Unlabeled type 1 interferon expedites B-cell autoimmunity and anti-drug antibody formation during anti-TNF therapy

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Anti-drug antibodies (ADA) are biomarkers of type 2 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 (ATL). Moreover, ADA's are associated with increased frequencies of anti-drug antibodies (ADA). We have previously shown that TNF inhibition shifts the equilibrium of TNF and type 1 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, although not the anti-IL12/21 ustekinumab was associated with an increase of antibacterial antibodies (ANA) in psoriasis patients. In vitro, anti-TNF treated plasmacytid dendritic cells propelled cell activation and enhanced IgG production, an effect that was critically dependent on type I interferon. In a mouse model of lupus, anti-TNF accelerated ANA formation, while the early glomerular IgG deposition and serum-creatinine increase, suggesting a pathogenic role for the dysbalance of TNF and type 1 interferon in ATL. Besides increased ADA, ustekinumab 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, unlabeled type 1 interferon production might unleash B-cell mediated autoimmunity and facilitates ADA formation and secondary loss of efficacy.

How important is the speed of response to biological therapy?

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Psoriasis is a chronic inflammatory disease that affects around 1-3% of the adult population. The most common type, psoriatic vulgaris, is a consequence of genetic susceptibility and has multiple triggers. Immunological and genetic studies have identified cytokines such as TNF-a, IL-17 and IL-23 as key factors in the pathogenesis of psoriasis and becomes targets for the new biologic therapies. We present the case of a 65-year-old patient, smoker, who presents for an itch rash consisting of erythematous plaques with thick, silvery scales affecting the palms and soles. Also, all fingernails and toenails presented pitting, onycholysis, subungual hyperkeratosis, oil drop discoloration and splinter hemorrhages, with an evolution of about one year. The nail changes were impressive, therefore the patient had functional impairment. The patient was on multiple therapies with topical medication, PUVA therapy and methotrexate for 3 months, but without significant therapeutic success. Following highly modified scores, it was decided to initiate treatment with ixekizumab (Taltz), an anti-IL-17A monoclonal antibody. After 3 months, at a clinical evaluation, it was noticed an improvement of the palmoplantar and nail psoriatic lesions and an increase of the quality of life. Psoriasis vulgaris is a complex disorder of the skin and immune system, the purpose of the treatment being the remission of the lesions and prevention of the complications such as psoriatic arthropathy by using a safe and effective therapy for the patient, initiated as soon as possible in the evolution of the disease.

Unraveling the kinetics and cellular contributions in type 2 immune responses in atopic dermatitis

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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 appears to be driven by specific immune system responses in the context of a dysregulated skin microbiome. Identification of the key players and their interactions could pave the way to newer treatment options. In this study, we aimed to unravel the kinetics and cellular contributions in type 2 immune responses in AD. A mouse model of AD was established by treatment of BALB/c mice with dinitrochlorobenzene (DNCB) to induce atopic dermatitis. Both DNCB and adjuvant potentiated the production of IL-4 and IL-13, which is a hallmark of type 2 immune responses. A novel approach was taken by using IL-4 reporter mice, which allows the identification of IL-4 producing cell types in vivo. Using this approach, we found that type 2 immune responses were induced early after the treatment with DNCB and persisted during the progression of AD. The early appearance of type 2 immune responses was accompanied by increased mRNA expression of IL-13, IL-4, CCL17 and CCL22, 6 days after treatment. Skin-draining lymph nodes mimicked the previously described dynamics of IL-4 producing cell types, suggesting a pivotal role for lymph node-draining cells in the induction of type 2 immune responses. Furthermore, the increased IL-4 and IL-13 expression was associated with increased expression of IL-4 and IL-13 receptors on monocytes, suggesting a potential role for these cells in the regulation of type 2 immune responses. These findings provide novel insights into the kinetics and cellular contributions in type 2 immune responses in AD and highlight the importance of targeting type 2 immune responses for the treatment of AD.

C10R16F2 is specifically expressed by pathogenic Th2 cells in atopic dermatitis

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Pathogenic Th2 cells are a recently described subgroup of pathogenic Th2 cells that are characterized by a specific cytokine profile and high expression of CD25. We hypothesized that C10R16F2 (C10orf16f) is a novel marker for pathogenic Th2 cells in atopic dermatitis (AD). 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 (C10R16F2) 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 C10R16F2 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 cells express higher levels of C10R16F2 than Th1 and Th17 cells. In addition, C10R16F2 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 C10R16F2 is a perinuclear protein that is rapidly downregulated by IL-2 signaling. Finally, C10R16F2 was found to be expressed by T cells infiltrating lesional skin of atopic dermatitis. In conclusion, C10R16F2 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 C10R16F2 in human Th2 cells. Based on the close association of C10R16F2 with pathogenic Th2 cells, these studies may have therapeutic implications for type 2-driven disease in the skin and beyond.

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 besides proinflammatory cytokines like TNF-alpha, IL-23 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 recombinant IL-1 receptor antagonist, over 12 weeks. Skin severity improved from PASI 11 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.

Cutaneous kinase activity correlates with treatment outcomes following PI3K delta inhibition in mice with experimental pemphigus diseases

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Pemphigus diseases (PD) comprise a group of autoimmune disorders characterized by pathological cutaneous inflammation and subepidermal blistering. PD are caused by autoimmune thymus-derived targeting structural proteins of the dermal-epidermal junction. Skin-bound immune complexes trigger recruitment of myeloid cells, engagement of Fcγ receptors, and activation of specific kinases. Selective blockade of PI3K can alleviate disease manifestation in mouse models of autoimmune disease. Here, we evaluated the treatment efficacy of parsaclisib, a selective PI3Kdelta inhibitor, in in-vivo and in-vivo models of epidermolysis bullosa acquisita (EBA) and mucous membrane pemphigus (MMP). We demonstrated that parsaclisib dose-dependently inhibited keratinocyte and skin-specific expression of MMP in vivo and mouse 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. Pasaclisib 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 pathogenic role of PI3Kδ as a target for PD. Our study confirmed potential of harnessing cutaneous kinase activity present in lesional PD correlates with disease severity, suggesting the potential activity of PI3Kδ blockade with parsaclisib as a treatment option.