transcriptomic and proteomic profiling indicates that PD-1 blockade response in cSCC is associated with chemokine-enriched, LAMP3+ myeloid-lymphoid interaction zones at the tumor-stroma interface. These immune-stromal niches may serve as baseline biomarkers of PD-1 sensitivity and provide a framework for rational immunotherapy design in cSCC.

Kategorie: Tumor Immunology
Präsentationsart: Poster

Abstract-ID: 223

Alpha-MSH reduces Myeloid-Derived Suppressor Cell Numbers: Implications for Local and Adjuvant Immunotherapy in Skin Cancer?

A. Arndt[1], U. Raap[2], T. Luger[3], K. Loser[1]

[1] Carl von Ossietzky University, Institute of Immunology, Oldenburg, Germany

[2] Carl von Ossietzky University, Division of Experimental Allergy and Immunodermatology, Oldenburg, Germany

[3] University of Münster, Department of Dermatology, Münster, Germany

Skin cancer, encompassing malignant melanoma (MM) and non-melanoma entities such as basal (BCC) and squamous cell carcinoma (SCC), remains among the most prevalent malignancies in Europe. While ultraviolet (UV) radiation and genetic predisposition are well-established risk factors, immune dysregulation also plays a pivotal role in disease progression. Myeloid-derived suppressor cells (MDSCs) are key immunosuppressive populations that impair anti-tumor immunity by suppressing $CD8^+$ T cell activity and promoting regulatory T cell expansion. Targeting MDSCs therefore represents a promising strategy to restore effective immune responses and improve therapeutic outcomes. Notably, UV-induced factors like the neuropeptide alpha-melanocyte-stimulating hormone (alpha-MSH), best known for its role in pigmentation, also modulate immune responses in the skin. Previous findings have shown that alpha-MSH can enhance the cytotoxicity of peripheral blood mononuclear cells (PBMCs) from melanoma patients, though the underlying mechanisms are not fully understood.

In this project, we therefore focused on the interaction between alpha-MSH and MDSC, aiming to clarify whether alpha-MSH can influence MDSC generation, expansion, or functional activity, and thereby potentially influence anti-tumor immunity. Remarkably, *in vitro* generated MDSC via stimulation with granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-6 (IL-6) were significantly reduced in numbers upon treatment with alpha-MSH. Further phenotypic analysis of MDSC key expression markers like inducible nitric oxide synthase (iNOS) and transforming growth factor beta (TGF-beta) revealed no major alterations following alpha-MSH treatment. Functionally, *in vitro* generated MDSC consistently suppressed $CD8^+$ T cell proliferation in CFSE-based assays, however alpha-MSH did not modify the suppressive activity. To further explore the interaction between MDSCs and skin tumor cells, co-cultures of *in vitro* generated MDSCs and a melanoma cell line were established. Intriguingly, MDSCs displayed a cytotoxic effect towards the melanoma cells that was independent of alpha-MSH exposure. To gain deeper mechanistic insight, functional and phenotypic differences between alpha-MSH treated MDSC and control cells were further characterized on gene expression level with bulk RNA sequencing. Moreover, Seahorse assays were performed with regard to potential changes in the metabolic activity of alpha-MSH treated MDSCs.

Collectively, our findings demonstrate that alpha-MSH significantly reduced the numbers of *in vitro* generated MDSCs. Hence alpha-MSH might be a potential candidate for future development towards a local adjuvant therapy in skin cancer. Ongoing studies are extending these observations to MDSCs treated with alpha-MSH from BCC, SCC, and MM patients, including NDP-MSH, a more stable synthetic analog.

Kategorie: Tumor Immunology
Präsentationsart: Poster

Abstract-ID: 224

Neutrophil Extracellular Traps (NETs) Impair T Cell-Mediated Antitumor Response in 3D Human Melanoma Models

Michalaki, G [1]; Zhao, F. [2]; Ghorbani, F.[3]; Kött, J. [4]; Weishaupt, C. [5]; Schedel, F. [6]

