

Exosomes as therapeutic delivery vehicles for intervertebral disc degeneration: Mechanisms and applications

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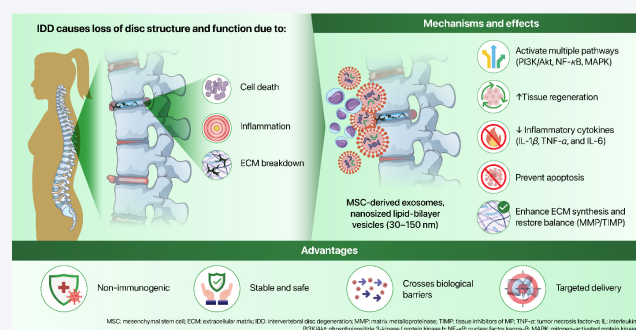
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 **Cite this article:** *Nano Research*, 2026, 19, 94908923. <https://doi.org/10.26599/NR.2026.94908923>

ABSTRACT: Lumbar intervertebral disc degeneration (IDD) is one of the primary causes of chronic low back pain. Its pathogenesis involves a complex cascade of interconnected molecular events, including inflammation, extracellular matrix dysregulation, oxidative stress, autophagy imbalance, apoptosis, and cellular senescence. Regenerative biological therapies, such as gene therapy, growth factors, cell-based injections, and tissue-engineered constructs, have attracted widespread attention for directly addressing IDD. Among these, direct injection of exosomes into degenerative discs is a promising and rapidly advancing strategy. As cell-derived nanoscale vesicles, exosomes exhibit low immunogenicity, low toxicity, ability to cross biological barriers, and excellent carrier properties, making them highly attractive for IDD treatment. In this review, we comprehensively discuss the biological characteristics of exosomes, including their sources, secretion mechanisms, and core advantages. We further summarize the mechanisms of action and key signaling pathways of exosomes from various sources. Finally, we address current challenges and propose future research directions.

KEYWORDS: lumbar intervertebral disc degeneration, mesenchymal stem cells, animal-derived exosomes, plant-derived exosomes, miRNA, drug delivery systems



1 Introduction

Low back pain (LBP) is one of the major concerns associated with the aging population [1], imposing a heavy burden on individuals and society [2]. Intervertebral disc (IVD) degeneration (IDD), a disease directly linked to aging [3], is a major risk factor for LBP. Multiple factors can contribute to IDD, including mechanical load and injury [4], insufficient nutrient supply [5], smoking [6], obesity [7], genetics [8], diabetes [9], and muscle-fat infiltration [10]. IDD is primarily characterized by the destabilization of the extracellular matrix (ECM) homeostasis and reduced cell density [11]. The IVD is a fibrocartilaginous tissue that connects adjacent vertebrae and consists of an inner core (nucleus pulposus, NP, rich in proteoglycans) and an outer region (annulus fibrosus, rich in collagen). The cartilage endplates (CEPs) are located at the upper

and lower ends of the IVD and connect to adjacent vertebrae, forming a "vertebra-disc-vertebra" transitional structure. The two main types of NP cells (NPCs) are notochordal and mature, with these notochordal cells originating from the embryonic notochord. With increasing age, notochordal cells decrease in number and are replaced by mature NPCs. The ECM of the NP is produced by NPCs derived from notochordal precursors/progenitor cells and it consists of water, proteoglycans, and collagen. These components absorb shock and maintain the mechanical load-bearing capacity of the IVD; however, the quantity of these components also gradually decreases with advancing age.

The IVD is the largest avascular tissue in mammals. The lack of vasculature translates to NPCs existing in a physiologically hypoxic microenvironment. In IDD, this microenvironment is disrupted, resulting in the accumulation of reactive oxygen species (ROS), and with NPCs experiencing oxidative stress. These events culminate in oxidative damage, the induction of pathogenic signaling pathways, and aberrant secretion of inflammatory molecules, i.e., cytokines. These cytokines trigger a series of pathogenic responses in NPCs, promoting autophagy, senescence, and apoptosis [12]. Both hypoxia and oxidative stress can activate autophagy. Autophagy

Received: April 1, 2026; **Revised:** May 25, 2026

Accepted: June 8, 2026

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induced by oxidative stress promotes NPC apoptosis [13], whereas autophagy stimulated by hypoxia protects against NPC apoptosis [14]. The loss of stem and progenitor cell markers, ECM imbalance, exacerbated inflammatory response, abnormal proliferation of sensory nerves and angiogenesis, and abnormalities in related signaling pathways are key factors in IDD occurrence and progression [15]. In conclusion, inflammation, dysregulation of ECM, oxidative stress, autophagy, cellular senescence, and apoptosis collectively constitute the key pathogenic determinants of IDD (Fig. 1) [16].

Surgery is the mainstream treatment for LBP and leg pain caused by IDD that is refractory to conservative treatment. It can alleviate symptoms and improve function, but it cannot fundamentally reverse IDD progression; it may even further exacerbate IDD in some cases [17]. Therefore, new treatments are required to reverse IDD progression. Stem cells, which exhibit self-proliferation and directed differentiation at the degenerative site, are widely applied in regenerative medicine [18]. Exosomes, as a type of nanocarrier, exhibit low immunogenicity, low toxicity, strong ability to cross biological barriers, and excellent carrier properties. They are an effective strategy for IDD repair and have garnered widespread research interest [19, 20].

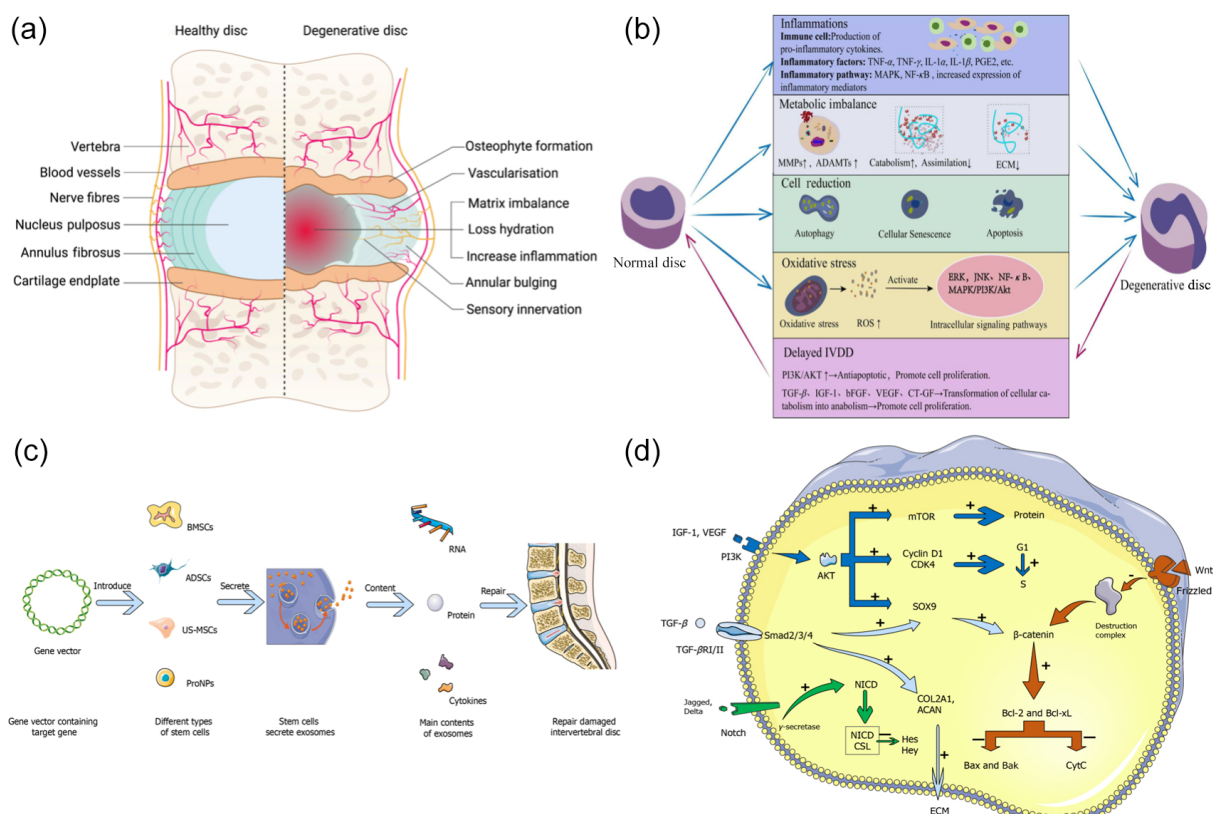
To elaborate systematically on the potential of exosomes as therapeutic vehicles for IDD, this article will begin by introducing the fundamental concepts of exosomes, including their biogenesis, biological characteristics, and core advantages. It will then delve into a categorized discussion of the mechanisms of action and related signaling pathways of exosomes from different sources, such

as mammalian-derived exosomes (MDEs) and plant-derived exosomes, in treating IDD. Finally, the article will conclude by summarizing the current limitations and challenges in the field and proposing future research directions, aiming to provide a theoretical foundation and practical guidance for further in-depth studies.

