Uniliated type I interferon expresses B-cell autoimmunity and anti-drug antibody formation during anti-TNF therapy

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Anti-TNF therapy is associated with the development of 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 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-nucleotides (ANA) in psoriasis patients. In-vitro, anti-TNF treated plasmacytoid 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 and early glomerular IgG-separation 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, uniliated 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 that affects 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, IL-17 and IL-23 as key factors in the pathogenesis of psoriasis and as 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 erythematos plaques with thick, silver scales affecting the palms and soles. Also, all fingers 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 was started on etanercept, a nonselective tumor necrosis factor inhibitor, at the time of the hospitalization, the patient had a form of severe psoriasis with a PASI score of 11, 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 adalimumab. The patient was treated with infliximab, adalimumab and etanercept. The patient had continued to present with disease activity.

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

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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 depends on the action of type 2 immune responses and 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 and IL-5 cytokines 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 the IL-4-producing cell types such as Th2 cells, eosinophils and natural killer (NK) cells, accompanied by an 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. Moreover, increased mRNA expression of IL-13, CCL17 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 confirm this finding by pointing to a shift within the microbial hostmicrobiota characterized by a predominance of Firmicutes. This is consistent with the known pathophysiology of AD. In addition, this study demonstrates that IL-22 and IL-23 synergistically induce the increased expression 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 pemphigus diseases

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Pemphigus diseases (PD) comprise a group of autoimmune diseases characterized by distinct cutaneous inflammation and subepidermal blistering. PD are caused by autoantibodies targeting structural proteins of the dermal-epidermal junction. Skin-bound immune complexes trigger recruitment of myeloid cells, engagement of Fc receptors, and activation of specific kinases. Selective blockade of PI3K can alleviate disease manifestations in mouse models of autoimmune diseases. Here, we evaluated the treatment efficacy of parsaclisib, a selective PI3Kδ inhibitor, in in-vivo and in-vivo models of epidermolysis bullaosa acquisita (EBA) and mucous membrane pemphigus (MMP). We demonstrated that parsaclisib dose- dependently impaired generation of reactive oxygen species (ROS) from both human and mouse dermal fibroblasts and reduced skin inflammation in mouse models of PD. Parsaclisib significantly improved the extent of skin and/or oral disease in a murine model of MMP. Furthermore, parsaclisib reduced the frequency of FcγR+ myeloid cells and reduced skin inflammation in EBA mouse models. In conclusion, PI3Kδ inhibition with parsaclisib is a promising therapeutic strategy for the treatment of PD and other autoimmune skin diseases.

C1ORF162 is specifically expressed by pathogenic Th2 cells in atopic dermatism

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Psoriasis vulgaris is a complex disorder of the skin and immune system. The purpose of the treatment is to control the severity of the disease and improve quality of life. In recent years, biologic therapies targeting specific cytokines such as tumor necrosis factor (TNF) have revolutionized the management of psoriasis. However, the pathogenesis of psoriasis is not fully understood and novel therapeutic approaches are needed. C1ORF162 is a new gene that is specifically expressed by pathogenic Th2 cells and is 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.