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REVIEW ARTICLE

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From molecular regulation to tissue repair: hydrogels in the fight against intervertebral disc degeneration

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ABSTRACT

Background: Intervertebral disc degeneration (IVDD) is a leading cause of low back pain and involves multiple pathological processes, including cell apoptosis, senescence, oxidative stress–inflammation imbalance, and extracellular matrix (ECM) metabolic disorders. Current treatments such as pharmacotherapy, physical therapy, and surgery primarily relieve symptoms but fail to reverse the degenerative process and often carry the risk of complications.

Methods: This review systematically summarizes recent advances in the functional design and therapeutic applications of hydrogels for IVDD, with a focus on delivery systems, microenvironment modulation, and stimulus-responsive mechanisms. *In vivo* studies and preliminary clinical findings are also reviewed.

Results: Hydrogels have emerged as a promising strategy for IVDD regenerative therapy due to their excellent biocompatibility, injectability, and dynamic responsiveness. Acting as multifunctional platforms, hydrogels can precisely deliver stem cells, exosomes, and nucleic acid drugs, regulate apoptotic pathways (e.g. Bax/Bcl-2, Caspase-3), suppress pro-inflammatory cytokines (e.g. TNF-α, IL-1β), and promote ECM synthesis (e.g. collagen II and proteoglycans). Additionally, the incorporation of antioxidant nanoparticles and stimuli-responsive systems allows for effective remodeling of the degenerative microenvironment and interruption of the oxidative stress–inflammation feedback loop. Hydrogels fabricated using 3D bioprinting techniques with biomimetic architectures further improve mechanical stability, preserve disc height, and delay progression of degeneration. Preliminary clinical studies have confirmed the safety and therapeutic potential of hydrogels in IVDD treatment.

Conclusions: Hydrogels demonstrate a multidimensional therapeutic potential ranging from molecular regulation to tissue repair. They hold great promise as a regenerative medicine strategy for precise and effective treatment of IVDD.

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1. Introduction

The intervertebral disc (IVD) is an important biomechanical element of the spine, consisting of three functionally integrated elements: nucleus pulposus (NP), annulus fibrosus (AF), and cartilaginous endplate (CEP), which provide biomechanical stability, movement of loads, and supply of fluids to the IVD [1]. The NP is a gel-like structure rich in water and proteoglycans, which plays an important role in distributing pressure in the spine [2]. The primary role of the NP distributes mechanical load and compensates for spinal pressures experienced while performing daily activities and reduces stress to the spine and intervertebral disc [3]. The annulus fibrosus is composed of several layers of interlaced collagen fibers to

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provide superior elasticity and tensile strength. The AF can tolerate shear and tensile loading while providing protection to the NP [4,5]. The vertebral bodies are connected to the intervertebral disc through cartilaginous endplates that sit above and below the IVD. They primarily act to regulate the transportation of nutrients and transmit pressure between the IVD and the vertebral bodies to ensure IVD stability [6]. These elements work together to allow the spine to remain flexible, absorb loads, provide stability while tolerating loads associated with daily activities [7].

As individuals age, gain weight, or adopt unhealthy lifestyles (e.g. prolonged sitting, improper weight-bearing), intervertebral discs gradually undergo degeneration (Intervertebral Disc Degeneration, IVDD). IVDD is a multifactorial degenerative disease characterized by senescence and apoptosis of NP cells, degradation of extracellular matrix (ECM) components such as collagen and proteoglycans, and persistent activation of inflammatory cytokines [8,9]. Along with aging, apoptosis of nucleus pulposus cells(NPCs) and annulus fibrosus cells is one of the major mechanisms of IVDD develops, proteoglycans, and therefore water content, progressively decrease in the NP, which weakens its pressurizing-buffering capacity, and leads to a notable decrease in the degeneration of biomechanical properties of the disc [1,10]. The excessive expression of matrix-degrading enzymes, such as matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), exacerbates the degradation of ECM within the annulus fibrosus (AF) and NP. This not only compromises the mechanical stability of the intervertebral disc, but also increases the risk of NP displacement, which may ultimately lead to disc herniation [11]. Chronic inflammatory responses can also be characterized in IVDD. During the process of degeneration, inflammatory factors such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1) are released, which subsequently activate a number of different immune system cells, including macrophages and T cells, to induce local tissue inflammation [12]. These inflammatory responses not only exacerbate the damage to disc tissue but may also cause nerve root compression, leading to severe pain [13]. Chronic inflammation can also promote oxidative stress, which can lead to further increases of nucleus pulposus cells((NPCs) and annulus fibrosus cells apoptosis through the formation of free radicals, and therefore exacerbates the degenerative process [14,15]. The overlapping of these pathological mechanisms not only affects the biomechanical properties of the disc but also limits spinal mobility, ultimately severely impacting patients' quality of life [16]. The clinical manifestations of IVDD primarily include chronic low back pain. In certain cases, degenerative changes may lead to disc herniation, which in turn can cause radicular symptoms such as radiating leg pain. The severity of these symptoms is closely associated with the progression of disc degeneration [17]. Current treatment options for IVDD include conservative approaches, minimally invasive treatments, and surgical interventions [18]. Conservative treatment mainly alleviates symptoms through medications, physical therapy, and lifestyle adjustments, such as pain relievers, anti-inflammatory drugs, and traction, heat therapy or guided exercises. However, these methods often only provide symptomatic relief and fail to fundamentally repair the degenerated disc structure [19]. Minimally invasive treatments and surgical interventions, such as disc removal and spinal fusion, can effectively reduce pain and improve quality of life, but these methods are associated with higher risks of complications, postoperative recurrence, and negative impacts on spinal biomechanics [20,21]. Therefore, there is an urgent need for a treatment approach that not only repairs the degenerated disc structure but also restores its biomechanical function. In recent years, hydrogels, as emerging biomaterials, have shown promising potential in the treatment of IVDD [22]. Hydrogels are generally regarded as having excellent biocompatibility, degradability, and mechanical support capabilities, along with the ability to mimic the hydration characteristics of native intervertebral discs. These properties make them highly promising candidates for bearing biomechanical loads, relieving tissue pressure, and promoting tissue regeneration. However, their biocompatibility varies depending on their material composition, which will be elaborated in the following sections [23,24]. The hydrated nature of hydrogels allows them to replicate the biomechanical properties of natural intervertebral discs, providing support and alleviating the mechanical loads generated during IVDD [25].

In addition, hydrogels could act as delivery carriers for drugs and cells that deliver anti-inflammatory drugs, stem cells, or growth factors to the degenerated disc area to foster tissue repair. Stem cells or NPCs within hydrogels, for example, are capable of proliferating and differentiating within the disc and restoring function to the NPCs and slowing or reversing the degenerative process [26,27]. Smart responsive hydrogels are also able to sense local changes in the environment (e.g. pH, temperature) and subsequently release drugs or biological factors to enhance the therapeutic effect [28,29]. With these

technologies, hydrogels could not only reduce symptoms, but at the same time engender biological repair and regeneration of the intervertebral disc itself [19].

This review intends to provide a systematic perspective on recent research advancements of hydrogels in IVDD therapy by providing innovative strategies in multifunctional design, drug and cell delivery systems, microenvironment chemistry, and smart responsive hydrogels. To better facilitate valuable references to future studies and eventually clinic application, we provide a comprehensive review of recent literature making it easier to evaluate potential multi-integration of therapeutic characteristics targeted at IVDD therapy.

2. Pathological mechanisms of IVDD and treatment challenges

2.1. Multifactorial pathological mechanisms of IVDD

IVDD is a multifactorial condition involving cellular dysfunction, molecular imbalance, and altered biomechanics. These mechanisms jointly disrupt disc homeostasis and drive degeneration. (Figure 1). The following sections will discuss the pathological processes in an ordered manner based on three main dimensions: abnormal cell death, molecular metabolic dysregulation, and mechanical microenvironment imbalance.

