Mesenchymal stem cell-derived exosomes: therapeutic opportunities and challenges for spinal cord injury

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Abstract
Spinal cord injury (SCI) often leads to serious motor and sensory dysfunction of the limbs below the injured segment. SCI not only results in physical and psychological harm to patients but can also cause a huge economic burden on their families and society. As there is no effective treatment method, the prevention, treatment, and rehabilitation of patients with SCI have become urgent problems to be solved. In recent years, mesenchymal stem cells (MSCs) have attracted more attention in the treatment of SCI. Although MSC therapy can reduce injured volume and promote axonal regeneration, its application is limited by tumorigenicity, a low survival rate, and immune rejection. Accumulating literature shows that exosomes have great potential in the treatment of SCI. In this review, we summarize the existing MSC-derived exosome studies on SCI and discuss the advantages and challenges of treating SCI based on exosomes derived from MSCs.

Keywords: Spinal cord injury, Mesenchymal stem cells, Exosomes, MicroRNAs

Introduction
SCI is a serious neurological disease because patients often suffer from poor quality of life. In addition to motor and sensory impairment, patients also have bladder dysfunction, an respiratory distress and may die [1]. According to the definition of the International Spinal Cord Society, SCI is divided into traumatic spinal cord injury and non-traumatic spinal cord injury [2]. The economic impact of SCI on patients is enormous [3]. Current treatments for SCI include surgical decompression [4–6], hemodynamic therapy [7–9], corticosteroids [10, 11], and invasive spinal cord pressure monitoring [12–14]. However, these methods do not completely restore the function of the injured spinal cord, and it is urgent to find a new method for treating SCI.

The role of mesenchymal stem cells (MSCs) in SCI has been extensively studied, but many studies have shown that MSCs have many drawbacks, and their therapeutic effects are more likely to be related to paracrine action. Exosomes are important mediators of cell-cell communication and participate in many pathological processes. The therapeutic potential of exosomes in SCI has attracted more and more attention in recent years.

This review mainly introduces the potential mechanisms of exosomes derived from MSCs in SCI. Given the unique role of exosome miRNAs derived from MSCs, we will introduce them separately. We will also discuss the prospects and challenges of MSC-derived exosomes, as MSC-exosomes may become a promising treatment method for SCI in the future.
The pathology of SCI
The pathological process of SCI includes two consecutive processes of primary and secondary injury [15, 16]. Primary injury is defined as the immediate mechanical injury to the spinal cord, which is an irreversible process [17, 18]. Mechanical injury leads to rupture of the axonal membranes and the release of inhibitory decomposition products from the myelin sheath, such as neurite outgrowth inhibitor protein A, myelin-associated glycoprotein, oligodendrocyte myelin glycoprotein, and chondroitin sulfate proteoglycan, which are all powerful axonal regeneration inhibitors [19–25]. Physical force is the main cause of the primary injury, and this force includes forms of compression, contusion, tear, or tension [26, 27]. The secondary injury is delayed and progressive. Inflammatory cells release inflammatory cytokines due to the destruction of the blood spinal cord barrier (BSCB) [28, 29]. Secondary injury includes electrolyte abnormalities and the release of reactive oxygen species (ROS) and excitatory amino acids, which, in turn, lead to ischemia, edema, and cell necrosis, and apoptosis at the injured site [30–39]. Secondary injury is generally more complicated than the primary injury.

Exosomes and MSC-derived exosomes
Exosomes, one of the main subclasses of extracellular vesicles that can be released into the extracellular environment, are secreted by almost all types of cells and exist widely in body fluids [40, 41]. Exosomes have clear biophysical and biochemical parameters, so they are suitable for routine laboratory tests [40, 42, 43]. The diameter of exosomes is generally 30–150 nm, and their density is 113–119 g mL$^{-1}$ [44].

The biogenesis of exosomes can be divided into different stages (Fig. 1), including the formation of early endosomes through invagination of the plasma membrane, the formation of late endosomes through cargo selection, and the formation of multivesicular bodies (MVBs)
from late endosomes. MVBs contain intraluminal vesicles (ILVs). The fusion between MVBs and the plasma membrane results in the release of the MVB contents called exosomes [45–47]. The endosomal sorting complex required for transport (ESCRT) is an important system during exosomal biogenesis [48, 49]. However, the formation of exosomes is not entirely dependent on the ESCRT complex [50].

