



Repair of Spinal Cord Injury; Mesenchymal Stem Cells as an Alternative for Schwann Cells

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Received March 2, 2018; **Revised** May 24, 2018; **Accepted** May 29, 2018; **Online Published** June 20, 2018

Abstract

Spinal cord injury (SCI) is one of the most severe types of disabilities that has a limited capacity to repair; therefore, medical interventions are essential to the treatment of injuries. Cell transplantation is one of the remarkable strategies for the treatment of spinal cord injury. Transplantation of Schwann cells (SCs) has shown a great promising result for SCI but harvesting SC is limited due to donor complications and limited cell collection capacity. However, the use of stem cells to differentiate into SCs can reduce the risks associated with the use of mature cells in the grafting process. Mesenchymal stem cells can differentiate to various type cells. They are as easily accessed source with high growth rate and low immunogenicity; therefore, these properties make them an interesting source for cell therapy. These cells can be transdifferentiated into SC-like cells in neuronal induction media. Accordingly, many studies demonstrated that mesenchymal cells are well suited for cell therapy of SCI. This article briefly discusses the treatment of SCI by cell transplantation and the benefits of using Mesenchymal stem cells as an alternative for SCs.

Keywords: Spinal Cord Injury, Cell Transplantation, Mesenchymal Stem Cell, Schwann Cell

Citation: Moosazadeh Moghaddam M, Bonakdar S, Shokrgozar MA, Faghihi S. Repair of spinal cord injury; mesenchymal stem cells as an alternative for Schwann cells. J Appl Biotechnol Rep. 2018;5(2):42-47. doi:10.29252/jabr.05.02.01.

Introduction

Spinal cord injury (SCI) is one of the most severe types of disabilities, which due to its negative impacts on motor control abilities, has a major impact on patient's life and causes the person to face a wide range of constraints.^{1,2} The statistics show that the incidence rates of developed countries ranged from 13 to 163 per million people while the rates of non-developed countries varied from 13 to 220 per million people. In addition, the prevalence of SCI is 490 to 526 per million population among developed countries and for non-developed countries, reported prevalence is about 440.³ On the other hand, the cost of caring for a SCI is also huge. For example, the annual cost of spinal cord injuries is estimated to be more than \$9 billion in America and a tetraplegia patient will cost over 900 000 in the first year and \$ 170 000 over the next years.⁴ In Iran, there are more than 2000 SCI veterans due to Iraq-Iran war and more than 15 000 cases of spinal cord injuries have been diagnosed until today. According to the studies, the most common causes of spinal cord injuries include injuries during driving and sports, violent acts and war injuries, falling from heights, some diseases, and medical incidents. Complications due to spinal cord injuries include loss of complete or partial movement ability (such

as walking) and sensation in the affected area and the more upper body is engaged, the more will be the complications.^{5,6} However, injured spinal cord axons have the ability to restore themselves, but the maximum axon growth is about one millimeter, although this restoration process is not happening at a satisfactory level. On the other hand, the glial scars formation and the lack of growth stimulating symptoms such as semaphorin and ephrin and on the contrary the existence of inhibition signals like myelin sheath components (myelin-associated glycoprotein, Nogo-A) are regarded as inhibitory factors of axon growth.⁷ Therefore, considering the extent and intensity of the disabilities caused by spinal cord injuries and their increased incidence, numerous efforts have been made in order to elevate the effects of mentioned damages. The effective treatment of the injury depends on the type and severity of the damage, although the high costs of treatment can affect the process of healing.^{8,9} The use of cell therapy is one of the solutions that have been widely considered in the last 2 decades due to the high growth rate of regenerative medicine based on tissue engineering and stem cell.^{10,11}

Cell Transplantation Therapy for Spinal Cord Injury

The utilization of cell therapy is one of the used strategies

for treatment of SCI which includes embryonic tissue transplantation, use of Schwann mature cells, and embryonic, bone marrow, nervous stem cells, and olfactory ensheathing cells (OECs).^{11,12} In some cases gene therapy and insertion of genes such as *NT-3*, *BDNF*, *NGF*, which play an important role in restoring spinal cord injuries, into stem cells or mature cells such as fibroblasts is also used.^{13,14} Considering the progress in stem cells and restorative medicine, stem cell therapy compared to the use of mature cells is one of the most important and remarkable therapies for SCI or other injuries and diseases because of long-term self-renewal ability of stem cell and the possibility of genetic manipulation.^{15,16} However, access to an appropriate stem cell source is one of the most limitations and their differentiation into target cells is one of the key steps in using these cells for treatment purposes.

