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Chapter

Mesenchymal Stem Cells for Clinical Use after Spinal Cord Injury

Karla Soria-Zavala, Julián García-Sánchez and Roxana Rodríguez-Barrera

Abstract

Since multipotential and immunoregulatory properties were identified in mesenchymal stem cells (MSCs) in the twentieth century, they have been proposed as an effective therapy for many degenerative and traumatic diseases such as spinal cord injury (SCI). SCI is a devastating event with a high mortality rate that evokes the loss of motor and sensory functions due to neurochemical imbalance and an exacerbated immune response as a consequence of the initial mechanical damage, which in conjunction creates a hostile microenvironment that inhibits neuronal circuitry restoration. This chapter pretends to lead the reader towards the immunomodulatory, differentiation, and tissue repairing capacities of MSCs that allow them to be a valuable candidate for clinical trials. In the first section, the physiopathology of SCI will be addressed; after that, the chapter will review the general aspects of MSCs such as origin, molecular markers, and the different mechanisms by which MSCs can heal the target tissues. Finally, we will discuss clinical trials involving autologous MSC transplantation and their limitations.

Keywords: SCI, MSCs, clinical trials

1. Introduction

Spinal cord injury (SCI) is an important clinical problem with significant socioeconomic impact worldwide.

SCI is a catastrophic event involving damage to the spinal cord (SC) that causes morphological and physiological changes leading to biomechanical and functional disorders in patients [1]. This condition induces acute and chronic inflammatory processes that can result in temporary or permanent repercussions including paraplegia, quadriplegia, or even death [2].

The pathophysiology of SCI is very complicated, and it consists of a primary and a secondary phase. The primary phase occurs immediately after the damage to the SC causing cell death at the epicenter of the injury as well as the beginning of the pro-inflammatory response [3]. The secondary phase starts 2 hours after the damage and can last up to 6 months. During this phase the extent of the injury increases in response to the augmented pro-inflammatory factors which contribute to induce local edema, ischemia, vascular alterations, ionic dysregulations, and oxidative

stress [3, 4]. These prejudicial mechanisms persist during the chronic stages of the injury, and although their intensity is diminished, the neurological function continues to decline [5]. Most of the post-traumatic neuronal degeneration involves an uncontrollable cascade of destructive mechanisms that are still incompletely understood and remain a challenge for scientists [6].

The current therapy for SCI involves surgical decompression and steroid administration; however, both of them only show minimal efficiency, and the need for an effective therapy is continuously rising [7]. Therefore, the transplantation of stem cells as a novel therapeutic approach has received increasing attention due to their promising results in neurological recovery in SCI [8–10]. Among them, mesenchymal stem cells (MSCs) demonstrate to be a valuable promising therapy due to their significant autocrine and paracrine activity which help to induce the proliferation and differentiation of different cell types and to exert immunomodulatory effects in the microenvironment of the host [6, 11]. MSCs, anti-inflammatory molecules, and trophic factors are capable of supporting axonal growth to promote angiogenesis, remyelination, and protection against apoptotic cell death [12]. Furthermore, MSCs possess a varied spectrum of therapeutic properties such as neuroprotection after glutamate excitotoxicity [13, 14], reduction in protein levels associated with stress and reactive oxygen species [15] and pro-inflammatory cytokines [16], M1 macrophage polarization to the M2 pro-repair activated phenotype [17], secretion of neurotrophic factors [16, 18, 19], and their ability to produce numerous exosomes.

In addition, MSCs have minimal immunoreactivity towards the host as well as a limited chance of developing a tumor and are particularly appealing due to their wide range of advantages over other types of stem cells [20]. Finally, we will discuss clinical trials of improvement using autologous and allogeneic MSCs after acute and chronic SCI.

2. General aspects of MSCs

MSCs are adult stem cells with self-renewing and differentiation abilities. These cells can be isolated from different sources (bone marrow, adipose tissue, umbilical cord (UC), and amniotic fluid) and are easily preserved without raising any ethical issue [21]. Mammalian bone marrow is the best understood niche that harbors hematopoietic stem cells (HSCs), and MSCs are believed to provide the basis for the physical structures of the niche [22]. Moreover, MSCs are defined as multipotent cells that are thought to regulate the self-renewal, proliferation, and differentiation of the HSCs through the production of cytokines and intracellular signals that are initiated by cell-to-cell interaction. Lastly, MSCs can differentiate into cells from different lineages, such as osteoblasts, cartilage cells, fibroblasts, muscle cells, fat cells, and neurons [23, 24].

3. Markers of MSCs

Most researchers have suggested minimal criteria to define MSCs. The International Society for Cellular Therapy (ISCT) established specific criteria in order to identify unique populations of MSCs [25].

1. MSCs must be plastic adherent when maintained under standard culture conditions.

2. MSCs must be positive for CD105, CD90, CD73, CD29, CD44, CD71, and CD106 and be negative for the expression of hematopoietic markers such as CD34, CD45, HLA-DR, CD14, MHC-II, CD11b, and CD14 and express low levels of MHC-I.

3. MSCs must differentiate in vitro at least in osteoblasts, adipocytes, and chondroblasts [25, 26].

4. MSCs: biological properties

MSCs are well known for their ability to differentiate into numerous cell lineages, but, besides their cell multipotential reprogramming capacity, they promise to be an effective candidate therapy in clinical trials for different human pathologies due to their successful homing, immunomodulation, and tissue repairing [27]. Moreover, exosomes from MSCs are being considered the most important factor of the therapeutic effects of MSCs as they could be used as molecule exchangers and natural drug delivery vehicles [28].

4.1 Homing and chemotactic activity

Several studies have shown that MSCs are capable of migrating selectively and exert homing capabilities to different organs [29, 30]. Even if they are transplanted by local or systemic pathways, MSCs are principally guided to damaged tissues by the coordinate expression of specific receptors and ligands that allow them to reach their desired target and effectuate different mechanisms [31]. Additionally, MSCs possess a high chemotactic activity that increases the recruitment of different cells. Indeed, fibroblasts accelerate migration, proliferation, and integrin expression in response to MSC secretome [32, 33]. Similarly, neutrophils increase migration rate and immunological response when they are stimulated with MSCs after microbial challenge in vitro [34, 35]. In murine SCI models, the MSC-grafted SC has proven to amplify granulocytes and antigen-presenting cell recruitment in early stages by a wide variety of cytokines and chemokines such as CXCL10, CXCL12, CXCL1, and CL5 to boost SC recovery [34, 36].

