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Identification of α2 -Macroglobulin as a Master Inhibitor of Cartilage-Degrading Factors That Attenuates the Progression of Posttraumatic Osteoarthritis.

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Abstract

OBJECTIVE:
To determine if supplemental intraarticular α2 -macroglobulin (α2 M) has a chondroprotective effect in a rat model of osteoarthritis (OA).

METHODS:
Using Western blotting, mass spectrometry, enzyme-linked immunosorbent assay (ELISA), and immunohistochemistry, α2 M was identified as a potential therapeutic agent through a comparison of α2 M concentrations in serum, synovial fluid (SF), and cartilage from normal subjects and patients with OA. In cultured chondrocytes, the effects of α2 M on interleukin-1 (IL-1)-induced cartilage catabolic enzymes were evaluated by Luminex assay and ELISA. In vivo effects on cartilage degeneration and matrix metalloproteinase 13 (MMP-13) concentration were evaluated in male rats (n = 120) randomized to 1 of 4 treatments: 1) anterior cruciate ligament transection (ACLT) and saline injections, 2) ACLT and 1 IU/kg injections of α2 M, 3) ACLT and 2 IU/kg injections of α2 M, or 4) sham operation and saline injections. Rats were administered intraarticular injections for 6 weeks. The concentration of MMP-13 in SF lavage fluid was measured using ELISA. OA-related gene expression was quantified by real-time quantitative polymerase chain reaction. The extent of OA progression was graded by histologic examination.

RESULTS:
In both normal subjects and OA patients, α2 M levels were lower in SF as compared to serum, and in OA patients, MMP-13 levels were higher in SF than in serum. In vitro, α2 M inhibited the induction of MMP-13 by IL-1 in a dose-dependent manner in human chondrocytes. In the rat model of ACLT OA, supplemental intraarticular injection of α2 M reduced the concentration of MMP-13 in SF, had a favorable effect on OA-related gene expression, and attenuated OA progression.

CONCLUSION:
The plasma protease inhibitor α2 M is not present in sufficient concentrations to inactivate the high concentrations of catabolic factors found in OA SF. Our findings suggest that supplemental intraarticular α2 M provides chondral protection in posttraumatic OA.