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Chapter

Strategies to Repair Spinal Cord Injuries: Single Vs. Combined Treatments

Vinnitsa Buzoianu-Anguiano and Ismael Jiménez Estrada

Abstract

Several experimental strategies have been developed in past years for the repair of damages evoked in axons, myelin, and motor functions by spinal cord injuries. This chapter briefly reviews some of such strategies. On the one hand, it examines individual procedures, such as: tissue or cell transplants (i.e. evolving cells of the olfactory glia or mesenchymal cells), implants of biomaterials (fibrine and chitosan), application of enzymes (chondroitinase and ChABC), growth factors (brain-derived neurotrophic factor, BDNF; neurotrophin-3, NT-3; or glial-derived neurotrophic factor, GDNF), and drugs (myocyclines or riluzole) among others, that induce different recovery degrees in axonal regeneration, myelination, and motor performance in experimental animals. On the other hand, it also examines the recent strategy of combining some of the previous experimental procedures to potentialize the positive effects evoked by each one in experimentally spinal cord lesioned animals and explores the possible use of this strategy in future preclinical research for the treatment of spinal cord lesions.

Keywords: spinal cord injury, cell therapy, tissue transplants, biomaterials, axonal regeneration, neuroprotection, remyelination, motor function, exogen factors

1. Introduction

It is known that the regenerative potential of the central nervous system (CNS) is limited by both extrinsic and intrinsic factors, which restrict axonal growth in adult animals. These factors include proteins associated with myelin or with the formation of a fibroglial scar, which creates a physical and chemical barrier. This barrier secretes factors from the extracellular matrix that prevents axonal growth after a traumatic spinal cord injury (TSCI) [1].

Among the myelin-associated molecules, there are NogoA, myelin-associated glycoprotein (MAG), and oligodendrocyte-associated glycoprotein (OMgp). It has been shown that, after a TSCI, these proteins favor the inhibition of axonal and neuritic growth as well as the formation of collaterals. In addition, they can form aberrant connectivity [2].

The inhibitory activity of NogoA, MAG, and Omgp after a TSCI occurs by the activation of these proteins by binding to their NGR1 receptor, which can be anchored to the GPI protein (**Figure 1**). This receptor has been reported to be specific for these proteins, promoting the inhibitory effect for axonal growth after TSCI [3]. When

