

Review

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Review

Stem Cell-Derived Extracellular Vesicle-Mediated Therapeutic Signaling in Spinal Cord Injury

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Abstract: Mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) have emerged as a promising therapeutic strategy for spinal cord injury (SCI). These nanosized vesicles possess unique properties such as low immunogenicity and the ability to cross biological barriers, making them ideal carriers for delivering bioactive molecules to injured tissues. MSC-EVs have been demonstrated to exert multiple beneficial effects in SCI, including reducing inflammation, promoting neuroprotection, and enhancing axonal regeneration. Recent studies have delved into the molecular mechanisms underlying MSC-EV-mediated therapeutic effects. Exosomal microRNAs (miRNAs) have been identified as key regulators of various cellular processes involved in SCI pathogenesis and repair. These miRNAs can influence inflammation, oxidative stress, and apoptosis by modulating gene expression. This review summarizes the current state of MSC-EV-based therapies for SCI, highlighting the underlying mechanisms and potential clinical applications. We discuss the challenges and limitations of translating these therapies into clinical practice, such as inconsistent EV production, complex cargo composition, and the need for targeted delivery strategies. Future research should focus on optimizing EV production and characterization, identifying key therapeutic miRNAs, and developing innovative delivery systems to maximize the therapeutic potential of MSC-EVs in SCI.

Keywords: Spinal cord injury; mesenchymal stem cell; extracellular vesicle; miRNA; signaling pathway; therapeutic effects; bio-scaffold

1. Introduction

Spinal cord injury (SCI) is a devastating condition with limited therapeutic options, often leading to long-term disability and impaired quality of life [1]. Repairing SCI involves addressing complex pathophysiological mechanisms and complications related to nerve regeneration within the nervous system [2]. The etiology of SCI encompasses primary and secondary injuries [3], initially manifesting as mechanical damage to the spinal cord, followed by the influx of cells and their biological reactions to the primary injury [4]. This process engages various systems, including the nervous, immune, and vascular systems, resulting in inflammatory responses, scar formation, neural cell death,

demyelination, ischemia, oxidative stress, hemorrhage, etc. Repairing the damaged spinal cord is significantly challenging, with several approaches available for promoting neuroprotection, angiogenesis, immunomodulation, and axonal regeneration [5,6].

The therapeutic benefits of MSCs in treating SCI are attributed to their paracrine mechanism supported by both *in vivo* and *in vitro* studies in rat SCI [7]. In Figure 1, MSC-secreted nano-sized EXs can potentially decrease inflammation and cell death, promote angiogenesis, and facilitate functional behavioral recovery in rat SCI [8–10]. Also, the immune system does not perceive EXs as foreign bodies, making them more suitable for clinical application [11]. In addition, EVs hold promise for repairing injured spinal cord tissues through several mechanisms: angiogenesis [12] and axon formation [13], regulating inflammation and the immune response [14], inhibiting apoptosis [15], and maintaining the BSCB’s integrity [16]. MSC-EXs may thus be a promising cell-free therapeutic approach for SCI treatment, mainly because of their paracrine effects as evidenced by studies in rat SCI [7] and *in vitro* cell culture experiments [8]. The limitations of existing therapeutic options for SCI highlight the necessity for innovative treatment strategies. This review article examines the preparation, functions, mechanisms, and challenges associated with different EVs in SCI treatment.

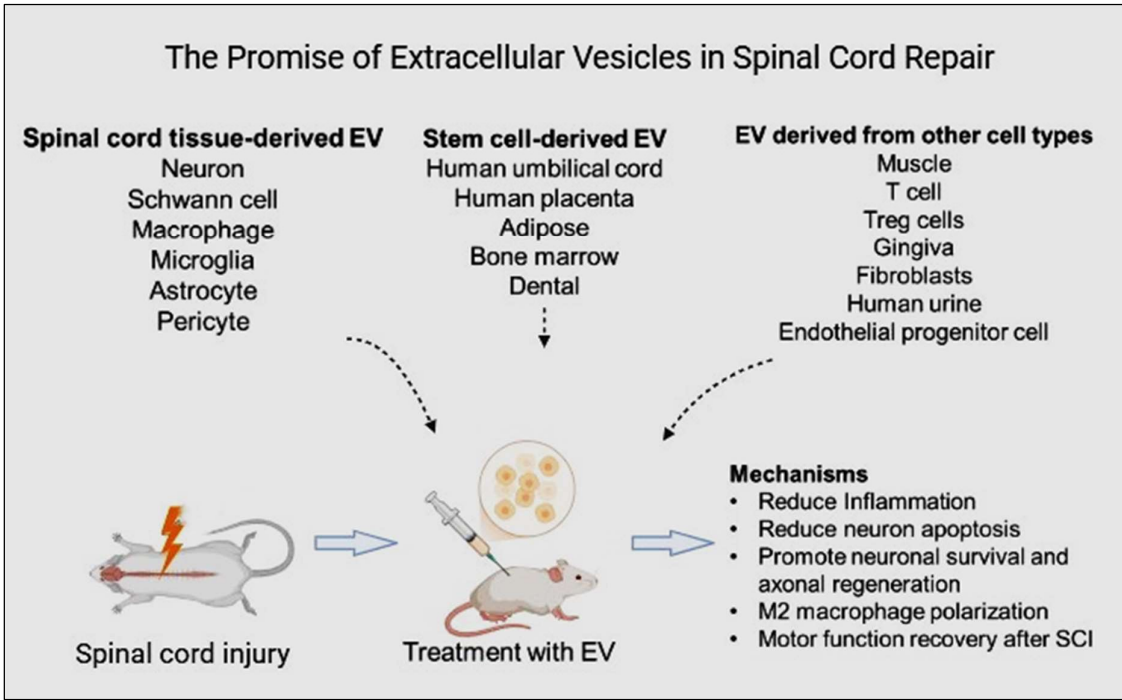


Figure 1. Illustration of extracellular vesicle-mediated therapeutic mechanisms for spinal cord injury repair. Various types of extracellular vesicles, including mesenchymal stem cell-derived exosomes, neuronal microvesicles, and macrophage-derived exosomes, hold promise for spinal cord repair. These vesicles can exert therapeutic effects by reducing inflammation, promoting axonal regeneration, and enhancing neurogenesis (Created with BioRender.com).

2. Extracellular Vesicles: Potential Mediators in Spinal Cord Injury

Extracellular vesicles (EVs) are emerging as a promising therapeutic strategy in regenerative medicine, including SCI [17,18]. These nanosized, membrane-bound particles, ranging from 40 to 1000 nanometers in diameter, are released by various cell types and carry diverse bioactive molecules [19]. Exosomes, a specific subtype of EVs originating from the endocytic pathway, are particularly enriched in proteins, lipids, and nucleic acids. These molecules can influence cellular behavior, promote tissue repair, and modulate immune responses. Given their potential to target injured tissues and deliver therapeutic payloads, EVs offer a promising avenue for developing innovative

treatments for SCI. While EVs have gained significant attention in scientific research, a comprehensive bibliometric analysis of their role in SCI is lacking. To address this gap, this study aims to systematically analyze the therapeutic effects of mechanisms related to EVs and SCI.

Exosomes (EXs), typically 30–150 nm in diameter, are continuously released into the extracellular environment and contain diverse biomolecules, including lipids, proteins, and nucleic acid [20]. These are crucial for intercellular communication because they carry a diverse array of active components, including proteins (e.g., TSG101, AIP1/ALIX, 1-integrin, CD81, CD63, ICAM-1, and MFG-E8), lipids (e.g., cholesterol, phosphatidylserine, phosphatidylinositol, sphingomyelin, and phosphatidylcholine), and nucleic acids (e.g., mRNA, miRNA, noncoding RNAs, and DNA) [21,22]. EXs are signaling elements released naturally from a mesenchymal stem cell (MSC), facilitating cell-to-cell communication by transporting genetic materials and proteins to the recipient cells, thereby initiating beneficial processes [23]. Notably, neurons, glial, and immune cells can also produce EXs to regulate biological processes following nerve injury [24]. Table 1 & 2 demonstrates the effects of stem cell-derived EVs in SCI.

