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Mesenchymal stem cells in the treatment of spinal cord injuries: A review

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Abstract

With technological advances in basic research, the intricate mechanism of secondary delayed spinal cord injury (SCI) continues to unravel at a rapid pace. However, despite our deeper understanding of the molecular changes occurring after initial insult to the spinal cord, the cure for paralysis remains elusive. Current treatment of SCI is limited to early administration of high dose steroids to mitigate the harmful effect of cord edema that occurs after SCI and to reduce the cascade of secondary delayed SCI. Recent evident-based clinical studies have cast doubt on the clinical benefit of steroids in SCI and intense focus on stem cell-based therapy has yielded some encouraging results. An array of mesenchymal stem cells (MSCs) from various sources with novel and promising strategies are being developed to improve function after SCI. In this review, we briefly discuss the pathophysiology of spinal cord injuries and characteristics and the potential sources of MSCs that can be used in the treatment of SCI. We will discuss the progress of MSCs application in research, focusing on the neuroprotective properties of MSCs. Finally, we will discuss the results from preclinical and clinical trials involving stem cell-based therapy in SCI.

Key words: Spinal cord injury; Mesenchymal stem cells; Bone marrow stromal cells; Umbilical cord derived mesenchymal stem cells; Adipose tissue derived mesenchymal stem cells

Core tip: Despite our deeper understanding of the molecular changes that occurs after the spinal cord injury (SCI), the cure for paralysis remains elusive. In this review, the pathophysiology of SCI and characteristics and potential sources of mesenchymal stem cells (MSCs) that can be used in the treatment of SCI were discussed. We also discussed the progress of application of MSCs in research focusing on the neuroprotective properties of MSCs. Finally, we discussed the results from preclinical and clinical trials involving stem cell-based therapy in SCI.

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INTRODUCTION

Traumatic spinal cord injury (SCI) continues to be a devastating injury to affected individuals and their families and exacts an enormous financial, psychologi-

cal and emotional cost to them and to society. Despite years of research, the cure for paralysis remains elusive and current treatment is limited to early administration of high dose steroids and acute surgical intervention to minimize cord edema and the subsequent cascade of secondary delayed injury[1-3]. Recent advances in neurosciences and regenerative medicine have drawn attention to novel research methodologies for the treatment of SCI. In this review, we present our current understanding of spinal cord injury pathophysiology and the application of mesenchymal stem cells (MSCs) in the treatment of SCI. This review will be more useful for basic and clinical investigators in academia, industry and regulatory agencies as well as allied health professionals who are involved in stem cell research.

Direct mechanical damage to the spinal cord usually results in either partial or total loss of neural functions such as sensory perception and mobility[4]. The prevalence of people with SCI who are alive in the United States in 2013 is estimated to be approximately 273000[5]. According to census data, motor vehicle accidents (36.5%), falls (28.5%), and acts of violence (14.3%) are the most frequent causes of SCI since 2010. The average age at injury is 42.6 years and 80.7% of spinal cord injuries occur in males. Among those injured since 2010, 67.0% are Caucasian, 24.4% African American, 0.8% Native American and 2.1% Asian. The most frequent neurologic category at discharge of persons reported to the database since 2010 is incomplete tetraplegia (40.6%), followed by incomplete paraplegia (18.7%), complete paraplegia (18.0%) and complete tetraplegia (11.6%). Less than 1% of SCI patients experienced complete neurologic recovery by the time of hospital discharge. Over the last 20 years, the percentage of SCI patients with incomplete tetraplegia spinal cord injury has increased while the more devastating complete paraplegia and complete tetraplegia numbers have decreased[5]. Whether complete or incomplete injury, SCI is a devastating condition that not only paralyzes the affected individuals but also exacts tremendous emotional, social and financial burdens[6]. These patients also face increased risks of cardiovascular complications, deep vein thrombosis, osteoporosis, pressure ulcers, autonomic dysreflexia and neuropathic pain[3]. The limitation of any clinical treatment success is most likely due to the complex mechanisms of SCI and the relative inability of the human body to repair or regenerate neurons in the spinal cord[7].

PATHOPHYSIOLOGICAL FEATURES AFTER SCI

The pathophysiological processes that underlie SCI comprise the primary and secondary phases of injury[1,8]. Initial physical trauma to the spinal cord includes traction injury, compression forces and direct mechanical disruption of neural elements. Immediate microvascular injuries with central gray hemorrhage and disruption of cellular membrane and blood-spinal cord barrier are followed by edema, ischemia, release of cytotoxic chemicals from inflammatory pathways and electrolyte shifts. Subsequently, a secondary injury cascade is triggered that compounds the initial mechanical injury with necrosis and apoptosis that are injurious to surviving neighboring neurons, further reducing the chance of recovery of penumbra neurons and rendering any functional recovery almost hopeless[3,8]. Pathophysiological processes that occur in the secondary injury phase are responsible for exacerbating the initial damage and creating an inhibitory milieu that is hostile to endogenous efforts of repair, regeneration and remyelination. These secondary processes include inflammation, ischemia, lipid peroxidation, production of free radicals, disruption of ion channels, axonal demyelination, glial scar formation, necrosis and programmed cell death[3]. The post-trauma inflammatory response plays a critical role in the secondary phase after SCI through modulation of a series of complex cellular and molecular interactions[9]. After SCI, the blood-spinal cord barrier is disrupted due to hemorrhage and local inflammation[10]. The activation and recruitment of peripheral and resident inflammatory cells including microglial cells, astrocytes, monocytes, T-lymphocytes, and neutrophils promotes the development of secondary damage following SCI[11]. This secondary injury can be subdivided into the acute-phase (2 h-2 d), the sub-acute phase (days-weeks), and the chronic phase (months-years), each with distinct different pathophysiological processes[12-14]. These changes include edema, ischemia, hemorrhage, reactive oxygen species (ROS) production and lipid peroxidation, glutamate-mediated excitotoxicity, ionic dysregulation, blood-spinal-cord barrier permeability, inflammation, demyelination, neuronal cell death, neurogenic shock, macrophage infiltration, microglial activity, astrocyte activity and scar formation, initiation of neovascularization, Wallerian degeneration, glial scar maturation, cyst and syrinx formation, cavity formation and schwannosis. The end of spontaneous post-SCI changes is identified as a pathophysiological phenomenon with solid glial scar formation, syrinx formation, and neuronal apoptosis[15]. However, endogenous repair and regenerative mechanisms do occur during the secondary phase of injury to minimize the extent of the lesion (through astrogliosis), reorganize blood supply through angiogenesis, clear cellular debris, and reunite and remodel damaged neural circuits, and as such, offer exploitable targets for therapeutic intervention[3], the most promising of which is stem cell-based therapy[16].

