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Mesenchymal Stem Cell-Derived Therapeutics for Intervertebral Disc Degeneration: From Paracrine Mechanisms to Clinical Translation

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Abstract

Intervertebral disc degeneration (IVDD) is a leading cause of low back pain and disability worldwide, imposing a substantial socioeconomic burden. Current treatments primarily address symptoms without halting disease progression, necessitating the development of regenerative therapies. Mesenchymal stem cells (MSCs) have emerged as a promising therapeutic approach due to their differentiation potential, immunomodulatory properties, and paracrine activity. However, challenges including poor cell survival, immune rejection, and tumorigenic risks have prompted investigation into cell-free alternatives, particularly MSC-derived exosomes (MSC-Exos) and conditioned media. This comprehensive review synthesizes recent advances in MSC-based therapeutics for IVDD, examining molecular mechanisms including inhibition of apoptosis, suppression of oxidative stress and ferroptosis, modulation of inflammation, promotion of extracellular matrix synthesis, and regulation of cellular senescence. We critically evaluate the therapeutic potential of MSC-Exos, which offer advantages of lower immunogenicity, enhanced stability, and targeted delivery of bioactive molecules including miRNAs and proteins. Emerging strategies including microenvironment-educated exosomes, genetically engineered MSCs, smart hydrogel delivery systems, and peptide-functionalized scaffolds are discussed. We address current challenges in clinical translation, including standardization of isolation protocols, dosing optimization, and safety considerations. While numerous preclinical studies demonstrate efficacy and early clinical trials have shown feasibility and initial safety, rigorous phase III trials are needed to confirm clinical benefit. Despite these obstacles, MSC-derived therapeutics represent a paradigm shift in IVDD treatment, of-

fering the potential for disease modification rather than symptomatic management, though this potential remains to be definitively proven in large-scale human studies.

Keywords

Intervertebral Disc Degeneration, Mesenchymal Stem Cells, Exosomes, Cellular Senescence, Regenerative Medicine

1. Introduction

Low back pain (LBP) affects approximately 80% of adults during their lifetime, with healthcare expenditures exceeding $100 billion annually in the United States alone [1]. Intervertebral disc degeneration (IVDD) is the primary pathological contributor to LBP, characterized by progressive structural and biochemical changes within the intervertebral disc (IVD) that compromise biomechanical function [2].

Spanning the spinal column, the intervertebral discs confer both mobility and resistance to mechanical stress. Despite the disparate roles of their three constituent components—the nucleus pulposus (NP), annulus fibrosus (AF), and cartilaginous endplates These structures act synergistically to maintain disc integrity [3]. The NP maintains disc hydration and load-bearing capacity through its hydrophilic properties [4]. IVDD is characterized by progressive loss of NP cells (NPCs), extracellular matrix (ECM) degradation, altered cellular metabolism, and a shift toward a catabolic phenotype driven by inflammatory mediators including interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and matrix metalloproteinases (MMPs) [5].

Current treatment modalities provide symptomatic relief but fail to address the underlying pathophysiology [6]. Surgical approaches are associated with significant complications including recurrent disc herniation and adjacent segment disease. These limitations have driven investigation into biological and regenerative strategies targeting the root causes of IVDD.

Mesenchymal stem cells (MSCs) have garnered considerable attention due to their multilineage differentiation potential, immunomodulatory properties, and capacity to secrete trophic factors [7]. Preclinical studies demonstrate that MSC transplantation can attenuate IVDD progression by inhibiting apoptosis, promoting ECM synthesis, and modulating inflammatory responses [8]. However, challenges including poor cell survival in the harsh disc microenvironment, limited retention, and concerns regarding tumorigenicity and immune rejection have prompted exploration of cell-free approaches [9].

MSC-derived exosomes (MSC-Exos), nano-sized extracellular vesicles (30 - 150 nm) containing proteins, lipids, and nucleic acids, have emerged as a promising alternative that retains therapeutic benefits while mitigating cell-associated risks

[10]. Exosomes mediate intercellular communication by transferring bioactive molecules to recipient cells, regulating gene expression and modulating cellular functions [11].

