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Th17 cells: interactions with predisposing factors in the immunopathogenesis of inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD) is a chronic inflammatory state of the GI tract of unknown etiology. Classically, tissue injury in IBD is thought to be primarily mediated by Th1 cells in Crohn's disease or Th2 cells in ulcerative colitis. The discoveries of new subsets of T-helper cells, especially Th17 cells, have revolutionized our understanding of the disease immunopathology. Th17 cells seem to affect both innate and adaptive immune responses by the release of regulatory cytokines. Understanding the role of Th17 cells in IBD pathogenesis and targeting their regulatory cytokines may provide potential therapeutic approaches for the treatment of IBD in the future.

Keywords

Crohn's disease; inflammatory bowel disease; interleukin-17; Th17; UC; CD; T-helper cells; ulcerative colitis

Th17 cells: new players in inflammatory bowel disease immunopathogenesis

Inflammatory bowel disease (IBD) is an inflammatory condition of GI tract that is chronic, remitting and relapsing and also progressive in its course. IBD includes two major clinical entities, ulcerative colitis (UC) and Crohn's disease (CD). The specific etiology of IBD is unknown. However, the pathogenesis and clinical course of IBD is affected by many factors, broadly categorized as genetic susceptibility of the patient, intestinal flora, various lifestyle issues and the patient's immune system [1].

The immune system is the principal mediator in IBD pathogenesis and its clinical picture. Genetic mutations causing aberrant immune responses towards environmental factors (most

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importantly towards gut bacterial flora) are largely believed to be responsible for IBD pathogenesis. Nevertheless, different environmental factors can cause an increase in the incidence of IBD by altering the immune responses in different ways that are not fully understood [2,3].

The immune system can be divided into innate and adaptive immunity. The main cellular components of innate immunity are macrophages, neutrophils, natural killer cells and epithelial cells, while adaptive immunity primarily consists of B lymphocytes (responsible for humoral immunity) and T lymphocytes (responsible for cell-mediated immunity). T lymphocytes are further subdivided into $CD4^+$ (T helper [Th]) cells and $CD8^+$ (cytotoxic T) cells. Complex immunological interactions occur between innate and adaptive immune systems, which may play a critical role in the pathogenesis of IBD, as shown in animal studies [4,5]. This interaction is tightly regulated. Rapid progress in the field of immunology has led to the discovery of many new Th cell subsets. These newly discovered cell lineages play an important role in immune regulation, mainly by cytokine production. One of these Th subsets, Th17 cells, has gained particular attention due to its proinflammatory role in mucosal immune responses and their involvement in autoimmune disorders. In this review, we will discuss different functions of the newly discovered Th17 cell, its relationship with other Th subsets and its potential role in the pathogenesis of IBD.

Th17 discovery

Traditionally, Th cells ($CD4^+$ cells) are divided into two subsets; Th1 and Th2 cells based on initial bioassays, protein expression studies and the cytokines production. Apart from immune response regulation, they were linked to different immune-mediated diseases like autoimmunity and allergy; Th1 responses were seen to be mediating autoimmunity [6] and Th2 cells appeared to be involved in allergy and asthma [7]. To understand the sequence of events leading to Th17 discovery, we will briefly review the development of T-cell subsets. Th cell development begins in the thymus while the functional differentiation of Th cells start when the cell comes in contact with activated antigen-presenting cells (APCs), such as dendritic cells (DCs) in the mucosa. APCs, as well as other immune cells, produce either IL-12 and drive the naive $CD4^+$ cells to become IFN-γ-producing Th1 cells, or IL-4 to induce Th2 cells producing IL-4, IL-5 and IL-13. The Th1 and Th2 axis was very useful for the explanation of autoimmunity and allergy; however, the role of Th1 as the sole driver of autoimmunity was questioned when injections of IFN-γ or IL-12, the driving force for Th1 development, prevented the development of autoimmune disease in animal studies [8,9]. This contradicts the link of Th1 with autoimmunity, hence suggesting the possibility of other pathways involved in its pathogenesis.

