IL-23 and monocyte interactions redirect human Th17.1 cells to an IL-17A^{high}IFNγ^{high} pathogenic profile

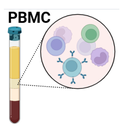
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Purpose

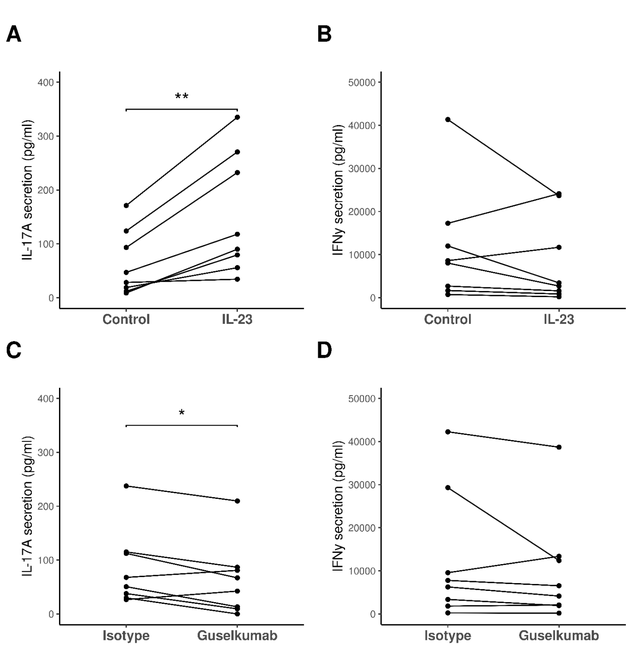
IL-23–targeted therapies have demonstrated clinical efficacy in psoriatic arthritis (PsA), primarily through the reduction of IL-17A–driven inflammation. Therefore, most studies focus on the high IL-17A producing CCR6+CXCR3-CCR4+ classical Th17 cells, leaving the effect of IL-23 inhibition in human Th17.1 underexplored. Th17.1 express CCR6+CXCR3+CCR4-, are traditionally characterized by high IFNγ and low IL-17A production and are considered highly pathogenic in autoimmune diseases. The aim of this study is to characterize the role of IL-23 on human memory Th17.1 cells.

Methods and Results

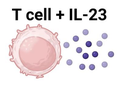
1 IL-23 regulates IL-17A but not IFNγ in PBMC of treatment-naïve PsA patients



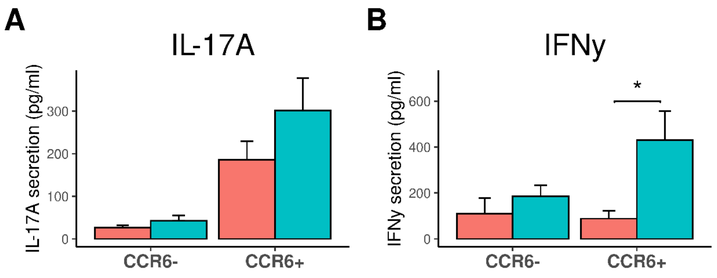
PBMCs from PsA patients are stimulated with αCD3/28 for three days. Adding IL-23 to the stimulation induced IL-17A, while adding anti-IL-23 significantly reduces IL-17A secretion.



2 IL-23 induces IFNγ in human memory CCR6+ T cells



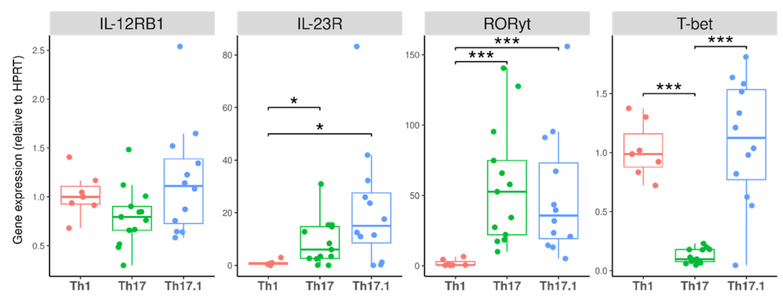
CCR6- and CCR6+ memory T cells were stimulated with αCD3/28 for three days



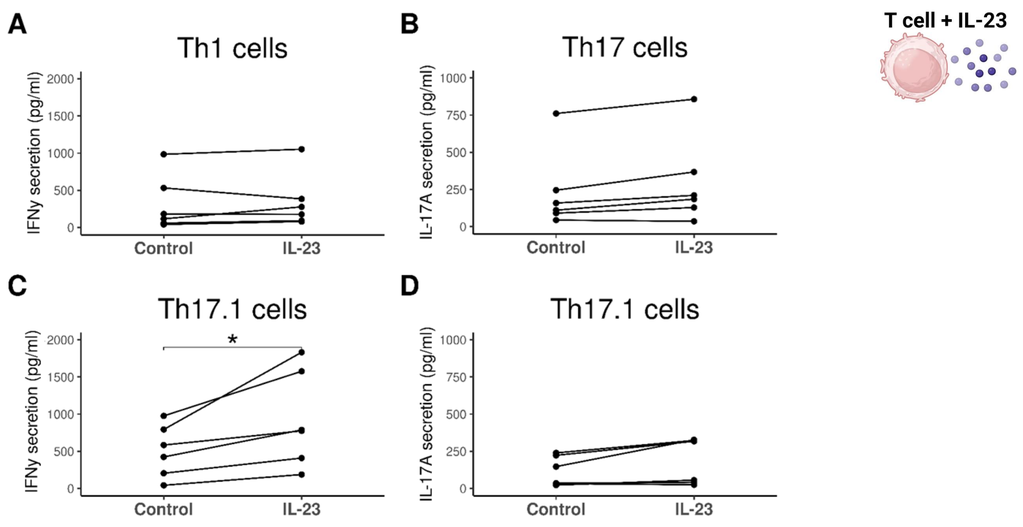
Both human Th17 and Th17.1 cells express the IL-23 receptor ex vivo



