

Exosomes-Based Nanotherapeutic Strategies: An Important Approach for Spinal Cord Injury Repair

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Abstract: The repair and functional regeneration of spinal cord injury (SCI) remains a major challenge and focal point in regenerative medicine. Following SCI significant inflammation and neuronal damage occur. Conventional drug therapies often fail to precisely target the injured areas and cannot cross the blood-spinal cord barrier, severely limiting therapeutic efficacy. Therefore, precision therapeutics are crucial to improve the prognosis of SCI patients. In recent years, exosomes have gained widespread attention as natural delivery vehicles due to their low immunogenicity, high biocompatibility, and efficient delivery capabilities. Exosomes can effectively cross cell membranes and target specific cells, playing an important role in intercellular signaling. This makes them highly promising for precision therapies in SCI. By engineering exosomes for targeted delivery, new strategies can be developed for drug delivery, gene therapy, and personalized treatment after SCI. We aimed to review the biological functions of exosomes derived from different cell sources and discuss the role in tissue repair following SCI. Additionally, we explore the prospects and potential of exosomes in clinical SCI applications, to provide valuable research insights to improve functional recovery and long-term health management for SCI patients in the future.

Keywords: spinal cord injury, exosomes, nanodelivery, inflammation, nerve injury, non-coding RNA

Introduction

Spinal cord injury (SCI) results in immediate damage to neurons and axons, triggering a cascade of secondary pathological events.¹ These events lead to sensory, motor, and autonomic dysfunction below the level of injury. Furthermore, high-level SCI may cause respiratory difficulties.² SCI can be classified into complete and incomplete injuries based on the location and severity of the damage. Complete SCI results in total loss of function below the level of injury, leaving patients unable to perceive or control the parts of the body below the injury site. In contrast, patients with incomplete SCI may retain some function below the injury level, maintaining the ability to perceive certain sensations or partial motor capabilities.³ Currently, the incidence of new SCI cases continues to rise globally, imposing a significant economic burden on patients and society.⁴ The prognosis of SCI depends on the severity of the injury and the extent of preserved function. The pathological process of SCI can be divided into primary and secondary injuries. Primary injury is an instantaneous and irreversible process caused by initial mechanical compression, while secondary injury involves inflammatory infiltration and neuronal apoptosis, which can persistently expand the lesion area, further exacerbating the progression of SCI.⁵ Surgical intervention and hormone therapy remain the primary approaches during the acute phase following SCI.⁶ However, despite advancements in the treatment of SCI, the limited regenerative capacity of the spinal cord means that there is currently no fully effective treatment capable of completely restoring spinal cord function, and clinical outcomes remain poor. Long-term health management for patients poses significant challenges. Consequently, the search for safe, effective, and sustainable long-term treatment methods has become a crucial area of research.

The Main Pathological Processes of Secondary Injury

Damage to Blood Vessels, Ischemia, and Hypoxia After SCI

The blood supply to the spinal cord is disrupted during the early stages of primary injury. Due to excessive hemorrhage and neurogenic shock, patients with SCI often experience impaired perfusion and ischemia at the lesion site. After the blood vessels are damaged, the activation of multiple pathways can lead to systemic damage, causing a significant increase in extracellular glutamate levels, triggering excitotoxicity.⁷ Additionally, blood perfusion in the tissue can increase the permeability of the blood-spinal cord barrier (BSCB), promote the production of reactive oxygen species (ROS), and induce inflammation. Direct alterations to the BSCB endothelial cells can also facilitate the infiltration of immune mediators, leading to edema.⁸

The Inflammatory Response After SCI

Inflammatory response is a critical component of secondary injury, with inflammation infiltration dependent on the time course of injury and the activation state of immune cells.⁹ Following SCI, astrocytes, resident microglia, endothelial cells, and peripherally derived immune cells secrete harmful products, mediating activation of the immune system and the inflammatory response. Some studies indicate that inflammatory cytokines are upregulated within hours after injury, subsequently triggering the infiltration of exogenous and local cells.¹⁰ Moreover, these infiltrating immune cells can further produce and secrete other chemokines and cytokines that regulate the immune response, creating a detrimental inflammatory cycle.¹⁰ During the initial phase of inflammation (0–2 days), astrocytes, blood-derived neutrophils, and microglia are recruited to the injured area. Approximately 3 days post-injury, the second phase begins, during which circulating phagocytes and lymphocytes are recruited to the injury site. Activated macrophages, microglia, and other cells can stimulate T lymphocytes, thereby contributing to immune protection.¹¹ CD4⁺ helper T lymphocytes promote the generation of B lymphocytes by producing various factors.¹² The inflammatory response triggered by these cells plays a critical role in the progression of SCI.

Cell Death After SCI

Cell death is a critical process in secondary injury. Furthermore, as a result of mechanical damage caused by primary injury, the death of neurons and glial cells continues throughout the acute and subacute stages of injury.¹³ Necrosis and apoptosis are two important mechanisms of cell death.¹⁴ Necrosis is triggered by various factors, including the accumulation of blood-derived toxic substances, increased glutamate, ion imbalance, and excessive ATP depletion.¹⁵ Apoptosis is a programmed cell death process that can occur through extrinsic and intrinsic pathways based on the triggering mechanisms. The extrinsic pathway is activated by triggering death receptors, while the intrinsic pathway is regulated through the dynamic coordination of intracellular apoptosis-related proteins.¹⁶ Apoptosis typically occurs in areas distant from the injury site. In rat models of SCI, apoptosis can occur as early as 4 hours post-injury and peaks at 7 days.¹⁷ Therefore, modulating the necroptosis pathway appears to be a strategy for neuroprotection following SCI.

Scar Formation After SCI

Following SCI, astrocytes, pericytes, and fibroblasts are activated, promoting the development of glial/fibrotic scars. The upregulation of TGF- β enhances astrocyte activation and the subsequent formation of glial scar borders, as well as the deposition of fibronectin and laminin.¹⁸ Additionally, the transcription factor STAT3 plays a crucial role in establishing the glial scar border, which helps isolate infiltrating cells from entering the lesion core.¹⁹ However, the role of scars is complex. Glial scars have beneficial effects, such as repairing the damage to the BSCB caused by inflammation and isolating toxic substances from the injury site. Astrocytes simultaneously support axonal growth.²⁰ Conversely, persistent scar formation induced by astrocytes impedes the regeneration and repair process of the spinal cord during the subacute and chronic stages of injury.¹¹ Secretory products like proteoglycans produced by activated astrocytes can also interact with various harmful molecules and exert detrimental effects.²¹ The neural plasticity of mammals has been increasingly supported by numerous studies. When reactive astrocytes are transplanted into a naive spinal cord, they revert to a naive astrocyte state. Similarly, when they are transplanted into an injury site, they transform into scar-forming astrocytes.²² This indicates that the environment determines the phenotype of astrocytes, thereby influencing the inhibitory functions mediated by glial scars. In summary, SCI can be caused by a multitude of factors including traffic accidents, falls from

height, violent injury, and sports injury. After SCI, a series of pathological changes occur in the injured area, leading to abnormal responses in multiple body systems (Figure 1, All figures were drawn by Figdraw).

Exosomes as Acellular Therapy

The pathophysiological mechanisms following SCI are complex, involving the participation of various cells in different pathological processes within the injury zone.²³ Moreover, the functions of these cells and their signaling communication vary across different stages of injury. With advancements in medical technology, emerging therapies have brought potential hope for the treatment of SCI. Exosomes, leveraging their natural biological properties, hold significant potential in terms of safety, targeting ability, drug delivery efficiency, and functional diversity, particularly in the fields of precision medicine and personalized therapy.²⁴ As naturally occurring nanoscale vesicles derived from cells, exosomes carry a variety of proteins, lipids, nucleic acids, and bioactive small molecules, enabling intercellular communication and material exchange.²⁵ Extracellular vesicles (EVs) are membranous vesicles commonly found in a variety of body fluids and cells.²⁶ Typical EVs can be divided into three types: microvesicles, exosomes, and apoptotic bodies.²⁷ Studies have focused on the two main types of EVs (exosomes and microvesicles), and the release of these vesicles plays an important role in signal communication and molecular transmission between cells.²⁸ Exosomes (approximately 50–100 nm in diameter) have been reported as acellular structures and are formed by the invagination of the membrane into endosomes, followed by the formation of multivesicular bodies, which fuse with the plasma membrane, releasing EVs called exosomes.²⁹ Exosomes are widely distributed in the human body, and can be obtained from bodily fluid systems such as blood, urine, sweat, saliva, cerebrospinal fluid, and milk. The most commonly used method to obtain them is

