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REVIEW

IL-17/IL-17 receptor system in autoimmune disease: mechanisms and therapeutic potential

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ABSTRACT

IL-17 (interleukin-17), a hallmark cytokine of Th17 (T-helper 17) cells, plays critical roles in host defence against bacterial and fungal infections, as well as in the pathogenesis of autoimmune diseases. The present review focuses on current knowledge of the regulation, functional mechanisms and targeting strategies of IL-17 in the context of inflammatory autoimmune diseases. Evidence shows that IL-17 is highly up-regulated at sites of inflammatory tissues of autoimmune diseases and amplifies the inflammation through synergy with other cytokines, such as TNF (tumour necrosis factor) α. Although IL-17 was originally thought to be produced mainly by Th17 cells, a newly defined T-cell subset with a specific differentiation programme and tight regulation and several other cell types (especially innate immune cells) are also found as important sources for IL-17 production. Although IL-17 activates common downstream signalling, including NF-κB (nuclear factor κB), MAPKs (mitogen-activated protein kinases), C/EBPs (CCAAT/enhancer-binding proteins) and mRNA stability, the immediate receptor signalling has been shown to be quite unique and tightly regulated. Mouse genetic studies have demonstrated a critical role for IL-17 in the pathogenesis of variety of inflammatory autoimmune diseases, such as RA (rheumatoid arthritis) and MS (multiple sclerosis). Importantly, promising results have been shown in initial clinical trials of monoclonal antibodies against IL-17 or its receptor (IL-17R) to block IL-17-mediated function in treating autoimmune patients with psoriasis, RA and MS. Therefore targeting IL-17/IL-17R, IL-17-producing pathways or IL-17-mediated signalling pathways can be considered for future therapy in autoimmune diseases.

Key words: autoimmune disease, defence, inflammation, interleukin-17 (IL-17), T-helper 17 (Th17).

Abbreviations: AHR, aryl hydrocarbon receptor; APC, antigen-presenting cell; BATF, basic leucine zipper transcription factor ATF-like; BBB, blood–brain barrier; CCL, CC chemokine ligand; CD, Crohn's disease; CIA, collagen-induced arthritis; CNS, central nervous system; CSF, colony-stimulating factor; CXCL, CXC chemokine ligand; DC, dendritic cell; DN, double-negative; DSS, dextran sodium sulfate; EAE, experimental autoimmune encephalomyelitis; Foxp3, forkhead box p3; G-CSF, granulocyte colony-stimulating factor; G-CSF, granulocyte CSF; GM-CSF, granulocyte/macrophage CSF; GWAS, genome-wide association studies; IBP, IRF4-binding protein; IFN, interferon; IL, interleukin; IL-6R, IL-6 receptor; IL-17R, IL-17 receptor; IL-23R, IL-23 receptor; IRF4, IFN regulatory factor 4; JNK, c-Jun N-terminal kinase; LTi-like cell, lymphoid-tissue inducer-like cell; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; MEF, mouse embryonic fibroblast; MIP, macrophage inflammatory protein; miRNA, microRNA; MS, multiple sclerosis; NFAT, nuclear factor of activated T-cells; NF-κB, nuclear factor κB; IκB, inhibitor of NF-κB; IKK, IκB kinase; NK, natural killer; NKT, NK T-cell; iNKT cell, invariant NKT cell; NOD, non-obese diabetic; PBMC, peripheral blood mononuclear cell; PGE_2, prostaglandin E_2; RA, rheumatoid arthritis; RANKL, receptor activator of NF-κB ligand; ROR, retinoic acid-receptor-related orphan receptor; Runx1, runt-related transcription factor 1; SEFIR, SEF/IL-17R; SLE, systemic lupus erythematosus; STAT, signal transducer and activator of transcription; T1DM, Type 1 diabetes mellitus; TCR, T-cell receptor; TCR, T-cell receptor; TGFβ, transforming growth factor β; TAK1, TGFβ-activated kinase 1; Th cell, T-helper cell; TILL, TIR (Toll/IL-1R)-like loop; TNBS, trinitrobenzene sulfonic acid; TNF, tumour necrosis factor; BAFF, B-cell-activating factor belonging to the TNF family; TNFR, TNF receptor; TRAF, TNFR-associated factor; T_{reg}-cell, regulatory T-cell; nT_{reg}-cell, natural T_{reg}-cell; UC, ulcerative colitis.

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INTRODUCTION

IL (interleukin)-17A (or IL-17) was cloned by a subtractive hybridization screen in a rodent T-cell library in 1993 [1], and was then recognized as an inflammatory cytokine produced by T-cells and exerted its function mainly on myeloid cells and mesenchymal cells to induce the expression of G-CSF [granulocyte CSF (colony-stimulating factor)], IL-6 and certain chemokines, which in turn recruited neutrophils to infectious sites [2,3].

In 1986, Mosmann and Coffman [4] introduced the concept of distinct types of Th cells (T-helper cells), which was based on their distinct cytokine secretion and function. IL-12-activated Th1 cells secrete IFN (interferon)-γ, which mediates cellular immunity, whereas Th2 cells produce IL-4, IL-5 and IL-13, which mediate humoral immunity (Figure 1). However, some intriguing phenomena were observed that cannot be explained by the Th1/Th2 paradigm. IFN-γ- and IL-12-deficient mice were unexpectedly found to be more susceptible to EAE (experimental autoimmune encephalomyelitis), a mouse model for MS (multiple sclerosis) [5,6]. This paradox remained elusive until the discovery of the third helper T-cell subset, the Th17 subset, which produces IL-17A, IL-17F, IL-21 and IL-22 (Figure 1). It is now known that Th17 cells play a major role in EAE development. As the Th1-related cytokines (IFN-γ and IL-12) inhibit Th17 development, mice with a deficiency in Th1 cytokines are more susceptible to EAE, probably due to increased Th17 cells. Importantly, recent findings have demonstrated that both Th1 and Th17 cells can independently induce EAE, probably through different mechanisms [7–10].

In addition to Th17 cells, several innate immune cell types are described as sources for IL-17, including $\gamma\delta$ T-cells, NK cells (natural killer cells), NKT cells (NK T-cells), macrophages, DCs (dendritic cells), neutrophils, mast cells and lymph tissue inducer cells [11]. IL-17 exerts various functions in host defence, autoimmune diseases, allergy, transplantation, obesity and diabetes, and malignancy [12–30]. In the present review, we will summarize the sources, signalling pathways and biological characteristics of IL-17, its roles in the pathogenesis of autoimmune diseases and the therapeutic potential by targeting IL-17/IL-17R (IL-17 receptor) axis.

IL-17 EXPRESSION AND REGULATION

Following the discovery that IL-23 promotes the secretion of IL-17 by amplifying differentiated Th17 cells, which was recognized as the major source of IL-17 *in vivo* [31,32], further investigations have demonstrated that IL-23 can also induce IL-17 expression in RAG (recombination-activating gene)-deficient mice which lack both B- and T-cells, suggesting that there is an existence of innate IL-17-producing cells [33]. Now, it is believed that IL-17 can be expressed by adaptive $\alpha\beta$ T-cells, as well as the innate $\gamma\delta$ T-cells, iNKT cells (invariant NKT cells), LTi (lymphoid-tissue inducer)-like cells and myeloid cells [11]. In the present review, we mainly summarize the regulation of Th17 cells, especially mouse Th17 cells which have been investigated intensively.

After Th17 cell was discovered, a number of reports rapidly followed describing the factors involved in the differentiation and regulation of the Th17 lineage. Mouse Th17 cell differentiation is driven by TGFβ (transforming growth factor β), IL-1β (or IL-1) and IL-6. Although IL-23 is required to expand and stabilize the cell population [34–40], Th17 cell differentiation is regulated by the transcription factors STAT (signal transducer and activator of transcription) 3, RORγt [ROR (retinoic acid-receptor-related orphan receptor) γt], IRF4 (IFN regulatory factor 4), AHR (aryl hydrocarbon receptor), BATF (basic leucine zipper transcription factor ATF-like) and Runx1 (runt-related transcription factor 1) [41–53]. In addition to IL-17A, mouse Th17 cells produce IL-17F, IL-21 and IL-22 to mediate various functions [16,45,54,55]. Described below are the well-defined positive and negative regulators for mouse Th17 differentiation and IL-17 production (Figure 1).

Positive regulators

RORγt and RORα

RORγt, which is a splice variant of RORγ expressed in T-cells [48,56], was identified as the linage-specific transcription factor for Th17 cells [42], as T-bet and GATA3 are the lineage-specific transcription factors for Th1 and Th2 cells respectively [57,58]. However, although reduced, IL-17-producing cells are not absent in RORγt-deficient mice. Another ROR family member, RORα, was subsequently discovered to have a redundant role with RORγt in promoting Th17 cell differentiation, as deficiency of both RORα and RORγt completely inhibited Th17 cell generation *in vitro* and *in vivo* [47]. RORγt and RORα are both strongly induced by IL-6 or IL-21 in the presence of low amounts of TGFβ [41]. However, the mechanisms by which RORγt and RORα regulate IL-17 production have not yet been fully elucidated.

