Histol Histopathol (2021) 36: 907-920

**http://www.hh.um.es**

Histology and Histopathology
*From Cell Biology to Tissue Engineering*

**REVIEW** **Open Access**

# Cell therapy and delivery strategies for spinal cord injury

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**Summary.** Spinal cord injury (SCI) is a complex neuropathological condition that represents a major challenge for clinicians and scientists due to patient's functional dysfunction and paralysis. Several treatments have been proposed including biological factors, drugs and cells administered in various ways. Stem cells arise as good candidates to treat SCI since they are known to secrete neurotrophic factors, improving neuro-regeneration, but also due to their role in modulating the inflammatory process, favoring a pro-regenerative status. There are several types of cells that have been tested to treat SCI in experimental and clinical studies, but we still face many unanswered questions; one of them is the type of cells that can offer the best benefits and, also the ideal dose and administration routes. This review aimed to summarize recent research on cell treatment, focusing on current delivery strategies for SCI therapy and their effects in tissue repair and regeneration.

**Key words:** Spinal cord injury, Cell transplantation, Delivery routes

## Introduction

Despite intense research in laboratories all over the world, traumatic lesions to the spinal cord represent a major challenge for clinicians and scientists. The incidence of traumatic spinal cord injury (SCI) in the United States is roughly 17,330 new cases per year, with an estimate of 291,000 people living with SCI today; most of them affect men (78%) with an average age of 43 years old. Car crashes account for most of them (39.3 %), followed by falls (31.8 %) and violent acts (13.5 %), among other causes (Fehlings, 2019). Depending on the type of injury (incomplete or complete) and where the lesion occurs (cervical, thoracic, or lumbar levels), the consequences can range from minor symptoms to either paraplegia or tetraplegia, which are always accompanied by functional deficits that significantly limit daily life activities (Fehlings, 2019). The incidence of spinal cord injury in Brazil is unknown, as there are no national epidemiological studies. The most consistent data are those of the Sarah Network of Rehabilitation Hospitals, which carries out continuous epidemiological studies of their attendance. In a survey conducted in 2019, through interviews with hospitalized patients, it was found that 20.8% of hospitalizations in the units of the network were motivated by external causes, such as accidents and violence itself. Traffic accidents were the first external cause of hospitalization, with 47.7% of cases. Aggressions (including firearms, bladed weapons, and physical aggression) constitute the second external cause of hospitalization, 22.6% of cases. Falls, 15.5%, diving accidents, 4.5%, impacts by heavy objects, 2.7%, among others, 7.0%, also appear as external causes in this research.

After a traumatic lesion to the spinal cord, a series of events take place in the injured parenchyma. The spinal cord is comprised of neuronal cell bodies (motor, sensory, autonomic and interneurons), glial cells (astrocytes, oligodendrocytes, microglia, and ependymal cells), occasional immune cells, extracellular matrix and blood vessels. All these components are affected at the lesion epicenter (injury site), leading to neuronal death, glia activation and/or death, Wallerian degeneration of the affected axons, blood vessel disruption and an important inflammatory process. During the first few hours after a lesion, the distal stumps of the affected nerve fibers undergo a self-destructive process called Wallerian degeneration; neurons and glial cell bodies which are directly affected by the traumatic lesion will die, with deleterious consequences to the morphology and function of the spinal cord (Ruff et al., 2008; Mietto et al., 2015). After this primary phenomenon, a secondary cascade of events occurs amplifying tissue injury, both rostral and caudally. These events are characterized by hemorrhage, due to blood vessels direct insult, edema, cell death, excitotoxicity, lipid peroxidation, demyelination of surviving myelinated fibers, activation of apoptosis, cavitation and scar

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DOI: 10.14670/HH-18-350

formation, and, finally, by an intense inflammatory reaction that may last for months (Oyinbo, 2011).

Neuroinflammation after SCI is a prominent process that is regarded as being both beneficial and detrimental, depending on the state of activation of the immune cells and the clinical phase after injury. There is a variety of cell types that participate in the neuroinflammation after SCI, including leucocytes (neutrophils), microglia, astrocytes, macrophages, and T- and B-lymphocytes. Neutrophils are the first cells to invade the spinal cord parenchyma and exert their function by releasing proinflammatory cytokines (IL-1 $\beta$, IL-6, TNF-$\alpha$) and chemokines (MIP-1, MCP-1) that attract macrophages from the peripheral blood. The second wave of inflammation includes the arrival of macrophages and T- and B lymphocytes into the tissue injury, where they exert their function. Depending on macrophages/microglia activation status, their function can increase axon regeneration but can also exacerbate tissue damage. M1 macrophages/microglia act by releasing pro-inflammatory cytokines and reactive oxygen species (ROS) exacerbating inflammation and tissue damage. On the other side, M2 macrophages/microglia secrete anti-inflammatory cytokines, and, therefore, are considered pro-regenerative (Chen and Bisby, 1993; David et al., 1995).

