REVIEW

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The function of interleukin 17 in the pathogenesis of rheumatoid arthritis

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Abstract

Interleukin (IL)-17 is a 30- to 35-kDa homodimeric polypeptide cytokine cloned in 1993 and originally named cytotoxic T lymphocyte-associated antigen-8 (CTLA-8). Sequencing the human genome resulted in the discovery of an additional five members of the IL-17 family that were consecutively named IL-17B to IL-17F. IL-17A is exclusively produced by a newly identified $CD4^+$ T-helper subset that was recently named Th17. Differentiation of these cells from naïve $CD4^+$ T cells requires both TGF-β and IL-6. IL-15 and, especially, IL-23 are required for these cells' survival and efficient IL-17 production. IL-17 binding to an IL-17 receptor expressed on epithelial, endothelial, and fibroblastic stromal cells triggers the activation of transcription factor NF-κB and mitogen-activated protein kinase (p-38), which in turn results in the secretion of IL-1, TNF-α, IL-6, IL-8, or prostaglandin E_2. The IL-17 family plays a key role in the regulation of immune and inflammatory response, in the homeostasis of several tissues, and the progression of autoimmune diseases. In addition, IL-17 exerts synergistic effects with TNF-α and IL-1 in the induction of joint inflammation and cartilage and joint destruction. Given these properties, it is not surprising that in certain pathological conditions, for example rheumatoid arthritis, Th17 cells emerge as a new pathological cell type that, by IL-17 production and release, contributes to their pathogeneses.

Key words: interleukin 17, family and receptors of IL-17, function of IL-17, rheumatoid arthritis.

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INTRODUCTION

The list of potential inflammatory mediators important in the pathogenesis of rheumatoid arthritis (RA) has been extended by yet another cytokine, i.e. interleukin (IL)-17 [15, 39]. IL-17-producing T lymphocytes have been shown to comprise a distinct lineage of proinflammatory T-helper cells known as T-helper-17 (Th17) cells, distinct from Th1 and Th2 cells, that are probably involved in the pathogenesis of many autoimmune and inflammatory diseases [9, 11, 23]. Overproduction of the proinflammatory cytokine IL-17 was found in RA synovium and synovial fluids, where this cytokine plays a pathogenic role because of its association with bone destruction [3, 13, 18]. RA is a chronic autoimmune disease characterized by destruction of articular cartilage, progressively destructive joint inflammation, and synovial hyperplasia [15, 16, 18]. The autoimmune response in RA is initiated by the activation of antigen-specific T cells, particularly $CD4^+$ T-helper cells (Th). Naive $CD4^+$ cells differentiate into Th1 and Th2 cells, which are the dominant cell types in the synovial filtrate of patients with RA [29]. Interactions between synoviocytes and Th1 lymphocytes and monocytes lead to the production of the pivotal proinflammatory cytokines IL-1 and tumor necrosis factor (TNF)-α, which stimulates osteoblasts to produce IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF), which regulate osteoclast formation [4, 5, 23].

Recent studies have shown that IL-17 acts synergistically and additively with IL-1 and TNF-α [9]. This cytokine alone and also in combination with TNF-α and IL-1 induces the synthesis of IL-6, IL-8, and TSG-6 by fibroblasts-like synoviocytes [13]. As IL-17 shares properties with TNF-α and IL-1 cytokines, it may contribute to bone and cartilage damage and affect both osteoclast- and chondrocyte-mediated resorption [5, 23].

IL-17 FAMILIY MEMBERS AND THEIR RECEPTORS

IL-17 is a proinflammatory cytokine that is secreted as a dimer, principally by a restricted set of cells, i.e. activated T cells with the phenotype of $CD4^+CD45RO$ human memory T cells or mouse $TCR\alpha^+CD4^-CD8^-$ thymocytes [23, 24, 25]. IL-17, originally cloned and described by Rouvier et al. in 1993 [30] and named CTLA8, was subsequently renamed IL-17 and finally IL-17A [17]. IL-17A is 30- to 35-kDa glycosylated homodimeric polypeptide [4] whose gene is located on chromosome 6p12. IL-17A is expressed in T cells. This cytokine encodes a 155-amino-acid sequence containing an N-terminal signal peptide and exhibits 72% amino-acid sequence identity with a viral protein encoded by open reading frame 13 of the gene of the T-lymphotropic herpesvirus saimiri [3, 24, 37, 38]. Human IL-17A displays significant (62%) structural homology with mouse and rat IL-17A, both having remarkably conserved glycosylation sites [17].