2.1.1. Cellular mechanisms

Cellular Senescence: The aging of NP is a primary driver of the initiation and progression of IVDD. Wnt signaling, which can be activated by hypoxia, nutrient deprivation, and genetic predisposition, brings about the depletion of Tie2/GD2-positive NPCs progenitor cells and triggers NPCs to take on senescent characteristics. These phenotypes are characterized by a reduction in ECM synthesis and an increase in the secretion of matrix metalloproteinases (MMPs) [30]. The absence of ACE2 expression can accelerate NPCs senescence and the progression of IVDD *via* the TGFβ2/Smads signaling pathway by upregulating the expression of Serpine1 (PAI-1) [31]. In an acidic microenvironment, activation of the acid-sensing ion channels ASIC1/ASIC3 triggers the p53-p21/p27 and p16-Rb1 pathways, inducing senescence in

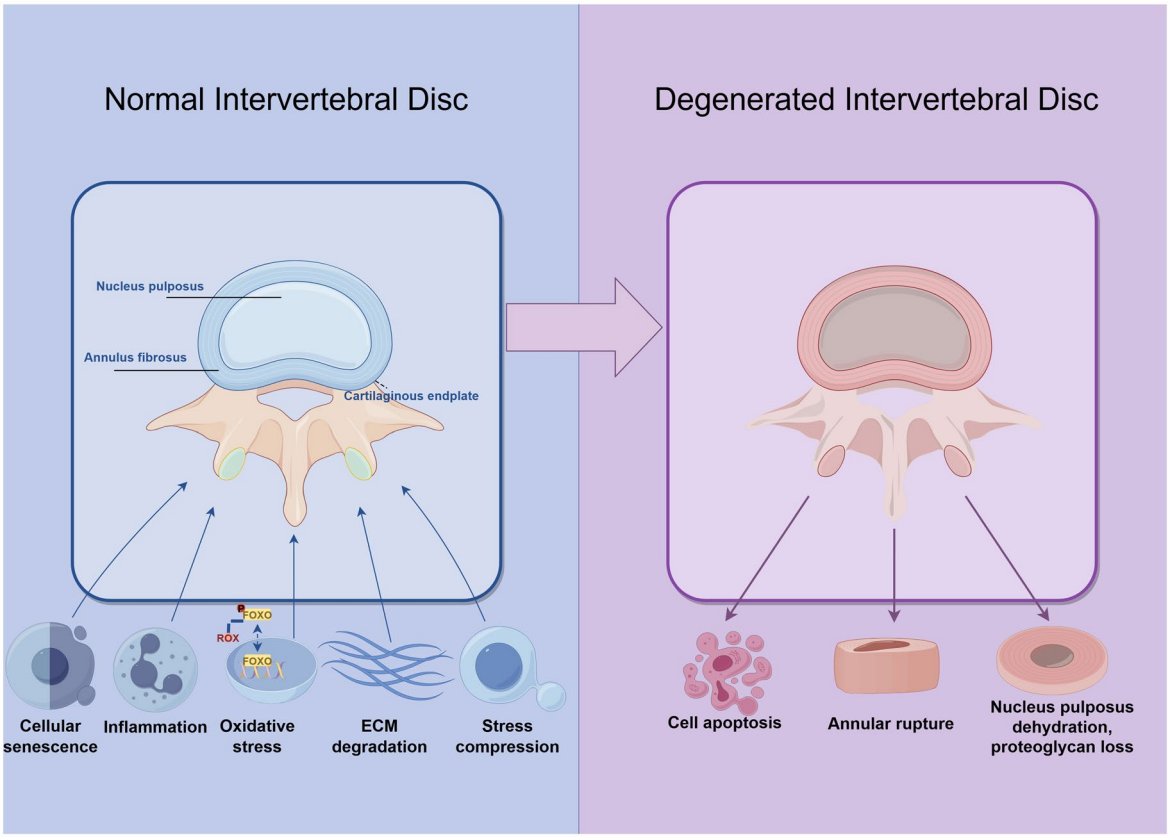

Figure 1. Pathogenetic mechanisms underlying IVDD.

mesenchymal stem cells within the nucleus pulposus cells(NPCs) [32]. Impaired chaperone-mediated autophagy (CMA) leads to abnormal accumulation of phospholipase Cγ1 (PLCG1), which, through the p53/p16 pathway, drives calcium overload-dependent senescence [33]. Mitochondrial dysfunction induces cell cycle arrest *via* the p53-p21 pathway, while the cGAS-STING pathway triggers the release of mtDNA, initiating an inflammatory response. These pathways synergistically promote the formation of the senescence-associated secretory phenotype (SASP) and ECM degradation [34]. Both the p53 signaling pathway (hsa04218) and the PI3K-AKT signaling pathway (hsa04151) activate DNA damage responses, amplify oxidative stress, and promote the release of ECM-degrading enzymes, thereby inducing NPs senescence and ECM breakdown, thus advancing the pathological course of IVDD [35]. Cell Apoptosis: Mitochondria-dependent apoptosis, characterized by Bax/Bcl-2 imbalance and eventual Caspase-3 activation, cooperates with the NF-κB pathway, leading to NPs death [36]. Overexpression of miR-22-3p significantly increases NPs apoptosis (flow cytometry results, $p < 0.001$), accelerating the progression of IVDD [37]. DJ-1 deficiency impairs mitochondrial autophagy, leading to cytochrome C leakage and activation of the Caspase-3-dependent apoptosis pathway (TUNEL assay results, $p < 0.001$) [38,39]. Inactivation of Nrf2 inhibits the expression of antioxidant genes (such as HO-1 and SOD), and the accumulation of ROS triggers mitochondria-dependent apoptosis [40]. Disruption of endoplasmic reticulum (ER) phagy indirectly activates apoptosis pathways by destabilizing ER homeostasis [41]. Cell Pyroptosis: ROS activation of the NLRP3 inflammasome leads to cleavage of GSDMD by Caspase-1 and the release of IL-1β, directly damaging NPs and exacerbating the inflammatory microenvironment [42]. PRDM1 promotes NPs pyroptosis by activating CASP1 transcription and inhibiting mitochondrial autophagy [43].

2.1.2. Molecular mechanisms

Oxidative Stress: Hypoxia leads to sustained activation of HIF-1α, and the accumulation of ROS causes mitochondrial respiratory chain damage and mtDNA oxidation, resulting in a vicious cycle [44]. ROS can induce DNA damage and G1-phase cell cycle arrest *via* the ATM-Chk2-p53 and MAPK/Akt pathways, while upregulating MMP-1/3/9 and ADAMTS-5 expression, thereby inhibiting ECM synthesis [45]. Inflammatory Response: Pro-inflammatory factors, such as TNF-α and IL-1β, increase the expression of MMPs/ADAMTS *via* the NF-κB pathway, promote macrophage infiltration, and activate the NGF/BDNF-ASIC3 pain pathway, establishing a harmful cycle of 'inflammation-matrix destruction-neuroplasticity' [13]. The p38 MAPK signaling pathway mediates the release of IL-6/TNF-α and the M1 polarization of macrophages, accelerating NPs apoptosis [46]. ECM Metabolism Dysregulation: TNF-α/IL-1β upregulates the expression of MMP3 through the NF-κB pathway, leading to the degradation of collagen II and proteoglycans [47]. Overactivation of MMPs/ADAMTS family members (e.g. ADAMTS-4/5) can cause collagen I deposition and water loss, reducing the mechanical properties of the intervertebral disc [43]. Disruption of circadian genes (e.g. BMAL1, Per2) exacerbates ECM degradation through autophagy imbalance [48].

2.1.3. Biomechanical mechanisms

Biomechanics plays a complex and multifaceted role in the progression of IVDD, involving structural alterations of the disc, deterioration of mechanical properties, and interactions with underlying biological mechanisms.

During IVDD, the intervertebral disc undergoes a loss of hydration, degradation of extracellular matrix (ECM), and disruption of the annulus fibrosus structure, which collectively compromise its biomechanical integrity. These changes result in abnormal load distribution, reduced disc height, and increased mechanical stress on surrounding tissues, further exacerbating cellular dysfunction and inflammatory cascades [49]. Studies have shown that as degeneration advances, the range of motion (ROM) of the degenerated spinal segment is significantly reduced, while the ROM of adjacent normal segments increases due to compensatory hypermobility. This imbalance in motion and load distribution imposes excessive mechanical stress on adjacent segments, accelerating their degeneration and contributing to adjacent segment disease (ASD) [50]. In addition, intradiscal pressure (IDP) in degenerated discs markedly decreases, whereas adjacent segments exhibit elevated IDP. This shift in pressure distribution further undermines the biomechanical stability of the spinal motion segment [51].

Importantly, mechanical loading also exerts significant effects on the biological behavior of disc cells. High-intensity mechanical strain can stimulate nucleus pulposus and annulus fibrosus cells to secrete

inflammatory cytokines and matrix-degrading enzymes, thereby promoting ECM degradation, inflammation, and apoptosis – processes that collectively drive disc degeneration [5]. Mechanical stress activates SPP1 in macrophages, inhibits the PERK/ATF4 axis, and reduces the secretion of the anti-inflammatory cytokine IL-10, exacerbating inflammation and ECM degradation [52]. Mechanical stimulation activates the Piezo1 ion channel, triggering ER stress and oxidative stress, which in turn activates the NLRP3 inflammasome, promoting IL-1β/IL-18 release and pyroptosis. Additionally, mechanical stimulation inhibits the SOST gene and activates the Wnt/β-catenin pathway, upregulating MMP3/MMP13 expression, leading to ECM degradation, and blocking PINK1/Parkin-mediated mitochondrial autophagy, resulting in ROS accumulation, mitochondrial dysfunction, and cellular aging/apoptosis. This cascade of events, involving NF-κB and SIRTs family dysregulation, amplifies inflammation, oxidative damage, and matrix metabolism disruption, collectively driving IVDD [53]. The research on the mechanisms of IVDD is specifically summarized in Table 1.

2.2. Limitations of traditional treatment strategies

Pharmacological and Physical Therapies: Long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) in the treatment of IVDD can lead to gastrointestinal side effects [54]. The efficacy of physical therapy (e.g. traction) for IVDD is limited by patient heterogeneity, and there is a lack of evidence for long-term

Table 1. Summary of mechanisms underlying IVDD.

