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REVIEW

Potential role of Th17 cells in the pathogenesis of inflammatory bowel disease

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Abstract

The etiopathology of inflammatory bowel disease (IBD) remains elusive. Accumulating evidence suggests that the abnormality of innate and adaptive immunity responses plays an important role in intestinal inflammation. IBD including Crohn's disease (CD) and ulcerative colitis (UC) is a chronic inflammatory disease of the gastrointestinal tract, which is implicated in an inappropriate and overactive mucosal immune response to luminal flora. Traditionally, CD is regarded as a Th1-mediated inflammatory disorder while UC is regarded as a Th2-like disease. Recently, Th17 cells were identified as a new subset of T helper cells unrelated to Th1 or Th2 cells, and several cytokines [e.g. interleukin (IL)-21, IL-23] are involved in regulating their activation and differentiation. They not only play an important role in host defense against extracellular pathogens, but are also associated with the development of autoimmunity and inflammatory response such as IBD. The identification of Th17 cells helps us to explain some of the anomalies seen in the Th1/Th2 axis and has broadened our understanding of the immunopathological effects of Th17 cells in the development of IBD.

Key words: Crohn's disease; Inflammatory bowel disease; Interleukin-17; Interleukin-23; Th17 cells; Ulcerative colitis

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INTRODUCTION

Current evidence strongly suggests that inflammatory bowel disease (IBD) arises from a disruption of mucosal immune homeostasis in genetically susceptible individuals, resulting in altered processing of enteric antigens, pathogenic T cell activation, and chronic inflammation[1-3]. Although the etiology of IBD remains unclear, accumulating evidence has indicated that dysfunction of the mucosal immune system plays an important role in the pathogenesis of IBD. Among a variety of inflammatory cells in the gut, mucosal $CD4^+$ T cells are thought to play a central role in both the induction and persistence of chronic inflammation by producing proinflammatory cytokines. Studies have indicated that Th1-related cytokines [e.g. tumor necrosis factor (TNF), interferon (IFN)-γ, interleukin (IL)-12] as well as Th17-associated cytokines (e.g. IL-17A, IL-21, IL-23) are markedly increased in inflamed mucosa of CD, whereas the cytokine profiles in inflamed areas of UC seem to exhibit increased production of the Th2 cytokines such as IL-5 and IL-13[1-3]. These proinflammatory cytokines are potent *in vitro* stimulators of intestinal mucosal effector functions including T cell and macrophage proliferation, adhesion molecule expression, chemokine expression, and secretion of other proinflammatory cytokines.

Th17 CELLS AND THE DIFFERENTIATION REGULATION

$CD4^+$ T cells play an important role in the initiation of immune responses by providing help to other cells and by taking on a variety of effector functions during immune reactions. Upon antigenic stimulation, naive $CD4^+$ T cells are activated, expand and differentiate into different effector subsets such as Th1 and Th2 cells

characteristic of the production of distinct cytokines and effector functions[4,5]. Th1 cells produce IFN-γ and lymphotoxin and can mobilize the cellular arm of the immune system to combat intracellular pathogens. Th2 cells secrete IL-4, IL-13, and IL-25, which are essential for the generation of appropriate classes of antibodies and for the elimination of extracellular pathogens[4,5].

The identification of the IL-17 family of cytokines as well as the IL-23-mediated expansion of IL-17-producing T cells uncovered a new subset of Th cells, designated as Th17 cells[6,7]. Th17 cells require specific cytokines and transcription factors for their differentiation. Although the function of this cell subtype is not completely elucidated, emerging data suggest that Th17 cells may play an important role in host defense against extracellular pathogens, which are not efficiently cleared by Th1-type and Th2-type immunity. The first pathogen implicated in a Th17 response was observed in human Lyme arthritis caused by *Borrelia burgdorferi*, in which *B. burgdorferi*-derived lipopeptides could stimulate the production of IL-17A by T cells from synovial fluid, leading to a Th17 lineage differentiation[8]. Previous work has demonstrated that Th17 cells with specificity for self-antigens lead to severe autoimmunity in various animal models. In the murine model of psoriasis, evidence has shown that Th17 cells along with their upstream cytokines (e.g. IL-23) and their downstream effector cytokines (e.g. IL-22) might play a critical role in the pathogenesis of psoriasis[9,10]. Moreover, increased levels of IL-17 produced by Th17 cells have been observed in murine models of rheumatoid arthritis and correlate with more severe joint damage[11].

