Novel chondro-protective mechanisms of hyaluronic acid: down-regulation of ADAMTS-7 and ADAMTS-12, and reduced COMP release from articular cartilage

Minoru Takasaki, Jun-ichi Fukushi, Yukihide Iwamoto
Department of Orthopaedic Surgery, Graduate School of Medical Sciences, Kyushu University
*Contact author: takasaki@ortho.med.kyushu-u.ac.jp

Objective: Hyaluronic acid (HA) is known to down-regulate matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinases with thrombospondin motifs (ADAMTSs) in both chondrocytes and synoviocytes, and widely used for both osteoarthritis and rheumatoid arthritis patients in the clinical settings. However, it is not well understood whether HA could protect articular cartilage from proteolytic degradation. Cartilage oligomeric matrix protein (COMP) is a noncollagenous extracellular matrix protein consisting articular cartilage, and released from matrix by proteolytic degradation in the presence of MMPs and ADAMTSs. In this study, we examined whether HA could inhibit the proteolytic release of COMP from articular cartilage.

Methods: Bovine articular cartilage was cut into small pieces and incubated with RPMI in the presence of IL-1beta and synovium-derived SW982 cells, with or without HA. COMP levels were measured using ELISA. SW982 cells were also incubated with IL-1beta in the presence of HA, then mRNA was extracted, and the expression levels of MMP-3, ADAMTS-4, -5, -7, and -12 were examined using real-time PCR.

Results: Proteolytic release of COMP from bovine cartilage samples was up-regulated about 2-fold over the control level when incubated with SW982 for 3 days. This up-regulation was significantly inhibited in the presence of HA. In SW982 cells, the expression levels of MMP-3, ADAMTS-7 and ADAMTS-12 were increased about 3- to 5-fold over the control levels when stimulated with IL-1beta. HA also significantly inhibited these IL-1beta-induced up-regulation of proteases.

Conclusions: Chondro-protective effects of HA were observed in this study. HA suppressed proteolytic release of COMP from articular cartilage stimulated by IL-1beta and SW982 cells. This inhibitory effect is thought to be a result from down-regulation of MMP3.