Published in final edited form as:

Neurochem Res. 2010 June ; 35(6): 940–946. doi:10.1007/s11064-009-0091-9.

Synergy of IL-23 and Th17 Cytokines: New Light on Inflammatory Bowel Disease

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Abstract

Inflammatory bowel diseases (IBDs), including Crohn's disease and ulcerative colitis, involve an interplay between host genetics and environmental factors including intestinal microbiota. Animal models of IBD have indicated that chronic inflammation can result from over-production of inflammatory responses or deficiencies in key negative regulatory pathways. Recent research advances in both T-helper 1 (Th1) and T-helper 17 (Th17) effect responses have offered new insights on the induction and regulation of mucosal immunity which is linked to the development of IBD. Th17 cytokines, such as IL-17 and IL-22, in combination with IL-23, play crucial roles in intestinal protection and homeostasis. IL-23 is expressed in gut mucosa and tends to orchestrate T-cell-independent pathways of intestinal inflammation as well as T cell dependent pathways mediated by cytokines produced by Th1 and Th17 cells. Th17 cells, generally found to be proinflammatory, have specific functions in host defense against infection by recruiting neutrophils and macrophages to infected tissues. Here we will review emerging data on those cytokines and their related regulatory networks that appear to govern the complex development of chronic intestinal inflammation; we will focus on how IL-23 and Th17 cytokines act coordinately to influence the balance between tolerance and immunity in the intestine.

Keywords

Inflammatory bowel disease (IBD); IL-23; IL-17A; IL-17F; IL-22

Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract involving aberrant activation of innate and adaptive immune responses. IBD affects approximately 1.4 million individuals in the United States. Although the true etiology of IBD is unclear, clinical and experimental studies demonstrate a breakdown in intestinal homeostasis with the development of aberrant inflammatory responses to intestinal bacteria [1]. One line of evidence for this model of perturbed host-microbial interactions is that treatment with antibiotics has a modest effect on improving disease activity. Other evidence implicates LPS and additional bacterial products which are recognized by a class of pattern-

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Special issue article in honor of Professor Armen Galoyan.

recognition-receptor (PRR) known as Toll-like receptors (TLRs) and nucleotide oligomerization domain-containing protein (NOD)-like receptors (NLRs). These PRRs trigger complex signaling cascades leading to host protective responses through activation of transcription factors such as nuclear factor κ B (NF- κ B). Although the innate immune response may be important especially in the early phase of colitis, recent research has focused on the role of the adaptive immune response in the development of IBD. With the discovery of the Th1 and Th2 cell subsets of CD4⁺ T cells, it became clear that the differentiation of CD4⁺ T cells into mature T-cell subsets is critical for the maintenance of immunity at mucosal sites. Blockade of the inflammatory cytokine tumor necrosis factor- α (TNF- α) has been shown to be highly effective in some cases, however many patients are “non-responders”. Moreover, there is concern that sustained neutralization of TNF- α could result in enhanced susceptibility to infection, addressing the need of more specific therapeutic approaches. Thus, the study of cytokines in IBD is hoped to reveal better therapeutic targets.

Among the inflammatory cytokines implicated in IBD pathogenesis, much interest has focused on two recently identified cytokines: IL-23 and IL-17. IL-23, a key driver of intestinal inflammation [2-5], shares the p40 subunit with the earlier described cytokine IL-12. The activity of IL-23 induced by anti-CD40 appears to play a key role in the intestine immunopathology, whereas IL-12 has more systemic inflammatory effects [4], indicating a tissue-specific role for IL-23 in the gut inflammatory response. In addition, recent genetic studies in humans identified IL-23 receptor (IL-23R) variants that were associated with both small intestinal (ileal CD) and large intestinal (UC) inflammation [6]. IL-17 (also known as IL-17A), was the key to the identification (and naming) of Th17 cells, which are associated with host defense against infectious agents, as well as chronic inflammation. The interplay of Th17 cells and IL-23 plays critical roles in the pathogenesis of organ-specific autoimmune diseases and inflammatory diseases. In humans, IL-23 and IL-1 are sufficient for Th17 differentiation [7], while in mice, IL-23 acts on IL-23R-expressing differentiated Th17 cells to induce their population expansion in vitro and in vivo but does not influence Th17 differentiation [8-10]. Mice with a combined deficiency in IL-23 together with inducible T-cell co-stimulator (ICOS) failed to express IL-17A in models of autoimmune disease.

