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.

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KEYWORDS
Th17; IL-17; IL-23; Inflammatory bowel disease (IBD); Crohn's disease; Ulcerative colitis

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. 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. 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. 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.

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...
large quantities of interferon (IFN)-γ under the stimulus of interleukin (IL)-12. By contrast, in UC the inflammatory response is associated with exaggerated production of Th2 cytokines, such as IL-4 and IL-13. 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. 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. 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 is instructed, at least in mouse, by the dual actions of TGF-β and IL-6, and requires the activity of the transcription factors retinoic acid-related orphan receptor (ROR) γt and RORα. However, IL-23 is necessary for expanding and/or maintaining Th17 cell responses. IL-25, IL-27, and the Th1-associated transcription factor, T-bet, have been reported to cross-regulate Th17 responses. Differentiation of human Th17 cells would seem to rely on IL-1, IL-6, and IL-23. The factors produced by mouse and human Th17 cells are similar and include IL-17, IL-17F, IL-21, and IL-22.

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. 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 chemotactic protein-1, monocyte-inhibitor protein (MIP)-3α), cyclooxygenase-2, and tissue-degrading matrix metalloproteinases (MMPs) by several cell types. 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.

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. 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. 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. 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. Indeed, IL-21 has been reported to expand the ongoing Th1 cell response in CD, to stimulate gut fibroblasts to secrete MMPs, and to induce colonic epithelial cells to produce MIP-3α, a chemokine that has been involved in the recruitment of activated T cells and dendritic cells in the gut. IL-22 is also highly expressed in mucosal samples of patients with active CD and to a lesser degree of patients with UC. 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. Moreover, IL-22 enhances the expression of TNF-α, IL-8, and β-defensin (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. 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. Moreover, IL-22 enhances the expression of TNF-α, IL-8, and β-defensin (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.

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). 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, 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...
colitis, showed that IL-17F deficiency results in reduced colitis, whereas IL-17A knockout mice develop more severe disease. Although more work is needed in this area, the available data would seem to suggest that IL-17F rather than IL-17A is crucial in sustaining inflammation in chemically-induced colitides.

Th17 cells have been also involved in the pathogenesis of colitis induced by transfer of a cecal bacterial antigen-specific C3H/HeJ/Bir (C3Bir) CD4(+) T-cell line to C3H/HeSnJ SCID mice. In this model, gut inflammation associated with enhanced production of IL-17, and adoptive transfer of IL-17-secreting T cells to SCID recipients resulted in a marked gut inflammation, as compared to that caused by transfer of Th1 cells. Administration of mice with a monoclonal anti-IL-23p19 prevented and treated active colitis, downregulated the synthesis of a broad array of inflammatory cytokines and chemokines in the colon, and promoted apoptosis of colitogenic Th17 cells. By using a novel model of CD8+ T cell-dependent colitis, Tajima et al. have recently shown that a single adoptive transfer of naive CD8+ T cells into syngeneic Rag-deficient mice was followed by rapid spontaneous proliferation of these cells in the mesenteric lymph nodes and severe colitis. Analysis of cytokine-secreting CD8+ T cells in the mesenteric lymph nodes showed the existence of IL-17 and IFN-γ-double-positive cells. Notably, adoptive transfer of naive CD8+ T cells derived from either IL-17- or IFN-γ-knockout mice associated with a remarkably less severe colitis, raising the intriguing possibility that IL-17 and IFN-γ can cooperate to cause pathology in this model of colitis.

In line with these findings, we recently showed that IL-21-deficient mice were largely protected against the development of DSS colitis and TNBS-relapsing colitis. This protection was associated with a reduced colonic expression of several Th17-related genes, including IL-17A, IL-17F, and ROR-γt, consistent with the role of IL-21 in promoting Th17 cell differentiation. Additionally, blockade of IL-21 activity with a specific IL-21R-fusion protein reduced intestinal inflammation and Th17 response during the course of DSS colitis.

