Role of interleukin-17 in the pathogenesis of rheumatoid arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is a systemic autoimmune disorder with an unknown etiology. It typically affects the peripheral synovial joints symmetrically. The roles of T and B cells, macrophages, plasmocytes, host tissue cells (synoviocytes, chondrocytes), and osteoclasts in RA are more defined. In RA, cytokines secreted by cells implicated in adaptive and natural immunity have important roles in causing inflammation, articular destruction, and other comorbid diseases related to RA**.** Other than the clear roles of interleukin (IL)-1 and tumor necrosis factor α, there are other cytokines that are suspected of having roles in the pathogenesis of RA, IL-17 for instance. Interleukin-17 is a proinflammatory cytokine, produced by Th17 cells, and has pleiotropic effects on various cells contributing to the pathogenic condition of RA. Several studies showed that this cytokine maintains the inflammation and causes more destruction of joint cartilage. Advances in the understanding of the role of IL-17 elicits the idea to modulate IL-17 and/or Th17 cells as the potential targets of therapy in RA.

Rheumatoid arthritis (RA) is a systemic autoimmune disorder indicated by chronic polyarthritis and synovitis that results in joint damage. It typically affects the peripheral synovial joints symmetrically. The clinical course of the disease is prolonged and accompanied by systemic complains.[1,2] The manifestations are varied and early intensive management is needed to prevent joint damage and physical handicap.[3] The disease had been described by Landre Beauvais since 1800 and the terminology of RA was first introduced by Garrod in 1859.[2]

The etiology of RA is still unknown despite advances in the understanding of its pathogenesis. Several aspects that are also suspected of having roles in the pathogenesis of RA are as follows: (1) genetic factor or specific gene polymorphism; (2) pathogenic immune response and infectious agent-induced inflammation; (3) autoimmunity toward synovium and cartilage components; (4) interference of regulation of proinflammatory cytokines production; and (5) transformation of constituent cells in the synovial into tissue invasive, autonomous cells.[4]

The perception that RA pathogenesis is a multifactorial process that needs a combination of genetic, environmental, and immune factors, has been accepted by most experts. However, the understanding of how the components are correlated with each other is still unclear. There is a possibility that those factors have roles as risk factors. They, combined with other factors, can cause the disease through mechanisms and pathways that are not yet fully understood.[4,5]

Synovial membrane in RA contains activated T cells and B cells, macrophages, and plasmocytes. It is also known that host tissue cells, such as synoviocytes, chondrocytes, and osteoclasts, are also involved in mediating bone and joint cartilage damages. Recruitment process, activation, and effectors of each contributors mentioned earlier are regulated through a network of cytokines.[6–8]

ROLE OF CYTOKINES IN RHEUMATOID ARTHRITIS

Cytokines are protein secreted by cells implicated in adaptive and natural immunity that regulate various fundamental processes of the cells, such as inflammation, tissue reparation, cell growth, fibrosis, angiogenesis, and immune response. To understand about the role of cytokines in RA, comprehensive analysis is needed. Tissue availability from pathogenic site (synovial joint) facilitates investigation and identification of role of cytokines.[9,10]

In RA, cytokines secreted by those cells have important roles in causing inflammation, articular destruction, and other comorbid diseases related to RA. Disease activity is also closely related to cytokines changes.[5,6,11]

Interleukin (IL)-1 and tumor necrosis factor α (TNFα) are major proinflammatory cytokines that have roles in inflammation in RA; both have overlapping roles such as causing inflammation, promoting inflammatory cells' adhesiveness, and causing angiogenesis and bone resoption. Tumor necrosis factor α is a cytokine secreted by macrophage and is the center of cytokines that have roles in pathogenesis of RA.[5] Brennan et al[6] reported higher level of IL-1 in synovial culture of RA patients than that of osteoarthritis patients. Treatment with anti-TNFα monoclonal antibody can suppress IL-1 level. Further studies showed that suppression of TNFα also decreases other

cytokines production such as granulocyte macrophage colony-stimulating factor (GM-CSF), IL-6, IL-8, and IL-9. It shows that there is a coordinated cytokine network in causing an inflammation.[5,6]

There is an imbalance between proinflammatory and anti-inflammatory cytokines, in which the proinflammatory ones are dominant. Raza et al[12] reported that the level of proinflammatory cytokines produced by T cell, macrophage, and fibroblast, such as IL-2, IL-4, IL-13, IL-17, IL-15, basic fibroblast growth factor, and epidermal growth factor increase more evidently in RA patients as compared to non-RA arthritis patients.