In general, the applied cell therapy techniques in order to repair SCI can be summarized in the following cases^{17,18}:

- Transplantation of peripheral nerve
- Transplantation of Schwann cells (SCs)
- Transplantation of olfactory nervous system cells
- Transplantation of embryonic CNS tissue
- Transplantation of embryonic stem/progenitor cells
- Transplantation of adult stem/progenitor cells
- Transplantation of engineered stem/progenitor cells
- Transplantation of activated macrophages

In 1999, for the first time, German researchers by employing embryonic stem cells (ESCs) derived from glial precursors showed that a protective myelin sheath could be formed in the rat-damaged spinal cord.¹⁹ In addition, other studies showed that these cells could improve the rat's SCI at a very limited level. In 2000, for the first time, olfactory stem cells were used for repairing SCI in rats.²⁰ Since then, many studies have reported the use of stem cells and tissue engineering to repair these injuries with different levels of recovery.²¹⁻²⁶ Here is a variety of studies due to the complexity of the spinal cord tissue and the lack of complete recognition of the effective repair process at the clinical level. However, the use of SCs is one of the options that has been considered in recent years for the treatment and repair of spinal cord injuries due to the considerable potential of these cells including²⁷⁻²⁹:

- Produce growth factors, which stimulate some nerve fiber (axon) regeneration
- Produce components of the extracellular matrix, which supports regenerating axons
- Surround and re-insulate (re-myelinate) axons that lost their insulation after injury
- Restore axonal communication upon re-myelination
- Spontaneously enter the spinal cord after SCI

Although, there are limitations for transplanted SCs such as (1) need to provide a neurotransmitter for extraction and transplantation of SCs, (2) the possibility of secondary damage during the isolation and receipt of primary SCs, (3) possibility of immunogenic responses, and (4) the need for long-term cell cultivation and proliferation processes. Accordingly, the use of stem cells to differentiate into SCs can reduce the risks associated with the use of mature cells in the grafting process.

Stem cells can be characterized based on their differentiation potential including totipotent, pluripotent, unipotent, and

adult stem cells. Totipotent stem cells can form an entire embryo including the extraembryonic tissues. Pluripotent stem cells can trigger the three embryonic germ layers: mesoderm, endoderm, and ectoderm. Unipotent or progenitor stem cells can only differentiate into one defined cell type and adult stem cells are capable of multi-lineage differentiation in cells of only one germ layer.^{30,31} The differentiation potential of stem cells is related to their developmental stage so that the potential of differentiation decreases from an ESC to a specialized tissue stem cell. In addition, induced pluripotent stem cells (iPSC) as a type of pluripotent stem cell can be generated directly from adult cells.³²⁻³⁴

So far, many studies have been done on the use of stem cells to repair spinal cord injuries by differentiating stem cells into SC. In these studies, various types of stem cells have been evaluated based on development stage including tissue source and iPSC. Table 1 presents different sources of stem cells that have been evaluated for SCI.¹⁸