The IL-17 cytokine family is a recently discovered group of cytokines, which includes six members, IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (or IL-25) and IL-17F, and act *in vitro* and *in vivo* as potent proinflammatory cytokines[6]. IL-17 can induce the expression of proinflammatory cytokines (such as IL-6 and TNF), chemokines (such as KC, MCP-1 and MIP-2) and matrix metalloproteases, which mediate tissue infiltration and tissue destruction[12]. It is also involved in the proliferation, maturation and chemotaxis of neutrophils[13]. In agreement with this point, mice deficient in the IL-17 receptor (IL-17R) are more sensitive to lung bacterial infection because of reduced recruitment of neutrophils to the lung[14]. In contrast, overproduction of IL-17 in the lungs leads to chemokine expression and tissue inflammation infiltrated by large amounts of leukocytes[15]. Moreover, IL-17 is able to costimulate T cells and enhance the maturation of dendritic cells[16]. Taken together, these data indicate that IL-17 has pleiotropic activities, functions through the adaptive and innate immune system to promote immune response, and plays an important role in immune responses.

Several cytokines have been reported to be associated with the development and/or proliferation of Th17 cells. Neutralization of IFN-γ and IFN-α *in vitro* increases the number of IL-17-producing cells generated by IL-23 stimulation. The number of Th17 cells is further increased by the addition of an IL-4-neutralizing antibody, indicating that IL-4 and IFN-γ could inhibit the IL-23-driven expansion of Th17 cells[17]. IL-2, a cytokine important for growth and survival of Th1 and Th2 subsets, is also involved in the long-term expansion and survival of Th17 cells, since restimulation of differentiated Th17 cells with IL-2 could abolish IL-17 production and induce IFN-γ production[18]. In addition, the differentiation of Th17 cells might also require costimulatory signals distinct from those involved in the differentiation of Th1 and Th2 cells. These studies of the costimulatory requirements of Th17 cells were undertaken to determine which costimulatory molecules are important for IL-6- and TGF-β-mediated differentiation of Th17 cells. However, recent work has also demonstrated that Th1-derived IFN-γ could trigger antigen-presenting cells to produce IL-23 and then induce memory Th17 cell expansion in a B7-H1-independent manner[19]. These data indicate that this complex differentiation of Th17 cells may be dependent on various cytokine milieu.

IL-23 is a heterodimeric protein, which is a member of the IL-12 family of cytokines. It is composed of a p19 subunit in addition to a p40 subunit, which is also a component of IL-12[20]. IL-23 functions through the receptor-signaling complex, which is composed of its distinct receptor (namely IL-23R) and IL-12Rβ1[21]. Because IL-23 and IL-12 share a common p40 subunit and IL-12Rβ1, IL-23 may function like IL-12 to trigger Th1 response. However, p19-deficient mice could contribute to normal Th1 response but could not promote the production of IL-17 cells[22]. Other work has demonstrated that Th17 cells are absent in IL-23$^{-/-}$ mice, and could not be amplified and survive albeit in the presence of normal Th17 cells *in vivo*[23]. Studies have shown that IL-23R is not expressed on naïve T cells, therefore IL-23 could not induce naïve T cells to differentiate into Th17 cells, but could promote Th17 cells amplification[24]. These data imply that IL-23 could provide survival signaling to induce the differentiation of Th17 cells. Recently, increasing evidence has shown that IL-1β and IL-23 are required for the generation of Th17 cells and differentiation[23]. Naive T cells stimulated with TGF-β plus IL-6 could secrete large amounts of IL-17, whereas IL-23 could trigger the proliferation of Th17 cells from activated memory T cells, only the combination of IL-6 plus TGF-β is sufficient to induce differentiation of Th17 cells from naive T cells[25]. Moreover, IL-1β and TNF could increase the number of Th17 cells generated *in vitro* in the presence of IL-6 plus TGF-β[26]. These data suggest that an inflammatory milieu could regulate the expression of IL-23R on Th17 cells and thereby allow IL-23 to sustain and strengthen the Th17 phenotype.

