Review

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Vascular ingrowth in intervertebral disc degeneration

Mechanistic insights, current progress, and therapeutic perspectives

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Abstract: Intervertebral disc degeneration (IDD), a primary cause of low back pain, currently lacks therapeutic strategies capable of halting its progression or promoting disc regeneration. Vascular ingrowth is the hallmark pathological feature of IDD, which arises from annulus fibrosus (AF) injury and accelerates degenerative processes through intricate interactions with inflammation and extracellular matrix degradation. This review summarizes the characteristics of vascular ingrowth in IDD, including differential vascular distribution between normal and degenerative discs, spatiotemporal dynamics of progressive invasion, and its association with pain via neurovascular co-invasion. The key underlying mechanisms involve the activation of pro-angiogenic factors (e.g., vascular endothelial growth factor [VEGF]), regulation by miRNA networks (e.g., miR-140-5p), macrophage-mediated coupling of inflammation and angiogenesis, and the dual roles of stress pathways and hypoxia-inducible factor signaling in driving pathological vascularization. Current research employs *in vivo* models (e.g., puncture- or fixation-induced degeneration), *in vitro* vascular co-culture systems, as well as advanced imaging techniques to dissect the process of vascular ingrowth in IDD. Aimed at counteracting pathological angiogenesis and halting the progression of IDD, emerging therapeutic strategies have been developed, including VEGF interventions, miRNA-targeted therapies, modulation of the inflammatory microenvironment, and multi-target combinatorial regimens. Despite substantial advances in understanding vascular ingrowth, several critical unresolved issues remain, including the unclear causal relationship between vascular ingrowth and IDD progression, species-specific disparities in preclinical models, and challenges in optimizing therapeutic timing and target selection. Future research will focus on addressing these gaps, with key priorities including single-cell analysis of vascular heterogeneity, mechanobiological coupling with vascularization, biomaterial-based precision regulation, and the establishment of standardized clinical translation pathways. In summary, vascular ingrowth is a critical driver of IDD, and mechanistic insights gained herein support its potential as a therapeutic target. Addressing current challenges will accelerate the translation of novel strategies into clinical practice for effective IDD management.

Keywords: low back pain, intervertebral disc degeneration, vascular ingrowth

1. Introduction

Intervertebral disc degeneration (IDD) is a major cause of low back pain, a prevalent chronic disease that severely impairs patients' quality of life.[1] As the primary factor leading to disability in the elderly population, the disease burden caused by IDD is increasingly heavy.[2] Currently, clinical treatments mainly include conservative therapies and surgical interventions. However, conservative treatments only alleviate symptoms, while surgical methods such as lumbar fusion carry the risk of accelerating adjacent segment degeneration.[3] More critically, none of the existing treatment modalities can effectively promote intervertebral disc regeneration or halt the degenerative process.[4] This therapeutic gap underscores the urgent clinical need for in-depth research into the pathological mechanisms of IDD.[1,4]

The intervertebral disc, as the largest avascular organ in the human body, has had its vascularization identified as a characteristic pathological change in IDD.[5,6] When the annulus fibrosus (AF) is damaged, disrupting the blood-disc barrier, angiogenesis and immune cell infiltration form a vicious cycle, accelerating the progression of IDD

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and triggering a series of clinical symptoms.[7] Studies have shown that vascular ingrowth not only brings abnormal innervation but also interacts with pathological processes such as extracellular matrix (ECM) degradation and inflammatory microenvironment formation.[8,9] Notably, vascular invasion is closely associated with the accumulation of senescent cells in degenerative intervertebral discs and the continuous release of senescence-associated secretory phenotype.[10] This vascular-senescence axis may constitute a key mechanism for the persistent progression of IDD.[11]

Research on vascular ingrowth mechanisms holds multiple theoretical values: first, it reveals the rules of microenvironmental transformation of intervertebral discs from "immune privilege" to "vascularization"[7]; second, this process involves multi-level regulation such as vascular endothelial growth factor (VEGF) signaling, miRNA regulatory networks, and macrophage polarization[12,13]; more importantly, angiogenesis has cross-talk with core mechanisms of IDD such as mitochondrial dysfunction and oxidative stress.[14,15] These findings provide molecular targets for the development of anti-vascular therapies, such as innovative strategies by regulating the balance of M1/M2 macrophage polarization[12,13] or utilizing exosome-mediated intercellular communication.[6] Although current regimens such as anti-VEGF therapy still face challenges such as timing selection,[16] multi-target synergistic interventions combined with biomaterial delivery systems show therapeutic potential to reverse the degenerative process.[17–20]

