REVIEW

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Spinal cord regeneration using dental stem cell-based therapies

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Spinal cord injury (SCI) is traumatic central nervous system damage resulting in a motor and sensory dysfunction that usually causes a severe and permanent paralysis. Today, the treatment of SCI principally includes surgical treatment, pharmacological treatments and rehabilitation therapies, which target secondary events determining only some clinical improvements in patients. SCI is still a worldwide problem in the clinic and remains a big challenge for neuroscientists and neurologists throughout the world. Therefore, new therapies able to restore the function of the injured spinal cord are urgently needed for SCI patients. An interesting approach to overcome the growth inhibiting properties present in the injured spinal cord is to transplant cells with reparative and protective properties such as mesenchymal stem cells. In this context, human dental-derived stem cells represent a promising new cell source for cell-based therapies. It has been shown that dental-derived stem cells isolated from dental pulp, named dental pulp stem cells or stem cells from human exfoliated deciduous teeth induce functional improvement after SCI in animal models. This review summarises the current state of the literature regarding the use of dental-derived stem cells for spinal cord repair and regeneration and highlights the neuroprotective effects of these cells when administered after spinal cord injury.

Key words: spinal cord injury, dental pulp stem cells, human exfoliated deciduous teeth, spinal cord regeneration, spinal cord defects

INTRODUCTION

Spinal cord injury (SCI) is a devastating neurological disorder resulting in the permanent sensory and motor dysfunctions due to loss of glia, neurons and the incomplete axonal regeneration after injury (Silva et al., 2014; Ahuja et al., 2017). SCI varies in incidence around the world, depending on the land transport, type of infrastructure, culture and socioeconomic levels between countries (Lee et al., 2014). The complicated pathophysiology of SCI has been extensively studied in recent years and it includes; myelin loss, inflammatory response, oxidative stress, activation of various cytokines, cell death and axonal degradation (Hu et al., 2016; Hayta and Elden, 2018; Alizadeh et al., 2019). It has been shown that patients suffering from SCI have multiple clinical problems including sensory and motor function loss and several secondary complications such as obesity, depression, bowel and bladder dysfunction as well as urinary tract infections (Jensen et al., 2007; Bianco et al., 2016). Moreover, SCI patients possess socioeconomic problems and require extensive medical attention due to the complexities of the secondary conditions caused by this injury (Doulames and Plant, 2016).

The pathophysiology of SCI is a biphasic event characterised by an initial primary injury followed by a secondary phase of injury (Oyinbo, 2011). Primary mechanical injury is the consequence of dislocation and disruption of the vertebral column, which causes the direct disruption of axons, neurons, glia and blood

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vessels. This is followed by a secondary damage phase characterized by multiple injury processes, including inflammation, glutamate excitotoxicity, apoptosis and free radical-induced cell death (Oyinbo, 2011). After SCI, the inflammatory response is the major component of secondary injury, which includes the activation of resident microglia and the recruitment of macrophages from the bloodstream to the site of the injury resulting in neuron death as well as in axonal degeneration and demyelination (Yamamoto et al., 2014). The influx of inflammatory cells including neutrophils and lymphocytes also induces the formation of glial scars, and therefore the reduction of neuronal function (Zhou et al., 2014; Shultz and Zhong, 2017). Therefore, during the secondary phase, some processes destroy neurons that were not damaged in the primary phase.

Although modern medicine today has increased the survival of patients affected by SCI, the life quality of SCI patients still remains poor due to little advancement in ameliorating related dysfunctions such as neurogenic shock, respiratory difficulties, alterations in ion and neurotransmitter levels and inflammation (Zhang et al., 2013; Doulames and Plant, 2016). Currently, the treatment of SCI principally includes surgical treatment, pharmacological treatments and rehabilitation therapies that target secondary events, determining only some clinical improvements in patients (Sadowsky and McDonald, 2009; Raslan and Nemecek, 2012; Kim et al., 2017) It has been shown that conventional therapies for SCI on rare occasions are able to promote an acceptable level of functional recovery (Luo et al., 2018). Moreover, current therapeutic strategies such as surgical decompression and pharmacological intervention, as well as therapeutic hypothermia, are not satisfactory in treating SCI completely (Gazdic et al., 2018; Mukhamedshina et al., 2019). Therefore, SCI is still a worldwide problem in the clinic and remains a big challenge for neuroscientists and neurologists (Dietrich, 2015; Yuan et al., 2019).

