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The potential role and trend of HIF-1α in intervertebral disc degeneration: Friend or foe? (Review)

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Abstract. Lower back pain (LBP) is one of the most common reasons for seeking medical advice in orthopedic clinics. Increasingly, research has shown that symptomatic intervertebral disc degeneration (IDD) is mostly related to LBP. This review first outlines the research and findings of studies into IDD, from the physiological structure of the intervertebral disc (IVD) to various pathological cascades. The vicious cycles of IDD are re-described in relation to the analysis of the relationship among the pathological mechanisms involved in IDD. Interestingly, a 'chief molecule' was found, hypoxia-inducible factor-1α (HIF-1α), that may regulate all other mechanisms involved in IDD. When the vicious cycle is established, the low oxygen tension activates the expression of HIF-1α, which subsequently enters into the hypoxia-induced HIF pathways. The HIF pathways are dichotomized as friend and foe pathways according to the oxygen tension of the IVD microenvironment. Combined with clinical outcomes and previous research, the trend of IDD development has been predicted in this paper. Lastly, an early precautionary diagnosis and treatment method is proposed whereby nucleus pulposus tissue for biopsy can be obtained through IVD puncture guided by B-ultrasound when the patient is showing symptoms but MRI imaging shows negative results. The assessment criteria for biopsy and the feasibility, superiority and challenges of this approach have been discussed. Overall, it is clear that HIF-1α is an indispensable reference indicator for the accurate diagnosis and treatment of IDD.

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Contents

1. Introduction

Lower back pain (LBP) is one of the most common reasons for seeking medical advice in orthopedic clinics. World Health Organization statistics revealed that patients with LBP cost up to 100 billion dollars each year in the United States (1). According to a report, 68-85% of individuals worldwide experience LBP at least once in their lifetime (2) and 5% ultimately go on to develop chronic LBP (CLBP) (3). This is associated with severe pain and disability, and is a heavy economic burden on society (4). Increasingly, studies have shown that one of the main symptoms associated with intervertebral disc (IVD) degeneration (IDD) is CLBP (5-8). A number of researchers have reported that genetic factors accounted for >68% of the pathogenic factors that are associated with IDD, although a variety of factors can lead to IDD (9-11). IDD is the pathological basis of disc herniation, and it is likely to increase the susceptibility of disc herniation (12,13). The spontaneous disappearance, or decrease in size, of a herniated disc in patients displaying clinical symptoms have been reported on numerous times in the past, but there has been an increasing number of cases, even in patients showing large herniated discs (14-16). One of the common features of these patients is that the individuals are relatively young and it was observed that herniated disc tissue retraction, or even disappearance through MRI (14-16). Recently, Gao *et al* (16) reported on a woman in her 40s whose herniated disc tissue self-absorbed 8 months after the initial diagnosis of lumbar disc herniation. This phenomenon cannot be explained by biomechanics. Therefore, exploring the mechanism of IDD from a genetic perspective is necessary in order to solve the current clinical problems of CLBP

Anatomically, the IVD consists of the central nucleus pulposus (NP) enriched in proteoglycans, the peripheral annulus fibrosus (AF), and the endplates of hyaline cartilage at the upper and lower ends (17). From the cross-section, IVD can be observed as four concentric areas: The outer AF; the inner AF; the transition zone; and the central NP (18). The IVD is essentially an avascular structure because vascular structures are only visible in the outer AF; they are not in NP tissue and these structures are separated by a thick layer of avascular AF (19). Blood vessels from the lumbar artery terminate at the cartilage endplate, with only a small amount of blood vessels infiltrating the cartilage endplate and the outer third of the AF zone, but none of these vessels penetrate the NP and inner AF (17,20,21). NP cells (NPCs) are morphologically analogous to chondrocytes, and have similar histological and physiological structures to the articular cartilage (22). Therefore, NPCs are largely dependent on capillary diffusion through the cartilage endplates for oxygen exchange, nutrient acquisition and metabolic waste transport (23,24). In addition to the complex structure, there is an oxygen concentration gradient around the avascular IVD where the partial pressure of oxygen in the IVD central region is as low as 1% (25). The oxygen partial pressure of degenerate tissue is lower than that of normal IVD tissue (26). Accumulating evidence has revealed that hypoxic environments play a crucial role in maintaining the physiological functions of IVDs, including cell metabolism and matrix synthesis (4,21,27-29). Therefore, NPCs adapt to survive in hypoxic microenvironments under physiological conditions (23). This hypoxic environment may affect the activity of a series of genes related to cell adaptation for survival in hypoxic microenvironments (24). Hypoxia-inducible factor-1α (HIF-1α) is one of the most essential transcriptional regulators of cell adaptation to hypoxic environments (30). Feng *et al* (28,29) found that the expression of HIF-1α in human NPCs was significantly increased under hypoxic conditions compared with normoxic conditions. Richardson *et al* (31) demonstrated that HIF-1α was markedly expressed in degenerative IVD tissue.

HIF-1α is ubiquitously expressed in almost all cells in the human body. Benita *et al* (32) proposed that HIF-1α has the potential to regulate 81 genes under hypoxic conditions in a number of cell types. It has also been found to play a vital role in the occurrence and progression of numerous diseases, including myocardial-cerebral ischaemia (33-35), tumours (33,36) and chronic degenerative diseases (4,21,29,37-39). IDD is identified as the most common chronic spinal degenerative disease; the pathogenesis of IDD is mainly related to the destruction of cells, in terms of both biochemistry and structure (24,40). Thus far, the mechanisms of HIF-1α in IDD have been widely reported. HIF-1α is a marker of NPCs involved in: The synthesis and catabolism of the extracellular matrix (ECM) (4,28,29,41); promoting angiogenesis (41,42); regulation of NPC apoptosis (43); inflammatory responses (41); provision of NPC energy metabolism (31,44); modulation of NPC autophagy (45); NPC transplantation (46,47); regulation of extracellular dystrophic calcification of NP (48); and regulation of the expression of matrix metalloproteinases (MMPs) (49-52). However, in addition, a comprehensive analysis of HIF-1α in other tissues or cells found that HIF-1α may also influence the occurrence and progression of IDD by participating in the process of spontaneous absorption of herniated disc tissue (52) and regulatory networks of non-coding RNAs (Tables I and II) (53). Despite extensive research in this area, the precise mechanism of IDD remains mostly unknown. Therefore, this article summarizes the reported findings on the potential role and possible mechanisms of HIF-1α in IDD, as well as predicting the trends in development. Moreover, an early precautionary diagnosis and treatment method has been proposed.