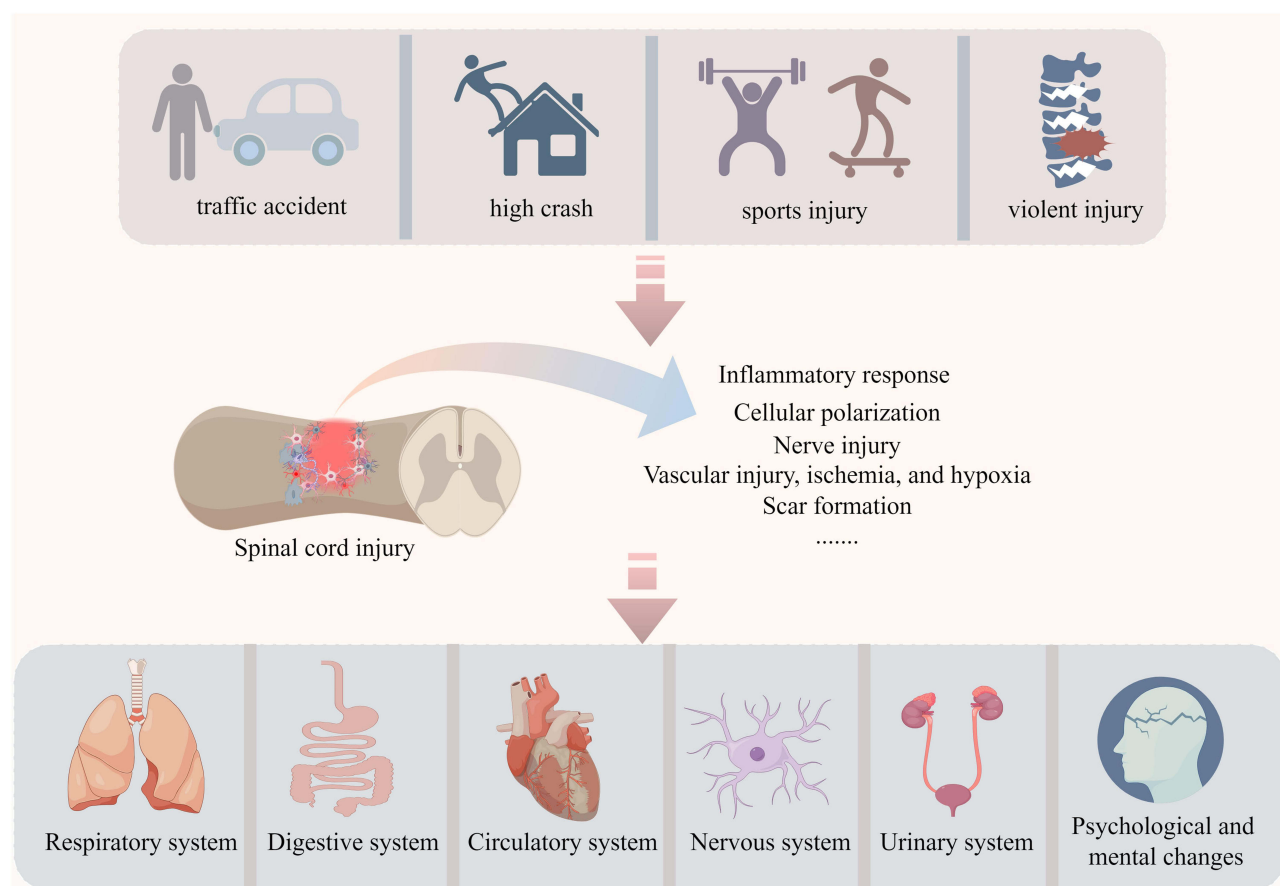


Figure 1 SCI can be caused by various factors such as traffic accident, high crash, violent injury, and sports injury. After SCI, the injured area undergoes a series of pathological changes, including inflammatory responses, cell polarization, neural damage, vascular injury, ischemia, hypoxia, and scar formation. Additionally, SCI can trigger abnormal reactions and alterations in multiple systems, including the respiratory, digestive, circulatory, nervous, and urinary systems, as well as psychological and mental health.

ultracentrifugation.³⁰ Exosomes are composed of many types of proteins, lipids and nucleic acids. The proteins include major histocompatibility complex (MHC)-II, integrin, differentiation cluster, four transmembrane proteins and heat shock protein (Hsp). Lipids mainly include sphingomyelin and cholesterol. Nucleic acids include miRNA, circRNA, mRNA and lncRNA.³¹ The source, extraction, and structure of exosomes are described in Figure 2. Exosomes can achieve intercellular communication and material exchange functions, and their main mechanism of action is through receptor ligand binding, direct membrane fusion, and endocytosis. Exosomes are also closely related to the progression of various diseases, including cancer, immune diseases, and neurological diseases.^{32–34} Exosomes also lack growth and proliferation ability, have low tumor risk, high membrane transport efficiency, and can cross the BSCB to reach the injured site of the spinal cord. Therefore, exosomes may have great potential and advantages in the treatment of SCI. The research progress of exosomes in SCI treatment can be regarded from three viewpoints: the source of exosomes, the non-coding RNA in exosomes and the engineering modification of exosomes. Exosomes strongly associated with the progression of various diseases, including cancer, immune disorders, and neurological diseases. Following SCI, exosomes play a pivotal role in

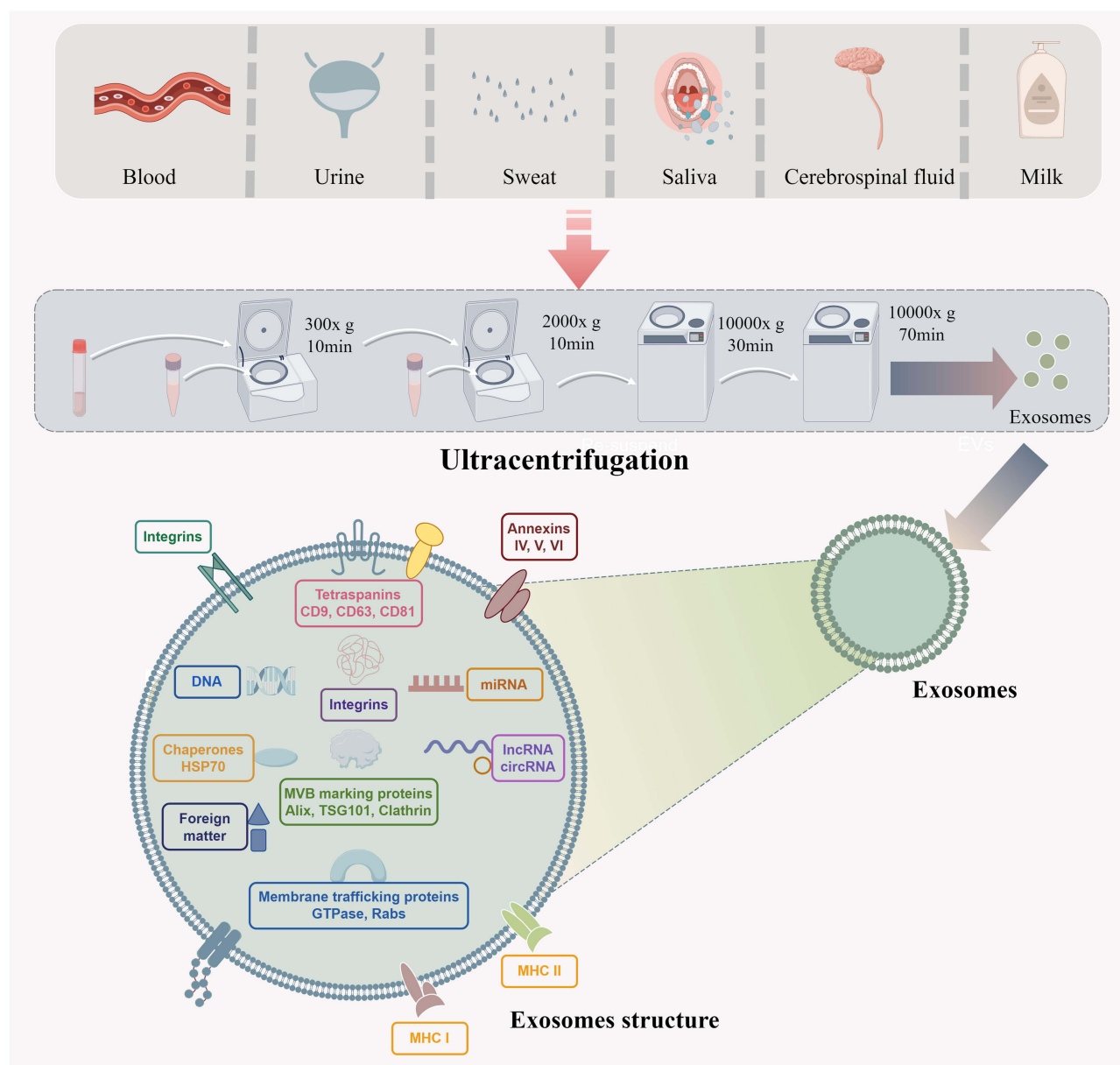


Figure 2 The origin, extraction, and structure of exosomes.

promoting neuroprotection, alleviating inflammatory responses, and enhancing the regenerative capacity of neurons. Additionally, exosomes can modulate the activity of immune cells such as glial cells and macrophages, thereby contributing to the improvement of the post-SCI immune microenvironment and reducing the occurrence of secondary injuries.

Local ischemia after SCI is a critical factor that hampers neural repair. Exosomes, carrying various small bioactive molecules, can enhance vascular stability and reduce the disruption of the BSCB. They also promote endothelial cell migration and angiogenesis, which are essential for restoring blood supply and supporting tissue regeneration. Moreover, exosomes exhibit high biocompatibility and low immunogenicity, allowing them to avoid the adverse effects commonly associated with traditional drugs and therapies. Their natural lipid bilayer structure enables exosomes to maintain stability *in vivo* and effectively cross the blood–brain barrier (BBB), a property crucial for treating neurological conditions like SCI. This appears to offer new strategies for the treatment of SCI.

The Function of Exosomes From Different Sources in SCI Diseases

Schwann Cell Derived Exosomes

In recent years, increasing evidence has demonstrated a connection between mitochondrial dysfunction and acute central nervous system (CNS) injury.³⁵ Therefore, maintaining normal mitochondrial function is crucial for neuronal cell stability. Schwann cells (SCs) contribute positively to nerve repair by clearing myelin sheath and axonal debris, as well as facilitating axonal growth and proliferation.³⁶ Recently study indicated that SCs-Exo can stimulate mitochondrial autophagy mediated by the AMPK pathway, thereby reducing oxidative stress, inflammation, and cell necrotic apoptosis.³⁷ Pan et al showed that SCs-Exo suppress the expression of EGFR and inhibit the Akt/mTOR signaling pathway, thereby enhancing autophagy levels and exerting a protective effect on SCI.³⁸ Furthermore, SCs-Exo treatment inhibits the occurrence of M1 polarization in LPS-stimulated bone marrow-derived macrophages (BMDMs). Additionally, a composite hydrogel patch prepared with SCs-Exo and methylprednisolone can promote the transition of M1 macrophages to the M2 phenotype, suppress neuronal apoptosis, and enhance neuronal survival.^{39,40} The delivery of SCs-Exo to astrocytes can increase TLR2 expression and reduce CSPG deposition in the injured area. Intravenous injection of SCs-Exo effectively decreases scar formation following SCI.^{41,42} In terms of angiogenesis, SCs-Exo can be internalized by bEnd.3 cells and promote angiogenesis via integrin- β 1.⁴³

