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REVIEW

Mesenchymal Stem Cell-Derived Exosomes: A Promising Therapeutic Strategy for Spinal Cord Injury

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Abstract: Spinal cord injury (SCI) is a central nervous system injury caused by external forces or pathological factors, and traumatic SCI is the most common. If not treated promptly, traumatic SCI can cause secondary injury and neuroinflammation, leading to the proliferation of glial cells and formation of glial scars. Clinically, SCI is usually treated with surgical intervention, pharmacological therapy, or rehabilitation. However, good outcomes cannot be guaranteed. Therefore, SCI repair remains a central focus in neurotraumatic injury research. With an in-depth study of stem cells in nerve injury repair, stem cells and exosomes secreted by them have brought new hope for SCI treatment. Exosomes secreted by stem cells are small nano-sized vesicles, approximately 30–150 nm in diameter, that contain lipids, proteins, and nucleic acids. They can cross the blood-brain barrier (BBB) or blood-spinal cord barrier (BSCB) through the blood system, and the proteins or nucleic acid molecules they carry promote nerve repair. Existing studies have demonstrated that exosomes exert therapeutic effects on SCI through multiple mechanisms: miRNA-mediated modulation of inflammatory responses, promotion of axonal regeneration and angiogenesis, inhibition of glial scar formation and apoptosis, as well as regulation of target cell gene expression via signal transduction pathways mediated by their carried signaling molecules. Although exosome research has yielded promising results in animal models of SCI, significant challenges remain in their clinical translation. Future research should focus on optimizing exosome production, improving purity, elucidating their precise mechanisms of action, and advancing their clinical translational applications.

Keywords: spinal cord injury, mesenchymal stem cell, exosomes, therapeutic strategy

Introduction

Spinal cord injury (SCI) is a central nervous system injury caused by external forces or pathological factors. It is a serious neurological disorder that causes dysfunction of limb movement, sensation, and autonomic nervous system below the site of injury. According to statistics on the Global Burden of Disease (GBD), more than 20.6 million people were affected by SCI worldwide in 2019, with approximately 0.9 million new cases each year.[1,2] SCI is usually caused by impact or compression. According to etiological factors, SCI can be divided into traumatic and nontraumatic SCI. Based on pathological changes following injury, SCI can be divided into primary and secondary injuries. Primary injury refers to neuronal damage directly caused by the impact, whereas secondary injury results from inflammation of the spinal cord after the primary injury, which promotes the formation of glial cells and glial scars. The formation of glial scars hinders the development of new neural circuits, making it difficult to fully repair the injured spinal cord, and presents a challenge that needs to be overcome for effective SCI repair. Currently, the primary treatment for SCI includes surgical intervention, pharmacological therapy, and rehabilitation. However, regardless of the treatment method, desired therapeutic effects cannot be achieved. Recently, remarkable progress has been made in SCI repair through intrathecal injections of nerve growth factor (NGF), stem cells, genetically modified stem cells, and stem cell exosomes.[3,4]

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SCI can lead to irreversible functional damage caused by neuronal damage and the disruption of neuronal connections at the injury site. In SCI repair research, researchers aim to generate new neurons through the proliferation and differentiation of stem cells, thereby repairing damaged or dead neurons, and establishing new neural circuits. However, the microenvironment formed after SCI often causes transplanted stem cells such as neural stem cells (NSCs) to differentiate into glial cells rather than neurons.[5] Therefore, repairing SCI by differentiating stem cells into neurons is challenging, and remodeling the microenvironment after SCI is crucial. Within the inflammatory microenvironment of the spinal cord after SCI, the benefits of stem cell transplantation arise mainly from the components secreted by the stem cells. Consequently, the direct isolation and injection of stem cell-derived exosomes represent a new strategy for SCI repair.

Exosomes are small nanosized vesicles formed by endocytosis in eukaryotic cells. They fuse with the cell membrane and are released into the extracellular environment with an average diameter of approximately 30–150 nm.[6] Almost all eukaryotic cells produce exosomes. Exosomes secreted by eukaryotic cells can be isolated and purified from the culture medium. After separation and purification, they can be preserved at low temperatures, facilitating their application in SCI treatment. In SCI treatment, exosomes can cross the blood-spinal cord barrier (BSCB) to reach the SCI site because of their unique biological properties,[7] offering unique advantages over traditional cell transplantation methods.

Studies have shown that mesenchymal stem cell exosomes (MSC-Exos) play a crucial role in tissue repair and regeneration by promoting cell proliferation, migration, and differentiation and participating in processes such as angiogenesis and immune modulation.[8,9] In addition, exosomes can influence the function and fate of receptor cells by delivering cell-signaling molecules.[10] MSC-Exos have shown promise in SCI repair. For example, in neurodegenerative diseases, exosomes promote survival and axonal growth of nerve cells, thereby contributing to neural repair.[11,12] As a new cell-free treatment strategy, MSC-Exos represent a new method for the treatment of SCI, and have broad application prospects.

Mesenchymal stem cells (MSCs) are currently the most extensively studied type of stem cell. Compared with stem cells from other sources, MSCs offer several advantages, including abundant sources such as umbilical cord mesenchymal stem cells (UC-MSCs), bone marrow mesenchymal stem cells (BM-MSCs), adipose-derived mesenchymal stem cells (AD-MSCs), and menstrual blood-derived endometrial stem cells (MenSCs).[13,14] Furthermore, MSCs possess strong expansion capabilities, low tumorigenicity, and significantly better safety profiles and clinical applicability compared to stem cells from other sources.[13]

A key mechanism underlying stem cell therapy for nerve injury is the secretion of bioactive factors, such as proteins, cytokines, and chemokines, as well as the release of extracellular vesicles (EVs).[15] Exosomes, a type of EV, offer advantages over live cell therapy by avoiding post-infusion embolization, tumorigenicity, and survival issues.[16] Importantly, in the nervous system, while cells can not cross the blood-spinal cord barrier (BSCB), exosomes are nanosized vesicles that can penetrate the BSCB to reach the site of SCI.[16] This represents a significant advantage of exosome therapy over cell therapy.

Studies have shown that MSC-Exos exhibit low immunogenicity, making them suitable for allogeneic use without the need for human leukocyte antigen (HLA) matching.[17] Secondly, MSC-Exos are enriched with reparative miRNAs, such as miR-431-3p, miR-423-3p, and miR-338-5p, providing a rich molecular "toolbox" for disease treatment.[18–20] Specifically, miR-431-3p can promote neuronal axonal regeneration,[18] miR-423-3p inhibits ferroptosis and inflammatory responses,[19] and miR-338-5p reduces neuronal apoptosis.[20] This article reviews the research progress of MSC-Exos in the treatment of SCI, aiming to provide a reference for future research and clinical translation.