4.2 Microenvironment immunomodulation

MSCs have proven to regulate the immune response through cell-to-cell contact and by the secretion of soluble mediators including cytokines, prostaglandins, enzymes, and proapoptotic and antiapoptotic molecules [27, 37–39]. Different studies involving MSC transplantation in exacerbated immune response models such as peritonitis and ulcerative colitis ameliorate inflammation by reducing the expression levels of pro-inflammatory cytokines such as interleukin-1 beta, interleukin-12, interleukin-6, and tumor necrosis factor-α (TNFα). In addition, these cells exert a decrease of the classical phenotype M1 marker and an increase of the alternative phenotype M2, as well as a marked macrophage reprogramming from M1 to M2 [17, 40–42]. Moreover, MSCs can suppress T cell activation and proliferation by downregulating the expression of costimulatory molecules on the surface of dendritic cells [43], interleukin-10, transforming growth factor-B (TGFβ), nitric oxide, and indoleamine 2,3-dioxygenase enzyme production in response to inflammation as well as interleukin-2 absorption [37, 44, 45]. Similarly, B cell activation can be disturbed, and the regulatory B cell phenotype can be promoted [46, 47].

4.3 Tissue repairing and regeneration

MSCs participate in repairing many tissues, mostly by the secretion of TGFβ and vascular endothelial growth factor (VEGF) to promote angiogenesis [48], extracellular matrix remodeling, and reduction of the scar formation in chronic wounds [49, 50]. Similarly, in pathologies where gliosis, demyelination, and neuroinflammation occur, MSCs have shown neuroprotective activities such as vascular stabilization and angiogenesis by tight junction protein expression [51], neuronal suppression apoptosis [52, 53], glia hypertrophy prevention [54], and promotion of myelinization by the activation of oligodendrocyte precursor cells [53, 55]. Additionally, MSCs promote synaptic transmission [56], neurite outgrowth, and axonal sprouting mostly by excretion of trophic factors including brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) [12, 57]. SCI models motor skills are increased [58] inclusively; bladder and erectile dysfunction improvement have been reported [59, 60].

4.4 Multipotential capacity

Originally it was believed that MSCs could exclusively differentiate into cells from the mesodermal lineage [23, 24]; however, in the last 20 years many authors have proven that a proper microenvironment can promote greater plasticity and that MSCs from different sources can differentiate into dermal, neural, or glial cells in vitro and in vivo when they are exposed to neurotrophic factors and specific cytokines [61–63]. Smooth muscle and endothelial cells derived from MSCs can be detected and improve heart functions in ischemic myocardium models [64]. Also, skin, articular cartilage, and bone regeneration have been reported, but mostly when MSCs are combined with natural and artificial scaffolds or when genetically modified [65–67]. In order to achieve CNS regeneration, different sources of MSCs and culture methods have been tested in murine SCI models; however, transplants have demonstrated to improve functional recovery by differentiation into neurons, astrocytes, but mostly oligodendrocytes [54, 55, 58].

4.5 Exosomes as mechanisms for cell-to-cell communication and drug delivery vehicles

Exosomes are extracellular vesicles released by many cells, including MSCs. Their length is between 30 and 100nm, and they can bind to cells through receptor and ligand interaction or by fusion with the target cell membrane to deliver high amounts of cytokines, growth factors, microRNAs, and mRNAs capable of modifying peptide and protein synthesis [60]. Thus, the derived MSC exosomes could be the most attractive therapy in SCI models since neuronal differentiation from MSCs remains poor [58, 68] and several studies show that the regenerative and anti-inflammatory mechanisms are mostly mediated by paracrine factors [27, 36, 69–71]. Furthermore, MSC exosomes are natural drug delivery vehicles that can be modified and produced in high quantities [28, 72, 73]. MSCs have proven to be safe in many different preclinical studies; however, clinical trials involving exosomes in SCI therapy are not yet recruited due to the fact that optimal MSC culture conditions and protocols for exosome isolation is still to be established (www.clinicaltrials.gov).

5. MSCs in the clinic

The promising results of MSCs in preclinical studies encouraged their use in humans; however, the results obtained in the clinical trials still remain controversial

and do not replicate what was previously reported in experimental animal studies. In this section we will review the results obtained from the main clinical trials involving MSC transplantation as well as their type of application, properties, limitations, and future directions.

Most of the first clinical studies describing reporting the application of MSCs were focused on describing the transplantation technique, the safety, and the evidence of any adverse reactions. Moviglia et al. conducted a preliminary report that described the intra-arterial administration of bone marrow (BM) MSCs (BM-MSCs) in two patients with chronic SCI in combination with neurorehabilitation programs. Patient 1 presented paraplegia at the eighth thoracic vertebra (T8) with a sensitive level corresponding to T6, while patient 2 presented severe quadriplegia with a lesion that extended from his third to fifth cervical vertebrae (C3–C5) and a sensitive level corresponding to C2. After 6 months, both patients improved their motor and sensory functions without having any secondary effects. The motor level of patient 1 now corresponds to his first sacral metamere (S1) and his sensitive level to the fourth sacral metamere (S4), while sensory and motor functions from patient 2 reached T1–T2 [74]. Similar results, in terms of the safety, were obtained in a pilot study conducted by Pal et al., where 30 patients with complete cervical or thoracic SCI (ASIA scale rating system class A) received intrathecal injections of MSCs via lumbar puncture and none of them presented any adverse effects in the following 1–3 years [75]. However, only the patients with less than 6 months of thoracic-level injury experienced improvement in their quality of life and degree of independence according to Barthel's Index (BI). Despite these improvements, there was no significant change in the ASIA score and in magnetic resonance imaging (MRI). Furthermore, due to the homing abilities of the MSCs, Ra et al. also tested the toxicity, tumorigenicity, and therapeutic potential of the intravenous administration of adipose tissue-derived MSCs in eight patients with more than 12 months of SCI. After 3 months the therapy demonstrated to be safe and not promoting tumor growth [76]. In addition, this study described limited motor recovery where only one patient with ASIA A demonstrated improvement to ASIA grade C. Lastly, other studies have also demonstrated the safety and lack of evidence of any severe adverse reactions with the intrathecal administration of MSCs [77, 78].