IL-17 was the first discovered member of the IL-17 family. Another five members of the IL-17 family (IL-17B–F) have been discovered by large-scale sequencing of the human genome [24, 25, 34]. The different IL-17 family members seem to have very separate expression patterns, suggesting distinct biological roles. IL-17 and IL-17F share the highest degree of homology, about 50%, while IL-17B, IL-17C, IL-17D, and IL-17E share only 16–30% identity at the primary sequence level and are mapped to a different chromosome (Table 1). Characterization of the biological activities of IL-17B and IL-17C reveals that they differ completely from the established activities of IL-17. IL-17B is moderately expressed in normal human adult pancreas, stomach, spinal cord, and small intestine, while the expression of IL-17C is much more restricted and has a different expression profile, being detected in the adult prostate, thymus, and spleen and fetal kidney libraries [17, 22, 24]. Expression of IL-17D was found in skeletal muscle, neuronal cells, and prostate and, in contrast to IL-17, it is not induced in activated T or B cells [17]. The most varied known member of the IL-17 family is IL-17E, which is expressed in the brain, prostate, lung, and testis [20].

The IL-17 receptor (IL-17R) is also interesting because it has a unique primary structure different from any other known cytokine receptor. It is a type I transmembrane protein consisting of a 293-amino-acid extracellular domain, a 21-amino-acid transmembrane domain, and a 525-amino-acid cytoplastic tail and is approximately 130 kDa in weight [7, 17, 28]. While IL-17 is expressed by T cells, IL-17R is expressed in virtually all cells and tissues. Studies by Silva et al. [32] have shown that mRNA for IL-17R can be detected in T and B cells, epithelial cells, fibroblasts, marrow stromal cells, and myelomonocytic cells. However, Moseley et al. [28] showed that the IL-17R protein itself may be detected in vascular endothelial cells and in peripheral blood T cells from humans. Four additional receptors for the IL-17 family have been detected in various cell types, described and mapped to chromosome 3 (Table 2); these are IL-17RB to E [7, 17, 24]. IL-17RB has been shown to bind to IL-17B and IL-17E and is expressed in human kidney, liver, brain, pancreas, and intestines. IL-17RC, also called IL-17RL (receptor-like), shares 22% identity and 34% similarity with IL-17R and is expressed in human prostate, liver, kidney, cartilage, and heart. Finally, IL-17RE is expressed in human prostate, brain, and pancreas [9, 17, 28]. However, the receptor for IL-17F cytokine is unknown. All these

Table 2. The human IL-17 receptors

Receptor	Alternate name	Chromosomal location
IL-17R	IL-17AR	22q11.1
IL-17RB	IL-17RH1/IL-17ER	3p21.1
IL-17RC	IL-17RL	3p25.3
IL-17RD	hSEF	3p21.2
IL-17RE	IL-17RH1/IL-17RB	3p25.3

Table 1. The human IL-17 superfamily [17, 20, 22, 24, 28, 34]

Cytokine	Other name	Chromosomal location	Homology of murine to human (%)	Major functions
IL-17	IL-17A, CTLA-8	6p12	62	stimulated epithelial, endothelial, and fibroblastic stromal cells, inflammation, bone metabolism
IL-17B	CX1	5q32-34	88	induce IL-6 in human foreskin fibroblasts, cytokine secretion, induce TNF-α and IL-1β from a monocyte line
IL-17C	CX2	16q24	83	induce TNF-α and IL-1β from a monocyte line, induce IL-6 in human foreskin fibroblasts, regulation of Th1 cytokines
IL-17D	IL-27	13q11	78	cytokine secretion
IL-17E	IL-25	14q11.1	81	induce production of IL-8, regulator of Th2 response
IL-17F	ML-1	6p12	77	regulation of Th1 cytokines

receptors are well conserved in the mouse, with 68–90% similarity at the protein level between the mouse and human [28]. Both IL-17 cytokines and their receptors play important roles in the homeostasis of tissues and the progression of disease.