2. HIF families

HIFs belong to the Per-Arnt-Sim family; they are heterodimeric proteins composed of α and β subunits. The α subunit predominantly determines the activity of HIF, which is regulated by the oxygen-dependent degradation (ODD) domain in its central region, and thus can regulate gene expression depending on the level of oxygen tension (54). The β subunit is expressed in the nucleus, where it has roles in maintaining the stability of HIF structure and biofunctions, but it is not regulated by oxygen tension (55). There are three isoforms of HIF-α, HIF-1α, HIF-2α and HIF-3α (56-58). HIF-1α and HIF-2α have similar mechanisms of action in different cell types because they have extensive sequence homology and contain two ODD domains (56). Therefore, they are closely related to each other and can activate gene transcription that is dependent on the hypoxia responsive elements (HREs) (56). HIF-3α has a unique structure, containing only one ODD domain; it is spliced selectively and modulated via HIF-1α (57,58). A number of studies have shown that the metabolism of HIF-α is associated with oxygen concentration in numerous cell types (33,34,36). Under normoxic conditions, the α subunit is hydroxylated and subsequently activates prolyl hydroxylase (PHD), which is then rapidly degraded via the ubiquitin-proteasome pathway (33). However, when the cells are exposed to hypoxic-ischaemic conditions, PHD activity is reduced and the degradation of the α subunit is inhibited (33,59). Thus, HIF-1α rapidly expands and gradually accumulates in the cytoplasm (33,59). Then, it enters the nucleus and binds to HIF-1β to form an ectopic dimer, HIF-1, which recognizes and binds to the conserved sequence of HREs to activate the transcription of target genes (60). The α subunits of HIF-1α and HIF-2α have non-overlapping regions that have different biofunctions and even completely converse effects. Firstly, HIF-1α is ubiquitously expressed in almost all cells in the human body, while HIF-2α appears to be expressed in specific tissues, mainly the lung, heart, kidneys and liver in adults (61,62). Secondly, HIF-1α, but not HIF-2α, has been shown to markedly regulate the expression of the key enzymes involved in the glycolytic pathway (44). Furthermore, HIF-1α exclusively regulates adenosine triphosphate (ATP) production and mediates macrophage migration, infiltration and bacterial

Table I. HIF-1α is involved in the regulatory network of non-coding RNAs.

Author, year	RNA type	Tissues/cells	Signal pathways	Investigated processes	(Refs.)
Liu *et al*, 2015	miRNAs	Rat brain	miR-335/HIF-1α	Death	(35)
Serocki *et al*, 2018		Various endothelial cells	miR-155 and miR-18a/HIF-1α	Angiogenesis and hypoxia; proliferation and migration	(188)
Wang *et al*, 2015	lncRNAs	Human nucleus pulposus cells	RP11-296A18.3/miR-138/HIF-1α	Proliferation and ECM synthesis	(53)
Bao *et al*, 2018		Human vascular endothelial cells	LINC00657/miR-590-3p/HIF-1α/VEGF/MMP2	Angiogenesis	(189)
Liang *et al*, 2017	circRNAs	Human breast cancer	circDENND4C/HIF-1α	Proliferation	(186)
Du *et al*, 2017		Human and mice hearts	circ-Foxo3/HIF-1α	Senescence	(187)
Dang *et al*, 2017		Human vascular endothelial cells	circ_0010729/miR-186/HIF-1α	Proliferation and apoptosis	(190)
Liu *et al*, 2017		Human osteosarcoma endothelial cells	circRNA_103801/HIF-1α/VEGF	Cancer pathway	(191)

HIF-1α, hypoxia-inducible factor-1α; ECM, extracellular matrix; VEGF, vascular endothelial growth factor; MMP2, matrix metalloproteinase 2; miR, microRNA; lncRNA, long non coding RNA; circRNA, circular RNA.

Table II. CircRNAs involved in intervertebral disc degeneration.

Author, year	CircRNAs	Expression	Cell type	Signal pathways	Investigated processes	(Refs.)
Guo *et al*, 2018	circ-GRB10	Downregulated	Human nucleus pulposus cell	circ-GRB10/miR-328-5p/ERBB2	Apoptosis	(192)
Cheng *et al*, 2018	circ-VMA21	Downregulated	Human and rat nucleus pulposus cell	circ-VMA21/miR-200c/XIAP	Apoptosis and inflammation	(125)
Wang *et al*, 2018	circ-4099	Upregulated	Human nucleus pulposus cell	circ-4099/miR-616-5p/Sox9	ECM synthesis and inflammation	(184)

ECM, extracellular matrix; miR, microRNA; circRNA, circular RNA; XIAP, X-linked inhibitor of apoptosis protein.

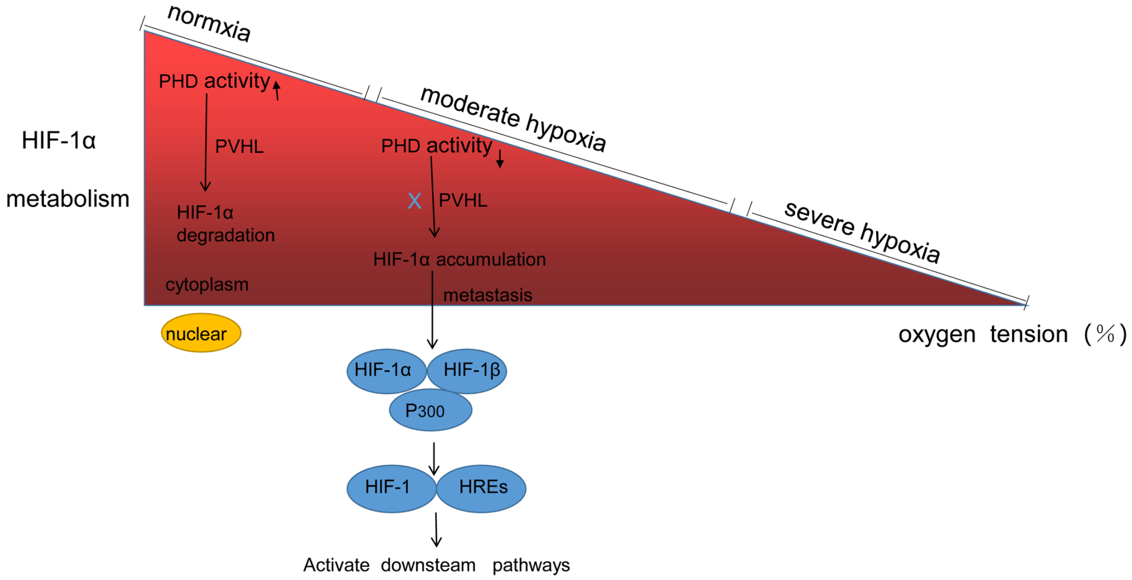

Figure 1. HIF-1α metabolism. HIF-1 belongs to the Per-Arnt-Sim family, heterodimeric proteins composed of α and β subunits. Under normoxia, the α subunit is hydroxylated and subsequently activates PHD, which is then degraded HIF-1α via pVHL. However, the PHD activity is reduced during moderate and severe hypoxia, following which the degradation of the α subunit is inhibited, so HIF-1α gradually accumulates in the cytoplasm. HIF-1α then enters the nucleus and binds to HIF-1β to form an ectopic dimer, HIF-1, which recognizes and binds to HREs to activate the downstream target genes. HIF-1α, hypoxia-inducible factor-1α; PHD, prolyl hydroxylase; HREs, hypoxia responsive elements; pVHL, protein von HippeI-Lindau.

killing during acute inflammation responses, while HIF-2α mainly mediates tumour-associated inflammation and appears to play a greater role than HIF-1α in cytokine production (63). Thirdly, the metabolism of HIF-1α and HIF-2α in NPCs is also different. PHD family members include PHD1, PHD2 and PHD3 (64). The degradation of HIF-1α and HIF-2α is mainly mediated by the 26S proteasome, which is not associated with oxygen tension (65). In addition, HIF-1α is mainly degraded by the oxy-PHD2 pathways, whereas the degradation of HIF-2α is associated with PHD3 pathways (21,65). Lastly, HIF-1α has an antitumour effect, but HIF-2α mainly promotes tumour progression (44,66). Therefore, it is more meaningful to study the mechanism of HIF-1α in IDD, and the metabolism of HIF-1α is shown in Fig. 1.

