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TOPIC HIGHLIGHT

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Neurotrauma and mesenchymal stem cells treatment: From experimental studies to clinical trials

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Abstract

Mesenchymal stem cell (MSC) therapy has attracted the attention of scientists and clinicians around the world. Basic and pre-clinical experimental studies have highlighted the positive effects of MSC treatment after spinal cord and peripheral nerve injury. These effects are believed to be due to their ability to differentiate into other cell lineages, modulate inflammatory and immunomodulatory responses, reduce cell apoptosis, secrete several neurotrophic factors and respond to tissue injury, among others. There are many pre-clinical studies on MSC treatment for spinal cord injury (SCI) and peripheral nerve injuries. However, the same is not true for clinical trials, particularly those concerned with nerve trauma, indicating the necessity of more well-constructed studies showing the benefits that cell therapy can provide for individuals suffering the consequences of nerve lesions. As for clinical trials for SCI treatment the results obtained so far are not as beneficial as those described in experimental studies. For these reasons basic and pre-clinical studies dealing with MSC therapy should emphasize the standardization of protocols that could be translated to the clinical set with consistent and positive outcomes. This review is based on pre-clinical studies and clinical trials available in the literature from 2010 until now. At the time of writing this article there were 43 and 36 pre-clinical and 19 and 1 clinical trials on injured spinal cord and peripheral nerves, respectively.

Key words: Neurotrauma; Stem cell therapy; Mesenchymal stem cells; Pre-clinical studies; Clinical trials

Core tip: Basic and pre-clinical studies have highlighted the positive effects of mesenchymal stem cell (MSC) treatment after spinal cord injury (SCI) and nerve trauma. There are many pre-clinical studies on MSC treatment for SCI and nerve injuries. However, the same is not true for clinical trials, particularly those concerned with nerve trauma. As for clinical trials for SCI, the results obtained so far are not as beneficial as those described in experimental studies. For these reasons basic and pre-clinical studies dealing with MSC therapy should emphasize the standardization of protocols that could be translated to the clinical set with consistent and positive outcomes.

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SPINAL CORD LESION: MECHANISMS OF DEGENERATION AND REGENERATION

Spinal cord injury (SCI) causes motor and sensory deficits that impair functional performance, and significantly impacts expectancy and quality of life of affected individuals. The estimated annual global incidence of SCI is 15-40 cases per million inhabitants[1]. In addition to the sensory and functional deficits, spinal cord injury also causes great economic impact on the whole society and it is estimated that this impact is greater than 4 billion dollars per year[2].

SCI results from primary and secondary injury mechanisms. Primary injury refers to the immediate physical injury to the spinal cord as a consequence of laceration, contusion, compression, and contraction of the neural tissue[3]. Pathological changes resulting from primary injury mechanisms include severed axons, direct mechanical damage to cells, and ruptured blood vessels. Secondary injury is responsible for the expansion of the injury site which, in turn, limits the restorative process[4,5]. Specific secondary sequel include alterations in local ionic concentrations, loss of regulation of local and systemic blood pressure, reduced spinal cord blood flow, breakdown of the blood-brain barrier, penetration of serum proteins into the spinal cord, inflammatory responses (alterations in chemokines and cytokines), apoptosis, excitotoxicity, calpain proteases activation, neurotransmitter accumulation, production of free radicals/lipid peroxidation, and imbalance of activated metalloproteinases. These changes lead to demyelination, ischemia, necrosis, and apoptosis of spinal cord parenchyma[5]. These intrinsic responses to tissue injury contribute to an environment that is inhibitory to axonal regrowth[6]. As a consequence of these negative influences when axons in the central nervous system (CNS) are damaged they mount a poor regenerative response.

An injury in the central nervous system generally leads to transection of some nerve fibers as well as damage to the surrounding tissues. The distal ends of the damaged axons form dystrophic growth cones that are exposed to a glial hostile microenvironment. During the initial phase of lesion, inhibitors associated with intact myelin oligodendrocyte and myelin debris, such as NOGO (no go), MAG (myelin associated glycoprotein) and OMGp (oligodendrocyte myelin glycoprotein) proteins can restrict axonal growth[7]. In addition, the recruitment of inflammatory cells and astrocytes, in an attempt to restore the blood-brain barrier, leads to the formation of glial scar, which is usually accompanied by cavities filled with astrocytes secreted substances, such as chondroitin sulfate proteoglycans, which also acts as axon growth inhibitory molecules[8,9]. Furthermore, there is also a lack of trophic factors in the lesion milieu due to intrinsic changes in neurons such as atrophy and death after axonal injury. Together, all these inhibitory molecules form a glial microenvironment which is hostile to axonal repair[2,4,10,11].