MSC THERAPY AFTER SCI

An array of new and promising strategies is being developed to improve function after SCI. At present, two main therapeutic strategies, cell-based and gene-based therapies

are being investigated to repair the injured mammalian spinal cord. At this time it appears that neither strategy by itself is efficacious, whereas a combinatory strategy appears to be more promising. The targeting of an array of deleterious processes within the tissue after SCI will require a multi-factorial intervention, multi-phasic polytherapy such as the combination of cell- and gene-based approaches[17]. This review focuses only on stem cell-based therapy. Cell-based therapy faces numerous challenges including selection of a SCI model, timing and mode of cell implantation, location of cellular injection and their subsequent migration, survival, transdifferentiation, immune incompatibility and rejection, and tracking of implanted cells[17]. Cellular therapies for SCI repair may involve modification or recruitment of endogenous cells *in vivo*, harvest and/or alteration *ex vivo* of endogenous cells that are subsequently implanted as autogeneic graft or transplanted into the injured organism as allogeneic or xenogeneic grafts. Transplanted stem cells promote neural regeneration and rescue impaired neural function after SCI by parasecreting permissive neurotrophic molecules at the lesion site to enhance the regenerative capacity thereby providing a scaffold for the regeneration of axons and replacing lost neurons and neural cells[17]. Mesenchymal stem cells have recently been advocated as a promising source for cellular repair after central nervous system (CNS) injury[15]. MSCs, also known as marrow stromal cells[18] or mesenchymal progenitor cells[19] are self-renewing, multipotent progenitor cells with the capacity to differentiate into several distinct mesenchymal lineages[20]. These cells are multipotent adult stem cells present in all tissues as part of the perivascular population. As multipotent cells, MSCs can differentiate into different mesodermal tissues ranging from bone and cartilage to cardiac muscle[21]. Several small clinical trials have investigated the efficacy and safety of MSCs in diseases including chronic heart failure, acute myocardial infarction, hematological malignancies and graft *vs* host disease. Pre-clinical evidence suggests that MSCs exert their beneficial effects largely through immunomodulatory and paracrine mechanisms[22].

MSCs are favored in stem cell therapy for SCI for the following reasons: (1) ease of isolation and cryopreservation[23], (2) maintenance of viability and regenerative capacity after cryopreservation at -80 ℃[24], (3) rapid replication with high quality progenitor cells and high potential of multilineage differentiation[25], and (4) minimal or no immunoreactivity and graft-versus-host reaction of transplanted allogeneic MSCs[26]. MSCs were initially identified in bone marrow and later in muscle, adipose and connective tissue of human adults[21]. Bone marrow and umbilical cord blood are rich sources of these cells, but MSC have also been isolated from fat[27], skeletal muscle[28], human deciduous teeth[29], and trabecular bone[30]. Mesenchymal stem cells are ideally suited to address many pathophysiological consequences of SCI[3]. The major goals for the therapeutic use of stem cells is regeneration of axons, prevention of apoptosis and replacement of lost cells, particularly oligodendrocytes, in order to facilitate the remyelination of spared axons[31]. In this review, we touch upon the therapeutic applications of MSCs after SCI.

BONE MARROW STROMAL CELLS

Bone marrow-derived mesenchymal stem cells (BMSC) differentiate into cells of the mesodermal lineage but also, under certain experimental conditions, into cells of the neuronal and glial lineage. Their therapeutic translation has been significantly boosted by the demonstration that MSCs display significant anti-proliferative, anti-inflammatory and anti-apoptotic features. These properties have been exploited in the effective treatment of experimental autoimmune encephalomyelitis (EAE), experimental brain ischemia and in animals undergoing brain or spinal cord injury[32]. Several investigators have reported that MSCs possess immunosuppressive features[33-36]. These immunosuppressive properties, in combination with the restorative functions of BMSC reduce the acute inflammatory response to SCI, minimize cavity formation, as well as diminish astrocyte and microglia/macrophage reactivity[37-39]). BMSC transplantation in an experimental SCI model has been shown to enhance neuronal protection and cellular preservation *via* reduction in injury-induced sensitivity to mechanical trauma[39]. It was suggested that the beneficial effects of MSCs on hindlimb sensorimotor function may, in part, be explained by their ability to attenuate astrocyte reactivity and chronic microglia/macrophage activation[39]. These significant results demonstrated the potential of MSCs to serve as attenuators of the immune response. It was proposed that as attenuators, MSCs could potentially serve in an immunoregulatory capacity in disorders in which chronic activation of immune cells, such as reactive astrocytes and activated microglia/macrophages play a role. Studies by Hofstetter *et al*[40], indicated that transplanted MSC attenuates acute inflammation and promotes functional recovery following SCI. Ohta *et al*[41], suggested that BMSCs reduced post-SCI cavity formation and improved behavioral function by releasing trophic factors into the cerebrospinal fluid (CSF) or by direct interaction with host spinal tissues. Infusion of transplants through CSF provides no additional traumatic injury to the damaged spinal cord and BMSCs might be administered by lumbar puncture to the patients. Lumbar puncture can be done without severe invasion, so BMSCs can be repeatedly administered to maintain their effects. This study has demonstrated for the first time that the transplantation of BMSCs through CSF can promote the behavioral recovery and tissue repair of the injured spinal cord in rats, thus providing a road map for the clinical autograft of BMSCs without severe surgical infliction to human patients[41]. In another study, human mesenchymal stem cells (hMSCs) isolated from adult bone marrow were found to infiltrate primarily into the ventrolateral white matter tracts, spreading to adjacent segments

rostro-caudal to the injury epicenter, and facilitate recovery from SCI by remyelinating spared white matter tracts and/or by enhancing axonal growth[42]. In our laboratory, we used mesenchymal stem cells from rat bone marrow to evaluate the therapeutic potential after SCI in rats[43]. We observed that caspase-3 mediated apoptosis after SCI on both neurons and oligodendrocytes was significantly downregulated by BMSC. Treatment with BMSC had a positive effect on behavioral outcome and better structural integrity preservation as seen in histopathological analysis. BMSC secrete protective factors that prevent neuronal apoptosis through stimulation of endogenous survival signaling pathways, namely PI3K/Akt and the MAPK/ERK1/2-cascade. Overall, these findings demonstrate that BMSC trigger endogenous survival signaling pathways in neurons that mediate protection against apoptotic insults. Moreover, the interaction between stressed neurons and BMSC further amplifies the observed neuroprotective effect[44].