SCI

Types of SCI

SCI can be categorized into two major types based on etiological factors: traumatic and nontraumatic.[21] Traumatic SCI is the most common type, often resulting from external forces such as traffic accidents, falls, or impacts (Figure 1). In contrast, nontraumatic SCI is relatively rare and is usually associated with neurological diseases that lead to spinal cord dysfunction.[21–24] Depending on the location, SCI can be further classified into cervical, thoracic, lumbar, and sacral injuries.[25] SCI outcomes vary

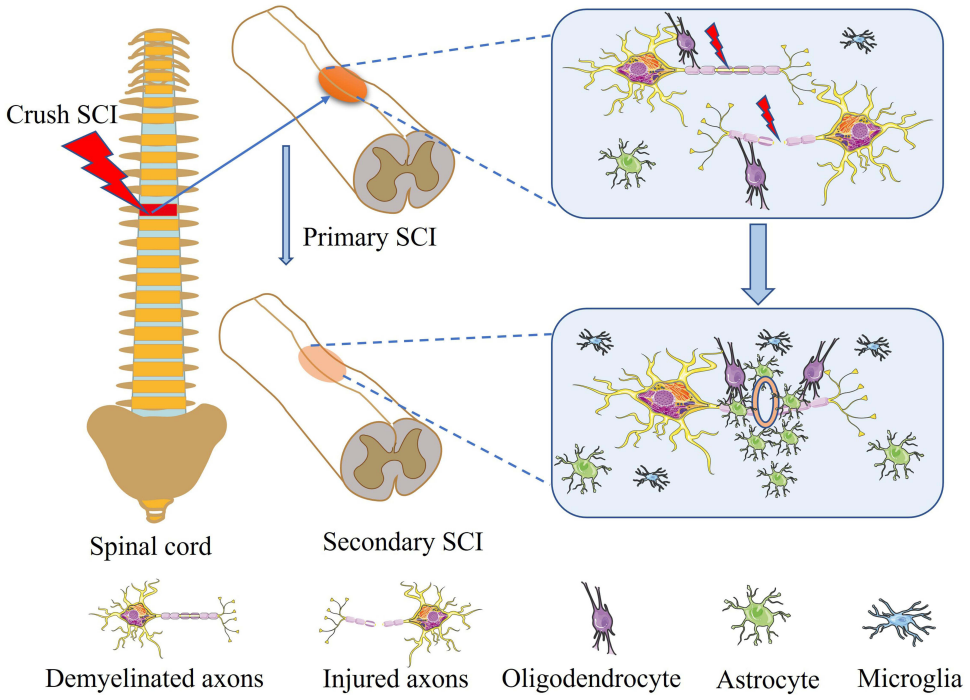

Figure 1 Pathophysiological processes after SCI.
Note: Spinal cord injury (SCI) is commonly traumatic, resulting in demyelination or axonal injury of spinal cord neurons due to crushing. The injured area is affected by cellular damage, which activates glial cell proliferation, leading to inflammation. Finally, glial scars form at the site of injury.

depending on the injury site, with cervical SCI generally resulting in more severe consequences than sacral SCI.[26] Cervical SCI can cause damage to the motor and sensory nerves, severely affecting the motor and sensory functions of the limbs below the site of injury and even leading to tetraplegia.[27] SCI can be classified as complete or incomplete.[28] Complete SCI leads to total loss of spinal cord function below the site of injury, often resulting in complete paralysis, whereas incomplete SCI retains some degree of function below the site of injury, potentially leading to partial or unilateral paralysis.[24] Based on the pathological changes following injury, SCI can be divided into primary and secondary.[29,30] Primary SCI refers to the initial injury caused by direct trauma, such as contusions, whereas secondary SCI occurs as a result of pathological changes following primary injury, such as inflammation and glial scar formation.[31,32] The optimal treatment time for SCI is in the primary injury phase.[33]

Pathophysiological Process of SCI

If not treated in a timely manner, the primary SCI triggers a series of pathological changes. (1) Inflammatory response: After SCI, the immune system is activated, leading to proliferation and accumulation of immune cells such as neutrophils and macrophages.[34] These cells release inflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1), which exacerbate the inflammatory response.[35,36] (2) Cell apoptosis: Changes in the microenvironment at the site of injury, such as oxidative stress, expression of inflammatory factors, and reduced levels of neurotrophic factors, may induce neuronal apoptosis.[37,38] Due to the poor regenerative ability of neurons, this process leads to irreversible pathological changes that complicate SCI repair.[29,39] (3) Formation of glial scars: After SCI, astrocytes and microglia are activated in an inflammatory environment.[40] Proliferation of these cells leads to the formation of glial scars, which act as barriers to prevent the spread of inflammation. However, they also inhibit axonal growth and re-establish damaged neural circuits, thereby affecting neuronal function and posing a substantial obstacle to SCI repair.[40–42] Neuroinflammation and glial scars are pivotal barriers to post-SCI repair (Figure 1).[43]

Therapy Methods and Limitations of SCI

Current clinical treatments for SCI include surgical intervention, pharmacological therapy, and rehabilitation therapy; however, each treatment has its own limitations.[29] (1) Surgical treatment: Surgery primarily aims to relieve spinal cord

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compression, as in cases of contusion-induced SCI. Although surgical removal of compressive elements can prevent further injury, it cannot reverse the sustained damage. Additionally, surgical procedures carry inherent risks, such as secondary injury during the removal of compressive tissues, postoperative inflammation, and tissue adhesion, which may further complicate SCI repair.[44,45] Surgical treatment is also a common method used after severe traumatic SCI, usually to promptly remove nerve compression caused by trauma and foreign objects, in order to reduce further nerve damage. (2) Pharmacological therapy: Commonly used drugs for SCI include neuroprotective and neuroregenerative agents such as corticosteroids, gangliosides, and nerve growth factors.[33,45–48] These drugs mainly play a role in neuroprotection and promoting self-repair, and the damage to neurons in the central nervous system is non-renewable. Therefore, once the neurons are damaged, drug treatment cannot achieve good therapeutic effects. (3) Rehabilitation therapy involves physical and occupational therapies to stimulate neural activity and enhance functional recovery.[49–51] However, the efficacy of rehabilitation therapy in patients with severe SCI is limited.[29,52] (4) Combined therapy: A combination of these methods is often used.[53,54] For example, in contusion-induced SCI, surgical decompression is followed by pharmacological support for neural recovery and subsequent rehabilitation therapy, leading to improved outcomes.[44]

These treatment methods offer value for SCI management from specific perspectives but are hindered by inherent limitations. A primary challenge lies in regenerating damaged neurons: within the central nervous system (CNS), neurons poor regenerative capacity post-injury, resulting in incomplete recovery with existing approaches. To address this, researchers have explored neural stem cells (NSCs) for SCI therapy, aiming to induce their differentiation into neurons. However, studies reveal that the inflammatory microenvironment of SCI redirects NSCs differentiation toward glial cells rather than neurons.[5] This suggests that harnessing stem cells to generate neurons for SCI treatment may not be viable. Additionally, the limited availability of human NSCs constrains research progress in this area.

In clinical practice, MSCs, such as UC-MSCs and AD-MSCs, are more readily accessible. This accessibility has spurred extensive investigation into MSCs for treating various diseases, including SCI. Given that NSCs fail to differentiate into neurons under SCI conditions, it is plausible that MSCs may similarly lack this capacity. Instead, MSCs are hypothesized to exert therapeutic effects via their secreted factors or extracellular vesicles. Consequently, research into MSC-based therapies and their exosomes for SCI treatment has garnered significant interest.

MSCs and Exosomes

MSCs

MSCs are multipotent stem cells derived from the mesoderm that can self-renew and differentiate into various cell types.[55,56] MSCs can be isolated from a wide variety of tissues. Although the biological characteristics and functions of MSCs may vary depending on the tissue source, they possess the fundamental properties of MSCs.[57] In vitro and in vivo experiments have demonstrated that MSCs exhibit strong proliferative and self-renewal capacities, with osteogenic and adipogenic potential, but without tumorigenicity, which ensures their safety for therapeutic applications.[58,59] Numerous studies have demonstrated the anti-inflammatory potential of MSCs.[60] Research has shown that MSC-Exos can inhibit glial scar formation after SCI.[61] Furthermore, studies have revealed that MSCs regulate neuronal ferroptosis by inhibiting the mitochondrial pathway to alleviate SCI.[62] Multiple studies have indicated that MSCs play a role in the repair of SCI not only through their direct action but also through the extracellular vesicles and exosomes secreted by them. Research has demonstrated that 3D cultured MSC-Exos effectively reduce SCI-induced inflammation and glial scarring.[63] Studies have shown that small extracellular vesicles derived from MSCs affect the phenotype of astrocytes through miR-21, thereby promoting recovery from SCI.[64] Owing to their small diameter, MSC-exos can traverse the BBB or BSCB of the CNS and repair SCI via vein or local injection, a characteristic that has garnered considerable attention and research in recent years.

