IL-23 and Autoimmunity: New Insights into the Pathogenesis of Inflammatory Bowel Disease

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Crohn’s disease, ulcerative colitis, genome-wide association studies, Th17 cells, intestine

Abstract
The intestinal immune system has the challenge of maintaining both a state of tolerance toward intestinal antigens and the ability to combat pathogens. This balance is partially achieved by reciprocal regulation of proinflammatory, effector CD4⁺ T cells and tolerizing, suppressive regulatory T cells. Inflammatory bowel disease (IBD) comprises Crohn’s disease (CD) and ulcerative colitis (UC). Genome-wide association studies have linked CD to a number of IL-23 pathway genes, notably IL23R (interleukin 23 receptor). Similar associations in IL-23 pathway genes have been observed in UC. IL23R is a key differentiation feature of CD4⁺ Th17 cells, effector cells that are critical in mediating antimicrobial defenses. However, IL-23 and Th17 cell dysregulation can lead to end-organ inflammation. The differentiation of inflammatory Th17 cells and suppressive CD4⁺ Treg subsets is reciprocally regulated by relative concentrations of TGFβ, with the concomitant presence of proinflammatory cytokines favoring Th17 differentiation. The identification of IL-23 pathway and Th17 expressed genes in IBD pathogenesis highlights the importance of the proper regulation of the IL-23/Th17 pathway in maintaining intestinal immune homeostasis.
INTRODUCTION

The demonstration of genetic associations in the interleukin 23 (IL-23) pathway in multiple chronic inflammatory disorders, including inflammatory bowel disease (IBD), has coincided with significant advances in the understanding of its key role in host defense and organ-specific autoimmunity. Evidence for the importance of the IL-23 pathway in IBD has come from mouse models of IBD, in which IL-23 deficiency or blockade protects from disease (1–3), as well as human IBD (4–9). In particular, genetic polymorphisms in the IL-23 receptor, IL23R, represent one of the strongest associations in Crohn’s disease (CD) and are also associated in ulcerative colitis (UC) (10), psoriasis (11), and ankylosing spondylitis (12). In this review, we integrate advances from human genetics with advances in the understanding of IL-23, with a particular focus on its role in Th17 cells, a subset of CD4+ T cells that is important in organ-specific autoimmunity.

CROHN’S DISEASE AND ULCERATIVE COLITIS: CLINICAL FEATURES

CD and UC represent the two major subtypes within idiopathic IBD and share clinical, epidemiologic, and genetic features. Both are chronic, often relapsing inflammatory disorders of the gastrointestinal tract. Patients typically suffer from diarrhea, abdominal pain, rectal bleeding, malnutrition, and diminished health-related quality of life. The incidence of IBD is highest in the second to fourth decades of life, and it is estimated that over one million Americans are affected (13). Patients with IBD are more likely to also have other chronic inflammatory diseases, including primary sclerosing cholangitis, ankylosing spondylitis, psoriasis, and multiple sclerosis (14).

CD may be distinguished from UC by the distribution of intestinal inflammation. In CD, the inflammation is often transmural, focal, discontinuous, and asymmetric in distribution. The distribution of inflammation in UC is typically continuous, symmetric, and confined to the superficial mucosa and submucosa. CD most commonly involves the ileum and colon but can affect any region of the gut. UC always involves the rectum, and inflammation may extend as far as the cecum in a contiguous pattern (15). CD is associated with granulomas in ~30% of cases and the deeper, transmural involvement of inflammation observed can be associated with the development of strictureguring and fistulous complications, whereas UC is typically not associated with these features.

Medical therapies for both CD and UC include the use of aminosalicylates, antibiotics, immunosuppressives (azathioprine, methotrexate), corticosteroids, and monoclonal antibodies directed toward blockade of pathways contributing to the inflammatory process, with anti-TNF antibodies dramatically improving medical therapies for both CD and UC. One third of patients with UC eventually require total proctocolectomy (removal of the colon and rectum to treat UC or its complications), and up to 57% of patients with CD required one or more surgeries to remove portions of their small or large intestines in the period prior to anti-TNF therapy (16). For these reasons, there is a significant need to more efficiently prioritize, test, and apply improved medical therapies for these disorders.

