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Involvement of the IL-23/IL-17 axis and the Th17/Treg balance in the pathogenesis and control of autoimmune arthritis

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Abstract

The T helper (Th) cell subsets are characterized by the type of cytokines produced and the master transcription factor expressed. Th1 cells participate in cell-mediated immunity, whereas Th2 cells promote humoral immunity. Furthermore, the two subsets can control each other. Thereby, Th1-Th2 balance offered a key paradigm in understanding the induction and regulation of immune pathology in autoimmune and other diseases. However, over the past decade, Th17 cells producing interleukin-17 (IL-17) have emerged as the major pathogenic T cell subset in many pathological conditions that were previously attributed to Th1 cells. In addition, the role of CD4⁺CD25⁺ T regulatory cells (Treg) in controlling the activity of Th17 and other T cell subsets has increasingly been realized. Thereby, examination of the Th17/Treg balance in the course of autoimmune diseases has significantly advanced our understanding of the pathogenesis of these disorders. The differentiation of Th17 and Treg cells from naïve T cells is inter-related and controlled in part by the cytokine milieu. For example, transforming growth factor β (TGF β) is required for Treg induction, whereas the same cytokine in the presence of IL-6 (or IL-1) promotes the differentiation of Th17. Furthermore, IL-23 plays a role in the maintenance of Th17. Accordingly, novel therapeutic approaches are being developed to target IL-23/IL-17 as well as to modulate the Th17/Treg balance in favor of immune regulation to control autoimmunity.

Paradigm shift from Th1-Th2 to Th17-Treg

For over two decades, the T helper 1-T helper 2 (Th1-Th2) paradigm was used as a framework to characterize human diseases [1, 2]. After CD4⁺ T cells are activated by antigen, the cells expand and polarize into either Th1 cells that produce interferon- γ (IFN γ), interleukin-2 (IL-2), and lymphotoxin (LT) or Th2 that produce IL-4, IL-5, IL-9 and IL-13 [3]. The cytokine milieu present during T cell activation plays a role in the differentiation of naïve T cells into specific T cell subsets. IFN γ and IL-12 induce the differentiation of naïve T cells into Th1 cells, whereas IL-4 promotes the differentiation into Th2 cells. The Th1

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cells participate in a cellular response that targets intracellular pathogens, whereas the Th2 cells provide help to the B cells leading to the production of antibodies, which target extracellular pathogens [2, 4]. The master transcription factor of Th1 cells is T-box transcription factor expressed in T-cells (T-bet) and it is inhibited by IL-4. In contrast, GATA-binding protein 3 (GATA-3) is necessary for Th2 differentiation and it is inhibited by IFN γ . The cross regulation of the two Th subsets is the hallmark of the Th1-Th2 paradigm.

The Th1-Th2 paradigm had to be expanded and revised with the discovery of IL-23, which shares the p40 subunit with IL-12, and thereby, was responsible for many of the immune effects that had previously been attributed to IL-12 [5]. IL-12 is a heterodimer composed of p35 and p40 subunits, whereas IL-23 is composed of a unique p19 and the shared p40 subunit, and IL-23 is very similar to IL-12 but is functionally different. Studies conducted in the mouse collagen-induced arthritis (CIA) model of human rheumatoid arthritis (RA) [6] revealed that mice lacking the p19 subunit of IL-23, but not those lacking the p35 subunit of IL-12, were protected from arthritis. It was also shown that IL-12-deficient mice had an increase in Th17 cells. Similar results were obtained in studies in the mouse experimental autoimmune encephalitis (EAE) model of human multiple sclerosis (MS) [5]. It was later shown that IL-23 did not directly induce the differentiation of Th17 cells, but it helped Th17 cells to expand and maintain their lineage [7]. Instead, it was shown that IL-6 and transforming growth factor- β (TGF β) were necessary for murine Th17 cell differentiation [8]. Since inducible T regulatory cells (iTreg) are differentiated by TGF β alone, a new paradigm has arisen in the form of Th17-Treg cell balance in controlling immune responses in health and disease.