This review provides a comprehensive overview of MSC-based therapeutics for IVDD, focusing on paracrine mechanisms, exosome-mediated effects, and emerging strategies for enhancing therapeutic efficacy.

Three Distinct MSC-Based Therapeutic Modalities for IVDD: Scope and Core Differences

Three separable therapeutic categories derived from mesenchymal stem cells (MSCs) have been investigated for intervertebral disc degeneration (IVDD): MSC transplantation (live cell therapy), MSC-conditioned medium (MSC-CM, crude cell-free secretome), and MSC-derived extracellular vesicles/exosomes (MSC-Exos/EVs, purified nanoscale secretory cargo carriers). All three exert regenerative effects primarily via paracrine signaling to suppress inflammation, oxidative damage, nucleus pulposus (NPC) apoptosis and senescence, while boosting extracellular matrix (ECM) anabolism; however, they differ fundamentally in formulation, safety profiles, manufacturing complexity, therapeutic persistence, and clinical translational maturity, as summarized in **Table 1**.

Table 1. Comparison of key features, mechanisms, advantages, limitations, and clinical translational stages of the three main MSC-based therapeutic modalities for IVDD.

Feature	MSC Transplantation (Live Cell Therapy)	MSC-Conditioned Medium (MSC-CM)	MSC-Derived Exosomes/EVs (MSC-Exos)
Core composition	Viable multipotent MSCs (bone marrow, adipose, umbilical cord, NP-derived)	Unpurified cell culture supernatant containing soluble growth factors, cytokines, loose protein complexes, trace EVs	Purified 30 - 150 nm endosomal nanovesicles loaded with defined miRNAs, proteins, lipids, mRNAs, lncRNAs
Primary therapeutic mechanisms	1) Direct differentiation into NP-like chondrocytic cells; 2) Sustained dynamic paracrine secretion responding to disc microenvironment; 3) Immunomodulation via cell-surface ligand interactions	Passive delivery of soluble trophic factors; no sustained de novo synthesis post-administration; mixed bioactive soluble cargo without targeted delivery vehicles	Cargo-specific epigenetic/transcriptional regulation in NPCs; targeted cell uptake via membrane fusion/endocytosis; precise delivery of functional miRNAs and antioxidant proteins (e.g., GPX4)
Key advantages	Endogenous adaptive secretion; dual differentiation + paracrine repair; robust anabolic signal output; completed human clinical trials confirm pain relief at 12-month follow-up	Simplified manufacturing (no vesicle purification); low technical barrier for preclinical screening; fully cell-free, eliminating live-cell risks	Minimal immunogenicity; no tumorigenic/ectopic ossification risk; stable cryopreservation; tunable cargo engineering; sustained local retention with hydrogel carriers; high target cell specificity

Continued

Major limitations	Poor survival in hypoxic, acidic degenerative disc microenvironment; cell leakage induces osteophyte formation; allogeneic immune rejection risk; batch variability in cell expansion; tumorigenesis theoretical risk	Heterogeneous, unstandardized bioactive composition; rapid clearance post-injection; high soluble factor degradation in vivo; undefined trace contaminants; limited tissue targeting capacity	Low total cargo yield per MSC batch; labor-intensive isolation/characterization protocols (per MISEV2018); immature clinical regulatory frameworks; uniform dosing standards not established for human intradiscal injection
Clinical translational stage	Multiple completed phase I/II human clinical trials (autologous/allogeneic BM-MSC intradiscal injection)	Exclusively preclinical in vitro/in vivo rodent models; no human trial data for IVDD	All IVDD studies remain preclinical; EV/exosome therapies validated clinically for other degenerative diseases, with safety benchmarks established
Cited core references	[7] [9] [12] [13]	[14] [15]	[10] [16]-[19]

2. Pathophysiology of Intervertebral Disc Degeneration

2.1. Cellular and Molecular Mechanisms

IVDD is a multifactorial process involving complex interactions between genetic predisposition, mechanical loading, aging, and environmental factors [20]. The hallmark of IVDD is a reduction in NPC numbers and function, leading to impaired ECM homeostasis. Apoptosis, autophagy, pyroptosis, and ferroptosis have all been implicated in NPC death [21].

