103 Unabated type I interferon expression in B-cell autoimmunity and anti–drug antibody formation during anti-TNF therapy
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Anti-TNF biologics are widely used in the treatment of numerous autoimmune diseases such as rheumatoid arthritis, Crohn’s disease, and psoriasis. However, TNF blockade as a therapy has its limitations. Besides an increased susceptibility to infections, 0.2–1% of patients develop anti-TNF-induced lupus erythematosus (ATEL). Moreover, TNF-α blockers are associated with increased frequencies of anti-drug antibodies (ADA). We have previously shown that TNF inhibition shifts the equilibrium of TNF and type I interferon towards an excessive type I interferon response. Here, we show that a similar pathomechanism underlies B-cell-mediated autoimmunity and the formation of ADA during anti-TNF treatment. In fact, adalimumab but not the anti-IL12/23 ustekinumab was associated with an increase of anti-nuclear antibodies (ANA) in psoriasis patients. In vitro, anti-TNF treated plasmacytoid dendritic cells produced cell death and enhanced IgG production, an effect that was critically dependent on type I interferon. In a mouse model of lupus, anti-CD45R0+B cell accumulation and ANA formation was accelerated and early glomerular IgG deposition and serum creatinine increase suggest a pathogenic role for the dysbalance of TNF and type I interferon in ATEL. Besides increased ANA, adalimumab also showed a significantly higher frequency of ADA as compared to ustekinumab, despite similar immunogenicity of the antibodies. ADA correlated with interferon-alpha serum levels in patients receiving adalimumab and, in a mouse model, the activation of the type I interferon pathway led to accelerated ADA formation during anti-TNF treatment. These findings indicate that, in patients treated with anti-TNFs, unabated type I interferon production might unleash B-cell-mediated autoimmunity and facilitates ADA formation and secondary loss of efficacy.

105 How important is the speed of response to biological therapy?
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Atopic dermatitis (AD) is a chronic inflammatory skin disease associated with skin barrier defects and microbial dysbiosis. The development and progression of AD critically depends on the role of different type 2 cytokine-producing cells in the development of AD beyond Th2 responses. In the long term, this project will clarify the role of different type 2 cytokine-producing cells in the development of AD beyond Th2 cells and develop new treatment strategies.

106 Molecular analysis of treatment-refractory pityriasis rubra pilaris uncovers an IL-1 signature with therapeutic proof-of-concept of the anti-IL-1 biological anakinra
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Pityriasis rubra pilaris (PRP) is a rare inflammatory skin disease phenotypically presenting features within the spectrum of psoriasis and atopic eczema. The pathogenesis is not fully understood but an activation of the interleukin (IL)-23 T-helper (Th) 17 axis has been shown, which currently presents as a promising treatment option. Here we present an in-depth molecular analysis of cytokine tissue profiling (nanotagging) of patients with PRP (during and post-inflammation) comparing to plaque-type psoriasis, atopic dermatitis and healthy controls. We could show that proinflammatory cytokines like TNF-alpha, IL-21 and IL-17, also IL-1 alpha and IL-1 beta were upregulated during disease course, which normalized after resolution of skin inflammation. Principal component analysis and pathway analysis are currently ongoing. Additionally, we performed serum cytokine analysis in all groups. In a patient with a second flare of PRP and a positive IL-1 signature, we applied anakinra, a receptor IL-1 receptor antagonist, over 12 weeks. Skin severity improved from PASI 11.4 to 2.6 (77% reduction). Digital special profiling (GeoMX) from serial biopsies are currently ongoing. In summary we could show for the first time, that targeting IL-1 in human PRP could be a treatment option in this subgroup of treatment-refractory patients.

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104 C1ORF162 is specifically expressed by pathogenic Th2 cells in atopic dermatitis
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Pathogenic Th2 cells are a recently described subgroup of allergen-specific Th2 cells that exhibit distinct cytokine signatures and are associated with severe atopic dermatitis. Understanding the unique biology of pathogenic Th2 cells holds the promise of identifying specific and novel therapeutic targets. The gene chromosome 1 open reading frame 162 (C1ORF162) has been repeatedly identified to be specifically expressed by pathogenic Th2 cells and its expression correlates with disease severity in atopic dermatitis. Yet, its function is completely unknown. Here, we characterized the cellular expression of C1ORF162 at the mRNA and protein level in primary human T cells. RNA sequencing and qPCR analysis confirmed that both in vitro and in vivo primed Th2 express higher levels of C1ORF162 than Th1 and Th17 cells. In addition, C1ORF162 expression in Th2 cells correlated with the expression of cytokines that are specifically expressed by pathogenic Th2 cells, such as IL-9 and IL-5. These findings were confirmed at the protein level by Western Blot and FACS analysis. Initial protein localization experiments and functional analyses suggest that C1ORF162 is a perinuclear protein that is rapidly downregulated by IL-2 signaling. Finally, C1ORF162 was found to be expressed by T cells infiltrating lesional skin of atopic dermatitis. In conclusion, C1ORF162 is consistently expressed in pathogenic Th2 cells and associated with disease severity in atopic dermatitis. Future experiments aim to further define the identity and function of C1ORF162 in human Th2 cells. Based on the close association of C1ORF162 with pathogenic Th2 cells, these studies may have therapeutic implications for type 2 driven disease in the skin and beyond.

107 Cuttingan kinase activity correlates with treatment outcomes following PPIK delta inhibition in mice with experimental pemphigus diseases
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Pemphigus diseases (PD) comprise a group of autoimmune diseases characterized by the development of auto-antibodies targeting structural proteins of the dermal-epidermal junction. Skin-bound immune complexes trigger recruitment of myeloid cells, engagement of Fcy receptors, and activation of specific kinases. Selective blockade of PPIK (P) can alleviate disease manifestation in mouse models of autoimmunes diseases. Here, we evaluated the treatment efficacy of parsaclisib, a selective PPIK64 inhibitor, in in-vitro and in-vivo models of epidermolysis bullosa acquisita (EBA) and mucous membrane pemphigoid (MMP). We demonstrated that parsaclisib dose-dependently decreased cytokine expression in human skin, decreased EBA and MMP skin immune complex-stimulated neutrophils. Furthermore, parsaclisib inhibited the dermal-epidermal separation induced in-vitro by co-incubation of immune complexes with polymorph nuclear cells. To investigate the effect of parsaclisib in-vivo, we used 3 experimental mouse models of PD. Parsaclisib significantly improved the extent of skin and oral lesions in immunization induced EBA and antibody transfer-induced MMP, but not antibody transfer-induced EBA. In line, kinase activity profiling of the mouse lesional skin further supported the concept that parsaclisib is a powerful therapeutic agent after PD. This study suggests a potential role of PPIK in EBA and MMP and immunization induced EBA. However, PPIK was absent within the kinase activation network of antibody transfer induced EBA. Taken together, our data provide evidence that global cutaneous kinase activity present in lesional PD correlates with disease severity, suggesting the potential activity of PPIK35 blockade with parsaclisib as a treatment option.