Given the complexity and diversity of the gut immune response, we will restrict this discussion to summarizing current understanding of proinflammatory cytokines, especially IL-23 and Th17 cytokines, in the pathogenesis of IBD and the relationship to the mucosal immune system.

Features of the Colon Mucosal Immune System

The intestinal tract contains large numbers of immune cells involved in the encounter with microbial antigens. Under normal conditions, the lumen of the intestine is covered by a layer of intestinal epithelial cells (IECs), which are joined together by tight junctions forming a protective layer impeding bacterial invasion [11]. There are several pathways for the immune system to encounter luminal antigens. First, M cells specialize in macromolecule transport via pinocytosis to the underlying immune tissue, where the antigens are picked up by APCs.

Then, intestinal bacterial-loaded DCs migrate to the mesenteric lymph nodes (MLNs) but not to other lymphoid compartments, constraining the antigen-specific response to a local level. Second, IECs can detect microbial products directly through Toll-like receptors (through Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD) receptors [12]. Third, IECs have major histocompatibility complex (MHC) molecules, receptors for different chemokines, and class-specific Fc receptors, allowing their integration and communication with the immune system. Fourth, IECs can secrete cytokines, a variety of chemokines, and other attractants of immune cells in response to pathogenic stimuli. Collectively, epithelial-cell derived factors can modulate intestinal immune responses through effects on antigen-presenting cells and lymphocytes.

In the colon, in addition to Peyer's patches, which are extensively investigated intestinal lymphoid structures, there are also specialized lymphoid structures, termed "isolated lymphoid follicles" (ILFs), which are thought to facilitate immune surveillance. ILF, containing M cells, DCs, B and T lymphocytes [13, 14], have been considered as an inductive site for mucosal immune responses. Since the number of commensal bacteria increases toward the distal end of the bowel, the colon has a higher antigenic load than the small intestine. Immune responses in the colon take place in three distinct compartments: the lamina propria, the ILFs scattered throughout the colon, and the MLNs [14]. The latter two sites may play important roles in initiating the immune response as well as dictating quantitative and qualitative features of the response. Cells in the lamina propria are involved in antigen sampling, and this site is also where effector cells accumulate during inflammation.

Both innate and adaptive arms of the immune system protect the colonic mucosa from infection. We will further discuss the adaptive immune response mediated via T cells, especially the key roles of proinflammatory cytokines in the formation and development of inflammatory bowel disease.

IL-23 and Colitis

Over 20 years ago, the T-helper 1 (Th1)/Th2 subsets were discovered and introduced a new era in cytokine biology. Since then, numerous studies have been carried out to identify upstream factors involved in the differentiation of distinct Th responses. The heterodimeric cytokine, IL-12, composed of a p35 and a p40 subunit, was shown to function as a mediator in promotion of Th1 responses and host defense against intracellular pathogens. The related heterodimeric cytokine, IL-23, comprised of IL-12p40 and an IL-23-specific p19 subunit [15], was identified in 2000. Whereas IL-12 is well known for promoting the IFN- γ -producing Th1 effector phenotype in the adaptive response, IL-23 is reported to promote "Th17" cells, named for their production of IL-17 and shown to be an effector lineage distinct from Th1 and Th2. IL-23 is produced by cells of the innate immune system such as DCs and macrophages in response to PRR stimulation or endogenous signals, indicating a potential role for T cells in reinforcement of the IL-23 response [16]. IL-23 signaling is mediated predominantly through the signaling adapter molecule signal transducer and activator of transcription 3 (STAT3). A functional receptor for IL-23 was identified several years after the discovery of the cytokine [17]. This receptor is also a heterodimer and

unsurprisingly shares one subunit, IL-12RM (binds IL-12p40), with the IL-12 receptor, the other subunit is the specific IL-23R. The receptor is expressed on T cells, natural killer cells, DCs and macrophages.

