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Breaking old paradigms: Th17 cells in autoimmune arthritis[☆]

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Abstract

Aberrant helper T cell activation has been implicated in the pathogenesis of an array of autoimmune diseases. In this review, we summarize evidence that suggests the involvement of a novel T cell subset, the Th17 lineage, in rheumatoid arthritis. In particular, we focus on the role of Th17 cells in inducing and perpetuating the chronic inflammation, cartilage damage, and bone erosion that are hallmark phases of joint destruction and consider current and emerging therapies that seek to disrupt the inflammatory Th17 network and shift the immune system back towards homeostasis.

Keywords

Th17; IL-17; Rheumatoid arthritis

Introduction

Effective immunologic homeostasis relies on a continual balance between a number of factors, including helper T (Th) cell activation and regulatory T cell (Treg) suppression. When homeostasis is disrupted and the immune system tips in favor of activation, the host becomes susceptible to autoimmunity. Although it was originally believed that many autoimmune disorders, including rheumatoid arthritis (RA) and multiple sclerosis, partially resulted from an aberrant Th1 response, several studies in mice that demonstrated the deleterious effects of interferon-gamma (IFN- γ) deficiency called the role of the Th1 lineage in autoimmune pathogenesis into question [1–3]. The recent discovery of another subset of helper T cells, termed Th17, breaks the long-accepted paradigms about T cell subsets in autoimmunity and has the potential to resolve the contradictory evidence regarding the role of Th1 cells. (For a schematic of T cell subsets, see Fig. 1.) Identified originally by their expression of the pro-inflammatory cytokine IL-17A (henceforth referred to as IL-17), Th17 cells have gained wide acceptance as a distinct subset of CD4⁺ cells with expression of unique master regulatory transcription factors retinoic acid receptor-related orphan receptor-gamma-t (ROR γ t) and ROR α [4,5]. Th17 cells are induced by a number of pro-inflammatory cytokines including IL-1, IL-6, and IL-23, and in turn these cells secrete anti-microbial peptides and pro-inflammatory cytokines such as TNF, IL-21, and IL-22. Interest in the relationship between Th17 cells and Tregs is growing rapidly given evidence that the relative proportions of each in the joint is a potential indicator of disease progression [6]; however, this subject will be mentioned only briefly. This review will focus on the mechanisms by which Th17 cells drive

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three overlapping phases of auto-immune arthritis: inflammation, cartilage destruction, and bone erosion.

Identification of Th17 cells as a principal mediator of autoimmune arthritis

Early observations of the inflamed tissue of rheumatoid arthritis led researchers to hypothesize that the disease was mediated by Th1 cells [7,8]. Reports that the infiltration of activated T cells enhances osteoclastogenesis in the joint, coupled with the identification of elevated Th1-associated factors (M-CSF, IL-10, and TNF) that induce osteoclastogenesis in synovial tissue, supported this notion [7–10]. However, the mechanism by which Th1 cells induced osteoclastogenesis remained unclear, and evidence ultimately emerged for an inhibitory effect of this subset on bone resorption. IFN- γ was found to suppress RANKL-dependent osteoclast formation by inducing the degradation of TRAF6, a molecule that links RANKL signaling to the differentiation of osteoclasts [1,2,11]. Other cytokines associated with Th1 cells, including GM-CSF, IL-12, and IL-18, were shown to inhibit bone resorption in vitro [12–14]. Thus, although Th1 cells express RANKL [15], it appeared that the expression of IFN- γ and other prototypical Th1 cytokines would have a net inhibitory effect on osteoclastogenesis, which has been confirmed in co-culture systems [3]. Furthermore, several studies in animal models of autoimmune arthritis suggest a protective role for IFN- γ during disease pathogenesis. Although initial studies showed that IFN- γ produced heterogeneous effects depending on the timing of its application [16,17], more recent studies demonstrate that IFN- γ -deficient mice exhibit increased susceptibility to and more severe manifestations of autoimmune arthritis [18,19]. Indeed, Vermeire et al. proposed that previous studies had linked administration of anti-IFN- γ to the attenuation, rather than the aggravation, of disease because administration of low-affinity antibody resulted in the formation of antibody-antigen complexes that hampered clearance of the cytokine and effectively augmented its availability to IFN- γ receptor [20]. Therefore, timing and dose appear to determine the effect of IFN- γ on disease, and the extent to which the presence of this cytokine in synovial fluid correlates with disease progression in RA remains unclear [21,22].

