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Clinical Consequences of Targeting IL-17 and T_H17 in Autoimmune and Allergic Disorders

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Abstract

The T_H17 lineage of T cells and its canonical cytokine IL-17 have been the focus of many recent studies in autoimmune, allergic, and infectious disease. In this review, we will briefly discuss the current knowledge about the role of these cells and IL-17 in a spectrum of disorders. It is clear that IL-17 plays pathogenic roles in certain conditions while the same pathway is critically important to immunity in others. Targeting of T_H17 cells or IL-17 therapeutically may impart many benefits, but this approach is not without potentially serious implications regarding host defense. These issues will be discussed herein as we evaluate pharmacological approaches targeting this pathway that are just beginning to be fully tested in human disease.

Keywords

Inflammation; Immunity; Host defense; Allergy; Asthma; Lung; Arthritis; Psoriasis; Lupus; Crohn disease; Pneumonia; Multiple sclerosis; IL-17; Th17; Autoimmune

Introduction

Naive CD4⁺ T cells originate in the thymus and can be activated following the recognition of antigenic peptides by MHC class II molecules on dendritic cells. During activation, CD4⁺ T cells assimilate signals from T cell receptors and co-stimulatory molecules in the presence of cytokines to determine their differentiation into multiple possible T effector cell lineages. T helper 17 (T_H17) cells are a T cell effector lineage of CD4⁺ T cells that have been described to produce high levels of the cytokines IL-17 and IL-22 [1]. IL-1, IL-6, and TGF- β are critical regulators of T_H17 cell differentiation. In addition, IL-23, produced by antigen presenting cells, has been shown to drive T_H17 cell regulation, proliferation, and cytokine production [2]. Key transcription factors that direct the lineage of T_H17 cells include STAT3, ROR γ and ROR α [3]. Conversely, Type I IFN, Type II IFN, and IL-27 negatively regulate T_H17 cell polarization and cytokine production [4-5]. In addition to IL-17 and IL-22, T_H17 cells produce IL-21 which promotes T_H17 cell lineage differentiation and

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Conflict of Interest

Keven M. Robinson, Michelle L. Manni, and Partha S. Biswas declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

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potentially acts as an auto feedback mechanism [6]. In addition to T_H17 cells, there are other cellular sources of IL-17 and IL-22 including T cells, cytotoxic T cells, invariant natural killer T cells, natural killer cells, and lymphoid tissue inducer cells [1].

IL-17 is a family of cytokines including IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25), and IL-17F [7]. IL-17A and IL-17F map to the same chromosome in both humans and mice (chromosomes 6 and 1, respectively). IL-17A and IL-17F induce the production of cytokines, chemokines, and metalloproteinases as well as recruit, activate, and regulate the migration of neutrophils [7]. There are multiple IL-17 receptors including IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE [8]. IL-17RA and IL-17RC bind both IL-17A and IL-17F [9]. IL-17RA is expressed on hematopoietic cells, osteoblasts, endothelial, and epithelial cells among others. IL-22 is a member of the IL-10 family of cytokines. The receptor for IL-22 is a heterodimer consisting of IL-10R2 and IL-22R and is expressed predominantly on endothelial and epithelial cells [10]. An endogenous antagonist of IL-22, IL-22 binding protein (IL22 BP), inhibits IL-22 driven STAT3 activation [11].

T_H17 immunity has been implicated in causing tissue inflammation in both autoimmune and allergic disease. T_H17 immunity also plays a critical role in host defense against multiple pathogens. While the T_H17 pathway may provide potential therapeutic targets to combat inflammatory diseases, this may allow for decreased protection by the host against invading pathogens.

IL-17, T_H17 cells and autoimmune disorders

IL-17 and T_H17 cells have been strongly implicated in the pathogenesis of autoimmune inflammatory diseases. In recent years, numerous mouse model studies as well as studies in humans have identified IL-17 as a key player in multiple autoimmune conditions described below.

Rheumatoid arthritis

Rheumatoid arthritis (RA), a chronic inflammatory arthritis, is characterized by the synovitis leading to the destruction of bone and cartilage. In fact, the presence of IL-17 producing cells in the inflamed synovium was first shown in RA. Subsequently, numerous mouse model studies have demonstrated the pathological role of IL-17 in this disorder. Indeed, administration of antibodies directed against IL-17A or its receptor IL-17RA protected mice from developing arthritis [12]. Furthermore, mice deficient in IL-17RA had diminished severity of experimental arthritis, indicating that IL-17 drives chronic inflammatory reactions in the joints [13]. These studies along with several preclinical studies have provided strong rationale to target IL-17 in the treatment of RA.

