CSCI Reference Library

Spinal Cord Injury

1. Stem cell therapy in spinal cord injury: Hollow promise or promising science?
Aimee Goel
Journal of Craniovertebral Junction & Spine 2016

Spinal cord injury (SCI) remains one of the most physically, psychologically and socially debilitating conditions worldwide. While rehabilitation measures may help limit disability to some extent, there is no effective primary treatment yet available. The efficacy of stem cells as a primary therapeutic option in spinal cord injury is currently an area under much scrutiny and debate. Several laboratory and some primary clinical studies into the use of bone marrow mesenchymal stem cells or embryonic stem cell-derived oligodentrocyte precursor cells have shown some promising results in terms of remyelination and regeneration of damaged spinal nerve tracts. More recently,laboratory and early clinical experiments into the use of Olfactory Ensheathing Cells, a type of glial cell derived from olfactory bulb and mucosa have provided some phenomenal preliminary evidence as to their neuroregenerative and neural bridging capacity. This report compares and evaluates some current research into selected forms of embryonic and mesenchymal stem cell therapy as well as olfactory ensheathing cell therapy in SCI, and also highlights some legal and ethical issues surrounding their use. While early results shows promise, more rigorous large scaleclinical trials are needed to shed light on the safety, efficacy and long term viability of stem cell and cellular transplant techniques in SCI.

2. Stem Cell-Based Therapy for Spinal Cord Injury
Volarevic, Vladislav; Erceg, Slaven; Bhattacharya, Shom Shanker; Stojkovic, Petra; Horner, Philip; Stojkovic, Miodrag
The Journal of Spinal Cord Medicine 2009

Stem cells (SCs) represent a new therapeutic approach for spinal cord injury (SCI) by enabling improved sensory and motor functions in animal models. The main goal of SC-based therapy for SCI is the replacement of neurons and glial cells that undergo cell death soon after injury. Stem cells are able to promote remyelination via oligodendroglia cell replacement to produce trophic factors enhancing neurite outgrowth, axonal elongation, and fiber density and to activate resident or transplanted progenitor cells across the lesion cavity. While several SC transplantation strategies have shown promising yet partial efficacy, mechanistic proof is generally lacking and is arguably the largest impediment toward faster progress and clinical application. The main challenge ahead is to spur on cooperation between clinicians, researchers, and patients in order to define and optimize the mechanisms of SC function and to establish the ideal source/s of SCs that produce efficient and also safe therapeutic approaches.

3. Continuous improvement after multiple mesenchymal stem cell transplantations in a patient with complete spinal cord injury.
Jarocha D, Milczarek O, Wedrychowicz A, Kwiatkowski S, Majka M.
Cell Transplant 2015

Interruption of spinal cord (SC) continuity leads to functional loss below the lesion level. The purpose of this study was to evaluate the safety and efficacy of bone marrow nucleated cell (BMNC) and multiple mesenchymal stem cell (MSC) transplantations in spinal cord injury (SCI). A patient with total SC interruption at the Th2-3 level underwent experimental therapy with BMNC and MSC transplantations followed with intensive neurorehabilitation treatment. At admission, 6 h after SCI, the patient was scored ASIA A, had a Th1 sensation level, paraplegia with sphincter palsy, and was without the ability to control trunk movement. Neurophysiology examination showed bilateral axonal damage to the motor and sensory neural fibers with no motor unit potentials or peripheral motor nerve conduction in the lower extremities. The standard therapy had been applied and had not produced any positive results. The patient was treated with autologous BMNCs injected intravenously (3.2×10(9)) and intrathecally (0.5×10(9)) 10 weeks after the SCI and with five rounds of MSCs every 3-4 months (1.3-3.65×10(7)) administered via lumbar puncture. Total number of transplanted MSC cells during the course of treatment was 1.54×10(8). There were no complications related to transplantations and no side effects related to the therapy during 2 years of treatment. The ASIA score improved from A to C/D (from 112 to 231 points). The sensation level expanded from Th1 to L3-4, and the patient's ability to control the body trunk was fully restored. Bladder filling sensation, bladder control, and anal sensation were also restored. Muscle strength in the left lower extremities improved from plegia to deep paresis (1 on the Lovett scale). The patient's ability to move lower extremities against gravity supported by the movements in quadriceps was restored. The patient gained the ability to stand in a standing frame and was able to walk with the support of hip and knee ortheses. Magnetic resonance imaging (MRI) revealed that at the Th2/Th3 level, where the hemorrhagic necrosis was initially observed, small tissue structures appeared. Our results suggest that repeated intrathecal infusions of MSCs might have the potential to produce clinically meaningful improvements for SCI patients.

