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REVIEW

How Advanced Are Exosomes as Cell-Free Therapeutics for Spinal Cord Injury?

Yaqi Wu[1,*], Yu Wang[1,*], Jun Zhou[2], Zhijian Tang[1], Lulu Huang[3], Shengwen Liu[1]

[1]Department of Neurosurgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China; [2]Institute of Material Polymer (IMP), University Claude Bernard Lyon 1, INSA Lyon, University Jean Monnet, CNRS UMR 5223, Villeurbanne Cedex F-69622, France; [3]Department of ICON Pharma Development Solutions (IPD), ICON Public Limited Company (ICON Plc), Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Shengwen Liu, Department of Neurosurgery, Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology, Jiefang Avenue 1095, Wuhan, Hubei, 430030, People's Republic of China, Tel +86-27-83662448, Fax +(86) (27) 83646605, Email liushengwent047@163.com

Abstract: Spinal cord injury (SCI) remains a leading cause of disability worldwide, characterized by complex pathophysiological processes involving primary mechanical damage and secondary cascades of inflammation, oxidative stress, and gliosis. Current cell-based therapies face challenges such as low survival rates, tumorigenicity, and immune rejection. Emerging evidence highlights exosomes—nanoscale extracellular vesicles derived from various cell types—as promising cell-free therapeutic agents. These exosomes mediate intercellular communication by transferring bioactive cargo and exhibit advantages such as low immunogenicity, stability, and blood-spinal cord barrier permeability. This review explores the neuroprotective roles of exosomes from diverse cellular sources in SCI repair. Key mechanisms include regulation of macrophage/microglia polarization, suppression of pyroptosis, promotion of vascularization, inhibition of glial scar formation and enhancement of axonal growth. Challenges remain in optimizing exosome yield, standardization, and clinical translation. Future directions emphasize multi-target therapies, biomarker exploration, and hybrid approaches combining exosomes from multiple. A combination of exosomes with biomaterials or stem cells would amplify the therapeutic effects and reduce the dosage of exosomes. This review underscores the potential of exosome-based therapies to revolutionize SCI treatment by addressing its multifaceted pathophysiology while circumventing risks associated with cell transplantation.

Keywords: exosomes, neuroprotection, spinal cord injury, macrophage polarization, axonal regeneration

Introduction

Spinal cord injury (SCI) typically results from mechanical disruption of neural circuits in the central nervous system, which causes impairments in motor, sensory, and autonomic functions.[1–3] The post-SCI pathophysiological progression can be categorized into two distinct phases: primary injury and secondary injury.[4] Primary injury refers to the immediate physical damage to spinal cord tissues, surrounding vasculature, and normal anatomical structures caused by external mechanical forces.[5] Secondary injury evolves through a series of complex cellular and molecular cascades, including reactive gliosis (proliferation of glial cells), oxidative stress, tissue edema, excitotoxic cellular damage, and sustained inflammatory responses.[6–8] The intricate interplay of these pathological mechanisms ultimately leads to failed neural regeneration, and to date, no clinically proven effective therapies exist for complete functional restoration.

In recent years, multiple cellular therapeutic candidates – including mesenchymal stem cells (MSCs),[9] Schwann cells,[10,11] endothelial progenitor cells,[12] microglia/ macrophages[13]- have been investigated for SCI regeneration. Emerging evidence suggests that combinatorial strategies integrating these cells with advanced biomaterials and pharmacological agents demonstrate particularly promising therapeutic potential.[14–16] Nevertheless, critical challenges persist, notably suboptimal cell survival rates, tumorigenic risks, immune-mediated rejection mechanisms, and unresolved ethical controversies surrounding cell sources, which collectively pose insurmountable barriers to clinical translation.[17]

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The therapeutic efficacy of cell transplantation in SCI is primarily mediated through paracrine mechanisms.[18] Exosomes (Exos), serving as key signaling vesicles in intercellular communication, constitute the principal mediators of these cellular paracrine effects. Compared with conventional cell-based therapies, Exos exhibit reduced immunogenicity while eliminating tumorigenic risks associated with transplanted cells. Over the past three decades, Exo-based interventions have emerged as a revolutionary frontier in SCI research, garnering substantial scientific attention.[13,19–21] These nano-sized vesicles demonstrate cell type-specific molecular cargo (DNA, RNA, and proteins) that dictates their functional heterogeneity and distinct therapeutic mechanisms in SCI management. Notably, Exos have been engineered as nanoscale delivery platforms for low-molecular-weight therapeutics in preclinical investigations.[13,22–24] Crucially, their inherent phospholipid membrane encapsulation confers enhanced stability during systemic circulation and facilitates blood-brain barrier (BBB) penetration – a critical advantage for central nervous system targeting.[25] These unique properties, combined with superior biocompatibility and minimal immunotoxicity, have positioned Exos as multifunctional tools for both diagnostic applications and therapeutic innovations, with several candidates advancing through clinical translation pipelines.[26]

This review systematically examines the therapeutic landscape of Exo-based SCI interventions, with particular emphasis on: 1) Comparative analysis of cellular derivation sources, 2) Mechanistic insights into neural repair processes, and 3) Current technological advancements in Exos engineering. This synthesis aims to bridge critical knowledge gaps in exosomal therapeutics while informing the development of targeted therapeutic strategies for SCI regeneration.

What Do We Understand About Exosomes?