1 Michalaki, G. University Clinic Münster, Department of Dermatology, Münster, Germany

2 Zhao, F. University Clinic Duisburg-Essen, Department of Dermatology, Essen, Germany

3 Ghorbani, F. University Clinic Duisburg-Essen, Department of Dermatology, Essen, Germany

4 Kött, J. University Medical Center Hamburg-Eppendorf, Department of Dermatology and Venereology, Hamburg, Germany

5 Weishaupt, C. University Clinic Münster, Department of Dermatology, Münster, Germany

6 Schedel, F. University Clinic Münster, Department of Dermatology, Münster, Germany

Background
T cell-directed immunotherapies have transformed oncologic treatment, yet many patients fail to achieve long-term responses.In the tumor microenvironment, $CD8^+$ T cells exert cytotoxic effects against tumor cells, while neutrophils modulate immune activation and suppression. Neutrophil extracellular traps (NETs) filamentous structures composed of chromatin DNA, histones, and granule proteins, are crucial components of innate immune defense but may also promote immunotherapy resistance and tumor progression. NET deposits have been described in primary and metastatic melanoma, yet their role in modulating melanoma progression and T cell activity remains poorly understood.

Methods
This study investigates the interaction of NETs with three-dimensional human melanoma spheroids, employing neutrophils and autologous T cells to model the immune-tumor microenvironment. Human melanoma spheroids were incubated with activated neutrophils to induce NET formation and subsequently exposed to autologous T cells.

Results
Confocal imaging revealed that NETs formed a dense barrier around tumor cells, impairing T cell-mediated tumor killing. Application of differentially acting NET inhibitors including GSK484, DNase I, and CIT-013 degraded or inhibited the formation of NETs, enabled immune cell-tumor cell contact, and enhanced cytotoxic function.

Conclusion
Our findings indicate that excessive NET formation benefits immune exclusion, inhibiting T cell-mediated antitumor immune responses in 3D tumor models. The established model can be utilized for further studies on how neutrophils and NETs shape the melanoma microenvironment. By targeting NETs, T cell efficacy may be improved, offering a promising strategy to enhance the therapeutic response to immunotherapy in melanoma and potentially other tumors.

Kategorie: Tumor Immunology
Präsentationsart: Poster

Abstract-ID: 225

Targeting TAMs via the glucocorticoid receptor sensitizes melanoma to immunotherapy

Landwehr, C.[1]; Krug, J.[1]; Cetkovic, A.[2]; Rocca, Y.[1]; A. Riedel, A.[2]; Schmieder, A.[1]

1 Department of Dermatology, Venereology and Allergology, University Hospital Würzburg, Germany.

2 Mildred-Scheel-Early-Career-Centre, Institute for Virology and Immunology, University Würzburg, Germany.

Background

Melanoma is among the five most prevalent malignancies worldwide. Immune checkpoint inhibitors (ICIs) have been shown to be an effective treatment for metastatic melanoma, with a consequent improvement in patient survival. However, the occurrence of massive immune-related side effects, in addition to the development of resistance, limits the efficacy of this treatment in half of the patients.

Regulatory T cells, myeloid-derived suppressor cells, and tumor-associated macrophages (TAMs) are components of the immunosuppressive tumor microenvironment (TME), which contributes to therapeutic resistance to ICIs. TAMs can be categorized into an immunoreactive M1-like phenotype and a protumoral, immunosuppressive M2-like phenotype. In many tumors, a high percentage of TAMs is associated with a poor prognosis.

Targeting of M2-like TAMs is currently being investigated as a potential therapeutic approach to overcome ICI resistance, with some groups using lipid nanoparticles (LNPs) to target M2-like macrophages via CD163.

Methods

For *in vitro* analyses, bone marrow-derived macrophages were isolated and directly stimulated with macrophage-colony stimulating factor and an M1/M2 stimulus for 72 h. Three days after isolation, the cells were stimulated either with the same stimulus or repolarized with the opposing stimulus. On day six, the cells were characterized using flow cytometry. In addition, functional assays such as tumor phagocytosis or antigen processing analysis were performed.

In vivo, YUMM1.7 cells were injected subcutaneously into the flank of C57BL/6J mice. When the tumor was palpable, LNPs were injected three times and αPD-1 antibodies twice per week. The tumor size was measured twice per week. The mice were euthanized 2.5 weeks after the injection of the tumor. The excised tumor was then further processed for flow cytometry analysis.

Results

Our approach aims to change the polarization state from M2-like TAMs to anti-tumorigenic M1-like TAMs. *In vitro*, the inhibition of the glucocorticoid receptor (GR) by αCD169 coated LNPs carrying mifepristone (Mife-LNPs) altered the polarization state of macrophages leading to an M1-like state. In addition, the GR KO reduced phagocytic ability and increased antigen processing in macrophages.