Almost a decade ago, a new member of the IL-12 family, IL-23, was described. Soon after, its role in the development of autoimmune diseases was established. In 2003, animal studies showed mice lacking IL-23 were resistant to autoimmune disease; however, mice lacking IL-12 but expressing intact IL-23 suffered from a severe form of autoimmune disease [10]. These surprising results supported the idea that IL-23 may be acting independently of IL-12 on a different population of lymphocytes to mediate autoimmunity. It was also seen that IL-23 stimulates the production of IL-17, a proinflammatory cytokine, from a subpopulation of T cells, designated as Th17 cells, based on their characteristics and specific cytokine production [11].

Multiple studies in humans have described the role of Th17 cells, IL-17 and IL-23 in the pathogenesis of several autoimmune diseases. Their results were comparable to the data in animal models [12–15].

Other recently discovered Th cells include follicular T helper cells, natural regulatory T cells, induced regulatory T cells, Th9 and $CD4^+CD28^{null}$ T cells [16,17]. Immune regulation was first presented by Mosmann *et al.* [18]; however, with new Th cells (especially Th17 cells) playing a central role in immunopathogenesis, our understanding of immune regulation has changed significantly.

Th17 development

Upon contact with APCs, naive $CD4^+$ cells have the potential to differentiate into Th1, Th2, induced regulatory T cell and Th17 cells. APCs control this differentiation through their effector cytokines. These cytokines transmit their signals by binding with the Jak–STAT pathway. When a cytokine binds to its receptor, it activates transcription factors belonging to the STAT family (seven members), which determines the fate of the cells by regulating gene expression [19].

STAT-3 has been shown to regulate various genes involved in the development of Th17 cells in both humans and mice. These transcription factors not only regulate the genes producing Th17 cytokines (IL-17, IL-21) and IL-23 receptors, but also three other transcription factors that are necessary for Th17 differentiation, namely RoRγt, IRF4 and Batf [20].

Retinoid receptors are an important group of nuclear transcription factors. Whereas RoRγ is universally expressed, a transcript denoted RoRγt, is solely expressed in lymphoid cells, and is critical for T-cell development. Two members of retinoic acid orphan receptors (RoRγt and RoRα) are preferentially expressed in Th17 cells and are critical for their differentiation and development; their deletion results in a complete absence of Th17 cells [20]. Similarly, Th1 cell development is promoted by STAT-4 and transcription factor T-bet, Th2 cells require STAT-6 and transcription factor Gata-3, and Treg cells need STAT-5 and transcription factor FoxP3 [19].

Characterization of Th17 cells

Th17 cell development is controlled by different cytokines and in turn, after stimulation, they secrete their own cytokines that control the functions of other cells during the immune response. In the following section, we describe the mechanisms of stimulation of Th17 cells and the effects of different cytokines secreted by these cells on different tissues.

Stimulation of Th17 cells

Several cytokines have been shown to stimulate Th17 cell development and function, notably TGF-β, IL-6, IL-23, IL-21 and IL-1β [21].

The initial phase of Th17 cell development is mainly regulated by IL-6 and TGF-β. IL-6 is produced by many APCs and T cells. It activates the STAT-3 pathway as described above and leads to increased expression of Th17 cytokines, IL-23 receptors and RoRγt. Additionally, TGF-β upregulates the transcription factors FoxP3 and RoRγt, leading to the development of Treg or Th17 cells from $CD4^+$ cells. It is believed that IL-6 signaling is important in blocking FoxP3-mediated suppression of RORγt, which ultimately results in the formation of Th17 cells instead of Treg cells [21]. IL-1β, produced by various cells, is also an important stimulant of Th17 cells in the presence of IL-6 and TGF-β [22]. IL-21, a member of the IL-2 cytokine family produced by Th17 cells, stimulates further development of Th17 cells in the presence of TGF-β. It engages with its receptor and increases the transcription factor IRF4, which promotes cell development. This pathway seems to work independently of the IL-6/TGF-β pathway [23]. In humans IL-1 as well as IL-23, mainly

produced by DCs, help in the development and expansion of Th17 cells by engaging with the STAT-3 pathway [22,24].