Although the blocking of TNFα and IL-1 shows good response, there is still the possibility of failing to control the disease course of RA. It shows that there are other factors that also have roles, IL-17 for instance. Interleukin-17 is suspected of having role because firstly, it is similar to TNFα in its proinflammatory characteristic and secondly, it is produced by T cells, while the role of T cells is not yet fully understood.[6,13]

ROLE OF INTERLEUKIN-17 IN RHEUMATOID ARTHRITIS

Interleukin-17 is a cytokine produced by T cells. It was first assumed as a product of Th1 cells, but then it was found that IL-17 is produced by Th17 cells which are similar to Th1 cells as derivation of CD4+ Th cells pathway. The differentiation into Th-17 cells is influenced by IL-23, IL-6, and IL-1B and it undergoes negative regulation influenced by IL-4, IL-10, and interferon γ (IFNγ).[13–16] Interleukin-17 is a member of IL-17 superfamily which consists of 6 members: IL-17A to IL-17F. Interleukin-17A is the strongest of them and is also known as IL-17. Interleukin-17 is a protein with a molecular weight of 17 kDa and secreted in dimeric form with 155 amino acids.[16,17]

Interleukin-17 is a proinflammatory cytokine and has pleiotropic effects on various cells, including macrophages and fibroblasts, and is a strong candidate for effector cytokine contributing to the pathogenic condition of RA.[18–20] Chabaud et al[21] and Kohno et al[22] measured IL-17 level of synovial tissue supernatant of RA patients, osteoarthritis patients, and healthy people. They found high level of IL-17 in RA patients, but not in osteoarthritis patients nor in healthy people. Shahrara et al[23] also found similar result. Higher levels of IL-17 in serum and in synovium of RA patients were also reported.[15,18] A study by Chabaud et al[21] showed that intra-articular injection of IL-17 to mice will induce joint cartilage degradation, while Jovanovic et al[25] reported treatment with IL-17 can initiate and maintain the inflammatory response.

Interleukin-17 is produced by cells of immune system that have roles in inflammatory process in RA patients.[13] It will stimulate the transcription activity of nuclear factor-κB and IL-6 and the secretion of IL-8 by fibroblast, endothelial cells, and epithelial cells, and induce T cell proliferation.[17,26] Furthermore, IL-17 will stimulate synoviocytes to produce GM-CSF and prostaglandin E2, which means that IL-17 may have a role in promoting mediators in arthritis pathogenesis and functions as the controller of inflammatory response.[17,27] Interleukin-17 will stimulate macrophages' production of IL-1 and TNFα,[25] support the production of IL-1–mediated IL-6 by synoviocytes, and the synthesis of IL-1, IL-6, and IL-8 induced by TNFα.[17] It shows that IL-17 synergizes with TNFα and IL-1, and the combination of those three will cause more tissue destruction.[23,26]

A study in mice showed the role of IL-17 in causing joint inflammation. Interleukin-17–deficient mice showed the important role of IL-17 in the activation of T cell-mediated immune responses. Interleukin-17–deficient mice that were induced to have arthritis showed evident inflammatory suppression, as well as prevention of the development of destructive arthritis in IL-1 receptor antagonist deficient mice after inactivation of IL-17.[17,28]