3. Extraction and Identification of Extracellular Vesicles

The isolation of EV from biological sources like body fluids and cell cultures can vary depending on the exosome origin and size. Five primary isolation methods have been documented: ultracentrifugation, size-based separation, *in situ* polymer precipitation, immunoaffinity capture, and microfluidic approaches [25]. Ultracentrifugation currently dominates as the most frequent method in Figure 2 [26]. While various extraction techniques exist, they often have limitations like low yield and insufficient purity. Furthermore, characterizing EV involves a multi-faceted approach [27]. Techniques to identify and analyze exosomes encompass morphological assessments (transmission electron microscopy, scanning electron microscopy, cryo-electron microscopy, atomic force microscopy), particle size determination (nanoparticle tracking analysis, dynamic light scattering), surface marker analysis (trypsin digestion, mass spectrometry, enzyme-linked immunosorbent assay (ELISA)), and protein expression profiling (Western blot analysis, flow cytometry) [26]. This necessitates further research into optimized extraction methods to enable large-scale exosome production for clinical applications.

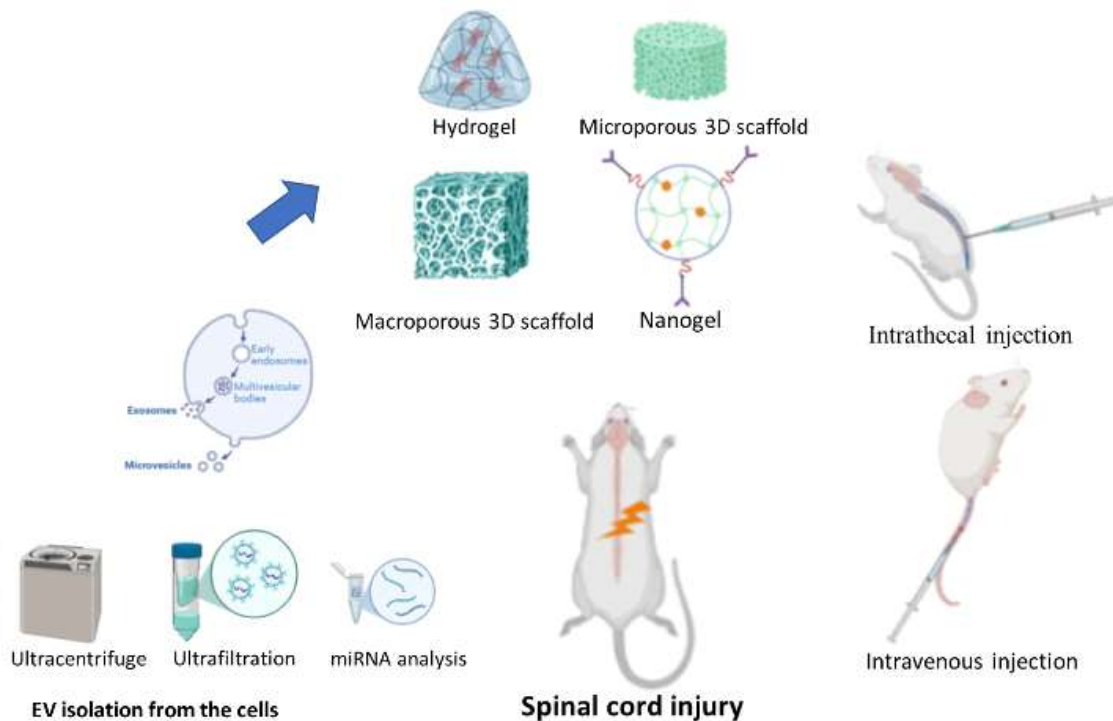


Figure 2. An overview of extracellular vesicle (EV) isolation, their miRNA analysis, and application of various bio-scaffolds and injections (created with BioRender.com).

4. Routes of Administration and Biomaterial Approaches for Extracellular Vesicle Delivery in Spinal Cord Injury

Administration routes for exosomes in rodent SCI models include intrathecal injection for direct delivery to the injury site, maximizing local effects and minimizing systemic side effects. Intravenous injections allow for systemic distribution, while epidural injection targets the spinal cord with fewer complications [28]. Compared to other routes like intrathecal injection, tail vein injection is generally less technically demanding and less likely to cause complications [29]. Tissue engineering has introduced biomaterial scaffolds (Figure 2) to deliver EXs. These scaffolds provide a supportive environment for EXs and stimulate neuronal axon growth [30]. At the SCI site, regenerative biomaterials can fill the cavities, deliver healing drugs, and provide adsorption sites for host cells [31]. Currently, the three main biomaterial scaffold types used for SCI are 3D-printed scaffolds, nanomaterial-based scaffolds, and biodegradable polymer scaffolds [31]. Moreover, the biodegradable polymer scaffolds, composed of agarose, chitosan, collagen, and fibronectin, have been tested in animal models [32,33]. The collagen scaffold-encapsulated HucMSC-EXs can be designed using dual bio-specific peptides to help neural stem cell migration and paclitaxel delivery in SCI rats, by promoting nerve regeneration, reducing scar deposition, and facilitating functional recovery [34]. In a rat model, EXs embedded with an alginate scaffold have anti-inflammatory, antinociceptive, and pro-neurotrophic properties in spinal nerve ligation injury-induced pain [35]. Overall, various administration routes for exosomes in SCI have been explored, including intrathecal, intravenous, and epidural injections. Recent advancements in tissue engineering have introduced novel approaches, such as incorporating exosomes within biomaterial scaffolds. These scaffolds, often composed of biodegradable polymers, provide a controlled release mechanism for exosomes, enhancing their therapeutic efficacy and promoting tissue regeneration.

5. Extracellular Vesicle miRNAs in Spinal Cord Injury Repair

MiRNAs regulate gene expression and play a unique role in nerve injury and regeneration [36]. Furthermore, exosomal miRNAs and neurotransmitter receptors can regulate synaptic transmission, neuronal excitability, and plasticity in the injured spinal cord, thereby preserving neuronal function and promoting functional recovery [37,38]. Moreover, stem cell EXs can stimulate endogenous neurogenesis [12] and oligodendrogenesis in the injured spinal cord by delivering trophic factors, extracellular matrix proteins, and developmental signaling molecules [39]. Additionally, miRNAs play a significant role in decreasing nerve apoptosis mediated *via* EXs. The distribution of miRNAs in SCI represents a promising therapeutic approach and can serve as potential biomarkers for nerve injuries [36]. Studies have shown that specific miRNAs, such as miR-16-5p [40], miR-125b-5p [41,42], miR-21-5p [43], etc., are involved in regulating processes relevant to rat SCI. A previous review has revealed miRNA transport via EXs in various cells and their significant protective effects in SCI [44]. Table 3 shows the therapeutic effects of EVs miRNAs in SCI. Therefore, Exosomal miRNAs exert a significant influence on neuronal function, regeneration, and survival following SCI. Understanding the complex interplay between miRNAs and exosomes provides crucial insights for developing novel therapeutic strategies to improve functional outcomes in patients with SCI.

6. Unlocking Therapeutic Potential: Mesenchymal Stem Cell-Derived Extracellular Vesicles in Spinal Cord Injury Recovery via Potential Signaling Pathways

6.1. Human Umbilical Cord Mesenchymal Stem Cell-Derived Extracellular Vesicles

Human umbilical cord mesenchymal stem cell-derived exosomes (HucMSC-EXs), the primary cell population neighboring the umbilical vessels, modulate antigen-presenting cells and T-cell apoptosis [45,46]. HucMSC-EXs mitigate apoptosis at the SCI site, downregulate inflammatory factors, and promote angiogenesis and axonal growth by activating the Wnt/ β -catenin signaling pathway, while simultaneously inhibiting microglia and astrocyte activation [46]. Moreover, HucMSC-EXs can induce the polarization of M1 macrophages toward the M2 phenotype [47]. HucMSC-EXs on neuropathic pain, achieved by inhibiting the TLR2/MyD88/NF- κ B signaling pathway in spinal microglia in a rat chronic constriction injury [48]. This effect involves the EX-mediated interference with Rsad2 expression, inhibiting microglial activation [48]. Additionally, the protective effects of HucMSC-EXs in rat SCI are mediated by the BCL2/Bax and Wnt/ β -catenin signaling pathways [45]. Furthermore, EXs transfer miR-199a-3p/145-5p into neurons in SCI rats, affecting tropomyosin receptor kinase A (TrkA) ubiquitination and promoting the nerve growth factor (NGF)/TrkA signaling pathway [46].