MSCs secrete more exosomes than other cells [51]. MSC-derived exosomes not only express tetraspanins as common exosomal surface markers (CD81, CD63, and CD9) but also express heat shock proteins (HSP60, HSP70, and HSP90), ALG-2 interacting protein X (Alix), tumor susceptibility gene 101 (Tsg101), and adhesion molecules (CD29, CD44, and CD73) [41, 52] (Fig. 1). MSC-derived exosomes, like general exosomes, carry a complex cargo, including proteins, nucleic acids, and lipids [53, 54] (Fig. 1). In addition to cytoplasmic proteins, there are a considerable number of membrane proteins [44, 55, 56], and proteins found in lipid rafts (Flotillin-1 and Flotillin-2) [57, 58]. Exosomes are also rich in nucleic acids, which play an essential role in changing the fate of recipient cells. Among them, micro-RNAs (miRNAs) have been researched the most [59, 60]. miRNAs encapsulated in MSC-exosomes mainly exist in the form of their precursors [61]. Emerging evidence shows that the efficacy of MSC treatment results mainly from paracrine effects, rather than transdifferentiation and implantation of MSCs. Therefore, MSC-derived exosomes containing various paracrine mediators can be used as a cell-free therapeutic strategy [62]. And we launch the idea that MSC-exosomes have great potential to promote functional recovery and their contents may serve as biomarkers in SCI.

Treat SCI with exosomes derived from MSCs
Exosomes derived from MSCs are easier to obtain and store and are subject to little ethical restriction compared with MSCs [63]. The volume of exosomes is significantly smaller than that of MSCs, so they will not be captured by lung and liver tissues, and they can penetrate the BSCB [64]. Therefore, attention has recently focused on the use of exosomes to treat SCI (Table 1). We have summarized the existing studies on MSC-derived exosomes to treat SCI. The specific mechanisms are as follows (Fig. 2).

Anti-inflammatory effects of exosomes derived from MSCs
The relative levels of pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α, and anti-inflammatory factors are related to the functional recovery of patients with SCI [83, 84]. Thus, the composition of the pro-inflammatory and anti-inflammatory environments is highly correlated with the prognosis after SCI and inhibiting the formation of the pro-inflammatory environment is a major strategy for treating SCI. Romanelli et al. [66] reported that exosomes derived from human umbilical cord mesenchymal stem cells (hUCMSC-exosomes) directly interact with activated microglia in vitro and inhibit the expression of pro-inflammatory cytokines during secondary injury. Intravenous injection of hUCMSC-exosomes into an SCI rat model inhibits the expression of IL-1β and IL-6, but also inhibits the formation of scars, thereby contributing to the recovery of motor function. Neuroinflammation is characterized by the activation of resident immune cells initiated by various external stimuli, and this activation is mediated by an important protein complex-inflammasome called the nucleotide-binding domain-like receptor protein 3 (NLRP3) inflammasome that plays a key role in the secondary injury of SCI [85]. The NLRP3 inflammasome is located in the cytoplasm and is assembled by NLRP3, an apoptosis-associated speck-like protein containing a caspase recruitment domain, and caspase-1. It is involved in the regulation of the natural immune response [86, 87]. Some recent studies have shown that the activity of the NLRP3 inflammasome increases in traumatic brain injury and SCI models [85, 88, 89]. The NLRP3 inflammasome may be triggered and upregulated after SCI [88, 90, 91]. Inhibiting activation of the NLRP3 inflammasome promotes functional recovery after SCI in rats [88, 90–93]. Huang et al. [65] discovered that exosomes derived from epidural fat mesenchymal stem cells (EFMSCs) promote the recovery of neural function and reduce injured volume. The molecular mechanism is that systemic administration of EFMSC-exosomes into an SCI model significantly inhibits the activation of NLRP3 inflammasomes and reduces the expression of inflammatory cytokines. In addition, EFMSC-exosomes reduce the pro-apoptotic protein (Bcl-2-associated X protein, Bax) after SCI, while upregulating the expression of anti-apoptotic protein (B cell lymphoma-2, Bcl-2). Sun et al. [76] obtained similar results. They found that exosomes derived from hUCMSCs reduce the levels of the inflammatory cytokines TNF-α, IL-6, interferon-γ, and granulocyte colony-stimulating factor while increasing the levels of the anti-inflammatory cytokines IL-4 and IL-10.