Polymorphisms in the IL-23 receptor have been associated with susceptibility to inflammatory bowel diseases (IBDs) in man. In mice, there are a number of models of IBD, and IL-23 plays various roles in these different models. Although IL-23 can promote Th17 cells, it can also mediate innate intestinal inflammation independent of effector T cells. Thus IL-23 was required for intestinal inflammation to develop in T cell deficient RAG^{-/-} mice treated with an agonistic anti-CD40 monoclonal antibody. In this model, there is both intestinal inflammation, which requires IL-23, as well as a systemic inflammatory response. The latter includes splenomegaly, increases in serum cytokines, wasting disease, and inflammatory infiltrates in the liver, is independent of IL-23, but requires TNF- α and IL-12 [4]. Another mouse IBD model is intestinal bacterial infection by *Helicobacter hepaticus*, a Gram-negative microaerophilic bacterium that colonizes the crypts of the cecum and the colon, in immune deficient RAG^{-/-} mice [3]. In this model, expression of IL-23p19 and IL-12p40 mRNA, but not of IL-12p35, was significantly increased in the cecum and colon of *H. hepaticus* infected (*Hh*⁺) 129SvEvRAG^{-/-} mice. Treatment with anti-p19 was effective in ameliorating colon inflammation. A surprising increase in expression of IL-17A from non-T cells was induced in these mice. Like the anti-CD40 model, *H. hepaticus* also triggered a systemic inflammatory response, but unlike that model, this systemic response was dependent on IL-23.

IL-23 is also closely associated with T-cell-mediated colitis. In a well-established T cell-dependent model of IBD, naive CD4⁺CD45RB^{high} T cells isolated from C57BL/6 mice were adoptively transferred into age-matched cohorts of syngeneic RAG^{-/-} recipient mice, p40^{-/-}RAG^{-/-} mice (lacking both IL-12 and IL-23), p35^{-/-}RAG^{-/-} mice (lacking only IL-12), or p19^{-/-}RAG^{-/-} mice (lacking only IL-23) (3). Development of intestinal inflammation was greatly dampened in p40^{-/-}RAG^{-/-} recipients as well as in p19^{-/-}RAG^{-/-} recipients, confirming that IL-23 was essential in this T-dependent IBD model. IL-10^{-/-} mice develop IBD, and blockade of IL-12p40 but not IFN- γ could attenuate established colitis in these mice, again implicating IL-23 but not the IL-12p70/IFN- γ axis. Other studies also reported that IL-23 plays a crucial role in T-cell dependent colitis in a number of models including spontaneous and *H. hepaticus*-induced colitis in mice deficient in IL-10 or IL-10 signaling, respectively [18]. Although in most mouse models of colitis, IL-23 is proinflammatory, in TNBS (2,4,6-trinitrobenzen sulfonic acid) colitis, which is T-cell mediated, IL-23 is anti-inflammatory because it appears to suppress IL-12 in that model. In addition, IL23-specific deficient mice (p19KO) were highly susceptible for the development of experimental T cell-mediated TNBS colitis intestinal inflammation [19]. Furthermore, IL-23 can also restrain regulatory T-cell responses in the gut (discussed below). However, even though IL-23 is clearly a central mediator of intestinal inflammation, there may be additional IL-23-independent inflammatory pathways that also contribute to disease.

Th17 Cytokines Associated with Colitis

Although the Th17 cell clearly is involved in a number of mouse models of inflammatory pathology, the relative function of the cytokines these cells produce still remain unclear. The hallmark of Th17 cells is the expression of IL-17A, but additional cytokines are also produced by these cells as identified by microarray [20]. In addition to IL-17A and IL-17F, these cells also express IL-22, IL-21 and CCL20 (ligand of CC-chemokine receptor 6). The expression of IL-21 is induced by IL-6 in a STAT3-dependent manner [21, 22], while CCL20 is induced by IL-17A and can facilitate the localization of immune cells to the gut [23]. The following discussion will focus on the cytokines initially identified with Th17 cells: IL-17A, IL-17F and IL-22.