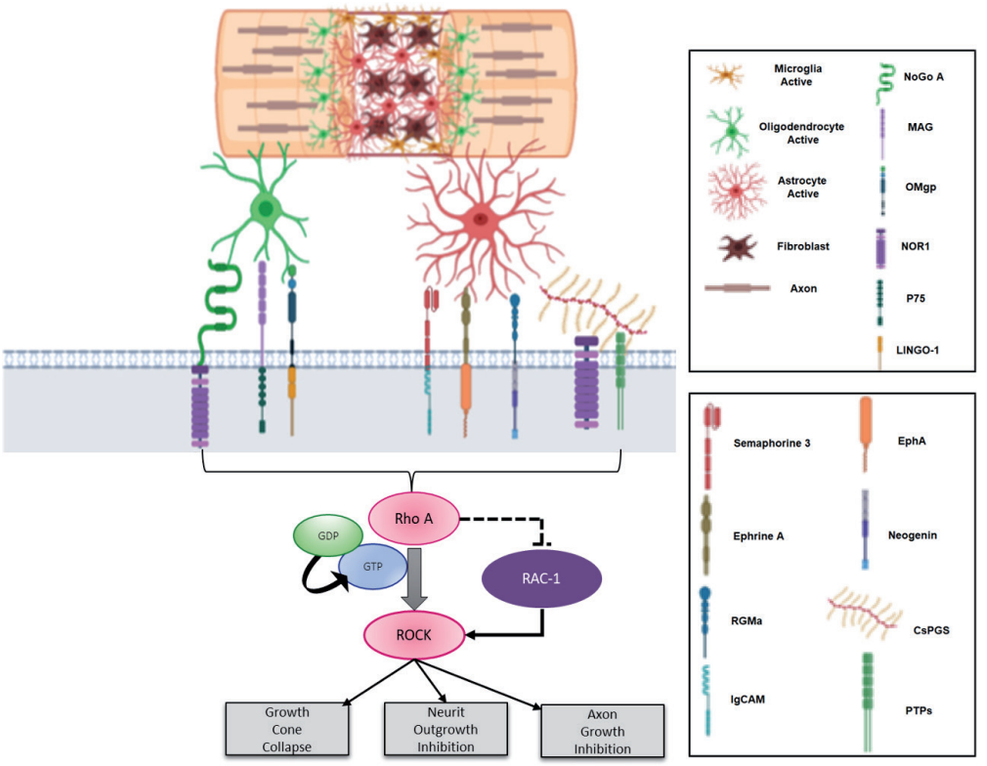

Figure 1.
Molecules that inhibit axonal growth. After a TSCI in the injury area, a fibroglial scar forms forming a physical barrier preventing axonal growth. At the same time, a chemical barrier is initiated by the activation of molecules such as MAG, NogoA, and OMgp secreted by reactive oligodendrocytes, which bind with their NGR1, P75, and Lingo receptors; or molecules secreted by reactive astrocytes such as Semaforin 3, Ephrine A, RGMa, and CsPG that also bind to their receptors such as IgCAM, EphA, Neoginine, NGR1, and PTPs; the union of these receptors with their ligands causes the activation of the RhoA pathway by GDP-GTP phosphorylation promoting the activation of ROCK kinase favoring the collapse of the axonal cone, inhibition of neuritic growth, and inhibition of axonal growth.

NgR1 is anchored to its GPI protein, in its intracellular domain, different co-receptors are activated that favor the activation of axonal inhibition signaling. In this activation, the two molecules P75 (molecule belonging to the TNF receptor) and TOY (LINGO-1) are involved. Activation of this co-receptor complex favors the activation of a RhoA kinase, which activates another ROCK kinase, in turn promoting the activation of LIM. This LIM kinase can activate the cofilin factor, thus causing the collapse of the axonal cone and depolymerization of the actin filaments [3, 4].

On the other hand, the glial reaction, which happens after the injury, promotes the recruitment of the microglia, oligodendrocyte precursors, meninges cells, and astrocytes in their reactive form at the site of the injury [5]. The result of this cell migration is the formation of a physical barrier, the fibroglial scar, which has the function of isolating the area of injury from the rest of the tissue, secreting factors that cause axonal growth to be inhibited in order to avoid aberrant connectivity. The factors that are present in the glial scar are: tenacines, semaphorins, ephrines, and chondroitin sulfate proteoglycans [1]. These molecules that are expressed from the extracellular matrix after a TSCI promote inhibition of axonal and neuritic growth as well as collapse of the axonal cone [6, 7].

The activation of all these molecules is due to an RHO-(RhoA) kinase; by activating the RhoA signaling pathway, it causes a decrease in the activity of RAC1 kinase, through binding to the PTP receptor (transmembrane protein tyrosine phosphatase), in addition to LAR and NGR1 and 3 leukocyte-related phosphatase. This causes RhoA to be phosphorylated from Rho-GDP to Rho-GTP, activating ROCK kinase, thereby promoting inhibition of axonal growth (**Figure 1**; [6, 7]).