Exos biogenesis originates from the inward budding of endosomal membranes, initiating multivesicular body (MVB) formation.[27] The process begins with plasma membrane invagination creating early Exos containing transmembrane proteins and cytoplasmic components. These sorting organelles undergo maturation coordinated by endoplasmic reticulum-Golgi network interactions, ultimately progressing to late Exos. Subsequent recruitment of the endosomal sorting complex required for transport machinery facilitates intraluminal vesicle (ILV) generation within MVBs. These ILVs (future Exos) face two distinct fates: lysosomal/autophagic degradation through organelle fusion, or extracellular release via calcium-dependent MVB-plasma membrane docking and exocytosis (Figure 1).[28]

Based on biogenesis pathways and physical characteristics, extracellular vesicles are classified into three subtypes: (1) Exos (40–100 nm): ESCRT-dependent formation from endosomal system; (2) Microvesicles (100–500 nm): direct shedding from plasma membrane; (3) Apoptotic bodies (500–1000 nm): caspase-mediated blebbing during programmed cell death.[29] Ubiquitous Exo secretion has been documented across diverse cell populations, including immune lineage cells as dendritic cells,[30] macrophages,[31] B lymphocytes[32] and T lymphocytes.[33] Others as MSCs, endothelial, epithelial cells and cancer cells also produce Exos.[34] These nano-carriers transport biomolecular cargo (DNA species, coding/non-coding RNAs, functional proteins) through systemic circulation via hematogenous and cerebrospinal fluid routes, enabling targeted intercellular communication.[35]

Exosome Therapy for Spinal Cord Injury: Cellular Source-Dependent Effects

Mesenchymal Stem Cells Derived Exosomes

MSCs isolated from bone marrow (BM-MSCs), umbilical cord blood (UCB-MSCs), and adipose tissue (AD-MSCs) have been extensively investigated for SCI repair.[36] MSC-Exos lack cell nuclei and organelles but recapitulate the therapeutic benefits of their parent cells – including enhanced axonal regeneration, blood-spinal cord barrier (BSCB) integrity restoration, immunomodulation, and pro-angiogenic effects – while circumventing critical limitations such as alloimmune responses, tumorigenic potential, and ethical constraints.[37]

Emerging comparative studies reveal significant functional heterogeneity among MSC-Exos based on tissue origin. AD-MSC-Exos demonstrate superior angiogenic capacity compared to BM-MSC-Exos, potentially attributed to their unique miRNA profiles (eg, miR-125a enrichment) that enhance endothelial cell migration.[38] Dental pulp MSC-derived Exos (DP-MSC-Exos) outperform UCB-MSC-Exos and BM-MSC-Exos in promoting endogenous neurogenesis and axonal elongation.[39]