Regeneration of central nervous fibers after a traumatic lesion is possible but extremely limited; the idea that the CNS fibers can regenerate arose from the seminal works of Santiago Ramon y Cajal (Ramón y Cajal, 1928) and David Aguayo (David and Aguayo, 1981, 1985), who provided evidence that following a traumatic injury, central neurons are able to regenerate their axons if a favorable microenvironment is provided to them. With these concepts in mind, many researchers have been working on strategies that can improve the potential of central neuron cell bodies to regenerate and extend their neurites and, also, counteract the inhibitory effect of the microenvironment and modulate the inflammatory process, which can otherwise, worsen the tissue injury. Stem cells arise as good candidates to treat SCI since they are known to secrete neurotrophic factors, improving neuroregeneration, but also due to their role in modulating the inflammatory process, favoring a pro-regenerative status (Vismara et al., 2017; Veneruso et al., 2019). There are several types of stem cells that have been tested to treat SCI in experimental and clinical studies, but we still face many unanswered questions; one of them is the type of stem cells that can offer the best benefits and also the ideal doses and administration routes (dos Santos Ramalho et al., 2018, 2019).

This review will summarize recent research on stem cell treatment and different delivery routes for SCI. We will include data on animals' pre-clinical experimental studies and human clinical trials during the last ten years (2010-2020). All references cited in this review were recovered from the Medline database. The following terms were used in the search: stem cell AND spinal cord injury; intravenous stem cell AND spinal cord injury; intraperitoneal stem cell AND spinal cord injury; intrathecal stem cell AND spinal cord injury. Review articles were excluded.

## Stem cell-based therapies for SCI

Cell therapy is a promising strategy in the treatment of spinal cord injury and exerts therapeutic effects through mechanisms that target events occurring during the primary and secondary phases of SCI. Some of these mechanisms are cell replacement and neurotrophic support, which are crucial to enhance neuronal regeneration and survival (Vismara et al., 2017; Veneruso et al., 2019). Besides, some cell types are beneficial because they provide immunomodulation, downregulation of inhibitory molecules, regulation of glial scar and by providing scaffold support for the regeneration of axons (Tetzlaff et al., 2011).

Several cell types have been indicated as feasible candidates for transplantation after spinal cord injury. There are several studies using neural stem and progenitor cells (Cao et al., 2010; Hawryluk et al., 2014), Schwann cells (Sparling et al., 2015), olfactory ensheathing cells (Takeoka et al., 2011), embryonic stem cells (Marques et al., 2010), induced pluripotent stem cells (Führmann et al., 2018) and mesenchymal stem cells (de Almeida et al., 2015; Massoto et al., 2020) as treatment for spinal cord injury.

After transplantation, cells are hypothesized to mediate functional improvements after SCI through a variety of mechanisms, including trophic support, immunomodulation, axon regeneration, and myelin regeneration. The neural progenitor cell transplantation resulted in neurogenesis and integration into functional circuits (Ogawa et al., 2002; Okano et al., 2003; Rossi et al., 2010). Considering embryonic stem cells (ESCs), their mechanism of action can be considered quite advantageous, because these cells can differentiate into cells of ectodermal origin such as neurons and glial cells (Gazdic et al., 2018). These cells also replaced oligodendrocytes that were able to remyelinate axons and consequently restore locomotion (Keirstead et al., 2005). The mesenchymal stem cells (MSCs), olfactory ensheathing cells (OECs) and Schwann cells (SCs) have also shown benefits. These cells survive for a long time after transplantation and they present neurotrophin production that is considered an important aspect for regeneration (de Almeida et al., 2015; dos Santos Ramalho et al., 2018) because it provides trophic support to injured host cells. These cells also modulate inflammatory reactions by cytokine production. OECs can also form myelin sheaths that can wrap axons and give support to neurite outgrowth (Sasaki et al., 2011a,b). Similarly, Schwann cells are also capable of forming myelin sheaths around the regenerated axons and this can explain the enhancement in regeneration after transplantation (Kocsis et al., 2002). Concerning the use of iPSC, the action mechanisms consist of the

ability of these cells to differentiate into neural progenitor cells, neurons, oligodendrocytes and astrocytes at the same time underlining the integration of transplanted cells into the site of injury (Lukovic et al., 2012).

### *Neural stem and progenitor cells (NSPCs)*

Neural stem and progenitor cells (NSPCs) are considered multipotent progenitors isolated from the central nervous system of fetal or adult tissue and they frequently grow as neurospheres. Considering cell transplantation, they present some advantages, such as their renewal capacity and the differentiation in neural cell phenotypes (neurons, oligodendrocytes and astrocytes) after transplantation to injured spinal cord (Tarasenko et al., 2007). In addition, they can also modulate immune and inflammatory responses (Ottoboni et al., 2015).

NPSCs were able to survive up to 10 weeks after transplantation and they integrated along white-matter, expressed myelin basic protein and remyelinated axons after SCI (Karimi-Abdolrezaee et al., 2006). Recently, a study performed on rhesus monkeys showed regenerated axons that formed synapses into grafts, and functional improvement, several months after NSPC transplantation (Rosenzweig et al., 2018). One disadvantage of NSPCs is the difficulty of the extraction process, because these cells are deeply located in the adult brain and the region is not easily accessible for harvesting and, hence, for autologous transplantation. Given the practical and ethical limitations of this scenario, an alternative to this process is the generation of the neural progenitors from embryonic stem cells (ESCs) or induced pluripotent stem cells (IPSCs).