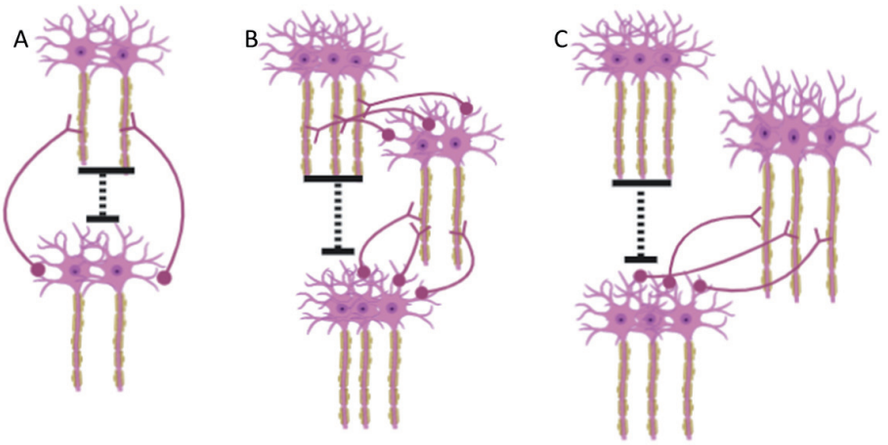

Figure 2.
Diagram of the proposed strategies for reinnervation after a spinal cord injury. (A) Long distance axonal regeneration; (B) short-distance regeneration; (C) growth of preserved axons.

Other molecules that intervene in the repulsive environment after a TSCI are the axonal repulsive guidance molecules (RGM), especially the RGMa isoform, which inhibits neuritic growth present at the site of injury (**Figure 1**). It can also cause poor axonal growth and loss of functionality [6, 8]. RGMa is activated when it binds to its neoginin receptor, causing an activation of RHO-GEF (guanine exchange factor), which in turn activates RhoA kinase. This sparks the activation of another ROCK kinase through the phosphorylation of a GTP (guanosine triphosphate). This in turn triggers the regulation of various proteins such as MCL (myosin light chain), which promotes the inhibition of neuritic growth, the LIM kinase, which causes the activation of the actin and cofilin polymerization factor, and CRMP-2 (collapsing 2 response mediator protein), which causes inhibition of neuritic growth and inhibition of axonal growth [6].

As we have seen, all these signals foster a repulsive environment for axonal growth after a spinal cord injury, which nullifies the regenerative capacity of the CNS. Some hypotheses have been proposed for reinnervation after a spinal cord injury: (1) long-distance regeneration via creating an appropriate synaptic connection by branching off new axons, which could make new connections with target cells, from originally damaged axons; (2) short-distance regeneration via enabling the formation of collateral branches that can form synaptic contacts with neighboring cells, which, in turn, can connect with the target cells of the damaged axons; and (3) growth of preserved axons which can maintain a connection with the target cells from the site of injury (**Figure 2**) [3].

2. Simple treatments that improve axonal regeneration and locomotive function

Based on the previous hypotheses, strategies have been designed with, among others, tissue transplants, biomaterials, cell therapies, and exogenous factors to favor axonal regeneration, remyelination, and improvement of locomotor function in animal models with a TSCI. We will discuss some of these strategies in this chapter.

Predegenerated peripheral nerve (PPN) transplants have been used to repair injuries to the peripheral nervous system (PNS), by being used as a bridge to promote axonal regeneration and re-functionalization [9], favoring axonal regeneration and refunctionalization after a TSCI, since they act as a neuroprotector in the

medulla after transplanting it [10]. Moreover, it helps as a guide for axons to grow through the nerve and connect to both proximal and distal axons [11–14].

Axonal growth occurs due to the permissive microenvironment derived from Schwann cells and macrophages present in PPNs, which secrete growth factors such as GDNF, BDNF, NGF, NT-3, NT-4, and GM-CS [15–17]. In addition, Schwann cells form Bügner bands, which support axonal growth [18–20].

3. Use of inert bridges

The use of biomaterial bridges has been an attractive alternative for neuroregeneration. Inert bridges are temporary structures that support cell and tissue growth. These materials are biodegradable, they can foster mechanical strength, they can be fibers or porous channels, and they have the capacity of cell adhesion [21]. Hydrogels, which are biocompatible implants for repair after a TSCI, also form bridges for regeneration as well as preventing fibroglial scar formation, thus promoting a permissive environment for regeneration. Third-dimensional nanofibers have also been designed, which provide better cell adhesion and promote migration, cell proliferation, and differentiation [21].

