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REVIEW

The pathogenicity of Th17 cells in autoimmune diseases

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Abstract

IL-17-producing T helper (Th17) cells have been implicated in the pathogenesis of many inflammatory and autoimmune diseases. Targeting the effector cytokines IL-17 and GM-CSF secreted by autoimmune Th17 cells has been shown to be effective for the treatment of the diseases. Understanding a molecular basis of Th17 differentiation and effector functions is therefore critical for the regulation of the pathogenicity of tissue Th17 cells in chronic inflammation. Here, we discuss the roles of proinflammatory cytokines and environmental stimuli in the control of Th17 differentiation and chronic tissue inflammation by pathogenic Th17 cells in humans and in mouse models of autoimmune diseases. We also highlight recent advances in the regulation of pathogenic Th17 cells by gut microbiota and immunometabolism in autoimmune arthritis.

Keywords IL-17 · GM-CSF · Th17 cells · Autoimmune arthritis · EAE · Rheumatoid arthritis

Introduction

CD4+ T helper (Th) cells play pivotal roles in the tissue destruction of many inflammatory and autoimmune diseases such as multiple sclerosis (MS), rheumatoid arthritis (RA), psoriasis, and inflammatory bowel diseases [1]. Among Th subsets, interleukin-17 (IL-17)-producing Th (Th17) cells are classified as an inflammatory Th subset, resulting in chronic tissue inflammation and subsequent organ failure [2, 3]. Indeed, some biologic agents targeting the effector cytokines of Th17 cells have been approved for the treatment of certain immune-mediated diseases and we will see the expansion of diseases, which could be treatable by them. Therefore, understanding the differentiation and pathogenic functions of Th17 cells is crucial for the development of a novel immunotherapy for Th17-associated inflammatory diseases. Here, we focus on how Th17 cells acquire the terminal effector function, in particular, the pathogenicity in disease models and how environmental cues modulate Th17 cells that orchestrate chronic tissue inflammation in SKG mice, an animal model of RA. Finally, we discuss the role of gut microbiota and immunometabolism in modulating Th17 cells of patients with RA.

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Induction of Th17 cells

The differentiation and pathogenic functions of Th17 cells are regulated by numerous internal and external signals (Fig. 1). The differentiation of Th17 cells from naïve Th cells is initiated by stimulation with professional antigen-presenting cells (APCs) and particular cytokines including IL-6, IL-21, and TGFβ [4–7]. Following the upregulation of the lineage-defining transcription factors RORγt and RORα mediated by IL-6-JAK-STAT3 axis [8–12], Th17 cells produce the signature cytokines IL-17A, IL-17F, and IL-22, which are essential for mucosal host defense against extracellular bacteria and fungi by inducing anti-microbial peptides from epithelial cells and also recruit neutrophils by inducing chemokines under inflammation [13]. Hence, the deficiency of IL-6, IL-21, TGFβ, or RORγt impairs the differentiation of Th17 cells and subsequent Th17-mediated immunity [6, 8, 14]. However, the effect of TGFβ signaling in vitro is complicated with respects to Th17 effector function and could inhibit the function of autoimmune Th17 cells [15].

