A59 SYNDECAN-4 REGULATES CARTILAGE DEGRADATION IN OSTEOARTHRITIS

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Cartilage breakdown by loss of proteoglycans is one of the hallmarks of osteoarthritis (OA). The aggrecanase ADAMTS-5 has been shown to be responsible for proteoglycan loss in arthritic mouse cartilage. However, the mechanisms that lead

to ADAMTS-5 activation during cartilage remodelling are poorly understood.

Based on recent data that have implicated transmembrane heparan sulfate proteoglycans in matrix turnover, we analysed the relationship between syndecan-4 and ADAMTS-5 in osteoarthritic cartilage and in different animal models of OA. To study syndecan-4 in OA, we surgically achieved joint instability in syndecan-4-/- mice (Sdc4–/–), wild-type controls and wild-type animals treated with a Sdc4-specific antibody. We determined the severity of the induced cartilage damage by Mankin scores, proteoglycan loss and collagen type X staining. Staining for syndecan-4 and ADAMTS generated aggrecan neo-epitopes and matrix metalloproteinase 3 (MMP-3) was performed in cartilage sections of these mice. For in vitro studies, femur cartilage caps isolated from 3–weeks-old wild-type and Sdc4–/– mice were used to analyse interleukin 1 (IL1)-induced proteoglycan loss (dimethylmethylene blue assay), ADAMTS activity (aggrecan-neo-epitope ELISA), gene expression (real-time PCR) and mitogen-activated protein kinase (MAPK) activation (immunoblot). Interaction of Sdc4 and ADMATS-5 was determined by co-immunoprecipitation from arthritic chondrocytes.

There was a strong upregulation of syndecan-4 in human and rodent OA cartilage. Analysis of osteoarthritic changes in mice revealed a correlation between collagen type X and Sdc4 staining in dedifferentiated hypertrophic chondrocytes. Sdc4–/– OA mice had a significant reduction in Mankin scores and a reduction in the loss of proteoglycans. This was accompanied by significantly reduced staining for ADAMTS-generated aggrecan neo-epitopes and an increase in MMP-3 staining in Sdc4–/– mice. ADAMTS-5 expression was upregulated by IL1 equally in wild-type and Sdc4–/– femur cap cartilage; however, MMP-3 expression was lower in Sdc4–/– OA cartilage. IL1-induced proteoglycan loss was significantly reduced in Sdc4–/– cartilage. Intra-articular injection of Sdc4-blocking antibodies prevented OA-induced cartilage damage, proteoglycan loss and MMP-3 expression to the same extent as in Sdc4–/– mice. In vitro blocking syndecan-4 inhibited IL1-induced proteoglycan loss, ADAMTS protease activity and extracellular signal-regulated kinase 1 and 2 (ERK 1/2) phosphorylation. Sdc4 directly binds ADAMTS-5 and regulates ADAMTS-5 activation through MMP-3 expression, as an MMP inhibitor reduced ADAMTS-mediated aggrecan cleavage.

Our data show for the first time that syndecan-4 controls early cartilage damage by hypertrophic OA chondrocytes through activation of ADAMTS-mediated cleavage of aggrecan. Inhibition of syndecan-4 may therefore constitute a promising strategy to interfere with osteoarthritic cartilage damage.