

Intervertebral Disc Degeneration: A Comprehensive Review of Pathophysiological Mechanisms, Diagnostic Advances, and Evolving Clinical Management Protocols

Arjun Sinkemani^{1*}, Shuang Zhang²

¹Department of Human Anatomy, School of Basic Medical Sciences, Shandong Medical and Pharmaceutical University, Yantai, China

²Office of Asset Management, Shandong Medical and Pharmaceutical University, Yantai, China
Email: *sinkemani@hotmail.com

How to cite this paper: Sinkemani, A. and Zhang, S. (2026) Intervertebral Disc Degeneration: A Comprehensive Review of Pathophysiological Mechanisms, Diagnostic Advances, and Evolving Clinical Management Protocols. *International Journal of Clinical Medicine*, 17, 295-318.
<https://doi.org/10.4236/ijcm.2026.1710021>

Received: September 16, 2026

Accepted: October 19, 2026

Published: October 22, 2026

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Abstract

Intervertebral disc degeneration (IVDD) is a progressive, multifactorial condition in which the cellular and extracellular matrix architecture of the disc deteriorates. It is a leading global cause of chronic low back pain and disability. Its pathophysiology involves a complex interplay among cellular senescence, inflammatory signaling, oxidative stress, mitochondrial dysfunction, and impaired mechanotransduction. Recent studies have clarified the roles of mitophagy and programmed cell death pathways such as pyroptosis and ferroptosis, as well as the critical influence of the disc microenvironment on disease progression. Diagnosis depends mainly on magnetic resonance imaging, although emerging biomarkers and advanced imaging techniques may allow earlier detection. Clinical management follows a stepwise approach, starting with conservative measures and advancing to surgery for refractory cases. Traditional treatments focus on symptom relief, whereas emerging regenerative strategies including stem cell therapies, senolytics, and biomaterial innovations aim to modify the degenerative cascade at the molecular level. This review summarizes current knowledge of IVDD pathogenesis and assesses contemporary clinical management protocols together with promising biological therapies.

Keywords

Intervertebral Disc Degeneration, Cellular Senescence, Mitophagy, Inflammation, Extracellular Matrix, Mechanotransduction, Stem Cell Therapy, Hydrogels, Spinal Fusion, Regenerative Medicine

1. Introduction

Intervertebral disc degeneration (IVDD) imposes a substantial global health burden. It is the main structural correlate of chronic low back pain and a leading cause of years lived with disability worldwide [1] [2]. Progressive loss of disc structural integrity characterizes the condition, encompassing degradation of the nucleus pulposus (NP), delamination and tearing of the annulus fibrosus (AF), and calcification or fracture of the cartilaginous endplate (CEP) [3]. IVDD naturally results from biological aging and cumulative physiological loading; nevertheless, genetic predisposition, metabolic dysfunction, and aberrant mechanical stress can accelerate its progression [4] [5].

The clinical and socioeconomic implications of IVDD are profound. Degenerative disc changes appear in a large proportion of adults, and their prevalence rises markedly with age [6]. The correlation between radiographic degeneration and clinical symptoms, however, is notoriously inconsistent, as imaging features of degeneration are frequently observed in asymptomatic individuals [7] [8]. Understanding the molecular and cellular mechanisms that distinguish physiological aging from pathological degeneration is therefore critically needed [9] [10]. Such mechanisms represent potential molecular discriminators, which could explain why some individuals with radiographic degeneration remain asymptomatic while others develop symptomatic disease.

Current management of IVDD spans a range of therapeutic philosophies, from conservative symptom relief to surgical stabilization [11]-[13]. Nevertheless, these approaches have limitations, including variable efficacy, risks of reoperation, and a lack of disease-modifying effects. These shortcomings have driven strong interest in biological strategies that target the underlying pathophysiological cascades [7] [14].