Exosomes

Exosomes are nanoscale membrane vesicles secreted by cells, with diameters ranging from 30 to 150 nm.[65,66] They are widely present in bodily fluids and play a crucial role in intercellular communication.[65,66] Exosomes contain various types of biologically active molecules such as lipids, proteins, DNA, and RNAs, which mediate intercellular information transmission and regulate intercellular signal transduction.[67–69] The exosome formation process is complex (Figure 2).

The membranes of parental cells or intracellular membrane structures bud inward or outward to form early endosomes. Early endosomes mature into late endosomes. Some small vesicles in the late endosomes sag inward to form multivesicular bodies (MVBs). These small vesicles are precursors of exosomes. Subsequently, multivesicular bodies fuse with lysosomes and are degraded. They can also fuse with the cell membrane to release small internal vesicles (exosomes) into the extracellular environment (Figure 2). Exosome biogenesis is regulated by various molecular mechanisms, including endosomal sorting complexes required for transport (ESCRT)-dependent and-independent pathways.[70,71]

Similar to the cell membrane, the exosomal membrane is composed of a lipid bilayer that protects its contents.[6] Exosomes contain a complex array of components, including lipids, proteins, nucleic acids, and metabolic products, all of which are derived from parent cells.[72] Therefore, the parent cell type determines the composition and function of exosomes. For example, exosomes from tumor cells can induce malignant proliferation of normal cells, whereas exosomes from immune cells can regulate immune responses and enhance immune defenses.[73–75] Studies have shown that the injection of antigen- or peptide-bearing exosomes induces antigen-specific naïve CD^{4+} T-cell activation in vivo.[76] Therefore, exosomes play an important role in both physiological and pathological processes and in-depth studies can provide new strategies for disease treatment.

MSC-Derived Exosomes (MSC-Exos)

MSC-Exos not only inherit some of the biological functions of MSCs but also possess unique advantages that make them highly promising for therapeutic applications. Compared to exosomes from other sources, MSC-Exos exhibit stronger tissue repair and regenerative capacities. Studies have shown that MSC-Exos contain multiple proteins with multiple functions, including transmembrane proteins, signaling proteins, heat shock proteins (HSP60, HSP70, and HSP90), and MHC class I and class II proteins.[77,78] Additionally, MSC-Exos contain transmembrane proteins (CD9, CD63, and CD81).[61] MSC-Exos contain numerous nucleic acids, including mRNAs, miRNAs, mitochondrial DNA, piRNAs, ncRNAs, ribosomal RNA, and snRNAs.[79,80] These factors participate in cell signal transduction, regulate gene

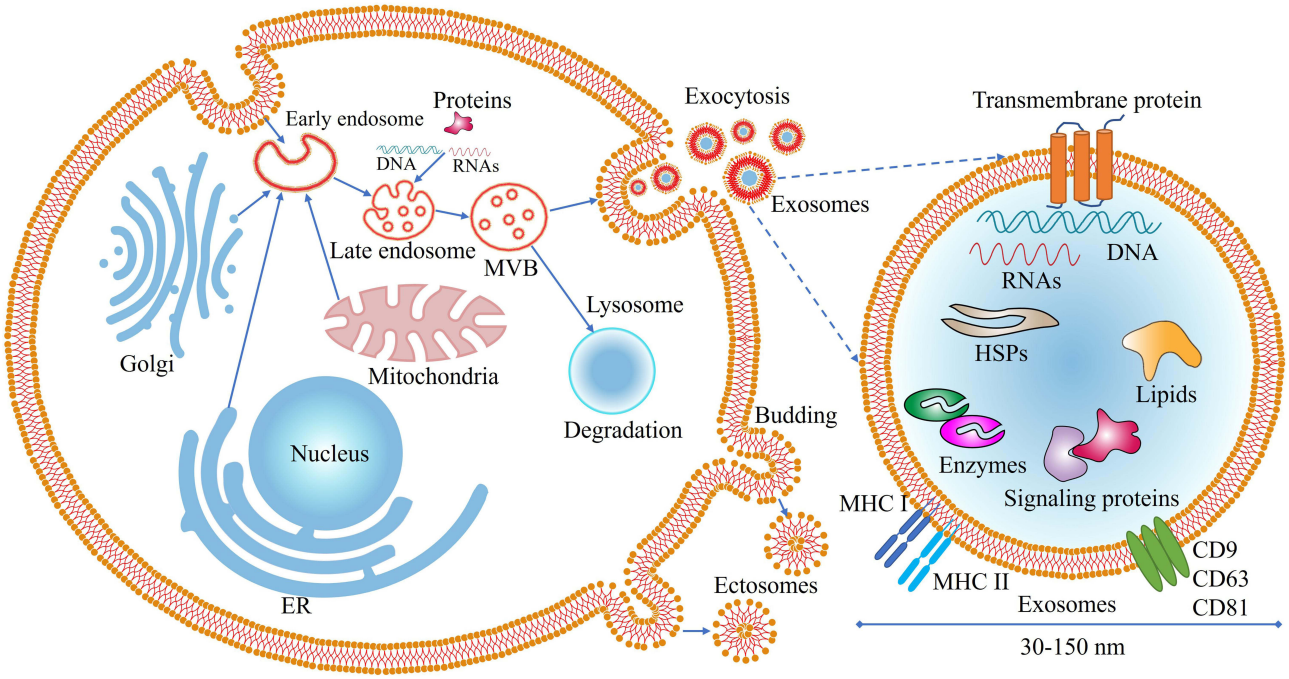

Figure 2 The process of exosome formation.

Notes: The parental cell membrane sprouts inward to form early endosomes, and the budding of organelles inside the cell can also form early endosomes. Early endosomes further form late endosomes, which, in turn, form MVBs. MVBs may fuse with lysosomes to either degrade or fuse with the cell membrane to release vesicles and form exosomes. The cell membrane can also sprout outward to form ectosomes. These contain proteins, lipids, and nucleic acids. The diameter of the exosomes ranges from 30 to 150 nm. Abbreviations: MVBs, multivesicular body; ER, endoplasmic reticulum; HSP, heat shock protein.

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expression, and promote cell proliferation, migration, and differentiation, thereby accelerating tissue repair and regeneration (Figure 2). For example, in skin injury models, local application of MSC-Exos substantially enhanced wound healing, increased angiogenesis, and promoted collagen synthesis, with better effects than exosomes from other cell sources[81–83] Additionally, MSC-Exos regulate the synthesis and degradation of the extracellular matrix and maintain the tissue structure and function.[84,85]

MSC-Exos also possess robust immunomodulatory properties.[86,87] The immunoregulatory functions of MSCs are largely mediated by extracellular vesicles (EVs).[88] MSC-Exos can inhibit the activation and proliferation of T and B lymphocytes, modulate the function of macrophages and dendritic cells, and reduce inflammatory responses and immune rejection.[89] This immunomodulatory effect makes MSC-Exos valuable for the treatment of autoimmune diseases and organ transplantation.

Compared with MSCs, MSC-Exos offer better stability and safety. As extracellular vesicles, exosomes have a relatively stable structure and maintain their biological activity in various environments. The preparation and storage of MSC-Exos are relatively simple.[90] They can be isolated and purified using methods such as ultracentrifugation, ultrafiltration, and immunomagnetic beads and can be stored long-term at appropriate temperatures.[91] MSC-Exos exhibit improved targeting capabilities. Research has shown that MSC-Exos can specifically recognize and bind to target cells through surface molecules such as integrins and transmembrane proteins, thereby achieving precise regulation of target cells.[86]

In summary, MSC-Exos possess strong tissue-repair capabilities, notable immunomodulatory effects, good stability, good safety, and strong targeting abilities. These characteristics make them highly promising therapeutic agents with broad application prospects in the treatment of SCI and other diseases.