Mesenchymal Stem Cells as an Alternative for Schwann cell Transplantation

Bone marrow and adipose-derived stem cells (ADSCs) as mesenchymal stem cells (MSCs), which also derived from peripheral blood, placenta and umbilical cord, the lung, and the heart, are multipotent stromal cells that can differentiate to various type cells such as osteoblasts, chondrocytes, and adipocytes. They are as easily accessed source with high growth rate, low immunogenicity and a favorable ethical profile and better safety that can differentiate to all mesodermal lineage cells, therefore these properties make them an interesting source for cell therapy.^{35,36} MSCs can be transdifferentiated into SC-like cells in neuronal induction media.^{37,38} On the other hand, studies have shown that SCs that differentiated from MSCs enhance and support neurite outgrowth, axonal surviving and remyelination.³⁹ In many studies, MSCs is considered as a brilliant cell for the treatment of central nervous system.^{40,41} In addition, transplantation of SCs derived from mesenchymal stem cells as a potentially useful treatment for SCI is also confirmed.^{42,43} Studies have shown that MSCs can produce various growth factors, neuroprotective cytokines and chemokines (Figure 1) such as vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), fibroblast growth factor (FGF), nerve growth factor (NGF), and brain-derived neurotrophic factor (BDNF), which enhances functional benefits associated with MSC transplantation.^{42,44} Accordingly, MSCs are an efficient source of HGF suggested that the therapeutic effects of MSC transplantation are partly mediated by HGF secretion. This factor blocked secretion of transforming growth factor- β (TGF- β) from activated astrocyte cells and prevented expression of specific chondroitin sulfate proteoglycan (CSPG) species. Studies demonstrated that transplantation of HGF-overexpressing MSCs significantly decreased expression of neurocan and glycosaminoglycan chain deposition around hemisection lesions in the spinal cord.^{42,45,46} Also in animal models, HGF-MSCs showed an increase in axonal growth and improvement in functional recovery, which confirms that HGF can act as an attractive signal for the guidance of axon

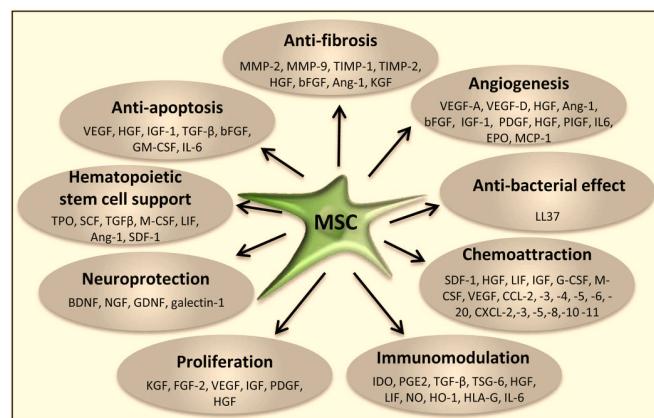
Table 1. Comparison of Different Sources of Stem Cells Used for Peripheral Nerve Regeneration¹⁸

Stem Cell	Classification	Advantage	Disadvantage	Preclinical or Clinical	Use Mechanism
ESCs	Pluripotent stem cells	Homogenous, no detrimental impact of age and disease, unlimited cell number, better differentiation potential, and longer lasting proliferation capacity	Teratoma formation, ethical dilemma	Preclinical	Myelination and/or neurotrophic factors
BMSCs	Multipotent cells	Easily accessible without ethical concerns	Lower capacity of proliferation and differentiation, invasive procedure for autologous harvesting	Preclinical	Myelination, neurotrophic factors
ADSCs	Multipotent stem cells	Easy to harvest, higher proportion and superior proliferation	Differentiation potential towards adipocytes	Preclinical	Myelination, neurotrophic factors, reduce inflammation
NSCs	Multipotent stem cells		Difficult to be harvested	Preclinical	Replace SCs
Fetal-derived stem cell	Multipotent stem cells	Less immunoreactivity	Cell bank for storage	Preclinical	Augmented blood perfusion and enhanced intraneural vascularity
HFSCs	Multipotent stem cells	Abundant and accessible source, differentiate into pure human SC population	Difficult to isolate	Preclinical	Replace SC myelination, neurotrophic factors
DPSCs	Multipotent stem cells	Stronger harvesting and proliferation potential, as well as greater clonogenic potential	Require storage	Preclinical	Replace SC myelination, neurotrophic factors
SKP-SCs	Multipotent cells	Easy to harvest	Long time to differentiate	Preclinical	Replace SC myelination
MDSPCs	Progenitor cells	Abundant and accessible source	Limited research	Preclinical	Neurotrophic factors
iPSCs	Pluripotent stem cells	Inducible from easily obtainable somatic cells	Subdued efficiency and enhanced variability during the differentiation process, epigenetic memory from the original somatic cells, chromosomal aberrations, stronger tumorigenicity	Preclinical	Replace SC myelination, neurotrophic factors

ESCs: embryonic stem cells; BMSCs: bone marrow-derived stem cells; ADSCs: adipose-derived stem cells; NSCs: neural stem cells; HFSCs: hair follicle stem cells; DPSCs: dental pulp stem cells; SKP-SCs: skin-derived precursor stem cells; MDSPCs: muscle-derived stem/progenitor cells; iPSCs: induced pluripotent stem cells; SC: Schwann cell.