Psoriasis and Psoriatic arthritis

Psoriasis and Psoriatic arthritis are chronic inflammatory conditions that affect skin and distal joints, respectively. Strong genetic associations with IL-23R gene polymorphism indicate a pathogenic role of T_H17 cells in these conditions [14]. Psoriatic patients have high expression of IL-17, IL-23, IL-22, and IL-6 in skin biopsy samples [15-17]. Thus, these disorders are the subject of clinical trials that target to test the effectiveness of IL-17 inhibitors. In addition to IL-17, T_H17 cells derived IL-22 likely plays a pathogenic role in IL-23 mediated skin inflammation, making IL-22 a therapeutic target in psoriasis [17].

Ankylosing spondylitis

Ankylosing spondylitis is an inflammatory joint disease that affects the spine. In contrast to RA, analysis of bone-biopsy samples revealed mast cells as the primary producer of IL-17 in ankylosing spondylitis patients [18].

Multiple Sclerosis (MS)

MS is a chronic inflammatory disease that leads to brain inflammation and myelin destruction. Mouse models studies have strongly implicated the pathogenic role of IL-17 and T_H17 cells in brain inflammation, and an IL-17A-targeted auto-vaccine prevented experimental autoimmune encephalomyelitis [19]. The fact that *IL-17A* gene is overexpressed in the brains of MS patients, makes IL-17 a potential drug target in MS [20].

Systemic Lupus Erythematosus (SLE)

SLE is a systemic autoimmune condition leading to end-organ damage. In recent years, multiple lines of evidence identified IL-17 as a key player in the pathogenesis of SLE. Lupus mice deficient in IL-17 or IL-17 receptors were shown to be protected from lupus nephritis [21]. Further supporting the role of IL-17 in lupus, elevated plasma levels of IL-17 have been reported in SLE patients that correlated with disease activity in some studies [22]. Moreover, the fact that genetic associations identified in SLE to date involve T_H17-related pathways providing a solid justification to target IL-17 and other T_H17 related cytokines, such as IL-21, in lupus [22].

Crohn disease

Crohn disease is a type of inflammatory bowel disease (IBD) that may affect any part of the gastrointestinal tract. Unlike other autoimmune conditions described above, mouse models of IBD have revealed conflicting results. In these studies, both pro-inflammatory and potentially protective roles of IL-17 have been described [23-24]. However, polymorphisms in the IL-23R gene have been linked with Crohn disease, and biopsy samples revealed high expression of IL-17 together with IL-23, IL-22, and IL-6, indicating several potential therapeutic targets for this disease [25].

Targeting IL-17 and T_H17 cells in autoimmune disorders

Over the past decade the discovery of anti-TNF- α biologics have significantly improved the treatment of multiple autoimmune diseases [26]. Because TNF- α and IL-17 have shared synergistic functions, the rationale for testing IL-17 inhibitors in the clinic is often based on the concept that patients who do not respond or inadequately respond to TNF- α inhibitors (about 30% of the patients) may have an IL-17-driven disease [26]. To this end, several strategies have been implemented to neutralize IL-17 and T_H17 cells in autoimmune patients and are depicted in Figure 1.

RA

In RA, secukinumab (anti-IL-17A mAb) induced an ACR20 response rate of 46%, compared to 20% with placebo treatment and was considered to be encouraging enough to start a Phase III clinical trial which is currently ongoing [27]. A separate Phase II trial with ixekizumab (anti-IL-17A mAb) in RA led to a decrease in clinical parameters as early as 1 week [28].

Psoriasis

A significant reduction in the skin lesions was observed in psoriatic patients following a single injection of secukinumab in a Phase I clinical trial [27]. Additionally, in a Phase II

trial, subcutaneous injection of brodalumab (anti-IL-17RA mAb) in 198 patients demonstrated encouraging results with 77% of patients showed a 75% improvement and 72% showed a 100% improvement in skin lesions at week 12 [29].