Research Progress of MSCs and MSC-Exos in SCI Repair

MSCs are multipotent cells found in various tissues, such as the bone marrow, adipose tissue, and umbilical cord. They can self-renew and differentiate into multiple cell types including osteoblasts, adipocytes, and chondrocytes. MSCs have extensive potential in tissue repair, immune modulation, disease treatment, and other applications. Numerous studies have explored the application of MSCs in regenerative medicine, stem cell therapy, and drug development.

Umbilical Cord Mesenchymal Stem Cells (UC-MSCs)

UC-MSCs are stem cells extracted from umbilical cord tissue that can self-renew and differentiate into various cell types that constitute the human tissues and organs. UC-MSCs can form fat, bone, and cartilage. Their non-invasive harvesting, low immunogenicity, and ability to secrete cytokines give UC-MSCs unique advantages in clinical applications.[92,93] In clinical applications, UC-MSCs promote vascular remodeling, inhibit inflammation, regulate apoptosis, and release beneficial factors.[94] Studies have shown that the differentiation, migration, and protective properties of UC-MSCs are superior to those of other stem cells. In addition, UC-MSCs have been used to treat various neurodegenerative diseases, laying the foundation for their clinical application.[95,96]

In the SCI contusion model, exosomes derived from human umbilical cord stem cells (hUC-MSCs) are injected intravenously. Research has shown that these exosomes have a positive effect on motor function in rats after SCI while reducing cell apoptosis. Exosome treatment downregulates the number of astrocytes and microglia, suggesting a reduction in SCI-induced inflammation. The Bcl-2/Bax and Wnt/β-catenin signaling pathways are involved in the SCI repair process and may mediate the protective effect of exosomes derived from hUC-MSCs, whereas exosome transplantation activates the Wnt/β-catenin signaling pathway.[97] Although exosomes are effective therapeutic agents for traumatic SCI, their mechanism of action remains unclear. Studies have shown that hUC-MSC-derived exosomes can improve motor function through their anti-apoptotic and anti-inflammatory effects. MiR-199a-3p/145-5p is a relatively highly expressed microRNAs (miRNAs) in exosomes. In *vivo* experiments showed that exosomal miR-199a-3p/145-5p upregulated TrkA expression at SCI sites and improved SCI motor function, indicating that exosomes derived from UC-MSCs may be a promising treatment for SCI.[98] To investigate the repair effects of extracellular vesicles derived from hUC-MSCs (hUC-MSC-EVs) on SCI, researchers have established rat models of SCI and transplanted hUC-MSC-EVs. By observing the motor function and morphology of spinal cord tissue in SCI rats, researchers found that rats treated with

hUC-MSC-EVs showed substantial recovery in motor function and reduced necrosis, nuclear pyknosis, and cavities. Studies have shown that inhibiting miR-29b-3p or overexpressing PTEN can reverse the repair effect of EVs in SCI. This suggests that hUC-MSC-EVs improve motor function in rats with SCI through the miR-29b-3p/PTEN/Akt/mTOR axis, thereby promoting neural function repair in SCI rats.[99]

Bone Marrow Mesenchymal Stem Cells (BM-MSCs)

BM-MSCs have multiple differentiation potentials and can differentiate into osteoblasts, chondrocytes, and adipocytes.[100] Their strong proliferative and multidirectional differentiation abilities provide favorable conditions for transplantation in SCI treatment.[101] In addition, BM-MSCs transplanted into SCI sites can not only survive for extended periods but also promote the growth of nerve axons and angiogenesis, playing a key role in the treatment of SCI.[102,103]

After SCI, the spinal cord sustains severe morphological damage and a partial loss of motor function. Promotion of axonal regeneration is crucial for SCI treatment. BM-MSCs promote neuroprotection, nerve regeneration, and myelin sheath regeneration by reconstructing the spinal cord microenvironment.[104]

Studies have shown that the therapeutic effect of MSCs is because of their ability to regenerate the microenvironment and paracrine signaling, rather than their differentiation capabilities. BM-MSC transplantation may promote recovery after SCI through paracrine effects.[105] Following SCI, complement levels increase and exosomes extracted from BM-MSCs mainly accumulate at injured sites and combine with microglia to inhibit complement synthesis.[106] In the spinal cord ischemia-reperfusion injury (SCIRI) model, the expression of Ern1 was upregulated, and the polarization level of M2 macrophages was downregulated. Exosomes derived from BM-MSCs carrying the MiR-124-3p target, downregulate Ern1, thereby enhancing M2 macrophage polarization. This process inhibits apoptosis and mitigates SCIRI-induced tissue and nerve damage.[107] Exosomes derived from BM-MSCs can inhibit the secretion of pro-inflammatory factors through the nuclear factor kappa B (NF-κB) signaling pathway, reduce neuroinflammation, improve the BBB behavioral score in rats, and enhance their motor function, thus contributing to SCI treatment.[108,109] Overexpression of G protein-coupled receptor kinase 2 interacting protein 1 (GIT1) in BM-MSCs improves the effects of exosomes on traumatic SCI in rats. Unlike the injection of exosomes into the tail vein, overexpression of GIT1 exosomes effectively inhibits glial scarring and neuronal death, promotes axonal regeneration, and plays a crucial role in SCI treatment.[110]

Adipose-Derived Mesenchymal Stem Cells (ADMSCs)

ADMSCs are widely used in biomedical research and in clinical applications. These pluripotent stem cells can undergo multidirectional differentiation and can be isolated from adipose tissue. ADMSCs exhibit various biological characteristics including multidirectional differentiation potential, immune regulatory functions, and tissue repair capabilities.[111–113] Owing to their wide availability, ease of acquisition, amplification, and preservation as well as their low immunogenicity and minimal ethical and legal concerns, ADMSCs have become a popular research topic in recent years.[114] Recently, ADMSC-derived exosomes (ADMSC-Exos) have received increasing attention. These exosomes have various biological functions, such as anti-apoptotic, antioxidant, angiogenic, and immune response regulation.[115–118] Breakthroughs have been achieved in the diagnosis and treatment of immune diseases, skin repair, and regenerative engineering.[119] The therapeutic benefits of ADMSC-Exos have been confirmed in many diseases.[120] In addition, ADMSCs promote the transformation of M1 macrophages into M2 macrophages.[121]

Studies have shown that ADMSC-Exos under hypoxic conditions (Hypo-Exo) can substantially reduce the formation of cavities in the SCI area of rats and improve functional recovery of hind limbs after injury. The mechanism by which miR-499a-5p in Hypo-Exo reduces neuronal apoptosis after SCI involves targeting c-Jun N-terminal kinase 3 (JNK3) to regulate the JNK3/c-jun apoptotic signaling pathway.[122] In addition, ADMSC-derived sEVs inhibit SCIRI-induced neuronal apoptosis, tight junction protein degradation, and endoplasmic reticulum (ER) stress. ADMSC-sEVs may contain tumor necrosis factor-stimulated gene-6, whose overexpression inhibits ER stress in vivo by modulating the PI3K/AKT pathway.[123]

Menstrual Blood-Derived Endometrial Stem Cells (MenSCs)

MenSCs are a type of stem cell with abundant sources, simple isolation and culture methods, and considerable application value in disease treatment. They are involved in adipogenesis, osteogenesis, chondrogenesis, and neural and cardiac differentiation.[124–126] Studies have shown that MenSCs transplantation accelerates neuronal recovery at the injury site, inhibits glial cell formation and microglial activation at the injury site, reduces inflammatory factor expression, and improves the inflammatory microenvironment to achieve functional recovery of SCI. The mechanism by which MenSCs promote functional recovery of SCI may not involve their differentiation into neurons or glial cells, but rather the secretion of factors that improve the SCI microenvironment and facilitate the recovery of SCI.[127]

In summary, the research results of the above-mentioned types of MSC-Exos in SCI indicate that key biological functions include providing neuroprotection and promoting locomotor function recovery. Mechanistic studies have shown that MSC-Exos can reduce neuroinflammation and neuronal apoptosis (Table 1).