Many different strategies have been tried to find efficacious treatments for SCI. In this context, it has been shown that stem cells hold great promise for the treatment of SCI due to their neuroprotective and neuroregenerative properties (Gazdic et al., 2018; Mukhamedshina et al., 2019).

For example, embryonic stem cells, adult stem cells such as neural stem cells, mesenchymal stem cells and induced pluripotent stem cells have been extensively studied as potential therapeutics candidates for spinal cord injury. However, the use of embryonic stem cells and induced pluripotent stem cells in the clinic is currently limited because they possess ethical and safety concerns (Volarevic et al., 2018). For example, the use of the four transcription factors OCT3/4, Sox2, Klf4 and c-Myc to induce the pluripotent state of the cells could cause teratomas after transplantation (Nakamura and Okano, 2013; Deng et al., 2018). Importantly, the human central nervous system possesses limited regenerative capacity despite the presence of neural stem cells in the spinal cord (Mead et al., 2017; Beyer et al., 2019).

Cells such as mouse embryonic stem cells and induced pluripotent stem cells have been shown to differentiate into oligodendrocytes, astrocytes and neurones when transplanted in SCI (Guillaume and Zhang, 2008; Khazaei et al., 2017). However, both cells possess ethical concerns that limit their application. In addition, embryonic stem cells heterologous transplantation may cause graft rejection whereas induced pluripotent stem cells can lead tumorigenesis after injection (Pearl et al., 2011; Zhang et al., 2012).

Mesenchymal stem cells such as those derived from bone marrow-derived mesenchymal stem cells, Wharton's jelly and adipose tissues represent an alternative source of pluripotent stem cells able to repair spinal cord injury (Hofstetter et al., 2002; Kang et al., 2006; Mohamadi et al., 2019). Hofstetter et al. (2002) show that bone marrow-derived mesenchymal stem cells, when transplanted into rats rendered paraplegic by SCI, are able to improve the functional recovery of injured spinal cord (Hofstetter et al., 2002) whereas Mohamadi et al. (2019) obtained similar results by using the anti-inflammatory potential of Wharton's jelly mesenchymal stem cells. In addition, also Kang et al. (2006) observed that the intravenous injection of oligodendrocyte precursor cells (OPCs) derived from rat adipose tissues can improve motor function in an experimental model of rat SCI. Taken together these data highly suggest that mesenchymal stem cells could be a suitable cell source for spinal cord repair.

Moreover, human Wharton's jelly mesenchymal stem cells combined with spinal cord porcine–ECM (SC-ECM) and urinary bladder-ECM (UB-ECM) have been used to evaluate the ability of such constructs to repair spinal cord in an acute model of SCI (Tukmachev et al., 2016). Importantly, although SC-ECM and UB-ECM hydrogels induced significant neuroregenerative and immunomodulatory effects after SCI, the combination of mesenchymal stem cells with SC-ECM/UB ECM did not significantly improve the regeneration of injured spinal cord in terms of ingrowth of axons and formation of blood vessels with respect to SC-ECM alone.

Currently, dental derived stem cells due to their ability for neurogenic differentiation are considered to be an attractive cell source for SCI regeneration. Outlined below is a brief overview on the recent progress and future perspectives on the use of dental stem cells for SCI treatment.

Use of dental derived stem cells (DSCs) for the treatment of SCI

Numerous populations of mesenchymal stem cells have been discovered in several dental tissues, and they are generally called dental stem cells (Karamzadeh and Eslaminejad, 2013). To date, different human dental stem cells have been isolated and characterised including dental pulp stem cells (DPSCs) (Gronthos et al., 2000), stem cells from human exfoliated deciduous teeth (Miura et al., 2003), stem cells from apical papilla (SCAPs) and dental follicle progenitor cells (DFPCs) (Morsczeck et al., 2005).

The centre of each tooth contains a cavity pulp chamber made up of a soft connective tissue, known as dental pulp, which is rich in odontoblasts, blood vessels, nerve fibres, immune cells and mesenchymal stem cells; called dental pulp stem cells (DPSCs) (Yamamoto et al., 2014). Importantly, the isolation of mesenchymal stem cells from dental pulp is convenient and easy, with no trauma and therefore, they can be considered as a source of stem cells suitable for transplantation (Taghipour et al., 2011).