This review offers a comprehensive synthesis of current knowledge on IVDD pathophysiology, diagnostic modalities, and clinical management protocols, with particular emphasis on the evolving interface between molecular understanding and therapeutic innovation.

2. Pathophysiological Mechanisms of Intervertebral Disc Degeneration

2.1. Structural and Cellular Organization of the Healthy Disc

The intervertebral disc is a specialized fibrocartilaginous structure. It comprises three distinct anatomical regions: the central NP, the surrounding AF, and the CEP that interfaces with adjacent vertebral bodies [15]. Within the NP, a gelatinous tissue, proteoglycans—particularly aggrecan—bind water molecules and generate the osmotic pressure necessary to resist compressive loads [7]. Concentric lamellae of collagen fibers, arranged in alternating oblique orientations, form the AF, providing tensile strength and resistance to torsional and shear forces [15]. Acting as a semi-permeable barrier, the CEP regulates nutrient transport while preventing vascular invasion into the avascular disc [7] [16].

Phenotypic heterogeneity characterizes the cellular constituents across anatomical regions. Notochordal cells predominate in the NP during early life but are gradually replaced by chondrocyte-like NP cells with skeletal maturity [15] [17]. The AF contains fibroblast-like cells in outer lamellae and chondrocyte-like cells in inner regions, while the CEP is populated by chondrocytes [18] [19]. These cells reside within a hypoxic, avascular environment, relying primarily on anaerobic metabolism and diffusion from vertebral capillaries for nutrient supply [7]. The intervertebral disc comprises three anatomically and functionally distinct regions, each with unique compositional features that are progressively altered during degeneration. **Table 1** summarizes the normal composition of each disc region and the characteristic age-related degenerative changes that occur within each compartment.

Table 1. Intervertebral disc structure, composition, and age-related degenerative changes.

Disc Region	Normal Composition	Age-Related Degenerative Changes	Reference
Nucleus Pulposus (NP)	Water content 70% - 90%; rich in proteoglycans (aggrecan) and type II collagen; high osmotic pressure maintains disc hydration	Proteoglycan loss → dehydration; water content decreases; hydrostatic pressure drops; load-bearing capacity impaired	[15] [20]
Annulus Fibrosus (AF)	15 - 25 concentric lamellae of type I collagen; fibers at ~30° to vertebra, intersecting at ~60°; outer layers denser, inner layers more elastic	Collagen/elastin disorganization; fiber disruption; translamellar bridge degradation; increased shear stress susceptibility	[15]
Cartilaginous Endplate (CEP)	Thin hyaline cartilage (~0.6 mm); semi-permeable barrier; regulates nutrient diffusion; chondrocyte-populated	Calcification, thinning, microfracture; nutrient diffusion impairment; Modic changes (Type I inflammatory, Type II fatty, Type III sclerotic)	[15] [21]
Age-Associated Progression	Younger individuals: higher water content, NP area lighter on T2-weighted MRI	Significant positive linear relationship between age and cumulative Pfirrmann score ($R^2 = 0.4205$; $p < 0.0001$)	[22]

2.2. Extracellular Matrix Degradation and Metabolic Imbalance

The hallmark of IVDD at the biochemical level is disruption of equilibrium between anabolic and catabolic processes governing extracellular matrix (ECM) turnover [7] [23]. Degenerative discs exhibit diminished synthesis of proteoglycans and type II collagen alongside upregulated expression of matrix metalloproteinases (MMPs) and aggrecanases [5] [23]. This catabolic shift results in progressive loss of proteoglycan content, reduced water-binding capacity, and impaired hydrostatic pressurization of the NP [15] [24].

This catabolic imbalance is driven largely by inflammatory mediators. Degenerative disc tissues contain elevated levels of interleukin-1 beta (IL-1 β) and tumor necrosis factor-alpha (TNF- α). These cytokines stimulate MMP expression and, at the same time, suppress ECM synthesis [25] [26]. They also induce the expres-

sion of further inflammatory mediators, thereby creating a self-perpetuating inflammatory milieu. As a result, immune cells are recruited into the disc space, which is normally immune-privileged [27]. The nuclear factor kappa-B (NF- κ B) signaling pathway serves as a critical downstream mediator of these inflammatory effects, and its activation correlates with degenerative severity [28] [29].