IL-17A

The IL-17 family consists of six structurally related isoforms: IL-17A (also known as “IL 17”), IL-17F, IL-17B, IL-17C, IL-17D, and IL-17E (also known as IL-25) [24]. Of the family members, IL-17A and IL-17F are most closely related, sharing 55% homology. IL-17A binds to and signals through IL-17 receptor A (IL-17RA), a member of an IL-17R family that is widely expressed by mesenchymal cells such as epithelial cells, endothelial cells and fibroblasts [25]. Moreover, IL-17RA can also form a heterodimer with IL-17RC, another member of the IL-17R family [26], suggesting that there is an additional form(s) of IL-17 receptors with a different affinity for IL-17s and/or different signal-transduction pathways. Although Th17 cells can mediate IBD in some models, the IL-17 cytokines themselves appear to have both pathogenic and protective actions in IBD.

IL-17A expression has been associated with many inflammatory diseases, such as rheumatoid arthritis, asthma and systemic lupus erythematosus (SLE). Initial studies showed that some genes encoding several chemokines, including CC-chemokine ligand 2 (CCL2), CCL7, CCL20 and CXC-chemokine ligand 1 (CXCL1), as well as the genes encoding matrix metalloproteinase 3 (MMP3) and MMP13, were significantly upregulated in mouse fibroblasts after treatment with IL-17A [20, 27]. Furthermore, IL-17RA-deficient mice showed impaired host defense against mycobacterial infection due to a significant decrease in the amount of granulocyte colony-stimulating factor (G-CSF; also known as CSF3). Although Th17 cells are the best-characterized source of IL-17A during adaptive immune responses and perhaps during chronic inflammatory responses, other cell types can also express IL-17A, including CD8⁺ T cells. However, a causative relationship between IBD and IL-17A remains controversial. Early studies showed that most of (90%) the IL-17A KO mice survived dextran sodium sulfate (DSS) treatment in the DSS-induced acute colitis model [28] in which epithelial damage and inflammatory infiltrates were not obvious. When (TNBS) was administered to IL-17RA KO mice, it was found that the TNBS-induced colitis was attenuated in the receptor gene KO animals [29]. Although the proinflammatory properties of IL-17A have been inferred from the induction of CXC chemokines and other chemoattractants from both endothelial and epithelial cells, a recent study from Richard Flavell's group suggested the opposite: transfer of *Il7a*^{-/-} CD45RB^{hi} CD25⁻CD4⁺ T cells induced an overly aggressive inflammatory response in *Rag1*^{-/-} recipients [30]. Similarly, the *Il7ra*^{-/-} (IL-17A receptor knockout) CD45RB^{hi} CD4⁺ T cells also elicited an accelerated

wasting disease in *Rag1*^{-/-} recipients. These findings demonstrate that surprisingly, in IBD IL-17A can mediate protection, rather than pathology, at least in the CD45RB^{hi} transfer model of colitis. In addition, administration of a neutralizing anti-IL-17A antibody, the DSS-induced colitis in mice aggravated, suggesting that IL-17A may play an inhibitory, rather than enhancing, role in the development of experimental colitis [31]. Since different results were obtained from different mouse colitis models, it will be important to clarify the source and action of IL-17A in the specific phases of the immune response.

IL-17F

The *IL-17F* gene is located in the same chromosomal region as IL-17A in mice and in humans and may have derived from a gene-duplication event. Although there is considerable knowledge about the function of IL-17A, little is known about the regulation and function of IL-17F. IL-17F was first found to be expressed by Th17 cells that were induced to proliferate with IL-23 [32]. Similar to IL-17A, IL-17F was reported to induce the expression of various cytokines, chemokines and adhesion molecules by human airway epithelial cells, vein endothelial cells and fibroblasts, but IL-17F had significantly weaker activity than IL-17A [33]. Human IL-17F does not bind to human IL-17RA and their mouse counterparts only associated weakly in vitro, but recently, IL-17RC (a member of the IL-17 receptor family) was reported to be a receptor for IL-17F [34]. Interestingly, IL-17A also binds to IL-17RC. Similarly, it is not clear whether IL-17A and IL-17F homodimers, as well as the IL-17A/F heterodimers, preferentially interact with IL-17RA and IL-17RC homodimers or heterodimers. Elucidation of the receptor usage by these cytokines will help to reveal the differential roles of IL-17-family members in the regulation of inflammation.