Ankylosing spondylitis

Results obtained from a Phase II study demonstrated the safety and efficacy of secukinumab for the treatment of ankylosing spondylitis [30].

Crohn disease

Phase II clinical trials of brodalumab and secukinumab in Crohn disease have been terminated due to the fact that they failed to improve disease symptoms and in some patients even increased the disease activity [31].

In recent years, multiple studies have associated IL-17 and T_H17 cells in the pathogenesis of number of chronic inflammatory diseases. Thus, therapeutic strategies to block this pathogenic cytokine are now in place to confirm whether these observations are indeed correct in human subjects. Based on these observations, monoclonal antibodies targeting IL-17 or IL-17 receptor components have been designed, and the results of these clinical trials are now being released. So far the results obtained from clinical trials have been encouraging and inhibition of IL-17 activity can be seen as a new treatment option for patients with chronic inflammatory diseases. However, the difficulty in predicting patients' responses to IL-17 targeted therapy is a major problem in refining the response rate and safety of these targeted therapies. A major effort is now in progress to better select patients with inflammatory disease mediated by IL-17 and/or T_H17 cells.

T_H17 and IL-17 in Asthma

In addition to autoimmune roles, T_H17 cells and IL-17 are thought to play a pathogenic role in allergic airway disease. Asthma is a common chronic respiratory disease affecting as many as 5% of the world population and between 8-10% of the US population.

Corticosteroids and long-acting β_2 -agonists are the mainstay for asthma treatment, although subsets of asthmatics (as many as 10%) respond poorly to standard therapy [32-34]. T_H17 cells may play a critical role in non-canonical T_H2 asthma pathogenesis, especially in asthmatics with severe, steroid-resistant disease. This subset of asthmatics is often characterized by neutrophilia in the presence or absence of classical T_H2-induced inflammation [35]. The presence of airway neutrophilia correlates to asthma severity and patients with neutrophilic inflammation exhibit decreased improvement in FEV₁ (forced expiratory volume) and airway responsiveness following steroid treatment [36-38].

Furthermore, neutrophils are known to be largely steroid-insensitive and glucocorticoids are known to inhibit neutrophil apoptosis, which may account for the increase in neutrophils observed in the lungs [39-40]. On the other hand, neutralization of TNF- α , a potent stimulator of chemotaxis of neutrophils, was not effective at limiting severe asthma treated with high doses of corticosteroids [41]. Based on this, limiting neutrophilic inflammation alone may not be an effective method for treating severe disease.

IL-23 and Asthma

The T_H17 pathway has been linked to severe asthma and thus, methods to directly reduce T_H17 cells and their effectors may serve as potential therapeutic targets for the treatment of this refractory disease. IL-23 is thought to have an important role in severe asthma as it is a key molecule for T_H17 cell propagation. In a murine asthma model, IL-23 levels were elevated in lung homogenates and IL-23p19 mRNA was induced upon antigen inhalation in the lungs of antigen-sensitized mice [42]. In this study, IL-23 also enhanced antigen-induced

activation of both T_H17 and T_H2 cells and administration of anti-IL-23p19 antibodies lessened airway inflammation and T_H2 cytokine production [42]. Thus, targeting IL-23 availability by down regulating its expression as well as other cytokines, such as IL-6 and IL-1 that drive T_H17 cell expansion, may aid in the treatment of T_H17 -dependent diseases.

IL-17 and asthma

T_H17 cytokines downstream of IL-23 are also known to contribute to asthma pathogenesis. Antigen recruited T_H17 cells secrete proinflammatory cytokines (IL-17A, IL-17F, IL-22), resulting in steroid-insensitive allergic airway disease (i.e. neutrophilia, airway hyperresponsiveness, mucus production) in mice [43]. IL-17 is also known to be strongly upregulated in asthma as serum and airway IL-17 mRNA and protein levels are found to be elevated in asthmatics [44-47]. The increased levels of IL-17 in the lung directly correlated with disease severity (i.e. increased AHR to methacholine) [48]. Further, IL-17 also plays a critical role in driving neutrophil influx into the airways and is implicated in airway remodeling, which are more prominent in chronic steroid-resistant disease [45, 49]. Studies have also indicated IL-23-induced T_H17 cell effector function was impaired in gene variant carriers of the protective allele IL-23R R381Q resulting in significantly reduced IL-17A production and STAT3 phosphorylation, which supports a critical role for the IL-23/IL-23R signaling in generating pathogenic T_H17 responses [50]. As the T_H17 pathway is critical for the development of severe asthma, the design of new therapies aimed at targeting this pathway may be advantageous.