2 Molecular mechanisms of intervertebral disc degeneration

2.1 Inflammatory

Following structural disruption of the disc, macrophages infiltrate via neovascularization and, under local microenvironmental stimuli, polarize into pro-inflammatory M1 phenotypes (secreting tumor necrosis factor- α (TNF- α), interleukin-1 beta (IL-1 β), IL-6, etc.) or anti-inflammatory M2 phenotypes (secreting IL-10, transforming growth factor beta (TGF- β), etc.), with the M1/M2 imbalance being a key determinant of uncontrolled inflammation [21]. Pro-inflammatory cytokines, predominantly TNF- α and IL-1 β , not only self-amplify the inflammatory cascade but also directly mediate subsequent pathological damage by activating NF- κ B and MAPK signaling pathways. These inflammatory factors induce apoptosis, pyroptosis, ferroptosis, and stress-induced premature senescence (upregulating p16 and p53), resulting in massive loss of functional IVD cells, such as nucleus pulposus cells. They also strongly upregulate matrix metalloproteinases (e.g., MMP-1/3/13) and a disintegrin and metalloproteinase with thrombospondin



motifs (ADAMTS), leading to degradation of critical matrix components like proteoglycans and type II collagen that far exceeds synthesis, which directly accounts for the structural breakdown of the IVD [16]. Although M2 macrophages can promote extracellular matrix repair, their effects are limited in an inflammation-dominated milieu. TNF- α and IL-1 β can induce mitochondrial dysfunction, causing excessive accumulation of reactive oxygen species (ROS); oxidative stress and inflammation thereby form a vicious positive feedback loop that further drives cellular senescence and matrix degradation. Inflammatory cytokines induce high expression of nerve growth factor (NGF) and vascular endothelial growth factor (VEGF), which promote the ingrowth of pain-related nerve fibers into the ruptured annulus fibrosus and neovascularization, representing a major source of discogenic low back pain. Underlying this cascade, aberrant DNA methylation modifications, dysregulated histone modifications mediated by enzymes such as sirtuin 6 (SIRT6) or enhancer of zeste homolog 2 (EZH2), and the abnormal regulation of inflammatory pathways by non-coding RNAs, including miRNAs and lncRNAs, collectively constitute the profound epigenetic basis for sustained inflammatory activation [22].

2.2 Dysregulation of extracellular matrix

The extracellular matrix (ECM) is a highly dynamic structure that is present in all tissues and continuously undergoes controlled remodeling, a process primarily mediated by proteases such as matrix metalloproteinases (MMPs) and ADAMs [23]. The balance between ECM anabolism and catabolism is critical for IVD homeostasis. During intervertebral disc degeneration, the metabolic homeostasis of the ECM is disrupted, with catabolism substantially exceeding anabolism. Under the stimulation of pro-inflammatory cytokines (such as TNF- α and IL-1 β), adipokines (such as leptin) and aberrant mechanical loading, the expression and activity of matrix metalloproteinases (MMPs, e.g., MMP-1, MMP-3 and MMP-13) and ADAMTS (e.g., ADAMTS-4 and ADAMTS-5) are markedly elevated. These enzymes act in a concerted manner, leading to excessive degradation of the major components of the ECM, in particular type II collagen and aggrecan. Under an inflammatory milieu, oxidative stress and nutrient deprivation, nucleus pulposus cells undergo apoptosis, pyroptosis, ferroptosis and stress-induced premature senescence, resulting in a substantial reduction in the number of functional cells responsible for matrix synthesis. In degenerated nucleus pulposus cells, the glycolytic pathway, which supplies critical precursors (such as uridine diphosphate N-acetylglucosamine (UDP-GlcNAc)) and energy for proteoglycan synthesis, is suppressed, leading to a shortage of both energy and substrates for anabolism. Concurrently, advanced glycation end products (AGEs) that accumulate under hyperglycemic and oxidative stress conditions form non-enzymatic cross-links between collagen fibers, rendering the matrix stiff and less elastic, and further impeding normal matrix repair. Following the degradation of negatively charged aggrecan, the osmotic pressure of the nucleus pulposus declines, causing a decrease in water content; consequently, the disc fails to effectively buffer mechanical loads, thereby exacerbating structural deterioration. Under sustained abnormal mechanical and inflammatory signals, the original type II collagen is progressively replaced by type I collagen, and the nucleus pulposus transforms from a gel-like structure into disorganized fibrous tissue, ultimately losing its intrinsic biomechanical function [16, 24, 25].

2.3 Oxidative stress

In IDD, oxidative stress is a critical driver of multiple downstream pathological processes [26]. ROS is a general term used to describe chemicals formed by the incomplete reduction of oxygen, mainly including hydroxyl radicals ($\cdot\text{OH}$), singlet oxygen ($^1\text{O}_2$), superoxide anion ($\cdot\text{O}_2^-$), and hydrogen peroxide (H_2O_2) [27]. Mitochondrial dysfunction and endoplasmic reticulum (ER) stress lead to excessive accumulation of ROS, while the activity of antioxidant systems such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) declines, weakening antioxidant defense capacity and causing an imbalance in intracellular redox homeostasis. Excessive ROS activate NF- κB and MAPK signaling pathways, upregulate the expression of MMPs and ADAMTS, and accelerate the degradation of type II collagen and aggrecan; concurrently, they suppress matrix anabolism by inhibiting the PI3K/Akt pathway. At the level of cell fate, ROS, through induction of activating transcription factor 4 (ATF4)/C/EBP homologous protein (CHOP) transcription, promotion of mitochondrial permeability transition pore (mPTP) opening, and activation of the receptor-interacting protein 1 (RIP1)/receptor-interacting protein 3 (RIP3) pathway, trigger apoptosis, pyroptosis, and programmed necrosis of NP cells; they also promote stress-induced premature senescence via the p53-p21 and p16-Rb pathways, and senescent cells further deteriorate the local microenvironment through the senescence-associated secretory phenotype (SASP). Moreover, ROS serve as an important upstream signal for NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome activation, promoting the maturation and release of pro-inflammatory cytokines such as IL-1 β , forming a positive feedback loop of "oxidative stress-inflammation-matrix degradation" that continuously amplifies catabolic reactions. Ultimately, non-enzymatic cross-linking of collagen fibers by advanced glycation end products formed under oxidative conditions renders the matrix stiff and less elastic, leading to loss of water-binding capacity in the NP and progressive deterioration of the biomechanical function of the IVD [28, 29].

2.4 Autophagy

Autophagy is the process by which cells degrade and recycle proteins and organelles to maintain intracellular homeostasis [30]. Autophagy exhibits a characteristic dual role in IDD, with its activity tightly regulated by key signals such as AMP-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR) and PTEN-induced putative kinase 1 (PINK1)/parkin RBR E3 ubiquitin-protein ligase (Parkin). Under physiological conditions, autophagy maintains redox homeostasis by promoting the degradation of damaged mitochondria and misfolded proteins, thereby effectively inhibiting apoptosis, premature senescence, and ECM degradation in NPCs, functioning as an intrinsic protective barrier. However, once autophagic flux becomes excessively elevated or lysosomal degradation is impaired, this protective effect shifts to a pro-death mechanism, accelerating cell loss. Furthermore, autophagy and pyroptosis exhibit reciprocal functional inhibition, whereby activation of autophagy restricts NLRP3 inflammasome activity, thereby attenuating pyroptosis-mediated inflammatory injury. Therefore, the precise regulation of autophagy is crucial for maintaining NPC homeostasis and retarding IDD progression [31, 32].

2.5 Apoptosis

NPC apoptosis represents a central cellular event in the

pathogenesis of IDD and is executed through the convergent actions of the intrinsic mitochondrial pathway, the ER stress pathway, and the extrinsic death receptor pathway [16]. The mitochondrial pathway relies on B-cell lymphoma 2 (BCL-2) family-mediated mitochondrial outer membrane permeabilization (MOMP), resulting in cytochrome *c* release and subsequent caspase-9/-3 cascade activation. The ER stress pathway amplifies pro-apoptotic signaling via the protein kinase R-like endoplasmic reticulum kinase (PERK)/CHOP and inositol-requiring enzyme 1 α (IRE1 α)/c-Jun N-terminal kinase (JNK) axes, with CHOP simultaneously upregulating pro-apoptotic BCL-2 proteins and promoting ER-to-mitochondria calcium flux. The death receptor pathway, through death-inducing signaling complex (DISC)-mediated caspase-8 activation, directly triggers executioner caspases and engages the mitochondrial pathway via BH3-interacting domain death agonist (Bid) cleavage to truncated Bid (tBid), forming a signal amplification loop. These pathways exhibit distinct dominance at different stages of degeneration, collectively driving the massive loss of NPCs. The consequent reduction in matrix-synthesizing cells, coupled with the release of pro-inflammatory mediators and enhanced expression of ECM-degrading enzymes such as MMPs and ADAMTS, disrupts the balance between ECM anabolism and catabolism, promotes inflammation, and ultimately precipitates the structural deterioration and biomechanical failure of the intervertebral disc. Furthermore, the intimate crosstalk between apoptosis and other cell death modalities, including pyroptosis and autophagy, as well as the co-activation of the NLRP3 inflammasome, constitutes a multimodal regulatory network that further accelerates the degenerative cascade [33].