Mechanism Category	Mechanistic	Signaling Pathways/ Molecular Mediators	Mechanistic Features	Cellular/Tissue-Level Outcomes	Ref
Cellular Senescence	Hypoxia and nutrient deficiency activate Wnt p53/p21 and pathways, inducing NPCs senescence	Wnt, p53/p21, PI3K-Akt, ACE2, TGFβ2/Smads	Progressive, associated with DNA damage and altered secretory phenotype	Decreased function and ECM synthesis in NPCs,with structural senescence	[31,32,34]
Apoptosis	Mitochondrial and NF-κB pathways mediate apoptosis	Bax/Bcl-2, Caspase-3, NF-κB, DJ-1, AIF, ER-phagy	Programmed cell death regulated by oxidative and mitochondrial signaling	Cell loss and impaired tissue regenerative capacity	[37–39]
Pyroptosis	ROS activates NLRP3 and CASP1, leading to GSDMD-mediated pyroptosis	NLRP3, Caspase-1, GSDMD,	Inflammation-dependent membrane rupture distinct from apoptosis	Membrane rupture, inflammatory cytokine release, and accelerated degeneration	[42,43]
Oxidative Stress	Hypoxia and ROS accumulation cause mitochondrial and DNA damage, suppressing ATP synthesis	HIF-1α, p53, ATM/ Chk2, MAPK, Nrf2, DJ-1	Disruption of both ROS and mitochondrial functions across multiple pathways	Induced apoptosis, impaired autophagy, and ATP depletion	[40]
Inflammatory Response	Pro-inflammatory cytokines (TNF-α, IL-1β) promote MMP activation and immune cell infiltration	NF-κB, IL-1β, TNF-α, IL-6, p38MAPK	Early activation leading to downstream degenerative cascades	Matrix destruction, pain sensitization, and sustained inflammation	[30,46]
Extracellular Matrix (ECM) Metabolic Imbalance	NF-κB and JAK/STAT3 signaling enhance MMP and ADAMTS expression, degrading type II collagen	NF-κB, JAK/STAT3, MMP3/13, ADAMTS4/5, Aggrecan, COL2A1	Primarily inflammation-mediated, challenging to reverse	ECM degradation, dehydration, and decreased mechanical integrity	[43]
Circadian Rhythm Disruption	Disruption of circadian clock genes (BMAL1, CLOCK, REV-ERBα) impairs autophagy	BMAL1, CLOCK, REV-ERBα, C/EBPβ	Imbalance in regulatory control of circadian timing	Insufficient autophagy and ongoing ECM degradation	[48]
Mechanical Stress	Mechanical stress activates Piezo1, Wnt/β-catenin, and NF-κB pathways, inducing oxidative stress and inflammation	Piezo1, Wnt/β-catenin, NF-κB, NLRP3, PERK/ATF4	Coupled mechano-biochemical signaling affecting multiple levels	Pro-inflammatory response, pyroptosis, ROS accumulation, and ECM damage	[52,53]

Abbreviations. Wnt: Wingless-related integration site; PI3K-Akt: Phosphoinositide 3-kinase – Protein kinase B pathway; ACE2: Angiotensin-Converting Enzyme 2; TGFβ2/Smads: Transforming Growth Factor beta 2/SMAD signaling proteins; Bax/Bcl-2: Bcl-2-associated X protein/B-cell lymphoma 2; Caspase-3: Cysteine-aspartic acid protease 3; NF-κB: Nuclear Factor kappa-light-chain-enhancer of activated B cells; DJ-1: Parkinsonism associated deglycase; AIF: Apoptosis-inducing factor; NLRP3: NOD-, LRR- and pyrin domain-containing protein 3; GSDMD: Gasdermin D; HIF-1α: Hypoxia-Inducible Factor 1-alpha; ATM/Chk2: Ataxia Telangiectasia Mutated/Checkpoint Kinase 2; MAPK: Mitogen-Activated Protein Kinase; Nrf2: Nuclear factor erythroid 2–related factor 2; IL-1β: Interleukin 1 beta; TNF-α: Tumor Necrosis Factor alpha; p38MAPK: p38 Mitogen-Activated Protein Kinase; JAK/STAT3: Janus Kinase/Signal Transducer and Activator of Transcription 3; MMP3/13: Matrix Metalloproteinases 3 and 13; ADAMTS4/5: A Disintegrin and Metalloproteinase with Thrombospondin Motifs 4/5; COL2A1: Collagen Type II Alpha 1; BMAL1: Brain and Muscle ARNT-Like 1; CLOCK: Circadian Locomotor Output Cycles Kaput; REV-ERBα: Nuclear Receptor Subfamily 1 Group D Member 1; C/EBPβ: CCAAT/Enhancer Binding Protein beta; Piezo1: Mechanosensitive Ion Channel Piezo Type 1; PERK/ATF4: Protein kinase RNA-like endoplasmic reticulum kinase/Activating Transcription Factor 4.

effectiveness [55]. Surgical Interventions: Although procedures such as disc removal and spinal fusion can relieve nerve compression and improve clinical symptoms in the short term, they alter the distribution of biomechanical loads, significantly increasing the risk of adjacent segment degeneration [20]. Regenerative Medicine Challenges: In the treatment of IVDD, bioactive substances often suffer from short durations of action and rapid local drug clearance, making it difficult to maintain effective therapeutic concentrations, thereby significantly limiting their clinical efficacy [56]. Stem cell therapy faces challenges, including low post-implantation cell survival, the hostile disc microenvironment that inhibits cell adaptation and functional differentiation, and insufficient safety data [57].

2.3. Emergence of hydrogels as a novel treatment strategy

Hydrogels, as an emerging therapeutic strategy, have demonstrated significant potential in the treatment of IVDD in recent years. Current research primarily focuses on developing hydrogel systems with excellent biocompatibility, injectability, and controlled release properties, aimed at delivering drugs, gene regulatory sequences, or cellular therapeutics to promote disc regeneration [58,59].

3. Hydrogel materials Science: from fundamental properties to precision design

3.1. Core properties of hydrogels and the needs for IVDD repair

Hydrogels have garnered significant attention for their application in IVDD repair, with their core properties-including pore structure, degradation rate, biocompatibility, and mechanical characteristics-directly influencing their effectiveness in IVDD treatment [60,61]. The core properties of hydrogels are summarized in Table 2. Current research is focused on developing hydrogels with ideal mechanical properties, high biocompatibility, and controllable degradation rates, to mimic the ECM of the intervertebral disc and promote tissue regeneration [62,63].

Within these properties, the pore structure of hydrogels plays a significant role in cell survival, proliferation, and ECM deposition. Hydrogels with appropriate porosity can better mimic the natural ECM microenvironment of the body, driving cell migration, nutrient transfer, and the synthesis of the matrix, which will enhance the regenerative repair capacity of hydrogels used in degenerated discs [64,70]. The degradation rate of the hydrogel ultimately determines its time in the body, in addition to the rate at which drugs or cells embedded in the hydrogels can be released. An ideal degradation rate should coincide with the rate of tissue regeneration, in which case it would be too fast to complete repair, or too slow, inducing inflammation and limiting the reconstruction of new tissues [65,71]. Biocompatibility is the primary basis for the safe implantation of hydrogels in the IVDD microenvironment. Biocompatibility encourages cell activity, limits inflammatory responses, and promotes ECM reconstruction and functional repair, ultimately contributing to significant long-term repair [62,66]. The mechanical properties of hydrogels, especially their elastic modulus, are also significant for replicating the mechanical environment of the intervertebral disc. An elastic modulus closely resembling the natural NPCs tissue elastic modulus will

Table 2. Core properties of hydrogels and their relevance to IVDD repair.

Core Property	Scientific Function	Relevance to IVDD Repair	Ref.
Porous Structure	Provides 3D support for cell adhesion, migration, and ECM synthesis	Mimics ECM microenvironment of NPCs; promotes cell viability and matrix deposition	[64]
Degradability	Controlled degradation and release profile to match tissue regeneration timeline	Maintains structural integrity while relieving mechanical stress, avoiding overly rapid or excessively slow degradation.	[65]
Biocompatibility	Compatibility with host tissues and cells; non-toxic and non-immunogenic	Supports cell viability, reduces inflammation, promotes functional repair	[66]
Mechanical Properties	Elastic modulus close to native NPCs for mechanical integrity	Restores biomechanical stability; prevents collapse or annulus stress	[67]
Injectability	Facilitates minimally invasive administration *via* syringe injection	Enables localized, targeted therapy; improves clinical operability	[68]
viscosity	Combines elasticity and viscosity to accommodate dynamic loads	Simulates load-bearing behavior of discs; cushions impact and delays degeneration	[69]

Abbreviations: 3D: Three-dimensional; ECM: Extracellular Matrix; NPCs: Nucleus Pulposus Cells; IVDD: Intervertebral Disc Degeneration.

promote NPCs migration, NPCs aggregation, and ECM synthesis, which will help reconstruct the structural integrity and function of tissue [67]. Ideally, hydrogels would also display viscoelasticity resembling disc tissues, which would buffer load, maintain mechanical homeostasis, and mitigate the potential for further annulus fibrosus degeneration due to pathological load stress [64,68,69].

The ability to inject hydrogels has considerable potential for minimally invasive treatments because it allows for focal delivery of therapeutic agents, an appealing clinical advantage of hydrogels in IVDD therapy [60,68]. This discussion emphasizes that the design of hydrogels has to be holistic, taking the microstructure, biological behavior, and mechanical properties of the hydrogels into account for a systematic treatment of complex pathological conditions of IVDD [66,67,72]. The therapeutic effects of hydrogels in IVDD have been extensively validated by numerous studies. The following section summarizes their properties and current research progress (Figure 2).