Lu *et al*[45], investigated the nature of the chronic scar and its ability to block axon growth by testing the hypothesis that chronically injured spinal cord axons can regenerate through the gliotic scar in the presence of local growth-stimulating factors. BMSC, genetically modified to secrete neurotrophin-3 (NT-3) were injected into the lesion site of rats with cervical SCI[45]. It was observed that a modest number of axons penetrated through the chronic scar that contained a mixture of inhibitory and growth stimulating factors. Furthermore, robust axonal growth can be induced by the local provision of neurotrophic factors without resecting the chronic scar. In another study, Urdzíková *et al*[46], have shown that treatment with different cell populations obtained from bone marrow (MSCs, BMCs and the endogenous mobilization of bone marrow cells) has a beneficial effect on behavioral and histological outcomes after SCI. However, it is not clear whether the injection of MSCs, BMCs or granulocyte-colony stimulating factor (G-CSF) treatment induces functional and morphological improvement through the same mechanisms of action. Transplanted MSCs mollify the inflammatory response in the acute setting and reduce the inhibitory effects of scar tissue in the subacute/chronic setting to provide a permissive environment for axonal extension. In addition, grafted cells may provide a source of growth factors to enhance axonal elongation across spinal cord lesions[47]. Down-regulation of TNF-α expression in macrophages/microglia was observed at an early stage after SCI in rats transplanted with a gelatin sponge (GS) scaffold impregnated with rat bone marrow-derived mesenchymal stem cells at the site of injury[48]. It was also shown that 3D gelatin sponge scaffolds allowed MSCs to adhere, survive and proliferate and also for fibronectin to deposit. *In vivo* transplantation experiments demonstrated that these scaffolds were biocompatible and MSCs seeded to the scaffolds played an important role in attenuating inflammation, promoting angiogenesis, and reducing cavity formation. Novikova *et al*[49], observed that differentiated BMSC provided neuroprotection for axotomized rubrospinal neurons and increased the density of rubrospinal axons in the dorsolateral funiculus rostral to the injury site. They suggested that BMSC induced along the Schwann cell lineage increased expression of trophic factors and have neuroprotective and growth-promoting effects after SCI[49]. Cizkova *et al*[50], standardized the intrathecal (IT) catheter delivery of rat MSCs after SCI in adult rats. Based on these results, it was suggested that repetitive IT transplantation, which imposes a minimal burden on the animals, may improve behavioral function when the dose, timing, and targeted IT delivery of MSCs towards the lesion cavity was optimized. Kang *et al*[51], indicated that therapeutic rat BMSCs in a poly (D,L-lactide-co-glycolide)/small intestinal submucosa scaffold induced nerve regeneration in a complete spinal cord transection model and demonstrated that functional recovery further depended on defect length.

Park *et al*[52] evaluated the therapeutic efficacy of combining autologous BMSC transplantation with granulocyte macrophage-colony stimulating factor (GM-CSF) by subcutaneous administration directly into the spinal cord lesion site of six patients with complete SCI. At the 6-mo and 18-mo follow-up periods, four of the six patients showed neurological improvements by two ASIA (American Spinal Injury Association) grade (from ASIA A to ASIA C), while another improved from ASIA A to ASIA B[52]. Moreover, BMSC transplantation together with GM-CSF was not associated with increased morbidity or mortality. In another clinical trial, the safety of autologous bone marrow cell implantation was tested in twenty patients[53]. Motor-evoked potential, somatosensory-evoked potential, magnetic resonance imaging, and ASIA scores were measured in a clinical follow-up. This study demonstrated that BMSC transplantation is a relatively safe procedure, and BMSC-mediated repair can lead to modest improvements in some injured patients. It is also anticipated that a Phase II clinical trial designed to test the efficacy will be initiated in the near future. In a study conducted by Deng *et al*[54], implantation of BMSC elicited *de novo* neurogenesis, and functional recovery in a non-human primate SCI model with rhesus monkeys achieved Tarlov grades 2-3 and nearly normal sensory responses three months after transplantation. Zurita *et al*[55], observed progressive functional recovery three months after SCI in paraplegic pigs injected with autologous BMSC in autologous plasma into lesion zone and adjacent subarachnoid space. Intramedullary post-traumatic cavities were filled by a neoformed tissue containing several axons, together with BMSC, that expressed neuronal or glial markers. Furthermore, in the treated animals, electrophysiological studies showed recovery of the previously abolished somatosensory-evoked potentials. Despite promising data, further research is needed to establish whether bone marrow cell treatments can serve as a safe and efficacious autologous source for the treatment of SCI[47]. However, the use of BMSC in SCI does present certain issues-migration beyond the injection site (for intraspinally delivered cells) is limited and

Table 1 Overview of effects of bone marrow stromal cells after spinal cord injury

Source of MSC	Main pathological features improved/repaired	Limitations/recommendations/conclusions	Ref.
Human	Axonal growth, partial recovery of function	Differences in donor or lot-lot efficacy of MSC	Neuhuber *et al*[37], 2005
Human	Axonal growth, significant behavioral recovery	Survival of BMSC grafts for longer duration	Himes *et al*[38], 2006
Human	Significant motor improvements in human patients	Autologous bone marrow cell transplantation with GM-CSF administration has no serious complications. More comprehensive multicenter clinical studies are recommended	Park *et al*[52], 2005
Human	Homing of MSC, functional recovery	Mechanisms of engraftment, homing, long-term safety	Cizkova *et al*[42], 2006
Rhesus monkey	*De novo* neurogenesis and functional recovery in rhesus monkeys	Synergetic effects of MSC implantation and locally delivered neurotrophic factors in rhesus SCI models	Deng *et al*[54], 2006
Pig	Improvement in somatosensory-evoked potentials, functional recovery in pigs	Possible utility of BMSC transplantation in humans suffering from chronic paraplegia	Zurita *et al*[55], 2008
Rat	No allodynia, anti-inflammatory, increase in white matter volume and decrease in cyst size, sensorimotor enhancements	Survival of MSC	Abrams *et al*[39], 2009
Rat	MSC form bundles bridging the lesion epicenter, functional recovery	Neuron-like MSC lacked voltage-gated ion channels for generation of action potentials	Hofstetter *et al*[40], 2002
Rat	Cavity reduction, functional recovery	Unknown trophic factors secreted by BMSC	Ohta *et al*[41], 2004
Rat	Downregulation of apoptosis, functional recovery	Intrinsic properties of MSC, microenvironment of the injured spinal cord, host-graft interactions	Dasari *et al*[43], 2007
Rat/gerbil	Activation of survival signaling pathways, neuroprotection	Neuroprotective factors released by BMSC, interactions between neurons and BMSC	Isele *et al*[44], 2007
Rat	Axonal regeneration, myelination of axons	Resection of the chronic scar	
Rat	Increase in spared white matter, functional recovery	Differences in mechanism of action of MSCs or BMCs (bone marrow cells) or G-CSF in inducing functional and morphological improvement	Urdzíková *et al*[46], 2006
Rat	Reduction in inflammation, promoting angiogenesis, and reducing cavity formation	GS scaffolds may serve as a potential supporting biomaterial for wound healing after SCI	Zeng *et al*[48], 2011
Rat	Extensive in-growth of serotonin-positive raphaespinal axons and calcitonin gene-related peptide-positive dorsal root sensory axons, attenuation of astroglial and microglial activity	Production of trophic factors support neuronal survival and axonal regeneration	Novikova *et al*[49], 2011
Rat	Functional recovery	Repetitive IT transplantation may improve behavioral function depending on optimization of dose, timing, and targeted IT delivery of MSCs	Cizkova *et al*[50], 2011
Rat	Axonal regeneration, functional recovery	Feasibility of therapeutic cell delivery using 3D scaffolds, especially in complete spinal cord transection	Kang *et al*[51], 2011
Rat	Partial improvement in ASIA score in human patients	Polymer hydrogels may become suitable materials for bridging cavities after SCI	Sykova *et al*[53], 2006

SCI: Spinal cord injury; MSC: Marrow stromal cell; IT: Intrathecal; CSF: Cerebrospinal fluid; GS: Gelatin sponge; BMSC: Bone marrow-derived mesenchymal stem cell.

inter-donor variability in efficacy and immunomodulatory potency might be reflected in variable clinical outcome[37], making BMSC evaluation as a therapy for SCI difficult[3]. The pathological improvements of BMSC after SCI are summarized in Table 1.

