HIF-1α: linking subchondral bone and cartilage as a therapeutic target in osteoarthritis

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Recent studies have identified subchondral bone deterioration as a critical factor in the degeneration of the overlying articular cartilage. This relationship is linked to abnormalities in the subchondral bone microenvironment and remodelling processes during osteoarthritis (OA). These processes include mechanical stimulation signals, chondrocyte apoptosis, matrix degradation, H-type vessel formation, and a complex balance between osteoclasts and osteoblasts, as well as the growth of sensory nerve axons.[1] Osteoclast overactivity and vascular invasion in subchondral bones are closely associated with abnormal bone remodelling and the progression of OA.[2]

Therefore, much research has been devoted to OA treatments that target osteoclast overactivation and H-type blood vessel proliferation in subchondral bone. However, osteoclast inhibition therapies, notably bisphosphonates, are controversial. In preclinical animal OA models, such drugs have shown significant protective effects on cartilage.[3] However, clinical trials have failed to show a significant improvement in pain, structure, or function in patients with OA compared with patients receiving placebo.[4] A possible plausible explanation is that bisphosphonates may be more suitable for OA patients with high bone turnover.

Similarly, as another potential therapeutic target for OA treatment, invasion of the vasculature has negative impacts on cartilage homeostasis. Endogenous knockout of angiogenesis-related factors such as platelet-derived growth factor-BB, as well as the use of exogenous vascular inhibitory drugs, can effectively prevent surgically induced OA progression by inhibiting subchondral vascularisation.[5-7] However, a potential issue is that osteoclast activation is often a normal physiological response to abnormal mechanical stress and microstructural damage within the subchondral bone, which triggers H-type angiogenesis. Although inhibiting H-type vessel formation might provide temporary relief from the adverse effects of blood vessels and oxygen on cartilage, it is uncertain whether such inhibition adversely affects osteogenesis-angiogenesis coupling and the normal physiological repair of subchondral bone microstructural damage. This might lead to long-term cartilage damage induced by abnormal mechanical signalling.

In a recent publication in *Science Advances*, Zhang et al.[8] underscored the significant role of hypoxia-inducible factor-1 alpha (HIF-1α) degradation in the degeneration of cartilage associated with OA. This study utilised both *HIF-1α* knockdown and *HIF-1α* stabilisation strategies (with dimethyloxalylglycine) in lymphocyte cytosolic protein 1 (*Lcp1*)-deficient and wild-type OA mouse models. Knockout of the *Lcp1* gene hinders angiogenesis, preserves a hypoxic environment within the joint, and decelerates OA progression.[9] Zhang et al.'s research[8] revealed that HIF-1α impacts articular cartilage independent of alterations in subchondral bone. Despite the decrease in bone remodelling attributed to *Lcp1* knockout, *HIF-1α* silencing accelerated the degeneration of articular cartilage and negated the protective effect in $Lcp1^{-/-}$ anterolateral cruciate ligament transection mice. Conversely, in wild-type anterolateral cruciate ligament transection mice, with a nonhypoxic environment with unhindered subchondral bone remodelling, dimethyloxalylglycine stabilised *HIF-1α* and decelerated OA progression.

Numerous studies have shown that HIF-1α is essential for the energetics, matrix synthesis, and functionality of chondrocytes in both normal and osteoarthritic cartilage. The deactivation of HIF-1α in OA models has been associated with increased chondrocyte apoptosis. Stabilising HIF-1α boosts the activity of sex-determining region Y-box 9, a crucial factor for the differentiation of mesenchymal stem cells into chondrocytes, and also diminishes hypertrophy and aids metabolic adaptation in

hypoxic environments, thereby playing a significant role in protecting articular cartilage. Furthermore, HIF-1α is vital for sustaining anaerobic glycolysis and boosting extracellular matrix synthesis. Consequently, stabilising HIF-1α effectively prevents chondrocyte apoptosis and degradation of the extracellular matrix, which leads to increased extracellular matrix synthesis and enhanced chondrocyte differentiation (**Figure 1**).[10]