Human Umbilical Cord Mesenchymal Stem Cells Derived Exosomes

Umbilical cord mesenchymal stem cells (UCMSCs) versatile stem cells found in neonatal umbilical cord tissue, are capable of differentiating into various types of tissue cells with high differentiation potential. UCMSCs hold significant clinical promise in tissue engineering applications, including the regeneration of bone, cartilage, muscle, tendon, ligament, nerve, liver, endothelium, and myocardium tissues.^{44,45} However, the function of hUCMSCs derived exosomes (hUCMSCs-Exo) in SCI remains unclear. Exosomes from hUCMSCs have great therapeutic potential in improving neuronal recovery after SCI. hUCMSCs-Exo decreased the activation of microglia and astrocytes in mice, and increased the motor function of SCI mice.⁴⁶ In *in vitro* and *in vivo* experiments, hUCMSCs-Exo effectively reduced the protein and mRNA expression levels of neurotoxic astrocyte markers C3 and Lcn2. Further mechanistic studies revealed that miR-146a-5p, by binding to IRAK1 and TRAF6, inhibits the expression of target genes, which is a crucial pathway through which hUCMSCs-Exo promote the recovery of motor function in mice.⁴⁷ In neurons, hUCMSCs-Exo- miR-146b inhibits the activation of the NF- κ B pathway by targeting TLR4, which can significantly alleviate the inflammatory injury to PC12 cells.⁴⁸ In addition, hUCMSCs-Exo can promote the transformation of M1 macrophages into M2 macrophages by downregulating inflammatory cytokines such as TNF- α , MIP-1 α , IL-6, and IFN- γ , as well as reducing ROS production. This process inhibits microglial apoptosis, thereby alleviating the inflammatory environment in the injured area.^{49,50} Isolating CD146+ CD271+ umbilical cord mesenchymal stem cells and obtaining hUCMSCs-Exo can reduce endothelial cell permeability, promote tight cell junctions, and enhance angiogenesis and BSCB integrity in the injured area following SCI.⁵¹ In summary, current findings indicate that hUCMSCs exert beneficial effects on inflammatory response, vascular regeneration, and neural recovery following SCI.

Endothelial Progenitor Cells Derived Exosomes

Endothelial progenitor cells (EPCs) are mainly derived from bone marrow and have the potential of multi-differentiation and stem cell-specific self-renewal. Bone marrow-derived EPCs promote the regeneration of blood vessels and nerve axons, migrate to organs or tissues with pathological damage, and promote tissue recovery.^{52,53} EPCs-Exo can be absorbed by BMDM *in vitro* and polarized towards an anti-inflammatory phenotype. *In vivo* experiments, intravenous injection of EPCs-Exo significantly reduced the proportion of M1 macrophages in the injured area and promoted an increase in M2 macrophages. Mechanistically, exosomes-derived miR-222-3p inhibits SOCS3 and activates the downstream JAK2/STAT3 pathway, thereby improving motor function recovery in mice.⁵⁴

Human Placental Mesenchymal Stem Cells Derived Exosomes

As reported by Zhou et al, exosomes derived from human placental mesenchymal stem cells (hPMSCs-Exo) can activate endogenous neural progenitor cells (NPCs), induce neural differentiation, and improve hindlimb motor function. Additionally, exosomes therapy promotes the recovery of urinary function by restoring neurogenic bladder function and reducing urinary retention in mice with SCI. This process may involve activation of MEK/ERK/CREB signaling pathways.⁵⁵ Conversely, the combined application of exosomes and hyperbaric oxygen promotes recovery after SCI in rats, and administration of hPMSCs-Exo promotes tube formation and migration of human umbilical vein endothelial cells (HUVECs).^{56,57}

Neurons and Neural Stem Cells Derived Exosomes

As neuronal synaptic function differentiates, the capacity for neural regeneration declines with age. Neuron-derived exosomes (Neurons-Exo) can enhance the activity of adjacent neurons, promote neuronal differentiation and the maturation of oligodendrocyte precursor cells (OPCs), and inhibit the toxic activation of A1 astrocytes and M1 microglia.⁵⁸ An miRNA array analysis revealed that miR-124-3p is the most enriched in neuron-derived exosomes, and MYH9 was identified as a downstream target gene of miR-124-3p. The miR-124-3p-MYH9 axis reduces neuroinflammation by modulating the PI3K/AKT/NF- κ B signaling pathway, thereby playing a role in SCI repair.⁵⁹ Neural stem cells derived exosomes (NSCs-Exo) derived VEGF-A promotes the angiogenic activity of SCMECs and the recovery of neurological function in mice.⁶⁰ In addition, NSCs-Exo-miR-374-5p activates neuronal autophagy response by targeting STK-4, thereby exerting a protective function against SCI.⁶¹ Three-dimensional (3D)-printed hydrogel patches loaded with GFR+ NSCs-Exo can activate the autophagy pathway, promote neural functional recovery, and facilitate neurite regeneration.⁶²

Microvascular Endothelial Cells Derived Exosomes

Microvascular endothelial cells are important cells that maintain the BSCB and angiogenesis.^{63,64} The inflammatory microenvironment may impair the survival of microvascular endothelial cells. Exosomes derived from endothelial cells (ECs-Exo) have demonstrated significant potential in promoting nerve regeneration during the repair of peripheral nerve injuries.⁶⁵ In SCI, ECs-Exo can promote the M2 polarization of microglia/macrophages and improve LPS-induced mitochondrial damage. *In vivo* injection experiments have demonstrated effective promotion of BMS scores and muscle strength recovery in mice. Through transcriptome sequencing and mass spectrometry analysis, exosomes-derived USP13, as a deubiquitinase, regulates microglial polarization and mitochondrial function by stabilizing I κ B α activity.⁶⁶ Hypoxic stimulation can increase the levels of angiogenic growth factors in cells, such as hypoxia-inducible factor-1 α (HIF-1 α), fibroblast growth factor, and transforming growth factor- β 1. Exosomes derived from hypoxically treated HUVECs have been shown to exhibit significant pro-angiogenic effects following SCI.⁶⁷ Studies have shown that macrophages are the primary cells that take up exosomes derived from ECs. Once inside macrophages, ECs-exo can promote the polarization of macrophages into the M2 subtype.⁶⁸ Conversely, pericytes are mesenchymal cells located outside vascular endothelial cells, surrounding the basement membrane of capillaries and small venules. Pericytes are not only closely related to vascular growth, stability, and repair but also play a role in neuroprotection, neural repair, and the regulation of inflammatory responses. In the CNS, pericytes, together with neurons, astrocytes, and vascular endothelial cells, form the neurovascular unit, which is crucial to maintaining the integrity of the BBB. Research indicates that ECs can uptake

exosomes derived from pericytes, thereby enhancing endothelial cell integrity and promoting the restoration of the BSCB.⁶⁹

Induced Pluripotent Stem Cells Derived Exosomes

Induced pluripotent stem cells (iPSCs) can control the self-renewal, proliferation, differentiation, apoptosis and metabolism of stem cells.⁷⁰ Injection of iPSCs-Exo in vivo can improve the M2 phenotypic transformation of M1 macrophages and promote motor recovery and neuronal regeneration in rats. Mechanically, miR-199b-5p was significantly expressed in iPSCs-Exo, and high expression of miR-199b-5p targeted HGF, inhibiting the activation of the PI3K signaling pathway, which is a key pathway for iPSCs-Exo to promote SCI repair.⁷¹ In addition, exosomes derived from induced pluripotent stem cell-derived neural stem cells (iPSC-NSCs) can inhibit microglia/macrophage pyroptosis and alleviate inflammatory responses.⁷²

Treg Cell Derived Exosomes

Regulatory T cells (Tregs) are a subset of T cells with significant immunosuppressive functions, characterized by the expression of Foxp3, CD25, and CD4. Treg cells are crucial to maintain peripheral tolerance, prevent autoimmunity, and limit chronic inflammatory diseases.^{73,74} Research has found that Treg cell infiltration and microglial cell apoptosis increase simultaneously after SCI. Diphtheria toxin injection of Foxp3 selectively consumes Treg cells, resulting in extensive microglial death in mice, as well as significant alterations to foot imprinting and BMS scores. The injection of Treg cells into the tail vein of mice alleviates the scorched death process of microglia and the loss of motor function. Bioinformatics analysis showed that miR-709 was significantly enriched in the exosomes secreted by Treg cells. Through online database prediction and experimental verification, it was clarified that the miR-709-NKAP axis was an important mechanism for the function of Treg-Exo.⁷⁴ In terms of angiogenesis, Treg-Exo can restore the integrity of the BSCB after SCI and reduce its permeability.⁷⁵

Macrophage/Microglial Derived Exosomes

M1 macrophages exacerbate the progression of SCI by releasing various pro-inflammatory factors.⁷⁶ Studies have shown that M1-derived exosomes treatment significantly increases ROS levels and mitochondrial fragmentation in bEnd.3 cells, and the M1-Exo-miR-155/SOCS6/p65 axis impairs mitochondrial function in bEnd.3 cells. When M1-Exo is injected in vivo, the recovery of motor function post-SCI is significantly hindered, as evidenced by BMS scores, footprint analysis, electrophysiological tests, and swimming tests. EB extravasation tests reveal that M1-Exo induces endothelial-mesenchymal transition (EndoMT) and aggravates the disruption of the BSCB.⁷⁷ In contrast, M2 macrophages release anti-inflammatory factors that promote the repair of damaged spinal cord tissue. Treatment with M2 macrophage-derived exosomes enhances angiogenesis and neurogenesis following SCI, reduces tissue damage, and improves functional recovery. This process is associated with the activation of the HIF-1/VEGF signaling pathway.⁷⁸ Similarly, peripheral macrophage-derived exosomes (PM-Exo) enhance autophagy and promote the polarization of anti-inflammatory microglia by inhibiting the PI3K/AKT/mTOR pathway, which is crucial for neuroprotection following SCI.⁷⁹

Microglia derived exosomes: The anti-inflammatory microglia (M2 microglia) have been shown to reduce inflammation and promote spinal cord recovery. However, the role of exosomes derived from M2 microglia in SCI therapy is unclear. Through a series of experiments, Zhou et al found that miR-672-5p is the key miRNA for the function of M2-Exo. By targeting AIM2 to inhibit ASC/ caspase-1 signal pathway, thus to reduce neuronal scorch death, promote axonal regeneration and the recovery of functional behavior in mice.⁸⁰ M2-Exo may exert this neuroprotective effect by inhibiting the NF- κ B pathway, thereby reducing A1 astrocyte activation and enhancing neuronal survival and axonal growth.⁸¹ LPS-induced activated microglial exosomes were collected and co-cultured with astrocytes. The results showed that the combination of exosomes-miR-145-5p and Smad3 could regulate the proliferation of astrocytes, which was closely related to scar formation after SCI.⁸²