motor to the target tissue.⁴⁵ In addition to growth factors, immunological cytokines are also involved in the process of stem cell therapy after SCI. According to the studies, transplantation of MSCs into a lesion spinal cord leads to a reduction in Tumor necrosis factor alpha (TNF α), interleukin 1 beta (IL-1 β , IL-2), IL-4, IL-6, and IL-12 secretion.^{47,48} In addition, implantation of MSCs inhibits second-phase neuronal injury by suppressing lymphocyte and microglia effects and reduces the inflammatory reaction in the local environment after SCI.⁴⁹ These results confirm that MSC administration can help to neuronal survival after lesion through cytokine release and immunomodulation. It has also been demonstrated that apoptosis-related pathways involved in SCI is affected after MSC transplantation. Accordingly, findings show that caspase-3-mediated apoptosis on neuron and oligodendrocyte cells following SCI is significantly downregulated by MSCs, which is regulated through stimulation of endogenous survival signaling pathways including PI3K/Akt, and the MAPK/ERK1/2-cascade.^{50,51}

Considering the contents mentioned above, it can be explained that mesenchymal cells are well suited for cell therapy of SCI. In this regard, many experiments in small and big SCI animal models have demonstrated the beneficial effects of MSCs from different sources.^{52,53} In addition, various studies are currently underway at various clinical stages using

**Figure 1.** Different Effects of the Soluble Paracrine Factors Secreted by MSCs (<https://anova-irm-stemcell-center.com>).

MMP: Matrix metalloproteinase; TIMP: Tissue inhibitors of metalloproteinases; HGF: Hepatocyte growth factor; FGF: Fibroblast growth factor; Ang-1: Angiopoietin 1; KGF: Keratinocyte growth factor; VEGF: Vascular endothelial growth factor; IGF: Insulin-like growth factors; TGF: Transforming growth factor; GM-CSF: Granulocyte-macrophage colony-stimulating factor; TPO: Thrombopoietin; SCF: Stem cell factor; LIF: Leukemia inhibitory factor; SDF-1: Stromal cell-derived factor 1; BDNF: Brain-derived neurotrophic factor; NGF: Nerve growth factor; GDNF: Glial cell line-derived neurotrophic factor; PDGF: Platelet-derived growth factor; EPO: Erythropoietin; MCP-1: Monocyte chemoattractant protein-1; CCL: Chemokine (C-C motif) ligand; CXCL: Chemokine (C-X-C motif) ligand; IDO: Indoleamine 2, 3-dioxygenase; PGE: Prostaglandin E2; TSG-6: TNF-stimulated gene 6 protein; HO-1: Heme oxygenase-1; HLA-G: Human leukocyte antigen G; IL: interleukin.

Table 2. Some Clinical Trials (Phase I, II, & III) Done Using MCSSs (<https://clinicaltrials.gov/>)

