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# The cell repair research of spinal cord injury: a review of cell transplantation to treat spinal cord injury

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## ABSTRACT

Through retrospective analysis of the literature on the cell repair of spinal cord injury worldwide, it is found that the mechanism of cell transplantation repairing spinal cord injury is mainly to replace damaged neurons, protect host neurons, prevent apoptosis, promote axonal regeneration and synapse formation, promote myelination, and secrete trophic factors or growth factors to improve microenvironment. A variety of cells are used to repair spinal cord injury. Stem cells include multipotent stem cells, embryonic stem cells, and induced pluripotent stem cells. The multipotent stem cells are mainly various types of mesenchymal stem cells and neural stem cells. Non-stem cells include olfactory ensheathing cells and Schwann cells. Transplantation of inhibitory interneurons to alleviate neuropathic pain in patients is receiving widespread attention. Different types of cell transplantation have their own advantages and disadvantages, and multiple cell transplantation may be more helpful to the patient's functional recovery. These cells have certain effects on the recovery of neurological function and the improvement of complications, but further exploration is needed in clinical application. The application of a variety of cell transplantation, gene technology, bioengineering and other technologies has made the prospect of cell transplantation more extensive. There is a need to find a safe and effective comprehensive treatment to maximize and restore the patient's performance.

## 1 Introduction

Spinal cord injury (SCI) is one of the most serious central nervous system injuries. Most SCI patients cannot take care of themselves, which brings huge medical burden to their families and the society. The incidence of SCI in the world is about 3.6~195.4 per million [1], which is higher in males than in females, and mostly are thorax or cervix related [2–6].

There are two main kinds of spinal cord injury. One is the primary injury, including neural cell damage and vascular destruction. The other is the secondary injury, including inflammation, excitotoxicity, edema, ischemia, chronic demyelination and the formation of

glial scars, etc., causing apoptosis and leading to increased damage [7, 8].

Surgical interventions, medication, symptomatic treatments, and hypothermia have been studied and applied to the treatment of SCI [9], but these methods are not effective in improving prognosis. Cell therapy can enhance the endogenous regeneration ability of spinal cord, which is attracting more and more attention [10].

## 2 The mechanism and method of cell transplantation

Cell transplantation therapy for spinal cord injury

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refers to transplanting cells into SCI patients by local direct transplantation, transvascular grafting or intrathecal injection for lumbar puncture transplantation to treat motor, sensory and autonomic dysfunction or complications caused by SCI. The repair mechanisms mainly include replacing the damaged neurons, protecting the host neurons, preventing apoptosis, promoting axonal regeneration, promotes myelination and synapse formation, or secreting nutrient factors to improve microenvironment [11–13]. Different transplantation methods have their own advantages and disadvantages. The most widely used method is the local transplantation, which is the most effective but also the most invasive, while the vascular transplantation is opposite [11, 12, 14]. It is generally believed that the optimal time for cell therapy is within 2–4 weeks after trauma. Transplantation of spinal cord injury microenvironment is not conducive to cell survival and function when conducted prior to 2 weeks, or to the self-recovery of spinal cord function after 4 weeks [15]. The cells for SCI repair can be fundamentally categorized as stem and non-stem cells. The stem cells include pluripotent adult stem cells, embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). The non-stem cells include olfactory ensheathing cells (OECs), Schwann cells and inhibitory interneurons.

### 3 Stem cell transplantation

#### 3.1 Pluripotent adult stem cells

The pluripotent adult stem cells for spinal cord injury mainly include bone marrow-derived mesenchymal stem cells (BMSCs), umbilical cord blood mesenchymal stem cells (UCB-MSCs), amniotic fluid-derived mesenchymal stem cells (AF-MSCs), adipose-derived mesenchymal stem cells (ADMSCs), oligodendrocyte precursor cells (OPCs) and neural stem/progenitor cells (NSPCs), etc.