2.6 Cellular senescence

Cellular senescence is a pivotal driver of intervertebral disc degeneration, initiated and propagated through multiple interconnected molecular mechanisms. The decline in the epigenetic regulator SIRT6 results in H3K9 hyperacetylation and defective DNA damage repair, causing persistent accumulation of γ -H2AX-marked lesions; together with impaired autophagy, this compromises the clearance of damaged components and establishes the senescent phenotype [34]. Concomitantly, compromised chaperone-mediated autophagy (CMA) function disrupts the degradation of phospholipase C gamma 1 (PLCG1), whose abnormal accumulation promotes intracellular calcium overload, which activates the p53/p21/p16 pathways via mitochondrial oxidative stress, forcing NPCs into irreversible senescence. The progressive loss of Klotho in progenitor cells during aging attenuates the SIRT6/nuclear factor erythroid 2-related factor 2 (NRF2)/heme oxygenase-1 (HO-1) antioxidant axis, exacerbating mitochondrial dysfunction and ROS accumulation, thereby exhausting endogenous regenerative capacity. Senescent cells, through the paracrine actions of the SASP (IL-6, IL-1 β , TGF- β , monocyte chemoattractant protein-1 (MCP-1), IL-8), not only intensify local inflammation but also upregulate MMPs and ADAMTS, shifting ECM metabolism toward catabolism, which together drive NP dehydration, fibrosis, and the irreversible structural and functional deterioration of the disc [35, 36].

3 What are exosomes?

In 1981, Trams et al. cultured shed vesicles with 5'-nucleotidase activity from various normal and tumor cell types. Exosomes were

initially described as having an average vesicle diameter of 500–1000 nm, and they typically contain a second population of vesicles with diameters of approximately 40 nm [37]. From 1976 to 1985, Sullivan et al. [38], Harding et al. [39], Hopkins and Trowbridge [40], and Johnstone et al. [41] observed the interaction between undegraded transferrin receptors and small vesicles (~ 50 nm in diameter) in reticulocytes. These structures were officially named "exosomes" by Johnstone in 1987 [42].

Extracellular vesicles (EVs) are secretory membrane structures with multiple subtypes, including exosomes, microvesicles, and apoptotic bodies (Fig. 2). Exosomes are the smallest secretory vesicles. Exosomes initially form as endocytic vesicles derived from the plasma membrane and mature into late endosomes via the Golgi complex. During this period, intraluminal vesicles accumulate, and cargo sorting into these vesicles occurs via endosomal sorting complex required for transport (ESCRT)-dependent and ESCRT-independent pathways. Reverse budding then produces multi-vesicular bodies (MVBs) that contain intraluminal vesicles. MVBs fuse with lysosomes or the plasma membrane. When they fuse with the plasma membrane, the internal vesicles (i.e., exosomes) are released into the extracellular space [43]. The latest Guidelines for the Minimal Information for Studies of EVs state that "The term 'exosome' refers to EVs from internal compartments of the cell that are released via the MVB, and the diameter of intraluminal vesicles of endosomes is generally smaller than 200 nm" [44].

4 Characteristics of exosomes

Controlling drug delivery to specific tissues and organs in the human body has long been a critical challenge in pharmaceutical research. For example, the blood-brain barrier constitutes a formidable obstacle to the entry of drugs into the brain. Early researchers placed their expectations on liposomal systems. However, they are easily recognized by the body as foreign substances, and liposomal macromolecules are usually degraded before reaching the target site [45]. As regenerative medicine has advanced, exosomes have emerged as superior drug carriers, with lower immunogenicity, lower toxicity, and the ability to cross biological barriers such as the blood-brain barrier [46].

4.1 Lower immunogenicity

Exosomes are organelle-sized. Unlike single proteins or small molecules, exosomes contain heterogeneous molecules that contribute to their superior distribution characteristics, pharmacokinetic profiles, and cellular uptake. Moreover, they are less complex than cells or organs, exhibit lower immunogenicity, and are easier to manipulate for therapeutic purposes. Research on the immunogenicity of exosomes and even EVs remains scarce. However, early clinical trials evaluated the effects of exogenous substances, exemplified by the use of autologous dendritic cell-derived EVs in cancer immunotherapy and allogeneic mesenchymal stem cell (MSC)-derived EVs for managing inflammation and promoting regeneration. In these trials, the vast majority of patients recorded only mild to moderate side effects [47]. Furthermore, when EVs purified from bovine milk were injected intravenously into mice, no adverse events occurred; only moderate cytokine release was observed [48]. Similarly, using blood cell-derived EVs in blood transfusion procedures caused no significant adverse reactions in most cases [49].

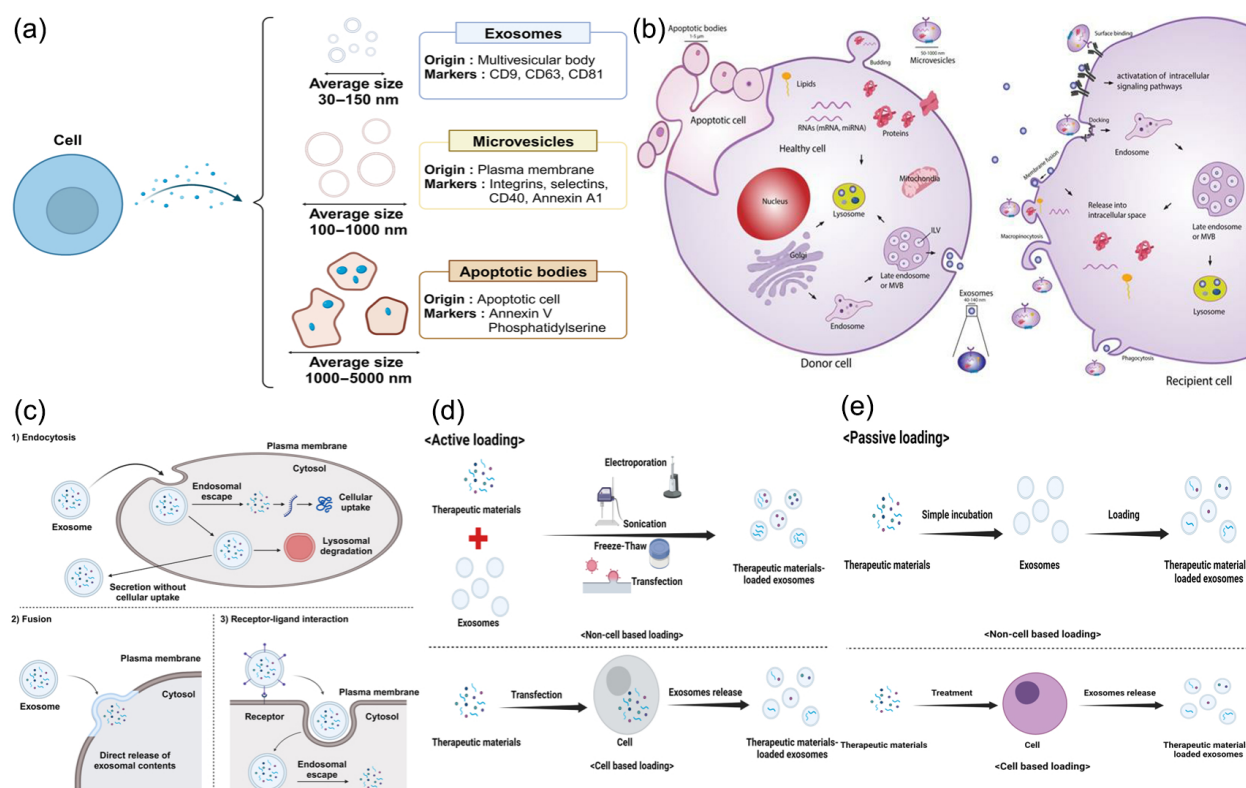


Figure 2 (a) Classification of extracellular vesicle [57], reproduced with permission from Ref. [57], © Kim, H. I. et al. 2024. (b) Schematic of biogenesis, secretion, and uptake of extracellular vesicles [43], reproduced with permission from Ref. [43], © Ivyspring International Publisher. All rights reserved 2026. (c) Cellular uptake pathways of exosomes. (d) Passive loading of therapeutic materials into exosomes. (e) Active loading of therapeutic materials into exosomes [57], reproduced with permission from Ref. [57], © Kim, H. I. et al. 2024.