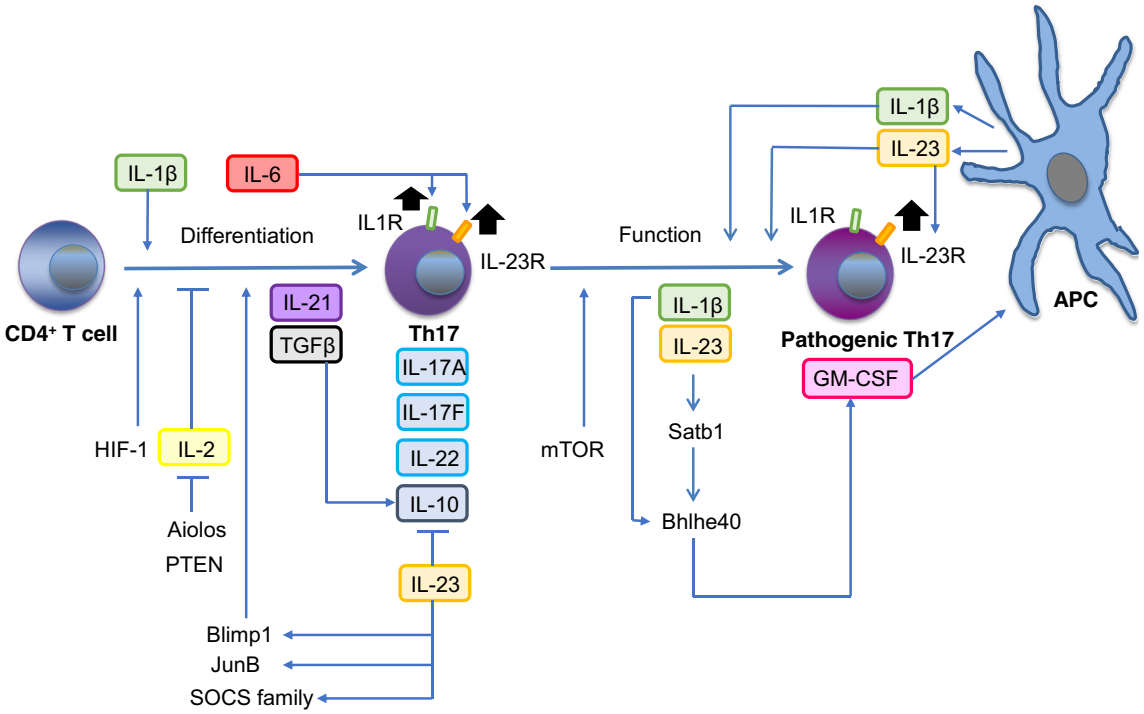

Fig. 1 The regulation of Th17 differentiation and effector function

Among negative regulators of Th17 induction such as Th1- and Th2-inducing cytokines, IL-2 is a key repressor of Th17 differentiation and IL-2-mediated STAT5 activation specifically inhibits production of IL-17 [16]. By contrast, phosphatase and tensin homolog (PTEN) and Aiolos (encoded by *Ikzf3*), which repress IL-2 expression in T cells, have been identified to promote the development of Th17 cells [17, 18].

Natural Th17 cells are normally present in the gut in a microbiota-dependent manner, maintain tissue homeostasis, and fight against pathogenic microbes [19]. This defense mechanism is mainly mediated by IL-17 and IL-22, which increase anti-microbial peptides from gut epithelial cells [20]. Intriguingly, Th17 cells in Peyer's patches can be converted into T follicular helper cells with high levels of Bcl6 and IL-21 expression, which support the differentiation of IgA-secreting B cells with antigen-specific properties [21]. These gut-specific Th17 cells are termed as "non-pathogenic Th17 cells" and are not associated with autoimmune reactions to self-antigens. However, when self-reactive Th cells are accidentally primed under Th17 conditions, additional environmental cues are able to modulate the effector profiles of autoimmune Th17 cells that cause the pathogenic outcome of targeted organs.

Pro-inflammatory cytokines to modulate the pathogenic function of Th17 cells

IL-1 and IL-23 are pro-inflammatory cytokines and are well-characterized as an enhancer and stabilizer of effector Th17 cells in autoimmune models, which predominantly express their corresponding receptors IL-1R1 and IL-23R, respectively [22–28]. Consistent with the importance of IL-1 and IL-23 in in vivo models, in vitro-polarized Th17 cells by stimulation with IL-6 and TGFβ are not able to induce Th17 cell-driven experimental autoimmune encephalomyelitis (EAE), an animal model of MS, whereas Th17 cells induced by IL-1β, IL-6, and IL-23 acquire the pathogenicity and elicit EAE [15]. One of the possible explanations about the difference between these in vitro conditions is that the treatment with IL-6 and TGFβ induces anti-inflammatory cytokine IL-10 in Th17 cells whereas IL-23 is critical for induction of the endogenous cytokine TGFβ3 by developing Th17 cells in addition to restraining IL-10 and in turn induces the pathogenicity of Th17 cells with high levels of T-bet, IL-23R, and GM-CSF [29, 30]. Furthermore, the single-cell RNA-sequencing analysis of ex vivo Th17 cells causing chronic inflammation in the central nervous system (CNS) of EAE mice identified *Gpr65*, *Toso*, and *Plzp* as novel genes promoting Th17 pathogenicity and CD5 antigen-like (CD5L) as a repressor of Th17 cell-mediated disease [31, 32]. IL-1 and IL-23 signaling also modulate the effector profile of Th17 cells through regulation of JunB and SOCS family members and induce highly pathogenic IL-17$^+$ IFNγ$^+$ and IL-17$^+$ GM-CSF$^+$ double-positive T cells, which have been shown to be originated from Th17 cells using a fate mapping strain [33–36]. It is of note that IL-23 is not required for the differentiation and maintenance of "non-pathogenic" Th17 cells in the gut and the functional plasticity toward T follicular helper cells [21].

Since naïve T cells do not express IL-1R and IL-23R [23, 37], their expression occurs during the initiation of Th17 differentiation in the presence of IL-6 whose signaling upregulates IL-1R1 and IL-23R expression via RORγt binding to the *Il1r1* locus and STAT3 binding to the *Il23r* locus, respectively [15, 24, 38]. STAT3 activation also increases miR-183-96-182 cluster, which dampens Foxo1 expression, a negative regulator of IL-1R1 and IL-23R expression [38]. Protein C receptor also represses IL-1R and IL-23R expression on Th17 cells [39]. On the other hand, RBPJ (downstream of Notch signaling) promotes IL-23R expression as a positive regulator and therefore RBPJ KO Th17 cells fail to show the pathogenicity [40].

Through integrating these positive/negative regulators and a positive feed-forward loop by IL-1β and IL-23 stimulation, Th17 differentiation are finally stabilized along with upregulation of IL-1R and IL-23R [15, 41]. Thus, IL-23R expression is the hallmark of effector Th17 cells and its signaling promotes Blimp-1 (encoded by *Prdm1*) expression in vivo and the pathogenicity of Th17 cells by increasing IL-17 and GM-CSF production in RORγt-, STAT3-, and p300-dependent manners [42].

Environmental stimuli to modulate the pathogenic function of Th17 cells

Environmental factors are implicated in the increased prevalence of autoimmune and allergic diseases, some of which are induced by Th17 cells. External signals such as environmental toxins, metabolic stress, and osmotic pressure substantially affect the immune system including the pathogenicity of Th17 cells.

