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MINI-REVIEW

Th17 immune response in IBD: A new pathogenic mechanism

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Abstract

Although traditionally associated with exaggerated Th1 or Th2 cell response, the gut inflammation occurring in patients with IBD is also characterized by production of cytokines made by a distinct lineage of T helper cells, termed Th17 cells. The discovery that this new inflammatory T-cell subset drives immune-mediated pathology and that the antigen-presenting cell-derived IL-23 is necessary for amplifying Th17 cell-associated inflammation has contributed to elucidate new pathways of intestinal tissue damage as well as to open new avenues for development of therapeutic strategies in IBD.

In this review, we discuss the available data regarding the involvement of Th17 cells and their interplay with other mucosal cell types in the modulation of intestinal tissue inflammation.

1. Introduction

Crohn's disease (CD) and ulcerative colitis (UC), collectively known as inflammatory bowel diseases (IBD), are chronically relapsing inflammatory diseases that affect the human digestive tract. The etiology of IBD is still unknown, but there is evidence that both CD and UC result from the interaction of genetic and environmental factors that ultimately promote an immunopathologic process leading to chronic inflammation.[1] Studies of experimental models of IBD also suggest that this immunopathologic process consists of an excessive and dysregulated immune response to components of the bacterial microflora.[2] CD4+ T cells play a major role in initiating and shaping this pathologic response. Consistent with this, T cell-directed therapies have been employed with clinical success in IBD patients.[3] Moreover, studies in animal models of IBD have shown that either targeted inhibition or over-expression of CD4+ T-cell gene products can alter the magnitude and outcome of the intestinal tissue-damaging inflammatory responses.[4,5]

The ability of CD4+ T cells to promote/expand the intestinal pathologic response is in part dependent on the production of distinct profiles of cytokines. In particular, the intestinal inflammation in CD is characterized by a predominant differentiation of T helper type 1 (Th1)-lymphocytes that produce

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large quantities of interferon (IFN)-γ under the stimulus of interleukin (IL)-12.[6,7] By contrast, in UC the inflammatory response is associated with exaggerated production of Th2-cytokines, such as IL-4 and IL-13.[6,8] Although simplified pathways are useful to understand disease processes, more complex networks of immune interactions are being appreciated in IBD. For instance, studies from several laboratories have recently contributed to shed light into the immune-regulatory role of another subset of Th cells, namely Th17 cells, in the pathogenesis of gut inflammation.[9–12] In this report, we will review the available data regarding the involvement of Th17 cell populations and their interplay with other mucosal cell types in the modulation of intestinal inflammation.

2. Th17 cell differentiation and effector functions

IL-17, also termed IL-17A, is the cytokine signature of Th17 cells. IL-17 is the founding member of the IL-17 cytokine family, which also contains IL-17B, IL-17C, IL-17D (IL-27), IL-17E (IL-25), and IL-17F.[13] The molecular requirements governing Th17 cell development and functions are not yet fully understood. Although initial studies suggested that the antigen-presenting cell-derived IL-23 was involved in the generation of Th17 cells, it is now clear that the early differentiation of Th17 cells occurs independently of signals from IL-23, and instead it is instructed, at least in mouse, by the dual actions of TGF-β1 and IL-6, and requires the activity of the transcription factors retinoic acid-related orphan receptor (ROR) γt and RORα.[14,15] However, IL-23 is necessary for expanding and/or maintaining Th17 cell responses.[16] IL-25, IL-27, and the Th1-associated transcription factor, T-bet, have been reported to cross-regulate Th17 responses.[17–19] Differentiation of human Th17 cells would seem to rely on IL-1, IL-6, and IL-23.[20] The factors produced by mouse and human Th17 cells are similar and include IL-17, IL-17F, IL-21, and IL-22.[13,21]

