Th17 Cells in autoimmune diseases

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Abstract Th17 cells are a new subset of CD4+ T cells involved in the clearance of extracellular pathogens and fungi. Accumulating evidence suggests that Th17 cells and their signature cytokines have a pivotal role in the pathogenesis of multiple autoimmune-mediated inflammatory diseases. Here, we summarize recent research progress on Th17 function in the development and pathogenesis of autoimmune diseases. We also propose to identify new small molecule compounds to manipulate Th17 function for potential therapeutic application to treat human autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, Sjögren’s syndrome, inflammatory bowel disease, and multiple sclerosis.

Keywords IL-17; Th17 cells; RORγt; autoimmune diseases; posttranslational modification; inhibitors

Introduction

Th17 cells have been identified as a new CD4+ T helper lymphocyte lineage following the promising discovery of the role of IL-23 in experimental autoimmune encephalomyelitis (EAE) [1] and collagen-induced arthritis (CIA) [2]. They are characterized according to their capacity to produce interleukin (IL)-17A (also called IL-17), IL-17F, and IL-22 [3]. Th17 cells are currently assumed to mediate host defense, especially against extracellular bacterial infections, and play an important role in the pathogenesis of autoimmune diseases [4]. In this review, we discuss our current understanding of the role of Th17 cells in autoimmune diseases, with a focus on rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren’s syndrome (SS), inflammatory bowel disease (IBD), and multiple sclerosis (MS).

Th17 cells

Naïve CD4+ T cells differentiate into diverse subsets of T helper cells depending on different cytokine milieu upon T-cell receptor (TCR) stimulation. Unlike the required cytokines for Th1 and Th2 differentiation, the combination of transforming growth factor-β (TGF-β) and IL-6 initiates the development of Th17 lineage in mice [5,6]. TGF-β favors the induction of Th17 under inflammatory milieu despite its role in the development of regulatory T cells [7]. IL-6 induces the production of IL-21, which subsequently amplifies the differentiation in an autocrine way [8]. IL-23 stabilizes the Th17 phenotype and maintains its ability to produce related cytokines [9]. By contrast, the role of TGF-β in the differentiation of human Th17 cells is controversial. Previous research suggested that human Th17 cells were induced by IL-1β plus IL-6 and suppressed by TGF-β [10]. More recent studies show that a combination of TGF-β, IL-1β, IL-6, and IL-23 is critical for human Th17 development [11,12].

The retinoic acid-related orphan receptor γt (RORγt), as the master transcription factor, orchestrates the differentiation of Th17 cells [13]. RORγt directs the transcription of IL-17A by directly binding to the IL-17A promoter, which is essential for the functions of this cell lineage [14]. Moreover, another related nuclear receptor RORα cooperates with RORγt to trigger greater Th17 response and upregulates the expression of IL-17A and IL-17F [15]. Moreover, other key transcription factors, including signal transducer and activator of transcription 3 (STAT3), interferon regulatory factor 4 (IRF4), and aryl hydrocarbon receptor (Ahr), have been identified as the pivotal factors during the differentiation and function of Th17 cells [16–18].

The key effector cytokine of Th17 cells is IL-17A [9].
The IL-17/IL-17R complex recruits the U-box-like E3 ubiquitin ligase Act1 to trigger intracellular signaling pathways through homotypic interactions. Binding of Act1 to tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6) and TGF-β-associated kinase 1 (TAK1) ultimately activates the canonical NF-κB pathway [19]. However, not all the Th17 are pathogenic; thus, TGF-β3 and IL-6 are attributed to the full pathogenic phenotype, which is IL-23 dependent [20].

**Th17 and RA**

RA is an autoimmune rheumatic disease characterized by inflammation of multiple joints, which eventually leads to progressive joint destruction and deformity. Immune cells infiltrate the synovium of RA following aberrant cytokine and chemokine signaling [21].

IL-17A cytokines are involved in the pathogenesis of RA, which has been well established both in animal models of autoimmune arthritis and RA patients. IL-17A has been detected both in the serum and synovial fluid (SF) of RA patients [22–24]. IL-17A induces the expression of receptor activator of the nuclear factor kappa B ligand (RANKL) to enhance osteoclastogenesis [25]. Anti-IL-17A treatment reduces the expression of RANKL, alleviates bone structural damage, and reduces disease progression in models [26]. Moreover, antibodies against IL-17A, such as secukinumab, have already been used in clinical trials [27,28]. Enhanced epigenetic modifications in RA patients lead to the production of IL-17A, which sustains the survival of synoviocytes and inflammatory cells. These effects initiate the expansion of Th17 cells [21]. However, mast cells were also found as the main producer of IL-17A in the synovial tissue of RA patients in a clinical study [23].

IL-17F, another Th17-specific cytokine, was significantly increased in RA patients versus healthy control. IL-17F, but not IL-17A, was reduced after methotrexate and anti-TNF treatment [29]. This result indirectly proved the role of Th17 cells in the development of RA. Spontaneous development of autoimmune arthritis in SKG mice, which resembles RA in humans, is accompanied with enhanced arthritogenic Th17 cells [30]. Higher frequencies of Th17 cells are observed in RA patients as compared with those from healthy groups [31–36] (Table 1). Th17 frequencies in RA SF mononuclear cells (SFMC) are higher than paired RA peripheral blood mononuclear cells (PBMC) [37]. Moreover, CCR6+ memory Th17 cells from early RA patients trigger pathogenic activation of RASFs, which elevates the production of proinflammatory cytokines and other relevant enzymes [33]. Interestingly, the frequency of Th17 cells in RA joints is low, which suggests that Th17 cells might not be the main producer of IL-17A within RA joints [37]. This finding might be explained by the proposal that Th17 cells are unstable and spontaneously convert to a Th1 phenotype [38]. The adoptive transfer of polarized Th17 cells induces severe, destructive polyarthritis in mice, and IL-17A produced by Th17 cells is attributed to the osteoclastogenic effects of Th17 cells [39]. In addition, Th17 cells could assist the B cell in producing autoantibodies [40]. A small fraction of Th17 cell lineage, which originates from CD25+Foxp3+CD4+ T cells, possesses more potent osteoclastogenic capability than conventional Th17 cells under arthritic conditions [41].

**Th17 and SLE**

SLE is a chronic systemic autoimmune disease characterized by dysregulation of the immune system, which leads to loss of self-tolerance with activation of autoreactive T and B cells [42]. Production of autoantibodies contributes to deposition of immune complexes and tissue injury.

In the past years, numerous studies have reported elevated serum IL-17A levels in SLE patients compared with healthy controls [43–46]. However, a weak correlation was found between IL-17A levels and SLE disease severity [37]. This finding might be explained by the finding that Th17 cells from early RA patients lead to the production of IL-17A, which sustains the survival of synoviocytes and inflammatory cells. These effects initiate the expansion of Th17 cells [21]. However, mast cells were also found as the main producer of IL-17A in the synovial tissue of RA patients in a clinical study [23].