

**P004** IL1-mediated loss of aggrecan from articular cartilage is MMP17 dependent

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ADAMTS4 can generate the osteoarthritis-associated NITEGE neoepitope resulting in aggrecan loss from articular cartilage. MMP17 (MT4-MMP) has been implicated in the activation of ADAMTS4. Hypothesis: MMP17 mediates the IL1 $\beta$  induced release of NITEGE neoepitope from human and murine articular cartilage.

MMP17 is expressed in OA and normal cartilage (mRNA and protein). IHC studies in human articular cartilage confirmed an association between MMP17 protein and NITEGE neo-epitope staining with both increased in areas of cartilage damage. Treatment of normal human cartilage with recombinant MMP17 protein increased both NITEGE generation in the cartilage and GAG loss into the media. IL-1 $\beta$  mediated GAG loss and increased NITEGE neoepitope in cartilage.

Our data showed MMP17 expression (mRNA) was increased in IL1 $\beta$  stimulated murine articular cartilage. Intra-articular injection of IL1 $\beta$  into C57bl6/Jax mice resulted in an increase in GAG and NITEGE into the synovial fluid and MMP17 knockout mice were protected against this increase. However, MMP17 knockout offered no protection in a surgically induced meniscectomy model. Although we have not demonstrated ADAMTS4 processing *per se* we have shown a link between MMP17 and NITEGE generation. In addition, we have demonstrated inhibition / absence of MMP17 protects against IL1 $\beta$  driven GAG loss in both human *in vitro* and in *in vivo* models.