4.2 Lower toxicity

Exosomes can target, recognize, bind to, and deliver cargo to specific cells. They generally do not accumulate in large, disorderly quantities in non-target cells or induce non-specific, widespread adverse effects. For instance, chimeric antigen receptor (CAR) exosomes released by CAR-T cells have demonstrated low toxicity in multiple experiments. *In vitro*, they exhibit specific cytotoxicity against tumor cells; *in vivo*, the treatment was well-tolerated with no observable adverse effects, while significantly curbing tumor growth across a range of mouse xenograft models. In programmed cell death protein 1 (PD-1)-related studies, programmed cell death-ligand 1 (PD-L1) inhibits CAR-T cells but does not affect the cytotoxic activity of CAR exosomes. In studies on cytokine release syndrome, CAR-T cells induce cytokine release syndrome-like toxicity, whereas CAR exosomes do not. Collectively, these findings indicate that CAR exosomes exhibit tumor-killing activity and low toxicity [50].

Similarly, MSC exosomes modified with "G-C"-rich tetrahedral DNA nanostructures are engineered to form decoy exosomes (Exo-TDNs). Experimentally, exosomes promote cell proliferation and have no obvious toxic effects. Additionally, Exo-TDNs can reduce chemotherapeutic drug toxicity to the heart, confirming their low toxicity and protective effect on cells [51]. However, although exosomes typically exhibit low toxicity, in certain cases, such as when they are derived from pathological cells, including tumor cells [52], they can promote tumor metastasis, disrupt the immune microenvironment, and cause other adverse effects, including toxicity [53, 54].

4.3 Crossing biological barriers

Exosomes are nanoscale microvesicles that can pass through small gaps between cells and small pores in biological membranes. They are endocytosis-derived lipid bilayer vesicles, offering good compatibility with biological membranes. When exosomes reach the cell membrane at biological barriers, they transfer their cargo (proteins, nucleic acids, etc.) into target cells through membrane fusion, crossing the barrier [54]. Exosome surfaces exhibit various proteins, some of which bind to specific receptors on cell surfaces found at biological barriers. This binding triggers intracellular signal transduction, prompting exosomal endocytosis or altering the tightness of intercellular junctions, thereby facilitating the passage of exosomes through the barrier [55].

4.4 Excellent carriers

Conceptualized on the basis of their lipid bilayer, exosomes are paracrine signaling vesicles that transport complex cargo, including proteins, nucleic acids, and lipids. The primary role of the bilayer is to safeguard nucleic acids and proteins against extracellular degradation as they are being transported [56]. Owing to their low immunogenicity, exosome effects may be enhanced by repeated administration. In contrast, for gene therapies delivered via viral vectors, such as adeno-associated virus, repeated administration can eventually trigger an immune response against the virus. Nanoparticles have a similar limitation: the human body eventually recognizes them as foreign with repeated administration [46]. The surface of exosomes carries various proteins and receptors that can specifically bind to corresponding ligands or receptors on the target

cell surface. Exosomes can also carry proteins, genetic materials, and small-molecule drugs [57], enabling targeted delivery to specific cells or tissues [53]. By modifying exosome-producing cells through genetic engineering, specific targeting molecules can be expressed on the exosomal surface, further enhancing their specificity and reusability [58].

5 Effects of exosomes from various sources on IDD

Exosomes have a wide range of sources, including immune cells (e.g., macrophages [59], dendritic cells [60], T lymphocytes [61], antigen-presenting cells [62]), stem cells (MSCs, neural stem cells [63]), tumor cells, epithelial cells [64], endothelial cells [64], and bodily fluids (e.g., blood [65], urine [66], cerebrospinal fluid [67], milk [68], saliva [69]). Exosomes are categorized as either natural or engineered depending on whether they have been artificially modified. Natural exosomes are classified into mammalian-derived exosomes (MDEs) and plant-derived exosome-like nanoparticles (PELNs). Engineered exosomes are derived from natural exosomes but are modified; these exosomes can be undergo specific modifications that enable their customization on demand to meet for specific applications, making them more widely used thereby expanding their utility in clinical research (Table 1). Exosomes are produced under healthy and tumor conditions; therefore, MDEs can be further subdivided into normal and tumor exosomes [70]. Among healthy exosomes, MSC-derived exosomes (MSC-Exos) are currently being studied extensively [71, 72]. In the MDE section, this article will focus on the therapeutic effect of MSC-Exos on IDD.

5.1 MDEs

MSCs are suitable for cell therapy and regenerative medicine and can also serve as carriers for gene and drug delivery due to their unique characteristics [72]. First, they can be easily isolated and conveniently obtained from tissues such as bone marrow, adipose tissue, and IVDs [79, 80]. Second, they can differentiate into functional cells of various mesenchymal and non-mesenchymal origins, which can repair and treat multiple diseases [81, 82]. Third, they can be extensively expanded in culture with their ability to differentiate remaining intact, meeting clinical demand for cells [83]. Fourth, they have low immunogenicity and can induce immunosuppression during transplantation, thereby aiding in the treatment of autoimmune disorders and preventing the rejection of transplanted organs [84]. Fifth, they can alleviate inflammation and facilitate disease treatment [85]. Sixth, after *in vivo* administration, they can migrate to damaged tissues, tumors, and metastatic sites to exert their effects, improving targeting and aiding tissue repair [86, 87]. In terms of IVD repair, MSCs can transform into NPCs and produce new ECM for the regeneration of IDD [88]. Additionally, stem cells reduce the inflammatory microenvironment in IDD by secreting paracrine anti-inflammatory factors and chemokines [89]. Exosomes derived from different mesenchymal stem cell sources possess distinct advantages and exert their therapeutic effects on IDD through different mechanisms (Table 2).

5.1.1 Bone marrow mesenchymal stem cell-derived exosomes (BMSC-Exos)

Inflammation and excessive oxidative stress are the leading causes of early IDD, and NPC apoptosis is a crucial contributor to IDD.

Table 1 Engineered exosomes

Customization	Classification	Fabrication	Refs.
Cargo loading	(i) Passive loading	(a) Incubation of exosomes with free drugs (b) Incubation of donor cells with free drugs	[73, 74]
	(ii) Active loading	(a) Sonication (b) Extrusion (c) Freeze-thaw (d) Electroporation (e) Incubation with membrane permeabilizers	
Surface engineering	(i) Genetic engineering	(a) Expression of viral or plasmid vectors using cellular synthesis machinery (b) Genetic modification of parent cells (c) Incorporation of multiple peptide-based targeting moieties	[74, 75]
	(ii) Covalent modification	(a) Thiol-maleimide (b) 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide/N-hydroxysuccinimide (c) Azide-alkyne cycloaddition (d) Amidation	
	(iii) Non-covalent modification	(a) Multivalent electrostatic interactions (b) Ligand-receptor interaction (c) Hydrophobic interaction/membrane engineering (d) Aptamer-based surface modification (e) Modification by anchoring cp05 peptide	
Artificial exosomes	(i) Hybrid exosomes	Fused liposome-exosomes	[77]
	(ii) Exosome mimics	(a) Cell extrusion (b) Cell membrane-cloaked nanoparticles	[78]

Bone marrow mesenchymal stem cells are the most extensively studied stem cells in tissue engineering and regenerative medicine. As carriers for intercellular communication, BM-MSC-derived exosomes (BM-MSC-Exos) influence NPCs by delivering various bioactive molecules, e.g., miRNAs, to mitigate pathological processes, including cell apoptosis, ECM metabolism, and inflammatory response [114]. Furthermore, BM-MSC-Exos can also repair damaged NPCs by delivering organelle components such as functional mitochondria or mitochondrial DNA [115]. A proportion of BM-MSCs can survive in degenerated mouse IVDs for up to 24 weeks and re-establish cartilaginous NP by stimulating endogenous notochordal cells to self-differentiate into a chondrocyte phenotype [116]. BM-MSC-Exos inherit the paracrine reparative functions of their parent cells, delivering bioactive molecules such as miRNAs and proteins to multi-targetedly suppress apoptosis, pyroptosis, ferroptosis, and senescence of NPCs, while promoting ECM synthesis, thereby comprehensively retarding IDD [117]. As a "cell-free" therapy, BM-MSC-Exos

