Nature Reviews Rheumatology | Published online 12 May 2016; doi:10.1038/nrrheum.2016.66

OSTEOARTHRITIS

Hypoxia protects against cartilage loss by regulating Wnt signalling

> HIF1α acts as a physiological regulator of Wnt signalling by limiting chondrocyte catabolic activities such as MMP13 production

New research links degradation of articular cartilage by matrix metalloproteinase 13 (MMP13) — a well-established process in osteoarthritis (OA) development — to the interaction of hypoxia-inducible factor 1α (HIF1α) with the Wnt signalling pathway. This finding by Bouaziz *et al.* sheds light on the hypoxic nature of cartilage tissue. "Because hypoxia inhibits Wnt signalling in other tissues, we speculated that physiological, low oxygen levels could negatively regulate Wnt signalling in cartilage, and loss of hypoxia could lead to increased Wnt signalling in OA," says Martine Cohen-Solal, corresponding author of the study.

Previous work showed that HIF1α has a crucial role in chondrocyte homoeostasis and differentiation, and that activation of β-catenin — a component of the Wnt pathway — leads to cartilage damage in OA. In line with these studies, Bouaziz *et al.* observed by immunohistochemistry that hypoxia and Hif1α expression were reduced in mice with OA compared with control mice.

To check whether HIF1α contributes to OA progression, the researchers used mice in which knockout of *Hif1a* could be specifically induced in chondrocytes. The advantage of this system relies on the fact that it "bypasses any confounding effects resulting from the alteration of the cartilage during skeletal development," explains Cohen-Solal. Results revealed that chondrocyte-specific loss of Hif1α in knockout mice exhacerbates OA cartilage lesions and increases Mmp13 protein levels compared with control mice.

Subsequently, the investigators dissected the molecular function of Hif1α *in vitro* using primary mouse chondrocytes. Silencing of *Hif1a* expression by short interfering RNA (siRNA) increased the transcription of *Mmp13* and other Wnt target genes. Co-immunoprecipitation and chromatin immunoprecipatation (ChIP) analyses of nuclear extracts further showed that Hif1α forms a complex with β-catenin, thus preventing the Wnt signalling pathway from activating downstream genes.

In summary, this study highlights the role of oxygen microenvironment in cartilage integrity during OA, showing that HIF1α acts as a physiological regulator of Wnt signalling by limiting chondrocyte catabolic activities such as MMP13 production. "Further research is needed to characterize the role of hypoxia in OA and to verify whether HIF1α represents a valid therapeutic target," concludes Cohen-Solal.

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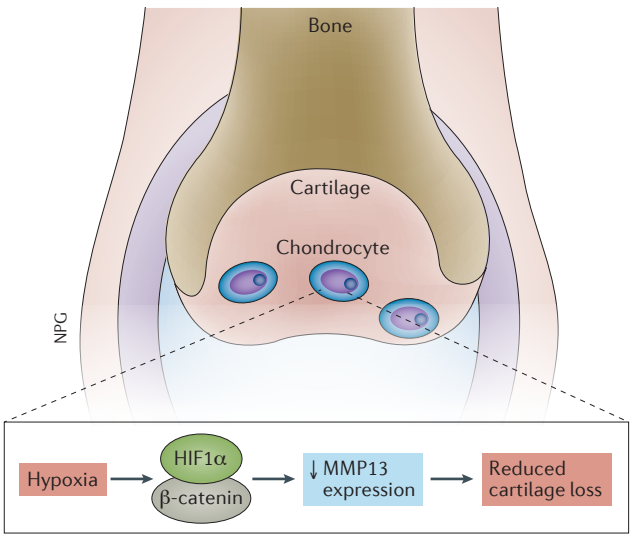

ORIGINAL ARTICLE Bouaziz, W. *et al.* Interaction of HIF1α and β-catenin inhibits matrix metalloproteinase 13 expression and prevents cartilage damage in mice. *Proc. Natl Acad. Sci. USA* http://dx.doi.org/10.1073/pnas.1514854113