

World Journal of *Stem Cells*

World J Stem Cells 2017 September 26; 9(9): 144-168



**REVIEW**

- 144 Stem cell therapy for nerve injury

Sayad Fathi S, Zaminy A

MINIREVIEWS

- 152 Role of aryl hydrocarbon receptor in mesenchymal stromal cell activation: A minireview

de Almeida DC, Evangelista LSM, Câmara NOS

ORIGINAL ARTICLE**Basic Study**

- 159 Murine hepatocellular carcinoma derived stem cells reveal epithelial-to-mesenchymal plasticity

Jayachandran A, Shrestha R, Dhungel B, Huang IT, Vasconcelos MYK, Morrison BJ, Ramlogan-Steel CA, Steel JC

ABOUT COVER

Editorial Board Member of *World Journal of Stem Cells*, Shimon Slavin, MD, Director, Professor, Department of Scientific and Medical , The International Center for Cell Therapy and Cancer Immunotherapy, Top Ichilov at the Weizman Center, Tel Aviv 64239, Israel

AIM AND SCOPE

World Journal of Stem Cells (*World J Stem Cells*, *WJSC*, online ISSN 1948-0210, DOI: 10.4252), is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJSC covers topics concerning all aspects of stem cells: embryonic, neural, hematopoietic, mesenchymal, tissue-specific, and cancer stem cells; the stem cell niche, stem cell genomics and proteomics, and stem cell techniques and their application in clinical trials.

We encourage authors to submit their manuscripts to *WJSC*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

INDEXING/ABSTRACTING

World Journal of Stem Cells is now indexed in PubMed, PubMed Central, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Biological Abstracts, and BIOSIS Previews.

FLYLEAF

I-V

Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Ya-Jing Lu*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Li-Jun Cai*
Proofing Editorial Office Director: *Jin-Lai Wang*

NAME OF JOURNAL
World Journal of Stem Cells

ISSN
ISSN 1948-0210 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Tong Cao, BM BCh, DDS, PhD, Associate Professor, Doctor, Department of Oral Sciences, National University of Singapore, Singapore 119083, Singapore

Oscar Kuang-Sheng Lee, MD, PhD, Professor, Medical Research and Education of Veterans General Hospital-Taipei, No. 322, Sec. 2, Shih-pai Road, Shih-pai, Taipei 11217, Taiwan

EDITORIAL BOARD MEMBERS
All editorial board members resources online at <http://www.wjgnet.com/1948-0210/editorialboard.htm>

EDITORIAL OFFICE

Xiu-Xia Song, Director
World Journal of Stem Cells
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>

PUBLISHER

Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>

PUBLICATION DATE

September 26, 2017

COPYRIGHT

© 2017 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non-commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

<http://www.wjgnet.com/bpg/gerinfo/204>

ONLINE SUBMISSION

<http://www.f6publishing.com>

Stem cell therapy for nerve injury

Sara Sayad Fathi, Arash Zaminy

Sara Sayad Fathi, Arash Zaminy, Department of Anatomical Sciences, School of Medicine, Guilan University of Medical Sciences, Rasht 41996-13769, Iran

Arash Zaminy, Neuroscience Research Center, School of Medicine, Guilan University of Medical Sciences, Rasht 41996-13769, Iran

Author contributions: Authors have contributed equally to the manuscript.

Conflict-of-interest statement: Authors declare no conflict of interest for this article.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Arash Zaminy, PhD, Department of Anatomical Sciences, School of Medicine, Guilan University of Medical Sciences, Rasht-Tehran Highway, Rasht 41996-13769, Iran. zaminy_a@gums.ac.ir
Telephone: +98-91-24796418
Fax: +98-13-33690036

Received: January 29, 2017

Peer-review started: February 13, 2017

First decision: May 11, 2017

Revised: June 29, 2017

Accepted: July 14, 2017

Article in press: July 17, 2017

Published online: September 26, 2017

microsurgery, some severe types of neural injuries cannot be treated without causing tension to the injured nerve. Thus current studies have focused on the new approaches for the treatment of peripheral nerve injuries. Stem cells with the ability to differentiate into a variety of cell types have brought a new perspective to this matter. In this review, we will discuss the use of three main sources of mesenchymal stem cells in the treatment of peripheral nerve injuries.

Key words: Cell-based therapies; Peripheral nerve injury; Stem cells; Mesenchymal stem cells; Bone marrow mesenchymal stem cells; Adipose-derived mesenchymal stem cells; Umbilical cord mesenchymal stem cells

© **The Author(s) 2017.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Mesenchymal stem cells (MSCs) can differentiate into many kinds of cell types including Schwann cells (SCs). Since there are limitations for the use of SCs in nerve injuries, it is necessary to know about substitute cell types. So far different sources of MSCs such as embryonic stem cells, bone marrow MSCs, adipose-derived stem cells, etc. have been studied and the existence of beneficial effects on nerve regeneration after injury has been confirmed. Here in this paper, we have collected the latest updates on the use of MSCs from different sources in peripheral nerve regeneration.

Sayad Fathi S, Zaminy A. Stem cell therapy for nerve injury. *World J Stem Cells* 2017; 9(9): 144-151 Available from: URL: <http://www.wjgnet.com/1948-0210/full/v9/i9/144.htm> DOI: <http://dx.doi.org/10.4252/wjsc.v9.i9.144>

Abstract

Peripheral nerve injury has remained a substantial clinical complication with no satisfactory treatment options. Despite the great development in the field of

INTRODUCTION

Cell-based therapy in Peripheral nerve injuries (PNIs) has become an important intercession which amends clinical outcome. Contrary to the central nervous system, the peripheral nervous system has the potential for

regeneration to a certain extent^[1]. Nevertheless, complete functional recovery is strongly dependent upon the severity of the injury, anatomical site of the injury, and the delay before any kind of applied intervention^[2].

What is PNI?

Any harm to the peripheral nerves interrupting their function would be classified as a PNI. In the case of PNI, the connection between the involved nerve fiber and the distal organ would be negatively affected and sometimes even lost, so the distal organ undergoes atrophy due to denervation. In 1%-3% of patients with a traumatic accident, a PNI will almost always be involved^[3,4]. It has been recognized in children suffering falls^[5,6], as a consequence of medical procedures such as surgeries, chemotherapy, radiation^[7-9] and sometimes it has been brought about some chronic conditions like diabetes and cancers^[10,11]. It can also occur as an iatrogenic injury^[12]. There are three main types of a condition causing PNI: Transection, tension, and compression^[13,14]. First of which is commonly caused by penetrating trauma, the second one occurs when a nerve is over-stretched and the third can be reversed if the condition caused the injury is stopped within 8 h. In this article we have mainly focused on transection injuries.

What happens in cellular and molecular level?

A series of cellular and molecular events take place in response to nerve injury. In severe transection injuries (grade V in Sunderland classification or neurotmesis in Seddon classification^[15,16]) caused by penetrating trauma, proximal and distal stumps of the injured nerve undergo pathological changes. "Wallerian degeneration" will occur in distal stump in which injured axons will turn into granule-like debris that will be later cleaned by macrophages^[17]. Proximal stump also firstly retracts back to node of Ranvier^[18] and then tries to reach the distal stump by giving rise to outgrowing axons^[19,20] while activated Schwann cells (SCs) transform into regenerating phenotype and proliferate in the distal stump to form longitudinal columns called "bands of Büngner" which are essential to guide the outgrowing axons^[21]. However, mentioned events along with the secretion of neurotrophic factors by SCs make a great environment for axonal stumps to meet, but the slow rate of axon regeneration which is location-dependent but is usually stated as 1 mm/d^[22], almost always fails these processes and leads to impotency of activated SCs^[23], misguidance of outgrowing axons and target organ atrophy due to prolonged lack of innervation^[24].