Table 2 Effects of exosomes from various sources on IDD

Source	Species	Route of administration	Delivered substance	Pathways	Therapeutic mechanism	Refs.
BM- MSC	Rat	Local injection (PLGA microspheres)	Hypoxia-inducible factor-1 α (HIF-1 α)	HIF-1 α /PPAR- γ	Inhibition of oxidative stress and NPC senescence	[90]
	Human	Intradiscal injection	miR-19b-3p	miR-19b-3p/ACSL4 & Wnt/ β -catenin & Hippo	Inhibition of ferroptosis and ECM degradation	[91]
	Rat	Local injection (GelMA hydrogel)	Mitochondria	Kif5b/Rab22a	Improvement of mitochondrial dysfunction and NPC senescence	[92]
	Rat	Intradiscal injection	miR-221-3p	miR-221-3p/DDIT4/NF- κ B	Inhibition of NPC senescence	[93]
	Human	Local injection (GelMA hydrogel)	miR-148a-3p & miR-152-3p	NF- κ B/FOXO3	Anti-inflammation, anti-senescence, and ECM remodeling	[94]
	Human	Intradiscal injection	BCL2 interacting protein 3 (BNIP3) protein	BNIP3/ANXA2/TFEB	Induction of mitophagy and improvement of mitochondrial quality control	[95]
AD- MSCs	Rat	Intradiscal injection (ECM hydrogel)	ND	p62/KEAP1/NRF2	Inhibition of ferroptosis	[96]
	Rat	Intradiscal injection (ECM hydrogel)	ND	NLRP3/Caspase-1/GSDMD	Inhibition of pyroptosis and ECM metabolic imbalance	[97]
	Rat	<i>In vitro</i> (cellular uptake)	ND	ND	Maintenance of ECM metabolic balance and anti-apoptosis	[98]
UC- MSCs	Human	Intradiscal injection	ND	p300/CBP-H3K27ac/FTO/Nrf2-m6A/YTHDF2	Inhibition of oxidative stress-induced LMP damage and NPC senescence	[99]
	Human	Intradiscal injection	miR-194-5p	miR-194-5p/TFAM	Repair of mitochondrial dysfunction and inhibition of oxidative stress	[100]
	Human	Local injection (HAMA hydrogel)	miRNAs	p53 signaling pathway	Reversal of NPC senescence and promotion of ECM synthesis	[101]
PL- MSCs	Human	Intradiscal injection	AntagomiR-4450	miR-4450/ZNF121	Anti-inflammation, anti-apoptosis, and ECM protection	[102]
NP- MSCs	Human (NP cells)	<i>In vitro</i> co-culture	miR-15a	miR-15a/MMP-3 & PI3K/Akt/Wnt/ β -catenin	Promotion of NP-MSC chondrogenic differentiation and ECM synthesis	[103]
	Human (degenerated NPCs)	Intradiscal injection	miR-27a-3p	miR-27a-3p/PPAR- γ /NF- κ B/PI3K/AKT	Induction of macrophage M1 polarization, promotion of inflammation and IVD degradation	[104]
CESCs	Rat	<i>In vitro</i> co-culture	miR-128-3p	miR-128-3p/TRAF6/NF- κ B	Inhibition of pyroptosis and inflammation	[105]
	Rat	Injectable hydrogel implantation (near CEP)	Sphk2 protein	Sphk2/PI3K/AKT/autophagy	Promotion of NPC autophagy and inhibition of senescence	[106]
	Human (senescent CECs)	<i>In vitro</i> co-culture/intradiscal injection	miR-29b-3p	miR-29b-3p/FOXO3	Induction of NPC oxidative stress injury and exacerbation of IDD	[107]
	Rat	<i>In vitro</i> co-culture/intradiscal injection	ND	PI3K/AKT/autophagy	Inhibition of NPC apoptosis and promotion of autophagy	[108]
	Rat	Autocrine/intradiscal injection	ND	HIF-1 α /Wnt/GATA4/TGF- β 1	Promotion of CESC migration and transdifferentiation into NPCs	[109]
USCs	Human	Intradiscal injection	MATN3 protein	TGF- β /SMAD&PI3K/AKT	Anti-senescence, promotion of NPC proliferation and ECM synthesis	[110]
	Human	Local injection (OSA/CMCS hydrogel)	DEPTOR protein	DEPTOR/mTORC1/SASP	Inhibition of SASP secretion and delay of IDD	[111]
iPSC	Human	Intradiscal injection	miR-100-5p	miR-100-5p/mTORC1	Promotion of M1-to-M2 macrophage re-polarization and disruption of the senescence-inflammation loop	[112]
	Human	Intradiscal injection	miR-105-5p	miR-105-5p/PDE4D/Sirt6	Activation of Sirt6 pathway, restoration of senescent NPC function, and inhibition of IDD	[113]

circumvent the risks of immune rejection, chromosomal variation, and aberrant differentiation associated with direct stem cell transplantation, offering higher biosafety [118]. More importantly, BM-MSC-Exos possess the potential for engineering optimization; through preconditioning with hypoxia or inflammatory stimuli, or in combination with biomaterial scaffolds for localized sustained release, they overcome the delivery bottleneck imposed by the avascular nature of the intervertebral disc, where therapeutics are otherwise rapidly cleared [119].

5.1.2 Adipose mesenchymal stem cell-derived exosomes

Besides facilitating energy storage, adipose tissue also exerts unique endocrinological effects [120]. Adipose tissue is primarily composed of mature adipocytes, but it also contains other cells, including adipose MSCs (AD-MSCs). AD-MSC-derived exosomes (AD-MSC-Exos) are derived from a widely available and easily accessible source; adipose tissue possesses abundant reserves and robust regenerative capacity. The minimally invasive harvesting procedure and fewer ethical constraints significantly reduce the isolation cost and complexity, thereby facilitating future clinical translation. The most common source for AD-MSC isolation is subcutaneous white adipose tissue from the abdomen, thighs, or hips/gluteal region [121]. ADSCs derived from subcutaneous adipose tissue represent an optimal reservoir of exosomes, exhibiting a higher osteogenic tendency and greater stemness properties compared to ADSCs from deep regions [122]. Due to the ease with which they can be extracted, AD-MSCs are widely used to treat musculoskeletal diseases [123].

5.1.3 Umbilical cord mesenchymal stem cell-exosomes (UCMSC-Exos)

BM-MSCs and AD-MSCs are preferentially isolated from adult tissues for MSC therapy [124]; however, their acquisition becomes harder with patient age due to increased surgical risks. In comparison, fetal UC-MSCs are easily acquired, with enhanced differentiation potential [125], lower immunogenicity [84], and reduced ethical risks, making them a potential first choice for IVD regeneration [126]. The umbilical cord is grayish white, covered by the amniotic membrane, and contains one vein, two arteries, and a colorless, translucent gelatinous matrix known as Wharton's jelly, which is derived from the extraembryonic mesoderm and protects the umbilical vessels. MSCs can be obtained from multiple compartments of the umbilical cord, including the amniotic epithelial membrane, subamnion, Wharton's jelly, and perivascular region. Therefore, MSCs can be classified into: (1) Wharton's jelly MSCs (WJ-MSCs), isolated by dissecting the arteries and extracting Wharton's jelly from the umbilical cord using a knife or forceps; (2) perivascular MSCs, isolated from circulating vascular cells via enzymatic digestion to enable cell dissociation and subsequent culture; (3) subamniotic MSCs, isolated by dissecting the umbilical cord lining with scissors or a scalpel and culturing the explants to obtain adherent cells; and (4) amniotic MSCs, isolated by dissecting the umbilical cord, immersing the amniotic membrane in an enzyme solution for cell dissociation, and subsequently expanding the cells in culture medium. Among these, WJ-MSCs have the best differentiation and drug delivery potential [127, 128]. However, limited research is available on WJ-MSCs as a natural exosome delivery system; most studies focus on modifying WJ-MSCs through bioengineering to generate engineered exosomes for IDD treatment [129].

5.1.4 Placenta mesenchymal stem cell-derived exosomes

Similar to UC-MSCs, placenta MSCs (PL-MSCs) exhibit lower immunogenicity and greater differentiation potential compared with BM-MSCs [130]. Furthermore, PL-MSCs can be induced into chondrocytes [131] and may even be directly induced into NPCs under hypoxic conditions [132]. Although limited research is available on PL-MSCs as carriers for delivering nucleic acid substances to treat IDD, PL-MSC-derived exosomes (PL-MSC-Exos) are reportedly abundant in miR-125b-5p, miR-30c-5p, and miR-23a-3p [133]. BM-MSC-Exos can also deliver miR-125b-5p to treat IDD, thus laying a foundation for future research on PL-MSCs.

5.1.5 Nucleus pulposus mesenchymal stem cell-derived exosomes/degenerated nucleus pulposus cells

NP tissue also contains MSCs. Similar to BM-MSCs, nucleus pulposus MSCs (NP-MSCs) can differentiate into chondrocyte-like cells [134] and adapt to harsh microenvironments, including hypertonic, hypoxic, and acidic conditions [135]. NP-MSCs derived from non-degenerative NP tissue are superior to those from degenerative tissue regarding the expression of stem cell markers, colony formation, migration, proliferation, and stemness gene expression [136].