2. Mechanistic insights and current progress

2.1. The characteristics of vascular ingrowth in IDD

The normal intervertebral disc, as the largest avascular organ in the human body, relies on a unique hypoxic state and an intact blood-disc barrier to maintain a healthy microenvironment.[21,22] Histological studies have shown that healthy nucleus pulposus (NP) tissue exhibits typical avascular characteristics, with only a small vascular network present in the outer AF.[21,22] However, during degeneration, damage to the AF leads to disruption of the blood-disc barrier, triggering significant angiogenesis.[23] This pathological change first occurs in the outer layer of the AF and gradually extends toward the NP as degeneration progresses.[11,22] It is worth noting that notochordal cells play a key role in maintaining the avascular state of the intervertebral disc, as their secreted inhibitory factors can effectively prevent vascular ingrowth.[11] Changes in the vascular distribution pattern of degenerative intervertebral discs also manifest as abnormal vascular morphology, including tortuous and dilated vessels and increased permeability, which promote inflammatory cell infiltration and matrix degradation (Table 1).[22,23]

The process of vascular invasion into the intervertebral disc exhibits distinct spatiotemporal dynamic characteristics. In the temporal dimension, angiogenesis is positively correlated with the degree of degeneration: early degeneration is mainly characterized by capillary proliferation in the outer 1/3 of the AF, while late-stage degeneration involves vascular invasion deep into the NP.[22,23] Animal model studies have shown that new blood vessel formation can be observed 2 weeks after AF puncture injury, peaking at 4–8 weeks.[16] Given that new blood vessels grow from the outside to the inside of the AF, and the original vascular network within the intervertebral disc is also distributed on the outside of the AF, a reasonable inference is that the ingrowth of blood vessels in the intervertebral disc originates from the proliferation and migration of the original vascular endothelial cells in the AF. However, the evidence based on spatial location is still unable to rule out the possibility that the endothelial cells of the newly formed blood vessels within the intervertebral disc may originate from adjacent tissues and other situations. The origin of the endothelial cells of the newly formed blood vessels within the intervertebral disc still needs to be further confirmed by lineage tracing evidence. In terms of spatial distribution, vascular invasion presents a progressive expansion pattern from the periphery to the center and from the ventral to the dorsal side, which is highly consistent with the distribution of mechanical stress.[18,22] Imaging techniques such as dynamic contrast-enhanced magnetic resonance imaging (MRI) (DCE-MRI) have confirmed that vascular invasion is accompanied by significant increases in blood flow and changes in vascular permeability, which can serve as early markers of degenerative progression.[21,24] Notably, angiogenesis and nerve fiber invasion often show a synergistic distribution, forming a special pathological pattern of "neuro-vascular co-invasion."[23]

Multiple clinical pathological studies have confirmed a significant correlation between vascular density and the degree of IDD. Quantitative histological analysis shows that the microvessel density of intervertebral

Table 1

Comparison of vascular characteristics in normal and degenerated intervertebral discs.

Characteristics	Normal IVD	Degenerative IVD
Vascular level	Mostly avascular	Significant angiogenesis
Vascular distribution	Only small vascular nets in outer AF	Significant angiogenesis from outer AF to NP
Anti-angiogenesis	Notochordal cells secreted antiangiogenesis factors	Notochord cells drops sharply or even disappear
Vascular morphology	Normal vessels	Tortuous and dilated vessels and increased permeability
Vascular function	Supplies nutrients and enables substance exchange	Promote inflammatory cell infiltration and matrix degradation

AF = annulus fibrosus, IVD = intervertebral disc, NP = nucleus pulposus.

discs with Pfirrmann grade III or higher degeneration is 3–5 times higher than that of the normal group.[22] Immunohistochemical studies have found that the expression levels of pro-angiogenic factors such as VEGF are positively correlated with vascular density and degeneration grade.[11] At the molecular level, abnormal expression of hypoxia-related markers such as hypoxia-inducible factor-2α (HIF-2α) in degenerative NP tissue is significantly associated with the degree of angiogenesis.[18,22] Clinical imaging studies have also confirmed that the vascular permeability parameter measured by DCE-MRI is positively correlated with the degree of IDD ($R = 0.72$, $p < 0.01$).[24] It is worth noting that the increase in vascular density is not only related to structural degeneration but also significantly correlated with the severity of pain symptoms, which may be associated with nociceptive stimulation caused by neurovascular co-invasion.[22,23]