Cellular senescence plays a pivotal role in IVDD, with senescent NPCs secreting pro-inflammatory cytokines and matrix-degrading enzymes that create a vicious cycle of tissue degradation [22]. p16INK4a and p53/p21 pathways are key regulators of senescence, with their activation contributing to age-related disc degeneration [22].

Oxidative stress is a critical driver, with excessive reactive oxygen species (ROS) promoting NPC apoptosis, senescence, and ECM degradation [23]. Emerging evidence implicates ferroptosis, an iron-dependent form of regulated cell death characterized by lipid peroxidation and GPX4 inactivation, in IVDD pathogenesis [21] [24].

2.2. The Role of Notochordal Cells

During embryonic development, the NP is populated by notochordal cells (NCs), which are essential for disc formation [25]. In humans, NCs disappear during early childhood and are replaced by chondrocyte-like NPCs. This transition correlates with the initiation of degenerative changes, suggesting NCs play a protective role [26].

Notochordal cells have been shown to secrete factors that stimulate NPC proliferation, proteoglycan synthesis, and ECM production [27] [28]. Notochordal

cell conditioned medium (NCCM) promotes MSC differentiation toward an NP-like phenotype, with enhanced expression of NP markers including aggrecan, collagen II, and SOX9 [27]. The loss of NCs during aging is thought to deprive the NP of these trophic factors, contributing to IVDD progression.

3. Mesenchymal Stem Cell Therapy for IVDD

3.1. Sources and Characteristics of MSCs

MSCs can be isolated from various tissues including bone marrow (BM-MSCs), adipose tissue (ADSCs), umbilical cord (UC-MSCs), and the NP itself [29]. BM-MSCs are the most extensively studied and have demonstrated safety and efficacy in preclinical models [30]. ADSCs offer advantages of abundant availability and less invasive harvest [31]. UC-MSCs represent an attractive allogeneic source with high proliferative capacity and low immunogenicity [32].

3.2. Mechanisms of Action

MSCs exert therapeutic effects primarily through paracrine signaling, secreting trophic factors that promote endogenous repair [14]. MSC-derived conditioned medium enhances NPC viability, proliferation, and ECM synthesis while inhibiting apoptosis and inflammation [15]. The MSC secretome contains growth factors (TGF-β, IGF-1, FGF-2), cytokines (IL-10, IL-6), chemokines, and extracellular vesicles that collectively modulate the disc microenvironment.

3.3. Clinical Translation

Several clinical trials have evaluated MSC transplantation for IVDD. A pilot study by Orozco *et al.* [12] demonstrated that autologous BM-MSC injection improved pain and disability scores at 12-month follow-up. Subsequent studies have reported similar improvements with allogeneic MSCs [33].

Despite promising results, challenges remain. MSC survival after intradiscal injection is poor due to the harsh disc microenvironment [9]. Cell leakage can lead to osteophyte formation [13]. These limitations have driven the development of cell-free approaches utilizing MSC-derived exosomes and conditioned media.

4. MSC-Derived Exosomes: Biogenesis, Composition, and Function

4.1. Biogenesis and Characterization

Exosomes are nano-sized (30 - 150 nm) extracellular vesicles of endosomal origin, formed through invagination of the endosomal membrane to produce intraluminal vesicles within multivesicular bodies [34]. Biogenesis is regulated by the ESCRT machinery and ESCRT-independent pathways [35]. MSC-Exos are characterized by exosomal markers including CD9, CD63, CD81, TSG101, and Alix [34].

4.2. Molecular Composition

MSC-Exos contain diverse bioactive molecules including proteins, lipids, and nucleic acids [36]. Proteomic analyses have identified proteins involved in cell adhesion, migration, proliferation, and immunomodulation [37]. Nucleic acid content includes mRNA, miRNA, lncRNA, circRNA, and DNA [11]. MicroRNAs are particularly important as exosomal effectors mediating therapeutic effects in IVDD [16] [38] [39].