IL-27 is another IL-12 family member and has been found to downregulate Th17 cell development[27,28]. IL-27 is a heterodimeric cytokine composed of Epstein-Barr virus-induced gene 3 (*EBI-3*) and p28 chains. Activation of T cells in the presence of IL-27 induces T-bet, a transcription factor critical for the differentiation of naive CD4$^+$ T cells into Th1 cells. However, IL-27R-deficient mice develop severe immunopathology resulting from a general dysregulation of effector T cell responses not restricted to any particular Th cell subtype[29,30]. The absence of IL-27-mediated signaling exacerbates

neuroinflammation, enhances the generation of Th17 cells and increases the number of IL-17-expressing T cells in inflamed tissue. The transcription of the two subunits of IL-27 is differentially regulated, leading to the immunosuppressive effects of IL-27. *EBI-3* is strongly induced by Toll-like receptors (TLRs) and the stimulation of TLR results in the binding of NF-κB complexes to a promoter region of the *EBI-3* gene, while activation of TRIF downstream of TLR3 or TLR4 is critical in the induction of p28[28]. IL-27, independently of IFN-γR and IL-6R signaling, can inhibit the differentiation of Th17 cells triggered by IL-6 and TGF-β. Previous work has demonstrated that T-bet and the suppressor protein SOCS3 are not involved in the IL-27-mediated inhibition of Th17 cells, but that the transcription factor STAT1 seems to be required for the suppressive effect of IL-27 on the development of Th17 cells[27,28].

RORγt, an orphan nuclear hormone receptor, is expressed by fetal lymphocyte tissue-inducer cells and participates in the formation of lymph nodes and Peyer's patches, intestinal lymphocyte tissue-inducer-like cells and immature thymocytes[31]. Interestingly, RORγt is also found to be expressed by differentiated Th17 cells and IL-17-producing T cells present in the intestinal lamina propria (LP). Consistent with this, Th17 cells are observed to be absent in RORγt-deficient mice, whereas transduction of naive T cells with a RORγt-encoding retrovirus could induce IL-17 production. These data indicate the importance of RORγt in the differentiation of Th17 cells[32]. In addition, a recent study has observed that RORγt-deficiency could not abolish Th17 cell generation and that Th17 cells also express high levels of another related nuclear receptor RORα[33]. Importantly, RORα deficiency results in reduced IL-17 expression, while coexpression of RORα and RORγ synergistically leads to Th17 cell differentiation. Thus, these data indicate that Th17 differentiation is directed by two lineage-specific nuclear receptors, RORα and RORγ[33].

PATHOGENIC ROLE OF Th17 CELLS IN IBD

It was widely believed that the chronic intestinal inflammation characteristic of human IBD is the consequence of pathogenic Th1 $CD4^+$ cell responses against the luminal flora, especially in CD, which in turn is driven by proinflammatory cytokines such as IL-12 and TNF[1-3]. Animal models of IBD support this hypothesis as intestinal inflammation could be blocked by treatment with monoclonal antibodies specific for IL-12 or TNF[34,35]. In recent years, studies on the Th17 cell subset has highlighted our understanding of the formation of human inflammatory diseases, which helps us to explain some of Th1/Th2 balance of abnormal phenomena, particularly in human IBD.

Evidence has shown that high numbers of $CD4^+$ Th17 cells are found in the colonic LP of the ileum and colon but not the duodenum, jejunum, mesenteric lymph nodes or spleen in conventionally-raised mice, and that these cells are highly infiltrated in inflamed areas of colitic mice[36,37]. Further analysis confirmed that commensal gut flora contribute to the expansion of these $CD4^+$ Th17 cells, leading to intestinal mucosal inflammation. In terms of mucosal immunity, the IL-23/IL-17 axis has been observed to play an important role in normal intestinal homeostasis, although the precise actions of these cytokines in the gut remain to be fully delineated. To date, IL-17 and other Th17-associated cytokines (e.g. IL-22, IL-23) have been found to have protective effects or pathogenic effects dependent on other effective factors in local tissue. Previous study has demonstrated that IL-23 is mainly expressed by LP dendritic cells in the terminal ileum of normal mice and the frequency of Th17 cells in the intestinal LP is markedly higher than their frequency in peripheral lymphoid tissues[38]. Evidence has shown that IL-23 may have important immune protective effects in the gut and that $IL\text{-}23^{-/-}$ mice exhibited enhanced susceptibility and mortality following infection with the intestinal bacterial pathogen *Citrobacter rodentium*[38]. Interestingly, *C. rodentium*-infected $IL\text{-}23^{-/-}$ mice still generate potent mucosal Th17 responses, suggesting that IL-23-mediated protective responses need not necessarily involve IL-17 production[25]. Similarly, although studies in various murine colitis models have implied that IL-23-driven intestinal pathology is associated with increased IL-17 production, a plethora of other inflammatory cytokines have also been found to be elevated in the inflamed colon, including IL-1β, IL-6, IFN-γ and TNF[39]. In many of the T cell-dependent IBD murine models, Th1 cells clearly predominated in inflamed mucosa and inhibition of Th1 responses could attenuate disease[1-3]. Moreover, the observations that IL-23 also drives chronic colitis mediated by cells of the innate immune system are also consistent with the hypothesis that IL-23-mediated intestinal inflammation need not necessarily involve Th17 cells[39,40].