These bridges can be made of biological materials such as collagen or fibronectin; or of natural polymers such as alignate, agarose, or chitosan; or they can also be composed of synthetic polymers such as polyhydroxy- , poly-2-hydroxyethylmethacrylate, or polyethylene glycol [22, 23].

It has been shown that these materials in TSCI models (contusions, transection, or hemisections) can favor and direct axonal growth, since they act as bridges [24, 25]. They have also been found to be compatible when used in combination with other treatments such as cell or trophic factors, promoting a permissive environment for this axonal growth [26–28]. Furthermore, it has been observed that they help the adhesion of oligodendrocytes, or Schwann cells, thus favoring remyelination of damaged axons [29].

4. Cellular therapy

The term cellular therapy (CT) refers to any type of strategy that uses cells as a therapeutic agent. Neural transplantation has been used to repair injured SC in both acute and chronic phases. The use of cell transplants has been a positive alternative for axonal regeneration. Different cell types have been used during these transplants such as: Schwann cells, olfactory ensheathing glia (OEG) cells, embryonic stem cells, hematopoietic cells, neural stem cells and bone marrow stromal cells (BMSCs) [30].

4.1 Schwann cells

In the PNS, unlike the CNS, regeneration is efficient due to the presence of Schwann cells (Cs). Cs have been used to perform transplants in different animal models since they are capable of: engulfing cellular debris, producing trophic factors necessary for the survival of the neuron (especially brain-derived neurotrophic factor (BDNF) and neurotrophin 4/5 (NT4/5)), secreting cell matrices of inhibitory molecules that help axonal regrowth, and producing myelin layers to envelop the naked axons and increase the impulse speed of nerve cells to improve their functioning [31]. In rodent models, Cs implants have been shown to foster remyelination, thus improving motor functions in contusion and complete section

injuries [32, 33]. Combination with other materials has also been shown to help guide axonal regrowth after a TSCI [34, 35].

4.2 Olfactory ensheathing glia cells

Olfactory ensheathing glia cells (OEG) are a type of glial cells that are present in the olfactory system of adult mammals. In both acute and chronic injuries, OEGs have been shown to have the ability to promote axonal regeneration and help restore axonal conduction after TSCI [36].

Ramón-Cueto et al. demonstrated that OEG aided in the regrowth of sensory axons after spinal injury [37]. Doucette et al. described the survival of the OEG after having transplanted them in brain [38]. In contusion and transection models, the ability of OEGs to help protect the tissue after transplantation has been demonstrated, since they promote axonal growth and favor the improvement of locomotor function [39, 40]. OEGs have been said to have similar properties to Schwann cells and astrocytes, which make them unique. This cell type has two important benefits: they can exist both inside and outside the central nervous system, and they can be in constant neurogenesis, producing sensitive neurons in both embryonic and adult stages in mammals [41].

4.3 Mesenchymal cells

Mesenchymal stem cells, or mesenchymal stromal cells (MSCs), are adult multipotent cells that have the capacity for self-renewal, proliferation, and differentiation. MSCs are an alternative for the experimental treatment of a spinal cord injury (contusions, transection, or ischemia). They have shown that they favor axonal regeneration and improve locomotor function [42–45]. They also have the ability to form bridging cell bundles at the TSCI epicenter [45–48] and can be differentiated both in vitro and in vivo in neurons, astrocytes, oligodendrocytes, Schwann cells, and microglia [49, 50].

