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Interaction with activated monocytes enhances cytokine expression and suppressive activity of human $CD4^+CD45RO^+CD25^+CD127^{low}$ regulatory T cells

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Introduction

Despite the high frequency of $CD4^+$ T cells with a regulatory phenotype ($CD25^+CD127^{low}FoxP3^+$) in the joints of patients with rheumatoid arthritis (RA), inflammation persists. Regulatory T cells (Tregs) can be converted into pro-inflammatory IL-17-producing cells by inflammatory mediators, particularly IL-1β.

Aim

To investigate whether activated monocytes, which are abundantly present in the rheumatic joint and potent producers of IL-1β, induce pro-inflammatory cytokine expression in Tregs and whether this impairs Treg function.

Materials and methods

The presence and phenotype of $CD4^+CD45RO^+CD25^+CD127^{low}$ T cells (memory Tregs) and $CD14^+$ monocytes in the peripheral blood (PB) and synovial fluid (SF) from patients with RA was investigated by flow cytometry. FACS-sorted memory Tregs from healthy controls were co-cultured with autologous *in vitro*-activated monocytes and anti-CD3 monoclonal antibody. Intracellular cytokine expression, phenotype and function were determined by flow cytometry, ELISA and proliferation assays.

Results

Patients with RA showed higher frequencies of $CD4^+CD45RO^+CD25^+CD127^{low}$ Tregs and activated $CD14^+$ monocytes in SF relative to PB. We demonstrate that activated monocytes induced an increase in the percentage of IL-17^+, IFNγ^+ and TNF-α^+, but also IL-10^+ Tregs. Blocking and reconstitution experiments revealed that the observed increase in IL-17^+ and IFNγ^+ Tregs was driven by monocyte-derived IL-1β, IL-6 and TNF-α and was mediated by both $CD14^+CD16^-$ and $CD14^+CD16^+$ monocyte subsets. Despite enhanced cytokine expression, cells maintained their $CD25^+FoxP3^+CD39^+$ Treg phenotype and showed enhanced capacity to suppress proliferation and IL-17 production by effector T cells.

Conclusion

Tregs exposed to a pro-inflammatory environment show increased suppressive activity.

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