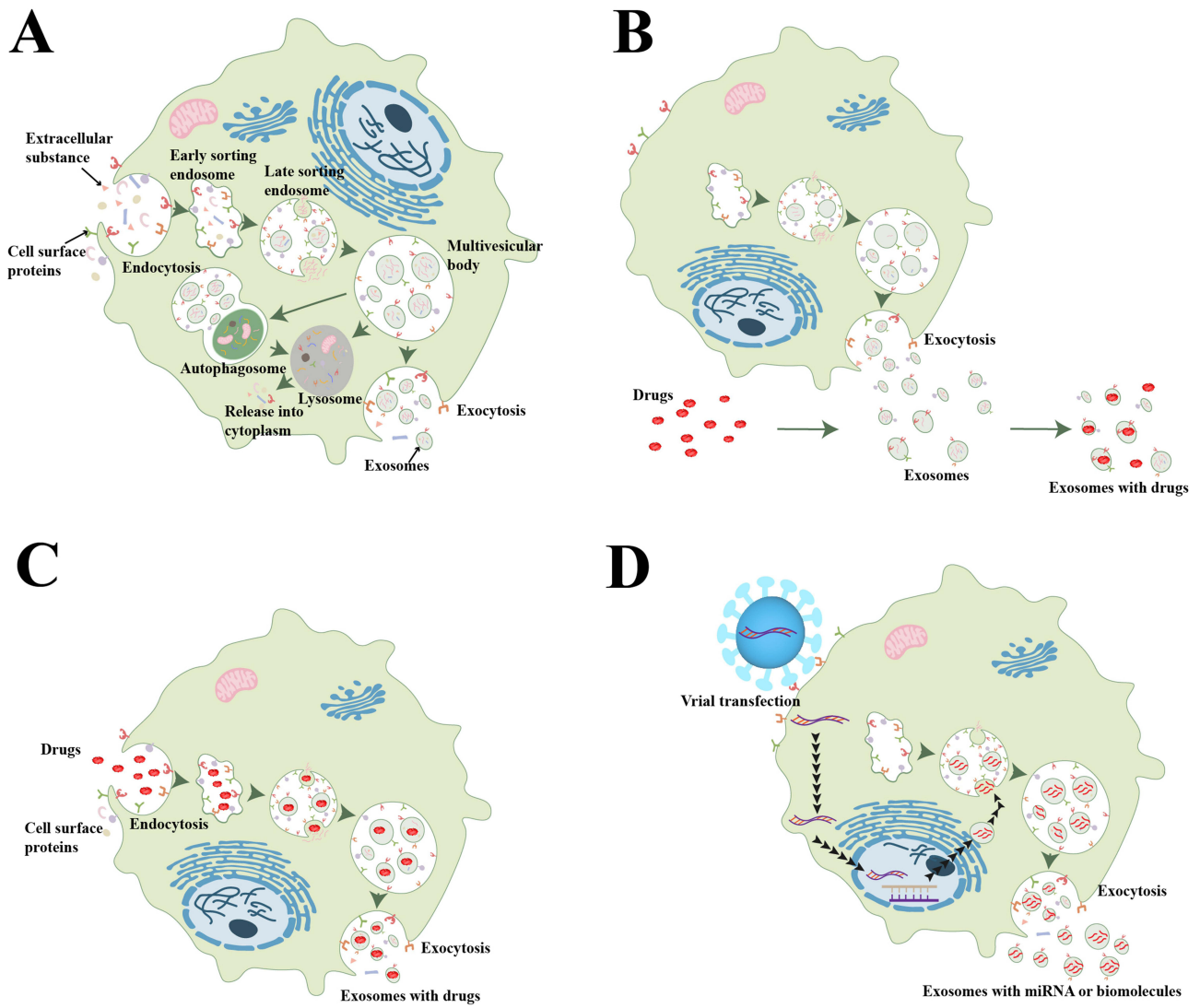

Figure 1 Biogenesis and modification of exosomes.(**A**). Biogenesis of exosomes. The early-sorting endosomes, are formed under the endocytosis of the cell membrane and contain cell membrane proteins and related substances in the internal environment of the cell. The Golgi apparatus, endoplasmic reticulum and mitochondria are also involved in the formation process. Early-sorting endosomes fuse with each other or further mature to form late-sorting endosomes, which then become multivesicular bodies under the action of the endosomal sorting complex required for transport. Multivesicular bodies contain several exosomes. Multivesicular bodies can be dissolved within the cell under the action of intracellular lysosomes and autophagosomes or fuse with the cell membrane to release exosomes outside the cell. (**B**). Incorporation of designated drugs directly into the exosomes. (**C**). Drugs can be uptake by the parental cells, which produce exosomes containing designated drugs. (**D**). Transfection of the parental cells with drugs-coding DNA to get exosomes loading with therapeutic agents expressed by the genes.

Emerging delivery modalities for MSC-derived Exos demonstrate distinct pharmacokinetic profiles and therapeutic outcomes in SCI management. Shaowei and et al established the neurotropic migration capacity of Exos through nasal-brain axis transport, demonstrating efficient BBB penetration via olfactory pathways.[40] The Exos of MSCs given intravenously were ingested by M2-type macrophages at the site of SCI, causing M2-type macrophages to continue to polarize and release TGF-β to restore the integrity of the BSCB.[41] Compared with intravenous infusion of MSCs, intravenous administration of Exos can reduce uptake by liver and lung tissues.[42,43] Of course, there are poor bioavailability of intravenously administered Exos and extensive secondary damage at the site of action. Min and et al used the 3D-exohydrogel hybrid microneedle array patch hydrogel to achieve precise and sustained release of Exos at the site of SCI. Such approach demonstrated a superior therapeutic advantage over the traditional way of directly attaching MSCs to the stroma. Exos implanted by this method have a higher Exo retention rate and are more conducive to neural regeneration in injured spinal cord.[44]

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Astrocytes Derived Exosomes

The ability of astrocytes to maintain the integrity of BSCB and to participate in neuronal signaling is partially mediated by Exos released from these cells.[25] Studies have shown that astrocyte-derived Exos are secreted in response to oxidative stress or hyperthermic conditions.[22] Furthermore, experiments using cultured astrocyte models have revealed that such vesicle secretion serves as a neuroprotective mechanism linked to synapsin release, thereby promoting neuronal survival.[45] Additionally, astrocyte-derived Exos contain numerous microRNAs (miRNAs) that contribute to neural repair processes following injury.[46] Notably, vimentin released in astrocytic Exos exhibits promising neuroprotective effects and enhances plasticity in the context of SCI treatment.[47]

Oligodendrocytes Derived Exosomes

Oligodendrocytes in the central nervous system primarily function to myelinate axons, forming insulating sheaths that facilitate the efficient propagation of nerve impulses. Early ultrastructural studies by Carsten et al identified MVBs localized predominantly at periaxonal sites within oligodendrocytes.[48] These cells secrete Exos enriched with myelin-associated components, including proteolipid protein (PLP), myelin oligodendrocyte glycoprotein (MOG), myelin basic protein (MBP), and 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNPase), all of which are essential for myelination.[49] Carsten et al further elucidated Exo-mediated bidirectional communication between neurons and oligodendrocytes. Specifically, neuronal activity-dependent glutamate release elevates intracellular Ca^{2+} levels in oligodendrocytes via NMDA and AMPA receptor activation, triggering Exo secretion. These oligodendrocyte-derived Exos are subsequently internalized by neurons, conferring protection against oxidative stress at both axonal and somatodendritic compartments.[50] Frohlich et al extended these findings by identifying catalase and superoxide dismutase as critical cargos in oligodendrocyte Exos that mitigate neuronal ischemic damage.[51]

Collectively, these findings indicate that oligodendrocyte-neuron crosstalk, mediated by Exos, plays a dual role in coordinating myelination and neuroprotection. Recent work by Kelly's team revealed that SIRT2 within mature oligodendrocyte Exos enhances axonal energy metabolism by deacetylating mitochondrial adenine nucleotide translocases 1/2 (ANT1/2), thereby boosting ATP production.[52] Conversely, Dirk et al reported an autoregulatory mechanism wherein oligodendrocyte Exos paradoxically suppress myelinogenesis through autocrine signaling,[53] highlighting the functional complexity of these vesicles.

Despite these advances, regulatory mechanisms governing oligodendrocyte Exo secretion remain poorly understood. Chieh et al investigated Rab GTPase-mediated Exo biogenesis, leveraging the phospholipid bilayer properties of Exos. Their study demonstrated that Rab35 inactivation via TBC1D10A-C targeting induces intracellular Exo accumulation in oligodendrocytes.[54] Nevertheless, whether Schwann cell-derived Exos in the peripheral nervous system share functional parallels with oligodendrocyte Exos warrants further investigation.