HucMSC-EVs reduce pathological changes, enhance motor function, and promote nerve repair in SCI rats through the miR-29b-3p/Phosphatase and TENsin homolog deleted on chromosome 10 (PTEN)/Protein kinase B (PKB), also known as Akt/mammalian target of rapamycin (mTOR) pathway in rat SCI [49]. Additionally, miR-146a-5p within HucMSC-EXs can ameliorate the neuroinflammatory response mediated by microglia by suppressing the Interleukin-1 receptor-associated kinases 1 (IRAK1)/TNF receptor-associated factor (TRAF6) pathway in murine model [50]. Moreover, HucMSC-EXs effectively improves lipopolysaccharide/hydrogen peroxide-induced oxidative stress and neuroinflammation by inhibiting the microglial NRF2/NF- κ B/NLRP3 signaling pathway in the LPS-treated mouse model [51]. Our recent article has published that HucMSCs-EXs-encapsulated Gelfoam shows promise in improving motor dysfunction and neuropathic pain induced by SCI, possibly by promoting nerve regeneration, remyelination, anti-inflammatory processes, and anti-apoptotic mechanisms [1]. Therefore, HucMSCs-EXs are a powerful solution for repairing spinal cord injuries, making them a top choice for recovery.

6.2. Human Placental Mesenchymal Stem Cell-Derived Extracellular Vesicles

The therapeutic potential of Human placental mesenchymal stem cell-derived exosomes (hPMSC-EXs) in rat SCI has been demonstrated through their activation of endogenous neural pluripotent cells (NPCs) and facilitation of neurogenesis, leading to motor and autonomic function restoration [52]. This vital process may involve the activation of the mitogen-activated protein kinase (MEK)/extracellular signal-regulated kinase (ERK)/cAMP-response element binding protein (CREB) signaling pathway, which has been implicated in alleviating rat nerve injury-induced neuropathic pain [52]. Furthermore, the synergistic effects of combining hPMSC-EXs treatment with hyperbaric oxygen enhance neuroprotective effects in SCI rats [53]. Moreover, intrathecal injection of hPMSC-EXs restores function, neuronal regenerative capacity, and anti-apoptotic potential during the acute phase of SCI [53]. Additionally, miR-26a-5p within hPMSC-EVs can regulate the Wnt5a/Receptor-like Tyrosine Kinase (Ryk)/calmodulin-dependent kinase II (CaMKII)/nuclear factor of activated T cells (NFAT) pathways, offering moderate anti-neuroinflammatory and neuropathic pain relief effects through the Wnt signaling pathway in a spared nerve injury mouse model [54]. These findings provide strong evidence for the therapeutic potential of hPMSC-EXs in SCI. Their ability to promote neurogenesis, enhance neuroprotection, and alleviate neuropathic pain suggests that hPMSC-EXs may offer a novel and promising approach to treating SCI. Further research is warranted to translate these preclinical findings into effective clinical therapies.

6.3. Adipose Mesenchymal Stem Cell-Derived Extracellular Vesicles

Adipose-derived mesenchymal stem cells (ASCs) are a promising source of regenerative medicine due to their ease of isolation, high proliferation capacity, and immunomodulatory properties [55]. ASC-derived EXs are nano-sized extracellular vesicles containing all neurotrophins, immunoregulatory, and angio-modulatory factors [55]. *In vitro* studies link ASC-EXs to a neuroprotective environment in neuronal differentiation and neuroregeneration. They stimulate PC12 cell migration/proliferation and inhibit apoptosis *via* PI3K/AKT pathway activation [56]. This effect could help to treat nerve injuries, as ADSC-EXs have been shown to promote significant repair of rat cavernous nerve injuries [57]. Hypoxia-conditioned ADSC-EXs significantly reduce neuronal apoptosis after the reperfusion (OGD/R) model *in vitro* [58]. Furthermore, it can reduce the formation of cavities in injured areas, leading to improved functional recovery of hind limbs in post-injury rats. The exosomal miR-499a-5p controls the JNK3/c-jun-apoptotic signaling pathway by affecting JNK3 and decreasing nerve apoptosis after rat SCI [58]. Furthermore, they promote functional recovery by reducing cavity formation in injured areas of rat SCI models. This neuroprotective effect is mediated by ADSC-EXs miR-499a-5p, which targets the JNK3/c-jun apoptotic signaling pathway, decreasing JNK3 expression and ultimately reducing nerve cell death after rat SCI [58].

The ADMSC-EXs prevent inflammation in M1 microglia and spinal cord tissues, promote M2 microglia expression, and stimulate the Nrf2/HO-1 pathway in rats with SCI [59]. ADMSC-EX can improve motor function recovery by activating the Nrf2/HO-1 pathway and microglial polarization [59]. In Figure 3, ADSC-EXs also prevent ferroptosis and promote recovery of vascular and neural functions after rat SCI *via* the NRF2/SLC7A11/GPX4 pathway [60]. These findings highlight the multifaceted therapeutic potential of ASC-EVs in SCI. Their ability to modulate multiple cellular processes, including neuroprotection, inflammation, and oxidative stress, suggests that ASC-EVs may offer a promising approach to repairing SCI. Additional research is needed to transform these preclinical findings into effective clinical treatments.

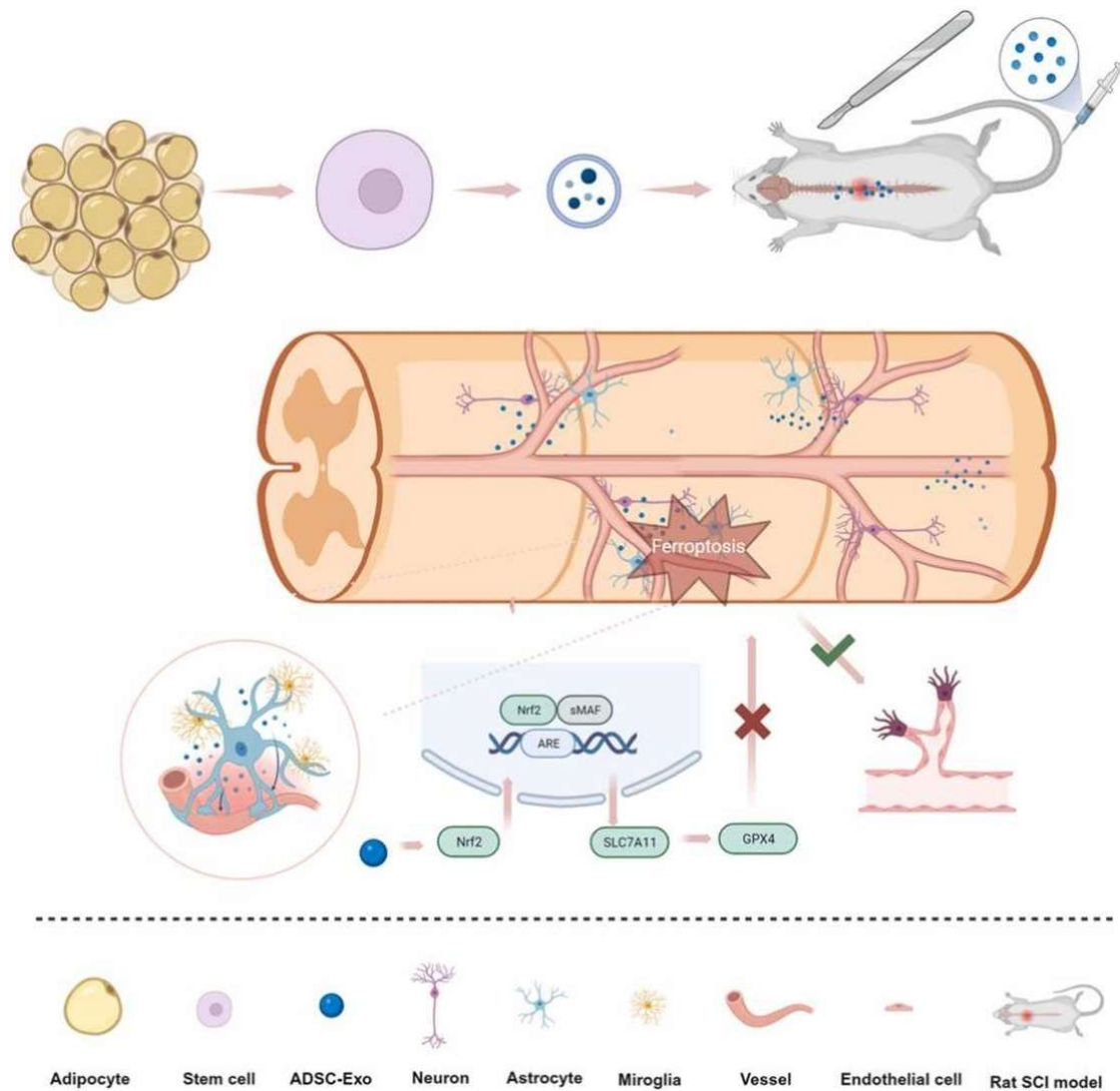


Figure 3. ADSC-EXs may inhibit ferroptosis and promote vascular and neural function recovery after SCI *via* the NRF2/SLC7A11/GPX4 pathway. Reprinted with permission from S. Wu, Z. Chen, Y. Wu, Q. Shi, E. Yang, B. Zhang, Y. Qian, X. Lian, J. Xu. Copyright 2024 Elsevier [60].