### *Embryonic stem cells*

Embryonic stem cells (ESCs) are derived from the inner cell mass of the preimplantation blastocysts and they express pluripotent stem cell surface antigens such as SSEA-3 and SSEA-4 (stage-specific embryonic antigens 3 and 4), and also express pluripotency-associated genes octamer-binding transcription factor 3/4 (OCT3/4), sex determining region Y box-containing gene 2 (SOX2), and NANOG (Thomson et al., 1998; Reubinoff et al., 2000). These markers' expressions are important to verify the maintenance of an undifferentiated pluripotent state for ESCs after the isolation process. These cells have a great capacity for proliferation and can differentiate into cells of ectodermal origin, such as neuronal and glial cells. And this can be regarded an advantage considering cell transplantation in the central nervous system. Some works have shown that transplantation of differentiated and pre-differentiated ESC to SCI resulted in cell survival and integration with host tissue and an enhancement in functional recovery (Keirstead et al., 2005; Nistor et al., 2005; Marques et al., 2010). Although the results are promising, there are some issues that need to be addressed, such as immune rejection possibility and risk of tumor formation after transplantation (Gazdic et al., 2018). These factors can be considered disadvantages for using these cells for transplantation in humans.

### *Induced pluripotent stem cells*

The use of iPSCs (induced pluripotent stem cells) has been particularly attractive because they avoid the ethical and moral concerns that involve other stem cells. Several cell types like fibroblasts, neural progenitor cells, keratinocytes, melanocytes, CD34+ cells, hepatocytes, cord blood cells and adipose stem cells have been used to produce iPSCs. The elected cell can influence the differentiation capacity of the resultant iPSCs, due to epigenetic memory and genetic variations of their original cell line and this fact must be considered regarding cell transplantation into the spinal cord. For applications in SCI, the iPSCs can be differentiated into neurons, oligodendrocytes, astrocytes, neural crest cells and mesenchymal stromal cells that act by replacing dead cells or providing trophic support in the host tissue (Kim et al., 2010, 2011; Hou et al., 2013; Khazaei et al., 2015).

### *Schwann cells*

Schwann cells (SCs) are the myelinating glia of the peripheral nervous system and these cells can guide regenerating axons after peripheral nerve injury. They also myelinate or ensheath regenerated axons, reduce cavity formation and secondary damage of tissue around the initial insult site and improve functional recovery (Williams et al., 2015).

However, the process of Schwann cell extraction has some characteristics that can be considered limitations for transplantation. There are several reported protocols to isolate Schwann cells from adult mammalian nerves, and most of these methods have great concerns about fibroblast proliferation and contamination. In addition, depending on the protocol used, the amount of Schwann cells obtained after purification is low. Thus, many nerves are needed to yield a satisfactory number of cells to be transplanted (Mauritz et al., 2004).

Even with some disadvantages as previously described, the use of SCs cells can be considered a promising therapy for spinal cord repair since cell transplantation provides a bridge across the lesion site, myelinates spared axons and reduces astrogliosis. In addition, electrophysiological assays showed that axons remyelinated by both Schwann cells and oligodendrocytes can conduct action potentials correctly, which makes it clear that the role of Schwann cells in the remyelination of preserved axons may contribute to animals' recovery. Another outstanding feature, showed by electron micrographs, is that Schwann cells remyelinate axons inside the central nervous system with

its typical morphology that includes a basement membrane and extracellular collagen deposition (Kocsis et al., 2002).

### *Olfactory ensheathing cells*

The olfactory ensheathing cells (OECs) are glial cells that support axon growth of olfactory neurons into the olfactory bulb. These cells are present in the lamina propria of the olfactory mucosa and ensheath some olfactory axons in bundles forming a fascicle, after they leave the olfactory epithelium. Although some studies have shown positive outcomes in regeneration after spinal cord injury, the results with these cells are still quite contradictory, and these variations may be related to the methods of extraction and purification of these cells prior to transplantation. If a robust purification process does not occur, the therapeutic potential of these cells will not be accomplished (Ekberg and St John, 2014; Yao et al., 2018).

The OEC transplantation has been proposed for SCI repair based on evidence that showed transplanted cell migration to damaged spinal cord tissue which contributed to remyelination, besides modulating neuroinflammation and tissue preservation (Zhang et al., 2019). On the other hand, a few authors have also demonstrated that OECs from adult rats do not form myelin nor exhibit a Schwann cell-like relationship with axons. These different outcomes may be due to the proportion of OECs during cell culture preparation before, and cellular purity (Plant et al., 2002; Yao et al., 2018).

### *Mesenchymal stem cells*

In this scenario of cell therapy, mesenchymal stem cells (MSCs) stand out because of their easy isolation from different sources like bone marrow, adipose tissue and umbilical cord, raising no ethical concerns and, also, for the limited risk of tumor development. These cells also present fast proliferation and a high multilineage differentiation can be obtained. Additionally, MSCs maintain the regenerative potential even after cryopreservation and present "homing properties", being able to migrate toward the lesion site (Kotobuki et al., 2004; Lee et al., 2005; Dasari et al., 2014; Cofano et al., 2019). MSCs also show important autocrine and paracrine activities that can stimulate proliferation, differentiation of several cells and, moreover, exert immunomodulatory, anti-inflammatory, and neuroprotective effects on the lesioned microenvironment (Baez-Jurado et al., 2019; Cofano et al., 2019).

Some studies have demonstrated positive results after using MSC transplantation to treat spinal cord injury (dos Santos Ramalho et al., 2018, 2019; Yousefifard et al., 2019; Massoto et al., 2020), even when treatment was performed in the chronic phase of the injury (Abrams et al., 2009; de Almeida et al., 2015).