Mesenchymal stem cells (MSCs) are the most widely used stem cells in pluripotent adult stem cells, and mostly exist in bone marrow, fat and pericarpal tissues (such as cord blood, amniotic membrane, placenta, etc.). MSCs can secrete a variety of growth factors, cytokines and neurotrophic factors, which improve the spinal cord microenvironment [16],

regulate immune response, support hematopoiesis, inhibit excessive inflammatory response, promote angiogenesis and tissue repair, anti-scarring tissue proliferation, anti-apoptosis, anti-inflammatory, and promote endogenous stem/progenitor cell proliferation and axonal growth [17, 18].

##### 3.1.1 Bone marrow-derived mesenchymal stem cells (BMSCs)

As the most commonly used MSCs, BMSCs are easy to isolate, culture and genetically transduce [17, 18]. Orthotopic transplantation is the major method used in preclinical experiments [19]. Jung et al. [20] compared the effects of autologous and allogeneic transplantation of BMSCs in dogs, and found that both methods can promote the functional recovery of SCI. Although autologous BMSCs transplantation can avoid immune rejection and graft-versus-host reaction in allogeneic transplantation, it is difficult to apply autologous stem cell transplantation in clinic because it takes too long from cell acquisition to cell transplantation [20].

##### 3.1.2 Umbilical cord blood mesenchymal stem cells (UCB-MSCs)

Umbilical cord blood stem cells have self-renewal and multi-differentiation potential, and the UCB-MSCs are the most widely used. UCB-MSCs are easy to proliferate and culture *in vitro*, and have good tolerance to animals and low risk of graft-versus-host disease after transplantation [21]. Studies have shown that the repair mechanisms of UCB-MSCs in SCI model include neurotrophs, anti-inflammatory, anti-apoptosis, angiogenesis, reduction of glial scar formation and chemotaxis [22], rather than differentiation into neurons [17]. UCB-MSCs have relatively fewer ethical controversies and a broader therapeutic potential than BMSCs [23].

##### 3.1.3 Amniotic fluid-derived mesenchymal stem cells (AF-MSCs)

AF-MSCs are derived from the amniotic membrane and amniotic fluid of the embryos, which protect embryos and help maintaining proper development of fetal organs, and are usually discarded after childbirth. Except for the characteristics of MSCs, AF-MSCs have unique traits such as non-tumorigenicity and low immunogenicity, for which AF-MSCs are widely used in regenerative medicine [24].

### 3.1.4 Adipose-derived mesenchymal stem cells (ADMSCs)

ADMSCs have a wide range of sources, and are easily acquired and cultured without ethical issues [25]. ADMSCs and BMSCs have similar properties and play important roles in promoting angiogenesis, wound healing, reducing inflammatory response and activating lymphocyte proliferation, and thus more and more clinical studies has applied ADMSCs transplantation to treating SCI. ADMSCs accumulates in the injured spinal cord through vein grafting, then activate cytokines and accelerate the recovery of motor function and tissue repair in rats [25]. Hur et al. [26] performed intrathecal autologous transplantation of ADMSCs in 14 patients with SCI, no serious adverse events were found during 8 months of follow-up, and some patients exhibited slight neurological improvement. Despite this, further verification of the safety and efficacy of this kind of cell therapy is needed.

### 3.1.5 Oligodendrocyte precursor cells (OPCs)

OPCs are a subpopulation of nerve cells that account for 5%~8% of central nervous system cells. They respond quickly after injury and proliferate fast, which makes them a potential source of oligodendrocyte replacement after SCI. Although effective oligodendrocyte replacement and adequate remyelination can significantly improve neurological function, endogenous remyelination is very difficult after trauma because of the adverse microenvironment and inflammatory changes after SCI [27, 28]. A clinical trial of patients with complete thoracic SCI has shown that transplantation of human embryonic stem cell-derived oligodendrocyte progenitor cell therapy product does not cause any adverse clinical observations, toxicity, allodynia or tumors, which suggests that OPC is also a good candidate [29].