Vaquero and colleagues have observed that after a TSCI, the use of MSCs and Schwann cells as therapy was beneficial not only because they observed axonal regeneration, but also because at different times (up to 9 months with transplantation), animals with severe contusions eventually recovered locomotive function (with a score of 16 on the BBB scale) [51–55]. Other studies have shown that MSCs give positive results when used in diseases or damage the nervous system by secreting growth factors such as neural growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), and hepatocyte growth factor (HGF). They can also secrete cytokines such as interleukin-6 (IL-6), colony stimulating factor 1 (CSF-1), monocyte chemoattractant protein (MCP), colony stimulating factor (CSF), and stromal cell derived factor (SDF-1) [42, 56]. In addition, they promote angiogenesis, proliferate after transplantation, aid neuronal survival, and decrease apoptosis [56]. Moreover, another important factor of MSCs is the immunomodulatory effect, since they are capable of secreting soluble inflammatory-mediating factors such as indolamine 2–3 dioxygenase (IDO), inducible nitric oxide synthase (iNOS), and homo-oxygenase 1. They can also secrete the human leukocyte G antigen, transforming factor (TGF-), interleukin 6 (IL-6), and prostaglandin E2. These soluble factors promote the inhibition of CD4+CD8+ T cells [57]. It has been shown in contusions and compressions that using MSCs helps decrease proinflammatory cytokines such as TNF- and IL-6, and promotes the secretion of anti-inflammatory cytokines such as IL-4, IL-10, and IL-13, which promotes the activation of M2 macrophages by fostering a neuroprotective environment [58, 59].

5. Exogenous factors

Neurotrophins are structural proteins consisting of four families, which are involved in events in the development of the CNS such as survival, differentiation, and axonal growth. Among these, we find neuronal growth factor NGF, neurotrophin 3 (NT-3), neurotrophin 4/5 (NT-4/5), and brain-derived growth factor (BDNF). These neurotrophins bind directly to Trk receptors (tropomycin kinase receptors): NGF binds to its TrkA receptor, BDNF and NT4/5 bind to the same TrkB receptor, and NT-3 binds to its TrkC receptor. They also have a high affinity for the p75 receptor, NTR [60].

Studies on contusions, transections, and hemisections have shown that the most studied neurotrophins are BDNF and NT-3. The use of BDNF has been seen to promote neuroprotection, form collateral branches, and promote plasticity [61]. It also favors axonal growth, thus improving locomotor function [62, 63]. Moreover, in different models of contusion, transection, and hemisections, it was demonstrated that the exogenous use of NT-3 favors axonal regrowth and improvement of locomotor function [64, 65].

As for NGF and NT4/5, they are the least studied within TSCI models. NGF has been shown to promote the growth of sensory axons [66, 67], and in a contusion study, it reduced neuronal death, thus promoting an improvement in locomotive function [68]. NT4/5, like BDNF, can promote neuroprotection and axonal growth in a full-section model [69].

Another factor used chondroitinase ABC (ChABC), an enzyme from the bacteria *Proteus Vulgaris*. ChABC can bind to the chains of the GAG glycosaminoglycans, within the disaccharides, which favors the digestion of chondroitin sulfates (CSPGs) [70]. It has been seen that both in hemisection and transection models, this enzyme favors axonal growth [71, 72]. Moreover, in the presence of growth factors such as NT-3 and BDNF, it promotes the proliferation of oligodendrocytes, increasing remyelination and favoring improvement in locomotor function [71, 73, 74].

6. Pharmacological use

Successful drug trials on animals have been carried out and have advanced to human clinical trials; however, none of them has shown a clear improvement on patients. Some of the drugs used in TSCIs will be mentioned.

Methylprednisolone (MPP) is a synthetic steroid from the glucocorticoid group, which is used for its immunosuppressive and anti-inflammatory properties. Its mechanism of action is to inhibit the formation of arachidonic acid and decrease inflammation. In studies of animals with a TSCI, it has been observed that the administration of MPP favors the reduction of apoptosis. It also induces the interaction with the glucocorticoid receptor HIF-1 , which decreases the damage of oligodendrocytes [75]. In clinical studies with acute injuries, the use of MPP has been shown to improve functionality and sensitivity when compared to patients who only took the placebo [76–78].