BMSCs Derived Exosomes

BMSCs are a type of cell with the potential to differentiate into bone, cartilage, fat, nerve, and muscle cells. Their therapeutic effects in neurological and inflammatory diseases have been widely reported.⁸³ Obtaining BMSCs-Exo for treatment can upregulate macrophage receptors with collagen structure (MARCO) in macrophages, enhance macrophage phagocytic ability, and promote neurological recovery after SCI.⁸⁴ It is worth mentioning that BMSCs-Exo is used to educate macrophages to promote angiogenesis and axonal growth after SCI.⁸⁵ In addition to the effects on macrophages, BMSCs-Exo can inhibit the activation of A1 astrocytes and reduce glial scar formation.⁸⁶ The overexpressed neurotrophic factor (NGF) in BMSCs-Exo can stimulate the differentiation of NSCs and promote axonal regeneration of neurons.^{87,88} Additionally, BMSC-Exo inhibits BSCB damage and pericyte pyrogenesis while maintaining BSCB integrity by regulating the TIMP2/MMP signal pathway and the NOD1 signal pathway.^{89,90}

Olfactory Ensheathing Cells Derived Exosomes

Transplantation of olfactory ensheathing cells (OECs) has been shown to play a beneficial role in SCI by the regulation of neuronal inflammation, neuronal survival and promoting angiogenesis.^{91,92} To further verify whether OECs-Exo are an important carrier for the function of OECs, extracted OECs-Exo were delivered to microglia and found that it can inhibit NF- κ B and c-Jun in vitro and reverse the M1 polarization of microglia. In vivo injection of OECs-Exo reduced neuronal death and promoted axonal survival after SCI.⁹³ This suggests that exosomes may serve as signaling molecules for OECs in the treatment of SCI.

Adipose Derived Multipotent Adult Stem Cells Derived Exosomes

Mesenchymal stem cells extracted from human epidural adipose (hEpiAD-MSc) tissue, typically obtained during posterior lumbar decompression surgery, have shown therapeutic potential. ADMSC-Exo can inhibit the expression of inflammatory factors in spinal cord tissue and M1 microglia while promoting the expression of M2 microglia.⁹⁴ After extraction and identification, hEpiAD-MSc-derived exosomes (hEpiAD-MSc-Exo) were injected into SCI rats through tail vein. The results showed that compared with the injury group, hEpiAD-MSc-Exo treatment significantly decreased the expression of inflammatory cytokines such as IL-1 β , IL-2 and TNF- α in the injured area, and promoted the improvement of neurotrophic related factors and BBB score in rats.⁹⁵ Conversely, the exosomes were obtained after anoxic treatment of AD-MSc. It was found that Hypo-exo significantly reduced neuronal apoptosis and cavity formation in the injured site of OGD model. Further microRNA sequencing analysis of exosomes shows that miR-499a-5p targeting JNK3/c-jun apoptosis signal pathway is the key mechanism.⁹⁶

Dental Pulp Stem Cells Derived Exosomes

Dental pulp stem cells (DPSCs) are usually extracted from discarded teeth.⁹⁷ Like the spinal cord, DPSCs also originates from the neural crest. DPSCs can differentiate into a variety of cells, such as neurons and glial cells, in vitro and in vivo.⁹⁸ The transplantation of hDPSCs can improve motor nerve function in rat SCI model. DPSCs can also produce neurotrophic factors to support nerve cell survival.⁹⁸ DPSCs-Exo has stronger immunomodulatory effects than BMSCs-Exo. Therefore, the exosomes derived from DPSCs may be an excellent candidate for the treatment of SCI.^{97,99} Furthermore, increased levels of ROS can promote the pro-inflammatory polarization of M1 macrophages. However, after treatment with exosomes derived from DPSCs both in vitro and in vivo, the exosomes are able to inhibit the polarization of M1 macrophages and alleviate inflammation and neuronal damage through the ROS-MAPK-NF- κ B p65 signaling pathway.¹⁰⁰ This study shows the potential hope of DPSC-Exo in SCI repair.

Here, we reviewed the biological functions of exosomes from different cell sources in SCI. Studies indicated that exosomes have diverse functions (Figure 3). Currently, most research still focuses on the roles of exosomes-derived non-coding RNAs in the mechanisms of inflammation, neuroregeneration, angiogenesis, and functional recovery in SCI. This highlights the potential clinical value of non-coding RNAs as key molecules that should not be overlooked in SCI repair. Therefore, we have provided a detailed explanation of the regulatory mechanisms of exosomes-derived non-coding RNAs in SCI.

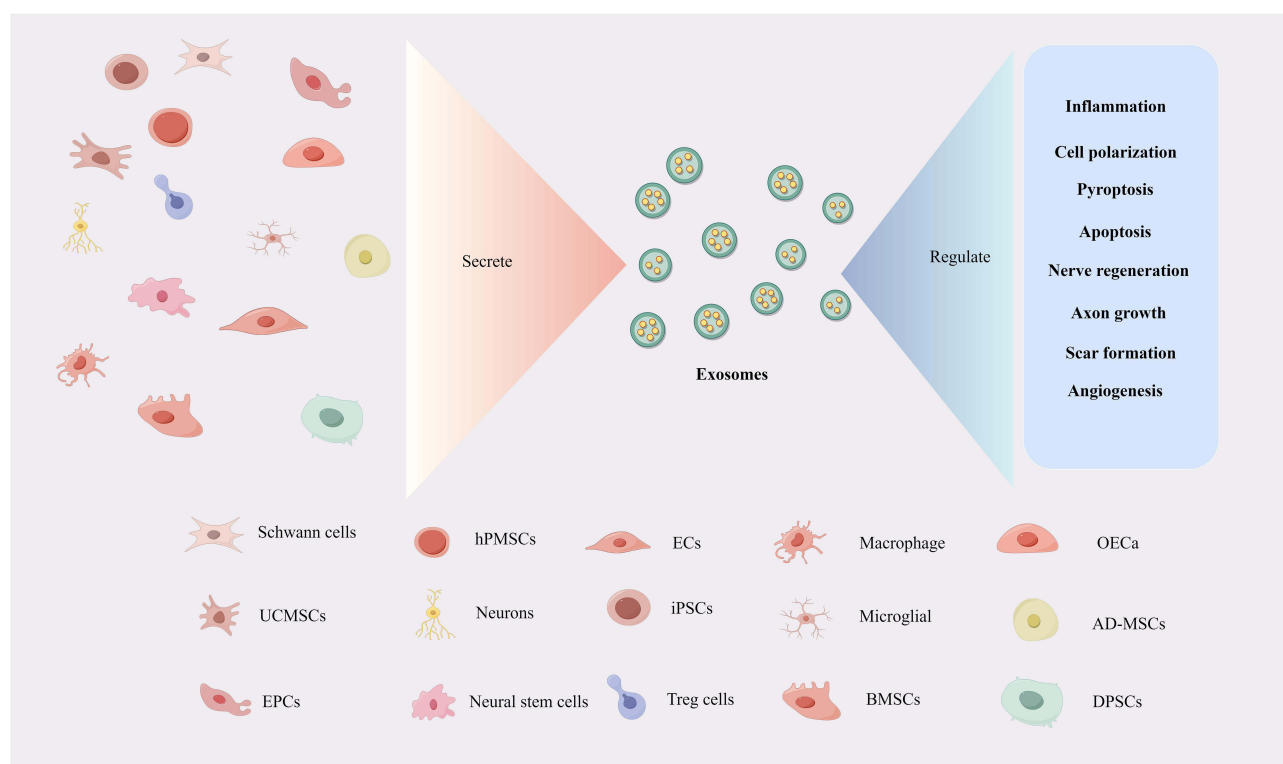


Figure 3 The biological functions of exosomes derived from different cell sources.

Exosomes Derived Non-Coding RNA

Although over 80% of the genome can be transcribed, only approximately 2% of the genome continues to be translated into proteins after transcription. Most remaining genomic sequences are transcribed into non-coding RNAs.¹⁰¹ Non-coding RNAs do not directly participate in protein synthesis, but they influence many physiological and pathological processes in organisms by regulating gene expression, cellular structure, signal transduction, and other aspects. Therapeutic strategies targeting miRNA, circRNA, or lncRNA are becoming part of precision medicine.

miRNA derived from exosomes: miRNA, also known as microRNA, is a short RNA molecule that is not involved in coding. It has a size of approximately 21–25 nucleotides and has the ability to attach to either the 3' "UTR or 5' UTR area of the target gene. This attachment leads to the downregulation of gene expression after transcription.¹⁰² Many different targeted mRNAs can be combined with the same miRNA. Conversely, the same mRNA can also be targeted by different miRNA.¹⁰³ miRNA can regulate gene expression and participate in the occurrence and development of many pathological conditions such as cancer, cardiovascular disease, endocrine system disease and nervous system disease.^{104–107} In SCI disease, miRNA from multiple exosomes sources plays an important role in the progression of SCI by combining with target genes. For example, BMCS- Exo-miR-9-5p promotes FGF2 expression by inhibiting HDAC5-mediated deacetylation, thereby inhibiting LPS-induced apoptosis, inflammation and ER stress in PC12 cells.¹⁰⁸ The exosomes were obtained from hypoxia-treated MSCs (HEXos). It was found that HEXos-miR-216a-5p could promote the transition from M1 phenotype to M2 phenotype of macrophages in vivo and in vitro by targeting TLR4.¹⁰⁹ Microglia-Exo-miRNA -151-3p regulates neuronal apoptosis and axonal regeneration by regulating p53/p21/CDK1 signal pathway.¹¹⁰ In addition, Exo-miRNA plays an important role in promoting anti-inflammatory macrophage polarization, neural stem cell proliferation and angiogenesis, maintaining SC repair-related phenotype and slowing cell pyrogenesis (all related Exo-miRNA are listed in Table 1). This indicates that Exo-miRNA can serve as an important molecule in SCI repair.

lncRNA derived from exosomes: long non coding RNA (lncRNA) with a length not exceeding 200 nucleotides and does not encode any peptides or proteins. lncRNA can regulate genes at three levels: epigenetic, transcriptional and post-transcriptional.¹⁴⁴ These lncRNA are involved in the progression of many diseases.^{145,146} The functional mechanisms of