Each T helper subpopulation has their unique combination of transcription factors

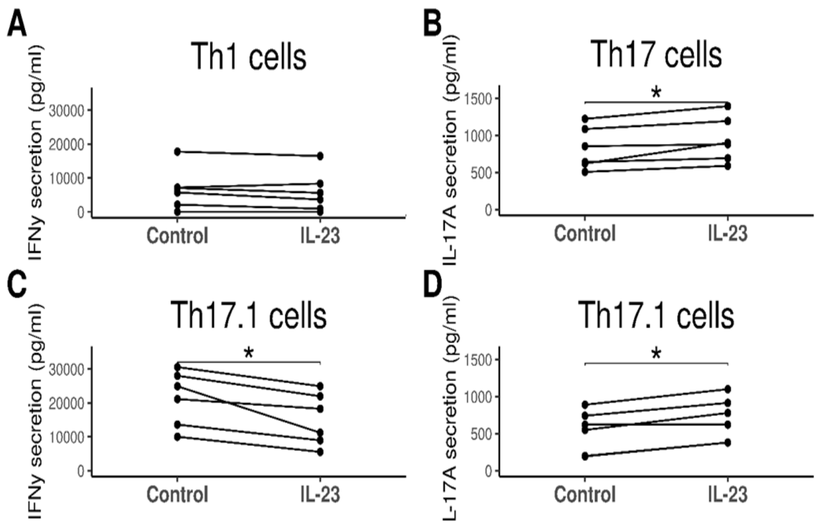


3 Human Th17.1 cells secrete more IFNγ upon IL-23 stimulation, while Th1 do not



Sorted human memory Th1, Th17 and Th17.1 cells are stimulated with αCD/28 with or without IL-23. Surprisingly, Th17.1 secrete more IFNγ upon IL-23 stimulation, while Th1 cells are not affected. No difference in IL-17A was found for any T cell population.

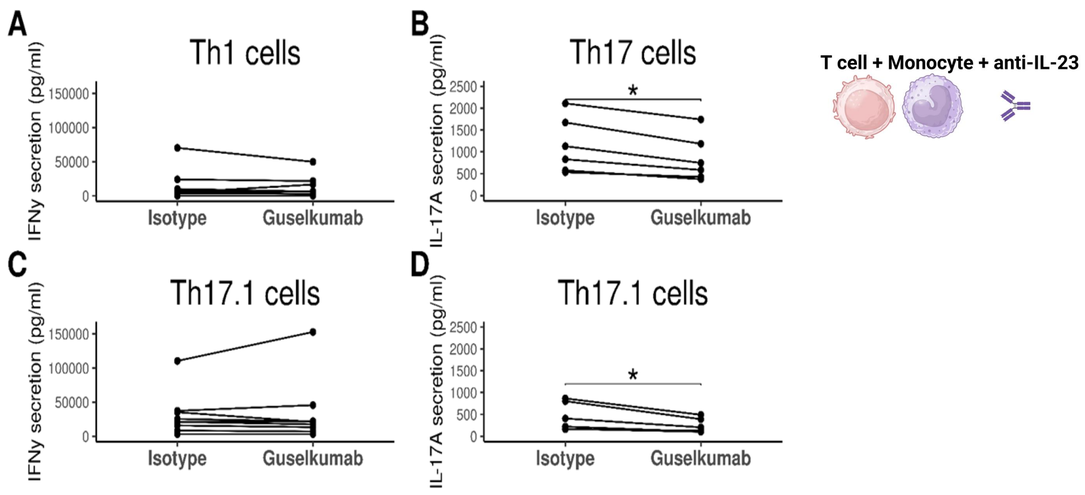
4 In coculture with monocytes, human Th17.1 cells secrete more IL-17A, but less IFNγ upon stimulation with IL-23





In coculture with monocytes, the effect of exogenous IL-23 stimulation changes IL-17A and IFNγ expression compared to culturing T cells alone.

5 Blocking IL-23 reduces IL-17A secretion in human Th17 and Th17.1 cells, but did not affect IFNγ production



Blocking monocyte-derived IL-23 shows physically relevant effects, highlighting the association between IL-23 and IL-17A in both Th17 and Th17.1 cells. However, the effect of IL-23 on IFNγ is no longer apparent.

Conclusion

IL-23R is expressed both in human Th17 and Th17.1 cells, yet IL-23 stimulation exerts distinct effects. IL-23 induces IFNγ in Th17.1 monocultures, while in Th17.1–monocyte cocultures IL-23 reduces IFNγ secretion, highlighting a complex interplay. Strikingly, Th17.1 secreted high levels of IL-17A upon coculture with monocytes, which is further amplified by IL-23, progressing to an IL-17A^{high}IFNγ^{high} state. These findings highlight the importance of IL-23 in Th17.1 cell plasticity and underscore the therapeutic relevance of IL-23 blockade in preventing the emergence of pathogenic IL-17A^{high}IFNγ^{high} Th17.1 cells.

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