4.3. Cellular Uptake and Function

Exosomes are taken up through multiple mechanisms including ligand-receptor interaction, endocytosis, and direct membrane fusion [40]. Upon internalization, exosomal cargo modulates cellular functions through post-transcriptional regulation and signaling pathway modulation [41]. MSC-Exos are efficiently internalized by NPCs, where they exert anti-apoptotic, anti-inflammatory, and pro-anabolic effects [16] [42].

5. Therapeutic Mechanisms of MSC-Exos in IVDD

MSC-derived exosomes exert their therapeutic effects through a coordinated network of molecular pathways that target the key pathological hallmarks of IVDD: apoptosis, ferroptosis, cellular senescence, inflammation, and ECM degradation. Understanding these mechanisms provides the rational basis for exosome engineering and optimization.

5.1. Inhibition of NPC Apoptosis

MSC-Exos potently inhibit NPC apoptosis through multiple mechanisms. Cheng *et al.* [16] demonstrated that BM-MSC-Exos deliver miR-21 to NPCs, inhibiting apoptosis by targeting PTEN and activating the PI3K/Akt pathway. MSC-Exos containing miR-532-5p inhibit TNF-α-induced apoptosis by targeting RASSF5 [38], while miR-142-3p attenuates IL-1β-induced apoptosis by targeting MLK3 [39].

5.2. Inhibition of Ferroptosis via Nrf2 and GPX4

Ferroptosis, an iron-dependent form of regulated cell death characterized by lipid peroxidation and GPX4 inactivation, has emerged as a critical mechanism in IVDD [21]. MSC-Exos counteract ferroptosis through two complementary mechanisms:

First, Chen *et al.* [17] demonstrated that MSC-Exos alleviate oxidative stress-induced ferroptosis by regulating the p62/KEAP1/NRF2 pathway. Mechanistically, MSC-Exos promote H3K27ac modification of the FTO promoter via increased p300/CBP histone acetyltransferase activity, enhancing chromatin accessibility and FTO expression. This reduces Nrf2 mRNA m6A methylation, enhancing NRF2 stability and transcriptional activity, which in turn upregulates antioxidant genes and restores GPX4 expression [17].

Second, Wu *et al.* [18] showed that microenvironment-educated exosomes (D-

EVs) are enriched with GPX4 protein, which is delivered directly to senescent NPCs to inhibit lipid peroxidation and prevent ferroptosis. This direct protein delivery mechanism represents a paradigm shift in exosome therapy, complementing the epigenetic regulation of endogenous antioxidant pathways.

5.3. Regulation of Cellular Senescence

MSC-Exos demonstrate potent anti-senescence effects through multiple pathways. Sun *et al.* [43] showed that induced pluripotent stem cell-derived MSC exosomes deliver miR-105-5p to senescent NPCs, targeting PDE4D and activating the Sirt6 pathway. Guo *et al.* [44] demonstrated that urine-derived stem cell exosomes containing MATN3 exert anti-senescence effects through TGF-β pathway activation. Additionally, Wu *et al.* [18] demonstrated that D-EVs exhibit enhanced targeting toward senescent NPCs through the CXCL10-CXCR3 chemokine axis, enabling selective delivery of anti-senescence cargo without activating NF-κB-mediated pro-inflammatory cascades.

5.4. Anti-Inflammatory Effects

MSC-Exos demonstrate potent anti-inflammatory effects through modulation of multiple pathways. Xia *et al.* [45] showed that BM-MSC-Exos reduce ROS, NLRP3 inflammasome activation, and inflammatory cytokine production. Exosomal miR-410 targets NLRP3, reducing NPC pyroptosis [46], while miR-223 downregulates IRAK1 to inhibit inflammatory responses [47].

5.5. Promotion of ECM Synthesis

MSC-Exos promote ECM synthesis through multiple mechanisms. Lu *et al.* [42] showed that BM-MSC-Exos upregulate anabolic genes (aggrecan, collagen II, SOX9) and downregulate catabolic genes (MMP-1, MMP-3). Exosomal miR-199a promotes ECM preservation by targeting GREM1 [48], while miR-532-5p inhibits ECM degradation by targeting RASSF5 [38]. The AMPK/SIRT1 pathway, activated by MOTS-c peptide in functional hydrogels, further promotes anti-apoptotic and anti-senescence effects through regulation of mitochondrial function and oxidative stress [49].