DPSCs, due to their neural crest origin, possess significant higher neural stem cell properties than those of bone marrow-derived mesenchymal stem cells (Huang et al., 2009; Karaöz et al., 2011) and can differentiate toward functionally active neurones (Arthur et al., 2008). Furthermore, they are attractive for their easy accessibility and potential for autologous transplantation (Giuliani et al., 2013). In addition, they can produce trophic factors including brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF), and ciliary neurotrophic factor (CNTF) that promote neuronal survival (Nosrat et al., 2001; Sakai et al., 2012). Moreover, Martens et al. (2014) have shown that human dental pulp stem cells (DPSCs) can be successfully differentiated into Schwann cells (SCs), a cell type important in the peripheral nerve regeneration. Since DPSCs are originated from migrating neural crest cells, they are physiologically predisposed to differentiate towards peripheral glial cells (Bianco et al., 2016). These results further indicate that DPSCs are good candidates for cell-based therapies as treatment for peripheral nerve injury.

In 2012, Sakai et al. showed that DPSCs and exfoliated deciduous teeth stem cells (SHEDs) possessed higher neuroregenerative activities than bone marrow-derived mesenchymal stem cells and improved the recovery of hind limb locomotor function when transplanted in a rat model of SCI. Specifically, they demonstrated that SHEDs can inhibit apoptosis of oligodendrocytes and neurones in the epicentre of SCI. Moreover, they have shown that SHEDs protect neurofilaments against degeneration, replace damaged or lost oligodendrocytes with functionally analogue cells and regenerate transected axons by paracrine mechanism (Sakai et al., 2012). These results clearly show that the multifaceted neuroregenerative potential of dental stem cells can ameliorate several aspects of functional recovery after SCI. Moreover, the potential effect of DPSCs in the regeneration of injured nerves after trauma was observed in a mouse model of compressive spinal cord injury by de Almeida et al. (2011). They have shown that the DPSCs transplanted in a rat model of SCI release trophic factors into the damaged tissue, induce the presence of axons, express some glial markers and improve locomotor functions. As a consequence, they conclude that DPSCs induce neuroplasticity and endogenous axon guidance in a mouse model of SCI (de Almeida et al., 2011). Also, dental stem cells derived from human apical papilla (SCAP), known as human apical papilla stem cells (SCAPs), hold great promise for the treatment of SCI. Work from de Berdt et al. (2015) shows that the transplantation of SCAPs into the injured rat spinal cord improves gait and reduces glial reactivity.

Recently, several independent research groups reported that dental stem cells show neuro-regenerative activity in a rat model of SCI. In another study, Taghipour and colleagues (2011) transplanted undifferentiated or neural induced SHEDs in a rat model of acute contused SCI. Interestingly, they observed that the transplantation of neural induced SHEDs enhanced a significant locomotor functional recovery in rats with a contused spinal cord. In particular, these authors showed that neural induced SHEDs expressed high levels of neurotrophins such GDNF, BDNF as well as NTF3, which was essential in the induction of axonal bridging beyond cellular grafts in the spinal cord after injury (Taghipour et al., 2011).

In a rat study conducted in 2015, human dental follicle cells (hDFCs) combined with PCL/PLGA electrospun material (AEM) were transplanted to restore the defect in rat spinal cord (Li et al., 2015). Results showed that implanted hDFCs combined with the AEM were able to survive and differentiate towards functional oligodendrocytes in this animal model of SCI. However, due to the small sample size (16 rats), the authors of this study did not observe significant functional improvements in rats transplanted with hDFCs seeded AEM, when compared to controls. They concluded that hDFCs could be considered as a suitable cell source for the treatment of spinal cord defects (Li et al., 2015).

One year later, Nicola et al. (2016) evaluated the effectiveness of stem cells isolated from human exfoliated deciduous teeth transplantation combined with treadmill training to treat rats with experimental SCI.

Results showed that SHEDs have a neuroprotective and anti-inflammatory action. In particular, these cells were able to promote functional recovery and increase neurofilament density near the lesion site after traumatic SCI. These findings demonstrated that grafted SHEDs in combination with treadmill training could also be considered as an effective therapy for the treatment of spinal cord lesions (Nicola et al., 2016).

Recently, the same type of cells, due to their potential for promoting functional recovery were used as a possible treatment strategy for SCI (Nicola et al., 2017). It was observed that SHEDs were able to reduce the overexpression of pro-apoptotic factor TNF-α as well as the neuronal loss over time. These results demonstrate that SHED transplantation after SCI contributes to tissue and motor neuron preservation by reducing the early neuronal apoptosis and interfering with the balance between anti- and pro-apoptotic factors (Nicola et al., 2017).