Therapeutic Strategy of MSC-Exos in SCI

Therapeutic Strategies of MSC-Exos or Modified MSC-Exos Separation Injection

The present study identified two strategies to study the effects of exosomes derived from widely used MSCs: UC-MSCs, BM-MSCs, ADMSCs, and MenSCs. The first strategy involves directly isolating and culturing MSCs, extracting exosomes, and injecting them into SCI sites in animal models or injecting them through the tail vein to observe their repair effects. The second strategy involves modifying or stimulating cultured MSCs with genes or peptides before isolating exosomes, which are then injected into the SCI site in animal models to observe their repair effects (Figure 3). To evaluate the repair effects, researchers have focused not only on the motor function of animals but also on axonal regeneration at the injury site, cell apoptosis, inhibition of glial cell formation, and transformation of activated microglia from M1 to M2 macrophages (Figure 3). Although the therapeutic strategy for the direct injection of MSC-Exos is simple, the inflammatory microenvironment in the SCI area may lead to degradation of MSC-Exos. Simultaneously, a single injection of MSC-Exos into the SCI area may have a limited action time, and multiple injections may increase the possibility of secondary trauma. However, it is difficult to determine the amount of MSC-Exos that reaches the SCI area through tail vein injection. Therefore, there are still many problems that need to be studied further regarding the delivery strategy of MSC-Exos for SCI treatment.

Therapeutic Strategies of MSC-Exos and Biomaterial Combination

Strategy of MSC-Exos Combined with Hydrogel Materials for Treatment of SCI

With the rapid developments in tissue engineering research, many biomaterials have been used for SCI repair. Injectable hydrogels have great application prospects and unique therapeutic plasticity in the treatment of severe SCI because they can fill pathological defects with minimal surgical trauma through in situ injection of flowable hydrophilic materials. In addition, hydrogels reduce inflammation and promote neuronal regeneration at the injured sites.[132,133] Injectable

Table 1 Research Progress of MSCs-Exos in SCI Repair

Type of Stem Cells	Exosome Separation Method	Exosome Diameter	Model Animal	Biological Effects	Mechanisms	Reference
UC-MSCs	Ultracentrifugation	30 −200 nm	Rats	Promote locomotor function recovery	Reduce the infammatory response; suppressed apoptosis of neurons	[97,128,129]
BM-MSCs	Exosome isolation kit	20–130 nm	Rats	Enhance locomotor capacity and neuron viability	Reduce the infammatory response; reduce neuron apoptosis	[106, 130]
ADSCs	Ultracentrifugation	127.2 nm	Rats	Improve the functional recovery of the hindlimbs of rats after injury	Reduce neuronal apoptosis	[122]
MenSCs	Ultracentrifugation	85 nm	Rats	Neuroprotective	Reduce oxidative factor (MDA) and proinfammatory cytokines	[131]

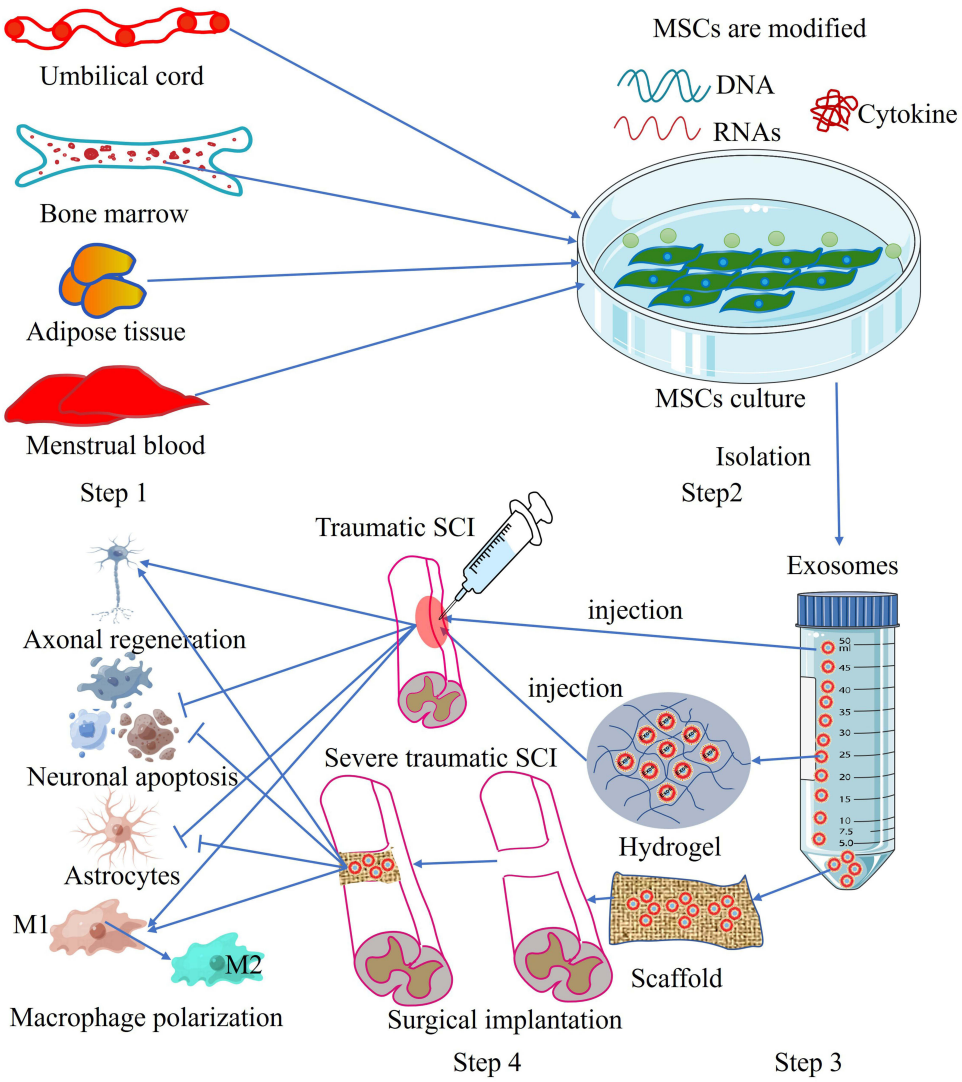

Figure 3 Therapeutic strategy of MSC-Exos in SCI.
Notes: The therapeutic process of SCI using exosomes is divided into four steps. The first step involves obtaining tissues (umbrella cord, bone marrow, adipose tissue, and menstrual blood). The second step involves the isolation and culture of stem cells from tissues. In stem cell cultures, gene modification or protein stimulation can be performed to obtain stem cells. The third step is the separation of exosomes. Exosomes were isolated from cell culture medium (via ultracentrifugation, ultrafiltration, and immunomagnetic bead separation). The fourth step was the injection therapy. The exosomes obtained can be directly injected into the intrathecal injury site or tail vein for SCI treatment, combined with biomaterials, and injected into the intrathecal injury, or surgical implantation site for treatment. After reaching the injury site, exosomes can play a role in SCI treatment in various ways, such as promoting axonal regeneration, inhibiting neuronal apoptosis, inhibiting the formation of astrocytes, and promoting the polarization of M1 type macrophages to M2 type macrophages.