5.6. Integration of Mechanistic Pathways

The therapeutic effects of MSC-Exos are mediated through an integrated network of signaling pathways. The PI3K/Akt pathway (via miR-21/PTEN), MAPK pathway (via miR-142-3p/MLK3), and NF-κB pathway are modulated to inhibit apoptosis and inflammation. The Nrf2 antioxidant pathway (via epigenetic regulation of FTO) and GPX4 (via direct protein delivery) synergize to inhibit ferroptosis. The CXCL10-CXCR3 axis enables targeted delivery to senescent cells, while TGF-β and Sirt6 pathways regulate senescence and ECM synthesis. This multi-targeted approach distinguishes exosome therapy from single-agent interventions and underlies its therapeutic potency.

6. Emerging Strategies for Enhanced Therapeutic Efficacy

6.1. Microenvironment-Educated Exosomes

Wu *et al.* [18] developed "domesticated exosomes" (D-EVs) by educating MSCs with senescent NPC conditioned medium. This approach yielded exosomes with enhanced targeting capabilities toward senescent NPCs, mediated by the CXCL10-CXCR3 chemokine axis. D-EVs were enriched with GPX4 protein, which directly inhibited ferroptosis and alleviated NPC senescence.

6.2. Genetically Engineered MSCs

Genetic modification of MSCs has been explored to enhance therapeutic potential. Khalid *et al.* [50] demonstrated that overexpression of SOX9 and TGF-β1 promoted chondrogenic differentiation and regenerated IVDD in vivo. Kim *et al.* [51] developed MSCs with a tetracycline-off system expressing TGF-β1, IGF-1, and BMP-7, demonstrating superior therapeutic effects.

6.3. Peptide-Functionalized Hydrogels

Lin *et al.* [49] engineered a MOTS-c-modified functional self-assembling peptide hydrogel that enhanced NP-MSC activity by activating the AMPK/SIRT1 pathway. This system demonstrated sustained MOTS-c release and promoted ECM synthesis, with in vivo validation showing preserved disc height and reduced degeneration.

6.4. Comparative Synthesis: Source, Cargo, and Delivery Determinants of Efficacy

Therapeutic efficacy depends on cell source, cargo, and delivery system. BM-MSCs are most studied, but urine-derived and iPSC-MSCs may offer superior anti-senescence effects. miRNAs targeting PI3K/Akt, NF-κB, and Nrf2 are consistently linked to benefit, yet GPX4 protein cargo directly inhibits ferroptosis. Smart hydrogels outperform bolus injection by enabling sustained release and targeting. Collectively, combinatorial engineering of cargo and delivery platform, rather than cell source alone, emerges as the priority.

7. Clinical Translation and Challenges

7.1. Current Clinical Status

Exosome-based therapies for IVDD are currently in preclinical stages, with no approved clinical trials specifically targeting IVDD. However, MSC-Exos have been evaluated in clinical trials for other conditions, including osteoarthritis, myocardial infarction, and wound healing [52] [53]. These studies have demonstrated safety and preliminary efficacy, supporting the potential for IVDD applications.

Several clinical trials have evaluated MSC transplantation for IVDD, providing proof-of-concept for cell-based approaches. Noriega *et al.* [33] conducted a randomized controlled trial of allogeneic BM-MSCs for IVDD, demonstrating safety

and potential efficacy at 12 months. Pettine *et al.* [54] reported 3-year follow-up data for autologous BM-MSC injection, showing sustained pain relief and functional improvement.

7.2. Regulatory and Manufacturing Challenges

Standardization of isolation, characterization, and quality control is essential [19]. Cell source, culture conditions, and isolation methods affect exosome yield, purity, and bioactivity. Regulatory pathways are still evolving, with classification as biological products or advanced therapy medicinal products [55].