Therapeutic strategies

In the case of transection injury, the Gold-Standard therapeutic strategy is to join the proximal and distal stumps of the damaged nerve through surgical interventions. Yet, when the gap is too wide to be repaired without stretching the nerve fiber, a nerve

graft or a conduit is needed to bridge the gap. Although nerve grafting is the gold standard technique^[20,25], this often leads to consequences such as donor site unwholesomeness for autologous grafts and graft rejection for heterologous grafts. On the other hand, conduits provide a guiding channel for axonal outgrowth and they can also serve as a vehicle to deliver essential growth factors and supporting cells^[20,26-29]. In recent years, cell transplantation has been proposed as a method of improving peripheral nerve regeneration. SCs activated in response to nerve injury, as previously described play a key role in Wallerian degeneration and formation of bands of Büngner. These features make SCs the most suitable supporting cell candidate to transplant, but regarding other important features of SCs such as the difficulty of harvest, the slow expansion in culture and a high immunogenicity^[30,31], SCs could not make the ideal supporting cells. So attentions have moved towards the use of differentiated and undifferentiated types of stem cells which have the capacity to transform into a variety of different cell types in presence of particular factors.

Use of stem cells

Stem cells are undifferentiated cells of an organism being capable of giving rise to indefinitely more cells of the same type, and other types of cells by differentiation. Stem cells commonly come from two main sources: Embryos (embryonic stem cells), which can be harvested during embryonic period and adult tissues (adult stem cells) that are available in all the tissues in the body. Stem cells are classified by their capability to differentiate into other cell types. Unipotent stem cells (like muscle stem cells) can only give rise to cells of their own type. Oligopotent stem cells can differentiate into a few cell types, like myeloid stem cells. Multipotent stem cells have the ability to differentiate into a nearly related type of cells, like hematopoietic stem cells which not only can produce red blood cells but also can give rise to white blood cells and platelets. Pluripotent stem cells can differentiate into almost all cell types and the examples include embryonic stem cells and the cells from ectodermal, mesodermal and endodermal layers. Totipotent stem cells are the only ones which are able to give rise to all possible cell types, the example is the first few cells that result from the division of the zygote and the fertilized zygote itself.

Mesenchymal stem cells

In this review we mainly focused on mesenchymal stem cells (MSCs), the multipotent stem cells which can be obtained from various sources such as bone marrow, umbilical cord and amniotic fluid, adipose tissue, and also teeth. These cells are characterized morphologically by a small cell body containing a round nucleus with a clear appearance and a prominent nucleolus. Cells have a few long cell processes and the cytoplasm contains Golgi apparatus, mitochondria, rough endoplasmic

reticulum and ribosomes. They are spread widely in the extracellular matrix containing a low amount of reticular fiber.

All-together, this paper will discuss the recent progress in the use of cell-based therapies and of interest the use of MSCs for peripheral nerve regeneration. It will summarize the perspectives of employing main sources of MSCs to speed up the healing process in injured peripheral nerves and involved mechanisms.

SURGICAL TECHNIQUES

The most common donor nerve used for autograft is Sural nerve which is a sensory nerve, hence it cannot be the proper choice for the repair of nerves with mixed motor and sensory or motor constituent^[20,32]. Regarding to the complications of nerve autografts, researchers have focused on using substitute options to bridge the wide gaps with no harm to nerve ends. Various absorbable biomaterials have been used to make conduits and authors worldwide reported different results^[20,26-29]. Conduits can be autogenous or synthetic. Autogenous conduits such as vein conduits sometimes accompanied by muscle or platelet-rich plasma components regardless of good outcomes require a donor site for harvesting^[33,34]. A wide range of synthetic conduits made of collagen, polycaprolactone, polyglycolic acid and polyester have also been studied. Taras *et al*^[35] used collagen conduits and reported good sensory nerves recovery. Wangenstein *et al*^[36] and Ashley *et al*^[37] showed that collagen conduits can have beneficial effects in clinical experiments as well as preclinical experiments with using them in trauma patients and infants with brachial plexus injuries respectively. They run a follow-up survey and monitored 5 infants with transplanted collagen conduits and reported significant motor recovery. Lohmeyer *et al*^[38] also used collagen conduits for nerve reconstruction and reported a 55% of two-point discrimination and 77% of protective sensation recovery. Boeckstyns *et al*^[39] used collagen tubules for recovery of the injured median and ulnar nerves and Sosa *et al*^[40] used collagen tubules containing platelet-rich fibrin for a patient with ulnar neuroma and both of them reported significant motor and sensory recovery. Mackinnon *et al*^[18] used polyglycolic acid tubes in 15 patients with 17 mm nerve gaps and found that despite 14% of them having poor recovery, 86% of them showed excellent (33%) and good (55%) signs of recovery. Battiston *et al*^[27] used polyglycolic acid conduits and muscle-vein conduits to see their difference healing properties. Results showed no significant difference between two groups. Weber *et al*^[41] evaluated the beneficial effects of polyglycolic acid tubes compared to neurotaphy and nerve autografts and reported that in gaps of less than 4 mm or more than 8 mm, polyglycolic acids provided better recovery. Despite great improvements in surgical techniques and instruments, this field will have to be more and more investigated to make an optimal combination of

cells and neurotrophic factors accompany a conduit to amend clinical outcomes.

IMPORTANT ROLE OF NEUROTROPHIC FACTORS

Axonal outgrowths are very slow to form and in severe cases it takes a long time for them to reach the distal stump, and on the other hand it is critical for activated SCs to innervate quickly in order to remain in their active form, thus administration of exogenous neurotrophic and growth factor with the ability of speeding up the mentioned processes has gathered attention. Neurotrophic factors are proteins which are necessary for many vital neural activities particularly in the regeneration of neurons after injuries^[42-45]. Brain-derived neurotrophin factor (BDNF) plays a key role after neural injuries and showed to have advantageous effects on outgrowing axons^[46,47]. Nerve growth factor (NGF) have also a beneficial effect on the elongation of outgrowing sensory axons additional to enhancing SCs motility^[48-50]. Glial cell line-derived neurotrophic factor (GDNF) acts like a chemoattractant for SCs^[48-50]. Sox11 is a very important transcription factor upregulating in response to PNI^[51]. Its expression can affect myelination and axonal elongation and levels of BDNF^[52-56]. It also can help with the survival of neurons through the expression of TNF receptor-associated factor-associated NF- κ B activator (TANK)^[51-55]. Vascular endothelial growth factor (VEGF) can improve outcomes of nerve regeneration through improving microcirculation^[57]. Insulin-like growth factor (IGF) found to have stimulant effects on mitosis of SCs and axonal elongation^[58]. Mohammadi *et al*^[59] used silicon tube with hepatocyte growth factor (HGF) filling and reported improved muscle atrophy. Li *et al*^[60] also reported that same beneficial properties of HGF in combination with acellular nerve allograft. Mohammadi *et al*^[61] reported improved recovery after using silicone tube filled with adrenocorticotropin hormone (ACTH). Emel *et al*^[62] have reported that IGF-1 has a better effect on PNI compared to Platelet-rich plasma. Regardless of how much it could be helpful to use the combination of conduits and neurotrophins, it is still important to hold SCs at their active form, because over a short period of time they lose their capacity for remaining active. Researchers have had invented methods to transplant newly activated SCs to the site of injury or to use cell types which are able to transform into SCs or SC-like cells to support the healing process.