Promotion of macrophage polarization
The therapeutic effect of MSC-exosomes has also been found to be related to the promotion of macrophage polarization. Macrophages are heterogeneous cells with extensive functional plasticity that have been divided into M1 and M2 types [94, 95]. M1 macrophages produce pro-inflammatory cytokines, ROS, and nitric oxide
| Study                  | Type of MSC     | Animal     | Exosome diameter | Administration | Biological effects                                                                 | Mechanisms of actions                                                                                                                                 |
|-----------------------|-----------------|------------|------------------|----------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| Huang et al. [65]     | Epidural Fat-MSCs | SD rats    | 60–130 nm        | Intravenous injection (IV) | Alleviate cell death, attenuate tissue damage, and improve neurological recovery | Inhibit NLRP3 inflammation                                                                                                                                 |
| Pasquale et al. [66]  | hUCMSCs         | SD rats    | –                | IV             | anti-inflammatory and anti-scarring activity                                          | Decrease the expression of pro-inflammatory cytokines and reduce astrogliosis and scarring.                                                                 |
| Huang et al. [67]     | BMSCs           | SD rats    | 20–130 nm        | IV             | Attenuate cellular apoptosis and inflammation. Promote angiogenesis                   | Attenuate Bax expression and upregulate Bcl-2 expression. U regulate pro-inflammatory cytokines and downregulate anti-inflammatory cytokines.        |
| Lu et al. [68]        | BMSCs           | SD rats    | –                | IV             | Attenuate neuronal cell death and improve motor recovery                               | Increases BSCB pericyte coverage and decreases BSCB permeability. Inhibit pericyte migration via the NF-κB p65 pathway.                          |
| Liu et al. [69]       | BMSCs           | SD rats    | 20–150 nm        | IV             | Attenuate neuronal cell apoptosis and lesion size. Suppressed glial scar formation and inflammation. Promote axonal regeneration. | Mir-29b regulate proteins involved in neuronal regeneration, such as NF200, GAP-43, and GFAP.                                                                |
| Wang et al. [70]      | BMSCs           | SD rats    | 30–150 nm        | IV             | Reduce SCI-induced A1 astrocytes                                                    | Inhibit the nuclear translocation of NF-κB p65.                                                                                                         |
| Yu et al. [71]        | BMSCs           | SD rats    | –                | IV             | Accelerate the motor function and promote neuronal regeneration. Alleviate histopathological damage. | Mir-21-5p downregulate expression of the pro-apoptotic target gene Fasl.                                                                                  |
| Zhou et al. [72]      | BMSCs           | Wistar rats | 40–160 nm        | IV             | Improve functional recovery and attenuate lesion size and apoptosis                  | Insulin resistance decreased mir-21 expression in MSCs. Overexpression of mir-21 in obese rat MSCs restored the protective effects.               |
| Ji et al. [73]        | BMSCs           | SD rats    | 30–100 nm        | IV             | Attenuate the protective effects of obese rat MSC-derived exosomes against SCI       | Mir-21 and mir-19b derived from the exosomes of hMSCs regulated the apoptosis and differentiation of neuron cells by regulating PTEN expression     |
| Xu et al. [74]        | hMSCs PC12 cells | SD rats    | –                | IV             | Suppresses the apoptosis of neuron cells and improve functional recovery             | Mir-21 facilitate post-SCI recovery and suppress neuron cell death                                                                                     |
| Kang et al. [75]      | –               | SD rats    | 40–110 nm        | IV             | Mir-21 facilitate post-SCI recovery and suppress neuron cell death                   | Mir-21 inhibit the expression of PTEN/PDCD4. Mir-21/PTEN/PDCD4 signaling pathways increased cell viability and inhibited cell death in vitro.    |
| Sun et al. [76]       | hUCMSCs         | C57BL/6 mice | 70 nm            | IV             | Promote locomotor functional recovery and reduce inflammation                        | Downregulate the inflammatory cytokines, such as TNF-α, MIP-1α, IL-6 and IFN-γ and trigger the macrophage Polarization from M1 to M2 phenotype. |
| Li et al. [77]        | BMSCs           | SD rats    | –                | IV             | Improved functional recovery, Reduced the lesion volume. Preserved neurons.         | Mir-133b activate ERK1/2, STAT3, and CREB. Inhibit RhoA expression.                                                                                  |
| Li et al. [78]        | BMSCs           | Wistar rats | –                | –              | Improve locomotor functional recovery and inhibit neuronal apoptosis.              | Activate the Wnt/β-catenin signaling pathway.                                                                                                          |
| Zhao et al. [79]      | BMSCs           | Wistar rats | 20–130 nm        | IV             | Improve functional recovery and reduce SCI-induced complement activation.          | Inhibit complement mRNA synthesis and release and inhibit activation of NF-κB signaling by binding to microglia cells.                          |
| Huang et al. [80]     | BMSCs           | SD rats    | 30–120 nm        | IV             | Improved functional recovery and reduced the lesion volume.                        | Promote angiogenesis and neurogenesis.                                                                                                                 |
| Study         | Type of MSC | Animal | Exosome diameter | Administration | Biological effects                                                                 | Mechanisms of actions                                                                 |
|--------------|-------------|--------|------------------|----------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Yuan et al. [81] | BMSCs       | SD rats | 30–150 nm        | IV             | Improved functional recovery and the axonal regeneration. Decreased the injury volume, retained the neuronal cells. | MIR-126 activates ERK1/2, STAT3 and CREB while inhibiting the expression of RhoA. |
| Gu et al. [82]   | BMSCs       | SD rats | 30–150 nm        | IV             | Improve the recovery of motor function. Reduce neuronal apoptosis.                   | The expression of proapoptotic protein caspase-3 is decreased while the antiapoptotic protein Bcl-2 is upregulated. BMSC-exosomes induces activation of autophagy after SCI. |
to promote tissue inflammation and injury. In contrast, M2 macrophages usually produce anti-inflammatory factors that reduce the ability of the injured site to produce pro-inflammatory molecules, thereby resulting in tissue remodeling. Macrophages can switch from one phenotype to another, which is induced by inflammatory factors after injury or infection [96, 97]. M1 macrophages have harmful effects in the injured spinal cord, while M2 macrophages promote axonal regeneration even in the presence of dominant inhibitory substrates [98, 99]. Most macrophages in the injured spinal cord are M1 macrophages, and only a few transient M2 macrophages exist [99]. The dominance of M1 macrophages and the decreased number of M2 macrophages after SCI aggravates the injury [98, 99]. Understanding these macrophage phenotypes and the characteristics of the

