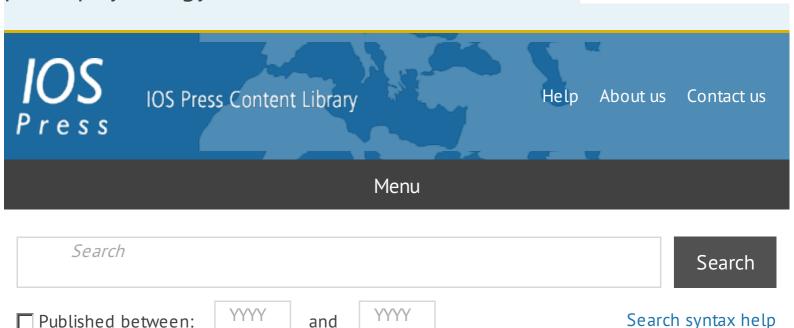
The role of cytokines in osteoarthritis pathophysiology.

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The role of cytokines in osteoarthritis pathophysiology

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Abstract: Morphological changes observed in OA include cartilage erosion as well as a variable degree of synovial inflammation. Current research attributes these changes to a complex network of biochemical factors, including proteolytic enzymes, that lead to a breakdown of the cartilage macromolecules. Cytokines such as ILĭ and TNF alpha produced by activated synoviocytes, mononuclear cells or by articular cartilage itself significantly up regulate metalloproteinases (MMP) gene expression. Cytokines also blunt chondrocyte compensatory synthesis pathways required to restore the integrity of the degraded extrecellular matrix (ECM). Moreover, in OA synovium, a relative deficit in the production of natural antagonists of the ILX1 receptor (ILX1Ra) has been demonstrated, and could possibly be related to an excess production of nitric oxide in OA tissues. This, coupled with an

upregulation in the receptor level, has been shown to be an additional enhancer of the catabolic effect of IL≥1 in this disease. IL≥1 and TNF≥≥ significantly up≥ regulate MMP≥3 steady≥state mRNA derived from human synovium and chondrocytes. The neutralization of IL≥1 and/or TNF≥≥ up≥regulation of MMP gene expression appears to be a logical development in the potential medical therapy of OA. Indeed, recombinant ILX1receptor antagonists (ILRa) and soluble IL⊠1 receptor proteins have been tested in both animal models of OA for modification of OA progression. Soluble IL■1Ra suppressed MMP■3 transcription in the rabbit synovial cell line HIGX82. Experimental evidence showing that neutralizing TNFXX suppressed cartilage degradation in arthritis also support such strategy. The important role of TNFXX in OA may emerge from the fact that human articular chondrocytes from OA cartilage expressed a significantly higher number of the p55 TNF\(\mathbb{Z}\) alpha receptor which could make OA cartilage particularly susceptible to TNFMalpha degradative stimuli. In addition, OA cartilage produces more TNFMM and TNFXX convertase enzyme (TACE) mRNA than normal cartilage. By analogy, an inhibitor to the p55 TNFXX receptor may also provide a mechanism for abolishing TNFXXXinduced degradation of cartilage ECM by MMPs. Since TACE is the regulator of TNFXX activity, limiting the activity of TACE might also prove efficacious in OA. ILX1 and TNFXX inhibition of chondrocyte compensatory biosynthesis pathways which further compromise cartilage repair must also be dealt with, perhaps by employing stimulatory agents such as transforming growth factor

▼ beta or insulin\(\mathbb{Z}\) like growth factor\(\mathbb{Z}\). Certain cytokines have antiinflammatory properties. Three such cytokines - IL

4, IL

10, and IL

13 - have been identified as able to modulate various inflammatory processes. Their antiinflammatory potential, however, appears to depend greatly on the target cell. Interleukin⊠4 (ILM4) has been tested in vitro in OA tissue and has been shown to suppress the synthesis of both TNFXX and ILX1X in the same manner as lowXdose dexamethasone. Naturally occurring antiinflammatory cytokines such as IL≥10 inhibit the synthesis of ILX1 and TNFXX and can be potential targets for therapy in OA. Augmenting inhibitor production in situ by gene therapy or supplementing it by injecting the recombinant protein is an attractive therapeutic target, although an in vivo assay in OA is not available, and its applicability has yet to be proven. Similarly, IL≥13 significantly inhibits lipopolysaccharide (LPS)≥induced TNF≥≥ production by mononuclear cells from peripheral blood, but not in cells from inflamed synovial fluid. ILX13 has important biological activities: inhibition of the production of a wide range of proinflammatory cytokines in monocytes/macrophages, B cells, natural killer cells and endothelial cells, while increasing IL

1Ra production. In OA synovial membranes treated with LPS, IL

13 inhibited the synthesis of IL≥1≥, TNF≥≥ and stromelysin, while increasing IL≥1Ra production. In summary, modulation of cytokines that control MMP gene up regulation would appear to be fertile targets for drug development in the treatment of OA. Several studies illustrate the potential importance of modulating ILX1 activity as a means to reduce the progression of the structural changes in OA. In the experimental dog and rabbit models of OA, we have demonstrated that in vivo intraarticular injections of the IL⊠Ra gene can prevent the progression of structural changes in OA. Future directions in the research and treatment of osteoarthritis (OA) will be based on the emerging picture of pathophysiological events that modulate the initiation and progression of OA.

Keywords: OA, proinflammatory cytokines, antiinflammatory cytokines, cytokine antagonists

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