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IL-17 and limits of success

Zahra Omidian[1,*], **Rizwan Ahmed**[1,*], **Adebola Giwa**[2], **Mohanraj Sadasivam**[1], **Thomas Donner**[2], **Abdel Rahim A. Hamad**[1]

[1]Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD 21205, United States.

[2]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21205, United States.

Abstract

Interleukin-17 (IL-17) is a potent proinflammatory cytokine that protects host against fungal and extracellular bacterial infections. On the other hand, excessive or dysregulated production of IL-17 underlines susceptibility to autoimmune disease. Consequently, blocking IL-17 has become an effective strategy for modulating several autoimmune diseases, including multiple sclerosis (MS), psoriasis, and rheumatoid arthritis (RA). Notably, however, IL-17 blockade remains ineffective or even pathogenic against important autoimmune diseases such as inflammatory bowel disease (IBD). Furthermore, efficacy of IL-17 blockade against other autoimmune diseases, including type 1 diabetes (T1D) is currently unknown and waiting results of ongoing clinical trials. Coming years will determine whether efficacy of IL-17 blockade is limited to certain autoimmune diseases or it can be extending to other autoimmune diseases. These efforts include new clinical trials aimed at testing second-generation agents with the goal of increasing efficiency, spectrum and ameliorating side effects of IL-17 blockade. Here we briefly review the roles of IL-17 in pathogenesis of selected autoimmune diseases and provide updates on ongoing and recently completed trials of IL-17 based immunotherapies.

Keywords

Interleukin-17; Autoimmune diseases; IL-17; immunotherapy; clinical trials

IL-17 plays an important role in the clearance of extracellular bacteria (e.g. Staphylococcus aureus, Clostridium rodentium, Klebsiella pneumonia) and fungal infections. However, members of the IL-17 family also also central players in driving autoimmunity. Dysregulated production of IL-17 can result in excessive pro-inflammatory cytokine production and chronic inflammation, leading to tissue damage and autoimmunity. Here we describe in brief details the roles of IL-17 in pathogenesis of selected autoimmune diseases and current or recently concluded clinical trials (Table 1) assessing the efficacy of IL-17-neutralizing antibodies (biologics) as immunotherapies.

Address correspondence to Abdel Hamad, ahamad@jhmi.edu; Ph 410-614-3021; Fax 410-614-3548 .
*First-Coauthor

Role of IL-17 in autoimmunity

The IL-17 family represents a distinct and complex cytokine signaling system that is highly conserved across vertebrate evolution [1–3]. To date, the IL-17 family has been shown to consist of six structurally-related ligands (IL-17A, B, C, D, E, and F) and five receptors (IL-17RA, RB/IL-25R, RC, RD/SEF and RE). IL-17A, often referred to only as IL-17, is the most intensively studied and characterized. IL-17 was initially thought to be produced exclusively by CD4 α T cells, but subsequently a variety of adaptive and innate immune cells have been found to produce IL-17 [4]. These include a subset of γδ T cells (γδ17), natural killer T cells (NKT17), and group 3 innate lymphoid cells (ILC3). Macrophages, dendritic cells and neutrophils have also been reported to secrete IL-17 in response to infection or in the context of tissue inflammation [5].

A common feature of both adaptive and innate lymphocytes that secrete IL-17 is the expression of the transcription factor, retinoic acid receptor-related orphan receptor-γt (RORγt) [6]. Cytokines and transcription factors that regulate Th17 cell differentiation are distinct from those regulating differentiation of Th1 and Th2 cells [7]. Although the majority of the Th17 pathway components are similar, it is now well-established that the conditions that promote and regulate the Th17 differentiation are different in mice and humans [8, 9]. The IL-23 along with IL-1β cytokines, however, play critical roles in Th17 development in both mice and humans [10–13]. Additionally, TGF-β (transforming growth factor β) plays an important role in promoting differentiation of Th17 cells in mice, but its role in human Th17 development remains controversial [9, 14]. On the other hand, IL-6 is often used to induce in vitro differentiation of mouse Th17 cells and STAT3-mediated activation of the RORγt transcription factor and to alleviate Foxp3-mediated inhibition of the Th17 program [15, 16]. However, IL-6 does not seem to be absolutely required for generation of human Th17 [17]. Similarly, IL-21 activates STAT3 and can act in an autocrine manner to promote murine Th17 differentiation [18, 19], but it remains controversial whether there is an absolute requirement for IL-21 for differentiation of mouse Th17 cells[20, 21]. In humans, IL-21 to act in synergy with TGF-β to promote generation of Th17 cells[22], but it noteworthy that IL-21 in combination with TGF-β and IL-6 had been described to promote a mixed Th17/Tfh (follicular helper T cell) phenotype[23].

Role of IL-17 in pathogenesis of Type 1 Diabetes (T1D)

The non-obese diabetic (NOD) mouse has been instrumental in studying the pathogenesis of [24]T1D [25, 26]. NOD mice develop normally, but start to develop insulitis after the age of 4 to 5 weeks due to islet infiltration by autoreactive T cells, B cells, and macrophages. The insulitis remains benign for a variable period of time that precedes the attack and destruction of insulin-producing β-cells by autoreactive T cells leading to insulin deficiency and hyperglycemia [24, 27–29]. The role of IL-17 in the pathogenesis of autoimmune diabetes is not yet fully understood. For example, IL-17 knockout NOD mice display delayed onset of diabetes and reduced severity of insulitis[30]. Moreover, NOD mice lacking both IL-17 and IFN-γ receptors showed enhanced protection from overt hyperglycemia (not insulitis) when compared to IL-17 single-knockout NOD mice[31, 32]. The authors of the latter study concluded that the IL-17 and IFN-γ pathways synergize to initiate beta cell destruction.

Another study showed that adoptive transfer of highly purified islet antigen specific Th17 polarized BDC2.5 transgenic T cells leads to the induction of T1D in NOD/SCID (Severe Combined Immunodeficiency) mice [33]. However, *in-vivo* instability of these cells and their conversion to the Th1-like cells in NOD/SCID mice precludes a definitive conclusion that the Th17 cells are directly involved in the pathogenesis of autoimmune diabetes in NOD mice[34, 35].

In humans, there is clinical data supporting a pathogenic role for Th17 cells in the development of T1D. Patients with T1D present with elevated plasma levels of IL-17 increased circulating IL17-producing T cells and islet antigen-specific Th17 cells [36]. Pancreatic lymph nodes (PLN) from T1D patients have an increased frequency of Th17 cells and analysis of islets obtained from recently deceased T1D patients expressed high levels of transcription factor RORγt and IL-17A[37]. In combination with IL-1β and IFN-γ, IL-17 mediates increased β-cell apoptosis in human pancreatic islet cells in vitro [38]. Thus, clinical data suggests that IL-17-producing cells may be pathogenic in the early stages of the disease and therapeutic strategies targeting Th17 cells could be a viable option for the treatment of T1D. Clinical data also provides a strong rationale to test agents that can suppress multiple pro-inflammatory axes simultaneously in the early phases of T1D. Currently, a phase I/II trial (Table 1) led by Jan P. Dutz's group in collaboration with the JDRF Canadian Clinical Trials Network (CCTN) is evaluating the efficacy of ustekinumab in new-onset T1D subjects[39]. Ustekinumab is a monoclonal antibody that targets the human p40 subunit thereby inducing blockade of both IL-17 and IFN-γ signaling pathways. Ustekinumab is currently approved for the treatment of psoriasis and if proved to be efficacious in T1D, could be utilized in the clinical setting for diabetes patients (Table 1). There are ongoing clinical trials for PF-06342674 to evaluate the immunogenicity, tolerability, safety, and pharmacokinetics in adult's patients with Type 1 Diabetes [https://clinicaltrials.gov/ct2/show/NCT02038764 and Table 1].

Role of IL-17 in Multiple Sclerosis (MS)

Multiple sclerosis (MS) is a chronic immune-mediated demyelinating disease of the central nervous system (CNS) characterized by focal lymphocytic infiltration, leading to the damage of myelin and axons [40]. Several recent findings from studies using animal models and MS patients indicate that Th17 cells, instead of Th1/Th2 cells, are critical players in the disease development [41, 42]. Most of the animal studies are undertaken using the well-characterized experimental autoimmune encephalomyelitis (EAE) model. Landmark studies in 2003 show that the IL-23-induced Th17 production plays a central role in the pathogenesis of EAE [43]. Additional evidence for the role of Th17 cells in driving EAE was shown in mice with targeted deletion of STAT3 in the $CD4^+$ T cell compartment (CD4-STAT3KO), which became resistant to the development of EAE due to their inability to generate Th17 cells[44]. Additionally, adoptive transfer of antigen-specific Th17 cells, but not Th1 cells isolated from established EAE donors induced severe EAE in recipient mice [45]. It is noteworthy that γδT cells provide an early source of innate IL-17 and create an amplification loop for IL-17 secretion by Th17 cells[46].