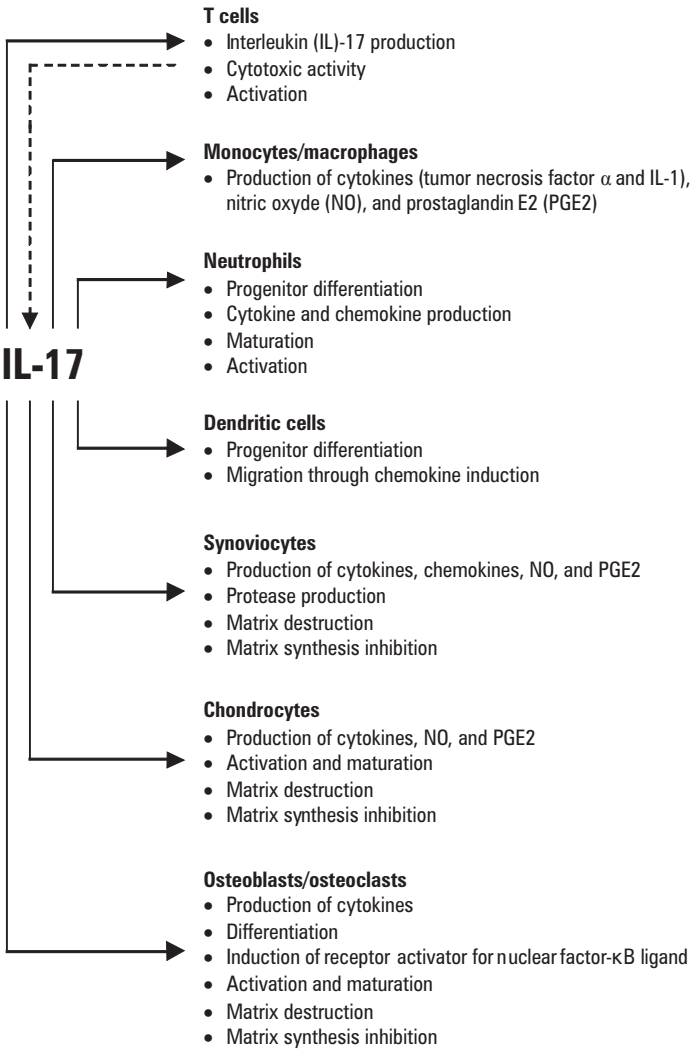

Figure 1 Effects of interleukin-17 on various cells implicated in rheumatoid arthritis. (Adapted from Miossec et al, 2003)[3]

Interleukin-17 has double effects in joint cartilage, such as blocking the metabolism of chondrocytes in intact joint cartilage and inducing proteoglycan destruction. Matrix synthesis by chondrocytes is suppressed by increasing nitric oxyde production. Interleukin-17 also stimulates aggrecanase activity to degrade the matrix of joint cartilage.[24,29] Cai et al[29] explained that the effect is independent of IL-1 and will be even greater if it synergizes with IL-1. Van Bezooijen et al[30]

also showed that IL-17 synergizes with TNFα to induce joint cartilage destruction. Meanwhile, Koshy et al[31] stated that to stimulate release of metalloproteinase, IL-17 can work by itself or combined with proinflammatory cytokines produced by macrophage (IL-1 and TNFα).

Interleukin-17 is a cytokine of T cell which is potent in stimulating osteoclastogenesis. Interleukin-17, combined with TNFα, will increase osteoclastic resorption and the expression of receptor activator for nuclear factor-κB ligand (RANKL) in osteoblasts. RANKL is a regulator of osteoclastogenesis and can be blocked by osteoprotegerin (OPG).[8,32] Lubberts et al[17] also found that in IL-17–deficient mice, there was an obvious suppression of bone erosion if induced to be chronic arthritis. It seems that the mechanism of IL-17 to stimulate bone erosion is through loss of balance between RANKL and OPG.

In animal model, increase of IL-17 in joint with arthritis will cause influx of polymorphonuclear cells; thus, there will be a release of oxygen radical and proteolytic enzymes from those cells. This condition will aggravate the destruction of exposed joint.[30] On the contrary, Yamada et al[33] found that Th1, but not Th17 cells, predominate in the joints of patients with rheumatoid arthritis. In spite of that, murine studies using IL-17 inhibitor or anti–IL-17 monoclonal antibody showed promising results.[34–36] In addition, a recent study by Genovese et al[37] found that a humanized anti–IL-17 monoclonal antibody, added to oral disease-modifying antirheumatic drugs improved signs and symptoms of RA, with no strong adverse safety signal noted.

