

## 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 auto-crine 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) $\alpha$  production [6]. Although it needs to be demonstrated that this results in joint damage in RA, the well-studied capacities of TNF $\alpha$  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. TNF $\alpha$  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. TNF $\alpha$  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. TNF $\alpha$  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, TNF $\alpha$  was not tested as an inducer of chondrocyte produced IL-7, nor did IL-7 stimulation lead to TNF $\alpha$  production by chondrocytes. This suggests that the chondrocyte IL-7/IL-7R pathway is independent from and additive with a TNF $\alpha$ -driven pathway. This is supported by recent findings demonstrating TNF $\alpha$ -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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