SCs IN NERVE REGENERATION

SCs actively produce cell adhesion molecules, neurotrophins and growth factors and they can also serve as a scaffold allowing axonal sprouts to grow through their basal lamina^[63-66]. They can also produce regulatory factors to help axonal outgrowth^[67,68]. Despite promising results in preclinical experiments, clinical studies did

not gain good results because the difficulties with harvesting^[68,69] and culture of SCs^[70] and the fact that prolonged denervated SCs lose their ability to stimulate regeneration^[71].

STEM CELLS USED IN PNIs

Because of stem cells' potentials they have become a source of cells which act as an alternative for SCs in peripheral nerve regeneration^[70,72-74]. Stem cells as previously described, are biological progenitor cells which are undifferentiated and are able to produce more undifferentiated stem cells like themselves through mitosis. In addition, they can differentiate into almost all kinds of cell type depending on trophic and tropic factors they are exposed to. In the case of nervous system, stem cells have the ability to differentiate into supporting cells including oligodendrocytes, astrocytes, microglia, SC-like cells, and neurons themselves^[75]. They can be differentiated *in vitro* before transplantation, and can also be transplanted in their undifferentiated form allowing to differentiate *in vivo* at the site of injury. An ideal choice of stem cell would be depended on the important features of the cells, like the ease of harvesting through noninvasive procedures, rapid expanding in culture and low immunogenicity^[30,31]. Many kinds of stem cells with different sources have been studied, among them, MSCs having mentioned features, have been suggested as a potential cell type to enhance nerve regeneration. MSCs are multipotent stromal cells which can differentiate into a variety of cell types. Three main sources of MSCs will be discussed in following sections.

Bone marrow mesenchymal stem cells

Several studies have reported that bone marrow mesenchymal stem cells (BMSCs) can be induced to differentiate into mesodermal, ectodermal and endodermal lineage^[76-80]. Interestingly they can differentiate into SC-like cells and ameliorate neural regeneration by releasing neurotrophic and growth factors, BDNF, GDNF, myelin basic protein^[81] and by regulating SCs behavior^[82]. These good effects seem to be irrelevant to their differentiation state because both differentiated and undifferentiated BMSCs represent positive molecular, electrophysiological, histological and behavioral effects in preclinical experiments^[83]. Regarding some problems in harvesting BMSCs like the need of performing invasive and painful procedures that might yield a low number of cells, BMSCs have some disadvantages in clinical studies. Wang *et al.*^[84] compared the combination of BMSC-SCs and Adipose-derived stem cell SCs (ADSC-SCs) with acellular grafts to bridge the sciatic gaps of 15 mm and reported the greater regeneration recovery at the presence of BMSC-SCs and ADSC-SCs. Hu *et al.*^[85] used BMSC seeded grafts for the recovery of 50 mm median nerve injury in monkeys and found that the healing process with good functional and morphological outcomes was close to autografts. Cuevas *et al.*^[86,87] found that using

BMSCs have beneficial effects on rat models of PNI with injured sciatic nerves. They have also run a follow-up experiment to assess the healing process and reported a significant improvement in sciatic nerve-injured rats with transplanted BMSCs compared to control group. Chen *et al.*^[81] used silicon conduits filled with BMSCs and assessed the recovery process measuring the number of growing axons and muscle atrophy along with walking test and reported their beneficial effects on mentioned indices highlighting the role of neurotrophic factors and myelin basic protein upregulation and not the increase in the number of SCs. Haghighat *et al.*^[88] and Mohammadi *et al.*^[89] also showed that using vein conduits with undifferentiated BMSCs can cause a significant increase in the number and diameter of growing axons and functional improvement consequently. Studies showed that differentiated BMSCs can have a better impact when used in combination with acellular nerve allografts rather than undifferentiated BMSCs^[90]. It has been demonstrated that using BMSCs in PNIs can have similar outcomes as in use of autografts. Studies showed that BMSCs can possibly improve the outcome of nerve regeneration by modulating the behavior of SCs along with expressing neurotrophins^[82]. Caddick *et al.*^[79] found that BMSCs can be induced to differentiate into SC-like cells representing SCs markers such as S100, P75, and GFAP. It has been reported that with the use of cytokines, rat BMSCs can be transformed into SC-like cells which were capable of myelinating PC12 cells *in vitro* after 2 wk as well as increasing the myelinated axons in a rat model of PNI after 3 wk^[91]. It has been shown that BMSCs apply their beneficial effects in a dose-dependent manner^[92].

Adipose-derived mesenchymal stem cells

Adipose-derived mesenchymal stem cells (ADSCs) are another source of multipotent stem cells with the ability of transforming into all three germinal layers^[93,94] and additionally has been showed to give much greater numbers of cells compared to other adult tissues^[95], with minimally invasive surgical procedures and a very simple isolation protocol including washing; diffusing with the aid of enzymatic agents; centrifugation and removal of red blood cells (RBCs). This protocol gives a cellular fraction containing various cell types. Among them, ADSCs of interest adhere to the plastic wall of the container and proliferate quickly, so it can be easily recognized and separated from other cells. Studies showed that ADSCs can be induced to express glial cell markers such as S100B, GFAP and P75 neurotrophin receptors *in vitro*^[69]. Also in the case of ADSCs, it has been demonstrated that *in vitro* differentiation into SCs could not bring any further melioration probably because of ADSCs natural capacity of *in vivo* differentiation into SCs^[65]. Di summa *et al.*^[65] demonstrated that ADSC-SCs, as well as BMSC-SCs, can be used for the repair of rat sciatic nerve injury and since unlike the BMSCs, ADSCs can be easily harvested and expanded, they would be a better choice in PNI injuries. Erba *et al.*^[96] transplanted undifferentiated

ADSCs in poly-3-hydroxybutyrate conduit to assess the axonal outgrowth and the transplanted cells capacity to transform at the site of injury. They reported the increase in the number of SCs and regeneration however researchers could not detect any transformation into neither glial nor neural cells. A similar result has been reported by Santiago *et al*^[97] and the possible mechanism suggested by the authors through which the regeneration has been enhanced, was the expression of neurotrophins. Other similar results have been reported by other researchers^[98,99]. Wei *et al*^[100] showed that ADSC filled conduits have the same regenerative effects in rat sciatic nerve injury as SC filled conduit. Researchers found that ADSCs cannot be differentiated into SCs *in vivo* despite *in vitro* differentiation^[101]. It has been demonstrated that undifferentiated ADSCs can release neurotrophins but at a lower extent^[102]. Oliveira *et al*^[103] used polycaprolactone conduits seeded with MSCs and showed the improvement of myelination and function compared with empty conduits. Another research group used collagen conduits with collagen gel containing ADSCs filling and results showed that improvement was similar to nerve autografts^[104].