Another drug used is riluzole, a benzothiasilic anticonvulsant, which acts as a blocker of sodium channels. Fehlings and colleagues compared the effect of riluzole with phenytoin in an acute contusion injury model, where they observed promoted functional recovery [79]. In studies with patients with acute injury, riluzole has been observed to prompt sensory and locomotor improvement [80].

Minocycline, a second-generation synthetic tetracycline, has also been used as an antibacterial agent. This medication can stay in the CNS longer than the usual tetracycline since it can cross the blood-brain barrier. It can act as a neuroprotector

Biomaterials. 2009;**30**:169-179. DOI: 10.1016/j.biomaterials.2008.09.017

[16] Höke A, Gordon T, Zochodne DW, Sulaiman OAR. A decline in glial cell-line-derived neurotrophic factor expression is associated with impaired regeneration after long-term Schwann cell denervation. Experimental Neurology. 2002;**173**:77-85. DOI: 10.1006/exnr.2001.7826

[17] Michalski B, Bain JR, Fahnestock M. Long-term changes in neurotrophic factor expression in distal nerve stump following denervation and reinnervation with motor or sensory nerve. Journal of Neurochemistry. 2008;**105**:1244-1252. DOI: 10.1111/j.1471-4159.2008.05224.x

[18] Ribeiro-Resende VT, Koenig B, Nichterwitz S, Oberhoffner S, Schlosshauer B. Strategies for inducing the formation of bands of Büngner in peripheral nerve regeneration. Biomaterials. 2009;**30**:5251-5259. DOI: 10.1016/j.biomaterials.2009.07.007

[19] Tom VJ, Houle JD. Peripheral nerve graft-mediated axonal regeneration. In: Neural Regeneration. Elsevier Inc.; 2015. DOI: 10.1016/B978-0-12-801732-6.00019-7

[20] Zhang Y, Campbell G, Anderson PN, Martini R, Schachner M, Lieberman AR. Molecular basis of interactions between regenerating adult rat thalamic axons and Schwann cells in peripheral nerve grafts. I. Neural cell adhesion molecules. The Journal of Comparative Neurology. 1995;**361**:193-209. DOI: 10.1002/cne.903610202

[21] Tsintou M, Dalamagkas K, Seifalian AM. Advances in regenerative therapies for spinal cord injury: A biomaterials approach. Neural Regeneration Research. 2015;**10**:726-742. DOI: 10.4103/1673-5374.156966

[22] Raspa A, Pugliese R, Maleki M, Gelain F. Recent therapeutic approaches for spinal cord injury. Biotechnology and Bioengineering. 2015;**113**:253-259. DOI: 10.1002/bit.25689

[23] Sakiyama-Elbert S, Johnson PJ, Hodgetts SI, Plant GW, Harvey AR. Scaffolds to promote spinal cord regeneration. In: Handbook of Clinical Neurology. 1st ed. Elsevier B.V; 2012. DOI: 10.1016/B978-0-444-52137-8.00036-X

[24] GÜnther MI, Weidner N, MÜller R, Blesch A. Cell-seeded alginate hydrogel scaffolds promote directed linear axonal regeneration in the injured rat spinal cord. Acta Biomaterialia. 2015;**27**:140-150. DOI: 10.1016/j.actbio.2015.09.001

[25] Tsai EC, Dalton PD, Shoichet MS, Tator CH. Matrix inclusion within synthetic hydrogel guidance channels improves specific supraspinal and local axonal regeneration after complete spinal cord transection. Biomaterials. 2006;**27**:519-533. DOI: 10.1016/j.biomaterials.2005.07.025

[26] Taylor L, Jones L, Tuszynski MH, Blesch A. Neurotrophin-3 gradients established by lentiviral gene delivery promote short-distance axonal bridging beyond cellular grafts in the injured spinal cord. The Journal of Neuroscience. 2006;**26**:9713-9721. DOI: 10.1523/JNEUROSCI.0734-06.2006