### 3.1.6 Neural stem/progenitor cells (NSPCs)

NSPC, which is an ideal candidate for SCI transplantation, are derived from immature cells in the nervous system. NSPCs have high ability in self-renewal duplication, and can migrate to the injury sites after transplantation. Compared with other stem cells, their unique advantage is that they can differentiate and regenerate to functional neurons, and suffer from

low tumorigenic risk.

NSPCs can significantly improve the functional recovery of the animal spinal cord transection and contusion models. Immediate transplantation of NSPCs after SCI to the mice showed a better effect than transplantation 35 days later [30]. Different transplant pathways have different effects. Cheng et al. [31] transplanted human NSPCs into a rat contusion model and found that distal transplantation improved functional recovery in rats, but no significant functional recovery was seen in orthotopic transplantation. Some researchers have also explored the safety of NSPCs transplantation. Curtis et al. [32] had transplanted human spinal cord neural stem cells (NSI-566) into 4 patients with chronic SCI, and observed no serious adverse reactions during 18~27 months after transplantation, 2 patients even showed 1~2 levels of functional improvement.

## 3.2 Embryonic stem cells (ESCs)

ESCs can be induced and differentiate into neural stem cells, which are able to differentiate into neurons and glia. The initial agreement from multiple clinical trials has been reached, that is, human ESC-based therapies are safe and promising [33]. Although embryonic stem cells are the best candidates in theory, their application potential is limited by sources of origin, ethical issues, and potential tumorigenic risks [17, 34, 35]. Studies have also shown that regenerative axons cannot cross the injury sites, thus they have limited recovery effects on nerve function [36].

## 3.3 Induced pluripotent stem cells (iPSCs)

The iPSCs can be obtained from patients themselves without ethical and immunological rejection problems [35]. Its therapy mechanism is similar to those of other cells [37]. It is generally believed that cells which survive after transplantation can differentiate into mature neurons and integrate into the host's neural pathways, reducing the extent of lesions and promoting angiogenesis to improve SCI in rat models [38]. However, this technology may cause uncontrolled cell proliferation and tumor formation risks, and not all iPSCs transplantation studies have yielded beneficial results [35].

## 4 Non-stem cell transplantation

### 4.1 Olfactory ensheathing cells (OECs)

Compared with other cells, OECs can migrate long distance in the central nervous system, making regenerative axons to get through the interface between the graft and the host, so they may be the “most promising candidate cell” [39, 40]. OECs can relieve neuropathic pain and improve sensory function caused by SCI [41]. However, the efficacy and safety of the cell transplantation application is still controversial, and the ethical problems of olfactory ensheathing cell transplantation from the embryonic olfactory bulb still exist.

### 4.2 Schwann cells

Schwann cells are autologous cells with low immunogenicity and can grow well after transplantation. Schwann cells can secrete a variety of neurotrophic factors and growth factors. These factors can nourish and protect intact nerve cells, promote axonal regeneration and regenerate axonal myelination, and reduce spinal cord regeneration disorders [42]. Clinical trials have shown that transplantation of autologous Schwann cells into patients with subacute SCI is safe and has significant therapeutic potential and prospects [43]. The problems to be solved are their short survival period and the limited migration distance [42].

### 4.3 Inhibitory interneurons

Neuropathic pain (NP) is a chronic debilitating disease caused by neurodegeneration after SCI, and about 59% of SCI patients may experience such chronic pain [16]. Although there are a variety of drugs used in the treatment of SCI-NP, their medical effect is not optimistic, and the side effects are inevitable [44, 45]. Cell therapy can alleviate the mechanical hypersensitivity reaction in rodents and alleviate SCI-NP, which brings a new idea for the treatment of SCI-NP [44].