3.2. Functionalized design targeting the pathological mechanisms of IVDD

Based on the pathological mechanisms discussed in Section 2.1, including ECM degradation, oxidative stress, and the inflammatory microenvironment, various therapeutic strategies have been developed. In the following subsections, we introduce hydrogel-based therapeutic approaches that primarily target these pathological mechanisms, aiming to mitigate IVDD and restore disc function.

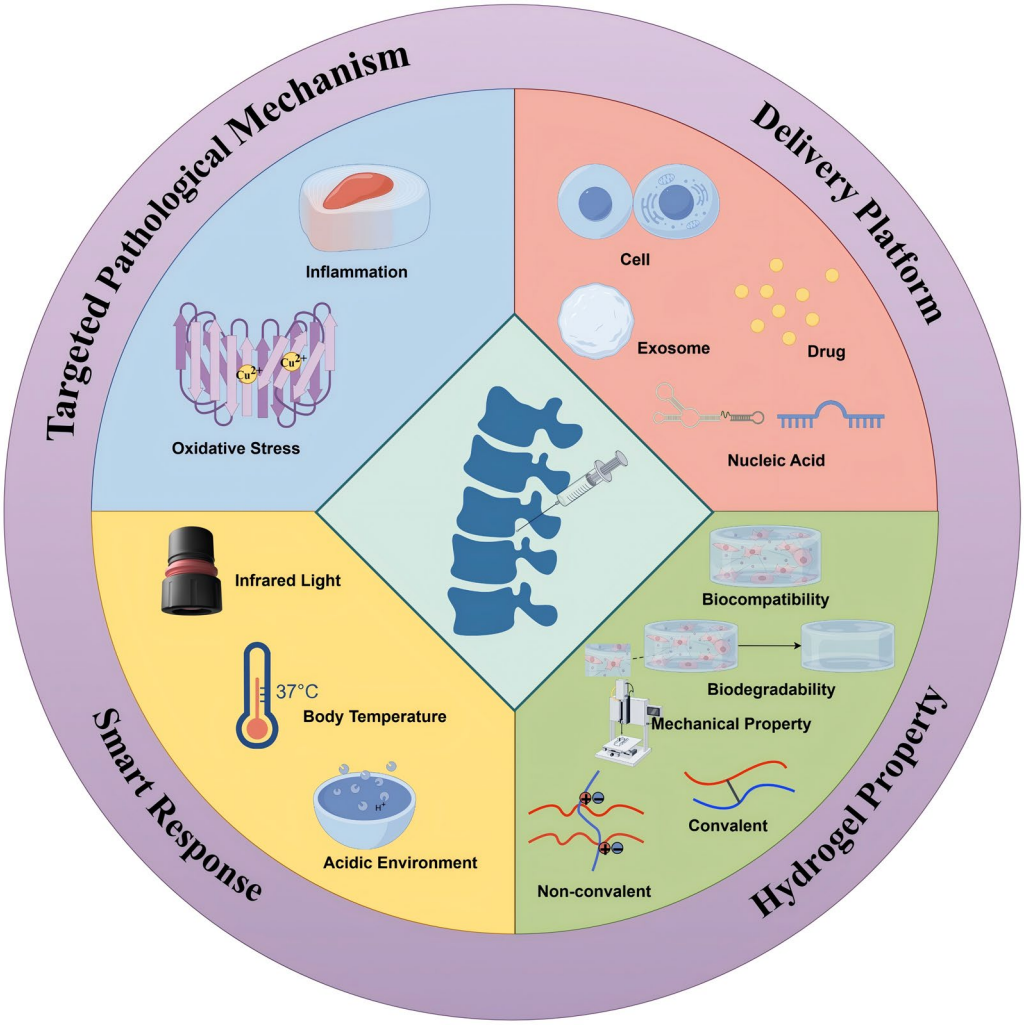

Figure 2. Properties of hydrogels and their applications in IVDD treatment.

3.2.1. Cell and molecular delivery platforms

Treatment approaches for IVDD demand a precise intervention to address its multifactorial pathobiological mechanisms. Given that cell senescence and apoptosis contribute significantly to IVDD as described in Section 2.1.1, hydrogels, with their injectability and biocompatibility and tunable properties, have been designed as an ideal platform for delivering cells, exosomes, and nucleic acids. .The following section will systematically build on the functionalized design of hydrogels in the context of the latest research to facilitate pro-cell and molecular therapy.

3.2.1.1. Cell delivery: promoting regeneration and functional recovery. Cell-based therapies play a fundamental role in the regenerative treatment of IVDD. Various cell types – including AF cells, NPCs, and MSCs – have been delivered using hydrogels to restore disc structure and function. For example, Panebianco et al. developed a composite system composed of fibrin-genipin cross-linked hydrogel (FibGen) and oxidized alginate microbeads (OxAlg MBs), which carried annulus fibrosus cells (AF cells). This system provided immediate mechanical support through the high-modulus FibGel, while the OxAlg microbeads gradually released the cells, promoting long-term ECM synthesis and significantly reducing the risk of herniation in a bovine tail organ culture model [73]. Similarly, Barcellona et al. used laminin-mimetic peptide-modified hydrogels to deliver NPCs into the degenerated intervertebral disc, successfully restoring disc height and ECM components (such as proteoglycans) in a rat model, indicating that the physicochemical properties of the hydrogel are crucial for maintaining cell phenotype [74]. Furthermore, Zhou et al. developed a collagen type II/chondroitin sulfate (CCSA) hydrogel system to deliver ADSCs, which, through gene expression modulation, induced the differentiation of ADSCs into NP-like cells, significantly improving the water content and tissue structure of degenerated NPCs [75]. Choi et al. encapsulated Wharton's jelly mesenchymal stem cells (WJ-MSCs) in a hyaluronic acid-methylcellulose (HAMC) hydrogel, significantly enhancing cell survival rates, and delaying degeneration by inhibiting ECM degradation and promoting anabolic metabolism [76].

3.2.1.2. Exosome delivery: modulating the microenvironment and suppressing inflammation. Exosomes, by carrying active molecules such as microRNA and proteins, can precisely regulate cell metabolism and inflammation. However, their rapid *in vivo* clearance limits their therapeutic effectiveness. Xing et al. developed a thermosensitive decellularized ECM hydrogel (dECM@exo) loaded with ADSC-derived exosomes. This system not only repaired ECM leakage *via in situ* gelation but also inhibited MMPs activity and alleviated cell pyroptosis by releasing exosomes, effectively maintaining the homeostasis of the disc microenvironment in animal models [77]. Li et al. further analyzed the potential of gelatin-methacryloyl (GelMA) hydrogels as exosome carriers, highlighting their photosensitivity and tunable mechanical properties that support cell regeneration [78].

In conclusion, the above research demonstrates that hydrogels, as delivery platforms for cells, exosomes,exhibit multidimensional therapeutic potential: cell delivery replenishes degenerated intervertebral disc cells, exosome delivery modulates microenvironment homeostasis, and nucleic acid delivery targets the inhibition of degeneration pathways. Therefore, hydrogels show promising prospects as multifunctional delivery platforms for cells, exosomes, and nucleic acids in the treatment of IVDD.

3.2.2. Anti-inflammatory and antioxidant strategies

As described in Section 2.1, oxidative stress and chronic inflammation are key drivers in the progression of intervertebral disc degeneration (IVDD). Hydrogels, as versatile delivery platforms, have shown great potential in targeting and modulating these pathological processes. Their core design strategy lies in the integration of anti-inflammatory and antioxidant agents, enabling precise injection and sustained release at the lesion site. This allows for targeted intervention in critical signaling pathways – particularly the NF-κB and NLRP3 inflammasome cascades – thereby disrupting the vicious cycle of 'inflammation–oxidative stress–cell apoptosis'.

3.2.2.1. Anti-inflammatory strategies: disrupting the NF-κB–inflammasome axis. The inflammatory cascade in IVDD is primarily mediated by cytokines such as IL-1β and TNF-α, which activate NF-κB and NLRP3 inflammasome signaling.This article finds that hydrogels that can provide these pathway inhibitors have already demonstrated the effect of reshaping the inflammatory microenvironment.

For instance, pH-responsive HAMA microspheres releasing IL-1Ra achieved precise inhibition of IL-1 signaling, alleviating inflammation in degenerated NPCs [28]. TA nanoparticle-modified hydrogels suppressed TNF-α expression while supporting ECM homeostasis [79]. KGN and IL-10 co-delivered *via* GelMA hydrogels exhibited dual regulation of inflammatory signaling and matrix metabolism, significantly improving disc repair [80]. Moreover, dual-network hydrogels incorporating Mg^{2+} and HA-histidine complexes enhanced the resilience of NPCs under inflammatory stress, suggesting a promising strategy to improve cell function in hostile microenvironments [81].