Another exciting study investigated the effects of DPSCs transplantation combined with chitosan scaffolds into an SCI rat model. Importantly, this transplantation resulted in the marked recovery of hind limb locomotor functions after SCI (Zhang et al., 2016). This positive effect was justified on the basis that neurotrophic factors such as NGF, BDNF, NT-3 and GDNF secreted from transplanted DPSCs were able to improve the neurological outcome and enhance the neural regeneration. Based on this data, it was concluded that DPSCs transplantation could be considered a suitable candidate for treating SCI and also that chitosan scaffolds could be a suitable vehicle to transport DPSCs to the site of spinal cord injury (Zhang et al., 2016).

In a recently published paper, three types of dental stem cells including, DPSCs, dental follicle stem cells (DFPCs) and stem cells from apical papilla (SCAPs) were used to treat a rat model of SCI. Data showed that all type of dental stem cells described above, especially DFSCs, have the potential to promote functional recovery after injury and repair the completely transected spinal cord (Yang et al., 2017). The authors hypothesised these dental stem cells were able to reduce the inflammatory response by inhibiting the expression of interleukin-1β, promote neurite regeneration by inhibiting the expression of ras homolog gene family member A (RhoA), and reduce the progressive haemorrhagic necrosis by inhibiting the sulfonylurea receptor 1 (SUR-1) (Yang et al., 2017).

In 2018, two independent groups reported that DPSCs could be used as new cell source and new therapeutic strategy for the treatment of SCI. In the first study, Kabatas et al. (2018) showed that DPSCs transplanted into a rat with SCI were able to differentiate into nerve cells and recover the damaged spinal cord. In the second study, Luo and colleagues analysed the effects of a thermosensitive heparin-poloxamer (HP) hydrogel containing DPSCs and basic fibroblast growth factor (bFGF) on neuron restoration after SCI. The results showed that the combination of HP hydrogel, DPSCs and bFGF had a significant impact on spinal cord repair and regeneration and could be considered a novel therapeutic strategy for functional recovery, neuron repair and tissue regeneration after spinal cord injury (Luo et al., 2018).

Although the MSC-based strategies seem to be promising, an effective treatment for patients with SCI has not been established so far (Bianco et al., 2016). Today, several clinical trials are evaluating the potential of transplantation of mesenchymal stem cells isolated from bone marrow, umbilical cord and adipose tissue for the treatment of SCI (clinicaltrials.gov numbers NCT02981576, NCT01274975, NCT03521336, NCT03505034, NCT03925649). Their principal objectives are to assess the safety of autologous mesenchymal stem cells transplantation and to determine if the functional, anatomic and physiological outcome measures are improved after mesenchymal stem cells transplantation in patients with SCI. However, until now dental stem cells have not yet been used in clinical trials for the treatment of SCI. Therefore, clinical trials are necessary to prove the beneficial effects of DSCs on human spinal cord regeneration and repair.

The neuroprotective effect is an important mechanism by which DSCs improve the functional recovery after SCI

It has been shown that DSCs such as SHED are able to express the glial marker SB100 and the early neural precursor cell marker vimentin when cultivated in vitro, whereas they are able to stimulate the presence of neural progenitor cells and reduce the early astrocytic hypertrophy when transplanted in the spinal cord of injured rats (Nicola et al., 2019). This experimental model of SCI shed light on the fact that transplanted SHEDs can influence glial scar formation and astrocytic reaction.

Glial scar formation after SCI interferes with functional recovery and neural regeneration due to the inhibitory microenvironment of the injured spinal cord (Yuan and He, 2013). It has been hypothesized that the functional recovery observed in the animal model of SCI transplanted with SHEDs is mediated by paracrine signalling that reduces glial scar formation (Nicola et al., 2019). Therefore, SHEDs have neuroprotective effects when administered after spinal cord injury.

Similarly, it has been shown that also DPSC and SCAP due to their neurotrophic and neuroprotective proper-

ties can promote functional recovery after SCI (Nosrat et al., 2001; Mead et al., 2013; De Berdt et al., 2018). All these studies highlight the neuroprotective potential of DSCs. The understanding of the exact mechanisms related to functional recovery by DSCs is important for the development of new strategies for spinal cord regeneration.