7.3. Reproducibility Limits and Heterogeneity

A major translational barrier is the striking lack of reproducibility across studies. Isolation methods (ultracentrifugation, size-exclusion chromatography, precipitation) yield exosome populations with divergent purity and cargo [19], while culture conditions and harvest timing further compound variability [34]. Potency assays lack consensus, with disparate readouts (apoptosis, ECM synthesis, antioxidant effects) obscuring cross-study comparison [16]-[18]. Dose reporting is inconsistent (mass, particle count, arbitrary units), and outcome measures in animal models are non-uniform [56]. Harmonized reference materials, standardized potency assays, and consensus reporting guidelines are urgently needed to bridge mechanistic insights and clinical translation [19].

7.4. Dosing and Administration

Studies have used exosome doses ranging from 10 - 100 μg/mL [16]. Intradiscal injection is the primary route, but retention is poor, necessitating sustained-release systems [18]. Hydrogel delivery systems show promise in improving retention and controlled release.

7.5. Safety Considerations

MSC-Exos are generally considered safe due to low immunogenicity and lack of tumorigenic potential [10]. However, careful evaluation of biodistribution, clearance, and off-target effects is essential. Standardized donor screening and quality control ensure product safety and consistency.

8. Future Directions

8.1. Personalized Exosome Engineering

Based on patient-specific disease characteristics, exosomes could be engineered to deliver optimal cargo combinations. Yuan *et al.* [57] demonstrated that exosomes derived from human placental MSCs carrying antagomiR-4450 alleviate IVDD through upregulation of ZNF_{121}.

8.2. Combination Therapies

Combining MSC-Exos with biomaterials, growth factors, or small molecules may

enhance therapeutic efficacy. Zhang *et al.* [58] demonstrated that combined hydrogel and MSC therapy improves outcomes in moderate-severity disc degeneration.

8.3. Large Animal Models and Clinical Trials

Preclinical validation in large animal models is essential before clinical translation. The porcine model is particularly relevant due to similarities in disc anatomy and biomechanics [56]. Clinical trials are needed to establish safety and efficacy in humans.

8.4. Non-Coding RNA Therapeutics

Synthetic miRNAs or miRNA inhibitors could be delivered directly or through engineered exosomes to modulate specific pathways. Zhu *et al.* [38] [39] demonstrated that exosomal miR-532-5p and miR-142-3p target key pathways in IVDD.

8.5. Multi-Omics Analysis

Comprehensive multi-omics analysis of MSC-Exos and their effects on NPCs will accelerate understanding of mechanisms and identification of therapeutic targets. Wu *et al.* [18] used transcriptomic and proteomic analysis to identify GPX4 as a key effector molecule in D-EVs.

9. Conclusions

Mesenchymal stem cell-derived exosomes represent a paradigm shift in the investigational treatment of intervertebral disc degeneration, offering the potential for disease modification rather than symptomatic management. Preclinical evidence indicates that MSC-Exos retain therapeutic benefits while mitigating cell-associated risks, providing a safe and potentially scalable platform that warrants further investigation.

The therapeutic effects observed in vitro and in animal models are mediated through multiple mechanisms, including inhibition of apoptosis and ferroptosis, regulation of cellular senescence, suppression of oxidative stress and inflammation, and promotion of ECM synthesis. Exosomal miRNAs target key signaling pathways including PI3K/Akt, MAPK, NF-κB, and Nrf2.

Emerging strategies including microenvironment-educated exosomes, genetically engineered MSCs, and smart hydrogel delivery systems have shown promise in enhancing targeting, cargo specificity, and sustained release in preclinical settings. The identification of key effector molecules provides a rational basis for exosome engineering, though these approaches remain at an early stage of development.

Despite compelling preclinical data and early clinical feasibility studies demonstrating initial safety and tolerability, significant challenges remain in standardization, dosing optimization, and clinical validation. Current clinical evidence supports the safety and feasibility of MSC-based approaches but does not yet establish

definitive efficacy for IVDD. Rigorous, large-scale, randomized controlled trials are essential to translate these findings into established clinical practice.

Future directions include personalized exosome engineering, combination therapies, and well-designed clinical trials with appropriate endpoints. With continued progress, MSC-derived exosomes have the potential to transform IVDD treatment; however, this potential must be confirmed through robust clinical investigation. If successful, such therapies could reduce the burden of low back pain and improve quality of life for millions worldwide.

Conflicts of Interest

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

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