STAT3

STAT3 conditional knockout mice with STAT3 deletion in T-cells have impaired Th17 differentiation, whereas overexpression of a constitutively active form of STAT3 in T-cells can increase IL-17 production [44,47]. Importantly, loss of STAT3, which is the critical downstream transcription factor of the IL-6 and IL-21 signalling pathways, markedly decreased RORγt and RORα expression and impaired Th17 differentiation

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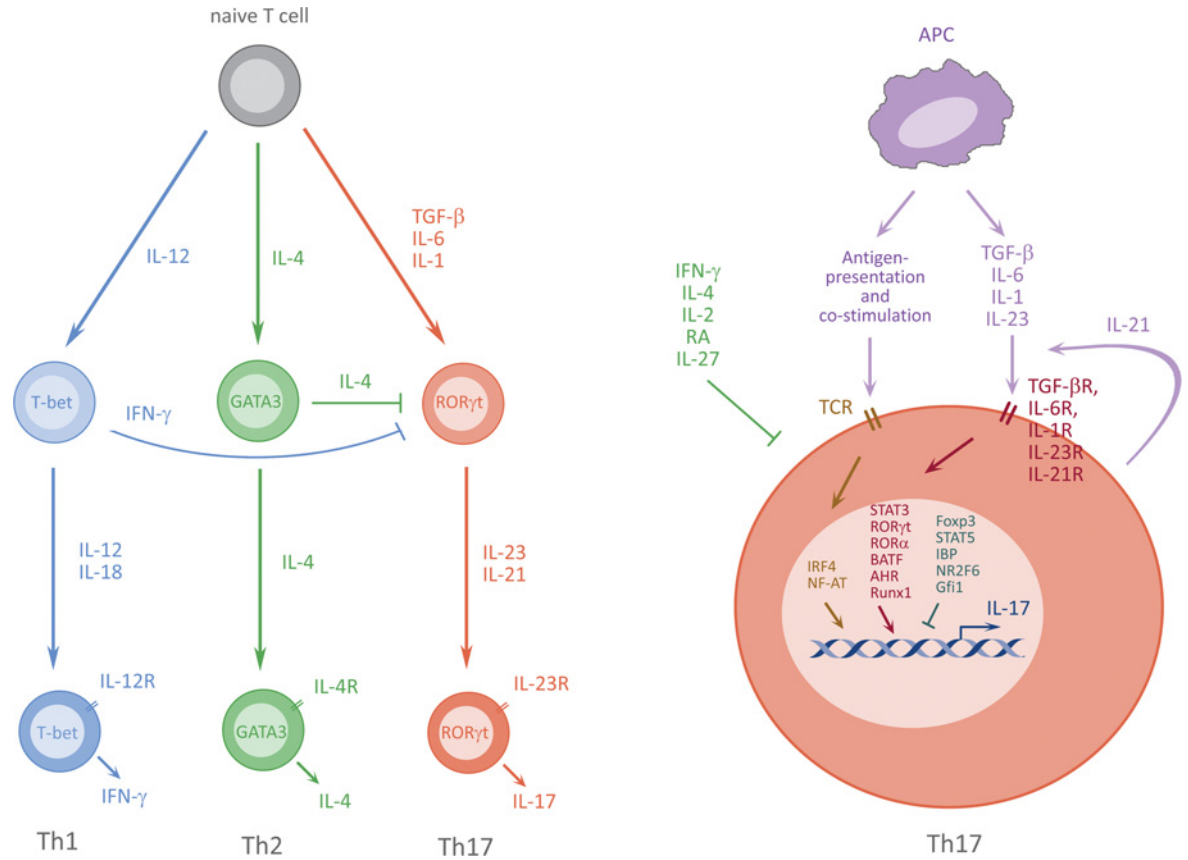

Figure 1 Differentiation of mouse Th17 cells and regulation of IL-17 expression

Left-hand panel, näive mouse T-cells can be differentiated into three subsets of effector Th cells. Differentiation of each subset is under the control of a distinct set of cytokines. IL-12 and IL-4 promote Th1 and Th2 differentiation respectively, whereas the Th17 differentiation is under the control of APC-secreted TGFβ, IL-6, IL1, IL23 and self-secreted IL21. The Th17 differentiation pathway is inhibited by IFN-γ and IL4. Tbet, GATA3 or RORγt is the linage-specific transcription factors of Th1, Th2 and Th17 respectively. Right-hand panel, Detailed regulation of mouse Th17 differentiation and IL-17 expression. *In vivo*, Th17 differentiation requires antigen presentation and co-stimulation, and activation of APCs to produce TGFβ, IL6, IL1, IL23 and IL21. This initial activation results in the activation and up-regulation of STAT3, RORγt and other transcriptional factors to induce IL17 production. After rounds of proliferation and differentiation in the lymph node, polarized Th17 cells, with the stable expression of RORγt, are ready to migrate into target tissues. The transcription factors or regulators that positively or negatively regulates IL-17 production are shown inside the nucleus. The cytokines that indirectly inhibit Th17 differentiation are also shown in green outside of the cell.

[44,46,59]. Moreover, STAT3 also binds directly to the IL-17 and IL-21 promoters [45,60]. STAT3 and RORγt seem to co-operate in the regulation of IL-17 expression depending on the availability of both transcription factors [41].

IRF4

IRF4, which is induced by TCR (T-cell receptor) activation, has been reported to be associated with the differentiation of the Th1 and Th2 subsets [61,62]. It is also found to be required for the differentiation of Th17 cells [49]. IRF4-deficient T-cells failed to induce RORγt expression and could not be differentiated into Th17 cells in the presence of TGFβ plus IL-6 [49]. Consistently, IRF4-deficient mice failed to generate Th17 cells *in vivo* and were resistant to EAE induction [49].

Other transcription factors that are also involved in full commitment of T-cells to the Th17 lineage, including BATF, Runx1, AHR, IKKα {IκB [inhibitor of NF-κB (nuclear factor κB)] kinase α}, IκBζ and NFATc1 [NFAT (nuclear factor of activated T-cells) c1] [50–53,63–65] (Figure 1). Recent reports have shown that the microRNA *miR-326* also regulates the differentiation of Th17 cells by targeting the negative regulator Ets1 [66].

Negative regulators

Foxp3 (forkhead box P3)

Foxp3 is a specific marker of nT_{reg} cells [natural T_{reg}-cells (regulatory T-cells); a lineage of T-cells] and a/iT_{reg}-cells (adaptive/induced T_{reg}-cells) [67-69]. Animal studies show that Foxp3-expressing T_{reg}-cells are a specialized subpopulation of T-cells which suppress

activation of the immune system and thereby maintains tolerance to self-antigens. Th17 and T_{reg}-cell developmental programmes are interconnected reciprocally. Upon TCR stimulation, a naive T-cell can be driven to express Foxp3 and become a T_{reg} cell in the presence of TGFβ. However, in the presence of TGFβ plus IL-6 or IL-21, the T_{reg}-cell developmental pathway is abrogated; instead T-cells develop into Th17 cells. Reports have shown Foxp3 physically associates with both RORγt and RORα to antagonize the functions of each other [70,71].

STAT5

STAT5 is a critical downstream transcription factor of IL-2, which is important for T-cell survival. Genetic deletion or antibody blockade of IL-2 promoted differentiation of the Th17 cell subset *in vivo*. Whereas STAT3 is a key positive regulator of RORγt and Th17 differentiation, deletion of STAT5 resulted in enhanced Th17 cell development, probably due to the abolishment of an IL-2-mediated suppressive effect [72]. The inhibitory effect of STAT5 on Th17 differentiation may also be due to its competitive binding with STAT3 to the same locus encoding IL-17 [73].

IBP (IRF4-binding protein)

IBP was cloned by yeast two-hybrid using IRF4 as bait [74]. IBP is broadly expressed in the immune system and can be detected in both T- and B-cell compartments [74]. Mice deficient in IBP spontaneously developed SLE (systemic lupus erythematosus)-like systemic autoimmunity in one study [75] or rapidly developed RA (rheumatoid arthritis)-like joint disease and large-vessel vasculitis in another study [76]. The pathology was associated with the inappropriate synthesis of IL-17 and IL-21. Mechanistically, IBP sequestered IRF-4 and prevented it from targeting the transcriptional regulatory regions of the genes that encode IL-17 and IL-21 [76].

Other transcription factors are also reported to negatively regulate Th17 differentiation, including the nuclear orphan receptor NR2F6, which directly interfered with the transcriptional activity of the NFAT-dependent IL-17A cytokine promoter [77], Gfi1 (growth factor independent 1), which inhibited RORγt activity [78], and eomesodermin, which directly bound to the proximal region of both the RORγ and IL17a promoters to suppress Th17 differentiation [79] (Figure 1). There are also some indirect inhibitory transcription factors, such as Ets-1, which does not bind to the IL-17 promoter or interfere with early signalling events of cytokines for Th17 differentiation, but is dependent on the inhibitory effect of IL-2 [80].

Many cytokines are also involved in the tight control of Th17 differentiation and IL-17 production. IL-2 inhibits Th17 differentiation though the downstream transcription factor STAT5 [72]. Retinoic acid inhibits the IL-6-driven Th17 differentiation and promotes T_{reg}-cell differentiation, thus regulating the balance of T_{reg}-cells and Th17 [81]. IL-27 inhibits the production of IL-17A and IL-17F by suppressing the expression of the Th17-specific transcription factor RORγt in a STAT1-dependent manner [82,83]. IFNγ and IL-4, the cytokines for Th1 and Th2 lineage respectively, also mediate transcriptional-factor-dependent inhibition of Th17 lineage [84] (Figure 1).

In addition to the effect in Th17 cells, RORγt has been shown to induce the transcription of IL-17 in innate IL-17-producing cells [11]. Although IL-6-dependent STAT3 activation is thought to be crucial for RORγt expression and development of Th17 cells, examination of *Il6*$^{-/-}$ mice revealed several innate subsets of IL-17-producing cells that arise independently of IL-6, including iNKT cells, $\gamma\delta$ T-cells, LTi-like cells and NK-like cells [11]. Another important transcriptional regulator that regulates innate IL-17-producing cells is AHR. It has been suggested that AHR can co-operate with RORγt to induce maximal amounts of IL-17 and IL-22 production and to inhibit TGFβ-induced FoxP3 expression [52,53]. AHR was shown further to interact with STAT1 and STAT5 to suppress STAT1- and STAT5-mediated negative effects and thus enhance the effects of IL-23- and RORγt-dependent functions [52,53].

Sources of IL-17 may vary in different types of inflammatory pathogenesis [11,41]. In autoimmunity, adaptive antigen-specific Th17 cells were thought to be the major source of IL-17 [41,85] and, usually, a polarized effector Th17 cell population takes up to 5 days *in vivo* [11]. Early IL-17 produced by innate $\gamma\delta$ T-cells has been shown to directly induce production of IL-23, IL-1, IL-6 and TGF-β in APCs (antigen-presenting cells) [86], which are crucial factors for the development of pathogenic Th17 cells. Moreover, in a CNS (central nervous system) autoimmune model, when $\gamma\delta$ T-cells were depleted during immune priming, fewer antigen-specific Th17 cells developed *in vivo* [86], suggesting that innate IL-17 produced early during immune priming could influence the generation of antigen-specific Th17 cells and exacerbate autoimmunity. In infection, a $\gamma\delta$ T-cell subset has been implicated as a primary source of early IL-17 production in the lungs during *Mycobacterium bovis* and *M. tuberculosis* infection [87,88], or in the skin during *Staphylococcus aureus* infection [89]. In a tissue injury model, resident iNKT-cells can expand rapidly and produce IL-17 following mitogen-induced injury by PMA skin painting [90].

