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Distinct roles of interleukin-17 and T helper 17 cells among autoimmune diseases

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ABSTRACT

Background: Interleukin (IL)-17 and T helper 17 (T_H17) cells, a distinct subset of $CD4^+$ T cells which promotes the expression of IL-17, mediate host defensive mechanisms to various infections and are involved in the pathogenesis of autoimmune diseases including inflammatory bowel disease (IBD), psoriasis, and rheumatic diseases. IL-17 inhibitors have shown to be effective in psoriasis, but failed to demonstrate response in IBD. Further, clinical trials of IL-17 inhibitors reported some cases of new onset IBD. We aim to discuss the roles of IL-17 and T_H17 cells among autoimmune diseases and the possible immunological mechanisms of new onset IBD in patients undergoing IL-17 inhibitors.

Methods: A non-systematic literature review using PubMed/Medline.

Results: IL-17 inhibitors, which either target IL-17 A (secukinumab and ixekizumab) or the IL-17 receptor (brodalumab), have demonstrated clinical benefits in plaque psoriasis, psoriatic arthritis, or axial spondyloarthritis. However, secukinumab and brodalumab have shown no clinical benefit in Crohn's disease and led to frequent serious adverse events including worsening of Crohn's disease. Further, some cases of new onset IBD were reported in clinical trials of IL-17 inhibitors. Consistently, an animal model of colitis has demonstrated that IL-17 can directly inhibit the development of T helper 1 (T_H1) cells and T_H1 cells can induce aggressive colitis in the absence of IL-17 signaling.

Conclusions: IL-17 and T_H17 cells might have protective rather than pro-inflammatory roles in the intestine. IL-17 inhibition may induce inflammation in the intestine by favoring T_H1 pathways, which explain the lack of response to IL-17 inhibitors in IBD.

1. Introduction

The interleukin (IL)-17 family is composed of six molecules with IL-17A (generally called as IL-17) and IL-17F being the main family members [1]. T helper 17 (T_H17) cells are identified as a distinct subset of $CD4^+$ T cells which promote the expression of IL-17A, IL-17F, and IL-22 [2–4]. These effector cytokines mediate host defensive mechanisms to various infections including bacteria and fungi [5], and are involved in the pathogenesis of several autoimmune diseases [6]. In mouse models of experimental autoimmune encephalitis, IL-23 was shown to be required for the differentiation of T_H17 cells *in vivo* [7,8]. In addition, transforming growth factor-β and IL-6 are also important cytokines to induce retinoid-related orphan receptor (ROR)-γτ (RORC in human), which is a master regulator of T_H17 cells in mice [9,10]. While natural killer cells, mast cells, innate lymphoid cells, and neutrophils are other cellular sources of IL-17, the respective contribution of IL-17 produced by such different cell types to the disease pathogenesis is still unclear [2].

Several experimental animal models [11–13] demonstrated that IL-17 and T_H17 cells play important roles in the pathologies of inflammatory bowel disease (IBD), psoriasis, and rheumatic diseases, suggesting that IL-17 can be a potential therapeutic target [2]. Indeed, monoclonal antibodies targeting IL-17A (secukinumab and ixekizumab) or an antibody against the IL-17 receptor (brodalumab) have demonstrated clinical benefits and been approved for patients with plaque psoriasis [14–16], psoriatic arthritis [17–22], or axial spondyloarthritis [23,24]. However, randomized, double-blind, placebo-controlled trials (RCTs) of secukinumab or brodalumab in patients with Crohn's disease (CD) have been terminated due to lack of clinical benefit and frequent serious adverse events including worsening of CD in the treatment group

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[25,26]. Further, clinical trials of IL-17 inhibitors in patients with autoimmune diseases other than IBD reported some cases of new onset IBD [27].

In this review, we discuss the roles of IL-17 and T_H17 cells in animal IBD models and patients with IBD and other autoimmune inflammatory conditions, and the possible immunological mechanisms of new onset IBD in patients undergoing IL-17 inhibitors.

2. The role of IL-17/T_H17 cells in IBD

In the pathogenesis of IBD, CD is primarily mediated by T_H1 cells and ulcerative colitis (UC) by T_H2 cells [27]. T_H17 cells and their cytokines are crucial mediators in both conditions [27,28]. Although increased levels of IL-23, T_H17 cells, and IL-17 were found in intestinal mucosa, plasma, and serum of patients with IBD, both CD and UC [29], either protective or pro-inflammatory roles of IL-17 or T_H17 cells have been shown in animal models of IBD.