ADIPOSE TISSUE-DERIVED MESENCHYMAL CELLS

Adipose tissue is abundant in the body and contains a stromal fraction rich in stem- progenitor cells capable of undergoing differentiation into osteogenic, chondrogenic, and adipogenic lineages[56]. The *in vitro* as well as *in vivo* properties of adipose tissue-derived stromal cells (ADSCs) resemble those of MSCs obtained from bone marrow, and the liposuction procedure employed to harvest ADSCs is minimally invasive for the patient[57]. Kang *et al*[58], reported that intravenous infusion of oligodendrocyte precursor cells (OPCs) derived from rATSC autograft cells improved motor function in rat models of SCI. Moreover, cytoplasmic extracts prepared from adipose tissue stromal cells (ATSCs) inhibit H_2O_2-mediated apoptosis of cultured spinal cord-derived neural progenitor cells (NPCs) and improved cell survival[59]. ATSCs extracts mediated this effect by decreasing caspase-3 and c-Jun-NH2-terminal kinase (SAPK/JNK) activity, inhibiting cytochrome c release from mitochondria and reducing Bax expression levels in cells. Direct injection of ATSCs extracts mixed with matrigel into the spinal cord immediately after SCI also resulted in less apoptotic cell death, astrogliosis and hypo-myelination and showed significant functional improvement. Zhang *et al*[60], showed that ADSCs can differentiate into neural-like cells *in vitro* and *in vivo*. However, neural differentiated ADSCs did not result in any better functional recovery than did undifferentiated ones following SCI. Ryu *et al*[61], evaluated the implantation of allogenic adipose-derived stem cells (ASCs) for the improvement of neurological function in a canine SCI model. Using both *in vitro* and *in vivo* injury models, Oh *et al*[62], confirmed that hypoxic

Table 2 Overview of effects of Adipose tissue-derived mesenchymal cells after spinal cord injury

Source of MSC	Main pathological features improved/repaired	Limitations/recommendations/conclusions	Ref.
Human	Functional recovery	Interaction between engrafted rATSC-OPCs and endogenous spinal cord-derived NPCs promotes host injury repair	Kang *et al*[58], 2006
Human	Improvement in both the cell survival and the gene expression of the engineered NSC observed in SCI rats	Hypoxia preconditioning strategy and combined stem cell/gene therapies can be used to augment the therapeutic efficacy at target injury sites	Oh *et al*[62], 2010
Human	mNSCs transplanted into rat spinal cords with AT-MSCs showed better survival rates than mNSCs transplanted alone	Co-transplantation of mNSCs with AT-MSCs may be a more effective transplantation protocol to improve the survival of cells in the injured cord	Oh *et al*[63], 2011
Human	Transplantation of 3DCM-ASCs into the injured spinal cord significantly elevated the density of vascular formations and enhanced axonal outgrowth at the lesion site, functional recovery	Transplantation of 3DCM-ASCs may be an effective stem cell therapy	Oh *et al*[64], 2012
Human	No toxicity of hAdMSCs in immunodeficient mice, none of 8 male patients developed any serious adverse events related to hAdMSC transplantation in phase Ⅰ clinical trial	Systemic transplantation of hAdMSCs appears to be safe and does not induce tumor development. Slow intravenous infusion of autologous hAdMSCs may be safe in SCI patients	Ra *et al*[66], 2011
Human	Increase in BDNF levels, increased angiogenesis, preserved axons, decreased numbers of ED1-positive macrophages, reduced lesion cavity formation, functional recovery in rats	Compared with hBMSCs, hADSCs may be a better source of MSCs for cell therapy for acute SCI because of their relative abundance and accessibility	Zhou *et al*[67], 2013
Dog	Significant improvement in nerve conduction velocity based on SEP, partial improvement in neurological functions of dogs	ASCs in spinal cord injuries might be partially due to neural differentiation of implanted stem cells	Ryu *et al*[61], 2009
Dog	Anti-inflammation, anti-astrogliosis, neuronal extension, neuronal regeneration, functional recovery	The combination of Matrigel and NMSC produced beneficial effects	Park *et al*[65], 2012
Rat	Reduced apoptotic cell death, astrogliosis and hypo-myelination, functional recovery	ATSC extracts may provide a powerful autoplastic therapy for neurodegenerative conditions in humans	Kang *et al*[59], 2007
Rat	Neural differentiated ADSCs did not result in better functional recovery than undifferentiated ones following SCI	*In vitro* neural transdifferentiation of ADSCs might therefore not be a necessary pre-transplantation step	Zhang *et al*[60], 2009
Rat	Functional recovery	Predifferentiation of ASCs plays a beneficial role in SCI repair	Arboleda *et al*[57], 2011
Rat	Axonal regeneration, remyelination, functional recovery	Adipose tissue-derived Schwann cells can support axon regeneration and enhance functional recovery	Zaminy *et al*[68], 2013

OPCs: Oligodendrocyte precursor cells; NPCs: Neural progenitor cells; NSC: Neural stem cell; SCI: Spinal cord injury; MSC: Marrow stromal cell; AT: Adipose tissue; 3DCM-ASCs: Three-dimensional cell mass transplantation of adipose-derived stem cells; hAdMSCs: Human Adipose tissue-derived mesenchymal stem cells; NMSC: Neural-induced mesenchymal stem cells; ATSC: Adipose tissue stromal cell; ADSCs: Adipose tissue-derived stromal cells; BMSC: Bone marrow-derived mesenchymal stem cell.

preconditioning (HP)-treated adipose tissue-derived mesenchymal stem cells (HP-AT-MSCs) increased cell survival and enhanced the expression of marker genes in DsRed-engineered neural stem cells (NSCs-DsRed). Based on their findings, it was suggested that the co-transplantation of HP-AT-MSCs with engineered neural stem cells (NSCs) can improve both cell survival and gene expression of the engineered NSCs. This novel strategy can be used to augment the therapeutic efficacy of combined stem cell and gene modulation therapy for SCI. In another study, Oh *et al*[63], examined the effects of co-transplanting mouse neural stem cells (mNSCs) and adipose tissue-derived mesenchymal stem cells (AT-MSCs) on mNSC viability. It was observed that mNSCs transplanted into rat spinal cords with AT-MSCs showed better survival rates than mNSCs transplanted alone, thereby suggesting that co-transplantation of mNSCs with AT-MSCs is a more effective strategy to improve the survival of transplanted stem cells into the injured spinal cord. In a more recent study, the same group investigated the effectiveness of a three-dimensional cell mass transplantation of adipose-derived stem cells (3DCM-ASCs) in hind limb functional recovery by the stimulation of angiogenesis and neurogenesis[64]. These results revealed a significantly elevated density of neovascular formations through angiogenic factors released by the 3DCM-ASCs at the lesion site, enhanced axonal outgrowth, and significant functional recovery. These findings suggest that transplantation of 3DCM-ASCs may be an effective stem cell transplantation modality for the treatment of spinal cord injuries and neural ischemia. In a similar study, Park *et al*[65], observed that a combination of matrigel and neural-induced mesenchymal stem cells (NMSC) reduced the expression of inflammation and/or astrogliosis markers and improved hind limb function in dogs with SCI. The predifferentiation of ASCs plays a beneficial role in SCI repair by promoting the protection of denuded axons and cellular repair that was induced mainly through paracrine mechanisms[57]. The propensity of proliferation and the potential of unchecked differentiation of stem cells raised the concern of inherent tumorigenicity and toxicity. Ra *et al*[66], observed that systemic transplanta-