CELLULAR SOURCES AND REGULATION OF IL-17

IL-17 is produced by $TCR\alpha^+CD4^-CD8^-$ as well as by $CD4^+$ activated memory ($CD45RO^+$) T cells (Th17 cells) [1, 12, 18, 37]. Th17 cells have been identified as a unique subset of Th cells that develops along pathways that are distinct from the Th1 and Th2 differentiation pathways (Fig. 1) [12, 33]. Several recent studies have shown that two cytokines, IL-15 and IL-23, are potent regulators of IL-17 production. The role of IL-15, which is produced by synoviocytes, in regulating IL-17 has yet to be determined, but as IL-15 is important in the maintenance of T cells of the memory subset, the IL-15-IL--17 axis may play a key role in chronic inflammation [39]. Compared with IL-15, IL-23 produced by activated dendritic cells (DCs) and macrophages, is a much stronger regulator of IL-17 and is a crucial factor in autoimmune inflammation to the central nervous system, but is not essential for the development of Th17 [12, 24]. The transcriptional factors critical for the development of Th1 and Th2 cells are not required for the induction of Th17 cells. The key transcriptional factor essential for the development of Th17 cells is the orphan nuclear receptor RORγt [11, 12, 33]. Moreover, we can distinguish two Th17-cell differentiation pathways, one IL-23 dependent and the other IL-23 independent, in which TNF-α, IL-1, IL-6, and transforming growth factor (TGF)-β take part [12]. TGF-β is an important regulator of the differentiation of both tissue-damaging Th17 cells, when collaborating with IL-6, and as an activator of anti-inflammatory Treg, when acting without IL-6 [2, 26]. However, IL-23, though necessary for Th17 differentiation, was still required for the survival and expansion of Th17 cells [8].

BIOLOGIC FUNCTIONS AND SIGNALING PATHWAYS OF IL-17

Functionally, IL-17 has been classified as a proinflammatory mediator responsible for inducing inflammatory effectors in target cells [7]. IL-17 may play an