2.1. Animal colitis models showing protective functions of IL-17/T_H17 cells in IBD

In a dextran sulfate sodium colitis model, an experimental mouse model of UC [30], blocking of IL-17 activity using anti-IL-17 antibody enhanced the expression of *tumor necrosis factor* (*TNF*)-*α*, *interferon* (*IFN*)-*γ* and *IL-6*, and the infiltration of T cells ($CD3^+$ cells, particularly $CD4^+$ T_H cells) and granulocytes-monocytes in the intestinal mucosa, resulting in the progression of severe colitis [31]. They also found that recombinant IL-17 attenuated the effect of anti-IL-17 antibody [31].

In another study assessing the function of IL-17A in a T-cell transfer model of colitis, they transferred $CD45RB^{high}CD25^-CD4^+$ T cells from *IL-17A*-knockout (KO) mice or wild type mice into *Rag*-KO recipients and demonstrated that *IL-17A*-deficient $CD45RB^{high}$ T cells induced an aggressive wasting colitis with a higher expression of genes encoding T_H1-type cytokines in the colon. They also found that *IL-17 receptor*-KO $CD45RB^{high}$ donor T cells elicited an accelerated wasting disease in *Rag*-KO recipients [32], suggesting a protective role for IL-17A in the T-cell transfer colitis model. It has been also postulated that IL-17A can directly inhibit developing T_H1 cells by suppressing the expression of key T_H1-effector genes and T_H1 cells can induce aggressive colitis in the absence of IL-17 signaling (Fig. 1) [33].

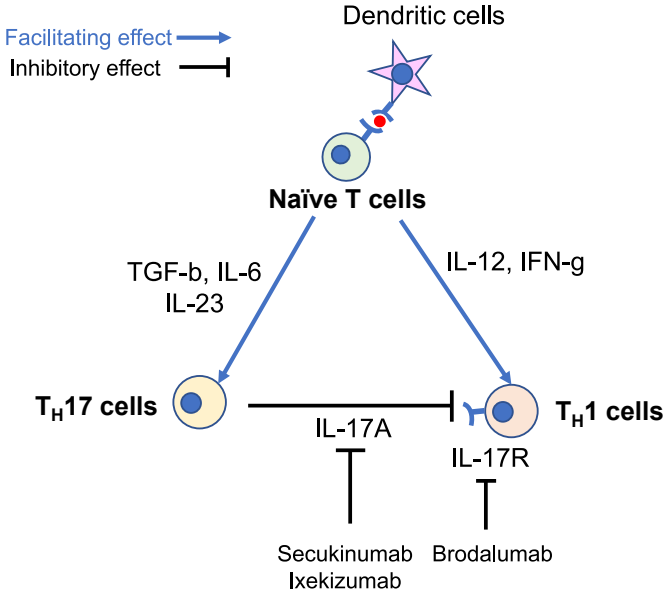

Fig. 1. The possible immunological mechanism to explain how interleukin-17 inhibitors can induce new onset inflammatory bowel disease. IFN, interferon; IL, interleukin; IL-17R, interleukin-17 receptor; TGF, transforming growth factor; T_H17 cells, T helper 17 cells; T_H1 cells, T helper 1 cells.

2.2. Animal colitis models showing pro-inflammatory functions of IL-17/T_H17 cells in IBD

In a colitis model in which $CD25^-CD4^+$ T cells were transferred to immunodeficient SCID mice, the development of colitis was associated with an increase in IL-17A-producing T_H17 cells in the spleen, mesenteric lymph nodes, and lamina propria [34]. On the other hand, the expression of IL-17F declined in the T_H17 cells in the spleen and mesenteric lymph nodes, suggesting that IL-17F was inversely corelated with the activity of colitis in this model [34]. This study also found that simultaneous neutralization of IL-17A and IL-17F ameliorated colitis, whereas neutralization of IL-17A or IL-17F alone was inefficient *in vivo*, suggesting overlapping and interdependent proinflammatory roles of these cytokines in colitis pathology [34].