Umbilical cord mesenchymal stem cells

Regarding ethical concerns with the use of umbilical cord mesenchymal stem cells (UC-MSCs) and limitation of its availability, there is still proofs which show they are superior to other adult stem cell with different sources: First, they can be collected in great numbers without causing any harm to donor simply from discardable tissues after childbirth; second, as they will be collected at the perinatal period, they are less likely to have genetic damages^[105]; third, they are younger than other adult stem cells so they can undergo higher number of mitosis and can be much more expanded in culture^[106]; fourth, while they lack HLA-II, they have much lower immunogenic properties compared to other adult stem cells^[107]. Matsuse *et al*^[108] used tubes filled with SC-like cells which have been previously formed as a result of UC-MSCs differentiation and showed that they can promote axonal regeneration. Same results have been demonstrated by Kuroda *et al*^[109] and Pereira *et al*^[110]. Peng *et al*^[111] demonstrated that SC-like cells can secrete BDNF, Neurotrophin-3, and NGF *in vitro* and when combined with PC12 cells, axonal growth was seen.

CONCLUSION

To improve peripheral nerve regeneration for better sensory and motor recovery, the use of stem cells and especially MSCs would be greatly helpful. These cells not only can differentiate into SCs *in vitro* but also are able to transform into SCs directly at the site of injury. Furthermore, administration of stem cells, can regulate the activity of native SCs, modify the inhibitory regenerative environment, improve myelination and cell

survival and enhance neurotrophic activity. In summary, MSCs with such suitable properties as the ease of harvesting especially in the case of ADSCs and the lower risk of immunogenic activities have got a great potential to improve the regeneration process. Thus, for sure by further investigations, significant improvements in neural regeneration by the help of MSCs will be obtained.

REFERENCES

- 1 **Chen ZL**, Yu WM, Strickland S. Peripheral regeneration. *Annu Rev Neurosci* 2007; **30**: 209-233 [PMID: 17341159 DOI: 10.1146/annurev.neuro.30.051606.094337]
- 2 **Scheib J**, Höke A. Advances in peripheral nerve regeneration. *Nat Rev Neurol* 2013; **9**: 668-676 [PMID: 24217518 DOI: 10.1038/nrneurol.2013.227]
- 3 **Noble J**, Munro CA, Prasad VS, Midha R. Analysis of upper and lower extremity peripheral nerve injuries in a population of patients with multiple injuries. *J Trauma* 1998; **45**: 116-122 [PMID: 9680023]
- 4 **Taylor CA**, Braza D, Rice JB, Dillingham T. The incidence of peripheral nerve injury in extremity trauma. *Am J Phys Med Rehabil* 2008; **87**: 381-385 [PMID: 18334923 DOI: 10.1097/PHM.0b013e31815e6370]
- 5 **Bekelis K**, Missios S, Spinner RJ. Falls and peripheral nerve injuries: an age-dependent relationship. *J Neurosurg* 2015; **123**: 1223-1229 [PMID: 25978715 DOI: 10.3171/2014.11.JNS142111]
- 6 **Missios S**, Bekelis K, Spinner RJ. Traumatic peripheral nerve injuries in children: epidemiology and socioeconomics. *J Neurosurg Pediatr* 2014; **14**: 688-694 [PMID: 25303155 DOI: 10.3171/2014.8.PEDS14112]
- 7 **Pereira S**, Fontes F, Sonin T, Dias T, Fragoso M, Castro-Lopes JM, Lunet N. Chemotherapy-induced peripheral neuropathy after neoadjuvant or adjuvant treatment of breast cancer: a prospective cohort study. *Support Care Cancer* 2016; **24**: 1571-1581 [PMID: 26384827 DOI: 10.1007/s00520-015-2935-y]
- 8 **Brull R**, Hadzic A, Reina MA, Barrington MJ. Pathophysiology and Etiology of Nerve Injury Following Peripheral Nerve Blockade. *Reg Anesth Pain Med* 2015; **40**: 479-490 [PMID: 25974275 DOI: 10.1097/AAP.0000000000000125]
- 9 **Wu SG**, Huang SJ, Zhou J, Sun JY, Guo H, Li FY, Lin Q, Lin HX, He ZY. Dosimetric analysis of the brachial plexus among patients with breast cancer treated with post-mastectomy radiotherapy to the ipsilateral supraclavicular area: report of 3 cases of radiation-induced brachial plexus neuropathy. *Radiat Oncol* 2014; **9**: 292 [PMID: 25499205 DOI: 10.1186/s13014-014-0292-5]
- 10 **Antoine JC**, Camdessanché JP. Peripheral nervous system involvement in patients with cancer. *Lancet Neurol* 2007; **6**: 75-86 [PMID: 17166804 DOI: 10.1016/S1474-4422(06)70679-2]
- 11 **Callaghan BC**, Cheng HT, Stables CL, Smith AL, Feldman EL. Diabetic neuropathy: clinical manifestations and current treatments. *Lancet Neurol* 2012; **11**: 521-534 [PMID: 22608666 DOI: 10.1016/S1474-4422(12)70065-0]
- 12 **Kömürçü F**, Zwolak P, Benditte-Klepetko H, Deutinger M. Management strategies for peripheral iatrogenic nerve lesions. *Ann Plast Surg* 2005; **54**: 135-139; discussion 140-142 [PMID: 15655461]
- 13 **Kim DH**, Murovic JA, Tiel RL, Kline DG. Mechanisms of injury in operative brachial plexus lesions. *Neurosurg Focus* 2004; **16**: E2 [PMID: 15174822]
- 14 **Burnett MG**, Zager EL. Pathophysiology of peripheral nerve injury: a brief review. *Neurosurg Focus* 2004; **16**: E1 [PMID: 15174821 DOI: 10.3171/foc.2004.16.5.2]
- 15 **Seddon H**. Three types of nerve injury. *Brain* 1943; **66**: 237-288 [DOI: 10.1093/brain/66.4.237]
- 16 **Sunderland S**. A classification of peripheral nerve injuries producing loss of function. *Brain* 1951; **74**: 491-516 [PMID: 14895767 DOI: 10.1093/brain/74.4.491]