hydrogels have the characteristics of avoiding complex surgeries on large wounds, filling irregular gaps, delivering drugs, and carrying stem cells, exosomes, and neurotransmitters. Simultaneously, they have the advantages of good biocompatibility, biodegradability, and low immunogenicity and have attracted increasing attention.[134]

At present, injectable hydrogels used for biomedical materials have a wide variety of physical and chemical properties, and numerous studies have directly utilized these as biomaterials for damage repair, including cells, small-molecule drugs, or protein factors that can be used for damage repair by loading biomaterials.[135] Biomaterials play dual roles in SCI repair: self-repair and load component repair. Simultaneously, biomaterials can effectively fill and adhere to void tissues.[136] In addition, biomaterials play a role in the delivery and sustained release of the loaded components. If MSC-Exos were used in SCI repair research, they could play a role in sustained release and protection. If MSC-Exos are directly injected into the site of injury, the SCI environment will degrade them, which cannot guarantee a sustained effect. However, the combination of biomaterials can solve this problem (Figure 3).

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Strategy of MSC-Exos Combined with Biomaterial Scaffolds for Treatment of SCI

Biomaterial scaffolds have also been widely used in SCI repair in recent years. Studies have demonstrated that plant-derived lignocellulosic scaffolds coated with poly-L-ornithine (PLO) can support locomotor recovery and neural tissue repair in a rat model of SCI.[137] Additionally, a novel collagen-based biomaterial scaffold can specifically bind to paclitaxel-loaded exosomes, thereby promoting SCI regeneration and repair.[138]

A key distinction between biomaterial scaffolds and hydrogels lies in their application: biomaterial scaffolds are pre-formed and then implanted, whereas hydrogels can be injected and undergo in situ gelation to fill defects. Biomaterial scaffolds typically require a longer degradation period. In cases of SCI where the lesion area is large and structural support is necessary, biomaterial scaffolds are the preferred choice. These scaffolds are pre-fabricated into specific shapes based on the SCI lesion site and subsequently loaded with cells, exosomes, or drug molecules. This approach not only provides structural support but also delivers therapeutic effects (Figure 3).

Both biomaterial scaffolds and hydrogels have been extensively used for SCI treatment, each offering distinct advantages and disadvantages. Biomaterial scaffolds excel in providing pre-formed, porous three-dimensional frameworks. These frameworks can supply substantial mechanical strength and oriented channels within the disrupted spinal cord tissue, guiding axons to extend over long distances along these channels. They also enable robust anchoring and sustained release of drugs or exosomes. Thus, they are particularly suitable for SCI treatments requiring structural support and long-term therapeutic delivery. However, their implantation necessitates open surgery, and they exhibit poor adhesion to irregular wound surfaces. In contrast, hydrogels offer the advantage of injectability and in situ gelation, allowing them to conform perfectly (100%) to the shape of the injury cavity with minimal surgical trauma. Their limitations include low mechanical strength (inability to withstand suturing or compression) and small pore sizes, which are less conducive to the long-distance directional growth of axons. Therefore, when combining MSC-Exos with biomaterials for SCI treatment, the selection of either hydrogel or biomaterial scaffold should be tailored to the specific characteristics of the SCI (Figure 3).

Therapeutic Mechanism of MSC-Exos in SCI

Compared with MSCs, MSC-Exos possess distinct advantages in SCI repair. As nanoscale particles, exosomes can efficiently cross the BSCB and directly target cells at the SCI lesion site. Their functional effects are primarily mediated through the release of signaling proteins or RNAs that regulate target cell activities (Figure 4). Their released signaling proteins, such as NGF, can act as signaling molecules, binding to receptors on the surface of target cells and triggering intracellular signaling pathway changes, thereby regulating cell growth and proliferation (Figure 4). Notably, RNAs play a crucial regulatory role: target cells internalize exosomes via endocytosis, leading to the release of encapsulated RNAs including miRNAs, circRNAs, and lncRNAs into the cytoplasm. These RNAs then modulate gene expression in target

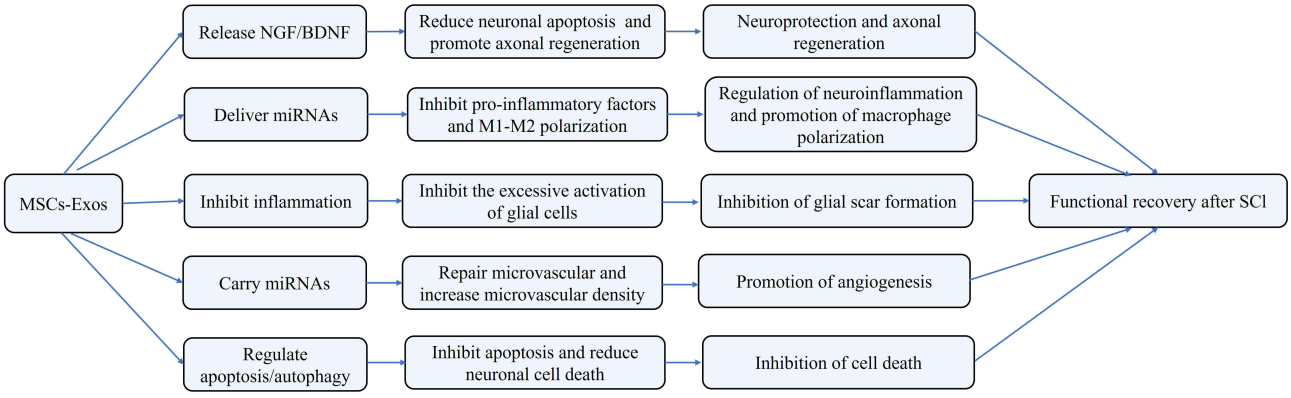

Figure 4 Diagram of the repairing effect of MSC-Exos on SCI.
Abbreviations: NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor.

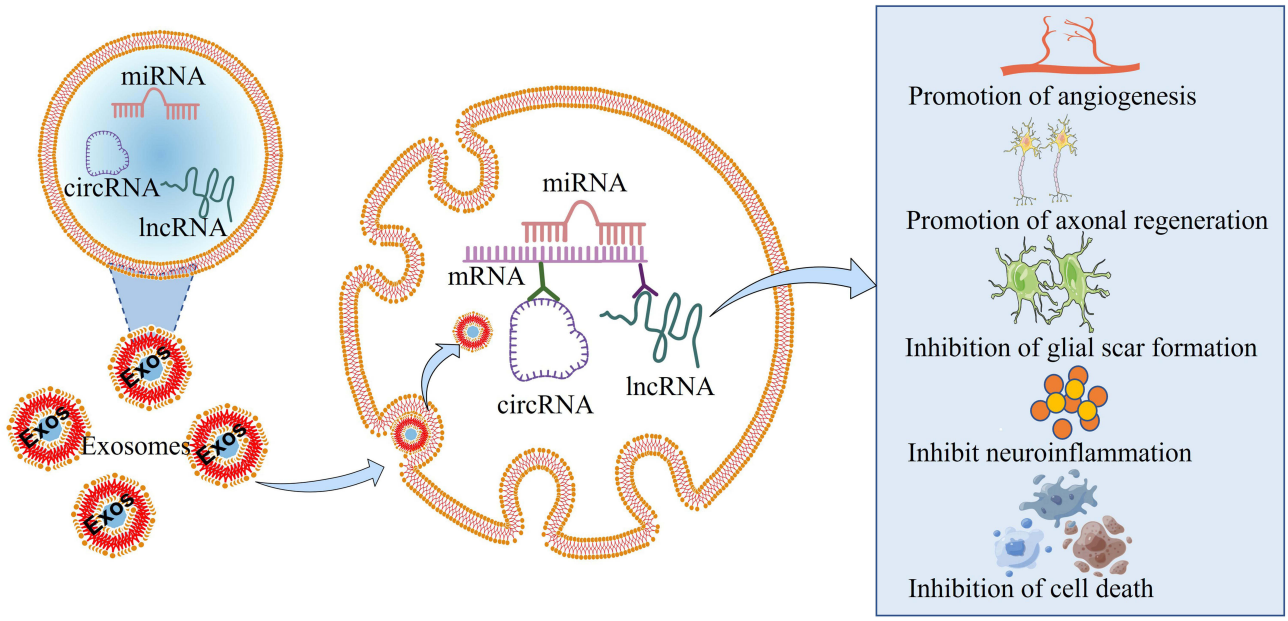

Figure 5 MSC-Exos RNA for SCI repair pathway (Reference[16]).
Abbreviations: mRNA, Messenger RNA; miRNA, microRNA; lncRNA, Long Non-Coding RNA; circRNA, circular RNA.