3. Vicious cycle pathways

It is generally hypothesized that disrupting the diffusion of oxygen, nutrients and metabolic waste in the IVD space is the most critical mechanism in the occurrence and progression of IDD (24,67). With the occurrence of IDD, the amount of water in the NP tissue is reduced, following which the diffusion of oxygen, nutrients and metabolic waste is restricted. The oxygen tension is lower in the IVD microenvironment in the wake of poor diffusion, following which the production of lactate is increased through anaerobic metabolism (24). The excretion of lactate is blocked so it gradually accumulates, decreasing the pH of the IVD microenvironment, which further affects cellular metabolism and biofunction (24). Thus, NPC quantity and viability is decreased, and the synthesis and decomposition of ECM are unbalanced; this imbalance decreases the intradiscal pressure, transforms the biomechanics from hydrostatic stress to shear stress and decreases the IVD height, which further aggravates the progression of IDD (24,40). Therefore, the first important vicious cycle is established. The low oxygen tension activates the expression of HIF-1α, which subsequently enters into the hypoxia-induced HIF pathways (Fig. 2). The HIF pathways are dichotomized as friend and foe pathways according to the oxygen tension of the IVD microenvironment (Figs. 3 and 4).

The second vicious cycle centers on cartilage endplate calcification (CEC). A previous study indicated that the degree of CEC is associated with the severity of IDD (68). When the water content in NP tissue decreases, pyknotic substances are deposited in the cartilage endplate, which gradually calcifies; the permeability of cartilage endplate declines and then enters into the vicious cycle (Fig. 2) (25,69). Notably, there is an association between angiogenesis and CEC, but the mechanism by which angiogenesis aggravates CEC remains unclear (70).

4. Potential role of HIF-1α

ECM metabolism. An IVD is a fibrous cartilage pad between the vertebral bodies that resists pressure from the spine and allows for slight movement of the spine (71). Peripheral AF cells and central NPCs from IVDs exhibit different morphology and functional expression. AF cells are similar to fibroblasts in morphology and contain higher levels of collagen type I (COL1), which accounts for ~68% of the dry weight of AF (67,71,72). NP is enriched in collagen type II (COL2) and proteoglycans; COL2 accounts for ~20% of the dry weight of NP, and aggrecan (ACAN) is the major component of proteoglycans, which constitute 50% of the wet weight of NP (22,71,72). ACAN contains a large quantity of chondroitin sulfate (CS), which primarily binds to water molecules and is responsible for maintaining the moisture and mechanical load of IVD; it is necessary for IVD to exert its physiological functions and bear stress (73-75). Collagen imparts tensile strength to IVD by forming a network of collagen fibres that encloses the proteoglycans (72). Therefore, it is more

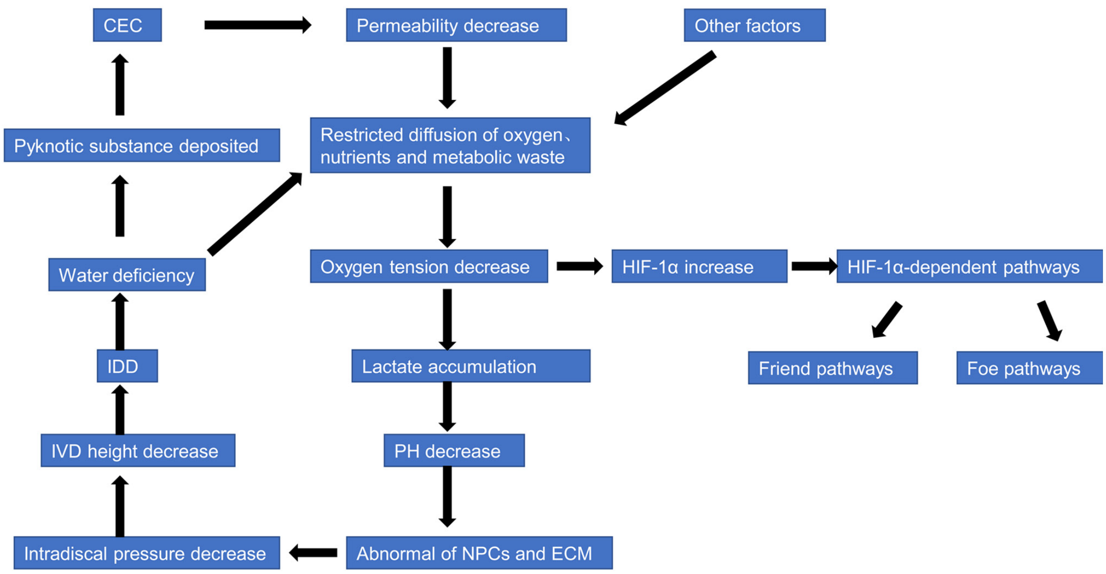

Figure 2. Vicious cycle pathways. The center of the vicious cycle pathways is restricted diffusion of oxygen, nutrients and metabolic waste. Two critical factors contributing to these restrictions are the decrease of cartilage endplate permeability and water deficiency of IVD. The oxygen tension is lower in the IVD microenvironment as a result of poor diffusion. This low oxygen tension establishes the vicious cycle pathways and promotes the expression of HIF-1α, which subsequently enters into the hypoxia-induced HIF pathways. The HIF pathways are dichotomized as friend and foe pathways according to the oxygen tension. IVD, intervertebral disc; HIF-1α, hypoxia-inducible factor-1α; CEC, cartilage endplate calcification; IDD, IVD degeneration; NPC, nucleus pulposus cells; ECM, extracellular matrix.