The cellular source of IL-17 and its role in synovial inflammation and bone damage in arthritis

IL-17 is a pro-inflammatory cytokine (Table 1), which is known to be an important contributor to the development and progression of RA and other autoimmune diseases (Table 2) [9–11]. IL-17 is a signature cytokine of CD4 $^{+}$ Th17 cells. However, IL-17 also can be produced by CD8 $^{+}$ T cells, natural Th17 cells, innate lymphoid cells (ILCs), $\gamma\delta$ T cells, natural killer (NKT) cells, and neutrophils [9, 12]. Of these, two subsets of cells deserve special mention. Natural Th17 cells are present in the skin and mucosa and they can produce IL-17 in response to IL-1 and IL-23 [9, 13]. As with adaptive Th17, natural Th17 also develop in the thymus. ILCs, which are found in the gut and skin, can produce IL-17 in response to inflammatory cytokines and stress [9, 14, 15]. Unlike natural Th17 cells, ILCs develop in the bone marrow.

The IL-17 family of cytokines consists of 6 members, IL-17A-F (Table 1) [16]. The most widely studied of the family members is the IL-17A. IL-17A and IL-17F signal through a heterodimeric receptor complex that includes the IL-17RA and IL-17RC. IL-17RA is found ubiquitously but can only signal in the presence of IL-17RC [17]. The IL-17RA/RC complex signals through tumor necrosis factor receptor-associated factor 6 (TRAF6) leading to activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), mitogen-activated protein kinase (MAPK), and other pathways and production of

inflammatory mediators [9, 18–20]. Various cytokines, chemokines and other mediators of inflammation increase the expression of IL-17. This cytokine has been shown to have a cooperative or an antagonistic relationship with other pro-inflammatory cytokines such as IFN γ [21–24].

IL-17 directly aggravates arthritic inflammation by binding to its receptor (IL-17RA/IL17RC) on immune cells as well as fibroblasts, osteoblasts, synoviocytes and endothelial cells, and stimulating them to produce more pro-inflammatory cytokines, chemokines and other inflammatory mediators including nitric oxide (NO), prostaglandins, and matrix metalloproteinases (MMPs) [10, 23, 25–28]. IL-17 works synergistically with other pro-inflammatory cytokines, mainly IL-1, IL-6 and tumor necrosis factor- α (TNF- α) to increase the production of diverse mediators of inflammation. IL-17 itself acts as a chemotactic factor and promotes immune cell infiltration into the arthritic synovium. In addition, IL-17 facilitates neovascularization by stimulating fibroblasts to secrete vascular endothelial growth factor (VEGF), by promoting blood vessel growth, and by activating endothelial cells.

Osteoclastic bone resorption is another characteristic feature of arthritis besides inflammation. Molecular pathways involving the receptor activator of NF-Kappa B (RANK) and its ligand, RANK ligand (RANKL), play a critical role in regulating osteoclastogenesis in the joints in RA. IL-17 plays a major role in driving osteoclastogenesis [10, 23, 25–28]. IL-17 upregulates RANK on osteoclast precursors and thereby increases their sensitivity to RANKL. Also, IL-17 induces the production of RANKL. Furthermore, IL-17 induces the expression of macrophage-colony stimulating factor (M-CSF), which is required for the differentiation and survival of osteoclasts.

