ABSTRACTS

Indolent primary cutaneous B-cell lymphomas resemble persistent antigen reactions without signs of dedifferentiation

RH01

Johannes Griss[1], Sabina Gansberger[1], Inigo Oyarzun[1], Stefanie Porkert[1], Matthias Farlik[1], Wolfgang Weninger[1], Werner Dolak[2], Constanze Jonak[1], Patrick M. Brunner[3]

[1]Medizinische Universität Wien, Universitätsklinik für Dermatologie, Wien, Österreich, [2]Medizinische Universität Wien, Universitätsklinik für Innere Medizin III, Wien, Österreich, [3]Icahn School of Medicine at Mount Sinai, Department of Dermatology, New York, Vereinigte Staaten

Einleitung / Background: Primary cutaneous B-cell lymphomas comprise a heterogeneous group of extranodal non-Hodgkin lymphomas. While primary cutaneous diffuse large B-cell lymphoma - leg type (pcDLBCL-LT) is highly aggressive, the two other subtypes, primary cutaneous follicle centre lymphoma (pcFCL) and primary cutaneous marginal zone lymphoma (pcMZL), also termed primary cutaneous marginal zone lymphoproliferative disorder, usually follow an indolent course.

Methodik / Methods: We here present a comprehensive single-cell RNA-sequencing study of pcFCL, pcMZL, and pcDLBCL-LT skin lesions in comparison to samples from benign reactive B-cell rich lymphoid proliferation (rB-LP) lesions, gastric MALT lymphoma, nodal FCL, and nodal DLBCL.

Ergebnisse / Results: Our data show that pcMZL and pcFCL, as well as rB-LP, showed a persistent germinal centre reaction within the expanded clone. By contrast, malignant clones of pcDLBCL-LT and gastric MALT lesions lacked these features. Therefore, pcMZL may represent a non-malignant reaction against a yet to be determined antigen. Conversely, in pcFCL, B cells show a significantly larger clonal expansion, presumably through acquisition of a driver mutation. Nevertheless, these clones were still undergoing continuous somatic hypermutation. This may be linked to the lack of further differentiation of B cells in pcFCL, in contrast to nodal FCL, and may cause its indolent clinical course.

Schlussfolgerung / Conclusion: In contrast to pcDLCBL-LT, our data thus indicate that pcMZL and pcFCL, similar to rB-LP are characterised by a functional germinal centre reaction likely driven by antigen recognition which supports the classification of pcMZL as a lymphoproliferative disease. Therefore, our suggests a new pathomechanism for indolent primary cutaneous B cell lymphoma.

Mite be a problem? Resistance to scabicides in *Sarcoptes scabiei var. hominis* mites

RH02

Markus Wiesmüller[1], Julia Walochnik[2], Damian Meyersburg[3], Alireza Abdolrasouli[4], Cielo Pasay[5], Maximilian Egg[1], Alessandra Handisurya[1]

[1]Medizinische Universität Wien, Universitätsklinikum für Dermatologie, Wien, Österreich, [2]Medizinische Universität Wien, Zentrum für Pathophysiologie, Infektiologie und Immunologie, Institut für Spezifische Prophylaxe und Tropenmedizin, Wien, Österreich, [3]Uniklinikum Salzburg, Universitätsklinikum für Dermatologie und Allergologie, Salzburg, Österreich, [4]King's College Hospital, Department of Medical Microbiology, London, Vereinigtes Königreich, [5]The Australian Defence Force Malaria and Infectious Disease Institute Laboratory, QIMR Berghofer Medical Research Institute, Brisbane, Australien

Einleitung / Background: Increasing evidence has sparked a debate on the resistance of *Sarcoptes scabiei var. hominis* mites to antiscabietic therapy with permethrin. This study investigates mites derived from Austria and other countries for the presence of mutations in the voltage-sensitive sodium channels (*Vssc*), known to be associated with knockdown resistance (kdr), and for alterations in the detoxification pathway of permethrin.

Methodik / Methods: Mites' DNA was genotyped in three distinct regions of the *Vssc*, which constitute the putative binding site for permethrin. In addition, the mRNA expression of distinct enzymes responsible for the detoxification of permethrin (GSTmu I-III, GSTdelta I-III, P-Glycoprotein) was evaluated via qPCR in comparison to permethrin-naive control mites.

Ergebnisse / Results: The previously identified kdr-associated M918L mutation was detected in 100% of the mites collected in Austria and northern Europe. Additionally, three novel, not yet identified mutations (P18T, T742I, E747D) present within the *Vssc* were identified, whose biological relevance are currently under investigation. Furthermore, gene expression analyses revealed significantly elevated mRNA levels of the GSTmu and GSTdelta detoxification enzymes compared to mites, which had never encountered permethrin. The most prominent increases were observed in the GSTdelta II (up to 24700-fold) and GSTdelta I (up to 3700-fold) isoforms.

Schlussfolgerung / Conclusion: The results indicate that several mechanisms are present in the current *Sarcoptes scabiei var. hominis* mite population that could contribute to the observed loss of sensitivity to permethrin. Given the emergence of therapy-refractory mites, resistance may have slowly evolved in the past years, which may be decisive for future therapy management of scabies-infested patients.