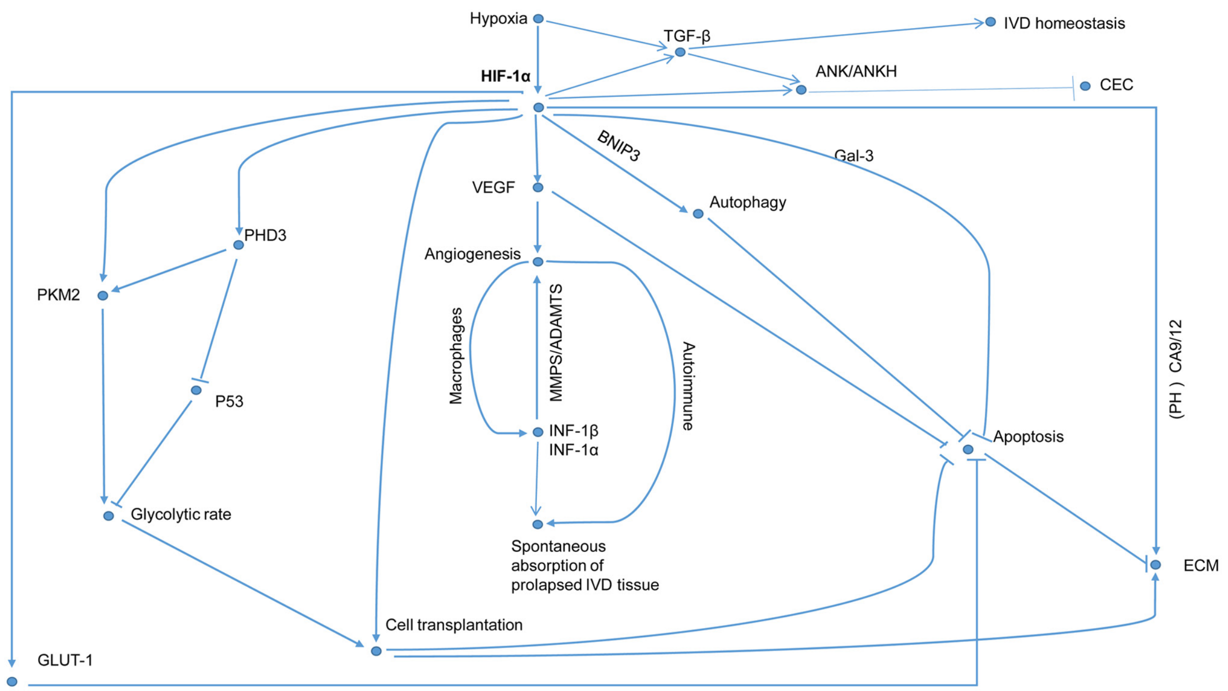

Figure 3. Friend pathways. During moderate hypoxia, the friend role of HIF-1α is increasingly reinforced as oxygen tension gradually decreases. There are a number of pathways in this process, but the end point is the upregulation of ECM synthesis. HIF-1α, hypoxia-inducible factor-1α; ECM, extracellular matrix; PKM2, pyruvate kinase M2; GLUT-1, glucose transporter 1; PHD3, prolyl hydroxylase 3; VEGF, vascular endothelial growth factor; INF-1, eukaryotic initiation factor 4A; MMPS, matrix metalloproteinases; ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; BNIP3, BCL2 interacting protein 3; TGF-β, transforming growth factor-β; IVD, intervertebral disc; ANK/ANKH, progressive ankylosis; Gal-3, galectin 3; CEC, cartilage endplate calcification; CA, carbonic anhydrase.

meaningful to study NPCs than AF cells. Interestingly, the content and distribution of various collagens changes with IDD, while IVD ageing will not cause this change. In the early stages of degeneration, collagen content usually increases in the region of its distribution (76,77). COL1 begins to appear in the nucleus, and collagen types IV and X can be detected with the aggravation of IDD; the expression of COL2 was not detected in the endplate (76,77). Accumulating evidence suggests that ECM plays an important role in supporting the NP-integrated structure and biofunctions, as well as mediating

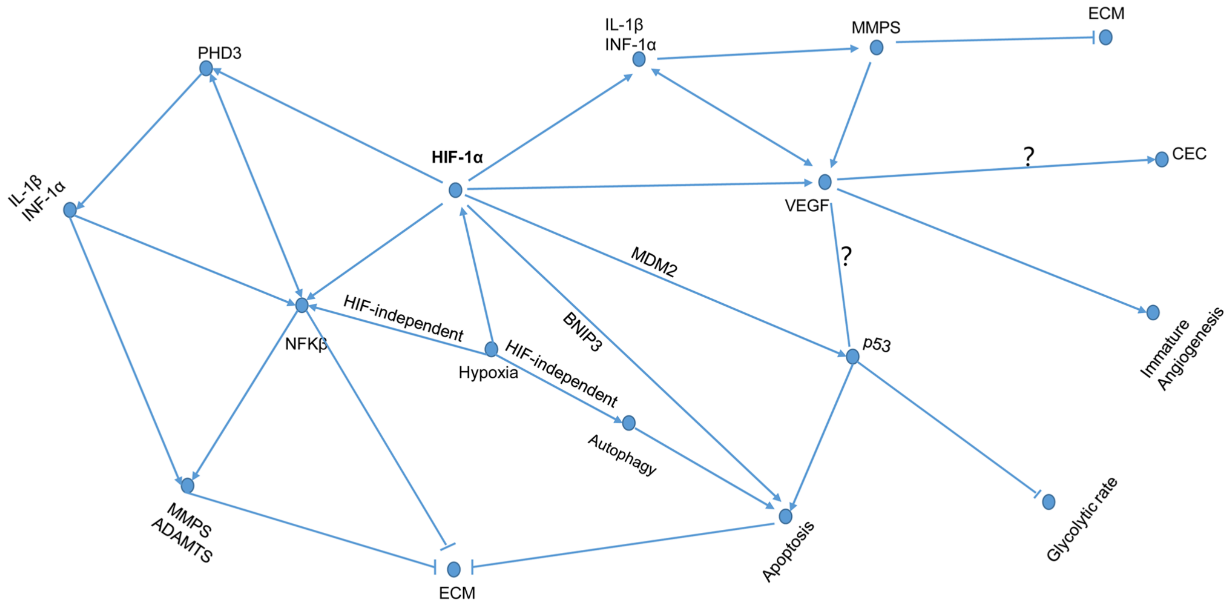

Figure 4. Foe pathways. During severe hypoxia, the foe role of HIF-1α is increasingly reinforced as the oxygen tension gradually decreases. HIF-1α, hypoxia-inducible factor-1α; IL, interleukin; PHD3, prolyl hydroxylase 3; INF-1, eukaryotic initiation factor 4A; MMPS, matrix metalloproteinases; ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; ECM, extracellular matrix; BNIP3, BCL2 interacting protein 3; MDM2, mouse double minute 2 homolog; NFKβ, nuclear factor κβ; VEGF, vascular endothelial growth factor; CEC, cartilage endplate calcification.

NP tissue morphogenesis, homeostasis, repair and remodelling (25,77,78). A number of factors cause the degradation and decreased synthesis of the ECM, leading to a downregulation in the water content of NP tissue; thus, the IVD height and the capability of bearing mechanical loads decrease further, which will ultimately trigger IDD (79).

Hypoxia significantly increased the phenotype of NPCs while having little effect on AF, indicating that HIF-1α can be used as marker of NPCs (28,29). Richardson *et al* (31) found that HIF-1α is expressed in NPCs rather than AF cells, further demonstrating that the use of HIF-1α for phenotypic identification of NPCs is scientific and justified. However, there is still controversy surrounding the findings concerning the regulation of ECM metabolism by HIF-1α. Over the years, an increasing number of studies have shown that hypoxia can induce numerous cells to upregulate HIF-1α to promote ECM synthesis, including NPCs (4,28,29,80), chondrocytes (81-83), fibroblasts (84) and mesenchymal stem cells (83). Animal and human studies have suggested that the content of ECM synthesis has a negative association with the degree of hypoxia (Figs. 3 and 4) (28,29,85-87). The ideal level of hypoxia for reinforcing NPC survival is 1% physiological oxygen concentration (85). Ishihara and Urban (87) reported that the synthesis of glycosaminoglycan (GAG) in bovine NPCs significantly increased as the oxygen tension in the medium gradually decreased. Furthermore, Liu *et al* (80) found that HIF-1α increases the expression of COL2 and ACAN via the mediation of the NOTCH1 signalling pathway. Interestingly, however, Cigognini *et al* (88) found that although HIF-1α was activated at 2% oxygen tension, no increase in ECM synthesis was observed, which suggested that HIF-1α is not the only factor that promotes ECM synthesis. Another study showed that O_2 is essential for the synthesis of GAG in bovine NPCs (89). In complete anaerobic conditions, bovine NPCs express little GAG (89). These two different results may be attributed to different cell-specific endogenous factors, including age, sex, histologic origin and the severity of the damage model (88). Exploring and analysing the ways in which HIF-1α promotes or inhibits ECM synthesis in NPCs, and finding the most critical mechanism for regulating HIF-1α should be the focus of future research.