As subsequent studies increasingly pointed to a beneficial role for IFN- γ in animal models [20,23–25], other research elucidated the roles of IL-12 and IL-23 in autoimmune inflammation. The uneven contributions of the p35 subunit unique to IL-12 and the p40 subunit shared between IL-12 and IL-23 to the pathogenesis of various experimental autoimmune disorders was confirmed by ensuing studies that implicated IL-23 in the progression of disease and indicated the deleterious effects of IL-12 deficiency [26–28]. Further supporting the role of the IL-23-IL-17 axis, a link between IL-17 and the development of autoimmune arthritis began to emerge. Analysis of RA synovial fluid demonstrated elevated levels of IL-17 [29–31] while various animal models of autoimmune arthritis underscored a pathogenic role for IL-17/IL-17R signaling [32,33]. In particular, studies in IL-17 knock-out or deficient mice demonstrated that IL-17 is indispensable for spontaneous disease development through the priming of autoantigen-specific T cells as well as the generation of a pro-inflammatory cytokine milieu in joints [34,35]. In concurrence with these findings, local over-expression of IL-17 exacerbates joint destruction in collagen-induced arthritis (CIA) and chronic streptococcal cell wall arthritis [36,37]. Thus, mounting evidence implicates IL-17 as a crucial cytokine in both the induction of local inflammation and the joint destruction that characterizes the synovial tissue of autoimmune arthritis.

Mechanisms of IL-17 driven joint destruction

Inflammation

Th17-driven inflammation during host defense markedly resembles the inflamed synovial tissue in RA and other forms of autoimmune arthritis. The RA synovium is characterized by

elevated levels of IL-6, TNF, and IL-1 β along with nitric oxide (NO) and prostaglandin E2 (PGE2) [38]. Th17 cells, and IL-17 in particular, have been shown to synergize with or upregulate each of these pro-inflammatory factors. IL-17 mediates the induction of IL-6 and IL-8 in both adult RA and juvenile idiopathic arthritis [39,40]; these cytokines are associated with inflammation in synovial fluid and activate fibroblast-like synoviocytes through the phosphatidylinositol 3-kinase/Akt and NF- κ B pathways [39,41,42]. Additionally, IL-17 induces the expression of cyclooxygenase-2 (COX-2) in synoviocytes, a stress response molecule conducive to the high levels of PGE2 observed during inflammation [43,44]. Although in vitro cultures have suggested a regulatory role for PGE2 [44,45], experimental models of arthritis demonstrate that deficiency in COX-2 or the major inducible PGE2 synthetase attenuates acute and chronic inflammation [25,46]. Furthermore, PGE2 favors the expansion of the Th17 lineage by shifting the dendritic cell phenotype away from the IL-12 axis in favor of IL-23 [47,48]. Through synergy with TNF, IL-17 has also been proposed to induce the alternative complement pathway proteins C3 and factor B, both of which are upregulated in RA synovial tissue [49]. Abnormalities in the activation of the alternative complement pathway have been observed in RA synovium [50] and have been implicated in pathogenesis in autoimmune arthritis models [51,52]. In addition, IL-17 activates RA synovial fibroblasts through the PI2K/Akt, p38 MAPK, and NF κ B signaling pathways, inducing the IL-23-specific subunit, IL-23p19, in a probable positive feedback loop [53]. Two other members of the IL-17 cytokine family, IL-17B and IL-17C, have also been implicated in chronic inflammation in an experimental model of arthritis; CD4⁺ T cells transduced with IL-17B or IL-17C exacerbated murine CIA to the same degree as IL-17, and both cytokines stimulated the expression of pro-inflammatory IL-1 β , IL-6, TNF, and IL-23 [54]. Although comparatively few studies have examined the relationship between IL-17 and the autoantibodies characteristic of RA, recently B cell-activating factor (BAFF), associated with autoantibody production, and an associated family member TNFSF13 (or APRIL) have been demonstrated to regulate the production of IL-17 in CIA [55–57]. Taken together, these data are consistent with the localization of CD4⁺ T cells to the inflammatory pannus tissue formed during CIA [58]. However, qualifying these reports, a recent animal study suggests that IL-17 can only augment the inflammatory reaction rather than initiate it [59].