[27] Tobias CA, Han SSW, Shumsky JS, Kim D, Tumolo M, Dhoot NO, et al. Alginate encapsulated BDNF-producing fibroblast grafts permit recovery of function after spinal cord injury in the absence of immune suppression. Journal of Neurotrauma. 2005;**22**:138-156. DOI: 10.1089/neu.2005.22.138

[28] Zhang J, Lu X, Feng G, Gu Z, Sun Y, Bao G, et al. Chitosan scaffolds induce human dental pulp stem cells to neural

differentiation: Potential roles for spinal cord injury therapy. Cell and Tissue Research. 2016;**12**:1-14. DOI: 10.1007/s00441-016-2402-1

[29] King VR, Phillips JB, Hunt-Grubbe H, Brown R, Priestley JV. Characterization of non-neuronal elements within fibronectin mats implanted into the damaged adult rat spinal cord. Biomaterials. 2006;**27**:485-496. DOI: 10.1016/j.biomaterials.2005.06.033

[30] Watt FM, Driskell RR. The therapeutic potential of stem cells. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences. 2010;**365**:155-163. DOI: 10.1098/rstb.2009.0149

[31] Garza-Castro OD, Martínez-Rodríguez HG, Gabriela S. Schwann cell precursor transplant in a rat spinal cord injury model. Revista de Investigacion Clinica. 2018;**70**:88-95. DOI: 10.24875/RIC.18002466

[32] Guest JD, Rao A, Olson L, Bunge MB, Bunge RP. The ability of human Schwann cell grafts to promote regeneration in the transected nude rat spinal cord. Experimental Neurology. 1997;**148**:502-522. DOI: 10.1006/exnr.1997.6693

[33] Zurita M, Aguayo C, Bonilla C, Vaquero J. Co-cultivo de células madre adultas mesenquimales y células de Schwann en presencia de membranas de policarbonato. Neuroscience Letters. 2007;**5**:103-109

[34] Liu S, Sandner B, Schackel T, Nicholson L, Chtarto A, Tenenbaum L, et al. Regulated viral BDNF delivery in combination with Schwann cells promotes axonal regeneration through capillary alginate hydrogels after spinal cord injury. Acta Biomaterialia. 2017;**1**:1-14. DOI: 10.1016/j.actbio.2017.07.024

[35] Oudega M, Xu X-M. Schwann cell transplantation for repair of the adult spinal cord. Journal of Neurotrauma. 2006;**23**:453-467. DOI: 10.1089/neu.2006.23.453

[36] Lim PAC, Tow AM. Recovery and regeneration after spinal cord injury: A review and summary of recent literature. Annals of the Academy of Medicine, Singapore. 2007;**36**:49-57

[37] Ramón-Cueto A, Plant GW, Avila J, Bunge MB. Long-distance axonal regeneration in the transected adult rat spinal cord is promoted by olfactory ensheathing glia transplants. The Journal of Neuroscience. 1998;**18**:3803-3815

[38] Smale KA, Doucette R, Kawaja MD. Implantation of olfactory ensheathing cells in the adult rat brain following fimbria-fornix transection. Experimental Neurology. 1996;**137**:225-233

[39] López-Vales R, Forés J, Navarro X, Verdú E. Chronic transplantation of olfactory ensheathing cells promotes partial recovery after complete spinal cord transection in the rat. Glia. 2007;**55**:303-311. DOI: 10.1002/glia.20457

[40] Torres-Espín A, Redondo-Castro E, Hernández J, Navarro X. Bone marrow mesenchymal stromal cells and olfactory ensheathing cells transplantation after spinal cord injury—A morphological and functional comparison in rats. The European Journal of Neuroscience. 2014;**39**:1704-1717. DOI: 10.1111/ejn.12542

[41] Mackay-sim A. Olfactory ensheathing cells and spinal cord repair. Glia. 2005;**54**:8-14