3.2.2.2. Antioxidant strategies: scavenging ROS and restoring redox balance. Researchers try to use a hydrogel material with antioxidant properties that reduces oxidative damage and helps cells better resist external pressure. The experimental results show that this hydrogel has a clear effect on restoring the redox balance in cells. EGCG-modified gelatin hydrogels reduced ROS-mediated NPC injury and improved cell viability [82]. BPQD-loaded microspheres (GM@CS-BP) attenuated ASIC3 activation and reduced H_2O_2 levels by over 200%, preserving ECM integrity [83]. Additional systems such as fucoidan-GelMA microspheres (Fu@GelMA-MS) and dynamic HA-NCSN/Cu hydrogels modulated NRF2 or TGF-β/Smad pathways to enhance antioxidant capacity and matrix regeneration [84,85]. Hybrid release systems combining TA and resveratrol in PLGA-PEG-PLGA hydrogels provided temporal control over inflammation and oxidative stress, resulting in sustained ECM repair [86].

3.2.2.3. Nucleic acid-mediated modulation: precision targeting of degenerative pathways. The advantage of these methods is that they can regulate inflammatory reactions and oxidation signals very accurately. If you put them into the hydrogel, it can also bring more benefits, because the hydrogel can provide a way to provide localized and continuous drug administration, so that the treatment effect will be better.siRNA-loaded G5-PBA@Gel hydrogels effectively silenced p65, blocked NLRP3 activation, and reduced pyroptosis in NPCs [87]. Antagomir-204-3p delivered *via* ZOG hydrogels suppressed apoptosis and improved mechanical integrity [67]. miR-5590-loaded DNA hydrogels activated autophagy and preserved matrix homeostasis [88]. Advanced platforms integrating miR-21 inhibitors and mitochondrial-targeting peptides (ss-31) within TA nanogels modulated the Spry1–cGAS–STING axis to achieve dual inflammation–oxidation control [86,89]. Similarly, Klotho circRNA-NT-LNPs combined with hydrogels reversed senescent NPC phenotypes, offering a strategy to combat age-associated disc degeneration [90].

These hydrogel drugs can simultaneously deal with the inflammation and oxidation caused by IVDD, and they can control the redox reaction by accurately sending the drug to the place where it is needed, and the redox reaction can be controlled. In this way, it can alleviate the symptoms of the degeneration of the disc, and solve the problem from the root cause, providing a more comprehensive solution to the treatment of the disease.

3.2.3. ECM protection and regeneration

ECM degradation, particularly of aggrecan and collagen II, was discussed in Section 2.1.4.Hydrogels, as functional carriers, have become key tools in repairing ECM homeostasis by integrating strategies such as inhibition of ECM degradation factors, delivery of pro-synthetic biomolecules, gene regulation, and biomimetic microenvironment construction. The following section systematically discusses the mechanisms and applications of hydrogels in ECM protection and regeneration, based on the latest research advancements.

3.2.3.1. Inhibition of ECM degradation enzyme activity and inflammatory regulation. Excessive ECM degradation is primarily mediated by MMPs and ADAMTS, while the inflammatory microenvironment exacerbates ECM breakdown. Dynamic nanohybrid peptide hydrogels (NHPH) significantly reduce ECM degradation and promote its remodeling by scavenging pro-inflammatory ROS and inhibiting MMP activity [91]. Similarly, LAPONITE®-crosslinked pNIPAM-co-DMAc hydrogels (NPCsgel) loaded with enzyme inhibitors (such as collagenase and aggrecanase ABC inhibitors) restore the homeostasis of collagen and proteoglycans by inhibiting the activities of MMP-3 and ADAMTS4 [92]. A hydrogel system based on tannic acid nanoparticles (TA NP) delivers Antagomir-21 to silence MMP gene expression and scavenge ROS, further restoring ECM metabolic balance [79]. Furthermore, BPQD-modified gelatin methacrylate

(GelMA) microspheres (GM@CS-BP) inhibit the expression of acid-sensitive ion channel-3 (ASIC-3) and inflammatory factors, reducing MMP expression and remodeling ECM homeostasis [83].

3.2.3.2. Delivery of bioactive molecules to promote ECM synthesis. Growth factors (such as TGF-β3, BMP-2) and small molecules (such as Kartogenin, KGN) activate ECM synthesis pathways. Photosensitive dextran methacrylate-fucoidan composite hydrogels (DexMA-Fucoidan) promote ECM metabolism and suppress inflammation by activating the CAV1-YAP mechanical transduction axis, significantly enhancing the synthesis of collagen II and proteoglycans [93]. Graphene oxide (GO)-self-assembled peptide hybrid hydrogels loaded with TGF-β3 release the growth factor through GO, upregulating the expression of collagen II and aggrecan in NPCs, promoting the deposition of NP-specific ECM [94]. KGN and IL-10 co-loaded GelMA hydrogels (KGN + IL-10@GelMA) enhance antioxidant capacity by activating the NRF2 pathway, while also promoting collagen II synthesis, thereby delaying the degeneration process [80]. Fucoidan-functionalized GelMA microspheres (Fu@GelMA-MS) restore redox balance by activating the NRF2 pathway, significantly delaying the degeneration process [84]. Additionally, a gel-based hydrogel loaded with platelet-rich plasma (PRP) and simvastatin (SIM) nanomiscelles (HAMC) inhibits inflammation and promotes ECM regeneration, showing good biocompatibility and tissue repair potential in subcutaneous implantation experiments [95]. Chondroitin sulfate (CS)-modified intervertebral disc-derived ECM hydrogels enhance the secretion of sGAG and collagen II by nasal chondrocytes (NCs), simulating the natural NPs microenvironment to support ECM regeneration [96].

3.2.3.3. Gene regulation and ECM metabolic balance. Gene therapy can precisely repair the ECM by regulating the expression of ECM-related genes. PEG hydrogels loaded with Agomir874 restore ECM synthesis/degradation balance by downregulating MMP expression, improving the degenerative disc microenvironment [97]. M2c macrophage-derived exosomes (M2c-Exos) loaded in hyaluronic acid hydrogels (M2c-Exos@HA) regulate ECM metabolism through the miR-124/CILP/TGF-β axis, significantly increasing collagen II and aggrecan content [98]. Decellularized NPCs matrix hydrogels (DNP-G) integrate the integrin-RhoA/LATS/YAP1 signaling pathway to induce MSCs to differentiate into NP-like cells, promoting ECM-specific regeneration [99]. KGN-enhanced dynamic self-healing hydrogels activate the NRF2 pathway, restore the redox balance in NP cells, and promote collagen II synthesis, significantly improving ECM metabolic imbalance in a puncture-induced IVDD model [100]. Additionally, PEMF (pulsed electromagnetic field) therapy provides a novel approach for gel-based therapies by activating the SIRT1-autophagy signaling network to inhibit ECM degradation [101].

3.2.3.4. Construction of biomimetic ECM microenvironment. Biomimetic materials are designed to simulate the composition and structure of natural ECM, providing the biochemical and mechanical signals necessary for cell regeneration. 3D hydrogels based on collagen type II and hyaluronic acid (HA) can guide WJ-MSCs to differentiate into NP-like cells, significantly enhancing the synthesis of collagen II and proteoglycans [102]. Decellularized matrix (DCM) hydrogels (e.g. DNP-G and DAF-G) retain the protein composition and spatial properties of natural ECM, inducing MSCs to differentiate directionally through tissue-specific microenvironments, promoting ECM regeneration in NPCs or annulus fibrosus [99,103]. Self-assembling peptide hydrogels (SAPHs), due to their high biocompatibility and ECM biomimetic characteristics, are widely used in NPCs spheroid culture, significantly enhancing ECM synthesis and tissue repair capacity [104,105].

In conclusion, hydrogels provide a comprehensive solution for IVDD treatment, ranging from molecular regulation to tissue biomimicry, through various multimodal strategies targeting ECM protection and regeneration. Notable progress has been made in strategies such as inhibition of ECM degradation enzymes (e.g. MMP inhibitors), delivery of pro-synthetic molecules (e.g. TGF-β3/KGN), gene regulation (e.g. miRNA/exosomes), and the construction of biomimetic microenvironments (e.g. DCM/self-assembling peptides).

3.2.4. Mechanical adaptation and dynamic response

The pathological microenvironment of IVDD is characterized by dynamic changes, such as acidic pH, hypoxia, and abnormal mechanical load. As a result, developing hydrogels with mechanical adaptability and dynamic response capabilities has become a core strategy for repair. This section focuses on the current research advancements in the mechanical adaptation design of hydrogels, their dynamic response mechanisms, and their application in synergistic therapies.