Table 1 The Mechanism of Non-Coding RNA Derived From Exosomes in Regulating SCI

Source	Names	Pathways	Function	Ref
hUCMSCs-Exo	miR-146 b	miR-146b-TLR4/ NF- κ B	Reduce neuronal apoptosis	[48]
ECs- Exo	miR-467b-3p	miR-467b-3p-PTEN/PI3K/mTOR	Regulate macrophage polarization	[68]
EPCs- Exo	miR-222-3P-	miR-222-3P-SOCS3 / JAK2 / STAT3,	Regulate macrophage polarization	[54]
BMSC- Exo	miR-199a-5p	miR-199a-5p -GSK-3 β / β -catenin	Promote NSC proliferation	[111]
iPSCs-Exo	miR-199b-5p	miR-199b-5p-Hgf/PI3K	Regulate macrophage polarization	[71]
Treg cell- Exo	miR-709	miR-709-NKAP	Regulate microglia pyroptosis	[74]
BMSCs- Exo	miR-137	No mention	Promote neuron viability	[112]
hUCMSCs- Exo	miR-146a-5p	Traf6/Iraki/NF κ B	Reduce the toxicity of neurotoxic astrocytes	[47]
NSCs- Exo	miR-374-5p	miR-374-5p- SKT-4	Suppress neuronal cell apoptosis	[61]
BMSC- Exo	MiR-146a	No mention	Reduce neuron apoptosis	[113]
BMSC- Exo	miR-9-5p	miR-9-5p-HDAC5/FGF2	Reduce neuron apoptosis	[108]
M2 microglial -Exo	miR-672-5p	miR-672-5p -AIM2/ASC/Caspase-1 Signaling	Inhibit neuronal pyroptosis	[80]
Microglia-Exo	miR -151-3p	miR-151-3p -p53/p21/CDK1	Inhibit neuronal pyroptosis	[110]
ADSCs-Exo	miR-499a-5p	JNK3/c-jun-apoptotic signaling	Reduce neuronal apoptosis	[96]
Microglia-Exo	miR-145-5p	miR-145-5p-Smad3	Inhibite astrocyte proliferation	[82]
BMSCs- Exo	miR-145-5p	miR-145-5p- TLR4/NF- κ B	Reduce inflammation	[114]
BMSCs- Exo	miR-338-5p	miR-338-5p -Cnr1/Rap1/Akt	Reduce neuronal apoptosis	[115]
BMSCs- Exo	miR-26a	PTEN/AKT/mTOR	Promote axonal regeneration	[116]
MI-polarized macrophages- Exo	miR-155	miR155/SOCS6/p65 axis	Impairing mitochondrial function in vascular endothelial cells	[77]
BMSCs- Exo	microRNA-125a	miR-125a-IRF5	Promote M2 macrophage polarization	[117]
hUCMSCs- Exo	miR-199a-3p/145-5p	miR-199a-3p/145-5p-Cblb/Cbl/NGF/TrkA	Promote neurite outgrowth	[118]
BMSCs- Exo	microRNA-181c	microRNA-181c -PTEN/ NF κ B	Reduce inflammation	[119]
Neuron- Exo	miR-124-3p	miR-124-3p/MYH9	Suppressing the activation of neurotoxic microglia and astrocytes	[59]
BMSCs-Exo	miR-544	No mention	Improve functional recovery	[120]
BMSCs- Exo	miR-216a-5p	miR-216a-5p -TLR4/NF- κ B/PI3K/AKT	Promotes M2 microglial polarization	[109]
BMSCs- Exo	miR-126	No mention	Promote angiogenesis and neurogenesis	[121]
BMSCs- Exo	miRNA-29 b	No mention	Promoted neuronal regeneration	[122]
BMSCs- Exo	miR-21	miR-210-PTEN/PDCD4	Reduce neuronal apoptosis	[123]
ADSCs- Exo	miR-133b	No mention	Axon regeneration	[124]

(Continued)

Table 1 (Continued).

Source	Names	Pathways	Function	Ref
BMSCs-Exo	miR-497-5p	TXNIP/NLRP3 axis	Reduce neuronal apoptosis	[125]
PLASMA-Exo	miR-138-5p	SOX4	Regulate microglial polarization	[126]
BMSCs-Exo	miR-219-5p	UBE2Z/NRF2 axis	Suppress neuronal cell ferroptosis	[127]
BMSCs-Exo	miR-146a	IRAK1/TRAF6/NF- κ B p65 axis	Reduce inflammation	[128]
NSCs- Exo	let-7b-5p	LRIG3	Alleviate microglial/macrophage pyroptosis	[72]
BMSCs-Exo	miR-17-92	No mention	Suppress the apoptosis and inflammation of nerve cells	[129]
BMSCs-Exo	miR-26a-5p	EZH2	Reduce neuronal apoptosis	[130]
BMSCs-Exo	miR-21a-5p	PELI1	Alleviate microglial/macrophage pyroptosis	[131]
BMSCs-Exo	miR-125a-3p	No mention	Mitigated neutrophil activation	[132]
BMSCs-Exo	miR-431-3p	RGMA	Promote axonal regeneration	[133]
NSCs-Exo	miR-34a-5p	HDAC6	Promotes neural regeneration	[62]
Pericyte-Exo	miR-210-5p	JAK1/STAT3 axis	Promote the repair of the BSCB	[69]
Treg cell- Exo	miR-2861	IRAK1	Promote the repair of the BSCB	[75]
BMSCs-Exo	miR-216a-5p	TLR4/NF- κ B axis	Suppresses inflammation	[134]
UCMSC-Exos	miR-501-5p	MLCK	Promote the repair of the BSCB	[51]
BMSCs-Exo	circ_0006640	miR-382-5p/IGF-1 axis	Inhibit cell apoptosis and inflammation	[135]
ADSCs-Exo	circ-Vvdfy3	miR-423-3p/GPX4 axis	Inhibit cell ferroptosis	[136]
BMSCs-Exo	circ_003564	No mention	Attenuates inflammasome-related pyroptosis	[137]
BMSCs-Exo	circZFHX3	circZFHX3-miR-16-5p / IGF-1	Reduce cell injury	[138]
BMSCs-Exo	lncGm36569	lncGm36569/miR-5627-5p/FSP1	Suppress neuronal cell Ferroptosis	[139]
BMSCs-Exo	lncRNA TCTN2	lncRNA TCTN2-miR-329-3p/IGF1R	Inhibit cell apoptosis and inflammation	[140]
ADSCs-Exo	lncGm37494	lncGm37494-miR-130b-3p / PPAR γ	Promotes M2 microglial polarization	[141]
BMSCs-Exo	lncRNA PTENP1	lncRNA PTENP1-miR-21/miR-19b/PTEN	Promotes neuronal apoptosis	[142]
ADSCs-exos	lncRNA LRR75A-AS1	FDFT1	Inhibits inflammation	[143]

lncRNA include decoying lncRNA, guiding lncRNA, scaffold lncRNA, stabilizing lncRNA, and competitive endogenous lncRNA (ceRNA). Among them, ceRNA is the classical mechanism by which lncRNAs function.¹⁴⁷ The ceRNA hypothesis means that RNA transcripts with the same miRNA reaction element can compete with each other and bind to the same miRNA, and hinder the binding of miRNA to the target gene through sponge adsorption.¹⁴⁸ In SCI studies, lncGm37494 was significantly expressed in the exosomes of hypoxic treated adipose mesenchymal stem cells. Upregulation of Exo-lncGm37494 can inhibit miR-130b-3p and promote PPAR γ expression and phenotype transformation of microglia from M1 to M2.¹⁴¹ Transfection of knockdown lncRNA PTENP1 exosomes in PC12 cells can promote

the upregulation of miR-21/miR-19b and down-regulate the expression of PTEN to inhibit neuronal apoptosis.¹⁴² Moreover, Exo-lncRNA TCTN2/miR-329-3p/IGF1R inhibits LPS-induced apoptosis, inflammation and oxidative stress, while the lncGm36569-miR-5627-5p/FSP1 pathway inhibits iron degradation.^{139,140}

circRNA derived from exosomes: Aside from lncRNA, circRNA, as an important member of the non-coding family, functions in SCI repair by competing with miRNA. As reported by Tian et al, Exo-circZFHX3 regulated the expression of IGF-1 by adsorbing miR-16-5p, which increases the viability of BV-2 cells treated with LPS and inhibits apoptosis, inflammation and oxidative stress *in vitro*.¹³⁸ In an *in vivo* experiment, Exo-circZFHX3 treatment was shown to reduce the area of SCI damage and promote the functional recovery of mice.¹⁴⁹ In another report, Exo-circle003564 can reduce the process of neuronal pyroptosis, but the specific mechanism remains to be elucidated.¹³⁷ Here, we elucidate the impact of non-coding RNAs derived from exosomes on SCI, and summarize the sources and functions of all non-coding RNAs in Table 1.

A number of studies focus on exosomes-derived non-coding RNAs, suggesting that the ncRNAs carried by exosomes play important biological roles in intercellular communication, regulation of gene expression, cell differentiation and apoptosis, as well as epigenetic repair (Figure 4). This provides an explanation for the possible mechanisms of exosomes functions and lays a favorable foundation for the future development of effective molecular drugs targeting SCI repair.