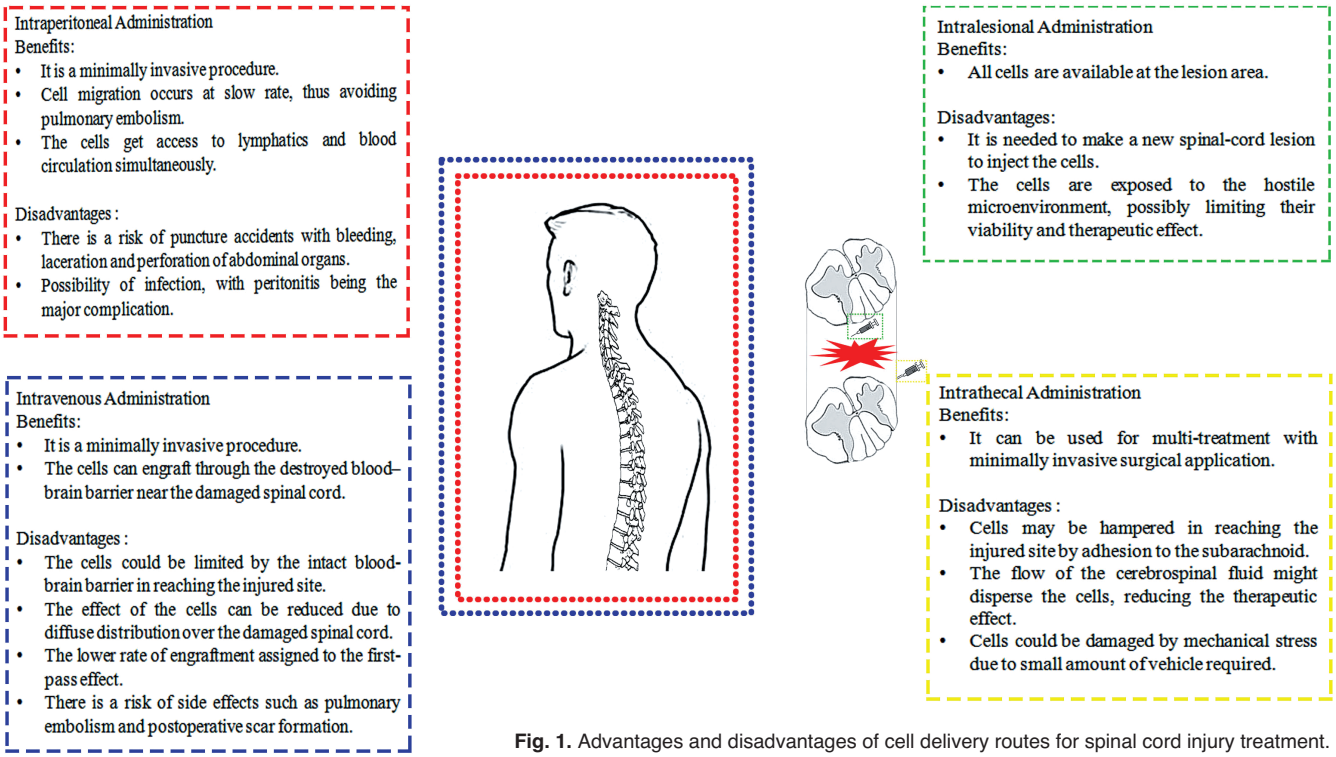


**Fig. 1.** Advantages and disadvantages of cell delivery routes for spinal cord injury treatment.

## Delivery strategies

Different delivery strategies have been proposed to administer therapeutic cells into the injured spinal cord (Fig. 1). Most preclinical and clinical studies concerning SCI treatment have used intralesional administration of stem cells and reported positive results, but in the last decade, several clinical studies have also used the intrathecal route; intravenous, intrathecal and, more recently, intraperitoneal routes were also adopted in preclinical models. Table 1 is a summary of preclinical and clinical studies using different cell types and routes of administration for spinal cord injury, from 2010 until now.

### *Intralesional administration*

Intralesional delivery is the most used route for stem cell administration after spinal cord injury. Several studies have demonstrated an improvement in locomotor function after local cell administration (Marques et al., 2010; Hawryluk et al., 2011; Zhou et al., 2013; de

**Table 1.** Summary of pre-clinical (white background) and clinical (gray background) studies using cell therapy for spinal cord injury.