4. Human mesenchymal stem cells modulate inflammatory cytokines after spinal cord injury in rat.

Urdzíková LM, Růžička J, LaBagnara M, Kárová K, Kubinová Š, Jiráková K, Murali R, Syková E, Jhanwar-Uniyal M, Jendelová P.

International Journal of Molecular Sciences 2014

Transplantation of mesenchymal stem cells (MSC) improves functional recovery in experimental models of spinal cord injury (SCI); however, the mechanisms underlying this effect are not completely understood. We investigated the effect of intrathecal implantation of human MSC on functional recovery, astrogliosis and levels of inflammatory cytokines in rats using balloon-induced spinal cord compression lesions. Transplanted cells did not survive at the lesion site of the spinal cord; however, functional recovery was enhanced in the MSC-treated group as was confirmed by the Basso, Beattie, and Bresnahan (BBB) and the flat beam test. Morphometric analysis showed a significantly higher amount of remaining white matter in the cranial part of the lesioned spinal cords. Immunohistochemical analysis of the lesions indicated the rearrangement of the glial scar in MSC-treated animals. Real-time PCR analysis revealed an increased expression of Irf5, Mrc1, Fgf2, Gap43 and Gfap. Transplantation of MSCs into a lesioned spinal cord reduced TNFα, IL-4, IL-1β, IL-2, IL-6 and IL-12 and increased the levels of MIP-1α and RANTES when compared to saline-treated controls. Intrathecal implantation of

MSCs reduces the inflammatory reaction and apoptosis, improves functional recovery and modulates glial scar formation after SCI, regardless of cell survival. Therefore, repeated applications may prolong the beneficial effects induced by MSC application.

5. Transplantation of mesenchymal stem cells promotes an alternative pathway of macrophage activation and functional recovery after spinal cord injury.
Nakajima H, Uchida K, Guerrero AR, Watanabe S, Sugita D, Takeura N, Yoshida A, Long G, Wright KT, Johnson WE, Baba H.
Journal of Neurotrauma 2012

Mesenchymal stem cells (MSC) derived from bone marrow can potentially reduce the acute inflammatory response in spinal cord injury (SCI) and thus promote functional recovery. However, the precise mechanisms through which transplanted MSC attenuate inflammation after SCI are still unclear. The present study was designed to investigate the effects of MSC transplantation with a special focus on their effect on macrophage activation after SCI. Rats were subjected to T9-T10 SCI by contusion, then treated 3 days later with transplantation of 1.0×10(6) PKH26-labeled MSC into the contusion epicenter. The transplanted MSC migrated within the injured spinal cord without differentiating into glial or neuronal elements. MSC transplantation was associated with marked changes in the SCI environment, with significant increases in IL-4 and IL-13 levels, and reductions in TNF-α and IL-6 levels. This was associated simultaneously with increased numbers of alternatively activated macrophages (M2 phenotype: arginase-1- or CD206-positive), and decreased numbers of classically activated macrophages (M1 phenotype: iNOS- or CD16/32-positive). These changes were associated with functional locomotion recovery in the MSC-transplanted group, which correlated with preserved axons, less scar tissue formation, and increased myelin sparing. Our results suggested that acute transplantation of MSC after SCI modified the inflammatory environment by shifting the macrophage phenotype from M1 to M2, and that this may reduce the effects of the inhibitory scar tissue in the subacute/chronic phase after injury to provide a permissive environment for axonal extension and functional recovery.