Microglia/Macrophages Derived Exosomes

Following SCI, disruption of the BSCB triggers a complex cascade involving microglial activation and infiltration of peripheral blood-derived macrophages. These microglia/macrophages exhibit two primary polarization states: the proinflammatory M1 phenotype and the anti-inflammatory M2 phenotype, with their phenotypic plasticity being critically regulated by the evolving pathological microenvironment post-SCI.[55]

The divergent roles of Exos secreted by polarized microglia/macrophages in spinal cord repair have been extensively investigated. Notably, Exos derived from M1 and M2 phenotypes exert opposing effects on SCI pathophysiology.[56] Substantial evidence indicates that M2 macrophages promote angiogenesis through multiple mechanisms. For instance, Peng et al demonstrated that microglia-derived Exos mitigate oxidative stress in spinal microvascular endothelial cells by activating the KEAP1/NRF2/HO-1 signaling axis, thereby enhancing angiogenesis.[57] While this study did not explicitly identify the microglial phenotype involved, subsequent work by Luo et al systematically investigated the therapeutic potential of M2 macrophage-derived Exos. Their in vitro experiments revealed that M2 Exos significantly enhance the angiogenic capacity of spinal cord microvascular endothelial cells. Moreover, sustained delivery of these Exos via hydrogel scaffolds at injury sites promoted vascular regeneration and functional recovery in SCI models.[58] Complementary findings by Song et al identified miR-124 in M2 microglial Exos as a key mediator of neuroprotection,

demonstrating its ability to downregulate ubiquitin-specific protease 14 (USP14), thereby reducing ischemic infarct volume and neuronal apoptosis in cerebral ischemia models.[59] Zhang et al further engineered M2 macrophage-derived extracellular vesicles co-loaded with nerve growth factor (NGF) and curcumin, which synergistically attenuated neuroinflammation and improved motor function in SCI rats.[60] In a mechanistic study, Wang et al revealed that M2 bone marrow-derived macrophage Exos inhibit neuronal apoptosis in SCI mice via miR-421-3p-mediated suppression of the mTOR pathway, highlighting their role in regulating autophagy.[61]

Contrastingly, M1-derived Exos exhibit detrimental effects. Ge et al reported that Exos from polarized M1 macrophages exacerbate BSCB disruption by enhancing mitochondrial reactive oxygen species (ROS) production and endothelial-mesenchymal transition (EndMT) in vascular endothelial cells, a process driven by exosomal miR-155.[62] This pro-inflammatory effect extends to remyelination processes, as co-culture experiments demonstrated that M1 microglial Exos inhibit oligodendrocyte precursor cell (OPC) recruitment and remyelination, whereas pro-regenerative microglial Exos enhance these reparative processes.[56]

Intriguingly, peripheral macrophage-derived Exos may modulate central nervous system repair through cross-talk with resident microglia. A recent study revealed their capacity to induce microglial autophagy via PI3K/AKT/mTOR pathway inhibition, driving polarization toward the anti-inflammatory M2 phenotype.[63]

Neurons Derived Exosomes

Neuronally derived Exos exhibit a unique miRNA repertoire distinct from the endogenous miRNA profile of their parental neurons. A notable example is miR-124-3p—a central nervous system (CNS)-enriched miRNA—which demonstrates targeted delivery to astrocytes and efficient cellular internalization capacity.[64] Beyond maintaining neural homeostasis and modulating neuron-glia interactions under physiological conditions, neuronal Exos suppress post-traumatic activation of microglia and astrocytes in SCI models, ultimately enhancing locomotor recovery. Mechanistically, miRNA microarray analyses revealed significant enrichment of miR-124-3p in neuronal Exos, functioning through dual pathways: (1) inactivation of myosin heavy chain 9 (MYH9), and (2) modulation of the PI3K/AKT/NF-κB signaling cascade.[65]

Exosomes of Other Cell Origin

Exos from alternative cellular sources have shown therapeutic potential in SCI treatment. Intravenous administration of Schwann cell-derived Exos (SCDEs) in SCI murine models upregulated Toll-like receptor 2 (TLR2) expression on astrocytes while reducing chondroitin sulfate proteoglycan (CSPG) deposition in the extracellular matrix (ECM). Mechanistic studies implicated NF-κB/PI3K signaling activation as the driver of TLR2 elevation.[66] SCDEs additionally demonstrated capacity to polarize macrophages/microglia toward anti-inflammatory phenotypes, thereby attenuating neuroinflammation post-SCI.[11] Parallel therapeutic effects have been observed with Exos from olfactory ensheathing cells.[67]

Notably, regulatory T (Treg) cell-derived Exos—a $CD4^+$T cell subset critical for immune homeostasis—effectively suppress microglial pyroptosis and subsequent inflammatory cascades in SCI.[68] Vascular endothelial cell Exos enhance Schwann cell myelination through miR-199-5p upregulation and coordinated activation of the PI3K/AKT/PTEN (phosphatase and tensin homolog) pathway.[69] Furthermore, pericyte-derived Exos mitigate multiple SCI-associated pathologies, including edema, BSCB leakage, hypoxia, oxidative stress, and neuronal apoptosis.[70]

Modified Exosomes

Multiple engineering strategies have been developed to enhance the therapeutic efficacy of Exos through cargo loading (Figure 1). The primary approach involves passive diffusion, where naïve Exos are incubated with lipophilic small molecules to facilitate drug encapsulation.[71] However, due to the inherent saturation of endogenous proteins and nucleic acids in native Exos, this method exhibits limited loading capacity.[72] For RNA delivery, electroporation enables active incorporation of specific nucleic acids into exosomal vesicles. Hydrophilic macromolecules such as proteins can be loaded via membrane permeabilization using agents like saponin. Notably, Gao et al achieved 17.13 ± 1.64% berberine loading efficiency in M2 macrophage-derived Exos through iterative ultrasonication, demonstrating sustained drug release over 48 hours.[73]