6.4. Bone Marrow Mesenchymal Stem Cell-Derived Extracellular Vesicles

The bone marrow mesenchymal stem cell-derived exosomes (BMSC-EXs) have emerged as promising therapeutics for SCI due to their multifaceted effects on various cellular pathways [61]. When administered intravenously, exosomes can influence the function of macrophages in the injured spinal cord tissue by targeting M2-type macrophages [62]. In rat models of traumatic brain injury, BMSC-EXs have demonstrated neuroprotective effects by reducing lesion size, improving neurobehavioral outcomes, and modulating inflammation and cell death processes [63]. BMSC-EXs administration enhances macrophage phagocytosis by targeting myelin debris, facilitating functional recovery post-SCI [61,64]. Moreover, they modulate A1 astrocyte activation via the nuclear factor-kappaB (NF- κ B) pathway, contributing to a conducive environment for recovery in the rat SCI model [65]. The Wnt/ β -catenin signaling pathway, known for its involvement in cell proliferation, neurodevelopment, and tissue repair, has also been implicated in SCI recovery, as it has shown great potential in promoting tissue repair and inhibiting neuronal apoptosis in rat SCI [66]. Additionally, the BCL2/Bax and Wnt/ β -catenin signaling pathways play crucial roles in the pathophysiology of rat SCI, further highlighting the complexity of the molecular mechanisms involved [45].

Delivery of miRNA-133b-modified BMSC-EXs has shown promise in reducing injury volume, promoting axonal regeneration, and activating key signaling molecules, including ERK1/2, STAT3, and CREB, thereby aiding in functional recovery after traumatic SCI in rat models [67]. The encapsulation of BMSC-EXs within electro-conductive hydrogels enhances their therapeutic efficacy by modulating the M2 microglial polarization *via* the NF- κ B pathway using neural stem cell and dorsal root ganglion *in vitro* cell culture [68]. This modification promotes neuron and oligodendrocyte differentiation while inhibiting astrocyte differentiation, ultimately leading to increased axon outgrowth through the PTEN/PI3K/AKT/mTOR pathway in the SCI mouse model [68]. Furthermore, BMSC-EXs significantly reduce the CD68+ microglia numbers, promote neuron-axon regeneration, and improve locomotor recovery in the early stages of the mice SCI model [68].

The administration of BMSC-EVs enriched with miR-23b modulates the TLR4/NF- κ B signaling pathway, reducing inflammatory processes and subsequently ameliorating SCI rats [69]. Additionally, BMSC-EXs promote miR-145-5p expression and inhibit TLR4/NF- κ B pathway activation in both SCI rats and PC12 cells, suggesting their potential to prevent inflammation and related pathway activation [70]. Moreover, the sonic hedgehog (SHH) signaling pathway, which is crucial for neuronal regeneration post-injury, has been targeted using BMSC-SHH-EX, which has shown promising effects in promoting neuronal recovery and inhibiting astrocyte activation-related pathology after rat SCI [71]. Additionally, BMSC-EX attenuates BSCB disruption by modulating the tissue inhibitor of the metalloproteinases-2 (TIMP2)/matrix metalloproteinase (MMP) pathway, offering another avenue for therapeutic intervention in the SCI rat model [72]. Furthermore, NGF-overexpressing BMSC sheet-derived EXs repair SCI in the mouse model by facilitating neural stem cell differentiation and axonal regeneration [73]. Moreover, BMSC-EVs exhibit significant therapeutic potential in SCI by modulating multiple cellular pathways, including inflammation, neurogenesis, and axonal regeneration. These findings underscore the importance of continued research to translate the therapeutic potential of BMSC-exosomes into effective clinical treatments for SCI.

6.5. Dental Mesenchymal Stem Cell-Derived Extracellular Vesicles

Dental mesenchymal stem cell-derived exosomes (DSC-EXs) exhibit diverse functions, underscoring their dynamic role in intercellular communication and therapeutic potential across various pathological conditions [74]. These EXs have been implicated with many functions such as immunomodulation, neuroprotection, anti-inflammatory responses, angiogenesis, osteogenesis, and modulation of cell death in mouse SCI models [74,75].

Figure 4 illustrates the capacity of DSC-EX to mitigate macrophage M1 polarization, particularly in the context of SCI, *via* the ROS-MAPK-NF κ B P65 signaling pathway, suggesting their therapeutic utility in reducing secondary damage associated with the rat SCI model [76]. In the context of ischemia/reperfusion-induced cerebral injury, DSC-EX demonstrates anti-inflammatory effects, potentially mediated by the inhibition of the HMGB1/TLR4/MyD88/NF- κ B pathway, highlighting their neuroprotective capabilities in mice transient middle cerebral artery occlusion injury [77]. These findings demonstrate the multifaceted therapeutic potential of DSC-EXs across various pathologies, including SCI. Their ability to modulate inflammation and protect against cellular damage suggests that DSC-EXs may offer a novel and promising approach to treating SCI. Further research is crucial to successfully translate these preclinical findings into effective clinical therapies.

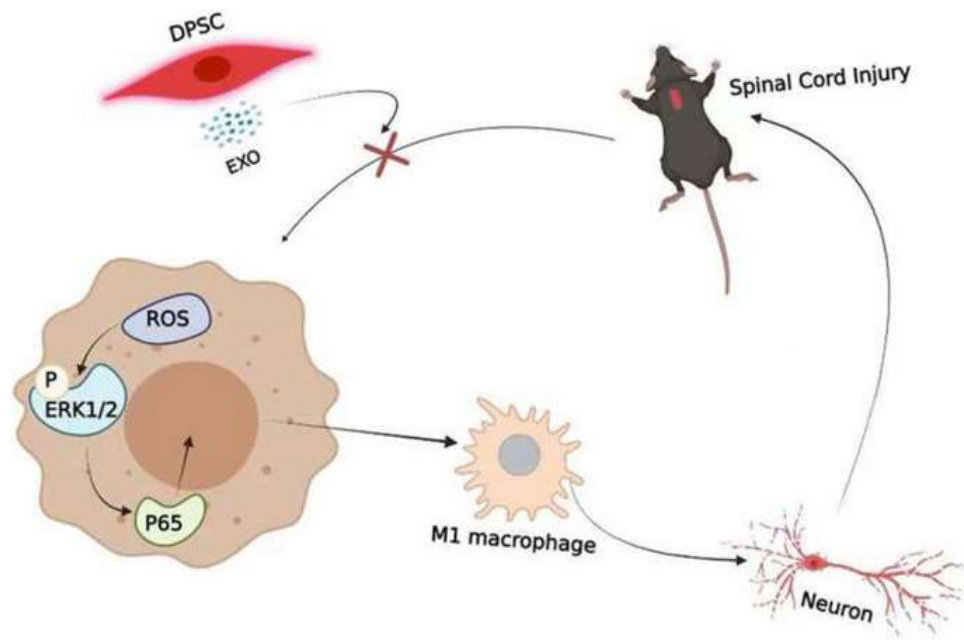


Figure 4. Dental pulp stem cell (DPSC)-derived exosomes can reduce macrophage M1 polarization through the ROS-MAPK-NF-κB P65 signaling pathway in SCI treatment. Disrupting the cycle between ROS and M1 macrophage polarization might also be a potentially effective treatment, as it reduces secondary damage. Reprinted with permission from Liu, C., Hu, F., Jiao, G., Guo, Y., Zhou, P., Zhang, Y., Zhang, Z., Yi, J., You, Y., Li, Z., Wang, H., Zhang, X. (2022). Copyright 2022 Journal of Nanobiotechnology, Springer Nature [76].