Consistent with the results in mice, studies in humans have established a significant role for IL-17 in the pathogenesis of MS. Th17 cells are detected at high frequencies in the cerebrospinal fluid (CSF) and peripheral blood of patients, especially during an acute neurological episode as compared to patients with non-inflammatory neurological diseases[47]. IL-17 production is increased in the perivascular lymphocytes, astrocytes and oligodendrocytes located in the active areas of MS lesions in the CNS indicating that IL-17 is involved in the early phase of MS[48]. An increased proportion of IL-17A mRNA was observed in the brain of MS patients in both acute and chronically progressing lesions, but not in normal non-inflamed specimens[49–51]. The levels of GM-CSF, which is essential for Th17 responses, have also been shown to be elevated in the CSF and blood of MS patients [42].

The first evidence that blocking IL-17 may be efficacious in ameliorating lesion activity in MS came from the treatment of patients with secukinumab. Interestingly, secukinumab was found to be safe with no serious adverse events and no anti-secukinumab antibodies were detected in treated patients [52, 53]. Another phase II study that was launched to examine the efficacy and safety of secukinumab in patients with relapsing-remitting MS was initiated (NCT01874340). Unfortunately, this clinical trial had been terminated prematurely because another anti-IL-17 fully human monoclonal antibody, CJM112, was shown to have better potential for treating MS patients[54]. Currently, a phase II proof-of-concept study (MABINGO) is being initiated to evaluate the efficacy of CJM112 relative to fingolimod in controlling brain MRI disease activity in MS patients transitioning from natalizumab treatment[55], (See table 1).

Role of IL-17 in pathogenesis of Psoriasis

Psoriasis is a chronic skin disease resulting from the dysregulated interactions between keratinocytes and infiltrating immune cells, and is characterized by dermal hyperplasia[56]. A causal link between IL-17 and psoriasis was first documented in mice. Deletion of genes encoding either IL-23 or IL-17 significantly decreased the progression of psoriasis in mice [57]. Mice injected with IL-17-blocking or -neutralizing monoclonal antibodies decreased downstream signaling of 1L-17 and Th17 cells and significantly reduced epidermal hyperplasia[58]. The major role of IL-17 in psoriasis in humans was first identified in the genome-wide association studies that linked IL-23 and Act1 polymorphisms to psoriasis, which regulates IL-17 production and IL-17-mediated signaling, respectively[59]. Although Th17 cells has been considered the primary source of IL-17, IL-17-producing γδT cells (γδ17) have been identified as a lead source of IL-17 involved in the activation of keratinocytes in psoriasis[58]. Patients with severe psoriasis have high frequencies of γδ17 T cells in psoriatic skin lesions[60]. The clearest evidence for a role of IL-23/Th17 in psoriasis was elucidated by studies documenting higher serum and lesion levels of IL-17 in psoriasis patients when compared to controls. One of these studies described a correlation between IL-17 levels and disease severity. Generalized pustular psoriasis patients with more severe disease were observed to have the highest serum levels of IL-17. RNA levels of IL-17A, IL-17C and IL-17F are elevated within psoriatic lesions and vary with disease severity.

Recent clinical studies that block IL-17A demonstrate its importance in psoriasis pathogenesis[61]. Currently, secukinumab has been approved for plaque psoriasis treatment and there are ongoing Phase III trials of isekizumab and brodalumab [62], (Table 1).With these successes, quests for new agents to target IL-17 in psoriasis are still ongoing. However, a recent phase Ib/IIa trial of fynomab (COVA322), which targets both IL-17 and TNF-α was discontinued due to safety concerns [25]. Despite this, the quest for an ideal biologic to treat psoriasis continues.

Role of IL-17 in pathogenesis of Rheumatoid Arthritis (RA)

RA is a chronic systemic autoimmune disease that is characterized by inflammatory damage to multiple joints with bone and cartilage destruction, pannus formation and hyperplastic synovium in the affected joints [18, 63, 64]. There is a positive correlation between IL-17, disease activity, and Th17 cells, which expand and produce more IL-17 in blood of patients with active disease [65].In addition, γδ T cells are also a major source of IL-17. Hu *etal* group's [31] has indicated that increases in IL-17-producing γδ T cells correlated with disease development and induction of inflammatory responses. IL-17 mRNA and protein expression were higher in the joints of RA patients as compared to healthy individuals [66, 67]. Moreover, serum and synovial levels of IL-17 correlated with disease activity[68]. IL-17 also plays a vital role particularly in the early stage of the disease by stimulating the fibroblast-like synoviocytes (FLS) to produce vascular endothelial growth factor (VEGF) [69], which leads to an increase in vascularity in mouse joints and promotes the growth of blood vessels [70]. IL-17 also provokes the secretion of other proinflammatory cytokines including, IL-8, IL-6, and Prostaglandin E2 [71]. In mice, increased expression of IL-17 by viral infections enhanced collagen-induced arthritis and accelerated joint destruction as well as synovial inflammation [70]. Furthermore, Th17 promotes osteoclastic bone erosion during collagen arthritis by provoking the expression of the receptor activator of nuclear factor-kB ligand (RANKL). IL-17 significantly increases the RANKL/osteoprotegerin (OPG) ratio [72]. Moreover, intra-articular injection of IL-17 in the joints of healthy mice led to inflammation and depletion of cartilage proteoglycans causing tissue degradation [73, 74]. Similarly, long-term intraarticular injection of IL-17 using gene transfer reproduced symptoms of rheumatoid arthritis.

Interestingly, antibody blockade of IL-17 (ixekizumab and secukinumab) or its receptor IL-17RA (brodalumab) protected against the development and manifestations of arthritis in patients with RA [75], (Table 1). In patients with RA, secukinumab induced an ACR20 (American College of Rheumatology standard scale to measure the amount of improvement in RA in designated joints after treatment) response rate of 46% when compared to the 20% using placebo treatment in their Phase III clinical trial [76], also see Table 1. Use of another IL-17 drug (ixekizumab) showed that inhibition of IL-17A could minimize the clinical parameters in as early as one week after the start of treatment. The Phase II trial with ixekizumab showed a 75% reduction in skin lesions in RA patients at week 12 as compared to placebo group with an 8% reduction [76, 77].

Previously, TNFα has been shown to be a key cytokine in the collagen-induced arthritis model. Although TNF contributes to the pathogenesis of the early stages of the disease, it is

not involved in the later stages of the disease. Contrarily, IL-17 seems to play a role in more than just the early stages of other chronic disease[78]. Since TNFα and IL-17 have shared functions, the rationale for testing IL-17 inhibitors in the clinical setting is often based on the concept that patients who do not respond to TNF inhibitors may have an IL-17-driven disease. This finding is another indication that IL-17 contributes to the chronicity of the disease.

Other IL-17A-targeting drugs include SCH-900117, CNTO6785 and bimekizumab, which are in Phase I to Phase III of their clinical trials (Table 1). Another randomized, placebo-controlled, phase II, dose-ranging study has been carried out to evaluate the immunogenicity, pharmacokinetics, safety and efficacy of CNTO6785, which is the human monoclonal antibody to interleukin 17A in rheumatoid arthritis patients with insufficient response to methotrexate (MTX) therapy (Table 1). Their study showed that although CNTO6785 was well-tolerated, it was not clinically efficacious in RA patients with insufficient response to MTX. However, it did suggest that due to the favorable safety profile, CNTO6785 could be a potential treatment candidate for other autoimmune diseases [79], also see Table 1.