CONCLUSIONS

SCI is a disabling and irreversible condition that results in a loss of sensory-motor function and the disruption of autonomic function (Lee and Thumbikat, 2015). Currently, there are no effective treatments for SCI due to the complicated pathophysiology of SCI (Sakai et al., 2012). Therefore, the development of a treatment for SCI is one of the major challenges in biomedical research (Rowland et al., 2008; Lee and Thumbikat, 2015).

In cell therapy for SCI, various cells have been used including Schwann cells (SCs), neural stem cells, olfactory ensheathing cells (OECs) and bone marrow-derived mesenchymal stem cells (Dasari et al., 2014; Bianco et al., 2016; Gómez et al., 2018; Lin et al., 2018). However, all these types of cells possess some disadvantages and show unsatisfactory performance in repairing large-scale lesions of an organ; therefore, new cell sources are necessary to improve the SCI regeneration (Bianco et al., 2016). In this context,

Table I. Studies that assessed the use of dental pulp stem cells for spinal cord repair and regeneration.

Dental stem cells (DSCs)/scaffold	Animal model	Remarks	Year	References
Dental pulp stem cells (DPSCs)	Mouse model of compressive spinal cord injury	DPSCs induce neuroplasticity and endogenous axon guidance in a mouse model of SCI	2011	(de Almeida et al., 2011)
SHEDs	SCI rat model	Transplantation of SHED or its derivatives could be a suitable candidate for the treatment of SCI	2011	(Taghipour et al., 2011)
Dental pulp stem cells (DPSCs); exfoliated deciduous teeth stem cells (SHEDs)	Injured rat spinal cord	DPSCs and SHEDs possessed higher neuroregenerative activities than BMSCs and provided significant benefits for SCI; DSCs can ameliorate several aspects of functional recovery after SCI	2012	(Sakai et al., 2012)
human apical papilla stem cells (SCAPs) injected with a fibrin hydrogel	Injured rat spinal cord	Transplantation of SCAPs into the injured rat spinal cord improves gait and reduces glial reactivity	2015	(De Berdt et al., 2015)
Dental follicle cells (DFCs) with electrospun PCL/PLGA material	SCI rat model	hDFCs can be a candidate resource in neural regeneration	2015	(Li et al., 2015)
SHEDs	Injured rat spinal cord	SHEDs might be an effective therapy to spinal cord lesions, with possible anti-inflammatory action	2016	(Nicola et al., 2016)
DPSCs and chitosan scaffolds	SCI rat model	Transplantation of DPSCs together with chitosan scaffolds into an SCI rat model resulted in the marked recovery of hind limb locomotor functions.	2016	(Zhang et al., 2016)
SHEDs	SCI rat model	SHED transplantation in rat model of SCI interferes with the balance between pro- and anti-apoptotic factors and reduces early neuronal apoptosis, what contributes to tissue and motor neuron preservation and hind limbs functional recovery	2017	(Nicola et al., 2017)
Human dental follicle stem cells (DFSCs), stem cells from apical papilla (SCAPs) dental pulp stem cells (DPSCs)	SCI rat model	DFSCs, demonstrated the potential in repairing the completely transected spinal cord and promote functional recovery after injury	2017	(Yang et al., 2017)
Dental Pulp-Neural Crest Stem Cells (hDP-NCSCs)	SCI rat model	hDP-NCSCs might be an effective strategy to improve functional recovery following spinal cord trauma	2018	(Kabatas et al., 2018)
Thermosensitive heparin-poloxamer (HP) hydrogel containing DPSCs and bFGF	Injured rat spinal cord	Hydrogel containing DPSCs and bFGF had a significant impact on spinal cord repair and regeneration	2018	(Luo et al., 2018)

