Interleukin-34: A Potential Diagnostic and Therapeutic Target for Rheumatoid Arthritis

To the Editor:

Recently, we read with great interest the article titled "Increased Levels of Interleukin 34 in Serum and Synovial Fluid Are Associated with Rheumatoid Factor and Anticyclic Citrullinated Peptide Antibody Titers in Patients with Rheumatoid Arthritis," published in *The Journal of Rheumatology*¹, showing that serum levels of interleukin 34 (IL-34) were positively correlated with rheumatoid factor (RF) and anticyclic citrullinated peptide antibody (anti-CCP) titers, but not with systemic osteoporosis and radiographic joint damage in rheumatoid arthritis (RA). Further, IL-34 levels were significantly increased in the serum of patients with RA ($p < 0.001$) or ankylosing spondylitis ($p < 0.001$) compared with controls². These studies bring new insights that IL-34 may play a crucial role in the pathogenesis of RA, and serum levels of IL-34 may be diagnostic and therapeutic targets in RA.

To date, it is well known that RA is characteristic of the expansion of the synovium and the infiltration of the inflammatory cells coupled with the destruction of adjacent articular cartilage and bone³. Although the exact causes of RA remain unknown, immunological dysregulation by inflammatory cytokines has been shown to be involved in driving the inflammation and synovial cell proliferation that result in joint destruction in patients with RA.

IL-34 is a recently discovered cytokine that increases monocyte viability and enhances macrophage proliferation through colony-stimulating factor receptor⁴. It has been reported^{1,5} that elevated levels of IL-34 have been observed in the joint tissue, serum, synovial fluid, and fibroblast-like synoviocytes of patients with RA. Interestingly, elevated levels of IL-34 were also detected in early RA (disease duration ≤ 6 mos)² and a significant association was found between IL-34 expression and synovitis severity⁶. Of greatest interest, significant positive correlations were found between IL-34 levels, inflammation variables (such as erythrocyte sedimentation rate and C-reactive protein), antibodies production (such as RF and anti-CCP), and disease activity indexes (such as tender joint count and the Disease Activity Score at 28 joints)⁷. The proinflammatory cytokines play a dual role in the pathogenesis of RA that can promote inflammation and the destruction of bone. It was found that IL-34 increased IL-6 and chemokine levels in human whole blood⁸. Similarly, Moon, *et al* also agreed that IL-34 concentration in synovial fluid correlated significantly with IL-6 and the receptor activator of nuclear factor- κ B (NF- κ B) ligand levels in RA¹. Moreover, Tian, *et al* showed for the first time that IL-34 induced the production of IL-17 by activated peripheral blood mononuclear cells from patients with RA⁷. On the other hand, tumor necrosis factor (TNF)- α or IL-1 β should stimulate IL-34 expression through the NF- κ B and c-Jun N-terminal kinase pathway in synovial fibroblasts⁶. Hwang, *et al*⁵ also proved that the production of IL-34 was upregulated by TNF- α in RA. Another study showed that IL-34 could promote osteoclastogenesis *in vitro*⁹. IL-34 would contribute to the

persistent expression of proinflammatory cytokines, and accelerate inflammation and the destruction of bone in RA.

Taken together, available evidence suggests that IL-34 may play a potential role in RA. However, further studies are needed to comprehensively extend the role of IL-34 in RA, and the development of therapeutic agents targeting IL-34 may be a promising diagnostic and therapeutic target for RA.

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