Although effective treatments for SCI remain limited, there have been many studies in recent years that have promised for the future from a clinical translational perspective. In general, basic science, preclinical, and clinical studies are aimed at overcoming the factors that are involved in impeding recovery from SCI. Current research is aimed at preventing secondary injury, promoting regeneration, and replacing destroyed spinal cord tissue. In particular, a variety of therapies have been addressed to alter neuro-inflammation[12-14], reduce free radical damage[15-17], reduce excitotoxic damage to neurons[18,19], improve blood flow[20,21], and counteract the effects of local ionic changes[20,22-25]. Current experimental studies and the knowledge of clinical situations provide us with a better understanding of the complex interaction of the pathophysiologic events after SCI. Future approaches should involve strategies aimed at blocking the multiple mechanisms of progressive pathogenesis in SCI and therefore promoting neuroregeneration.

Methylprednisolone (MP), a glucocorticoid, is the only current pharmacotherapy approved for SCI in the human clinic. Although therapy with methylprednisolone has been shown to be protective, its efficacy is limited and it only marginally improves outcomes[14]. Recent advances in SCI research have led to a variety of novel experimental therapeutic strategies. The approach based on cell therapy using various lineages of stem cells has been considered as the most potential for the treatment of spinal cord injuries[26]. Cell transplantation after spinal cord injury has several goals, among them, filling the cavity of the lesion to make a bridge that joins the edges of conserved areas, restore dead cells (neurons or myelinating cells) and make a favorable environment for axonal regeneration. Our laboratory employed *in vivo* experiments using predifferentiated embryonic stem cells[27], human dental pulp stem cells[28], and mesenchymal stem cell (MSC) (data not published) as a therapy for compressive spinal cord injury in mice, and our results show that these treatments lead to positive and similar functional and morphological responses. Among these lineages, mesenchymal stem cells have strengths such as easy extraction and cultivation, and do not involve ethical and moral issues, making them one of the favorite lineages for spinal cord injury treatment.

MSC THERAPY FOR SPINAL CORD LESION: FROM EXPERIMENTAL STUDIES TO CLINICAL TRIALS

MSC transplantation has been extensively investigated by several groups and these cells can be considered a feasible candidate for treatment of central nervous system diseases because they have characteristics that address the multifactorial events that occur after SCI. These cells have anti-inflammatory, immunomodulatory[29] and neu-

roprotective[30] effects. It has also been shown that MSC can secrete trophic factors thus exerting a paracrine effect that can stimulate axon regeneration contributing to functional recovery enhancement.

Concerning the paracrine effect, some groups have identified the ability of these cells in secreting pro-survival factor such as insulin-like growth factor (IGF) brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), granulocyte-macrophage colony stimulating factor (GMCSF), fibroblast growth factor-2 (FGF2) and transforming growth factor beta (TGF-β)[31-33]. In addition, MSC can be combined with gene therapy, by introducing genes to generate molecules with great therapeutic potential in promoting neuron survival and regeneration[34]. Table 1 is a summary of preclinical studies using MSC for spinal cord injury, from 2010 until now.

Sources of MSC

MSC reside in a range of adult tissues that are easily accessible such as bone marrow, adipose tissue, skin, and even peripheral blood[34]. Most of the studies in SCI use MSC derived from bone marrow and adipose tissue, but it is also possible to get MSC from a perinatal source like umbilical cord blood, umbilical cord matrix[74], amniotic fluid and placenta[75-77]. MSC can be extracted from these tissues and plated to be used in autologous transplantation, minimizing the rejection risk.

Studies using MSC extracted from bone marrow in rodents have demonstrated a beneficial effect of cell transplantation after SCI. The beneficial effect of MSC is usually attributed to secretion of neurotrophic factors[78,79] and anti-inflammatory cytokines[71,80,81]. Studies performed with pigs[82] and monkeys[83] showed that MSC can promote axonal growth and sprouting, corroborating the previous results in rodents, thus supporting the clinical use of MSC.

MSC extracted from adipose tissue is considered an attractive source of cells due to easiness of isolation, obtention of a large amount of cells per donor, and also due to the fact that this tissue is usually discarded after liposuctions. In SCI models, treatment with these cells have resulted in cell survival, neuroprotection, attenuation of secondary damage, axonal regeneration, decrease of gliosis, angiogenesis and enhanced functional recovery[61,84-90]. A comparative study using MSC extracted from both bone marrow and adipose tissue after SCI found that both sources of MSC expressed similar surface protein markers, but animals that received adipose tissue cells presented higher levels of tissue BDNF, increased angiogenesis, higher number of preserved axons and a decrease in the number of macrophages, suggesting that the use of MSC extracted from adipose tissue is a better candidate for SCI treatment[41]. However, this is not a consensus and should be further investigated because in another comparative study published in 2012, the authors did not find any difference between animals that received MSC derived from bone marrow or adipose tissue, in terms of axonal regeneration, neuroprotection and functional recovery after a compression lesion in dogs[51].

Despite being less investigated in terms of SCI treatment, MSC extracted from perinatal tissues also present a therapeutic potential. Human umbilical cord blood cells (hUCBC) transplantation in rats submitted to an injury, resulted in differentiation of these cells into neural cells and downregulation of the fas/caspase-3 pathway in neurons and oligodendrocytes, and also increased levels of anti-apoptotic proteins[91,92].