Angiogenesis. The process of forming new capillaries from existing blood vessels is called angiogenesis (90). Vascular endothelial growth factor (VEGF) is the most important factor in angiogenesis (91). VEGF regulates vascular maturation (92), alters ECM expression (93), increases vascular permeability (94), promotes endothelial cell proliferation and maintains vascular function (94). The oxygen tension of the cell survival environment is an important factor in the regulation of VEGF expression and angiogenesis (41). Hypoxia can stabilize the post-transcriptional levels of HIF-1α, and HIF-1α directly induces VEGF expression under hypoxic conditions (41,95,96). HIF1-α can also indirectly regulate VEGF expression via modulating its own transcriptional activity through E/D-rich carboxy-terminal domain-2 (a p300 binding protein) (97). In addition, interleukin (IL)-8 (98), basic fibroblast growth factor (bFGF) (99,100) and transforming growth factor-β (TGF-β) (100) also have strong angiogenic effects, and these factors are downstream target genes of HIF-1α. TGF-β also activates bFGF and maintains IVD homeostasis (101,102). Interestingly, TNF-α (103,104), IL-1β (41,105) and MMPs (106,107) also play important and complex roles in the regulation of angiogenesis. In endothelial cells, TNF-α promotes angiogenesis by increasing the expression of VEGF, IL-8 and bFGF (103). MMP-2 may promote angiogenesis, whereas MMP-9 may block angiogenesis by converting plasminogen into an angiogenesis inhibitor (106,107). It is noteworthy that hypoxia has a dual role in angiogenesis to avoid over-activation of the HIF-1α/VEGFA axis during hypoxia in order to maintain the surrounding environment and biofunction of cells (108).

Studies have indicated that HIF-1α and VEGF are directly involved in the entire process of angiogenesis (109). The *VEGF* gene may increase the susceptibility to IVD degeneration, and VEGF expression is also positively correlated with the severity of IVD degeneration (110). With regard to the role of angiogenesis in IDD, different scholars hold different perspectives. Some scholars hypothesize that angiogenesis may be the adaptive response of the body to deal with various stresses or injuries to repair degenerative IVD tissue (Fig. 3). Long *et al* (111) found that the expression of VEGF in human IVD tissues is time-specific, and that there is differential expression in different developmental stages of IVD. This is clearly related to the observation that IVD undergoes partial vascularization, devascularization and revascularization (111). Vascularized IVD tissue not only increases blood circulation and improves the nutrition of NPCs, but also plays an important role in the spontaneous absorption of prolapsed IVD tissue (104,107,112). Neovascularization facilitates the infiltration of inflammatory cells, such as macrophages, into NP tissues (9,112,113). The prolapsed IVD tissue can be phagocytosed by macrophages or dissolved via autoimmune reactions (112,113). Various cytokines, such as TNF-α and IL-1β, can also be synthesized by macrophages and other cells to promote both MMPs and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), in order to digest ECM components of prolapsed tissues to mitigate IDD (112,113). Activated MMPs can stimulate VEGF expression and promote the vascularization of IVD (107). Other scholars hypothesize that angiogenesis may accelerate IDD (Fig. 4). Uncontrolled and immature angiogenesis is the cause of a variety of diseases (89). Although HIF-1α promotes angiogenesis, it may promote immature angiogenesis to trigger IDD. VEGF may have a combinatory effect with the *p53* gene to promote IDD (114). p53 induces apoptosis by directly combining with HIF-1α (115) and is ubiquitously considered a pro-apoptotic gene (116). The association between HIF-1α and p53 is so complex that it has not been elucidated, but it is clear that p53 is motivated by HIF-1α to reduce glycolytic rates under severe or chronic hypoxia (36). Pyruvate kinase M2 (PKM2) reinforces the transactivation of HIF-1α and glycolytic rates via interaction with PHD3 (117). It could be that HIF-1α safeguards p53 against degradation via mouse double minute 2 homolog (MDM2) (81). Furthermore, in mild hypoxic conditions, HIF-1α degradation of p53 is associated with PHD3, while MDM2 is not involved in this process (118). Interestingly, p53-enhanced HIF-1α ubiquitination and degradation is involved in the malfunction of cell mitochondria (119). PHD3 is a critical regulator of HIF-1α, p53 and NF-κB pathways (9,21,118,120). HIF-1α upregulates the expression of PHD3, while PHD3 consolidates the transcriptional activity of HIF-1α (21). PHD3 upregulates the TNF-α-induced NF-κB/p65 signaling activity to reinforce the expression of ADAMTS-5 and MMP-13; additionally it can downregulate the expression of the genes *ACAN* and *COL2* (9,121). Fujita *et al* (120) first showed that the expression of PHD3 is mediated by NF-κB-dependent, but not HIF-1α-dependent inflammatory cytokines in NPCs. PHD3 decreases the activity of p53, playing a crucial role in the reciprocal negative correlation between the p53 and NF-κB pathways (118). Another possible mechanism is that activated MMPs and ADAMTS may digest ECM components in non-prolapsed IVD tissues (111). In addition, angiogenesis can also aggravate IDD by promoting CEC (113).

Inflammation. During IDD, the accompanying aseptic inflammatory response within the NP is another important pathological phenomenon (121). The expression of a number of pro-inflammatory cytokines secreted by IVDs and other cells, such as TNF-α (8,74,121), IL-1β (8,74,121-125) and IL-6 (121) are upregulated in IDD. These cytokines promote the progression of IDD by increasing the expression of MMPs (8,40,125), degrading ECM (8,74,125), promoting angiogenesis (103-105), enhancing NPC apoptosis (123-125) and deteriorating IVD tissue (Fig. 4) (8). IL-1β is considered to be the most important cytokine involved in multiple pathological processes of IDD (8,122). IL-1β and TNF-α can reduce the biosynthesis of ECM (including CS, COL2 and ACAN), and enhance the expression of MMPs and pro-apoptotic proteins by stimulating non-coding RNAs (74,125,126). Additionally they can also upregulate the expression of ADAMTS-4/5 to enhance ECM degradation through MAPK and NF-κB signaling pathways (8,125,127). Interestingly, they also activate the Notch pathway to maintain NPC homeostasis by mediating MAPK and NF-κB signaling pathways (128). In addition, IL-1β induces NPC apoptosis and autophagy through the mitochondrial pathway, as well as activating the NF-κB signaling pathway to promote NPC apoptosis, and inhibit the expression of ACAN and COL2 (123-125). Notably, Risbud and Shapiro (8) elucidated that there are three distinct but overlapping inflammation response stages in IDD, of which the second stage emphasizes the role of angiogenesis in transporting various inflammatory cytokines into IVD tissue to further amplify the inflammatory responses that were established in the first stage. Here, we propose a hypothesis that HIF-1α may be predominantly involved in the second stage to regulate the inflammation response of the IVD microenvironment (129).

Increasingly, research suggests that there is a sophisticated and tight relationship between hypoxia, HIF-1α, inflammation and angiogenesis (Fig. 4) (39,130). The NF-κB cascade is an inflammatory signaling pathway. Hypoxia activates both the canonical HIF-dependent pathway and the NF-κB signaling pathway by enhancing inhibitor of NF-κB kinase subunit β (IKKβ) activity (an NF-κB inhibitor) and decreasing PHD-dependent hydroxylation, as IKKβ contains sequences that are similar to hydroxylation sites for binding of PHD to HIF-1α (39,130). Notably, IKKβ is also potentially hydroxylated by PHD on account of its particular structure (39). From this perspective, HIF-1α is involved in activating the NF-κB signalling pathway (130). Moreover, NF-κB also stabilizes HIF-1α expression under normoxic conditions and activates HIF-related pathways (39,130). Konisti *et al* (39) and Oliver *et al* (130) demonstrated the interaction between the NF-κB signalling pathway and HIF-related pathways, which together induce and amplify the inflammatory cascade, and also promote angiogenesis. Previously, it has been confirmed that the expression of HIF-1α is upregulated in inflammatory diseases, such as osteoarthritis (37,131) and rheumatoid arthritis (37,39,131). In 2003, Cramer *et al* (129) conditionally knocked out HIF-1α in mouse bone marrow cells, and found that the production of ATP and biofunction of macrophages decreased significantly, thus further demonstrating that HIF-1α controls the inflammatory response via regulating the glycolytic metabolic pathway and plays a key role in the early stage of inflammatory cell infiltration. Subsequently, in 2010, Imtiyaz *et al* (63) found that the production of ATP is exclusively regulated via HIF-1α, but not HIF-2α. Firstly, NPCs survive in a hypoxic microenvironment, and the expression of HIF-1α is upregulated in IDD (23,28,29). Secondly, NPCs are primarily powered via the anaerobic glycolysis pathway (132). Finally, IDD is often accompanied by aseptic inflammatory response in NPCs (122). Therefore, in this article it is hypothesized that the hypoxia-HIF-inflammatory pathway is involved in the regulation of IDD. Further investigation is needed to elucidate the above hypothesis.