3.2.4.1. Mechanical adaptation: mimicking the mechanical properties of natural discs. The mechanical stability of the intervertebral disc relies on the elasticity of the NPCs and the tensile distribution in the annulus fibrosus. Traditional hydrogels often fail to maintain intervertebral disc height over time due to insufficient mechanical properties [106]. Recent studies have significantly improved the mechanical properties of hydrogels through material composites and crosslinking strategies. For instance, Wei et al. developed a three-crosslinked hydrogel (OHA-DA-PAM/CMP/TGF-β1) that combines the synergistic effects of oxidized hyaluronic acid-dopamine-polyacrylamide to achieve tensile strength (>1 MPa) and self-healing ability similar to natural annulus fibrosus, effectively resisting the dynamic loads of the intervertebral disc [107]. To further optimize the compatibility between hydrogels and the biomechanical environment of the intervertebral disc, Cai et al. proposed a mechanical adaptability strategy by developing a dual-network hydrogel system (PVA-DN) with tunable viscoelastic properties. Under dynamic compression conditions, this hydrogel effectively supported the proliferation and adhesion of NPCs, activated the expression of specific ECM components, and improved the inflammatory microenvironment by inhibiting the IL-17 signaling pathway. *In vivo* studies in rats demonstrated that the hydrogel could restore the function of degenerated intervertebral discs [23]. Wang et al. systematically reviewed the application of various polysaccharide-based materials – such as hyaluronic acid, alginate, and chitosan – in intervertebral disc regeneration, emphasizing their excellent biocompatibility and their ability to provide both mechanical support and microenvironmental regulation for the nucleus pulposus [19]. In addition, Chopra et al. proposed the use of biomimetic proteoglycans (PGs) to enhance the water-retention capacity and anti-degradation properties of disc tissue. By structurally modifying these PGs to incorporate bioactive peptide sequences, they achieved the potential to restore intervertebral disc mechanical function even in the absence of cellular or nutritional support, offering a novel perspective for orthobiologic strategies [108]. These studies indicate that the elastic modulus, adhesiveness, and fatigue resistance of hydrogels must be precisely matched to the mechanical demands of different regions of the intervertebral disc to provide long-term stable mechanical support. Mechanical stimulation and cellular mechanotransduction also show a synergistic effect, as hydrogels adapted to mechanical forces can transmit mechanical signals to regulate cellular behavior.

3.2.4.2. Dynamic response: smart adaptation to pathological microenvironment. Dynamic response hydrogels can autonomously adjust their physical state or function according to physicochemical changes in the intervertebral disc microenvironment, such as pH, ROS levels, or temperature. For example, Li et al. developed a fucoidan-methyl methacrylate-dextran (DexMA) composite hydrogel that undergoes a sol-gel phase transition under acidic pH and activates ECM synthesis in NPCs *via* the CAV1-YAP mechanical transduction pathway [93]. Bonetti et al. reviewed methylcellulose (MC) thermoresponsive hydrogels that undergo *in situ* gelation under body temperature, protecting cells from shear force damage and controlling drug release kinetics *via* thermal response [109]. Additionally, Bu et al. designed a HA-NCSN/Cu dynamic hydrogel that uses Cu^{2+}/Cu^{+} redox reactions to generate photothermal effects, locally increasing temperature under near-infrared light stimulation and co-regulating the TGF-β/Smad pathway to promote collagen regeneration [85]. These smart response mechanisms not only improve the targeting of treatments but also prevent the failure risks associated with the static properties of traditional materials.

To balance mechanical adaptation and dynamic response, multi-scale composite strategies have become a research hotspot. For instance, Cheng et al. developed an OPF/SMA-PLGA dual-drug controlled release hydrogel that loads IL-4 and kartogenin into PLGA microspheres, achieving sequential regulation of anti-inflammatory and regenerative effects while providing mechanical support [65]. Gao et al. proposed a stimulus-responsive composite hydrogel system integrating gel scaffolds and nanoparticles, using multi-level responses (such as pH, enzymatic degradation) to achieve dynamic balance between mechanical properties and drug release [63]. This type of design overcomes the functional limitations of single materials, providing new strategies for precise treatment in complex pathological microenvironments.

3.3. Cutting-edge technologies empowering hydrogel design-3D bioprinting

3D bioprinting technology provides a revolutionary solution for constructing biomimetic intervertebral disc scaffolds by precisely controlling material deposition and structural assembly. Its core advantage lies in its ability to replicate the complex hierarchical structure of the intervertebral disc (such as the angular layer arrangement of the AF and the NP-annulus fibrosus interface), while integrating functionalized hydrogels to promote cell adhesion, differentiation, and tissue regeneration. Traditional 3D printing

techniques are limited by resolution, making it challenging to precisely simulate the concentric angular layered structure of the AF. The introduction of electrohydrodynamic 3D printing significantly improves printing precision, successfully producing high-resolution polycaprolactone (PCL) scaffolds with angular layer designs highly similar to natural AF. The mechanical compatibility was validated through finite element analysis [110]. Similarly, the combination of 3D printing with electrospinning technology allows for the creation of directional porous fiber bundles supported by polylactic acid (PLA) frameworks, mimicking the mechanical response characteristics of the AF. Simultaneously, the hydrogel loaded with BMSCs mimics NPCs, achieving high structural and functional matching with the natural intervertebral disc [111].

The design of bioinks for 3D-printed hydrogels is a key technological breakthrough. Sulfated hydrogels (e.g. sulfated chondroitin sulfate, sulfated heparin-modified) have gained attention due to their excellent bioactivity. They not only maintain the phenotype of NPCs and chondrocyte cells but also enable the controlled release of growth factors, providing support for the repair of the intervertebral disc microenvironment [112]. Additionally, composite hydrogel sealants, by integrating 3D-printed thermoplastic polyurethane (TPU) meshes with tough hydrogels, precisely match the shape and mechanical properties (elastic modulus, fracture toughness) of AF defects. This combination effectively prevents herniation recurrence and restores biomechanical function in bovine intervertebral disc models [113]. These achievements lay an important foundation for clinical translation.

As a viable material for treating IVDD, hydrogel design has evolved from single-function systems to multimodal synergistic frameworks. By regulating porous structure, degradation kinetics, and mechanical compatibility, hydrogels not only mimic the biomechanical properties of natural intervertebral discs but also achieve targeted modulation of the degenerative microenvironment through functional components such as anti-inflammatory/antioxidant molecule delivery, ECM metabolic regulation, and cellular/exosome loading. The integration of dynamically responsive hydrogels (e.g. pH/ROS-sensitive systems) with 3D bioprinting technology further advances the construction of biomimetic architectures and enables personalized therapeutic strategies. The functionalized design of hydrogels in the treatment of IVDD has evolved into a multidimensional synergistic therapeutic framework (Table 3). By loading cells (e.g. MSCs), exosomes, or nucleic acids (siRNA/miRNA) to target and modulate apoptosis and inflammatory pathways, integrating antioxidant nanoparticles (e.g. EGCG, BPQDs) and anti-inflammatory factors (e.g. IL-1Ra) to scavenge reactive oxygen species (ROS) and block inflammatory cascades, and utilizing growth factors (e.g. TGF-β3) or enzyme inhibitors to maintain ECM synthesis-degradation balance, hydrogels effectively mimic the physiological biomechanical microenvironment through mechanically adaptive and dynamically responsive designs, enabling on-demand therapeutic delivery. 3D bioprinting further advances the construction of personalized regenerative architectures. The integration of these pioneering strategies has unveiled novel pathways for achieving precise repair and functional reconstruction in IVDD therapy, marking a pivotal transition from theoretical exploration to clinical translation in disc regeneration medicine.

4. Hydrogel therapy for IVDD: translational applications

4.1. Key findings from preclinical research

Preclinical animal model studies have shown that hydrogel interventions can significantly slow down the progression of IVDD and promote tissue repair. In small animal models, such as rat needle puncture-induced IVDD models, hydrogel injection effectively maintains disc height and water content. MRI imaging results show that the T2-weighted signal intensity of intervertebral discs in the hydrogel-treated group was significantly higher than in the degenerative control group, with corresponding Pfirrmann degeneration scores being lower, indicating that the water content of the NP and disc structure were preserved [60]. Additionally, X-ray or micro-CT measurements confirmed that hydrogels could partially restore the damaged disc height, with the disc height index (DHI) approaching that of the normal group within a few weeks after surgery, while the untreated group showed continued decline in DHI [87]. Histological evaluations further confirmed the effectiveness of the hydrogel treatment: H&E and Safranin O-Fast Green staining showed that the morphology and matrix composition of the NPCs in the hydrogel group were close to normal, with a clear annulus fibrosus-NP boundary and higher proteoglycan content. In contrast, the degenerative control group exhibited collapse in the NPCs region, sparse cells, and significantly weakened matrix staining [119].

Table 3. Hydrogel-based delivery systems for IVDD therapy.