Table 1. Comparative therapeutic efficacy of different cell types and their extracellular vesicles in animal models of spinal cord injury.

| Cell type/ EV type | Animal model | Delivery route | Signaling pathways | Functions | Reference |
|--------------------|---------------------------------|----------------------------|----------------------------|----------------------------------------------------------------------------------------------------|-----------|
| HucMSC-EXs | Rat chronic constriction injury | Intrathecal injection | TLR2/MyD88/NF-κB | Attenuates neuropathic pain | [48] |
| HucMSC-EXs | Rat spinal cord injury | Tail vein injection | Wnt/β-catenin | Mitigates apoptosis downregulates inflammatory factors and promotes angiogenesis and axonal growth | [45,46] |
| HucMSC-EXs | Rat spinal cord injury | Intravenous administration | BCL2/Bax and Wnt/β-catenin | Productive effects of SCI | [45] |
| HucMSC-EXs | LPS-treated mouse model | Tail vein injection | NRF2/NF-κB/NLRP3 | Reduces oxidative stress and neuroinflammation | [51] |
| HPMSC-EXs | Rat spinal cord injury | Tail vein injection | MEK/ERK/cAMP-CREB | Endogenous neurogenesis activation enhances recovery from spinal cord injury | [52] |
| ADSC-EXs | Rat spinal cord injury | Tail vein injection | Nrf2/HO-1 | Prevents inflammation in M1 | [59] |

| | | | | | |
|--------------------------------------------------|--------------------------------------------------------|----------------------------|------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|------|
| | | | | microglia and spinal cord tissues | |
| ADSC-EXs | Rat spinal cord injury | Tail vein injection | NRF2/SLC7A11/GPX4 | Prevents ferroptosis and promotes recovery of vascular and neural functions | [60] |
| ADMSC-EXs | Mice spinal cord injury | Tail vein injection | NF- κ B light-chain enhancer (related to STAT activity) to inhibit NF- κ B | Repairs SCI <i>via</i> Shifting microglial M1/M2 Polarization | [78] |
| BmMSC-EXs | Rat spinal cord injury | Tail vein injection | Wnt/ β -catenin | Inhibits neuronal apoptosis and promotes motor function recovery | [79] |
| BmMSC-EXs | Rat spinal cord injury | Intravenous administration | Wnt/ β -catenin | Plays crucial roles in SCI | [45] |
| Bone MSC-EXs | Mice spinal cord injury | Tail vein injection | TLR4–NF- κ B and activating the PI3K–AKT | Exosome-shuttled miR-216a-5p from hypoxic pre-conditioned MSC repairs traumatic SCI | [7] |
| BMSC-SHH-EXs | Rat spinal cord injury | Intravenous injection | Sonic Hedgehog (SHH) | Promotes neuron recovery and inhibits astrocyte activation | [71] |
| BmMSC-EXs | Rat acute spinal cord injury | Intravenous injection | TIMP2)/MMP | Therapeutics intervention in acute SCI | [72] |
| BmMSC-EXs | Rat diabetic nephropathy model | Tail vein injection | JAK2/STAT3 | Protective effects of diabetic nephropathy and its possible mechanism | [80] |
| miR-216a-5p was enriched in MSC-derived exosomes | Rat spinal cord injury | Tail vein injection | TLR4/NF- κ B/PI3K/AKT | Repairs traumatic SCI by suppressing the activation of A1 neurotoxic reactive astrocytes | [67] |
| DSC-EXs | Rat spinal cord injury | Tail vein injection | ROS-MAPK-NF- κ B P65 | Suppresses M1 macrophage polarization | [76] |
| DSC-EXs | Mice transient middle cerebral artery occlusion injury | Tail vein injection | HMGB1/TLR4/MyD88/NF- κ B | Promotes anti-inflammatory and neuroprotective effects | [77] |

HucMSC-EXs: Human umbilical cord mesenchymal stem cell-derived exosome; BmMSC-EXs: Bone marrow mesenchymal stem cell-derived exosome; ADMSC-EXs: Adipose stem cell-derived exosome; DSC-EXs: Dental stem cell-derived exosome.

7. Exploring Therapeutic Potential: Spinal Cord Tissue-Derived Extracellular Vesicles in Spinal Cord Injury

7.1. Neural Stem Cell-Derived Extracellular Vesicles

Many studies recommend that transplantation of neural stem cell-derived exosomes (NSC-EXs) can enhance the motor, sensory, and autonomic nerve function in SCI [34,81,82]. Table 2 summarizes several investigations demonstrating NSC-EX’s neuroprotective and reparative effects in SCI. These EXs have been shown to protect neuronal function, mitigate neurocognitive impairment, and promote rat SCI repair [34,83]. Exosomes derived from induced pluripotent stem cell-derived neural progenitor cells exhibit neuroprotective effects against oxygen- and glucose-deprived neurons by modulating the PTEN/AKT signaling pathway and promoting neurite outgrowth in embryonic rat cortical neuron cultures [83]. Furthermore, NSC-EX-loaded with FTY720 positively affects rat SCI by regulating the PTEN/AKT pathway [84]. Notably, NSC-EXs have also been found to suppress neuronal cell death by activating autophagy via the miR-374-5p/STK-4 axis in SCI mice [85]. Moreover, NSC-EXs have shown promising outcomes in reducing the size of the spinal cord cavity, enhancing microvascular regeneration, and improving Basso mouse scale scores in the SCI mice model [86]. In the SCI mice model, NSC-EX injection mitigates microglial PTEN/AKT activation and astrocyte activation, while promoting the maturation of oligodendrocyte progenitor cells [87]. Additionally, NSC-EXs can facilitate spinal cord repair by modulating the cellular microenvironment of neuron cell culture *in vitro* study [87]. These findings highlight the multifaceted therapeutic potential of NSC-EXs in SCI. Their ability to modulate multiple cellular processes, including neuroprotection, neurogenesis, and glial cell function, suggests that NSC-EXs may offer a promising avenue for developing novel therapies for SCI.

Table 2. Cellular signaling pathways are activated by spinal cord tissue-derived extracellular vesicles in spinal cord injury.

| Cell type/EV type | Injury model | Delivery route | Signal pathways | Therapeutic effects | Reference |
|-------------------|-----------------------------------|------------------------------------------|-------------------------------|-----------------------------------------------------------------------------------------|-----------|
| MG-EXs | Mice spinal cord contusive injury | Exogenous administration | p53/p21/CDK1 | Regulates neuronal apoptosis and promotes axonal growth | [88] |
| MG-EXs | Mouse spinal cord injury | Tail vein injection | Keap1/Nrf2/HO-1 | Promotes functional recovery after SCI | [89] |
| MP-EXs | Mouse spinal cord injury | Locally administrated at the injury site | Wnt/ β -Catenin | Promotes angiogenesis after SCI. | [90] |
| MP-EXs | Rat spinal cord contusion injury | Tail vein injection | PI3K/AKT/mTOR | Attenuates anti-apoptosis suppresses BSCB disruption and functional recovery after SCI. | [91] |
| MP-EXs | Rat spinal cord injury | Tail vein injection | miR-23a-3p/PTEN/PI3K/AKT axis | Phenotypic switch of macrophages in the immune microenvironment | [92] |
| SC-EXs | Mice spinal cord | Tail vein injection | NF- κ B/PI3K | Stimulates the expression of TLR2 in astrocytes | [93] |

| | | | | | |
|---------|---------------------------------|-----------------------------------|----------------------------|-----------------------------------------------------------------------------------------------|------|
| | contusion injury | | | after SCI and reduces the deposition of CSPGs. | |
| SC-EXs | Rat spinal cord injury | Tail vein injection | vincristine receptor B | Reduces apoptosis and promotes recovery of motor function | [94] |
| SC-EXs | Rat spinal cord contusion model | Tail vein injection | SOCS3/STAT3 | Attenuates inflammation | [95] |
| PC-EXs | Mice spinal cord injury | Tail vein injection | PTEN/Akt | Improves endothelial barrier function under hypoxic conditions and protects endothelial cells | [96] |
| NSC-EXs | Rat spinal cord injury | Tail vein injection | PTEN/AKT | Promotes functional recovery of SCI | [84] |
| NSC-EXs | Rat acute spinal cord injury | Tail vein injection | miR-219a-2-3p/YY1 | Inhibits neuro-inflammation and promotes neuroprotection | [97] |
| AC-EVs | Spinal cord injury | <i>In vitro</i> PC12 cell culture | Hippo pathwayMOB1-YAP axis | Promotes neurite elongation | [98] |

MG-EX: Microglial cell-derived exosome; MP-EXs: Macrophage cell-derived exosome; SC-EXs: Schwann cell-derived exosomes; PC-EXs: Pericyte cell-derived exosome; NSC-EXs: Neuron stem cell-derived exosome; AC-EXs: Astrocyte cell-derived exosome; SCI: Spinal cord injury; BSCB: Blood–spinal cord barrier.