Cellular infiltrates

IL-17 may intensify local inflammation by promoting angiogenesis and subsequently recruiting innate immune cells to the joint. In in vitro cultures of tissue outgrowths that modeled the pannus characteristic of RA, Wakisaka et al. found that the RA synovium-derived T cells necessary for the formation of these outgrowths strongly expressed the lymphocyte adhesion molecules LFA-1 and CD2, the ligands of synovial cell ICAM-1 and LFA-3, respectively [60]. These lymphocytes also constitutively expressed IL-17, while the surrounding synovial macrophages and fibroblasts produced IL-15, a known stimulus of IL-17 [60,61]. IL-17 dose-dependently increases the production of vascular endothelial growth factor (VEGF) in RA fibroblast-like synovial cells in vitro, and stimulates this expression additively with TNF, suggesting that these cytokines act through independent pathways [62,63]. Additionally, IL-17 can upregulate the constitutive release of other angiogenic factors from synovial fibroblasts, including KGF, HGF, and HB-EGF, all of which are involved in the proliferation of endothelial cells [64].

IL-17-induced angiogenesis lays the foundation for the recruitment of neutrophils, macrophages and T cells to the joint, and local over-expression of IL-17 has been shown to augment the influx of polymorphonuclear leukocytes into the joints in CIA [65–67]. IL-17 regulates neutrophil activity through a combination of granulopoiesis, chemokine induction, and neutrophil survival during host defense [68,69] and may likewise be responsible for the influx of inflammatory neutrophils that occurs in the RA synovium. Indeed, following

stimulation by IL-17, RA fibroblast-like synovial cells upregulate the chemotactic factors IL-8, Gro- α , and Gro- β [70]. After pretreatment of RA synovial fibroblasts with IL-17 and TNF, subsequent co-culture of these cells with neutrophils effectively doubled neutrophil lifespan through the inhibition of apoptotic pathways [71]. Additionally, IL-17 has been linked to the upregulation of IL-16, a chemoattractant cytokine for CD4⁺ monocytes, and monocyte-chemoattractant protein-1 (MCP-1), and thus may also be involved in the influx of inflammatory macrophages in the synovium [72–74]. IL-17 has also been implicated in the recruitment of CD4⁺ T cells from peripheral blood, in part through induction of IL-8 and IL-16 [72,75]. In addition, TNF and IL-1 β , both of which synergize with IL-17, enhance IL-15 production from RA fibroblast-like synoviocyte cell lines, and IL-15 appears to promote the proliferation of lymphocytes in models of pannus [60,76]. The synergy between monocyte-derived IL-1 β and TNF and T cell-derived IL-17 also causes the upregulation from RA synoviocytes of CCL20, a protein involved in the chemotaxis of T cells and immature dendritic cells [77]. IL-17 thus appears to enhance inflammation in the joint through multiple pathways. In addition to inducing a highly inflammatory cytokine milieu, it drives angiogenesis and the subsequent recruitment of innate immune cells that further amplify inflammation.

Cartilage destruction

The structure and composition of articular cartilage are maintained by resident chondrocytes; for this reason, the formation of RA pannus and the subsequent degradation of articular cartilage are of particular import. Local inflammation has long been implicated in triggering and exacerbating cartilage destruction in rheumatic joints. Two downstream mechanisms by which such degradation occurs have been elucidated: the simultaneous inhibition of proteoglycan and collagen synthesis and the catabolism of the extracellular matrix. It is thought that inflammation in the adjacent synovial tissue and fluids evokes changes in the metabolic activity of chondrocytes [78].