Moving forward, Sykova et al. conducted a nonrandomized phase I/phase II clinical trial comparing the functional improvement and safety of intra-arterial versus intravenous administration of BM-MSCs in 20 patients with SCI at the cervical or thoracic level. The clinical characterization described 15 patients with ASIA grade A and 5 patients with ASIA grade B (incomplete SCI). Both intra-arterial group (n=7) and the intravenous group (n=13) contained patients with acute and chronic phases of SCI. The study found significant functional improvements (motor and sensory) in five acute patients and only in one chronic patient. In the intra-arterial group, all four subacute patients exhibited a significant improvement in their ASIA score or Frankel score as well as a marked recovery of motor and somatosensory evoked potentials (MEPs and SEPs). However, in the intravenous group, only one patient demonstrated an improved ASIA score as well as electrophysiology results. Interestingly most of the patients who had functional improvements received the administration of the MSCs close to the injury site suggesting that the administration route through the vertebral artery or into the cerebrospinal fluid might lead to the best outcome. This study also describes that 3–4 weeks after the injury appears to be the best therapeutic window to administer the cells [79]. These results are also supported by another study carried out by Park et al. where they showed improved motor and sensory function in 5 out of 6 patients who received intraspinal implantation of BM-MSCs 7 days post-injury in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF)

[80]. Four patients demonstrated a significant improvement in their American Spinal Injury Association Impairment Scale (AIS) grades from A to C, while one patient improved to AIS B from A. Lastly this study also describes those 3–4 weeks after the injury appears to be the best therapeutic window to administer the cells [79].

As many studies supported the safety of this therapy, more scientists focused on comparing and trying to find different types of MSC transplantation. Geffner et al. reported eight thoracic SCI cases (four acute and four chronic) with the administration of BM-MSCs through many different administration routes such as intravenous, intraspinal, and directly into the spinal canal in order to assure that the cells will reach their target. Over the course of 2 years, patients showed significant improvements in their quality of life measured by the BI score as well as certain motor recovery measured by the ASIA, Ashworth, and Frankel scores. All four patients of the acute group experienced an improvement in the ASIA score from A to C, while chronic patients had a lesser recovery improving from an ASIA score of B–C to C–D. Improvement of bladder control was the most important aspect in augmenting their quality of life; however, there were also many other important motor improvements, which cannot be correctly represented in the ASIA score [81]. In addition, other studies furtherly support the therapeutic potential of MSCs in improving the urinary functions of SCI patients which majorly contributes to increasing their self-care ability [82, 83]. This study also demonstrated the feasibility and safety of multiple administration routes. Moreover, the study conducted by Jeon et al. discussed the effectiveness of the intraspinal application of BM-MSCs in 10 patients with complete cervical SCI. After 6 months 6 patients demonstrated motor improvements in the upper limbs by measuring electrophysiological parameters (electromyography, nerve conduction velocity, SEP, MEP) as well as morphological changes described by magnetic resonance imaging (MRI) at the site of the lesion. In addition, three out of those six patients exhibited a significant increase in the performance of daily tasks. However, the ASIA/Frankel motor grade remained the same and did not reflect these motor improvements. This study also reported the absence of any major adverse effect or neoplasm growth over the course of 3 years, furtherly supporting the safety of this therapy [84].

Karamouzian et al. conducted one of the first studies to introduce a control group in the field of MSCs and SCI. This nonrandomized clinical trial discussed their therapeutic potential by comparing the outcome of 11 patients (7 males and 4 females with mean age of 33.3 ± 8.9 years) with complete subacute SCI who received BM-MSC transplantation via lumbar puncture with a control group (n=20). Five patients in the study group and 12 patients in the control group presented spinal fracture at T12 and L1 levels, while the remaining patients presented a lesion between T1 and T11. After almost 3 years of follow-up, five patients of the experimental group and three patients of the control group exhibited noticeable recovery (a two-grade improvement from baseline, i.e., from ASIA A to C); however, the results were statistically borderline, and there is no clear evidence of the therapeutic potential of these MSCs [85]. In a similar study, Dai et al. discussed the effectiveness of BM-MSCs in complete and chronic SCI. This study randomly assigned 40 patients with complete and chronic SCI into a treatment group (n=20) and a control group (n=20). After 6 months of follow-up, 50% of the treatment group demonstrated significant motor recovery as well as an improvement in ASIA score and in electrophysiological examinations. In addition, most of the patients in the treatment group exhibited a significant clinical improvement in terms of the amount of residual urinary volume, pinprick sensory, and light touch, while the control group did not exhibit any significant motor or sensorial improvements [82]. Both of these studies suggest that BM-MSCs might help improve neurological function

in complete and chronic SCI, and they present no evidence of any severe complications or major adverse events in any of the patients.

Although stem cell therapy has demonstrated that they possess the therapeutic potential to be combined with neurorehabilitation, Cheng et al. analyzed the effect of UC-MSCs in comparison with neurorehabilitation and self- healing in 34 patients with thoracolumbar SCI and AIS A grading. Patients were divided into three groups: the UC-MSC treatment group, the rehabilitation group, and the control group. After 6 months around 70% of the patients in the treatment group experienced a significant motor recovery and noticeable improvement in muscle tension and self-care ability which involves an increase in the strength of the abdomen, waist, and lower limbs. Meanwhile, only 36% of the patients treated with neurorehabilitation exhibited certain improvements in these aspects, and the control group showed no significant changes in motor recovery, sensation, or self-care ability. In terms of bladder functions, the treatment group showed a decrease in residual urinary volume and maximum detrusor pressure as well as an increase in bladder capacity and urinary flow in comparison with the other two groups [86]. Later on, El-Kheir et al. decided to compare the use of BM-MSCs in combination with physical therapy with the use of physical therapy alone in 70 chronic cervical and thoracic SCI patients (25 AIS A and 45 AIS B) in a phase I/phase II controlled single-blind clinical trial. After 18 months of follow-up, 46% of the stem cell therapy group exhibited functional improvement and an increase in both motor and dermatome scores by the ASIA and AIS scoring as well as a significant improvement in motor, pinprick, and light touch sensory and functional independence scores over the treated group with physical therapy alone [87]. These studies suggest that BM-MSCs can be combined with additional therapies in order to boost their therapeutic potential.