Human Th17 cells and other IL-17 sources

Shortly after the recognition of factors that promote differentiation of mouse Th17 cells, efforts were made to generate human IL-17-producing CD4$^+$ T-cells. Similar to their mouse counterparts, human Th17 cells also express the master regulator RORC2, the human homologue of RORγt [91,92], and overexpression of

RORC2 in cord blood CD4$^+$ T-cells induces the expression of IL-17A, IL-17F and IL-26, but not IL-22 [93]. The role of other Th17-associated transcription factors in the development of human Th17 cells has been characterized relatively poorly. It is known that the transduction of human cord blood cells with RORA increases IL-17 expression [93], suggesting that, as in mice, this factor may co-operate with RORC2 to induce Th17 cells. STAT3 also appears to be critical for the development of human Th17 cells on the basis of evidence from patients with hyper-IgE sydrome, who carry autosomal-dominant mutations in *STAT3*. T-cells from these patients fail to differentiate into Th17 cells *in vitro* due to a lack of IL-6-stimulated STAT3 activation and consequently RORC2 expression [94,95]. AHR is also expressed by human Th17 cells [52], but it is not known whether it contributes to their development.

The differentiation conditions of human Th17 cells appear almost the same as mouse Th17 cells, such as IL-6, IL-1, IL-23 and IL-21 [41,85]; however, there are some arguments on the requirement of TGF-β for human Th17 differentiation. In the 2007, several studies claimed that TGF-β was dispensable for the differentiation of human Th17 cells [40,92]. One argument raised is that perhaps the human cells are not quite as naïve as their mouse counterparts. Several new reports have investigated this out by using naïve cord blood T-cells and have proved evidence that TGF-β is essential for the differentiation of human Th17 cells from naïve T-cells as well. TGF-β is required to induce RORC, but its expression and function are inhibited by excess TGF-β [93,96,97].

Given the perplexing data from human cells and the complex effects of TGF-β, the requirement of TGF-β for mouse Th17 differentiation has been revisited. In T-cells deficient in T-bet and STAT6 expression, IL-6 alone induces IL-17 production, even in the absence of TGF-β signalling [98]. This has been interpreted to indicate that TGF-β acts indirectly to regulate IL-17 by suppressing factors that drive other cell fates [99], especially Th1 and Th2 cell differentiation. In addition, the IL-23 R (IL-23 receptor) is induced in the absence of TGF-β, and addition of IL-23 induces receptor expression further. Consequently, the combination of IL-1, IL-6 and IL-23 is able to induce IL-17 production in a TGF-β-independent manner [100]. Consistent with these findings, Th17 cells are also present in the gut of mice with deficient TGF-β signalling [100,101].

In addition to the classic Th1 and Th17 subgroups, a mixed Th1-Th17 subgroup has been identified, which expresses both Tbet and RORC [85], showing the plasticity of Th1 and Th17 cells, similar to mouse system. It is quite common to observe IL-17/IFNγ double producers in lesion tissues in the setting of autoimmunity [102,103]. Besides this, there is even plasticity between Th17 cells and T_{reg}-cells [104]. As more states of CD4 T-cell differentiation are uncovered, their flexibility of differentiation is beginning to be recognized. The differentiation plasticity of T-cell subsets has recently been described, i.e. a committed T-cell subset can be reprogrammed to other T-cell subsets depending on cytokine environment [105].

In humans, IL-17 may also have innate sources. $\gamma\delta$ T-cells have been found to accumulate in acute MS lesions [106], as well as in the cerebrospinal fluid of patients with recent-onset MS [107], suggesting that innate cells may also have a role in human disease. Furthermore, human NKT cells treated with IL-23 *in vitro* produced IL-17 [108], and RORC$^+$ NK-like cells and LTi-like cells also could produce IL-17 [109,110].

IL-17R EXPRESSION AND SIGNALLING

IL-17 cytokine family consists of six members, IL-17A–IL-17F, with IL-17A and IL-17F sharing the highest degree of homology. The IL-17R family contains five receptor subunits, IL-17RA–IL-17RE [111,112]. Both IL-17 members and IL-17Rs have little homology to other known cytokines or cytokine receptors, and are thus classified as new cytokine and cytokine receptor families. IL-17A and IL-17F can form homodimers (IL-17A/IL-17A, or IL-17F/IL-17F) or heterodimers (IL-17A/IL-17F). Both IL-17A and IL-17F bind to the IL-17RA (also named as IL-17R) and IL-17RC heterodimeric complex to transduce downstream signalling. Human IL-17A has been shown to have higher affinity for IL-17RA than IL-17F, whereas human IL-17RC has a similar binding affinity for both IL-17A and IL-17F. However, mouse IL-17RC preferably binds to IL-17F [2,112,113]. IL-17Rs contain certain conserved structural motifs, including an extracellular fibronectin III-like domain and a cytoplasmic SEFIR (SEF/IL-17R) domain [114]. Different from other IL-17Rs, IL-17RA contains two extra domains, a TILL [TIR (Toll/IL-1R)-like loop] domain close behind SEFIR domain and an Distal domain in the C-terminus. IL-17RA appears to be a common subunit in the IL-17R family to form heterodimeric complexes with other IL-17Rs. [115]. Study of the crystal structure has shown that IL-17RA binds to IL-17F in a 1:2 stoichiometry. The mechanism of IL-17 cytokine and receptor complex formation has shown unique and involved the engagement of IL-17 by two fibronectin-type domains of IL-17RA. Binding of the first receptor to IL-17 modulated the affinity and specificity of the second receptor-binding event, thereby promoting heterodimeric compared with homodimeric complex formation [116]. IL-17RA is expressed ubiquitously, with particularly high levels in haemopoietic tissues [2,117]; however, the main responsive cells to IL-17 are epithelial cells, endothelial cells and fibroblasts, although macrophages and DCs are also responsive [112,118]. In contrast with IL-17RA,

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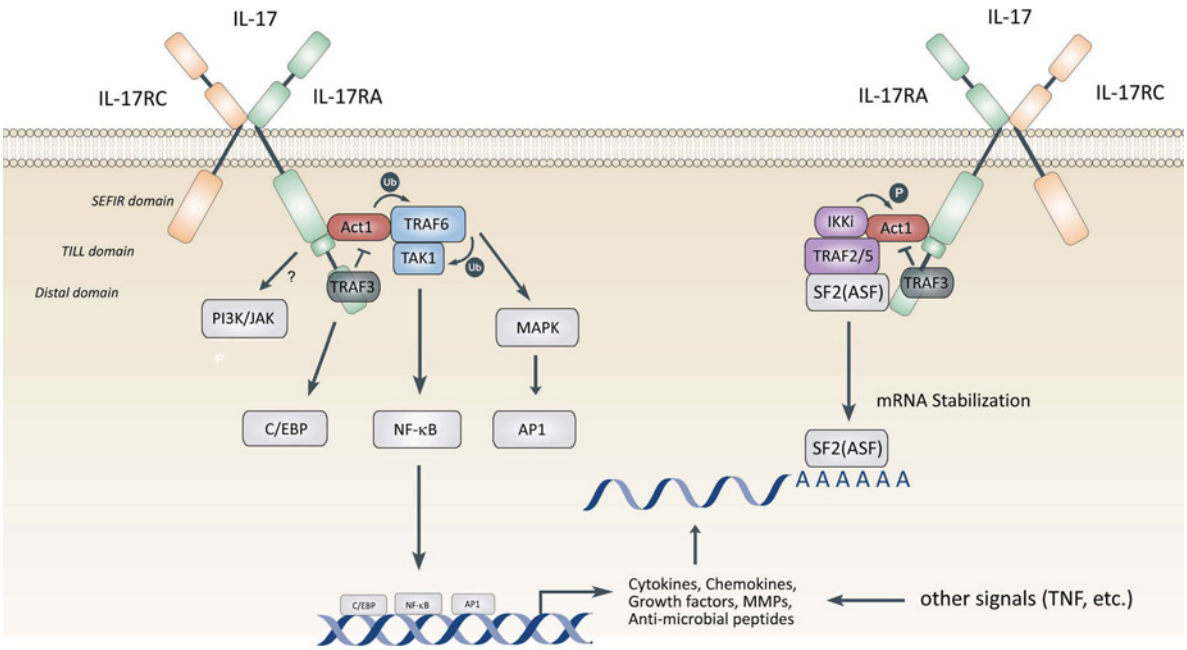

Figure 2 IL-17R-mediated signalling pathways

The IL-17R complex is composed of IL-17RA and IL-17RC. Both IL-17RA and IL-17RC have a SEFIR domain. IL-17RA has two extra domains called the TILL domain and Distal domain. Left-hand side, upon IL-17 stimulation, IL-17RA and IL-17RC form a heterodimeric complex to recruit Act1 through the SEFIR domain interaction. Act1 then associates with TRAF6 though its TRAF-binding sites to recruit TRAF6 to the IL-17R complex. Act1 also functions as an E3 ubiquitin ligase to polyquiquitinate TRAF6. TRAF6 also acts as an E3 ubiquitin ligase probably to polyubiquitinate (Ub) the TAK1 complex, leading to IKK and NF-κB activation. The IL-17-induced Act1 signalling complex also activates MAPKs and induces C/EBP expression. IL-17 probably activates the JAK/PI3K pathway. All of the IL-17-stimulated pathways lead to the activation of transcription factors such as C/EBPs, NF-κB and AP1 (activator protein 1) to induce gene transcription. In contrast, TRAF3 is an proximal negative regulator of the IL-17R and suppress IL-17-mediated downstream events through interfering with the formation of the receptor signalling activation complex IL-17R–Act1–TRAF6. Right-hand portion, IL-17 stimulation can form another complex Act1–IKKi–TRAF2–TRAF5–SF2 to mediate TRAF6-independent mRNA stability for IL-17- and TNF-mediated synergy of certain chemokines (such as KC) and potential cytokine induction.

IL-17RC expression is low in haemopoietic tissues and high in the prostate, liver, kidney, thyroid and joints [119,120]. The differential expression of IL-17RA and IL-17RC may provide a mechanism for the tissue-specific function by IL-17.

IL-17 has been shown to activate many common downstream signalling pathways, including NF-κB, the MAPKs (mitogen-activated protein kinases) JNK (c-Jun N-terminal kinase), p38 and ERK (extracellular-signal-regulated kinase), C/EBPs (CCAAT/enhancer-binding proteins), PI3K (phosphoinositide 3-kinase) and JAK (Janus kinase)/STATs. Another important function of IL-17 is that it can stabilize the mRNA of some pro-inflammatory cytokines and chemokines induced by TNF [121–124]. Recent studies have begun to unravel some of the important signalling intermediates in IL-17-induced pathways, which are described below and in Figure 2.