2.2. The molecular mechanisms underlying vascular ingrowth in the intervertebral disc

VEGF is a key molecule regulating vascular ingrowth in the intervertebral disc. Studies have shown that macrophages can secrete endogenous VEGF through the VEGF-VEGFR2 signaling pathway, inducing angiogenesis under ischemic conditions.[25] In IDD models, the expression level of VEGF is positively correlated with vascular density, and inhibition of VEGF or VEGFR2 signaling can significantly disrupt macrophage-related vascular formation (Fig. 1).[25] In addition, the interleukin (IL)-1β signaling pathway promotes the transcription of VEGF-A through signal transducer and activator of transcription3 and nuclear factor kappa-B pathways, and it has been confirmed in acute limb ischemia models that macrophage IL-1β expression is crucial for VEGF-A-induced blood flow recovery.[26] Notably, platelet-derived growth factor-BB, another pro-angiogenic factor, has also been found to be secreted by macrophages and involved in the process of IDD.[22]

MicroRNAs (miRNAs) play an important regulatory role in the vascularization of IDD. Studies have found that the expression level of miR-140-5p in NP extracellular vesicles is negatively correlated with angiogenesis in IDD, and its mechanism may be related to the regulation of the downstream Wnt/β-catenin pathway.[18] There is also evidence that miR-21 inhibitors can exert regenerative effects on NP tissue through anti-inflammatory effects.[27] During macrophage polarization, upregulation of exosomal miR-21b has been confirmed to be associated with angiogenesis regulation.[28] In addition, studies have found that certain pathogens can alter the miRNA abundance of host cells by regulating the macrophage transcription factor c-Myc, providing a new perspective for understanding miRNA regulatory networks in the intervertebral disc microenvironment.[29]

Oxidative stress is defined as an abnormally elevated level of reactive oxygen species generated by endogenous or exogenous factors, which results in an imbalance in redox homeostasis.[30] During the process of IDD, oxidative stress mainly occurs in NP cells, which can trigger cellular senescence and apoptosis, inflammatory accumulation, and ECM degradation.[15] Endoplasmic reticulum stress occurs when the homeostasis of the endoplasmic reticulum is disrupted, leading to the accumulation