Equally important, El-Kheir et al. described that thoracic SCI patients with smaller lesions and lower duration of the injury had a higher increase of functional improvement in comparison with patients with cervical SCI [87]. Similar results were obtained in the study carried out by Mendonca et al. which demonstrated a statistically significant correlation between the neurological recovery and both the level and size of the injury in patients with chronic (>6 months) thoracic or lumbar SCI. In addition, after the intra-lesion administration of BM-MSCs, all of the 14 patients demonstrated certain improvements in tactile sensitivity and 8 subjects showed some improvement in the motor functions of the lower limbs reflected by an improvement in their ASIA grading from A to B or C [88].

As the amount of beneficial but limited results grew, the amount of the transplanted MSCs and number of administrations started to gain attention. Vaquero et al. conducted a series of clinical trials involving different numbers of MSC administrations in SCI. The first study consisted of a clinical trial involving 12 patients with complete (ASIA A) and chronic thoracic SCI who received two separate transplantations of BM-MSCs in the subarachnoid space. All patients exhibited certain degree of sensorial improvement (pinprick sensitivity and light touch sensitivity), and 50% of the patients showed motor activity below the injury level according to clinical and neurophysiological studies (SEPs and MEPs). More than 30% of the patients improved their AIS A score from A to B or C, and 83% of the patients presented improvement in urodynamic function including possibility of voluntary micturition (5 patients), increased bladder capacity at filling in (8 patients), decreased detrusor pressure at bladder filling in (9 patients), and increased bladder compliance (10 patients). In addition, they hypothesize that the clinical improvement was dose-dependent [89]. The second study consisted of 10 patients with incomplete (ASIA B and C) cervical, thoracic, and lumbar SCI who received 4 subarachnoid administrations of MSCs. Besides the variable degree of sensorial and motor improvement, after 12 months of the first dosage almost all the

patients showed noticeable improvements in bowel and bladder control as well as evidence of muscle reinnervation in electromyographic studies. Furthermore, half of them demonstrated a decrease in spasticity by the Penn and Ashworth scales, and after the third dosage of MSCs, all the patients exhibited an increase in the values of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), glial-derived neurotrophic factor (GDNF), ciliary neurotrophic factor (CNF), and neurotrophin 3 (NT-3) and neurotrophin 4 (NT-4). However, the difference with the basal mean concentration was not statistically significant [90]. Lastly, their third study consisted of a phase II clinical trial with the administration of three intrathecal injections of MSCs in nine patients with chronic SCI. However, this time 44.4% of the patients demonstrated important improvements in voluntary muscle contraction, motor power, spasm, spasticity, neuropathic pain, and sexual function (IANR-SCIFRS scale) along with evidence of muscle reinnervation. In addition, more than half of the patients showed improved somatosensory and motor evoked potentials [91]. Taken all together, Vaquero and colleagues demonstrate that the subarachnoid administration of MSCs is a safe procedure and that the clinical improvement may increase in a dose-dependent manner. These results were furtherly supported by a study carried out by Oh et al. where a single intramedullary administration of MSC in 16 patients with chronic SCI ASIA B demonstrated very limited therapeutic efficacy. Only two patients demonstrated enhanced motor recovery [92].

6. Study limitations and future directions for MSCs

Overall, the use of MSCs in SCI appears to be safe and without any major evidence of severe adverse reactions. However, the results obtained in the clinical trials so far do not concrete the promising results obtained in the preclinical trials. This may be due to the fact that preclinical studies normally utilize specific animal models with standardized protocols to produce the injury as well as preestablished treatments and timing of the transplantation which cannot be replicated in a human study. In clinical trials, most of these conditions depend heavily on chance, the traumatic event, and the emergency setting which may differ a lot from the controlled atmosphere of an animal experiment. In addition, there is a great lack of phase III clinical trials due to financial and ethical reasons. As mentioned before, one of the few phase III clinical trials held by Oh et al. showed weak and limited therapeutic efficacy [92]. Further investigation is needed to determine accurate parameters for its clinical use in SCI such as optimal therapeutic protocols involving type, preparation, number of cells administered, timing of transplantation, and administration route.

On the other hand, thanks to the technological revolution, scientists have now started to investigate the use of MSCs in combination with new biomaterials in order to promote tissue repair and to improve cell survival [6]. A study conducted by Xiao et al. analyzed the therapeutic effect of MSC transplantation in combination with a collagen scaffold which is known to support cell migration and adhesion [93]. After the transplant the injury status of the patients changed from ASIA A to ASIA C accompanied by a significant improvement in motor, sensory, and urinary functions [94]. Furthermore, the possibility of combining MSCs with hydrogels is particularly appealing due to their capacity to be injected with minimal invasion and to be loaded with specific drugs that can be furtherly released in a controlled manner [95]. Moreover, MSCs' ability to induce the production of neurotrophic, immunomodulating, and neuroprotective factors needs further investigation in order to be fully understood and furtherly enhanced, aiming to improve the clinical outcomes. Lastly, the homing properties of the MSCs could be useful to transport specific target drugs to the site of the lesion and thus acting as a vector [96].

7. Conclusion

In conclusion, MSCs represent a practical therapy in the search for a new treatment for SCI; this may be due to the fact that MSC therapy presents a large spectrum of favorable assets that make it particularly appealing. First, MSCs can be isolated from non-embryonic tissues (BM, adipose tissue, UC, and amniotic fluid, among others) via noninvasive techniques and are easily preserved and expanded in vitro. Furthermore, MSCs possess migratory properties that allow them to be administered through different routes and have minimal immunoreactivity towards the host, as well as a limited chance of developing a tumor. Numerous clinical trials have demonstrated their safety for transplantation in humans as well as their lack of any major side effects. However, an enormous improvement in motor recovery and sensory function is still missing, bringing out that additional investigation and new phase III clinical trials are needed in order to fully understand the mechanism of action of MSCs as well as the pathological mechanisms which prevent the restoration of neural circuits in SCI. Lastly, the use of combinatory strategies with specific drugs, biomaterials, or neurorehabilitation may be the key factor to translate their promising results into the clinical practice.