Role of IL-17 in the pathogenesis of Systemic Lupus Erythematosus (SLE)

SLE is a chronic and heterogeneous autoimmune disease that is characterized by the presence of autoantibodies against various autoantigens leading to damage in tissues such as the skin, joints, and kidneys. Several factors, including environmental influences, molecular mediators, various immune cells, and genetic susceptibility loci lead to the development and progression of lupus [80]. Recent studies have demonstrated that IL-17 and Th17 cells play a pivotal role in SLE progression in both mouse models and patients [81]. Other preclinical studies showed that lupus-prone mice (MRL/lpr) had an expansion of Th17 cells and increased expression of IL-17A mRNA, which correlated to increased disease activity [82]. In addition, lymphocytes from lymph nodes, splenocytes, including double negative (DN) T cells of MRL/lpr mice produced significantly higher levels of IL-17 than lymphocytes from the control MRL/MPJ mice [83]. In addition, B6/lpr mice had significantly more Th17 cells than the control mice. Similarly, autoimmune BXD2 mice had an increased level of IL-17 than wild-type mice.

There are several potential targets for therapy in SLE. Interactions among $CD4^+$ T cells can be disrupted by blocking IL-17 signaling. This can be seen in IL-17 receptor-deficient mice, which had decreased B cell development in germinal centers and reduced humoral responses [84]. Plasmacytoid dendritic cells and monocytes play an important role in the production of other cytokines (i.e. IL-23) that stimulate the production of IL-17 [85]. Increased levels of IL-6 and IL-23 have been reported in both the tissue and serum of patients with SLE along with increased levels of IL-17-producing cells [86]. Additionally, $\alpha\beta TCR^+CD^-CD8^-$ double negative (DN) T cells, which is a small T cell subset in mice and healthy individuals[87] produce IFN-γ, IL-1β, and a significant fraction of IL-17 along with the increased numbers of γδ T cells in the peripheral blood of SLE patients. However, despite knowledge of factors contributing to the pathogenesis of SLE and numerous endeavors to develop efficacious treatment for patients with SLE, there is still a paucity of approved medications. The only approved treatment over that last 60 years for SLE patient is

belimumab, which is a human monoclonal antibody that inhibits B-cell activating factor (BAFF). Although, IL-17 has not yet been therapeutically targeted in human SLE, ustekinumab treatment could yield potential improvements in cutaneous lupus [80]. There are still ongoing clinical trials with composite endpoints for SLE that may progress in capturing clinically meaningful therapeutic responses [88].

Role of IL-17 in the pathogenesis of Hashimoto's thyroiditis (HT)

HT is one of the most prevalent autoimmune thyroid diseases (AITD). It is characterized by autoantibody production, lymphocyte infiltration, and fibrosis of the thyroid gland that lead to tissue inflammation and cell destruction [89, 90]. Activation of $CD4^+$ T cells, especially Th17 cells, plays a critical role in the pathogenesis of HT. These cells are characterized by the surface expression of CCR6, IL-23R, IL-12R-beta2, CD49, and CD161. In addition to IL-17A and IL-17F, Th17 cells produce IL-21, IL-9, IL-22, and TNFα. IL-17 also induces the expression of other proinflammatory cytokines (IL-6, IL-8, GM-CSF, G-CSF), metalloproteinases, and chemokines. Patients with HT have increased numbers of $CD4^+$ T cells in the interstitium [91, 92] and increased serum concentrations of IL-6 and IL-23, which promote Th17 differentiation [91, 93]. Similarly, high levels of Th17 cells in untreated children with HT suggests their participation in development of HT [94]. Moreover, Li et al [95] noted a vigorous relation between the concentration of IL-17 and stromal fibrosis of the thyroid, suggesting that elevated IL-17 promotes local inflammation and causes atrophy of thyrocytes and fibrosis. Additionally, there is an increased level of IL-17 mRNAs in PBMCs of HT patients [96]. Recent studies have shown a significant positive correlation between percentage of Th17 cells and level of Thyrotropin stimulating antibodies (TSAbs) [94, 97] as well as a positive correlation between the proportions of $CD4^+$ $IL17^+/CD4^+$ $CD25^+$ $CD127^-$ $FoxP3^+$ T cells and levels of TSAbs in newly diagnosed GD (Graves' disease) patients. There was also a positive correlation between the thyroperoxidase (TPO) and thyroglobulin (TG) antibodies and $CD4^+$ $CD161^+$ $CD196^+/CD4^+$ $CD25^+$ $CD127^-$ T cells in untreated Hashimoto's thyroiditis patients, which supports a role of Th17 in the progression of autoimmune thyroid diseases [97]. Besides Th17 cells, IL-17-producing γδ T cells have also been identified as a significant source of IL-17 in the thyroid tissue of patients with HT that may account for 55 % of $CD3^+$ T cells in inflamed glands [98]. As discussed above, IL-17 and Th17 could play a vital role in the pathogenesis of HT and could be a potential target for prevention and treatment.

Role of IL-17 in pathogenesis of Inflammatory Bowel Disease (IBD)

IBD is a chronic relapsing inflammatory disorder that leads to chronic gastrointestinal inflammation and includes ulcerative colitis (UC) and Crohn's disease (CD) [99]. It has been shown that IBD patients with inflamed gastrointestinal mucosa show immense Th17 cell infiltration and monocytes/macrophages that produce Th17-related cytokines. In both UC and CD tissues, there are high levels of IL-17-producing cells and upregulation of RNA transcripts for IL-17A and IL-17F in inflamed guts when compared with healthy controls. Other studies have indicated a positive correlation between the severity of disease and levels of IL-17-secreting PBMCs in UC patients [99–101]. Other groups have shown that IL-23- and IL-17-producing intestinal lymphocytes were remarkably increased in UC and CD. IFN-

γ production was also enhanced by γδ T cell activation providing a source of IL-17 production in PBMCs of IBD patients [102, 103].

Indeed, understanding the important role of lL-17 in the pathogenesis of IBD could pave the way to the development of therapeutic targets in the IL-17 pathway. Since the role of IL-17 has been established in the pathogenesis of IBD, recent drug development strategies are focused on using IL-17-neutralizing mAbs. IL17R knockout mice have shown substantial protection against trinitrobenzenesulfonic acid- (TNBS-)-induced colitis when compared with the wild-type mice[104]. Furthermore, colonic inflammation due to acute TNBS colitis has been attenuated in mice overexpressing an IL-17R IgG1 fusion protein after induction of TNBS [104]. Blockade of IL-17 in animal models of IBD as well as in humans, however, has led to controversial results. As a consequence, current clinical trials are focused on combined IL-17A and IL-17F inhibition. (See Table 1). Vidofludimus (SC12267, 4SC-101) is a recent oral immunomodulator that inhibits dihydroorotate dehydrogenase (DHODH) and targets IL-17A and IL-17F and IFN-δ by impairing the NFκB and JAK/STAT pathways [105]. Since it has been used for clinical trials, the efficacy, safety, and tolerability of vidofludimus in IBD patients have been proved in phase 2 double-blind, randomized, multicenter placebo-controlled trials and dose-finding studies. The safety and efficacy evaluation of vidofludimus calcium have been analyzed in moderate-to-severe ulcerative colitis patients for induction and maintenance therapy (ClinicalTrials.gov identifier (NCT number): NCT03341962). Secukinumab, a human anti-IL-17A antibody, has failed to have any significant efficacy in CD patients [106, 107]. In Crohn's patients, brodalumab and secukinumab have been administrated for clinical trials and unexpectedly, increased disease activity and subsequently failed the trial [108]. Thus, there is a lot to be learned about IL-17 in IBD and deciphering of why IL-17 blockade is yet to provide remedy for IBD patients.

Role of IL-17 in Celiac disease (CD)

CD is a prototypic CD4 T cell-dependent disease that leads to an intolerance of dietary gluten [109]. Several factors contribute to the pathogenesis of CD. HLA-DQ2 is a strong genetic determinant that is expressed in more than 90% of CD patients, whereas HLA-DQ8 molecules are expressed by the rest of celiac patients [110]. The production of cytokines following the activation of T cells plays a critical role in the development of CD [111]. A number of cytokines have been implicated in the pathogenesis of CD. Increased levels of IL-6 and IL-17 have been reported in patients with CD [112, 113]. Another study on patients with IBD and CD, found increased levels of IL-17, IL-21 and IFN-γ in their cohort [112]. It is apparent from these and other studies that IL-17 is a potential contributor to CD development whose pathogenic role is a focus in several ongoing investigations. Ex vivo experiments have shown that intracellular IL-17A is produced from CD4 T cell as well as CD8 T cells in biopsy samples in response to peptic-tryptic digest of gliadin [113]. Indeed, they have demonstrated that in the small bowel context of CD, gliadin-reactive CD4+ T cells are the main source of IL-17A [114, 115]. While Th17 primarily produces IL17, specific Treg cell populations, which are increased in lymphocytic colitis have also been found to be producing IL-17 in the mucosa of CD, UC and IBD patients. In addition, another study showed that mRNA levels of IL-17A, IFN γ, and Foxp3 in untreated CD patients were significantly higher than their levels patients treated for CD [116]. These results support a

role of IL-17 in the pathogenesis of CD and potential use it in monitoring of clinical progression.