- 17 **Waller A.** Experiments on the section of the glossopharyngeal and hypoglossal nerves of the frog, and observations of the alterations produced thereby in the structure of their primitive fibers. *Philos Trans R Soc Lond* 1850; **140**: 423-429 [DOI: 10.1098/rstl.1850.0021]
- 18 **Maggi SP,** Lowe JB 3rd, Mackinnon SE. Pathophysiology of nerve injury. *Clin Plast Surg* 2003; **30**: 109-126 [PMID: 12737347 DOI: 10.1016/S0094-1298(02)00101-3]
- 19 **Geuna S,** Raimondo S, Ronchi G, Di Scipio F, Tos P, Czaja K, Fornaro M. Chapter 3: Histology of the peripheral nerve and changes occurring during nerve regeneration. *Int Rev Neurobiol* 2009; **87**: 27-46 [PMID: 19682632 DOI: 10.1016/S0074-7742(09)87003-7]
- 20 **Lee SK,** Wolfe SW. Peripheral nerve injury and repair. *J Am Acad Orthop Surg* 2000; **8**: 243-252 [PMID: 10951113]
- 21 **Bungner OV.** Über die Degenerations und Regenerationsvorgänge an Nerven nach Verletzungen. *Beitr Pathol Anat* 1891; **10**: 321-387
- 22 **Trojaborg W.** Rate of recovery in motor and sensory fibres of the radial nerve: clinical and electrophysiological aspects. *J Neurol Neurosurg Psychiatry* 1970; **33**: 625-638 [PMID: 5478945 DOI: 10.1136/jnnp.33.5.625]
- 23 **You S,** Petrov T, Chung PH, Gordon T. The expression of the low affinity nerve growth factor receptor in long-term denervated Schwann cells. *Glia* 1997; **20**: 87-100 [PMID: 9179594 DOI: 10.1002/(SICI)1098-1136(199706)20:23.O.CO;2-1]
- 24 **Fu SY,** Gordon T. Contributing factors to poor functional recovery after delayed nerve repair: prolonged denervation. *J Neurosci* 1995; **15**: 3886-3895 [PMID: 7751953]
- 25 **Pabari A,** Lloyd-Hughes H, Seifalian AM, Mosahebi A. Nerve conduits for peripheral nerve surgery. *Plast Reconstr Surg* 2014; **133**: 1420-1430 [PMID: 24867724 DOI: 10.1097/PRS.0000000000000226]
- 26 **Sabongi RG,** Fernandes M, Dos Santos JB. Peripheral nerve regeneration with conduits: use of vein tubes. *Neural Regen Res* 2015; **10**: 529-533 [PMID: 26170802 DOI: 10.4103/1673-5374.155428]
- 27 **Battiston B,** Geuna S, Ferrero M, Tos P. Nerve repair by means of tubulization: literature review and personal clinical experience comparing biological and synthetic conduits for sensory nerve repair. *Microsurgery* 2005; **25**: 258-267 [PMID: 15934044 DOI: 10.1002/micr.20127]
- 28 **Siemionow M,** Bozkurt M, Zor F. Regeneration and repair of peripheral nerves with different biomaterials: review. *Microsurgery* 2010; **30**: 574-588 [PMID: 20878689 DOI: 10.1002/micr.20799]
- 29 **Liao C,** Zheng R, Wei C, Yan J, Ding Y, Wang G, Li Z, Zhang Z. Tissue-engineered conduit promotes sciatic nerve regeneration following radiation-induced injury as monitored by magnetic resonance imaging. *Magn Reson Imaging* 2016; **34**: 515-523 [PMID: 26686023 DOI: 10.1016/j.mri.2015.12.004]
- 30 **Azizi SA,** Stokes D, Augelli BJ, DiGirolamo C, Prockop DJ. Engraftment and migration of human bone marrow stromal cells implanted in the brains of albino rats—similarities to astrocyte grafts. *Proc Natl Acad Sci USA* 1998; **95**: 3908-3913 [PMID: 9520466]
- 31 **Walsh S,** Midha R. Practical considerations concerning the use of stem cells for peripheral nerve repair. *Neurosurg Focus* 2009; **26**: E2 [PMID: 19435443 DOI: 10.3171/FOC.2009.26.2.E2]
- 32 **Nichols CM,** Brenner MJ, Fox IK, Tung TH, Hunter DA, Rickman SR, Mackinnon SE. Effects of motor versus sensory nerve grafts on peripheral nerve regeneration. *Exp Neurol* 2004; **190**: 347-355 [PMID: 15530874 DOI: 10.1016/j.expneurol.2004.08.003]
- 33 **Manoli T,** Schulz L, Stahl S, Jaminet P, Schaller HE. Evaluation of sensory recovery after reconstruction of digital nerves of the hand using muscle-in-vein conduits in comparison to nerve suture or nerve autografting. *Microsurgery* 2014; **34**: 608-615 [PMID: 25088084 DOI: 10.1002/micr.22302]
- 34 **Kim JY,** Jeon WJ, Kim DH, Rhyu IJ, Kim YH, Youn I, Park JW. An inside-out vein graft filled with platelet-rich plasma for repair of a short sciatic nerve defect in rats. *Neural Regen Res* 2014; **9**: 1351-1357 [PMID: 25221591 DOI: 10.4103/1673-5374.137587]
- 35 **Taras JS,** Jacoby SM, Lincoski CJ. Reconstruction of digital nerves with collagen conduits. *J Hand Surg Am* 2011; **36**: 1441-1446 [PMID: 21816545 DOI: 10.1016/j.jhsa.2011.06.009]
