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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

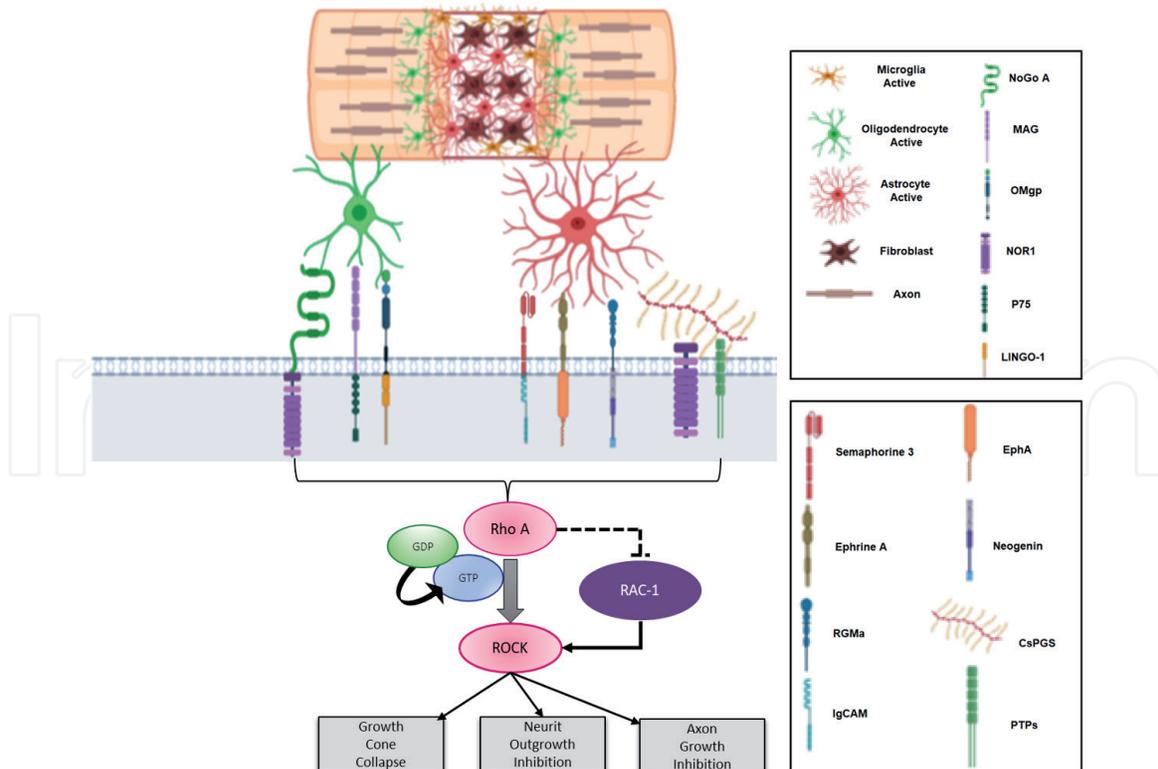


Figure 1.

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 Semaphorin 3, Ephrine A, RGMa, and CsPG that also bind to their receptors such as IgCAM, EphA, Neogenine, 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 α 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]).