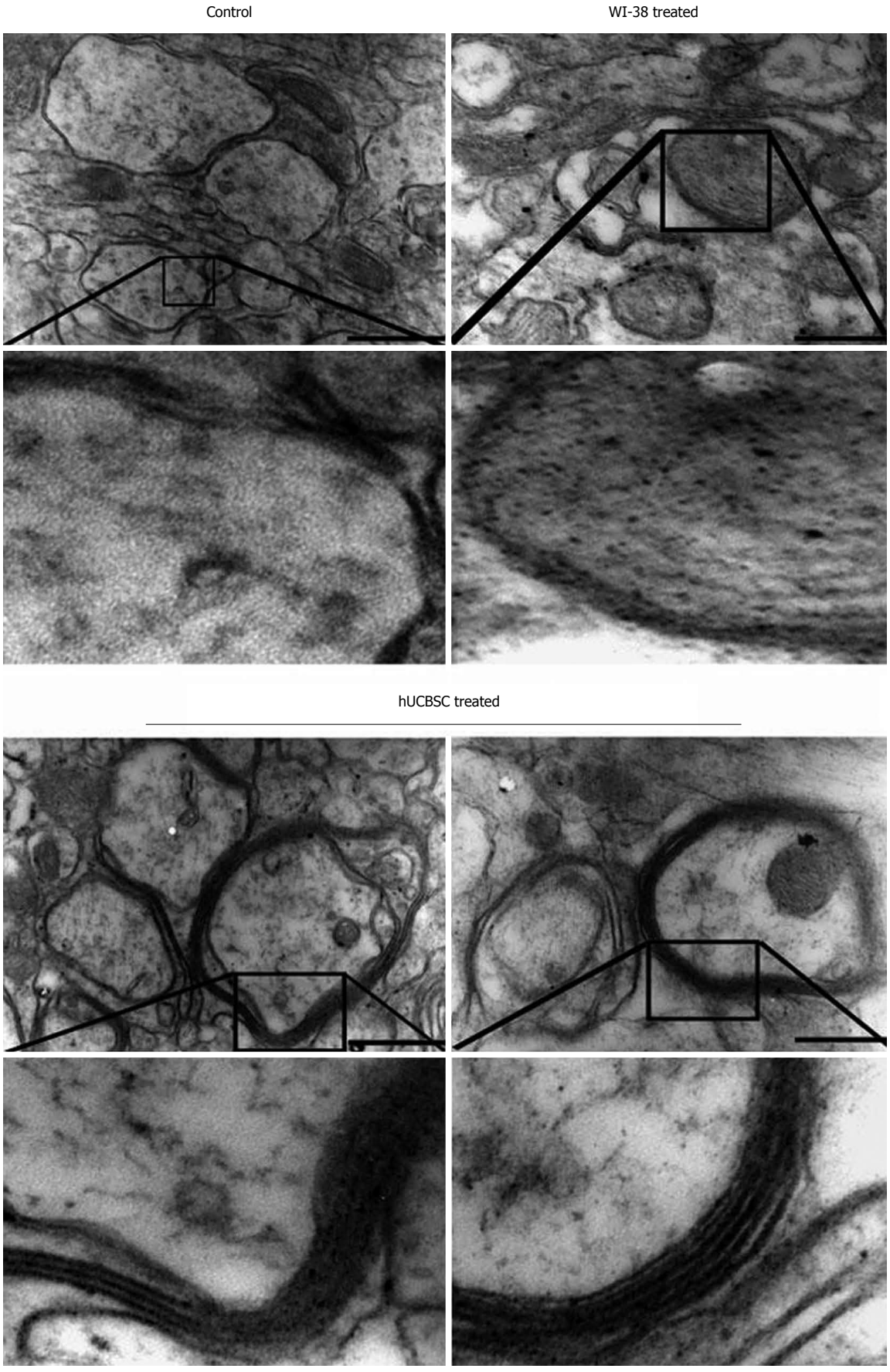

Figure 1 Transmission electron micrographs of shiverer mice brain showing thin and fragmented myelin around the axons in control and WI-38- implanted mice. In contrast, human umbilical cord blood-derived mesenchymal stem cells-treated shiverer brains showing myelin with several layers. Images are representatives of the several sections obtained from 3 different animals (n = 3). Scale bar = 33000. *Stem Cells Dev* 2011; **20**: 881-891.