2.3. Cellular Senescence and Programmed Cell Death

Accumulating evidence implicates cellular senescence as a central driver of IVDD pathogenesis [30]. Senescent disc cells exhibit irreversible growth arrest, altered metabolic activity, and a senescence-associated secretory phenotype (SASP) characterized by release of pro-inflammatory cytokines and matrix-degrading enzymes [31] [32]. The accumulation of senescent NP cells, AF cells, and CEP chondrocytes contributes to the degenerative microenvironment through both cell-intrinsic functional decline and paracrine effects [30] [31]. Markers of senescence, including p16INK4a, p21, and senescence-associated β -galactosidase, are elevated in degenerative disc tissues [30] [33] [34].

Multiple forms of programmed cell death contribute to loss of viable disc cells during degeneration. Apoptosis, mediated through both intrinsic and extrinsic pathways, is well-documented in degenerative NP tissues. More recently, pyroptosis, a caspase-1-dependent inflammatory cell death and ferroptosis, an iron-dependent form of lipid peroxidation-mediated death have been implicated in IVDD pathogenesis [35]-[37]. The NLRP3 inflammasome plays a significant role in IVDD pathogenesis by promoting pyroptosis in NP cells, thereby exacerbating local inflammation [36] [38].

2.4. Oxidative Stress and Mitochondrial Dysfunction

The hypoxic and acidic microenvironment of the degenerative disc predisposes cells to oxidative stress, characterized by excessive reactive oxygen species (ROS) production and impaired antioxidant defenses [39]. Mitochondrial dysfunction, resulting from accumulated damage to mitochondrial DNA and respiratory chain components, amplifies ROS generation and diminishes ATP production [40] [41]. Excessive ROS activates multiple signaling cascades, including the p38 MAPK pathway, that culminate in ECM degradation, inflammatory cytokine expression, and cellular apoptosis [42] [43].

Mitophagy, the selective autophagic removal of damaged mitochondria, plays a crucial protective role in IVDD by promoting ECM production, inhibiting ECM degradation, and reducing apoptosis and senescence [44]. However, excessive mitophagy may be detrimental to cells, and the regulatory mechanisms governing appropriate versus excessive mitophagy remain unclear [44]. This is echoed by the NLRX1 study, which demonstrated that mitochondrial collapse occurred in NLRX1-defective NP cells and switched on the compensatory PINK1-PRKN pathway that led to excessive mitophagy and aggressive NP cell senescence [45]. Targeting mitophagy represents a promising therapeutic strategy for maintaining IVD cell

homeostasis and slowing IVDD progression [44] [46].

2.5. Mechanotransduction and Biomechanical Factors

The disc is exquisitely sensitive to its mechanical environment, and abnormal loading patterns contribute to IVDD pathogenesis [47]. Mechanotransduction pathways convert mechanical stimuli into biochemical signals regulating gene expression and cellular behavior [48]. The Hippo-YAP pathway has emerged as a critical mediator of mechanical responses in disc cells [49]. Altered Hippo signaling in degenerative discs may contribute to the phenotypic shift of NP cells toward a catabolic, senescent state [50] [51].

Transient receptor potential (TRP) channels, particularly TRPV4, serve as mechanosensors in disc cells [52]. Piezo1, a mechanosensitive ion channel, has been identified as a key mechanical sensing target in lumbar disc degeneration, with experimental evidence supporting its therapeutic potential [53]. Excessive mechanical stimulation activates these channels, leading to calcium influx, inflammatory mediator release, and NP cell damage [40] [54]. Genetic or pharmacological inhibition attenuates degeneration in animal models, suggesting potential therapeutic targets [52] [53].