The aryl hydrocarbon receptor (AhR) is a ligand-dependent transcription factor and senses many environmental toxins and endogenous ligands such as tryptophan metabolites. AhR is specifically induced under Th17 culture conditions and AhR ligation enhances production of IL-17 and IL-22 by effector Th17 cells [43, 44].

Metabolic cues regulate the function and differentiation of innate and adaptive immune cells. Metabolic demands dramatically increase during T cell activation and proliferation. The transcription factor hypoxia-inducible factor 1 (HIF-1), a key metabolic sensor, controls, in particular, a glycolytic pathway during Th17 differentiation and the effector function of Th17 cells through directly activating RORγt and IL-17 [45, 46]. The kinase complex mTORC1 is also known to be a central regulator of transcriptional pathways mediated by metabolic stress and contributes to the differentiation and effector function of Th subsets. The pathogenic phenotype of Th17 cells expressing T-bet and IFN-γ is partly regulated by mTORC1 signaling and therefore deletion of mTORC1 after Th17 differentiation reduces EAE severity [47].

A high salt diet widely spreads over the world and is associated with modern diseases. Serum glucocorticoid kinase 1 (SGK1), a serine/threonine kinase, can be induced in a high salt concentration under Th17 culture conditions and promotes IL-23R expression and stabilization of Th17 cells by deactivating Foxo1, the antagonist of Th17 cells. Thus, SGK1 activation in Th17 cells promotes autoimmune Th17 responses by upregulating GM-CSF [48, 49]. Taken together, environmental factors have a robust impact on accelerating the pathogenic function of Th17 cells.

GM-CSF, a key pathogenic cytokine in autoimmune tissue inflammation

GM-CSF is recently highlighted as the pathogenic cytokine of Th17 cells. The role of GM-CSF in EAE model was first reported in 2001, in which blockade of GM-CSF showed resistance to the EAE induction, but the critical source of GM-CSF in immune cells was not investigated in details [50]. There was the first report that among Th subsets infiltrating into the CNS after EAE induction, some of Th cells showed IL-17A^{+} GM-CSF^{+} double-positive producer [51]. The critical function of IL-23 signaling directing encephalitogenic Th17 cells has been reported to drive GM-CSF production, which causes local tissue inflammation [41, 52]. Because T cells do not express GM-CSF receptor [41], GM-CSF affects non-T cells. GM-CSF first acts on CNS-infiltrating myeloid cells such as dendritic cells (DCs), monocytes, and macrophages which in turn secrete pro-inflammatory cytokines such as IL-6 and IL-23, both of which upregulate IL-23R expression, amplifying IL-23-mediated pathogenic circuit to directly cause neurological pathogenicity and establishing local tissue inflammation by recruiting inflammatory macrophages in the CNS [51, 53]. GM-CSF also activates CCR2^{+} monocytes, monocyte-derived DCs and microglia in the brain to produce IL-1β [54, 55]. Since microglia have a potential to produce IL-23, they could participate the IL-23-IL-17 immune axis in Th17 cell-mediated tissue inflammation [56].

The transcription factor Bhlhe40, whose expression is initiated by CD28 signaling and enhanced by IL-1R1 signaling in T cells, has been identified as the direct driver of GM-CSF expression and Bhlhe40 KO mice were shown to be resistant to EAE due to impaired production of GM-CSF from pathogenic T cells [57, 58].

We recently identified special AT-rich binding protein 1 (Satb1), a genome organizer, as a crucial regulator of the pathogenic function of encephalitogenic tissue Th17 cells, while Satb1 was dispensable for the differentiation of Th17 cells [59]. To elucidate a specific role of Satb1 in Th17 cells, we generated *Il17a*^{Cre}*R26R*^{eYFP}*Satb1*$^{fl/fl}$ conditional knock out (Th17^{Satb1CKO}) mice, in which Cre-mediated deletion of *Satb1* occurs in Th17 cells upon their differentiation into IL-17-expressing eYFP^{+} CD4^{+} T cells. We found that

Th17^{Satb1CKO} mice after EAE induction had impaired Th17 cells with low levels of GM-CSF expression and as a result, Th17^{Satb1CKO} mice were resistant to EAE. Mechanistically, Satb1 specifically bound to the active promoter region of the *Bhlhe40* locus and upregulated GM-CSF production in encephalitogenic Th17 cells. This machinery was pathogenic Th17-dependent in inflamed tissue because Satb1-sufficient gut Th17 cells did not express GM-CSF. We also observed that in vitro re-stimulation of draining LN eYFP$^+$ Th17 cells from EAE mice with IL-23, but not IL-1β or IL-6 increased Satb1 expression, whereas TGF-β restrained its effect, suggesting that IL-23 signaling in chronic inflammation upregulates Satb1 expression in Th17 cells. In addition, Satb1 specifically promoted the effector function of Th17 cells in the CNS by inhibiting PD-1 expression. Considering that IL-1 signaling directly upregulates Bhlhe40, IL-1 and IL-23 signaling synergistically enhance GM-CSF production and the encephalitogenicity of Th17 cells by increasing Bhlhe40 and Satb1 expression, respectively.