In vivo, the inhibition of the GR by Mife-LNPs in combination with αPD-1 resulted in a reduced tumor growth and weight, increased mature macrophages, increased activated $CD8^+$ T cells, and reduced exhausted $CD8^+$ and $CD4^+$ T cells. Furthermore, a single exposure of tumor-bearing mice to Mife-LNPs resulted in a decline in $CD163^+$ macrophages, and a decrease in monocytes and macrophages two days after treatment. Interestingly, only a reduction in peripheral macrophages and not tissue- resident macrophages was observed.

Conclusion
Summing up, the results of this study suggest that GR inhibition is a promising target to sensitize melanoma to ICIs. Future investigations will focus on the impact of peripheral macrophages in our tumor mouse model.

Kategorie: Tumor Immunology
Präsentationsart: Poster

Abstract-ID: 226

Comprehensive target identification platform reveals aberrant splicing induced HLA peptides as potential tumor-exclusive targets for immunotherapy

Bernhardt,M. [1], Hoffmann, S. [1], Hailemariam-Jahn, T. [1], Lamer, S.[2], Schlosser,A. [1], Schilling, B.[1]

1 Department of Dermatology, Venerology, Allergology, Univesity Hospital Frankfurt am Main
2 Center for Functional Proteomics, Goethe University Frankfurt

Immunotherapies have revolutionized melanoma therapy regimes, in particular the introduction of checkpoint inhibitors (ICIs). ICIs restore the capacity of CD8 positive (CD8+) T cells to destroy tumor cells selectively in a HLA-I peptide specific manner, making HLA-I peptides key targets for immunotherapy. In this project, we focused on the comprehensive identification of HLA peptide targets to improve cancer-immunotherapy by applying peptide vaccination, transgenic T cells or ImmTACs (Immune mobilizing monoclonal T cell receptors Against Cancer).
Our aim was to identify shared HLA peptides that directly derive out of aberrant oncogenic processes and to further validate their immunogenicity. As cryptic HLA peptides are often recurrently detected among patients, we primarily focused on this novel class of antigens.
Oncogenesis is freqeuntly accompanied by dysregulated RNA splicing events. Accumulating evidence suggests that neoantigens derived from aberrant splicing events, such as intron retentions or generation of new exon-exon-junctions, might represent promising targets for cancer immunotherapy. Here, we used a quantitative mass spectrometric approach to study the generation of aberrant-splicing-induced HLA-peptides (ABSINDH-peptides).
Pre-mRNA splicing was manipulated pharmacologically in melanoma cell lines. All experiments were conducted using metabolic isotope labeling followed by immunoaffinity purification and quantitative mass spectrometry-based analysis of HLA-I peptides.
By applying this technique, we were able to detect the formation of dozens of neoantigens upon splicing-modulation. Most of these peptides derived from intron retentions, which led to an extension of the coding sequence (CDS) into intronic regions.
A systematic comparison with tumor and benign immunopeptidomes revealed that out of all ABSINDH-peptides identified, a fraction of ~20% was detected in tumor cells *ex vivo* but not in healthy controls, indicating that this group of tumor exclusive ABSINDH-peptides was present naturally in tumors without further manipulating the splicing machinery of these tumors.
Interestingly, a substantial part of ABSINDH -peptides was identified in melanoma patients, indicating that aberrant splicing occuring in cutaneous melanoma might contribute to targetable neoantigens.
We screened the most promising tumor-exclusive ABSINDH-peptides in *in vitro* priming assays and indeed, some of them induced positive T cell responses. Considering that these tumor-exclusive ABSINDH-peptides were recurrently presented among different tumor patients and even in different tumor entities, they represent a new class of shared neoantigens with potential for immunotherapeutic exploitation.
We are currently performing T cell receptor sequencing and aim to identify T cell receptor sequences that recognize texABSINDH-peptides. This enables to further study the tumor killing efficacy and tumor specificity of these antigens and might pave the way for new T cell receptor-based therapies for melanoma and other malignancies.