Act1

Act1 (also called CIKS) was cloned out as an NF-κB activator and IKK-associated adaptor [125,126]. Genetic studies have demonstrated Act1 plays dual roles in the regulation of immune responses. Although Act1 negatively regulates CD40- and BAFF (B-cell-activating factor belonging to the TNF family)-mediated B-cell survival and autoimmunity [127,128], Act1 is an essential adaptor molecule in the IL-17-mediated signalling pathways and regulates IL-17-mediated autoimmune diseases [129,130]. An earlier bioinformatics study found that IL-17R and Act1 consist of a SEFIR domain, which is likely for protein–protein interactions, hinting at a potential role of Act1 in IL-17-mediated function [114]. Indeed, Act1 functions though its SEFIR domain to associate with IL-17Rs to mediate downstream signalling. In addition to the SEFIR domain, Act1 also contains two TRAF [TNFR (TNF receptor)-associated factor]-binding sites, a helix-loop-helix domain at the N-terminus, and a U-box-like region and a coiled-coil domain at the C-terminus. Act1 forms complex with downstream signalling molecules TRAF6 and TAK1 (TGFβ-activated kinase 1) upon IL-17 stimulation [129]. As IL-17RA has no predicted TRAF6-binding site, it is likely that Act1 associates with TRAF6 through its TRAF-binding sites to recruits TRAF6 to IL-17R. Interestingly, Act1 has been shown to be a novel

U-box-like E3 ubiquitin ligase, whose activity is essential for IL-17-mediated signalling pathways and inflammatory gene expression. By utilizing the Ubc13–Uev1A E2 complex, Act1 mediates Lys^{63}-linked ubiquitination of TRAF6, which is critical for the ability of TRAF6 to mediate IL-17-induced NF-κB activation. As TRAF6 is also an E3 ubiquitin ligase, it is likely that it polyubiquitinates the TAK1 complex to activate IKKs for NF-κB activation, as shown similarly in IL-1β-mediated signalling [131]. In addition to NF-κB activation, Act1 also mediates IL-17-induced MAPK activation and C/EBP induction pathways. The functional mechanism of Act1 in these pathways still remains to be determined. *In vivo* studies have shown that Act1 plays an essential role in the development of EAE, similar to the phenotype in IL-17-deficient mice [30,129]. Further mechanistic studies have shown that, although Th17 cells were robustly generated in Act1-deficient mice and could normally infiltrate the CNS of Act1-deficient mice, the haemogenously derived lymphocytes, neutrophils and macrophages could not be recruited into the CNS, suggesting that IL-17-mediated signalling in the CNS is critical for inflammatory gene induction to recruit lymphocytes for the pathogenesis of EAE [129,132].

TRAF6

TRAF6, a critical adaptor in TLR (Toll-like receptor)- and TNF family-mediated signalling, was found to be the first intermediate signalling molecule in IL-17R signalling and was shown to be essential for IL-17-mediated NF-κB and JNK activation through studies of TRAF6-deficient MEFs (mouse embryonic fibroblasts) [133]. Consistently, IL-17-induced IL-6 was abolished in the TRAF6-deficient MEFs [133]. TRAF6 has been found to be a substrate of Act1 E3 ubiquitin ligase, and the ubiquitination of TRAF6 was critical for downstream signalling [131]. TRAF6-deficient mice are embryonic-lethal and the *in vivo* function for TRAF6 in IL-17-mediated signalling and inflammatory pathogenesis is still lacking.

mRNA stability

IL-17 can synergize with TNFα to induce inflammatory factor expression. It is believed that post-transcriptional effects through mRNA stability play a major role in the synergistic induction of some pro-inflammatory genes such as *Cxcl1* (CXC chemokine ligand 1; KC) and *Cxcl2* [CXC chemokine ligand 2; MIP2 (macrophage inflammatory protein 2)]. Interestingly, Act1 is required for IL-17-mediated stability of *Cxcl1* mRNA induced by TNFα, whereas TRAF6 was actually dispensable for IL-17-induced mRNA stability, although it is required for IL-17-induced NF-κB and JNK activation and inflammatory gene induction, suggesting that key linkers for Act1-mediated mRNA stability in IL-17 signalling are still missing [121,134]. Interestingly, more recent studies have indeed identified a TRAF6-independent signalling complex for IL-17-induced mRNA stability. IKKi (also named IKKε), a kinase involved in type I IFN production for antivirus, was shown to be important for IL-17-induced phosphorylation of Act1, which is critical for the formation of the Act1–TRAF2–TRAF5 complex to mediate IL-17-induced mRNA stability through dissociation of ASF (alternative splicing factor) from mRNA [135,136]. Apart from mRNA stability, the synergistic effect of IL-17 and TNFα in IL-6 production has been shown at least partially though the co-operative induction of C/EBPs at the promoter level. In addition to TNFα, IL-17 has been shown to have synergistic effects with many others factor, including IL-1β, IL-22, IFN-γ, oncostain M, CD40, BAFF, LTα and vitamin D3 [137]. The synergistic mechanisms remain to be determined at different levels such as transcription and post-transcription.

JAK/STAT pathway

One report has shown that IL-17 can activate the JAK1/2 and PI3K pathway, which co-ordinate with the NF-κB-activating pathway of Act1/TRAF6/TAK1 for gene induction, especially for host defence genes, such as human defensin 2 in human airway epithelial cells [138]. Another study has observed that STAT3 was critical for IL-17-mediated CCL (CC chemokine ligand) 11 expression in human airway smooth muscle cells [139]. However, more direct evidence for the roles of the JAK/PI3K and JAK/STAT pathways in IL-17 signalling is needed to avoid secondary effects of IL-17-induced cytokines, such as IL-6, which can strongly activates JAKs.

Negative regulators

One important question is whether and how IL-17 signalling is strictly controlled to adequately prevent inflammatory disorders. It has been shown that blockade of the PI3K pathway led to the up-regulation of IL-17RA, which could potentially enhance IL-17 signalling [140]. It has also been shown that IL-17R signalling activates ERK to phosphorylate Thr^{188} of C/EBPβ, which is required for Thr^{179} phosphorylation of C/EBPβ by GSK3β (glycogen synthase kinase 3β). The dual phosphorylation of C/EBPβ inactivates itself, resulting in the suppression of IL-17-mediated downstream gene induction. The two phosphorylation events are probably activated through different signalling pathways, as they require different domains in the IL-17R [141]. Our recent findings shows that TRAF3 is a negative regulator of IL-17R proximal signalling. TRAF3 greatly suppressed IL-17-induced NF-κB and MAPK activation, and subsequent production of inflammatory cytokines and chemokines by interfering with the formation of the receptor signalling activation complex IL-17R–Act1–TRAF6 [142]. TRAF3 also markedly

inhibited IL-17-induced expression of inflammatory cytokine and chemokine genes *in vivo* and consequently delayed the onset and greatly reduced the incidence and severity of EAE [142]. More recently, we found that persistent stimulation with IL-17 resulted in β-TrCP (β-transducin repeat-containing protein)-mediated ubiquitination of Act1 for its subsequent degradation, and consequently desensitization of IL-17R signalling, indicating a new desensitization mechanism of IL-17 signalling for the prevention of persistent inflammation [143]. Although recent studies have started to dissect the negative regulation of IL-17 signalling, further research is still needed for the thorough understanding of IL-17 control signalling at different levels.

BIOLOGICAL FUNCTIONS OF IL-17

Although we have some knowledge of the signal transduction downstream of IL-17, what is the biological function of IL-17? As introduced earlier, both adaptive $\alpha\beta$ T-cells and the innate $\gamma\delta$ T-cells, NK cells, iNKT cells, LTi-like cells, macrophages, DCs, neutrophils and mast cells are the major cellular source of IL-17 [11]. Most experimental evidence to date suggests a role for IL-17 in local tissue inflammation, mainly via the induced release of pro-inflammatory cytokines and chemokines. In addition to cytokines and chemokines, IL-17 has also been shown to induce the production of other genes, including growth factors, antimicrobial peptides and MMP (matrix metalloproteinase) enzymes in epithelial cells, endothelial cells, fibroblasts, osteoblasts, macrophages and DCs [43,144] (Figure 3). In this section, we briefly discuss what is known about IL-17-mediated physiological functions.

Chemokines

Stimulation with rIL-17A (recombinant IL-17A) protein causes the production and release of CXCL1 [KC or GRO (growth-related oncogene)-α], CXCL2 (MIP2), CXCL5, CXCL8 (IL-8), CXCL10 [IP10 (IFN-inducible protein 10)], CCL2 [MCP1 (monocyte chemotactic protein 1)] and CCL20 (MIP3a) in different human cell types [3,118,145–149]. CXCL1, CXCL5 and CXCL8 potentially mediate the biological function of IL-17 by attracting neutrophils *in vivo* [12,148,150,151]. Interestingly, CCL20 is the ligand of CCR6 (CC chemokine receptor 6), which is selectively expressed in Th17 cells [152], indicating a positive-feedback loop for IL-17 by recruiting more IL-17-producing cells to inflammatory sites. Although CCL2 enables IL-17 to mediate accumulation of monocytes [153], its functional importance in the accumulation of monocyte-lineage cells remains to be characterized.

Pro-inflammatory cytokines

A number of studies have shown that IL-17 induces tissue inflammation through stimulating pro-inflammatory cytokines [2,154,155]. IL-17 was first found to stimulate IL-6 production in fibroblasts and epithelial cells in 1995 [2]. Interestingly, IL-6 is also demonstrated to be essential for Th17 differentiation, suggesting a positive-feedback circuit induced by IL-17 [156]. IL-17 also induces the production of other pro-inflammatory cytokines, such as TNFα and IL-1β [155], and in turn synergizes with them to induce a large amount of inflammatory factors. This synergy is very likely to have bearing for the pathogenesis of several inflammatory diseases. For example, co-stimulation of human airway epithelial cells with IL-17 and TNFα enhances the release of CXCL8 and CXCL1 [147,148]. There is also evidence of IL-17A synergizing with IL-1β in activating the promoter of the CXC chemokine CINC (chemokine cytokine-induced neutrophil chemoattractant) in rat intestinal epithelial cells [153].

Other pro-inflammatory mediators

Studies have also shown that IL-17 could induce NOS (NO synthase) and COX (cyclo-oxygenase), triggering an increase in NO and PGE_2 (prostaglandin E_2) in various cell types [157,158]. PGE_2 and NO have been well-studied and implicated as mediators of inflammatory diseases. IL-17 caused a dose-dependent enhancement of IFNγ-triggered NO synthesis in both mouse and rat primary astrocytes. IL-17 also synergized with exogenous IL-1 and TNF for astrocyte NO production [157]. It is similarly reported that IL-1, TNF and IL-17 synergistically up-regulate NO and PGE_2 production in explants of human osteoarthritic knee menisci [158].