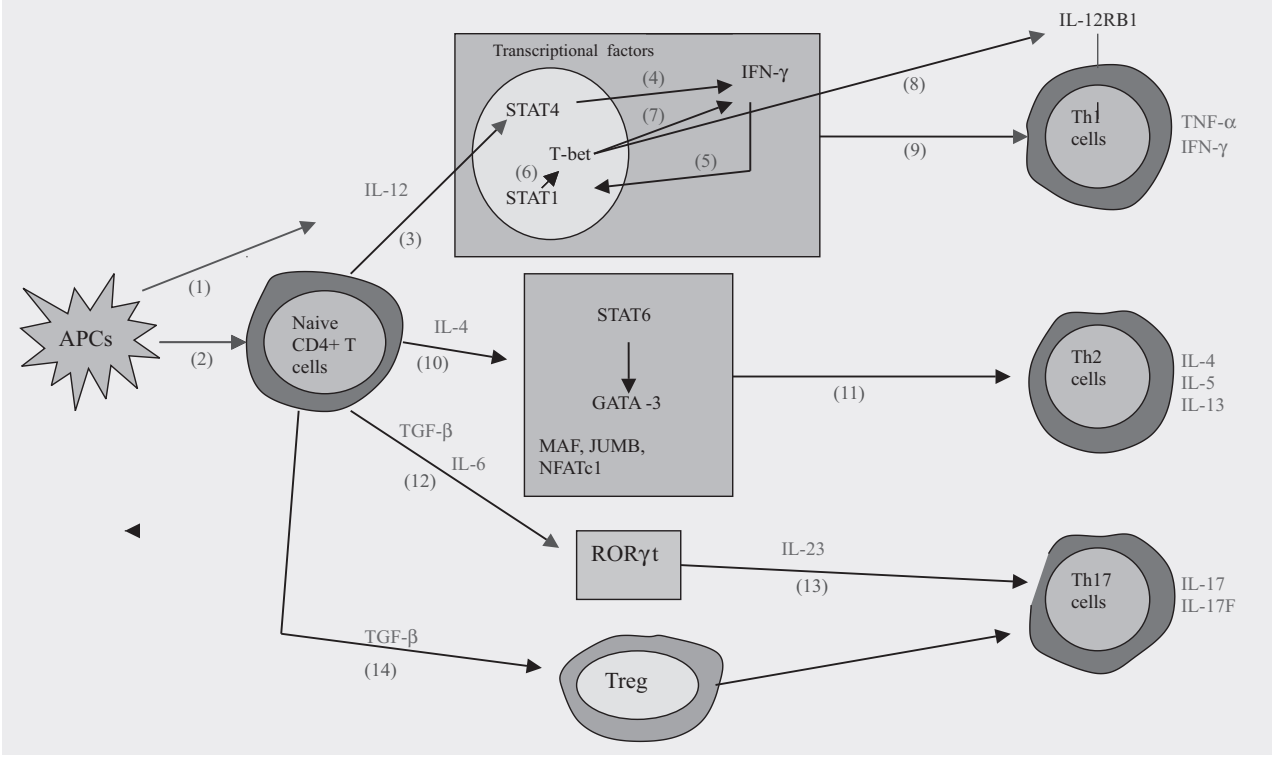

Fig. 1. The development of IL-17-producing $CD4^+$ T cells. Activated antigen-presenting cells (APCs) produce IL-12 (1) and activate naive $CD4^+$ T cells through the expression of certain surface molecules such as co-stimulators (2). IL-12 causes the activation of the signal transducer and activator of transcription 4 (STAT4) (3), which is necessary for the optimal production of IFN-γ (4) and, together with STAT1 (5), stimulates T-bet expression (6). T-bet is a master regulator of Th1 differentiation and is crucial for optimal expression of IFN-γ (7) and IL-12Rβ1 (8). IL-12, through the transcription factors, regulates Th1 cell lineage differentiation (9). IL-4, through STAT4 (10), increases the expression of GATA-3 and determines Th2 cell differentiation (11). TGF-β and IL-6 acting together induce the differentiation of $CD4^+$ naive T cells into Th17 cells (12). IL-23, through RORγt, induces the expression of and is required for the survival of Th17 cells (13). A TGF-β dose (in the absence of IL-6) triggers the differentiation of Treg cells (14), which inhibit autoimmunity and protect against tissue injury.

upstream role in T cell-triggered inflammation by upregulating some of the gene products involved in cell activation, growth, and proliferation [14, 23]. It exhibits pleiotropic biological activities on various cell types, including epithelial, endothelial, and fibroblastic stromal cells, neutrophils, and macrophages. IL-17 stimulates these cells to secrete several cytokines, such as IL-6, IL-8 (CXCL8), G-CSF, IL-1β, and TNF-α, and a key mediator of inflammation, prostaglandin E_2 (PGE_2) [19, 23]. IL-17 appears to exert an adaptive and synergistic effect with IL-1β and TNF-α in cartilage, synovium, and meniscus [10, 28]. IL-17 shares transcriptional pathways with IL-1β and TNF-α. It can activate the transcription factor NF-κB and mitogen-activated protein kinases, including extracellular signal-related kinase (ERK)1 and ERK2, p38, and c-Jun N-terminal kinase [24] in synoviocytes and chondrocytes. The involvement of Janus kinase/signal transducer and activator of transcription and TNF-receptor-associated factor 6 has been suggested to transmit IL-17 signaling in a human monocyte cell line and embryonic fibroblasts [10]. IL-17 may be a major regulator responsible for the communication between T cell activation and inflammatory response and it is associated with the degradation of articular cartilage and destruction of bone because it stimulates the production of the MMP-1 and MMP-13 collagenases in chondrocytes, the degradation of proteoglycans, and the expression of IL-6 and leukemia inhibitory factor in fibroblast-like cells of the synovium [13, 14, 19, 28]. IL-17 can upregulate nitric oxide production in osteoarthritic cartilage, in fetal bone, and in cultured chondrocytes and osteoblasts from both normal and osteoartritic cartilage [28, 39]. Because IL-17 can enhance matrix degradation by inducing the release of cartilage proteoglycan and collagen fragments, it may be an important catabolic mediator in tissue degradation. At the same time, IL-17 also inhibits the synthesis of new collagen and proteoglycans [28]. The list of the biological effects of IL-17 also includes triggering the production of IL-12, IL-10, IL-1R, and stromelysin in human peripheral blood macrophages [21, 39]. This cytokine is associated with many inflammatory disorders, including RA, inflammatory bowel disease, *Helicobacter pylori* infection, asthma, unstable angina, psoriasis, airway inflammation, and allograft rejection [17].