Exos can also be bioengineered at the progenitor cell level to display surface-targeting ligands or acquire specialized functionalities. One strategy involves preloading parental cells with therapeutic agents, which are subsequently packaged into secreted Exos. For example, Cui et al achieved 45.2% encapsulation efficiency and 19.7% loading capacity for resveratrol in M1 microglia-derived Exos. These engineered vesicles exhibited reduced pro-inflammatory cytokine levels (IL-1β and TNF-γ) compared to naïve Exos, along with enhanced resveratrol stability and anti-inflammatory efficacy in SCI mice following intravenous administration.[74] This method not only preserves drug bioactivity but also leverages the exosomal phospholipid bilayer to improve BSCB penetration.[73] Alternatively, genetic modification of parent cells enables endogenous production of therapeutic cargo. Lai et al engineered miR-146a-5p-overexpressing human umbilical cord mesenchymal stem cells (hUCMSCs), whose Exos mitigated neurotoxic astrocyte activation and enhanced neuronal survival in SCI rats.[75]

Exosomal functional diversity is further influenced by parental cell culture conditions.[76,77] Liu et al demonstrated that hypoxia-preconditioned MSC-Exos outperformed normoxic counterparts in restoring motor function post-SCI, a effect attributed to miR-216a-5p-mediated microglial M1/M2 polarization.[77] Furthermore, combining hypoxic Exos with biomaterial hydrogels synergistically enhanced angiogenesis and neural repair.[78] TGFβ1 (transforming growth factor) -preconditioned MSC Exos significantly promoted M2 microglial polarization, neuroprotection, and functional recovery in SCI mice, whereas untreated MSC Exos showed attenuated effects.[79] These findings underscore the necessity of standardized Exo production protocols for clinical translation.

With their inherent biocompatibility and engineerability, Exo-based drug delivery systems represent a frontier in precision medicine for SCI.[80,81] Strategic cargo loading and surface modifications offer novel pathways for clinical application of these intelligent biomaterials (Figure 2).

Potential Mechanisms Involved in Repair of Spinal Cord Injury by Exosomes

Relieving Inflammation and Pyroptosis

SCI initiates a cascade of inflammatory responses, predominantly characterized by robust activation of proinflammatory M1 macrophages/ microglia. Consequently, rebalancing the M1/M2 macrophage/microglia polarization equilibrium emerges as a pivotal therapeutic strategy for SCI (Figure 3). Exos demonstrate remarkable capacity to modulate this polarization shift, driving the conversion from M1 proinflammatory to M2 anti-inflammatory phenotypes.[82]

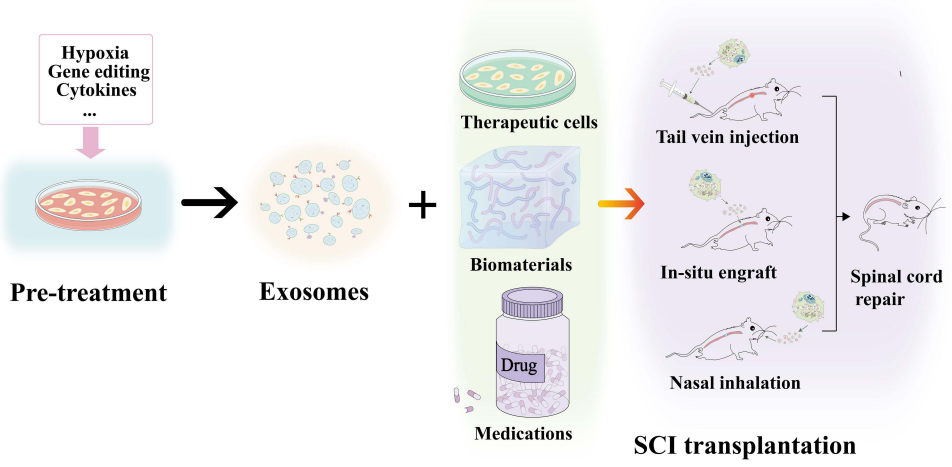

Figure 2 Combinatorial approaches of exosomes for spinal cord injury (SCI) repair.Cells can be genetically engineered or subjected to modified culture conditions (eg, hypoxic stimulation or growth factor supplementation), enabling the same cell lineage to generate distinct exosome subtypes. These exosomes may be incorporated into biomaterial-based hydrogels, combined with pharmacological agents, or co-administered with therapeutic cells to enhance SCI repair efficacy through systemic delivery (eg, tail vein injection and nasal inhalation) or localized therapeutic strategies (eg, direct transplantation at the lesion site).