- 36 **Wangenstein KJ,** Kalliaianen LK. Collagen tube conduits in peripheral nerve repair: a retrospective analysis. *Hand (NY)* 2010; **5**: 273-277 [PMID: 19937145 DOI: 10.1007/s11552-009-9245-0]
- 37 **Ashley WW Jr,** Weatherly T, Park TS. Collagen nerve guides for surgical repair of brachial plexus birth injury. *J Neurosurg* 2006; **105**: 452-456 [PMID: 17184076 DOI: 10.3171/ped.2006.105.6.452]
- 38 **Lohmeyer JA,** Kern Y, Schmauss D, Paprottka F, Stang F, Siemers F, Mailaender P, Machens HG. Prospective clinical study on digital nerve repair with collagen nerve conduits and review of literature. *J Reconstr Microsurg* 2014; **30**: 227-234 [PMID: 24338485 DOI: 10.1055/s-0033-1358788]
- 39 **Boeckstyns ME,** Sørensen AI, Viñeta JF, Rosén B, Navarro X, Archibald SJ, Valsø-Solé J, Moldovan M, Krarup C. Collagen conduit versus microsurgical neurotaphy: 2-year follow-up of a prospective, blinded clinical and electrophysiological multicenter randomized, controlled trial. *J Hand Surg Am* 2013; **38**: 2405-2411 [PMID: 24200027 DOI: 10.1016/j.jhsa.2013.09.038]
- 40 **Sosa I,** Reyes O, Kuffler DP. Immunosuppressants: neuroprotection and promoting neurological recovery following peripheral nerve and spinal cord lesions. *Exp Neurol* 2005; **195**: 7-15 [PMID: 15935348 DOI: 10.1016/j.expneurol.2005.04.016]
- 41 **Weber RA,** Breidenbach WC, Brown RE, Jabaley ME, Mass DP. A randomized prospective study of polyglycolic acid conduits for digital nerve reconstruction in humans. *Plast Reconstr Surg* 2000; **106**: 1036-1045; discussion 1046-1048 [PMID: 11039375]
- 42 **Fu SY,** Gordon T. The cellular and molecular basis of peripheral nerve regeneration. *Mol Neurobiol* 1997; **14**: 67-116 [PMID: 9170101 DOI: 10.1007/BF02740621]
- 43 **Kemp SW,** Walsh SK, Midha R. Growth factor and stem cell enhanced conduits in peripheral nerve regeneration and repair. *Neurol Res* 2008; **30**: 1030-1038 [PMID: 19079977 DOI: 10.1179/174313208X362505]
- 44 **Zheng M,** Kuffler DP. Guidance of regenerating motor axons in vivo by gradients of diffusible peripheral nerve-derived factors. *J Neurobiol* 2000; **42**: 212-219 [PMID: 10640328]
- 45 **Boyd JG,** Gordon T. Neurotrophic factors and their receptors in axonal regeneration and functional recovery after peripheral nerve injury. *Mol Neurobiol* 2003; **27**: 277-324 [PMID: 12845152 DOI: 10.1385/MN:27.3:277]
- 46 **Griesbeck O,** Parsadanian AS, Sendtner M, Thoenen H. Expression of neurotrophins in skeletal muscle: quantitative comparison and significance for motoneuron survival and maintenance of function. *J Neurosci Res* 1995; **42**: 21-33 [PMID: 8531223 DOI: 10.1002/jnr.490420104]
- 47 **English AW,** Wilhelm JC, Ward PJ. Exercise, neurotrophins, and axon regeneration in the PNS. *Physiology (Bethesda)* 2014; **29**: 437-445 [PMID: 25362637 DOI: 10.1152/physiol.00028.2014]
- 48 **Johnson BN,** Lancaster KZ, Zhen G, He J, Gupta MK, Kong YL, Engel EA, Krick KD, Ju A, Meng F, Enquist LW, Jia X, McAlpine MC. 3D Printed Anatomical Nerve Regeneration Pathways. *Adv Funct Mater* 2015; **25**: 6205-6217 [PMID: 26924958 DOI: 10.1002/adfm.201501760]
- 49 **Cao X,** Shoichet MS. Defining the concentration gradient of nerve growth factor for guided neurite outgrowth. *Neuroscience* 2001; **103**: 831-840 [PMID: 11274797 DOI: 10.1016/S0306-4522(01)00029-X]
- 50 **Cornejo M,** Nambi D, Walheim C, Somerville M, Walker J, Kim L, Ollison L, Diamante G, Vyawahare S, de Bellard ME. Effect of NRG1, GDNF, EGF and NGF in the migration of a Schwann cell precursor line. *Neurochem Res* 2010; **35**: 1643-1651 [PMID: 20623378 DOI: 10.1007/s11064-010-0225-0]
- 51 **Jankowski MP,** Cornuet PK, McIlwrath S, Koerber HR, Albers KM. SRY-box containing gene 11 (Sox11) transcription factor is required for neuron survival and neurite growth. *Neuroscience* 2006; **143**: 501-514 [PMID: 17055661 DOI: 10.1016/j.neuroscience.2006.09.010]
- 52 **Jankowski MP,** McIlwrath SL, Jing X, Cornuet PK, Salerno KM, Koerber HR, Albers KM. Sox11 transcription factor modulates peripheral nerve regeneration in adult mice. *Brain Res* 2009; **1256**: 43-54 [PMID: 19133245 DOI: 10.1016/j.brainres.2008.12.032]
- 53 **Jing X,** Wang T, Huang S, Glorioso JC, Albers KM. The transcription factor Sox11 promotes nerve regeneration through activation of the regeneration-associated gene *Sprr1a*. *Exp Neurol* 2012; **233**: 221-232 [PMID: 22024412 DOI: 10.1016/j.expneurol.2011.10.005]

