L.F. da Rocha Jr, *et al* reply

To the Editor:

We thank Xie and colleagues for their comments[1] on our article[2] and for applying expertise to this question of interleukin 22 (IL-22) as a possible therapeutic target in rheumatoid arthritis (RA) and as a promising candidate biomarker.

Novel cytokines have emerged recently as contributing to the pathogenesis of autoimmune diseases. Knowledge about the role of IL-22 in autoimmune diseases is increasing and may reveal new therapeutic options for modulation of this cytokine. The role of IL-22 has been investigated in other inflammatory autoimmune diseases, such as psoriasis[3] and psoriatic arthritis[4], systemic sclerosis[5], and systemic lupus erythematosus[6].

In RA, IL-22 is also a promising candidate biomarker as a predictor of disease activity. We demonstrated that higher serum levels of this cytokine are associated with more severe disease[2]. The association of IL-22 with bone erosions supports the idea that this cytokine may play a role in destructive bone disease. IL-22 may also be associated with pannus formation[4].

Th17 and Th22 subsets are major sources of IL-22. These cell lineages were significantly increased in the peripheral blood of patients with inflammatory arthritis, such as ankylosing spondylitis and RA[7,8]. Although we did not investigate these cell subsets, we were able to show that IL-22 levels are high in patients with RA, indicating a role of this cytokine within the complex and heterogeneous pathogenesis of RA.

New strategies for RA treatment focusing on IL-22 may reveal alternative therapies for those patients who remain refractory to current therapeutic modalities. Antibodies to this cytokine might become available in the future. The monoclonal antibody fezakinumab, which modulates expression of IL-22, has been studied in a Phase II trial, but the study was discontinued[9]. The role of IL-22 in protection against bacterial infection should be kept in mind[10]. The nuclear receptor peroxisome proliferator–activated receptor-γ agonists currently under study may also represent a molecular target in autoimmune diseases such as RA, as they were found to suppress the expression of IL-22[11].

The benefit of rituximab, a monoclonal antibody directed to CD20 antigen on B cells, is recognized in the treatment of RA. In a recent study of 12 patients with active RA disease who were resistant to TNF blockade, lower mRNA levels of IL-22 in synovial tissue were described after rituximab treatment[12]. Thus, IL-22 suppression is probably one of the mechanisms involved in rituximab therapy. The Janus kinase inhibitor tofacitinib has been shown to be an inhibitor of IL-22 expression, and may represent a strategy in the treatment of RA[13].

Finally, genetic studies would be helpful in clarifying the role of IL-22 in RA as a biomarker or as a potential therapeutic target.

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