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

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Anti-TNFs are key agents 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 (ATL). Moreover, anti-TNFs 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 toward 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-nucleosomal antibodies (ANA) in psoriasis patients. In vitro, anti-TNF treated plasmacytoid dendritic cells produced 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 by early glomerular IgG-deposition and serum-creatinine increase, suggesting a pathogenic role for the dysbalance of TNF and type I interferon in ATL. 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, unlabeled type I 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 affecting around 1-3% of the adult population. The most common type, psoriasis vulgaris, is a consequence of genetic susceptibility and has multiple triggers. Immunological and genetic studies have identified cytokines such as TNF-α, IL-17 and IL-23 as key factors in the pathogenesis of psoriasis and potential targets for the new biologic therapies. We present the case of a 65-year-old patient, smoker, who presents for an itchy 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 discolouration and splinter hemorhages, with an evolution of about one year. The nail changes were impressive, therefore the patient had functional impairment. The patient does not have arthralgias, a nonspecific feature for the significant nail involvement. At the time of the hospitalization, the patient had a form of severe psoriasis with a PASI score of 11.6, DLIQ score of 27 and NAPSI score of 118. The blood tests were normal. Histopathological examination revealed highly suggestive changes to establish the diagnosis of psoriasis vulgaris. The patient followed numerous 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 isekizumab (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 arthritis 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 critically depends on different types of type 2 immune responses. We aimed to disclose the kinetics and cellular contributors of type 2 immune responses in AD, focusing on the action of type 2 immune mediators. However, the identity of these immune cells as well as their chronological appearance in the establishment of AD are still elusive. This project aims to disclose the kinetics and cellular contributions of type 2 immune responses in AD, focusing on the dynamics of interleukin (IL)-4 induction during skin inflammation in pre-clinical models. To mimic skin barrier impairment, mice were subjected to repeated tape stripping (TS) of their shaved back skin. Medium containing Staphylococcus aureus (S. aureus) was applied to induce microbial dysbiosis. Both conditions were induced either alone or in combination at defined time points. Using IL-4 reporter mice, we found that TS as well as the combination of TS and S. aureus increased the appearance of IL-4-producing cell types such as Th2 cells, eosinophils and natural regulatory T cells. The skin, accompanied by an increased mRNA expression of IL-13, CCL1 and IL-6 was detected at early time points, accompanied by downregulation of skin barrier-forming proteins within the combined treatment with TS and S. aureus. Analyses of the skin microbiome of WT mice affirm this finding by pointed to a shift within the microbial homeostasis characterized by a predominance of Staphylococcus and Propionibacterium after TS. This points to a potential role of S. aureus and/or microbial dysbiosis acting synergistically to induce the increased appearance of specific IL-4-producing cell types, as well as other features of AD. 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.

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

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Pemphigoid diseases (PD) comprise a group of autoimmune disorders characterized by skin and mucosal inflammation and subepidermal blistering. PD are caused by autoreactive antibodies targeting structural proteins of the dermal-epidermal junction. Skin-bound immune complexes trigger recruitment of myeloid cells, engagement of FcγR receptors, and activation of specific kinases. Selective blockade of PI3K can alleviate disease manifestation in mouse models of autoimmune diseases. Here, we evaluated the treatment efficacy of parasilub, a selective PI3Kδ inhibitor, in in-vitro and in-vivo models of epidermolysis bullosa acquisita (EBA) and mucous membrane pemphigoid (MMP). We demonstrated that parasilub dose-dependently inhibited inflammatory cytokine and chemokine production in EBA and MMP patient skin complex-stimulated neutrophils. Furthermore, parasilub inhibited the dermal-epidermal separation induced in-vitro by co-incubation of skin complexes with polymorph nuclear cells. To investigate the effect of parasilub in-vivo, we used 3 experimental mouse models of PD. Parasilub significantly improved the extent of skin and/or 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 that parasilub is an effective treatment of mouse PD. Thus, PI3Kδ signaling plays a role in the pathogenesis of EBA and MMP and immunization induced EBA. However, PI3Kδ was absent within the kinome 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 PI3Kδ blockade with parasilub as a treatment option.