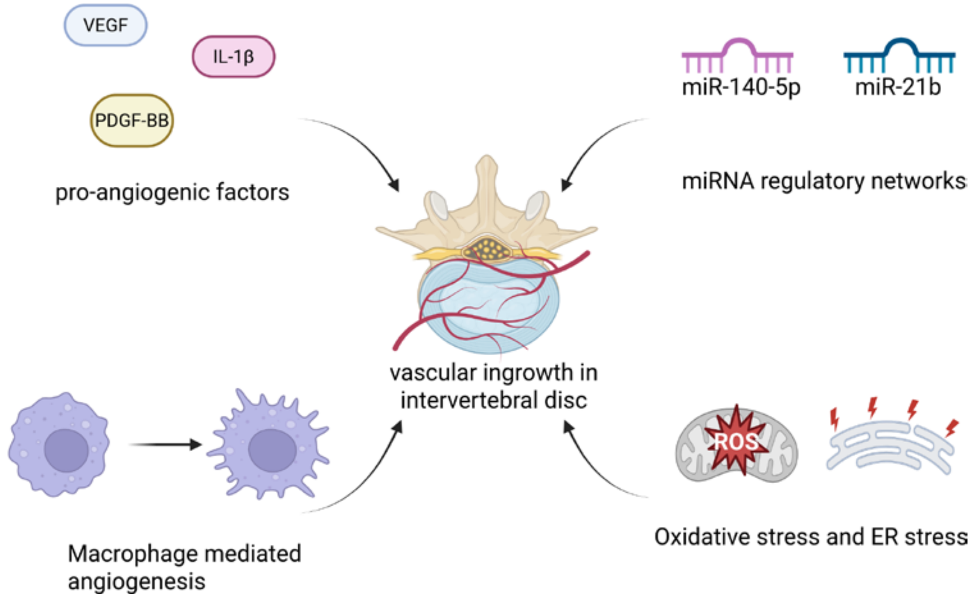

Figure 1. The molecular mechanisms underlying vascular ingrowth in the intervertebral disc. The molecular mechanisms of vascular ingrowth in intervertebral discs involve multiple aspects: VEGF, a key pro-angiogenic factor, is secreted by macrophages via VEGF-VEGFR2 signaling, with its expression correlating with vascular density; IL-1β and PDGF-BB also play roles. miRNA networks (e.g., miR-140-5p, miR-21b) regulate angiogenesis. Macrophages mediate inflammation-angiogenesis coupling, with M1/M2 polarization affecting vascular endothelial cell functions. Oxidative and endoplasmic reticulum stress regulate angiogenesis, with antioxidants showing potential. Images were created by Biorender. PDGF = platelet-derived growth factor; VEGF = vascular endothelial growth factor.

of unfolded or misfolded proteins.[31] This triggers the unfolded protein response, and if it persists over an extended period, it may cause cell death via oxidative stress or mitochondrial dysfunction. Endoplasmic reticulum stress plays a key role in the progression of IDD, which can induce apoptosis and pyroptosis of NP cells and also promote disc degeneration through mitochondrial interaction.[32]

Both oxidative stress and endoplasmic reticulum stress play important regulatory roles in the vascularization of IDD. Meanwhile, oxidative stress and endoplasmic reticulum stress disrupt the immune homeostasis of intervertebral discs by inducing the release of pro-inflammatory cytokines (such as tumor necrosis factor α [TNF-α], IL-1β) and recruiting pro-inflammatory immune cells such as macrophages, neutrophils, and mast cells.[33] Studies have shown that hydrogels with broad-spectrum antioxidant activity can restore tissue redox and immune homeostasis by regulating macrophage phenotypes.[34] In addition, endoplasmic reticulum stress can affect the expression of pro-angiogenic factors such as VEGF through the unfolded protein response pathway, but the specific mechanism in the field of IDD still needs further research.[34] Notably, certain flavonoids such as kaempferol-3-O-rutinoside can exert anti-inflammatory effects by inhibiting VEGF-C-mediated macrophage migration,[35] suggesting that oxidative stress regulation may be a potential target for intervening in vascular ingrowth (Fig. 1).

2.3. The relationship between the vascular ingrowth and IDD

During IDD, angiogenesis and ECM degradation form a mutually reinforcing vicious cycle. Studies have shown that the increased oxygen content brought by new blood vessel formation disrupts the original hypoxic adaptation state of NP cells. Under the condition of dysregulated HIF-1α, it triggers ECM metabolic disorders and accelerated degradation.[36] Meanwhile, abnormal expression of HIF-2α in degenerative NP cells is found to be closely related to the upregulation of the angiogenic factor VEGF-A, which further exacerbates ECM destruction by promoting the migration of vascular endothelial cells.[28,37] Fragments generated by ECM degradation can act as pro-angiogenic signals, stimulating more vascular ingrowth and forming a positive feedback loop.[9,38] It is worth noting that this interaction also involves the participation of various extracellular ligands and signaling pathways, including the synergistic effects of angiogenic factors such as platelet-derived growth factor and fibroblast growth factor.[27]

During the progression of IDD, angiogenesis is often accompanied by abnormal ingrowth of nerve fibers, forming a phenomenon of neurovascular co-invasion. This synergistic invasion accelerates the degenerative process through multiple mechanisms: on the one hand, new blood vessels provide scaffolds and nutritional support for nerve fiber growth; on the other hand, neuropeptides released by invading nerve endings can stimulate local inflammatory responses, further activating angiogenic signals.[8] Therefore, the ingrowth of nerves and angiogenesis also form a vicious cycle. Studies have shown that activation of the Toll-like receptor 4/HIF-1α signaling pathway in degenerative NP tissue not only promotes angiogenesis but also creates a microenvironment suitable for nerve ingrowth by upregulating the expression of inflammatory factors.[39] The co-invasion of this neurovascular unit also leads to abnormal transmission of pain signals, constituting an important pathological basis for discogenic pain.[40,41] Specifically, nerve endings that grow into degenerated intervertebral discs express nociceptive receptors (such as TrkA), which generate pain signals upon stimulation by inflammatory factors.[42] Concurrently, local accumulation of pain-inducing metabolites—such as lactate and adenosine triphosphate—within degenerated discs can directly activate pain pathways.[43]