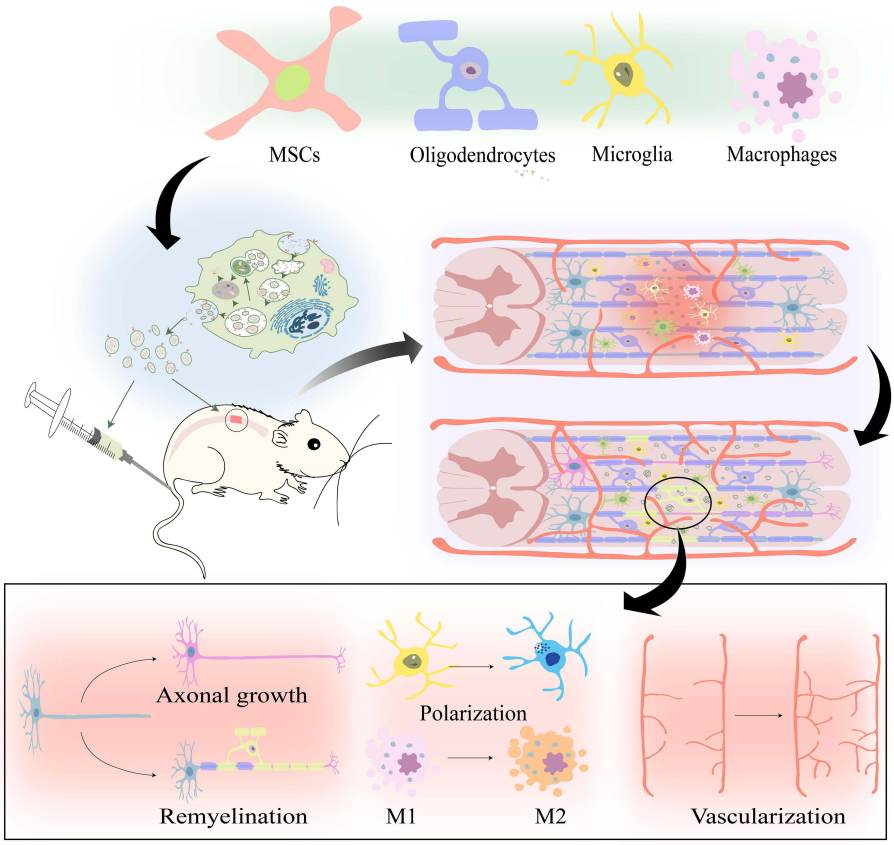

Figure 3 Mechanisms of exosomes from different cellular sources for the treatment of spinal cord injury.The primary repair mechanisms involve promoting axonal regeneration, enhancing myelin sheath formation, shifting macrophage/microglia polarization toward the M2 anti-inflammatory phenotype, and facilitating vascularization to maintain blood-spinal cord barrier integrity.

Mechanistic studies reveal multifactorial regulation of phenotypic switching. Yuan et al demonstrated dose-dependent effects of endothelial progenitor cell-derived Exos on macrophage polarization, where exosomal miR-222-3p activated the SOCS3/JAK2/STAT3 axis to enhance M2 marker expression and improve functional recovery in SCI models.[12]

The therapeutic potential of M2-derived Exos extends beyond immunomodulation. Wang et al identified miR-421-3p enrichment in M2 macrophage Exos as a critical mediator of neuroprotection, suppressing neuronal apoptosis via mTOR pathway inhibition and autophagy activation.[61] Complementary findings show peripheral macrophage Exos promote M2 microglial polarization through PI3K/AKT/mTOR-mediated autophagy induction, amplifying reparative responses post-SCI.[63]

In recent years, there have been several studies on the role of MSC-derived Exos in inhibiting pyroptosis in SCI. It has been found that miR-21a-5p in BMSC derived Exos positively regulates the autophagy of macrophages/microglia by reducing Pellino 1 expression, thereby inhibiting their pyroptosis and enhancing the recovery of locomotor functions.[83] Besides, Exos can also inhibit pericyte pyroptosis via suppressing NF-κB activation after SCI, and increase the content of endothelial tight junction proteins such as Claudin-5, Occludin, and ZO-1 to reduce neurological damage.[84]

Emerging strategies combine immunomodulation with pyroptosis inhibition. Treg cell-derived Exos carrying miR-709 target NKAP (NF-κB activating protein) to mitigate microglial pyroptosis, synergistically reducing neuroinflammation.[68] Advanced engineering approaches further enhance therapeutic efficacy. Zhang et al developed dual-functional Exos co-loaded with NGF and curcumin onto M2 macrophage Exos, achieving combined anti-inflammatory and neuroprotective effects that surpass single-modality treatments[60] (Table 1).

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Table 1 A Summary of Exosomes From Different Cellular Resources for Repair of SCI

Cellular Resource of Exosomes	Mechanisms of Spinal Cord Repair	Delivery Ways	Limitation
Dental pulp mesenchymal stem cell[39]	Promoting the regeneration and differentiation of neuronspromoting axonal regenerationimproving motor, sensory, and urinary reflex	Local implantation	Need further system safety evaluation and pharmacological testingneed to research in the regeneration of complex tissues
Bone marrow mesenchymal stem cell[41]	Repair Blood-spinal cord barrier (BSCB) ImmunomodulationMolecular regulationFunctional recovery	Tail intravenous injection: one dose or fractionated doses	Limitations of the administration protocolIncomplete clarification of the mechanism of actionLimitations in targetingSpecies differences: need human researchUnknown long-term safety
Bone marrow mesenchymal stem cell[43]	Inhibition of glial scar formationAnti-inflammatoryNeuroprotectivePromotion of nerve repairNeuroelectrophysiologyFunctional recovery	Tail intravenous injection: siRNA-loaded exosomes	Loading efficiency and stabilityUnclear mechanism of exosome actionLimitation of delivery efficiencySpecies differences: need human researchUnknown long-term safety
Bone marrow mesenchymal stem cell[44]	Anti-inflammatoryImmunomodulatoryInhibition of glial scar formationTissue repairFunctional recovery	Local implantation:GelMA-MN@3D-Exo	Delivery efficiency and stabilityInsufficient depth of mechanismClinical transformation obstaclesLimitation of application scope
Astrocyte[46]	Anti-inflammatoryImprovement of neurological functionAlleviating the degree of brain injury	Intracerebroventricular injection: exosomes enriched with miR-873a-5p	Exosome delivery efficiency and targetingInsufficient depth of mechanismObstacles in clinical translationSpecies differences: need human researchUnknown long-term safety
Oligodendrocytes[49]	Amelioration of depressive-like behaviorsRestoration of hippocampal neurogenesisEnhancement of synaptic plasticity	Tail intravenous injection	Limitations in research scopeUnclear dosage and physiological effectsInsufficient mechanism verificationLack of electrophysiological evidenceGender singularity
Microglia[57]	Antioxidative stressPromotion of endothelial cell survival and functionPromotion of vascular regenerationImprovement of neurological function recovery	Tail intravenous injection	Unclear exosome componentsLimitations of experimental modelsRoom for optimization in delivery methodsObstacles to clinical translationInsufficient depth in mechanism research
M2 macrophage[58]	Enhancement of vascular endothelial cell function in vitroPromotion of vascular regeneration in vivoImprovement of spinal cord function recovery	Local implantation: Hydrogel-mediated sustained release of M2-Exos	Incomplete elucidation of the complexity of exosome componentsLimitations of the experimental modelRoom for optimization of the delivery systemObstacles to clinical translationInsufficient depth of mechanism research
M2 BV2[59]	In vitro protection of neuronsReduction of infarct volumeImprovement of neurological functionInhibition of neuronal apoptosis	Tail intravenous injection	Incomplete elucidation of the complexity of exosome componentsLimitations of the experimental modelRoom for optimization in delivery methodsObstacles to clinical translationInsufficient depth in mechanism research
M2 macrophages[60]	Regulation of macrophage polarizationPromotion of neuron survivalImprovement of axon and myelin sheath repairFunctional recovery	Tail intravenous injection	Incomplete elucidation of the complexity of exosome componentsLimitations of the experimental modelRoom for optimization of the delivery systemObstacles to clinical translationInsufficient depth of mechanism research