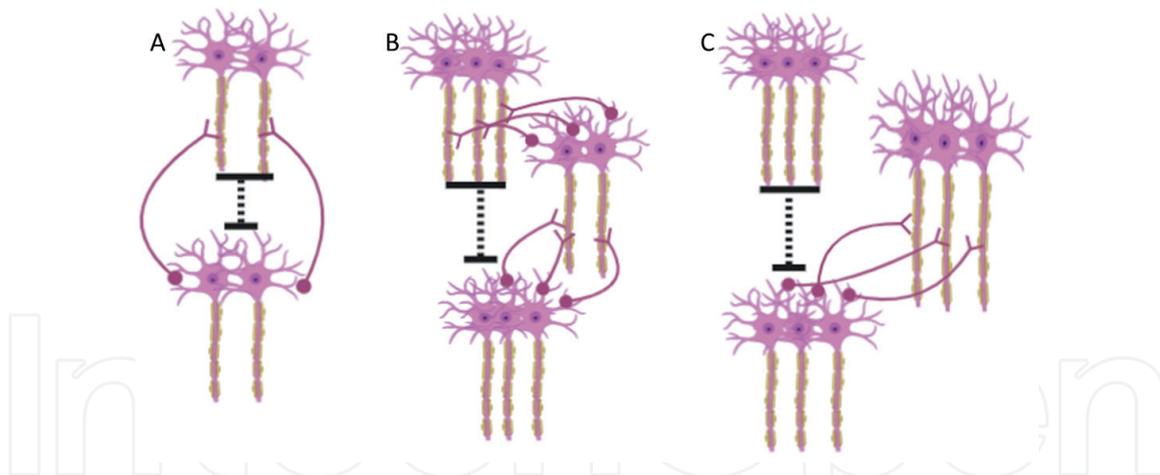


Figure 2.
Diagram of the proposed strategies for reinnervation after a spinal cord injury. (A) Long distance axonal regeneration; (B) short-distance regeneration; (C) growth of preserved axons.

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 alginate, agarose, or chitosan; or they can also be composed of synthetic polymers such as polyhydroxy- α , 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 β (TGF- β), 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- α 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 (tropomyosin 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 is 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 TSIs 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 α , 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 benzothiazilic 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

by reducing inflammation and preventing cell death [81]. In studies with patients with acute cervical and thoracic injuries, it was observed that the administration of minocycline did not cause side effects in patients. Additionally, in patients with cervical injuries, it improved locomotor function when compared to patients who took only the placebo. However, in patients with thoracic lesions, no changes were observed. In this study, it was concluded that the effect of minocycline with more patients should be evaluated to verify its efficacy [82].

7. Combined treatments

As described in previous paragraphs, the use of different strategies as simple treatments in TSCI models promotes neuroprotection, axonal growth, and remyelination of damaged axons, and facilitates the improvement of locomotor function. Therefore, it has been determined that the combination of different strategies should be able to more effectively facilitate axonal growth and remyelination, helping to increase locomotor function.

The effect of using PPN transplantation in combination with ChABC or growth factors has been evaluated. It was shown that the animals with combined treatment had a greater number of regenerated axons and an increase in the improvement of locomotor function, unlike those animals with simple treatment [83, 84]. It was also demonstrated that by, in comparison with single treatments, combining PPN with FGF α , and PPN with ChABC, a favorable microenvironment was formed, increasing axonal growth [11, 85].

The effect of MSCs combined with chitosan bridges or with growth factors such as the granulocyte colony-stimulating factor (G-CSF) has also been studied, and it was observed that animals on combined treatments, compared to simple treatments, had greater axonal growth, thus improving locomotor function [46, 86]. In a chronic phase compression model, the combination of MSCs with ChABC increased axonal growth in comparison to single treatments [87].

It was also observed that animals, after 2 months of PPN and MSC transplants in a full-section model, had a greater number of growing axons by detecting GAP43 as well as an improvement in remyelination by detection of PBM and by electron microscopy, unlike animals treated with simple transplantation [88]. When making a triple combination of PPN with MSCs and ChABC, an increase in axonal regeneration was observed after 3 months, improving locomotor function [89].

On the other hand, the combination of ChABC with growth factors such as BDNF and NT-3 can promote greater axonal growth and favor the proliferation of oligodendrocytes, thus increasing remyelination compared to animals that only had separate treatments [71, 73, 74]. Also, in a full section model in the acute phase, the combination of ChABC with NT-3 increased axonal growth and improved locomotor function, unlike groups with single treatments [73]. It was also demonstrated in a chronic transection model that a ChABC injection with rehabilitation inhibited the formation of chondroitin sulfates, promoting increased axonal growth, unlike single treatment groups [72].

8. Clinical trials

Independent of the type of traumatic spinal lesion (contusion, compression, or sectioning), the treatment of a spinal cord injury patient often begins at the site of the accident. Emergency personnel must gently and quickly immobilize and check the vital signs (urine retention, respiratory, and cardiovascular difficulty and formation