IL-17 mRNA has been found to be highly expressed in inflamed mucosa from both UC and CD patients, and immunohistochemistry revealed that CD68-positive cells express IL-17[41]. Recent work[42] has also demonstrated that most of the transcripts for Th17-related cytokines were increased in both UC and CD compared to normal controls, but more abundant in UC than in CD. In contrast, up-regulation of IFN-γ mRNA was marked in CD LP $CD4^+$ T cells. Up-regulation of IL-23p19 mRNA was detected in colonic mucosa from both UC and CD patients. The significance of Th17 immunity in UC was further supported by the finding that recombinant IL-23 actually enhanced IL-17 production by LP $CD4^+$ T cells in UC, but had a lesser effect on LP $CD4^+$ T cells in CD. Since the Th1 pathway has been reported to antagonize the Th17 pathway *via* various mechanisms, IFN-γ or IL-12 could actually suppress IL-17 production by human LP $CD4^+$ T cells. Therefore, we can hypothesize that excess IFN-γ production by Th1 cells in CD patients may negatively affect the IL-17 production by Th17 cells in CD, despite the fact that Th17 cells are present in CD mucosa.

A previous report has shown that IL-23 can enhance IFN-γ production by LPMCs from CD patients and that the mucosal IL-23p19 expression levels were correlated with IL-17 in UC and IFN-γ in CD[43]. These results

suggest that IL-23 may enhance the production of distinct cytokines between UC and CD patients, thereby contributing to the local Th1/Th17 balance in IBD. Additionally, IL-21, belonging to the IL-2 family, has been described to play an important part in the differentiation and maintenance of Th17 cells[44,45]. Comparing the Th1, Th2, and Th17 subsets, the largest amounts of IL-21 are produced by Th17 cells. IL-21 produced by differentiating Th17 cells may act in a positive feedback loop, which amplifies the precursor frequency of Th17 cells[44,45]. Recently, our study found that IL-21 facilitated IBD $CD4^+$ T cells to differentiate into Th17 cells, characterized by increased expression of IL-17A and RORγt. Thus, we proposed that IL-21 might be involved in the pathogenesis of IBD and blockage of IL-21R signaling may have therapeutic potential in IBD[46].

The exact role of IL-17 and Th17 cells in intestinal pathology and homeostasis is currently not well understood. IL-17 may have some protective functions in the epithelial layer, as it has been shown to fortify tight junction formation between epithelial cells *in vitro*[47], and treatment of mice with anti-IL-17 neutralizing antibody actually enhanced the severity of colitis induced by administration of dextran sodium sulphate[48]. In contrast, a recent study comparing the ability of Th1 and Th17 cells to induce colitis in mice has proven that Th17 cells are significantly more pathogenic than their Th1 counterparts[49].

So far, there have been few studies that have employed selective blockade of IL-17 during intestinal inflammation. However, in $IL\text{-}10^{-/-}$ mice, treatment with anti-IL-17 specific antibody had little impact on colitis unless anti-IL-6 antibody was also co-administered[48], suggesting that IL-17 may synergize with other inflammatory mediators in the gut. Recent studies have highlighted further potential heterogeneity within Th17 cell populations by demonstrating that some may even secrete IL-10[50], a factor known to inhibit intestinal inflammation. Thus, it is possible that the actions of Th17 cells may differ dependently on other factors that may be present in the local environment. In the normal intestine, the primary function of Th17 cells may be like sentinels which contribute to maintaining epithelial barrier function, whereas in sites of chronic intestinal inflammation, high levels of IL-23 may activate their full pathogenic and antibacterial functions.

CONCLUSION

Through the potential role of Th17 cells in IBD animal models of chronic intestinal inflammation as well as in human IBD, target therapy directed against the Th17/IL-17 axis may have a therapeutic role in the treatment of intestinal mucosal inflammation. However, the precise mechanisms of the Th17/IL-17 axis in intestinal homeostasis should be further elucidated in murine models and human IBD patients.

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