Kategorie: Tumor Immunology
Präsentationsart: Poster

Abstract-ID: 227

AHR-deficient tumour cells escape CD8+ T cell immune therapy

S. Gellert [1]; M. Celebi [1]; A. Buzzai [1]; B. Kruse [1]; W. Li [1]; A. Braun [1]; K. Knauth [1]; S. Bonifatius [1]; M. von Wricz Rekowski [1]; F. Cansiz [2]; S. Weinert [3]; M. Mengoni [4]; M. Böttcher [5]; D. Mougiakakos [5]; A. Tasdogan [2]; T. Tüting [1]

1 Department of Dermatology, University of Magdeburg, Magdeburg, Germany

2 Department of Dermatology, University Hospital Essen, Essen, Germany

3 Department of Cardiology, Magdeburg, Germany

4 Department of Dermatology, University Clinic Schleswig-Holstein, Lübeck, Germany

5 Department of Haematology, Magdeburg, Germany

The aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor first identified for its capacity to bind and detoxify dioxins, toxic by-products of industrial processes. Beyond its role in xenobiotic metabolism, the AHR responds to numerous endogenous ligands and regulates key physiological processes such as cellular differentiation and immune homeostasis in the skin. Recent findings implicate AHR signalling in promoting melanoma progression and treatment resistance. Here, we examine the hypothesis that cancer cell-intrinsic AHR activity constrains the efficacy of T cell-based immunotherapy.

To test this hypothesis, we disrupted the AHR gene in HCmel12 mouse melanoma cells using CRISPR/Cas9 genome editing and applied our established CD8+ T cell adoptive cell therapy (CD8 ACT) protocol. This therapeutic regimen combines chemotherapeutic preconditioning with the adoptive transfer of melanoma-specific CD8+ T cells, recombinant adenoviral vaccination, and adjuvant intratumoural stimulation of innate immunity using the synthetic nucleic acids polyI:C and CpG.

Unexpectedly, the CD8 ACT treatment was considerably less effective against established HCmel12 AHR KO melanomas compared to HCmel12 CRISPR ctrl tumours. High-resolution spectral flow cytometry of single-cell suspensions from melanomas 7 days post-CD8 ACT treatment revealed an increased infiltration of macrophages and neutrophils exhibiting an immunosuppressive phenotype in HCmel12 AHR KO tumours compared to HCmel12 CRISPR ctrl tumours. Notably, a substantial number of late tumour escape variants emerged in CD8 ACT-treated HCmel12 AHR KO melanomas. To investigate underlying mechanisms, we conducted long-term in vitro stimulation of the HCmel12 AHR KO cell lines with interferon gamma. After 14 days of continuous IFNg exposure, these cells lost their responsiveness, characterized by downregulation of MHC class I and II molecules and resistance to IFNg/TNFa-induced cell death.

These findings reveal a novel role of cancer cell-intrinsic AHR signalling in modulating the tumour immune microenvironment and promoting immune escape through acquired loss of interferon responsiveness, highlighting potential challenges for T cell-based immunotherapies in melanoma.

Kategorie: Tumor Immunology
Präsentationsart: Oral Presentation & Poster

Abstract-ID: 228

ImmTACs Against Skin Cancer: From Molecular Design to Translation

Engel, M. [1]; Atilla Aydin, S. [1]; Primke, K. [1]; Levagina, P. [1]; Sinnberg, T. [1]; Eigentler, T. [1]

1 Charité – Universitätsmedizin Berlin, Department of Dermatology, Venereology and Allergology, Berlin, Germany,

Background
Immunotherapies have revolutionized cancer treatment, yet their efficacy in advanced skin malignancies remains limited. Immune-mobilizing monoclonal TCRs against cancer (ImmTACs) combine high-affinity, tumor-specific T-cell receptors with antibody fragments to recruit and activate effector cells. The clinical success of Tebentafusp in HLA-A*02:01-positive patients with metastatic uveal melanoma demonstrates the therapeutic potential of this molecule class. However, translation of the ImmTAC format to other skin cancer entities or alternative effector mechanisms has hardly been explored, particularly in the academic setting.

Objectives
This project aims to establish and apply a modular platform for the development and preclinical evaluation of novel ImmTAC constructs targeting rare and therapy-resistant skin cancers.

Methods
A bimodular plasmid backbone enables rapid exchange of TCR and CD3 domains via Golden-Gate assembly. Constructs are expressed in HEK293 cells and screened for functionality using co-cultures of gp100-positive, HLA-A*02:01-expressing tumor cells and reporter Jurkat T cells. Active candidates are further characterized with PBMCs from healthy donors and patient-derived material from an institutional biobank. In a second phase, additional tumor-associated antigen-binding domains and alternative effector domains, such as CD16 to engage NK cells, are integrated and compared functionally. Selected TCRs undergo affinity optimization using AI-based in-silico modeling (TCRmodel2, TPepRet). Future work includes validation in humanized mouse models expressing e.g. human CD3 or CD16A to assess immune activation and antitumor efficacy in vivo.