MMPs. MMPs are endopeptidases of the ECM that have the ability to degrade almost all known components of the ECM in IVDs (133,134). Structurally, MMPs can be divided into six main sections: Gelatinase (MMP-2 and MMP-9); collagenase (MMP-1, MMP-8, MMP-13 and MMP-18); matrix degradation element (MMP-3, MMP-10 and MMP-11); matrilysins (MMP-7 and MMP-26); transmembrane and GPI-linked MT-MMP (MMP-14, MMP-15, MMP-16, MMP-17, MMP-24 and MMP-25); and glassy lectin (MMP-21), as well as other types of MMPs (MMP-24) (133,135-137). Functionally, a variety of studies have shown that different types of MMPs, including MMP-2 (134,138-142), MMP-9 (134,139,143), MMP-13 (144), MMP-14 (145) and MMP-16 (146) are negatively correlated with the ECM level of degenerated NP and can promote IDD via the induction of ECM degradation. The most studied MMP is MMP-2, and upregulation of its expression is significantly associated with IDD (137-140). As early as 1997, Crean *et al* (134) found that the expression levels of MMP-2 and MMP-9 were related to the extent of IVD degeneration. Kozaci *et al* (138) found that MMP-2 was upregulated in the early stages of degenerative disc disease, and could promote IDD by degrading COL2. Roberts *et al* (139) found that the expression of MMPs was the most abundant in blood vessels and cell clusters of degenerative IVDs, and was associated with the grade of IDD on the macroscopic level. Rutges *et al* (140) reported that increased MMP-2 activity during disc degeneration was associated with MMP-14 expression. Micro (mi)RNAs are a class of small non-coding RNA regulators. A number of miRNAs have distinct expression profiles in human normal and degenerative IVDs (143,144). They promote the apoptosis or ECM degradation of NPCs in IVD to regulate IDD progression via the targeted regulation of MMPs (144,145). Xu *et al* (143) found that miRNA-133a was involved in the regulation of IVD degeneration by negatively regulating the expression of MMP9 indirectly, and outlined the role of the miRNA-133a/MMP9/COL2 axis in the pathophysiology of IDD. Ji *et al* (145) demonstrated that miRNA-193a-3p may participate in disc degeneration via the targeted regulation of MMP-14. Zhang *et al* (146) reported that miRNA-155 inhibits the ECM degradation of NP and reverses IVD degeneration by targeting negative regulation of MMP-16 expression. At the same time, MMP-16 is involved in MMP-2 activation (147). The expression of MMP-2 was upregulated by HIF-1α in numerous cell types (49-52,148). Wu *et al* (52) found that the expression of HIF-1α and MMP-2 increased in degenerated lumbar IVD, and that there was a significant association between them. Therefore, in the present review, it is hypothesized that HIF-1α may also increase MMP-2 activity in degenerated NPCs. However, the mechanism by which HIF-1α promotes MMP-2 expression remains unclear. Inflammatory cytokines such as IL-1β (121,149) and TNF-α (121,142,149) stimulate the expression of MMP-2 in the degenerative tissues of IVD. In summary, it is hypothesized that the HIF-1α/IL-1β and TNF-α/MMP-2/ECM axes may play an important role in the development of IDD (Fig. 4).

Energy metabolism. NPCs are mainly dependent on anaerobic glycolysis to synthesize ATP to maintain energy metabolism in the absence of oxygen (132). HIF-1α regulates ATP production and can be involved in the regulation of glycolytic metabolism by stimulating the expression of glycolytic genes (43,63,129). Glucose transporter (GLUT), located on the cell membrane, assists cells to take up glucose and plays an important role in glycolysis (31,150-152). There are numerous subunits of GLUT, of which GLUT-1 is the most widely studied in IDD. It has been shown that the overexpression of GLUT-1 reduced hypoxia-induced apoptosis (151). In addition, GLUT-1 provides energy for transplanted cells under hypoxia (Fig. 3) (150). Richardson *et al* (31) found that the expression of GLUT in NPCs is positively correlated with the expression of HIF-1α and the severity of IDD. The upregulation of HIF-1α increased the expression of GLUT-1, GLUT-3 and GLUT-9 in NPCs; however, this association has not been observed in AF cells (31). Furthermore, HIF-1α is involved in regulating the expression of a series of genes in the anaerobic glycolysis pathway, such as 6-phosphofructo-2-kinase (152), PKM2 (117), phosphoglycerate kinase-1 (119) and lactate dehydrogenase (119). HIF-1α is also involved in regulating mitochondrial energy metabolism (153,154). Papandreou *et al* (154) found that HIF-1α also activates pyruvate dehydrogenase kinase-1 in hypoxia and thereby inhibits mitochondrial function. In addition, HIF-1α-induced mitochondrial autophagy decreases the quantity of mitochondria to reduce oxygen consumption (155). However, non-mitochondrial oxygen consumption was found to be regulated via protein-tyrosine phosphatase-1B in breast cancer under hypoxia (156). Whether HIF-1α is involved in the above process remains unknown.

Autophagy. Autophagy is a non-apoptotic, programmed cell death that leads to the self-digestion and degradation of unwanted proteins and organelles to prevent cellular stress and maintain cell function (157). Cells can resist apoptosis and senescence by activating autophagy, which alleviates the progression of certain chronic degenerative diseases (158-162). Autophagy plays a crucial role in the pathogenesis of a number of degenerative diseases, including osteoarthritis (158) and IDD (159-162). The autophagy-related genes or proteins beclin 1, cathepsin B, damage-regulated autophagy modulator 1 and p65 were highly expressed in degenerated IVD tissues compared with normal, healthy IVD tissues (163). Autophagy is a physiological response to hypoxia in cells, and has a complicated relationship with hypoxia (164,165). HIF-dependent autophagy enhances cell survival during physiological hypoxia or mild hypoxia (Fig. 3), while autophagy reinforces cell death via a HIF-independent pathway in severe hypoxia or even anoxia (Fig. 4) (164). Accumulating evidence indicates that HIF-1α induces autophagy via the activation of BCL2 interacting protein 3 (BNIP3) in different mammalian cell types (155,164,166,167). Follicle-stimulating hormone can induce autophagy of mouse granulosa cells through the AKT-mTOR signalling pathway, and HIF-1α is a key factor in mediating this process (167).

