Specific targeting of IL-6 signalling pathway: a new way to treat IBD?


Abstract 1
The pro-inflammatory cytokine interleukin (IL)-6 can bind to cells lacking the IL-6 receptor (IL-6R) when it forms a complex with the soluble IL-6R (sIL-6R) (trans signalling). Here, we have assessed the contribution of this system to the increased resistance of mucosal T cells against apoptosis in Crohn’s disease (CD), a chronic inflammatory disease of the gastrointestinal tract. A neutralizing antibody against IL-6R suppressed established experimental colitis in various animal models of CD mediated by type 1 T-helper cells, by inducing apoptosis of lamina propria T cells. Similarly, specific neutralization of sIL-6R in vivo by a newly designed gp130-Fc fusion protein caused suppression of colitis activity and induction of apoptosis, indicating that sIL-6R prevents mucosal T-cell apoptosis. In patients with CD, mucosal T cells showed strong evidence for IL-6 trans signalling, with activation of signal transducer and activator of transcription 3, bcl-2 and bcl-xl. Blockade of IL-6 trans signalling caused T-cell apoptosis, indicating that the IL-6–sIL-6R system mediates the resistance of T cells to apoptosis in CD. These data indicate that a pathway of T-cell activation driven by IL-6–sIL-6R contributes to the perpetuation of chronic intestinal inflammation. Specific targeting of this pathway may be a promising new approach for the treatment of CD.

Abstract 2
Proinflammatory cytokines have been demonstrated to play a crucial role in the pathogenesis of Crohn’s disease (CD). Among those cytokines, strong expression of IL-6 has been repeatedly demonstrated. To examine the role for IL-6 in the pathogenesis of CD, we introduced anti-IL-6R mAb to a murine model of colitis. Colitis was induced in C.B-17-scid mice transferred with CD45RB<sup>+</sup> CD4+ T cells from BALB/c mice. Anti-IL-6R mAb or rat IgG was administered weekly after T cell transfer. ICAM-1 and VCAM-1 expression were analyzed by immunohistochemistry. Colonic cytokine expression was determined by RT-PCR. Mice treated with mAb showed normal growth, whereas controls lost weight. The average colitis score was 0.64 for mAb-treated mice and 1.80 for controls. T cell expansion in treated mice was less remarkable than in the controls. Colonic ICAM-1 and VCAM-1 expression were markedly suppressed by mAb. IFN-γ, TNF-α, and IL-1 mRNA were reduced by the treatment. The results presented here show a crucial role for IL-6 in the pathogenesis of murine colitis and suggest a therapeutic potential of anti-IL-6R mAb for treatment of human CD.

Comment
More than 200 cytokines have been identified that bind to specific receptors expressed on the surface of the target cells. They are able to trigger intracellular signalling cascades leading to the control of gene expression involved in the cellular response. Although a lot of detailed information on the signalling cascade and effects of specific cytokines on various cells has accumulated over the past few years, our understanding of cytokine functions in vivo remains very poor.

These uncertainties are particularly illustrated by the case of interleukin (IL)-6. The in vivo functions of this cytokine remain debated, IL-6 being considered alternatively as a pro- or anti-inflammatory cytokine, or sometimes as a key factor to polarise Th2 cells. Moreover, the IL-6 signalling is particular involving a phenomenon called trans signalling. Briefly, the receptor for IL-6 consists of two subunits: a ligand binding component (IL-6R) and a signal-transducing glycoprotein 130 (gp130), which is a member of the cytokine receptor superfamily (including also IL-11 and the leukaemia inhibitory factor). A soluble form of the ligand specific chain (sIL-6R), when complexed to IL-6, is capable of binding to the membrane bound gp130 and thus can elicit a signal-transduction involving STAT-3. This phenomenon called trans signalling introduced a novel aspect of cytokine action (fig 1).

In Crohn’s disease (CD), IL-6 is present at high levels in both serum and intestinal tissues. Increased levels of IL-6R and gp130 expression have been also demonstrated in peripheral lymphocytes of patients with CD together with an enhancement of serum sIL-6R. IL-6 signalling playing potentially a crucial role in the pathogenesis of CD, the therapeutic potential of antibodies against IL-6R (anti-IL-6R Ab), which block both the transmembrane and soluble forms of IL-6R, has been evaluated.

In the study by Yamamoto et al, colitis was induced by CD45RB<sup>+</sup> CD4+ T cell transfer in scid mice. Anti-IL-6R Ab was administered intraperitoneally just after T cell transfer and then weekly for 8 weeks. Anti-IL-6R Ab prevented wasting disease and the development of macroscopic and histological lesions. This treatment suppressed also the massive accumulation of ICAM-1 positive cells in the lamina propria and the expression of ICAM-1 and VCAM-1 by vascular endothelial cells. Expansion of both colonic and splenic transferred CD4+ T cells observed in the recipient untreated scid mice was also reduced as well as the colonic expression of TNF-α, IL-1β and IFN-γ mRNA without modification for the production of TGF-β1.
IL-10 and IL-4 mRNA. This study provides evidence that IL-6 signalling plays a crucial role for the pathogenesis of murine colitis.

The second study published by Atreya et al confirms and extends these results. The authors showed high production of IL-6 and sIL-6R by purified lamina propria cells of patients with CD and UC together with increased serum levels of IL-6-sIL-6R complexes. In contrast, only a small fraction of T cells in patients with IBD expressed membrane bound IL-6R. However, there was an activation of the IL-6 pathway in these T cells as reflected by an increased expression and nuclear translocation of the IL-6 dependent STAT-3 signalling and a considerable induction of two anti-apoptotic STAT-3 dependent genes namely bcl-2 and bcl-xl. As IL-6 is known to rescue T cells from apoptosis, the authors next tested a neutralising antibody against human IL-6R which actually induced lamina propria T cell apoptosis.10 The authors next tested a neutralising antibody bcl-2 and bcl-xl. As IL-6 is known to rescue T cells from apoptosis, the authors next tested a neutralising antibody against human IL-6R which actually induced lamina propria T cell apoptosis.10

In conclusion, specific targeting of the IL-6 signalling pathway may be a new way to treat CD or inflammatory diseases characterised by increased production of IL-6.

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