

Anti-TNF α antibodies induce regulatory macrophages in an Fc region dependent manner

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Introduction

The introduction of anti-tumour necrosis factor alpha (anti-TNF α) agents has been an important breakthrough in the treatment of Crohn's Disease (CD). However, not all anti-TNF α agents are effective in CD, suggesting that neutralizing soluble TNF α is not the most important mechanism of action in CD. The aim of this study was to examine the mechanism of action of anti-TNF α *in vitro*.

Methods

Induction of apoptosis in T cells and a mixed lymphocyte reaction (MLR) was determined by annexin V staining or a Caspase 3 activity assay. Inhibition of proliferation was measured with a ³H thymidine incorporation assay. To evaluate the phenotype of macrophages, cytokine profiles were determined by CBA, proliferation in a secondary MLR was measured by ³H thymidine incorporation and expression of markers was measured with flowcytometry.

Results

None of the anti-TNFs showed effects on proliferation or apoptosis in activated T cells grown in isolation. Infliximab and adalimumab reduced proliferation in an MLR, whereas etanercept and certolizumab did not. This effect was completely abolished after blocking Fc receptors. Also, infliximab F(ab')₂ fragment, lacking the Fc region, did not inhibit proliferation in an MLR whereas certolizumab Ig (with an Fc region) gained the ability to inhibit proliferation, indicating a role for the Fc receptor in this assay. Anti-TNFs induced a new population of

macrophages in an Fc region dependent manner. These macrophages appeared to have a strong immunosuppressive phenotype, in terms of their capacity to inhibit proliferation of activated T cells, production of anti-inflammatory cytokines and the expression of the regulatory macrophage marker CD206.

Conclusion

We show that anti-TNFs can induce of regulatory macrophages in an Fc region dependent manner. Regulatory macrophages have immunosuppressive properties and play an important role in wound healing. This mechanism of action of anti-TNFs may play a role in mucosal healing in patients with IBD.