7.2. Schwann Cell-Derived Extracellular Vesicles

EXs released from different phenotypic Schwann cells (mature myelinating, repair, and hypothetical dysfunctional repair SCs) carry distinct cargoes with different functions [99,100]. Treatment with Schwann cell-derived exosomes (SC-EXs) reduces oxidative stress and inflammation after SCI, alleviates necroptosis, and enhances mitochondrial functionality. It also promotes mitophagy in injured PC12 cells [100]. Repair SCs secrete EXs that can enhance axonal regeneration after a nerve injury. Also, it holds significant promise for SCI repair due to the intrinsic regenerative capacity of Schwann cells in the peripheral nervous system [100]. In particular, repair SC-derived EXs contain miRNA-21 that leads to down-regulation of phosphatase and tensin homolog (PTEN) and phosphoinositide 3-kinase (PI3K) activation in the neuron cell culture [24]. Furthermore, the repair of SC-EXs increases cell viability and inhibits the apoptosis of neurons in the rat SCI model [101]. SC plays a constructive role in nerve repair and promotes axonal proliferation and de-differentiation, myelin sheath elimination, and axonal debris [102]. SC-EXs can enhance axon regeneration and mitigate inflammation through *in vitro* stimulation with a combination of fibroblast growth factor, neuregulin-1, and platelet-derived growth factor-AA [103]. It can also contribute to axon protection by enhancing autophagy and anti-apoptotic effects *via* the EGFR/Akt/mTOR signaling pathway in the rat SCI model.

Contrarily, SC-EX can stimulate the expression of TLR2 in astrocytes after SCI and reduce the deposition of CSPGs through NF-κB/PI3K signaling, thereby promoting functional recovery after SCI in mice [93]. Ren et al. revealed that SC-EX with MFG-E8 modifies macrophage/microglial polarization to reduce inflammation and enhance motor function *via* the SOCS3/STAT3 pathway after SCI contusion in a rat model [95]. The skin precursor SC-EXs triggered axonal outgrowth and regeneration of motor and sensory neurons through the PI3K/protein kinase B/mammalian target of rapamycin/ribosomal protein S6kinase β-1 (PI3K/Akt/mTOR/p70S6K) signaling pathway in peripheral nerve injury (PNI) and SCI in rat dorsal root ganglion and sensory neurons culture *in vitro*

[104]. SC-EXs also showed a neuroprotective effect on neurons by blocking the caspase-3 cell death pathway, consistent with axonal regeneration and promoting cell survival in motor neurons *in vitro* study [105]. The skin precursor-derived SC-EVs enhanced neuron growth and survival, particularly in oxygen-glucose-deprivation-injured rat sensory neurons from dorsal root ganglion, through miR-21-5p's regulation of the PTEN/PI3K/Akt pathway [104]. SC-EVs demonstrate significant therapeutic potential in SCI. By modulating key signaling pathways and influencing cellular processes such as inflammation and neurogenesis, SC-EVs contribute to improved functional recovery after SCI.

7.3. Macrophage-Derived Extracellular Vesicles

The peripheral macrophages efficiently promote anti-inflammation in injured areas and are the significant factors that support healing after *in vitro* study of anti-inflammatory microglial polarization following autophagy induction [91]. Furthermore, it highlights the potential of Macrophage-derived exosomes (MP-EXs) in modulating the anti-inflammatory process by stimulating microglial autophagy *via* inhibition of the PI3K/AKT/mTOR signaling pathway in rat SCI [91]. MP-EXs-loaded baicalin has been found to improve solubility and brain targeting ability, leading to significant neuroprotection in ischemic stroke patients through the antioxidative pathway [106]. In another study, OTULIN derived from macrophage 2-derived EXs emerges as a crucial mediator in facilitating angiogenic effects by directly deubiquitinating β -catenin and inducing the expression of genes associated with angiogenesis in spinal cord microvascular endothelial cells after mouse SCI [90].

In the SCI mice model, M2-derived EXs-loaded berberine had anti-inflammatory and anti-apoptotic effects by repolarizing macrophages from the M1 to M2 phenotype [107]. Particularly, EXs M2 macrophage alleviated tissue damage, enhanced functional recovery, and increased angiogenesis after the SCI rat model [108]. Also, it can improve tube migration, proliferation, and formation, and partially activate the HIF-1/VEGF signaling pathway through *in vitro* study of brain endothelial cell lines [108]. M2 macrophage-derived EXs may promote M2 macrophage polarization *via* the miRNA-mRNA network, making them a promising therapeutic agent for SCI immune microenvironment *in vitro*. The miR-23a-3p/PTEN/PI3K/AKT axis is notable in the network shown in the SCI rat model [92]. In conclusion, MP-EXs particularly those derived from M2 macrophages, exhibit significant therapeutic potential in SCI. They can modulate the inflammatory response by promoting anti-inflammatory macrophage polarization, inhibiting inflammation, and enhancing angiogenesis. These findings suggest that MP-EVs may offer a promising approach for improving functional recovery after SCI.

7.4. Microglia-Derived Extracellular Vesicles

Microglia, a type of neuroglia analogous to macrophages in the brain and spinal cord, are recognized as pivotal contributors to the pathophysiology of mice SCI [109]. The miR-151-3p is highly expressed in Microglia-derived exosomes (MG-EXs), and thus, it exerts a neuroprotective effect during SCI repair [64]. Concurrently, MG-EXs can activate the p53/p21/CDK1 signaling cascade, thereby regulating neuronal apoptosis and promoting axonal growth after contusive mouse SCI [64]. Additionally, MG-EXs may function as an antioxidant by activating the Keap1/Nrf2/HO-1 pathway, thereby facilitating functional recovery in the SCI mouse model [89]. Furthermore, MG-EXs miR-124-3p can potentially mitigate neuronal degeneration and improve cerebral outcomes via the Rela/ApoE signaling pathway [110]. Moreover, cell-polarization shifts from the M1 to M2 phenotype may occur in various subsets of microglial and monocyte cells after SCI in mice. M2 MG-EXs enhance neuron survival and protection, promote motor function recovery, and reduce the lesion area size [111]. Lastly, neuroprotection is influenced by reduced A1 astrocyte activation by inhibiting NF- κ B signaling pathway activation in mice SCI [111]. Overall, MG-EVs play a crucial role in the pathophysiology of SCI. They can exert neuroprotective effects by regulating neuronal apoptosis, activating antioxidant pathways, and modulating microglial polarization. These findings suggest that MG-EVs may offer a promising therapeutic target for improving functional outcomes after SCI.

7.5. Astrocyte-Derived Extracellular Vesicles

Astrocytes can play a pivotal role in the nervous system, such as neuron nourishment, promoting synapse construction, synaptic pruning *via* phagocytosis, regulation of cerebral blood flow, and homeostasis maintenance [112]. A1 and A2 reactive astrocytes are distinctive in acute neurotic conditions after mouse cortex stab injury [113]. A1 astrocytes are strongly neurotoxic, whereas A2 astrocytes might deal with neuro-protective effects by increasing the neurotrophic factors by microglial cells *in vitro* [114]. The Astrocyte-derived exosomes (AC-EXs) treated with semaphorin 3A-I enhance the axonal outgrowth and PTGDS expression *via* neuronal Rnd1/R-Ras/Akt/glycogen synthase kinase 3 β (GSK-3 β) signaling and promotes axon regeneration and stroke recovery in traumatic brain injury (TBI) in rats [115]. In the SCI rat model, AC-EVs facilitate tissue repair, decrease fibrosis, and enhance limb function and walking ability [116]. EVs derived from LPS-stimulated astrocytes (LPS-AS-EVs) exhibited enhanced neurite outgrowth *in vitro* and improved motor function recovery *in vivo* compared to EVs from unstimulated astrocytes (AS-EVs) in an SCI rat model [98]. Mechanistically, both AS-EVs and LPS-AS-EVs modulated the Hippo pathway in PC12 cells by increasing monopole spindle binding protein 1(MOB1) and decreasing Yes-associated protein (YAP), thereby promoting neurite elongation [98]. This finding suggests that LPS-stimulated astrocytes release EVs that enhance neuronal repair through the MOB1-YAP axis, providing a potential therapeutic avenue for SCI treatment [98]. While studies have explored the therapeutic potential of AC-EVs in TBI, their application in SCI remains limited. However, given the similarities in injury mechanisms and treatment approaches between TBI and SCI, both of which are central nervous system injuries, we anticipate a surge in research investigating AC-EVs-mediated repair of SCI. We believe that AC-EVs hold significant promise as therapeutic agents for SCI.