Neuropathic pain may be the result of hypersensitivity to nociceptive neurons induced by increased neurotrophic factors and neuroinflammation, spinal cord structural reorganization and inhibition of interneuronal loss [46]. Medial ganglionic eminence

(MGE) cells and GABAergic interneurons can complement inhibitory interneurons, restore GABAergic neuron function, inhibit mechanical hypersensitivity, and improve pain symptoms in patients. MGE is located in the ventral lateral ventricular wall of the brain and consists of many types of precursor cells. GABA precursor cells, the main source of GABAergic intermediate neurons in cortex and hippocampus, account for the majority [47]. When transplanted into the spinal cord of mice model and migrate to the injured site and differentiate into GABAergic interneurons and oligodendrocytes, MGE cells integrate with the host spinal cord to normalize the mechanical threshold and alleviate the SCI-NP [48, 49]. However, this treatment does not alleviate the pain caused by the chemical damage model [48].

Although MGE progenitor cells and interneuron-like cells have been produced from mouse and human stem cells, little is known about the way to reduce tumorigenesis, the time it takes to function after transplantation, or the long-term effects after transplantation [14]. Experiment on larger animal models is also rare.

## 5 Trends in cell therapy

As mentioned above, there are many limitations in the transplantation of only one type of cell. In order to improve the survival rate of transplanted cells and maximize their effect, the application of gene therapy, bioengineered scaffolds and drugs, and multiple cell transplantation are increasingly gaining the attention and recognition of researchers. The key to elevating these methods is to establish a good interaction environment between cells, scaffolds and bioactive molecules to promote the repair of damaged tissues more effectively [14].

### 5.1 Cell transplantation combined with gene therapy

The basic strategy of gene therapy for spinal cord repair is to transcribe specific genes to the site of injury, creating a good microenvironment [14]. Transgenic stem cells can not only improve the ability of cells to differentiate, but also express a large number of specific neurotrophic factors and reconstruct the spinal nerve circuit [50]. Many animal SCI model studies combined

with gene therapy, such as NT-3 over-secreting BM-SCs [51] and hUCB-MSCs [52], CSF-induced BM-SCs [53], Schwann-like cells after BM-SCs being induced by sciatic nerve fragments [54], etc. They have all been proved to be better than simply transplanting cell in promoting functional recovery.

However, gene expression induction in cells often increases the risk of tumor formation [55]. Before these therapies can be used in clinical trials, extensive animal studies are needed to ensure the safety of gene therapy in combination with cell transplantation.

### 5.2 Cell therapy combined with tissue engineering scaffold

Tissue-surgical scaffolds with sufficient tissue compatibility can be used to connect the upper and lower neuronal pathways and improve the microenvironment, promote axonal regeneration [56]. Combining with cell transplantation can increase cell viability and increase differentiation efficiency, and provide appropriate transfer factors to optimize therapeutic effects [55, 57, 58]. Many natural and synthetic tissue engineering scaffolds combined with cell transplantation to treat SCI have achieved certain effects, such as agarose, sodium alginate, chitosan, collagen, fibrin, fibronectin, methylcellulose, PGA/PLA/PLGA/PLCL, matrigel, polyethylene glycol/polyoxyethylene ether, etc.[11, 19, 58]. Some new technologies also bring opportunities to the treatment of SCI, such as biomimetic 3D-printed scaffolds [59].

The perfect combination of tissue engineering materials and stem cells is not easy to achieve, and more research will be done in the future to create ideal tissue engineering scaffolds that allow transplanted cells to migrate into the host spinal cord tissue, while nerve cells and axons from the host spinal cord tissue can grow into the stent to maximize the motor function of patients with SCI [56].

### 5.3 Combined transplantation of different type of cells

By combining different type of cells in transplantation, it is possible to exert complementary effects by utilizing their respective physiological characteristics. There are many studies suggesting that different types of stem cell combinations can repair the spinal cord more effectively than single cells during transplantation

after SCI [60]. Because different types of cells may secrete different neurotrophic factors and promote axonal regeneration in the injured area [56].

Instead of simply increasing the number of nerve cells, increasing the secretion of neurotrophic substances, promoting the growth of damaged axons, angiogenesis, adjusting the balance between pro-apoptotic factors and anti-apoptotic factors, and reducing the volume of damaged tissues are increasingly used in animal experiments and clinical trials. More and more attention has been paid to the cell transplantation therapy of SCI [60]. While more research is still needed to determine the optimal combination of different stem cell types, numbers, and densities to achieve optimal functional recovery after SCI.