Category	Hydrogel Type	Key Payload/Mechanism	Main Functions	Ref
Composite Hydrogel	Genipin-crosslinked fibrin + oxidized alginate microbeads	AF cells + RGD-functionalized microbeads	Provide mechanical support; protect cells from crosslinking toxicity; maintain phenotype; promote ECM synthesis	[73]
Bioactive Peptide-functionalized Hydrogel	PEG-based hydrogel (functionalized with IKVAV and AG73)	NPCs; IKVAV and AG73 enhance cell adhesion and phenotype maintenance	Promote NPCs viability and biosynthetic activity; maintain disc height and endplate organization; improve cell retention	[74]
Natural Composite Hydrogel	Type II collagen/chondroitin sulfate hydrogel + Genipin crosslinking	ADSCs induced to differentiate into NPCs	Promote ADSC differentiation; restore disc height, hydration, and ECM composition	[75]
KGN-loaded Hydrogel	GelMA, dynamic hydrogels, PLGA-GelMA, thermosensitive hydrogels	Loaded with KGN; activates Nrf2 or CBFβ-RUNX1 pathways; promotes NP-like differentiation and antioxidant defense	Antioxidant, anti-inflammatory, promotes ECM synthesis and NP regeneration	[80]
Gene Therapy Delivery System	Agomir-loaded PEG hydrogel	Agomir874 (mimics miR-874), downregulates MMPs	Regulates ECM metabolic balance, inhibits MMPs activity	[97]
Tissue Engineering Cell Delivery System	3D hydrogel with collagen and hyaluronic acid	WJ-MSCs	Induces ECM-like structure, reconstructs NPs environment	[102]
Exosome/Microtissue Delivery System	Hydrogel supporting spheroid formation	NPCs spheroid (mediated by N-cadherin and ITGβ1 signaling)	Enhances ECM synthesis and cell integration	[105]
Decellularized Scaffold-type Hydrogel	Native decellularized matrix hydrogel (various tissues)	Retained ECM components (e.g. GAGs, collagens)	Preserves native ECM bioactivity, promotes tissue integration	[107]
Drug-Releasing Hydrogel	Thermosensitive PLGA-PEG-PLGA hydrogel	Bevacizumab (anti-VEGF monoclonal antibody)	Locally inhibit VEGF expression; downregulate MMP3, upregulate COL II; delay degeneration	[114]
Combined Drug + Stem Cell Hydrogel	HAMA (hyaluronic acid methacrylate)	BMSCs + Salvianolic Acid B; activates JAK2-STAT3 pathway	Protect BMSCs from apoptosis; enhance cell survival; improve IVD structural integrity	[115]
Thermo-responsive Hydrogel	ELPs, PNIPAm, Pluronic F-127	LCST-driven phase transition, enhances stiffness post-injection	Injectable and stiffens *in situ*; improved therapeutic delivery	[116]
Metal NP-Hydrogel Composite	Ag, Au, Pt NP-doped Hydrogel	NPCs reinforce mechanical strength, enable self-healing and actuation	Tunable mechanical reinforcement, antimicrobial and sensing function	[117]
Ultrasound-responsive Hydrogel	Micelle/Nanoparticle-loaded Thermo/Acoustic Hydrogel	Ultrasound-induced mechanical disruption triggers drug release	Non-invasive deep tissue drug activation *via* acoustic stimuli	[118]

Abbreviations: RGD: Arginine-Glycine-Aspartic Acid; PEG: Polyethylene Glycol; IKVAV: Isoleucine-Lysine-Valine-Alanine-Valine; AG73: Peptide AG73 (sequence from laminin α1 chain); KGN: Kartogenin; PLGA: Poly(lactic-co-glycolic acid); CBFβ: Core-Binding Factor Subunit Beta; RUNX1: Runt-Related Transcription Factor 1; HA: Hyaluronic Acid; CS: Chondroitin Sulfate; Smad: Mothers Against Decapentaplegic Homolog; NT-LNP: Nucleus Targeting-Lipid Nanoparticle; PRP: Platelet-Rich Plasma; Agomir: Chemically Modified miRNA Mimic; WJ-MSCs: Wharton's Jelly Mesenchymal Stem Cells; GO: Graphene Oxide; ACAN: Aggrecan; ITGβ1: Integrin Beta-1; PEMF: Pulsed Electromagnetic Field; SIRT1: Sirtuin 1; YAP1: Yes-Associated Protein 1; DNP-G: Decellularized Nucleus Pulposus ECM Hydrogel; GAGs: Glycosaminoglycans; VEGF: Vascular Endothelial Growth Factor; BMSCs: Bone Marrow-Derived Mesenchymal Stem Cells; HAMA: Hyaluronic Acid Methacrylate; ELPs: Elastin-Like Polypeptides; PNIPAm: Poly(N-isopropylacrylamide); LCST: Lower Critical Solution Temperature.

Corresponding histological degeneration scores decreased significantly after hydrogel intervention, and in some studies, the histological scores in the hydrogel-treated group were close to those of healthy discs, significantly better than the untreated degenerative discs [120]. These results consistently demonstrate that the introduction of hydrogels in small animal IVDD models, such as rats, can restore the structural and functional integrity of intervertebral discs, significantly alleviating degeneration [64].

Studies in large animal models further validated the effectiveness of hydrogel treatment for IVDD. In a moderate IVDD model in goats (chemically induced enzymatic degeneration), simple hydrogel injection reduced the expression of inflammatory factors such as TNF-α in the NPCs. When combined with mesenchymal stem cells, hydrogel application led to a 10% recovery in disc height within a short period post-surgery and improved histological structure [121]. In other models, hydrogel combined with autologous stem cell implantation demonstrated stable repair effects during long-term follow-up: compared to untreated degenerative discs, hydrogel therapy maintained near-normal disc height and anatomical structure at six months, with NPCs density and distribution approaching normal levels [122]. Histological analysis using the Hoogendoorn scoring system showed that the degeneration score in the hydrogel treatment group was significantly lower than in the injury control group, with a significant difference observed at six months post-surgery. Although the difference somewhat narrowed by twelve months, it still remained significant, suggesting that hydrogel therapy delayed the degeneration process over the long term [123]. In conclusion, the key evidence from animal experiments

demonstrates the therapeutic potential of hydrogels for IVDD: in both small rodent models and larger vertebrate models, hydrogels can preserve disc height and water content, improve histological morphology, and restore the balance of the disc microenvironment (reducing inflammation and catabolism, promoting matrix regeneration). These effects collectively alleviate or even reverse the pathological changes associated with disc degeneration.

4.2. Clinical translation cases and challenges

In recent years, hydrogels and their combination with cell therapies have shown promising preliminary results in the clinical translation of IVDD treatment. Zhang et al. conducted a randomized, dose-escalation, placebo-controlled, double-blind phase II clinical study, enrolling 100 patients with single-level discogenic low back pain to evaluate the efficacy and safety of autologous adipose-derived mesenchymal stem cells (ADMSCs) combined with hyaluronic acid hydrogel. The primary endpoints included visual analog scale (VAS) pain scores, Oswestry Disability Index (ODI), Japanese Orthopaedic Association (JOA) scores, SF-36 quality of life scores, and MRI imaging indicators (Modic classification, Pfirrmann grading, disc height, etc.), with a follow-up period of up to 24 months. This study is currently in the implementation stage, and the results are eagerly awaited [124]. Another FDA-approved phase I/II clinical study, conducted by Gornet et al. was a multi-center, double-blind, randomized controlled trial involving 60 symptomatic disc degeneration patients. Participants received a single intradiscal injection of high-dose or low-dose allogenic disc progenitor cells, acellular carriers, or placebo. The high-dose cell group showed a significant reduction of 62.8% in pain VAS scores at 52 weeks ($p = 0.0005$), and the effect was maintained at 104 weeks. Additionally, this group showed a significant increase in disc volume on MRI (average increase of 249 mm^3 at 52 weeks, 402 mm^3 at 104 weeks, $p = 0.028$), suggesting the potential benefits of combining hydrogel scaffolds with cell therapy. In contrast, the low-dose and placebo groups showed no significant improvement, indicating that the therapeutic effect is closely related to the cell dose [125]. In addition to cell-based combination strategies, hydrogel monotherapies have also yielded encouraging results in clinical translation. In a multicenter, open-label study, a novel modified hyaluronic acid hydrogel (HYADD4-G) was administered *via* intradiscal injection to 23 patients with Pfirrmann grade III–IV lumbar disc degeneration. Over a 24-week follow-up, patients demonstrated a significant reduction in low back pain, with mean visual analog scale (VAS) scores dropping from 67.1 mm to 29.1 mm ($p < 0.0001$). Notably, improvements were also observed in disc hydration levels on MRI, as well as in patient-reported functional outcomes including Roland-Morris Disability Questionnaire (RMDQ) and EQ-5D quality-of-life scores. No serious adverse events were reported, and the overall safety profile was favorable, confirming that HYADD4-G is well tolerated as a stand-alone therapy [126].

Hydrogels have also demonstrated positive effects in clinical treatment. Overall, clinical translation studies on hydrogel therapy for IVDD have preliminarily confirmed its advantages in pain relief, functional improvement, and radiological restoration. As a biomaterial, hydrogels can be used alone for rapid symptom relief or as scaffold materials in combination with stem cells or immune cells to provide long-term tissue repair potential. However, most current clinical studies are still in the early stages, with limitations such as small study sizes, limited follow-up periods, and insufficient evidence for structural improvement on imaging. Moreover, the complexity of preparing and applying hydrogel-cell combination therapies presents challenges for clinical translation. In clinical treatment, there are still many problems that need to be solved. Because the disc usually bears a lot of pressure, ordinary hydrogels are prone to structural damage or uneven force over a long period of time, so that the effect will be worse. Now there are some new methods, such as using a double-net structure of hydrogels or a composite of nano-materials [127]. However, their long-term performance under actual physiological loading conditions in the human body still lacks systematic validation1.If the hydrogel contains collagen, degradation-producing substances, or chemical crosslinking agent residues, it may cause inflammation or be encased by body tissue, so that it cannot be well combined with the surrounding tissue. Now we are mainly studying some methods, such as slowly releasing anti-inflammatory drugs in the material, and adding some special polypeptides to the surface, Nevertheless, these approaches have not yet shown ideal outcomes and still require further confirmation through comprehensive immunological evaluations [128]. The requirements are also very high, so the cost goes up, and it will be more difficult to pass

medical approval [129]. Therefore, larger-scale, longer-term randomized controlled trials are needed to determine the optimal dosage, treatment duration, and long-term safety of hydrogel and cell combination therapies, advancing their transition from clinical research to widespread clinical practice [126].