7.6. Pericyte-Derived Extracellular Vesicles

Pericyte-derived exosomes (PC-EXs) can protect the endothelial cells and endothelial BSCB in hypoxic conditions *via* the PTEN/AKT pathway after mice SCI [96]. Notably, PC-EXs can increase the blood flow and oxygen supply to the damaged area and improve motor function after SCI [96]. Pericyte proliferation may occur through the S1P/S1PR3 pathway, leading to significantly reduced glial scar formation and improved locomotor recovery after SCI in rats [117]. In addition, S1P/S1PR3 signaling promoted pericyte proliferation *via* the Ras/pERK pathway, as shown by the reduced pericyte proliferation with CAY10444, an S1PR3 inhibitor. [117]. Thus, PC-EVs demonstrated the significant therapeutic potential in SCI by promoting endothelial function, enhancing blood flow, and stimulating pericyte proliferation, ultimately leading to reduced glial scarring and improved functional recovery.

8. Therapeutic Potential of Extracellular Vesicles from Other Cell Types in Spinal Cord Injury

The activation of the JAK2/STAT3 pathway by miR-214-containing exosomes derived from muscle-derived stem cells may facilitate the regeneration and repair of peripheral neurons following a rat sciatic nerve crush injury, potentially through the inhibition of PTEN [118]. T cell-derived exosomes can modulate immune responses, as evidenced by the enrichment of RAS signaling pathway proteins in exosomes from activated T cells, leading to ERK phosphorylation [119]. Gingiva-derived MSC-EXs successfully regenerate the sciatic nerve in rodent models [120]. A recent study found that EXs derived from fibroblasts can promote retinal ganglion cell neurite growth by activating mTOR and promoting Wnt10b in neuron cell culture *in vitro* [121]. These studies play a role in axonal regrowth and regenerative signaling [121]. Additionally, human menstrual blood-derived mesenchymal stem cell-derived exosomes demonstrated the potential to promote axon regeneration in a rat model of SCI [122]. EXs from human urine stem cells show promise for regeneration, aiding spinal cord recovery by fostering angiogenesis through Angiopoietin-like 3 transfer in the contusion SCI mouse model [123]. EXs derived from Treg cells can encapsulate and

transport miR-2861, thereby modulating the expression of IRAK1 to influence BSCB integrity and motor function following SCI in mice [124]. Pericyte-derived exosomes containing miR-210-5p have been shown to enhance endothelial barrier function by inhibiting JAK1/STAT3 signaling. This mechanism, linked to reduced lipid peroxidation and improved mitochondrial function, offers a promising therapeutic target for restoring the BSCB after SCI [125]. Locally administered gingival mesenchymal stem cell-derived EVs enhanced nerve regeneration and functional recovery in injured mice by upregulating c-JUN, a key gene for Schwann cell repair [126]. Endothelial progenitor cell-derived exosomes containing miR-222-3p modulated macrophage polarization via the SOCS3/JAK2/STAT3 pathway, improving functional recovery in mice with SCI [127]. Hence, EVs derived from diverse cellular sources exhibit potent regenerative properties, influencing key cellular processes, including immune modulation, angiogenesis, and the regulation of crucial signaling pathways. These findings underscore the significant therapeutic potential of EVs for SCI.

9. Exploring the Role of Bioinformatics in Advancing Stem Cell-Derived Extracellular Vesicle Studies

Bioinformatics (BI) is a scientific subdiscipline using computer technology to collect, store, analyze, and disseminate biological information [128]. Post-SCI, BI analysis can help identify the hub ferroptosis genes, including STAT3, JUN, TLR4, ATF3, HMOX1, MAPK1, MAPK9, PTGS2, VEGFA, and RELA, and the potential drugs targeting ferroptosis to repair SCI in rats [129]. The integrated BI analysis, including differential expression gene, gene ontology enrichment, KEGG pathway analysis, and protein-protein interaction network, has helped to reveal that the Sema3A/NRP1 signaling may regulate the development of oligodendrocytes post-SCI, thereby affecting functional recovery [130]. For SCI-induced neuropathic pain in a murine model [131], 592 differentially expressed genes with a significantly altered expression were found, with CCL3 showing the highest upregulation, and 209 pathways changed significantly based on the results of the KEGG analysis with MAPK signaling pathway [132].

9.1. Unveiling Therapeutic Pathways via microRNA Analysis in Extracellular Vesicles Transplanted Rodents

miRNAs can regulate cell differentiation, proliferation, and apoptosis, and are closely linked with pathological processes (inflammation, demyelination, oxidative stress, and neural apoptosis) after SCI [66]. Engineered non-vesicular nanoparticles offer a complementary approach for delivering bioactive molecules, including miRNAs [133]. These precisely tailored particles overcome the limitations of EVs by enabling the encapsulation of specific cargo, enhancing stability in circulation and at the target site, and facilitating targeted delivery to desired cell types through functionalization [133]. Although EXs are known to transfer various bioactive molecules, including microRNAs and proteins, to recipient cells, the associated mechanism of exosome-mediated SCI repair still needs further exploration [134,135]. Thus, RNA sequencing was performed to identify the key pathways, and gene analyses can help to differentiate groups (Table 1, 2 & 3). Li *et al.* revealed improved survival of neurons and motor function after the systemic injection of miRNA-133b EX, which moderately activates the CREB, STAT3, ERK1/2, and RhoA signaling in rat SCI [13]. Also, MSC-EXs miRNA-133b considerably promotes the expression of GFAP, MBP, NF, and GAP43 expression, prompting axon regeneration and improving functional recovery in SCI animals [136]. Furthermore, it can deliver miR-133b to increase neurite growth and stimulate neuronal plasticity and functional recovery [137]. The umbilical MSC-EXs miR-199a-3p/145-5p can help in 'the functional recovery of the SCI in a rat model *via* the mediated NGF/TrkA signaling pathway [46]. Weihua *et al.* recommended that miR-216a-5p from MSC-EXs involves microglial polarization [7]. Hung *et al.* suggested that miR-21 plays a significant role in nerve regeneration and protection in stroke [138]. Emerging evidence indicates that exosomal miR-423-5p, originating from osteoblasts activated by cerebrospinal fluid pulsation

stress, plays a pivotal role in enhancing endothelial cell angiogenesis through the modulation of the DUSP8/ERK1/2 signaling pathway [139].

Table 3. Possible signal pathways involved in different types of microRNA from mesenchymal stem cells (MSCs)-derived extracellular vesicles.

| Cell type/ EV type | Exosome Cargo | Delivery route | Injury model | Signaling pathways | Functions | Reference |
|-----------------------|------------------------|----------------------------------|---------------------------------------------|--------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|-----------|
| HucMSC- EXs | miR-145- 5p | Tail vein injection | Rat spinal cord injury | TLR4/NF-κB | Regulates inflammation | [70] |
| HucMSC- EXs | miR-199a- 3p/145-5p | Tail vein injection | Rat spinal cord injury | NGF/TrkA | Promotes neuroprotective and functional recovery | [46] |
| MP-EXs | miR-155 | Tail injection | Mouse contusive spinal cord injury | NF-κB; miR- 155/SOCS6/p65 axis | Ensures the transport network between macrophages and vascular endothelial cells after SCI | [140] |
| MSC-EXs | miR-338- 5p | Tail vein injection | Rat spinal cord injury | Cnr1/Rap1/Akt | Reduces apoptosis and promotes neuronal survival | [141] |
| ADSC-EXs | miR-133b | Tail intravenous injection | Rat spinal cord injury | - | Promotes axonal regrowth and motor function recovery | [13] |
| BmMSC- EXs | miR-23b | Caudal vein injection | Rat spinal cord injury | targeting TLR4 and inhibiting NF-κB pathway activation | Alleviates spinal cord injury | [69] |
| BmMSC- EXs | miR-544 | Intravenous injection | Rat spinal cord injury | - | Reduces the number of apoptotic neurons | [142] |
| BmMSC- EXs | miR-125a | Intravenous injection | Rat spinal cord injury | - | Promotes M2 macrophage polarization | [143] |

HucMSC-EXs: Human umbilical cord mesenchymal stem cell-derived exosome; BmMSC-EXs: Bone marrow mesenchymal stem cell-derived exosome; ADSC-EXs: Adipose stem cell-derived exosome; SCI: Spinal cord injury.