IL-22

IL-22 is a cytokine whose expression increases during differentiation from Th0 cells to Th17 conditions. IL-22 was initially termed “IL-10-related T-cell-derived stimulator” (IL-TIF) when it was first identified by Dumoutier et al. as a gene induced in mouse T lymphoma cells by IL-9 with 22% amino acid identity with IL-10. IL-22-expressing T cells generated in vivo co-express IL-17A and IL-17F. The IL-22 receptor is part of the type 2 cytokine receptor family and consists of two subunits, IL-22R1 and IL-10R2 [35]. IL-10R2 is widely expressed on immune cells (T, B, and NK cells), unlike IL-22R1 which is present on a variety of nonimmune tissues: skin, lung, small intestine, liver, colon, kidney, and pancreas [36]. Expression of IL-22R1 is upregulated on intestinal epithelial cells by stimulation with the proinflammatory mediators LPS, IL-1 β , and TNF- α .

IL-22 was first suggested to be a proinflammatory cytokine acting downstream of IL-23. For example, in psoriasis, this IL-23 to IL-22 pathway was implicated in acanthosis (thickening of the skin) and dermal inflammation through the activation of STAT3 [37]. However several lines of evidence suggest that, in the gut, IL-22 has more of a restorative than pathogenic role. IL-22 transcripts are elevated in biopsies of subjects with Crohn's disease compared to those with ulcerative colitis [38]. In a mouse model of ulcerative colitis, disease was improved via an IL-22 gene delivery method [39]. This improvement was thought to be secondary to IL-22-enhanced mucus production and goblet cell replacement, leading to the maintenance of this external barrier at the epithelial surface. This role of epithelial barrier

protection by IL-22 was investigated in mice infected with *Citrobacter rodentium* which induces intestinal inflammation [39]. IL-22 knockout mice had significantly increased mortality compared to wild-type control mice and disrupted epithelial barrier integrity, indicating IL-22 is pivotal for host defense against this pathogen. This protective pathway appeared to involve IL-23 induction of IL-22 in non-T cells. The downstream mediators of the protective function of IL-22 could be accounted for by induction of the antimicrobial proteins RegIII β and RegIII χ in colonic epithelial cells [40].

Although IL-22 has been termed a “Th17 cell cytokine”, as noted above, the relevant source can be non-T cells in early host defense against bacterial infection. One such alternative source of IL-22 in the intestine appears to be a subset of natural killer (NK) cells that are NKp46⁺ [41, 42]. These NK cells localize in cryptopatches in intestinal mucosa and were found to be dependent on transcription factor ROR γ t as well as commensal gut microflora for differentiation and IL-22 production [42]. It is proposed that these IL-22-producing NK cells in the gut function in host defense by inducing antimicrobial peptides and in epithelial tissue repair.

Thus, Th17 cells are clearly capable of inducing intestinal inflammation, it remains to be determined which Th17 cell effector cytokines actually mediate the inflammatory response. Although initial studies implicated IL-17A itself based on the capacity of blocking IL-17A and IL-6 to ameliorate colitis in IL-10-deficient mice [5], several groups [30, 43] concluded that IL-17A production by T cells was dispensable for T-cell transfer colitis. One candidate for pathogenesis by Th17 cells is IL-17F. Although IL-17A and IL-17F have overlapping activities in some systems, there is evidence for differential activities in the gut. In an acute model of colitis, IL-17A mediated a protective role [30], while IL-17F appeared to play a pathogenic role at least in DSS induced colitis model [44].