Author details

Karla Soria-Zavala, Julián García-Sánchez and Roxana Rodríguez-Barrera*
Centro de Investigación en Ciencias de la Salud (CICSA), Universidad Anáhuac México Campus Norte, Huixquilucan, México

*Address all correspondence to: roxana.rodriguezb@anahuac.mx

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References

[1] Ahuja CS, Wilson JR, Nori S, Kotter MRN, Druschel C, Curt A, et al. Traumatic spinal cord injury. Nature Reviews. Disease Primers. 2017;**3**:17018

[2] Jain NB, Ayers GD, Peterson EN, Harris MB, Morse L, O'Connor KC, et al. Traumatic spinal cord injury in the United States, 1993-2012. Journal of the American Medical Association. 2015;**313**(22):2236-2243

[3] Norenberg MD, Smith J, Marcillo A. The pathology of human spinal cord injury: Defining the problems. Journal of Neurotrauma. 2004;**21**(4):429-440

[4] Kwon BK, Tetzlaff W, Grauer JN, Beiner J, Vaccaro AR. Pathophysiology and pharmacologic treatment of acute spinal cord injury. The Spine Journal. 2004;**4**(4):451-464

[5] Bravo G, Ibarra A, Guizar-Sahagun G, Rojas G, Hong E. Indorenate improves motor function in rats with chronic spinal cord injury. Basic & Clinical Pharmacology & Toxicology. 2007;**100**(1):67-70

[6] Cofano F, Boido M, Monticelli M, Zenga F, Ducati A, Vercelli A, et al. Mesenchymal stem cells for spinal cord injury: Current options, limitations, and future of cell therapy. International Journal of Molecular Sciences. 2019;**20**(11):2698

[7] Wilson JR, Tetreault LA, Kwon BK, Arnold PM, Mroz TE, Shaffrey C, et al. Timing of decompression in patients with acute spinal cord injury: A systematic review. Global Spine Journal. 2017;**7**(3 Suppl):95S-115S

[8] Keirstead HS, Nistor G, Bernal G, Totoiu M, Cloutier F, Sharp K, et al. Human embryonic stem cell-derived oligodendrocyte progenitor cell transplants remyelinate and restore locomotion after spinal cord injury. The Journal of Neuroscience. 2005;**25**(19):4694-4705

[9] Jin MC, Medress ZA, Azad TD, Doulames VM, Veeravagu A. Stem cell therapies for acute spinal cord injury in humans: A review. Neurosurgical Focus. 2019;**46**(3):E10

[10] Oliveri RS, Bello S, Biering-Sørensen F. Mesenchymal stem cells improve locomotor recovery in traumatic spinal cord injury: Systematic review with meta-analyses of rat models. Neurobiology of Disease. 2014;**62**:338-353

[11] Baez-Jurado E, Hidalgo-Lanussa O, Barrera-Bailón B, Sahebkar A, Ashraf GM, Echeverria V, et al. Secretome of mesenchymal stem cells and its potential protective effects on brain pathologies. Molecular Neurobiology. 2019;**56**(10):6902-6927

[12] Quertainmont R, Cantinieaux D, Botman O, Sid S, Schoenen J, Franzen R. Mesenchymal stem cell graft improves recovery after spinal cord injury in adult rats through neurotrophic and pro-angiogenic actions. PLoS One. 2012;**7**(6):e39500

[13] Lu S, Lu C, Han Q, Li J, Du Z, Liao L, et al. Adipose-derived mesenchymal stem cells protect PC12 cells from glutamate excitotoxicity-induced apoptosis by upregulation of XIAP through PI3-K/Akt activation. Toxicology. 2011;**279**(1-3):189-195

[14] Voulgari-Kokota A, Fairless R, Karamita M, Kyrargyri V, Tseveleki V, Evangelidou M, et al. Mesenchymal stem cells protect CNS neurons against glutamate excitotoxicity by inhibiting glutamate receptor expression and function. Experimental Neurology. 2012;**236**(1):161-170

[15] Lanza C, Morando S, Voci A, Canesi L, Principato MC, Serpero LD, et al. Neuroprotective mesenchymal stem cells are endowed with a potent antioxidant effect in vivo. Journal of Neurochemistry. 2009;**110**(5):1674-1684

[16] Zhou C, Zhang C, Chi S, Xu Y, Teng J, Wang H, et al. Effects of human marrow stromal cells on activation of microglial cells and production of inflammatory factors induced by lipopolysaccharide. Brain Research. 2009;**1269**:23-30

[17] Nakajima H, Uchida K, Guerrero AR, Watanabe S, Sugita D, Takeura N, et al. Transplantation of mesenchymal stem cells promotes an alternative pathway of macrophage activation and functional recovery after spinal cord injury. Journal of Neurotrauma. 2012;**29**(8):1614-1625

[18] Crigler L, Robey RC, Asawachaicharn A, Gaupp D, Phinney DG. Human mesenchymal stem cell subpopulations express a variety of neuro-regulatory molecules and promote neuronal cell survival and neuritogenesis. Experimental Neurology. 2006;**198**(1):54-64

[19] Hawryluk GW, Mothe A, Wang J, Wang S, Tator C, Fehlings MG. An in vivo characterization of trophic factor production following neural precursor cell or bone marrow stromal cell transplantation for spinal cord injury. Stem Cells and Development. 2012;**21**(12):2222-2238

[20] Lu LL, Liu YJ, Yang SG, Zhao QJ, Wang X, Gong W, et al. Isolation and characterization of human umbilical cord mesenchymal stem cells with hematopoiesis-supportive function and other potentials. Haematologica. 2006;**91**(8):1017-1026

[21] Dasari VR, Veeravalli KK, Dinh DH. Mesenchymal stem cells in the treatment of spinal cord injuries: A review. World Journal of Stem Cells. 2014;**6**(2):120-133

[22] Miura Y, Gao Z, Miura M, Seo BM, Sonoyama W, Chen W, et al. Mesenchymal stem cell-organized bone marrow elements: An alternative hematopoietic progenitor resource. Stem Cells. 2006;**24**(11):2428-2436

[23] Le Blanc K, Davies LC. MSCs-cells with many sides. Cytotherapy. 2018;**20**(3):273-278

[24] Uccelli A, Moretta L, Pistoia V. Mesenchymal stem cells in health and disease. Nature Reviews. Immunology. 2008;**8**(9):726-736

[25] Chamberlain G, Fox J, Ashton B, Middleton J. Concise review: Mesenchymal stem cells: Their phenotype, differentiation capacity, immunological features, and potential for homing. Stem Cells. 2007;**25**(11):2739-2749

[26] Squillaro T, Peluso G, Galderisi U. Clinical trials with Mesenchymal stem cells: An update. Cell Transplantation. 2016;**25**(5):829-848