GENETIC EPIDEMIOLOGY OF CD AND UC

The importance of genetic factors in disease pathogenesis was first suggested through the observation that cases of IBD tended to cluster within families. The relative risk to siblings compared to general population risk ranges from 30 to 40 for CD and from 10 to 20 for UC (17). Furthermore, the relative risk for UC to siblings of a CD proband was observed to be 3.9, and the converse risk given a UC...
proband was observed to be 1.8. Taken together, these epidemiologic data suggest a genetic model of IBD in which some risk alleles will be unique to either CD or UC, and other risk alleles will be common to both. That genetic factors contribute to disease pathogenesis is definitively established through twin studies, which demonstrate a significantly higher rate of disease concordance in monozygotic twins than dizygotic twins, and higher concordance rates for CD (20%–50% monozygotic concordance, 0%–7% dizygotic twin concordance) than UC (14%–19% monozygotic concordance, 0%–5% dizygotic concordance) (18–21). That monozygotic twin concordance is significantly less than 100% reflects the roles of developmental and environmental factors in disease expression.

By definition, expression of complex genetic disorders does not follow a simple Mendelian pattern of inheritance (e.g., autosomal recessive, autosomal dominant), and no single genetic variant alone drives disease expression. Instead, multiple genetic loci of varying statistical significance and functional effects have been associated with both CD and UC. The engine for these discoveries has been the application of the genome-wide association (GWA) study to large case-control cohorts, which has recently resulted in the identification of >30 distinct genetic loci associated with CD (22). The magnitude of the association effects, as well as the certainty with which given genes and specific causal alleles can be assigned in these regions, varies broadly. However, genes of both the innate and adaptive immune system have been implicated in IBD. Genes of the innate immune system associated with CD and not UC include NOD2 and the autophagy genes, ATG16L1 (autophagy) (23, 24) and IRGM (immunity related GTPase M protein) (25, 26). On the other hand, multiple genes involved in IL-23 signaling as well as Th17 cell subsets have been identified in both CD and UC, notably the IL23R, interleukin 12A (IL-12A, p40), and STAT3 (signal transducer and activator of transcription) (22).

THE INTESTINAL IMMUNE SYSTEM: BALANCE BETWEEN EFFECTOR AND REGULATORY CD4⁺ T CELL SUBSETS

The central challenge of the intestinal immune system is balancing defense with tolerance: responding to pathogens while coexisting with resident bacteria and food antigens (27). It is believed that, in IBD, an inappropriate, overactive mucosal immune response to resident intestinal bacteria mediates intestinal tissue damage in genetically susceptible hosts (15). Antigen-presenting cells in the intestinal mucosa are continuously sampling intraluminal intestinal antigens from both food and bacteria. Upon exposure to certain antigens, antigen-presenting cells migrate to the mesenteric lymph nodes and Peyer’s patches, where they interact with naïve T lymphocytes, resulting in their activation, clonal expansion, and differentiation (Figure 1). The outcome of this differentiation process in the intestinal lymphoid structures depends on the nature and context of the antigen presented. As a result, there is a continuous balance between differentiation toward various regulatory T cell outcomes (tolerance) and specific effector T cells that enhance host defense against particular pathogens (defense).

The functional requirement for T cells to combat distinct pathogens, such as intracellular microbes, extracellular bacteria, fungi, and helminthic parasites, led to the hypothesis that diverse T cell effector functions would be mediated by distinct cell subsets. This hypothesis was subsequently confirmed through the identification of distinct CD4⁺ helper T cell subsets characterized by specific cytokine profiles. The Th1 subset (Th1) mediates cell-mediated immunity against intracellular microbes via secretion of interferon gamma (IFNγ) and tumor necrosis factor alpha (TNFα), resulting in macrophage activation and IgG production. In contrast, Th2 cells produce IL-4, IL-5, and IL-13, enhancing host defense against helminthic parasites via production of mast cells, eosinophils, and IgE (28).
This classification has been modified recently following the characterization of Th17 cells, which mediate defense against a broad range of pathogens, including extracellular Gram-positive and Gram-negative bacteria, and fungi (29). Th17 cells secrete IL-17A, IL-17F, IL-21, IL-22, IL-26, and TNFα (Figure 2), as well as various chemokines, which then enhance neutrophil responses and mucosal defenses, such as antimicrobial peptide expression (β-defensins). The importance of Th17 cytokines in mediating defenses at mucosal surfaces is observed with both pulmonary [Klebsiella (30)] and intestinal [Citrobacter (31)] pathogens.

