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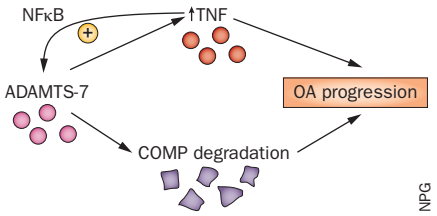
OSTEOARTHRITIS

Positive feedback between ADAMTS-7 and TNF in OA

ADAMTS-7, a member of the ADAMTs (a disintegrin and metalloproteinase with thrombospondin motifs) family, has been shown previously to degrade cartilage oligomeric matrix protein (COMP), which is a key component of cartilage. However, until now, the *in vivo* role of ADAMTS-7 in cartilage degradation and progression of osteoarthritis (OA) was unknown. A paper from Lai *et al.* published in *Annals of the Rheumatic Diseases* now reveals that, in addition to degrading COMP, ADAMTS-7 mediates cartilage destruction by increasing expression of TNF, which in turn, via the NFκB signalling pathway, upregulates the expression of ADAMTS-7.

The authors generated transgenic mice that overexpressed *Adamts-7* in cartilage and also *Adamts-7* small interfering RNA knockdown mice, so they could investigate the effects of overexpressing or blocking expression of ADAMTS-7 *in vivo*. First, the phenotype of healthy transgenic mice was assessed: "This is the first paper



demonstrating that targeted overexpression of ADAMTS-7 in chondrocytes induces chondrodysplasia in young mice but an OA-like phenotype in aged mice," explain Xiu-Ping Yu and Chuan-Ju Liu, lead authors on the paper.

Next, destabilization of medial meniscus surgery (a surgically-induced model of OA) was performed. Surgery led to more severe cartilage breakdown and accelerated OA progression in the *Adamts-7* transgenic mice compared with wild-type mice. By contrast, the *Adamts-7* knockdown mice had less cartilage breakdown than wild-type mice and were protected against surgically-induced OA. "These experiments provide *in vivo* evidence that ADAMTS-7 has an important role in cartilage and OA development," state Yu and Liu.

Finally, the molecular pathways involved were investigated. *Adamts-7* overexpression led to increased expression of TNF and metalloproteinases associated with the development of OA. In addition, via NFκB , TNF induced the expression of *Adamts-7* resulting in a positive feedback loop encouraging cartilage destruction and OA progression.

"These discoveries have not only provided insight into the role of metalloproteinases in skeletal and joint biology, but may also lead to identification of new therapeutic targets to treat chronic degenerative disorders," conclude Yu and Liu.

Jenny Buckland

Original article Lai, Y. *et al.* ADAMTS-7 forms a positive feedback loop with TNF-a in the pathogenesis of osteoarthritis. doi:10.1136/annrheumdis-2013-203561