Tolerogenic dendritic cells regulate T cells via TGFβ

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Introduction

Tolerogenic dendritic cells (TolDC) are a recently developed experimental cellular immunotherapy for rheumatoid arthritis (RA), currently undergoing clinical trial. RA is an autoimmune disease characterised by chronic inflammation and degradation in synovial joints, affecting ~1% of adult population worldwide.

Dendritic cells (DC) are potent antigen presenting cells that activate or tolerate T cells, depending on the maturation state of DC. Mature DC (MatDC) initiate inflammation by activating effector T cells which secrete inflammatory cytokines (e.g. IFN-γ). In contrast, TolDC which are immature or semi-mature, induce immune tolerance by regulating T cells.

Aims

1. Establish the role of TGFβ in the mechanism by which TolDC regulate CD4+ T cells.

2. Investigate the responsiveness of synovial T cells from RA patients to TGFβ and regulation by TolDC.

Results 1

- TolDC suppressed inflammatory cytokine IFN-γ and proliferation of CD4+ T cells. Suppression of IFN-γ was reversed by TGFβ inhibition.

- CD4+ T cells primed by TolDC displayed low IFN-γ and IL-10 secretion on restimulation by MatDC. T cell hyporesponsiveness was reversed by TGFβ inhibition.

Results 2

- Expression of TGFβ receptor II and responsiveness of TGFβ receptors were similar between healthy and RA CD4+ T cells.

- IFN-γ and proliferation of RA synovial T cells were suppressed by TolDC.

Conclusion

1. TGFβ is an important cytokine in tolerogenic function of TolDC, and potentially a quality control marker in TolDC generation.

2. T cells from RA are responsive to TGFβ at receptor level and to TolDC.

Methods

Independent experiments were conducted with DCs and T cells derived from different donors. Results are expressed as median for n ≥ 4 and analysed by Mann-Whitney test.