The miRNAs regulate the expression of related proteins by upregulating or down-regulating target genes that are altered after SCI. For example, the changes in miR-10a, miR-10b, miR-142-3p, miR-338, and miR-133 contents after SCI are closely related to the pathogenesis of the disease [144]. BmMSC-EXs inhibit the NF-κB pathway by upregulating miR-23b targeting TLR4, participating in the process of oxidative stress, alleviating the inflammatory response after SCI, and improving the motor function of rats after SCI [69]. miR-29a/199B inhibits the RGMA/STAT3 axis and promotes neural function repair in rats post-SCI [145]. NSC-EXs regulate astrocyte and microglia activation through miR-124-3p to protect against traumatic SCI [146]. The overexpression of miR-223 decreased the protein expression levels of interleukin (IL)-1β, IL-18, NLRP3, ASC, and caspase-1, and regulated the transformation of macrophages between types in injured spinal cords of mice with chronic sciatic nerve injury [147]. Additionally, miR-20a, miR-21, miR-497, miR-494, miR-223, miR-29b, miR-320, and miR-124 were involved in cell apoptosis after SCI [148–151]. Furthermore, miR-133b, miR-20a, and miR-124 were involved in promoting angiogenesis and regulating nerve repair after SCI [152–

154]. MSCs-EXs can reduce cell proliferation and neuronal ferroptosis caused by hypoxia [155]. This is done by inhibiting neuronal cell ferroptosis through the miR-5627-5p/FSP1 axis, thereby reducing neuronal dysfunction [155].

Exosomal miR-124-3p from neurons can reduce the activation of M1 microglia in mice after SCI *via* PI3K/AKT/NF- κ B signaling [146]. Huang et al. discovered that exosomal miR-494 prevented inflammation and neuron apoptosis in the injured area, supporting nerve generation and motor function recovery in rats with SCI [149]. This review highlights the critical role of miRNAs within EVs in modulating various cellular processes involved in SCI repair. miRNAs encapsulated within EVs derived from multiple sources, including mesenchymal stem cells, neural stem cells, and macrophages, regulate key signaling pathways such as NF- κ B, PI3K/AKT, and ERK1/2, influencing inflammation, neurogenesis, angiogenesis, and cell survival. These findings underscore the therapeutic potential of utilizing and manipulating exosomal miRNAs to enhance functional recovery after SCI. Further research is crucial to elucidate the precise mechanisms of miRNA action within the injured spinal cord and to translate these findings into effective clinical therapies for SCI.

10. Clinical Studies

Despite limitations in search terms and incomplete data, the surge in EV-related clinical trials (471 since 1999) reflects the growing interest in their therapeutic potential. One promising example is NCT03675885, which evaluates the safety and efficacy of stem cell-derived exosomes for SCI. This trial's initial results demonstrate some patient's sensory improvements and motor recovery, highlighting the potential for clinical translation [156]. While we anticipate no change in our conclusions, it may be necessary to repeat this analysis later to identify trends in these trials. A further limitation is that our search terms were not exhaustive, focusing only on "extracellular vesicles" and "exosomes," the most common terms for small EVs. However, other relevant subcategories exist, such as oncosomes, microsomes, and ectosomes, which could also be explored in future studies. Finally, clinicaltrials.gov lacks strict reporting requirements, resulting in many vague and incomplete study records. This analysis serves as a preliminary assessment of the current landscape of EV clinical trials to guide future research in SCI.

11. Navigating Future Insights and Anticipated Challenges

11.1. Future Insights

1. Enhanced targeting and delivery: Advancements in engineering will enable precise targeting of stem cell exosomes to injured spinal cord regions and specific cell types, maximizing therapeutic efficacy [157].
2. Synergistic Therapies: Integrating EVs with biomaterials, growth factors, and other therapies can significantly improve tissue repair and functional recovery [66].
3. Personalized Medicine: Tailoring EV therapies to individual patients, utilizing omics technologies to select optimal donors and optimize exosome composition, can improve treatment outcomes [158].
4. Non-invasive Monitoring: Implementing non-invasive imaging and biomarker assays will provide valuable insights into exosome biodistribution, persistence, and therapeutic response, guiding treatment optimization.

11.2. Challenges

Establishing standardized protocols for EV isolation, purification, and characterization is imperative to ensure the reproducibility and comparability of preclinical and clinical studies [66].

12. Conclusions

MSC-derived EVs represent a promising therapeutic avenue for SCI due to their multifaceted mechanisms of action and unique ability to traverse biological barriers. Existing pre-clinical research suggests the potential benefits of MSC-EVs in promoting tissue repair, attenuating inflammation, and enhancing functional recovery in SCI models. However, further investigation is warranted to understand their therapeutic potential fully. Nevertheless, the growing bodies of evidence supporting the therapeutic potential of MSC-EVs offer hope for developing novel and effective treatments for SCI.

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Abbreviations

| | |
|------------|----------------------------------------------------------------|
| MSC-EVs | Mesenchymal stem cell-derived extracellular vesicles |
| MSC-EXs | Mesenchymal stem cell-derived exosomes |
| SCI | Spinal cord injury |
| miRNAs | Micro RNAs |
| BSCB | Blood spinal cord barrier |
| HucMSC-EXs | Human umbilical cord mesenchymal stem cell-derived exosomes |
| hPMSC-EXs | Human placental mesenchymal stem cell-derived exosomes |
| ADSC-EXs | Adipose mesenchymal stem cell-derived exosomes |
| BMSC-EXs | Bone marrow mesenchymal stem cell-derived exosomes |
| DSC-EXs | Dental mesenchymal stem cell-derived exosomes |
| NSC-EXs | Neural stem cell-derived exosomes |
| SC-EXs | Schwann cell-derived exosomes |
| MP-EXs | Macrophage-derived exosomes |
| MG-EXs | Microglia-derived exosomes |
| AC-EXs | Astrocyte-derived exosomes |
| PC-EXs | Pericyte-derived exosomes |
| TLR2 | Toll-like receptor 2 |
| NF-κB | Nuclear factor kappa-light-chain-enhancer of activated B cells |
| Rsd2 | Radical SAM domain-containing 2 |
| BCL2 | B-cell lymphoma 2 |
| Bax | Bcl-2-associated protein x |
| TrkA | Tropomyosin receptor kinase A |
| NGF | Nerve growth factor |

| | |
|-----------|--------------------------------------------------------------------------------------|
| IRAK1 | Interleukin-1 receptor-associated kinases 1 |
| TRAF6 | TNF receptor-associated factor 6 |
| NRF2 | Nuclear factor erythroid 2-related factor 2 |
| NLRP3 | Nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 |
| NPCs | Neural pluripotent cells |
| MEK | Mitogen-activated protein kinase |
| ERK | Extracellular signal-regulated kinase |
| CREB | cAMP-response element binding protein |
| OGD/R | Oxygen-glucose deprivation/reperfusion |
| Nrf2/HO-1 | Nuclear factor erythroid-2 related factor 2/heme oxygenase |
| PI3K/Akt | Phosphatidylinositol 3-kinase/Protein kinase B |
| SLC7A11 | Solute carrier family 7 member 11 |
| GPx4 | Glutathione peroxidase 4 |
| PTGDS | Prostaglandin D2 synthase |
| Rnd1 | Rho Family GTPase 1 |
| R-Ras | R-Ras gene |
| S1P | Sphingosine-1-phosphate |
| SIPR3 | Sphingosine-1-phosphate receptor 3 |
| Sema3A | Semaphorin 3A |
| NRP1 | Neuropilin 1 |
| SOCS6 | Suppressor of cytokine signaling 6 |
| Rap1 | Repressor/Activator Protein 1 |
| Cnr1 | Cannabinoid receptor gene |
| KEGG | Kyoto Encyclopedia of Genes and Genomes |
| STAT3 | Signal transducer and activator of transcription 3 |
| JUN | Jun proto-oncogene or enhancer-binding protein |
| HMOX1 | Heme oxygenase 1 |
| PTGS2 | Prostaglandin-Endoperoxide Synthase 2 |
| VEGFA | Vascular endothelial growth factor A |
| RELA | v-rel avian reticuloendotheliosis viral oncogene homolog A |
| CCl3 | C-C Motif Chemokine Ligand 3 |
| PTEN | Phosphatase and tensin homolog |
| SHH | Sonic hedgehog |
| TIMP2 | Tissue inhibitor of metalloproteinases-2 |
| MMP | Matrix metalloproteinase |
| ROS | Reactive oxygen species |
| MAPKs | Mitogen-activated protein kinases |
| Cdc42 | Cell division control protein 42 homolog |
| HMGB1 | High mobility group box 1 |
| EGFR | Epidermal growth factor receptor |
| mTOR | Mammalian target of rapamycin |

PKB also known as Protein kinase B
AKT
PI3Ks Phosphoinositide 3-kinases
DUSPs dual-specificity phosphatases

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