

Stem cell-based therapies to treat spinal cord injury: a review

Zhongju Shi^{1,2}
Hongyun Huang³
Shiqing Feng^{1,2}

¹Department of Orthopaedics, Tianjin Medical University General Hospital, ²Institute of Neurology, Key Laboratory of Post-Neuroinjury Neuro-Repair and Regeneration in Central Nervous System, Ministry of Education, Tianjin City, Tianjin, ³Institute of Neurorestoratology, General Hospital of Armed Police Forces, Beijing, People's Republic of China

Abstract: Spinal cord injury (SCI) is a devastating condition and major burden on society and individuals. Currently, neurorestorative strategies, including stem cell therapy products or mature/functionally differentiated cell-derived cell therapy products, can restore patients with chronic complete SCI to some degree of neurological functions. The stem cells for neurorestoration include neural stem cells, mesenchymal stem cells, embryonic stem cells, induced pluripotent stem cells, etc. A better understanding of the merits, demerits and precise function of different stem cells in the treatment of SCI may aid in the development of neurorestorative strategies. However, the efficacy, safety and ethical concerns of stem cell-based therapy continue to be challenged. Nonetheless, stem cell-based therapies hold promise of widespread applications, particularly in areas of SCI, and have the potential to be novel therapeutics, which contributes to the repair of SCI. This review mainly focused on recent advances regarding the stem cell-based therapies in the treatment of SCI and discussed future perspectives in this field.

Keywords: spinal cord injury, neural stem cells, bone marrow-derived mesenchymal stem cells, adipose-derived stem cells, embryonic stem cells, induced pluripotent stem cells

Introduction

Spinal cord injury (SCI) is a devastating condition resulting from traumatic accidents with a high morbidity and mortality, and there are no effective treatments available by conventional treatments.¹⁻³ Currently, neurorestorative strategies, including cell therapy (stem cell products or mature/functionally differentiated cell-derived cell therapy products according to classification of US Food and Drug Administration,⁸⁵ neurostimulation/neuromodulation, neuroprosthesis, neurotization or nerve bridging, neurorehabilitation and combined therapies, can restore patients with chronic complete SCI to some degree of neurological functions.⁴ From the inception of the Orphan Drug Act in 1983 through March 31, 2010, the Office of Orphan Products Development received 27 applications for orphan designation of stem cell-based products (SCBPs); the sources of orphan-designated SCBPs include human embryonic stem cells (hESCs), fetal porcine cells, peripheral blood, umbilical cord blood, mesenchymal tissue, olfactory tissue and bone marrow.⁵ The weight-bearing nature and flexible nature of vertebrae make it particularly susceptible to general SCI.⁶ SCI is characteristically composed of primary injury and secondary injury.⁷ The primary phase is a direct consequence of physical trauma to the spinal cord, and it can cause the discontinuation of axonal projections to release neurotoxic compounds and inflammatory mediators that contribute to neuronal and oligodendroglial cell

Correspondence: Shiqing Feng
Department of Orthopaedics, Tianjin Medical University General Hospital, 154 Anshan Road, Heping District, Tianjin 300052, People's Republic of China
Tel/Fax +86 22 2718 3812
Email sqfeng@tmu.edu.cn

death.⁸ The secondary pathological injury is a complex damage in the cellular level and occurs over the hours, days and even weeks following the initial injury, including loss of myelin, degeneration of axons and formation of a glial scar that inhibits spontaneous regeneration, and these processes can cause a significant degeneration and consequent functional loss.^{8,9} Furthermore, some factors can contribute to the events after primary SCI, including unbalance of ion, glutamate release and lipid peroxidation.¹⁰ Until now, a considerable amount of research has been carried out to find a more effective way to restore SCI functions. However, there is still no neuroprotective and regenerative therapies for the injured spinal cord.