5.1.6 Cartilage endplate stem cell-derived exosomes

The CEP is key to nutrient supply and mechanical stability within the IVD. Under physiological conditions, the CEP is hypoxic and avascular; the hypoxic microenvironment promotes chondrogenesis of CEP stem cells (CESCs) while inhibiting osteogenesis [137]. However, IDD is characterized by vascular proliferation, which disrupts the hypoxic environment and increases CEP ossification, further exacerbating IDD [138]. Progenitor cells have been shown to also be present in the degenerated CEP [139]. CESCs promote their own migration to the IVD and their differentiation into NPCs through autocrine exosomes, thereby inhibiting IDD [140, 141]. Among the stem cells derived from various anatomical regions of human degenerated IVDs, CESCs possess the strongest osteogenic and chondrogenic potential [142]. Currently, most studies focus on the paracrine effects of CESC-Exos, whereas few studies investigate their role as delivery systems.

5.1.7 Urine mesenchymal stem cell-derived exosomes

Urine MSCs (USCs) can be isolated from the sediment of midstream urine samples. Compared with stem cells from other sources, USCs are conveniently obtained [143] and have fewer ethical considerations. However, the exact origin of USCs is not fully clear. Zhang et al. suggested that they may originate from glomerular parietal epithelial cells [144]. USC-derived exosomes (USC-Exos) have demonstrated initial efficacy in treating musculoskeletal diseases [142, 145], but research on their role in treating IDD still lags behind that on BM-MSCs and other stem cells.

5.1.8 Induced pluripotent mesenchymal stem cell-derived exosomes

Induced pluripotent MSCs (iPSCs) are pluripotent cells with properties similar to those of embryonic stem cells and are generated by reprogramming somatic cells (such as skin or blood cells) using specific genetic reprogramming technologies. Since Yamanaka et al. first reprogrammed somatic cells into iPSCs in

2006 [146], iPSC technology has rapidly transformed regenerative medicine, disease research, drug screening, and personalized medicine, reshaping modern biomedicine. The advent of iPSCs is a major milestone in biomedicine. It circumvents the long-standing ethical dilemmas associated with ESC research [147], providing scientists with a source of pluripotent stem cells that does not rely on embryos, enabling related research to flourish in a broader and more flexible context and offering immense potential for clinical applications. Using iPSC technology, researchers can convert a patient's own somatic cells into iPSCs, which are then induced to differentiate into various functionally specific cells. These cells can precisely target damaged tissues to repair injuries and replace diseased cells [148]; theoretically, they may even enable organ regeneration and functional recovery [149–151]. Compared with MSCs from other sources, iPSCs can replicate indefinitely without losing pluripotency [152], and they carry a lower tumorigenic risk than the most commonly used BM-MSCs [153]. Meanwhile, iPSC-Exos are also readily amenable to monitoring [154]. iPSC-Exos have already achieved remarkable results in musculoskeletal repair [155, 156]; however, their potential in IDD treatment awaits further exploration.

5.1.9 Synovium mesenchymal stem cell-derived exosomes

Synovium MSCs (SMSCs) are derived from synovial tissue. In 2001, De Bari et al. first isolated MSCs from human synovium, demonstrated that these cells possess stem cell characteristics and *in vitro* multilineage differentiation potential, and accordingly named them SMSCs. Compared with BM-MSCs, SMSCs have superior

expansion potential; human SMSCs can proliferate even after the 10th passage, independently of donor age [157]. Among MSCs derived from human bone marrow, synovium, periosteum, skeletal muscle, and adipose tissue, SMSCs exhibit the strongest chondrogenic potential [158]. This may relate to actin organization in SMSCs, which regulates the TGF- β 1 and SMAD pathways to induce chondrogenesis [159]. Current research on SMSC-derived exosomes (SMSC-Exos) is primarily focused on cartilage regeneration [160] and the treatment of arthritis [161]. Although no studies exist on using SMSC-Exos for IDD treatment, existing research suggests that microtubule stabilization is a promising area for further investigation. In NPCs, microtubule stabilization promotes collagen type II (COL2) synthesis by suppressing Yes-associated protein/ transcriptional coactivator with PDZ-binding motif (YAP/TAZ) expression and activity through the Hippo pathway, thereby driving matrix production [162]. In SMSCs, microtubule stabilization inhibits YAP expression and activity, activates the TGF- β /SMAD pathway, enhances SRY-box transcription factor 9 (SOX9) and COL2 expression, and promotes chondrogenesis [163, 164].

5.1.10 Tumor-derived exosomes (TDEs)

TDEs are EVs secreted by tumor cells [165]. The bioactive molecules they carry, such as proteins, nucleic acids, and lipids, are important in tumor initiation, progression, metastasis, and the shaping of the tumor microenvironment (Fig. 3) [166]. TDEs are generally not used to treat IDD clinically; instead, they may promote it. Regarding the inflammatory response, although TDEs

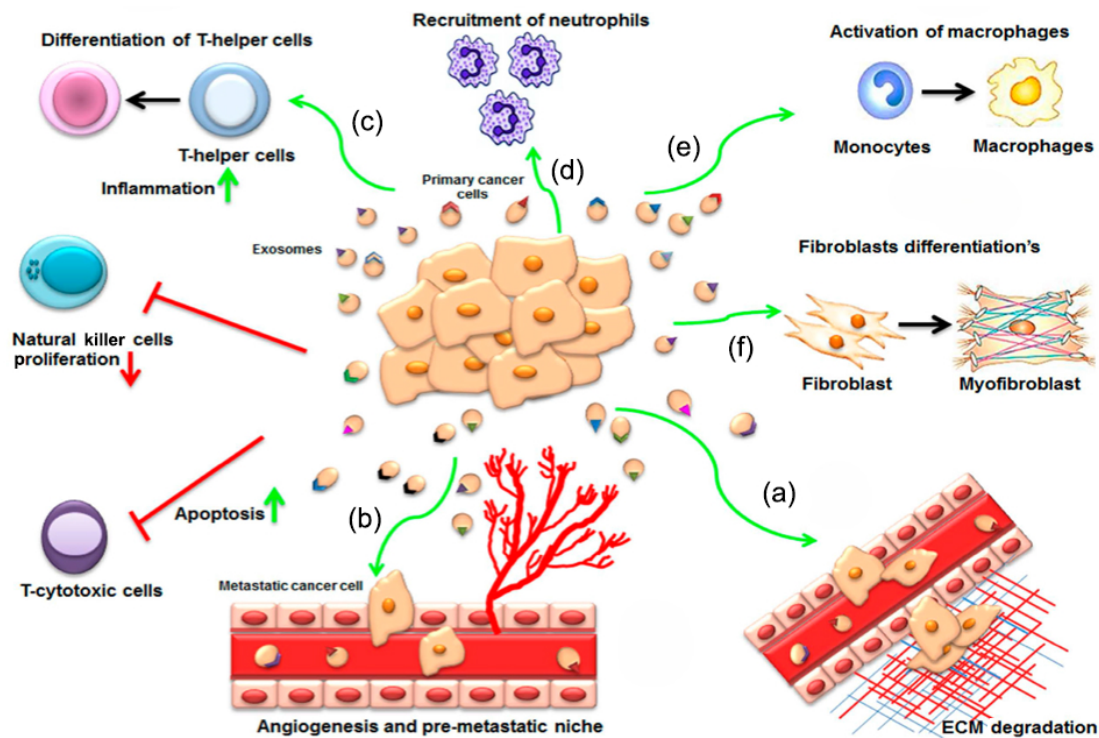


Figure 3 Tumor-derived exosomes orchestrate tumorigenesis, progression, and metastasis by transferring oncogenic cargo to remodel the local and distant microenvironments. Their multifaceted functions include: (a) traveling to distant organs to foster pre-metastatic niche formation; (b) stimulating angiogenesis through the induction of endothelial and stromal cell differentiation; (c) facilitating immune evasion via immunosuppressive effects, such as inducing cytotoxic T-cell apoptosis, impairing natural killer cell proliferation, and promoting T-helper cell differentiation into a regulatory T-cell phenotype; (d) recruiting bone marrow-derived cells to nascent tumor sites to support cancer development; (e) activating and polarizing tumor-associated macrophages (TAMs), which in turn secrete a plethora of pro-tumorigenic factors to support growth and invasion; and (f) reprogramming normal fibroblasts into cancer-associated fibroblasts with myfibroblastic features [165], reproduced with permission from Ref. [165], © M. H. R. et al. Licensee MDPI, Basel, Switzerland 2017.

can induce regulatory macrophages to polarize toward the M2 phenotype [167], which has certain anti-inflammatory effects, TDEs themselves can deliver pro-inflammatory cytokines such as IL-6 and TNF- α into the IVD microenvironment [168]. These pro-inflammatory cytokines activate immune cells (e.g., macrophages) in the IVD, inducing their polarization into the pro-inflammatory M1 phenotype [169] and releasing additional inflammatory mediators, thereby initiating an inflammatory cascade. The inflammatory environment directly damages IVD cells and inhibits the synthesis of ECM components (e.g., type II collagen and proteoglycans) while upregulating the expression and activity of MMPs to drive ECM degradation, ultimately impairing the structure and function of the IVD. Furthermore, TDEs can induce angiogenesis and increase vascular permeability [170], which may disrupt the physiologically hypoxic IVD microenvironment. TDEs can also comprehensively suppress the immune system, disrupt the functions of various immune cells, and create a microenvironment conducive to tumor growth [171]. Consequently, the body cannot generate a supportive immune environment for the treatment of IDD; instead, immune suppression may cause an uncontrolled local inflammatory response, further exacerbating IDD.