The continuous synthesis of proteoglycans and collagens by resident chondrocytes are critical functions that sustain the structural integrity of cartilage. Multiple studies have identified the capacity of IL-17 to disrupt such anabolism [79–81], although the mechanisms by which this occurs remain unclear. One study that examined chondrocyte function in tissues from multiple species and disease states found that the potency of IL-17 relative to IL-1 β , a known repressor of chondrocyte anabolism, depends on the species and culture conditions tested [79]. Along with uncertainty about its relative strength, questions remain about the particular pathways through which IL-17 inhibits proteoglycan and collagen synthesis. The emerging picture suggests that IL-17-driven suppression of matrix synthesis involves a unique pathway from the one initiated by IL-1 β [79,81] and may involve the upregulation of leukemia inhibitory factor [82,83]. Also, controversy remains over the contribution of nitric oxide to the loss of proteoglycan synthesis in chondrocytes [80,81,84]. IL-4 alone or in combination with IL-10 can protect matrix formation when used as a pretreatment for cartilage explants exposed to IL-17 [85]. Further studies are needed to clarify the specific mechanisms by which IL-17- and IL-1 β drive the suppression of chondrocyte metabolism.

IL-17 also appears to play an active role in the induction of cartilage matrix breakdown through the dysregulation of chondrocyte metabolism [86]. Shalom-Barak et al. described the prolonged activation of NF- κ B and all three subgroups of MAP kinases—ERK, JNK, and p38—in chondrocytes following exposure to IL-17 [87]. These pathways regulate the expression of genes associated with joint inflammation and damage, such as matrix metalloproteinases (MMP), which degrade extracellular matrix and are implicated in RA pathogenesis [88]. In particular, IL-17 has been reported to induce the expression of MMP-2, MMP-3, MMP-9, and MMP-13 [79,89,90]. However, Cai et al. called into question the extent to which the upregulation of these molecules by IL-17 contributes to RA pathogenesis, given that IL-17

primarily stimulates production of the pro-enzymatic, and thus inactive, form of some of these factors [79]. Instead, the study indicated a greater role for aggrecanases in the degradation of articular cartilage. TNF, IL-1 β , IL-17, and IFN- γ strongly upregulate S100A8 from murine chondrocytes, and S100A8-stimulated chondrocytes upregulate the expression of various MMPs and aggrecanases [91]. In addition, IL-17 alone or in concert with IL-1 β can induce or synergize with other degradative enzymes and molecules, including nitric oxide (NO), prostaglandin E2 (PGE2), and oncostatin M to further damage articular tissue [81,92,93].

Bone erosion

The joint destruction that follows in the wake of synovial inflammation and cartilage degradation is primarily brought about by osteoclasts, members of the monocyte/macrophage lineage that are formed by multiple cellular fusions of mononuclear precursors. Osteoclasts are considered terminally differentiated cells and can be derived from myeloid precursors, differentiated tissue macrophages, and various intermediates of this lineage, following stimulation by RANKL and M-CSF [94]. Early studies of co-culture systems underscored the requirement for cell-to-cell contact between mesenchymal cells, such as osteoblasts, and hematopoietic osteoclast precursors for osteoclast formation. However, a decade passed before the membrane-bound osteoclast differentiation factor expressed by mesenchymal cells (and CD4⁺ T cells) was cloned and subsequently termed RANKL [1,14].

