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Inhibition of IL-1? activity using IL-1RII

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Cheryl Smythe,[Aff1]

Aff1 Imperial College Faculty of Medicine, London, UK

Keywords

adenovirus, chondrocyte, IL-1RII, IL-1?, nitric oxide, osteoarthritis, PGE_2, synoviocyte

Context

Interleukin-1? (IL-1?) is constitutively produced 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. In normal and OA-affected human cartilage, expression of innate antagonist regulators of IL-1 is deficient. Therefore, inhibition of IL-1? action using the IL-1? type II receptor (IL-1RII), which acts as a decoy receptor, would have therapeutic potential. Indeed, IL-1?-induced nitric oxide (NO) and prostaglandin E_2 (PGE_2) production by chondrocytes, synoviocytes and epithelial cells has been shown to be significantly inhibited by soluble IL-1RII. In this study, the authors have further examined the effects of reconstituting IL-1RII deficient ($IL\text{-}1RII^-$) cells with IL-1RII using adenoviral gene transfer.

Significant findings

IL-1? mRNA and protein expression is 10-fold greater in OA than normal cartilage. $IL\text{-}1RII^+$ cells expressed significant amounts of both intracellular and secreted IL-1RII. IL-1?-induced PGE_2 secretion was inhibited in $IL\text{-}1RII^+$ chondrocytes and OA synoviocytes compared to untransfected controls. IL-1?-induced IL-6 and IL-8 production and tumour necrosis factor (TNF)-a-induced PGE_2 production in $IL\text{-}1RII^+$ A549 human epithelial cells was inhibited. Induction of IL-1? mRNA by IL-1? was also inhibited in these cells. Membrane bound IL-1RII was shown to block IL-1? activity more effectively than soluble (s)IL-1RII. OA-affected cartilage incubated with $IL\text{-}1RII^+$ synovial cells, but separated by a buoyant chamber insert, showed reduced levels of spontaneous and IL-1?-induced PGE_2 and NO production. Furthermore the IL-1?-mediated reduction in proteoglycan synthesis was reversed by paracrine sIL-1RII. Human OA-affected cartilage was used to generate $IL\text{-}1RII^-$ and $IL\text{-}1RII^+$

chondrocytes that were then transplanted onto the autologous cartilage. OA-affected cartilage transplanted with human IL-1RII^{+} chondrocytes showed inhibition of spontaneous and exogenous IL-1?-induced NO, PGE_2, IL-6 and IL-8 production and a reversal of IL-1?-mediated reduction in proteoglycan production; controls transplanted with IL-1RII^{-} cells showed none of these effects.

Comments

This study is an extension of the group's earlier work that demonstrated that IL-1?-induced NO and PGE_2 production by chondrocytes, synoviocytes and epithelial cells is inhibited by soluble IL-1RII (see Additional information). These publications implicate the therapeutic use of IL-1RII in the treatment of OA. The current study identifies the paracrine action of transgenic IL-1RII, which would allow transduced synovial cells to also inhibit IL-1?-mediated events in nearby cartilage. However the evaluation of transgenic IL-1RII expression in an animal model of OA now needs to be carried out.

Methods

Chondrocyte isolation, culture and transplantation, synovial cell isolation, recombinant adenovirus construction, immunostaining, RT-PCR and real-time PCR, assays for PGE_2, nitrite and proteoglycan synthesis

Additional information

Attur MG, Dave M, Cipolletta C, Kang P, Goldring MB, Patel IR, Abramson SB, Amin AR: **Reversal of autocrine and paracrine effects of interleukin 1 (IL-1) in human arthritis by type II IL-1 decoy receptor. Potential for pharmacological intervention.** *J Biol Chem* 2001, **275**:40307-40312 (Paper%20report).

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