**025**

**Imiquimod-induced psoriatic inflammation can be attenuated by the application of a Liver X receptor agonist through the production of pro-resolution molecule**

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Psoriasis, a T cell-mediated autoimmune skin disease, is characterized by the dysregulation of various pro-inflammatory mediators. We evaluated the effects of the liver X receptor (LXR) agonist GW3965 in the imiquimod (IMQ)-induced psoriasis-like skin inflammation model. GW3965 treatment significantly suppressed the skin inflammation and the expression of pro-inflammatory cytokines by dermal immune cells. GW3965 also reduced the number of infiltrating leukocytes, which included neutrophils, T cells, and macrophages. These results suggest that GW3965 may be a potential therapeutic agent for psoriasis.

**026**

**The impaired suppressive activity and altered response to IL-33 of regulatory T cells in a psoriasis model may be due to decreased ST2 expression**

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Interleukin 33 (IL-33), initially described as an alarmin, is released by cells following cell damage and mediates numerous functions in infections and inflammatory diseases by activating both the innate and the adaptive immune system. IL-33, however, can also act in an immunosuppressive fashion by inducing regulatory T cells (Treg). Enhanced IL-33 levels are found both in the skin and the serum of psoriatic patients. On the other hand, in psoriasis Treg appear to be impaired in their suppressive function. To study whether "psoriatic" Treg are impaired in their response to IL-33, we utilized the imiquimod (IMQ)-induced psoriasis-like model. IL-33 expression was elevated in both skin and serum of IMQ-treated mice, as compared with untreated mice and mice receiving vehicle. Treatment with GW3965 reduced IL-33 levels both in the skin and serum of IMQ-treated mice. Moreover, GW3965 reduced the skin inflammation of IMQ-treated mice. IL-33 may be a novel therapeutic target in psoriasis.

**027**

**IL-31 is predominantly produced by effector memory TH2-polarized CRTH2+ T cells co-when compared to low anti-SE IgA patients and controls. Increased IFN**

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Postscript: A skin inflammatory disorder known for its hallmark of having abnormal keratinocyte differentiation. In psoriatic skin, the expression of liver X receptors (LXR) and LXR, a nuclear receptor family of transcription factors has been shown to be down-regulated. In addition, LXR plays an integral part in the control of keratinocyte differentiation. However, very few studies have been conducted to understand the role of LXR during skin inflammation. We hypothesized that LXRs in the skin can interfere the immune cascade in the induction of psoriatic inflammation. We first evaluated imiquimod (IMQ)-induced psoriatic inflammation in murine ear skin that was simultaneously treated with or without an LXR agonist (GW3965) for 11 days. We found that IMQ-induced skin inflammation was milder in mice treated with GW3965 than in mice treated with its vehicle. In addition, qPCR analysis demonstrated that the gene expression levels of pro-resolution mediators (ABC1A, MetK, and TGF-β) in the IMQ-treated skin were higher in the LXR agonist-treated group than in the control group. We also performed lipidomics analysis to understand the role of the LXR agonist for the generation of lipid mediators in the skin. The levels of key immune recruitment lipid mediators (leukotriene D4 and prostaglandin E2) in the skin lesions were lower in the LXR agonist-treated group than in the control group. To further illustrate the role of LXRs for the immune cell recruitment in psoriatic skin inflammation, we performed whole mount skin imaging. We observed that neutrophil recruitment in the IMQ-treated skin was markedly lower in the LXR agonist-treated group compared to the control group. These results suggest that the activation of LXRs can alleviate psoriatic skin inflammation via the generation of pro-resolution molecules and the regulation of the synthesis of lipid mediators.

**028**

**The activation status of nuclear factor x in type 2 conventional dendritic cells before therapy correlates with clinical response to adalimumab**

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Biologic therapies have revolutionised the treatment of psoriasis. Nevertheless, clinical response to therapy is unpredictable. Thus, there is a need to identify biomarkers predictive of response to enable patient stratification. Here, we investigate the effects of adalimumab (TNF-α inhibitor) on the activation of nuclear factor κB (NF-κB) in the mononuclear cell compartment of psoriasis patients during the early phase of therapy. We hypothesize that monitoring the activation of the transcription factor downstream of the cytokine neutralized by a biologic can guide the discovery of predictive biomarkers. Whole blood (n=16) and peripheral blood mononuclear cell (PBMC) samples, obtained from psoriasis patients at baseline and weeks 1, 4, and 12 after commencing treatment, were stimulated with TNF or LPS. NF-κB nuclear translocation was quantified by imaging flowcytometry and Western blotting. Clinical response was defined as 75% reduction in baseline psoriasis area severity index (PASI75) at week 12. TNF-induced NF-κB translocation in T cells, dendritic cells (DCs), monocytes and neutrophils, while LPS, activated monocytes, DCs and neutrophils at baseline. In patients receiving adalimumab, TNF activation was significantly inhibited at each time point in T cells (92% at week 1, p<0.001), and to a lesser extent, in DCs (55% at week 1, p=0.05) compared to baseline but did not change in monocytes or neutrophils. As expected, adalimumab did not affect LPS-induced NF-κB translocation at baseline in the DC of patients who did not reach PASI75, as compared to patients reaching PASI75 (FDR<0.01). Importantly, this finding was replicated in an extended cohort of patients receiving adalimumab, where we detected increased LPS-induced NF-κB phosphorylation at baseline in type 2 conventional DC (cDC2) of patients not reaching PASI75 (FDR<0.01). Taken together, these data suggest that clinical response to adalimumab may depend on the baseline NF-κB activation status of cDC2.