Growth factors

IL-17 induces the production and release of at least two different CSFs *in vitro*, including G-CSF in venous endothelial cells and fibroblasts, as well as GM-CSF (granulocyte/macrophage CSF) in bronchial epithelial cells from humans [147]. IL-17A induces G-CSF by both increasing its transcription and stabilizing its mRNA in mouse fibroblasts *in vitro* [159]. IL-17 stimulation caused a strong expansion of a neutrophil lineage or neutrophilia through G-CSF, and neutralization of IL-17 is associated with granulopenia defects and susceptibility to infection [3,160].

Tissue-remodelling factors

IL-17 can induce MMPs, including MMP1, MMP3, MMP9 and MMP13, which play important roles in extracellular matrix destruction and tissue damage in RA or tumorigenesis [161]. IL-17 also increases membrane expression of RANKL (receptor activator of NF-κB ligand) in osteoblasts [162], which in turn promotes osteoclastogenesis and subsequent bone destruction.

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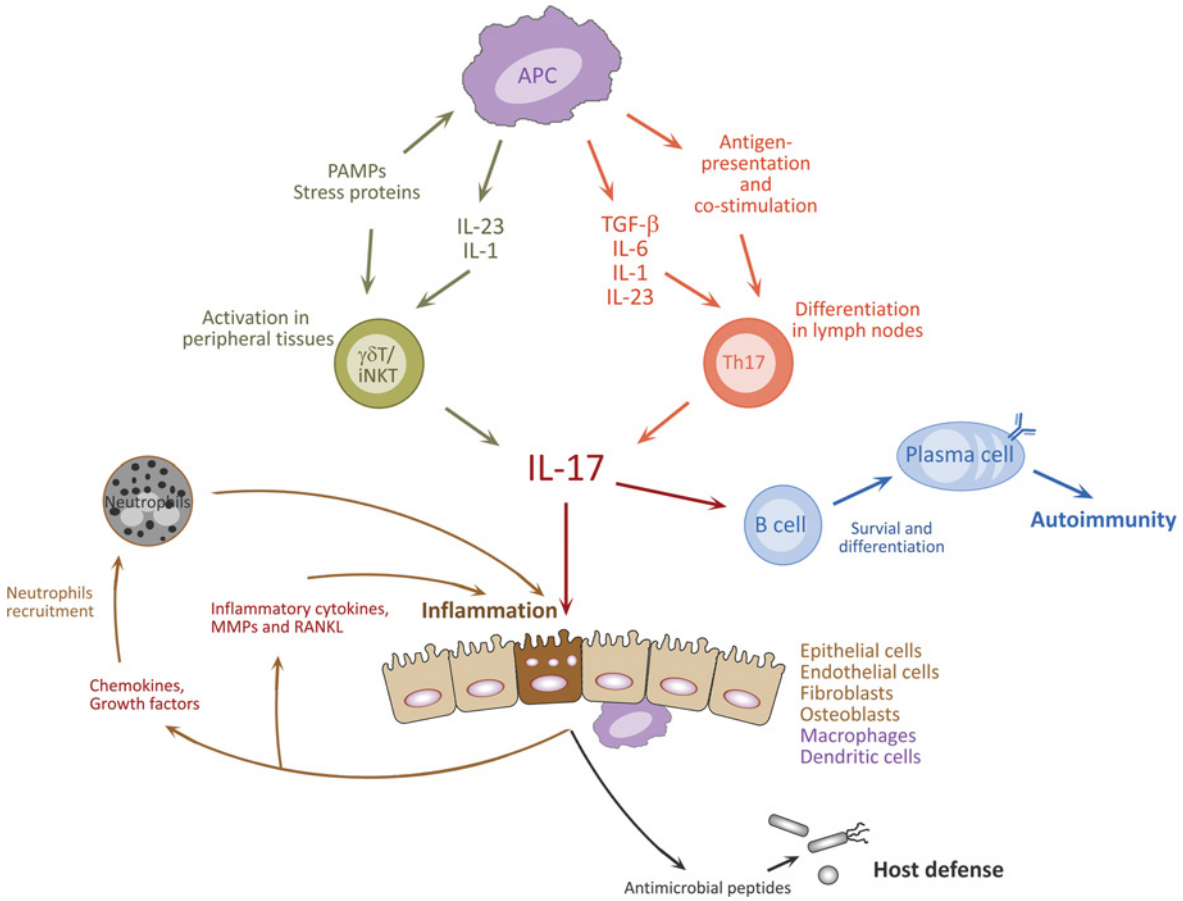

Figure 3 Biological functions of IL-17

Pathogen infections or other stress conditions could promote APCs, such as DCs and macrophages, to produce inflammatory cytokines. These cytokines are required for differentiation and expansion of either innate or adaptive IL-17-producing cells, such as Th17, Tc17 ($CD8^+$ T-cells), $\gamma\delta$ T-cells, iNKTs and LTi cells. IL-17 induces inflammatory cytokines, chemokines, growth factors, MMPs and RANKL in various cell types of target tissues, resulting in neutrophil recruitment to mediate tissue inflammation and damage. IL-17 also promotes the survival and expansion of B-cells and the differentiation of B-cells into antibody-producing plasma cells. This may leads to autoimmunity and pathogenesis, as seen in lupus. IL-17 also acts directly on epithelial cells of peripheral tissues to promote release of defensins, regenerating (REG) proteins and S100 proteins, which have antimicrobial activities and protect the host against infections.

Antimicrobial peptides

In addition to contributing to inflammatory pathogenesis, IL-17 is also critical for host defence. IL-17 induces the expression of various antimicrobial peptides, such as β-defensins and S100 proteins, in the lung, skin and gut [54,163,164]. Studies have suggested that β-defensin can function as a ligand for CCR6, recruiting DCs and T-cells [165]. IL-17 also induces acute-phase proteins such as LCN2 (lipocalin 2)/24p3, which exerts its antimicrobial function by binding to bacterial siderophores [166].

B-cell regulation

Besides the functions of IL-17 on non-lymphoid lineage cells, IL-17 has been shown to regulate the functions of B-cells. In the BXD mouse model of autoimmunity, exacerbated IL-17 secretion caused spontaneous development of germinal centres before the production of pathogenic autoantibodies. Blocking IL-17 signalling disrupted germinal centre formation and reduced humoral responses [167]. IL-17 alone or in combination with BAFF promoted human B-cell survival, proliferation and differentiation into Ig-secreting plasma cells. This effect was mediated mainly through the NF-κB-regulated transcription factor Twist-1 [168].

PATHOLOGICAL ROLES OF IL-17 IN AUTOIMMUNE DISEASES

The aetiology of autoimmune diseases remains unclear. It is generally believed that the break of central and peripheral tolerance leads to the escape of autoreactive T- and B-cells from normal selection. These

autoreactive T- and B-cells are activated and expanded when they encounter their cognate 'self'-antigens and become pathogenic, resulting in humoral and cellular abnormalities. The pathogenic autoreactive lymphocytes eventually lead to organ-specific diseases or systemic autoimmune diseases through their infiltration into the tissues, which are followed by exacerbated inflammatory responses and tissue destruction [169–173]. Before the discovery of the Th17 subset, it was considered that Th1, Th2 and B-cells were the main mediators of pathology in autoimmunity. However, a number of studies have demonstrated the critical pathogenic role of Th17 cells and its hallmark cytokine IL-17 in autoimmune diseases [28–30].

Following the discovery of IL-17 and its biological functions, many studies have demonstrated that increased IL-17 expression is associated with inflammatory autoimmune diseases in either human patients or animal disease models [137,174,175]. Robust evidence shows that IL-17 mediates adverse effects in many autoimmune diseases such as RA, MS, SLE, IBD (inflammatory bowel disease) and psoriasis to name a few [176]. IL-17 also plays critical roles in host defence, as well as in the pathogenesis of other inflammation-related diseases such as allergy, transplantation, obesity and malignancy [12–30]. In this section, we will mainly discuss the roles of IL-17 in the pathogenesis of autoimmune diseases.

RA

RA is characterized by the proliferation of synovial fibroblasts, infiltration of $CD4^+$ T-cells and autoantibody-producing plasma cells, and joint and cartilage erosion. It has long been believed to be a Th1-cell-cytokine-mediated autoimmune disease, supported by the presence of IFNγ and TNFα in synovial lesions and peripheral blood [176]. However, the pathology of CIA (collagen-induced arthritis), a mouse model of RA, is much more severe in mice lacking IL-12 or IFNγ [177], arguing against the importance of Th1 cells in these diseases. Several subsequent studies have demonstrated that IL-23, rather than IL-12, is important for the development of CIA [32], suggesting the essential role of Th17 cells in this process. Furthermore, neutralizing IL-17 or its receptor in CIA mouse models reduces joint inflammation, cartilage destruction and bone erosion [178], whereas ectopic expression of IL-17 promotes collagen arthritis and aggravates joint destruction [179]. IL-17-deficient mice were indeed found to be resistant to CIA, confirming the critical role of IL-17 in CIA [180].

Consistently, studies in patients have shown that high levels of IL-17 and its receptor were found in the rheumatoid synovium of patients with RA compared with healthy controls or patients with osteoarthritis, and IL-17 can promote joint degradation in *ex vivo* models [181–187]. Moreover, a 2-year prospective study analysing synovial tissues in RA patients demonstrated that IL-17 and TNFα were synergistic prognostic factors for poor outcomes [188]. IL-17 promoted the recruitment of both neutrophils and monocytes by inducing various chemokines, resulting in the inflammatory pathology in RA [186]. Taken together, current findings clearly demonstrate a central role of IL-17 in the pathogenesis of RA or experimental arthritis.

The functional mechanisms of IL-17 in RA pathogenesis have been well investigated in recent years. It is generally regarded that IL-17, independently or synergistically with pro-inflammatory cytokines such as TNFα and IL-1β, stimulates various cell types, including fibroblast-like synoviocytes, chondrocytes/osteoblasts and monocytes/macrophages, to produce cytokines (TNFα, IL-1β and IL-6), chemokines (CXCL1, CXCL5 and CCL20), growth factors (GM-CSF) and other destructive mediators (NO, MMPs and RANKL), and consequently leads to the pathological features of RA, such as inflammation and destruction of cartilage and bone [3,181,189–192]. These factors either directly participate in local inflammation, cartilage damage and bone erosion, or indirectly participate in the inflammatory pathology through recruiting neutrophils and monocytes to the synovial tissue which can exacerbate inflammation [186,193] (Figure 3).

