Commentary

The role of HIF-1α in maintaining cartilage homeostasis and during the pathogenesis of osteoarthritis

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Abstract

As a consequence of the avascular nature of cartilage the microenvironment in which chondrocytes must exist is characterized by hostile conditions, most prominently very low levels of oxygen (hypoxia). In recent years, a vast number of papers reporting on the role of hypoxia in cartilage development and disease has been published. It is well established today that the principal mediator of cellular adaptation to hypoxia, the transcription factor hypoxia inducible factor (HIF)-1, is of pivotal importance for survival and growth arrest of chondrocytes during cartilage development as well as energy generation and matrix synthesis of chondrocytes in healthy as well as osteoarthritic cartilage. With this commentary we aim to briefly discuss the recently published literature in this field.

A recent study published in *Arthritis Research & Therapy* described that in articular chondrocytes catabolic and hypoxic stress are strong inducers of the transcription factor hypoxia-inducible factor (HIF)-1, which is the principal regulator of cellular adaptation to low oxygen levels [1]. Oxygen serves as a fundamental prerequisite for energy generation by oxidative phosphorylation. Cellular survival and function is significantly influenced by the distance to the capillary network, as the diffusion capacity of oxygen sharply decreases after about 200 μm. This phenomenon is of particular importance for avascular tissues like articular and epiphyseal cartilage. Previous studies have shown an average oxygen partial pressure of 40 to 50 mmHg in synovial fluids of normal joints, demonstrating the hypoxic nature of the articular chondrocytes' microenvironment [2-4]. Interestingly, osteoarthritic joints displayed further decreased oxygen levels, arguing for a causal, or at least supportive, role of hypoxia during the pathogenesis of osteoarthritis (OA) [3,4].

HIF-1, as the key molecule in the adaptive response of cells and tissues to low oxygen levels, is responsible for increased expression of erythropoietin, glucose transporters, glycolytic enzymes, pro-angiogenic factors and several other molecules involved in apotosis and cell proliferation [5]. Several groups have demonstrated that HIF-1 is of pivotal importance in a diverse set of physiological and pathological conditions such as tumorigenesis, inflammation, cell survival in ischemic tissues and development of the growth plate as well as other organ systems [6,7]. The active subunit HIF-1α confers oxygen responsiveness and is hydroxlyated by oxygen sensitive prolyl-hydroxylases (PHD1-3) under normoxic conditions, followed by targeting of the von Hippel-Lindau protein and degradation through the proteasome [5]. In many cell types, oxygen levels lower then 6% lead to nuclear accumulation of HIF-1α and heterodimerization with HIF-1β (also known as ARNT (aryl hydrocarbon nuclear translocator)). The so-formed HIF-1 complex binds to hypoxia responsive elements of target genes, thereby regulating their transcription.

By real-time PCR analyses, Yudoh and colleagues [1] have demonstrated that HIF-1α transcripts are increased in degenerated cartilage compared to macroscopically intact cartilage within one joint. These novel and important findings confirm our own studies and those of other groups on the presence and distribution of HIF-1α and its target genes (encoding phosphate glycerate kinase-1, glucose transporter-1 and vascular endothelial growth factor (VEGF)-A) that show an increased number of chondrocytes stainable for the transcription factor and its target genes during the course of OA [8-10]. The authors further extended their investigation on the role of HIF-1 by performing several *in vitro* experiments confirming previous studies by us and other independent groups. In these previous studies, it has been shown that HIF-1α accumulates and translocates into the nucleus after exposing chondrocytes to low oxygen levels and inflammatory cytokines [11-13]. In addition, Pufe and colleagues [14] have

HIF = hypoxia inducible factor; OA = osteoarthritis; VEGF-A = vascular endothelial growth factor A.

reported that mechanical overload of bovine cartilage discs leads to an increased expression of VEGF-A via HIF-1. In conclusion, the α-subunit of HIF-1 is stabilized and HIF-1 activity is significantly increased in chondrocytes by hypoxic, inflammatory and mechanical stress. Thus, in articular chondrocytes, HIF-1 acts not solely as a hypoxia-inducible transcription factor, but seems to constitute a stress-inducible factor eventually protecting articular chondrocytes from potentially deleterious microenvironmental conditions.

Using RNA-interference, Yudoh and colleagues [1] further analyzed the role of HIF-1 in chondrocytic energy generation, matrix synthesis and cell survival. During hypoxic and normoxic conditions, functional inactivation of HIF-1α in the presence of interleukin-1β resulted in a significantly increased number of apoptotic chondrocytes. These *in vitro* data are in accordance with the *in vivo* observations described by Schipani and colleagues [15]. Loss of HIF-1α in all cartilaginous elements using the Cre/loxP-technology of conditional tissue knock-out led to distinctive defects in the center of most long bone growth-plates reaching from the articular cap to the hypertrophic zone. In addition, Schipani and colleagues demonstrated that HIF-1α null chondrocytes around these central defects of murine growth-plates were not able to survive this developmental hypoxia and underwent massive cell death [15]. Thus, the work by Yudoh and colleagues adds further experimental evidence for the suggested role of HIF-1 in protecting chondrocytes from cell death induced by pro-inflammatory cytokines. Finally, Yudoh and colleagues showed that HIF-1α is necessary for anaerobic energy generation and proteoglycan synthesis by articular chondrocytes, an observation that confirms our previously published data using murine growth plate chondrocytes [11].

Conclusion

The results provided in the study by Yudoh and colleagues and previous reports by us and other groups strongly support the notion that HIF-1 is of pivotal importance in cartilage development and homeostasis. Furthermore, given the decreased oxygen levels and presence of inflammatory mediators during the course of OA, a causal role for HIF-1 in preventing cartilage damage is reasonable to assume. It seems likely that OA chondrocytes, which are metabolically activated, rely on HIF-1 to instigate anaerobic ATP generation via increased glucose uptake and utilization in order to compensate for the accelerated energy consumption during OA. In conclusion, the study by Yudoh and colleagues, in concert with previous reports, further characterized HIF-1 as a central factor for chondrocyte survival amidst the hostile microenvironmental conditions of OA, most prominently hypoxia, low pH, high lactic acid concentration and exposure to inflammatory cytokines.

Competing interests

The author(s) declare that they have no competing interests.

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