

P011 Calcium pentosan polysulfate increases levels of TIMP-3 in cartilage

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The hallmark feature of osteoarthritis is breakdown of the cartilage extracellular matrix, abrogating its articulating and compressive functions. Breakdown of the matrix proteoglycan aggrecan is an early and crucial event, hindering the ability of the tissue to withstand compression and exposing the structural collagen fibers to subsequent proteolytic attack. Aggrecan breakdown is thought to be mediated largely by the ADAMTS family of metalloproteinases, whose physiological inhibitor is TIMP-3.

The sulfated synthetic glycosaminoglycan calcium pentosan polysulfate (CaPPS) has been reported to protect cartilage against aggrecan breakdown, but the mechanism is not understood. Here we show that CaPPS increases TIMP-3 levels in porcine cartilage explants, as well as in primary chondrocytes and the chondrosarcoma cell line HTB94. Heparin causes a similar increase in TIMP-3 levels in the medium of HTB94, while non-sulfated glycosaminoglycans such as hyaluronic acid, desulfated heparin, chondroitin sulfate and dermatan sulfate do not. In HTB94, TIMP-3 mRNA levels are unaffected by heparin, but TIMP-3 protein accumulates within 3h of heparin or CaPPS addition, and disappears within 48h of their removal. Levels of TIMP-1 and TIMP-2 are unaffected. This study implies that CaPPS protects the cartilage matrix by increasing levels of TIMP-3 within the tissue, thus inhibiting ADAMTS-mediated aggrecan breakdown.