Th17 cell-derived cytokines are supposed to play an important role in the protection of the host against various bacteria and fungi, particularly at mucosal surfaces, given their ability to enhance the recruitment and facilitate the activation of neutrophils, and stimulate the production of defensins by epithelial cells.[22,23] On the other hand, there is evidence that uncontrolled and persistent effector Th17 cell responses can cause pathology in various organs, because Th17 cytokines can promote the synthesis of inflammatory cytokines (e.g. IL-1, IL-6, TNF-α, GM-CSF), chemokines (e.g. IL-8, CXCL1, CXCL8, monocyte chemoattractant protein-1, monocyte-inhibitor protein (MIP)-3α), cyclooxygenase-2, and tissue-degrading matrix metalloproteinases (MMPs) by several cell types[13,24] (Fig. 1). IL-23 is absolutely required for providing Th17 cells a pathogenic phenotype. In fact, in the absence of IL-23, Th17 cells may have regulatory functions that correlate, in part, with their ability to produce IL-10.[25]

3. Expression of Th17 cytokines in human IBD

The first report on IL-17 producing cells in IBD came from a study in which it was shown that the inflamed gut of patients with CD and patients with UC contained high levels of IL-17-secreting cells in comparison to normal colonic mucosa or colonic samples of patients with ischemic colitis.[11] By immunohistochemistry, it was shown that, in active UC, IL-17-expressing cells were located mainly within the lamina propria, while in active CD, these cells were scattered throughout the submucosa and muscularis propria. Major sources of IL-17 were CD3+T cells and CD68+ cells. Moreover, IL-17 was found to be enhanced in the serum of IBD patients. These results were confirmed by the demonstration that RNA transcripts for IL-17A and IL-17F were up-regulated in the inflamed mucosa of UC patients and CD patients.[11,26] By flow-cytometry analysis of mucosal lymphocytes, Annuziato et al. demonstrated that the number of IL-17-producing T cells is higher in CD than in normal gut mucosa, and that some of these cells produce also IFN-γ.[27] In vitro treatment of such cells with IL-12 resulted in enhanced expression of T-bet and IFN-γ, and down-regulation of RORγt and IL-17. Although irrefutable evidence now indicates that the production of IL-17 is not sufficient to define the Th17 subset, the above findings suggest that T cells can co-express both Th1- and Th17-cytokine signatures, and that IL-17-secreting T cells can be induced to differentiate in fully-polarized Th1 cells.

The inflamed mucosa of IBD patients contains high levels of other Th17-related cytokines. In both CD and UC tissue there is enhanced production of IL-21, a cytokine that is capable of regulating the activity of multiple immune and non-immune cell types.[28] Indeed, IL-21 has been reported to expand the ongoing Th1 cell response in CD,[28] to stimulate gut fibroblasts to secrete MMPs,[29] and to induce colonic epithelial cells to produce MIP-3α,[30] a chemokine that has been involved in the recruitment of activated T cells and dendritic cells in the gut[31,32] (Fig. 1). IL-22 is also highly expressed in mucosal samples of patients with active CD and to a lesser degree of patients with UC.[33] Like other Th17 members, IL-22 stimulates colonic fibroblasts to make inflammatory cytokines (e.g. IL-6, IL-8, IL-11, and leukemia inhibitory factor), chemokines, and MMPs.[33] Moreover, IL-22 enhances the expression of TNF-α, IL-8, and β-defensin[34] (Fig. 1). By using an in vitro wounding assay, Brand et al. showed that IL-22 stimulates the migration of colonic cells by a PI-3 kinase-dependent mechanism, thus suggesting that IL-22 can promote intestinal barrier integrity.[34]

4. Involvement of Th17 cells in the pathogenesis of experimental colitis

Studies in IL-17 receptor A (IL-17RA) knockout mice demonstrated that IL-17 is necessary for the development of acute gut inflammation induced by intrarectal administration of trinitrobenzenesulfonic acid (TNBS),[35] a T cell-mediated colitis showing striking similarities with CD. Consistently, blockade of IL-17 signaling by an IL-17RA IgG1 fusion protein significantly attenuated colonic inflammation and prevented weight loss after TNBS administration in mice. In this context it is noteworthy that IL-17RA mediates the functional activities of both IL-17A and IL-17F,[36] thus making difficult to establish the exact contribution of these cytokines in the pathogenesis of TNBS-colitis. Studies in other models of colitis, such as the dextran sulfate sodium (DSS)-induced