5.2 Plant-derived exosome-like nanoparticles (PELNs)

PELNs are nanoscale membranous vesicles secreted by plant cells. Research on these natural exosome-like vesicles dates back to 1967, when the release of small vesicles from carrot cells was observed using an electron microscope [172]. However, after this observation, research on PELNs experienced a period of stagnation. As researchers recognized the challenges in obtaining ADEs, including the lack of unified, standardized methods for exosome isolation, purification, identification, and quality control [173], research into PELNs has garnered a lot of interest. The biological genesis of PELNs encompasses three pathways (Fig. 4): the vacuolar,

the MVBs, and the exocyst-positive organelle (EXPO) pathways. The MVBs pathway is considered fundamental in PELN biogenesis. The vacuolar pathway involves the fusion of newly discovered vacuoles containing hydrolases and defensive components with the plasma membrane, and may be linked to the MVBs pathway. The EXPO pathway represents an unconventional secretion route in plants characterized by a double-membrane EXPO that mediates exocytosis from the cytoplasm to the cell wall [174].

Compared with MDEs, PELNs have similar surface charge, morphology, and content composition [175]. PELNs likewise contain miRNAs, lipids, and proteins, functioning as extracellular messengers that mediate intercellular communication (Table 3). However, PELNs can be extracted from various edible plants, such as vegetables, fruits, spices, and herbs, with broad availability and low extraction costs [176]. Their yield is significantly higher than that of ADEs: for example, 1 g of tomatoes yields 1.119×10^{10} particles, whereas 1 g of cabbage and red cabbage yield 1.504×10^{11} and 1.098×10^{11} particles, respectively [177]. This high yield facilitates large-scale production and cost reduction. Additionally, under controlled artificial conditions, food additives can increase the yield of PELNs [178].

Excellent stability is another key advantage of PELNs. For example, PELNs derived from ginger slices exhibit similar inhibitory effects on IL-1 β secretion and caspase-1 autocleavage across various temperatures, indicating that they retain activity despite changes in storage temperature [179]. In a simulated gastrointestinal environment, ginger-derived exosome-like nanoparticles showed changes in size and zeta potential in stomach-like (pH 2.0) and intestinal-like (pH 6.5) solutions but remained structurally stable overall, maintaining integrity and functions when administered via the gastrointestinal tract [180]. *In vitro*, PELNs from various plants (e.g., strawberries, ginseng, ginger, and blueberries) showed low cytotoxicity and high cell viability across

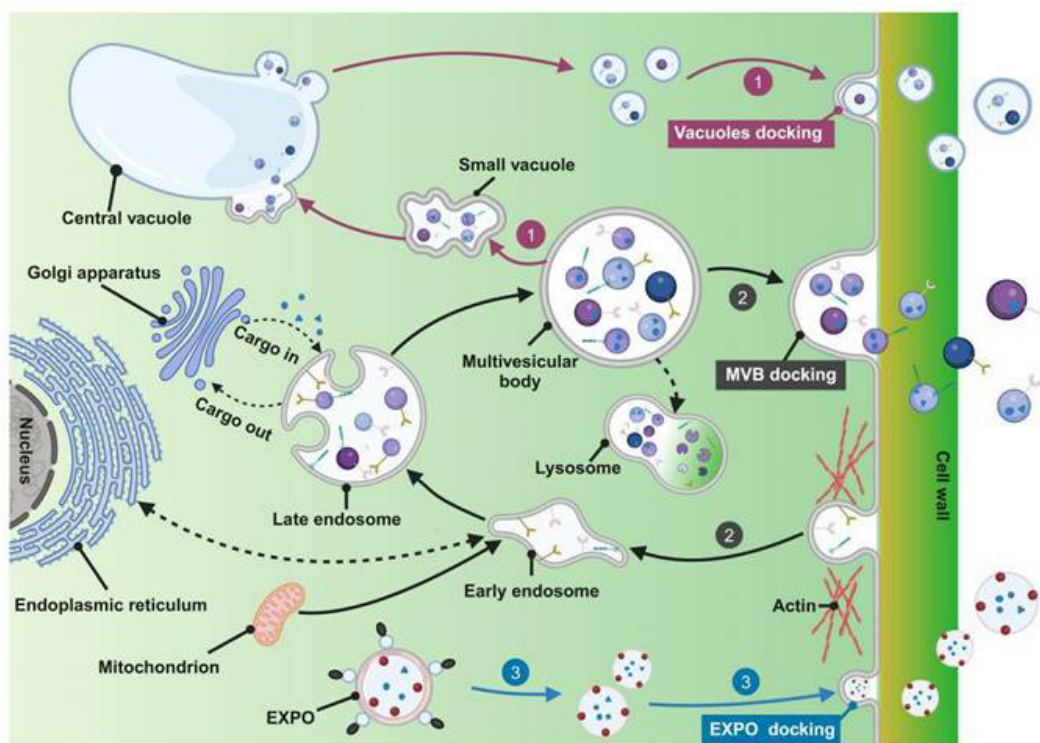


Figure 4 Biogenesis of PELNs. (1) Vacuolar pathway; (2) MVBs pathway; (3) EXPO pathway [174], reproduced with permission from Ref. [174], © Zhao, B. et al. 2024.

Table 3 Summary of PELNs

Natural compounds	Sources	Toxicity and side effects	Refs.	Mechanisms of action	Refs.
Resveratrol	<i>Veratrum album</i> , <i>Vitis</i> , <i>Ampelopsis</i> , <i>Polygonum</i> , <i>Arachis</i> , <i>Cassia</i> , <i>Sophora</i> , <i>Veratrum</i> , <i>Eucalyptus</i>	Nephrotoxicity (animal models); gastrointestinal upsets (human); poor <i>in vivo</i> pharmacokinetics	[186–188]	Inhibits NF- κ B inflammatory pathway; activates AMPK/SIRT1 signaling pathway to induce autophagy and reduce MMP-3 expression; blocks IL-6/JAK/STAT3 pathway; scavenges ROS; inhibits MMP-13	[189–194]
Quercetin	Onion, capers, green tea, apples, broccoli, red leaf lettuce, cherries, <i>Ginkgo</i> , American elderberry, <i>Hypericum</i>	ND		Activates autophagy via inhibiting p38 MAPK/mTOR pathway; activates miR-34a/SIRT1 signaling pathway to prevent oxidative stress-induced senescence of NP-MSCs; inhibits Nrf2/NF- κ B pathway; activates SIRT1-autophagy pathway; stabilizes HIF1A protein; exerts synergistic effect with dasatinib in IDD treatment; targets peroxisome proliferator-activated receptor alpha (PPARA)	[195–201]
Naringin	<i>Citrus grandis</i> , <i>Citrus paradisi</i> , <i>Citrus sinensis</i>	ND	[202, 203]	Activates PI3K/Akt signaling pathway; increases expression of autophagy-related proteins (LC3 and beclin-1), decreases p62 expression, and activates AMPK signaling pathway; inhibits NF- κ B signaling pathway; activates SIRT3-mediated mitophagy	[197, 204–206]
Curcumin	<i>Curcuma longa</i> L.	Gastrointestinal upsets	[207]	Decreases expression of iNOS, COX-2, TGF- β 1/2, MMP-9, and BDNF; increases LC3-II/LC3-I ratio and enhances autophagy	[208, 209]
Andrographolide	<i>Andrographis paniculata</i>	Reproductive toxicity; nephrotoxicity	[210–212]	Blocks TLR4/MyD88/NF- κ B signaling pathway to inhibit NP cell apoptosis and ECM degeneration; blocks NF- κ B signaling pathway to inhibit NP cell apoptosis and inflammation; activates MAPK/Nrf2/HO-1 signaling pathway and suppresses static mechanical pressure-induced ROS	[213–215]
Apigenin	<i>Apium graveolens</i> L.	ND		Activates autophagy via AMPK/mTOR signaling pathway	[216]
Maslinic acid	Jujube, loquat leaf, hawthorn, pomegranate, sage	ND		Inhibits PI3K/Akt and NF- κ B signaling pathways	[217]
Amygdalin	Peach, plum, loquat, apple, waxberry, almond	Decomposes into benzaldehyde and hydrocyanic acid <i>in vivo</i>	[210]	Inhibits NF- κ B signaling pathway and inflammatory response	[218]
Baicalein	<i>Scutellaria baicalensis</i>	ND		Promotes PI3K/Akt signaling and attenuates TNF- α	[219, 220]

various concentrations [181]. *In vivo*, administering of PELNs in healthy mice had no effect on liver enzyme levels, renal function, intestinal morphology, or intestinal immune cell composition; additionally, no morphological or pathological changes were observed across multiple tissues [180], thereby confirming their safety and biocompatibility. Although PELNs show promising anti-inflammatory [182], immunomodulatory [183], and anti-tumor effects [184], few studies have focused on the use of PELNs in the treatment of IDD [185]. However, using natural compounds from plants for the treatment of IDD is a current research hotspot and a promising future research direction.