Tolerance to self and intraluminal antigens is a central requirement for the intestinal immune system, which constitutes the major contact point with the external environment. There are multiple mechanisms through which the intestinal immune system mediates this tolerance, and perturbations in these mechanisms contribute to autoimmunity and chronic inflammation. A key mechanism of intestinal tolerance involves the function of FoxP3+ regulatory T cells (Tregs). FoxP3-defective mice develop a lymphoproliferative disease with early mortality. Transfer of FoxP3+ Tregs can rescue the disease. Along these lines, transfer of effector T cell subsets depleted of Tregs into lymphopenic mice results in autoimmunity and intestinal inflammation, which can be abrogated by the simultaneous infusion of Tregs (32). These studies emphasize the importance of the balance between effector and regulatory subsets in maintaining intestinal immune homeostasis.

The differentiation and regulation of the CD4+ T cell effector and regulatory subsets are characterized by distinct transcriptional regulatory programs, each associated with distinct inducing cytokines and master transcriptional
Multiple IL-23 pathway and Th17-relevant genes are associated with CD. TGFβ and proinflammatory cytokines such as IL-1 and IL-6 play a key, initial role in Th17 cell differentiation. IL-23 is probably involved in multiple stages of Th17 lineage fate, including in differentiation, expansion, and stabilization of Th17 cells. Key transcription factors required include retinoic acid-related orphan receptor (ROR)γt and STAT3. The expression of IL23R and CCR6 represent phenotypic features of IL-17-expressing cells. Amplification of this process is further accelerated by the autocrine growth factor, IL-21, which also signals through STAT3. Upon engagement of IL-23 to its receptor complex (composed of IL23R and IL12RB1), sequential activation of JAK2 and STAT3 occurs. The cytokines secreted by Th17 cells lead to a combination of inflammatory, regulatory, and epithelial restitution functions. The asterisk represents genes that have been associated with CD.

**Figure 2**

Multiple IL-23 pathway and Th17-relevant genes are associated with CD. TGFβ and proinflammatory cytokines such as IL-1 and IL-6 play a key, initial role in Th17 cell differentiation. IL-23 is probably involved in multiple stages of Th17 lineage fate, including in differentiation, expansion, and stabilization of Th17 cells. Key transcription factors required include retinoic acid-related orphan receptor (ROR)γt and STAT3. The expression of IL23R and CCR6 represent phenotypic features of IL-17-expressing cells. Amplification of this process is further accelerated by the autocrine growth factor, IL-21, which also signals through STAT3. Upon engagement of IL-23 to its receptor complex (composed of IL23R and IL12RB1), sequential activation of JAK2 and STAT3 occurs. The cytokines secreted by Th17 cells lead to a combination of inflammatory, regulatory, and epithelial restitution functions. The asterisk represents genes that have been associated with CD.

**Factors** The IL-12/IFNγ and IL-4 cytokines induce differentiation of Th1 and Th2 subsets, respectively. T-bet and GATA-3 represent the key transcription factors that drive much of the subsequent Th1 and Th2 differentiation programs, respectively. In fact, there is a critical, continuous cross-regulation between Th1, Th2, Th17, and Treg subsets. Furthermore, differentiation of Th17 cells shares many features with differentiation of Tregs; for example, TGFβ is a key inducing cytokine for both subsets. TGFβ favors FoxP3+ Treg differentiation, whereas addition of IL-1, IL-6, and IL-21 to TGFβ induces IL23R expression and leads to a distinct outcome of Th17 cell differentiation (Figure 1). IL-23 contributes to the differentiation of Th17 cells in some (33–36) but not all studies, and it is important for their expansion and stabilization (3, 31, 37–42). By definition, Th17 cells express IL-17, which exerts its proinflammatory effects, at least partially, by inducing neutrophil recruitment and granulopoiesis (43). The observation of increased expression of IL-23, IL-17, and other Th17 pathway members in the intestinal lamina propria of patients with CD (4–9, 44–46) provides further support for the in vivo importance of the IL-23 signaling pathway in human IBD. Tight control of the reciprocal relationship between Tregs and Th17 cells mediates self tolerance and prevents tissue inflammation, which is perturbed in IBD. GWA studies in CD have established multiple genes of the IL-23 pathway and the Th17 pathway. The most significant CD gene association in the pathway reported thus far is to the IL23R gene. The tightly regulated expression and function of IL23R, notably with respect to the Treg-Th17 cell lineage fate decisions, highlights its key role in autoimmunity and IBD.