T Cell Phenotypes in Asthma

Although distinct asthma phenotypes are being established, some asthmatics present with disease with multiple inflammatory processes or clinical characteristics of more than one phenotype. For instance, many asthmatics present with both sputum neutrophils and eosinophils [35]. Further, although steroid-resistant asthma may be neutrophil dependent, lavage eosinophils were also related to severe therapy-resistant asthma in children, as elevated T_H2 cytokines correlated with significantly lower lung function [51-52]. In contrast, other studies have noted that conventional steroid treatments are effective in reducing the number of T_H2 cytokine producing cells and increasing those that highly express T_H1 cytokines in steroid-resistant asthma [53-54]. These mixed inflammatory processes imply the involvement of multiple immune pathways contributing to disease pathogenesis. The immunological mechanisms of T_H1 , T_H2 and T_H17 responses are still emerging, and the impact of targeting one lineage over another is unknown.

Despite T cell fate determination, recent discoveries have emphasized that T cells are phenotypically unstable. For instance, it is apparent from both *in vitro* and *in vivo* studies that some T cells can produce both IFN- and IL-17 [55]. In addition, T_H17 cells can produce IL-21 and IL-22 in the absence of IL-17 [56]. It is also recognized that T_H17 cells as well as other T cell subsets produce the immunosuppressive cytokine IL-10; thus, not all T_H17 cells may be pathogenic [57]. The plasticity of T cell differentiation is thought to be cytokine-regulated and also is suggested to play a role in modulating inflammatory diseases [58]. This phenomenon is also thought to occur in humans. Human circulating memory T_H cells co-expressing IL-17/IL-4 have been identified in asthmatics [59]. Further, circulating T_H cells from healthy controls and asthmatics were found to express multiple transcription factors [60]. Together, these data support the concept that individual T_H cells may have a flexible phenotype and multiple functions *in vivo*. Therefore, therapies targeting a single pathway may influence the T cell phenotype or inflammatory milieu limiting one phenotype, while promoting another. In asthmatics with mixed neutrophil and eosinophil inflammation, neutralizing the T_H17 pathway may isolate or promote T_H2 -like disease, resulting in a more steroid responsive phenotype. Together, this emphasizes the complexity of the

immunological mechanisms of severe asthma and that multiple innate and adaptive immune pathways and cells may have a role in disease pathogenesis. Pharmacological studies targeting IL-23 and IL-17 are currently underway in asthmatics.

T_H17 immunity and Host Defense

Although the T_H17 axis may be detrimental or pathogenic in autoimmune and allergic disease, its protective role in host defense must be considered. T_H17 cells and effector cytokines play a key role in protecting against pathogenic microorganisms at the mucosa. IL-17A promotes inflammation by inducing macrophage and neutrophil chemokines and growth factors including granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), CXCL1 (keratinocyte chemoattractant or KC), CXCL2 (macrophage inflammatory protein or MIP-2), CXCL5 (LIX), CXCL8 (IL-8), CXCL9 (MIG), CXCL10 (IP-10), and CCL-2 (MCP-1) [1]. In addition, IL-17 and IL-22 can induce production of several antimicrobial peptides (AMPs) including serum amyloid A, lipocalin-2, α -defensins, S100 proteins, and RegIII [61-62]. Each of these functions has been shown to play critical roles in immunity against a diverse group of pathogens.