EPIDEMIOLOGY, ETIOLOGY, AND CLINICAL ASPECTS OF RA

RA is a chronic inflammatory autoimmune disease characterized by joint involvement leading to deformity, disability, and even to death [29]. RA usually presents as a polyarthritis affecting small joints or small and large joints. In its early stages the disease is characterized by pain and swelling, but not by deformity and damage. However, the disease remains active and uncontrolled inflammation causes deformity and instability of joints. The typical rheumatoid deformities are ulnar deviation of the fingers, swan neck, and boutonniere deformities. The chronic inflammation process leads to hyperplasia of the synovial lining cells that interacts with blood-derived mononuclear cells [10, 13]. The inflammation is responsible for stimulating the destructive process in the joint. The inflamed synovial membrane contains macrophages, DCs, synovial fibroblasts, and T lymphocytes. Synovial macrophages play a key role in joint destruction and inflammation [29]. The pathogenesis of inflammation and tissue destruction in RA is characterized by cell interactions between blood-derived cells, such as T lymphocytes, monocytes, B lymphocytes, and DCs [5, 6].

RA is classified among the systematic autoimmune diseases because of the presence of rheumatoid factor (RF), IgM anti-IgG autoantibodies that react with the Fc fragment of altered IgG, and other autoantibodies such as anti-CCP antibodies (CCP-cyclic citrullinated peptide). Both RF and anti-CCP antibodies are present in serum and in the joints [35]. Serum RF is clearly associated with florid disease activity and much of the serum RF is produced by activated plasma cells within the inflamed RA synovium [36]. The sensitivity of RF is 60–80% in RA and the specificity is rather low since RF is also widely detected in many other conditions, such as chronic liver disease, infectious diseases, and various connective tissue diseases, and even in healthy people [27]. However, anti-CCP antibodies are more sensitive and specific then RF, and they are also better predictors than RF of the progression of joint damage [35].

RA is a disease of unknown etiology that affects about 1–3% of the population. Although the disease affects people all over the world, some populations demonstrate particularly high or low prevalence [36]. Women are affected three times more frequently than men. The familial RA appears in about 10–30% of patients and in 20–40% of monozygotic twins. Genetic factors such as the HLA DRB1 and IgG genes can be associated with familial aggregation and it is possible that many different genes are involved in RA's pathogenesis. Genetic factors not only play an important role in the susceptibility and severity of the disease, but may also serve as a useful prognostic tool in the management of RA [29].