The HIF signaling pathway exhibits a complex dual regulatory role in the process of vascular ingrowth in the intervertebral disc. Under physiological conditions, HIF-1α is crucial for NP cells to adapt to the hypoxic environment, protecting cells from oxidative stress damage and maintaining ECM homeostasis.[44,45] However, under degenerative conditions, sustained activation of HIF-1α can promote the expression of angiogenesis-related genes, driving pathological angiogenesis.[46,47] Notably, HIF subtypes show differential regulation: HIF-1α mainly exerts a protective effect, while HIF-2α tends to promote degenerative progression, participating in vascular formation and hypoxic response regulation by upregulating target genes such as carbonic anhydrase IX and VEGF-A.[28,37] This double-edged sword effect is also reflected in the regulation of the immune microenvironment by HIF, which can both protect against excessive inflammatory responses and potentially promote angiogenesis and ECM remodeling under chronic inflammatory conditions.[46,48] In response to this complexity, the latest research attempts to balance HIF signaling by precisely regulating oxygen tension, such as using a laccase-mediated oxygen depletion strategy to establish a controllable hypoxic microenvironment, providing new ideas for therapeutic intervention[36] (Fig. 2).

2.4. Technical approaches for studying vascular ingrowth in intervertebral disc

Animal models are of irreplaceable value in IDD research. The currently commonly used puncture induction method simulates the human IDD process by destroying the integrity of the AF, and studies have shown that this method can effectively induce vascular ingrowth.[49] In rat models, puncturing the AF with a 21G needle can lead to the invasion of vascular endothelial cells into the NP region, accompanied by upregulated expression of the pro-angiogenic factor VEGF.[50] The fixation induction method simulates the degenerative process through mechanical

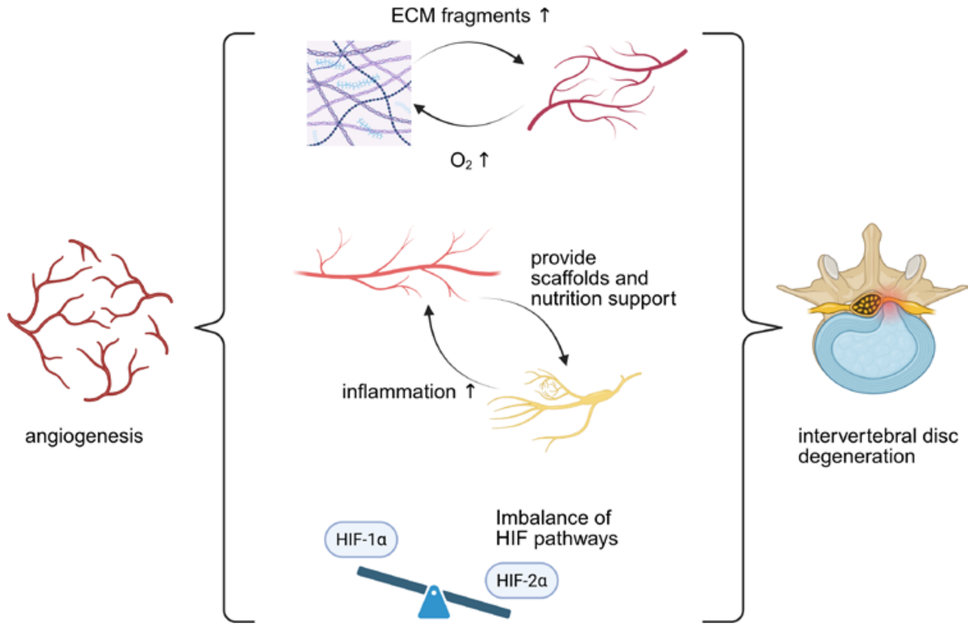

Figure 2. The relationship between the vascular ingrowth and IDD. During IDD, angiogenesis and ECM degradation form a mutually reinforcing vicious cycle. Meanwhile, angiogenesis is often accompanied by abnormal ingrowth of nerve fibers, forming a phenomenon of neurovascular co-invasion. The hypoxia-inducible factor (HIF) signaling pathway exhibits a complex dual regulatory role in the process of vascular ingrowth in the intervertebral disc. Images were created by Biorender.