M2 macrophages[61]	In vitro protection of neuronsPromotion of motor function recoveryReduction of neuronal apoptosis	Tail intravenous injection	Incomplete elucidation of the complexity of exosome componentsLimitations of the experimental modelRoom for optimization of the delivery methodObstacles to clinical translationInsufficient depth of mechanism research
M1 macrophages[62]	Promotion of EndoMTImpairment of mitochondrial functionDisruption of BSCB integrityImpediment to motor function recovery	Tail intravenous injection	Incomplete elucidation of the complexity of exosome componentsLimitations of the experimental modelInsufficient targeting of delivery methodsObstacles to clinical translationInsufficient depth of mechanism research
Peripheral macrophage[63]	Promotion of anti-inflammatory phenotype polarizationActivation of autophagy and inhibition of the PI3K/AKT/mTOR pathway. Improvement of motor functionReduction of tissue damageInhibition of inflammatory response	Tail intravenous injection	Incomplete elucidation of the complexity of exosome componentsLimitations of the experimental modelInsufficient targeting of the delivery methodObstacles to clinical translationInsufficient depth of mechanism research
Neuron[65]	Inhibition of M1 microglia activationInhibition of A1 astrocyte activationImprovement of motor functionReduction of tissue damageInhibition of neuroinflammation	Tail intravenous injection	Incomplete elucidation of the complexity of exosome componentsLimitations of the experimental modelInsufficient targeting of the delivery methodObstacles to clinical translationInsufficient depth of mechanism research
Schwann cells[66]	Activation of Toll like receptor 2 expressionImprovement of cell functionImprovement of motor functionReduction of tissue damageInhibition of scar formation	Tail intravenous injection	Incomplete elucidation of the complexity of exosome componentsLimitations of the experimental modelInsufficient targeting of the delivery methodObstacles to clinical translationInsufficient depth of mechanism research
Olfactory Ensheathing Cells[67]	Inhibition of M1 polarizationImprovement of motor functionProtection of neurons and axonsRegulation of the immune microenvironment	Local injection	Incomplete elucidation of the complexity of exosome componentsLimitations of the experimental modelInsufficient targeting of the delivery methodObstacles to clinical translationInsufficient depth of mechanism research
Treg cells[68]	Inhibition of pyroptosis activationImprovement of motor functionReduction of pyroptotic damageEnhancement of therapeutic effect	Intrathecal injection	Incomplete elucidation of the complexity of exosome componentsLimitations of the experimental modelInsufficient targeting of the delivery methodObstacles to clinical translationInsufficient depth of mechanism research
Human umbilical vein endothelial cells[69]	Enhanced proliferation, migration, and anti-apoptosisUpregulation of functional moleculesIn vivo promotion of nerve regenerationImprovement of motor functionStructural repairLong-term retention	Local multi-site injection	Incomplete elucidation of the complexity of exosome componentsLimitations of the experimental modelInsufficient targeting and optimization of delivery methodsObstacles to clinical translationInsufficient depth of mechanism research
Pericytes[85]	Improvement of motor functionAlleviation of pathological damageInhibition of cell apoptosisIncrease of blood perfusionProtection of BSCB	Tail intravenous injection	Incomplete elucidation of the complexity of exosome componentsLimitations of the experimental modelInsufficient targeting of the delivery methodObstacles to clinical translationInsufficient depth of mechanism research

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Enhance Vascularization

After SCI, mechanical disruption of microvasculature at the lesion site compromises BSCB integrity, triggering inflammatory cascades that impede tissue repair.[86] Revascularization plays a dual therapeutic role by restoring tissue perfusion to alleviate hypoxia and providing structural guidance for axonal regrowth (Figure 2).[87]

MSC-derived Exos enhance angiogenesis through coordinated activation of PI3K/AKT and MAPK/ERK1/2 signaling pathways, which upregulate vascular endothelial growth factor (VEGF) expression to stimulate endothelial cell proliferation and migration.[88] Li et al demonstrated that 15-minute hypoxic preconditioning of human umbilical vein endothelial cells (HUVECs) generates Exos capable of accelerating MSC-mediated tubulogenesis in vitro (2-hour capillary-like structure formation) and enhancing vascular regeneration in SCI rats.[76]

M2 macrophage-derived Exos exhibit potent pro-angiogenic properties during SCI recovery. RGD peptide-engineered $CD163^{+}$ macrophage Exos selectively deliver TGF-β to neovascular endothelial cells, synergistically promoting BSCB restoration and angiogenesis.[89] Proteomic analyses reveal OTULIN-enriched M2 Exos activate Wnt/β-catenin signaling via β-catenin stabilization, establishing a positive feedback loop for vascular regeneration.[58]

Notably, microglial Exo functionality depends on cellular phenotype. While Peng et al reported microglia-derived Exos mitigate endothelial oxidative stress via KEAP1/NRF2/HO-1 pathway activation[57] (Table 1).

How Emerging Exosome Therapy Can Facilitate Axonal Regeneration?