| Route of administration | Source | References |
|---|---|---|
| Intralesional | Embryonic stem cells | Marques et al., 2010 |
| Intralesional | Neural differentiated and undifferentiated-MSC | Pedram et al., 2010 |
| Intralesional | Bone marrow-MSC | Alexanian et al., 2010; Gu et al., 2010; Zhang et al., 2010; Sasaki et al., 2011a,b; Shi et al., 2011; Zeng et al., 2011; Hara et al., 2012; Kaynaklı et al., 2012; Wei et al., 2012; Boido et al., 2014; de Almeida et al., 2015 |
| Intralesional | Human bone marrow-MSC | Fang et al., 2010; Park et al., 2010; Alexanian et al., 2011; Choi et al., 2012; Hodgetts et al., 2013 |
| Intralesional | Human mesenchymal precursor cells | Hodgetts et al., 2013 |
| Intralesional | Umbilical cord-MSC | Park et al., 2011 |
| Intralesional | Human umbilical cord derived-MSC | Hu et al., 2010; Lee et al., 2011; Shang et al., 2011; Park et al., 2012c; Schira et al., 2012; Zhilai et al., 2012; Roh et al., 2013 |
| Intralesional | Bone marrow stromal cells, Schwan cells | Zhang et al., 2011 |
| Intralesional | Bone marrow-MSC, Adipose derived-MSC | Zhou et al., 2013 |
| Intralesional | Adipose derived-MSC | Kokai et al., 2014 |
| Intralesional | Bone marrow-MSC induced into Schwann cells | Zaminy et al., 2013 |
| Intralesional | Neural precursor cells, Bone marrow stromal cells | Hawryluk et al., 2011 |
| Intralesional | Neural induced adipose derived-MSC | Park et al., 2012b |
| Intralesional | Neural stem cells | Lu et al., 2012 |
| Intralesional | Induced pluripotent stem cells-derived neural progenitors | Ruzicka et al., 2017 |
| Intravenous | Human brain stromal cells | Badner et al., 2016 |
| Intravenous | Bone marrow-MSC | Osaka et al., 2010; Chen et al., 2012; Kang et al., 2012; Quertainmont et al., 2012; Morita et al., 2016; White et al., 2016; Oshigiri et al., 2019; Yasuda et al., 2020 |
| Intravenous | Adipose derived-MSC | Barriga et al., 2013; Ohta et al., 2017 |
| Intravenous | Human amniotic-MSC | Zhou et al., 2020 |
| Intravenous | Olfactory bulb ensheathing cells | Zhang et al., 2019 |
| Intravenous | Human placental/umbilical blood cells | Ryabov et al., 2014 |
| Intravenous | Human umbilical cord-MSC | Seo et al., 2011 |
| Intravenous | Human multipotent adult progenitor cells | DePaul et al., 2015 |
| Intravenous | Term-birth human umbilical cord perivascular cells, first-trimester human umbilical cord perivascular cells, adult bone marrow-MSC | Vawda et al., 2019 |
| Intrathecal | Bone marrow-MSC | Cizkova et al., 2011 |
| Intrathecal | Human Wharton's Jelly-MSC | Krupa et al., 2018; Mohamadi et al., 2019 |
| Intrathecal | Human umbilical cord-MSC | Yang et al., 2020 |
| Intraperitoneal | Bone marrow-MSC | dos Santos Ramalho et al., 2019 |
| Intralesional, intravenous | Bone marrow-MSC | Kim et al., 2013 |
| Intralesional, intrathecal, intravenous | Human bone marrow-MSC | Shin et al., 2013 |
| Intralesional, intrathecal, intravenous | Neural stem/progenitor cells | Takahashi et al., 2011 |
| Intravenous, intraperitoneal | Bone marrow-MSC | dos Santos Ramalho et al., 2018 |
| Intralesional | Schwann cells | Saberi et al., 2011; Anderson et al., 2017 |
| Intralesional | Bone marrow-MSC | Park et al., 2012a; Dai et al., 2013 |
| Intralesional | Olfactory ensheathing cells | Tabakow et al., 2013 |
| Intralesional | Umbilical cord blood-derived mononuclear cell | Zhu et al., 2016 |
| Intralesional | Spinal-cord-derived neural stem cell | Curtis et al., 2018 |
| Intrathecal | Bone marrow-MSC | Karamouzian et al., 2012; Vaquero et al., 2018 |
| Intrathecal | Umbilical cord-MSC | Cheng et al., 2014 |
| Intrathecal | Adipose derived-MSC | Hur et al., 2016 |

MSC: Mesenchymal stem cell.

Almeida et al., 2015).

Both single cell source and co-transplants have been intralesionally administered as a viable alternative for the treatment of SCI. Co-transplantation of bone marrow stromal cells and Schwann cells reduced the size of cystic cavities, promoted axonal regeneration and hind limb functional recovery in comparison to Schwann cells or bone marrow stromal cell transplantation alone (Zhang et al., 2011). Several studies have shown that intralesional administration from a single cell source can be beneficial after SCI. Lu and coworkers showed that the intralesional transplantation of neural stem cells after spinal cord transection in rats led to a significantly accelerated axonal growth at the injury site and improved axonal conduction (Lu et al., 2012). In another study (Kokai et al., 2014), adipose-derived mesenchymal stem cells were directly transplanted into the parenchyma of the spinal cord and the animal's body function was restored. Recently, Ruzicka and colleagues observed beneficial effects of induced pluripotent stem cell-derived neural progenitors, intraspinally administrated, on preserving the host tissue, reducing the glial scar, increasing axonal sprouting, and promoting motor functional recovery after compressive spinal cord injury (Ruzicka et al., 2017).

Although most studies on SCI treatment have used direct injection into the injured site and it has been favorable, this administration route has limitations, because it may make a new spinal-cord lesion to inject the cells but also exposes delivered cells to hostile environments that might limit their viability and therapeutic effect (Sasaki et al., 2011; Veneruso et al., 2019). Furthermore, when local administration is translated to clinical practice, major surgery is required to expose the spinal cord, which could be harmful to physically debilitated patients (Shin et al., 2013). Despite this disadvantage, it is important to note that the cells can be administered at the moment the injury site is inspected, immediately after the lesion, in order to treat the patient in the acute phase of injury.