stress overload. A Sprague–Dawley rat cervical spine fixation model shows that continuous compression can lead to a decrease in intervertebral disc height and promote angiogenesis.[21] It is worth noting that there are differences in the vascularization patterns generated by different induction methods: the puncture model mainly shows local vascular invasion, while the fixation model presents diffuse vascular proliferation.[50] In addition, local injection of enzymes such as papain and chondroitinase at the intervertebral disc can simulate the degradation process of the ECM and induce a chemically-induced IDD model.[51] The removal of the spinous process and the superior and inferior articular processes can induce rapid IDD by triggering spinal instability.[52] With the development of genetic engineering technology, various gene knockout mice, such as Sox9, Runx2, HIF1α, and Arpc2, have been found to have typical spontaneous IDD trends and have been developed as mature animal models for IDD.[53,54]

In vitro co-culture systems provide a controllable experimental platform for studying vascular ingrowth mechanisms. A co-culture model of human umbilical vein endothelial cells and AF cells has confirmed that exosomes derived from degenerative AF can significantly promote vascular formation.[6] In a three-dimensional culture system, direct contact between NP cells and vascular endothelial cells can activate the nuclear factor kappa-B signaling pathway, leading to increased expression of matrix metalloproteinases.[6] The application of microfluidic chip technology has further enabled dynamic observation of the angiogenesis process, and studies have found that hypoxic conditions can promote endothelial cells to penetrate the Matrigel matrix, simulating the AF barrier.[18] These *in vitro* systems not only verify the paracrine interaction between intervertebral disc cells and vascular endothelial cells but also provide an efficient platform for drug screening.[55]

Advanced imaging technologies provide noninvasive evaluation methods for intervertebral disc vascularization research. Diffusion tensor imaging can sensitively detect microvascular infiltration in early degenerative intervertebral discs by analyzing the anisotropy of water molecule diffusion.[56] The quantitative parameter Ktrans of DCE-MRI is significantly positively correlated with histologically measured vascular density, confirming that this technology can effectively evaluate changes in intervertebral disc vascular permeability.[49] Raman spectroscopy has recently been applied to intervertebral disc research, which can not only identify the spatial distribution relationship between microplastic pollutants and vascularization but also detect the degradation characteristics of collagen fibers.[57] Multimodal image fusion technology combined with cathepsin-activated near-infrared probes enables real-time visualization of vascular ingrowth processes at the *in vivo* level.[56,58]

2.5. Advances in therapeutic strategies against vascular ingrowth in IDD

VEGF plays a key role in vascular ingrowth during IDD. Studies have shown that VEGF-C forms a vicious cycle with inflammatory factors in the degenerative microenvironment, which can not only serve as a diagnostic marker but also may become a molecular therapeutic target.[59] Experimental anti-VEGF therapy has shown that the combined application of Prussian blue nanoparticles and VEGF can regulate oxidative stress under inflammatory conditions, protect VEGF bioactivity, and thereby improve angiogenesis efficiency.[55] In peripheral nerve regeneration research, Schwann cells overexpressing VEGF-A can promote microenvironmental vascularization, and this combined strategy provides new ideas for intervertebral disc repair.[57] In addition, acidic microenvironment-responsive hydrogels can achieve rapid release of VEGF, and this spatiotemporal controlled release technology provides an important reference for local drug delivery in the intervertebral disc.[60]

MiRNA regulatory networks play an important role in IDD. Studies have found that miR-21 inhibitors can exert regenerative effects by counteracting pathological changes during the degenerative process.[61] miRNA microarray analysis shows that there is a specific miRNA expression profile in degenerative intervertebral disc tissue, among which molecules such as miR-532 may become potential intervention targets.[62] miRNA therapy faces the challenge of rapid degradation *in vivo*, and exosome-based delivery systems are currently being developed, which can protect miRNAs and achieve targeted delivery.[63] Notably, miRNAs can not only directly regulate the degenerative process but also affect the microenvironment by regulating immune cells such as macrophages, providing a theoretical basis for the development of combined therapeutic strategies.[64,65]