Human Th17 cells and their role in neuroinflammation

Similar to mouse Th17 cells, the differentiation of human Th17 cells in vitro requires IL-1, IL-6, IL-23, and TGFβ. Several studies initially demonstrated that IL-1β, IL-6, and IL-23 but not TGFβ were sufficient to induce the differentiation of human Th17 cells [60, 61]. However, careful assessments later reconciled the role of TGFβ in human Th17 differentiation, showing that TGFβ, IL-23, and IL-1β (or IL-6) under serum-free conditions were essential in driving Th17 differentiation because culture medium contained serum-derived TGFβ or AhR ligands [62, 63]. Consistent with mouse Th17 cells, IL-23 plays the major role in human Th17 differentiation as human naïve CD4$^+$ T cells can immediately respond to IL-23 and the IL-23R expression is further upregulated by IL-23 signals in the presence of additional IL-1β [62, 64]. Furthermore, dominant-negative mutations in STAT3, a key transcription factor downstream of IL-6 and IL-23 signaling, were responsible for disease manifestations of hyper-immunoglobulin E syndrome and impaired IL-17 production and the differentiation of Th17 cells, supporting roles of STAT3 in IL-6 and IL-23 signaling pathways and Th17 differentiation in humans [65, 66].

Before the discovery of Th17 subset, IL-17 was identified as the highest-ranking gene expressed in the CNS of MS patients [67]. It is of note that accumulation of Th17 cells were the first wave of T cells infiltrating the CNS [68], followed by the infiltration of DCs, macrophages, and other cells, which further promote and sustain tissue inflammation. In addition, a number of studies have shown that a single nucleotide polymorphism (SNP) in IL-23R is linked to a number of human autoimmune diseases [1], indicating that IL-23 signaling is essential for evoking a pathogenic feature in Th17 cells. IL-23 is also associated with the risk of MS [69, 70]. Since GM-CSF have a pivotal role in Th17 cells for encephalitogenicity in mice [41, 52], the findings that there were elevated levels of GM-CSF in the cerebrospinal fluid and serum of active MS patients with relapsing-remitting type and increased GM-CSF production of T cell from the peripheral blood and brain lesion of MS suggest a crucial role of GM-CSF in disease manifestations and tissue inflammation [71, 72].

The pathogenicity of Th17 cells in autoimmune arthritis models

RA is a systemic autoimmune disease that affects about 1% of general population worldwide, characterized by chronic joint inflammation and bone destruction [73]. Although the exact pathogenesis remains to be determined, it has been recognized that Th subsets play an important role in RA pathogenesis based on human leukocyte antigen (HLA)-DRB1 identified as the strongest disease risk gene, abundant T cells and macrophages infiltrating into synovial membrane in RA patients, and presence of circulating autoantibody such as rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA) [73–76]. When the Th1/Th2 paradigm dominated in the pathogenesis of autoimmune diseases before the discovery of Th17 cells, RA as well as MS was previously thought to be Th1-mediated diseases. However, the levels of Th-1-mediated cytokines such as IFN-γ in RA synovium were relatively low compared with those of TNF-α, IL-1, or IL-6 derived from inflammatory macrophage- and fibroblast-like synoviocytes (FLS) [77, 78]. The importance of these macrophage- and FLS-derived proinflammatory cytokines in RA is evident based on the efficacy of anti-cytokine therapy, such as anti-TNF or anti-IL-6 therapy, which brought a paradigm shift in RA treatment.

The discovery of Th17 cells have shed new insights into how inflammatory Th subsets contribute to the initiation of RA and form a proinflammatory cytokine network, leading to chronic inflammation, in particular, in animal models of autoimmune arthritis. There are several murine models to understand the pathogenesis of RA. Firstly, collagen-induced arthritis (CIA), which is induced by immunizing mice with type II collagen and whose pathogenicity is totally dependent on the generation of anti-collagen autoantibodies, is one of the well-established arthritis models. K/BxN mice, another model of arthritis, develop spontaneous arthritis mediated by the arthritogenic anti-glucose-6-phosphate isomerase (GPI) autoantibody [79, 80]. It has been demonstrated that IL-17 plays a pathogenic role to a greater or lesser extent in these murine models. However, with regard to T cell-dependent, but not autoantibody-dependent autoimmune arthritis, SKG mice are a suitable model to focus how T cells mediate autoimmune arthritis [81–83].

The SKG strain of mice on a BALB/c background bears a point mutation in ζ-associated protein-70 (ZAP-70), a key TCR-proximal signaling molecule, and spontaneously develops Th cell-mediated autoimmune arthritis in a microbially conventional environment, which immunopathologically resembles human RA [84, 85]. The mutation of the ZAP-70 gene alters the threshold for positive and negative selection of T cells in the thymus, leading to the production of self-reactive (arthritogenic) T cells and development of autoimmune arthritis [84–86]. SKG mice also frequently develop extra-articular lesions such as interstitial pneumonitis, rheumatoid nodules and vasculitides and show the production of autoantibodies such as RF and ACPAs, as seen in human RA [84]. Interestingly, SKG mice do not develop spontaneous arthritis under a specific-pathogen-free condition, yet can be induced by stimulation of innate immunity via Toll-like receptors, the Dectin pathway, or complement activation pathways, for example, by injection of fungal products such as zymosan and mannan, or, by provoking homeostatic proliferation of self-reactive T cells under lyphopenic conditions [87, 88]. Synovial inflammation in SKG mice is characterized by abundant infiltration of Th cells, which can adoptively transfer the disease into lymphopenic mice such as *Rag2*$^{-/-}$ mice, showing the disease dependency on Th cells. Recently, we succeeded to newly identify an arthritogenic self-antigen, 60S ribosomal protein L23a (RPL23A), by isolating arthritogenic effector Th cells from SKG arthritic joints and screening their TCR repertoires with an arthritogenic potential in retrogenic mice system. In addition, anti-RPL23A autoantibody was specifically detected in sera from patients with RA, which would support a similar molecular basis of the pathogenicity between SKG arthritis and human RA [89].

