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TNF-inhibitor drugs regulate human pathogenic Th17 cells through induction of IL-10

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Background

TNF-α inhibitor (TNFi) therapy has revolutionized the treatment of immune-mediated inflammatory diseases, including rheumatoid arthritis (RA). IL-17-producing CD4+ T-cells (Th17 cells) are considered important contributors to the pathogenesis of RA. Here we investigated the effects of TNFi drugs on the function and plasticity of human Th17 cells.

Methods

The frequency of cytokine-expressing cells was assessed by flow cytometry. For functional studies, CD4+ T-cells and autologous CD14+ monocytes were co-cultured with anti-CD3 mAb in the absence or presence of different TNFi drugs. Cytokine secretion assays were used to re-sort cytokine-producing CD4+ T-cells.

Results

Ex vivo analysis of patients with RA on TNFi therapy revealed an enrichment of Th17 cells in peripheral blood compared to those on disease-modifying anti-rheumatic drugs or healthy controls. However, we also found an increase in IL-10-producing CD4+ T-cells. The enrichment in IL-17+ and IL-10+ CD4+ T-cells, including IL-17+IL-10+ co-expressing CD4+ T-cells, was recapitulated *in vitro* by the addition of TNFi drugs (adalimumab, infliximab, etanercept, and certolizumab) to human monocyte/CD4+ T-cell co-cultures. IL-10 induction was independent of FcγR binding, IL-10 and CD4+CD25+ Tregs. TNFi-induced Th17 cells were functionally distinct as shown by an ability to modulate CD14+ monocytes in an IL-10-dependent manner. We report the identification of a transcription factor that is strongly associated with IL-10 expression in TNFi-induced IL-17+ CD4+ T-cells, and show that overexpression of this transcription factor drives IL-10 expression in primary CD4+ T-cells.

Conclusions

TNFi drugs may exert their anti-inflammatory role, at least in part, by promoting Th17 plasticity through the induction of IL-10 expression in pathogenic Th17 cells.

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