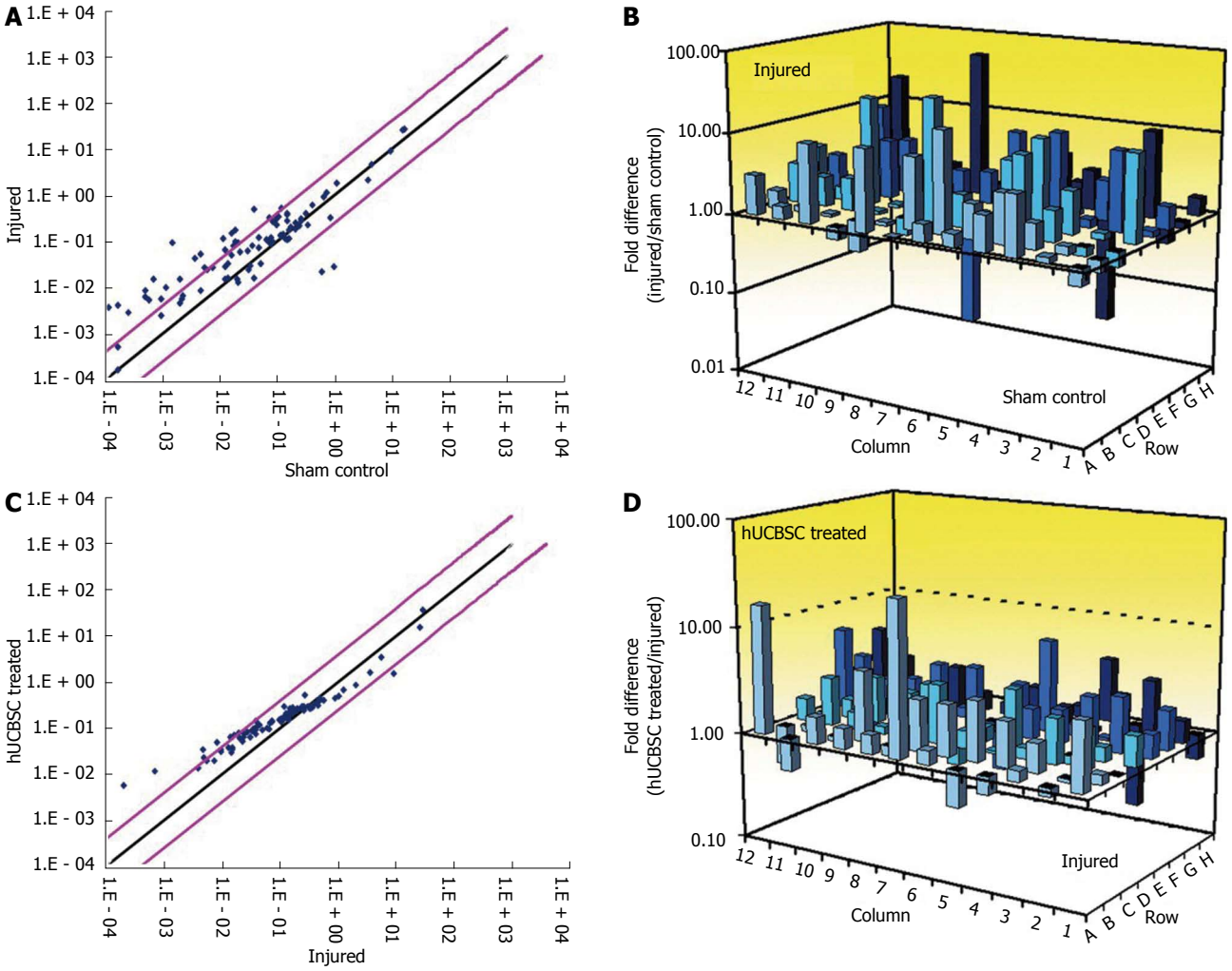

Figure 2 Microarray analysis of apoptotic genes after spinal cord injury. Total RNA was extracted from sham control, 3-wk post-spinal cord injury (SCI), and 3-wk post-SCI plus human umbilical cord blood-derived mesenchymal stem cells (hUCBSC)-treated tissues, reverse-transcribed, and the corresponding cDNA was loaded into a 96-well plate. In each group, RNA from at least three different animals was pooled together. A and C: Representative scatter plots show the validity of the experiment and the expression level of each gene in the control *vs* injured and injured *vs* hUCBSC-treated samples; B and D: These 3D profile graphs show the fold difference in expression of each gene between sham control *vs* injured and injured *vs* hUCBSC-treated samples. These experiments were performed in duplicate (hUCBSC, human umbilical cord blood-derived mesenchymal stem cells; SCI, spinal cord injury). *J Neurotrauma* 2009; **26**: 2057-2069.

tion of human Adipose tissue-derived mesenchymal stem cells (hAdMSCs) appeared to be safe and did not induce tumor development as none of the patients developed any serious adverse events related to hAdMSC transplantation during the three-month follow-up. Zhou *et al*[67], compared mesenchymal stromal cells from human bone marrow and adipose tissue for the treatment of spinal cord injury and suggested that hADSCs would be more appropriate than hBMSCs for transplantation to treat SCI. Recently, Zaminy *et al*[68], proved that adipose tissue-derived Schwann cells can modulate the hostile environment of the damaged spinal cord and generate a more stimulating environment to support axon regeneration and enhance functional recovery (Table 2).

HUMAN UMBILICAL CORD BLOOD-DERIVED MSCS

Human umbilical cord blood-derived mesenchymal stem cells (hUCBSC) offer great potential for novel therapeutic approaches targeted against many CNS diseases. Previous studies have reported that hUCBSC are beneficial in reversing the deleterious effects of SCI, even when infused five days after injury[69]. Transplanted hUCBSC differentiate into various neural cells and induce motor function improvement in SCI rat models[70]. In our laboratory, hUCBSC transplanted in rats one week after SCI were shown to transdifferentiate into neurons and oligodendrocytes and also to downregulate Fas-mediated apoptosis[71,72]. These transdifferentiated oligodendrocytes facilitated the secretion of neurotrophic hormones NT3 and BDNF and synthesized MBP and PLP, thereby promoting the remyelination of demyelinated axons in the injured spinal cord[71]. We observed that hUCBSC treatment increased myelin basic protein *in vitro* in PC-12 cells, which are normally not myelinated. To further confirm the ability of transplanted hUBCSC in remyelination, we injected hUBCSC into shiverer mice brains. This study

Table 3 Changes in the expression of apoptotic genes and inhibitors after spinal cord injury and human umbilical cord blood stem cells treatment

UniGene	GenBank	Gene name	Fold change after SCI	Fold change after hUCBSC treatment
Rn. 36696	NM_022698	Bad	3.12 ± 1.34	-1.47 ± 0.14
Rn. 14598	NM_053812	Bak1	2.28 ± 0.99	1.36 ± 0.79
Rn. 13007	NM_031328	Bcl10	8.83 ± 1.91	1.51 ± 1.45
Rn. 19770	NM_133416	Bcl2a1	7.95 ± 1.98	1.79 ± 0.75
Rn. 10323	NM_031535	Bcl2l1	2.13 ± 0.85	-2.01 ± 0.89
Rn. 162782	NM_022684	Bid	2.45 ± 1.27	1.86 ± 0.99
Rn. 89639	NM_057130	Bid3	5.43 ± 1.06	2.62 ± 0.75
Rn. 38487	NM_053704	Bik	4.41 ± 0.64	3.58 ± 0.14
Rn. 92423	XM_226742	Birc1b	25.84 ± 0.85	3.01 ± 0.67
Rn. 64578	NM_023987	Birc3	10.14 ± 1.06	3.01 ± 0.78
Rn. 54471	NM_022274	Birc5	-2.84 ± 1.98	4.57 ± 1.14
Rn. 55946	NM_057138	Cflar (Flip)	3.12 ± 1.77	-1.20 ± 0.86

Results are expressed as mean ± SD. hUCBSC: Human umbilical cord blood stem cells; SCI: Spinal cord injury. Refer Dasari *et al*[75].