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**Fig. 2** The therapeutic effects of exosomes derived from different MSCs in the treatment of SCI. MSCs can be obtained from bone marrow, the umbilical cord, the amniotic membrane, and adipose tissue. Exosomes derived from MSCs have anti-inflammatory and anti-apoptotic effects, as well as inhibit A1 astrocytes, promote axonal regeneration and macrophage polarization, and protect the BSCB from spinal cord injury.
chemical microenvironment after SCI will help to clarify how macrophages participate in the pathogenesis of SCI and to find new treatment strategies. Few reports are available about exosomes secreted by MSCs that promote the polarization of macrophages to treat SCI. One study reported that exosomes derived from hUCMSCs trigger the polarization of macrophages from the M1 phenotype to the M2 phenotype [76]. Lankford et al. [100] also demonstrated that intravenously injected MSC-derived exosomes quickly reach the injured spinal cord, rather than the uninjured spinal cord, and bind specifically to M2 macrophages, demonstrating that M2 macrophages can alleviate SCI.

**Reduction in A1 astrocytes**

Astrocytes are very important in the process of SCI, as they can hinder or promote recovery of the CNS [101–104]. In 2017, Liddelow et al. [105] discovered that two types of reactive astrocytes, called A1 and A2 astrocytes, are induced by neuroinflammation and ischemia, respectively. A2 astrocytes play a protective role by upregulating the expression of certain neurotrophic factors, while A1 astrocytes are rapidly formed after SCI, and have neurotoxic effects on myelin, synapses, and neurons. Therefore, inhibiting A1 astrocytes is a potential treatment for SCI. A study published in 2019 confirmed that bone marrow mesenchymal stem cell (BMSC)-derived exosomes effectively promote functional recovery after SCI. One of the potential mechanisms may be to inhibit the activation of A1 neurotoxic reactive astrocytes [69]. These results suggest that applying exosome-derived MSCs may be a promising strategy for treating SCI.

A1 astrocyte marker (complement C3) will upregulate in a nuclear factor kappa B (NF-κB)-dependent manner [106]. Some studies have shown that NF-κB signaling is widely activated by a variety of pro-inflammatory agents, such as cytokines (TNF-α and IL-1) and ROS [107, 108]. In addition, the secondary inflammation of SCI is regulated by the NF-κB pathway [109], and inhibiting the NF-κB signaling pathway promotes functional recovery after SCI [110]. Wang et al. [111] reported that BMSC-derived exosome treatment effectively reduces SCI-induced A1 astrocytes by inhibiting nuclear translocation of NF-κB p65.

