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Regulation of IL-1 by IL-1 decoy receptor

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Keywords

Cartilage, chondrocyte, IL-1, IL-1 decoy receptor, osteoarthritis

Context

Interleukin (IL)-1 is produced by synovial cells and chondrocytes in osteoarthritis (OA)-affected cartilage and plays a key role in the pathogenesis of the disease by inducing and maintaining an imbalance of cartilage homeostasis and extracellular matrix synthesis. IL-1 responses are regulated by a number of proteins. The IL-1 type I receptor (IL-1RI) and receptor accessory protein (IL-1RAcp) are required for IL-1 signalling across the cytoplasmic membrane. Furthermore, IL-1 signalling is antagonised by both the IL-1R antagonist (IL-1ra), which binds the IL-1R without inducing a biological response, and the IL-1R type II (IL-1RII), which lacks a cytoplasmic domain and therefore acts as a decoy receptor, inhibiting IL-1 activity. In this study the authors have characterised the expression of these IL-1 regulators in normal and OA cartilage and determined whether IL-1RII could inhibit IL-1 action and therefore prevent cartilage destruction.

Significant findings

IL-1RI and IL-1RAcp are expressed in both normal and OA-affected cartilage, while the antagonists IL-1RII and IL-1ra are not. IL-1RII was stably transfected into a human chondrocyte line. These cells expressed both surface IL-1RII and soluble IL-1RII (sIL-1RII). sIL-1RII could specifically block both IL-1?-induced nitric oxide (NO) and prostoglandin E_2 production by bovine and human OA chondrocytes and IL-1?-mediated inhibition of proteoglycan synthesis. Autocrine IL-1? gene expression was also inhibited in IL-1RII transfected cells compared to nontransfected controls. sIL-1RII was more effective than sIL-1RI in neutralising the action of endogenous autocrine IL-1 in OA cartilage. IL-1-induced PGE_2 expression in both human synovial and epithelial cells was also blocked by sIL-1RII.

Comments

This study demonstrates that the IL-1 decoy receptor, IL-1RII, can effectively attenuate IL-1-mediated inflammatory responses in chondrocytes, synovial cells and *ex vivo* cartilage, therefore identifying it as a potential therapeutic target for the treatment of OA. Inhibition of bone and cartilage damage has already been reported following treatment with the IL-1ra. Further experiments using animal models of OA will determine whether treatment with either endogenous or transgenic IL-1RII is also effective in blocking cartilage destruction *in vivo*.

Methods

Chondrocyte and synovial cell culture, cartilage organ culture, northern blot analysis, gene array analysis, PGE_2 and nitrite assays

References

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