Regarding clinical tests, most of them use the intralesional route for cell injection. A study of patients (n=33) with cervical and thoracic SCI (AIS A and B) reported partial sensorimotor recovery and no adverse events or associated tissue abnormalities after autologous Schwann cell transplantation (Saberi et al., 2011). Park and colleagues used repeated bone marrow-derived mesenchymal stem cell injections directly into the spinal cord and demonstrated that three of ten patients presented a motor improvement, and significant magnetic resonance changes and electrophysiological results (Park et al., 2012a). These results are similar to those obtained by Dai and coworkers, who also demonstrated a clinical improvement in patients that received autologous MSC transplantation (Dai et al., 2013). A phase I/IIa clinical trial of human OECs in chronic SCI confirmed no adverse events up to 3 years following transplant. However, no functional improvements were seen (Tabakow et al., 2013). However, another phase I/II clinical trial that transplanted umbilical cord blood-derived mononuclear cells (UCB-MNC) into 28 patients with chronic complete SCI demonstrated that at about a year after treatment, walking index of SCI, and spinal cord independence measure scores improved: 15/20 patients walked 10 m and 12/20 did not need assistance for bladder management or bowel management. Furthermore, five patients converted from complete to incomplete SCI (Zhu et al., 2016). Anderson and colleagues at the Miami Project to Cure Paralysis reported the results of a phase I open-label, nonrandomized, nonplacebo-controlled trial of autologous SCs harvested from a sural nerve (within 5-30 days postinjury) and injected into the epicenter of the SCI lesions (within 4-7 weeks of injury) in persons (n=6) with complete paraplegia (T3-11). At 1-year post-transplantation, there were no reported significant surgical, medical, or neurological safety concerns (Anderson et al., 2017). More recently, a phase I study tested the feasibility and safety of human-spinal-cord-derived neural stem cell (NSI-566) transplantation for the treatment of chronic SCI. All patients tolerated the procedure well and there have been no serious adverse events up to 18-27 months post-grafting. In two subjects, one to two levels of neurological improvement were detected using International Standards for Neurological Classification of Spinal Cord Injury motor and sensory scores (Curtis et al., 2018).

### *Intravenous administration*

In view of the limitations that the intralesional cell administration presents, it is worthwhile to seek alternative approaches that are minimally invasive as well as effective. Consistent with this idea, intravenous administration, through the tail or the femoral veins, has been introduced (Zhang and He, 2014; Badner et al., 2016; Morita et al., 2016; dos Santos Ramalho et al., 2018).

There are some experiments that indicate that intravenous transplantation of cells has good effects on SCI, like that of Ohta and colleagues, which showed that intravenously transplanted adipose-derived mesenchymal stem cells (AdMSCs) gradually accumulated in the injured spinal cord, where cytokines such as CINC-1 activated ERK1/2 and Akt, leading to functional recovery in rats that underwent contusive spinal cord injury (Ohta et al., 2017). Olfactory bulb ensheathing cells (OECs) transplanted by intravenous route were observed in the hemisectioned spinal cord 10 min after administration; moreover, the rats that received OECs transplantation exhibited a prominent reduction in inflammatory responses, increased neurogenesis and remyelination, and significant improvement in motor function, compared to the control group (Zhang et al., 2019). Recently, Zhou and coworkers demonstrated that human amniotic mesenchymal stem cells (hAMSCs) transplanted in the tail vein were able to migrate to the

injured spinal cord. Compared with the control group, hAMSC transplantation significantly decreased the numbers of ED1 macrophages/microglia and caspase-3 cells, and reduced levels of inflammatory cytokines, such as tumor necrosis factor alpha, interleukin-6 and IL-1β. In addition, hAMSC administration significantly attenuated Evans blue extravasation, and promoted angiogenesis and axonal regeneration. hAMSC injection also significantly improved functional recovery after contusive spinal cord injury in rats (Zhou et al., 2020).

Despite so many positive outcomes, there are some inconsistencies regarding the arrival of the cell at the injury site. According to Takahashi and colleagues, intravenous cell therapy is not optimal for treating localized damage of the central nervous system such as spinal cord injury, because the stem cells might be limited by the blood-brain barrier in reaching the injured site, and diffuse distribution over the damaged spinal cord and the lower rate of engraftment assigned to the first-pass effect, i.e., filtering by spleen, lung, and liver might reduce the potential effect (Takahashi et al., 2011). However, Shin and coworkers say that the cells are expected to engraft through the destroyed blood-brain barrier near the damaged spinal cord (Shin et al., 2013). Furthermore, important side effects were observed with this route, such as pulmonary embolism (Jung et al., 2013; Veneruso et al., 2019); besides that, some mice transplanted by femoral vein injection might also have suffered from postoperative scar formation producing hip joint contracture, as reported in the study of Takahashi and coworkers (Takahashi et al., 2011).

No clinical trials published in the last decade were found with cell administration by intravenous route.

### *Intrathecal administration*

Intrathecal injection of cells is performed by lumbar puncture and the cells reach the lesion site through the cerebrospinal fluid. This procedure can also be used for multi-treatment with repeated minimally invasive surgical application (Cizkova et al., 2011; Krupa et al., 2018).