The umbilical cord matrix, also known as Wharton's jelly, possesses a stem cell population that present some advantages in comparison to other sources because they can proliferate more rapidly and extensively than adult MSC[76,93] and also because they are easily obtained after normal and cesarean births, with low risk of viral contamination[94,95]. Other advantage is the possibility of using them for allogenic transplantation because they act by suppressing immune response and are, therefore, considered non-immunogenic cells[96]. Some studies using umbilical cord matrix-derived MSC indicated that these cells can survive in the injury site and promote repair and recovery after SCI. This improvement is attributed to immunomodulatory and trophic effects through secretion of glial-derived neurotrophic factor (GDNF), BDNF and nerve growth factor (NGF) which are known as supporters of cell survival and regeneration[54,97].

The amniotic fluid cells constitute another source of MSC, which are obtained from discarded post-partum tissue, without any ethical objections about their use. They present similar proliferation and differentiation patterns in comparison to adult MSC[98,99]. According to few studies, these cells are able to enhance cell survival and axon myelination and improve hind limb function, after transplantation in SCI models[100]. Some studies have also demonstrated the immunomodulatory effect and trophic support provided by these cells after SCI[101,102].

Issues regarding the quantity and best via of administration of MSC for SCI

Two important questions that should be addressed when we discuss MSC and its efficacy in treating central nervous system disorders are: the ideal quantity of cells and the best administration *via* Concerning the cell quantity, the literature presents several studies using different amount of cells. In terms of cell administration, most transplantation is delivered directly into the injury site or adjacent to it, by injecting few microliters of cell suspension[103]. Attempts have been made to inject cells intravenously or intraperitoneally in order to decrease tissue damage and, thus, avoiding subjecting the individual to another surgical intervention.

There are several studies that injected different quantity of cells with similar results. Apart from the difference on the quantity of cells, there are other points that make the comparison among these studies difficult, such as the diversity of lesion models, animal types and route of cell administration. For example, Cizkova and colleagues[104]

Table 1 Summary of pre-clinical studies using mesenchymal stem cell for spinal cord injury

Animal	Lesion type	Cells source	Route of administration	Effects on CNS regeneration	Ref.
Rat	Contusion	Human mesenchymal precursor cells	Lesion site	Improvement in functional recovery and tissue sparing and reduction of cyst volume	[35]
Rat	Contusion	Human bone marrow-MSC	Lesion site , intracisternal, intravenous	Improvement in functional recovery	[36]
Rat	Hemisection	Bone marrow-MSC induced into Schwann Cells	Lesion site	Improvement in locomotor and sensory scores, axonal regeneration and remyelination	[37]
Rat	Contusion	Bone marrow-MSC	Lesion site , intravenous	Improvement in locomotor scores and NGF expression	[38-40]
Rat	Transection to the dorsal columns and tracts	Bone marrow-MSC, adipose derived-MSC	Lesion site	Improvement in locomotor scores, increased angiogenesis, preserved axons, decreased numbers of ED1-positive macrophages and reduced lesion cavity formation	[41]
Rat	Hemisection	Human umbilical cord-derived MSC	Lesion site	Suppress mechanical allodynia, and this effect seems to be closely associated with the modulation of spinal cord microglia activity and NR1 phosphorylation	[42,43]
Rat	Hemisection	Human bone marrow-MSC	Lesion site	Improvement in locomotor scores, shorter latency of somatosensory-evoked potentials and differentiation into various cells types	[44]
Rat	Hemisection	Bone marrow-MSC	Lesion site	Improvement in locomotor scores and reduced lesion cavity formation	[45]
Mouse	Compression	Bone marrow-MSC	Lesion site	Improvement in locomotor and sensory scores and reduced lesion volume	[46]
Rat	Contusion	Human bone marrow-MSC	Lesion site	Improvement in functional recovery, tissue sparing and reduction in the volume of lesion cavity and in the white matter loss	[35,47-49]
Rat	Contusion	Human umbilical cord-MSC	Lesion site	Improvement in functional recovery, reduction of the extent of astrocytic activation and increased axonal preservation	[50]
Dog	Compression	Bone marrow, adipose, Wharton's jelly, umbilical cord derived-MSC	Lesion site	Improvement in functional recovery, increased numbers of surviving neurons, smaller lesion sizes and fewer microglia and reactive astrocytes in the epicenter of lesion	[51]
Rat	Compression	Bone marrow-MSC	Intravenous	Improvement in functional recovery, increase of NGF expression, higher tissue sparing and density of blood vessels	[52]
Rat	Contusion	Human umbilical cord-MSC	Lesion site	Improvement in functional recovery, endogenous cell proliferation and oligogenesis, and smaller cavity volume	[53,54]
Rat	Transection	Human-MSC	Lesion site	Improvement in functional recovery, increased amplitude of motor-evoked potentials, differentiation into neural cells	[55,56]
Rat	Contusion	Bone marrow-MSC	Lesion site	Improvement in functional recovery, preservation of axons, less scar tissue formation and increase in myelin sparing; higher levels of IL-4 and IL-3 and higher numbers of M2 macrophages, and reduction in TNF-α and IL-6 levels, and in numbers of M1 macrophages	[57-60]
Dog	Compression	Neural-induced adipose derived-MSC	Lesion site	Improvement in functional recovery and neuronal regeneration, and reduction of fibrosis	[61]
Mouse	Transection	Bone marrow-MSC	Lesion site	Improvement in functional recovery and neuronal survival, reduction of cavity volume and attenuation of inflammation, promotion of angiogenesis and reduction of cavity formation	[62-64]
Rat	Compression	Bone marrow-MSC	Lesion site	Improvement in functional recovery, up-regulation of VEGF mRNA expression, increase in angiogenesis and prevention of tissue atrophy	[65-67]
Rat	Compression	Human umbilical cord-MSC	Lesion site	Improvement in functional recovery, increase in the intensity of 5-HT fibers and in the volume of spared myelination; decrease in the area of the cystic cavity	[68]
Dog	Compression	Umbilical cord-MSC	Lesion site	Improvement in functional recovery, promotion of neuronal regeneration and reduction of fibrosis	[69]
Dog	Compression	Human umbilical cord-MSC	Lesion site	Improvement in functional recovery and remyelination	[70]
Rat	Contusion	Bone marrow-MSC	Intrathecal	Improvement in functional recovery	[71]
Rat	Contusion	Human bone marrow-MSC	Lesion site , lumbar puncture	Improvement in functional and sensory recovery	[72]
Rat	Contusion	Neural differentiated and undifferentiated MSC	Lesion site	Improvement in functional recovery and reduction of cavitation	[73]