IL-23 and the IL-23/IL-17 axis

IL-23 is a member of the IL-12 cytokine family and it is mainly secreted by activated macrophages and dendritic cells (DCs). The levels of IL-17 and IL-23 are elevated in the serum and synovial fluid of patients with RA, and these levels positively correlate with the disease severity [29–31]. However, these cytokines are barely detectable in healthy joints and in the joints of patients with osteoarthritis. There are other pieces of support for the strategic role of IL-23 in several autoimmune diseases including RA. For example, naïve T cells do not express the receptor for IL-23 (IL-23R), but this receptor is expressed on activated Th17 cells. IL-23 not only acts on conventional $\alpha\beta$ T cells, but also on innate cells such as $\gamma\delta$ T cells and cells of myeloid origin. Furthermore, IL-23 is required for the amplification and stabilization of Th17 cells. IL-23 signals through Janus kinases (e.g., JAK2 and non-receptor tyrosine-protein kinase (Tyk2)) and signal transducer and activator of transcription (STATs) (STAT3 and STAT4). Sustained IL-23 signaling in T cells is of importance for maintaining ongoing inflammation [7]. Differentiated Th17 cells are maintained and expanded primarily by IL-23 [7, 8, 32]. In $\gamma\delta$ T cells, IL-23 promotes IL-17 production and to a lesser extent can do this without the engagement of the T cell receptor (TCR) [33]. Thus, both IL-23 and IL-17 form a new axis through Th17 cells, which play an important role in autoimmunity and chronic inflammation [9]. Examples of some diseases in

which Th17 cells and their cytokine products play a role in disease pathogenesis are shown in Table 2 [9, 20, 34].

The cytokine milieu for Th17 differentiation and the activity of Th17 cells

A primary source of IL-17 is the Th17 cell, which is characterized by the expression of the master transcription factor retinoic acid receptor-related orphan receptor gamma t (ROR γ t). Th17 cells differentiate from naïve T cells in the presence of different cytokine combinations in mice and humans [35]. In mice, TGF β and IL-6 have been shown to be sufficient for Th17 differentiation. IL-21 can also pair with TGF β to differentiate murine Th17 cells [36]. In humans, Th17 differentiation occurs in the presence of IL-1 β paired with either IL-6 or IL-23 [37, 38]. It was later shown that this type of differentiation occurs in T central memory cells, but that IL-21 and TGF β combine to differentiate naïve T cells into Th17 cells [39]. IL-6 and IL-21 both signal through STAT3, highlighting the importance of STAT3 in Th17 differentiation. In addition, since Th17 cells can produce IL-21 besides IL-17, IL-21 may have an autocrine effect in promoting Th17 responses.

The Th17 cells direct immune responses against extracellular bacteria and fungi and some intracellular pathogens (Table 2). IL-17A and IL-17F produced by Th17 cells aid the migration of neutrophils and other myeloid cells to sites of infection by inducing the production of chemokines (e.g., IL-8) [40]. These cytokines play a vital role in immunity against fungal infections, such as those caused by *Candida albicans* [41–46]. Genetic deficiency of IL-17RA (autosomal recessive) or IL-17F (autosomal dominant) has been reported in a subset of patients with chronic mucocutaneous candidiasis (CMC) characterized by infection primarily by *C. albicans* and sometimes by *Staphylococcus aureus* [43, 44]. Recently, the role of natural Th17 and $\gamma\delta$ T cells, but not by ILCs, in providing innate immunity against *C. albicans* infection in mice has been elaborated [45]. The clearance of *S. aureus* in the nasal mucosa has also been shown to be Th17-dependent and mediated via IL-17A production and neutrophil influx [47]. These findings are of relevance in understanding the pathogenesis of mucosal immunity against oral pathogens. In other studies, it has been shown that mycobacteria and *Pneumocystis carinii* induce IL-23 production by infected antigen-presenting cells (APCs). Furthermore, knocking out p19 of IL-23 or neutralizing IL-17 prevents the clearance of *P. carinii*, further supporting the role of Th17 cells in anti-fungal immune response [48]. In addition, it has been shown that IFN α promotes Th17 effector response, while inhibiting Treg activity, thus favoring an inflammation-promoting milieu [49].

The phenotype, cellular differentiation, and activity of Treg cells

The Treg cells are of CD4⁺ CD25⁺ Foxp3⁺ phenotype. CD25 represents the IL-2 receptor alpha (IL-2R α), whereas Forkhead box 3 (Foxp3) is the intracellular transcription factor expressed by these cells. Treg cells belong to two subsets: natural Tregs (nTreg) and inducible Tregs (iTreg). A large proportion of Treg cells develop in the thymus (nTreg) when a developing T cell binds to self-antigen with high-affinity. The second population of Treg cells differentiates in the periphery (iTreg) from naïve T cells following activation by an antigen [50]. Based on the location of their development, the terms thymically-derived

Treg (tTreg) and peripheral Treg (pTreg) are now being used in favor of the terms nTreg and iTreg, respectively [50, 51].