2.6. Cartilage Endplate Dysfunction and Nutrient Supply Impairment

As the primary route for nutrient and oxygen diffusion into the avascular disc, the CEP plays a critical role in IVDD pathogenesis [55]. Calcification, thinning, and microfracture, degenerative changes in the CEP, compromise this diffusion pathway, leading to nutrient deprivation, lactate accumulation, and pH reduction [56] [57]. Such metabolic derangements further impair cell function and accelerate the degenerative cascade [21]. Modic changes, observed on MRI as signal alterations in vertebral endplates and adjacent bone marrow, reflect CEP inflammation and are associated with discogenic pain [55]. Providing a framework that integrates disc signal, endplate integrity, and adjacent marrow response, the disc-endplate-bone marrow complex (DEBC) classification has been proposed [58].

2.7. Genetic Predisposition

A substantial heritable component to IVDD has been established through family and twin studies, with genetic factors estimated to explain a considerable share of the variance in imaging-defined degeneration severity [59]. Heritability estimates for radiographic phenotypes, however, should not be equated with individual clinical risk. Rather than predicting whether a given individual will develop symptomatic discogenic pain or require intervention, they describe population-level variance attributable to genetic factors. Mendelian randomization analyses have identified causal associations between specific genetic variants and IVDD risk [60]. Altered susceptibility has been linked to polymorphisms in genes encoding ECM structural components, inflammatory mediators, and matrix-degrading enzymes

[61]. Some studies have associated the CILP polymorphism rs2073711 with radiologic disc degeneration, yet these associations appear population-dependent and have not been consistently replicated across all cohorts [62] [63]. Genetic findings should therefore be interpreted as susceptibility modifiers, not deterministic predictors of clinical disease.

2.8. Macrophage Involvement and Immune Microenvironment

Table 2. Key pathophysiological mechanisms of intervertebral disc degeneration.

Mechanism Category	Key Molecular Mediators	Functional Consequences	Reference
ECM Degradation	MMP-1, MMP-2, MMP-3, MMP-9, MMP-13, MMP-14; ADAMTS-4, ADAMTS-5	Aggrecan cleavage; proteoglycan loss; collagen network disruption; reduced NP hydration and hydrostatic pressure	[20]
Cellular Senescence & SASP	p16/p21 upregulation; γ H2AX positivity; SA- β -gal activity; SASP factors (IL-1 β , IL-6, IL-8, MMP-3/13, ADAMTS)	Suppressed type II collagen/aggrecan synthesis; amplified catabolic microenvironment; chronic inflammation	[69]
Oxidative Stress & Mitochondrial Dysfunction	ROS overproduction (mitochondrial ETC, NADPH oxidases); impaired mitophagy (PINK1/PRKN-dependent); mitochondrial fission imbalance	DNA damage; lipid peroxidation; ATP depletion; apoptosis and ECM degradation; self-reinforcing vicious cycle	[41]
Inflammatory Signaling	IL-1 β , TNF- α , NF- κ B pathway; MAPK (p38, JNK, ERK); NLRP3 inflammasome	MMP/ADAMTS upregulation; chemokine release; M1 macrophage polarization; pyroptosis (caspase-1, IL-18)	[20] [70]
Novel Cell Death Pathways	Pyroptosis (NLRP3/caspase-1/IL-1 β); ferroptosis (iron-dependent lipid peroxidation, GPX4/NRF2 dysregulation)	Depletion of viable disc cell pool; intensified inflammatory/oxidative injury; compromised reparative capacity	[20]
CEP Inflammation & Modic Changes	Modic Type I (inflammatory: T1 low, T2 high); Type II (fatty: T1 high, T2 high); Type III (sclerotic: T1 low, T2 low)	Impaired nutrient/oxygen supply to IVD; pathological damage to disc development; accelerated IVDD progression	[21]
Epigenetic Regulation (m6A)	N6-methyladenosine (m6A) modification; interaction with noncoding RNAs	Regulation of RNA methylation, matrix integrity; influence on inflammation and stress responses	[71]

