REVIEW ARTICLE

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Exosome Therapy in Spinal Cord Injury: A Review

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Abstract

Background: Injuries to the spinal cord (SCI) are one of the most detrimental central nervous system (CNS) injuries in developing countries. Today, treatment is one of the major issues facing the medical profession, and to date, there is no known promising treatment capable of fully healing injuries. There are various methods to repair and improve SCI, including the use of stem cells particularly mesenchymal stem cells (MSCs). Various studies have been performed on applying these cells in the treatment of SCI, whose results have confirmed the efficacy of using these cells specifically due to the paracrine secretion of these cells including growth factors, chemokines, cytokines, and small extracellular vesicles. Interestingly, among these paracrine molecules, exosomes may have the maximum therapeutic value and as such is widely investigated by researchers.

Aim: to fully focus on the usage of stem cell-derived extracellular vesicles on the healing of SCI in animal models.

Conclusion: Taken together, the extracellular nanovesicles have promising therapeutic potentials and their use in the treatment of SCI has been rapidly growing. In this review, we elucidated the effect of exosomes derived from bone marrow MSCs in SCI.

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Introduction

Spinal Cord Injury (SCI) today is one of the most debilitating neurological injuries in societies, and several victims of SCI may die before reaching the hospital. People who are hospitalized are also at risk of dying from infection after one year. It also imposes huge costs on governments and families. Studies suggest that the most common cause of SCIs is traffic accidents. Despite the current treatments to eliminate the complications of SCI, no definite cure has been found so far. Complications after CNS injury, especially the spinal cord, are one of the most important challenges facing the healthcare sector in both developed and developing countries. The annual incidence of SCI around the world has been reported to range from 3.6 to 195 cases per million. This injury is reported to be more common in men than in women (1). In Iran, the prevalence of SCI is 318 per million (2). This injury can partially or completely destroy the three main actions of the spinal cord, including movement, sensation, and reflexes (1, 3, 4). Functional defects are caused by damages to axonal fringes, loss of neurons, activation of astrocytes and microglia, and degeneration of oligodendrocytes (5).

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Although treatments such as drug therapy, gene therapy, cell therapy hypothermia, and tissue-engineering scaffolds have been studied to induce repair, none of them have completely eliminated the side effects so far (6).

SCI has primary and secondary phases. The primary phase occurs due to mechanical pressure while the second phase may occur after the initial phase, following the onset of inflammatory cascades (7, 8). Studies have shown that free radical formation and lipid peroxidation in SCI causes a rapid and severe oxidative stress and neuroinflammatory response which may result in neuronal death and decreased blood flow causing edema and inflammation (9, 10). Thus, inflammation as a key factor in SCI is due to the activation of microglia and releasing pro-inflammatory cytokines which may cause neuronal damage (8, 11-14). Different pharmacological therapies can partially control the secondary phase of SCI by preventing the production of inflammatory factors and free radicals, which can reduce the complications in SCI models.

MSC-based therapies in SCI and their associated barriers

One of the promising therapies in the treatment of SCI is the use of stem cells (7, 15-19). MSCs are multipotent cells that can be obtained from a variety of sources including bone marrow, peripheral blood, cord blood, and adipose tissue. Today these cells serve as a promising source for the cellular treatment of damaged cells (20-25). Basically, the therapeutic application of these cells after SCI can reduce the volume of cavities created in the spinal cord, replace dead cells, and create a favorable environment for axonal repair (26). Studies on rodents have shown that MSCs cells can contribute to the expression of factors such as neurotrophins, germination, and axonal regrowth. They can also lead to the healing of damaged tissues by improving vascular blood flow (27, 28). Research has also shown that the beneficial therapeutic effects of these cells are due to their paracrine secretion, but the precise mechanism of their efficacy has not yet been elucidated. One of the frequently mentioned barriers to MSCs application is their large size and inability to cross the blood-brain barrier, as well as their poor survival at the site of the injury; they disappear shortly after due to paracrine secretions of these cells, such as the secretion of molecules such as growth factors, chemokines, cytokines and small extracellular vesicles (23, 24, 29-32).