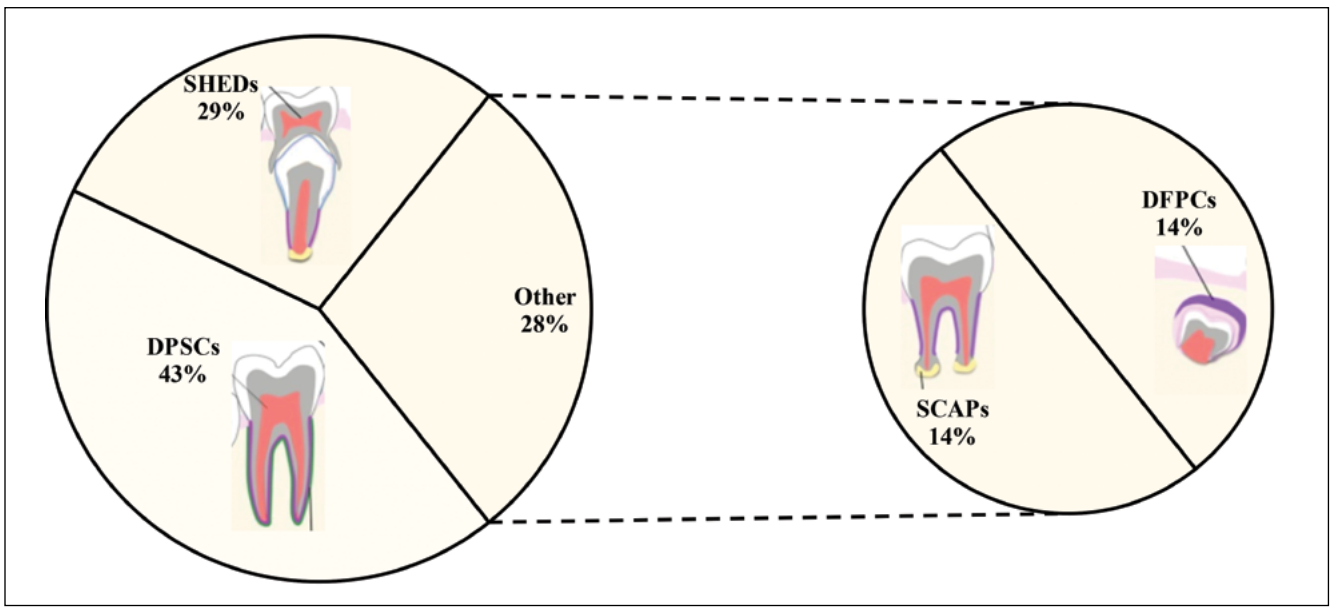

Fig. 1. Type of DSCs used in pre-clinical studies for the treatment of SCI. The diagrams depict the type of DSCs used for the transplantation of DSCs (percentage). DSCs (dental stem cells); DPSCs (dental pulp stem cells); exfoliated deciduous teeth stem cells (SHEDs); stem cells from apical papilla (SCAPs); human dental follicle stem cells (DFSCs), Spinal cord injury (SCI).

it has been shown that dental derived stem cells (DSCs), such as dental pulp stem cells (DPSCs), stem cells from human exfoliated deciduous teeth (SHEDs), dental follicle cells (DFCs) and stem cells from apical papilla (SCAPs) can reconstruct spinal cord defects (Fig. 1; Table I). Importantly, DSCs possess intrinsic advantages in the therapy of SCI compared to mesenchymal stem cells from other sources because they can actively secrete anti-inflammatory and immunomodulatory factors and possess potent tissue regenerative properties (Sakai et al., 2012).

For example, it has been shown that SHEDs show robust immunomodulatory properties that effectively ameliorated several immune diseases such as colitis or systemic lupus erythematosus (SLE) (Yamamoto et al., 2014). Furthermore, they derive from the cranial neural crest and express various differentiation markers