We reported that arthritis in SKG mice was highly dependent on Th17 cells since the cell transfer of IL-17-deficient SKG Th cells into T cell-deficient mice completely failed to induce arthritis. Supporting this finding, IL-6-deficient SKG mice were highly resistance to arthritis induction due to impaired T cell differentiation into Th17 cells. Although Th1 cells along with Th17 cells are also detected in SKG inflamed synovium, IFN-γ deficient SKG mice rather exacerbate arthritis, because Th17 differentiation is inhibited by Th1- or Th2-associated cytokines such as IFN-γ or IL-4 and IFN-γ deficient conditions expand arthritogenic Th17 cells [82].

We have proposed a possible mechanism of how self-reactive (arthritogenic) Th cells become effector Th17 cells, migrate to synovium and initiate joint inflammation in SKG mice. Self-reactive T cells become activated in the periphery via recognition of class II MHC/self-peptide complexes expressed by APCs, and stimulate APCs through CD40/CD40L interaction to upregulate CD80/CD86, which further activate these T cells to proliferate. Activated APCs secrete a large amount of IL-6 (also IL-1, IL-23, and TNFα), together with surrounding tissue-derived TGF-β, that induces the differentiation of effector Th17 cells. Expanded arthritogenic Th17 cells predominantly express CCR6 and migrate to joints in response to CCL20, the ligand of CCR6, which is secreted by activated FLSs. Indeed, treatment with anti-CCR6 blocking mAb significantly inhibits the infiltration of Th17 cells into joints and reduces the severity of arthritis in SKG mice. In vitro, CCL20 expression in synoviocytes is promoted by IL-17, IL-1β, or TNFα, whereas IFN-γ or IL-4 inhibits its expression. Thus, once arthritogenic Th17 cells are activated and recruited into joints to initiate inflammation, synoviocytes further recruit Th17 cells in a feed-forward mechanism by which CCL20 production is augmented by proinflammatory cytokines such as IL-17, IL-1β, or TNFα derived from both activated synoviocytes and Th17 cells (Fig. 2). Expression of CCR6 in Th17 cells and CCL20 in synoviocytes are also observed in RA patients with a significant correlation between the amounts of IL-17 and CCL20 in RA joints [90]. Furthermore, recent genome-wide association study (GWAS) studies identified CCR6 as a disease susceptibility gene of RA, which together implies the pathogenicity of Th17 in RA and a shared mechanism of Th17 recruitment in inflamed joints [91].

Although Th17 cells are responsible for initiating autoimmune arthritis, it remained unclear how Th17 cells participate in "chronic" tissue inflammation. Recently, we demonstrated that GM-CSF is a crucial mediator in forming chronic joint inflammation in SKG mice and how Th17 cells orchestrate this "GM-CSF-cytokine network." GM-CSF can be produced by various cell types including endothelial cells, fibroblasts, and activated T cells upon receiving immune stimuli, and is a key proinflammatory cytokine for the activation of macrophages and dendritic cells [92]. GM-CSF is abundantly seen in RA synovium, which is a reasonable observation to explain highly activated macrophages in RA joints, indicating its importance in the pathogenesis of RA [93, 94]. As expected, GM-CSF was crucial for arthritis induction in SKG mice since *Csf2*$^{-/-}$ SKG mice completely failed to develop arthritis, regardless of the presence of activated Th17 cells [95]. Adoptive T cell transfer experiment showed that T cell-derived GM-CSF, although it augmented arthritis, was dispensable for inducing arthritis, while non-T cell-derived GM-CSF was indispensable. Using bone marrow chimeras, the crucial source of GM-CSF was identified in radio-resistant stromal cells, including FLSs, and synovial-resident innate lymphoid cells (ILCs). Inhibition or loss of GM-CSF production in either radio-resistant stromal cells or ILCs significantly reduced the severity of arthritis. In vitro, FLSs upregulate GM-CSF secretion in response to recombinant IL-17 stimulation. In addition, adoptive transfer of wild type (WT), but not *Il17a*$^{-/-}$ SKG Th cells into *Rag2*$^{-/-}$ mice significantly induced *Csf2* (also *Ccl20* and *Il6)*, in synoviocytes, which together imply that arthritogenic Th17 cells in joints stimulate FLSs via IL-17 and promote GM-CSF production. ILCs reside in healthy