Table 4 Changes in the expression of caspase-related and nuclear factor-κB-related apoptotic genes after spinal cord injury

UniGene	GenBank	Gene name	Fold change after SCI	Fold change after hUCBSC treatment
Rn. 37508	NM_012762	Casp1	9.14 ± 1.70	1.27 ± 0.78
Rn. 81078	NM_130422	Casp12	2.91 ± 1.34	1.46 ± 0.68
Rn. 10562	NM_012922	Casp3	3.56 ± 0.92	1.18 ± 0.84
Rn. 88160	NM_031775	Casp6	3.34 ± 1.06	1.46 ± 0.79
Rn. 53995	NM_022260	Casp7	2.81 ± 1.27	2.81 ± 1.21
Rn. 54474	NM_022277	Casp8	3.84 ± 1.20	1.62 ± 0.89
Rn. 32199	NM_031632	Casp9	2.86 ± 0.71	1.36 ± 0.62
Rn. 67077	NM_053362	Dffb (Cad)	32.94 ± 0.78	2.72 ± 0.84
Rn. 16183	NM_152937	Fadd	2.21 ± 0.78	1.51 ± 0.73
Rn. 162521	NM_139194	Tnfrsf6 (Fas)	10.87 ± 1.77	1.79 ± 0.67
Rn. 44218	NM_053353	CD40lg	15.91 ± 0.99	3.46 ± 0.78
Rn. 160577	NM_080769	Lta (Tnfb)	28.67 ± 0.07	2.06 ± 0.68
Rn. 2275	NM_012675	TNF-α	7.17 ± 1.63	2.36 ± 1.03
Rn. 11119	NM_013091	Tnfrsf1a (TNFR1)	2.53 ± 1.48	1.22 ± 0.78
Rn. 83633	NM_130426	Tnfrsf1b (TNFR2)	5.25 ± 1.56	3.01 ± 0.99
Rn. 25180	NM_134360	Tnfrsf5 (CD40)	4.26 ± 1.84	1.99 ± 0.78
Rn. 54443	NM_030989	Tp53 (P53)	3.46 ± 1.41	-1.12 ± 0.61
Rn. 18545	XM_341671	Tradd	5.62 ± 1.13	1.46 ± 0.59
Rn. 136874	AI406530	Traf1	4.12 ± 1.34	2.06 ± 0.84

Results are expressed as mean ± SD. hUCBSC: Human umbilical cord blood stem cells; NF-κB: Nuclear factor-κB; SCI: Spinal cord injury. Refer Dasari *et al*[75].

clearly demonstrated that transplanted hUCBSC survived, migrated *in vivo* and myelinated genetically denuded axons in shiverer mice brains. The expression level of myelin basic protein, a major component of the myelin sheath, was significantly elevated in *vivo* and *in vitro* as revealed by Western blotting, reverse transcription polymerase chain reaction, immunohistochemistry, immunocytochemistry, and fluorescent *in situ* hybridization results. Further, transmission electron microscopic images of hUCBSC-treated shiverer mice brains showed several layers of myelin around the axons compared with a thin and fragmented layer of myelin in untreated animals (Figure 1). Moreover, the frequency of shivering was diminished one month after hUCBSC treatment. Our results strongly indicated that hUCBSC transplantation played an important role in re-myelination and could be an effective therapeutic approach for demyelinating or hypomyelinating disorders[73]. Furthermore, apoptotic pathways mediated by caspase-3, Fas and TNF-α were downregulated by hUCBSC[72,74]. The locomotor scale scores in hUCBSC-treated rats were significantly improved as compared to those of the control injured group. To further extend our studies, we utilized RT-PCR microarray and analyzed 84 apoptotic genes to identify the genetic modulation that occurred after traumatic SCI and after hUCBSC transplantation[75]. We observed that the genes involved in inflammation and apoptosis were up-regulated (TNF-α, TNFR1, TNFR2, Fas, Bad, Bid, Bid3, Bik, and Bak1) in the injured rat spinal cords, whereas genes such as XIAP, which are involved in neuroprotection, were up-regulated in the hUCBSC-treated rats (Figure 2, Tables 3 and 4). Our findings from co-cultures of cortical neurons with hUCBSC and blocking of the Akt pathway by a dominant-negative Akt and Akt-inhibitor IV confirmed that the mechanism underlying hUCBSC neuroprotection involved activation of the Akt signaling pathway. These results suggested the neuroprotective potential of hUCBSC against glutamate-induced apoptosis of cultured cortical neurons[74]. Both the *in vivo* and *in vitro* studies supported our hypothesis that the therapeutic mechanism of hUCBSC was remyelination of demyelinated axons and inhibition of the neuronal apoptosis during the repair phase of the injured spinal cord. Veeravalli *et al*[76] reported the involvement of tissue plasminogen activator (tPA) after SCI in rats and the role of hUCBSC. The tPA expression and activity were studied *in vivo* in rats after SCI and in *vitro* in rat embryonic spinal neurons in response to injury with staurosporine, hydrogen peroxide and glutamate. Infusion of hUCBSC downregulated tPA activity *in vivo* in rats as well as *in vitro* in the spinal neurons. Furthermore, MMP-2 is upregulated after hUCBSC treatment in spinal cord injured rats and in spinal neurons injured either with staurosporine or hydrogen peroxide. Also, hUCBSC-induced upregulation of MMP-2 diminished the formation of the glial scar at the site of injury along with reduced immunoreactivity to chondroitin sulfate proteoglycans. This upregulation of MMP-2 levels and reduction of glial scar formation by hUCBSC treatment after SCI created an environment more favorable for endogenous repair mechanisms[77] (Figure 3). Kao *et al*[78], suggested that hUCB derived-$CD34^+$ cells can induce angiogenesis and endo/exogenous neurogenesis in SCI. In addition, Chen *et al*[79] recently showed that hUCB stem cells have the ability to secrete multiple neurotrophic factors. Their study demonstrated an elevation of neuroprotective cytokine serum IL-10 levels and a decrease in TNF-α levels after hUCB stem cells infusion. Moreover, both GDNF and VEGF could be detected in the injured spinal cord

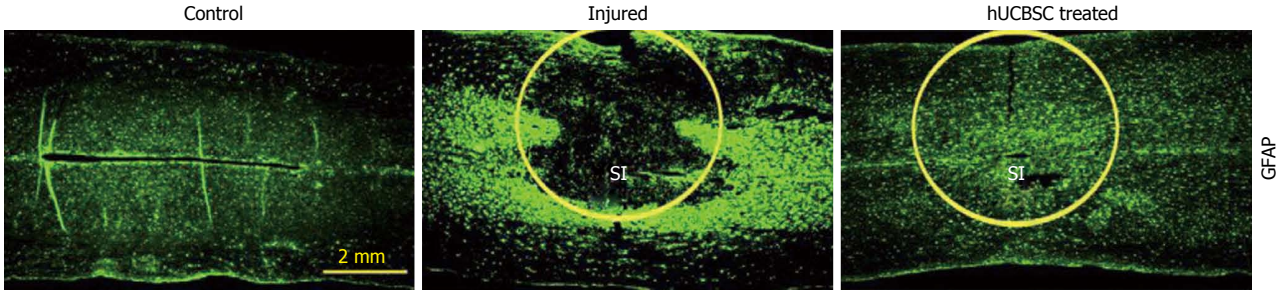

Figure 3 Reduction of inflammation in human umbilical cord blood- derived mesenchymal stem cell-treated spinal cords of rats. Immunohistochemical comparison of control, injured (21 d after spinal cord injury) and human umbilical cord blood- derived mesenchymal stem cells-treated spinal cord sections was performed to analyze the expression of reactive astrocytes at the site of injury. GFAP immunoreactivity is more evident and is localized at the lesion epicenter in the injured spinal cords. Astrogliosis is reduced in human umbilical cord blood- derived mesenchymal stem cells-treated sections. SI: Site of injury. *Neurobiol Dis* 2009; **36**: 200-212.

