Editorial

Role of interleukin-7 in degenerative and inflammatory joint diseases

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Abstract

IL-7 is known foremost for its immunostimulatory capacities, including potent T cell-dependent catabolic effects on bone. In joint diseases like rheumatoid arthritis and osteoarthritis, IL-7, via immune activation, can induce joint destruction. Now it has been demonstrated that increased IL-7 levels are produced by human articular chondrocytes of older individuals and osteoarthritis patients. IL-7 stimulates production of proteases by IL-7 receptor-expressing chondrocytes and enhances cartilage matrix degradation. This indicates that IL-7, indirectly via immune activation, but also by a direct action on cartilage, contributes to joint destruction in rheumatic diseases.

IL-7 is well-known for its strong immunostimulatory properties, in particular for the role it has in T and B cell homeostasis in mice and T cell homeostasis in humans. Less well-studied is the role of IL-7 in (immuno)pathology, in particular its role in joint diseases. In the previous issue of *Arthritis Research and Therapy*, Long and colleagues [1] demonstrate that IL-7 protein is produced by articular chondrocytes. Production is increased upon stimulation with fibronectin fragments and a combination of IL-1 and IL-6. Most interestingly, endogenous production of IL-7 by cartilage tissue is higher when obtained from older donors or from patients with osteoarthritis (OA). Through chondrocyte-expressed IL-7 receptor (IL-7R), this IL-7 is demonstrated to induce production of matrix metalloproteinase (MMP)-13 associated with enhanced release of proteoglycans from cartilage matrix. Thus, it has been suggested that IL-7 contributes in an autocrine manner to joint tissue destruction in OA and other joint diseases.

In support of a role for IL-7 in OA, it was recently shown that in synovial tissue of a substantial proportion of OA patients, IL-7 is expressed at a significant level (albeit lower than in rheumatoid arthritis patients) [2]. This IL-7 is considered to contribute to cartilage destruction indirectly through activation of inflammatory cells that secrete catabolic cartilage-destructive mediators, contributing to joint destruction. It has now been suggested that IL-7 is involved in cartilage destruction not only indirectly via inflammatory cells but also directly via IL-7R-expressing chondrocytes. However, although factors such as fibronectin fragment, and IL-1 and IL-6 induce IL-7, the (patho)physiological triggers for IL-7 production by human articular chondrocytes *in vivo* remain to be determined. Mechanical stress is one of the mechanisms that should be considered. Definitive proof should be provided by blockade of the IL-7/IL-7R pathway, limiting intrinsic degenerative cartilage destruction *in vitro* and *in vivo*, preferably in experimental models of degenerative joint damage that mimic OA but with minor inflammation [3]. This is of particular importance since the amounts of IL-7 produced by chondrocytes in the experiments described by Long and colleagues are below the amounts needed to induce MMP-13 production and matrix degradation.

Irrespective of this, the data from the study of Long and colleagues underline the role of IL-7 in the induction of joint pathology in rheumatic diseases. It was recently demonstrated that IL-7, apart from its role in T cell development in humans, can stimulate inflammatory T cells to produce tissue destructive cytokines that have a catabolic effect on cartilage and bone [4-7]. Together these studies suggest that IL-7 promotes joint destruction especially in patients that suffer from inflammatory (auto)immune diseases, many of which have increased IL-7 levels. Thus it was demonstrated that IL-7 induced T cell-dependent activation of monocytes/macrophages is associated, amongst other things, with tumour necrosis factor (TNF)α production [6]. Although it needs to be demonstrated that this results in joint damage in RA, the well-studied capacities of TNFα in this respect strongly

IL = interleukin; IL-R = IL receptor; MMP = matrix metalloproteinase; OA = osteoarthritis; TNF = tumour necrosis factor.

suggest that this will be the case. TNFα is a potent inhibitor of cartilage matrix synthesis and an inducer of cartilage degradation (by activation of MMPs), processes that lead to loss of cartilage integrity. TNFα also activates fibroblasts to produce catabolic factors such as cytokines and MMPs that indirectly facilitate cartilage destruction. IL-7 has also recently been shown to induce T cell-dependent osteoclast formation from monocytes. TNFα and RANKL (receptor activator of nuclear factor kappa B ligand) are crucial mediators in this IL-7-driven osteoclast formation [7]. Interestingly, in the study of Long and colleagues, TNFα was not tested as an inducer of chondrocyte produced IL-7, nor did IL-7 stimulation lead to TNFα production by chondrocytes. This suggests that the chondrocyte IL-7/IL-7R pathway is independent from and additive with a TNFα-driven pathway. This is supported by recent findings demonstrating TNFα-independent IL-7-driven inflammatory and bone-destructive activity [6,7].

IL-7 is also able to regulate joint pathology by T cell-driven immune activation in the absence of a clear inflammatory response. Experimental data have recently demonstrated the strong potential of IL-7 to facilitate bone loss. IL-7R-deficient mice display increased bone volume and bone density [8]. In contrast, IL-7-overexpressing transgenic mice are characterized by expanded bone marrow cavities with focal osteolysis of cortical bone and eroded bone surfaces [9]. In addition, estrogen deficient mice (induced by ovariectomy) are characterized by increased IL-7-driven T cell-dependent bone loss [10].

By giving a first glimpse of the direct effects of IL-7 on chondrocytes, the study of Long and colleagues contributes to our knowledge on the broad range of IL-7/IL-7R-driven pathways. In addition to its role in inflammation driven joint destruction, and its potential role in T cell-driven bone loss in the absence of prominent inflammation, direct harmful effects on cartilage can be added to the list of catabolic properties of IL-7. In this respect, the IL-7/IL-7R-stimulated pathology is a target of interest for the treatment of rheumatic diseases such as rheumatoid arthritis, osteoporosis and OA.

Competing interests

The authors declare that they have no competing interests.

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