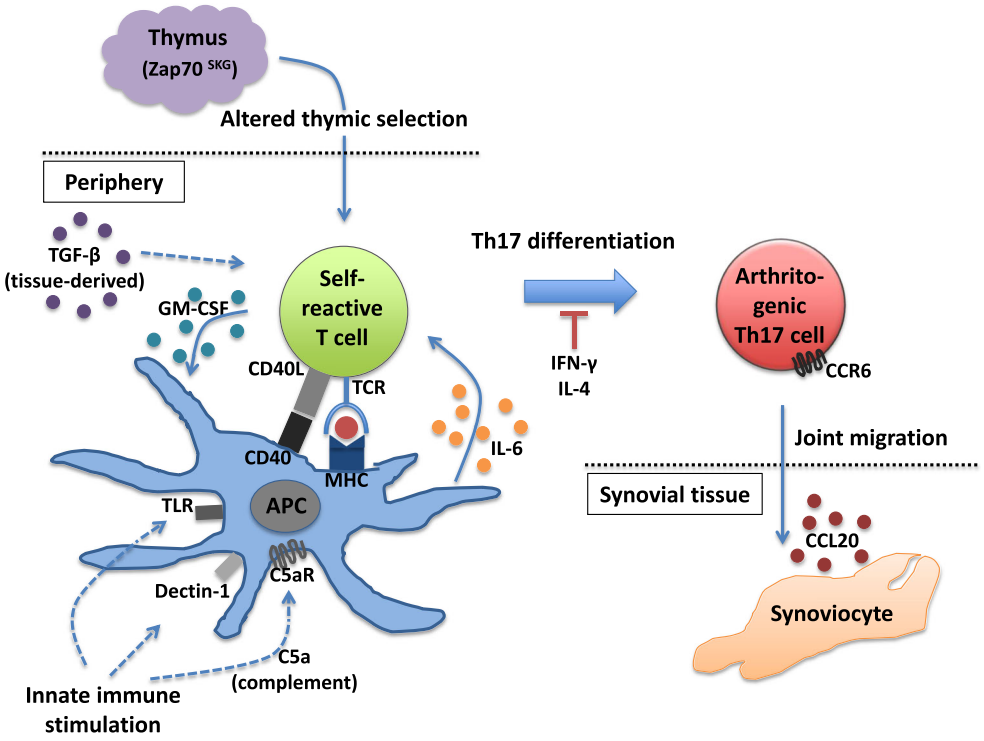

Fig. 2 A possible mechanism of self-reactive Th17 differentiation in SKG mice

joints of SKG (or even other healthy mouse strains), but when arthritis occurs, GM-CSF-producing ILCs specifically expand in the joints. Predominant population of GM-CSF-producing synovial ILCs expresses Gata-3 and/or IL-13, which are the master transcription factor and signature cytokine of ILC2s. Indeed, in vitro, when synovial ILCs are treated with a combination of IL-2 and IL-33, GM-CSF production is significantly enhanced as well as IL-13 and IL-5 production. Furthermore, these synovial ILCs highly express Toll-like receptor 9 (TLR9) and synergistically upregulate GM-CSF production in response to CpG DNA, a ligand of TLR9, in combination with IL-33, but not CpG DNA alone. Expression of functional TLR9 in synovial ILCs indicates that they may sense mitochondrial DNA, possibly released as one of endogenous damage-associated molecular patterns (DAMPs). Taken together, unlike mechanisms of GM-CSF production in FLSs, synovial ILCs sense IL-2, IL-33, and self DNA, which can be produced by arthritogenic Th17 cells and released from necrotic cells in inflamed joints, leading to GM-CSF production (Fig. 3) [95].

In the SKG arthritis model, induction of arthritis is fully dependent on Th17 cells. The key early event to initiate joint inflammation seems to be stimulating tissue stromal cells via IL-17 produced by arthritogenic Th17 cells migrating into joints. Expanded Th17 cells then orchestrate a GM-CSF-centric cytokine network, which results in the activation of synovial macrophages, leading to chronic inflammation and joint destruction.

Human Th17 cells in rheumatoid arthritis

As we have discussed above, there are several observations that support the pathogenesis of Th cells in RA. The efficacy of CTLA4-Ig treatment in RA indicates a central role of Th cells. In addition, recent GWAS study further identified RA risk loci that are linked to T cell function (e.g., PTPN22, CD28, CD40), and are even more specific to Th17-associated molecules such as CCR6 [91, 96–100]. However, the role of Th17 cells in RA is not as clear as animal models yet. Many reports agree that levels of IL-17 are increased in synovial fluid (SF) and synovial tissue (ST) in RA [101–104]. Kirkham et al. reported that the levels of IL-17 expression in ST are predictive of joint damage in RA patients, which could be the result of enhanced osteoclasts activation mediated by IL-17-rich environment [105]. However, it is controversial whether Th17 cells increase in the peripheral blood, SF, or ST in RA [106–110]. Furthermore, it was reported in ST that the vast majority of IL-17-secreting cells were not Th17 cells, which is one of the major differences from animal models of arthritis. The exact sources of IL-17 in ST remain unclear [101, 111]. Hueber et al. reported that the major source of IL-17 was synovial mast cells, which promote IL-17 production in stimuli by TNFα, IgG complexes or C5a, whereas Kan et al. later reported that the number of IL-17-producing mast cells and the frequency of IL-17-producing mast cells among all the IL-17$^+$ cells in ST were comparable between RA and osteoarthritis (OA) patients, raising a question to the contribution of synovial mast cells as a source of IL-17 [111, 112].