Cytokines secreted by Th17 cells

Th17 cells are characterized by the secretion of important effector cytokines such as IL-17A (also known as IL-17), IL-17F, IL-22 IL-21, and IFN-γ.

IL-17A and IL-17F are structurally very similar, being proinflammatory in nature; these cytokines play important roles in combating infections and mediating autoimmunity [25,26]. Both cytokines activate the cellular components of innate immunity (epithelial cells, fibroblasts, keratinocytes and endothelial cells) to carry out their functions. Suboptimal production of these cytokines, due to defects in Th17 cells, can lead to increased bacterial infections in humans. Also, blocking IL-17A improved many autoimmune diseases such as rheumatoid arthritis, psoriasis and uveitis, suggesting its role in autoimmunity [25]. IL-22, a member of the IL-10 family, is mainly produced by Th subsets including Th17 and Th1 cells [27]. Unlike other Th17 cytokines, IL-22 does not mediate immune regulation by interacting with other B and T cells; instead it mainly affects the cells in barrier surfaces of the body such as epithelia of the respiratory and gastrointestinal system, and skin. This cytokine appears to enhance the protective ability of the barrier at these sites by enhancing innate immune response [28]. IL-21, a member of the IL-2 family, is mainly produced by Th and NK cells [29], and acts on various other cellular components of innate and adaptive immunity [30–32]. It not only promotes the development of B cells into plasma cells [33] but also expands cytotoxic T cells [34], NK cells and helps in Th17 development [35]. It also has inhibitory effects on some APCs such as DC [36].

Briefly, IL-21 has multiple functions and its target cells include members from both innate and adaptive arms.

Role of Th17 cells in regulation of the immune responses

Two intriguing features of Th17 cells further elaborate their importance in immune regulation, which are their relationship with Treg cells and their plasticity. Treg cells are known for their immunosuppressive function, preventing excessive damage during infection and harmful reactions against self-antigens. Th17 and Treg cells seem to negatively impact each other's development. Th17 cells can inhibit Treg expansion by producing IL-21; similarly IL-10 produced by Treg cells suppresses Th17 cell development [1]. A fine balance between these immunosuppressive Treg cells and pro-inflammatory Th17 cells is essential for appropriate immune responses that do not cause self-damage and are also able to prevent damage from harmful pathogens.

Recent reports showed that Th17 cells are not one of the most stable cells and under various influences can undergo transformation into other Th subsets [37,38]. This ability to convert and then produce different Th cytokines is called plasticity. Plasticity is an important feature of Th17 cells that seems to help maintain homeostasis and balance in immune responses [16].

The interaction between Th17 and Th1 pathways in IBD is still controversial [39]. In a recent data report from our laboratory [Ali Raza A, Shata MT, Ahmed K *et al*. The numbers of IFN-γ secreting T cells in peripheral blood stimulated by anti-CD3 or lipopolysaccharide in inflammatory bowel disease patients significantly correlated with disease severity in Crohn's disease but not in ulcerative colitis (2011), Submitted] as well as other laboratories [40], the increase in IL-17 production was only significantly enhanced in UC, while IFN-γ production was enhanced in CD. This might indicate that IFN-γ may mediate Th1

inflammation in CD and Th17-mediated disease in UC, or that the capacity for producing IL-17 by Th17 may be disturbed by the enhanced Th1 cytokines in the CD intestinal mucosa [40].

Role of Th17 cells in the gut mucosal immune barrier

Th17 cells play an important role in the gut mucosal barrier by affecting the innate and adaptive responses [41]. Mucosal Th17 cells regulate the integrity of the physical barrier by epithelial cells, through chemotaxis of neutrophils and macrophages to prevent against invading pathogens. Its effector cytokines further stimulate the tight junction formation in the mucosal epithelial cells, thus providing resistance to bacterial translocation across gastrointestinal mucosa into the bloodstream [41,42]. Evidence of this important barrier function can be observed in HIV-positive patients who lack Th17 cells and have increased risk of bacteremia from intestinal translocation [41]. Th17 cells also affect the cellular components of the immune system by recruiting neutrophils to the site of inflammation, stimulating antimicrobial peptide production from epithelial cells, increasing matrix metalloproteinase production from fibroblasts, enhancing immunoglobulin production from B cells and regulating different T cells. Thus, Th17 cells contribute to the mucosal barrier by several mechanisms that help the host against invading pathogens.