- 54 **Bonilla IE**, Tanabe K, Strittmatter SM. Small proline-rich repeat protein 1A is expressed by axotomized neurons and promotes axonal outgrowth. *J Neurosci* 2002; **22**: 1303-1315 [PMID: 11850458 DOI: 10.3410/f.1005790.69855]
- 55 **Salerno KM**, Jing X, Diges CM, Davis BM, Albers KM. TRAF family member-associated NF-kappa B activator (TANK) expression increases in injured sensory neurons and is transcriptionally regulated by Sox11. *Neuroscience* 2013; **231**: 28-37 [PMID: 23201825 DOI: 10.1016/j.neuroscience.2012.11.034]
- 56 **Hong EJ**, McCord AE, Greenberg ME. A biological function for the neuronal activity-dependent component of Bdnf transcription in the development of cortical inhibition. *Neuron* 2008; **60**: 610-624 [PMID: 19038219 DOI: 10.1016/j.neuron.2008.09.024]
- 57 **Mohammadi R**, Ahsan S, Masoumi M, Amini K. Vascular endothelial growth factor promotes peripheral nerve regeneration after sciatic nerve transection in rat. *Chin J Traumatol* 2013; **16**: 323-329 [PMID: 24295576 DOI: 10.3760/cma.j.issn.1008-1275.2013.06.001]
- 58 **Mohammadi R**, Esmail-Sani Z, Amini K. Effect of local administration of insulin-like growth factor I combined with inside-out artery graft on peripheral nerve regeneration. *Injury* 2013; **44**: 1295-1301 [PMID: 23747124 DOI: 10.1016/j.injury.2013.04.014]
- 59 **Mohammadi R**, Masoumi-Verki M, Ahsan S, Khaleghjoo A, Amini K. Improvement of peripheral nerve defects using a silicone conduit filled with hepatocyte growth factor. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2013; **116**: 673-679 [PMID: 24237722 DOI: 10.1016/j.oooo.2013.07.006]
- 60 **Li Z**, Peng J, Wang G, Yang Q, Yu H, Guo Q, Wang A, Zhao B, Lu S. Effects of local release of hepatocyte growth factor on peripheral nerve regeneration in acellular nerve grafts. *Exp Neurol* 2008; **214**: 47-54 [PMID: 18680744 DOI: 10.1016/j.expneurol.2008.07.007]
- 61 **Mohammadi R**, Yadegarazadi MJ, Amini K. Peripheral nerve regeneration following transection injury to rat sciatic nerve by local application of adrenocorticotrophic hormone. *J Craniomaxillofac Surg* 2014; **42**: 784-789 [PMID: 24342732 DOI: 10.1016/j.jcms.2013.11.012]
- 62 **Emel E**, Ergün SS, Kotan D, Gürsoy EB, Parman Y, Zengin A, Nurten A. Effects of insulin-like growth factor-I and platelet-rich plasma on sciatic nerve crush injury in a rat model. *J Neurosurg* 2011; **114**: 522-528 [PMID: 21029038 DOI: 10.3171/2010.9.JNS091928]
- 63 **Terenghi G**. Peripheral nerve regeneration and neurotrophic factors. *J Anat* 1999; **194** (Pt 1): 1-14 [PMID: 10227662 DOI: 10.1046/j.1469-7580.1999.19410001.x]
- 64 **Rodríguez FJ**, Verdú E, Ceballos D, Navarro X. Nerve guides seeded with autologous schwann cells improve nerve regeneration. *Exp Neurol* 2000; **161**: 571-584 [PMID: 10686077 DOI: 10.1006/exnr.1999.7315]
- 65 **di Summa PG**, Kingham PJ, Raffoul W, Wiberg M, Terenghi G, Kalbermatten DF. Adipose-derived stem cells enhance peripheral nerve regeneration. *J Plast Reconstr Aesthet Surg* 2010; **63**: 1544-1552 [PMID: 19828391 DOI: 10.1016/j.bjps.2009.09.012]
- 66 **Terenghi G**. Peripheral nerve injury and regeneration. *Histol Histopathol* 1995; **10**: 709-718 [PMID: 7579822]
- 67 **Fawcett JW**, Keynes RJ. Peripheral nerve regeneration. *Annu Rev Neurosci* 1990; **13**: 43-60 [PMID: 2183684 DOI: 10.1146/annurev.ne.13.030190.000355]
- 68 **Thompson DM**, Buettner HM. Oriented Schwann cell monolayers for directed neurite outgrowth. *Ann Biomed Eng* 2004; **32**: 1120-1130 [PMID: 15446508 DOI: 10.1114/B:ABME.0000036648.68804.e7]
- 69 **Kingham PJ**, Kalbermatten DF, Mahay D, Armstrong SJ, Wiberg M, Terenghi G. Adipose-derived stem cells differentiate into a Schwann cell phenotype and promote neurite outgrowth in vitro. *Exp Neurol* 2007; **207**: 267-274 [PMID: 17761164 DOI: 10.1016/j.expneurol.2007.06.029]
- 70 **Walsh S**, Biernaskie J, Kemp SW, Midha R. Supplementation of acellular nerve grafts with skin derived precursor cells promotes peripheral nerve regeneration. *Neuroscience* 2009; **164**: 1097-1107 [PMID: 19737602 DOI: 10.1016/j.neuroscience.2009.08.072]
- 71 **Dedkov EI**, Kostrominova TY, Borisov AB, Carlson BM. Survival of Schwann cells in chronically denervated skeletal muscles. *Acta Neuropathol* 2002; **103**: 565-574 [PMID: 12012088 DOI: 10.1007/s00401-001-0504-6]
- 72 **Amoh Y**, Kanoh M, Niiyama S, Hamada Y, Kawahara K, Sato Y, Hoffman RM, Katsuoka K. Human hair follicle pluripotent stem (hfPS) cells promote regeneration of peripheral-nerve injury: an advantageous alternative to ES and iPS cells. *J Cell Biochem* 2009; **107**: 1016-1020 [PMID: 19507228 DOI: 10.1002/jcb.22204]
- 73 **Schaakxs D**, Kalbermatten DF, Raffoul W, Wiberg M, Kingham PJ. Regenerative cell injection in denervated muscle reduces atrophy and enhances recovery following nerve repair. *Muscle Nerve* 2013; **47**: 691-701 [PMID: 23504573 DOI: 10.1002/mus.23662]
- 74 **Tohill M**, Mantovani C, Wiberg M, Terenghi G. Rat bone marrow mesenchymal stem cells express glial markers and stimulate nerve regeneration. *Neurosci Lett* 2004; **362**: 200-203 [PMID: 15158014 DOI: 10.1016/j.neulet.2004.03.077]
- 75 **Ladak A**, Olson J, Tredget EE, Gordon T. Differentiation of mesenchymal stem cells to support peripheral nerve regeneration in a rat model. *Exp Neurol* 2011; **228**: 242-252 [PMID: 21281630 DOI: 10.1016/j.expneurol.2011.01.013]
- 76 **Tohill M**, Terenghi G. Stem-cell plasticity and therapy for injuries of the peripheral nervous system. *Biotechnol Appl Biochem* 2004; **40**: 17-24 [PMID: 15270703 DOI: 10.1042/BA20030173]
- 77 **Barry FP**, Murphy JM. Mesenchymal stem cells: clinical applications and biological characterization. *Int J Biochem Cell Biol* 2004; **36**: 568-584 [PMID: 15010324 DOI: 10.1016/j.biocel.2003.11.001]
- 78 **García-Castro J**, Trigueros C, Madrenas J, Pérez-Simón JA, Rodríguez R, Menendez P. Mesenchymal stem cells and their use as cell replacement therapy and disease modelling tool. *J Cell Mol Med* 2008; **12**: 2552-2565 [PMID: 19210755 DOI: 10.1111/j.1582-4934.2008.00516.x]
- 79 **Caddick J**, Kingham PJ, Gardiner NJ, Wiberg M, Terenghi G. Phenotypic and functional characteristics of mesenchymal stem cells differentiated along a Schwann cell lineage. *Glia* 2006; **54**: 840-849 [PMID: 16977603 DOI: 10.1002/glia.20421]
- 80 **Bajada S**, Mazakova I, Richardson JB, Ashammakhi N. Updates on stem cells and their applications in regenerative medicine. *J Tissue Eng Regen Med* 2008; **2**: 169-183 [PMID: 18493906 DOI: 10.1002/term.83]
- 81 **Chen CJ**, Ou YC, Liao SL, Chen WY, Chen SY, Wu CW, Wang CC, Wang WY, Huang YS, Hsu SH. Transplantation of bone marrow stromal cells for peripheral nerve repair. *Exp Neurol* 2007; **204**: 443-453 [PMID: 17222827 DOI: 10.1016/j.expneurol.2006.12.004]
- 82 **Wang J**, Ding F, Gu Y, Liu J, Gu X. Bone marrow mesenchymal stem cells promote cell proliferation and neurotrophic function of Schwann cells in vitro and in vivo. *Brain Res* 2009; **1262**: 7-15 [PMID: 19368814 DOI: 10.1016/j.brainres.2009.01.056]
- 83 **Wakao S**, Hayashi T, Kitada M, Kohama M, Matsue D, Teramoto N, Ose T, Itokazu Y, Koshino K, Watabe H, Iida H, Takamoto T, Tabata Y, Dezawa M. Long-term observation of auto-cell transplantation in non-human primate reveals safety and efficiency of bone marrow stromal cell-derived Schwann cells in peripheral nerve regeneration. *Exp Neurol* 2010; **223**: 537-547 [PMID: 20153320 DOI: 10.1016/j.expneurol.2010.01.022]
- 84 **Wang Y**, Zhao Z, Ren Z, Zhao B, Zhang L, Chen J, Xu W, Lu S, Zhao Q, Peng J. Recellularized nerve allografts with differentiated mesenchymal stem cells promote peripheral nerve regeneration. *Neurosci Lett* 2012; **514**: 96-101 [PMID: 22405891 DOI: 10.1016/j.neulet.2012.02.066]
- 85 **Hu N**, Wu H, Xue C, Gong Y, Wu J, Xiao Z, Yang Y, Ding F, Gu X. Long-term outcome of the repair of 50 mm long median nerve defects in rhesus monkeys with marrow mesenchymal stem cells-containing, chitosan-based tissue engineered nerve grafts. *Biomaterials* 2013; **34**: 100-111 [PMID: 23063298 DOI: 10.1016/j.biomaterials.2012.09.020]
- 86 **Cuevas P**, Carceller F, Dujovny M, García-Gómez I, Cuevas B, González-Corrochano R, Díaz-González D, Reimers D. Peripheral nerve regeneration by bone marrow stromal cells. *Neurol Res* 2002; **24**: 634-638 [PMID: 12392196 DOI: 10.1179/016164102101200564]
- 87 **Cuevas P**, Carceller F, García-Gómez I, Yan M, Dujovny M. Bone marrow stromal cell implantation for peripheral nerve repair. *Neurol Res* 2004; **26**: 230-232 [PMID: 15072644 DOI: 10.1179/016164104225013897]
- 88 **Haghighat A**, Mohammadi R, Amini K. Transplantation of

