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RHEUMATOID ARTHRITIS

TNF disables T_{REG}-cell function through FOXP3 modification

Regulatory T (T_{REG}) cells have a crucial role in the prevention of autoimmunity. In rheumatoid arthritis (RA), the immunosuppressive functions of these cells are known to be impaired, but what causes this defect? One answer might be TNF-induced dephosphorylation of the key T_{REG}-cell transcription factor, FOXP3, according to a recent study published in *Nature Medicine*.

> **"...can TNF inhibitors restore T_{REG}-cell function?"**

The authors of this study first demonstrated that synovial fluid from patients with RA diminishes the suppressive activity of T_{REG} cells obtained from healthy individuals. Next, using a series of blocking antibodies, they confirmed that TNF was the main factor responsible for this effect, and they set out to explore the underlying mechanisms.

Focusing initially on the role of FOXP3, the investigators found that *in vitro* activation of T_{REG} cells results in FOXP3 phosphorylation. This post-translational modification (at a specific residue) was crucial for the full repressive activity of FOXP3, as measured by changes in IL-2 production. Intriguingly, the levels of FOXP3 phosphorylation were lower when the T_{REG} cells were treated with either TNF or synovial fluid from patients with RA, suggesting that downregulation of FOXP3 phosphorylation mediates the impact of TNF on T_{REG} cells. With additional *in vitro* experiments, the authors established that in the presence of high TNF levels, as occur in patients with RA, the expression of the protein phosphatase PP1 is upregulated in T_{REG} cells through the NFκB pathway. PP1 then dephosphorylates FOXP3, resulting in defective T_{REG}-cell suppressive activity.

So, can TNF inhibitors restore T_{REG}-cell function? To find out, the researchers analysed the effects of the TNF-blocking antibody infliximab on T_{REG} cells in ten patients with RA. Although the numbers of T_{REG} cells in the patients' peripheral blood did not change, the treatment restored the levels of FOXP3 phosphorylation and PP1 in these cells to values similar to those observed in T_{REG} cells from healthy individuals. These changes were associated with an improvement in T_{REG}-cell suppressive activity, together with decreased numbers of effector T cells expressing the proinflammatory cytokines IL-17 and IFNγ. Jingwu Zhang, the lead author of the study, concludes that the results provide "a powerful mechanistic explanation as to why TNF blockers work in RA as a disease-modifying treatment".

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Original article Nie, H. *et al.* Phosphorylation of FOXP3 controls regulatory T cell function and is inhibited by TNF-α in rheumatoid arthritis. *Nat. Med.* doi:10.1038/nm.3085