Table 5 Overview of effects of umbilical cord blood-derived mesenchymal stem cells after spinal cord injury

Source of MSC	Main pathological features improved/repaired	Limitations/recommendations/conclusions	Ref.
Human	Stem cells migrated to injured areas, functional recovery	hUCB may be a viable source of stem cells for treatment of neurological disorders	Saporta *et al*[69], 2003
	Axonal regeneration, functional recovery	HUCBs and BDNF reduced the neurological function deficit to a moderate degree for SCI rats	Kuh *et al*[70], 2005
	Stem cells secrete neurotrophic hormones and remyelinating proteins, axonal remyelination	Studies on long-term survival of hUCBSC and remyelination are recommended.	Dasari *et al*[71], 2007
	Repair and maintenance of structural integrity of the injured spinal cord, downregulation of apoptosis, functional recovery	Role of hUCBSC in maintaining structural integrity and thereby promoting the long-term survival of neurons and oligodendrocytes in the injured spinal cord	Dasari *et al*[72], 2008
	Downregulation of neuronal apoptosis	Modulation of the micro environment of the injured spinal cord by application of hUCBSC might be a potential therapeutic modality	Dasari *et al*[75], 2009
	Downregulation of elevated tPA activity/ expression in SCI rats	tPA is involved in secondary pathogenesis following spinal cord injury	Veeravalli *et al*[76] 2009
	Upregulation of MMP2, reduction of glial scar	hUCBSC treatment after SCI upregulates MMP-2 levels and reduces the formation of the glial scar	Veeravalli *et al*[77], 2009
	GDNF and VEGF were secreted in the injured spinal cord after transplantation of $CD34^+$ cells	$CD34^+$ cell therapy may be beneficial in reversing the SCI-induced spinal cord infarction and apoptosis and hindlimb dysfunction	Kao *et al*[78], 2008
	Serum IL-10 levels increased, TNF-α levels decreased, functional recovery	Recovery of SCI-induced hind limb dysfunction is by increasing serum levels of IL-10, VEGF and GDNF in SCI rats.	Chen *et al*[79] 2008
	Infarct size and blood vessel density at the injured site were significantly different in the treated group, functional recovery	Transplantation of CD34(+) HUCBCs during acute phase could promote functional recovery better than during subacute phase after SCI by raising blood vessel density	Ning *et al*[80], 2013

MSC: Mesenchymal stem cell; SCI: Spinal cord injury; IL: Interleukin; TNF-α: Tumor necrosis factor-α; hUCB: Human umbilical cord blood; hUCBSC: Human umbilical cord blood-derived mesenchymal stem cell.

after the transplantation of hUCBSC, thereby promoting angiogenesis and neuronal regeneration. Recently, Ning *et al*[80], showed that transplantation of $CD34^+$ HUCBCs during the acute phase could promote functional recovery better than during the subacute phase after SCI by raising neovascular density. These multifaceted protective and restorative effects from hUCB grafts may be interdependent and act in concert to promote therapeutic recovery for SCI (Table 5). Nevertheless, clinical studies with hUCBSC are still limited due to concerns about safety, mode of delivery, and efficiency. Among these concerns, the major histocompatibility in allogeneic transplantation is an important issue that needs to be addressed in future clinical trials for treating SCI[16].

HUMAN WHARTON'S JELLY/UMBILICAL CORD MATRIX CELLS

There are two main populations of cells with a mesenchymal character within the human umbilical cord: Wharton's jelly mesenchymal stem cells (WJ-MSCs) and human umbilical cord perivascular cells (HUCPVCs)[81]. Wharton's jelly cells (WJ-MSCs) can proliferate more rapidly and extensively than adult BMSCs (for a detailed review refer to Vawda and Fehlings, 2013). Yang *et al*[82], examined the effects of human umbilical mesenchymal stem cells (HUMSC) transplantation after complete spinal cord transection in rats. They observed that transplanted HUMSCs survived for 16 wk and produced large amounts of human neutro-

Table 6 Overview of effects of Wharton's jelly/umbilical cord matrix cells after spinal cord injury

Source of MSC	Main pathological features improved/repaired	Limitations/recommendations/conclusions	Ref.
Human	Survival of transplanted HUMSCs 16 wk, secretion of human neutrophil-activating protein-2, neurotrophin-3, basic fibroblast growth factor, glucocorticoid induced tumor necrosis factor receptor, and vascular endothelial growth factor receptor 3 in the host spinal cord	Transplantation of HUMSCs is beneficial to wound healing after SCI in rats	Yang *et al*[82], 2008
	Axonal regeneration, neuroprotective action by grafted cells, functional recovery	Co-grafted HUMSCs and BDNF may be a potential therapy for SCI	Zhang *et al*[83], 2009
	hUCMSCs survive, migrate, and produce GDNF and neurotrophin-3, functional recovery	Studies on dose-dependent effects of hUCMSCs transplantation on SCI are required	Hu *et al*[84], 2010
	Increased intensity of 5-HT fibers, increased volume of spared myelination, decreased area of cystic cavity, functional recovery	NT-3 enhanced therapeutic effects of HUMSCs after clip injury of the spinal cord.	Shang *et al*[85], 2011

MSC: Mesenchymal stem cell; SCI: Spinal cord injury; hUCBSC: Human umbilical cord blood-derived mesenchymal stem cell.

phil-activating protein-2, neurotrophin-3, basic fibroblast growth factor, glucocorticoid induced tumor necrosis factor receptor, and vascular endothelial growth factor receptor 3 in the host spinal cord. Zhang *et al*[83], used an animal model of transected SCI to test the hypothesis that co-grafted human umbilical mesenchymal stem cells-derived neurospheres (HUMSC-NSs) and BDNF can promote morphologic and functional recoveries of the injured spinal cord. Recovery of hindlimb locomotor function in SCI rats was significantly enhanced in human umbilical cord mesenchymal stem cells-grafted animals at five weeks as compared to control sham-grafted animals[84]. Using a rat model for clip SCI, Shang *et al*[85], showed that Neurotrophin-3 (NT-3) genetically modified human umbilical mesenchymal stem cells (NT-3-HUMSCs) promoted the morphologic and functional recovery of injured spinal cords (Table 6). Although these studies involved thoracic SCI model, these positive findings will most likely apply to cervical SCI as well[3].

CONCLUSION

Therapeutic application of MSCs represents a promising approach in the treatment of spinal cord injury. Nevertheless, cell-based therapy for SCI in its nascent stages is facing several challenges including translational clinical issues, regulatory and ethical concerns, as well as modalities of transplantation, timing, safety and efficacy of the transplanted cells. A better understanding is also needed of the mechanisms of action and the behavior of stem cells in the pathological environment after transplantation in order to determine the best time frame and the most efficient routes for cell delivery after the injury[86]. Although several clinical trials utilize MSCs transplantation for the treatment of SCI, the ultimate value of a translational approach needs continued exploration of basic scientific knowledge of SCI and proven therapeutic efficacy *via* rigorous controlled, randomized, double blind, multicenter clinical trials.

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