[27] Baberg F, Geyh S, Waldera-Lupa D, Stefanski A, Zilkens C, Haas R, et al. Secretome analysis of human bone marrow derived mesenchymal stromal cells. Biochimica et Biophysica Acta, Proteins and Proteomics. 2019;**1867**(4):434-441

[28] Chen TS, Arslan F, Yin Y, Tan SS, Lai RC, Choo AB, et al. Enabling a robust scalable manufacturing process for therapeutic exosomes through oncogenic immortalization of human ESC-derived MSCs. Journal of Translational Medicine. 2011;**9**:47

[29] Devine SM, Cobbs C, Jennings M, Bartholomew A, Hoffman R. Mesenchymal stem cells distribute to a wide range of tissues following systemic

infusion into nonhuman primates. Blood. 2003;**101**(8):2999-3001

[30] Gao J, Dennis JE, Muzic RF, Lundberg M, Caplan AI. The dynamic in vivo distribution of bone marrow-derived mesenchymal stem cells after infusion. Cells, Tissues, Organs. 2001;**169**(1):12-20

[31] Nitzsche F, Müller C, Lukomska B, Jolkkonen J, Deten A, Boltze J. Concise review: MSC adhesion cascade-insights into homing and transendothelial migration. Stem Cells. 2017;**35**(6):1446-1460

[32] Smith AN, Willis E, Chan VT, Muffley LA, Isik FF, Gibran NS, et al. Mesenchymal stem cells induce dermal fibroblast responses to injury. Experimental Cell Research. 2010;**316**(1):48-54

[33] Sarojini H, Estrada R, Lu H, Dekova S, Lee MJ, Gray RD, et al. PEDF from mouse mesenchymal stem cell secretome attracts fibroblasts. Journal of Cellular Biochemistry. 2008;**104**(5):1793-1802

[34] Brandau S, Jakob M, Bruderek K, Bootz F, Giebel B, Radtke S, et al. Mesenchymal stem cells augment the anti-bacterial activity of neutrophil granulocytes. PLoS One. 2014;**9**(9):e106903

[35] Brandau S, Jakob M, Hemeda H, Bruderek K, Janeschik S, Bootz F, et al. Tissue-resident mesenchymal stem cells attract peripheral blood neutrophils and enhance their inflammatory activity in response to microbial challenge. Journal of Leukocyte Biology. 2010;**88**(5):1005-1015

[36] Neirinckx V, Agirman G, Coste C, Marquet A, Dion V, Rogister B, et al. Adult bone marrow mesenchymal and neural crest stem cells are chemoattractive and accelerate motor recovery in a mouse model of spinal

cord injury. Stem Cell Research & Therapy. 2015;**6**:211

[37] Laing AG, Fanelli G, Ramirez-Valdez A, Lechler RI, Lombardi G, Sharpe PT. Mesenchymal stem cells inhibit T-cell function through conserved induction of cellular stress. PLoS One. 2019;**14**(3):e0213170

[38] Sato K, Ozaki K, Oh I, Meguro A, Hatanaka K, Nagai T, et al. Nitric oxide plays a critical role in suppression of T-cell proliferation by mesenchymal stem cells. Blood. 2007;**109**(1):228-234

[39] Cantinieaux D, Quertainmont R, Blacher S, Rossi L, Wanet T, Noël A, et al. Conditioned medium from bone marrow-derived mesenchymal stem cells improves recovery after spinal cord injury in rats: An original strategy to avoid cell transplantation. PLoS One. 2013;**8**(8):e69515

[40] Song WJ, Li Q, Ryu MO, Ahn JO, Bhang DH, Jung YC, et al. TSG-6 released from intraperitoneally injected canine adipose tissue-derived mesenchymal stem cells ameliorate inflammatory bowel disease by inducing M2 macrophage switch in mice. Stem Cell Research & Therapy. 2018;**9**(1):91

[41] Song JY, Kang HJ, Hong JS, Kim CJ, Shim JY, Lee CW, et al. Umbilical cord-derived mesenchymal stem cell extracts reduce colitis in mice by re-polarizing intestinal macrophages. Scientific Reports. 2017;**7**(1):9412

[42] Nakajima K, Obata H, Iriuchijima N, Saito S. An increase in spinal cord noradrenaline is a major contributor to the antihyperalgesic effect of antidepressants after peripheral nerve injury in the rat. Pain. 2012;**153**(5):990-997

[43] Zhang Y, Ge XH, Guo XJ, Guan SB, Li XM, Gu W, et al. Bone marrow Mesenchymal stem cells inhibit the function of dendritic cells by

secreting Galectin-1. BioMed Research International. 2017;**2017**:3248605

[44] Rasmusson I, Ringdén O, Sundberg B, Le Blanc K. Mesenchymal stem cells inhibit lymphocyte proliferation by mitogens and alloantigens by different mechanisms. Experimental Cell Research. 2005;**305**(1):33-41

[45] Nasef A, Chapel A, Mazurier C, Bouchet S, Lopez M, Mathieu N, et al. Identification of IL-10 and TGF-beta transcripts involved in the inhibition of T-lymphocyte proliferation during cell contact with human mesenchymal stem cells. Gene Expression. 2007;**13**(4-5):217-226

[46] Cho KA, Lee JK, Kim YH, Park M, Woo SY, Ryu KH. Mesenchymal stem cells ameliorate B-cell-mediated immune responses and increase IL-10-expressing regulatory B cells in an EBI3-dependent manner. Cellular & Molecular Immunology. 2017;**14**:895-908

[47] Asari S, Itakura S, Ferreri K, Liu CP, Kuroda Y, Kandeel F, et al. Mesenchymal stem cells suppress B-cell terminal differentiation. Experimental Hematology. 2009;**37**(5):604-615

[48] Bronckaers A, Hilkens P, Fanton Y, Struys T, Gervois P, Politis C, et al. Angiogenic properties of human dental pulp stem cells. PLoS One. 2013;**8**(8):e71104

[49] Wan J, Xia L, Liang W, Liu Y, Cai Q. Transplantation of bone marrow-derived mesenchymal stem cells promotes delayed wound healing in diabetic rats. Journal Diabetes Research. 2013;**2013**:647107

[50] Berry MF, Engler AJ, Woo YJ, Pirolli TJ, Bish LT, Jayasankar V, et al. Mesenchymal stem cell injection after myocardial infarction improves myocardial compliance. American Journal of Physiology. Heart and Circulatory Physiology. 2006;**290**(6):H2196-H2203