Th17 cells and IL-17 in particular have been increasingly implicated in the bone degradation that occurs in inflamed joints. On the heels of the identification of RANKL as the long-sought after osteoclast differentiation factor [95] came evidence for IL-17's ability to enhance osteoclast differentiation and functional activity through the upregulation of RANKL and other osteoclastogenic factors [3,14]. Local over-expression of IL-17 in mice with CIA significantly elevates expression of RANKL and its receptor, thereby altering the synovial ratio of RANKL to its decoy ligand, osteoprotegerin (OPG) [36]. In co-cultures of murine osteoblasts and bone marrow cells, IL-17 up-regulates osteoblast-derived prostaglandin E2, a known stimulus of osteoclastogenesis, and in cultured RA synoviocytes, inhibition of IL-17 reduces osteoclast differentiation by 80% [31]. It also seems likely that IL-17 synergizes with other cytokines, such as TNF, IL-6, and IL-23, all of which have been implicated in enhanced osteoclastogenesis [96–98]. Recently, Hashizume et al. found that the IL-17- and TNF-driven induction of RANKL on RA fibroblast-like synoviocytes occurs through IL-6 signaling and requires the presence of soluble IL-6R as fibroblasts do not express endogenous IL-6R [99]. Thus it appears that IL-17 results in bone erosion by elevating the expression (directly and indirectly) of RANKL on osteoclast-supporting cells to facilitate local formation of osteoclasts.

TNF and IL-1 β appear to induce bone erosion partially through RANKL-independent mechanisms [100,101], raising the question as to whether IL-17 exhibits only partial dependency on RANKL as well. Indeed, addition of the RANKL decoy receptor OPG even at high concentrations only partially inhibits synergistic IL-17 and TNF osteoclastic resorption [102]. Recent evidence highlights the importance of the alternative Wnt pathway in bone remodeling, but as yet no evidence suggests overlap between Wnt and the IL-17 network [103]. The mechanisms by which IL-17 stimulates RANKL-independent osteoclastic formation and function remain to be determined. Figure 2 depicts the aforementioned mechanisms of Th17 cell-driven synovial inflammation, cartilage destruction, and bone erosion.

Current and emerging therapies

Cytokines involved in the Th17 network, including IL-6, IL-1 β and TNF, have been targeted in therapies for RA, although to date no clinical trials have tested the efficacy of anti-IL-17 treatment directly. The synergy between IL-17 and TNF may partially explain the efficacy of

TNF inhibitors in attenuating the symptoms of RA (for review of TNF inhibition, see Feldmann et al.) [104]. Although two separate studies reported that infliximab does not lower the gene expression or serum levels of IL-17, the administration of TNF inhibitors has been demonstrated to reduce serum levels of IL-6 and IL-15, both of which induce IL-17 [105, 106]. Furthermore, TNF blockade in CIA increases the absolute number of pathogenic Th1 and Th17 cells but inhibits their accumulation in the joint, thus abrogating inflammation and attenuating disease [107]. A novel pyrazoleanilide derivative, Y-320, inhibits the IL-15-driven production of IL-17 and ameliorates CIA, but this molecule has not yet been tested in humans [108].

Looking ahead, further elucidation of the Th17 network may result in novel therapies specifically designed to redress the imbalance between Th17 cells and Tregs that is characteristic of diseased synovium [6]. Mouse models suggest that the vitamin A metabolite all-*trans* retinoic acid may be one such factor [109,110], and treatment of murine experimental autoimmune encephalomyelitis with retinoic acid suppresses disease by lowering the ratio of Th17 to Tregs in draining lymph nodes [109]. Although it has been speculated that retinoid therapy may similarly help restore the balance between Th17 cells and Tregs in autoimmune arthritis, Beehler et al. cautioned that retinoic acid may not be strong enough to ameliorate disease for cases of advanced arthritis [111].

The frequency of cardiovascular disease in patients with RA and the immunomodulatory activity of statins led to the hypothesis that statin treatment might attenuate rheumatic disease [112]. Clinical trials have supported a therapeutic role for statins in RA (for review, see Paraskevas) [113]; however, the mechanisms by which statins abrogate disease remain unclear. Both fluvastatin and simvastatin induce apoptosis in RA synoviocytes [114,115], and simvastatin has been reported to downregulate the production of IL-6 and IL-8 from RA fibroblast-like synoviocytes [116,117]. In light of this, and a report that simvastatin inhibits the expansion of the Th17 lineage by interfering with its transcription factor and downregulating IL-6 and IL-23 from human monocytes, a principle mechanism by which statins attenuate RA may be through the suppression of IL-17-driven inflammation [118].