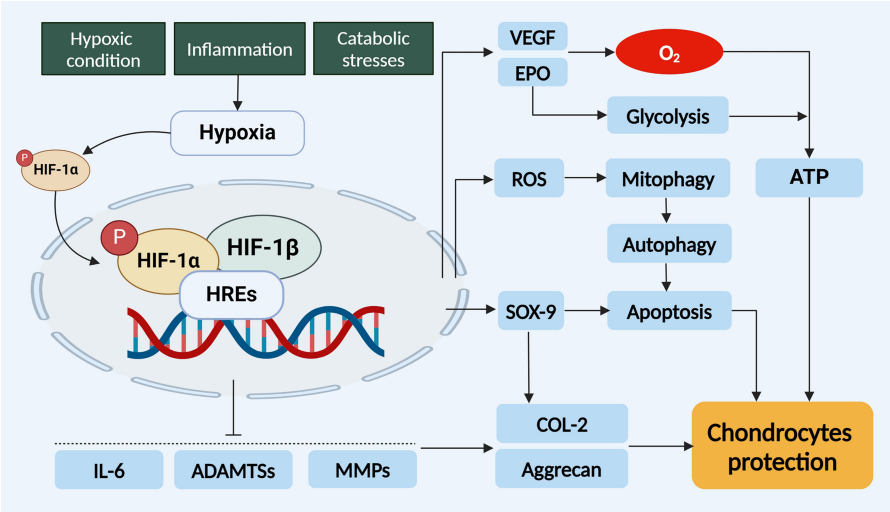

Figure 1. Regulatory mechanisms of hypoxia signalling and HIF-1α on chondrocytes of OA. Reprinted from Zeng et al.[10] ADAMTS: a disintegrin and metalloproteinase with thrombospondin motifs; ATP: adenosine triphosphate; COL-2: type II collagen; EPO: erythropoietin; HIF-1α: hypoxia-inducible factor-1 alpha; HRE: hypoxia response element; IL-6: interleukin-6; MMP: matrix metalloproteinase; ROS: reactive oxygen species; SOX-9: SRY (sex determining region Y)-box transcription factor 9; VEGF: vascular endothelial growth factor.

Although HIF-1α has a positive effect on cartilage, its impact on subchondral bone turnover remains unclear. Zhang et al.'s further investigation[8] indicated that neither knockdown nor stabilisation of HIF-1α markedly influenced subchondral bone remodelling, H-type vessel formation, or sensory nerve innervation. The role of HIF-1α in bone turnover, especially in osteoclastogenesis, is complex and has yielded inconsistent results across various studies. While some studies have reported increased differentiation and fusion following HIF-1α stimulation, others have reported decreases in differentiation and fusion.[10] Although these findings are conflicting, it is acknowledged that HIF-1α enhances the resorptive activity of osteoclasts.[11] This makes the strategy of stabilising HIF-1α contradictory to approaches that inhibit osteoclast activity. However, HIF-1α-induced vascular endothelial growth factor-related angiogenesis leads to a high-oxygen environment, which, when combined with osteoblast-mediated modulation of the receptor activator of nuclear factor-kappa B ligand-to-osteoprotegerin ratio, can suppress the continuous activation of osteoclasts.[12, 13] Furthermore, stabilising HIF-1α, as opposed to directly inhibiting vascularization, not only protects cartilage but also prevents the disruption of osteogenesis-angiogenesis coupling in the normal physiological bone turnover process. This finding aligns with Zhang et al.'s finding,[8] emphasising the complex role of HIF-1α in the pathology and treatment of OA.

In summary, in OA models, cartilage degeneration persists and worsens even after a significant reduction in the number of osteoclasts. Moreover, the findings of Zhang et al.[8] underscore the significance of the timing of interventions for OA treatment. The optimal window for administering anti-osteoclast agents is in the initial stages of OA, when osteoclast activity is significantly heightened. However, during the advanced stages of OA development, these agents prove ineffective in reversing the formation of H-type vessels or disrupted hypoxic conditions within the joint. Consequently, maintaining a hypoxic environment in cartilage and stabilising HIF-1α in chondrocytes is a viable approach to potentially delaying the progression of OA, regardless of alterations in the subchondral bone. This approach highlights the critical importance of timing and targeting in anti-osteoclastic and HIF-1α-stabilising interventions. Despite some uncertainties, targeting HIF-1α continues to be a promising direction for future research and treatment strategies in OA.

Author contributions

WF: Conceptualization, resources, writing-review & editing, supervision, project administration; KZ: writing-original draft, review & editing. Both authors approved the final version of the manuscript.

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The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this work.
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