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Role for IL-18 in rheumatoid arthritis

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Keywords

Collagen-induced arthritis, IL-18, rheumatoid arthritis

Context

IL-18 is a novel cytokine with potent IFN-?-inducing activities that is involved in Th1 cell differentiation. Th1-mediated immune responses are known to play an important role in the pathogenesis of RA. However, the specific cytokine mediators and their relative roles in the initiation and maintenance of Th1 cell responses in RA synovium are not clear. To examine the expression of IL-18 and its receptor in RA synovial tissues and their potential functional effects within the synovial joint.

Significant findings

IL-18 and IL-18R were detected within RA synovial tissues. Addition of IL-18 to synovial cultures *in vitro* promoted the synthesis of GM-CSF, TNF-a, and NO. Levels of TNF-a were further augmented by the addition of IL-12 and/or IL-15. Furthermore, IL-18 together with IL-12 and IL-15 induced significant levels of IFN-? in these cultures. IL-18 induced TNF-a and IFN-? synthesis was suppressed by anti-inflammatory cytokines, IL-10 and TGF-?. IL-18 synthesis was induced by pro-inflammatory cytokines such as TNF-a and IL-1?. *In vivo*, administration of IL-18 to DBA/1 mice immunised with collagen II in incomplete Freund's adjuvant enhanced the development of an erosive inflammatory arthritis.

Comments

The study describes the expression of a pro-inflammatory cytokine, IL-18 and its receptor (IL-18R) in rheumatoid arthritis (RA) synovial tissues. The functional role of this cytokine was evaluated both *in vitro* (in a cell culture system) and *in vivo* (in an animal model of arthritis). In culture, IL-18 alone could promote the synthesis of granulocyte-macrophage colony-stimulating factor (GM-CSF), tumour necrosis factor alpha (TNF-a) and nitric oxide (NO). Furthermore, IL-18 together with IL-12 and IL-15

augmented the synthesis of IFN-? and TNF-a. Monokines such as TNF-a and IL-1? induced IL-18 expression, suggesting a positive feedback loop that could potentially promote Th1 cell development. *In vivo*, IL-18 was found to facilitate the development of an erosive inflammatory arthritis in a collagen-induced arthritis (CIA) mouse model. The data clearly document a pro-inflammatory role for IL-18 in the pathogenesis of arthritis.

Methods

Human IL-18 cDNA was cloned and expressed in bacteria, and the biological activity of the purified protein was determined by its ability to induce IFN-? synthesis in peripheral blood mononuclear cell culture. Monoclonal and sheep polyclonal anti-IL-18 specific antibodies were generated. Synovial membranes, synovial fluids and blood samples from RA and osteoarthritis patients were used for the study. The expression of IL-18 and its receptor was evaluated by RT-PCR, immunocytochemistry, FACS, and the functional effects of IL-18 on the synthesis of TNF-a and IFN-? were determined by an ELISA assay. IL-18 was administered (intraperitoneally) together with type II bovine collagen emulsified in incomplete Freund's adjuvant (intradermally) to DBA/1 mice to study the role of IL-18 in the pathogenesis of inflammatory arthritis.

References

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