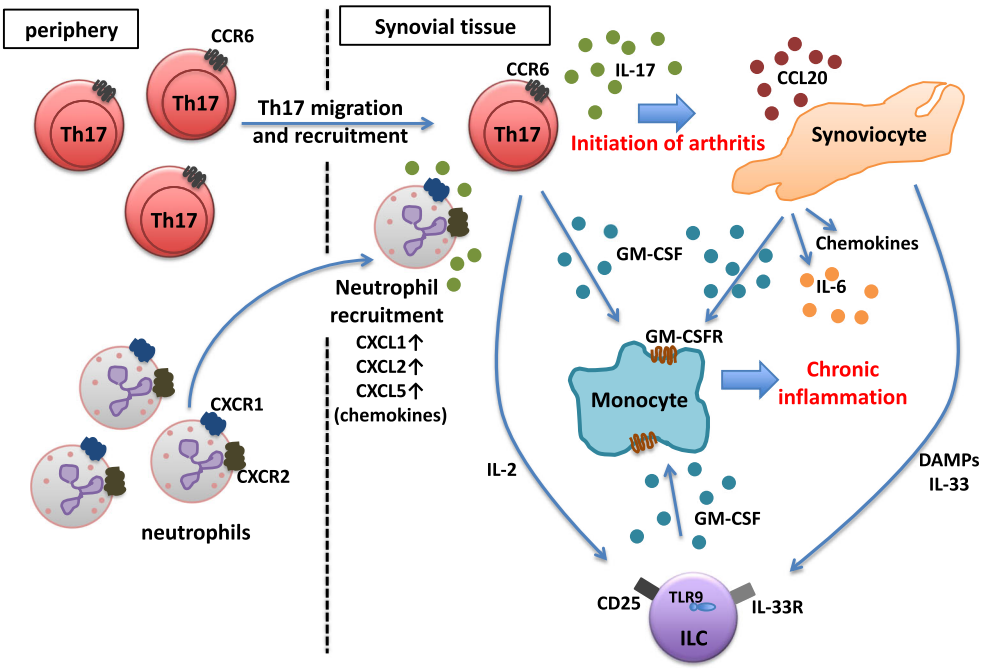

Fig. 3 Th17 cells orchestrate chronic joint inflammation in SKG mice

Furthermore, the frequencies of Th1 cells among CD4+ T cells in SF and ST of RA patients are much larger than those of Th17 cells [81, 110]. However, the plasticity of Th17 cells toward Th1-like cells may be able to give a possible explanation for this observation. Nistala et al. showed the presence of IFN-γ-producing Th17 cells (hereafter Th17/Th1) in SF from patients with juvenile idiopathic arthritis (JIA), which express both Th1 and Th17 transcription factors such as T bet and RORC2 [113]. They also demonstrated in vitro that Th17 cells can be converted to Th17/Th1-cell phenotype in IL-12^{high} TGFβ^{low} conditions that resembles the SF environment of JIA. Furthermore, TCRβ (TRBV) repertoire analysis revealed that synovial Th17/Th1 cells share TCRβ repertoire oligoclonality with Th17 cells, indicating that Th17/Th1 cells may be deviated from Th17 cells. Moreover, CD161, one of the surface marker of Th17 cells in human as well as CCR6, is expressed not only in Th17/Th1 cells, but also in a number of Th1 cells in SF. These findings together suggest that a certain subpopulation of IFN-γ-producing CD4+ T cells in arthritic joints may originate from Th17 cells, which shift to Th1-like phenotype via an intermediate state of Th17/Th1 cells, when they encounter a IL-12^{high} TGFβ^{low} environmental cue in the local inflammatory site. In fact, there are accumulating evidence that IFN-γ^{+} ex-Th17 cells are enriched in SF of JIA and RA in comparison to peripheral blood [113–115]. In addition, recent studies revealed that approximately 80% of GM-CSF-producing CD4+ T cells in joints of JIA and RA co-express IFN-γ, but rarely express IL-17 [116, 117]. The majority of these IFN-γ^{+} GM-CSF^{+} CD4^{+} T cells express CD161, indicating that the subpopulation of IFN-γ^{+} ex-Th17 cells also actively produce GM-CSF [117].

As Th17 cells have been highlighted in the pathogenesis of RA, IL-17 inhibitors as a new potential biologic agent were trialed for RA treatment. In phase II trials, treatment with anti-IL-17 antibodies, secukinumab or ixekizumab, have demonstrated preliminary efficacy in RA with biologic-naïve or who failed to respond to TNF inhibitors or methotrexate [118–121]. However, in phase III trials, IL-17 inhibition showed no incremental benefit over the biologic agents currently approved to non-responders for TNF inhibitors [122, 123]. Although there is no clinical trial that has focused on evaluating the efficacy of IL-17 inhibitors in the onset or early stage of RA, these results indicate that IL-17 inhibitors alone are not sufficient enough to suppress ongoing chronic inflammation in established RA. Notably, it has been reported that higher levels of IL-17 in SF exist at the early stage of RA compared with the established stage and those of IL-17 in sera rather decreases after the onset of RA [124, 125]. Taking these findings together, Th17 cells may have different roles at different phases of RA. Th17 cells initiate joint inflammation via IL-17 by stimulating FLSs, promoting osteoclast differentiation and recruiting abundant neutrophils and more Th17 cells. However, soon after the onset of inflammation, a number of Th17 cells may become IFN-γ^{+} ex-Th17 cells in response to surrounding cytokine environments in the arthritic joints and simultaneously begin to actively secrete GM-CSF together with other GM-CSF-producing cells such as activated FLSs and synovial ILCs that synergistically provoke synovial macrophages to secrete a large amount of tissue destructive molecules and proinflammatory cytokines such as TNF-α or IL-6, leading to chronic inflammation. Thus, the pathogenesis of Th17 cells in RA may shift from "IL-17-producer," as an

initiator of the disease, into "GM-CSF-producer," as an organizer of chronic inflammation. GM-CSF has been highlighted as a key mediator in RA based on recent clinical trials using GM-CSF inhibitors for RA patients [126–129]. From our point of view, IL-17 inhibitors may show a better clinical outcome for early onset RA patients, although it is not easy to identify and test such patients in a clinical trial.