CNS: Central nervous system; MSC: Mesenchymal stem cell; TNF: Tumor necrosis factor; IL: Interleukin; NGF: Nerve growth factor; VEGF: Vascular endothelial growth factor.

demonstrated cell survival and enhancement in locomotor performance after MSC transplantation delivered by intravenous injection (one million cells in a volume of 0.5 mL of DMEM) in a model of balloon compressive injury in rats, while Sheth *et al*[105] performed cell transplantation (600000 cells in a volume of 6 μL) directly into the injury site after contusive injury in rats, and also observed an enhancement in locomotor function and a decrease in the lesion volume, indicating a neuroprotective effect of these cells. Thus, it is still difficult to determine the ideal quantity of cells and the best *via* for stem cell transplantation after SCI. The questions that arise from these studies are: Is there a minimum number of transplanted cells that can be used and yet giving the best results in terms of functional recovery? Can we get similar results with cells injected systemically in comparison to local injection? Studies using the same type of lesion and different amount of cells and administration *via* should be further undertaken in order to better clarify this issue.

Time point for cell transplantation

Other crucial issue that should be further addressed here is the time point for cell transplantation after lesion. This is important because the environment created after SCI is hostile for regeneration and can negatively influence cell survival and differentiation. Thus, depending on the time that the treatment is performed the results can be completely different. Most studies have been performed in acute or sub-acute phases, which means immediately or 1-2 wk after injury, respectively[35,103]. There are fewer studies in the SCI chronic phase, when cells are delivered in later stages, when the glial scar is already present[38,41].

Clinical trials

The clinical trials conducted for SCI comprise three different phases with human participation in all phases. The phase 1 trial begins with the administration of the cell transplants to a human subject with the aim to investigate the presence of adverse or toxic effects and treatment safety. People who participate in these trials may experience some risks and have limited benefits. In phase 2, the objective is to determine the potential and variability of a therapy in comparison with a control group. The participants are usually recruited and randomly assigned to the groups (experimental or control) and both, participants and investigators, do not know to which study they have been assigned to. The phase 3 clinical trials are usually the definitive clinical trial. The aim is to confirm the preliminary results obtained at the phase 2, with a statistically significant clinical benefit of the therapeutic intervention. The number of subjects is also larger and multiple study centers are involved[106,107]. The majority of the studies using MSC transplantation after spinal cord injury are in phase 1 or 2.

At the time of writing this article there were twenty clinical trials being either completed, ongoing or in the recruitment stage, using either adult or perinatal sources of mesenchymal stem cells in different phases of the disease, and most of them use autologous transplantation to minimize the risk of rejection. Table 2 list the clinical trials listed on the clinical trials.gov.

The number of clinical trials using MSCs for treatment of SCI is increasing, indicating that despite several questions that still need to be addressed at basic and pre-clinical levels, the MSC are considered potentially beneficial for translational studies.