Pathogenesis of IBD

IBD may affect the entire GI tract as in CD or colonic mucosa as in UC. Various genetic factors, gut flora and lifestyle factors play a dynamic role with the host immune system in the pathogenesis of IBD. Briefly, the development and course of IBD can be divided into four categories:

- Immune system
- Intestinal flora
- Genetic susceptibility
- Dietary and lifestyle factors

Immune system

Traditionally, CD has been linked with Th1 cells [43], and UC has been linked with Th2 cells [44], based on the cytokine environment and transcription factors found in their respective mucosa. However, several studies have recently shown that the inflamed gastrointestinal mucosa of patients with IBD has a massive infiltration of Th17 cells [45,46].

Th17 cells are mainly found in the mucosa of the GI tract, especially in the small intestine. This homing of Th17 cells could be affected indirectly by intestinal flora in the large intestine by priming the immune system, and stimulates the development and migration of Th17 to the small intestine [47,48]. Their location together with their plasticity and regulatory effects on other immune cells suggest its importance in mediating GI inflammation. A recent report showed that levels of IL-17 and Th17 were higher in patients with UC and CD compared with normal subjects and patients with ischemic colitis, and these Th17 cells were found abundantly in the mucosa and submucosa of UC and CD, respectively [45].

Recent data from our laboratory suggested a correlation between disease severity and levels of IL-17 secreted by PBMCs from UC patients but not from CD patients, suggesting a differential role of Th17 in these two categories of IBD diseases [49]. Various studies have shown increased production of Th17 cytokines (IL-21 and IL-22), which exacerbates

inflammation in IBD by promoting Th1 responses [50,51]. IL-23, also increased in IBD, promotes Th17 and Th1 responses, resulting in inflammation of the GI tract [51,52]. Based on the above observations, it is obvious that Th17 cells play an important role in IBD pathogenesis, which was solely attributed to Th1 and Th2 cells in the past.

Treg cells represent another type of Th cells that have an immunosuppressive function. Treg cells produce important anti-inflammatory cytokines such as IL-10 and TGF-β. Blocking the Treg cytokine, IL-10, led to the development of spontaneous GI tract inflammation in mice [53], possibly due to the inhibition of its suppressive effects on Th17 cells. Therefore, a fine balance needs to be maintained between Th17 and Treg cells in order to avoid excessive inflammation.

Intestinal flora

Humans are colonized by both beneficial and potentially pathogenic microorganisms. The human GI tract harbors more than 10^{14} microbes belonging to more than 1000 species. Most of these bacteria are found in the colon. Imbalances in the composition of the bacterial microbiota may be one of the factors in human disorders such as IBD. *Bacteroidetes* (Gram negative) and *Firmicutes* (Gram positive) make up the majority of the gut flora. This gut flora affects the development, composition and function of innate and adaptive immune responses [1]. In an animal model, it has been shown that *Bacteroides fragilis* protects from experimental colitis induced by a commensal bacterium with pathogenic potential. There is strong evidence that molecules of the bacterial microbiota can mediate the critical balance between health and disease [54].

The concept of intestinal bacteria as the initiator of immune response comes from observations in animal studies showing that mice in a germ-free state did not develop GI inflammation [55], and the T cells that were reactive against the intestinal flora caused colitis [56]. These microorganisms can also control the responses of Th17 and Treg cells, as shown by various studies [48,54,57,58] directly affecting the immune response [59,60].

Genetic susceptibility

Multiple genes have been linked to IBD pathogenesis. Recent advancements in genetic studies have led to the discovery of more genetic loci for IBD. Thus, approximately 60 genetic loci have been associated with IBD, roughly a third have been associated with UC, another third with CD, and the rest are common with both UC and CD [61]. These genetic studies also elaborate the recent discovery of the IL-23 and Th17 cell pathway. Among many genetic loci, important genes linking Th17 cells to IBD are the IL-23 receptor gene (associated with both UC and CD), IL-10 gene (associated with UC) and IL-17 receptor E-like (*IL-17REL*) gene (associated with UC) [24]. Other important genetic loci, not directly related to Th17, include NOD2 and TLR4 genes, which are associated with CD and influenced by IL-23 expression [1].