Recent studies are also focusing on the correlation between polymorphisms in IL-17 gene and CD. Indeed, IL-17A (197A/G) gene polymorphism had an impact on the development of acute myeloid leukemia, gastric carcinogenesis, and UC [117, 118]. However, similar studies in CD patients did not show a statistically significant association between the IL-17 (−197A/G) polymorphism and CD[119]. Another study looking at genetic variations (single nucleotide polymorphisms) of the IL4, IL5, IL9, IL13, IL17B and NR3C1 (GR) susceptibility loci of chromosome 5q (*CELIAC2)* found no significant allele or haplotype frequency differences between CD and control group [120]. Outside of those types of studies, there are currently no approved clinical trials investigating immunomodulatory therapeutics for CD perhaps likely because CD can be well-managed by dietary modification.

Concluding remarks

IL-17 is a significant contributor to the development and/or acute and chronic phases of several autoimmune diseases. Nonetheless, immunotherapies inhibiting this cytokine and its activity have been found to be efficacious in controlling and modulating severity of a limited numbers of autoimmune conditions. On other hand, it was outright pathogenic or ineffective in cases of other drugs. Understanding the mechanistic reasons behind these discrepancies will be very useful in expansion utilization of IL-17 in clinic. Additional efforts are currently focused on producing second generation therapies that are safer and more tolerable. Furthermore, efforts are also directed towards determining whether IL-17 blockade can be efficacious in treating other autoimmune diseases. The next few years will determine whether IL-17 based immunotherapy has reached its limits or whether its magic can be expanded and find opportunity in treating other conditions. We bet on the latter.

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References

[1]. Fujino S, Andoh A, Bamba S, Ogawa A, Hata K, Araki Y, Bamba T, Fujiyama Y, Increased expression of interleukin 17 in inflammatory bowel disease, Gut, 52 (2003) 65–70. [PubMed: 12477762]

[2]. Shin HC, Benbernou N, Esnault S, Guenounou M, Expression of IL-17 in human memory CD45RO+ T lymphocytes and its regulation by protein kinase A pathway, Cytokine, 11 (1999) 257–266. [PubMed: 10328864]

[3]. Kennedy J, Rossi DL, Zurawski SM, Vega F Jr., Kastelein RA, Wagner JL, Hannum CH, Zlotnik A, Mouse IL-17: a cytokine preferentially expressed by alpha beta TCR + CD4-CD8-T cells, J Interferon Cytokine Res, 16 (1996) 611–617. [PubMed: 8877732]

[4]. Kim JS, Jordan MS, Diversity of IL-17-producing T lymphocytes, Cell Mol Life Sci, 70 (2013) 2271–2290. [PubMed: 23052209]

[5]. Korn T, Oukka M, Kuchroo V, Bettelli E, Th17 cells: effector T cells with inflammatory properties, Semin Immunol, 19 (2007) 362–371. [PubMed: 18035554]

[6]. Monin L, Gaffen SL, Interleukin 17 Family Cytokines: Signaling Mechanisms, Biological Activities, and Therapeutic Implications, Cold Spring Harb Perspect Biol, 10 (2018).

[7]. Amatya N, Garg AV, Gaffen SL, IL-17 Signaling: The Yin and the Yang, Trends Immunol, 38 (2017) 310–322. [PubMed: 28254169]

[8]. Annunziato F, Cosmi L, Romagnani S, Human and murine Th17, Curr Opin HIV AIDS, 5 (2010) 114–119. [PubMed: 20543587]

[9]. Sallusto F, Zielinski CE, Lanzavecchia A, Human Th17 subsets, Eur J Immunol, 42 (2012) 2215–2220. [PubMed: 22949319]

[10]. Chung Y, Chang SH, Martinez GJ, Yang XO, Nurieva R, Kang HS, Ma L, Watowich SS, Jetten AM, Tian Q, Dong C, Critical regulation of early Th17 cell differentiation by interleukin-1 signaling, Immunity, 30 (2009) 576–587. [PubMed: 19362022]

[11]. McGeachy MJ, Chen Y, Tato CM, Laurence A, Joyce-Shaikh B, Blumenschein WM, McClanahan TK, O'Shea JJ, Cua DJ, The interleukin 23 receptor is essential for the terminal differentiation of interleukin 17-producing effector T helper cells in vivo, Nat Immunol, 10 (2009) 314–324. [PubMed: 19182808]

[12]. Wilson NJ, Boniface K, Chan JR, McKenzie BS, Blumenschein WM, Mattson JD, Basham B, Smith K, Chen T, Morel F, Lecron JC, Kastelein RA, Cua DJ, McClanahan TK, Bowman EP, de Waal Malefyt R, Development, cytokine profile and function of human interleukin 17-producing helper T cells, Nat Immunol, 8 (2007) 950–957. [PubMed: 17676044]

[13]. Zielinski CE, Mele F, Aschenbrenner D, Jarrossay D, Ronchi F, Gattorno M, Monticelli S, Lanzavecchia A, Sallusto F, Pathogen-induced human TH17 cells produce IFN-gamma or IL-10 and are regulated by IL-1beta, Nature, 484 (2012) 514–518. [PubMed: 22466287]

[14]. Romagnani S, Maggi E, Liotta F, Cosmi L, Annunziato F, Properties and origin of human Th17 cells, Mol Immunol, 47 (2009) 3–7. [PubMed: 19193443]

[15]. Bettelli E, Carrier Y, Gao W, Korn T, Strom TB, Oukka M, Weiner HL, Kuchroo VK, Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells, Nature, 441 (2006) 235–238. [PubMed: 16648838]

[16]. Geng J, Yu S, Zhao H, Sun X, Li X, Wang P, Xiong X, Hong L, Xie C, Gao J, Shi Y, Peng J, Johnson RL, Xiao N, Lu L, Han J, Zhou D, Chen L, The transcriptional coactivator TAZ regulates reciprocal differentiation of TH17 cells and Treg cells, Nat Immunol, 18 (2017) 800–812. [PubMed: 28504697]

[17]. Annunziato F, Cosmi L, Liotta F, Maggi E, Romagnani S, The phenotype of human Th17 cells and their precursors, the cytokines that mediate their differentiation and the role of Th17 cells in inflammation, Int Immunol, 20 (2008) 1361–1368. [PubMed: 18820263]

[18]. Korn T, Bettelli E, Gao W, Awasthi A, Jager A, Strom TB, Oukka M, Kuchroo VK, IL-21 initiates an alternative pathway to induce proinflammatory T(H)17 cells, Nature, 448 (2007) 484–487. [PubMed: 17581588]

[19]. Nurieva R, Yang XO, Martinez G, Zhang Y, Panopoulos AD, Ma L, Schluns K, Tian Q, Watowich SS, Jetten AM, Dong C, Essential autocrine regulation by IL-21 in the generation of inflammatory T cells, Nature, 448 (2007) 480–483. [PubMed: 17581589]

[20]. Coquet JM, Chakravarti S, Smyth MJ, Godfrey DI, Cutting edge: IL-21 is not essential for Th17 differentiation or experimental autoimmune encephalomyelitis, J Immunol, 180 (2008) 7097–7101. [PubMed: 18490706]

[21]. Sonderegger I, Kisielow J, Meier R, King C, Kopf M, IL-21 and IL-21R are not required for development of Th17 cells and autoimmunity in vivo, Eur J Immunol, 38 (2008) 1833–1838. [PubMed: 18546146]

[22]. Yang L, Anderson DE, Baecher-Allan C, Hastings WD, Bettelli E, Oukka M, Kuchroo VK, Hafler DA, IL-21 and TGF-beta are required for differentiation of human T(H)17 cells, Nature, 454 (2008) 350–352. [PubMed: 18469800]

[23]. Schmitt N, Liu Y, Bentebibel SE, Munagala I, Bourdery L, Venuprasad K, Banchereau J, Ueno H, The cytokine TGF-beta co-opts signaling via STAT3-STAT4 to promote the differentiation of human TFH cells, Nat Immunol, 15 (2014) 856–865. [PubMed: 25064073]

[24]. Abdel-Moneim A, Bakery HH, Allam G, The potential pathogenic role of IL-17/Th17 cells in both type 1 and type 2 diabetes mellitus, Biomed Pharmacother, 101 (2018) 287–292. [PubMed: 29499402]

[25]. Anderson MS, Bluestone JA, The NOD mouse: a model of immune dysregulation, Annu Rev Immunol, 23 (2005) 447–485. [PubMed: 15771578]

[26]. Xiao Z, Mohamood AS, Uddin S, Gutfreund R, Nakata C, Marshall A, Kimura H, Caturegli P, Womer KL, Huang Y, Jie C, Chakravarti S, Schneck JP, Yagita H, Hamad AR, Inhibition of Fas ligand in NOD mice unmasks a protective role for IL-10 against insulitis development, Am J Pathol, 179 (2011) 725–732. [PubMed: 21718680]

[27]. Li Y, Liu Y, Chu CQ, Th17 Cells in Type 1 Diabetes: Role in the Pathogenesis and Regulation by Gut Microbiome, Mediators Inflamm, 2015 (2015) 638470.