**Protecting the BSCB**

The BSCB is responsible for maintaining the normal function of the nervous system and its unique characteristics and functions are regulated by neurovascular unit cells [112]. The BSCB is formed by the basement membrane, pericytes, capillary endothelial cells, and astrocyte foot processes [113]. Pericytes, as a part of the neurovascular unit, are very important for maintaining the integrity and barrier properties of blood vessels. Jo et al. [114] showed that the ability of pericytes to maintain the stability of microvessels mainly occurs via three possible mechanisms: promoting the expression of endothelial tight junction proteins, regulating vesicle transport and body flow across cells, and moderating the tightness connection arrangement. In neurological diseases, such as stroke and ALS, there is increasing evidence indicating that abnormal migration of pericytes aggravates these diseases [115, 116]. In clinical practice and animal models, the destruction of the BSCB is usually the inevitable result of SCI [112]. After SCI, the blood vessels at the injured site are immediately destroyed, and the BSCB far away from the injured area is permanently destroyed [117]. Therefore, maintaining the integrity of the BSCB after SCI is a potential treatment. Previous studies have shown that intravenous injection of BMSCs promotes the functional recovery of SCI in rats and accelerates the restoration of BSCB integrity [68, 118]. Further research reported that the therapeutic effect of exosomes derived from BMSCs occurs via the NF-κB p65 pathway to inhibit the migration of pericytes, thereby maintaining integrity of the BSCB after SCI, leading to a reduction of neuronal cell apoptosis, axonal regeneration, and motor function [68]. Yuan et al. [119] directly used pericyte-derived exosomes to treat SCI and found that they reduce cell apoptosis, improve microcirculation in the spinal cord after injury, and prevent BSCB injury and edema.

**Exosomal miRNAs derived from MSCs in SCI**

MicroRNA (miRNA) is an endogenous non-coding RNA with a length of 20–24 nucleotides. After mature miRNAs are treated with dicer enzymes, they usually interact with target messenger RNAs (mRNAs) and bind to the 3’ end, leading to translational inhibition and degradation of these target mRNAs [120, 121]. Recently, some miRNAs have been identified as potential new targets for treating SCI, including miRNA-486, miRNA-21, and miRNA-126 [122–124]. Accumulating evidence reveals that exosomes with a bilayer membrane structure can be used as valuable carriers for targeting miRNAs at the SCI site. In addition, exosomes can penetrate the blood-brain barrier or BSCB to enhance the therapeutic effect of miRNAs [125]. MSCs secrete exosomes containing high levels of specific miRNAs by transfecting specific miRNA plasmids in advance [126]. Extensive studies have indicated that exosomes from MSCs carrying miRNAs have efficient repair effects on SCI. Exosomal miRNAs currently studied in SCI mainly include miRNA-21, miRNA-133b, and miRNA-126 (Fig. 3).

**MiRNA-21 of exosomes derived from MSCs in SCI**

MiRNA-21 expression increases in various injured tissues and organs, suggesting that miRNA-21 is closely
related to tissue injury [127–130]. Liu et al. [131] reported that miRNA-21 is unregulated in a rat model and reduces neuronal apoptosis by promoting activation of the PTEN-Akt signaling pathway and regulating the expression of the apoptosis-related proteins Bax, Bcl-2, caspase-9, and caspase-3 [132]. MiRNA-21 is one of the most common miRNAs secreted by exosomes derived from MSCs, and it is also the most studied exosomal miRNA for SCI therapeutic effects. Zhou et al. [72] determined that exosomes derived from miRNA-21-modified BMSCs significantly promote functional recovery and reduce lesion volume and apoptosis, which was mainly achieved by downregulating the expression of the pro-apoptotic gene FasL. The results of miRNA target analysis tools show that miRNA-21 contains a binding site complementary to the 3′ untranslated region of the FasL gene, indicating that the FasL gene is the direct target gene of miRNA-21. Xu et al. [74] reported that miRNA-21 of MSC-exosomes regulates apoptosis and differentiation of neurons in patients with SCI by downregulating the expression of PTEN, and that PTEN is a target gene of miRNA-21. Further research reported that miRNA-21 of exosomes derived from MSCs not only targets PTEN but also targets the tumor suppressor gene programmed cell death 4 (PDCD4). The miRNA-21/PTE/PDCD4 signaling pathway improves cell viability and inhibits cell apoptosis [75]. Ji et al. [73] showed that the weakened protective effect of exosomes derived from MSCs on SCI in obese rats was due to insulin resistance in the rats. Insulin resistance of MSCs reduces the level of miRNA-21 secreted by exosomes, which further strengthens the view that miRNA-21 is a potential molecule for treating SCI.