Dietary & lifestyle factors

The incidence of IBD has increased in recent years, in parallel with the changes in the surrounding environment. Major changes in diet, physical activity, obesity and increased smoking habits have been linked to increased incidence of IBD [62,63]. In a recent review, high dietary intakes of specific groups of food, including polyunsaturated fatty acids, ω-6 fatty acids and meat were found to increase the incidence of IBD. Conversely, people with a high fiber and fruit diet were associated with decreased risk of IBD [64]. Obesity seems to adversely affect the clinical course of UC [65], while its effect on CD has variable results

[63]. Interestingly, a recent animal study showed that obesity favors the development of Th17 cells, subsequently leading to severe colitis [62].

Expert commentary & five-year view

IBD is a chronic, debilitating illness with significant morbidity. Various environmental and genetic factors affect the initiation and progression of the disease. All these factors affect the immune system in one way or another, causing dysregulated immune response and tissue injury. The immune system being the main mediator of the extent and the type of tissue injury provides the basis for the future therapeutic interventions. Recent advances in the field of immunology have revolutionized our understanding of immune damage in IBD. New cellular components of the immune system have been discovered and described in the past decade. Through animal models, we gathered important information about these newly discovered cellular components of the immune system. Given some minor differences between the immunopathology of humans and animal models, more research aimed towards better characterization of these cellular components in human tissue is required. IBD has a complex pathophysiology and may represent more than one disease with different immunopathological mechanisms. With rapid progress in the immunology and genetic fields, our understanding of the mechanisms underlying the development of IBD has dramatically changed during the last decade. Gut microbiota, genetic associations and immune dysregulation are the focus of interest in IBD pathogenesis. Genome-wide association studies have helped us identify various high-risk groups in the population. Similarly, many ongoing studies are looking at the association between the gut microbiota and IBD pathogenesis. Finally, how to shift the immune balance towards tolerance from autoimmunity will be the cornerstone for IBD therapeutic interventions in the future. Th17 and Tregs, among other newly discovered T cells, hold much promise to understand the intricate balance between self-tolerance and autoimmunity. Th17 cells also hold a key position in IBD immunopathogenesis due to the location of the disease in the gastrointestinal mucosa and plasticity. In the next 5 years, targeted research on the development, characterization and behavior of the mucosal Th17 cells and their relationship with immunosuppressant cells will provide key information about the pathways responsible for IBD pathogenesis, which can serve as potential targets of future therapeutics. Blocking the secretion of Th17 cytokines have already shown promising results in alleviating various autoimmune diseases in humans. The same concept will be tested in the near future for IBD management, which could result in the development of very effective biological agents, which can work in resistant cases of IBD. Other immunomodulatory agents have been tested in IBD patients, including anti-IL-23R antibodies, as well anti-TNF-α antibodies that have shown promising results. It is expected that revolutionized lines of treatment in IBD patients will be developed within the next few years, building on our recent understanding of the immunopathology of IBD patients and the characteristic features of UC and CD.

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Key issues

- Inflammatory bowel disease (IBD) is a result of increased immune activation, which may lead to mucosal damage.
- Genome-wide association studies have revealed various mutations in the immune system that increase the risk of IBD development.
- IBD was thought to be a result of impaired functions of T-helper 1 (Th1) and T-helper 2 (Th2) cells, but recent advances have revealed important roles for T-helper 17 (Th17) and Treg cells.
- Various environmental factors may increase the activity of Th17 cells and may lead to mucosal damage and IBD development.
- Focused translational studies are required to define specific roles of newly discovered T-helper cells in IBD pathogenesis.

Learning objectives

Upon completion of this activity, participants should be able to:

- Describe the role of Th17 cells in regulating immune responses and in the gut mucosal immune barrier
- Describe factors involved in the pathogenesis of IBD
- Describe the regulatory cytokines of Th17 cells that could potentially offer future strategies to treat IBD