IL-10-KO mice have been used as a spontaneous colitis model [35]. When *IL-10*-KO mice were backcrossed with *IL-23p19*-KO *mice*, the colon was histologically disease free at 12 months of age, whereas *IL-10*-KO mice or *IL-10*-KO mice backcrossed with *IL-12*-KO mice showed active colitis by 3 months of age [36]. Further, they also transferred naïve T cells ($CD45RB^{high}CD4^+$) or memory T cells ($CD45RB^{low}CD4^+$) from *IL-10*-KO mice to *Rag*-KO mice to induce colitis and assessed the effect of recombinant IL-23 on colitis. They found that recombinant IL-23 accelerated colitis. Furthermore, this study revealed that IL-23 promoted productions of IL-17 and IL-6 by memory activated T cells from *IL-10*-KO mice with colitis and the combination of anti-IL-17 and anti-IL-6 antibodies significantly improved the severity of colitis induced by IL-23 [36]. Consistently, a T-cell transfer colitis model in which a cecal bacterial antigen-specific C3H/HeJBir $CD4^+$ T-cell line was transferred to C3H/HeSnJ SCID mice demonstrated that bacterial-reactive $CD4^+$ T_H17 cells were potent effector cells in chronic colitis and anti-IL-23 antibody prevented colitis [37].

2.3. Animal models modulating gut microbiotas

T_H17 cells are prominent in mucosal surface of the intestine in cooperation with other T cells to maintain intestinal homeostasis and protect against microorganisms [27,38]. An antibiotic treatment mice model in which conventional C57BL/6j mice were subjected to broad-spectrum antibiotics for 8 weeks showed decreased production of cytokines such as IL-17, IL-22, IFN-γ, and IL-10. These profound changes in the immune cells were restored by fecal microbiota transplantation [39], suggesting that IL-17 inhibition might interfere with its gut protective function [27].

Germ-free mice colonized with different microbiotas have been used to investigate the relationship between host and microbiotas and to understand microbiota-specific pro- or anti-inflammatory effects. T_H17 cells and $FoxP3^+$ regulatory T (Treg) cells are most highly induced upon microbiota colonization [40,41]. A study demonstrated that the colonization of germ-free mice with a single commensal microbe, segmented filamentous bacterium, was sufficient to induce T_H17 cells [42]. Previous studies have also shown that human fecal microbiotas from donors with IBD can induce intestinal inflammation in susceptible mice [43,44]. Britton et al. showed that mice colonized with microbiota derived from patients with IBD exhibited abundant mucosal T_H17 cells and a deficit in Treg cells, and susceptibility to disease in colitis which was induced upon transfer of naïve T cells into *Rag*-KO mice [44,45]. Further, they demonstrated that transplantation of healthy donor-derived microbiota suppressed mucosal T_H17 cells and protected mice from intestinal inflammation in this model [44].

2.4. Clinical trials of IL-17 inhibitors in patients with IBD

RCTs (phase II) of secukinumab or brodalumab in patients with moderate to severe CD have been conducted [25,26]. In a clinical trial of

secukinumab, 59 patients with CD (39 secukinumab and 20 placebo) were included [25]. This study demonstrated that patients treated with secukinumab experienced significantly worse outcomes as compared to those treated with placebo. The reduction of mean Crohn's disease activity index (CDAI) was greater in the placebo group compared to secukinumab [25]. Safety data up to week 18 showed that more patients experienced any adverse event in the secukinumab group than in the placebo group: 74% vs 50%, respectively, particularly for infections. Twenty infections were seen in 44% of patients with secukinumab, including four local fungal infections in four patients, whereas none in the placebo group. Severe adverse events (SAEs) were reported in 28% of patients in the secukinumab and 10% in the placebo groups. Of the seven SAEs suspected to be drug-related events, five events were worsening of CD, four in secukinumab and one in placebo treated patients [25]. This study suggested that inhibition of IL-17A by secukinumab was ineffective for patients with CD and IL-17A may have a protective function in CD.