Regulatory Network of IL23/Th17 Axis

The strong link between IL-23 and the Th17 response in vivo suggested that IL-23 was involved in the differentiation of Th17 cells. However, TGF- β and IL-6, rather than IL-23, were initially shown to be the key cytokines directing Th17 cell development. Subsequently, it was shown that other pro-inflammatory mediators such as IL-1 [45] and IL-21 could substitute for IL-6 during Th17 differentiation [46]. A recent study reported that the T cell-mediated colitis that develops in IL-10^{-/-} mice or in RAG^{-/-} recipients of IL-10^{-/-} CD4⁺ T cells was also dependent on IL-23 [3]. It now appears that IL-23 is unnecessary for the initiation of Th17 differentiation but is required at a crucial control point in the Th17 response. STAT3, which is activated by IL-23, was shown to be essential in the Th17 response. STAT3 binds to the *IL-17A* gene promoter, and it is proposed that STAT3 mediates IL-23-regulated expression of IL-17A. With the inactivation of STAT3, defects were found not only in IL-17A production, but also in the expression of IL-17F, IL-22 and IL-23R. In the absence of IL-23, there is a decrease in the accumulation of Th17 cells in vivo in response to inflammatory stimuli, suggesting a role for IL-23 in the expansion and/or maintenance of the Th17 response [47]. In human T cells, IL-23, together with TGF- β , IL-1 β and IL-6 were shown to induce Th17 differentiation and expression of IL-17A,

IL-17F, the IL-23R and the transcription factor ROR γ t which is required for Th17 differentiation [32].

IL-23 was shown to suppress expression of Foxp3 which induces regulatory T cell development [48]. If Foxp3 is present in T cells, it can divert differentiation away from Th17 because it binds ROR γ t and blocks its action. Since Foxp3⁺ROR γ t⁺ cells are found in the gut associated lymphoid tissue, it has been suggested that IL-23 acts on this intermediate cell, suppressing Treg development and thereby promoting Th17 development. Izcue et al. [42] recently reported that IL-23 reduces the frequency of Foxp3⁺ cells in the intestine and that IL-23 is dispensable for the pathogenesis of intestinal inflammation in the absence of regulatory T (Treg) cells. The crosstalk for IL-23/Th17 cytokines (Fig. 1) and Treg development is illustrated, showing a shared developmental pathway for these T-cell subsets.

Conclusion

Understanding the mechanisms underlying inflammatory diseases such as IBD has grown in recent years by combining human genetics with animal models. Key pathogenic pathways are the IL-23 axis and Th17 cytokines, which present attractive therapeutic targets. Although the functions of Th17 cytokines including IL-17A and IL-17F in the development of IBD still remain controversial regarding their pathogenic versus protective roles, most studies conclude that Th17 cells appear to mediate host protective immunity to some extracellular bacteria as well as eliciting potent inflammatory responses in several mouse models of IBD. Further insight into the role of specific Th17 cytokines could suggest targets for treatment of IBD but spare host defense. IL-23, involved in the conserved pathway in intestinal homeostasis, has been mainly considered to sustain Th17 cell responses in vivo. In the absence of IL-23, both Th1 and Th17-associated cytokines were decreased, showing that IL-23 promotes both types of responses in the bowel. Indeed, blockade of IL-23 is expected to not only inhibit chronic inflammatory pathways but also to promote Treg responses, favoring dominant tolerance. Interestingly, IL-23 is not necessary for intestinal inflammation if there are no Tregs in the system. Taken together, the immune response in the intestine displays a delicate balance between the TH17/IL-23 axis and the regulatory T cell response. Thus a complex network of cytokines that are produced by innate and adaptive immune cells mediates a spectrum of responses ranging from host defense to inflammatory pathology. Recent strides in understanding these mechanisms in mouse models will be evaluated for therapy in humans, offering new hope for the IBD patient.

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Fig. 1.

IL-23/Th17 axis modulates immune-cell function in intestinal epithelial cells. Th17 cells differentiate from naïve T lymphocytes under the stimulus of TGF- β , IL-6, IL-23 and IL-1 β . Once differentiated, Th17 autocrine IL-21 and its IL-23 receptor further promote the expansion of Th17 cell populations, while other Th17 cytokines including IL-17A, IL-17F and IL-22 signal other cells to either induce the production of CXC-chemokines or augment antimicrobial peptide production and defensins. In an alternative pathway, naïve CD4⁺ T cells can differentiate into Treg cells, characterized by Foxp3 which can inhibit the function of ROR γ t. Other cell types such as dendritic cells are also capable of elaborating IL-22. DC; Dendritic cells; TGF- β ; transforming growth factor- β