Gene expression profiles and immune cell composition of generalized pustular psoriasis and acute generalized exanthematous pustulosis

RH03

Theresa Benezeder[1], Natalie Bordag[1], Johannes Woltsche[1], Katharina Falkensteiner[1], Thomas Graier[1], Eva Schadelbauer[1], Lorenzo Cerroni[1], Peter Wolf[1]

[1]Medizinische Universität Graz, Univ. Klinik für Dermatologie und Venerologie, Graz, Österreich

Einleitung / Background: The clinical and histopathological features of generalized pustular psoriasis (GPP), a neutrophilic condition, overlap with those of acute generalized exanthematous pustulosis (AGEP), making a rapid and reliable distinction difficult. The aim of this study was to investigate the molecular differences between AGEP and GPP.

Methodik / Methods: In a multicenter team effort, we collected lesional FFPE skin biopsy samples from patients with AGEP (n=40), GPP (n=30), palmoplantar pustulosis (PPP; n=9), plaque psoriasis (PSO; n=8), cutaneous adverse drug reactions (ADR; n=12) and healthy control skin (HCO; n=9), then performed bulk RNA sequencing.

Ergebnisse / Results: The transcriptome profiles of AGEP and GPP largely overlapped, but showed differences to PPP, PSO, ADR and healthy skin. Analysis of immune response patterns showed that GPP samples had the highest expression of Th17- and neutrophil-related genes, while AGEP had higher expression of cytotoxicity-related genes. Furthermore, using CIBERSORTx, a computational deconvolution of RNA-Seq data, we found a higher number of neutrophils in GPP but a higher number of CD8+ T cells in AGEP samples.

Schlussfolgerung / Conclusion: We found a strong overlap between AGEP and GPP with subtle differences in the expression of immune marker genes. These data suggest that AGEP may be a drug-induced flare of GPP and therefore has more cytotoxic features than GPP.The data were obtained in collaboration with CEE GPP expert network members R. Čeović, J.-T. Maul, M. Marovt, V. Mateeva, B. Meier-Schiesser, D. Meyersburg, G. Ratzinger, A. Reich, L. Pavlovsky, K. Prillinger, J. Semakova and A. Szegedi, who provided clinical data, samples and other support.

Retrospektiver Vergleich der Prognose von Melanom-Patient:innen in Abhängigkeit von der Positivität des Sentinel-Lymphknotens in den Jahren 2013 bis 2023

RH04

Victoria Pernsteiner[1], Rebecca Ram[1], Eva Strauss[2], Sigrid Metz-Gercek[3], Norbert Sepp[1], Helmut Kehrer[1]

[1]Ordensklinikum Linz Elisabethinen, Abteilung für Dermatologie, Venerologie und Allergologie, Linz, Österreich, [2]Ordensklinikum Linz Elisabethinen, Klinische Studienzentrale, Linz, Österreich, [3]Ordensklinikum Linz Elisabethinen, Tumorzentrum Oberösterreich, Linz, Österreich

Einleitung / Background: Im Ordensklinikum Linz Elisabethinen wird eine Sentinel-Lymphknotenentnahme ab einer Tumordicke von 1 mm sowie unter bestimmten Voraussetzungen (Ulzeration, Alter < 40 Jahren) ab einer Tumordicke von 0,8 mm empfohlen.

Methodik / Methods: Retrospektiv analysiert wurden insgesamt 422 Patient:innen, denen bei Erstdiagnose eines malignen Melanoms in den Jahren 2013 bis 2023 ein Sentinel-Lymphknoten im Ordensklinikum Linz Elisabethinen entnommen worden war.

Ergebnisse / Results: Insgesamt ergab die histologische Untersuchung des Sentinel-Lymphknotens bei 52 Patient:innen (12,3 %) einen positiven und bei 370 Patient:innen (87,9 %) einen negativen Befund.

Bei 24 Patient:innen der Sentinel-positiven Gruppe (46,2 %) kam es zu einem Rezidiv mit regionalen Lymphknoten- oder Fernmetastasen. Es verstarben 15 der 52 Patient:innen (28,9 %). Bei den 370 Sentinel-negativen Patient:innen kam es bei 45 Patient:innen zu einem Rezidiv (12,2 %). Insgesamt verstarben in dieser Gruppe 50 der 370 Patient:innen (13,6 %). Die Dauer von der Erstdiagnose bis zum ersten Rezidiv war in der Sentinel-positiven Gruppe mit durchschnittlich 19,4 Monaten kürzer als in der Sentinel-negativen Gruppe mit durchschnittlich 33,7 Monaten.

Die Tumordicke lag am häufigsten zwischen 1 und 2 mm (53,3 %), wovon bei 8,0 % der Sentinel positiv war. Bei 49 Patient:innen mit Melanomen mit einer Tumordicke von ≤ 1 mm (11,6 %) war kein Lymphknoten metastatisch befallen. Mit 26,5 % war der Sentinel bei Patient:innen mit Melanomen mit einer Tumordicke von ≥ 4 mm (11,6 %) am häufigsten positiv.