Extracellular vesicles and their potential role

Extracellular vesicles are membrane-bound structures that can be secreted into the extracellular space by most cells. Evidence suggests that these structures play an important role in intercellular communication in physiological and pathological processes (33, 34). These vesicles are classified into exosomes (30 to 100 nm), microsomes or ectosomes (50 nm to 1 μm), and apoptotic bodies (50 nm to 5 μm) based on their intracellular origin and size. Exosomes are released through the attachment of multivesicular bodies (MVBs) to the plasma membrane and finally the extracellular environment, while exosomes are released by budding the plasma membrane into the extracellular space (34, 35). These secretory vesicles contain lipid, protein, mRNA, miRNA, noncoding RNAs and DNA depending on their origin. Today, the use of extracellular vesicles derived from MSCs has shown promising effects in the treatment of cardiovascular, hepatic, and renal disease (23, 24). Studies have suggested that these vesicles have the ability to cross biological barriers such as the blood-brain barrier and thus they have been utilized for therapeutic purposes in several neurological diseases. For instance, previous studies have shown that the use of curcumin-enriched extracellular vesicles can potentially reduce inflammatory conditions in

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the CNS (34, 36-38). It has been found that in pathological conditions of the nervous system like those in Alzheimer's, Huntington, Parkinson's, and Multiple Sclerosis, the secretion of these vesicles from damaged cells causes these diseases to spread (14,34). Almost all cells in the nervous system such as neurons (39-41), astrocytes (34, 41), microglia (41, 42) and oligodendrocyte are capable of secreting extracellular vesicles (41, 43). Recent studies have shown that exosomes derived from MSCs can reduce neuronal inflammation, encourage neural repair by angiogenesis and neurogenesis, and treat spatial learning disorders (44). These studies have shown that the use of exosomes in the treatment of brain injury is more beneficial than employing MSCs themselves. Unlike MSCs, extracellular vesicles are easy to transport and maintain without differentiation. The exact mechanism underlying the efficacy of exosomes over MSCs has not been elucidated, however, various drugs such as methylprednisolone with anti-inflammatory effects, riluzole with ion channels, G-CSF are used (15).

According to a study, the effect of systemic injection of bone marrow MSC-derived exosomes on apoptosis, inflammation, and angiogenesis after SI was investigated (23). They studied how the systemic injection of MSC-derived exosomes could improve SCI. The researchers developed the model of SCI by contusion at the level of the T10 vertebra. The animals were then divided into two groups of normal saline and exosome recipients (30 minutes post-injury via the tail vein). They extracted the exosomes from MSCs obtained from the bone marrow of male rats via ultracentrifugation. They found that the mice receiving exosomes had a better performance on the BBB test than the normal saline group. Furthermore, the results showed that the size of the lesion site was smaller in the exosome recipient group on 28 days post-injury (23). Also, in the exosome-treated group, the expression level of Bax protein was reduced, while the expression level of Bcl2 protein increased compared to the control group. In addition, in the exosome-treated group, the level of proinflammatory cytokines (IL-1β, TNF- α) decreased significantly, while the level of IL10 anti-inflammatory cytokines increased. Finally, the number of vessels in the exosome recipient group increased three days post-injury as compared with the control group (23). A study was conducted by Sun and colleagues (2018) to investigate the effect of umbilical cord-derived MSCs on the reduction of inflammation following SCI. In their study, they used C57BL/6 mice and developed a model of SCI by contusion at the level of T11-T12 vertebrae. The researchers prepared the MSCs used in the study from the cord and then cultured them. The culture media were collected by ultracentrifugation to extract the media. They divided the animals into three groups receiving PBS, 20 and 200 µg of the exosome. Exosomes were injected into the caudal vein 30 minutes post-injury. Behavioral tests showed that the 200 µg exosome group showed a better performance than the PBS group did. Also, the volume of the cavity created in the spinal cord was smaller in the aforementioned group compared to the 20 µg exosome group and the PBS recipient group. Examination of tissue sections from the spinal cord by immunofluorescence revealed that the ratio of M2 to M1 macrophages increased in the exosome recipient group. The results of in-vitro experiments also revealed that cord stem cell-derived exosomes are capable of converting M1 to M2 macrophages (45).

In 2018, Lankford et al. examined the intravenous injection of bone marrow MSCs-derived exosomes onto M2 macrophages in SCI. The researchers prepared and cultured MSCs from the bone marrow of Sprague-Dawley rats and added them to the DiR medium to label the exosomes. Then, the media were extracted by ultracentrifugation from the media medium. They developed the

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model of SCI through contusion at the level of the T9 vertebra. One week after injury, the exosomes were injected into the rats through the saphenous vein. They observed DiR-labeled exosomes in the secretory and caudal region of the lesion at a very low level. Also, by reconstructing the lesion site images via a three-dimensional method and specific staining of macrophage subtypes, it was found that the exosomes just below the M2 group were macrophages (25).

Kong and colleagues (2018) inspected the role of cerebrospinal fluid-derived exosomes in rats with SCI on in-vitro neuronal proliferation. In their study, they developed a model of SCI using the contusion method. They then collected cerebrospinal fluid from SCI mice and healthy mice and extracted the exosomes by ultracentrifugation. The researchers obtained the cells required for culture from the rat spinal cord. They then added them to one group of exosomes from SCI model mice and to another group of exosomes derived from healthy mice. They found that cells treated with exosomes derived from SCI mice showed more proliferation and increased ERK1/2 gene expression in these cells (3).