[28]. Fousteri G, Ippolito E, Ahmed R, Hamad ARA, Beta-cell Specific Autoantibodies: Are they Just an Indicator of Type 1 Diabetes?, Curr Diabetes Rev, 13 (2017) 322–329. [PubMed: 27117244]

[29]. Hamad AR, Ahmed R, Donner T, Fousteri G, B cell-targeted immunotherapy for type 1 diabetes: What can make it work?, Discov Med, 21 (2016) 213–219. [PubMed: 27115172]

[30]. Solt LA, Burris TP, Th17 cells in Type 1 diabetes: a future perspective, Diabetes Manag (Lond), 5 (2015) 247–250. [PubMed: 27708719]

[31]. Hu C, Qian L, Miao Y, Huang Q, Miao P, Wang P, Yu Q, Nie H, Zhang J, He D, Xu R, Chen X, Liu B, Zhang D, Antigen-presenting effects of effector memory Vgamma9Vdelta2 T cells in rheumatoid arthritis, Cell Mol Immunol, 9 (2012) 245–254. [PubMed: 22139198]

[32]. Bellemore SM, Nikoopour E, Schwartz JA, Krougly O, Lee-Chan E, Singh B, Preventative role of interleukin-17 producing regulatory T helper type 17 (Treg 17) cells in type 1 diabetes in non-obese diabetic mice, Clin Exp Immunol, 182 (2015) 261–269. [PubMed: 26250153]

[33]. Koarada S, Wu Y, Olshansky G, Ridgway WM, Increased nonobese diabetic Th1:Th2 (IFN-gamma:IL-4) ratio is CD4+ T cell intrinsic and independent of APC genetic background, J Immunol, 169 (2002) 6580–6587. [PubMed: 12444170]

[34]. Bending D, De la Pena H, Veldhoen M, Phillips JM, Uyttenhove C, Stockinger B, Cooke A, Highly purified Th17 cells from BDC2.5NOD mice convert into Th1-like cells in NOD/SCID recipient mice, J Clin Invest, 119 (2009) 565–572. [PubMed: 19188681]

[35]. Bellemore SM, Nikoopour E, Krougly O, Lee-Chan E, Fouser LA, Singh B, Pathogenic T helper type 17 cells contribute to type 1 diabetes independently of interleukin-22, Clin Exp Immunol, 183 (2016) 380–388. [PubMed: 26496462]

[36]. Baharlou R, Ahmadi-Vasmehjani A, Davami MH, Faraji F, Atashzar MR, Karimipour F, Sadeghi A, Asadi MA, Khoubyari M, Elevated Levels of T-helper 17-associated Cytokines in Diabetes Type I Patients: Indicators for Following the Course of Disease, Immunol Invest, 45 (2016) 641–651. [PubMed: 27611173]

[37]. Wang M, Yang L, Sheng X, Chen W, Tang H, Sheng H, Xi B, Zang YQ, T-cell vaccination leads to suppression of intrapancreatic Th17 cells through Stat3-mediated RORgammat inhibition in autoimmune diabetes, Cell Res, 21 (2011) 1358–1369. [PubMed: 21519350]

[38]. Wachlin G, Augstein P, Schroder D, Kuttler B, Kloting I, Heinke P, Schmidt S, IL-1beta, IFN-gamma and TNF-alpha increase vulnerability of pancreatic beta cells to autoimmune destruction, J Autoimmun, 20 (2003) 303–312. [PubMed: 12791316]

[39]. Marwaha AK, Tan S, Dutz JP, Targeting the IL-17/IFN-gamma axis as a potential new clinical therapy for type 1 diabetes, Clin Immunol, 154 (2014) 84–89. [PubMed: 24947953]

[40]. Gajofatto A, Turatti M, Investigational immunosuppressants in early-stage clinical trials for the treatment of multiple sclerosis, Expert Opin Investig Drugs, 27 (2018) 273–286.

[41]. Kolbinger F, Huppertz C, Mir A, Padova FD, IL-17A and Multiple Sclerosis: Signaling Pathways, Producing Cells and Target Cells in the Central Nervous System, Curr Drug Targets, 17 (2016) 1882–1893. [PubMed: 26953244]

[42]. Dos Passos GR, Sato DK, Becker J, Fujihara K, Th17 Cells Pathways in Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorders: Pathophysiological and Therapeutic Implications, Mediators Inflamm, 2016 (2016) 5314541.

[43]. Zhang GX, Yu S, Gran B, Li J, Siglienti I, Chen X, Calida D, Ventura E, Kamoun M, Rostami A, Role of IL-12 receptor beta 1 in regulation of T cell response by APC in experimental autoimmune encephalomyelitis, J Immunol, 171 (2003) 4485–4492. [PubMed: 14568921]

[44]. Liu X, Lee YS, Yu CR, Egwuagu CE, Loss of STAT3 in CD4+ T cells prevents development of experimental autoimmune diseases, J Immunol, 180 (2008) 6070–6076. [PubMed: 18424728]

[45]. Domingues HS, Mues M, Lassmann H, Wekerle H, Krishnamoorthy G, Functional and pathogenic differences of Th1 and Th17 cells in experimental autoimmune encephalomyelitis, PLoS One, 5 (2010) e15531.

[46]. McGinley AM, Edwards SC, Raverdeau M, Mills KHG, Th17cells, gammadelta T cells and their interplay in EAE and multiple sclerosis, J Autoimmun, (2018).

[47]. Chi LJ, Xu WH, Zhang ZW, Huang HT, Zhang LM, Zhou J, Distribution of Th17 cells and Th1 cells in peripheral blood and cerebrospinal fluid in chronic inflammatory demyelinating polyradiculoneuropathy, J Peripher Nerv Syst, 15 (2010) 345–356. [PubMed: 21199106]

[48]. Tzartos JS, Friese MA, Craner MJ, Palace J, Newcombe J, Esiri MM, Fugger L, Interleukin-17 production in central nervous system-infiltrating T cells and glial cells is associated with active disease in multiple sclerosis, Am J Pathol, 172 (2008) 146–155. [PubMed: 18156204]

[49]. Urshansky N, Mausner-Fainberg K, Auriel E, Regev K, Farhum F, Karni A, Dysregulated neurotrophin mRNA production by immune cells of patients with relapsing remitting multiple sclerosis, J Neurol Sci, 295 (2010) 31–37. [PubMed: 20541775]

[50]. Drulovic J, Savic E, Pekmezovic T, Mesaros S, Stojsavljevic N, Dujmovic-Basuroski I, Kostic J, Vasic V, Mostarica Stojkovic M, Popadic D, Expression of Th1 and Th17 cytokines and transcription factors in multiple sclerosis patients: does baseline T-bet mRNA predict the response to interferon-beta treatment?, J Neuroimmunol, 215 (2009) 90–95. [PubMed: 19695714]

[51]. Liu X, He F, Pang R, Zhao D, Qiu W, Shan K, Zhang J, Lu Y, Li Y, Wang Y, Interleukin-17 (IL-17)-induced microRNA 873 (miR-873) contributes to the pathogenesis of experimental autoimmune encephalomyelitis by targeting A20 ubiquitin-editing enzyme, J Biol Chem, 289 (2014) 28971–28986. [PubMed: 25183005]

[52]. Havrdova E, Belova A, Goloborodko A, Tisserant A, Wright A, Wallstroem E, Garren H, Maguire RP, Johns DR, Activity of secukinumab, an anti-IL-17A antibody, on brain lesions in RRMS: results from a randomized, proof-of-concept study, J Neurol, 263 (2016) 1287–1295. [PubMed: 27142710]

[53]. Orthmann-Murphy JL, Calabresi PA, Therapeutic Application of Monoclonal Antibodies in Multiple Sclerosis, Clin Pharmacol Ther, 101 (2017) 52–64. [PubMed: 27804128]

[54]. Bittner S, Wiendl H, Neuroimmunotherapies Targeting T Cells: From Pathophysiology to Therapeutic Applications, Neurotherapeutics, 13 (2016) 4–19. [PubMed: 26563391]

[55]. Wiendl H, Dahlke F, Bennett D, Rosenkranz G, Wolf C, Bar-Or A, IL-17 neutralization by subcutaneous CJM112, a fully human anti IL-17A monoclonal antibody for the treatment of relapsing-remitting multiple sclerosis: study design of a phase 2 trial, 2015.