Extracellular Bacteria

A role for T_H17 immunity against extracellular bacteria was initially explored in a murine respiratory model of gram-negative *Klebsiella pneumoniae* infection. Overexpression of IL-17A by adenovirus prior to *K. pneumoniae* infection resulted in increased production of G-CSF and MIP-2, enhanced bacterial clearance, and improved survival [63]. IL-17RA knockout ($-/-$) mice challenged with *K. pneumoniae* had increased mortality compared to controls. There was also a delay in neutrophil recruitment to the alveolar space, increased dissemination of bacteria, and decreased induction of G-CSF and MIP-2 [64]. IL-23p19 $-/-$ mice produced decreased amounts of IL-17A and IL-17F in response to *K. pneumoniae*, had increased mortality related to infection, and restored bacterial clearance after receiving exogenous IL-17A [65]. Subsequently, IL-22 was found to be crucial to early control of *K. pneumoniae*, in part related to the induction of the antimicrobial peptide lipocalin 2 [66]. T_H17 immunity also plays a protective role in the gut mucosa. IL-23 dependent T_H17 cells are required for protection against gram-negative *Citrobacter rodentium*. IL-17A, IL-17F, and IL17A/F $-/-$ mice had higher bacterial burden compared to controls [67]. IL-22 was also important to early *C. rodentium* infection, inducing antimicrobial peptides RegIII and RegIII γ , and exogenous RegIII improved survival of IL-22 $-/-$ mice infected with *C. rodentium* [68]. T_H17 immunity has been linked to oral mucosa host defense as IL-17R $-/-$ mice were more susceptible to the gram-negative *Porphyromonas gingivalis* [69]. T_H17 cytokines were elevated during infection with *Bordetella pertussis*, *Pseudomonas aeruginosa*, and *Helicobacter pylori*, although these models do not consistently reflect enhanced bacterial clearance [70-73]. Vaccine induced protection against *B. pertussis* and *P. aeruginosa*, however, are thought to be IL-17 dependent [74-75].

In addition to gram-negative bacteria, T_H17 immunity also guards against gram-positive extracellular bacteria. IL-17A and IL-17F are protective against *Staphylococcus aureus* mucocutaneous infections. IL-17R $-/-$ and IL-22 $-/-$ mice with *S. aureus* pneumonia had decreased bacterial clearance compared to wild-type controls. T_H17 and T cells make IL-17 in response to *S. aureus* pneumonia [76]. TCR $-/-$ mice had increased susceptibility to *S. aureus* pneumonia, attenuated neutrophil recruitment, and decreased production of cytokines [77]. Further, systemic depletion of IL-17A in mice resulted in attenuated bacterial clearance of *Streptococcus pneumoniae* that is associated with decreased neutrophil recruitment [78]. Immunization with pneumococcal antigen offers protection against primary colonization by *S. pneumoniae* via activation of IL-17 [79].

Intracellular Bacteria

While a protective role for T_H17 immunity in response to extracellular bacteria has emerged, the role for T_H17 immunity in host defense against intracellular bacteria remains more complex. A murine model of *Mycoplasma pneumoniae* infection revealed IL-23 dependent induction of IL-17A and IL-17F. When IL-23 was neutralized, there was decreased neutrophil recruitment and bacterial clearance [80]. In the *Chlamydia muridarum* respiratory model, IL-17 was required for bacterial clearance, reduced mortality, chemokine production, and neutrophil recruitment [81]. In the gut, infection with *Salmonella typhimurium* induced IL-17 and IL-22. IL-23p19 $-/-$ mice had decreased levels of IL-17, IL-22, Reg3 γ , and KC as well as reduced levels of neutrophil recruitment during *S. typhimurium* infection [82]. IL-17R $-/-$ mice had increased dissemination of *S. typhimurium* [83]. While the aforementioned intracellular bacteria require T_H17 immunity for protection, others use the T_H17 cytokines to mediate the inflammatory response and/or generate T_H1 responses. In pulmonary *Mycobacterium tuberculosis* and *Mycobacterium bovis* BCG infection, IL-17R $-/-$ and IL-23p19 $-/-$ mice were not more susceptible to infection, although the inflammatory response was altered and IL-17R $-/-$ mice had impaired granuloma formation to *Mycobacterium bovis* BCG [84-85]. The T_H17 axis likely plays an important role in vaccine-induced immunity against *Mycobacterium tuberculosis* [86]. Mice infected with pulmonary *Francisella tularensis* induce T_H17 cells in the lung [87], and both IL-17 and IL-23 were critical for clearance of *F. tularensis*. In addition, IL-17 helps drive the T_H1 response in pulmonary *F. tularensis* infection [88]. IL-17 has also been shown to promote the initial cytotoxic T cell response to *Listeria monocytogenes* in mice [89].