Macrophages play a dual role in IVDD, contributing to both degenerative progression and potential repair [64]. Within the degenerative disc microenvironment, recruited macrophages are polarized toward a pro-inflammatory M1 phenotype, releasing cytokines that exacerbate ECM degradation and cell death [64] [65]. M2-polarized macrophages, by contrast, exhibit anti-inflammatory and regenerative properties [66]. Promising therapeutic approaches for IVDD include strategies that target macrophage polarization, such as nanocarrier-based drug delivery and modulation of exosome communication [67] [68]. Extracellular matrix degradation, cellular senescence, oxidative stress, inflammatory signaling, and

novel cell death pathways together form a complex network of interrelated mechanisms underlying the pathogenesis of intervertebral disc degeneration. A consolidated overview of these key pathophysiological mechanisms, their principal molecular mediators, and their functional consequences within the degenerative cascade is provided in **Table 2**.

3. Clinical Presentation and Diagnostic Evaluation

For the purposes of this review, four related but distinct clinical entities should be distinguished. Radiographic IVDD refers to imaging evidence of disc dehydration, height loss, annular fissuring, endplate changes, or Pfirrmann grade progression, and may be asymptomatic. Discogenic axial low back pain refers to axial lumbar pain presumed to arise from a degenerated disc, typically without a dominant dermatomal radicular pattern. Disc herniation with radiculopathy refers to disc material compressing or irritating a nerve root, producing dermatomal pain, paresthesia, or weakness. Degenerative spinal stenosis refers to narrowing of the spinal canal, lateral recess, or neural foramen due to degenerative changes, often presenting with neurogenic claudication or radicular symptoms. Although these entities frequently coexist, they differ in diagnostic criteria, prognostic implications, and treatment approaches.

3.1. Clinical Manifestations

Axial low back pain is the cardinal symptom of IVDD. Patients often describe it as deep and aching, and prolonged sitting or activity tends to exacerbate it [72]. Pain may be referred to the buttocks and proximal lower extremities; typically, however, it does not follow a strict dermatomal distribution unless disc herniation compresses neural structures [13]. When radicular symptoms appear, they suggest concomitant nerve root irritation and may include sharp, shooting pain in a dermatomal pattern, paresthesias, and motor weakness [73] [74].

3.2. Imaging Modalities

For evaluating IVDD, magnetic resonance imaging (MRI) remains the imaging modality of choice, offering superior soft tissue contrast and the ability to characterize disc morphology, hydration status, and endplate changes [75] [76]. The Pfirrmann classification grades disc degeneration on T2-weighted sagittal images based on signal intensity, disc structure, and height [77] [78]. However, conventional MRI has limitations in detecting early degenerative changes and correlating findings with clinical symptoms [76] [79].

Advanced imaging techniques are being explored to address these limitations. The DEBC classification integrates disc signal, endplate integrity, and adjacent marrow response, potentially improving lesion-level stratification [58]. Emerging biomarkers identified through machine learning and bioinformatics analyses, including TAF13 and ceRNA network components, have been proposed as discovery-stage candidate biomarkers [31] [80] [81]. However, these candidates are de-

rived primarily from bioinformatics and retrospective dataset analyses and currently lack prospective clinical validation for diagnosis or disease monitoring. They should therefore be regarded as hypothesis-generating rather than clinically validated diagnostic tools.

3.3. Provocative Discography

Provocative discography remains a diagnostic option for identifying symptomatic disc levels when non-invasive imaging fails to establish clear correlation between structural findings and clinical symptoms [82] [83]. However, discography is invasive and its diagnostic validity has been questioned due to high false-positive rates [84]. Current guidelines recommend judicious use only in carefully selected patients being considered for surgical intervention [83] [85].