Engineering Modification of Exosomes

Engineering modifications of exosomes can enhance their stability and persistence in circulation (making them less prone to degradation or clearance), thereby prolonging their action time. Through engineering modifications, specific ligands

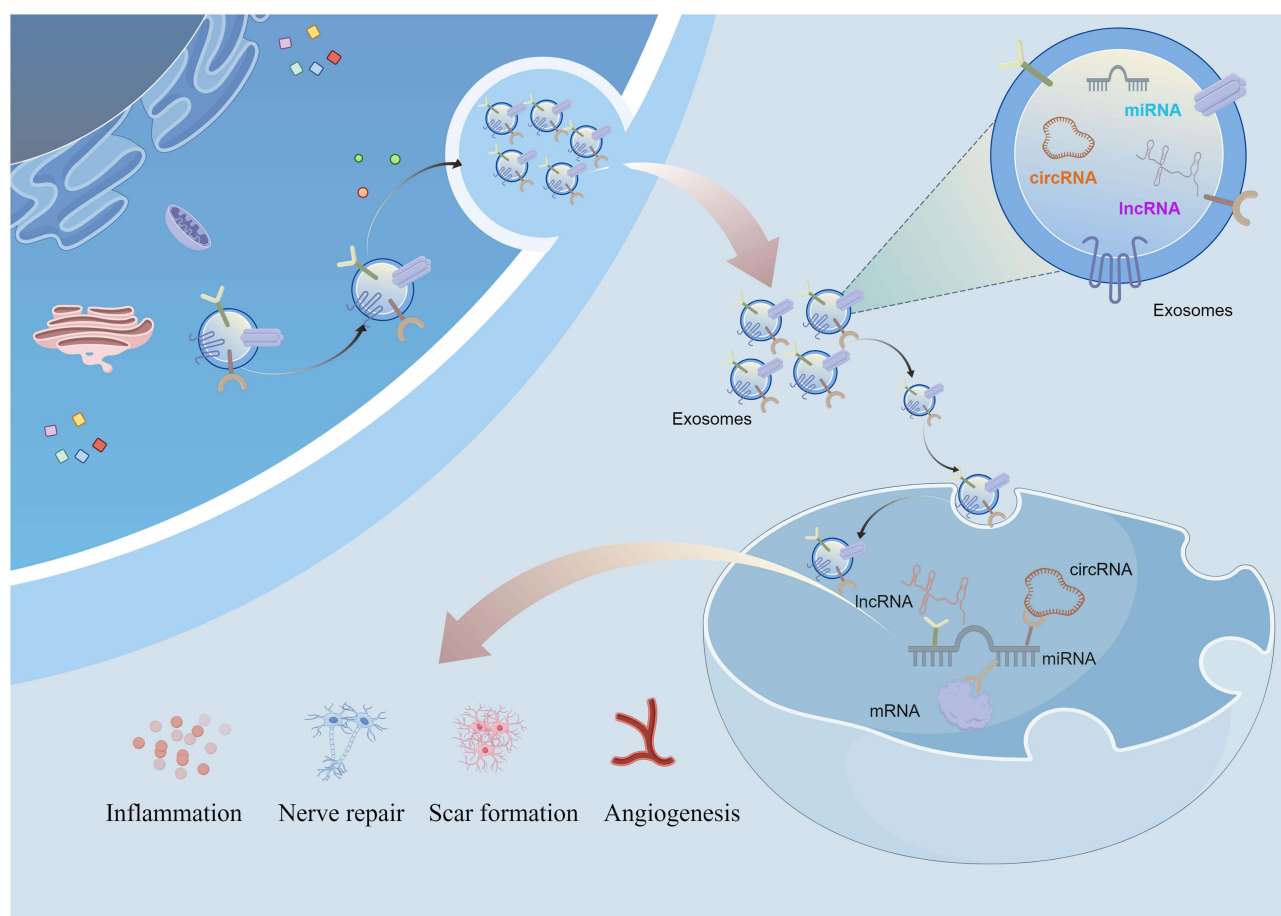


Figure 4 Exosomes-derived lncRNA, circRNA, and miRNA can regulate the inflammatory response, nerve damage, scar formation, and angiogenesis after SCI through the classical ceRNA mechanism.

(such as antibodies, peptides, or aptamers) can be introduced on the surface of exosomes, enabling them to precisely target specific cells or tissues, thereby improving therapeutic efficacy and reducing off-target effects. In addition, exosomes can be designed to carry multiple functional molecules (such as proteins, RNAs, and drugs), providing integrated therapeutic functions (Figure 5).

Hydrogel Loaded Exosomes

As a biomaterial with good biocompatibility and controllability, hydrogel is considered to be the best choice for loading exosomes.¹⁵⁰ The composition of hydrogel is similar to that of extracellular matrix (ECM), which provides a favorable culture environment for cells and is usually used as a scaffold for the treatment of SCI cystic cavity.¹⁵¹ The degradability and biocompatibility of different hydrogels are different. It is very important to select appropriate hydrogels or mix a variety of hydrogels according to different proportions for the sustained release of exosomes and to maintain activity. Spinal cord implantation of exosomes requires viscoelastic 3D materials and adhesive surface characteristics. A PPFLMLLLKGSTR peptide modified HA hydrogel (pGel) has been proposed to comprehensively regulate the SCI microenvironment by implanting exosomes and supplementing ECM in the interstitial space of transverse lesions. pGel improves 3D adhesion and retention of hMSC-derived exosomes. Exosomes are continuously released from the 3D pGel for approximately 11 days, and more than 90% of the EVs are finally released smoothly. pGel simulates ECM function *in vitro*, and has persistent retention and delivery functions for hMSC-Exo. Furthermore, Exo-pGel implantation effectively restores motor function and reduced inflammatory markers in SCI rats. Examination of the urinary system

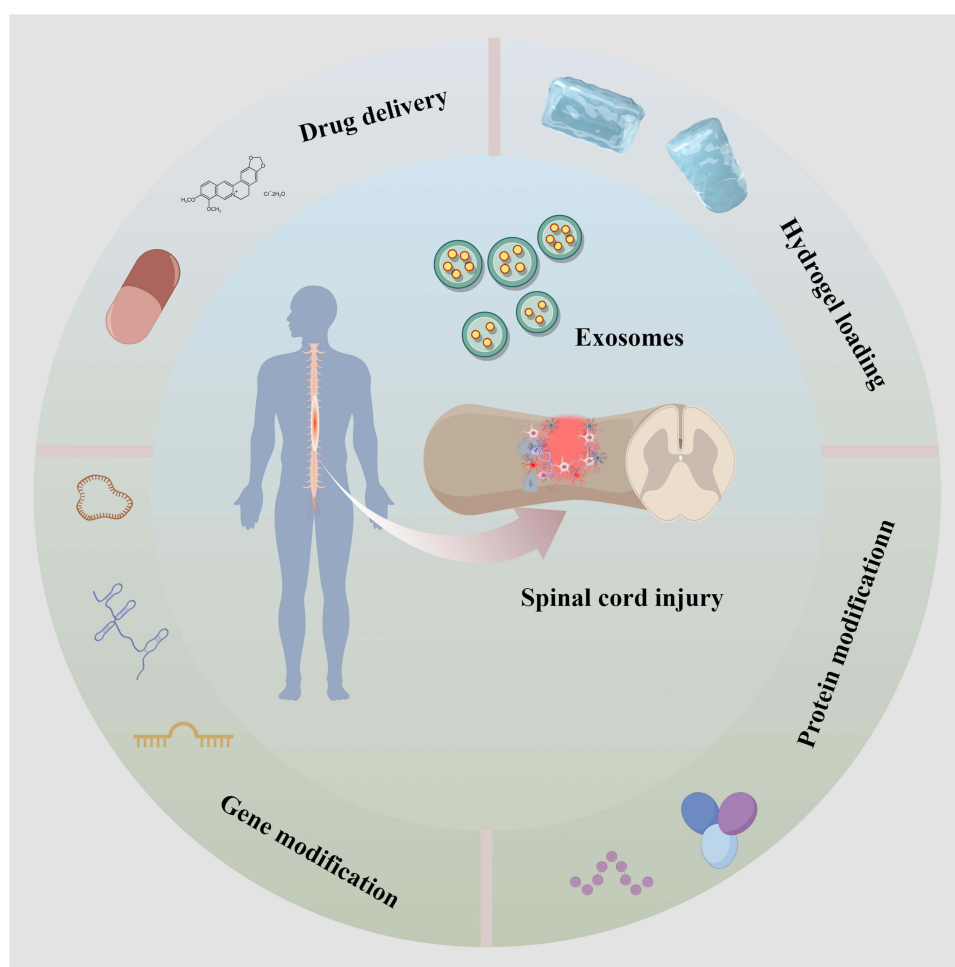


Figure 5 Hydrogel-loaded exosomes for sustained release or exosomes carrying various functional molecules (such as proteins, RNA, and drugs) exert repair functions in SCI.

has revealed that Exo-pGel has a significant function in the recovery of the urinary system.¹⁵² In 3D gelatin methacrylate hydrogel (GelMA), exosomes can be uniformly distributed on the hydrogel skeleton, while GelMA hydrogel shows a slow degradation rate and can release exosomes continuously for more than 14 days. GelMA loaded with exosomes was injected into damaged lesions, promoting the differentiation and extension of neurons *in vitro*, and alleviating the glial scar in the damaged lesions.¹⁵³

The biocompatibility of hydrogels is crucial for loading exosomes. Fiber gel has good safety and tissue adaptability in clinical application. Therefore, the UCMSCs-Exo and the BMSCs-Exo coated with fibrin gel are injected into the spinal cord transected area, which matches the mechanical strength of the spinal cord tissue and can effectively reduce oxidation and inflammatory microenvironment, promote the protection of nerve and urinary tissue, differentiation of OPCs and oligodendrocyte production *in vivo*.^{154,155}

3D-printed scaffolds are widely used in modern manufacturing, healthcare, engineering, and other fields, offering advantages such as personalized customization and complex manufacturing capabilities. The application of 3D-printed hydrogels loaded with plant-derived exosomes in SCI has shown positive effects in alleviating inflammatory responses and promoting nerve regeneration.¹⁵⁶ Compared with simple hydrogel loading, hydrogel combined with microneedle array patch can effectively reduce inflammation and glial scar caused by SCI by loading 3D cultured MSCs-Exo. In composite hydrogel, ubiquitin thioesterase otulin (OTULIN) derived from M2-Exos was embedded in light-cured mixed hydrogel (Gel+HA-NB) to form a local drug delivery system. The physicochemical properties show that the sol gel after 37 °C UV exposure provides a basis for local administration after SCI, and this porous structure hydrogel has good biocompatibility and biodegradability. M2-Exo-OTULIN injection *in vivo* had a positive effect on angiogenic activity.¹⁵⁷

Significantly, conductive hydrogel scaffolds have suitable swelling and mechanical properties, as well as excellent electrical conductivity similar to natural nerve tissue. Photocrosslinked gelatin methacrylate and polypyrrole (PPy) hydrogel constitute a double network conductive (GMP) hydrogel loaded with exosomes. The network has natural cell binding motifs such as Arg-Gly-Asp, which allow cells to grow in it. Covalent binding does not affect the structure and biological activity of the exosomes, and ensures that the exosomes is released slowly and continuously in the early stage of implantation. Exosomes were fixed into a GMP hydrogel network, which increased NSC compatibility of conductive hydrogel and promoted oligodendrocyte differentiation. The mechanism study shows that conductive hydrogels may regulate NSC differentiation and axonal regeneration through PTEN/PI3K/AKT/mTOR pathway.¹⁵⁸ The implantation of conductive hydrogels can trigger immune responses, and the persistent presence of conductive components may exacerbate early inflammation following acute SCI. Loading M2-Exos into conductive hydrogels can reduce post-injury inflammatory responses, promote neuronal survival, and mitigate the formation of glial scars.¹⁵⁹ In summary, conductive hydrogels that mimic the electrical transport properties of natural nerve tissue are highly beneficial for the repair of SCI.