Schlussfolgerung / Conclusion: Die Daten zeigen, dass ein signifikanter Unterschied hinsichtlich der Mortalität zwischen den beiden Gruppen besteht. Das rezidivfreie Überleben der Sentinel-negativen Gruppe ist signifikant länger.

Literatur / Literature: Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017;67(6):472-492. doi:10.3322/caac.21409

Hymenoptera venom-induced anaphylaxis patients with a clonal mast cell disease undergoing venom immunotherapy respond with senescent CD8$^+$ T_{EM} cells

RH05

Andrea Teufelberger[1], Urban Cerpes[1], Andrada-Renata Dan[1], Danijela Bokanovic[1], Regina Fink-Puches[1], Niklas Mahnke[2,3], Carolina Vera Ayala[2,3], Suk-yee Chu Wang[2,3], Polina Pyatilova[2,3], Kerim Fedai[2,3], Frank Siebenhaar[2,3], Birger Kränke[1], Peter Wolf[1]

[1]Medical University of Graz, Department of Dermatology and Venereology, Graz, Österreich, [2]Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Institute of Allergology, Berlin, Deutschland, [3]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Deutschland

Einleitung / Background: *Hymenoptera* venom immunotherapy (VIT) is usually effective in inducing long-life tolerance to the allergen. In patients with a clonal mast cell disease (CMD) and *Hymenoptera* venom-induced anaphylaxis (HVA), however, life-long VIT is recommended, as tolerance towards the venom is often lost after VIT termination. Differences in frequencies of blood lymphocytes between CMD and non-CMD patients might hint at a functional involvement of these cells in tolerance maintenance.

Methodik / Methods: Blood samples were collected from CMD and non-CMD patients with severe HVA (Ring and Messmer grade III or IV). These patients were either before VIT, or more than 3 years under VIT. Blood of non-anaphylactic CMD patients and healthy individuals served as controls. Serum tryptase, KIT D816V mutation, total IgE, and venom-specific IgE were measured to determine disease status. We quantified T and B memory- and regulatory cell subsets by flow cytometry.

Ergebnisse / Results: Most measured cell types were similar between all tested groups. VIT-treated CMD patients had more CCR7-CD8+ effector memory T cells (T_{EM}) and higher frequencies of senescent CD57+CD8+ T cells than untreated CMD patients. In contrast, VIT-treated non-CMD patients had slightly higher frequencies of the CCR7+CD8+ central memory T cells (T_{CM}) compared to untreated non-CMD patients and no increased frequencies of exhausted or senescent CD8+ T cells.

Schlussfolgerung / Conclusion: The observed difference in CD8+ T cell subsets between CMD and non-CMD patients during VIT suggests a different treatment response. Functional investigations of central and effector memory CD8+ T cells will give insights whether and how they influence immunological tolerance.

Tick feeding induces lymphatic emigration and pro-tolerogenic immune response in human epidermal Langerhans cells

RH06

Johanna Strobl[1], Lisa Kleissl[1], Sally Conolly[2], Laura Marie Gail[1], Sophie Weninger[1], Tobias Frey[3], Mateusz Markowicz[4], Klaus Schmetterer[3], Herbert Strobl[2], Hannes Stockinger[5], Michiel Wijnveld[5], Georg Stary[1]

[1]Medizinische Universität Wien, Universitätsklinik für Dermatologie, Wien, Österreich, [2]Medical University of Graz, Division of Immunology, Otto Loewi Research Center, Graz, Österreich, [3]Medical University of Vienna, Department of Laboratory Medicine, Wien, Österreich, [4]Austrian Agency for Health and Food Safety, AGES, Wien, Österreich, [5]Medical University of Vienna, Institute for Hygiene and Applied Immunology, Center for Pathophysiology, Infectiology and Immunology, Wien, Österreich

Einleitung / Background: Arthropods are evolutionally conserved disease vectors altering the host skin immune landscape during ectoparasitic feeding. An intact epidermal barrier including Langerhans cells (LCs) is pivotal for protection against ectoparasites including *Ixodes ricinus*.

Methodik / Methods: Here, we investigated the migration and polarization patterns of human LCs in response to clinical and experimental tick bite and infection with tick-borne *Borrelia burgdorferi*.

Ergebnisse / Results: Tick bites (TB) and tick saliva (TS) transmission re-program LCs to upregulate chemokine receptors and emigrate to the lymphatics. LCs primed with TS and tick-borne *B. burgdorferi* upregulate transcription factors IDO1 and IRF4, show blunted T helper(Th)-17 and Th-9 polarization when compared to *S. aureus*-stimulated LCs, and generate a response dominated by Th2 and regulatory T cells (Treg). Consistently, introducing TS and *B. burgdorferi* to an lymphoid tissue organoid model elicits Treg responses while abrogating effector T cells.

Schlussfolgerung / Conclusion: Collectively, our results reveal tick feeding to modulate the cutaneous immune repertoire by induction of tolerogenic LCs. These dampen the adaptive response to tick-borne pathogens by skewing T effector cell polarization in the lymph node.

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