Interestingly, some studies have suggested that the development of experimental arthritis in mice depends on environmental or infective factors, such as the indigenous microbe *Lactobacillus bifidus*, gut-residing SFB (segmented filamentous bacteria) and fungi [194–196]. These pathogens induce Th17 cell differentiation, secreting IL-17, and in turn result in arthritis, suggesting a link between innate immunity and autoimmune diseases.

MS

MS is a demyelinating disease characterized by autoimmune inflammation in the CNS. Accumulation of inflammatory immune cells from blood into the CNS results from their migration through the BBB (blood–brain barrier). Chronic inflammation of the brain leads to the destruction of myelin sheaths around the axons of the brain and spinal cord, resulting in the reduction of influx transmission and function loss so that the axons can no longer effectively conduct signals. As with CIA, Th1 cells were long thought to be responsible for EAE (a mouse model for MS) pathology, despite the fact that IFN$\gamma^{-/-}$, IFNγR (IFNγ receptor)$^{-/-}$, and IL-12p35$^{-/-}$ mice were susceptible [197–199]. Landmark studies comparing the IL-12p35$^{-/-}$ and IL-23p19$^{-/-}$ mice showed clearly that the IL-23-induced Th17 production was responsible for the pathology of EAE [200]. Further evidence for the role of Th17 cells in driving EAE was shown in STAT6/T-bet-double-knockout mice lacking Th1 and Th2 cells [98]. Furthermore, neutralization of IL-17 or IL-17 deficiency rendered the mice resistant to the induction of EAE [30,201]. IL-17RC (a receptor for both IL-17

and IL-17F)-deficient mice were also shown to have reduced EAE [202]. Adoptive transfer of pathological Th17 cells, but not Th1 cells, derived from established EAE mice induced severe EAE in recipient mice [200]. Taken together, these studies clearly suggest a central role of IL-17 or Th17 cells in EAE development. Interestingly, IL-17 produced by $\gamma\delta$ T-cells has also been suggested to play an important role in EAE development [86]. $\gamma\delta$ T-cells provide the early source of innate IL-17, which facilitate later adaptive Th17 cell generation by the induction of IL-6 and IL-23 secretion, suggesting that $\gamma\delta$ T-cells act in an amplification loop for IL-17 production by Th17 cells [86].

Consistent with observations in mouse models, extensive gene array studies have found that IL-17 was at the top list of genes found to be expressed in brain lesions from MS patients [203]. A significant increase in IL-17-positive T-cells in active MS lesions compared with inactive MS lesions has been found [204].

More recently, a study using conditional Act1-knockout mice demonstrated that the deletion of Act1 in neuroectoderm-derived cells (including astrocytes, oligodendrocytes and neurons), but not in endothelial cells or macrophages and microglia, delayed the onset and reduced the severity of Th17-cell-induced EAE. Furthermore, IL-17-mediated production of cytokines and chemokines was impaired in astrocytes from the CNS-restricted Act1-deficient mice [132], suggesting IL-17-mediated signalling in the CNS plays a critical role in EAE development. Although the exact pathogenic role of IL-17 in EAE or MS is still largely unknown, further studies have provided a picture where IL-17 could disrupt BBB tight junctions through the induction of ROS (reactive oxygen species) allowing autoreactive T-cells to enter the CNS [205,206]. Those T-cells are locally re-activated by resident APCs that present self-antigens and begin to secrete Th17 cytokines such as IL-17. Then IL-17 induces the expression of inflammatory genes in astrocytes, including CXCL1 and CXCL5 to attract neutrophils, CCL2 to attract monocytes, CCL20, a ligand for CCR6 expressed on Th17 cells, to recruit more Th17 cells [207], leading to an explosive inflammatory cascade associated with the onset of EAE.

SLE

SLE is a systemic multi-organ autoimmune disease characterized by autoantibody production. Patients with SLE develop immune responses against self-antigens and release autoantibodies which bind to the self-antigens to form immune complexes. The immune complex deposition in susceptible vascular beds, mostly in skin, joints and renal glomeruli, causes local inflammation and tissue damage, which amplifies the autoimmune response, creating a vicious circle [208,209]. Although lupus is traditionally considered mainly as a B-cell-mediated disease, recent reports have indicated that IL-17 is likely to be involved in the pathogenesis of lupus. IL-17 production is found high in MRL/lpr mice, which develop spontaneous lupus-like diseases [210]. In MRL/lpr mice, IL-17 mainly comes from DN (double-negative) TCR-$\alpha\beta^+$CD4$^-$CD8$^-$ T-cells. Interestingly, lymph node cells derived from MRL/lpr mice were able to cause glomerulonephritis when transferred into Rag1$^{-/-}$ mice without T- and B-cells. The pathological effect depended on pre-stimulation with IL-23, a critical cytokine for amplification of Th17 cells [210], whereas IL-23R deficiency prevents the development of lupus nephritis in C57BL/6-lpr/lpr mice, indicating the involvement of Th17/IL-17 in the pathogenesis [211]. There are other spontaneous lupus-like mouse strains, such as the BXD2 mouse strain, the Ets-1-deficient mice, BAFF-transgenic mice and NZBW mice. Studies in BXD2 mice have shown that IL-17 can drive the autoimmune disease through promoting the formation of spontaneous germinal centres, which is distinct from its pro-inflammatory effects [167]. Recently, two GWAS (genome-wide association studies) in SLE independently identified genetic variants in Ets-1 associated with SLE [212]. Interestingly, previous studies have found that Ets-1-deficient mice develop a lupus-like disease characterized by high titres of IgM and IgG autoantibodies, immune complex-mediated glomerulonephritis and local activation of complement [213]. In addition, in Ets-1-deficient mice, Th cells were differentiated more efficiently to Th17 cells. The deficient mice contained an abnormally high level of IL-17 transcripts in their lungs and exhibited increased mucus production by airway epithelial cells in an IL-17-dependent manner [80]. Evidence in patient samples indicates that IL-17 is highly expressed in patients with SLE. IL-17 was found to be increased in serum from patients with SLE and correlated with SLE disease activity [168,214,215]. Moreover, IL-17-producing T-cells were found to be increased in the peripheral blood of patients with SLE [215–217].

The exact pathogenic role of IL-17 in SLE is not clear. A study focusing on DN T-cells in SLE patients has shown that these DN T-cells are expanded in the peripheral blood of SLE patients and produce pro-inflammatory factors including IL-17, IFNγ and IL-1β [216,218], suggesting a direct pro-inflammatory activity of IL-17 and other cytokines in lupus nephritis. Interestingly, IL-17 has also been shown to synergize with BAFF to mediate B-cell survival, thereby increasing the number of autoantibody-producing cells [168,219] (Figure 3). Additionally, IL-17 induced the production of inflammatory cytokines as well as autoantibody in the PBMCs (peripheral blood mononuclear cells) of lupus patients with lupus nephritis [220]. Thus the pro-inflammatory activity of IL-17 and its impact on B-cells may explain its role in SLE pathogenesis.

Psoriasis

Psoriasis is a chronic skin disease resulting from the dysregulated interplay between keratinocytes and infiltrating immune cells, and is characterized by dermal hyperplasia. The critical role of IL-17 in psoriasis was highlighted in GWAS that linked IL-23R and Act1 polymorphisms to psoriasis, which regulates IL-17 production and IL-17-mediated signalling respectively [221,222]. A model of psoriasis was developed by intradermal injection of IL-23. Chan et al. [223] have shown that IL-23 stimulates epidermal hyperplasia via TNF- and IL-20R2 (IL-20 receptor 2)-dependent mechanisms, and anti-IL-17 treatment decreased G-CSF and MMP13, although it had no effect on erythema, mixed dermal infiltrate and epidermal hyperplasia associated with parakeratosis [223]. Zheng et al. [224] have shown that IL-22, another Th17 cytokine, was the factor mediating IL-23-induced dermal inflammation and acanthosis, findings which are supported by other studies [225,226]. However, Rizzo et al. [227] have reported that IL-23-mediated psoriasis-like epidermal hyperplasia is dependent on IL-17. Little hyperplasia was observed in IL-17$^{-/-}$ or IL-22$^{-/-}$ mice [227]. Nonetheless, IL-22 was likely to play a more important role in this psoriasis model. Interestingly, the positive results from a clinical trial with anti-IL-17 antibody treatment were obtained in psoriasis patients with the elevated expression of IL-17, IL-22 and IL-23 in psoriatic skin [92], suggesting the role of IL-17 in psoriasis.

A mechanism for the involvement of IL-17 in psoriasis may arise from the co-operation of IL-17 with IFNγ, TNFα, IL-22 or other stimuli to induce inflammatory cytokines, chemokines and antimicrobial peptides. IL-17 synergizes with IFNγ to induce ICAM-1 (intracellular adhesion molecule-1), IL-6 and IL-8 in human keratinocytes [228]. IL-17 in combination with TNFα induces inflammatory genes that are characteristic of psoriasis from human keratinocytes [229,230]. In addition, IL-17 together with IL-22 synergistically increases the expression of skin antimicrobial peptides, including β-defensin-2 (BD-2), S100A7 (psoriasin) and S100A8/9 (calprotectin) [54]. Interestingly, psoriasis patients are more resistant to skin infections than healthy people, perhaps as the result of the elevated production of antimicrobial peptides [137]. Furthermore, IL-17 and IL-22 induced keratinocytes to produce CCL20 (a ligand for CCR6) *in vitro* and *in vivo*, which is likely for the continuous recruitment of CCR6-positive Th17 cells in the psoriasis lesions [231].