According to PubMed database, in the last three years only three studies were published in "clinical trials" category, using MSC transplantation after SCI. One of them transplanted autologous bone marrow-derived MSC into the cerebrospinal fluid of patients with complete SCI. The authors described that 45% of the patients showed a recovery, but there was no difference between these patients and those from control groups; they emphasized that despite the fact that results were not positive, the transplantation was a feasible and safe technique, since patients did not present any adverse reaction[108]. On the other hand, Park *et al*[109] using the same cell source, and repeated cells injections directly into the spinal cord, demonstrated that three of ten patients presented a motor improvement, and significant magnetic resonance changes and electrophysiological results. These results are similar to those obtained by Dai *et al*[110] who also demonstrated a clinical improvement in patients that received autologous MSC transplantation. The results of these studies are not conclusive, and, unfortunately, not as good as those obtained in pre-clinical experiments. In spite of that, all of them emphasize mesenchymal stem cell clinical potential.

WALLERIAN DEGENERATION AND NERVE REGENERATION IN THE PERIPHERAL NERVOUS SYSTEM

Traumatic injury to nerves in the peripheral nervous system (PNS) is a large-scale problem annually affecting more than one million people worldwide. These injuries often result in pain and disabilities, owing to reduction in motor function and sensory perception. Moreover, the trauma can cause emotional, social and work-related disorders, and the affected individuals undergo a reduction in their quality of life[111,112].

While it is widely accepted that the PNS has an inherent potential for regeneration, functional recovery after a lengthy peripheral nerve injury (PNI) remains unsatisfactory[113]. After an extensive traumatic nerve injury with a large gap between the proximal and distal nerve stumps, a long period of time is required for regenerating axons to cross that gap. During that time, the ability of axotomized neurons to regenerate declines and Schwann Cells (SC) can no longer support regenerating neurons and their axons. As a result, regenerating axons fail to reach their target organs and the injury cannot be successfully repaired. In order to accelerate the rate of axonal growth many therapeutic strategies are being developed and in-

Table 2 Summary of clinical trials studies using mesenchymal stem cell for spinal cord injury

Title	Lesion type	Cells source	Phase of the study	Status	Effects on CNS regeneration
Clinical study of treatment for acute SCI using cultured bone marrow stromal cells	Cervical SCI	Autologous Bone marrow-MSC	Terminated	1/2	Rapid and remarkable recovery of ASIA B and C patients, but gradual or limited in ASIA A patients.
Autologous mesenchymal stem cell in SCI patients	Complete cervical or thoracic SCI	Autologous bone marrow-MSC	Enrolling by invitation	2	Not informed
Different efficacy between rehabilitation therapy and umbilical cord derived MSCs transplantation in patients with chronic SCI in China	Traumatic SCI	Umbilical cord derived-MSC	Recruiting	3	Not informed
A phase Ⅲ/Ⅳ clinical trial to evaluate the safety and efficacy of bone marrow-derived MSC transplantation in patients with chronic SCI	Cervical SCI	Autologous bone marrow-MSC	Recruiting	1/2	Not informed
Phase Ⅰ/Ⅱ trial of autologous bone marrow derived MSCs to patients with SCI	Traumatic thoracic or lumbar SCI	Autologous bone marrow-MSC	Recruiting Completed	1/2 1	Not informed
Safety of autologous adipose derived MSCs in patients with SCI	Clinical diagnosis of SCI (ASIA A to C)	Autologous Adipose derived-MSC			
The effect of intrathecal transplantation of autologous adipose tissue derived MSCs in the patients with SCI, phase I clinical study	Clinical diagnosis of SCI	Autologous Adipose derived-MSC	Recruiting	1	Not informed
Phase I, single center, trial to assess safety and tolerability of the intrathecal infusion of ex-vivo expanded bone-marrow derived MSCs for the treatment of SCI	Clinical diagnosis of SCI (ASIA A)	Autologous bone marrow-MSC	Active, not recruiting	1	Not informed
Study the safety and efficacy of bone marrow derived autologous cells for the treatment of SCI	Clinical diagnosis of SCI	Autologous bone marrow-MSC	Recruiting	1/2	Not informed
Surgical transplantation of autologous bone marrow stem cells with glial scar resection for patients of chronic SCI and intra-thecal injection for acute and subacute injury-a preliminary study	Complete spinal cord trans-section	Autologous bone marrow-MSC	Completed	1/2	Not informed
To study the safety and efficacy of autologous bone marrow stem cells in patients with SCI	SCI below C5 (ASIA A to C)	Autologous bone marrow-MSC	Recruiting	1/2	Not informed
Safety of autologous stem cell treatment for SCI in children	Clinical diagnosis of SCI (ASIA A to D)	Bone marrow-MSC	Recruiting	1	Not informed
Autologous bone marrow derived cell transplant in SCI patients	Traumatic SCI	Autologous bone marrow-MSC	Completed	1/2	Not informed
Phase 1 study of autologous bone marrow stem cell transplantation in patients with SCI	Traumatic thoracic or lumbar SCI	Autologous bone marrow-MSC	Not informed	1	Not informed
Phase I pilot study to evaluate the security of local Administration of autologous stem cells obtained from the bone marrow stroma, in traumatic injuries of the spinal cord	Traumatic SCI between C3 and L1	Autologous bone marrow-MSC	Recruiting	1	Not informed
Feasibility and safety of umbilical cord blood cell transplant into injured spinal cord: an open-labeled, dose-escalating clinical trial	Chronic SCI between C5 and T11 (ASIA A)	Umbilical cord blood mononuclear derived-MSC	Active, not recruiting	1/2	Not informed
Efficacy difference between rehabilitation therapy and umbilical Cord derived transplantation in patients with acute or chronic SCI in China	Clinical diagnosis of SCI	Umbilical cord derived-MSC	Not informed	2	Not informed
Safety and feasibility of umbilical cord blood cell Transplant Into Injured Spinal cord: an open-labeled, dose-escalating clinical trial	Chronic SCI between C5 and T11 (ASIA A)	Umbilical cord derived-MSC	Active, not recruiting	1/2	Not informed
Safety and effect of lithium, umbilical cord blood cells and the combination in the treatment of acute and sub-acute spinal cord injury : a randomized, double-blinded placebo-controlled clinical trial	Acute or Subacute traumatic SCI between C5 and T11 (ASIA A)	Umbilical cord derived-MSC	Active, not recruiting	1/2	Not informed