- undifferentiated bone-marrow stromal cells into a vein graft accelerates sciatic nerve regeneration in streptozotocin induced diabetic rats. *Curr Neurovasc Res* 2014; **11**: 230-241 [PMID: 24845854 DOI: 10.2174/1567202611666140520124754]
- 89 **Mohammadi R**, Azizi S, Delirez N, Hobbenaghi R, Amini K, Malekhetabi P. The use of undifferentiated bone marrow stromal cells for sciatic nerve regeneration in rats. *Int J Oral Maxillofac Surg* 2012; **41**: 650-656 [PMID: 22154576 DOI: 10.1016/j.ijom.2011.10.028]
 - 90 **Fan L**, Yu Z, Li J, Dang X, Wang K. Schwann-like cells seeded in acellular nerve grafts improve nerve regeneration. *BMC Musculoskelet Disord* 2014; **15**: 165 [PMID: 24885337 DOI: 10.1186/1471-2474-15-165]
 - 91 **Keilhoff G**, Stang F, Goehl A, Wolf G, Fansa H. Transdifferentiated mesenchymal stem cells as alternative therapy in supporting nerve regeneration and myelination. *Cell Mol Neurobiol* 2006; **26**: 1235-1252 [PMID: 16779672 DOI: 10.1007/s10571-006-9029-9]
 - 92 **Raheja A**, Suri V, Suri A, Sarkar C, Srivastava A, Mohanty S, Jain KG, Sharma MC, Mallick HN, Yadav PK, Kalaivani M, Pandey RM. Dose-dependent facilitation of peripheral nerve regeneration by bone marrow-derived mononuclear cells: a randomized controlled study: laboratory investigation. *J Neurosurg* 2012; **117**: 1170-1181 [PMID: 23039144 DOI: 10.3171/2012.8.JNS111446]
 - 93 **Zuk PA**, Zhu M, Mizuno H, Huang J, Futrell JW, Katz AJ, Benhaim P, Lorenz HP, Hedrick MH. Multilineage cells from human adipose tissue: implications for cell-based therapies. *Tissue Eng* 2001; **7**: 211-228 [PMID: 11304456 DOI: 10.1089/107632701300062859]
 - 94 **Kokai LE**, Marra K, Rubin JP. Adipose stem cells: biology and clinical applications for tissue repair and regeneration. *Transl Res* 2014; **163**: 399-408 [PMID: 24361334 DOI: 10.1016/j.trsl.2013.11.009]
 - 95 **Strem BM**, Hicok KC, Zhu M, Wulur I, Alfonso Z, Schreiber RE, Fraser JK, Hedrick MH. Multipotential differentiation of adipose tissue-derived stem cells. *Keio J Med* 2005; **54**: 132-141 [PMID: 16237275 DOI: 10.2302/kjm.54.132]
 - 96 **Erba P**, Mantovani C, Kalbermatten DF, Pierer G, Terenghi G, Kingham PJ. Regeneration potential and survival of transplanted undifferentiated adipose tissue-derived stem cells in peripheral nerve conduits. *J Plast Reconstr Aesthet Surg* 2010; **63**: e811-e817 [PMID: 20851070 DOI: 10.1016/j.bjps.2010.08.013]
 - 97 **Santiago LY**, Clavijo-Alvarez J, Brayfield C, Rubin JP, Marra KG. Delivery of adipose-derived precursor cells for peripheral nerve repair. *Cell Transplant* 2009; **18**: 145-158 [PMID: 19499703]
 - 98 **Widgerow AD**, Salibian AA, Lalezari S, Evans GR. Neuromodulatory nerve regeneration: adipose tissue-derived stem cells and neurotrophic mediation in peripheral nerve regeneration. *J Neurosci Res* 2013; **91**: 1517-1524 [PMID: 24105674 DOI: 10.1002/jnr.23284]
 - 99 **Kingham PJ**, Kolar MK, Novikova LN, Novikov LN, Wiberg M. Stimulating the neurotrophic and angiogenic properties of human adipose-derived stem cells enhances nerve repair. *Stem Cells Dev* 2014; **23**: 741-754 [PMID: 24124760 DOI: 10.1089/scd.2013.0396]
 - 100 **Wei Y**, Gong K, Zheng Z, Wang A, Ao Q, Gong Y, Zhang X. Chitosan/silk fibroin-based tissue-engineered graft seeded with adipose-derived stem cells enhances nerve regeneration in a rat model. *J Mater Sci Mater Med* 2011; **22**: 1947-1964 [PMID: 21656031 DOI: 10.1007/s10856-011-4370-z]
 - 101 **Sowa Y**, Kishida T, Imura T, Numajiri T, Nishino K, Tabata Y, Mazda O. Adipose-Derived Stem Cells Promote Peripheral Nerve Regeneration In Vivo without Differentiation into Schwann-Like Lineage. *Plast Reconstr Surg* 2016; **137**: 318e-330e [PMID: 26818322 DOI: 10.1097/01.prs.0000475762.86580.36]
 - 102 **Tomita K**, Madura T, Sakai Y, Yano K, Terenghi G, Hosokawa K. Glial differentiation of human adipose-derived stem cells: implications for cell-based transplantation therapy. *Neuroscience* 2013; **236**: 55-65 [PMID: 23370324 DOI: 10.1016/j.neuroscience.2012.12.066]
 - 103 **Oliveira JT**, Almeida FM, Biancalana A, Baptista AF, Tomaz MA, Melo PA, Martinez AM. Mesenchymal stem cells in a polycaprolactone conduit enhance median-nerve regeneration, prevent decrease of creatine phosphokinase levels in muscle, and improve functional recovery in mice. *Neuroscience* 2010; **170**: 1295-1303 [PMID: 20800664 DOI: 10.1016/j.neuroscience.2010.08.042]
 - 104 **Orbay H**, Uysal AC, Hyakusoku H, Mizuno H. Differentiated and undifferentiated adipose-derived stem cells improve function in rats with peripheral nerve gaps. *J Plast Reconstr Aesthet Surg* 2012; **65**: 657-664 [PMID: 22137687 DOI: 10.1016/j.bjps.2011.11.035]
 - 105 **Fairbairn NG**, Meppelink AM, Ng-Glazier J, Randolph MA, Winograd JM. Augmenting peripheral nerve regeneration using stem cells: A review of current opinion. *World J Stem Cells* 2015; **7**: 11-26 [PMID: 25621102 DOI: 10.4252/wjsc.v7.i1.11]
 - 106 **Cheng LN**, Duan XH, Zhong XM, Guo RM, Zhang F, Zhou CP, Shen J. Transplanted neural stem cells promote nerve regeneration in acute peripheral nerve traction injury: assessment using MRI. *AJR Am J Roentgenol* 2011; **196**: 1381-1387 [PMID: 21606303 DOI: 10.2214/AJR.10.5495]
 - 107 **Mauricio AC**, Gartner A, Armada-da-Silva P, Amado S, Pereira T, Veloso AP. Cellular Systems and Biomaterials for Nerve Regeneration in Neurotmesis Injuries. *InTech* 2011 [DOI: 10.5772/24247]
 - 108 **Matsuse D**, Kitada M, Kohama M, Nishikawa K, Makinoshima H, Wakao S, Fujiyoshi Y, Heike T, Nakahata T, Akutsu H, Umezawa A, Harigae H, Kira J, Dezawa M. Human umbilical cord-derived mesenchymal stromal cells differentiate into functional Schwann cells that sustain peripheral nerve regeneration. *J Neuropathol Exp Neurol* 2010; **69**: 973-985 [PMID: 20720501 DOI: 10.1097/NEN.0b013e3181eff6dc]
 - 109 **Kuroda Y**, Kitada M, Wakao S, Dezawa M. Mesenchymal stem cells and umbilical cord as sources for schwann cell differentiation: their potential in peripheral nerve repair. *TOTERMJ* 2011; **4**: 54-63 [DOI: 10.2174/1875043501104010054]
 - 110 **Pereira T**, Gärtner A, Amorim I, Almeida A, Caseiro AR, Armada-da-Silva PA, Amado S, Fregnan F, Varejão AS, Santos JD, Bartolo PJ, Geuna S, Luís AL, Mauricio AC. Promoting nerve regeneration in a neurotmesis rat model using poly(DL-lactide-ε-caprolactone) membranes and mesenchymal stem cells from the Wharton's jelly: in vitro and in vivo analysis. *Biomed Res Int* 2014; **2014**: 302659 [PMID: 25121094 DOI: 10.1155/2014/302659]
 - 111 **Peng J**, Wang Y, Zhang L, Zhao B, Zhao Z, Chen J, Guo Q, Liu S, Sui X, Xu W, Lu S. Human umbilical cord Wharton's jelly-derived mesenchymal stem cells differentiate into a Schwann-cell phenotype and promote neurite outgrowth in vitro. *Brain Res Bull* 2011; **84**: 235-243 [PMID: 21194558 DOI: 10.1016/j.brainresbull.2010.12.013]

P- Reviewer: Feng ZL, Isik AT, Zeng LF **S- Editor:** Ji FF
L- Editor: A **E- Editor:** Lu YJ





Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>