**Interleukin 12 (IL-12):** consists of two subunits, p35 and p40, the latter of which is shared with IL-23.
GENOME-WIDE ASSOCIATION STUDIES IN CD IMPLICATE MULTIPLE GENES ALONG THE IL-23 AND TH17 PATHWAY

The identification of genetic variants that are associated with common, complex genetic disorders has been greatly accelerated over the past couple of years through the application of GWA studies. GWA studies type several hundred thousand single nucleotide polymorphisms (SNPs) throughout the genome and have enormously advanced the number of genetic loci known to contribute to multiple complex disorders such as IBD. Because of the correlation patterns between human genomic SNPs, it is possible, in European-ancestry cohorts, to sample >80% of the common variation (defined here as having a minor allele frequency of >5%) using several hundred thousand SNPs selected on the basis of known correlation patterns (47). Because the association signals are relatively modest (e.g., conferring allelic odds ratios typically less than 1.5), very large case-control cohorts are required to distinguish true association signals from the background statistical noise generated by performing hundreds of thousands of statistical tests. The amount of genetic information generated through these approaches is orders of magnitude greater than that which was achievable before GWA studies. However, because of particular correlation patterns specific to various genomic regions, GWA studies cannot determine which gene or functional polymorphism is driving the observed association signal. With few exceptions, directly causal alleles have not been identified, and often the association signal encompasses multiple genes. The strongest CD association signals include IL23R (chromosome 1p31) and NOD2 (chromosome 16p12) (22).

Multiple SNPs in the IL23R gene region having distinct correlation patterns demonstrate association to CD, suggesting the presence of multiple independent risk and susceptibility alleles (10). IL23R consists of an extracellular domain with an N-terminal immunoglobulin-like domain and two cytokine receptor domains (48). Notable among the SNPs demonstrating association is the amino acid polymorphism, Arg381Gln, which is located in the cytoplasmic domain of the receptor (10). The less common glutamine allele of Arg381Gln confers approximately threefold protection against developing CD. In addition to the Arg381Gln SNP, a number of independent association signals are observed in intronic and intergenic SNPs contained within a haplotype block encompassing the C-terminal seven exons (of twelve) and extending into the intergenic region between IL23R and its close homolog, IL12RB2. Studies assessing whether CD-associated polymorphisms alter either expression or efficiency of IL-23-mediated signaling have yet to be reported.

The functional IL-23 receptor complex is composed of the IL23R and IL12RB1 (chromosome 19p13) subunits; the latter subunit is also part of the functional IL-12 receptor complex (48). The functional IL-23 cytokine is composed of p19 (IL-23A, chromosome 12q13) and p40 (IL-12B, chromosome 5q33) subunits; p40 is also part of the functional IL12 cytokine (49). The significance of the IL23R human genetic advances rests on the recent, increased understanding of the extent to which an intact IL-23 pathway is required for manifestation of intestinal inflammation in mouse models of IBD.

Of the top >30 gene CD association regions, four play a direct role in IL-23 signaling, namely IL23R, p40 (IL12B), STAT3, and JAK2 (48), ranked 1, 11, 12, and 30 in significance, respectively. In most cases, the associations do not directly implicate causal alleles, but, because of the local linkage disequilibrium patterns, likely identify the genes driving the association signals in these regions. IL12B (p40) is a constituent of both the functional IL-12 and IL-23 cytokines. Similar to CD, psoriasis has been associated with both IL12B and IL23R (11). JAK2 constitutively binds to IL23R, resulting in its own and IL23R tyrosine phosphorylation. This in turn results in the recruitment, phosphorylation, homodimerization, and nuclear translocation of STAT3 (48). STAT3 is a crucial but nonspecific...
transcription factor downstream of a number of pro- and anti-inflammatory cytokines. Taken together, these data demonstrate genetic association of multiple IL-23 pathway genes to CD susceptibility.