Stem cell transplantation was first applied to the patients with cancers of the blood and bone marrow in the 1950s.¹¹ Stem cells are defined as cells with the ability to renew themselves continuously and possess pluripotent ability to differentiate into many cell types under particular physiological conditions.¹² Stem cells are classified into embryonic stem cells (ESCs), fetal stem cells (FSCs) or adult stem cells (ASCs) based on their origin.¹³ Stem cell-based therapies hold promise of widespread applications particularly in SCI areas.¹⁴ The main advantage of stem cells for treating SCI is their self-renewal capacity. Cell transplantation is considered to be a feasible means to compensate for injury-induced cell and tissue loss following SCI.¹⁵

The goal of this brief review was to review the recent studies about stem cell-based therapies and advances in the SCI treatment. Further understanding of the potential of stem cell-based therapies may lead to additional therapeutic alternatives in SCI.

Neural stem cells (NSCs)

NSCs are multipotent populations with the ability to differentiate into neurons, oligodendrocytes and astrocytes.¹⁶ NSCs are derived from the central nervous system (CNS), including the subventricular zone, the dentate gyrus of the hippocampus and the central canal of the spinal cord.^{17,18} Many studies have explored the possibility of trying to promote functional recovery by transplanting NSCs after SCI. The grafted NSCs can differentiate into appropriate mature neurons.¹⁹ However, the transplanted NSCs maintain in the state of undifferentiation or are differentiated along the glial lineage after transplantation,²⁰ and the past research showed inconsistent results for functional recovery after transplantation. Several studies have overcome the environment unfavorable to neuronal differentiation and achieved good neuronal differentiation of grafted NSCs.^{21,22} Therefore, how

to promote the neuronal differentiation tends to be the most concerned thing for transplantation of NSCs.

NSCs-based therapies can not only fill lesion cavities but also provide a supportive substrate for axon regrowth.²³ Axon regeneration is considered as the one way to restore function after severe SCI.²⁴ A previous study confirmed that transplantation of NSCs can cause the long-distance outgrowth of axons from the graft.²⁵ However, this study showed that the axons could not regenerate beyond a limited distance within the transplant and enter the host spinal cord. Furthermore, demyelination is one major reason to contribute to functional deficits after SCI.^{26,27} After severe contusive SCI, surviving axons can exhibit demyelination because of the oligodendroglial cell death and limited oligodendrocyte renewal.^{28,29} Oligodendrocyte differentiation of endogenous neural stem cells is inadequate to promote remyelination after SCI. The implanted NSCs are capable of replacing lost oligodendrocytes and remyelinating spared axons and might be helpful to the restoration of function after SCI.^{30,31} Another study have also shown that transplantation of NSCs is effective to replace oligodendrocytes and promote the remyelination of surviving axons after SCI.³² Therefore, implantation of NSCs has been considered as a potential remyelination strategy for the treatment of SCI.

Mesenchymal stem cells (MSCs)

MSCs are multipotent prototype or stromal cells having multilineage potential that can differentiate into adipocytes, myocytes, osteocytes and chondrocytes, and the MSCs can be isolated from bone marrow, adipose tissue, placenta, amniotic fluid and umbilical cord.¹⁸ In the current review, we present our recent understandings on the applications of bone marrow-derived mesenchymal stem cells (BMSCs) and adipose-derived stem cells (ADSCs) in the treatment of SCI.

BMSCs are one of the most studied cell types for SCI.^{33,34} BMSCs can be isolated from bone marrow because of their property of tendency to adhere to tissue culture plastic.³⁵ BMSCs have the following advantages: easy to isolate and culture, low immunogenicity, pluripotency and capability to form different phenotypes.³⁶ Although previous studies have shown that the transplantation of BMSCs can increase sensory function after SCI, the effects on SCI-induced chronic neuropathic pain are unclear.^{37–39} BMSCs have been reported to overcome germ layer commitment and differentiate into neuron-like cells expressing neuronal markers.⁴⁰ The transplantation of BMSCs can promote the secretion of various immunoregulatory macromolecules that contribute to

