TARGET IDENTIFICATION

HIF2α central player in osteoarthritis

Osteoarthritis represents the most common form of arthritis. As the underlying process leading to cartilage destruction in osteoarthritis is poorly understood, current treatments are restricted to symptomatic relief. Now, two papers in *Nature Medicine* identify the transcription factor hypoxia-inducible factor 2α (HIF2α) as a central mediator of osteoarthritis development, providing important clues for deciphering the molecular processes underlying disease formation.

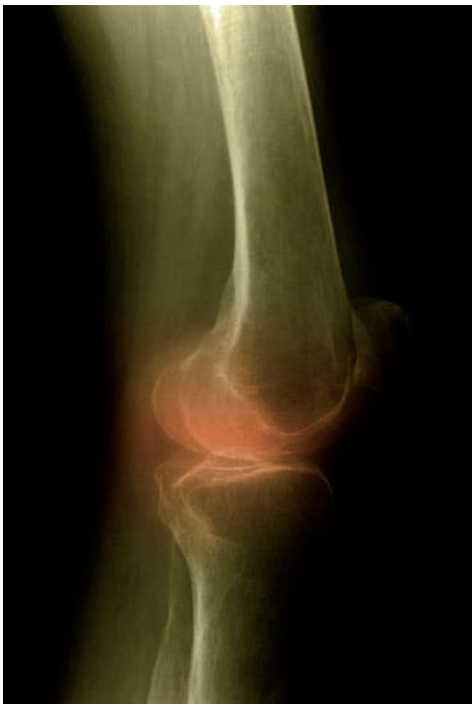
Cartilage destruction in osteoarthritis is known to be caused by an imbalance between the anabolic and the catabolic factors produced by chondrocytes, the unique cells that also synthesize cartilage-specific extracellular matrix components. The central steps in disease development are chondrocyte hypertrophy, followed by cartilage degradation and vascularization, leading to endochondral ossification.

Yang and colleagues used virtual screening of the human osteoarthritic cartilage UniGene library, followed by *in vitro* analysis of chondrocytes under pathological conditions, to find possible regulators of these processes. HIF2α was found to be induced by interleukin-1β (IL-1β) and other pro-inflammatory cytokines. Ectopic expression of HIF2α in primary chondrocytes resulted in an upregulation of catabolic regulators, including a range of matrix metalloproteinases known to be involved in osteoarthritic cartilage destruction. Conversely, a knockdown of HIF2α blocked IL-1β-induced expression of these catabolic factors.

In vivo experiments demonstrated that ectopic expression of HIF2α in mouse knee joints induced severe cartilage destruction, and similar results were obtained in transgenic mice with chondrocyte-specific overexpression of the HIF2α gene *Epas1*. Conversely, mice in which HIF2α was knocked down by small interfering RNA, as well as in mice with a heterozygous deletion of *Epas1*, were found to be resistant to experimental methods of osteoarthritis induction. The authors also examined HIF2α expression in osteoarthritic patients undergoing arthroplasty, and found that HIF2α levels were higher in damaged compared with undamaged areas of cartilage from the same patient.

Similar findings were reported by Saito and colleagues, who identified HIF2α in a screen for factors that induce the expression of type X collagen, which has a central role in endochondral ossification both in normal skeletal growth and in osteoarthritis development. The authors carried out an extensive analysis of HIF2α protein expression during chondrocyte differentiation, as well as an in-depth analysis of the molecular network around HIF2α in endochondral ossification. The physiological role of HIF2α in skeletal development, as well as its role in disease, was addressed in homozygous and heterozygous *Epas1* knockout mice. Interestingly, the authors also identified a sequence variation in the human *EPAS1* gene that shows an association with knee osteoarthritis.

Both studies identified pro-inflammatory cytokines, as well as the nuclear factor-κB (NF-κB) as upstream regulators of HIF2α. They also demonstrated that HIF2α is an extensive transcriptional regulator



of a wide range of downstream targets involved in the development of osteoarthritis. Mechanical stress may trigger disease by inducing NF-κB signalling and HIF2α expression in joint cartilage, leading to the transactivation of endochondral ossification-related molecules. Signals in the HIF2α axis could therefore represent exciting new targets for therapeutic strategies to abrogate cartilage destruction in osteoarthritis.

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ORIGINAL RESEARCH PAPERS Yang, S. *et al.* Hypoxia-inducible factor-2α is a catabolic regulator of osteoarthritic cartilage destruction. *Nature Med.* **16**, 687–693 (2010) | Saito, T. *et al.* Transcriptional regulation of endochondral ossification by HIF-2α during skeletal growth and osteoarthritis development. *Nature Med.* **16**, 678–686 (2010)