Several studies have shown positive results after the intrathecal administration of cells as spinal cord injury treatment. Mohamadi and colleagues reported that intrathecal transplantation of Wharton's jelly mesenchymal stem cells suppressed the NLRP1 inflammasome and significantly increased the number of normal-appearance neurons in the ventral horn of spinal cord. Noteworthy, these effects resulted in a significant improvement in motor function recovery, after compressive spinal cord injury in the rat (Mohamadi et al., 2019). Another study reported that human umbilical cord mesenchymal stem cells transplanted in the subarachnoid space in a rodent model of subacute incomplete spinal cord injury migrated towards the lesion epicenter and led to decreased astrogliosis, increased remyelination, and neuron regeneration with significant improvement in locomotion (Yang et al., 2020). A comparative study reported that intracisternal injection of bone marrow-derived mesenchymal stem cells (BMMSCs) gave greater functional improvement than intravenous or intralesional injection, although the latter gave the highest level of cell engraftment (Shin et al., 2013).

To determine in vivo distribution of cells injected into the lateral ventricle (LV), Won and colleagues injected Cy5.5 fluorescent dye or cells labeled with fluorescent magnetic nanoparticles (FMNPs) into LVs of rats with or without SCI and analyzed their in vivo distributions using in vivo optical imaging techniques. The presence of FMNP-labelled U87MG cells in the spinal cord was confirmed by quantitative PCR for human-specific sequence and immunohistochemistry staining using an antibody against human-specific antigen, indicating that LV injection can recapitulate intrathecal administration of stem cells for SCI patients (Won et al., 2018).

While intrathecal injection has been proposed to maximize the therapeutic outcome, this route also has disadvantages. Stem cells intrathecally injected may be hampered in reaching the injured site by adhesion to the subarachnoid space, and the flow of the cerebrospinal fluid might disperse the cells, reducing the therapeutic effect; moreover, stem cells might be damaged by mechanical stress due to the injection (Rossi et al., 2013; Veneruso et al., 2019).

With regard to the safety and efficacy of the intrathecal delivery in clinical tests, Karamouzian and coworkers confirmed the safety of MSCs in humans, in 2012, with a nonrandomized clinical trial comparing the results of autologous bone marrow cell (BMC) transplantation into cerebrospinal fluid (CSF) via lumbar puncture (LP) in 11 patients having complete SCI, with 20 patients as control group who received conventional treatment without BMC transplantation (high dose of methyl prednisolone and physiotherapy). None of the patients in the study and control group experienced any adverse reaction and complications, neither after routine treatment nor after cell transplantation, concluding that transplantation of autologous BMC via LP is a feasible and safe technique (Karamouzian et al., 2012). Cheng and colleagues demonstrated that umbilical cord mesenchymal stem cell transplantation via the intrathecal route is effective in the treatment for sequelae of thoracolumbar spinal cord injury in humans. Their method alleviated lower limb muscle tension, increased limb strength, and improved urinating function. The method's efficacy was more significant in comparison with rehabilitation therapy, and no adverse effects were found (Cheng et al., 2014). One recent study investigated the effect of intrathecal transplantation of autologously collected adipose-derived mesenchymal stem cells (AD-MSCs) in 14 patients with SCI. Functionality was measured using the ASIA motor and sensory scores, while corresponding electrophysiological studies included electromyography and MRI examinations. Following treatment, 10 of the 14 patients

exhibited sensory improvement; however, lesion size, as visualized by MRI, remained stable. Severe adverse events were also absent from all the patients treated with AD-MSCs (Hur et al., 2016). More recently, a phase 2 clinical trial in patients with chronic SCI who received three intrathecal administrations of MSCs and were followed for 10 months from the first administration showed that the treatment was well-tolerated, without any adverse events related to MSC administration. Patients showed variable clinical improvement in sensitivity, motor power, spasms, spasticity, neuropathic pain, sexual function or sphincter dysfunction, regardless of the level or degree of injury and age or time elapsed from the SCI (Vaquero et al., 2018).

### *Intraperitoneal administration*

An advantage of the intraperitoneal route is the slow rate of cell migration of cells administered in the peritoneal cavity, thus avoiding pulmonary embolism, a complication that can be fatal and that can occur by intravenous injection. The peritoneum is highly vascularized and therefore allows more cells to get access to lymphatics and blood circulation simultaneously; most of the absorption occurs via the mesenteric vasculature that flows into the portal vein (Wilson et al., 2010; Bazhanov et al., 2016); afterward, these cells can engraft to sites of tissue injury and inflammation.

The intraperitoneal route had been used before for mesenchymal stem cell (MSCs) injection in inflammatory diseases with positive results. In 2013, Yousefi and coworkers showed that intraperitoneal injection of MSCs was able to reduce the amount of aggressor inflammatory cells in the brain and ameliorated the severity of clinical scores in mice with experimental autoimmune encephalomyelitis (EAE) (Yousefi et al., 2013). After that, it was shown that intraperitoneal injection of MSCs was able to prevent almost completely the development of experimental autoimmune uveitis (EAU) in mice by suppressing Th1/Th7 immune responses, and to protect the retina from immune-mediated damage (Oh et al., 2014); and to suppress peritoneal inflammation by restoring the mesothelial layer and decreasing complement activation in fungal or yeast peritonitis in rat (Kim et al., 2014).