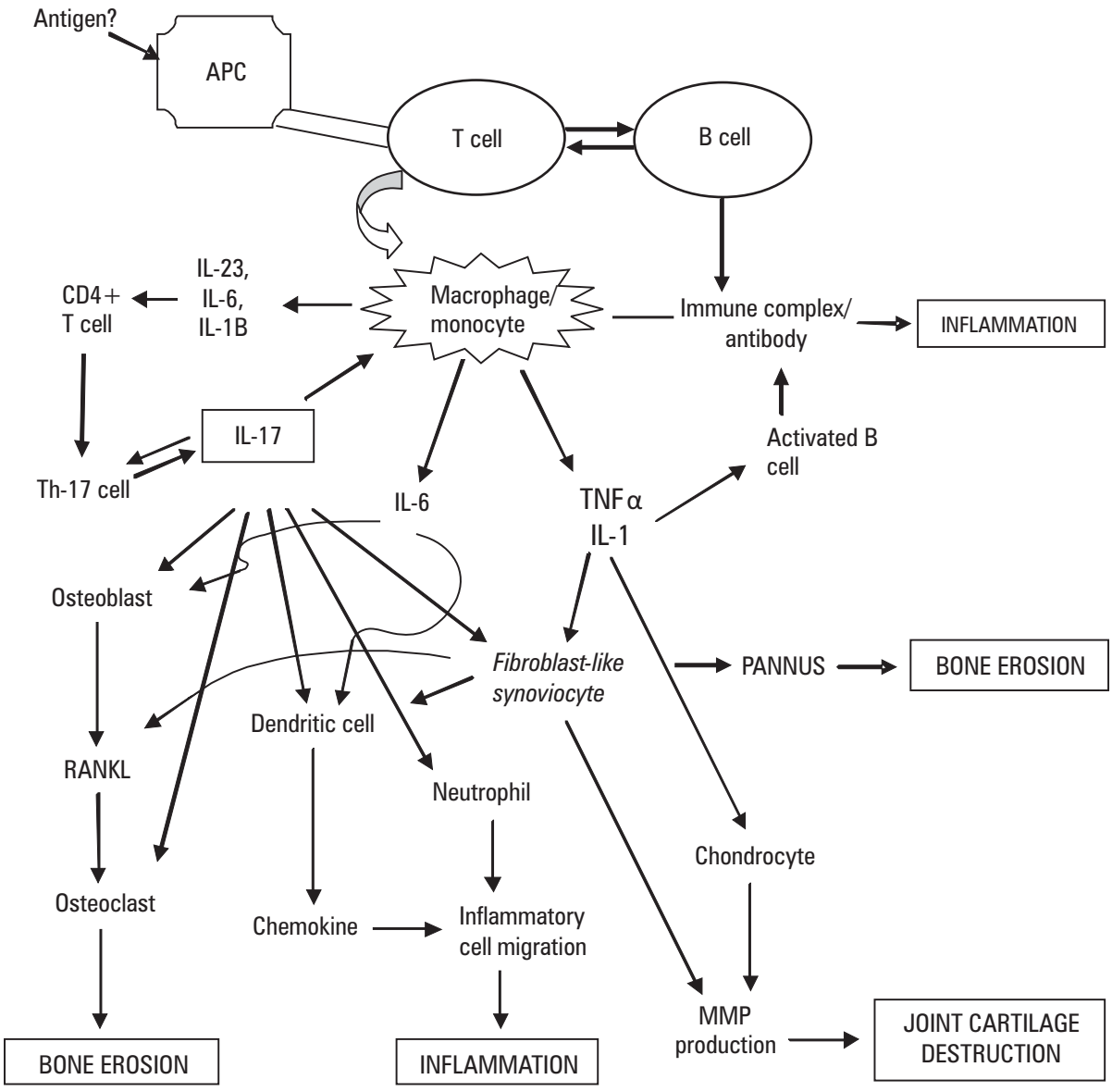

Figure 2 Role of interleukin-17 in the pathogenesis of rheumatoid arthritis. APC, antigen-presenting cell; IL, interleukin; TNFα, tumor necrosis factor α; RANKL, receptor activator for nuclear factor-κB ligand; MMP, matrix metalloproteinase.

CONCLUSION

Rheumatoid arthritis is indicated by chronic inflammation affecting connective tissues throughout the body, but it is mainly affecting diarthrodial joints. Roles of some cytokines are defined in the pathogenesis of RA. Other than the clear roles of TNFα and IL-1, there are many evidences that support the role of other cytokines; IL-17 is one of them. Several studies showed that this cytokine induces and maintains the inflammation, especially in RA. Advances in the understanding of the role of IL-17 elicits the idea to modulate IL-17 and/or Th17 cells as the potential targets of therapy in RA.

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