Macrophages as a therapeutic target in inflammatory bowel disease

Lessons learned from anti-TNF therapy

Houttuijn Bloemendaal, F.M.

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OUTLINE OF THE THESIS

This thesis aims to increase our understanding about the effector mechanism of anti-TNF therapy in inflammatory bowel disease (IBD). Although anti-TNF has become essential in the treatment of IBD, around 50 percent of patients do not respond so finding factors that could increase therapeutic efficacy or predict response are needed.\(^1\) IgG1 anti-TNF antibodies infliximab and adalimumab have shown to achieve mucosal healing in IBD patients, while unexpectedly, multiple differently designed anti-TNF agents failed to show clinical efficacy even though they demonstrated efficacy in other immune mediated diseases.\(^2\)\(^-\)\(^5\) This has questioned the effector mechanism of anti-TNF in IBD and suggests that additional factors besides TNF neutralization are necessary for therapeutic response. This thesis focusses on the requirement for Fcγ-receptor engagement by anti-TNF antibodies and evaluates the therapeutic efficacy of anti-TNF antibodies with increased Fc-binding affinity in vivo and in vitro. Mechanistically, we characterize the role of macrophages as Fc binding effector cells.

In chapter 1 we summarize the existing literature on the role of macrophages in the pathogenesis of IBD, macrophage behaviour during active intestinal inflammation and their role in therapeutics. In chapter 2 we study anti-TNF efficacy in a murine colitis model that lacks activating Fcγ-receptors. We then evaluate the therapeutic efficacy of hypo-fucosylated anti-TNF, an IgG1 anti-TNF with increased Fc-binding affinity, in vitro and in vivo. In the same models we measure CD206+ regulatory macrophage formation. We also compare Fcγ-receptor binding affinity between adalimumab and etanercept in vitro in the presence or absence of soluble TNF. In chapter 3 we compare IgG1 anti-TNF antibodies and etanercept in their ability to form immune complexes with soluble TNF. We determine the subsequent effects of Fcγ-receptor cross-linking by anti-TNF immune complexes on the production of IL-10 and IL-12/IL-23 by human inflammatory macrophages. In chapter 4 we investigate the necessity for macrophage IL-10 signalling in anti-TNF efficacy and CD206+ macrophage formation in vivo and in vitro. In chapter 5 we explore phenotypical differences directly ex vivo between mesenteric macrophages from Crohn’s disease patients compared to patients with ulcerative colitis and individuals without IBD. In chapter 6 our findings are discussed against the background of the current literature and this chapter also elaborates on future perspectives.