Taken together these findings suggest that Th17 cytokines are crucial factors for enhancing the effector phase of T-cell responses that causes intestinal tissue inflammation and damage.

5. IL-23 and colitis

IL-23 is constituted by the specific p19 subunit and shares the p40 subunit with IL-12. These observations and the demonstration that blockade of IL-12/IL-23p40 ameliorated colitis in mice prompted a clinical trial of treating CD with a monoclonal antibody against IL-12p40. Administration of such an antibody in patients with moderate and severe disease induced rates of response and remission of 75% and 38%, respectively. If the therapeutic effect of this novel reagent is due to the neutralization of IL-12 and/or IL-23 remains to be ascertained. However, studies conducted in various animal models of colitis would seem to indicate that IL-23 is more pathogenic than IL-12 in the gut. For instance, by backcrossing IL-10-deficient mice with mice lacking IL-12p35 or IL-23 p19, Yen et al. showed that IL-23 was essential for manifestation of chronic intestinal inflammation, whereas IL-12 was not. CD4+ T cells from IL-10/p19-knockout mice still produced large amounts of IFN-γ, thus indicating that Th1 responses developed normally in the absence of IL-23, but disease manifestations required the presence of IL-23. Moreover, administration of exogenous IL-23 in RAG mice reconstituted with naive CD4+ T cells caused a
more severe colitis that was associated with enhanced production of IL-6 and IL-17 and preventable by treatment of mice with a blocking IL-6 or IL-17 antibody. Although in this model, IL-6 and IL-17 were made by memory T cells, there is no doubt that some of the pathogenic functions of IL-23 in the gut are mediated by non-T cell populations. This was first shown by Powrie and coworkers who analyzed the effect of an agonistic anti-CD40 antibody or a blocking TGF-β receptor II and unable to respond to TGF-β-induced significant colitis when transferred to IL-23-deficient RAG mice. High levels of IFN-γ, but not IL-17, were seen in colitic mice, thus suggesting that IFN-γ might drive the chronic intestinal inflammation in this setting. Notably, transfer of Foxp3-deficient T cells to IL-23-deficient RAG mice caused severe colitis, thus indicating that IL-23 is not essential to the pathogenesis of intestinal inflammation, if counter-regulatory mechanisms are defective or absent. These later findings well fit with the notion that the requirement of IL-23 for the initiation and progress of gut inflammation varies depending on the model. In fact, acute colitis induced by TNBS is driven by IL-12 and negatively regulated by IL-23.

6. Conclusions

The recent discovery that, during gut inflammation, many of the functions traditionally attributed to IL-12 are actually due to IL-23, and that IL-23 contributes to immunopathology by acting in part on Th17 cells has provided a new picture of the way the local immune response can promote intestinal tissue damage. These new data suggest that, at least in theory, the IL-23/Th17 axis would be a better target for suppressing gut inflammation than IL-12/Th1 cytokines. However, some important issues remain to be resolved. For example, it is still unknown how Th17 cells are induced in human IBD and whether and how these cells interact in vivo with the other regulatory and effector mucosal T-cell subsets. It is unclear whether the various Th17 cytokines make qualitatively and quantitatively different contributions to the initiation and progress of gut inflammation or whether they are redundant in their ability to modulate specific inflammatory pathways. It remains also to be clarified why mice lacking IL-23 or specific Th17-related genes are differently susceptible to specific forms of experimental colitis. In normal conditions, Th17 cytokines are constitutively produced in the human and mouse gut, raising the possibility that these molecules may be involved in the maintenance of immunological homeostasis and/or in the control of specific inflammatory pathways. If this is the case, blocking Th17 cytokines could have deleterious rather than beneficial effects for the host. Finally, experimental studies are still necessary to ascertain whether prolonged treatment with Th17-cytokine antagonists can enhance the risk of infections and cancer, given that Th17 cytokines mediate host defensive mechanisms to bacteria and fungi (i.e. IL-17, IL-22) and exert antitumor activity (i.e. IL-21).

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