## 6 Summary and outlook

Cell therapy provides us with a new way to restore the function of SCI patients, but there are inevitably many problems. Research on cell repair of SCI is still at the primary stage and restrained to animal models, and current literature and clinical studies have not provided evidence for safe and effective consistency of this method. Despite the advances in molecular biology and cell detection techniques, the genetic stability of transplanted cells remains elusive, and potential cancer risk, autophagy, and promotion of tumor growth and viral transmission require further study [61]. The influencing factors in cell therapy for SCI include SCI model, cell source, dose, differentiation and transplantation time, transplantation route, etc. [37, 40], which make the results of most studies difficult to compare with each other. This leads to a different prognosis even for the same trial method [62]. There are animal or preclinical trials on cell transplantation for cervical SCI, which accounts for a large proportion of SCI morbidity [35]. The human nervous system, behavioral performance and biological difference, long-term effects after cell transplantation cannot be simulated or rigorously tested in animal experiments [46], so cell therapy is not currently used in clinical practice. For complete SCI, how to improve its limb function most effectively is also a huge challenge. There are no optimal protocols for different types and courses of SCI, and more preclinical studies will be needed in terms of cell preparation, cell type and number, and timing and route of administration.

At the same time, more clinical trials of evidence-based medical evidence are needed [63]. Most of the experimental studies have focused on the recovery of motor function in rats, with less attention to other dysfunctions such as neuropathic pain, bladder dysfunction, and spasm [64].

Finding a safe, appropriate, efficient and comprehensive treatment method will be the direction for future research. This requires international multi-center collaborative clinical trials to enable comparative analysis in more and more homogeneous patient populations, and accelerated transition of clinical trials into clinical applications. With the exploration of the molecular mechanisms of nerve regeneration of SCI in animal models and clinical environments, as well as the development of genetic and tissue engineering techniques, the prospect of cell repair of SCI will be even broader.