The differentiation of Treg requires TGF β [52]). TGF β signals through the TGF β receptor and SMAD family member proteins (human homologue of *Drosophila* Mad (Mad = Mothers against decapentaplegic) and the related *Caenorhabditis elegans* gene Sma) leading to Foxp3 expression. IL-2 has been shown to be indispensable for both Treg proliferation and differentiation [53]. IL-2 signals through the IL-2R and STAT5 to induce and maintain Foxp3 expression. This was evident following IL-2 treatment of cancer patients that resulted in an increase in Treg cells, followed by a decrease in Treg cells when IL-2 treatment was terminated [54]. Once the Treg cell differentiates, it upregulates the expression of CD25 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), but downregulates CD127 (representing IL-7R α) (in humans) [55].

Treg cells play an important role in the induction of tolerance and protection against autoimmunity [53, 55–57]. Treg cells suppress effector cells through a number of secreted and surface-expressed proteins. Evidence from different studies supports at least four main mechanisms of suppression [58–64]: cell-cell contact involving inhibitory surface molecules (CTLA-4 and lymphocyte-activation gene 3 (LAG-3)); inhibitory cytokines (TGF- β , IL-10); cytolytic activity (granzyme/perforin); and metabolic disruption (IL-2 deprivation). First, Treg cells express CTLA-4, which, in mice, has the ability to trans-endocytose CD80/CD86 from dendritic cells (DCs). This prevents DCs from activating and expanding the effector T cell population. Similarly, LAG-3, which is a CD4-related molecule that binds the major histocompatibility complex (MHC) class II molecule, limits the expansion of activated T cells in part via inhibiting the TCR signaling [64]. Second, Tregs produce anti-inflammatory cytokines (e.g., IL-10, TGF- β , and IL-35). Third, Tregs can mediate cytotoxicity of target cells via granzyme/perforin. Fourth, high-level expression of IL-2R on Treg cells is believed to deprive the effector T cells of IL-2 and inhibit their proliferation [58, 63]. The balance between the effector T cells and the regulatory T cells determines whether or not autoreactive cells are able to induce and propagate an autoimmune response (Figure 1).

The control of Th17 cells by Tregs and/or cytokines

The cytokines produced by Treg cells have been shown to inhibit Th17 development. Many cell types including Treg cells produce TGF β . At higher doses and in the absence of inflammatory cytokines (IL-6 and IL-1), TGF β promotes Foxp3 expression, which inhibits ROR γ t [65]. Recombinant IL-10 has been shown to limit Th17 differentiation in vitro, and IL-10 $^{-/-}$ mice have increased expression of IL-17 and IL-22 [66]. This was confirmed by the finding that Th17 cells from an RA patient treated with IL-10 in vitro had reduced expression of IL-17 and RORC, but increased expression of Foxp3 [67]. An additional mechanism of Th17 inhibition by Tregs was discovered when two different TNF α -inhibitors, adalimumab and etanercept, were tested on immune cells from an active RA patient. IL-10 and TGF β were sufficient to suppress IFN γ , but had much less effect on IL-17 production. Instead, the altered activation and expression of IL-6 by monocytes from RA patients correlated with the reduction in IL-17. Furthermore, co-culture of adalimumab-

treated Treg cells and monocytes identified an IL-10-independent mechanism of Th17 inhibition [68].

Other cytokines not typically produced by Treg cells that control Th17 differentiation are IL-4 and IL-27. IL-4 can inhibit IL-17 production by Th17 cells in a STAT6-dependent inhibition of STAT3. IL-4 cannot cause the already differentiated Th17 cells to become Th2 cells, but it can inhibit IL-17 production. However, this is short-lived as Th17 cells exposed to IL-4 for long-term become sensitized and downregulate IL-4R expression [69]. Next, IL-27 has been shown to antagonize Th17 development in vivo in a STAT-1-dependent, IFN γ -independent mechanism [70]. We have also shown that the injection of recombinant IL-27 limits autoimmune arthritis and IL-17 production in the rat adjuvant arthritis (AA) model of RA [23].