Gene Modified Exosomes Therapy

Gene therapy has shown good therapeutic effects in various diseases. As a signal carrier for intercellular communication, exosomes can freely pass through the BSCB without causing immune rejection, and can carry various molecules for substance delivery, thereby achieving widespread intercellular signaling communication.¹⁶⁰ Different genes can be loaded into exosomes to achieve therapeutic purposes. Engineered iPSCs-Exo loaded with miR-23b, miR-21-5p, and miR-199b-5p can alleviate inflammation in neurons stimulated by LPS and IFN- γ , significantly promoting the recovery of SCI.¹⁶¹ It is reported that miR-21 can regulate astrocyte polarization, glial scar formation and axonal growth after SCI.¹⁶² To effectively achieve the specificity and precision of miR-21 in the treatment of SCI, miR-21 was transiently overexpressed in CBD-Lamp2b-293T cells to obtain CBD-LP-Exo enriched with miR-21. The functional biomaterial scaffold of CBD-Lamp2b-miR-21- exosomes collagen-I was constructed by genetic engineering, and the scaffold was implanted into the body for SCI repair. Scaffolds promoted the continuous release of miR-21 into cells, inhibited apoptosis, improved neuronal survival and reduced the production of glial scars at SCI sites, showing excellent performance in SCI repair.¹⁶³

Netrin-1 is one of the earliest recognized axon guiding factors, which can initiate axon growth and branch formation, promoting the migration and survival of nerve cells.¹⁶⁴ Chemically modified information RNA (modRNA) refers to

mRNA synthesized *in vitro* using chemically modified bases, which is further transferred to target cells through liposomes or nanoparticles for protein translation and expression.¹⁶⁵ Using exosomes as carriers, loading modRNA^{modNetrin-1} encoding netrin-1 effectively alleviated LPS induced PC12 cell inflammation and necrosis, and tail vein injection of Exo-modRNA^{modNetrin-1} promoted nerve recovery.¹⁶⁶ In addition, miR-138-5p-modified UCMSC-Exo loaded in thermosensitive hydrogel can reduce neuronal apoptosis *in vivo* by inhibiting intracellular ROS levels through the Nrf2-keap1 signaling pathway.¹⁶⁷

Protein Modification of Exosomes

Although exosomes have shown a good therapeutic effect after SCI, the exosomes delivered to the injured area still lacks targeting. Usually, after being delivered to the damaged area, exosomes can enter various cells for signal transmission, resulting in a lack of specificity and effectiveness in treatment. Therefore, adding specific recognition peptides to the surface of exosomes can increase the targeting of exosomes delivery and accelerate the progress of SCI repair. However, lack of site targeting may lead to different therapeutic responses. Exosomes from autologous plasma (AP-Exo) have been used as functional cargo carriers and growth promoting peptides (ILP and ISP) and targeted peptides were loaded through CP05. Biological scaffolds based on AP-Exo can target and deliver AP-Exo through the BSCB, homing them to the SCI injury site, entering neurons in the damaged spinal cord, and promoting axonal regeneration.¹⁶⁸

Collagen, as the main component of the extracellular matrix, is superior to other materials in promoting cell adhesion and growth.^{169,170} Among them, linearly ordered collagen scaffold can guide the growth of nerve processes along its fibers and reduce the deposition of scar-related components in the injured site.¹⁷¹ The author of that study designed a new type of bio-specificity peptide that can effectively connect the collagen scaffold with mesenchymal stem cells derived exosomes (MExo). *In vivo* implantation of MExos can promote the migration of more NSCs to the center of the damaged area, which improves SCI recovery.¹⁷²

M2 macrophage-Exo have shown good anti-inflammatory effects *in vitro* and *in vivo*. Le-Lys-Val-Ala-Val (IKVAV) is the core functional peptide of laminin, which contributes to the survival, proliferation and differentiation of NSCs.¹⁷³ Viral macrophage inflammatory protein II (vMIP-II) is a broad-spectrum chemokine receptor-binding peptide. M2 macrophage-derived Exos modified with the vMIP-II-Lamp2b gene can target chemokine receptors highly expressed in injured spinal cord, inhibit chemokine signaling, reduce the production of pro-inflammatory factors, and regulate microglia/macrophage polarization to promote SCI repair.¹⁷⁴ Therefore, it is of great significance to prepare nano-reagents with both anti-inflammatory and nerve-targeted repair as ideal therapeutic drugs for SCI. IKVAV peptides were coupled to the surface of the M2 macrophage-Exo by copper-free cyclo-addition reaction and tail vein injection of exosomes showed that this new nano drug has excellent effects in promoting M2 macrophage polarization and NSCs differentiation.¹⁷⁵

Exosomes Loaded with Small Molecule Drugs

Drug therapy is an important means to deal with SCI. Drug treatment is traditionally via oral or intravenous infusion; however, when the drug passes through the blood circulation, because of the BSCB, it is difficult for the drug to be delivered to the damaged tissue, which greatly reduces the effectiveness of the drug. Therefore, it is critical to find a suitable drug carrier and deliver the drug to the injured area in an efficient and orderly manner. Because of their acellular structure, exosomes have the advantage of natural drug loading, so it has been regarded as the best drug carrier, and can be loaded with targeted drugs for specific diseases. PTEN is a well-known tumor suppressor, which has been identified as a key regulator of neuronal apoptosis and inflammation. Effectively knocking down the expression of PTEN can promote SCI repair.¹⁷⁶ In the study of Guo et al, it was found that intranasal delivery MSCs-Exo migrated through chemotaxis and had high affinity for neurons. PTEN-siRNA reagent was loaded into MSC-Exo (Exo-siPTEN) in a certain proportion to treat dorsal root ganglion (DRG) neurons. Compared with neurons treated with control siRNA, DRG neurons exhibited more complex, branched, and elongated morphology after 1 day of Exo-siPTEN treatment. This indicates that Exo-siPTEN can promote the growth of DRG neurons *in vitro*. *In vivo* experiments, nasal ExoPTEN treatment can induce motor, sensory, and bladder function recovery in SCI mice.¹⁷⁷

Berberine originates from the traditional Chinese medicine Huanglian and has various pharmacological effects, including anti-inflammatory, antioxidant, antibacterial, and neuroprotective effects.^{178,179} However, the short half-life and low efficiency of crossing the BBB seriously affect the pharmacological effects of berberine. To overcome these shortcomings, berberine was loaded Ber into M2-Exo and the -barrier penetration effect of exosomes was used to deliver drugs to SCI damaged areas for treatment. Experiments show that Exos- Berberine can reduce the expression of inflammatory factors such as TNF- α , IL-1 β and IL-6 and neuronal apoptosis, and promote the recovery of motor function.¹⁸⁰

FTY720 is a functional antagonist of sphingosine 1-phosphate receptor-1 (S1P1) and has immunomodulatory function.¹⁸¹ However, although the application of FTY720 has a positive effect on SCI, systemic administration easily causes serious adverse reactions.¹⁸² Therefore, NSCs-Exos were used as a carrier for FTY720 for SCI repair. The results showed that compared with the simple FTY720 reagent group, tail vein injection of NSCs-Exo-loaded FTY720 had a better effect on improving endothelial cell function, relieving apoptosis and spinal cord edema, and promoting the recovery of motor function in mice.¹⁸³ AM1241 is a selective CB2 receptor agonist that plays an important role in anti-inflammatory, neuroprotective, and analgesic functions. It has broad application prospects in the treatment of neurological diseases and chronic pain.¹⁸⁴ Exosomes-loaded AM1241 can activate the Nrf2/HO-1 signaling pathway, thereby reducing neuronal inflammation, oxidative stress, and apoptosis. It also contributes to promoting neural stem cell differentiation and motor function recovery.¹⁸⁵ Although the delivery system formed by loading small molecule drugs, proteins, and genes through EVs has shown certain therapeutic effects in SCI, exosomes still face issues as carriers such as poor targeting, short in vivo maintenance time, and off target. Further engineering transformation of exosomes is a necessary exploration for the development of exosomes therapy.

Exploration of Future Applications of Exosomes in SCI Non-Invasive Prognostic Markers

Patients with SCI often experience poor overall health and require long-term, repeated monitoring to assess their recovery status. Exosomes, which can be obtained from various body fluids such as blood, urine, and saliva, offer a rich source of biomarkers.¹⁸⁶ Compared to traditional biopsy or tissue sampling, the collection of exosomes is simpler, safer, and lower risk. Therefore, for high-risk or older adult patients, non-invasive exosomes-based detection provides a convenient and effective means of prognostic evaluation. Exosomes contain a variety of molecular information, including proteins, mRNA, miRNA, and DNA, which are determined by the state and function of their parent cells. As a result, these molecules exhibit high sensitivity and specificity, accurately and comprehensively reflecting cellular states and indicators such as inflammation, neural recovery, muscle strength, and sensory recovery.¹⁸⁷ By monitoring the dynamic changes in these biomarkers, treatment plans can be adjusted in a timely manner. Thus, exosomes can provide comprehensive and precise disease information, and the detection of these markers holds great potential for long-term monitoring and treatment efficacy evaluation in SCI patients.

The Diversified Administration Methods of Exosomes

Exosomes are naturally occurring nanoparticles with good biocompatibility and low immunogenicity. As an ideal drug delivery system, exosomes offer various administration methods, including intravenous injection, local administration, and oral administration.

Intravenous injection: Due to their ability to cross the BBB and be taken up by various cells, intravenous injection is a common method for exosomes-based drug delivery. Through intravenous injection, exosomes can rapidly enter the bloodstream and be transported to the injured area to exert their therapeutic effects. Additionally, exosomes can remain stable in the bloodstream and circulate for an extended period, making intravenous injection a promising approach for clinical treatment. However, most exosomes are metabolized by the liver and kidneys after intravenous injection, and only a small fraction of exosomes reach the injured area to exert their therapeutic effect. This significantly reduces the

effective therapeutic dose and may lead to systemic side effects. Therefore, intravenous injection requires close monitoring of the patient's overall condition.