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## References

- [1] Jazayeri SB, Beygi S, Shokraneh F, et al. Incidence of traumatic spinal cord injury worldwide: a systematic review. *Eur Spine J*. 2015, **24**(5): 905–918.
- [2] Kang Y, Ding H, Zhou HX, et al. Epidemiology of worldwide spinal cord injury: a literature review. *J Neurorestoratology*. 2017, **6**: 1–9.
- [3] Yang R, Guo L, Wang P, et al. Epidemiology of spinal cord injuries and risk factors for complete injuries in Guangdong, China: a retrospective study. *PLoS One*. 2014, **9**(1): e84733.
- [4] Burt AA. (iii) The epidemiology, natural history and prognosis of spinal cord injury. *Curr Orthop*. 2004, **18**(1): 26–32.
- [5] Kumar R, Lim J, Mekary RA, et al. Traumatic spinal injury: global epidemiology and worldwide volume. *World Neurosurg*. 2018, **113**: e345–e363.
- [6] Ackery A, Tator C, Krassioukov A. A global perspective on spinal cord injury epidemiology. *J Neurotrauma*. 2004, **21**(10): 1355–1370.
- [7] Tator CH, Fehlings MG. Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. *J Neurosurg*. 1991, **75**(1): 15–26.
- [8] Shende P, Subedi M. Pathophysiology, mechanisms and applications of mesenchymal stem cells for the treatment of spinal cord injury. *Biomed Pharmacother*. 2017, **91**: 693–706.
- [9] Forostyak S, Jendelova P, Sykova E. The role of mesenchymal stromal cells in spinal cord injury, regenerative medicine and possible clinical applications. *Biochimie*. 2013, **95**(12): 2257–2270.
- [10] Kim YH, Ha KY, Kim SI. Spinal cord injury and related clinical trials. *Clin Orthop Surg*. 2017, **9**(1): 1.
- [11] Oliveri RS, Bello S, Biering-Sørensen F. Mesenchymal stem cells improve locomotor recovery in traumatic spinal cord injury: systematic review with meta-analyses of rat models. *Neurobiol Dis*. 2014, **62**: 338–353.
- [12] Llewellyn-Smith IJ, Basbaum AI, Bráz JM. Long-term, dynamic synaptic reorganization after GABAergic precursor cell transplantation into adult mouse spinal cord. *J Comp Neurol*. 2018, **526**(3): 480–495.
- [13] Lu P, Woodruff G, Wang YZ, et al. Long-distance axonal growth from human induced pluripotent stem cells after spinal cord injury. *Neuron*. 2014, **83**(4): 789–796.
- [14] Lin XY, Lai BQ, Zeng X, et al. Cell transplantation and neuroengineering approach for spinal cord injury treatment: A summary of current laboratory findings and review of literature. *Cell Transplant*. 2016, **25**(8): 1425–1438.
- [15] Iyer NR, Wilems TS, Sakiyama-Elbert SE. Stem cells for spinal cord injury: Strategies to inform differentiation and transplantation. *Biotechnol Bioeng*. 2017, **114**(2): 245–259.
- [16] Wu GH, Shi HJ, Che MT, et al. Recovery of paralyzed limb motor function in canine with complete spinal cord injury following implantation of MSC-derived neural network tissue. *Biomaterials*. 2018, **181**: 15–34.
- [17] Zhou ZL, Zhang H, Jin AM, et al. A combination of taxol infusion and human umbilical cord mesenchymal stem cells transplantation for the treatment of rat spinal cord injury. *Brain Res*. 2012, **1481**: 79–89.
- [18] Shahrezaie M, Mansour RN, Nazari B, et al. Improved stem cell therapy of spinal cord injury using GDNF-overexpressed bone marrow stem cells in a rat model. *Biologicals*. 2017, **50**: 73–80.
- [19] Nejati-Koshki K, Mortazavi Y, Pilehvar-Soltanahmadi Y, et al. An update on application of nanotechnology and stem cells in spinal cord injury regeneration. *Biomed Pharmacother*. 2017, **90**: 85–92.
- [20] Jung DI, Ha J, Kang BT, et al. A comparison of autologous and allogenic bone marrow-derived mesenchymal stem cell transplantation in canine spinal cord injury. *J Neurol Sci*. 2009, **285**(1/2): 67–77.
- [21] Ballen KK, Gluckman E, Broxmeyer HE. Umbilical cord blood transplantation: the first 25 years and beyond. *Blood*. 2013, **122**(4): 491–498.
- [22] Bai LP, Li DT, Li J, et al. Bioactive molecules derived from umbilical cord mesenchymal stem cells. *Acta Histochem*. 2016, **118**(8): 761–769.