6 Current status and challenges

Exosomes are excellent delivery systems for treating IDD, yet their application is still challenging. Although MSC-Exos from mammalian sources have been widely used in research, their safety issues cannot be overlooked; MSCs can induce sarcoma or promote tumor growth [221], and they have underlying ethical concerns [222, 223]. Tumor-derived exosomes have the potential to regulate the polarization of macrophages toward the M2 phenotype [167], leading to a reduction in inflammation. However, their effectiveness and safety in IDD treatment remain to be investigated. Although several studies show that natural plant compounds are effective,

convenient, and safe for treating IDD, research on the use of PELNs for IDD is limited. A major bottleneck hindering clinical translation is the lack of scalable, reproducible manufacturing. Current yields from static cultures fall far below remain insufficient to meet clinical requirements, and the translation of academic theoretical protocols into pharmaceutical-grade production remains a major considerable challenge, including undefined quality attributes, donor variability, and the necessity for costly closed automated systems to minimize contamination risks [224]. While 3D dynamic bioreactors and combined isolation strategies like tangential flow filtration (TFF) with size-exclusion chromatography (SEC) have shown promise for increasing yield and purity, shear stress and membrane fouling remain unresolved issues that can compromise product integrity [225]. Furthermore, ultracentrifugation, still widely used as the gold standard, is time-consuming, non-scalable, and can damage vesicle structure, making it unsuitable for Good Manufacturing Practice (GMP)-compliant production [226]. Another critical barrier is the poor targeting ability of native exosomes, which are rapidly cleared by the mononuclear phagocyte system after systemic administration [227]. Although surface engineering can improve homing to the avascular IVD, this adds complexity to the manufacturing process complexity and necessitates deeper understanding of IVD-specific markers. In parallel, inefficient cargo loading remains a technical bottleneck;

active methods such as electroporation improve encapsulation but risk damaging the exosomal membrane and inducing cargo aggregation [57]. Furthermore, the field suffers from a lack of standardized quality control metrics. The intrinsic variability of MSCs-dependent on donor age, tissue source, and passage number-makes batch-to-batch consistency exceptionally difficult to achieve without rigorous, end-to-end quality assurance protocols [228]. Consequently, a universal platform or production model for manufacturing exosomes, either upstream or downstream, for any application is currently not feasible [229].

7 Conclusions

This review systematically summarizes the therapeutic effects of exosomes derived from diverse biological sources on IDD, with particular emphasis on the underlying signaling pathways. Our primary aim is to provide a conceptual framework for future mechanistic and translational investigations. Exosomes, as endogenous nanoscale carriers, possess a unique useful combination of attributes, including — low immunogenicity, minimal toxicity, remarkable high capacity to traverse biological barriers, and intrinsic drug delivery efficiency — that which collectively position them as highly promising therapeutic agents for IDD repair

Among mammalian-derived exosomes, BMSC-Exos remain the most intensively studied, largely owing to their robust self-renewal, multilineage differentiation potential, relative accessibility, and minor ethical concerns. However, their clinical scalability is constrained by donor age-related decline in functionality and the invasiveness of procurement. In contrast, UCMSC-Exos exhibit superior accessibility, enhanced differentiation capacity, lower immunogenicity, and reduced ethical hurdles, making them an attractive and potentially ideal source. iPSC-Exos represent another highly promising category with distinct advantages: they can be expanded indefinitely in culture without losing pluripotency, ensuring a virtually unlimited and uniform source; they carry lower tumorigenic risk compared with BM-MSCs; they can be derived from a patient's own somatic cells, thereby circumventing immune rejection; they avoid the ethical controversies associated with embryonic stem cells; and they are amenable to genetic engineering for stable production of customized exosomes. Nevertheless, research on iPSC-Exos in IDD remains limited, and challenges such as reprogramming efficiency, genomic stability, and scalable GMP-compliant production need to be addressed. PL-MSCs Placenta-derived and USC-Exosurine-derived MSC exosomes, although less explored, also show preliminary promise. Notably, PELNs have emerged as a novel alternative, offering abundant raw materials, high yield, excellent high physicochemical stability, and favorable biosafety profiles. Nevertheless, their application in IDD remains largely uncharted territory largely unexplored, representing a fertile ground for a key area for future research.

From a mechanistic perspective, exosomes from different sources carry a repertoire of bioactive cargoes-including microRNAs, long non-coding RNAs, and proteins-that coordinately modulate multiple signaling cascades. Through these pathways, exosomes concurrently inhibit nucleus pulposus cell apoptosis, delay cellular senescence, attenuate inflammatory responses, and promote extracellular matrix synthesis, thereby retarding or even reversing the degenerative process.

Despite these advances, several formidable challenges impede clinical translation. First, safety concerns persist regarding pro-

inflammatory or oncogenic factors present in some mammalian-derived exosomes, necessitating rigorous preclinical safety profiling. Second, the intrinsic heterogeneity of exosome populations and the lack of standardized, scalable, GMP-compliant isolation, purification, and characterization protocols remain critical bottlenecks. Third, inefficient cargo loading, poor innate targeting ability (leading to rapid clearance by the mononuclear phagocyte system), and batch-to-batch variability stemming from donor- and tissue-dependent differences in source cells collectively undermine the development of reproducible and reliable therapeutic products. Fourth, while PELNs offer distinct advantages, their mechanistic roles in IDD have barely been explored, and no consensus exists on optimal extraction, purification, or functional assessment methods for plant-derived vesicles.

In addition to naturally sourced exosomes, engineered exosomes have emerged as a versatile platform to address the inherent limitations of native vesicles. Through cargo-loading strategies and surface modification techniques, engineered exosomes can achieve enhanced targeting specificity, improved drug encapsulation efficiency, and controlled release kinetics. Furthermore, the integration of exosomes with biomaterial scaffolds-particularly injectable hydrogels such as GelMA, hyaluronic acid methacryloyl (HAMA), poly(lactic-co-glycolic acid) (PLGA) microspheres, or ECM-derived hydrogels-has demonstrated considerable promise for IDD therapy [230]. Hydrogels serve as sustained and localized delivery systems that protect exosomes from rapid clearance in the avascular disc microenvironment, as well as create a favorable niche for nucleus pulposus cell survival and extracellular matrix regeneration [231]. These exosome-hydrogel hybrid systems enable minimally invasive intradiscal injection, prolonged bioactivity, and synergistic effects with endogenous repair mechanisms [232]. Future efforts should focus on developing multifunctional hydrogels with tunable mechanical properties, disease-responsive release profiles, and immunomodulatory functions, as well as establishing standardized protocols for engineering exosomes with high batch-to-batch consistency.

Looking forward, we propose several priority directions. Fundamental studies should elucidate the molecular mechanisms of exosomes from understudied sources, especially PELNs, and dissect how specific cargo molecules engage distinct signaling pathways in different stages of IDD. Technological innovations are urgently needed to establish standardized, scalable, and GMP-compliant production systems, including advances in bioreactor-based culture, tangential flow filtration coupled with size-exclusion chromatography, and quality control metrics, such as particle size, zeta potential, marker protein expression, and potency assays.

In summary, exosomes, as an emerging therapeutic vehicle, open a new avenue for drug delivery and regenerative treatment of IDD. Although the translational research is still at an early translational stage, the convergence of advances in stem cell biology, nanotechnology, and materials science suggests that highlight the potential of exosome-based therapies have the potential to become a cornerstone of as promising candidates for precision medicine for in IDD management. The successful translation of these approaches will depend on require interdisciplinary collaboration, rigorous standardization, and a deep thorough understanding of the pathophysiological heterogeneity of IDD.

Data availability

Not applicable.

Acknowledgements

This work was supported by grants from the Jilin Provincial Department of Finance Projects (No. 2020SCZT033).

Declaration of competing interest

All the contributing authors report no conflict of interests in this work.

Author contribution statement

T. X.: Writing – review & editing, writing – original draft. M. C.: Writing – review & editing, writing – original draft. R. P. D.: Writing – review & editing. M. Y. K.: Writing – review & editing. Y. Q.: Writing – review & editing, writing – original draft.

Informed consent

Not applicable.

Ethics statement

Not applicable.

Use of AI statement

None.

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