Psoriasis, psoriatic arthritis (PsA), and ankylosing arthritis (AS) have been implicated in Th17-mediated autoimmune diseases in humans. Unlike RA, IL-17 inhibition shows marked clinical efficacies in psoriasis or PsA patients (also IL-12/23p40 inhibition) and AS patients, indicating the proof of concept in the pathogenesis of IL-17 in these diseases [130–134]. Further studies will be required to understand how IL-17-type/disease-specific tissue inflammation changes before and after the treatment with IL-17 inhibitors.

Regulation of Th17 cells by gut microbiota and immunometabolism in arthritis

There are accumulating evidence that the dysbiosis of gut microbiota is associated with various autoimmune diseases. Studies have shown that altered intestinal microbiota is observed not only in inflammatory bowel diseases, but also in organ-specific or systemic autoimmune diseases that affect internal organs, including type 1 diabetes, MS, and RA [135–140]. Autoimmune arthritis in murine models is also dependent on gut microbiota, for example, both K/BxN and SKG mice spontaneously develop arthritis in conventional conditions, but arthritis cannot be induced under germ-free (GF) conditions [87, 141]. Several studies have shown gut dysbiosis in RA patients. By using 16s rRNA gene sequencing, two reports revealed that *Prevotella copri* was significantly increased in RA patients, while *Bacteroides* was reduced. Maeda et al. demonstrated the disease-modifying role of *P. copri* in arthritis by generating gnotobiote SKG mice with *P. copri*, showing that *P. copri* induces CD4+ T cells in the large intestine to differentiate into Th17 cells, leading to production of arthritogenic Th17 cells and trigger autoimmune arthritis [138]. In contrast, another *Prevotella* species showed a beneficial role in humans. Marietta et al. demonstrated that *Prevotella histicola*, which is one of the commensal bacteria in the human gut, reduced the severity of arthritis in CIA model of HLA-DQ8-humanized mice [142]. Mice treated with *P. histicola* showed increased regulatory T cells (Treg) in the gut, suppressed antigen-specific Th17 response, and reduced the levels of prionflammatory cytokines, including IL-17 or TNF-α. These findings are intriguing in that therapeutic intervention of gut dysbiosis-targeting specific species may potentially be a new treatment for RA by regulating Th17 or Treg cells.

Immunometabolism plays a key role in the regulation of autoimmune T cells and T cell-mediated autoimmunity, including RA. Intriguingly, RA T cells fail to upregulate a glycolytic activity due to the insufficient induction of the key glycolytic enzyme PFKFB3, and shunt glucose toward the pentose-phosphate pathway. Impaired glycolysis induces a pyruvate^{low}ATP^{low} intracellular environment and increase the production of NADPH, resulting in reduction of reactive oxygen species (ROS) and upregulation of fatty acid synthesis [143, 144]. Using a chimeric mouse model generated by implanting human synovium and transferring human T cells into NOD/Scid/IL2Rγnull mice, Shen et al. reported that these altered metabolic conditions lead to overexpression of TKS5, a podosome scaffolding protein, which enables them to form tissue-invasive membrane structures, resulting in enhancement of T cell invasion into synovium [144]. Expression levels of TKS5 in activated CD4$^+$ CD45RA$^+$ T cells in RA patients were correlated with their disease activities. They demonstrated in the chimeric mice that regulating these altered metabolic conditions by supplementation of pyruvate or inhibiting fatty acid synthesis successfully rewired the tissue-invasive behavior of RA T cells. In addition, another report from the same group showed that reduction of ROS promotes T cell maldifferentiation into Th17 and Th1 cells [145]. ROS restoration by menadione treatment in the chimeric mice, significantly reduced IFN-γ or IL-17-producing T cells in the synovium. These observations suggest that regulating T cell metabolic condition may successfully control proinflammatory differentiation and behavior of RA T cells.

Concluding remark

The discovery of Th17 cells brought us a new insight into a molecular basis of autoimmune disorders beyond the Th1/Th2 paradigm and clinical applications for various immune-mediated diseases. However, it remains elusive how Th17 cells mediate tissue injuries and orchestrate chronic tissue inflammation at different target organs. A comprehensive single-cell atlas that will characterize the pathogenicity of Th17 cells at different inflamed organs will open a new avenue for a novel immunotherapy, which enables us to specifically manipulate the function of pathogenic Th17 cells in autoimmune disease, but preserve the immune homeostasis, for instance, in the gut, mediated by physiological Th17 cells.

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Compliance with ethical standards

Competing interests The authors declare that they have no competing interests.

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