Interleukin 22, a Potential Therapeutic Target for Rheumatoid Arthritis

To the Editor:

A recent report by Da Rocha, *et al* indicated that levels of interleukin 22 (IL-22) were increased in patients with rheumatoid arthritis (RA) compared with controls; levels of IL-22 correlated with Disease Activity Score (DAS28) and Clinical Disease Activity Index measures, rheumatoid factor positivity was correlated with higher levels of IL-22 in patients with RA, and the presence of bone erosions was associated with high IL-22 levels[1]. These findings suggest that IL-22 may be a good biomarker for assessment of activity in RA, and IL-22 seems to be a potential therapeutic target for RA.

Other studies have indicated the similar relationship between IL-22 and RA, where serum IL-22 levels were found to be increased in patients with RA compared with controls[2,3,4,5], and high IL-22 levels correlated with bone erosions[4]. The IL-22 concentration in synovial fluid was higher in patients with RA compared with controls[2,3]. In patients with RA, Th17 cells were recognized to produce higher IL-22[4]. Th22 cells also produced IL-22 and the expression of Th22 cells. IL-22 were significantly elevated in RA patients[5,6]. More importantly, Th17/22 cells showed positive correlations with IL-22, C-reactive protein, and DAS28 data[6]. In addition, natural killer (NK)-22 cells *in vitro* can secrete higher levels of IL-22 and tumor necrosis factor-α (TNF-α), and NK-22 supernatant can induce the proliferation of RA fibroblast-like synoviocytes (FLS); however, addition of IL-22 antibody plus TNF-α antibody inhibited the proliferation of FLS induced by the NK-22 supernatant[7]. *In vitro*, human recombinant IL-22 (rhIL-22) significantly increased proliferation of RA synovial fluid and FLS and production of monocyte chemoattractant protein-1[3,7,8], but an inhibitory effect of anti-IL-22R antibody on proliferation of FLS induced by rhIL-22 was found in RA[3]. Moreover, an experimental arthritis model (IL-1Ra–/–) displayed a progressive erosive arthritis characterized by upregulation of IL-22 in severely inflamed synovia; and anti-IL-22 treatment of IL-1Ra–/– mice significantly reduced the inflammation and bone erosions[9]. Similarly, in studies of collagen-induced arthritis (CIA), serum IL-22 levels were increased, and the specific IL-22RI was expressed in lymphoid tissue, including splenocytes. IL-22–/– mice were less susceptible to CIA than wild-type mice, as shown by their reduced incidence of arthritis and decreased pannus formation. Remarkably, the less severe form of arthritis in IL-22–/– mice was associated with increased production of collagen II-specific and total IgG antibodies. *In vitro*, IL-22 was found to promote osteoclastogenesis, a process that may contribute to its proinflammatory activity in CIA[10]. On the other hand, 1,25-dihydroxyvitamin D3 (1,25[OH]2D3) prevented corticosteroid-induced osteoporosis in patients with early RA, where 1,25[OH]2D3 directly modulated human Th17 polarization, accompanied by suppression of IL-17, TNF-α, and IL-22 production[11]. In patients with RA, rituximab reduced expression of IL-22 and Th17-positive cells in synovial tissue, and this correlated with better clinical outcomes. *In vitro*, rituximab strongly reduced IL-17 and IL-22 production induced by *Candida albicans*[12].

These findings suggest therapeutic potential for patients with RA, and suggest a role for IL-22 in development of RA. Further studies are needed to clarify the role of IL-22 in RA. Therapeutic agents targeting IL-22 might result in innovative new therapies for RA.

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