create regenerative microenvironments in the injured spinal cord.⁴¹ The immunoregulatory phenomenon was considered to be a multifactorial process that requires both direct intercellular contacts and contact-independent paracrine signaling governed through various molecules, including prostaglandin E2 (PGE2), interleukin 6 (IL-6), interleukin 10 (IL-10), inducible nitric oxide synthase (iNOS), indoleamine 2,3-dioxygenase (IDO), tumor necrosis factor-inducible gene 6 protein (TSG-6) and so on.⁴² These molecules participate in the processes of proliferation, differentiation, migration or apoptosis in different immune cells.⁴³ Furthermore, a previous study showed that infusion of BMSCs could lead to a more reducing cysteine (Cys) and glutathione (GSH) redox state and had antioxidant effects *in vivo*.⁴⁴ A previous study suggested that treatment with BMSCs had a positive effect on behavioral outcome and histopathological assessment after SCI.⁴⁵ In other studies, the authors injected BMSCs intravenously, and this could facilitate remyelination after SCI and locomotor recovery.^{46,47} Compared with intraspinal injection, intravenous injection has the advantage of minimally invasive and minimal hemorrhage incidence.⁴⁸ A recent study showed that using magnets could increase the targeting efficiency and enhance the efficiency of stem cell delivery in SCI.^{48,49} However, the underlying mechanisms of BMSCs' protective effects in SCI are still unclear and need to be further investigated.

ADSCs are isolated from the stromal vascular fraction (SVF) of adipose tissue, and they have a strong resemblance to BMSCs due to their common cell surface markers, similar gene expression profiles and similar differentiation potentials.^{50–52} ADSCs have recently been identified as alternative stem cells, and previous studies have shown that the cells could survive and integrate into the spinal cord.^{53,54} ADSCs have been an ideal choice for cell replacement therapy, and ADSCs have the following advantages: easy to isolate and culture, reliable biosafety and free of immunogenicity.^{55,56} A previous study that used rat models of spinal cord contusion injury showed that injection of ADSC-transdifferentiated motor neurons into the impact site and transplantation of glial cell line-derived neurotrophic factor–gelfoam complex into the myelin sheath after 7 days exhibited beneficial effects on recovery of motor function.⁵⁷ Transplanted ADSCs can significantly decrease astrocytic network and stimulate axonal sprouting.⁵⁸ Moreover, transplantation of three-dimensional (3D) cell mass of adipose-derived stem cells (3DCM-ADSCs) significantly improved functional recovery compared with transplantation of ASCs, and this finding may be effective for the treatment of SCI and neural ischemia.⁵⁹ Neurogenin-2

(Ngn2) is a gene that promotes neuronal differentiation, and a previous study showed that transplantation of Ngn2-overexpressed ADSCs can improve the local microenvironment and promote the functional recovery after SCI.⁶⁰ Therefore, this study suggested that ADSCs might provide an ideal source for further stem cell research with potential therapeutic application for SCI.

Embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs)

ESCs are pluripotent cells derived from the inner cell mass of a 1-week blastocyst.⁶¹ The chief difficulty with the use of ESCs is the immunogenicity, and then, ESCs can stimulate the immune response.⁶² Transplantation of ESCs may be a practical approach to treat SCI because they can be repeatedly passaged in culture and differentiated into neuronal or glial cells for transplantation.⁶³ ESCs can directly differentiate to oligodendrocytes and secrete trophic factors, such as hepatocyte growth factor and brain-derived neurotrophic factor (BDNF), which may be beneficial for promoting axonal regeneration and neurite outgrowth after SCI.⁶⁴ In another study, the implanted ESCs could not only restore lost myelin in the injured spinal cord but also differentiate into mature oligodendrocytes that were capable of myelinating axons.⁶⁵ Thus, at present, transplantation of hESC-derived neural cells, including neuron and oligodendrocytes, is a promising therapy for SCI.⁶⁶