5. Challenges and future directions in hydrogel research for IVDD treatment

5.1. The gap between material science and clinical needs

While hydrogels are widely regarded as promising for the treatment of IVDD, a significant gap still exists between their material properties and the practical demands of clinical applications. The first challenge is mechanical stability. The intervertebral disc is subject to repeated loading, and many hydrogels developed in the laboratory may suffer from fatigue fracture or displacement under long-term cyclic stresses *in vivo*. In fact, previous studies have shown that many hydrogels used for disc repair undergo deformation, migration, or even extrusion after implantation due to insufficient mechanical strength [106]. To enhance the mechanical properties of hydrogels, researchers are exploring material composites and engineered designs. For example, Li et al. introduced thermoplastic polyurethane (TPU) mesh as a framework in combination with tough hydrogels to create a fibrous ring defect sealing material. The orientation and volume fraction of TPU fibers were optimized to simulate the angular-layered structure and mechanical properties of the natural annulus fibrosus, significantly enhancing the durability and adhesion strength of the implant while reducing the risk of reherniation [113]. Similarly, Panebianco et al. designed a 'high-modulus scaffold + bio-microspheres' dual system: fibrin gel provided mechanical stability, while oxidized alginate microspheres loaded with NP provided long-term biological repair. The combination of the two balanced the dual needs for mechanical support and biological activity in disc repair, this system demonstrated good mechanical stability and no significant risk of reherniation in both *in vitro* bioreactor simulations and *ex vivo* bovine disc experiments [73]. These strategies help bridge the gap between the initial mechanical properties of hydrogels and the physiological load requirements of intervertebral discs.

The second challenge is biocompatibility and immune response. While synthetic polymer hydrogels offer excellent mechanical properties, their degradation products may induce an acidic microenvironment or foreign body reactions, leading to chronic inflammation that impairs tissue regeneration. On the other hand, natural hydrogels have high biological activity, but improper processing may leave antigenic components, causing immune rejection. Therefore, next-generation hydrogels are being designed with immune modulation functions to narrow the gap between materials and biological systems [130]. For example, using bio-derived materials and crosslinkers can reduce immunogenicity. A hydrogel made from decellularized NP matrix and crosslinked with low-concentration genipin demonstrated good biocompatibility, with the mechanical modulus equivalent to that of human NPCs. It supported the survival and differentiation of mesenchymal stem cells, effectively delaying IVDD in animal models [131]. On the other hand, hydrogels integrated with anti-inflammatory and antioxidant molecules actively alleviate the harmful microenvironment after implantation. For instance, a nanohybrid peptide hydrogel that continuously scavenges excess ROS and delivers pro-regenerative factors significantly inhibited the inflammatory cascade and remodeled the ECM microenvironment of degenerated discs, promoting tissue regeneration *in vivo* [91]. Similarly, a strong antioxidant composite of black phosphorus quantum dots and chitosan nanoparticles can neutralize the acidic and oxidative stress caused by oxygen metabolism imbalance, blocking the inflammatory feedback loop and promoting ECM reconstruction and tissue regeneration in the NP [83]. In summary, current multifunctional hydrogels, through mechanical enhancement, material composites, and biological activity regulation, have partially addressed the mismatch between material science and clinical needs. However, to achieve clinical translation, these designs still need long-term performance, safety verification, and standardization to ensure a better match between material properties, degradation, and the biomechanical environment of the patient's intervertebral disc.

5.2. Precision medicine and personalized treatment

Given the heterogeneity of IVDD lesions and patient variability, precision medicine is gradually being integrated into intervertebral disc regeneration treatment strategies. Patient-specific hydrogel designs

have become an important direction for development. Clinical imaging (such as MRI and CT) provides information on the disc's anatomy and degree of degeneration, and with the help of 3D modeling and biomanufacturing technologies, hydrogel implants can be customized to match the patient's disc anatomy, including personalized adjustments to shape, size, and mechanical properties. For example, studies have developed biomimetic artificial disc scaffolds where the fiber structure is stacked at a 60° angle to simulate the angular-layered structure of the patient's annulus fibrosus, double-network hydrogels are introduced into the scaffold to serve as a NP substitute, The overall mechanical behavior is highly similar to that of the natural intervertebral disc, and the pore size and mechanical strength can be adjusted according to digital models, making it suitable for patient-specific disc repair [111]. Similarly, for annular defects caused by disc herniation, Li et al. designed TPU-enhanced hydrogel sealing materials that can be customized according to the size and shape of the defect to ensure precise fitting and sufficient strength, in animal models, the implants integrated well with the surrounding tissues and reduced the risk of reherniation [113]. These patient-specific material designs based on anatomical features reflect the application of precision medicine in the development of intervertebral disc implants.

In addition to macroscopic structural matching, biological-level personalized treatment is also crucial. Different patients' is often driven by different molecular mechanisms, such as variations in inflammatory mediators, oxidative stress levels, and matrix-degrading enzyme activities. Therefore, hydrogel therapy is evolving toward 'on-demand response' and 'smart delivery' to achieve precise interventions based on the patient's pathological characteristics. Specifically, some new hydrogels are designed as stimuli-responsive materials to the disc's pathological microenvironment: they only release therapeutic factors when specific pathological signals are detected, enabling controlled drug/gene delivery in both space and time [132]. For example, Liu et al. constructed a pathological microenvironment-responsive hydrogel by conjugating the anti-inflammatory natural product EGCG to a gelatin scaffold using reversible borate ester bonds, when local inflammation, acidity, and elevated ROS occur in the disc, the borate ester bonds break, triggering EGCG release. This hydrogel showed accelerated drug release, ROS scavenging, and inflammation inhibition under high ROS and acidic conditions, effectively protecting NPCs from oxidative and inflammatory damage *in vitro* and maintaining disc height and tissue structure *in vivo* through microenvironment-triggered release [82]. This 'on-demand drug delivery' approach based on disease molecular markers (such as pH, ROS, and inflammatory factor levels) exemplifies precision treatment. Additionally, customized combination therapies for different patients also represent personalized treatment. Single strategies often cannot comprehensively reverse the degeneration process, so integrating cells, growth factors, and gene therapies into a single hydrogel platform can simultaneously target multiple pathological aspects. For example, Gao et al. suggested combining macroscale hydrogels with micro/nanoscale carrier particles to create a multi-scale delivery system, which could achieve synergistic delivery of cells, biomolecules, and nucleic acids, overcoming the limitations of single delivery modes such as large size, difficult performance control, and the need for surgical implantation [63]. Under this approach, many studies have attempted to integrate multiple therapies in hydrogels: such as loading stem cells and anti-inflammatory gene drugs together or combining multiple growth factors for sustained release, thus 'tailoring' treatment plans for the patient's specific pathological combination [77]. This personalized strategy is expected to improve the success rate of treating complex IVDD cases and is an important direction for future research and clinical translation.

5.3. Future technological integration prospects

Looking ahead, with the integration of multidisciplinary technologies, hydrogel therapy for IVDD will move toward a smarter and more efficient stage. Among them, AI-driven hydrogel design holds great promise. Traditional material development often relies on researchers' experience and repeated trial-and-error, which is time-consuming and labor-intensive. Machine learning algorithms, however, can mine hidden correlations between composition, structure, and performance from large experimental datasets and quickly select candidate formulas that meet specific mechanical and biological parameters. By building a hydrogel formula-performance database and training AI models to predict how different polymer ratios and crosslinking densities affect key parameters such as elastic modulus, degradation rate, and cell compatibility, the material development cycle can be greatly accelerated [133]. Especially in the case of intervertebral discs,

which involve multi-factorial degeneration, AI can perform multi-objective optimization – considering the mechanical support, nutrient delivery, and bioactive release of hydrogels, providing an integrated optimal design. Additionally, AI can assist in surgical decision-making and the creation of personalized treatment plans. Although AI applications in biomaterials are still in their infancy, some studies have already verified the feasibility of machine learning in optimizing 3D-printed scaffold structures and simulating biomechanical behaviors [134]. Therefore, it can be anticipated that in the future, AI will become a powerful tool in hydrogel development, helping researchers overcome the limitations of previous experiences and create more optimized and targeted intervertebral disc regeneration materials.

6. Conclusion

In summary, future IVDD treatment will present a trend of integration between 'materials+intelligence+bioengineering'. Hydrogel materials science will no longer develop in isolation but will deeply combine with AI design, advanced manufacturing (such as 3D bioprinting), micro-engineering chips, biotechnology, and other fields. This multi-technology synergy is expected to overcome current bottlenecks that are difficult to resolve within a single field. For example, AI-optimized hydrogel formulas can be precisely constructed into patient-specific implants through 3D printing, and then undergo functional and safety testing on intervertebral disc chips for rapid iterative optimization, ultimately forming candidate products for clinical trials. In this process, the integration of each new technology will further narrow the gap between laboratory research and clinical application. As the boundaries between disciplines gradually dissolve and technological innovations integrate, regenerative treatment for IVDD will enter a new era that is intelligent, efficient, and personalized, providing safer and more effective treatment options for patients.

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Data availability statement

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

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