The level of cellular autophagy changes accordingly as IVD degenerates and ages (160,164,168). There has been preliminary progress in the study of whether HIF-1α regulates IDD through autophagy in IVD cells under hypoxic conditions. On the one hand, Ye *et al* (168) found that the level of autophagy in rat NP tissues increased with age, and the level of autophagy was higher in the IDD model group compared with the control group. A number of studies have shown that NPCs exhibit lower autophagy activity in culture under hypoxia than in normoxia, which is contrary to studies in most other types of cells (45,164,168). Considering the special physiological environment and energy metabolism of NPCs, there is reason to consider that autophagy in NPCs under hypoxia should be different from that of other types of cells. Autophagy has a dual effect on the survival of NPCs in serum-free culture conditions; proper autophagy activity of cells promotes NPC survival, while excessive autophagy promotes NPC death (45). Hypoxia enhances NPC survival under serum-free culture conditions via the downregulation of excessive autophagy activity, including limiting the generation of reactive oxygen species and promoting the inactivation of the AMPK/mTOR signalling pathway; this process may be controlled by HIF-1α (45). On the other hand, contrary to previous investigations, Choi *et al* (169) confirmed that hypoxia enhances the non-classical autophagy of NPCs, and this process is not related to the mTOR and HIF-1α signalling pathways. This process does not affect the glycolytic metabolism of NPCs (169), which suggests that autophagy in NPCs may have other effects besides its classical degradation and recapture function. Therefore, further studies are needed to determine the physiological role of autophagy in NPCs and how it contributes to alleviate IDD.

Apoptosis. The biological activity of NPCs is indispensable for maintaining the stability and function of the IVD. Accumulating evidence suggests that excessive apoptosis and senescence of NPCs can lead to ECM degeneration in the NP, and it has been considered that it could be a therapeutic target in IDD (170,171). Gruber *et al* (171) studied postoperative specimens and found that the apoptosis of a large number of cells was detected in IVD, while active cells synthesize degraded ECM components, impeding cell growth and communication by altering the environment surrounding NP. It is becoming increasingly evident that HIF-1α is widely involved in the regulation of NPC survival. The positive correlation between the expression of HIF-1α and NPC apoptosis was analyzed in patients with disc herniation (43). In this review it is hypothesized that the survival state of NPCs is related to the severity of hypoxia under hypoxic environments; there is an oxygen threshold beyond which the expression of pro-apoptotic proteins and VEGF is reinforced. Moritz *et al* (59) and Liu *et al* (35) also found that HIF-1α has a dual function *in vivo*, and the alternative function of HIF-1α depends on the oxygen tension (Figs. 3 and 4). Some pro-apoptotic proteins, such as BNIP3, are downstream target genes of HIF-1α (166). BNIP3 can induce the apoptosis of NPCs via the mitochondrial pathway, and it is also involved in inducing mitochondrial autophagy, promoting cells to adapt to various metabolic reactions and exerting anti-apoptotic benefits (155). Forkhead box O3 (FOXO3a), which regulates resistance to various stresses and promotes cell survival, decreases the expression of BNIP3 by promoting the activity of the transcription cofactor cbp/P33 interacting transactivator 2 to inhibit apoptosis (172). In addition, inflammatory cytokines, decreased energy metabolism, ECM imbalance and angiogenesis, all promote apoptosis in varying degrees.

Increasingly, investigations have tended to support that HIF-1α enhances the NPCs adaptability to hypoxia and consolidates NPC survival under hypoxic conditions. The HIF-1α/VEGF pathway plays a vital role in maintaining the ECM balance of NPCs and promoting NPC survival (42). The function of VEGF is also restricted to the VEGF/membrane bound VEGF receptor-1 axis (173). The NPCs derived from progenitor cells were vulnerable to apoptosis in hypoxic conditions due to their inability to induce the expression of HIF-1α (174). After proteoglycans were added, the activation of HIF-1α was subsequently consolidated, and the susceptibility of progenitor cells to apoptosis induced by hypoxia was reduced (174). HIF-1α inhibits Fas ligand-mediated apoptosis by reinforcing the activation of the galectin-3 promoter (175). In addition, HIF-1α can enhance the expression of carbonic anhydrase (CA)-12 to increase the synthesis of the ECM of NP (4). HIF-1α is also involved in CA9/12-mediated bicarbonate cycling to maintain the pH stability of NP (176).

Dystrophic calcification. Although IVD is enriched in collagen fibrin and moisture, abnormal pyknotic substances are not deposited within NP under physiological conditions (48). The dysregulation of inorganic phosphate metabolism plays a key role in CEC (177), and its expression level can be used to assess the degree of CEC (178). The progressive ankylosis protein homolog gene (ANK) is a phosphate transporter that can prevent mineralization by regulating the transport of inorganic phosphates (48,179). ANK is involved in the local control of mineralization in bone, cartilage and the calcified tissue area of growth plates (179,180). Malnutrition mineralization caused by abnormal expression of ANK can lead to the occurrence of chronic diseases such as osteoarthritis (179,180) and IDD (48,181). Sohn *et al* (182) found that ANK is mainly expressed on the surface and hypertrophic areas of joints and cartilage, which indicates that the expression of ANK is oxygen-dependent. Zaka *et al* (183) demonstrated that the expression of *ANK* in growth plate chondrocytes depends on the regulation of HIF-1α. However, Skubutyte *et al* (48) found that ANK was highly expressed in calcified areas of cartilage endplates enriched in blood supply and in NP tissues lacking blood supply, suggesting that there is an intrinsic difference in the regulation of ANK between the NP and the growth plate. A previous study found that HIF-1α or HIF-2α directly negatively regulate the expression of ANK, indicating that the expression of HIF-1α or HIF-2α can maintain the physiological level of ANK under physiological conditions, thereby preventing the occurrence of dystrophic mineralization and promoting NPCs to adapt to the hypoxic environment (48). Interestingly, although the expression of HIF proteins is not related to oxygen tension, silencing HIF further increases the expression of ANK during hypoxia, indicating that hypoxia can also regulate can regulate TGF-β expression to modulate ANK promoter activity in a HIF-independent manner (Fig. 3) (48).

Transplantation. Cell transplantation repair or even reconstruction of degenerate IVD could be used to treat IDD. Wang *et al* (184) injected NPCs into an established IDD mouse model and found that transplanted NPCs can counteract apoptosis, increase the expression of ECM and promote NPC migration to the damaged area, thereby alleviating IDD. Yang *et al* (46,47) found that the isolation, expansion and culture of human degenerate NPCs can successfully preserve the regenerative capacity of NPCs during hypoxia. The expression of HIF-1α is enhanced under hypoxia, which can promote cell proliferation and maintain the functional phenotype of NPCs. Therefore, it is necessary to isolate and amplify NPCs during hypoxia to pave the way for post-cultivation or cell transplantation. The energy metabolism of transplanted NPCs relies on the HIF-1α-GLUT1 pathway (Fig. 3) (150).

5. HIF-1α development trends

Spontaneous absorption of prolapsed IVD tissues. An increasing number of studies have reported herniated disc tissue retraction or even disappearance in patients with lumbar disc herniation previously diagnosed by MRI (14-16). Macrophages, angiogenesis, MMPs and inflammatory cytokines play an important role in this process (104,107,112,113). HIF-1α mediates macrophage infiltration, and their role in acute inflammation response, via the regulation of ATP production (63). HIF-1α also enhances the phagocytic activity of M1 macrophages and the expression of pro-inflammatory cytokines and VEGF (8,130,185). Due to the network regulatory relationships among HIF-1α and angiogenesis, MMPs and inflammatory cytokines (Fig. 3), in this review it is hypothesized that HIF-1α may be involved in regulating the spontaneous absorption of prolapsed IVD tissue. The possible mechanisms need further research.