iPSCs are a type of pluripotent stem cells that can be created from adult somatic cells by “reprogramming” via the transduction of pluripotency genes.⁶ iPSCs are envisaged as advanced source for cell replacement therapy in regenerative medicine.⁶⁷ The key advantage of iPSCs for human cell therapy is avoiding immune rejection, ethical constraints and tissue donation.⁶⁸ However, iPSCs have the potential for uncontrolled proliferation and even tumor formation after transplantation in SCI models.⁶⁹ Therefore, a careful screening of oncogenic capacity is essential prior to transplantation. Some previous studies have developed useful and attractive methods to solve the problem of tumorigenicity. Itakura et al⁷⁰ found that immunoregulation could ablate tumors that are formed after transplantation, and this probably has to do with the infiltration of inflammatory cells, such as lymphocytes and microglia. Another study showed that inhibition of Notch signaling could induce the NPCs to more mature cells with limited proliferation.⁷¹ Furthermore, a recent study showed that neuroepithelial-like stem cells from human iPSCs (hiPS-It-NES cells) could differentiate into neural lineages in the

mouse model of SCI and promote functional recovery of hind limb motor function after transplantation.⁷² Romanyuk et al⁷³ used a rat model of thoracic contusion in SCI, and the result showed that transplantation of neural precursors derived from human iPSCs (iPSC-NPs) 1 week after SCI promoted tissue sparing and improvement in motor function. The transplantation field of iPSCs is rapidly progressing, and transplantation of iPSCs' products can produce functional recovery by replacing lost cells and/or modulating the microenvironment; yet iPSCs should be transplanted with caution because of the safety of the cell lines and the risk of tumor formation, which can be harmful to patients.

Problems to overcome in the application of stem cells for SCI

In this review, we focus on the stem cell therapies that have the potential to repair the injured spinal cord, and the comparison between different types of stem cells is summarized in Table 1. Although recently stem cell therapies have made great progress and are widely accepted in the treatment of SCI for promoting morphological recovery and functional recovery via various mechanisms (Figure 1), but they still face great challenges. First, the insufficient sources and ethical constraints concerning stem cells greatly hindered their clinical application.¹⁵ Although iPSCs are envisaged as an advanced source for cell replacement therapy without these problems, yet studies with animals are urgently required to demonstrate the efficacy and safety of replacement therapy of iPSCs. Moreover, the issue of stem cell tumorigenicity needs to be considered. Second, the transplanted stem cells often

maintain in the state of undifferentiation, and the neuronal induction efficiencies are lower than desirable. The inhibitory microenvironment of injured spinal cord is mainly due to local expression of inhibitory factors and glial scar, and the microenvironment can limit the regenerative capacity of endogenous or transplanted cells.^{74,75} Therefore, how to improve the microenvironment after SCI is related to the survival and differentiation of transplanted stem cells.

Furthermore, another problem is that the transplanted stem cells must be able to make right connections with the host neural network. During recent decades, with the development of tissue engineering, engineered biomaterials have been explored for their ability to support axonal regrowth and neuronal differentiation, and more and more biomaterials are applied to stem cell-based replacement

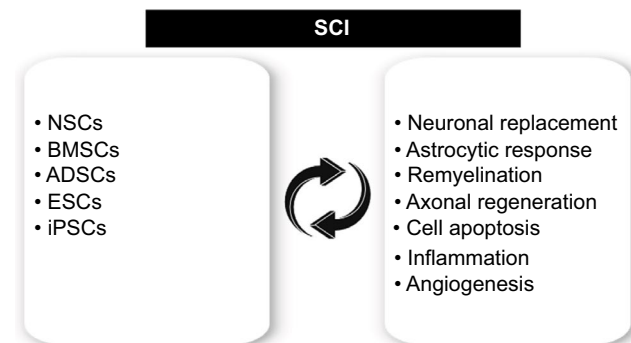


Figure 1 Major stem cell sources and the therapeutic focus of transplantation of stem cells in SCI.

Abbreviations: SCI, spinal cord injury; BMSCs, bone marrow-derived mesenchymal stem cells; ADSCs, adipose-derived stem cells; ESCs, embryonic stem cells; iPSCs, induced pluripotent stem cells.