cells, contributing to multiple repair processes such as promotion of angiogenesis, enhancement of axonal regeneration, inhibition of glial scar formation, suppression of neuroinflammation, and prevention of cell death (Figure 5).

However, the mechanisms underlying MSC-Exo repair are not fully understood. Based on existing research, the mechanisms discussed in the following sections may contribute to SCI repair.

Neuroprotection and Axonal Regeneration

MSC-Exos are rich in various growth and neurotrophic factors such as NGF and brain-derived neurotrophic factor (BDNF). These factors reduce neuronal apoptosis, and promote neuronal survival and axonal regeneration. Studies have shown that treatment of primary retinal cultures with BM-MSC-Exos has substantial neuroprotective and neuritogenic effects.[139] In addition, some studies have shown that exosomes derived from early stage rat BM-MSCs have neuroprotective potential.[140] Furthermore, hUC-MSC exosomes have been shown to promote axonal regeneration by delivering miRNAs.[141] These findings collectively support the neuroprotective and axonal regenerative effects of MSC-Exos, as demonstrated in numerous experiments.

In summary, the repair mechanism of SCI by MSC-Exos in this pathway may involve the following: NGF released by MSC-Exos binds to receptors on the surface of neural cells. This binding activates the PLC/Akt signaling pathway, thereby promoting neural cell growth, or activates the Ras/ERK and JAK/STAT signaling pathways to enhance cell proliferation (Figure 6A and B).

Regulation of Neuroinflammation and Promotion of Macrophage Polarization

After SCI, the inflammatory response hinders repair. MSC-Exos regulate immune cell activity, reduce inflammation, and create a favorable microenvironment for nerve repair. Studies have shown that exosomes derived from hUC-MSCs can inhibit neuroinflammation and reduce neural deficits caused by stroke via their miRNAs.[142] Additionally, MSC-Exos have a certain effect on nerve injury because they can reduce inflammation by controlling the heterogeneity of macrophages, which is regulated by the p38 MAPK/NF-κB pathway.[143] Human placental MSC-derived exosomes (hplMSC-Exos) can regulate inflammation by regulating the TLR4-mediated NF-κB/MAPK and PI3K signaling pathways, indicating that hplMSC-Exos can act as a new strategy for inflammatory treatment.[144] Numerous studies have demonstrated the role of MSC-Exos in immune regulation.[145–147]

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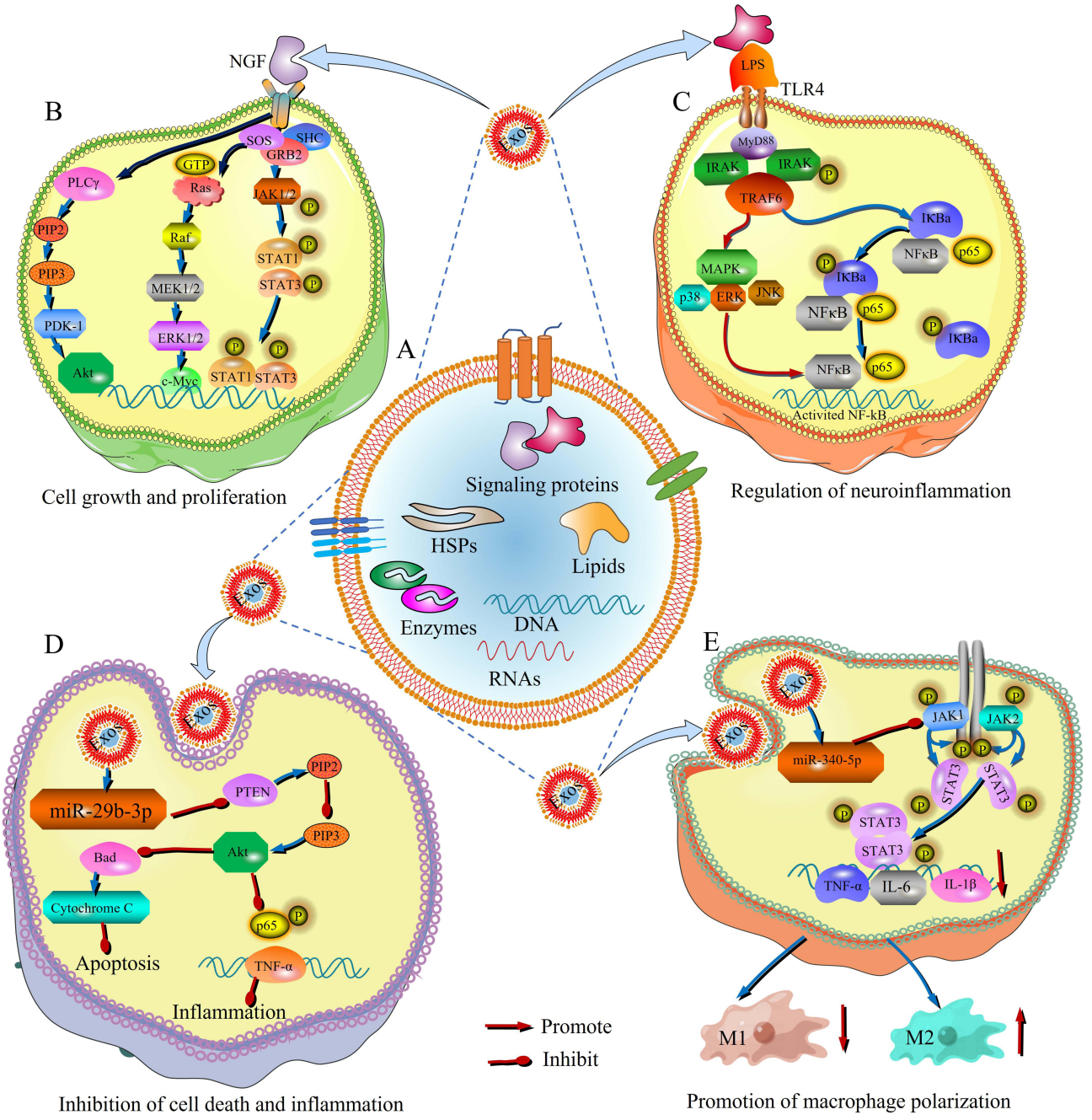

Figure 6 Mechanism of MSC-Exos on SCI repair.
Notes: (**A**) MSC-Exos, mesenchymal stem cells exosomes; MSC-Exos can exert therapeutic effects by promoting cell growth and proliferation (**B**) regulation of neuroinfammation (**C**) inhibition of cell death and inflammation (**D**) promotion of macrophage polarization (**E**).