The dynamics of the Th17/Treg balance in the course of arthritis

It has been reported that Th17 cells are significantly increased in the peripheral blood of RA patients compared to healthy controls [71–75]. However, the pattern of change in Treg cell number and/or function in RA is not fully clear [76]. Some investigators have shown either a decrease [71–73, 77] or no change [78] in the frequency of Tregs, while others have reported an increase [79] in Treg in the peripheral blood of RA patients [80]. Comparative evaluation of Treg frequency in the synovial tissue/joints versus peripheral blood has revealed two types of patterns. Most of the reports indicate increased Treg in synovial tissue [78, 79, 81], while some others show reduced Treg [77, 82, 83] compared to peripheral blood.

It has been reported by several investigators that Treg are functionally defective in RA [84–87], while few investigators observed that Treg are not defective in their suppressive activity [78, 79]. The suppressive function of Treg cells is controlled by the phosphorylation of Foxp3, and TNF α has been shown to reduce this phosphorylation leading to an increase in IL-17 response [88]. Furthermore, the effect of TNF α could be reversed by anti-TNF α antibody treatment. Recent studies have shown that defective Treg function in RA might be attributable to dysregulated methylation of an enhancer region upstream of the Foxp3 locus [85]. Another set of studies have revealed that deficiency in Treg function in RA involves defects in the expression and function of CTLA-4 [86] and epigenetic modifications resulting in failure to activate the immunosuppressive indoleamine 2, 3-dioxygenase (IDO)-mediated pathway [87].

In general, the lower Th17/Treg ratio in healthy controls versus active RA patients supports the role of Treg in autoimmune pathogenesis in arthritis. A decrease in Treg function may be associated with an increase in the severity of arthritis. Interestingly, various treatment regimens such as non-depleting anti-CD4 antibody [89], IL-21 [90], or anti-IL-6 receptor antibody [91] in animal models of RA, and anti-IL-6 receptor antibody (tocilizumab) [92], anti-TNF α antibody [68, 88], or combination therapy using methotrexate and etanercept [73] in RA patients have been shown to correct the disturbed Th17/Treg imbalance [80]. Furthermore, a differential effect of anti-TNF α modalities was observed in a study comparing adalimumab and etanercept: Treg of patients treated with adalimumab, but not those treated with etanercept showed suppressive effect on Th17 cells [68]. The effect of

anti-TNF therapy on Th17/Treg balance has also been observed in a model of uveitis [93]. In that study, anti-TNF therapy inhibited the differentiation of Th17 cells and thereby, altered the Th17/Treg balance in favor of immune suppression. Taken together, the results of the above-mentioned studies and the success of Treg adoptive therapy in animal models of RA and other autoimmune diseases have offered a convincing rationale for considering Treg supplementation as a therapeutic approach for RA [94, 95].

Paradoxical, regulatory role of IL-17 and IL-17-expressing T cells

We have described above the pathogenic role of IL-17 and Th17 cells. Three aspects of IL-17 and Th17 deserve special mention. First, that IL-17 is not equivalent to Th17, and vice versa [96]; second, both IL-17 and Th17 have been shown to expression anti-inflammatory activity under specific conditions [97, 98]; and third, a subset of Foxp3-expressing regulatory T cells have been shown to produce IL-17 [99, 100]. For example, IL-17-producing regulatory Th17 cells have been reported to modulate disease in an experimental model of type 1 diabetes (T1D) [97]. In another study, it has been shown that IL-17 displays an anti-inflammatory role in experimental autoimmune uveitis [98]. Finally, IL-17-producing regulatory T cells have been shown to possess suppressive activity [99, 100]. These new realizations show the complexities pertaining to the prototypic pro-inflammatory cytokine IL-17 and IL-17-producing T cells. Further studies are required to fully understand the dual role of these mediators of inflammation.