Fungi

During the unfolding of the AIDS epidemic, infection with *Pneumocystis carinii pneumonia* became more prevalent in this group characterized by a loss of CD4⁺ cells. Subsequently, *P. carinii* was linked to T_H17 immunity when IL-17 and IL-23 were found to enhance fungal clearance and induce production of chemokines [90]. In a murine model of pulmonary *Aspergillus fumigatus* infection, neutralization of IL-17 resulted in impaired fungal clearance [91]. It has also been proposed that the inflammation associated with T_H17 effector function during *A. fumigatus* infection results in a severe pathologic response and attenuates antifungal immunity [92]. In the oral mucosa, *Candida albicans* requires IL-17 and IL-23 for pathogen clearance. IL17R $-/-$ and IL-23p19 $-/-$ mice had impaired neutrophil recruitment and severe disease burden compared to controls [93]. Innate lymphoid cells have recently been identified as an emerging source of IL-17A and IL-17F in response to oral candidiasis [94]. Vaccine development aimed at fungal infections has found that T_H17 cells in mice were necessary to protect against *Blastomyces dermatitidis*, *Coccidioides posadasii*, and *Histoplasma capsulatum* [95].

Virus

During influenza infection, T_H17 immunity may play both a pathogenic and protective role. When challenged with H1N1 influenza, the inhibition of IL-17 signaling resulted in decreased weight loss and increased survival linked with decreased lung inflammation [96]. Conversely, challenge of IL-17 $-/-$ mice with highly pathogenic H5N1 influenza resulted in a lack of B cell recruitment, increased weight loss, enhanced lung immunopathology, and reduced survival [97]. Human rhinovirus has been found to synergize with IL-17 to induce IL-8 production by epithelial cells and may help recruit neutrophils, immature dendritic cells, and memory T cells to the airways [98]. Bacterial complications of viral disease are often associated with increased mortality. Mice infected sequentially with influenza and *S. aureus* resulted in influenza inhibition of subsequent T_H17 immunity and increased susceptibility to secondary *S. aureus* pneumonia [76]. Similarly, mice co-infected with influenza and *S. pneumoniae* resulted in a higher bacterial burden of *S. pneumoniae* and

decreased production of IL-17 [99]. It is clear from these numerous host defense studies discussed that blockade of IL-17 could be critically detrimental to pathogen clearance.

Conclusions

The literature is clear in demonstrating both pathogenic and protective roles for T_H17 cells and IL-17 in immunity. IL-17 plays an important role in the granulopoiesis and chemotaxis of neutrophils to the site of inflammation. It is attractive to target the IL-17 pathway in order to reduce inflammation and its detrimental effects. However, these innate immune cells are essential for mucosal host defense in many models. Additionally, IL-17 induces the expression of several genes that encode antimicrobial factors and chemokines in the epithelium and fibroblasts at the mucosal site. Thus, it is expected that targeting IL-17 or the IL-17 producing cells could lead to increased risk of infections with certain extracellular bacteria and fungi. Accordingly, patients with dominant-negative IL-17F or recessive IL-17R mutations suffer from mucocutaneous candidiasis [100]. Similarly, patients with STAT3 mutations display chronic *S. aureus* infections of the skin and lung. However, with the information available from early phases of clinical trials, no evidence of neutropenia or increased incidences of infection have been noted. Although a few sporadic cases of local *C. albicans* infection have been reported, the causal mechanism is still not clear and the role of IL-17 in these cases has yet to be confirmed. Nevertheless, an advantage of targeting IL-17 as opposed to blocking TNF- α in autoimmune conditions may be a reduced risk of infection with intracellular pathogens such as *M. tuberculosis* and *L. monocytogenes*. Although similar caveats may apply as IL-17 may also play critical roles in T_H1 priming against *M. tuberculosis*. Targeting IL-17 therapeutically brings with it many risks and concerns. It may prove better to fully identify downstream effectors of the IL-17 pathway that may be specifically targeted to achieve the desired benefits without the unintended consequences.

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Figure 1. Novel strategies to target IL-17 and TH17 cells in autoimmune disorders

The figure illustrates several ways in which members of the IL-17 protein and receptor family can be targeted and are already in use for clinical trials. This can be achieved by blocking the differentiation of TH17 cells using small molecule inhibitors or monoclonal antibody (mAb), directly targeting IL-17 family cytokines or their cognate receptors with mAbs, or inhibiting IL-17R signaling in target cells.