[51] Zacharek A, Chen J, Cui X, Li A, Li Y, Roberts C, et al. Angiopoietin1/ Tie2 and VEGF/Flk1 induced by MSC treatment amplifies angiogenesis and vascular stabilization after stroke. Journal of Cerebral Blood Flow and Metabolism. 2007;**27**(10):1684-1691

[52] Gu Y, Zhang Y, Bi Y, Liu J, Tan B, Gong M, et al. Mesenchymal stem cells suppress neuronal apoptosis and decrease IL-10 release via the TLR2/ NFκB pathway in rats with hypoxic-ischemic brain damage. Molecular Brain. 2015;**8**(1):65

[53] Wang F, Yasuhara T, Shingo T, Kameda M, Tajiri N, Yuan WJ, et al. Intravenous administration of mesenchymal stem cells exerts therapeutic effects on parkinsonian model of rats: Focusing on neuroprotective effects of stromal cell-derived factor-1alpha. BMC Neuroscience. 2010;**11**:52

[54] Yang C, Wang G, Ma F, Yu B, Chen F, Yang J, et al. Repeated injections of human umbilical cord blood-derived mesenchymal stem cells significantly promotes functional recovery in rabbits with spinal cord injury of two noncontinuous segments. Stem Cell Research & Therapy. 2018;**9**(1):136

[55] Jaramillo-Merchán J, Jones J, Ivorra JL, Pastor D, Viso-León MC, Armengól JA, et al. Mesenchymal stromal-cell transplants induce oligodendrocyte progenitor migration and remyelination in a chronic demyelination model. Cell Death & Disease. 2013;**4**:e779

[56] Bae JS, Jin HK, Lee JK, Richardson JC, Carter JE. Bone marrow-derived mesenchymal stem cells contribute to the reduction of amyloid-β deposits and the improvement of

synaptic transmission in a mouse model of pre-dementia Alzheimer's disease. Current Alzheimer Research. 2013;**10**(5):524-531

[57] Lu P, Jones LL, Tuszynski MH. BDNF-expressing marrow stromal cells support extensive axonal growth at sites of spinal cord injury. Experimental Neurology. 2005;**191**(2):344-360

[58] Cízková D, Rosocha J, Vanický I, Jergová S, Cízek M. Transplants of human mesenchymal stem cells improve functional recovery after spinal cord injury in the rat. Cellular and Molecular Neurobiology. 2006;**26**(7-8):1167-1180

[59] Albayrak Ö, Şener TE, Erşahin M, Özbaş-Turan S, Ekentok C, Tavukçu HH, et al. Mesenchymal stem cell therapy improves erectile dysfunction in experimental spinal cord injury. International Journal of Impotence Research. 2019

[60] Valadi H, Ekström K, Bossios A, Sjöstrand M, Lee JJ, Lötvall JO. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nature Cell Biology. 2007;**9**(6):654-659

[61] Woodbury D, Schwarz EJ, Prockop DJ, Black IB. Adult rat and human bone marrow stromal cells differentiate into neurons. Journal of Neuroscience Research. 2000;**61**(4):364-370

[62] Takizawa S. Differentiation of adult bone marrow cells into neurons and endothelial cells in rat brain after stroke in the presence of cytokines. Rinshō Shinkeigaku. 2003;**43**(11):830-831

[63] Kopen GC, Prockop DJ, Phinney DG. Marrow stromal cells migrate throughout forebrain and cerebellum, and they differentiate into astrocytes after injection into neonatal mouse brains. Proceedings of the National Academy of Sciences of the United States of America. 1999;**96**(19):10711-10716

[64] Jiang W, Ma A, Wang T, Han K, Liu Y, Zhang Y, et al. Homing and differentiation of mesenchymal stem cells delivered intravenously to ischemic myocardium in vivo: A time-series study. Pflügers Archiv. 2006;**453**(1):43-52

[65] De Bari C, Dell'Accio F, Luyten FP. Failure of in vitro-differentiated mesenchymal stem cells from the synovial membrane to form ectopic stable cartilage in vivo. Arthritis and Rheumatism. 2004;**50**(1):142-150

[66] Chen J, Chen H, Li P, Diao H, Zhu S, Dong L, et al. Simultaneous regeneration of articular cartilage and subchondral bone in vivo using MSCs induced by a spatially controlled gene delivery system in bilayered integrated scaffolds. Biomaterials. 2011;**32**(21):4793-4805

[67] Laverdet B, Micallef L, Lebreton C, Mollard J, Lataillade JJ, Coulomb B, et al. Use of mesenchymal stem cells for cutaneous repair and skin substitute elaboration. Pathologie Biologie. 2014;**62**(2):108-117

[68] Rooney GE, McMahon SS, Ritter T, Garcia Y, Moran C, Madigan NN, et al. Neurotrophic factor-expressing mesenchymal stem cells survive transplantation into the contused spinal cord without differentiating into neural cells. Tissue Engineering. Part A. 2009;**15**(10):3049-3059

[69] Huang JH, Yin XM, Xu Y, Xu CC, Lin X, Ye FB, et al. Systemic administration of exosomes released from mesenchymal stromal cells attenuates apoptosis, inflammation, and promotes angiogenesis after spinal cord injury in rats. Journal of Neurotrauma. 2017;**34**(24):3388-3396

[70] Liu W, Wang Y, Gong F, Rong Y, Luo Y, Tang P, et al. Exosomes derived from bone Mesenchymal stem cells repair traumatic spinal cord injury by suppressing the activation of A1 neurotoxic reactive astrocytes. Journal of Neurotrauma. 2019;**36**(3):469-484

[71] Lankford KL, Arroyo EJ, Nazimek K, Bryniarski K, Askenase PW, Kocsis JD. Intravenously delivered mesenchymal stem cell-derived exosomes target M2-type macrophages in the injured spinal cord. PLoS One. 2018;**13**(1):e0190358

[72] Yang J, Zhang X, Chen X, Wang L, Yang G. Exosome mediated delivery of miR-124 promotes neurogenesis after ischemia. Molecular Therapy--Nucleic Acids. 2017;**7**:278-287

[73] Cui GH, Guo HD, Li H, Zhai Y, Gong ZB, Wu J, et al. RVG-modified exosomes derived from mesenchymal stem cells rescue memory deficits by regulating inflammatory responses in a mouse model of Alzheimer's disease. Immunity & Ageing. 2019;**16**:10