Title	Status	Conditions	Interventions	Characteristics	Sponsor/Collaborators	Dates	Locations
Autologous Mesenchymal Stem Cells Transplantation for SCI-A Phase I Clinical Study	Completed	SCI	Mesenchymal Stem Cells	Study Type: Interventional Phase: Phase 1	-Armed Forces Bone Marrow Center, Rawalpindi, Pakistan -Armed Forces Institute of Regenerative Medicine	Study Start: June 2013	Armed Forces Bone Marrow Transplant Centre, Rawalpindi, Pakistan
Safety and Effect of Adipose Tissue Derived Mesenchymal Stem Cell Implantation in Patients With SCI	Completed	SCI	Autologous Adipose Tissue Derived MSCs Transplantation	Study Type: Interventional Phase: Phase 1, Phase: Phase 2	-Biostar -Korea University Anam Hospital	Study Start: January 2013	Korea University Anam Hospital, Seoul, Korea, Republic of
Administration of Expanded Autologous Adult Bone Marrow Mesenchymal Cells in Established Chronic Spinal Cord Injuries	Completed	SCI	Autologous Mesenchymal Bone Marrow Cell	Study Type: Interventional Phase: Phase 2	Puerta de Hierro University Hospital	Study Start: July 2015	Hospital Puerta de Hierro, Majadahonda, Madrid, Spain
Autologous Adipose Derived MSCs Transplantation in Patient With Spinal Cord Injury	Completed	SCI	Autologous Adipose Derived Mesenchymal Stem Cells	Study Type: Interventional Phase: Phase 1	Biostar	Study Start: July 2009	--
Intrathecal Transplantation Of Autologous Adipose Tissue Derived MSC in the Patients With SCI	Completed	SCI	Autologous Adipose Tissue Derived Mesenchymal Stem Cells	Study Type: Interventional Phase: Phase 1	Bukwang Pharmaceutical	Study Start: April 2012	Korea University Anam Hospital, Seoul, Seongbulgu, Korea, Republic of
Different Efficacy Between Rehabilitation Therapy and Stem Cells Transplantation in Patients With SCI in China	Completed	SCI	Mesenchymal Stem Cells	Study Type: Interventional Phase: Phase 3	General Hospital of Chinese Armed Police Forces	Study Start: June 2012	General Hospital of Chinese People's Armed Police Forces, Beijing, Beijing, China
Safety Study of Local Administration of Autologous Bone Marrow Stromal Cells in Chronic Paraplegia	Completed	SCI	Mesenchymal Stromal Cell Therapy	Study Type: Interventional Phase: Phase 1	Puerta de Hierro University Hospital	Study Start: March 2013	Hospital Puerta de Hierro, Majadahonda, Madrid, Spain
Subarachnoid Administration of Adult Autologous Bone Marrow Mesenchymal Cells Expanded in Incomplete (SCI)	Completed	SCI	Adult Autologous Mesenchymal Bone Marrow Cell	Study Type: Interventional Phase: Phase 1	Puerta de Hierro University Hospital	Study Start: May 2014	Hospital Puerta de Hierro, Majadahonda, Madrid, Spain
Cell Transplant in SCI Patients	Completed	SCI	Autologous Bone Marrow Transplant	Study Type: Interventional Phase: Phase 1, Phase 2	-Cairo University -Al-Azhar University -Medical Military Academy, Egypt -Alexandria University	Study Start: May 2005	Cairo University School of Medicine, Cairo, Egypt
Umbilical Cord Mesenchymal Stem Cells Transplantation to Patients With SCI	Recruiting	Nerve and Spinal Cord Injuries	Umbilical Cord Mesenchymal Stem Cells	Study Type: Interventional Phase:Phase 1, Phase 2	-Limin Rong -Third Affiliated Hospital, Sun Yat-Sen University	Study Start: January 2014	The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, Guangdong, China
Intrathecal Transplantation of UC-MSC in Patients With Late Stage of Chronic SCI	Recruiting	SCI	Umbilical Cord Mesenchymal Stem Cells	Study Type: Interventional Phase: Phase 2	-Third Affiliated Hospital, Sun Yat-Sen University -West China Hospital -Shanghai East Hospital	Study Start: January 1, 2018	The Third Affiliated Hospital, Sun Yat-Sen University, Guangzhou, Guangdong, China

* FAB117-HC is a medicinal product containing human allogeneic adipose derived adult mesenchymal stem cells expanded and pulsed with H2O2 and also HC016 cells.

MSCs that their results are promising for the treatment of spinal cord injuries. Table 2 presents some clinical studies that have been performed using MCSs.

Conclusions

The main goals of stem cell-based therapies for SCI are the neuron replacement and restoration of neurological, structural, and functional of the spinal cord after injury. This type of therapy is regarded as promising methods because of their effectiveness in the treatment of SCI. However, determination of an effective and specific type of stem cell (due to the existence of different types of stem cells) for cell replacement therapy in patients, which can be used as a renewable source, is one of the key steps in this process. Moreover, some issues such as their effectiveness, ethical considerations and being as a safe option in such therapies is still a challenge and must be considered. However with regard to the potential of MSCs, it seems that these cells can be a significant option for the treatment of spinal cord injury using cell therapy.

Authors' Contributions

SF and AMS designed and directed the studies. MMM and SB contributed to the selection and organization of the article's contents. MMM wrote the manuscript with input from all authors. All authors have given approval to the final version of the manuscript.

Conflict of Interest Disclosures

The authors declare no competing financial interest.

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