MSC: Mesenchymal stem cell; CNS: Central nervous system; SCI: Spinal cord injury.

vestigated. The identification of crucial elements responsible for successful regeneration in injured peripheral nerves will be quintessential in improving regenerative outcomes after peripheral and central nerve injuries.

Nerve trauma elicits a cascade of molecular, cellular, and ultrastructural responses which are necessary for degeneration and posterior regeneration, including: disruption of axonal conduction; increase in cell body metabolism and protein synthesis; degeneration of the distal stump of injured axons; dedifferentiation and pro-

liferation of SC; degradation of the myelin sheath; recruitment of macrophages to the site of injury[114], as well as the release of cytokines, neurotrophins and growth factors[115-117]. These events will allow rapid and efficient removal of the growth inhibitory cellular debris present in the injured peripheral nerve milieu, producing a favorable microenvironment for axonal growth[118].

After an injury the axon is divided into two segments: a proximal stump that remains in contact with the cell body, and a distal stump which is separated from the rest of the neuron. The distal nerve stump undergoes a cascade of events called "Wallerian degeneration"[119,120], which is initiated within 24 to 48 h by the entry of calcium in the axoplasm. Calcium influx activates proteases, such as calpains that promote cytoskeletal degradation and disintegration of axoplasm, myelin and axolemma[121,122]. The rupture of the blood-nerve barrier allows the entry of macrophages into the site of injury and, together with SC, these cells initiate intense phagocytosis and removal of degenerating axon and myelin debris. The barrier permeability decreases two weeks after the injury and then, in the fourth week, increases again in order to regain homeostasis after Wallerian degeneration[118].

Immediately after injury, the SC in the distal stump of the nerve begin the process of dedifferentiation. Even before axonal degeneration occurs, SC can modify its gene expression[123] and 48 h after injury, they decrease myelin protein expression, acquire a non-myelinating phenotype and begin to express genes related to regeneration, like growth associated protein 43 (GAP-43), neurotrophic factors and their receptors, neuroregulins and their receptors, and assume an intense proliferative activity[124,125]. About four days after injury SC reach their proliferation peak. These proliferative cells are confined within the tube formed by its own basal lamina and align forming the so called bands of Büngner. These bands columns will form a supportive substrate, providing clues that will guide axon growth toward the target organ, through the release of trophic factors. When SC contact the regenerating axons, the process of re-myelination is started[126].

The injury also causes a rapid arrival of signals from the damaged axons to the neuronal body resulting in an extraordinary change from a transmitting to a growth promoting phenotype. Cell body suffers a process called chromatolysis, which is characterized by swelling of the neuronal body and by dispersion of Nissl corpuscles[127,128]; These changes reflects variations in the metabolic activity of neurons which, as a result, fail to synthesize proteins required for neurotransmission, and start producing substances that are important for axonal sprouting and growth[129]. The regeneration that follows occurs *via* different mechanisms: the elongation of the distal end of injured axons and the growth of collateral axons from nodes of Ranvier in the proximal stump. However, the success of regeneration and target organ reinnervation depends mostly on the enhancement of the number of regenerating axons, the velocity of axon growth and on the ability of affected neurons to survive and acquire a regenerative phenotype.

In the clinical settings, reconstruction of transected peripheral nerve requires accurate microsurgical repair that connects the proximal and distal stumps of the nerve in a tension-free manner. In cases of injury with tissue loss, autologous peripheral nerve grafts, *i.e.*, autografts, is considered by neurosurgeons the gold standard technique, but unfortunately, even in these cases, the clinical results remain disappointing and, therefore, the search for better strategies is an urgent necessity. In cases of digital nerve lesions, biodegradable artificial nerve conduits are being used in the clinical settings, but their use is still limited to these thin nerves. An advantage of the use of these conduits is that they can be combined with other pro-regenerative strategies, such as the local injection of neurotrophic factors and cells.