[74] Moviglia GA, Fernandez Viña R, Brizuela JA, Saslavsky J, Vrsalovic F, Varela G, et al. Combined protocol of cell therapy for chronic spinal cord injury. Report on the electrical and functional recovery of two patients. Cytotherapy. 2006;**8**(3):202-209

[75] Pal R, Venkataramana NK, Bansal A, Balaraju S, Jan M, Chandra R, et al. Ex vivo-expanded autologous bone marrow-derived mesenchymal stromal cells in human spinal cord injury/paraplegia: A pilot clinical study. Cytotherapy. 2009;**11**(7):897-911

[76] Ra JC, Shin IS, Kim SH, Kang SK, Kang BC, Lee HY, et al. Safety of intravenous infusion of human adipose tissue-derived mesenchymal stem cells in animals and humans. Stem Cells and Development. 2011;**20**(8):1297-1308

[77] Hur JW, Cho TH, Park DH, Lee JB, Park JY, Chung YG. Intrathecal transplantation of autologous adipose-derived mesenchymal stem cells for treating spinal cord injury: A human trial. The Journal of Spinal Cord Medicine. 2016;**39**(6):655-664

[78] Satti HS, Waheed A, Ahmed P, Ahmed K, Akram Z, Aziz T, et al. Autologous mesenchymal stromal cell transplantation for spinal cord injury: A phase I pilot study. Cytotherapy. 2016;**18**(4):518-522

[79] Sykova E, Homola A, Mazanec R, Lachmann H, Konradova SL, Kobylka P, et al. Autologous bone marrow transplantation in patients with subacute and chronic spinal cord injury. Cell Transplantation. 2006;**15**(8-9):675-687

[80] Park HC, Shim YS, Ha Y, Yoon SH, Park SR, Choi BH, et al. Treatment of complete spinal cord injury patients by autologous bone marrow cell transplantation and administration of granulocyte-macrophage colony stimulating factor. Tissue Engineering. 2005;**11**(5-6):913-922

[81] Geffner LF, Santacruz P, Izurieta M, Flor L, Maldonado B, Auad AH, et al. Administration of autologous bone marrow stem cells into spinal cord injury patients via multiple routes is safe and improves their quality of life: Comprehensive case studies. Cell Transplantation. 2008;**17**(12):1277-1293

[82] Dai G, Liu X, Zhang Z, Yang Z, Dai Y, Xu R. Transplantation of autologous bone marrow mesenchymal stem cells in the treatment of complete and chronic cervical spinal cord injury. Brain Research. 2013;**1533**:73-79

[83] Kishk NA, Gabr H, Hamdy S, Afifi L, Abokresha N, Mahmoud H, et al. Case control series of intrathecal autologous bone marrow mesenchymal

stem cell therapy for chronic spinal cord injury. Neurorehabilitation and Neural Repair. 2010;**24**(8):702-708

[84] Jeon SR. Et al, Treatment of spinal cord injury with bone marrow-derived, cultured autologous mesenchymal stem cells. Journal of Tissue Engineering and Regenerative Medicine. 2010;**7**(3): 316-322

[85] Karamouzian S, Nematollahi-Mahani SN, Nakhaee N, Eskandary H. Clinical safety and primary efficacy of bone marrow mesenchymal cell transplantation in subacute spinal cord injured patients. Clinical Neurology and Neurosurgery. 2012;**114**(7):935-939

[86] Cheng H, Liu X, Hua R, Dai G, Wang X, Gao J, et al. Clinical observation of umbilical cord mesenchymal stem cell transplantation in treatment for sequelae of thoracolumbar spinal cord injury. Journal of Translational Medicine. 2014;**12**:253

[87] El-Kheir WA, Gabr H, Awad MR, Ghannam O, Barakat Y, Farghali HA, et al. Autologous bone marrow-derived cell therapy combined with physical therapy induces functional improvement in chronic spinal cord injury patients. Cell Transplantation. 2014;**23**(6):729-745

[88] Mendonça MV, Larocca TF, de Freitas Souza BS, Villarreal CF, Silva LF, Matos AC, et al. Safety and neurological assessments after autologous transplantation of bone marrow mesenchymal stem cells in subjects with chronic spinal cord injury. Stem Cell Research & Therapy. 2014;**5**(6):126

[89] Vaquero J, Zurita M, Rico MA, Bonilla C, Aguayo C, Montilla J, et al. An approach to personalized cell therapy in chronic complete paraplegia: The Puerta de Hierro phase I/II clinical trial. Cytotherapy. 2016;**18**(8):1025-1036

[90] Vaquero J, Zurita M, Rico MA, Bonilla C, Aguayo C, Fernández C, et al. Repeated subarachnoid administrations of autologous mesenchymal stromal cells supported in autologous plasma improve quality of life in patients suffering incomplete spinal cord injury. Cytotherapy. 2017;**19**(3):349-359

[91] Vaquero J, Zurita M, Rico MA, Aguayo C, Bonilla C, Marin E, et al. Intrathecal administration of autologous mesenchymal stromal cells for spinal cord injury: Safety and efficacy of the 100/3 guideline. Cytotherapy. 2018;**20**(6):806-819

[92] Oh SK, Choi KH, Yoo JY, Kim DY, Kim SJ, Jeon SR. A phase III clinical trial showing limited efficacy of autologous mesenchymal stem cell therapy for spinal cord injury. Neurosurgery. 2016;**78**(3):436-447. Discussion 47

[93] Tetzlaff W, Okon EB, Karimi-Abdolrezaee S, Hill CE, Sparling JS, Plemel JR, et al. A systematic review of cellular transplantation therapies for spinal cord injury. Journal of Neurotrauma. 2011;**28**(8):1611-1682

[94] Xiao Z, Tang F, Zhao Y, Han G, Yin N, Li X, et al. Significant improvement of acute complete spinal cord injury patients diagnosed by a combined criteria implanted with NeuroRegen scaffolds and mesenchymal stem cells. Cell Transplantation. 2018;**27**(6):907-915

[95] Vismara I, Papa S, Rossi F, Forloni G, Veglianese P. Current options for cell therapy in spinal cord injury. Trends in Molecular Medicine. 2017;**23**(9):831-849

[96] Wang LJ, Zhang RP, Li JD. Transplantation of neurotrophin-3-expressing bone mesenchymal stem cells improves recovery in a rat model of spinal cord injury. Acta Neurochirurgica. 2014;**156**(7):1409-1418