Table 1 Comparison between different types of stem cells

Types of stem cells	Therapeutic mechanisms and advantages	Disadvantages
NSCs	Neuronal replacement therapy Remyelinate the demyelinated axons Secrete neurotrophic factors Ameliorate T-cell receptor-mediated T-cell activation and inhibit signaling of inflammatory cytokines in immune cells	Undifferentiation or differentiation along the glial lineage after transplantation Ethical constraints
MSCs	Immunomodulation Anti-apoptotic effects Secrete neurotrophic factors and cytokines Permissive cellular substrate for promotion of host axonal growth Easily extracted and cultivated in large numbers No ethical constraints	Tumorigenicity
ESCs	Can be repeatedly passaged in culture Differentiate into neuronal or glial cells Secrete trophic factors	Immunogenicity Ethical constraints
iPSCs	Avoid immune rejection No ethical constraints and tissue donation	Tumorigenicity Genetic and epigenetic abnormalities

Abbreviations: NSCs, neural stem cells; MSCs, mesenchymal stem cells; ESCs, embryonic stem cells; iPSCs, induced pluripotent stem cells.

therapy of SCI. The biocompatible scaffold can provide 3D space; appropriate chemical, physical and mechanical properties for cell proliferation and differentiation and tissue formation and has the potential to transform the inhibitory microenvironment into a permissive transplant microenvironment, which further promotes axonal regrowth.^{76,77} Several types of biomaterials have been suggested for achieving improved functional recovery in the patients with SCI. In a recent study, implanting cetuximab-modified linear-ordered collagen scaffolds (LOCS) into SCI lesion sites in dogs could decrease chondroitin sulfate proteoglycan (CSPG) at the lesion site and results in neuronal regeneration and significant locomotion recovery.⁷⁸ Furthermore, new 3D culture systems have emerged recently that have demonstrated not only the feasibility of creating complex, organized spinal tissue but also how bioengineered 3D scaffolds can be used to control the transplant microenvironment.⁷⁹ A previous study demonstrated that a collagen/heparin sulfate scaffold fabricated by a 3D bioprinter could enhance the mechanical properties of collagen and provide continuous guidance channels for axons, which would improve the neurological function in the patients with SCI.⁸⁰ Moreover, nanoparticles can deliver the therapeutic molecules to the target tissue of interest and reduce the side effects of untargeted therapies in unwanted areas; hence, nanobiomedical systems are believed to be potential to provide new therapeutic availability for the treatment of SCI.⁸¹ Thus, combining neural tissue-engineered scaffolds with stem cell-based therapies can improve transplant efficacy and foster host tissue regeneration, and this combination is the future direction of the stem cell-based therapies following SCI.

Moreover, administration of drug or trophic factors is also a treatment strategy for promoting regeneration of injured spinal cord, and the combination therapy is expected to provide superior clinical effectiveness.⁸² Karimi-Abdolrezaee et al⁸³ added growth factors (epidermal growth factor, basic fibroblast growth factor, platelet-derived growth factor) to chondroitinase ABC (C-ABC) and administered them in the rats after SCI, and this treatment could enhance proliferation of endogenous NPCs, increase new vascular formation and suppress inflammatory reaction. In another study, semaphorin-3A inhibitor was administered to transect spinal cord of rats, and it could promote the elongation of neuronal axons and enhance the Schwann cell-mediated myelination and angiogenesis.⁸⁴

Taken together, although stem cell-based therapies had some problems at present, but they still have good developing prospects, and further investigations will be needed in order to improve the transition to the clinic.

Conclusion

The main goals of stem cell-based therapies for SCI are the neuron replacement and neurological, structural and functional restoration after SCI. Stem cell-based therapies hold great promise to become an effective therapeutic approach for SCI. Although there are a few different types of stem cells that can serve as a renewable cell source in cell-based therapy for patients suffering from SCI, yet which type of stem cells is most suitable for cell replacement therapy in patients with SCI still needs to be clarified. Furthermore, the efficacy, safety and ethical concerns of stem cell-based replacement therapy continue to be challenged.

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Disclosure

The authors report no conflicts of interest in this work.

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