- [23] Kern S, Eichler H, Stoeve J, et al. Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue. *Stem Cells*. 2006, **24**(5): 1294–1301.
- [24] Borghesi J, Ferreira Lima M, Mario LC, et al. Canine amniotic membrane mesenchymal stromal/stem cells: Isolation, characterization and differentiation. *Tissue Cell*. 2019, **58**: 99–106.
- [25] Ohta Y, Hamaguchi A, Ootaki M, et al. Intravenous infusion of adipose-derived stem/stromal cells improves functional recovery of rats with spinal cord injury. *Cytotherapy*. 2017, **19**(7): 839–848.
- [26] Hur JW, Cho TH, Park DH, et al. Intrathecal transplantation of autologous adipose-derived mesenchymal stem cells for treating spinal cord injury: A human trial. *J Spinal Cord Med*. 2016, **39**(6): 655–664.
- [27] Wu B, Sun L, Li PJ, et al. Transplantation of oligodendrocyte precursor cells improves myelination and promotes functional recovery after spinal cord injury. *Injury*. 2012, **43**(6): 794–801.
- [28] Li N, Leung GK. Oligodendrocyte precursor cells in spinal cord injury: A review and update. *Biomed Res Int*. 2015, **2015**: 235195.
- [29] Priest CA, Manley NC, Denham J, et al. Preclinical safety of human embryonic stem cell-derived oligodendrocyte progenitors supporting clinical trials in spinal cord injury. *Regen Med*. 2015, **10**(8): 939–958.
- [30] Kumamaru H, Saiwai H, Kubota K, et al. Therapeutic activities of engrafted neural stem/precursor cells are not dormant in the chronically injured spinal cord. *Stem Cells*. 2013, **31**(8): 1535–1547.
- [31] Cheng I, Githens M, Smith RL, et al. Local versus distal transplantation of human neural stem cells following chronic spinal cord injury. *Spine J*. 2016, **16**(6): 764–769.
- [32] Curtis E, Martin JR, Gabel B, et al. A first-in-human, phase I study of neural stem cell transplantation for chronic spinal cord injury. *Cell Stem Cell*. 2018, **22**(6): 941–950.e6.
- [33] Ilic D, Devito L, Miere C, et al. Human embryonic and induced pluripotent stem cells in clinical trials. *Br Med Bull*. 2015, **116**: 19–27.
- [34] Vismara I, Papa S, Rossi F, et al. Current options for cell therapy in spinal cord injury. *Trends Mol Med*. 2017, **23**(9): 831–849.
- [35] Goulão M, Lepore AC. IPS cell transplantation for traumatic spinal cord injury. *CSCR*. 2016, **11**(4): 321–328.
- [36] Young W. Spinal cord regeneration. *Cell Transplant*. 2014, **23**(4/5): 573–611.
- [37] Qin C, Guo Y, Yang DG, et al. Induced pluripotent stem cell transplantation improves locomotor recovery in rat models of spinal cord injury: a systematic review and meta-analysis of randomized controlled trials. *Cell Physiol Biochem*. 2018, **47**(5): 1835–1852.
- [38] Doulames VM, Plant GW. Induced pluripotent stem cell therapies for cervical spinal cord injury. *Int J Mol Sci*. 2016, **17**(4): 530.
- [39] Zhong WT, Bian KP, Hu YN, et al. Lysophosphatidic acid guides the homing of transplanted olfactory ensheathing cells to the lesion site after spinal cord injury in rats. *Exp Cell Res*. 2019, **379**(1): 65–72.
- [40] Chen L, Zhang Y, He X, et al. Comparison of intramedullary transplantation of olfactory ensheathing cell for patients with chronic complete spinal cord injury worldwide. *J Neurorestoratology*. 2018, **1**(6): 146–151.
- [41] Zheng ZC, Du XJ, Zhang KG, et al. Olfactory ensheathing cell transplantation inhibits P2X4 receptor overexpression in spinal cord injury rats with neuropathic pain. *Neurosci Lett*. 2017, **651**: 171–176.
- [42] Hosseini M, Yousefifard M, Baikpour M, et al. The efficacy of Schwann cell transplantation on motor function recovery after spinal cord injuries in animal models: A systematic review and meta-analysis. *J Chem Neuroanat*. 2016, **78**: 102–111.
- [43] Anderson KD, Guest JD, Dietrich WD, et al. Safety of autologous human schwann cell transplantation in subacute thoracic spinal cord injury. *J Neurotrauma*. 2017, **34**(21): 2950–2963.
- [44] Chen XM, Xue BH, Li YP, et al. Meta-analysis of stem cell transplantation for reflex hypersensitivity after spinal cord injury. *Neuroscience*. 2017, **363**: 66–75.
- [45] Fandel TM, Trivedi A, Nicholas CR, et al. Transplanted human stem cell-derived interneuron precursors mitigate mouse bladder dysfunction and central neuropathic pain after spinal cord injury. *Cell Stem Cell*. 2016, **19**(4): 544–557.
- [46] Blesch A. Human ESC-derived interneurons improve major consequences of spinal cord injury. *Cell Stem Cell*. 2016, **19**(4): 423–424.
- [47] Marín O. Cellular and molecular mechanisms controlling the migration of neocortical interneurons. *Eur J Neurosci*. 2013, **38**(1): 2019–2029.
- [48] Etlin A, Bráz JM, Kuhn JA, et al. Functional synaptic integration of forebrain GABAergic precursors into the adult spinal cord. *J Neurosci*. 2016, **36**(46): 11634–11645.
- [49] Bráz JM, Sharif-Naeini R, Vogt D, et al. Forebrain GABAergic neuron precursors integrate into adult spinal cord and reduce injury-induced neuropathic pain. *Neuron*. 2012, **74**(4): 663–675.
- [50] Wei GJ, An G, Shi ZW, et al. Suppression of MicroRNA-383 enhances therapeutic potential of human bone-marrow-derived mesenchymal stem cells in treating spinal cord injury via GDNF. *Cell Physiol Biochem*. 2017, **41**(4): 1435–1444.
- [51] Stewart AN, Kendziorski G, Deak ZM, et al. Transplantation of mesenchymal stem cells that overexpress NT-3 produce motor improvements without axonal regeneration following complete spinal cord transections in rats. *Brain Res*. 2018, **1699**: 19–33.
- [52] Shang AJ, Hong SQ, Xu Q, et al. NT-3-secreting human