IBD

IBD, including both CD (Crohn's disease) and UC (ulcerative colitis), are chronic relapsing inflammatory disorders of the gastrointestinal tract, caused in part by an deregulated immune response to intestinal bacteria followed by chronic inflammation. Local inflammation in the mucosa leads to the destruction of the lamina with complications such as perforations, internal or external fistulas. As with psoriasis, GWAS identified a series of Th17-related genes as IBD-associated genes, including IL-23R, STAT3 and CCR6, which regulate IL-17 production or Th17 attraction [232–234], suggesting the potential role of IL-17 in this disease. However, controversial results for the role of IL-17 have been observed in animal models of IBD, i.e. TNBS (trinitrobenzene sulfonic acid)- or DSS (dextran sodium sulfate)-induced colitis. IL-17RA$^{-/-}$ mice were resistant to colitis induced by intrarectal administration of TNBS [235], which is consistent with the findings that the overexpression of an IL-17R–IgG1 fusion protein significantly attenuated colonic inflammation after acute TNBS [235], indicating a pathogenic role of IL-17 in TNBS-induced colitis. However, neutralization of IL-17 with a monoclonal antibody aggravated DSS-induced colitis in mice [236]. Consistent with that, a later study showed that IL-17$^{-/-}$ mice developed more severe disease in DSS-induced colitis [201]. Both studies suggest a protective role of IL-17 in the development of DSS-induced colitis. In contrast, another study has shown that IL-17$^{-/-}$ mice had much less disease and mortality compared with wild-type controls, pointing to a pathological role of IL-17A [237]. In a T-cell transfer model to establish IBD in mice, adoptive transfer of Th17 cells resulted in more significant gut inflammation than that of Th1 cells [238]. In addition, inhibition of IL-17 in spontaneous colitis of IL-10$^{-/-}$ mice was inefficient in improving disease unless IL-6 was also neutralized [239]. Although the reasons for the discrepancies in these studies are not known at present, it is possible that intestinal microbial flora may have differed in these models and the chemicals used may have different characteristics as was suggested in a study showing differential cytokine profiles in DSS- compared with TNBS-induced colitis [240]. In addition, caution should be taken when analysing IL-17R$^{-/-}$ and IL-17$^{-/-}$ mice as they may not be functionally identical, since IL-17R is probably a common receptor for all members of the IL-17 cytokine family.

In humans, the expression of IL-17 was found to be elevated in patients with either CD or UD compared with healthy subjects or to patients with infectious or ischaemic colitis [241–243]. However, CD and UC may differ in some aspects of their pathogenesis. Some studies have found differences in the cytokine profile, with IL-17 being more associated with UC and IFNγ with CD [244]. More studies are needed to understand the exact role and mechanisms of IL-17 in IBD.

T1DM (Type 1 diabetes mellitus)

T1DM is a form of diabetes mellitus that results from T-cell-mediated autoimmune destruction of the insulin-producing β-cells of the pancreas. The subsequent lack

of insulin leads to increased blood and urine glucose. Cytotoxic $CD8^+$ T-cells are important contributors to β-cell death [245]. Th17 and IL-17 have been demonstrated to be involved in the development of autoimmune diabetes in animal models [246,247]. In NOD (non-obese diabetic) mice, a model of spontaneous autoimmune diabetes, inhibition of Th17 cells has been shown to improve autoimmune diabetes, and IL-17 neutralization suppressed the development of autoimmune diabetes [247]. In NOD/SCID (severe combined immunodeficiency) mice, *in vitro*-differentiated Th17 cells induced T1DM. However, the development of the diabetes was dependent on IFNγ, but not IL-17 [248], suggesting that Th17 cells were converted into Th1-like cells to secrete IFNγ under the lymphopenic conditions. A study with the antibody blockage of IL-17A or IL-17F showed they were also important for autoimmune diabetes in an adoptive transfer model of IL-23-induced Tc17 (IL-17 expressing $CD8^+$ cells) [249]. In humans, the role of IL-17 in T1DM is not known. Thus the precise role of IL-17 in T1DM remains to be elucidated.

Although both Il-17 and IL-17F require IL-17RA and IL-17RC to activate similar downstream signalling pathways for pro-inflammatory gene induction, *in vivo* studies have shown that IL-17 and IL-17F have differential roles and sometimes even opposite effects, as shown in the DSS-induced colitis model [201]. Although IL-17 was essential for the pathogenesis of EAE or asthma, IL-17F was shown not to be important for EAE initiation or even to negatively regulate the Th2 response. Whereas IL-17 played a protective role in DSS-induced colitis, IL-17F deficiency resulted in reduced colitis induced by DSS. In contrast with their differential pathogenic roles in autoimmune diseases, both IL-17A and IL-17F protect hosts from pathogens by inducing the production of chemokines, cytokines (such as G-CSF) and antimicrobial peptides in epithelial cells and keratinocytes. $IL\text{-}17^{-/-}IL\text{-}17F^{-/-}$ mice were more susceptible to spontaneous *S. aureus* infections compared with $IL\text{-}17^{-/-}$ or $IL\text{-}17F^{-/-}$ mice, and $IL\text{-}17RA^{-/-}$ mice had higher susceptibility to *Klebsiella pneumoniae* infection than $IL\text{-}17^{-/-}$ mice, suggesting that IL-17 and IL-17F have overlapping roles in these models [117,250]. Thus, although more evidence is needed, IL-17 appears to be more potent than IL-17F in inducing inflammatory responses during autoimmune pathogenesis, whereas both IL-17 and IL-17F seem to play important roles in host defence.

THERAPEUTIC POTENTIAL

Although each autoimmune disease has a quite different and complex aetiology and pathology, studies have clearly demonstrated the critical role of IL-17 in the pathogenesis of various systemic or organ-specific inflammatory autoimmune diseases, making IL-17 as an ideal common target. More advances have been made towards targeting IL-17/IL-17R, pathways regulating IL-17 expression or IL-17R-mediated downstream signalling pathways for therapeutic purposes (Figure 4).

Targeting IL-17/IL-17R

Targeting IL-17 or IL-17R is the most direct way to block IL-17-mediated functions. Currently, two anti-IL-17-blocking antibodies are under investigation in the clinic. One is AIN457, a humanized IL-17 antibody developed by Novartis, which has completed Phase I/IIa trials for psoriasis, RA and autoimmune uveitis, and is in Phase II trials for MS, CD and ankylosing spondylitis. The other is LY2439821, a humanized IL-17 antibody developed by Eli Lily, which is currently in Phase II trials for RA and psoriasis. Clinical studies show both AIN457 and LY2439821 improved signs and symptoms, with no strong adverse safety concerns observed [251,252]. Blocking IL-17R is also under investigation in the clinic. AMG-827, developed by Amgen, is a fully human monoclonal antibody to IL-17R and blocks IL-17R-mediated signalling. AMG-827 has completed Phase I trials for psoriasis and is now in Phase II trials for psoriasis, and Phase I/II trials for RA [193]. Since IL-17R appears to the common receptor subunit, its inhibition may affect the functions of other members of IL-17 family. Therefore targeting IL-17RC, which is also required for IL-17 signalling, could be more specific. Thus clinical trials hold promise for targeting IL-17/IL-17R for therapy of certain inflammatory autoimmune diseases.

Targeting upstream of IL-17

Clinical trials to inhibit Th17 cell development and thus IL-17 production have also been carried out. Several inflammatory cytokines, such as IL-1, IL-6 and IL-23, participate in the induction of IL-17-expressing cells. Neutralization of these cytokines or their receptors, for example by antibodies, may have therapeutic potential.

IL-1 and IL-6 are multifunctional cytokines which regulate many disease-associated processes. Their neutralization with antibodies has been useful in clinical settings even before the discovery that they are involved in the induction of the highly pro-inflammatory Th17 cell population. Tocilizumab, an IL-6R (IL-6 receptor) antibody developed by Hoffmann-La Roche and Chugai was successfully used for the treatment of RA and CD [253,254]. Anakinra, an IL-1R (IL-1 receptor) antagonist, has been successfully used for the treatment of RA [255]. Although it is largely unknown how the blocking antibody and antagonist function in the clinic, it is presumed that the observed therapeutic effects are, at least in part, due to inhibition of Th17 cell differentiation. It has been speculated that depleting IL-23, which is a key molecule for Th17 expansion and stabilization, may be more effective in down-regulating IL-17. IL-23 is a

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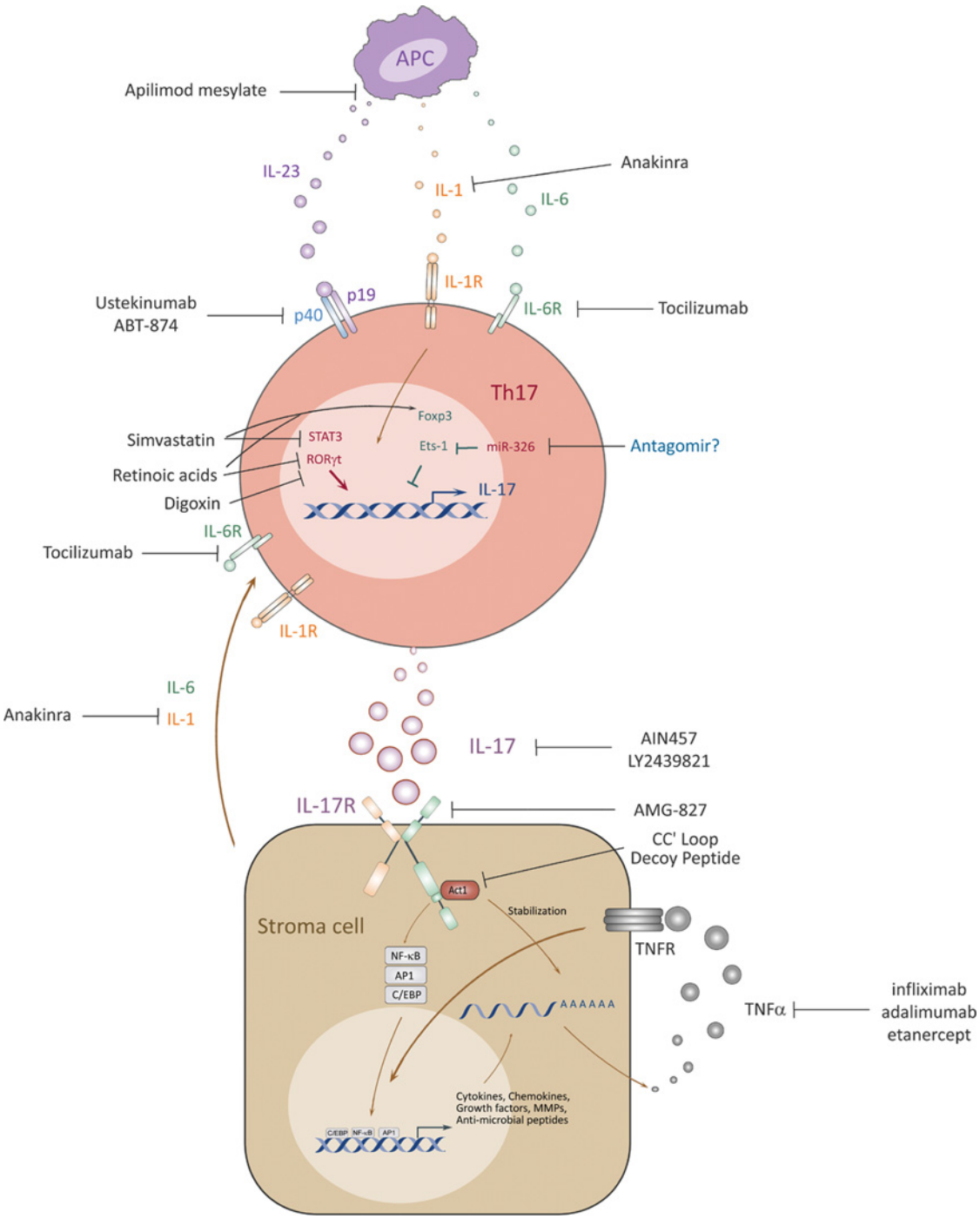