The inflammatory microenvironment of IDD is a key factor driving vascular ingrowth and matrix degradation. Studies have found that glycogen synthase kinase 3β deficiency can promote vasodilation through the adenosine 5'-monophosphate-activated protein kinase/HIF-2α/VEGF/VEGFR2 axis, while improving the local microenvironment and reducing inflammation.[66] Multifunctional hydrogel systems can simultaneously achieve broad-spectrum antioxidant and macrophage phenotype regulation, restoring tissue redox and immune homeostasis, and this multieffect regulation provides a new method for improving the degenerative microenvironment.[34] Therapeutic strategies targeting macrophages show promising prospects, and by regulating the balance of M1/M2 macrophages, intervertebral disc inflammation and neurovascular co-invasion can be effectively alleviated.[13]

Given the complex pathological mechanisms of IDD, single-target therapy is often limited in efficacy. The latest research has developed a multifunctional microparticle system targeting reactive oxygen species, pyroptosis, and ECM degradation, showing synergistic therapeutic effects.[67] Hydrogel-based delivery systems can achieve spatiotemporal controlled release of VEGF and bone morphogenetic protein-2: Early rapid release of VEGF promotes vascularization, and late sustained release of bone morphogenetic protein-2 promotes tissue repair. This sequential therapeutic strategy is worthy of being applied in intervertebral disc repair.[60] Exosome therapy, due to its natural messenger function and targeting, can simultaneously regulate multiple pathological processes such as inflammation, apoptosis, and autophagy, becoming one of the most promising multi-target therapeutic carriers.[68,69] Nanoparticle drug delivery systems can overcome the limitations of traditional therapies and provide personalized treatment options for IDD by precisely regulating multiple molecular pathways.[13]

3. Current challenges and future directions

Currently, there is still controversy regarding the exact role of vascular ingrowth in IDD. Although angiogenesis has been recognized as a pathological feature of IDD,[70] there is no consensus on whether it is the cause or result of degeneration. Some studies suggest that vascular ingrowth may accelerate the degenerative process by destroying the original immune privilege of the intervertebral disc, promoting immune cell infiltration and inflammatory responses.[64,71] However, there is also evidence that vascularization may be a passive phenomenon secondary to NP cell senescence and ECM degradation.[72] This ambiguity in causality makes therapeutic strategies targeting vascular ingrowth face the dilemma of an unclear theoretical basis. The application of single-cell sequencing technology will help reveal the complex dynamic changes in cell subsets in the IDD microenvironment.[72] Through single-cell transcriptome analysis, specific markers of pro-angiogenic endothelial cell subsets can be identified,[73] providing precise molecular targets for targeted intervention. In addition, this technology can also analyze the single-cell communication network of macrophage-endothelial cell interaction,[74] deepening the understanding of the microenvironmental heterogeneity of vascular ingrowth.

Therapies targeting vascular ingrowth face dual challenges: the grasp of timing windows and the complexity of multi-target synergy. On the one hand, anti-VEGF therapy may inhibit pathological angiogenesis in the early stage but may hinder physiological vascularization required for tissue repair when applied in the late stage.[6] Therefore, procedural control of angiogenesis is necessary. Specifically, angiogenesis should be inhibited in the early stage of IDD development to control inflammation. However, during the IDD repair stage, it is necessary to maintain sufficient microvessels to supply tissues and achieve the regeneration and repair of the intervertebral disc. On the other hand, angiogenesis forms a complex regulatory network with processes such as oxidative stress,[40,75] cellular senescence,[72,76] and inflammatory responses,[13,34] making single-targeted intervention often ineffective. Existing studies have shown that even if VEGF signaling is successfully inhibited, macrophage-derived pro-inflammatory factors can still maintain the angiogenic microenvironment.[12] This multi-system interaction makes therapeutic strategies need to comprehensively consider temporal dynamics and target combinations.[19,73] The development of intelligent biomaterials provides powerful tools for vascular regulation. Drug delivery systems based on injectable microscaffolds can achieve local sustained release of antiangiogenic factors while maintaining the mechanical properties of the intervertebral disc.[73,77] New polysaccharide-based hydrogels can synergistically achieve vascular inhibition and cell protection by simulating the natural NP microenvironment.[78] Future efforts should focus on developing composite materials with microenvironment-responsive properties, enabling them to dynamically regulate the release kinetics of therapeutic molecules according to the degree of degeneration.[13,79] Such materials also need to integrate pro-regenerative factors to balance the needs of anti-vascular therapy and tissue repair.[80]

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Ethical statement

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Conflicts of interest

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Author contributions

BDT is responsible for the organization of literature and the writing of manuscripts. CY put forward the main ideas and was responsible for proof reading the manuscript.

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