In terms of brodalumab, 130 patients with CD were randomized 1:1:1:1 to receive brodalumab (210, 350, or 700 mg at baseline and week 4) or placebo. At week 6, the rates of remission (CDAI $\leq$150) were 3% (210 mg), 15% (350 mg), 9% (700 mg), and 3% (placebo). However, there was no significant difference in the mean change from baseline in CDAI at week 6 between brodalumab and placebo groups. Notably, a higher rate of CD worsening was detected in the brodalumab group compared with the placebo group (25.0% vs 6.3%) [26]. This study did not demonstrate a meaningful efficacy of blocking of IL-17 receptor by brodalumab in patients with CD as well, leading to early termination of this study [26].

3. The role of IL-17/T_H17 cells in autoimmune inflammatory conditions other than IBD

3.1. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease, which can cause cartilage and bone damage [46]. IL-17 stimulates the production of IL-1 and TNF-α from human macrophages *in vitro* [47], resulting in IL-1-mediated IL-6 production by synoviocytes [48] and TNF-α-induced synthesis of IL-1, IL-6, and IL-8 in synovial fibroblasts [49]. Chronic inflammation via IL-17 is often associated with matrix destruction. IL-17 suppresses matrix synthesis by articular chondrocytes through enhancement of nitric oxide production [50], and also induces the production of matrix metalloproteinases from synoviocytes and chondrocytes [51,52], leading to cartilage destruction. Further, IL-17 is a potent stimulator of osteoclastogenesis as well [53]. IL-17 increases the expression of receptor activator of NF-κB ligand (RANKL) on osteoblasts and synoviocytes [54], which leads to increased RANK signaling in osteoclasts. IL-17 in combination with TNF-α also increased osteoclastic resorption *in vitro* [55]. These effects of IL-17 can cause bone damage in patients with RA. However, inhibition of IL-17 with secukinumab [56,57], ixekizumab [58], and brodalumab [59] have demonstrated only modest clinical benefits in patients with RA. As a result, these medications have not been approved for RA.

3.2. Psoriasis and psoriatic arthritis

Psoriasis is an inflammatory skin disease involving the skin and joints [60]. In the pathogenesis of psoriasis, complexes of host DNA and the epidermis-produced antimicrobial peptide LL-37 are thought to stimulate dermal plasmacytoid dendritic cells to produce IFN-α [61]. On the onset or exacerbation of psoriasis, activated dendritic cells produce TNF-α and IL-23 and amplifies inflammation through several inflammatory pathways including IL-23/T_H17 axis [60]. Skin biopsies taken from patients with psoriasis showed a high expression of IL-17 as well as IL-23, IL-22, IL-6 [62] and increased number of T_H1 and T_H17 cells were found in skin lesions [63]. Activated T_H17 cells also produce IL-17A, IL-17F, and IL-22 and induce keratinocyte proliferation and other clinical features of psoriasis [60]. Other cellular sources including mast cells and neutrophils also contribute to the production of IL-17 in affected skin lesions in patients with psoriasis [64]. Secukinumab [14], ixekizumab [15], and brodalumab [16] have demonstrated clinical benefits and been approved for moderate-to-severe plaque psoriasis.

Psoriatic arthritis is a form of inflammatory arthritis with destructive-joint features which may resemble the pathology of RA and occurs in up to 30% of patients with psoriasis [65]. Secukinumab [18–20] and ixekizumab [21,22] have also been approved for patients with psoriatic arthritis.

3.3. Axial spondyloarthritis

Axial spondyloarthritis is a chronic inflammatory disease that mainly affect the axial skeleton. It is a type of spondyloarthritis, which also includes psoriatic arthritis, arthritis associated with IBD, and reactive arthritis [66]. The term axial spondyloarthritis covers both patients who developed structural damage in the sacroiliac joints or spine visible on radiographs (radiographic axial spondyloarthritis, also termed ankylosing spondylitis) and patients without such structural damage, labeled as non-radiographic axial spondyloarthritis [66].

HLA-B27 is strongly associated with the pathogenesis of axial spondyloarthritis [67]. Further, it is clinically associated with IBD, psoriasis, or reactive arthritis in about 15–20% of cases [68], suggesting that barrier damages of intestinal mucosal or dermal surfaces and subsequent exposure of the immune system to microorganisms might be a relevant pathogenesis [66]. TNF-α and IL-17 appear to have relevant roles in pathogenesis as well. T_H17 cells and IL-17-producing innate immune cells, ILC3 cells, are involved in the inflammatory process of ankylosing spondylitis and IBD [27]. While ILC3 cells are mainly located in the intestinal mucosa of healthy individuals [27], a study demonstrated that gut-derived ILC3 cells were expanded in the peripheral blood, synovial fluid, and inflamed bone marrow of patients with ankylosing spondylitis, suggesting the presence of an active homing axis between the gut and the inflamed sacroiliac joints [69]. Furthermore, systemic overexpression of IL-23 in an animal model induced an enthesitis, resembling spondyloarthritis, suggesting that IL-23 might be a therapeutic target as well [70]. Secukinumab [23] and ixekizumab [24] have been approved in patients with axial spondyloarthrtiis.