Therapeutic approaches based on IL-17/IL-23 and Th17/Treg balance

Neutralization of IL-17/IL-23 for the treatment of arthritis

Therapeutic efficacy of IL-17 neutralization has been investigated in experimental models of RA and in RA patients [101–104]. In rat AA and mouse CIA models, treatment with anti-IL-17A alleviated symptoms of arthritis and afforded protection against bone damage [101]. Two IL-17A-neutralizing antibodies, secukinumab- a fully human monoclonal antibody of the IgG1/ γ isotype and ixekizumab- a humanized antibody of the IgG4 isotype, have been tested in the clinic. Both these antibodies improved clinical signs and symptoms, with no major adverse effects in RA, psoriatic arthritis (PsA), and ankylosing spondylitis [103, 105, 106]. Similarly, the efficacy and safety of brodalumab, a human monoclonal antibody against IL-17RA, was tested in a phase 2, randomized, double-blind, placebo-controlled study involving patients with PsA [104]. Brodalumab induced a marked improvement in patients with PsA. However, in one trial, this antibody was not much effective against RA [107]. IL-17RA is a common receptor subunit for IL-17 family member ligands (except for IL-17B), and blocking/inhibiting it may affect the functions of other members as well. Therefore, targeting the other receptor of IL-17, IL-17RC, is being considered for the control of autoimmune diseases.

Blocking IL-23, which is required for Th17 expansion and maintenance, has also been attempted as a potential therapeutic strategy. Ustekinumab, a human monoclonal antibody against IL-12/23 (p40 subunit), has been tested in patients with PsA and found to cause a significant reduction in the signs and symptoms of that disease [108–110]. Briakinumab and

guselkumab are other antibodies against IL-23, which are being tested in different diseases including PsA and Crohn's disease.

Inhibition of STAT3 and ROR γ t to control arthritis

STAT3 is a signaling protein that is activated by IL-6 and IL-21. It has been shown to bind to the IL-17A and IL-17F loci [111]. STAT3 $^{-/-}$ mice display a severe reduction in ROR γ t expression and Th17 development, leading to increased Treg cells [112]. Taken together, STAT3 directly regulates the differentiation of Th17 cells and targeting STAT3 is one way to reset the Th17/Treg cell imbalance seen in RA (Figure 1). There are a few examples in animal models that confirm that STAT3 inhibition limits autoimmune arthritis. STA-21 is a small molecule that inhibits the DNA binding of STAT3 [113]. Furthermore, natural products can also limit STAT3 signaling. For example, epigallocatechin-3-gallate (EGCG) [114] and Celastrol [115] are bioactive components of green tea and Celastrol, respectively, and they alter the Th17/Treg ratio in favor of Treg and limit arthritis by blocking STAT3 phosphorylation. Similar effects have been reported for grape seed proanthocyanidin extract [116] and haloguginone [117]; the latter is a synthetic analog of a natural herbal alkaloid.

When activated by IL-6 or IL-21, STAT3 increases the expression of ROR γ t. As the master regulator of Th17 cells, ROR γ t is a prime target to alter autoimmune arthritis. Naturally-derived digoxin and its synthetic derivatives [118], and synthetic SR1001 [119] have been shown to inhibit ROR γ t, which resulted in a reduction in Th17 cells in vitro and in vivo. This reduction in Th17 cells correlated with reduced autoimmune disease in mice [118, 119]. In contrast, the effect on Treg cells is less correlative and is dependent on which inhibitor is used.

Concluding remarks

Defining the IL-23/IL-17 axis and elaborating the differentiation and function of Th17 and Treg cells represent major advancements in immunology in the past decade. Knowledge of the biochemical and molecular pathways and cellular events driven by these mediators of inflammation has filled many gaps that the Th1/Th2 paradigm could not fully explain. However, it would be an oversimplification, albeit incorrect, to conclude by any criteria that functionally Th17/Treg has supplanted Th1/Th2 activities. In fact, the two systems are known to cooperate in certain situations, while being adversaries in others. Furthermore, IL-17 and Th17 have been shown to display anti-inflammatory activity in some situations, and IL-17-producing Treg have also been reported. These issues need to be addressed in future research.