6. Spinal cord injury in rats treated using bone marrow mesenchymal stem-cell transplantation
Yu-Bing Chen, Quan-Zhang Jia, Dong-Jun Li, Jing-Hai Sun, Shuang Xi, Li-Ping Liu, De-Xuan Gao, and Da-Wei Jiang
International Journal of Clinical and Experimental Medicine 2015

The aim of this study was to observe the effects of bone marrow mesenchymal stem-cell transplantation (BMSCs) in repairing acute spinal cord damage in rats and to examine the potential beneficial effects. 192 Wistar rats were randomized into 8 groups. Spinal cord injury was created. Behavior and limb functions were scored. Repairing effects of BMSCs transplantation was evaluated and compared. In vitro 4',6-diamidino-2-phenylindole (DAPI)-tagged BMSCs were observed, and whether they migrated to the area of spinal cord injury after intravenous tail injection was investigated. The expression of neuron-specific protein (NSE) on BMSCs was examined. Fifteen days after transplantation, the BMSCs-treated groups scored significantly higher in limb function tests than the untreated group. Pathological sections of the bone marrow after operation showed significant recovery in treated groups in comparison to the

control group. After transplantation, small amounts of fluorescent-tagged BMSCs can be found in the blood vessels in the area of spinal cord injury, and fluorescent-tagged BMSCs were diffused in extravascular tissues, whereas the DAPI-tagged BMSCs could not be detected,and BrdU/NSE double-labeled cells were found in the injured marrow. BMSCs improve behavioral responses and can repair spinal cord injuries by migrating to the injured area, where they can differentiate into neurons.

7. Long-term results of spinal cord injury therapy using mesenchymal stem cells derived from bone marrow in humans.
Park JH, Kim DY, Sung IY, Choi GH, Jeon MH, Kim KK, Jeon SR.
Journal of Neurosurgery 2012

BACKGROUND:
Although the transplantation of mesenchymal stem cells (MSCs) after spinal cord injury (SCI) has shown promising results in animals, less is known about the effects of autologous MSCs in human SCI.
OBJECTIVE:
To describe the long-term results of 10 patients who underwent intramedullary direct MSCs transplantation into injured spinal cords.
METHODS:
Autologous MSCs were harvested from the iliac bone of each patient and expanded by culturing for 4 weeks. MSCs (8 × 10) were directly injected into the spinal cord, and 4 × 10 cells were injected into the intradural space of 10 patients with American Spinal Injury Association class A or B injury caused by traumatic cervical SCI. After 4 and 8 weeks, an additional 5 × 10 MSCs were injected into each patient through lumbar tapping. Outcome assessments included changes in the motor power grade of the extremities, magnetic resonance imaging, and electrophysiological recordings.
RESULTS:
Although 6 of the 10 patients showed motor power improvement of the upper extremities at 6-month follow-up, 3 showed gradual improvement in activities of daily living, and changes on magnetic resonance imaging such as decreases in cavity size and the appearance of fiber-like low signal intensity streaks. They also showed electrophysiological improvement. All 10 patients did not experience any permanent complication associated with MSC transplantation.
CONCLUSION:
Three of the 10 patients with SCI who were directly injected with autologous MSCs showed improvement in the motor power of the upper extremities and in activities of daily living, as well as significant magnetic resonance imaging and electrophysiological changes during long-term follow-up.