[42] Lu P, Jones LL, Tuszynski MH. BDNF-expressing marrow stromal cells

Neuroscience. 2005;**11**:308-322. DOI: 10.1177/1073858405275175

[82] Casha S, Zygun D, McGowan MD, Bains I, Yong VW, John Hurlbert R. Results of a phase II placebo-controlled randomized trial of minocycline in acute spinal cord injury. Brain. 2012;**135**:1224-1236. DOI: 10.1093/brain/aws072

[83] Feng S-Q, Zhou X-F, Rush RA, Ferguson IA. Graft of pre-injured sural nerve promotes regeneration of corticospinal tract and functional recovery in rats with chronic spinal cord injury. Brain Research. 2008;**1209**:40-48. DOI: 10.1016/j.brainres.2008.02.075

[84] Fausto PG, Soares JG, de Freitas LM, de Paiva Cavalcanti JRL, Oliveira FG, Araujo JF, et al. Sciatic nerve grafting and inoculation of FGF-2 promotes improvement of motor behavior and fiber regrowth in rats with spinal cord transection. Restorative Neurology and Neuroscience. 2012;**30**:265-275. DOI: 10.3233/RNN-2012-110184

[85] Kuo H-S, Tsai M-J, Huang M-C, Chiu C-W, Tsai C-Y, Lee M-J, et al. Acid fibroblast growth factor and peripheral nerve grafts regulate Th2 cytokine expression, macrophage activation, polyamine synthesis, and neurotrophin expression in transected rat spinal cords. The Journal of Neuroscience. 2011;**31**:4137-4147. DOI: 10.1523/JNEUROSCI.2592-10.2011

[86] Luo J, Zhang H, Jiang X, Xue S, Ke Y. Combination of bone marrow stromal cell transplantation with mobilization by granulocyte-colony stimulating factor promotes functional recovery after spinal cord transection. Acta Neurochirurgica. 2009;**151**:1483-1492. DOI: 10.1007/s00701-009-0402-6

[87] Lee SH, Kim Y, Rhew D, Kuk M, Kim M, Kim WH, et al. Effect of the combination of mesenchymal stromal cells and chondroitinase ABC on chronic spinal cord injury. Cytotherapy. 2015;**17**:1374-1383. DOI: 10.1016/j.jcyt.2015.05.012

[88] Buzoianu-AnguianoV,Orozco-SuárezS, García-Vences E, Caballero-Chacón S, Guizar-Sahagún G, Chavez-Sanchez L, et al. The morphofunctional effect of the transplantation of bone marrow stromal cells and predegenerated peripheral nerve in chronic paraplegic rat model via spinal cord transection. Neural Plasticity. 2015:2015. DOI: 10.1155/2015/389520

[89] Buzoianu-Anguiano V, Rivera-Osorio J, Orozco-Suárez S, Angélica V-G, Elisa G-V, Stephanie S-T, et al. Single vs. combined therapeutic approaches in rats with chronic spinal cord injury. Frontiers in Neurology. 2020;**11**:1-11. DOI: 10.3389/fneur.2020.00136

[90] Badhiwala JH, Wilson JR, Kwon BK, Casha S, Fehlings MG. A review of clinical trials in spinal cord injury including biomarkers. Journal of Neurotrauma. 2018;**35**:1906-1917. DOI: 10.1089/neu.2018.5935

[91] Donovan J, Kirshblum S. Clinical trials in traumatic spinal cord injury. Neurotherapeutics. 2018;**15**:654-668. DOI: 10.1007/s13311-018-0632-5

[92] Kim YH, Ha KY, Kim SI. Spinal cord injury and related clinical trials. Clinics in Orthopedic Surgery. 2017;**9**:1-9. DOI: 10.4055/cios.2017.9.1.1

[93] Ahuja CSFM. Concise review: Bridging the gap: Novel neuroregenerative and neuroprotective strategies in spinal cord injury. Stem Cells Translational Medicine. 2015:1131-1143. DOI: 10.5966/sctm.2013-0207

[94] Badhiwala JH, Ahuja CS, Fehlings MG. Time is spine: A review of translational advances in spinal