Results and Expected Outcome
The modular approach allows standardized and comparable testing of ImmTAC variants. It provides a scalable experimental framework for assessing antigen specificity, immune activation, and effector function across different immune cell recruitment strategies. Combining molecular design, functional screening, and computational optimization will yield novel ImmTAC candidates and a validated workflow for TCR-based immunotherapies.

Conclusion
This project establishes an academically driven framework to systematically investigate T-cell receptor–based bispecifics. By enabling modular design and comparative evaluation of alternative effector mechanisms, it aims to expand the conceptual and methodological scope of TCR bispecific research and explore new applications for rare and treatment-resistant skin cancers.

Kategorie: Tumor Immunology
Präsentationsart: Poster

Abstract-ID: 229

Extracellular Vesicle Proteomics Reveals Baseline and Longitudinal Signatures of Melanoma Progression under Immune Checkpoint Inhibition

Carmen M.T. Roeper[1,2], Glenn Geidel[1,2], Daniel J. Smit[1,3], Lucija Ačkar[3], Bente Siebels[4], Hannah Voß[4], Hartmut Schlüter[4], Michaela Schweizer[5], Kilian Müller[4], Benjamin Deitert[1,2], Alessandra Rünger[1,2], Tim Zell[1,2], Ali Zeinal-Abedini[1,2], Isabel Heidrich[1,2,3], Stefan W. Schneider[1,2], Klaus Pantel[1,3], Julian Kött[1,2], Christoffer Gebhardt[1,2]

[1]Department of Dermatology and Venereology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[2]Fleur Hiege Center for Skin Cancer Research, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[3]Institute of Tumor Biology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[4]Center of Diagnostics, Section Mass Spectrometry and Proteomics, University Medical Center

Hamburg-Eppendorf, Hamburg, Germany

[5] Center for Molecular Neurobiology Hamburg (ZMNH), University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Introduction

Immune checkpoint inhibitors (ICI) have improved clinical outcomes in advanced melanoma, yet 40–50% of patients still experience disease progression, and reliable biomarkers capturing baseline risk and longitudinal treatment dynamics remain limited. Extracellular vesicles (EVs) mirror tumor–host interactions through their protein cargo, offering a promising liquid-biopsy source for identifying predictors of ICI response. This study aimed to define EV-based proteomic signatures associated with baseline outcome and progression patterns in melanoma patients undergoing ICI therapy.

Methods

Plasma EVs were isolated from 32 patients with advanced melanoma (AJCC IIIC–IV) receiving ICI treatment and classified into disease control and progressive disease groups based on radiologic assessment. EVs were collected at baseline, after six months on treatment, and at progression. EV characterization included nanoparticle tracking analysis and mass spectrometry–based proteomic profiling. Statistical analyses comprised differential abundance testing, PLS-DA, linear mixed-effects modeling, trajectory clustering, pathway enrichment, and survival modeling using Kaplan–Meier and Cox regression.

Results

Baseline EV proteomics revealed 640 proteins, with CRP and TTN emerging as the strongest discriminators between disease control and progressive disease. Both proteins were significantly elevated in patients with poor outcome and individually predicted shorter time to progression.

Longitudinal modeling identified 78 proteins with significant temporal shifts, forming four trajectory clusters with coordinated increases or decreases toward progression. CRP exhibited a pronounced decline from baseline to progression in non-responders, whereas TTN remained

consistently elevated at baseline, underscoring its role as a stable intrinsic high-risk marker in contrast to CRP's dynamic progression-related behavior. EV-associated pathways reflected alterations in immune activation, cell–cell communication, and DNA damage responses accompanying disease progression.

Conclusion

This work demonstrates that EV proteomics provides complementary insight into baseline stratification and the temporal biology of melanoma progression under ICI therapy. CRP and TTN represent promising baseline predictors of poor outcome, while longitudinal EV proteome remodeling highlights dynamic signatures associated with emerging resistance. EV-based proteomic biomarkers thus offer a minimally invasive approach for monitoring melanoma and may support personalized treatment strategies in the immunotherapy era.

Kategorie: Tumor Immunology
Präsentationsart: Poster