Commentary

Interleukin-7 deficiency in rheumatoid arthritis

Warren J Leonard

Laboratory of Molecular Immunology, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, USA

Corresponding author: Warren J Leonard, wjl@helix.nih.gov

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See related research by Ponchel *et al*., page 47 [http://arthritis-research.com/content/7/1/R80]

Abstract

Interleukin-7 (IL-7) is a stromal factor that is crucial for the development of T lymphocytes in humans and mice, and also B lymphocytes in mice. IL-7 can act as a T cell growth factor as well as a critical anti-apoptotic survival factor. The essential non-redundant role of this cytokine for T cell development *in vivo* is indicated by the phenotype of murine knockout models as well as by humans with a $T^-B^+NK^+$ form of severe combined immunodeficiency (SCID) resulting from mutations in IL-7 receptor α chain. IL-7 deficiency has now been found in patients with rheumatoid arthritis, a finding that relates not only to the T-lymphocyte status in this disease but also to the ability of patients with rheumatoid arthritis to recover from therapy-induced lymphopenia.

Rheumatoid arthritis (RA) is one of the most common human autoimmune diseases, with a prevalence of about 1%. Because of this high prevalence as well as the severely debilitating nature of the disease, considerable efforts have been devoted to the treatment of RA. In the current issue of this journal, Ponchel and colleagues [1] investigate the basis for the prolonged lymphopenia of $CD4^+$ T cells after lymphocyte-depleting therapy specifically of patients with RA in comparison with other disorders, and report that interleukin-7 (IL-7) is depleted.

The successful treatment of RA remains an area of considerable challenge. Therapeutic approaches in the past several decades have included corticosteroids, methotrexate, sulfasalazine, cyclophosphamid, cyclosporine, leflunomide, mycophenylate, and hydroxychloroquine; newer approaches include immune-based targeting of tumor necrosis factor-α (TNF-α) and interleukin-6 as well as the use of monoclonal antibodies to induce T-cell depletion [2–4].

The major pathology of RA occurs in the synovium, and it has been established that T cells and macrophages are the major cell types in the pannus and that fibroblast-like synoviocytes are also relevant in RA pathogenesis and represented in synovium/pannus [5]. The accessibility of synovial fluid has permitted the documentation of elevated levels of cytokines, including pro-inflammatory cytokines such as IL-1, TNF-α, and IL-6 and a large range of others [5]. The evidence in support of an immune basis has led to lympho-depleting therapies, including, for example, specific monoclonal antibodies or high-dose cyclophosphamide with autologous stem cell rescue. Whereas T-cell depletion is potentially an effective approach, it is crucial that the rescue can occur, and it is clear that this rescue requires IL-7, which can act as both a growth factor and survival factor and contributes to the expansion of both naive and memory T cells [6–8]. Although a critical 'cytokine network' related to RA has been extensively studied, IL-7 levels have previously been reported in major reviews as unknown [3,5], and IL-7 deficiency has hitherto not been associated with RA.

To investigate the basis for delayed repopulation, Ponchel and colleagues studied patients with RA and discovered, as reported in this issue, that circulating levels of IL-7 are diminished in patients with RA [1]. Moreover, they found that the number of cells containing T cell receptor excision circles (TRECs), which represents a measure of T-cell receptor gene rearrangement, was decreased. These findings were evident across a range of patients with RA and were not obviously affected by age or sex. The ability of bone marrow stromal cells to produce IL-7 in long-term culture also was diminished. Production of IL-7 was defective even when clinical remission was induced by blockade of signaling by

γ_c = common cytokine receptor γ chain; IL = interleukin; IL-7Rα = IL-7 receptor α chain; RA = rheumatoid arthritis; SCID = severe combined immunodeficiency; TNF-α = tumor necrosis factor-α; TRECs = T cell receptor excision circles.

TNF-α. This defect was restricted to IL-7 rather than its receptor (IL-7R) because the expression of the IL-7 receptor α chain (IL-7Rα) was normal, and peripheral blood mononuclear cells responded normally to exogenous IL-7.

Strikingly, when patients with RA were treated with chemotherapeutic regiments, there was defective recovery of both CD4 and CD8 T cell populations, including both naive and memory cells. This was associated with diminished TRECs. In contrast to patients with tumors, who had a lymphopenia-associated increase in IL-7, no such increase was found in the patients with RA.

IL-7 is a four-α-helical type I cytokine that binds to a receptor comprising IL-7Rα and the common cytokine receptor γ chain, γ_c [9,10]. γ_c is mutated in humans with X-linked severe combined immunodeficiency (X-linked SCID), in which T and NK cells are absent and B cells are present but non-functional. γ_c is also a component of the receptors for IL-2, IL-4, IL-9, IL-15, and IL-21, as well as IL-7, explaining the profound defects in X-linked SCID [9,11]. IL-7Rα is also a component of the receptor for thymic stromal lymphopoietin [12,13], a factor that preferentially affects the expansion of CD4 cells, whereas IL-7 affects both CD4 and CD8 cells [14,15]. Interestingly, mutations in IL-7Rα cause a form of SCID in which T cells are absent but the development of B and NK cells is normal [16]. It has been speculated that IL-7 deficiency would also result in SCID with a similar phenotype, but such patients have not yet been identified [6,9].

Whereas IL-7Rα-deficient SCID patients readily engraft bone marrow from haploidentical donors, the expectation is that this would not occur in IL-7 deficiency because the grafts would not be supported by the host stroma [6]. The study by Ponchel and colleagues [1] is important in supporting this speculation, but more importantly it identifies a clinical syndrome in which IL-7 deficiency affects T cell development *in vivo*. It is noteworthy that the defect in IL-7 production is partial, so one can only speculate about the nature of the defect that might evolve in a setting of complete IL-7 deficiency in humans.

Several important issues are raised by this study. First, given the difficulty in reconstituting T cells in patients with RA, therapeutic approaches that minimize the elimination of T cells are likely to be more desirable. Second, the basis for the defective IL-7 production in RA is unclear and is an interesting area for future investigation. In fact, very little is known about the regulation of the *IL7* gene, whereas recently information on both positive [17] and negative [18,19] regulation of *IL7R* gene expression in T cells has become available. Third, it will be crucial to determine whether the defect in IL-7 production in RA represents a global stromal cell defect or whether it is a relatively selective defect. In this regard, it will also be interesting to determine the levels of thymic stromal lymphopoietin in patients with RA. Thus, the study by Ponchel and colleagues [1] not only provides interesting information about IL-7 deficiency in patients with RA but also clearly indicates several areas in need of further investigation.

Competing interests

The author(s) declare that they have no competing interests.

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