AhR agonism by tapinarof regulates TH2 and TH17 cell function in human skin

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Introduction & Objectives:

The aryl hydrocarbon receptor (AhR) is a ligand-based transcription factor that plays a crucial role in skin homeostasis and skin barrier function. Tapinarof, a topical AhR agonist, has shown clinical efficacy in both psoriasis (PSO) and atopic dermatitis (AD) where it induced long lasting remissions. However, the anti-inflammatory mechanism of action of tapinarof is not fully understood.

Our aim was to study the mechanism of action of tapinarof on skin T cells in of patients with AD, PSO and allergic contact dermatitis (ACD).

Materials & Methods:

We established short-term human skin explant cultures from diseased AD, PS or ACD skin biopsies that we treated with tapinarof for 24h and then performed downstream analysis of skin T cells.

Results:

We observed highest expression of disease-relevant cytokines in the tissue-resident memory T (TRM) cell populations (IL-13+CD4+ TRM in AD and IL-17a+CD8+ TRM in PSO) previously shown to play a key role in disease progression, validating our ex vivo model. IL-13 and IL-17a were significantly reduced after tapinarof treatment in the respective diseases and populations. AhR agonism in ACD led to a significant reduction of IL-13 levels in TRM and CD4+ T-cells, while leaving IFN-g unchanged.

To uncover the mechanism of action of tapinarof we performed transcriptomic analysis of T-cells treated with tapinarof. As expected, tapinarof treatment resulted in a concerted upregulation of genes associated with AhR signaling pathway and cytochrome P450 response. Moreover, we confirm that IL13 and IL17A expression is reduced in response to tapinarof treatment.

In addition, RNAseq data revealed a downregulation of processes involved in T cell activation and metabolic enzymes in response to tapinarof treatment. sc-RNAseq experiments of T cells isolated from AD and PSO biopsies cultured in presence of tapinarof showed a similar metabolic impairment. Preliminary mechanistic studies of metabolism show a reduction of extracellular acidification rate (ECR) and oxygen consumption rate (OCR) in T cells after treatment with tapinarof, both in the resting and activated state.

Conclusion:

In summary, we established an ex vivo model to study the effect of tapinarof on skin T cells and found a significant reduction in disease-relevant cytokines in AD, PSO and ACD after tapinarof treatment. Furthermore, we show that tapinarof treatment leads to metabolic impairment affecting both glycolysis and oxidative phosphorylation in T cells, uncovering a previously unknown mechanism of action of tapinarof.