**MiRNA-133b of exosomes derived from MSCs in SCI**

MiRNA-133b plays an important role in neuronal differentiation, growth, and apoptosis [133–135]. Some studies have shown that overexpression of miRNA-133b promotes functional recovery after stroke in rats [136, 137]. In addition, studies on zebrafish and rodents have indicated that miRNA-133b is expressed in midbrain dopaminergic neurons where it regulates the production of tyrosine hydroxylase and dopamine transporters in patients with Parkinson’s disease [138]. In a study on the relationship between miRNA-133b and functional recovery after SCI in adult zebrafish, Yu et al. [139] showed that decreased expression of miRNA-133b is not conducive to the recovery of motor function and reduces neuronal axonal regeneration after using morpholino antisense oligonucleotides, which inhibit the expression of miRNA-133b.

Some molecules mediate the protective effect of miRNA-33b on SCI, such as signal transducer and activator of transcription 3 (STAT3), RhoA, and cAMP-response element-binding protein (CREB). STAT3 is distributed in astrocytes and neurons and is responsible for neuronal proliferation and differentiation as well as axonal regeneration [140, 141]. Activated STAT3 mediates inflammation caused by SCI [142]. RhoA is a member of the Rho family that is upregulated after SCI in rats and acts on Rho-associated kinase [143], which is its direct downstream effector. RhoA is related to the death of neurons [144]. The transcription factor CREB also plays an important role in axonal regeneration [145]. Activation of CREB is sufficient to overcome myelin inhibitors and promote axonal regeneration in vivo [146]. Qi et al. [147] demonstrated that miRNA-133b in exosomes significantly increases the STAT3 phosphorylation level, which is involved in axonal regeneration in the injured spinal cord of SCI rats. There is evidence that RhoA is a direct target of miRNA-133b [134]. In addition, miRNA-133b in exosomes released by MSCs promotes axonal growth [148]. Li et al. [77] further demonstrated this result and showed that systemic injection of miRNA-133b exosomes protects neurons and promotes the recovery of motor function after SCI, and this effect was at least
addition, overexpression of miRNA-544 in BMSC-ates the recovery of neuronal function after SCI. In these exosomes were intravenously injected into a SCI obtain exosomes that highly expressed miRNA-544 and [151] transfected rat BMSCs with miRNA-544 mimic to that has neuroprotective effects is miRNA-544. Li et al. expression of miRNA-25, thus indicating that miRNA- transfection of BMSCs to secrete exosomes with high mic spinal cord. This effect may be due to pre- from BMSCs have neuroprotective effects in the ische- recovery and reduce pathological damage of spinal cord showed that these exosomes accelerate motor functional after SCI, while increasing the level of miRNA-126 redu-uces inflammation and promotes angiogenesis and functional recovery. This process may be related to the downregulation of sprouty-related EVH1 domain-containing protein 1, phosphoinositol-3 kinase regulatory subunit 2, and vascular cell adhesion molecule 1 target gene expression. Some scholars have turned their attention to using exosomes derived from miRNA-126-modified MSCs to treat SCI. Huang et al. [80] demon-strated that exosomes containing miRNA-126 promotes angiogenesis and neurogenesis after SCI, as well as attenuates cell apoptosis, thereby promoting functional re-covery of an SCI rat model. Yuan et al. [81] indicated that systemic administration of exosomes derived from miRNA-126-modified MSCs promotes functional recovery and axonal regeneration. Similar to miRNA-21, it is likely that miRNA-126 activates ERK1/2, STAT3, and CREB while inhibiting the expression of RhoA.

