Inhibition by Hyaluronan of Collagenase Production through Nuclear Factor-κB Down-regulation in Rheumatoid Chondrocytes Stimulated with COOH-terminal Heparin-binding Fibronectin Fragment

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Introduction: Increased fibronectin fragments are thought to be involved in cartilage destruction in rheumatoid arthritis (RA) through their catabolic activities (1-3). At present, whether fibronectin fragments can activate nuclear factor (NF)-κB in RA chondrocytes remains unknown. In addition, hyaluronan (HA) effect on fibronectin fragment-activated intracellular pathways remains to be clarified. This study was aimed to examine the inhibitory effect of HA on collagenase production through NF-κB activation by COOH-terminal heparin-binding fibronectin fragment (HBFN-f) in RA chondrocytes.

Materials and Methods: RA cartilage was harvested from knee joint at replacement surgery, and chondrocytes were kept in monolayer or cartilage explant cultures in the presence of HBFN-f. Secreted levels of matrix metalloproteinase (MMP)-1 and MMP-13 in conditioned media were determined by immunoblot analysis. NF-κB activation and nuclear translocation were also evaluated by immunoblot analysis. Cultures were pretreated with 2700 kDa HA to evaluate the inhibitory effect on HBFN-f action.

Results: HBFN-f enhanced MMP-1 and MMP-13 in RA cartilage explant culture. The specific NF-κB inhibitor, BAY11-7085 confirmed the requirement of NF-κB for collagenase induction by HBFN-f. HBFN-f activated NF-κB, leading to NF-κB nuclear translocation in RA chondrocyte monolayer culture. Pretreatment with HA resulted in significant suppression of NF-κB phosphorylation and nuclear translocation by HBFN-f. HA also inhibited HBFN-f-stimulated production of MMP-1 and MMP-13 in RA cartilage explant culture.

Discussion: The present study clearly demonstrated that HBFN-f activated NF-κB in RA chondrocytes, while high molecular weight HA inhibited such activation. When HA is therapeutically introduced into RA joints, therefore, HA could suppress the catabolic actions of fibronectin fragments like HBFN-f as a potent NF-κB inhibitor.


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