[56]. Hanley TL, Yiu ZZ, Role of IL-17 in plaque psoriasis: therapeutic potential of ixekizumab, Ther Clin Risk Manag, 13 (2017) 315–323. [PubMed: 28352182]

[57]. AbuHilal M, Walsh S, Shear N, The Role of IL-17 in the Pathogenesis of Psoriasis and Update on IL-17 Inhibitors for the Treatment of Plaque Psoriasis, J Cutan Med Surg, 20 (2016) 509–516. [PubMed: 27207350]

[58]. Cai Y, Shen X, Ding C, Qi C, Li K, Li X, Jala VR, Zhang HG, Wang T, Zheng J, Yan J, Pivotal role of dermal IL-17-producing gammadelta T cells in skin inflammation, Immunity, 35 (2011) 596–610. [PubMed: 21982596]

[59]. Boutet MA, Nerviani A, Afflitto G. Gallo, Pitzalis C, Role of the IL-23/IL-17 Axis in Psoriasis and Psoriatic Arthritis: The Clinical Importance of Its Divergence in Skin and Joints, Int J Mol Sci, 19 (2018).

[60]. Giacomelli R, Parzanese I, Frieri G, Passacantando A, Pizzuto F, Pimpo T, Cipriani P, Viscido A, Caprilli R, Tonietti G, Increase of circulating gamma/delta T lymphocytes in the peripheral blood of patients affected by active inflammatory bowel disease, Clin Exp Immunol, 98 (1994) 83–88. [PubMed: 7923890]

[61]. Martin DA, Towne JE, Kricorian G, Klekotka P, Gudjonsson JE, Krueger JG, Russell CB, The emerging role of IL-17 in the pathogenesis of psoriasis: preclinical and clinical findings, J Invest Dermatol, 133 (2013) 17–26. [PubMed: 22673731]

[62]. Lai Y, Dong C, Therapeutic antibodies that target inflammatory cytokines in autoimmune diseases, Int Immunol, 28 (2016) 181–188. [PubMed: 26545932]

[63]. Giwa A, Ahmed R, Donner T, Yagita H, Hamad ARA, Editorial: Ying and Yang Members of the Tumor Necrosis Factor Superfamily: Friends or Foes in Immune-Mediated Diseases and Cancer, Front Immunol, 8 (2017) 1584. [PubMed: 29218044]

[64]. Van Boxel JA, Paget SA, Predominantly T-cell infiltrate in rheumatoid synovial membranes, N Engl J Med, 293 (1975) 517–520. [PubMed: 168488]

[65]. Notley CA, Inglis JJ, Alzabin S, McCann FE, McNamee KE, Williams RO, Blockade of tumor necrosis factor in collagen-induced arthritis reveals a novel immunoregulatory pathway for Th1 and Th17 cells, J Exp Med, 205 (2008) 2491–2497. [PubMed: 18936235]

[66]. Chabaud M, Durand JM, Buchs N, Fossiez F, Page G, Frappart L, Miossec P, Human interleukin-17: A T cell-derived proinflammatory cytokine produced by the rheumatoid synovium, Arthritis Rheum, 42 (1999) 963–970. [PubMed: 10323452]

[67]. Moran EM, Mullan R, McCormick J, Connolly M, Sullivan O, Fitzgerald O, Bresnihan B, Veale DJ, Fearon U, Human rheumatoid arthritis tissue production of IL-17A drives matrix and cartilage degradation: synergy with tumour necrosis factor-alpha, Oncostatin M and response to biologic therapies, Arthritis Res Ther, 11 (2009) R113. [PubMed: 19627579]

[68]. Rosu A, Margaritescu C, Stepan A, Musetescu A, Ene M, IL-17 patterns in synovium, serum and synovial fluid from treatment-naive, early rheumatoid arthritis patients, Rom J Morphol Embryol, 53 (2012) 73–80. [PubMed: 22395503]

[69]. Ryu S, Lee JH, Kim SI, IL-17 increased the production of vascular endothelial growth factor in rheumatoid arthritis synoviocytes, Clin Rheumatol, 25 (2006) 16–20. [PubMed: 16163444]

[70]. Lubberts E, Joosten LA, Oppers B, van den Bersselaar L, Coenen-de Roo CJ, Kolls JK, Schwarzenberger P, van de Loo FA, van den Berg WB, IL-1-independent role of IL-17 in synovial inflammation and joint destruction during collagen-induced arthritis, J Immunol, 167 (2001) 1004–1013. [PubMed: 11441109]

[71]. Fossiez F, Djossou O, Chomarat P, Flores-Romo L, Ait-Yahia S, Maat C, Pin JJ, Garrone P, Garcia E, Saeland S, Blanchard D, Gaillard C, Das Mahapatra B, Rouvier E, Golstein P, Banchereau J, Lebecque S, T cell interleukin-17 induces stromal cells to produce proinflammatory and hematopoietic cytokines, J Exp Med, 183 (1996) 2593–2603. [PubMed: 8676080]

[72]. Lubberts E, van den Bersselaar L, Oppers-Walgreen B, Schwarzenberger P, Coenen-de Roo CJ, Kolls JK, Joosten LA, van den Berg WB, IL-17 promotes bone erosion in murine collagen-induced arthritis through loss of the receptor activator of NF-kappa B ligand/osteoprotegerin balance, J Immunol, 170 (2003) 2655–2662. [PubMed: 12594294]

[73]. Dudler J, Renggli-Zulliger N, Busso N, Lotz M, So A, Effect of interleukin 17 on proteoglycan degradation in murine knee joints, Ann Rheum Dis, 59 (2000) 529–532. [PubMed: 10873962]

[74]. Chabaud M, Lubberts E, Joosten L, van Den Berg W, Miossec P, IL-17 derived from juxta-articular bone and synovium contributes to joint degradation in rheumatoid arthritis, Arthritis Res, 3 (2001) 168–177. [PubMed: 11299057]

[75]. Lubberts E, Koenders MI, Oppers-Walgreen B, van den Bersselaar L, Coenen-de Roo CJ, Joosten LA, van den Berg WB, Treatment with a neutralizing anti-murine interleukin-17 antibody after the onset of collagen-induced arthritis reduces joint inflammation, cartilage destruction, and bone erosion, Arthritis Rheum, 50 (2004) 650–659. [PubMed: 14872510]

[76]. Miossec P, Kolls JK, Targeting IL-17 and TH17 cells in chronic inflammation, Nat Rev Drug Discov, 11 (2012) 763–776. [PubMed: 23023676]

[77]. Genovese MC, Van den Bosch F, Roberson SA, Bojin S, Biagini IM, Ryan P, Sloan-Lancaster J, LY2439821, a humanized anti-interleukin-17 monoclonal antibody, in the treatment of patients with rheumatoid arthritis: A phase I randomized, double-blind, placebo-controlled, proof-of-concept study, Arthritis Rheum, 62 (2010) 929–939. [PubMed: 20131262]

[78]. Koenders MI, Lubberts E, van de Loo FA, Oppers-Walgreen B, van den Bersselaar L, Helsen MM, Kolls JK, Di Padova FE, Joosten LA, van den Berg WB, Interleukin-17 acts independently of TNF-alpha under arthritic conditions, J Immunol, 176 (2006) 6262–6269. [PubMed: 16670337]

[79]. Mease PJ, Jeka S, Jaller JJ, Kitumnuaypong T, Louthrenoo W, Mann H, Matsievskaia G, Soriano ER, Jia B, Wang C, Nie J, Hsia E, CNTO6785, a Fully Human Antiinterleukin 17 Monoclonal Antibody, in Patients with Rheumatoid Arthritis with Inadequate Response to Methotrexate: A Randomized, Placebo-controlled, Phase II, Dose-ranging Study, J Rheumatol, 45 (2018) 22–31. [PubMed: 29093159]

[80]. Crispin JC, Tsokos GC, IL-17 in systemic lupus erythematosus, J Biomed Biotechnol, 2010 (2010) 943254.

