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LETTER TO THE EDITOR

Discrepant hypoxia tolerance aggravates subchondral delamination in osteonecrosis of the femoral head

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Dear Editor,

We read the themed issue on osteonecrosis of the femoral head (ONFH) recently published by *International Orthopaedics* with great interest. Several articles discussed subchondral fractures and the ischemia-hypoxia loop of ONFH [1, 2]. Essentially, discrepant hypoxia tolerance between cartilage and subchondral structure aggravates subchondral delamination, which is a unique pathological feature of ONFH [3]. The mechanical failure of the femoral head is attributed to the disordered biological consequences.

Articular cartilage is devoid of blood vessels and subject to a harsh biomechanical environment. Articular chondrocytes (ACs) depend primarily on anaerobic metabolism, nourished by diffusion from the synovial fluid. ACs have been shown to be well adapted to the low oxygen conditions, which are embedded in an extensive extracellular matrix and exposed to a concentration of approximately 6% O_2 in the superficial layer, as well as the calcified layer less than 1% [4]. Moreover, increasing evidence suggests hypoxia not only promotes cartilage matrix formation and AC survival ability, but also benefits differentiation of mesenchymal stem cells (MSCs) toward chondrogenic lineage [5]. On the other hand, high pO_2 levels are osteogenic, showing that bone formation is dependent on a rich vascular supply. Previous studies demonstrated that hypoxia has profound inhibitory effects on osteoblasts, while strongly stimulates the number and size of osteoclasts. Ambient pO_2 levels below 2% result in near complete abolition of bone formation by inhibiting osteoblasts; conversely, osteoclastogenesis is elevated even in cultured gassed with 0.2% pO_2. The inhibition of osteogenesis in hypoxia is due to reductions in both growth and differentiation of osteoblasts, with inhibition of cell proliferation, collagen production, and alkaline phosphatase activity. The incidence of osteocytic and osteoblastic apoptosis is significantly increased in the femoral head during osteonecrosis, with the prolonged lifespan of osteoclasts. During the repair process, the imbalance between osteoclast-mediated bone resorption and osteoblast-mediated bone formation results in structural damage and collapse of the femoral head.

The crucial mediator of the adaptive response of cells to hypoxia is the transcription factor, hypoxia-inducible factor-1 (HIF-1), reported to be a key mechanism for coupling bone growth to angiogenesis, via increased expression of VEGF. Under hypoxia conditions, HIF-1α protein accumulates, translocates to the nucleus, and dimerizes with HIF-1β. The vessel formation increases in cartilage after ischemia induction in pig femoral head, with the upregulation of VEGF in chondrocytes mediated partially through HIF-1α. Moreover, the upregulation of VEGF may play an important role in stimulating the repair of the necrotic hypertrophic zone of the epiphyseal cartilage, as an essential step before endochondral ossification can be stored. HIF-1α activates Sox9 expression and enhances Sox9-mediated transcriptional activity following femoral head ischaemia, which may have a chondroprotective role.

Referring to the existing studies on hypoxia and HIF-1α in chondrogenesis and osteogenesis, a discrepant hypoxia tolerance between cartilage and subchondral structure can result in the detachment of cartilage and subchondral delamination in ONFH. The novel clue sheds light on the unique histopathological changes in ONFH, guiding us to develop ideal approaches to treat ONFH through modulation of discrepant tolerance of hypoxia.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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