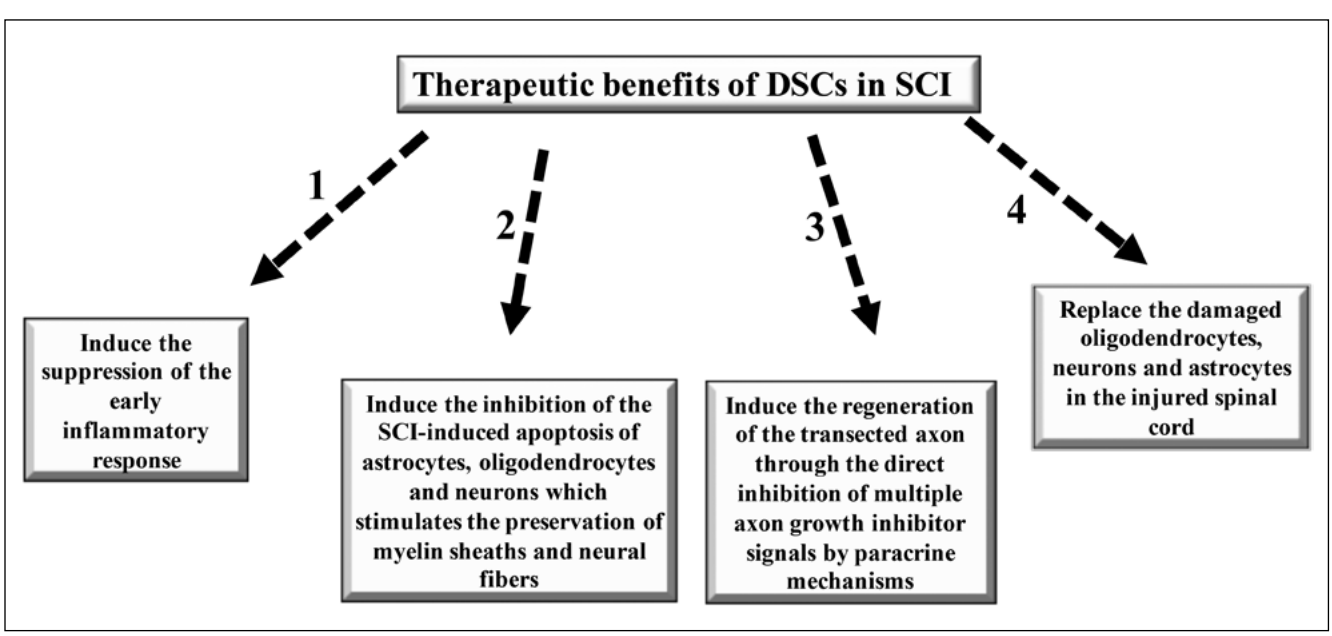

Fig. 2. Therapeutic benefits of dental stem cells (DSCs) in the treatment of spinal cord injury (SCI).

of neuroectodermal stem cells, and it was supposed that DSCs would contribute to neural regeneration (Gronthos et al., 2000; Miura et al., 2003). Importantly, the implantation of DPSCs into the transected rat spinal cords was able to induce a functional improvement by preserving axons and myelin sheaths. Moreover, this implantation was able to reduce the death of glia and neurons and promote the regeneration of transected axons by downregulating multiple growth inhibitors (Sakai et al., 2012; Snyder and Teng, 2012).

In addition, it was described that DSCs can stimulate the differentiation, migration and survival of the endogenous stem cells following central nervous system injury through the expression of neurotrophic factors, neurotrophins and their receptors (Bianco et al., 2016).

Regarding stem cells of tooth origin, most of the cell-based approach proposed for SCI injury so far are mainly based on the use of dental stem cells (DSCs) transplanted in rat models of SCI alone, or in combination with several types of scaffolds including fibrin hydrogel (De Berdt et al., 2015), chitosan scaffold (Zhang et al., 2016), electrospun PCL/PLGA material (Li et al., 2015) and thermosensitive heparin-poloxamer (HP) hydrogel (Luo et al., 2018).

The results described in this review clearly demonstrated that engrafted DSCs including DPSCs, SHEDs, DFSCs and SCAPs provide several therapeutic benefits for treating SCI (Table I).

From the analysis of the literature, it is possible to deduce that DSCs possess four important neuroregenerative activities. Firstly, DSCs can induce the suppression of the early inflammatory response (Yamamoto et al., 2014). Secondly, DSCs can induce the inhibition of SCI-induced apoptosis of astrocytes, oligodendrocytes and neurons, which stimulates the preservation of myelin sheaths and neural fibres (Sakai et al., 2012). In fact, the transplantation of dental pulp tissue into a hemisected spinal cord increased the number of surviving motor neurons (Nosrat et al., 2001). Thirdly, DSCs induce the regeneration of the transected axon through the direct inhibition of multiple axon growth inhibitory signals (Sakai et al., 2012). Finally, DSCs due to their capacity of differentiation into many cell lineages, can replace the damaged oligodendrocytes, neurons and astrocytes in the injured spinal cord (Sakai et al., 2012) (Fig. 2).

In conclusion, the immunomodulatory properties of DSCs, their neural crest origins and the expression of neurotrophic factors make these cells a suitable cell-source for treating the damaged central nervous system, particularly in repairing SCI.

Although DSCs transplantation represents a promising approach to treat spinal cord injury, additional studies are required to establish its therapeutic potential. This review highlights the fact that DSCs can offer therapeutic benefits for treating spinal cord injury through their efficacious neuroregenerative activities.

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