Figure 4 Therapeutic potential of targeting the IL-17/IL-17R axis for inflammatory autoimmune diseases

Various clinical approaches have been developed by targeting IL-17 itself, regulation of the upstream expression or downstream signalling pathways. IL-23 is a cytokine necessary for driving expansion of Th17 cells. Its availability can be diminished by anti-IL-23R p40 antibodies (Ustekinumab and ABT-874) or inhibitors of IL-23 production (Apilimod mesylate). The function of APC-induced or IL-17-induced IL-6 and IL-1 can be eliminated by anti-IL-6R antibodies (Tocilizumab) or IL-1 inhibitors (Anakinra) respectively. The transcriptional activity of the key factor RORγt for Th17 differentiation can be antagonized by a small molecule (Digoxin). Simvastatin and retinoic acids could repress the expression of STAT3 and RORγt respectively, and also enhance Foxp3 expression, which repress Th17 generation. miRNA inhibitors might also be considered to modulate IL-17 expression. Monoclonal antibodies AIN457 and LY2439821 targeting IL-17 or AMG-827 targeting IL-17RA have already been shown in clinical trials to be effective in treating certain autoimmune diseases. Effector functions of IL-17 could also be hampered by using peptides to block the interaction between Act1 and IL-17RA, or blocking antibodies for downstream induced genes such as TNFα (infliximab, adalimumab and etanercept), which also functionally synergizes with IL-17. It is tempting to speculate that dual blockade of IL-17 and TNFα might be a promising approach for efficiently treating autoimmune inflammatory diseases. AP1, activator protein 1.

heterodimeric cytokine that consists of two subunits, a specific p19 and a common p40, which is shared with IL-12. Ustekinumab and briakinumab (ABT-874), antibodies against the p40 chain developed by Centocord and Abbott Laboratories respectively, which reduce both Th17 and Th1 cells, were shown to have therapeutic potential in psoriasis, colitis and EAE in pre-clinical studies [256–258]. Improved effects of ustekinumab and briakinumab were observed in patients with severe psoriasis, as well as in CD, especially in those who did not respond to infliximab (anti-TNF-α antibody) [259–262]. However, ustekinumab failed in Phase II clinical trials in patients with RRMS (relapsing re-emitting MS) but detail of the mechanisms is unknown [263]. Targeting the pathways regulating IL-23 production is another way that may aid in the treatment of Th17-dependent diseases. Pre-clinical studies have showed that a small-molecule oral compound, apilimod mesylate (STA-5326), inhibited IL-23 and IL-12 production in human PBMCs *in vitro* [264], which was probably achieved by blocking the translocation of c-Rel, a member of the NF-κB transcription factors. This compound has been used for the treatment of active CD [265]. Directly depleting pathogenic Th17 cells could be also considered for therapeutic purpose. A study has shown that a depleting monoclonal antibody directed to surface LT-α (lymphotoxin-α) reduced both Th17 and Th1 cells and, consequently, suppressed EAE and CIA disease development [266].

Modulating intracellular pathways for Th17 differentiation using small molecules have also been considered in treating autoimmune diseases. Simvastatin, developed by Zocor and generics, is a hypolipidaemic drug used to control elevated cholesterol or hypercholesterolaemia. Treatment of mice with EAE with statins showed reduced severity and delayed onset of disease. It was recently demonstrated that simvastatin enhanced the expression of Foxp3 and inhibited RORγt, causing a reduction in IL-23 and IL-6 production and, in turn, inhibiting the production of IL-17 [267]. It was also suggested that simvastatin induced SOCS-3 (suppressor of cytokine signalling-3) to repress the induction of STAT3 and the subsequent activation of RORγt [267]. Retinoic acids and its analogues have been shown binding to RAR (retinoic acid receptors) and RXRs (retinoid X receptors), which belong to the same family of RORγt. Retinoic acid facilitates Foxp3$^+$ T_{reg}-cells and reduces IL-17-producing cells by enhancing TGF-β signalling and inhibiting the expression of IL-6Rs and IL-23Rs. In pre-clinical studies, retinoic acid ameliorated EAE by inhibiting the generation of Th17 cells [268]. It also reduced colon inflammation in biopsies from IBD patients and suppressed TNBS-induced colitis in mice by shifting the T_{reg}-cell/Th17 profile [269]. A recent study has demonstrated that digoxin and its derivatives suppressed Th17 cell differentiation by antagonizing RORγt activity [270]. Digoxin inhibited murine Th17 cell differentiation without affecting the differentiation of other T-cell lineages and was effective in delaying the onset and reducing the severity of autoimmune disease in mice [270]. Blocking or re-establishing miRNA (microRNA) may also be a promising new approach for the treatment of autoimmune diseases. A study has shown that the expression of *miR-326* was highly correlated with disease severity in patients with MS and in mice with EAE, and *in vivo* silencing of *miR-326* resulted in fewer Th17 cells and less EAE severity [66]. Resolvin E1, a product of $n-3$ fatty acids, inhibits the development of the airway inflammation and also promotes the resolution of this inflammation by regulating IL-23, IFN-γ and lipoxin A4 [271]. Steroids are the most commonly used agents for inflammatory diseases. The IL-17-induced release of IL-8, CXCL1 and CXCL6 from human bronchial epithelial cells might be sensitive to glucocorticoid receptor stimulation [146]. Yang et al. [272] have also shown that dexamethasone (an anti-inflammatory 9-fluoro-glucocorticoid) can inhibit the release of IL-17 and IFNγ in Vogt–Koyanagi–Harada Syndrome, which is an autoimmune disorder against melanocytes. Furthermore, the cytokine microenvironment affects the differentiation and plasticity of T-cell subsets (Th17, Th1, Th2 and T_{reg}-cells). Targeting strategies could also be considered to change the differentiation and re-differentiation programmes of those T-cell subsets, for example changing the cytokine profiles to let Th17 or Th1 cells re-differentiate into T_{reg}-cells for therapeutics.

Targeting downstream of IL-17

Blocking the intracellular signalling pathways of IL-17R is another approach to inhibit its biological activity. Using small molecules such as compounds, peptide inhibitors, siRNA (small interfering RNA) or miRNA, to target the essential adaptor Act1, or more specific signalling molecules affecting NF-κB, MAPK or mRNA stabilization, might be considered for future investigation to treat inflammatory autoimmune diseases. Recently, a CC' loop decoy peptide of Act1, which blocked the interaction between Act1 and IL-17RA, attenuated IL-17- and IL-25- induced inflammation [273], suggesting its potential for treatment of autoimmune diseases. IL-17 has been shown to stimulate IL-6 and IL-1 production, which are essential for Th17 differentiation. Thus their respective blocking antibodies tocilizumab and anakinra may also disrupt the positive-feedback circuit induced by IL-17 and, in turn, contribute to treatment [274]. IL-17 also induces the production of TNFα and synergizes with it to induce large amounts of inflammatory factors. The role of TNFα in the development and progression of RA, CD disease or psoriasis, and the therapeutic benefits of blocking this pro-inflammatory cytokine, are well established [275]. The blocking reagents include

antibodies such as infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia) and golimumab (Simponi), or etanercept, a fusion protein of TNFR2 and IgG_1. However, not all patients respond to anti-TNF therapy, indicating the potential involvement of other cytokines in the pathogenesis. Thus it would be interesting to know whether dual blockade of IL-17 and TNFα might be beneficial for treating these diseases. Besides, CCR6 and its ligand CCL20 are also potential targets for disrupting the chemotaxis of Th17 cells [207,276,277].

CONCLUSIONS AND PERSPECTIVES

IL-17, the signature cytokine secreted by Th17 cells, is required for host defence against extracellular bacterial and fungal infections, and contributes to the pathogenesis of various autoimmune inflammatory diseases. IL-17 has become an important target for treating different forms of inflammatory disorders. Recent clinical trials with agents that target IL-17/IL-17R, the upstream regulation pathways of IL-17 expression and the downstream signalling pathways of IL-17 hold promise for treating autoimmune diseases. However, targeting strategies to block Th17 differentiation and expansion could have a greater potential risk for impairing the defence of the patients because Th17 cytokines, such as IL-17F and IL-22, are critical for host innate immunity against infections. Such risk/side effects could be minimized by targeting IL-17 itself or its downstream signalling pathways. As IL-17 is also important for host defence, further investigations into IL-17-mediated signalling to dissect the inflammatory pathway compared with the host defence pathway, and subsequent immunological and pathogenic roles of potential signalling targets, will help in the development of more specific medicines for alleviating symptoms associated with autoimmune inflammatory diseases without compromising host defence.

There remain many unanswered questions with regard to the sources of IL-17, the IL-17R-mediated signalling and the role of IL-17 in autoimmunity. Although IL-17 can be produced by either innate immune cells or adaptive T-cells, the sources of IL-17 are not clear in different types of autoimmune diseases. It will also be important to address the specific roles of IL-17 in different cell types during autoimmune pathogenesis through conditional knockout mice. Although the differentiation plasticity of T-cell subsets is now appreciated, more work is still needed to fully understand the complex programming and re-programming before targeting the plasticity for potential therapy. While there is some knowledge of the IL-17R-mediated NF-κB activation pathway, other signalling pathways mediated by IL-17R are not well defined, such as MAPKs, C/EBPs and mRNA stability. Defining IL-17R-mediated signalling will provide potential new drug targets. We and others have found that IL-17C, another IL-17 member which binds to the IL-17RE–IL-17RA heterodimeric complex, is also important for host defence and autoimmunity [112,278–280]. Thus defining the roles and mechanisms of other IL-17 members will also provide potential new therapeutic targets.

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