[81]. Tabarkiewicz J, Pogoda K, Karczmarczyk A, Pozarowski P, Giannopoulos K, The Role of IL-17 and Th17 Lymphocytes in Autoimmune Diseases, Arch Immunol Ther Exp (Warsz), 63 (2015) 435–449. [PubMed: 26062902]

[82]. Xing Q, Wang B, Su H, Cui J, Li J, Elevated Th17 cells are accompanied by FoxP3+ Treg cells decrease in patients with lupus nephritis, Rheumatol Int, 32 (2012) 949–958. [PubMed: 21243492]

[83]. Zhang Z, Kyttaris VC, Tsokos GC, The role of IL-23/IL-17 axis in lupus nephritis, J Immunol, 183 (2009) 3160–3169. [PubMed: 19657089]

[84]. Hsu HC, Yang P, Wang J, Wu Q, Myers R, Chen J, Yi J, Guentert T, Tousson A, Stanus AL, Le TV, Lorenz RG, Xu H, Kolls JK, Carter RH, Chaplin DD, Williams RW, Mountz JD, Interleukin 17-producing T helper cells and interleukin 17 orchestrate autoreactive germinal center development in autoimmune BXD2 mice, Nat Immunol, 9 (2008) 166–175. [PubMed: 18157131]

[85]. Paley MA, Strand V, Kim AH, From mechanism to therapies in systemic lupus erythematosus, Curr Opin Rheumatol, 29 (2017) 178–186. [PubMed: 28118202]

[86]. Zickert A, Amoudruz P, Sundstrom Y, Ronnelid J, Malmstrom V, Gunnarsson I, IL-17 and IL-23 in lupus nephritis - association to histopathology and response to treatment, BMC Immunol, 16 (2015) 7. [PubMed: 25887118]

[87]. Martina MN, Noel S, Saxena A, Rabb H, Hamad AR, Double negative (DN) alphabeta T cells: misperception and overdue recognition, Immunol Cell Biol, 93 (2015) 305–310. [PubMed: 25420721]

[88]. Mahieu MA, Strand V, Simon LS, Lipsky PE, Ramsey-Goldman R, A critical review of clinical trials in systemic lupus erythematosus, Lupus, 25 (2016) 1122–1140. [PubMed: 27497257]

[89]. Duan J, Kang J, Deng T, Yang X, Chen M, Exposure to DBP and High Iodine Aggravates Autoimmune Thyroid Disease Through Increasing the Levels of IL-17 and Thyroid-Binding Globulin in Wistar Rats, Toxicol Sci, 163 (2018) 196–205. [PubMed: 29385629]

[90]. Esfahanian F, Ghelich R, Rashidian H, Jadali Z, Increased Levels of Serum Interleukin-17 in Patients with Hashimoto's Thyroiditis, Indian J Endocrinol Metab, 21 (2017) 551–554. [PubMed: 28670539]

[91]. Pyzik A, Grywalska E, Matyjaszek-Matuszek B, Rolinski J, Immune disorders in Hashimoto's thyroiditis: what do we know so far?, J Immunol Res, 2015 (2015) 979167.

[92]. Zha B, Huang X, Lin J, Liu J, Hou Y, Wu G, Distribution of lymphocyte subpopulations in thyroid glands of human autoimmune thyroid disease, J Clin Lab Anal, 28 (2014) 249–254. [PubMed: 24478186]

[93]. Kimura A, Kishimoto T, IL-6: regulator of Treg/Th17 balance, Eur J Immunol, 40 (2010) 1830–1835. [PubMed: 20583029]

[94]. Bossowski A, Moniuszko M, Idzkowska E, Dabrowska M, Jeznach M, Sawicka B, Borysewicz-Sanczyk H, Bossowska A, Rusak M, Bodzenta-Lukaszyk A, [Evaluation of CD4+CD161+CD196+ and CD4+IL-17+ Th17 cells in the peripheral blood of young patients with Hashimoto's thyroiditis and Graves' disease], Pediatr Endocrinol Diabetes Metab, 18 (2012) 89–95. [PubMed: 23146786]

[95]. Li D, Cai W, Gu R, Zhang Y, Zhang H, Tang K, Xu P, Katirai F, Shi W, Wang L, Huang T, Huang B, Th17 cell plays a role in the pathogenesis of Hashimoto's thyroiditis in patients, Clin Immunol, 149 (2013) 411–420. [PubMed: 24211715]

[96]. Shi Y, Wang H, Su Z, Chen J, Xue Y, Wang S, Xue Y, He Z, Yang H, Zhou C, Kong F, Liu Y, Yang P, Lu L, Shao Q, Huang X, Xu H, Differentiation imbalance of Th1/Th17 in peripheral blood mononuclear cells might contribute to pathogenesis of Hashimoto's thyroiditis, Scand J Immunol, 72 (2010) 250–255. [PubMed: 20696023]

[97]. Bossowski A, Moniuszko M, Idzkowska E, Grubczak K, Singh P, Bossowska A, Diana T, Kahaly GJ, Decreased proportions of CD4 + IL17+/CD4 + CD25 + CD127- and CD4 + IL17+/CD4 + CD25 + CD127 - FoxP3+ T cells in children with autoimmune thyroid diseases (.), Autoimmunity, 49 (2016) 320–328. [PubMed: 27206624]

[98]. Liu H, Zheng T, Mao Y, Xu C, Wu F, Bu L, Mou X, Zhou Y, Yuan G, Wang S, Zhou T, Chen D, Mao C, gammadelta Tau cells enhance B cells for antibody production in Hashimoto's thyroiditis, and retinoic acid induces apoptosis of the gammadelta Tau cell, Endocrine, 51 (2016) 113–122. [PubMed: 25994301]

[99]. Galvez J, Role of Th17 Cells in the Pathogenesis of Human IBD, ISRN Inflamm, 2014 (2014) 928461. [PubMed: 25101191]

[100]. Seiderer J, Elben I, Diegelmann J, Glas J, Stallhofer J, Tillack C, Pfennig S, Jurgens M, Schmechel S, Konrad A, Goke B, Ochsenkuhn T, Muller-Myhsok B, Lohse P, Brand S, Role of the novel Th17 cytokine IL-17F in inflammatory bowel disease (IBD): upregulated colonic IL-17F expression in active Crohn's disease and analysis of the IL17F p.His161Arg polymorphism in IBD, Inflamm Bowel Dis, 14 (2008) 437–445. [PubMed: 18088064]

[101]. Raza A, Shata MT, Letter: pathogenicity of Th17 cells may differ in ulcerative colitis compared with Crohn's disease, Aliment Pharmacol Ther, 36 (2012) 204; author reply 205. [PubMed: 22703461]

[102]. Kobayashi T, Okamoto S, Hisamatsu T, Kamada N, Chinen H, Saito R, Kitazume MT, Nakazawa A, Sugita A, Koganei K, Isobe K, Hibi T, IL23 differentially regulates the Th1/Th17 balance in ulcerative colitis and Crohn's disease, Gut, 57 (2008) 1682–1689. [PubMed: 18653729]

[103]. McVay LD, Li B, Biancaniello R, Creighton MA, Bachwich D, Lichtenstein G, Rombeau JL, Carding SR, Changes in human mucosal gamma delta T cell repertoire and function associated with the disease process in inflammatory bowel disease, Mol Med, 3 (1997) 183–203. [PubMed: 9100225]

[104]. Zhang Z, Zheng M, Bindas J, Schwarzenberger P, Kolls JK, Critical role of IL-17 receptor signaling in acute TNBS-induced colitis, Inflamm Bowel Dis, 12 (2006) 382–388. [PubMed: 16670527]

[105]. Herrlinger KR, Diculescu M, Fellermann K, Hartmann H, Howaldt S, Nikolov R, Petrov A, Reindl W, Otte JM, Stoynov S, Strauch U, Sturm A, Voiosu R, Ammendola A, Dietrich B, Hentsch B, Stange EF, Efficacy, safety and tolerability of vidofludimus in patients with inflammatory bowel disease: the ENTRANCE study, J Crohns Colitis, 7 (2013) 636–643. [PubMed: 23078909]