Secondary Wallerian degeneration after SCI in distal spinal cord segments disrupts excitatory signal transmission, perpetuating neurological deficits.[90,91] Axonal regeneration is further impeded by inhibitory microenvironmental factors, including CSPGs, Nogo-A, myelin-associated glycoprotein (MAG), and oligodendrocyte myelin glycoprotein (OMgp).[92]

Oligodendrocyte-derived myelin sheaths are essential for maintaining saltatory conduction. Emerging evidence highlights Exos as key mediators of post-SCI axonal regeneration, with oligodendrocyte Exos being particularly efficacious.[52,93,94] These vesicles deliver sirtuin 2 (SIRT2)—a NAD dependent deacetylase—from the myelin sheath's inner layers to axonal mitochondria, facilitating ATP production through mitochondrial deacetylation. This energy provision mechanism underscores Exos' role in neural network communication.[52,93]

Oxidative stress exhibits paradoxical effects on axonal regeneration. While PTEN inhibits regeneration, ROS generated post-injury can paradoxically promote axonal growth via NOX2-PI3K-p-Akt signaling-mediated PTEN inactivation. Direct administration of PTEN siRNA-loaded Exos to SCI sites enhances regeneration by suppressing this mTOR pathway inhibitor, thereby upregulating mTOR—a critical promoter of axonal growth.[40,95]

Bioengineered Exo composites demonstrate enhanced regenerative capacity.[96,97] Chitosan scaffolds synergize with fibroblast Exos to drive axonal regeneration via the TFAP2C/miR-132-5p/CAMKK1 axis.[96] Yan et al developed "Spinor" a DP-MSC assembly that autonomously releases Exos with dual anti-inflammatory and pro-regenerative properties, significantly improving axonal repair in SCI models[39] (Table 1).

Other Mechanisms

Astrocytes play a dual role in SCI repair, with their functional polarization critically influencing therapeutic outcomes. Proinflammatory A1 astrocytes—induced by inflammatory cascades post-SCI—exert neurotoxic effects through myelin sheath degradation and neuronal apoptosis, making their inhibition a promising therapeutic strategy.[98] Jiang et al demonstrated that miR-124-3p-enriched neuron-derived Exos effectively suppress A1 astrocyte activation, thereby enhancing functional recovery in SCI models.[65]

Fibrotic scar formation presents another major barrier to axonal regeneration. Combined treatment using MSC-derived Exos and bioactive hydrogels has shown efficacy in modulating the injury microenvironment, significantly suppressing fibrotic scar formation while promoting neural repair.[97] Furthermore, Schwann cell-derived Exos upregulate Toll-like receptor 2 (TLR2) expression on astrocytes via NF-κB/PI3K pathway activation, concurrently reducing CSPG deposition in the extracellular matrix.[66]

The Future Prospectives

Exos have emerged as a promising cell-free therapeutic modality for SCI, garnering significant attention in recent years.[99,100] Compared to conventional stem cell therapies, Exos offer distinct advantages including low immunogenicity, non-tumorigenicity, enhanced BSCB permeability, and logistical feasibility in transport/storage. Their engineerability further enables precision medicine through targeted delivery of regulatory RNAs (miRNAs, lncRNAs, circRNAs).[81,101] A Phase I clinical trial that intrathecal injection of allogeneic human umbilical cord MSC-derived Exos in 9 patients with complete subacute spinal cord injury was safe and well-tolerated, with significant improvements in neurological and functional conditions after 12 months of follow-up.[26] More related clinical studies are still underway, and with their unique ability to encapsulate and transport disease-specific molecules while traversing biological barriers, Exos hold immense promise as next-generation diagnostic biomarkers—offering unparalleled specificity and accessibility to revolutionize early disease detection and personalized medicine.[102] Nevertheless, clinical translation faces multifaceted challenges. The inherent complexity of intercellular communication limits the efficacy of single-target approaches, necessitating systematic exploration of multi-target mechanisms and therapeutic synergies. Critical translational gaps include:

1) Safety and pharmacokinetics considerations as comprehensive preclinical validation of Exo biocompatibility, biodistribution and in vivo half-life need to be explored; 2) Standardization of experiments by establishment of universal guidelines for dosage, administration routes and treatment regimens is required; 3) Manufacturing consistency of Exos by optimization of isolation protocols to ensure batch-to-batch purity and functional reproducibility is necessary;[103] 4) Mechanistic insights into Exo biogenesis to enhance yield without compromising cargo integrity are also important.[104] Future therapeutic strategies may integrate Exos with biomaterials or stem cells, while combinatorial approaches leveraging Exos from diverse cellular sources could address SCI's multifactorial pathology. Beyond therapeutics, emerging evidence supports their potential as diagnostic biomarkers for SCI progression and recovery prognostication.[105]

Conclusion

In conclusion, SCI remains a challenge in neural regeneration, with current therapeutic strategies failing to substantially improve patient prognoses. The post-SCI pathophysiological cascade represents a multifactorial interplay of degenerative and reparative processes, necessitating mechanistic elucidation to develop targeted interventions. Exo-based therapies emerge as a transformative paradigm, offering distinct advantages over cell transplantation by minimizing immunogenic risks while enabling targeted drug delivery across the BSCB. Their inherent capacity to mediate CNS intercellular communication and orchestrate multimodal repair mechanisms—including neuroprotection, immunomodulation, and axonal regrowth—positions Exos at the forefront of SCI therapeutics. Future progress hinges on: 1) Deciphering exosomal cargo-recipient cell interactions through multi-omics approaches; 2) Standardizing isolation protocols to enhance yield and functional consistency; 3) Establishing pharmacokinetic/ pharmacodynamic profiles for clinical dosing optimization. Addressing these challenges will bridge the translational gap, ultimately enabling precision Exo therapies tailored to SCI's spatial-temporal pathobiology.

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Disclosure

The authors report no conflicts of interest in this work.

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