HIF-1α may be a common relay station of non-coding RNAs. Numerous studies have reported that non-coding RNAs, including miRNAs, long non-coding (lnc)RNAs and newly discovered circular (circ)RNAs, play an important role in the occurrence and progression of IDD. More importantly, numerous non-coding RNAs are associated with HIF-1α (35,53,108,186-191), as shown in Table I. Liu *et al* (35) confirmed that miR-335 can directly regulate the expression of HIF-1α, and found that HIF-1α has a dual role in the regulation of cerebral ischaemia. Wang *et al* (53) found that lncRNA-RP11-296A18.3 enhances the expression of HIF-1α by sequestering miR-138, which in turn promotes human NPC proliferation and ECM synthesis. Serocki *et al* (188) reviewed the miRNAs and lncRNAs that can regulate the HIF-1α switch and found that they are mainly involved in process of cell proliferation, migration, angiogenesis and hypoxia. lncRNAs regulate HIF-1α directly (188) and can indirectly regulate HIF-1α expression by sequestering miRNAs (53,188,189). In the present review, the focus is mainly on the circRNAs that are associated with HIF-1α (180-191). Liang *et al* (186) found that the expression of circDENND4C was enhanced in breast cancer cells under hypoxia, and reduced after HIF-1α knockdown. Thus, indicating that HIF-1α mediates cell metabolism via regulating the expression of circRNA. Interestingly, circRNA mediates HIF-1α metastasis to reverse its biofunction (188). Du *et al* (187) reported that circ-Foxo3 was enriched in the cytoplasm and absorbs HIF-1α, which was originally highly expressed in the nucleus and translocated into the cytoplasm to promote cell senescence. Dang *et al* (190) found that circ_0010729 can sequester miR-186 to relieve the inhibitory effect of miR-186 on HIF-1α, thereby promoting vascular endothelial cell proliferation and migration, and inhibiting apoptosis. Liu *et al* (191) first studied the expression profile of circRNAs in osteosarcoma and found that circRNA_103801 expression was markedly upregulated. Functional enrichment analysis showed that it could play a role in cancer signalling pathways, such as HIF-1α, VEGF and angiogenesis (191). circRNAs have an effect on mitigating IDD (Table II) (125,126,192). Cheng *et al* (125) demonstrated that circVMA21 reduces inflammatory cytokine-induced NPC death and the expression of MMPs and ADAMTSs, as well as increasing the synthesis of COL2 and ACAN in *in vitro* experiments. Subsequently, the results of *in vivo* experiments were in accordance with the *in vitro* experiments, suggesting that the circVMA21/miR-200c/XIAP axis plays a crucial role in mitigating IDD (126). Guo *et al* (192) further demonstrated that the circ-GRB10/miR-328-5p/erb-B2 receptor tyrosine kinase 2 axis can also regulate NPC apoptosis. Wang *et al* (126) reported that TNF-α enhances the expression of circ-4099, which promotes the synthesis of SOX9 via the sequestering of miR-616-5p. However, these three experiments do have similar limitations; the key genes researched do not necessarily play a major role in IDD. As the purpose of studying the genes involved in IDD is so that the results can go on to be applied in the clinic, the key genes should be selected for study. In this review, it is questioned whether circRNAs participate in the regulation of IDD via modulating the HIF-1α switch. In summary, it is further speculated that HIF-1α may be a common relay site for non-coding RNAs regulating IDD. It is necessary to further investigate the role of the circRNA-miRNA-HIF-1α-MMP-ECM signalling pathway in regulating the progression of IDD.

Clinical conversion. Increasingly, patients with LBP in the clinic are shown to have protrusive or degenerative IVD via MRI imaging (14-16). Pfirrmann *et al* (193) mainly used MRI to classify the grade of the severity of IDD, without considering the microenvironmental factors of IVD. The IVD microenvironment has already become dysregulated before MRI shows positive results, such as protrusion or degeneration of the IVD (25,40,77). Thus, even if a negative result is detected by MRI, it cannot be ruled out that the IVD microenvironment has already deteriorated. Therefore, compared with Pfirrmann's ‘external grading’, the ‘internal grading’ of the degree of microenvironmental disturbance within IVD can easily be neglected before this type of patient has a positive result. Consequently, it is crucial to determine the 'internal grading' of the severity of IDD as soon as possible and to intervene early to block the vicious cycle of degeneration. This also opens up alternative avenues for patients who have results contradictory to MRI imaging. In view of the fact that IVD has no vascular structures (19,22), the diagnosis of the 'internal grading' of IDD relies on puncture only. Ultrasound-guided puncture has the advantages of accurate positioning, convenient operation, economy, and both diagnosis and treatment, as well as having clinical applicability (194). HIF-1α, as the most important molecule regulating the degeneration of human IVD (30), is a common relay station for the regulation of a number of non-coding RNA molecules (35,53,108,186-191). The various mechanisms affecting IDD interact with each other and ultimately regulate ECM metabolism (25,77-79). Therefore, the dysregulation of ECM metabolism is the most important mechanism affecting IDD. Water loss within the NP is an important feature of IDD (24,40,77). Although MMPs (49-52), inflammatory factors (8,103,125) and various related proteins (90,114,120,155) also play an important role in IDD, they are indirectly reflected by HIF-1α and ECM and may not be included in the evaluation index. Therefore, HIF-1α, ECM (the content and distribution of ACAN and COL2 and other collagens) and H_2O can be used as the evaluation criteria for the pathological diagnosis of the 'internal grading' of the degree of microenvironmental disorder in IVD. However, the challenges faced by this method should be noted. This includes how to puncture for the biopsy and its feasibility (why patients should take an invasive examination and where is the value). Therefore, further research is needed to demonstrate that early precaution and intervention can avoid advanced surgery. Additionally, another challenge concerns the determination of reference values of various evaluation indicators. circRNAs are tissue-specific and can serve as markers of disease (195) so greater challenges include further screening of circRNAs with markers that indirectly reflect the expression of HIF-1α and ECM, and then diagnose the degree of IDD through the drawing of blood.

6. Conclusions

In summary, this review put forward three invaluable and strongly indispensable research questions. Firstly, HIF-1α is a double-edged sword in modulating the occurrence and progression of IDD, which is related to the oxygen tension of the IVD microenvironment. The oxygen tension is gradually decreased with the progression of the vicious cycle. The HIF-dependent pathways play a friendly role during moderate hypoxia, while playing a foe role in severe hypoxia. Is it possible to alter the oxygen tension indirectly, in order to control the expression of HIF-1α and to treat IDD? Secondly, HIF-1α has the ability to regulate all other mechanisms involved in IDD, and it may also be a common relay station for a number of non-coding RNAs that regulate the progression of IDD. Does the circRNA-miRNA-HIF-1α-MMP2-ECM signalling pathway play a crucial role in regulating the progression of IDD? Thirdly, puncturing the IVD to obtain NP tissue for biopsy, guided by B-ultrasound, could be a novel and vital method for early diagnosis and treatment in cases where the patient is displaying symptoms but MRI is showing a negative result. So, how feasible is this diagnosis method? Why undergo an invasive examination, and where is the value? Can levels of HIF-1α, ACAN, COL2, VEGF and H_2O be used as evaluation criteria for the pathological diagnosis of the 'internal grading' of the degree of IVD microenvironmental dysregulation? Further research is needed to answer these questions in order to aid the clinical diagnosis and treatment of IDD.

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Authors' contributions

YL, SL and DP contributed to the concept and the design of the review. YL and DP wrote the manuscript. SL, GN and XX helped draft the manuscript and drew the figures. BX provided significant suggestions for the study. HZ, BZ, SZ searched the literature and collated important reference information. SF critically reviewed the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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