The role of STAT3 associations in IBD is likely to be complex. STAT3 both induces IL23R expression, being a key transcription factor for Th17 cell differentiation, and is itself activated by IL-23 signaling through the IL-23 receptor complex. This suggests that STAT3 activation (as measured by phosphorylation of the protein) would reflect an activated, inflammatory milieu. In support of this, increased STAT3 phosphorylation is observed in peripheral blood and lamina propria T cells from CD patients (44, 50–53). However, increased STAT3 phosphorylation likely reflects the effects of a complex inflammatory milieu involving both primary and secondary mechanisms. STAT3 is downstream of a broad array of both pro- and anti-inflammatory cytokines. Multiple cytokines besides IL-23 can activate STAT3, notably IL-6, IL-10, IL-21, IL-22, and IL-27 (54–56). Finally, STAT3 is involved in key suppressive functions, such that STAT3 deficiency in animal models can, in fact, result in colitis (57, 58).

In addition to genes along the IL-23 signaling pathway, there are two CD-associated genes that play a role in the Th17 cell subset, namely CCR6 and TNFSF15. CCR6 is expressed by immature dendritic cells and memory T cells; it is important for B cell differentiation and tissue-specific migration of dendritic and T cells during epithelial inflammatory and immunological responses (59). It has been shown that CCR6 and IL23R are selectively expressed by IL-17-producing cells (6, 33, 60–62). TNFSF15 is of particular interest because in a Japanese GWA study (63) it represented the most significant association, and therefore it is the most well-established example thus far of an association in CD that includes both European-ancestry (64, 65) and Asian populations (63). TNFSF15 has been shown to enhance IL-17-producing cell differentiation (66), although multiple studies have shown effects in Th1 and Th2 populations as well (8, 67–69).

The hypothesis that CD and UC have underlying genes in common has been confirmed with the demonstration of significant UC associations for multiple loci initially implicated in CD GWA studies. Of particular significance are UC associations to IL23R (10), IL12B (70, 71), and STAT3 (71), which suggest that alterations in the IL-23 pathway represent common pathogenic mechanisms between CD and UC. Further, the hypothesis that IBD and other autoimmune diseases share genes in common is also demonstrated now with associations in the IL-23 pathway.

**COMPLEX ROLE FOR IL-23 IN INTESTINAL IMMUNE HOMEOSTASIS**

Under physiological conditions, IL-23 is constitutively expressed in ileal mucosa, and IL-17-producing cells are highly enriched in intestinal tissues (72–74). The enriched Th17 cell population in the intestine may be due to a number of factors, including the resident intestinal bacteria (72). The dynamic balance and coregulation between the IL-23/Th17 pathway and Tregs is continuously in play in the intestinal environment. Intestinal Tregs increase in the absence of IL-23, indicating a role for IL-23 in their downregulation (75). Factors enriched in the intestinal environment influence this balance. For example, retinoic acid can inhibit the IL-6-driven induction of Th17 cells and promote anti-inflammatory Treg differentiation (76–79). Consistent with its high level of expression in intestinal tissues, the IL-23/IL-17 pathway is critical in mediating necessary bacterial defenses.

New insights concerning the ability of specific bacterial components or antigens to induce IL-23 relative to Th1- or Th2-related cytokines may shed light on the question of specificity. For example, IL-23 is induced in human dendritic cells stimulated with ligands for NOD2 and TLR2 (mimicking Gram-positive bacteria
and Mycobacteria tuberculosis) (80–82). IL23R is expressed on various cell populations; in addition to activated and memory T cells, IL23R expression on hematopoietic cells includes NK cells, NK T cells, eosinophils, dendritic cells, and macrophages (40, 48, 49, 83). These cell subsets are present within the intestinal lamina propria and contribute to ongoing maintenance of intestinal immune homeostasis. Furthermore, IL23R is expressed on epithelial cell populations, such as keratinocytes, where it can contribute to induction of antimicrobial peptide production (84). These antimicrobial peptides may well contribute to IL-23-mediated functions in the bacteria-dense environment of the intestine.

