Functional interrogation of immune cell types identified by single-cell RNA sequencing in alopecia areata

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Alopecia areata (AA) is an inflammatory disease in which autoreactive CD8+ T cells attack the hair follicle (HF) and result in non-scarring alopecia. Previous work from our lab, using both human samples and the graft-induced C3H/HeJ mouse model, established that CD8+ NKG2D+ T cells are the major pathogenic drivers of AA. However, the role of other immune cell types in disease is still unclear. Here, we characterized the major immune cell types in AA such as regulatory T cells (Tregs), non-Treg CD4+ T cells, and myeloid lineages in clinical samples. We performed single cell RNA-sequencing (scRNAseq) of CD45+ immune cells in skin from AA patients and control skin. The major pathogenic cell type in disease, and uncovered novel roles for myeloid lineages in AA onset.

IL-7 regulates the PD-1 signaling pathway via degradation by E3 ubiquitin ligase F-Box Protein 38

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The IL-7 signaling pathway plays an important role in T cell survival and it has been therapeutically targeted in several T cell-dependent autoimmune diseases. Here, we showed that C3H/HeJ mice with AA exhibited hair regrowth after anti-IL7RA treatment. Mechanically, we observed that IL7RA blockade significantly reduced the number of alopecic effector CD8+ T cells. We also found that C3H/HeJ mice treated with anti-IL7RA showed a significant increase in the frequency of PD-1+CD44+ T cells within the skin. Our results indicate that IL-7 might activate the function of PD-1 by downregulating the expression of PD-1 in T cells, however, the mechanism of this downregulation is still unclear. The F-box protein FBXO38, a member of the SCF ubiquitin ligase family, was highly expressed in PD-1+CD44+ T cells compared to PD-1−CD44− T cells. Using one of the highly expanded TCR sequences, we found that the degree of clonal expansion correlated with gene signatures suggestive of T cell activation and pathogenicity. Using this model, we discovered that IL-7 might decrease PD-1 expression by upregulating FBXO38. We generated TCR retrogenic mice, in which we cloned T cells with high expression of FBXO38 as a potential strategy to enhance IL-7-mediated regulation of FBXO38 expression.