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HIGHLIGHTS

- IL-17 produced by Th17 cells plays a vital role in the pathogenesis of arthritis.
- Th17/Treg imbalance contributes to the initiation and progression of arthritis.
- Neutralization of IL-17 and IL-23 is being explored for the treatment of arthritis.
- Various synthetic/ natural products are being tested for resetting Th17/Treg balance

Figure 1. Targeting IL-17, IL-23, and the Th17/Treg imbalance for the control of autoimmune arthritis

IL-17 drives inflammation and bone destruction in arthritis by promoting the cellular migration and activation of osteoclasts. One therapeutic approach in arthritis would be to limit the effects of IL-17. This can be achieved either by direct inhibition of IL-17 through the use of monoclonal antibodies against IL-17 or by indirect inhibition via blocking the function of the primary producer of IL-17, the Th17 cell. The use of inhibitors against STAT3 or RORγt could block the production of IL-17, and potentially might have the added effect of promoting the generation of inducible Treg (or pTreg) cells because of the antagonistic relationship between Th17 and Treg differentiation. Since pro-inflammatory Th17 cells express the IL-23R, antibodies against IL-23 may also be beneficial in targeting Th17-mediated autoimmune diseases.

Table 1

IL-17 Family of Cytokines

Member Name	Receptors	Homology with IL-17A (%)	Source
IL-17A	IL-17RA/RC	100	CD4+ T cells, CD8+ T cells, eosinophils, and neutrophils
IL-17B	IL-17RB	24	Pancreas, small intestine, stomach, and spinal cord
IL-17C	IL-17RA/RE	26	Human testis, thymus, spleen, and prostate
IL-17D	Unknown	30	Skeletal muscle, neuronal cells, prostate, and some resting CD4+ T lymphocytes
IL-17E (CD25)	IL-17RA/RB	16	Brain, lung, testis, prostate, and CD4+ T cells
IL-17F	IL-17RA/RC	50	CD4+ T cells
IL-17A/F (Heterodimer)	IL-17RA/RC	-	CD4+ T cells

This table is based on information from previously published reports [20, 120–127]

Table 2

Examples of diseases associated with cytokines secreted by Th17 cells

Disease category	Human disease	Animal model	Th17 cytokines involved	References
Autoimmunity	Rheumatoid arthritis (RA)	Collagen-induced arthritis, Adjuvant-induced arthritis, SKG model	IL-17A	[10, 25, 26]
	Multiple sclerosis (MS)	Experimental autoimmune encephalomyelitis	IL-17A, IL-17F	[128, 129] [130]
	Systemic lupus erythematosus (SLE)	MRL/lpr, NZB/W F1, BXD2	IL-17A	[131, 132]
	Psoriasis	Chronic proliferative dermatitis, transgenic cutaneous overexpression of cytokines, IL-23 injection i.d.	IL-17A, IL-22	[133–135]
	Inflammatory bowel disease (IBD)	Trinitrobenzenesulfonic acid-induced colitis, Dextran sulfate sodium-induced colitis	IL-17A, IL-17F	[136–138]
	Type 1 diabetes mellitus (T1D)	NOD mouse, STZ-induced Type 1 diabetes mellitus	IL-17A, IL-17F	[139, 140]
Allergy	Bronchial asthma	Allergen sensitization in BALB/c; RSV-induced asthma exacerbation	IL-17E (IL-25), IL-17F	[141–143]
Fungal/Bacterial infections and host defense	Chronic mucocutaneous candidiasis (CMC)	Oral/dermal infection of mice with <i>Candida albicans</i>	IL-17A, IL-17F	[43, 45, 46, 144]
	Pulmonary tuberculosis, pertussis, and pneumonia	Aerosol route to infect mouse, retropharyngeal instillation of the causative bacteria	IL-17A, IL-17F	[145, 146] [147]