Murine models of colitis have demonstrated a key role for the IL-23 pathway in mediating intestinal inflammation, either through deficiency or blockade of IL-23 (1–3, 75, 85, 86). Various cell populations, including monocyte-derived cells, contribute to the increase in IL-23 production during intestinal inflammation (87, 88). Furthermore, transgenic expression of IL-23 results in severe systemic inflammation, including in the small and large intestine (89). Along similar lines, bacterial-reactive CD4+ Th17 cells are potent effector cells in chronic colitis (1), as shown by their ability to transfer colitis to lymphopenic hosts. However, the intestinal tissue injury mediated by IL-23 can also be observed in the absence of IL-17, and furthermore, in the absence of T cells (75, 86). Finally, in addition to the proinflammatory cytokines secreted by Th17 lineage cells, cytokines that can contribute to inflammation downregulation are also secreted (e.g., IL-10 and IL-22), likely contributing to proper regulation of immune responses. For example, IL-22 can downregulate both liver (91) and intestinal (90) inflammation, and can contribute to restitution of mucus-producing goblet cells (90). Therefore, IL23/Th17 pathway cytokines can act in defenses against microbes at mucosal surfaces while simultaneously providing mechanisms for regulation of inflammation and epithelial restitution.

**DISEASE ACTIVITY AND INTESTINAL INFLAMMATION INDICES**

Understanding of the central role of the IL-23 pathway in IBD pathogenesis provides a new framework through which commonly utilized disease activity indices, such as levels of serum C-reactive protein (CRP), can be interpreted. In addition, potential new biomarkers can be evaluated on the basis of an improved understanding of disease mechanisms. The recognition that IBD represents a cascading series of inflammatory events provides a basis for utilizing serum acute-phase proteins to decide whether to “step up,” or increase potency of therapy. For example, CRP levels are utilized in clinical practice (92) and therapeutic trials to determine the efficacy of stepping up to anti-TNF therapies. CRP is a marker of systemic inflammation produced by hepatocytes after stimulation by the cytokine IL-6. Serum CRP levels tend to correlate with active CD but do not correlate as well with UC. It is possible that mesenteric adipose hypertrophy, described in CD but not UC, results in increased adipocyte production of IL-6, which is released into the portal circulation and stimulates hepatic CRP production. The importance of IL-6 in mediating both Th17 differentiation and systemic release of CRP may account, at least in part, for the clinical utility of serum CRP levels in reflecting intestinal disease activity and inflammation.

Measurements of serum cytokines may also reflect intestinal disease activity. Of particular interest here is a recent report utilizing a protein microarray. Increased p40 and TGFβ were two of the most predictive cytokines for CD in remission, and increased p40 (IL-12B) was the only single predictive cytokine for UC in remission (93). The finding of increased serum TGFβ in CD in remission is logical, given the central role of TGFβ in Treg-Th17 differentiation, with increased TGFβ concentrations favoring suppressive Treg differentiation (33). The finding of increased p40 (IL-12B) in IBD in remission is interesting as this cytokine subunit is common to both the functional IL-12
and IL-23 cytokines, which might suggest a role in active disease, as opposed to disease in remission. However, p40 subunits can combine to form homodimers (p80) that inhibit both IL-12 and IL-23 activity (94); it is speculated that increased serum p40, common to CD and UC in remission, may reflect the effects and expression of this inhibitory homodimer. Finally, increased serum IL-22 has been observed in CD, with significantly more modest serum elevations observed in UC. The application of improved biomarkers in IBD may benefit clinical practice and complement therapeutic trials.