Zhang and colleagues conducted a study in 2016 to investigate the effect of exosomes derived from bone marrow MSCs on functional recovery and neurovascular plasticity in rats following traumatic brain injury. To extract the exosomes, the researchers utilized bone marrow MSCs and extracted the exosomes by the Exo-Quick-Tc method after culturing these cells in the culture medium and collecting the optimum medium. The researchers used Wistar rats and developed the TBI model in CCI. They then divided the animals into three groups: sham, TBI + Exosom, and TBI + PBS, and injected the exosomes through the caudate vein the day after injury. They observed that the injection of exosomes improved spatial learning in TBI rats. It was also found that the rats receiving exosomes showed better sensory-motor improvement than controls did. In addition, it was found that the extent of angiogenesis was significantly enhanced in the exosome recipient group. In addition, neurogenesis was significantly amplified in the hippocampal dentate gyrus in this group. Finally, they discovered that the rate of cerebral inflammation in the expatriate recipient group was significantly reduced (44).

Elsewhere, Lai et al. (2010) examined the effect of exosomes secreted by MSCs on reducing ischemia-reperfusion injury of the heart muscle. The researchers cloned the animals to create an animal model of the left coronary artery and opened it 30 minutes later. They injected cultured media MSC cells containing paracrine secretions of the cells through the caudate vein of the animals for 5 min before re-opening the artery. According to the findings of their study, they suggested that the protective effects of MSCs are due to their paracrine secretions. Their results indicated that the animals receiving the exosomes had decreased the size of the heart muscle injury site, suggesting the ability of the exosomes to repair tissue damage (31).

Arslen et al. (2013) investigated the effect of MSCs-derived exosomes on ATP levels, oxidative stress, and the PI3K/AKT pathway in cardiac ischemia-reperfusion injury. In their study, they used C57BL6/J mice and developed the injury model by closing the animal's left coronary artery for 30 minutes and then re-opening it. They injected the extracted exosomes through the tail vein to the rats 5 minutes before the artery reopening. The results of their study showed that the exosomes reduced the size of the injury by interacting directly with the heart muscle cells. They also found that in the exosome recipient group, the left ventricular dilatation was prevented and cardiac function was also improved. In addition, their results showed that 30 minutes after reperfusion, the ratio of ATP/ADP and NADH/NAD+ increased significantly in the exosome recipient group,

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but the level of oxidative stress decreased significantly. The researchers also noted that phosphorylated AKT and GSK3 were phosphorylated significantly in the exosome recipient 1 hour after reperfusion while the pro-apoptotic signals decreased significantly. Exosomes also proved to reduce inflammation after injury (46).

A study to evaluate the effects of exosomes derived from adipose tissue-derived stem cells (ADSCs) on neuronal remodeling and sciatic nerve regeneration after injury was performed by Bucan and colleagues (2018). The researchers investigated the effects of exosomes on the growth of neuronal wastes in an in-vitro environment. They also injected the exosomes into the proximal and distal parts of the lesion after the injury to the sciatic nerve by Hamilton's syringe. The results of their in vitro studies showed that shoots in neuronal fractions increased significantly in the culture medium at 48 hours post-exposure to exosomes. In addition, the results of their in-vivo study also suggested that the exosome recipient group showed a higher degree of neurodegeneration (47).

Zhou and colleagues (2013) conducted a study to compare the therapeutic effects of bone marrow-derived stem cells with ADSC in the treatment of SCI. The researchers used 108 Wistar rats and divided the animals into three groups: PBS recipient, hBMSC recipient, and hADSC recipient. They then developed SCI at the level of the T9 vertebra. After the injury, the researchers injected the cells 2 mm above and below the injury site. The results of their study showed that ADSC significantly expressed higher levels of HGF, VEGF, and BDNF than bone marrow-derived stem cells did. They observed that animals receiving hADSC experienced better angiogenesis. In addition, the hADSC recipient group showed significantly better cortical and spinal cord regeneration than the hBMSC recipient group did. Also, in both groups of recipient stem cells, the volume of the cavity created was lower than in the control group, though this decrease was more pronounced in the hADSC recipient group. Meanwhile, the activity of microglia/macrophage cells in both recipient groups was lower than in the control group. BBB behavioral test results were better in hADSC recipients than in the other two groups. They eventually suggested that the use of hADSCs was a better option to help reduce SCI complications than employing hBMSCs (48).

Conclusion

Taken together, the extracellular nanovesicles have promising therapeutic potentials and their use in the treatment of SCI has been rapidly growing. In this review, we elucidated the effect of exosomes derived from bone marrow MSCs in SCI.

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Conflicts of Interest

The authors declare no conflicts of interest.

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