**001**

**Efectors functions of human T<sub>h</sub>9 cells depend on PPARγ-regulated glucose metabolism**

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T<sub>h</sub>9 cells, a subclass of T<sub>h</sub>2 cells, are crucial mediators of allergic skin inflammation. Their functions are characterized by expression of IL-9/IL-9R and rely on the transcription factor PPAR<sub>γ</sub> for full effector function. The functional role of PPAR<sub>γ</sub> in T<sub>h</sub>9 cells, however, remains unknown. As a first step toward the resolution of this question, the authors performed RNA-seq data from PPAR<sub>γ</sub>-inhibited T<sub>h</sub>9 cells revealed concerted downregulation of genes associated with T cell activation, glucose metabolism, and aerobic glycolysis. Accordingly, T<sub>h</sub>9 cells featured a higher glycolytic activity as compared to T<sub>h</sub>1 and T<sub>h</sub>2 cells. In turn, impairment of glycolysis led to downregulation of IL-9, but not IL-13 expression, thus emulating the effects of PPAR<sub>γ</sub> antagonism on cytokine production. Conversely, enhancing glycolytic activity by increasing glucose availability increased IL-9 levels, while leaving IL-13 expression unchanged. Mechanistically, PPAR<sub>γ</sub>- and glycolysis-related gene expression correlated with expression of various transcription factors (TCF19, GATA3, E2F1, E2F2, Oct4, Sf1). Collectively, these observations indicated a dichotomous regulatory role of glycolytic activity on IL-9 and IL-13 expression in activated T<sub>h</sub>9 cells that is dependent on PPAR<sub>γ</sub>-regulated glycolysis and mediated via mTORC1. In vitro and ex vivo studies on samples of allergic contact dermatitis indicated that this PPAR<sub>γ</sub>/mTORC1/IL-9 pathway was active in primary T<sub>h</sub>9 cells in human skin inflammation. Additionally, we found that tissue glucose levels were dynamically regulated in acute allergic skin inflammation, suggesting that in situ glucose availability might be linked to distinct immunological signals in vivo. In summary, our data propose that PPAR<sub>γ</sub> is a positive regulator of glucose metabolism in T<sub>h</sub>9 cells and that IL-9 expression is specifically dependent on tissue availability of glucose and cellular metabolic activity. These findings highlight a novel link between the metabolic environment in the tissue during inflammation and type 2 driven skin inflammation.

**002**

**The role of HIF-1α in the pathogenesis of psoriasis**

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On protein level, we confirmed that IL-9 prominently induced the expression of the mono- cellular population of IL-9-producing cells that do not produce IL-9. Unlike IL-17-producing cells, these IL-26-producing cells develop at early stages of TH17 differentiation and do not require TGF-β. However, when exposed to TGF-β, IL-26-producing cells transition into IL-17 producers, a process also observed in psoriatic skin lesions, where TGF-β is highly expressed by basal keratinocytes in close vicinity to IL-26-producing T cells. T-cell derived IL-26 was able to induce TGF-β expression in keratinocytes themselves, suggesting a mechanism by which TH17 cells control IL-17A responses in tissues via the expression of IL-26. Thus, our study identifies IL-26-producing cells as an early differentiation stage of TH17 cells that can further differentiate into IL-17A producing cells upon tumor infiltration via a paracrine loop involving TGF-β.

**003**

**Interleukin (IL)-26 drives pathogenic IL-17A responses through a TH17-keratinocyte crosstalk**

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IL-26 (IL-25) is a TH17 cytokine with known antimicrobial and pro-inflammatory functions and is highly expressed in tissues of TH17-mediated inflammatory diseases including psoriasis. However, the expression of IL-26 with respect to IL-17A and its precise function in the context of pathogenic TH17 responses are still unclear. In this study, we used flow cytometry-based fluorescent in situ hybridization of blood TH cells along with single-cell and spatial transcriptomics of psoriatic skin lesions to analyze the dynamic of the regulatory role of IL-26 expression in psoriasis. We show that in blood TH17 cells contain a large population of IL-26-producing cells that do not produce IL-17A. Unlike IL-17A-producing cells, these IL-26-producing cells develop at early stages of TH17 differentiation and do not require TGF-β. However, when exposed to TGF-β, IL-26-producing cells transition into IL-17 producers, a process also observed in psoriatic skin lesions, where TGF-β is highly expressed by basal keratinocytes in close vicinity to IL-26-producing T cells. T-cell derived IL-26 was able to induce TGF-β expression in keratinocytes themselves, suggesting a mechanism by which TH17 cells control IL-17A responses in tissues via the expression of IL-26. Thus, our study identifies IL-26-producing cells as an early differentiation stage of TH17 cells that can further differentiate into IL-17A producing cells upon tumor infiltration via a paracrine loop involving TGF-β.

**004**

**Cell-based therapy may be effective in alopecia areata: Preclinical evidence that autologous, peripheral regulatory T cells are preventive in human ex vivo and therapeutic in human in vivo models**

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Regulatory T cells (Tregs) have long been thought to exert protective, immunomodulatory functions in the CH50He) mouse model of alopecia areata (AA), while their role in human AA remains obscure. However, TGF-β-induced T cell receptor Treg (TGeff) cytokine profile of the predominant and more potent immunoinhibitory regulatory T cells. Given that we have recently identified ydT cells as important novel players in human AA pathophysiology, we have also found that ydT cells are preventive in human AA. Autologous circulating human ydT cells were generated by culture of PBMCs with IL-2, IL-15 and zoledronate for 7 days and thereafter the cultured cells were sorted by FACS/RIA, co-incubated with organ-cultured, stented human scalp hair follicles (HFs) that exhibit partial HF immune privilege (IP) collapse. 50 days after ydT injection in vivo, impressive hair regrowth was observed in all examined human xenotransplants, along with a significantly reduced perifollicular infiltrate and HF IP restoration. Ex vivo, ydT cells significantly reduced premature catagen and IP collapse induction (HA-ARCA regulation) by co-culture with activated CD63+NKGD2+ T cells (p<0.01). Importantly, ydT cells also significantly reduced AA-associated “danger” signals (MICa/B, CD10) increased proliferation and decreased apoptosis of hair matrix keratinocytes and increased the expression of HF IP guardians (TGF-β, IFN-γ) in the outer root sheath. Collectively these results confirm that autologous, blood-derived human ydT cells exert potent protective effects. Therapeutic effects on AA-affected human scalp hair follicles ex vivo and in vivo and thus deserve full clinical exploration as novel cell-based therapy in future AA management.