Local administration: Through local administration, exosomes and the small molecules they carry can reach higher concentrations at the site of injury. By targeting macrophages, microglia, astrocytes, and neurons, the precision and efficacy of local treatment can be increased, maximizing the therapeutic effect at the local site. Additionally, local administration significantly reduces the distribution of the drug in the systemic circulation, minimizing metabolism and clearance by organs such as the liver and kidneys, thus avoiding systemic side effects. This also reduces the damage to healthy tissues and improves patient tolerance. When exosomes are combined with local delivery systems (such as hydrogels and scaffolds), sustained release and long-lasting effects of the drug can be achieved. This reduces the frequency of administration and enhances patient compliance. Therefore, local exosomes delivery can lower the difficulty of treatment and improve patient acceptance. With the continuous development and maturation of exosomes technology and local delivery systems, their application prospects in clinical treatment after SCI will become even more extensive.

Oral administration: Oral administration is a non-invasive method that avoids the discomfort and potential complications associated with other delivery methods, such as injections. Patients can self-administer medications at home, enhancing the convenience of treatment, which is particularly important for the long-term management of chronic SCI. Additionally, the production, transportation, and use of oral medications are generally cost-effective, potentially reducing the overall medical expenses for patients. However, oral administration also faces challenges similar to intravenous delivery, such as systemic reactions. Moreover, the digestive system may affect the activity and stability of exosomes, posing a potential limitation.

Currently, the diversified administration methods of exosomes hold promise to meet the clinical application demands. In the long term, the suitability of exosomes for both short-term and long-term use in SCI patients remains uncertain. Whether exosomes should be adopted as a long-term strategy for SCI patients requires further exploration through extensive clinical prospective studies.

Exosomes Therapy in Personalized Medicine Model

The personalized medicine model for exosomes therapy is a new medical approach that is patient-centered and customizes treatment plans based on individual differences. In personalized medicine, treatment not only considers the patient's condition but also factors such as immune status, environmental influences, and lifestyle, to create tailored treatment strategies. By leveraging the unique properties of exosomes and integrating biotechnology and data analysis, highly personalized treatment plans are one of the optimal choices in the treatment of SCI. Treatment can involve extracting exosomes from the patient's cells (such as mesenchymal stem cells, immune cells, or tumor cells) to ensure biocompatibility and low immunogenicity, achieving personalized sourcing of exosomes. Moreover, based on the patient's genetic characteristics, the extent of the injury, and systemic response status, artificial intelligence technology can be used to optimize the design of exosomes and treatment plans. This involves surface targeting modifications and loading specific therapeutic molecules (such as miRNA, siRNA, proteins, or drugs) to design personalized local delivery systems, enabling highly precise treatment for the patient. In long-term health management, by monitoring the dynamic changes in exosomes in the patient's body fluids, it is possible to track treatment outcomes or adverse reactions, assess the effectiveness of treatment, and enable dynamic personalized therapy. This provides a new strategy for the development of precision medicine following SCI.

However, the rehabilitation process for SCI patients is slow. By combining exosomes therapy with exercise training, neural plasticity can be effectively enhanced. Tailoring the preparation and delivery of exosomes based on the patient's condition, along with dynamic safety assessments, holds promise to achieve long-term health management in these patients. However, the long-term effects and safety of exosomes therapy still need attention. First, the exosomes delivery system may accumulate in the body, and the long-term effects could be influenced by factors such as drug release control, exosomes stability, and cellular uptake. Second, immune response issues related to exosomes still exist, especially with prolonged use, which may trigger immune rejection. Additionally, exosomes may carry harmful substances or gene-editing tools, leading to off-target effects or the risk of tumor formation, particularly when they fail to precisely target the intended cells during delivery. When crossing the BBB, exosomes may introduce potential neurotoxicity. Therefore, the

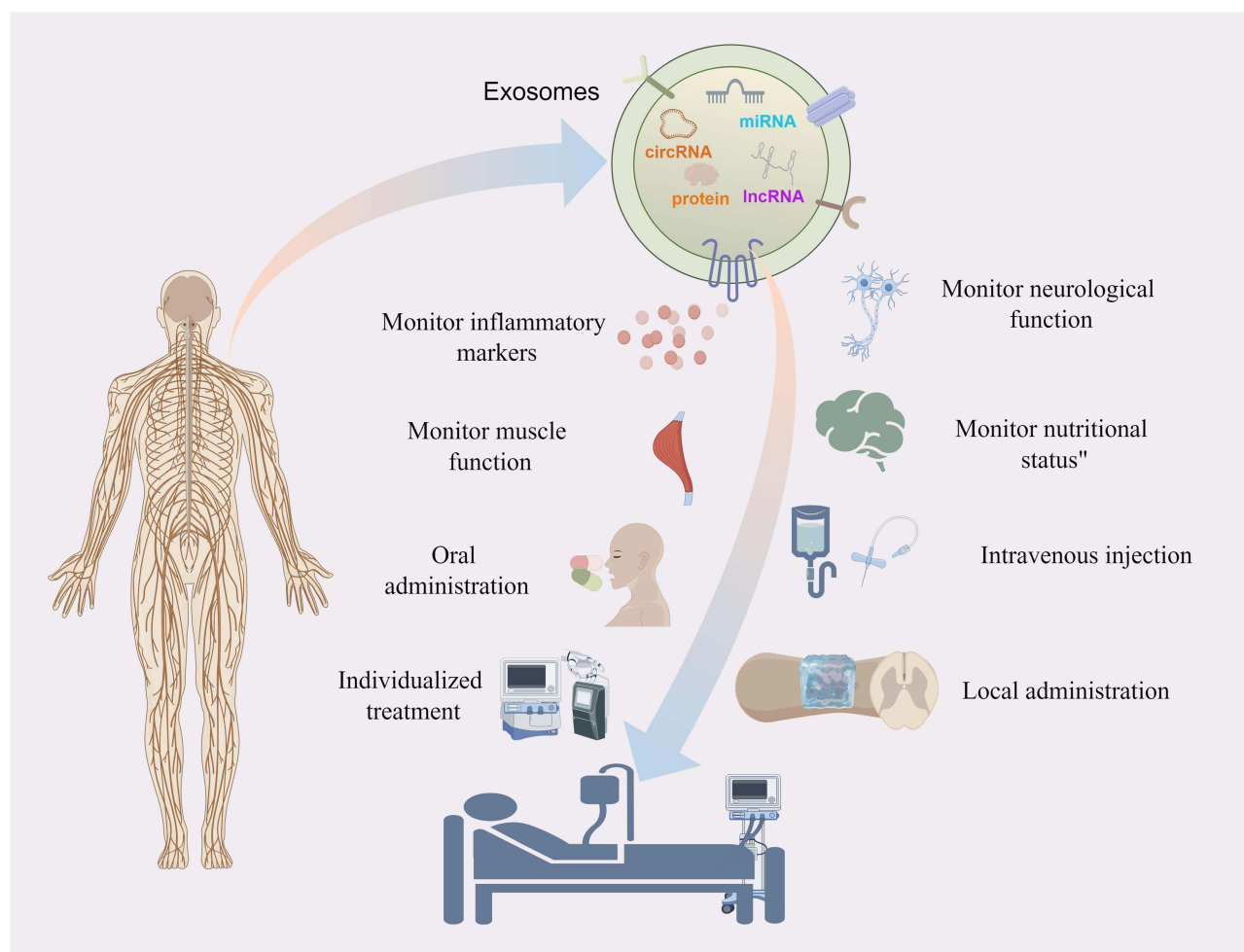


Figure 6 Exploring the significance of exosomes as prognostic biomarkers, diversified exosomes delivery methods, and personalized treatment in the future management of SCI.

long-term safety and efficacy of exosomes still need further evaluation and optimization to ensure their broad clinical application.

Challenges and Considerations in Exosomes Therapy

Despite the immense therapeutic potential of exosomes therapy, there are still numerous challenges and difficulties in its clinical translation. Exosomes commonly used in SCI treatment research are primarily derived from mesenchymal stem cells, peripheral blood, platelets, and other sources. While these sources offer certain functional advantages, the large-scale production of exosomes remains a major obstacle to their clinical application. Additionally, exosomes derived from different cell sources exhibit significant heterogeneity, and there is a lack of unified screening standards, leading to substantial batch-to-batch variability. Furthermore, there is no universally accepted optimal method for exosomes administration. Exosomes may produce different therapeutic effects in various experimental models and individuals, which is closely related to factors such as the patient's immune status, injury severity, exosomes source, and dosage. Moreover, existing animal experimental results are difficult to fully extrapolate to clinical research, and long-term use of exosomes may raise concerns regarding potential tumorigenicity, immune dysregulation, and other issues, for which systematic studies are still lacking.

To address the challenges in exosomes applications, we believe efforts should be made to promote automated and standardized purification processes, develop new technologies to improve purity and stability, and establish rigorous industry standards and clinical guidelines. The development of engineered exosomes, coupled with imaging technologies

(such as fluorescent tracing), can be used to monitor exosomes distribution within the body, enabling precise treatment. The development of personalized treatment strategies should also be pursued, selecting exosomes from specific sources based on the type of SCI and the clinical symptoms of the patient. Long-term toxicological assessments and gene expression profiling should be carried out to monitor the potential side effects of exosomes, clarifying their distribution, metabolism, and clearance pathways in the body. In conclusion, the standardization of exosomes applications holds great promise for clinical use in SCI.

Summary

The current status of SCI treatment and the various functions of exosomes derived from different cell sources in SCI have been summarized. Exosomes have significant therapeutic effects on the inflammation response, cell polarization, scar formation, angiogenesis, neuroregeneration, and axon formation following SCI. Exosomes play a crucial role in promoting SCI repair. Among them, various non-coding RNAs (such as miRNA, lncRNA, circRNA) in exosomes are key components that perform important biological functions and play a critical role in elucidating the specific mechanisms of exosomes. Additionally, researchers have made extensive efforts in engineering exosomes, including genetic modification, protein modification, hydrogel loading, and drug loading. These engineered modifications not only effectively enhance the long-term therapeutic effects of exosomes but also provide new directions and strategies for SCI treatment through novel nano-delivery systems formed by exosomes. Finally, we highlight the importance of exosomes as prognostic biomarkers and the diversification of exosomes delivery methods, and explore the value of personalized treatment in the future management of SCI (Figure 6).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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