Treatment	Function	Advantages	Disadvantages	References
Neuroprotective				
Methylprednisolone	Corticosteroid drug that reduces inflammation	It has been shown in patients with complete SCI that improves locomotor function	Adverse events, infections, pneumonia, sepsis	[90–92]
Minocycline	Tetracycline, second generation antibiotics, with anti-inflammatory, antioxidant and anti-apoptotic effects	In patients with incomplete acute lesions, only very few present improvements in motor functions	No side effects are present	[90–92]
Riluzole	Anti-epileptic drug that blocks excitotoxic, blocking sodium channels	Increased motor function of patients with incomplete acute injuries	Increments of liver enzymes	[90–92]
Gacycline	NMDA receptor agonist	Patients with incomplete acute injuries showed no motor or sensory improvement	No adverse effects	[90–92]
Neuroregenerative				
FGF	Growth factor that binds to heparin protein and stimulates axonal regeneration, survival of neurons and decreases the fibroglial scar	No changes in motor and sensory function were observed in patients with complete spinal cord lesions	No side effects	[91, 93–95]
Cethrine	Transferase C3, toxin produced by Clostridium botulinum that blocks Rho kinase	Promotes axonal regeneration and improves the motor function of patients with complete acute phase injuries	No adverse effects	[91, 93–95]
Anti-Nogo A	Nogo A is a myelin protein that inhibits neuronal growth. Anti-NogoA antibody that inhibits Nogo A and promotes axonal regeneration	In patients with complete acute phase injuries, they showed no differences in motor and sensory function	No adverse effects	[91, 93–95]
Ganglioside GM1	Gangliosides— acidic glycoproteins present in cell membranes, which favor axonal regeneration	In patients with incomplete acute injuries improves motor function	No adverse effects	[91, 93–95]
Schwann cells	Myelinating cells that function as an axonal support. They favor the myelination of axons in the PNS	In patients with chronic complete injury it has been shown to promote motor and sensory recovery	Produce few adverse effects, muscle spasms and non-permanent paresthesia	[91, 93–95]

Treatment	Function	Advantages	Disadvantages	References
Olfactory ensheathing cells	Glial cells, with astrocyte properties. Promote axonal regeneration and improves locomotor function	In patients with chronic complete injuries showed scarce improvement in motor function	No adverse effects	[91, 93–95]
Mesenchymal cells	Induce the secretion of growth factors and promotes axonal regeneration, myelination and improvement of function	In patients with chronic complete injuries, it has been shown to promote motor improvement	No adverse effects	[91, 93–95]
Neural precursor cells	Multipotent CNS cells that reduce inflammation, promote cell replacement, and promote axonal regeneration	Patients with complete chronic injuries shows few improvements in motor function	No adverse effects	[91, 93–95]
Oligodendrocyte progenitor cells	They are able to secrete growth factors, promote axonal myelination and improved locomotor function	In patients with chronic complete injuries improves their motor function	No adverse effects	[91, 93–95]

Table 1.
Clinical trials of treatments for spinal cord injuries.

of coagules in extremities) and prepare the patient for transport. In the clinic, doctors may apply anti-inflammatory drugs or lower the body temperature—a condition known as hypothermia—for 24–48 h to help prevent damaging inflammation. The patient is subjected to a careful medical inspection and examination, testing for sensory function and movement, and by asking some questions about the accident. In addition, X-rays, computerized tomography (CT) scanning, and/or magnetic resonance imaging (MRI) tests may be needed to reveal vertebral (spinal column) problems such as: tumors, fractures or degenerative changes in the spine, herniated disks, blood clots, or other masses that may be compressing the spinal cord. Often, a surgery intervention is necessary to remove fragments of bones, foreign objects, herniated disks, or fractured vertebrae that appear to be compressing the spine. Subsequently to these tests, doctors begin to analyze which treatment will be applied to the SCI patient.

Over the past few decades, several therapeutic strategies have been developed to target TSCI pathology in clinic, including single and combined treatments with the main objective to cover two important aspects: neuroprotection and neuroregeneration. **Table 1** summarizes several clinic trials used for the treatment of TSCI, which have advantages and disadvantages in their application. However, it needs to be mentioned that until now there are no effective treatments for TSCI, which promote complete regeneration and restoration of motor and systemic functions in humans. Since spinal cord injury research has relied on animal models to understand the mechanisms of disease and develop pre-clinical models of treatment, there is no successful translation from pre-clinical to patient interventions that could be attributed to the limited understanding of biological differences between human and animal model systems.

9. Conclusions

As it can be seen, in this chapter, some of the strategies used in models of spinal cord injury were discussed, showing that they favor axonal regeneration, remyelination, and improvement of locomotor function. However, they have been insufficient as single treatments for preclinical and clinical therapies, which leads us to propose that the best option when dealing with TSCIs is to use combined treatments to increase the beneficial effects of each of the strategies, which could yield optimal results in clinical practice.

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