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Review

Targets for new immunomodulation strategies in inflammatory bowel disease

Giovanni Monteleone *, Roberta Caruso, Francesco Pallone

Department of Systems Medicine, University of Rome "Tor Vergata," Rome, Italy

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ABSTRACT

Crohn's disease (CD) and ulcerative colitis (UC), the major forms of inflammatory bowel diseases (IBD) in human beings, are characterized by damage to the intestinal epithelium and deeper layers, which is caused by an excessive immune response directed against normal constituents of the gut microflora. In both IBD, the diseased tissue is heavily infiltrated with several subsets of leukocytes that produce huge amounts of inflammatory cytokines whose profiles varies not only between CD and UC but also during the evolution of the same disease. These recent discoveries together with the demonstration that the inhibition of some soluble cytokines is not beneficial in IBD have contributed to delineate new scenarios by which tissue damage is induced and perpetuated. We here review some of the major immunological defects documented in IBD and discuss why compounds inhibiting soluble cytokines were not beneficial in patients and how we can optimize therapeutic strategies with biologics.

Contents

1. Introduction

Inflammatory bowel disease (IBD) is the general term used to indicate two chronic and relapsing immune-mediated diseases of the gut, namely, Crohn's disease (CD) and ulcerative colitis (UC). CD develops mostly in the terminal ileum and colon but can involve all the portions of the alimentary tract and shows predominantly a mononuclear cell infiltrate with granuloma; the lesions are patchy and inflammation is typically transmural with deep fissuring ulcers. In contrast, in UC, the lesion is predominantly mucosal and continuous, and the infiltrate, dominated by neutrophils with crypt abscesses and epithelial damage, involves the colon [1].

The aetiology of both IBD remains unknown, even though a considerable amount of data have been accumulated to demonstrate that IBD is triggered by multiple environmental factors in genetically predisposed individuals and promoted by an exaggerated mucosal immune response directed against components of the gut microflora [2–4]. It is also becoming evident that, during IBD, tissue damage is mediated by an active interplay between immune and non-immune cells and that T cells and antigen presenting cells (APC, i.e., monocytes/macrophages and dendritic cells) play a key role in this pathogenic process [5]. This concept is supported not only by the fact that T cells and macrophages infiltrate heavily the diseased mucosa in both forms of IBD but also by the demonstration that these cell types mediate colitis in murine models of IBD and compounds targeting the functions of such cells are therapeutically useful for dampening the intestinal tissue-damaging inflammation. In this

* Corresponding author at: Department of Systems Medicine, University of Rome "Tor Vergata," Via Montpellier, 1, 00133 Rome, Italy. Tel.: +39 06 72596150; fax: +39 06 72596391.
E-mail address: Gi.Monteleone@Med.uniroma2.it (G. Monteleone).

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article, we review some of the major immunological defects documented in IBD and discuss why compounds inhibiting soluble cytokines were not beneficial in patients and how we can optimize immunomodulatory strategies.

2. Inhibitors of Th1- and Th17-type cytokines in CD

Most T cells infiltrating the intestinal lamina propria of CD patient are activated and produce huge amounts of inflammatory cytokines, such as interferon gamma (IFN-γ) [6]. These cells also express Stat4 and T-bet, two transcription factors necessary for the differentiation of T helper (Th)-type 1 cells [7,8]. CD-diseased mucosa contains macrophages and dendritic cells producing interleukin (IL)-12, the major inducer of Th1 in human beings, and other molecules, such as osteopontin, IL-15 and IL-18, which are able to amplify Th1 cell responses [9–12]. These findings together with the demonstration that Th1 cytokines are pathogenic in several murine models of colitis led to the development of antibodies blocking IFN-γ or IL-12/p40 [13–15]. However, results of 3 different clinical studies testing the efficacy of the anti-IFN-γ antibody fontolizumab showed that the blockade of IFN-γ was not beneficial in patients with active CD [16–18]. Similarly, two distinct neutralizing monoclonal anti-IL-12p40 antibodies were quite disappointing in patients with active CD, as these compounds were only slightly superior to placebo in inducing clinical remission [19,20]. However, one of these two IL-12p40 blockers, ustekinumab, appeared to be more effective than placebo in reducing clinical activity of CD patients resistant to anti-TNF antibodies [21]. The reason why fontolizumab and anti-IL-12p40 antibodies were not effective in all CD patients remains unknown, but it is conceivable that these negative results rely on the fact that CD-associated inflammation is sustained by additional pathways other than Th1 cytokines. Indeed, it is now well known that the gut of CD patients contains high numbers of Th17 cells, another subset of Th cells that secrete IL-17A, IL-17F, IL-22 and IL-26 [22–24]. In this context, it is, however, noteworthy that even the neutralization of IL-17A with the blocking antibody secukinumab was unsuccessful in active CD patients [25]. So the critical question is why Th1 and Th17 blockers failed in CD despite the potential of such cytokines to trigger and amplify inflammatory signals in the gut. While a definitive answer cannot be given, some novel data suggest some explanations. First, it is now evident that the production of both Th1 and Th17 cytokines can change with the evolution of the disease. Indeed studies in children with active CD and mice with experimental CD-like colitis have convincingly shown that the initial phases of the disease are marked by high levels of IL-12-induced IFN-γ while the late and established lesions are dominated by Th17 cytokines [26–28]. Therefore, taking this into account, we can speculate that fontolizumab could be useful at the earliest stages of the disease but not when lesions are established. It is also worth noting that Th1 and Th17 cytokines are mutually antagonistic [29], so the inhibition of IFN-γ with fontolizumab could suppress IFN-γ-driven inflammatory pathways but at the same time enhance Th17-induced inflammation. Similarly, the lack of beneficial effects in CD patients treated with secukinumab could rely on the fact that such antibody could stimulate IFN-γ production. A more rational approach for treating CD-related inflammation is thus to use compounds targeting simultaneously both Th1 and Th17 cells rather than a targeted approach aimed exclusively at one or the other. In theory, this goal could be reached with inhibitors of IL-21, a cytokine that is produced in excess in the intestine of patients with IBD and involved in the positive regulation of both Th1 and Th17 cytokines [30,31]. This hypothesis is supported by pre-clinical studies showing that IL-21-deficient mice are resistant to Th1/Th17-cell-driven colitis and blockade of IL-21 with an IL-21 receptor fusion protein inhibits experimental colitis in mice [31]. However, no study has yet tested the therapeutic effect of IL-21 blockers in IBD.