4. Clinical Management Protocols

Management should be tailored to the specific clinical syndrome rather than to radiographic IVDD alone. Asymptomatic radiographic degeneration generally requires no treatment. Discogenic axial low back pain is managed initially with conservative care, whereas disc herniation with radiculopathy and degenerative spinal stenosis may require distinct interventional or surgical strategies when neurological deficits or refractory symptoms are present. Throughout this section, treatment recommendations are therefore organized by the dominant clinical pathology.

4.1. Conservative and Non-Operative Management

Conservative management is the first-line approach for most patients with discogenic axial low back pain, particularly when neurological deficits are absent [86] [87]. Addressing modifiable risk factors includes lifestyle modification, such as weight reduction and smoking cessation [88] [89]. Physical therapy modalities include core strengthening, flexion-based exercises, and motor control training, with evidence supporting efficacy in reducing pain and improving function [90] [91]. Pharmacological management includes non-steroidal anti-inflammatory drugs (NSAIDs) as first-line agents, though long-term use is limited by gastrointestinal and cardiovascular risks [92]-[94]. Acetaminophen and muscle relaxants may provide adjunctive benefit [92] [95]. Opioid analgesics are generally discouraged for chronic discogenic pain due to risks of dependence and opioid-induced hyperalgesia [96] [97].

Treatment of radicular pain differs from that of axial discogenic pain. For disc herniation with radiculopathy, most patients improve with time, and initial management includes activity modification, analgesia, and physical therapy. Epidural corticosteroid injections may provide limited short-term relief in selected patients with radicular pain, particularly those with acute radicular symptoms, but evidence does not support them as disease-modifying therapy for IVDD, and their benefit is generally temporary [98] [99]. They should not be regarded as a substitute for definitive management when progressive neurological deficits, cauda

equina syndrome, or refractory radicular pain are present. For degenerative spinal stenosis, conservative care may include physical therapy, analgesia, and activity adjustment, but neurogenic claudication may be less responsive to axial pain-directed therapies [100] [101].

4.2. Surgical Management

Surgical indications should be separated by the dominant pathology. Lumbar decompression is indicated when disc herniation or degenerative stenosis causes neural compression with progressive neurological deficits, cauda equina syndrome, or disabling radicular or neurogenic claudicatory symptoms refractory to conservative care. Decompression primarily addresses neural compression and is not intended to treat discogenic axial pain *per se* [102] [103].

Fusion and disc arthroplasty are considered for selected patients with presumed discogenic axial low back pain after comprehensive conservative management has failed [104]. Unlike decompression, these procedures require more specific candidate selection, including careful exclusion of other pain generators, concordant imaging, and, in some cases, provocative discography or other diagnostic confirmation [105] [106]. Surgical intervention is indicated for patients with neurological deficits, cauda equina syndrome, or disabling pain refractory to comprehensive conservative care [72] [107]. Lumbar decompression is indicated when disc herniation or degenerative stenosis causes neural compression [108] [109]. Fusion techniques include posterolateral fusion (PLF), posterior lumbar interbody fusion (PLIF), transforaminal lumbar interbody fusion (TLIF), and anterior lumbar interbody fusion (ALIF) [110] [111]. For cervical disc degeneration with radiculopathy or myelopathy, anterior cervical discectomy and fusion represent a treatment option [112]. Selected patients may instead receive artificial disc replacement, which preserves motion and potentially reduces adjacent segment degeneration [113]-[115]. Critical to this approach, however, is appropriate patient selection.

4.3. Adjacent Segment Considerations

A significant long-term concern after spinal fusion is adjacent segment degeneration (ASD). Altered biomechanics at levels adjacent to a fused segment accelerate degenerative changes there [116] [117]. To reduce ASD risk, motion-preserving technologies have been developed, including disc arthroplasty and dynamic stabilization devices [118]-[121].

