OSTEOARTHRITIS

HIF-2 α drives osteoarthritis development

The pathogenesis of osteoarthritis (OA) involves endochondral ossification, a physiological mechanism in which avascular cartilage tissue converts into vascularized bone tissue as part of skeletal growth. This process is characterized by three fundamental steps—chondrocyte hypertrophy, cartilage degradation and vascular invasion, which involve the *COL10A1*, *MMP13* and *VEGFA* genes, respectively. Evidence from two studies in *Nature Medicine* now suggests that hypoxia-inducible factor 2 α (HIF-2 α), a protein known to be expressed in both hypoxic and vascularized tissues, is a central mediator of endochondral ossification and can promote OA development.

Taku Saito and colleagues, from the University of Tokyo, Japan, screened mouse chondrogenic ATDC5 cells and HeLa cells (harboring a *COL10A1* promoter fragment) with a panel of transcription factors, and identified HIF-2 α as the strongest activator of the *COL10A1* promoter. Further analysis revealed that the expression of *Epas1*, the gene encoding HIF-2 α , is increased during the differentiation of ATDC5 cells, as are the endochondral ossification-related mouse genes *Col10a1*, *Mmp13* and *Vegfa*. Furthermore, *Epas1*^{+/-} mice—which show growth retardation in embryogenesis and early life—had decreased *Col10a1*, *Mmp13* and *Vegfa* gene expression in their chondrocytes in comparison with wild-type mice, which could be restored by adenoviral overexpression of HIF-2 α .

Using an OA model in which instability is induced in the knee of wild-type and *Epas1*^{+/-} mice, the investigators noted that HIF-2 α deficiency caused a reduction in cartilage degradation, osteophyte formation and *Col10a1*, *Mmp13* and *Vegfa* gene expression. Furthermore, through sequence analysis of data from a Japanese cohort, the research team found a significant association ($P=0.013$) between knee OA and the presence of a single nucleotide polymorphism in the human *EPAS1* gene. Expression of

EPAS1 is driven by the p65 subunit of the transcription factor NF κ B, as determined by screening assays and site-directed mutagenesis. The authors hypothesize that mechanical stress might induce the NF κ B–HIF-2 α signal in joint cartilage, which then drives pathological endochondral ossification through the expression of *COL10A1*, *MMP13* and *VEGFA*. “The NF κ B–HIF-2 α signal controls not only the initial chondrocyte hypertrophy, but also subsequent cartilage degradation and vascular invasion steps of endochondral ossification in osteoarthritis, and so this signal might represent a therapeutic target,” explains Hiroshi Kawaguchi, the study’s lead investigator.

In a separate study, Siyoung Yang and co-workers, from three centers in Korea, identified *EPAS1* as a gene induced under pathological conditions by screening the human OA cartilage UniGene library. They subsequently showed *Epas1* to be upregulated in primary mouse chondrocytes treated with proinflammatory cytokines.

Further analysis demonstrated that HIF-2 α mediates the interleukin-1 β -induced expression of various catabolic factors in primary rabbit chondrocytes, including *MMP1*, *MMP3*, *MMP9*, *MMP12*, *MMP13*, *ADAMTS4*, *NOS2* and *PTGS2*. Indeed, expression of these factors could be enhanced by ectopic expression of *Epas1* and, conversely, blocked through the use of *Epas1*-specific small interfering RNA.

To examine the role of HIF-2 α in human disease, the researchers compared damaged and undamaged cartilage from 20 individuals with OA, and found elevated *EPAS1* messenger RNA and HIF-2 α protein levels in the damaged tissue. Expression of *EPAS1*, *MMP1*, *MMP9*, *MMP12*, *MMP13*, *ADAMTS4*, *NOS2* and *PTGS2* was also higher in damaged osteoarthritic cartilage compared with nonosteoarthritic control cartilage. Furthermore, the investigators could directly induce cartilage destruction

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by injecting *Epas1* into mouse and rabbit knee joints, strongly suggesting that the elevated levels of HIF-2 α observed in human osteoarthritic cartilage are critical in the pathogenesis of the disease.

Collectively, these studies present a novel role for HIF-2 α in endochondral ossification and the development of OA. Although *Epas1*^{+/-} mice displayed growth retardation in early life, they had no gross abnormalities of major organs, suggesting that inhibition of HIF-2 α activity might be a viable therapeutic option for OA with minimal adverse effects on normal skeletal growth. Indeed, efforts to target the NF κ B–HIF-2 α signal are underway. “We are now searching for the extracellular signal that lies upstream of HIF-2 α and either directly activates or suppresses it, because an extracellular protein might be easier to target than an intracellular transcription factor like HIF-2 α ,” says Kawaguchi.

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Original articles Saito, T. *et al.* Transcriptional regulation of endochondral ossification by HIF-2 α during skeletal growth and osteoarthritis development. *Nat. Med.* 16, 678–687 (2010) | Yang, S. *et al.* Hypoxia-inducible factor-2 α is a catabolic regulator of osteoarthritic cartilage destruction. *Nat. Med.* 16, 687–694 (2010)