ROLE OF IL-17 IN THE PATHOGENESIS OF RA

RA is an autimmune disease in which the activation of antigen-specific T cells, particularly $CD4^+$ Th cells, probably initiates the autoimmune response. Th cells can be divided into Th1 and Th2 subtypes according of their cytokine profiles and have different functional properties [1]. Th1 cells induce the production of IL-2, interferon (IFN)-γ, and TGF-β, which further stimulate the production of proinflammatory cytokines and induce cellular immunity. Th1 cells also play an important role in the elimination of intercellular pathogens

and tissue damage by the cytotoxic T cell response or by activating macrophages. Th2 cells secrete IL-4, IL-5, IL-6, IL-10, and IL-13 and activate self-reactive B cells to produce autoantibodies [1, 29]. Distinct from Th1 and Th2, Th17 cells have a crucial role in autoimmune inflammation and contribute to the differentiation and proliferation of osteoclasts, causing bone resorption. Th1 cells play a protective role in bone metabolism, while Th17 is destructive [33].

In the RA synovium, Th1 cells are predominant, but Th2 cells can also be found; moreover, Th1/Th0, but not Th2, cell clones isolated from rheumatoid synovium produce IL-17 [24]. IL-17 may be an important activator of T cell-driven inflammation and may thus contribute to the pathogenesis of RA [4]. IL-17 is spontaneously produced by RA synovial membrane cultures and high levels of it have been detected in the synovial fluid of patients with RA [24, 39]. However, the most predominant cytokines in RA synovial fluid, such as IL-6, IL-1β, and TNF-α, are derived from synovial fibroblasts and macrophages [18].

IL-17 shares many biological properties with TNF-α and IL-1β. The interaction of these cytokines sustained inflammatory processes within the joint and amplified the involvement of T cells in the pathogenesis of RA [13]. Moreover, the combination of IL-17 with IL-1β and TNF-α often leads to additive or synergistic effects which further increase their biological effects. IL-17 can increase IL-1 and TNF-α production by macrophages, but blocking IL-17 caused a decrease in IL-1 and TNF-α actions. These three cytokines may affect both osteoclast- and chondrocyte-mediated resorption and thereby mediate cartilage and bone destruction. They activate the common nuclear factors NF-κB in a variety of cell types, induce the receptor activator of NF-κB ligand (RANKL), which is a key regulator of osteoclastogenesis and the bone erosion process, and stimulate synovial fibroblasts, endothelial, and epithelial cells to secrete IL-6, IL-8, and PGE_2 [5, 6]. IL-17 induces the expression of RANKL in cultures of osteoblasts and mesenchymal cells; however, TNF-α and IL-1 induce RANKL on synovial fibroblasts [23, 24, 31]. Recent studies have shown that IL-17, TNF-α, and IL-1β alone or in combination can induce macrophage inflammatory protein-3α (MIP-3α) synthesis by the synovium and synoviocytes, which plays a role in mediating the inflammatory process by its ability to chemoattract immature dentritic cells and T cells [6]. IL-1β is a stronger inducer of MIP-3α, and addition of IL-17 to TNF-α exerted synergistic effects.

IL-17 plays a role not only in the early stages of RA, but also later, during disease progression, and it was detected at both the mRNA and protein level in RA synovium [4, 14]. However, the lack of correlation between levels of IL-17 in serum and synovial fluid of the same patient suggests that IL-17 is produced mainly locally in the synovium of RA patients [39]. IL-17 plays a role in cartilage destruction because it is a potent stimulator of osteoclastogenesis. IL-17 can inhibit the synthesis as well as stimulate the breakdown of type I collagen in RA synovium and bone explants and therefore plays an important role in joint inflammation and tissue destruction [18, 23].

CONCLUSION

IL-17 is the prototypical member of a fascinating new family of cytokines produced by RA synovium and inhibited by some Th2 cells. This family is involved in specific inflammatory processes leading to the mobilization of granulocytes. Especially IL-17A and IL-17F play a role in granulopoiesis and neutrophil accumulation and activation in the lung, central nervous system, joint space, and intestinal tissue. IL-17 production appears to be of great importance in inflammatory reactions in RA because its biological activity causes the induction of proinflammatory cytokines found in the RA synovium. IL-17 plays a role not only in the immune response, but also in the cartilage and tissue destruction in patients with RA. A deeper understanding of the actions of IL-17 seems necessary for an understanding of its functions and may be useful in the management of new methods in the treatment of RA.

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