Challenges and prospects
The main obstacles to the repair of an injured spinal cord include the weakened ability of axonal growth, insuffi-cient repair of endogenous cells, and the presence of inhibitory molecules at the injured site [153–156]. Over-coming these obstacles would lead to an ideal method for treating SCI. MSC transplantation seems to be an attrac-tive option. However, the direct transplantation of MSCs has potential risks. For example, one study re-port ed that BMSCs that have not been genetically modi-fied could have chromosomal abnormalities even during early passages, leading to the formation of malignant tu-mors [157]. Moreover, MSCs cannot differentiate into neurons. Immunochemistry, molecular marker, and cell morphology studies indicate that although MSCs have neuron-like characteristics after transplantation, it is difficult to regard them as real neurons [158, 159]. The expression of neuronal antigens may simply be due to the immature nature of the MSCs [160]. During in vitro culture, MSCs gradually lose their potential to proliferate and differentiate [161, 162]. According to current evi-dence, the curative effect of MSCs seems to be related to their paracrine activity but has little to do with the mechanism of cell replacement [163]. Moreover, the dis-advantages of MSCs, such as tumorigenesis, low survival rate, and immune rejection, make it difficult to continue the treatment of SCI using MSCs [164].

Similar to MSCs, MSC-exosomes have the same char-acteristics of homing to the injured tissue, and have the advantage of nanometer size, allowing them to pass through the BSCB and play an important role in the re-pair of the nervous system. More importantly, based on their relatively small molecular structure, natural mol-ecular transport characteristics, and good biocompati-bility, exosomes have shown great application potential as drug carriers in recent years. Traditional drugs often have a number of defects, such as poor water solubility, quick removal by the body, poor biocompatibility, unsat-isfactory distribution in vivo, and low permeability to cells, which limit their efficacy and clinical application. However, exosomes combine the advantages of cell and nanotechnology in drug delivery. For example, exosomes improve the stability of drugs; exosomes have a natural targeting ability based on donor cells when delivering drugs, and exosomes are nano-molecules with cell sur-face substances, so they have strong biological barrier
permeability and can selectively penetrate a tissue injury. Therefore, we speculate that exosomes will be a promising drug-delivery system to treat SCI. Another advantage of exosomes derived from MSCs is that they are not tumorigenic. No study has reported on the tumorigenesis potential of MSC-exosomes [165]. Although there is a lack of a direct comparison of the characteristics of exosomes derived from different MSCs in SCI models, we believe that umbilical cord mesenchymal stem cells (UCMSCs) may be one of the best sources because they are easier to obtain than BMSCs, and do not involve ethical issues.

Although exosomes have great potential to treat SCI, there are still a number of challenges that need to be addressed before exosome therapy for SCI can be used in clinical trials. First, the source of the exosomes must be determined, and the content and function of exosomes obtained under different culture conditions (such as hypoxia and growth factors) are also not consistent [166]. In addition, MSC-exosome separation methods must be standardized. There is no consensus on the method to separate exosomes, and different methods of separating exosomes have advantages and disadvantages. In fact, there are significant differences in protein and RNA contents among different separating methods [167]. The most commonly used method is ultracentrifugation, but the purity of exosomes obtained by this method is low, and the exosomes can be contaminated by other EVs with similar diameters [168], so it is necessary to explore a more efficient method. Another problem that needs to be solved is the storage, preservation, and transportation of exosomes. Although exosomes are more stable and suitable for long-term preservation than MSCs, a study published in 2018 showed that it is possible to purify exosomes by lyophilization [169]. This would help produce ready-to-use batches of exosomes, which could be easily transported; however, further research is needed to demonstrate whether lyophilization will change the characteristics of exosomes. Before exosomes can be used in clinical trials it will also be necessary to verify the half-life of freshly isolated and cryopreserved exosomes after injection. The contents of exosomes also need to be further studied to understand which components can be used to treat SCI and which may be harmful. Further research is needed to probe the relationship between injection frequency, dosage, and the therapeutic effect of MSC-exosomes to maintain the long-term effect, and whether single or multiple administrations will have a negative effect, which is very important for the correct use of exosomes to treat SCI. Research on the treatment of SCI with exosomes derived from MSCs is in the exploratory stage; the number of studies is small and most of them are based on rodents, particularly Sprague-Dawley rats. However, there are anatomical differences between human and rodent spinal cords. The SCI area of the rodent model is small, while the SCI area of humans is often larger, which leads to more tissue loss. Additionally, the human nervous system is more complex and more advanced than that of rodents. The process of human SCI is characterized by an immune response, a vascular response, an inflammatory reaction, and glial scar formation, which is also significantly different from SCI in rodents. Thus, the scope of research needs to be expanded further using larger animals (such as dogs) for research. In addition, although exosomes have a demonstrated therapeutic effect on SCI, the specific therapeutic mechanism and target are not exactly clear, and most studies have focused on the role of miRNAs; there is less research on the role of other components of exosomes, so further research is needed to clarify the therapeutic effects of exosomes. Furthermore, although MSC-exosomes are superior to MSCs in the treatment of SCI, the production technology for MSC-exosomes needs to be improved before it can be used in clinical practice. Studies have shown that MSCs secrete only a small number of exosomes (1–4 μg of exosome protein can be extracted from 10⁶ cells/day) [170]. Therefore, long-term cell culture and a large number of MSCs are needed to produce sufficient numbers of exosomes for clinical applications. However, the expression of growth factors decreases significantly in late-passage MSCs, which would reduce the therapeutic effect of growth factors and its mRNAs secreted by exosomes [171]. As mentioned earlier, the obstacles to SCI recovery include the weakened ability of axonal growth and insufficient endogenous cell repair but, unfortunately, current research on MSC-derived exosomes does not aid recovery through these mechanisms. In addition, there is a lack of research for horizontal comparison of exosomes from different MSCs in SCI, and the differences in the therapeutic efficacy of exosomes from different MSCs remain unclear.