- umbilical cord mesenchymal stromal cell transplantation for the treatment of acute spinal cord injury in rats. *Brain Res.* 2011, **1391**: 102–113.
- [53] Ye Y, Feng TT, Peng YR, et al. The treatment of spinal cord injury in rats using bone marrow-derived neural-like cells induced by cerebrospinal fluid. *Neurosci Lett.* 2018, **666**: 85–91.
- [54] Galhom RA, Hussein Abd El Raouf HH, Mohammed Ali MH. Role of bone marrow derived mesenchymal stromal cells and Schwann-like cells transplantation on spinal cord injury in adult male albino rats. *Biomed Pharmacother.* 2018, **108**: 1365–1375.
- [55] Hacein-Bey-Abina S, Von Kalle C, Schmidt M, et al. LMO<sub>2</sub>-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1. *Science.* 2003, **302**(5644): 415–419.
- [56] Muheremu A, Peng J, Ao Q. Stem cell based therapies for spinal cord injury. *Tissue Cell.* 2016, **48**(4): 328–333.
- [57] Agbay A, Edgar JM, Robinson M, et al. Biomaterial strategies for delivering stem cells as a treatment for spinal cord injury. *Cells Tissues Organs* (Print). 2016, **202**(1/2): 42–51.
- [58] Li XR, Fan CX, Xiao ZF, et al. A collagen microchannel scaffold carrying paclitaxel-liposomes induces neuronal differentiation of neural stem cells through Wnt/ $\beta$ -catenin signaling for spinal cord injury repair. *Biomaterials.* 2018, **183**: 114–127.
- [59] Koffler J, Zhu W, Qu X, et al. Biomimetic 3D-printed scaffolds for spinal cord injury repair. *Nat Med.* 2019, **25**(2): 263–269.
- [60] Xie XM, Shi LL, Shen L, et al. Co-transplantation of MRF-overexpressing oligodendrocyte precursor cells and Schwann cells promotes recovery in rat after spinal cord injury. *Neurobiol Dis.* 2016, **94**: 196–204.
- [61] Elboghady I, Hassanzadeh H, Stein BE, et al. Controversies and potential risk of mesenchymal stem cells application. *Semin Spine Surg.* 2015, **27**(2): 103–106.
- [62] Huang HY, Sharma HS, Chen L, et al. 2018 Yearbook of Neurorestoratology. *J Neurorestoratology.* 2019, **1**(7): 8–17.
- [63] Huang HY, Shanker S H, Lin C, et al. Review of clinical neurorestorative strategies for spinal cord injury: exploring history and latest progresses. *J Neurorestoratology.* 2018, **1**(6): 171–178.
- [64] Baastrup C, Maersk-Moller CC, Nyengaard JR, et al. Spinal-, brainstem- and cerebrally mediated responses at- and below-level of a spinal cord contusion in rats: evaluation of pain-Like behavior. *Pain.* 2010, **151**(3): 670–679.



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