More recently, a comparative study between the intravenous and the intraperitoneal routes demonstrated that the intraperitoneal injection has equivalent effects to the intravenous injection of MSCs in a model of spinal cord compressive injury in mice. In this study, the cells were able to reach the lesion site presenting evidence that systemic transplantation of MSCs, either by intraperitoneal or intravenous routes, has the potential to improve axonal myelination, white matter sparing and motor function after SCI, through the local release of trophic factors (dos Santos Ramalho et al., 2018). In 2019, the same authors emphasized the choice of intraperitoneal injection of stem cells as a viable alternative for SCI treatment, using mice with compressive spinal cord injury, and demonstrated functional and tissue improvement by intraperitoneal transplantation of 3 different doses of MSCs. The cells of the three MSC doses administered were able to migrate to the injury site, increase local expression of trophic factors, and enhance fiber sparing and/or regeneration, accompanied by substantial improvement in locomotor performance. Cell transplantation at medium ($8x10^5$) density showed the best therapeutic potential, leading to significant tissue and functional improvements compared to the minimum ($8x10^4$) and maximum ($8x10^6$) doses (dos Santos Ramalho et al., 2019).

To date, these are the only studies that used intraperitoneal cell injection after spinal cord injury. Therefore, further studies are needed to provide additional elucidation on this route of administration. The main disadvantages of this route include puncture accidents with bleeding, laceration and perforation of abdominal organs and infection, with peritonitis being the major complication. However, all these complications can be substantially minimized by the mastery of the application technique and by the appropriate antisepsis of the materials used (Bazhanov et al., 2016).

No clinical trials with cell administration by intraperitoneal route, published in the last decade, were found.

## Conclusions and perspectives

Immediately after a traumatic lesion to the spinal cord, a series of events take place in the injured parenchyma that causes progressive multifaceted neuropathology, becoming chronic after approximately 28 and 60 days, in animals and humans, respectively. Given the complexity of spinal cord injury, new strategies focus on therapies to counteract their diverse neuropathological events; multi-functional therapies may offer a promising new approach.

In this scenario, cell therapy, which has several beneficial effects, has proved to be a promising treatment in the last few years. Some mechanisms associated with cell therapy are cell replacement and neurotrophic support (Vismara et al, 2017; Veneruso et al, 2019). Moreover, some cell types are beneficial because they provide downregulation of inhibitory molecules and immunomodulation, regulation of glial scar and by providing scaffold support for the regeneration of axons (Tetzlaff et al., 2011). Different growth factors, chemokines, cytokines, extracellular matrix constituents and immunomodulatory molecules have been identified and characterized from different types of stem cells, and many of them show protective and regenerative activities when released in the injury

site (Veneruso et al., 2019).

The use of stem cells to influence micro-environments has been investigated in preclinical and clinical experiments. There are several studies using different cell types for spinal cord injury treatment, such as neural stem and progenitor cells (Cao et al., 2010; Hawryluk et al., 2014), Schwann cells (Sparling et al., 2015), olfactory ensheathing cells (Takeoka et al., 2011), embryonic stem cells (Marques et al., 2010), induced pluripotent stem cells (Führmann et al., 2018) and mesenchymal stem cells (de Almeida et al., 2015; Massoto et al., 2020). In most of these studies, cells were able to improve regeneration and locomotor recovery, regardless of the cell type used.

Among the several delivery strategies to administer therapeutic cells into the injured spinal cord, the intralesional route has been the most used (Marques et al., 2010; Hawryluk et al., 2011; Zhou et al., 2013; de Almeida et al., 2015), but intravenous (Zhang and He, 2014; Badner et al., 2016; Morita et al., 2016; dos Santos Ramalho et al., 2018), intrathecal (Cizkova et al., 2011; Krupa et al., 2018) and, more recently, intraperitoneal (dos Santos Ramalho et al., 2018; dos Santos Ramalho et al., 2019) routes were also used and all of them showed efficacy for the administration of cells after spinal cord injury, as well as tissue and functional recovery. Even though direct injection into the injured site has limitations because it can cause a new spinal-cord lesion and although the other routes of administration do not present this disadvantage, as they are systemic, all delivery strategies demonstrated in this review present some type of drawback, as previously demonstrated.

Although preclinical studies using cell therapy to treat SCI have shown important results, some impediments remain for clinical application. The protocols used in preclinical experiments are not standardized; cells from different origins and different routes of administration are tested, but rarely compared, creating variability. To overcome these limitations, a clinical-grade protocol must be adopted in preclinical experiments to ensure reproducibility of the procedure. In addition, there is an urgent need for more well characterized studies to identify the potential mechanisms underlying the paracrine action of the injected cells and how the route of administration can influence the arrival of the cells at the injured spinal cord and its effects on the lesion site. Altogether, it can be said that there are no gold-standard methods for spinal cord injury treatment that indicate not only the best cellular source but also the best route for administration.

*Acknowledgements.* Financial support: CAPES, Faperj and CNPq. This work was supported by Grant 465656/2014-5 from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Brasil; and also included a postdoctoral fellowship to Bruna dos Santos Ramalho. We acknowledge the support of ''National Institute of Science and Technology for Regenerative Medicine", CNPq, Brasil. B.S.R., F.M.A. and A.M.B.M. analyzed the data, and wrote the manuscript.

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Accepted June 10, 2021