Conclusions
In conclusion, the treatment of SCI is a great challenge, and there is no effective strategy to restore lost function. The pathological process of SCI is very complex and is the result of multiple factors, which hinders the development of treatments leading to a full recovery. Therefore, understanding the pathological mechanism is conducive to better treatments for SCI. Because of the poor plasticity and weak regenerating ability of the CNS, the recovery of neural function is greatly limited. As an intercellular
communication medium, exosomes are superior for treating SCI, particularly exosomes derived from MSCs. Exosomes derived from MSCs can pass through the BSCB and can be used as good drug carriers, which has great therapeutic potential in SCI. We must optimize MSC-derived exosomes to improve their therapeutic effect in SCI. More research is required to clarify the specific role of exosomes in SCI. If these problems can be solved, it will provide a comprehensive theoretical basis for the clinical transformation of MSC-derived exosomes in the treatment of SCI, and bring hope for clinical treatment of SCI.

Abbreviations
Alix: ALG-2 interacting protein X; Bax: Bcl-2-associated X protein; BBB: Blood-brain barrier; Bcl-2: B cell lymphoma-2; BMSCs: bone marrow mesenchymal stem cells; BSCB: Blood spinal cord barrier; CM: Conditioned medium; CNS: Central nervous system; CREB: cAMP-response element-binding protein; EFMSCs: Epidural fat mesenchymal stem cells; ESCRT: Endosomal sorting complex required for transport; GAP-43: Growth-associated protein 43; GFAP: Glial fibrillary acidic protein; hUCMSCs: Human umbilical cord mesenchymal; IV: Intravenous injection; hMSCs: Human mesenchymal stem cells; HSP: Heat shock proteins; IFN-y: Interferon-y; ILVs: Intraluminal vesicles; miRNAs: MicroRNAs; MSCs: Mesenchymal stem cells; MVs: Microvesicles; MVs: Multivesicular bodies; NF: Nuclearfactor; NF-kb: Nuclear factor kappa B; NLBP3: Nucleotide-binding domain-like receptor protein 3; PO: Parkinson’s disease; PDCD4: Programmed cell death 4; PTEN: Phosphate and tension homology deleted on chromosome ten; ROS: Reactive oxygen species; SCI: Spinal cord injury; STAT3: Signal transducer and activator of transcription 3; TLR4: Toll-like receptor 4; TNF-α: Tumor necrosis factor-α; Tsg101: Tumor susceptibility gene 101; UCMSCs: Umbilical cord mesenchymal stem cells

Acknowledgements
Not applicable.

Authors’ contributions
Zhan-jun Ma and Xue-wen Kang designed the study. Wen-zhao Liu and Jie-ru Li collected the literature. Wen-zhao Liu wrote the manuscript. Xue-wen Kang revised the manuscript for important intellectual content. All authors gave final approval.

Funding
This work was financially supported by the Chinese Medicine Administration Research Project of Gansu province (GZK-2019-46) and Cuying Technology Innovation Project of Lanzhou University Second and Cuying Scientific Training Program for Undergraduates of Lanzhou University Second Hospital (CYYZ2020-03). Hospital (CYY2019-MS10).

Availability of data and materials
Not applicable.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Received: 13 October 2020 Accepted: 7 January 2021

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