

INTERVIEW about

Interleukin-17
and arthritis
with

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What is the role of Interleukin-17 (IL-17) in the pathogenesis of rheumatoid arthritis?

Erik Lubberts: Rheumatoid arthritis (RA) is chronic systemic disorder that is characterized by autoimmunity, infiltration of joint synovium by activated inflammatory cells, synovial hyperplasia, neoangiogenesis and progressive destruction of cartilage and bone. RA is considered to be a systemic Th1-associated inflammatory joint disease and T cells comprise a large proportion of the inflammatory cells invading the synovial tissue.

Interleukin-17 (IL-17) is a T cell cytokine spontaneously produced by RA synovial membrane cultures. High levels have been detected in the synovial fluid of patients with RA. The

trigger for IL-17 is not fully identified. Although bioactive IL-17 is detected in RA and osteoarthritis (OA) synovial fluid, the levels of IL-17 were found to be higher in RA synovial fluid when compared with osteoarthritis (OA) synovial fluid (1,2). IL-17 stimulates transcriptional NF- κ B activity and IL-6 and IL-8 secretion in fibroblastic, endothelial, and epithelial cells, and induces T cell proliferation (3,4). Furthermore, it triggers human synoviocytes to produce GM-CSF, and PGE₂ (3), suggesting that IL-17 could be an upstream mediator in the pathogenesis of arthritis and may play a role in fine-tuning the inflammatory response.

What is known about the role of IL-17 in other inflammatory/autoimmune diseases?

Erik Lubberts: Apart from its role in autoimmune arthritis (5-7), IL-17 exhibit a potential role in other inflammatory diseases, such as lung, gut, and skin inflammation (8). IL-17 plays a role in T-cell-triggered inflammation by stimulating stromal cells to secrete various cytokines and growth factors associated with inflammation (3). IL-17 regulates gene expression and protein synthesis of the complement system. In addition, IL-17 stimulates granulopoiesis and is a strong inducer of neutrophil recruitment through chemokine release (8). Furthermore, IL-17 promotes angiogenesis. Studies in IL-17 deficient mice

revealed that this T cell cytokine played an important role in activation of T cells in allergen-specific T cell-mediated immune responses (9). Great diminished recruitment of neutrophils into lungs was found in mice with homozygous deletion of the IL-17 receptor in response to a challenge with a gram-negative pathogen (8). Elevated levels of IL-17 were found in other autoimmune diseases, such as experimental autoimmune encephalomyelitis (EAE) and patients with systemic sclerosis. However, further studies are needed to unravel the role of IL-17 in the pathogenesis of these autoimmune inflammations.

How important is the IL-17 receptor signaling?

Erik Lubberts: In contrast to the restricted expression of IL-17, the IL-17 receptor (IL-17R) is

ubiquitously expressed in virtually all cells and tissues. It is a type I transmembrane protein

that has no sequence similarity with any other known cytokine receptor (10). The exact mechanisms of IL-17 signaling are not fully elucidated. Binding of IL-17 to its unique receptor results in activation of the adapter molecule TNF receptor associated factor 6 (TRAF6), which is required for IL-17 signaling. IL-17 shares transcriptional pathways with IL-1 and TNF. It can activate NF- κ B and all three classes of MAP kinases including ERK1 and

ERK2, JNK, and P38. These pathways have been identified in synoviocytes and chondrocytes. Recent studies in mice have shown that IL-17R signaling is critical in driving the synovial expression of proinflammatory cytokines such as IL-1 and different metalloproteinases (11). Of interest, IL-17R signaling in radiation resistant cells in the joint is required for turning an acute macrophage-mediated inflammation into a chronic destructive synovitis (12).

Are other cytokines involved?

Erik Lubberts: T cell IL-17 is a strong inducer of other proinflammatory cytokines, such as TNF, IL-1, IL-6, and RANKL. IL-17 can synergize with these cytokines but probably acts directly as well. IL-17 enhances IL-1-mediated IL-6 production by RA synoviocytes *in vitro* as well as TNF α -induced synthesis of IL-1, IL-6 and IL-8 (6). This indicates that IL-17 synergizes with IL-1 and TNF and it has been shown that the combination of TNF α blockade with IL-1 and IL-17 blockade is more effective for controlling IL-6 production in RA synovium cultures (6). In line with the observations *in vitro* using RA synovial cocultures (6), combination blockade of TNF α and IL-17 suppressed ongoing CIA and is more effective than neutralizing TNF alone (unpublished data). In addition, IL-17

induces receptor activator of nuclear factor- κ B (NF κ B) ligand (RANKL) expression, which is an essential cytokine for osteoclastogenesis and bone resorption (7). Furthermore, when IL-17 is combined with other cytokines that are already thought to be important in arthritic disease (e.g. TNF α and IL-1), even more marked tissue destruction occurs (6,7). Of interest, TNF α -dependent arthritis can be circumvented by IL-17 (unpublished data). This underscores the potential of IL-17 to act additively or even synergistically with IL-1/TNF. Moreover, it also shows that T cell IL-17 can replace the proinflammatory/destructive function of IL-1/TNF, directly or via interplay with other macrophage-driven factors. These observations strongly implicate IL-17 as playing an important role in the disease pathogenesis of RA.

Do you believe that anti-IL-17 therapy is a new anti-rheumatic strategy?

Erik Lubberts: Data thus far strongly suggest IL-17 to be a novel target for the treatment of destructive arthritis. Since it is known that this T cell factor can have synergistic effects with proinflammatory mediators, it is tempting to speculate that IL-17 levels can make the difference whether or not a patient will respond to anti-TNF/anti-IL-1 therapy. Anti-IL-17 cytokine therapy might be an interesting new anti-rheumatic approach that may contribute to

prevent joint destruction additional to anti-TNF and anti-IL-1 therapy.

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