5. Emerging Biological and Regenerative Therapies

5.1. Cell-Based Therapies

Preclinical studies suggest that mesenchymal stem cell (MSC) therapies hold promise for IVDD. These cells can differentiate into disc-like cells, secrete anabolic growth factors, and modulate inflammatory responses [122] [123]. Investigators have examined MSCs from bone marrow, adipose tissue, and umbilical cord. Early clinical trials provide evidence that intradiscal injection can reduce

pain and improve disc hydration [124]. Stem cell-derived exosomes amplify analgesic effects by further modulating innate immunity and blocking nociceptive nerve ingrowth [123] [125]. Notochordal cell-based strategies are also under exploration, given their apparent resistance to degeneration [126]. As an intermediate state in the replacement of notochordal cells by NP cells, nucleus pulposus progenitor cells (NPPCs) may serve as a local reservoir for tissue maintenance and repair [127].

5.2. Senolytics and Pharmacological Interventions

Interest in senolytic agents that selectively eliminate senescent cells has grown, driven by the recognition of cellular senescence as a driver of IVDD [128] [129]. In animal models, preclinical studies demonstrate that senolytics can reduce SASP-related inflammation, attenuate ECM degradation, and improve disc function [128] [129]. Ferroptosis inhibitors, mitophagy modulators, and bioactive plant compounds targeting inflammatory signaling pathways represent other emerging pharmacological approaches [130]-[132].

5.3. Biomaterial and Tissue Engineering Approaches

Restoring disc structure and function may be possible through biomaterial innovations. Injectable hydrogels, deliverable minimally invasively, can augment NP hydration and mechanical function [133]. When damaged, self-healing hydrogels not only mimic the mechanical properties of natural intervertebral discs but also self-repair, maintaining stable functionality [133]. Scaffold-based approaches seek to replicate the native disc architecture. Strategies include electrospun nanofibers for AF repair and 3D-printed constructs with region-specific matrix composition [134]-[136]. For targeted drug delivery, nanocarriers can improve the pharmacokinetics and specificity of therapeutic agents while reducing systemic toxicity [137] [138].

5.4. Gene Therapy and Exosome-Based Strategies

Gene therapy approaches seek to modify the expression of specific genes involved in IVDD pathogenesis. Such modifications include delivering anabolic genes or silencing catabolic genes [139] [140]. As a promising cell-free therapeutic strategy, engineered extracellular vesicles (EVs) have attracted attention; MSC-derived exosomes, for example, exert anti-inflammatory effects by regulating macrophage polarization and inflammasome activity [125]. Largely preclinical at present, these technologies face challenges related to biocompatibility, degradation kinetics, and integration with native tissue that require resolution [125] [141] [142].

5.5. Translational Limitations

Promising preclinical results notwithstanding, regenerative therapies for IVDD face substantial translational limitations. Human evidence remains limited; most studies are small, heterogeneous, and often uncontrolled. Cell-based products and

extracellular vesicle preparations vary widely in source, isolation method, characterization, potency, and dosing. Such variability makes comparisons across studies difficult. Delivery to the avascular and mechanically loaded disc poses challenges, and retained cell viability, engraftment, and sustained biological activity remain uncertain. Durability of any regenerative effect is largely unknown, and long-term safety monitoring is required—particularly for intradiscal cell delivery, gene therapy, and engineered biomaterials. Before these therapies can be adopted into routine practice, rigorous, standardized, and adequately powered clinical trials with clinically meaningful endpoints are needed.

6. Conclusions

A complex, multifactorial disease process, intervertebral disc degeneration arises when aging, genetics, mechanical factors, and metabolic dysfunction converge to disrupt the delicate homeostasis of the disc microenvironment. Numerous potential targets for therapeutic intervention are offered by the pathophysiological mechanisms involved ECM degradation, cellular senescence, inflammation, oxidative stress, mitochondrial dysfunction, and altered mechanotransduction. Translating these molecular insights into clinically effective treatments, however, remains a formidable challenge.