New therapeutic approaches should have as a goal an increase of the intrinsic regenerative capacity of transected nerve fibers and a decrease of the extrinsic factors that limit regeneration of severed nerve fibers, thus creating an appropriate environment in which, axon elongation, remyelination and proper reinnervation of target organ may occur. A stem cell-based therapy represents an important new strategy to manage peripheral nerve injury. In the next part of this review we will discuss the potential use of mesenchymal stem cells, in promoting nerve regeneration.

MSC THERAPY IN PNS: FROM EXPERIMENTAL STUDIES TO CLINICAL TRIALS

A number of experimental studies have shown the potential of MSC to improve peripheral nerve regeneration following traumatic injuries[130-135]. These cells may act on nerve regeneration mainly by paracrine, neuro/axonoprotective, or immunomodulatory effects; by transdifferentiation into SCs; by cell-to-cell contact; or even by a combination of the above mechanisms[134]. However, most of the beneficial effects exerted by the MSC are strongly correlated with the production of neutrophic substances, such as FGF, NGF, ciliary neurotrophic facto, BDNF, GDNF among others[132,133,136,137].

Our group showed the presence of high levels of NGF-b in the in MSC *in vitro* suggesting that they are also able to express this potent neurotrophic factor *in vivo*; this result could represent one mean by which these cells acted on the enhancement of axon regeneration and remyelination, consequently contributing to the observed return of motor function[133]. In agreement with these findings, bone marrow-MSC locally injected in the mouse ischiatic nerve resulted in improvement of regeneration of sensory and motor axons[134]. Because these authors also observed that these cells were capable of increasing neurite outgrowth *in vitro* through NGF releasing, and that they presented low potential to differentiate into SC

in vivo, they suggested that the beneficial effects exerted by the implanted cells were mainly dependent on their trophic activity rather than their stemness potential[134]. In another work, our group also observed the benefits of bone marrow-MSC locally injected in the mouse median nerve following transection and conduit repair. This cell system was capable of increasing the number of both myelinated and unmyelinated fibers, preventing the muscle atrophy and, most importantly, improving functional performance[130].

It is also possible that MSC can act indirectly on nerve regeneration by modulating cellular behaviors such as inducing SC to survive, proliferate, produce neurotrophic factors and promote remyelination. A coculture system with rat bone marrow-MSC conditioned media and SC demonstrated cell-cell interactions despite no direct contact between the two population of cells. MSC not only favored survival and proliferation of SC but also induced them to express NGF, BDNF and NGF receptors[138]. This is an important MSC feature as it might indicates that MSC can relay and magnify neurotrophic function from stem cells to glia cells, thus improving peripheral nerve regeneration.

Besides rodents, larger animal models have also been used to investigate the effects of MSC-based therapy on more challenging nerve gaps. Few authors have shown the successful bridging of a 30 mm-long ischiatic nerve defect by means of a biodegradable conduit in dogs[139]. After six months of MSC implantation, they observed the reconstruction of ischiatic nerve trunk with restoration of nerve continuity, functional recovery for conducing electrical impulses and transporting materials, and muscle re-innervation, which lead to improvement of locomotion activities. Even more challenging, using a two-fold nerve gap in a similar experimental model but with addition of autologous MSC, the same group[140] demonstrated that the cellular treatment improved nerve regeneration and functional recovery in a manner comparable to the autograft-treated animals, which is considered by neurosurgeons the current gold standard for peripheral nerve repair.

As aforementioned, the great majority of the experimental studies of mesenchymal stem cell-based therapy on the peripheral nerve regeneration use rodents (mainly mice and rats) as animal models[130,133,134,138], perhaps because they are small size mammals and, consequently, easy to handle; also, they have been extensively used in the field of genetic engineering for a diversity of experimental trials of gain and loss of function as well as reporter assays. However, there are few studies using non-human primates such as cynomolgus and rhesus monkeys, which share high level of sequence homology with human genome, that have confirmed the feasibility of this cell system for improving nerve regeneration after severe nerve lesions. MSC transplantation into either allogeneic nerve grafts[141] or artificial conduits[142] for bridging severe upper extremity nerve defects in higher primates yielded structurally and functionally regenerated nerves; these studies proved to be safe and effective, thus giving great insight into the use of MSC in human clinics.

MSC obtained from human subjects have also been used in pre-clinical studies for promoting nerve regeneration, yielding promising results[143-145]. These studies are of great relevance because they address human MSC properties, clarifying their mechanisms of action, and also provide insight into their effects on peripheral nervous tissue recovery. Interestingly, the authors of these studies demonstrated that human MSC-based therapy improved peripheral nerve regeneration as well as functional recovery. However, McGrath *et al*[145] showed that MSC survived in the conduit and enhanced axonal regeneration only when transplantation was combined with the immunosuppressive treatment, cyclosporine A. As these results provide evidence of the nerve regeneration potential of human MSC, and taking into account that one of the great advantages of MSC is the possibility of auto transplantation without donor-site morbidity, they might encourage the use of this cell system for treating human peripheral nerve trauma.