While serum-based biomarkers hold the potential of broader clinical applications, monitoring of intestine-based expression levels of key inflammatory mediators provides an important, direct understanding of inflammatory mechanisms and responses to therapy. In human IBD, elevated expression of STAT3, phospho-STAT3, IL-17, IL-21, IL-22, and IL-23 is observed in colonic mucosa and lamina propria cells of CD and/or UC patients (4–9, 44–46). Lamina propria Th17 cells isolated from CD patients have been phenotypically characterized, demonstrating expression of IL23R, CCR6, and retinoic acid-related orphan receptor gamma tau (RORγτ), with some Th17 cells also expressing IFNγ (6). Furthermore, a unique macrophage subset in the human intestine that expresses IL-23, TNFα, and IL-6 is expanded in number and cytokine production in patients with CD (95). On the other hand, treatment of IBD patients leads to downregulation of these implicated inflammatory mediators. Anti-TNF treatment has been reported to result in downregulation of STAT3 phosphorylation in lamina propria mononuclear cells (51). Elevated IL-17 and IL-23 expression decreases after therapy of disease (e.g., steroids, anti-p40) (5, 96). While the IL23R genetic association studies in IBD strongly implicate Th17 cells in autoimmunity, Th1 cytokines are detected in inflamed tissues as well, and Th1 cells can readily transfer organ-specific autoimmunity (32), demonstrating that excessive or inappropriate CD4+ effector function generally can mediate end-organ inflammation such as in IBD.

**THERAPEUTIC IMPLICATIONS**

Given the key role of the IL-23 pathway in mediating intestinal inflammation, it is logical to consider blocking this pathway as a means of treating IBD. Administration of anti-p40, which blocks both IL-23 and IL-12 activities, has proved promising (97), with further studies ongoing. Because both these pathways are critical in mediating antimicrobial defenses and cross-regulating other cell subsets, risks of infectious complications and regulation of other immune cell subsets will need to be considered. Specific blockade of the IL-23 pathway through use of a monoclonal antibody against p19 was effective in both the prevention and treatment of a murine model of CD4+ T cell–mediated colitis (1). It remains to be determined if specific blockade of the IL-23 pathway will be safe and effective in humans. The identification of more subtle genetic contributions throughout the IL-23 pathway (IL-12B/p40, STAT3, JAK2, and PTPN2) (22) highlights the enormous complexity that contributes to interindividual differences in IL-23 functional responses. Although the contribution of IL-17 in intestinal inflammation is not fully defined, AIN457, a monoclonal anti-IL-17, is currently being evaluated for safety, tolerability, and efficacy in CD (98). Finally, while the application of potent monoclonal antibodies against key inflammatory mediators has revolutionized the treatment of IBD, it is interesting to note that simvastatin, a commonly utilized cholesterol-lowering agent that inhibits 3-hydroxy-3-methylglutaryl-CoA reductase, directly inhibits RORγτ expression (99). Given the relative safety and ubiquitous use of statins, it is important to better understand the effect of this class of medications on Th17-mediated aspects of inflammatory processes.

IBD is a complex genetic disorder that probably entails multiple different perturbations in the intestinal immune system leading to a manifestation of intestinal inflammation. Therefore, as we develop an understanding of the genetic, immune, and environmental mechanisms
leading to IBD in a given individual, we should be able to better target the specific inflammatory pathway mediating disease in that individual.

**SUMMARY POINTS**

1. The central challenge of the intestinal immune system is balancing defense with tolerance: responding to pathogens while coexisting with resident bacteria and food antigens (27). Dysregulation in either direction can result in intestinal inflammation.

2. IL-23/Th17 pathway genetic associations have been identified in both CD and UC, as well as other autoimmune disorders manifesting in tissue inflammation. These discoveries emphasize the importance of proper regulation of this immune pathway.

3. There is a dynamic cross-regulation between Th1, Th2, Th17, and Treg pathways. The proper balance of this cross-regulation is critical for optimizing defenses to microbes while simultaneously avoiding chronic tissue inflammation.

**FUTURE ISSUES**

1. Determine how the identified IL23R polymorphisms protect against IBD.

2. Determine the interactions and specificity between Th1 and Th17 pathways in mediating defenses against bacteria.

3. Determine if specific proteins in the IL-23 pathway can be used as biomarkers to aid in diagnosis, measurement of disease activity, and phenotypic classification of IBD.

4. Determine if therapeutic interventions targeting specifically the IL-23 and/or IL-17 pathway are useful in particular stages or phenotypes of IBD.

**DISCLOSURE STATEMENT**

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

**LITERATURE CITED**


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