Conclusion

The identification of IL-17 producing T cells as a distinct subset of pro-inflammatory helper T cells has broken down old paradigms concerning the role of Th1 cells in autoimmune disorders. Mounting evidence indicates a destructive role for IL-17 in various stages of rheumatoid arthritis: inflammation, along with the cartilage destruction and bone erosion that subsequently result. Furthermore, the efficacy of therapies that inhibit cytokines in the IL-17 network (IL-6, IL-1, and TNF) suggest the importance of the Th17 subset in autoimmune arthritis, a finding that may lead to future therapies that disrupt other signaling pathways in this network or target the imbalance between this lineage and the Treg subset. However, evidence against the centrality of Th17 cells in both experimental and rheumatoid arthritis has also been presented [8,119,120], and the possibility of a more regulatory capacity for Th17 cells has been raised [121]. Thus, it is prudent to be careful in assigning an essential and central role to this lineage in auto-inflammatory diseases [122]. Instead, it appears crucial to determine the details and resolve the inconsistencies surrounding the involvement of the Th17 network in autoimmune arthritis in order to design specific therapies that not only reduce inflammation but also impede joint destruction.

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Abbreviations

Th, T helper
 Treg, regulatory T cell
 RA, Rheumatoid Arthritis
 ROR γ t, retinoic acid receptor-related orphan receptor-gamma-t
 IFN- γ , interferon-gamma
 IL, interleukin
 TGF- β , transforming-growth factor beta
 M-CSF, macrophage-colony stimulating factor
 TNF, tumor necrosis factor
 RANKL, receptor activator of NF-kappa-B ligand
 TRAF6, TNF receptor-associated factor 6
 GM-CSF, granulocytemonocyte colony stimulating factor
 IL-17R, IL-17 receptor
 CIA, collagen-induced arthritis
 NO, nitric oxide
 PGE2, prostaglandin E2
 COX-2, cyclooxygenase-2
 MAPK, mitogen-activated protein kinase
 LFA, lymphocyte function-associated antigen
 ICAM-1, intercellular adhesion molecule-1
 VEGF, vascular endothelial growth factor
 KGF, keratinocyte growth factor
 HGF, hepatocyte growth factor
 HB-EGF, heparin-binding epidermal growth factor
 MCP-1, monocyte-chemoattractant protein-1
 CCL20, chemokine (C-C motif) ligand 20
 ERK, extracellular signal-regulated kinase
 JNK, Jun N-terminal kinase
 MMP, matrix metalloproteinase
 OPG, osteoprotegerin

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Figure 1.

Model of T cell subsets. Naïve CD4⁺ T cells commit to the Th1, Th2, Th17 or Treg lineages according to the composition of the local cytokine milieu. In the presence of TGF- β and IL-6 or IL-21 in mice and IL-1 β , IL-6, IL-23, and TGF- β in humans, naïve precursors develop into Th17 cells characterized by the expression of various pro-inflammatory factors, including IL-17A, IL-17F, and IL-6. Recent evidence suggests a certain degree of plasticity in the Treg lineage; reports indicate that the presence of activated dendritic cells can induce the loss of *Foxp3* expression and induce IL-17 production from Tregs.

Figure 2.

Schematic of the involvement of Th17 cells in rheumatoid arthritis. Infiltrating Th17 cells produce IL-17, which synergizes with other pro-inflammatory cytokines present in the synovial fluid, leading to (a) the activation of synovial fibroblasts and dendritic cells, leading to a local milieu conducive to Th17 development and further upregulating inflammation, (b) phenotypical modification of chondrocytes, resulting in the production of aggrecanases and MMPs that participate in cartilage destruction and (c) the upregulation of RANKL on osteoclast-supporting cells and synovial fibroblasts, which promotes bone erosion.