[106]. McLean LP, Cross RK, Shea-Donohue T, Combined blockade of IL-17A and IL-17F may prevent the development of experimental colitis, Immunotherapy, 5 (2013) 923–925. [PubMed: 23998727]

[107]. Wedebye Schmidt EG, Larsen HL, Kristensen NN, Poulsen SS, Lynge Pedersen AM, Claesson MH, Pedersen AE, TH17 cell induction and effects of IL-17A and IL-17F blockade in experimental colitis, Inflamm Bowel Dis, 19 (2013) 1567–1576. [PubMed: 23689808]

[108]. Symons A, Budelsky AL, Towne JE, Are Th17 cells in the gut pathogenic or protective?, Mucosal Immunol, 5 (2012) 4–6. [PubMed: 22071661]

[109]. De Re V, Magris R, Cannizzaro R, New Insights into the Pathogenesis of Celiac Disease, Front Med (Lausanne), 4 (2017) 137. [PubMed: 28913337]

[110]. Henderson KN, Tye-Din JA, Reid HH, Chen Z, Borg NA, Beissbarth T, Tatham A, Mannering SI, Purcell AW, Dudek NL, van Heel DA, McCluskey J, Rossjohn J, Anderson RP, A structural and immunological basis for the role of human leukocyte antigen DQ8 in celiac disease, Immunity, 27 (2007) 23–34. [PubMed: 17629515]

[111]. Stepniak D, Koning F, Celiac disease--sandwiched between innate and adaptive immunity, Hum Immunol, 67 (2006) 460–468. [PubMed: 16728270]

[112]. Ishihara K, Hirano T, IL-6 in autoimmune disease and chronic inflammatory proliferative disease, Cytokine Growth Factor Rev, 13 (2002) 357–368. [PubMed: 12220549]

[113]. Ortega C, Fernandez S, Estevez OA, Aguado R, Molina IJ, Santamaria M, IL-17 producing T cells in celiac disease: angels or devils?, Int Rev Immunol, 32 (2013) 534–543. [PubMed: 24040774]

[114]. Espinoza JL, Takami A, Nakata K, Onizuka M, Kawase T, Akiyama H, Miyamura K, Morishima Y, Fukuda T, Kodera Y, Nakao S, Japan Marrow Donor P, A genetic variant in the IL-17 promoter is functionally associated with acute graft-versus-host disease after unrelated bone marrow transplantation, PLoS One, 6 (2011) e26229.

[115]. Fina D, Sarra M, Caruso R, Del Vecchio Blanco G, Pallone F, MacDonald TT, Monteleone G, Interleukin 21 contributes to the mucosal T helper cell type 1 response in coeliac disease, Gut, 57 (2008) 887–892. [PubMed: 17965065]

[116]. Sjoberg V, Sandstrom O, Hedberg M, Hammarstrom S, Hernell O, Hammarstrom ML, Intestinal T-cell responses in celiac disease - impact of celiac disease associated bacteria, PLoS One, 8 (2013) e53414.

[117]. Arisawa T, Tahara T, Shibata T, Nagasaka M, Nakamura M, Kamiya Y, Fujita H, Nakamura M, Yoshioka D, Arima Y, Okubo M, Hirata I, Nakano H, The influence of polymorphisms of interleukin-17A and interleukin-17F genes on the susceptibility to ulcerative colitis, J Clin Immunol, 28 (2008) 44–49. [PubMed: 17828618]

[118]. Wrobel T, Gebura K, Wysoczanska B, Jazwiec B, Dobrzynska O, Mazur G, Kuliczkowski K, Bogunia-Kubik K, IL-17F gene polymorphism is associated with susceptibility to acute myeloid leukemia, J Cancer Res Clin Oncol, 140 (2014) 1551–1555. [PubMed: 24793548]

[119]. Akbulut UE, Cebi AH, Sag E, Ikbal M, Cakir M, Interleukin-6 and interleukin-17 gene polymorphism association with celiac disease in children, Turk J Gastroenterol, 28 (2017) 471–475. [PubMed: 28928101]

[120]. Ryan AW, Thornton JM, Brophy K, Daly JS, McLoughlin RM, O'Morain C, Abuzakouk M, Kennedy NP, Stevens FM, Feighery C, Kelleher D, McManus R, Chromosome 5q candidate genes in coeliac disease: genetic variation at IL4, IL5, IL9, IL13, IL17B and NR3C1, Tissue Antigens, 65 (2005) 150–155. [PubMed: 15713213]

Highlights

- IL-17 is becoming an important therapeutic target for autoimmune diseases, but yet to reach its full potentials as it inefficacious or outright pathogenic in cases of certain autoimmune diseases.
- Here we review the roles of IL-17 in selected autoimmune diseases and provide updates on ongoing or recently completed clinical trials aiming to extend therapeutic application of IL-17 blockade to other immunotherapies.

Table 1:

IL-17 and IL-17R Inhibitor Drugs*

Drug Name (Experiment Name)	Drug Type	Target	Disease	Study Status
Ustekinumab	Human monoclonal antibody	IL-17, IL-12, IL-23, IFN-ɣ	Psoriasis	Approved
			Crohn's Disease	Approved
			Type 1 Diabetes	Phase I/II
secukinumab	Human IgG1κ monoclonal antibody	IL-17A	Psoriasis	Approved
			Psoriatic Arthritis	Approved
			Ankylosing Spondylitis	Approved
			Rheumatoid Arthritis	Terminated
			Multiple Sclerosis	Terminated
			Crohn's Disease	Terminated
ixekizumab	Humanized IgG4 monoclonal antibody	IL-17A	Psoriasis	Approved
			Plaque Psoriasis	Approved
			Psoriatic Arthritis	Phase III
			Rheumatoid Arthritis	Phase II
brodalumab	Human monoclonal antibody	IL-17 Receptor	Psoriasis	Approved
			Moderate/Severe Crohn's Disease	Terminated
			Inflammatory Bowel Disease	Terminated
			Psoriatic arthritis	Phase III
			Rheumatoid Arthritis	Terminated
ABT-122	Human recombinant IgG1 (Dual variable domain immunoglobulin; DVD-Ig)	IL-17 TNF-α	Psoriasis	Phase II
			Rheumatoid Arthritis	
			Psoriatic Arthritis	
CJM112	Human IgG1 monoclonal antibody	IL-17A	Multiple Sclerosis	Phase II
risankizumab	Humanized monoclonal antibody	Binds to p19 subunit of IL-23A disrupting receptor activation and IL-23/17 axis	Psoriasis	Phase II
			Psoriatic Arthritis	
			Crohn's Disease	
briakinumab	Human $IgG_1λ$ monoclonal antibody	P40 subunit of IL-23 and IL-12	Moderate/Severe chronic Plaque Psoriasis	Terminated
			Crohn's disease	Phase II
bimekizumab	Humanized IgG1 monoclonal antibody	IL-17A IL-17F	Psoriasis	Phase III
			Psoriatic arthritis	
			Rheumatoid Arthritis	
			Inflammatory Bowel Disease	
BCD-085	Humanized monoclonal antibody	IL-17	Severe Psoriasis	Phase III
afasevikumab	Human monoclonal antibody (IgG1-κ)	IL-17A IL-17F	Multiple Sclerosis	Discontinued

Drug Name (Experiment Name)	Drug Type	Target	Disease	Study Status
perakizumab	Humanized monoclonal antibody (IgG1-κ)	IL-17A	Psoriatic arthritis	Phase I
RG7624	Human monoclonal antibody	IL-17A and/or IL-17F	Psoriasis	Phase I
SCH-900117	Human monoclonal antibody	IL-17A	Rheumatoid arthritis	Phase I
PF-06342674	Human monoclonal antibody	IL-17 receptor antagonist	Type 1 Diabetes	Phase I
			Multiple Sclerosis	
ABBV-257	Human monoclonal antibody; Dual-variable domain immunoglobulins 1	IL-17 TNF-α inhibitor	Rheumatoid Arthritis	Phase I
CNTO 6785	Human monoclonal antibody	IL-17A	Rheumatoid Arthritis	Phase II

* Lists IL-17 and IL-17 Receptor Inhibitor Drugs along with their targets, conditions approved for, and/or clinical trial status.