Contemporary clinical management of IVDD follows a stepwise approach. Conservative measures come first, and surgical intervention follows when necessary. Such approaches can provide symptomatic relief, yet they do not address the underlying degenerative processes. Disease modifying therapies that could alter the natural history of IVDD may emerge from regenerative medicine, but rigorous clinical trials are needed to establish safety and efficacy before routine adoption.

Priority should be given in future directions to identifying reliable biomarkers for early diagnosis and disease monitoring, developing patient specific therapeutic strategies based on genetic and phenotypic profiling, and designing clinical trials that rigorously evaluate both symptomatic and structural outcomes. Improving outcomes in this highly prevalent and disabling condition depends most on integrating molecular understanding with clinical management protocols.

Acknowledgements

ChatGPT version 5.5 was used for language polishing and grammar correction of this manuscript.

Author Contributions

Conceptualization, Arjun Sinkemani and Shuang Zhang; methodology, Arjun Sinkemani; software, Arjun Sinkemani; validation, Arjun Sinkemani and Shuang Zhang; formal analysis, Arjun Sinkemani; investigation, Arjun Sinkemani; resources, Shuang Zhang; data curation, Arjun Sinkemani; writing—original draft preparation, Arjun Sinkemani; writing—review and editing, Arjun Sinkemani and Shuang Zhang; visualization, Arjun Sinkemani; supervision, Arjun Sinkemani; pro-

ject administration, Arjun Sinkemani; funding acquisition, Arjun Sinkemani. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

ADAMTS—A Disintegrin and Metalloproteinase with Thrombospondin Motifs;
 AF—Annulus Fibrosus;
 ALIF—Anterior Lumbar Interbody Fusion;
 ASD—Adjacent Segment Degeneration;
 CEP—Cartilaginous Endplate;
 CILP—Cartilage Intermediate Layer Protein;
 DEBC—Disc-Endplate-Bone Marrow Complex;
 DNA—Deoxyribonucleic Acid;
 ECM—Extracellular Matrix;
 ERK—Extracellular Signal-Regulated Kinase;
 ETC—Electron Transport Chain;
 EVs—Extracellular Vesicles;
 GPX4—Glutathione Peroxidase 4;
 IL-1 β —Interleukin-1 Beta;
 IVD—Intervertebral Disc;
 IVDD—Intervertebral Disc Degeneration;
 JNK—c-Jun N-terminal Kinase;
 m6A—N6-methyladenosine;
 MAPK—Mitogen-Activated Protein Kinase;
 MMP—Matrix Metalloproteinase;
 MRI—Magnetic Resonance Imaging;
 MSC—Mesenchymal Stem Cell;
 NADPH—Nicotinamide Adenine Dinucleotide Phosphate;
 NF- κ B—Nuclear Factor Kappa-B;
 NLRP3—NOD-like Receptor Family Pyrin Domain Containing 3;
 NLRX1—NLR Family Member X1;
 NP—Nucleus Pulposus;
 NPPCs—Nucleus Pulposus Progenitor Cells;
 NRF2—Nuclear Factor Erythroid 2-related Factor 2;
 NSAIDs—Non-Steroidal Anti-Inflammatory Drugs;
 PINK1—PTEN-induced Kinase 1;
 PLF—Posterolateral fusion;
 PLIF—Posterior lumbar interbody fusion;
 PRKN—Parkin; RNA—Ribonucleic Acid;
 ROS—Reactive Oxygen Species;
 SASP—Senescence-Associated Secretory Phenotype;
 SA- β -gal—Senescence-Associated Beta-Galactosidase;
 TAF13—TATA-box Binding Protein Associated Factor 13;
 TLIF—Transforaminal Lumbar Interbody Fusion;
 TNF- α —Tumor Necrosis Factor-Alpha;
 TRP—Transient Receptor Potential;

TRPV4—Transient Receptor Potential Vanilloid 4;
YAP—Yes-Associated Protein; γ
H2AX—Gamma-H2A Histone Family Member X.