4. New onset IBD in patients undergoing IL-17 inhibitors

Many clinical trials of IL-17 inhibitors have been undertaken for patients with rheumatological and dermatological inflammatory conditions and demonstrated its clinical benefits as previously described. However, new onset of IBD cases following the treatment with IL-17 inhibitors have been reported [27,71,72]. Hence, our group conduced a systematic review with meta-analysis to assess the risk of new onset IBD with the use of IL-17 inhibitors. We included 38 RCTs with a total 12,614 patients treated with IL-17 inhibitors and 4076 treated with placebo. The 38 RCTs included eight studies of brodalumab (4588 patients), eight of ixekizumab (4485 patients), and 22 of secukinumab (7617 patients), respectively. The study population included psoriasis, psoriatic arthritis, RA, and ankylosing spondylitis [71]. We identified a total of 12 new cases of IBD (five cases of CD, seven cases of UC). All cases were reported in patients with IL-17 inhibitors (zero on brodalumab, four on ixekizumab, and eight on secukinumab). This corresponded to an incidence of 2.4 cases of new onset IBD per 1000 patient-years. However, statistically there was no difference in the risk of developing new onset IBD with IL-17 inhibitors compared with placebo (MH RD 0.00062, 95% CI -0.00072-0.0021, P = 0.35) [71]. Other recent studies including pooled analyses from clinical trials of ixekizumab [73], secukinumab [74], and a real-world study for patients with psoriasis treated with IL-17 inhibitors [75] have been conducted and showed low incidence of new onset IBD in patients with IL-17 inhibitors.

Further, an updated meta-analysis evaluating the risk of development of IBD under IL-17 inhibition was undertaken and demonstrated no differences in the pooled risk of new onset IBD in induction and maintenance studies of IL-17 inhibitors [76].

The pathogenesis of new onset IBD in patients undergoing IL-17 inhibitors is still unclear. Given that secukinumab and brodalumab frequently induced worsening of CD [25,26], IL-17 might have protective roles for patients with IBD. As previously stated, O'Connor et al. demonstrated that *IL-17A*-deficient CD45RB^{high} T cells induced an aggressive colitis with a higher expression of genes encoding T_H1-type cytokines [32], suggesting that IL-17 can directly inhibit the development of T_H1 cells by suppressing expression of key T_H1-effector genes and T_H1 cells can induce aggressive colitis in the absence of IL-17 signaling [33]. These evidences support that inhibition of IL-17 may induce inflammation in the gastrointestinal tract by favoring T_H1 pathways (Fig. 1) [72].

5. Conclusions

The roles of IL-17 and T_H17 cells in the intestine, skin, and joints are different. Given that clinical trials demonstrated significant clinical benefits of IL-17 inhibitors in patients with psoriasis, psoriatic arthritis, and axial spondyloarthritis, pro-inflammatory functions of IL-17 and T_H17 cells might predominate in the skin and joints. On the other hand, animal models of colitis showed either protective or pro-inflammatory roles of IL-17 or T_H17 cells. In human IBD, particularly CD, IL-17 might be protective for intestinal inflammation as IL-17 inhibitors worsened CD activity in the setting of clinical trials. IL-17 inhibitors have been used in clinical practice for autoimmune diseases other than IBD, however, physicians need to know that new onset IBD can develop via induction of T_H1 cell-mediated immune responses in patients undergoing treatment with IL-17 inhibitors. Hence, monitoring of gastrointestinal symptoms during the treatment of IL-17 inhibitors would be important to diagnose new onset IBD appropriately and to consider switching to alternative medications with different mechanisms.

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Author contribution

Literature search-SA, Figures and Tables-SA, Study design-SA, AS, Drafting of manuscript-SA, AS.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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