Thus, the results of pre-clinical studies highlighting the improved outcomes yielded by using MSC with the aim to repair a large nerve gap may increase the feasibility of translation of MSC-based therapy to clinical trials for peripheral nerve applications.

Table 3 summarizes the studies using MSC for nerve injuries, either in pre-clinical or clinical trials, since 2010 until now. To date, only one clinical trial has used autologous bone marrow mononuclear cells within silicone tubes to repair human median or ulnar nerves[146]. In this study scores for motor function, sensation and the effect of pain on function were better than those obtained from individuals that had the tubular nerve repair only; However, a possible limitation in this study is the fact that there was a difference between groups regarding the age of individuals and the length of follow-up after treatment, which could represent biases in this study. So, the interval between injury and treatment was always longer than 75 d, which could possibly limit the positive effects exerted by the cells on the nerve regeneration process. Another possible disadvantage of this work is that nerve conduits were made of silicone, a non-biodegradable material, thus requiring a second surgery to remove the conduit. In spite of these limitations cells-treated patients presented a better recovery compared to the untreated. The results of this study will, hopefully, encourage subsequent clinical studies to be conducted safely, with fewer biases, and with the association of the cellular treatment with suitable biodegradable conduits, thus preventing discomfort and complications generated from the use of silicone material.

Although important advances have been achieved in the use of stem cells for improving nerve regeneration, they are still limited to basic and pre-clinical trials. In addition, there are several variables among these studies, such as tissue source; methods of cell isolation, expansion and characterization; route of cell delivery; number

Table 3 Summary of pre-clinical and clinical studies using mesenchymal stem cell for peripheral nerve injury

Animal	Nerve	Lesion type	Cells source	Route of administration	Ref.
Mouse	Median	Transection	Bone marrow-MSC	Local	[147]
Mouse	Ischiatic	Transection	Bone marrow-MSC	Local	[148]
Mouse	Ischiatic	Transection	Embryonic stem cell derived-MSC	Local	[144]
Mouse	Ischiatic	Crush	Adipose derived-MSC	Intravenous	[149]
Mouse	Ischiatic	Transection	Bone marrow-MSC	Local	[131]
Rat	Ischiatic	Crush	Amniotic fluid derived-MSC	Local	[150]
Rat	Ischiatic	Crush	Amniotic fluid derived-MSC	Intravenous	[151-153]
Rat	Facial	Transection	Bone marrow-MSC	Local	[154,155]
Rat	Ischiatic	Crush	Bone marrow-MSC	Local	[156]
Rat	Ischiatic	Transection	Adipose derived-MSC	Local	[157-159]
Rat	Ischiatic	Transection	Umbilical cord derived-MSC	Local	[160,161]
Rat	Ischiatic	Transection	Bone marrow-MSC	Local	[145,158,162-169]
Rat	Cavernous	Traction	Bone marrow-MSC	Intracavernousal injection	[170]
Rabbit	Facial	Transection	Bone marrow-MSC	Local	[171]
Rabbit	Ischiatic	Traction	Bone marrow-MSC	Local	[172,173]
Pig	Ischiatic	Transection	Bone marrow-MSC	Local	[174]
Dog	Ischiatic	Transection	Bone marrow-MSC	Local	[140,175]
Dog	Ischiatic	Transection	Adipose derived-MSC	Local	[176]
Monkey	Median	Transection	Bone marrow-MSC	Local	[142]
Human	Median or ulnar	Transection	Bone marrow mononuclear cell fraction-MSC	Local	[146]

MSC: Mesenchymal stem cell.

of transplanted cells; therapeutic time window; animal and nerve models; type of injury; number of transplanted cells; and immunogenicity. These variables represent an important obstacle for comparing and contrasting study outcomes from different groups, thus hindering progress in the field.

In 2006, The International Society for Cellular Therapy proposed the development of a set of minimal criteria (adherence to plastic in standard culture conditions, expression of a number of markers and multipotent differentiation potential into osteoblasts, adipocytes and chondroblasts) for defining the MSC for research purposes[177]. Although this action represented a great attempt to allow for comparison of scientific studies among different groups, the criteria for mesenchymal cells from different species should be further considered and well-defined, in particular the non-human and human primate MSC.

CONCLUSION

Pre-clinical studies have shown the beneficial effects of MSC therapy in the neurotrauma field. Unfortunately, these effects are not usually seen in the clinical trials, and the results are far from being as good as those described in experimental studies. Therefore, there is an urgent need to seek for standardization of protocols in terms of source of cells, culture conditions, time of treatment after injury, number and *via* of administration of cells, plasticity and capability of human MSC after extraction and expansion in culture, among other concerns. Basic and pre-clinical studies focusing on these important points will, hopefully, be of great help in terms of their successful implementation in clinical trials.

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