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OSTEOARTHRITIS

Lack of *Nfatc1* and *Nfatc2*: a new mouse model of OA

"Advances in understanding osteoarthritis [OA] have been limited by the mouse models available," says Matthew Greenblatt, from Brigham and Women's Hospital and Harvard Medical School, Boston, "many of which either only develop mild-to-moderate disease or only develop disease after an extended period of time." A paper from Greenblatt *et al.*, published in *Proceedings of the National Academy of Sciences*, now describes "a new model of OA that avoids these limitations by developing early-onset severe disease, and also establishes a new role for NFATc1 in suppressing cartilage catabolism," he continues.

Previous research from the groups of Laurie Glimcher and others established a link between the nuclear factor of activated T cells (NFAT) family of transcription factors and OA: *Nfatc2*$^{-/-}$ mice develop ectopic cartilage around their synovial joints from ~3 months of age and develop OA at ~1–2 years of age. In the current paper, Greenblatt *et al.* investigated the role of another member of this family–NFATc1–in cartilage biology.

> "...the *Nfatc1*^{col2}*Nfatc2*$^{-/-}$ mice spontaneously developed severe OA, with many features of human disease..."

First, the researchers assessed the expression patterns of Nfatc1 *in vivo*. Nfatc1 protein was found to be expressed specifically in superficial articular chondrocytes in mice. In addition, levels of *NFATC1* RNA were reduced in lesional compared with nonlesional cartilage from patients with end-stage OA undergoing total knee joint replacement surgery.

These findings suggest that NFATc1 might act as an OA suppressor. To test this theory, mice that lack expression of *Nfatc1* specifically in chondrocytes were generated. These mice were no more susceptible to post-traumatic OA (destabilization of the medial meniscus model) than wild-type littermate controls, potentially due to redundancy between NFAT family members. To overcome the possible redundancy issue, mice that lack expression of both *Nfatc1* and *Nfatc2* in chondrocytes (*Nfatc1*^{col2}*Nfatc2*$^{-/-}$ mice) were generated. Within a few weeks of birth, the *Nfatc1*^{col2}*Nfatc2*$^{-/-}$ mice spontaneously developed severe OA, with many features of human disease, including proteoglycan loss, degradation of collagen and aggrecan, osteophyte formation, flattening of articular surfaces, thickening of the trabecular bone and joint instability.

"We intend use this mouse model of OA to determine the mediators of the different catabolic processes. In addition, this model could serve as a platform for us, and others, to test potential new drugs for OA patients," concludes Greenblatt.

Jenny Buckland

Original article Greenblatt, M. B. *et al.* NFATc1 and NFATc2 repress spontaneous osteoarthritis. *Proc. Natl Acad. Sci. USA* doi:10.1073/pnas.1320036110