Macrophages play a crucial role in the inflammatory response and tissue repair after SCI. Macrophages can be divided into two phenotypes, M1 and M2, which differ significantly in their functional and phenotypic characteristics. MSC-Exos can promote macrophage polarization towards M2, thereby exerting anti-inflammatory and tissue repair effects.[143] M1 macrophages can secrete large amounts of pro-inflammatory factors, such as IL-1β, IL-6, TNF-α, and inducible nitric oxide synthase (iNOS).[148–151] These pro-inflammatory factors can trigger strong inflammatory reactions, leading to local tissue damage and destruction. Simultaneously, M1 macrophages produce large amounts of reactive oxygen species, further damaging nerve cells and fibers and hindering the recovery of nerve function. M2 macrophages have anti-inflammatory functions and promote tissue repair. They can secrete anti-inflammatory factors such as IL-10 and

transform growth factor-β (TGF-β) and inhibit the inflammatory response.[150–152] In addition, M2 macrophages can phagocytose and clear necrotic tissues and cell debris, which helps maintain the stability of the microenvironment at the site of injury.[153,154] Many studies have shown that MSC-Exos can promote the polarization of M1 macrophages to M2 macrophages in SCI models, indicating that MSC-Exos have a regulatory effect on macrophage polarization.[155,156] Studies have shown that hUC-MSC exosomes alleviate SCI by regulating microglial polarization through miR-340-5p-mediated modulation of the JAK/STAT3 signaling pathway.[157]

Inhibition of neuroinflammation is the core issue in SCI repair. Following SCI, it leads to the death of cells at the injury site, which in turn triggers the occurrence of inflammation. The regulation of neuroinflammation by exosomes may mainly occur through the following aspects. Firstly, exosomes release signaling molecules that act on inflammatory signaling pathways, such as the TLR4-mediated MAPK/p38/ERK/JNK signaling pathway and the NFκB signaling pathway, to regulate the occurrence of neuroinflammation. Secondly, miRNAs in target cells regulate the signal transduction pathways of cell apoptosis or inflammation by inhibiting the activity of target molecules. For example, miR-29b-3p regulates the AKT signaling pathway by inhibiting PTEN, thereby inhibiting cell apoptosis or inflammation. miR-340-5p inhibits the expression of pro-inflammatory factors TNF-α, IL-6, and IL-1β by inhibiting the JAK1/STAT3 signaling pathway, thereby regulating macrophage polarization, leading to the polarization of M1-type macrophages to M2-type macrophages (Figure 6A and C–E).

Inhibition of Glial Scar Formation

Glial scarring hinders axonal regeneration. MSC-Exos may inhibit the excessive activation of glial cells, reduce the formation of glial scars, and create more favorable conditions for nerve regeneration. Studies have shown that exosomes derived from BM-MSCs can effectively inhibit inflammation, prevent neuronal apoptosis, reduce the number of reactive astrocytes, and induce glial scar formation.[158] In addition, they substantially upregulate several neurotrophic and anti-inflammatory factors, and promote motor recovery in rats with SCI.[158] Furthermore, studies have shown that over-expression of GIT1 in BM-MSC-Exos not only restrains glial scar formation and neuroinflammation after SCI but also attenuates neural apoptosis and promotes axonal regeneration in the injured area.[110] These results indicate that MSC-Exos inhibit glial scar formation via a relatively complex mechanism.

Promotion of Angiogenesis

A good vascular supply is crucial for SCI repair. Exosomes can promote angiogenesis, increase blood supply to injured areas, and provide nutrients and oxygen to nerve cells. Microvascular endothelial cells in the spinal cord are extensively damaged after SCI. Recent research has shown that exosomes isolated from NSCs-conditioned media can effectively ameliorate the vascular damage caused by SCI.[159] Exosomes increase microvascular density, reduce the SCI area, and alleviate motor dysfunction, indicating that exosomes derived from NSCs can be successfully applied as new regulatory factors in the treatment of SCI.[159] Studies have shown that hUC-MSC-derived exosomes carrying miR-126-3p promote angiogenesis.[160] Additionally, hUC-MSC-exos embedded in hydrogels accelerate bone repair by enhancing angiogenesis.[142]

Inhibition of Cell Death

SCI may lead to neuronal apoptosis, resulting in impaired neurological function. Exosomes can inhibit apoptosis, reduce neuronal cell death, and promote the recovery of neurological function by regulating the expression of apoptosis-related proteins and activating related signaling pathways. Research has shown that during SCI treatment, NSC-derived sEVs can upregulate the expression of autophagy-related proteins LC3B and beclin-1, reduce neuronal apoptosis and neuroinflammation, promote autophagosome formation, and promote functional recovery.[161] Studies have shown that hUC-MSC-derived exosomes improve ovarian function during natural aging by inhibiting apoptosis.[162] In a spinal cord injury model, MSC-Exos treatment attenuated cellular apoptosis and inflammation in the injured spinal cord.[155]

Other Possible Mechanisms

MSC-Exos have shown great potential as novel therapeutic agents for the treatment of SCI. They improve functional recovery after SCI through various mechanisms such as anti-apoptosis, anti-inflammation, angiogenesis promotion, and immune response regulation.[153] Research indicates that MSC-Exos mediate intercellular communication and enhance extracellular matrix remodeling and remyelination, all of which are favorable for SCI repair. As information carriers between cells, exosomes can convey signaling molecules and regulate gene expression and receptor cell function. This helps coordinate the collaborative action of different cell types in SCI repair. The factors present in exosomes can promote extracellular matrix remodeling, improve the organizational structure of the SCI site, and provide an appropriate scaffold for nerve repair. Exosomes may also promote axonal elongation and remyelination, thereby restoring nerve conduction.

The mechanisms by which MSC-Exos treat SCI have not yet been fully supported by sufficient experimental evidence. Further research is essential to provide more conclusive evidence regarding the mechanism of action of MSC-Exos in SCI repair. Therefore, further research is crucial to gain a deeper understanding of the specific mechanisms of MSC-Exos in SCI repair and their potential clinical application. At present, research on MSC-Exos is mostly based on experimental animal models, and clinical studies are rare. The main reason for this may be that its therapeutic mechanism for diseases is not fully understood. In addition, the large-scale production of MSC-Exos, different disease injection doses, purity, and clinical applications monitoring are also obstacles to its clinical applications.

Summary

Research on MSC-Exos has garnered widespread attention in recent years. They contain various bioactive substances, including proteins, nucleic acids, and lipids and have potential therapeutic value. Researchers are currently exploring the possibility of using MSC-Exos as drug delivery vectors. Exosomes exhibit good biocompatibility and stability, allowing them to penetrate biological barriers, deliver drugs to target cells or tissues, and improve therapeutic effects. For example, in the CNS, exosomes can cross the BBB or the BSCB to reach a target site, offering new hope for treating CNS diseases with exosome-based drug delivery.

Despite the progress in the study of MSC-Exos, some challenges remain. These include optimization of exosome isolation and purification methods to ensure the production of exosomes with high purity and activity. However, the mechanism of action of exosomes is not yet fully understood and requires further investigation. However, the safety and effectiveness of these clinical applications requires further experimental verification. Future research should focus on increasing the yield and quality of exosomes, exploring their mechanisms of action in detail, combining exosomes with biomaterials, and conducting preclinical and clinical studies to advance the application of MSC-Exos in disease treatment and regenerative medicine.

In summary, exosomes, as nano EVs, have broad prospects for clinical translation, but are still in their early stages. Key issues such as large-scale preparation, unified dosage and purity standards, and regulatory pathways are still blank. Future research needs to break through large-scale cell culture and exosome mass production technologies, establish standardized quality systems, which is expected to promote its transition from basic research to clinical applications.

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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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