8. Mesenchymal Stem Cell Graft Improves Recovery after Spinal Cord Injury in Adult Rats through Neurotrophic and Pro-Angiogenic Actions
Quertainmont R, Cantinieaux D, Botman O, Sid S, Schoenen J, Franzen R.
PLoS One 2012

Numerous strategies have been managed to improve functional recovery after spinal cord injury (SCI) but an optimal strategy doesn't exist yet. Actually, it is the complexity of the injured spinal

cord pathophysiology that begets the multifactorial approaches assessed to favour tissue protection, axonal regrowth and functional recovery. In this context, it appears that mesenchymal stem cells (MSCs) could take an interesting part. The aim of this study is to graft MSCs after a spinal cord compression injury in adult rat to assess their effect on functional recovery and to highlight their mechanisms of action. We found that in intravenously grafted animals, MSCs induce, as early as 1 week after the graft, an improvement of their open field and grid navigation scores compared to control animals. At the histological analysis of their dissected spinal cord, no MSCs were found within the host despite their BrdU labelling performed before the graft, whatever the delay observed: 7, 14 or 21 days. However, a cytokine array performed on spinal cord extracts 3 days after MSC graft reveals a significant increase of NGF expression in the injured tissue. Also, a significant tissue sparing effect of MSC graft was observed. Finally, we also show that MSCs promote vascularisation, as the density of blood vessels within the lesioned area was higher in grafted rats. In conclusion, we bring here some new evidences that MSCs most likely act throughout their secretions and not via their own integration/differentiation within the host tissue.

9. Mesenchymal stem cells in the treatment of spinal cord injuries: A review
Venkata Ramesh Dasari, Krishna Kumar Veeravalli, and Dzung H Dinh
World Journal of Stem Cells 2014

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.

10. Early transplantation of mesenchymal stem cells after spinal cord injury relieves pain hypersensitivity through suppression of pain-related signaling cascades and reduced inflammatory cell recruitment.
Watanabe S, Uchida K, Nakajima H, Matsuo H, Sugita D, Yoshida A, Honjoh K, Johnson WE, Baba H.
Stem Cells 2015

Bone marrow-derived mesenchymal stem cells (BMSC) modulate inflammatory/immune responses and promote motor functional recovery after spinal cord injury (SCI). However, the effects of BMSC transplantation on central neuropathic pain and neuronal hyperexcitability after SCI remain elusive. This is of importance because BMSC-based therapies have been proposed

for clinical treatment. We investigated the effects of BMSC transplantation on pain hypersensitivity in green fluorescent protein (GFP)-positive bone marrow-chimeric mice subjected to a contusion SCI, and the mechanisms of such effects. BMSC transplantation at day 3 post-SCI improved motor function and relieved SCI-induced hypersensitivities to mechanical and thermal stimulation. The pain improvements were mediated by suppression of protein kinase C-γ and phosphocyclic AMP response element binding protein expression in dorsal horn neurons. BMSC transplants significantly reduced levels of p-p38 mitogen-activated protein kinase and extracellular signal-regulated kinase (p-ERK1/2) in both hematogenous macrophages and resident microglia and significantly reduced the infiltration of CD11b and GFP double-positive hematogenous macrophages without decreasing the CD11b-positive and GFP-negative activated spinal-microglia population. BMSC transplants prevented hematogenous macrophages recruitment by restoration of the blood-spinal cord barrier (BSCB), which was associated with decreased levels of (a) inflammatory cytokines (tumor necrosis factor-α, interleukin-6); (b) mediators of early secondary vascular pathogenesis (matrix metallopeptidase 9); (c) macrophage recruiting factors (CCL2, CCL5, and CXCL10), but increased levels of a microglial stimulating factor (granulocyte-macrophage colony-stimulating factor). These findings support the use of BMSC transplants for SCI treatment. Furthermore, they suggest that BMSC reduce neuropathic pain through a variety of related mechanisms that include neuronal sparing and restoration of the disturbed BSCB, mediated through modulation of the activity of spinal-resident microglia and the activity and recruitment of hematogenous macrophages.