3. Which cytokine must we target in UC?

UC mucosa contains less Th1 cells than CD mucosa, but the amount of IFN-γ produced by T cells isolated from UC patients and maximally activated in vitro with anti-CD3/CD28 antibodies is greater than that produced by T cells isolated from the uninflamed colon of normal controls [6]. Moreover, in UC tissue, there is a predominant synthesis of IL-5 and IL-13, two cytokines made by Th2 cells, and elevated levels of Th17 cytokines [6,32].

Studies in the oxazolone model of colitis, which shows some similarities with UC, indicate that IL-13, produced by CD1-reactive natural killer T (NKT) cells, is crucial in the pathogenesis of this experimental gut inflammation [33,34]. Indeed, the elimination of NKT cells or neutralization of IL-13 prevents the development of colitis [33]. It has been also demonstrated that IL-13 can target intestinal epithelial cells and alters barrier function [32,33]. That IL-13 can be a potential therapeutic target in UC would seem also to be suggested by the demonstration that the benefit seen in UC patients treated with IFN-β is associated with a significant down-regulation in IL-13 production [35]. However, as indicated above, UC-related inflammation is also marked by the excessive production of Th17 cytokines and macrophage-derived cytokines (i.e., IL-6, IL-1 and TNF) [6,32]. Interestingly, patients who exhibit elevated levels of IL-6 and IL-17A do not respond to IFN-β [35], raising the possibility that therapeutic strategies blocking exclusively IL-13 could follow the pattern of blocking IFN-γ/IL-17A in CD and give disappointing results in UC patients.

Given the plethora of cytokines produced in the diseased mucosa of UC patients, it is conceivable that UC-related inflammation can be efficiently controlled by compounds inhibiting simultaneously multiple cytokines. This hypothesis is supported by the recent demonstration that the inhibition of the activity of Janus kinases (JAK) 1, 2 and 3 with the oral compound tofacitinib reduced the clinical and endoscopic activity of patients with active UC [36]. Further studies are, however, needed to confirm these promising results and ascertain whether the blockade of JAK can enhance the risk of severe side effects (e.g., leukopenia) as these kinases are involved in the control of leukocyte growth and survival [37].

4. Multiple factors contribute to the accumulation of leukocytes in the diseased tissue of IBD patients

Inflammatory cells are recruited from the blood stream to the diseased tissue of IBD patients as a result of enhanced production of chemoattractants within the inflammatory microenvironment. One such chemoattractant is the chemokine ligand 25 (CCL25), which is over-produced by the inflamed epithelium of CD patients and promotes homing of CC chemokine receptor 9 (CCR9)-expressing T cells to small intestine [38]. This pathway was initially supposed to be involved in the amplification of the intestinal inflammation because interfering with the CCR9/CCL25 axis, by neutralizing antibodies, was effective in SAMP1/YitFc mice, a spontaneous model of CD [39]. Similarly, some benefit was documented in patients with active CD treated with GSK-1605786, an oral antagonist of CCR9 [40]. However, data emerging from studies in the TNF ΔAU-rich element (TNF $^{\Delta ARE}$) mouse model of CD ileitis indicate that, in the absence of CCR9, TNF$^{\Delta ARE}$ mice develop a severe gut disease, compared with their CCR9-sufficient counterparts, which may be secondary to a deficiency of regulatory T cells, since CCR9 regulates also migration of regulatory T cells to sites of inflammation [41].

T-cell trafficking to the intestine is also regulated by interactions of integrins (e.g., α4β7) with cognate endothelial ligands. Monoclonal antibodies directed against either α4 (i.e., natalizumab) or β7 (i.e., vedolizumab) integrin have been tested with some benefit in patients with active phases of CD and UC [42–44], thus supporting the idea that the blockade of immune cell migration into the gut can be useful to suppress the IBD-related inflammation [45].