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REVIEW

Dental mesenchymal stem cells and neuro-regeneration: a focus on spinal cord injury

Gabriele Bonaventura[1] · Salvatore Incontro[2] · Rosario Iemmolo[1] · Valentina La Cognata[1] · Ignazio Barbagallo[2] · Erminio Costanzo[3] · Maria Luisa Barcellona[2] · Rosalia Pellitteri[1] · Sebastiano Cavallaro[1]

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Abstract

Regenerative medicine is a branch of translational research that aims to reestablish irreparably damaged tissues and organs by stimulating the body's own repair mechanisms *via* the implantation of stem cells differentiated into specialized cell types. A rich source of adult stem cells is located inside the tooth and is represented by human dental pulp stem cells, or hDPSCs. These cells are characterized by a high proliferative rate, have self-renewal and multi-lineage differentiation properties and are often used for tissue engineering and regenerative medicine. The present review will provide an overview of hDPSCs and related features with a special focus on their potential applications in regenerative medicine of the nervous system, such as, for example, after spinal cord injury. Recent advances in the identification and characterization of dental stem cells and in dental tissue engineering strategies suggest that bioengineering approaches may successfully be used to regenerate districts of the central nervous system, previously considered irreparable.

Keywords Human dental stem cells · Mesenchymal stem cells · Cell therapy · Spinal cord injury

Introduction

Regenerative medicine combines biomedical science and engineering approaches with the aim of restoring the biological function of damaged tissues and relies on the search of tissue sources to obtain cells useful in therapy approaches (Rodríguez-Lozano et al. 2011; Sedgley and Botero 2012).

A useful source of stem cells is characterized by mesenchymal stem cells (MSCs), since these are capable of self-renewal for a limited time *in vitro*. Within the vast class of MSCs, hematopoietic stem cells have been the best-studied and widely applied for over 40 years in clinical practice creating the background for bone marrow (BM) transplantation success (Wright et al. 2001). It has been demonstrated that, after bone marrow and adipose tissue, the oral cavity represents an excellent source of MSCs mainly localized in the periodontal ligament, dental follicle and in the dental pulp (Xiao and Nasu 2014).

In this review, we provide an overview of oral MSCs focusing on the use of hDPSCs for future applications in neural regeneration such as spinal cord injury repair.

Mesenchymal stem cells (MSCs): a brief description

MSCs, also known as mesenchymal stromal cells, are classified as multipotent stem cells, due to their capability to differentiate into various cellular lineages (Caplan 1991; Karaoz et al. 2013; Kopen et al. 1999).

Although the most studied source of MSCs derive from BM, MSCs can be extracted from a variety of tissues, including adipose tissue, umbilical cord, blood (Koch et al. 2007; Schuh et al. 2009), Wharton's jelly (Wang et al. 2004), amniotic fluid (Roubelakis et al. 2007), skeletal muscle tissue and periosteum (Kisiel et al. 2012), liver tissue (Najimi et al. 2017), lung tissue (Shi 2015), menstrual blood (Ren et al. 2016; Ulrich et al. 2013), gingiva and periodontal tissue (Mrozik et al. 2010; Otabe et al. 2012).

✉ Sebastiano Cavallaro
sebastiano.cavallaro@cnr.it

[1] Institute for Biomedical Research and Innovation, Italian National Research Council, Catania, Italy

[2] Department of Pharmaceutical Sciences, Section of Biochemistry, University of Catania, Catania, Italy

[3] Neurology Department, Cannizzaro Hospital, Catania, Italy

Different subtypes of cells have been isolated from dental tissue (Fig. 1). Dental mesenchymal stem cells (DMSCs) can be obtained from erupting primary teeth or extracted teeth, making their isolation simpler and less invasive than aspiration of BM-MSCs. Interestingly, they are considered pluripotent, showing peculiar characteristics related to their markers expression (such as *MYC* and *SOX2*) and morphological aspects depending on the area of extraction (Yalvac et al. 2010).

Dental pulp stem cells (DPSCs)

Human dental pulp stem cells (hDPSCs) originate from ectodermal cells that migrate from the neural tube into the oral region and differentiate into mesenchymal cells (Nuti et al. 2016). The staminal feature of hDPSCs in the adult tissue is preserved by the lack of environmental differentiation stimuli in the dental pulp, a niche sealed by mineralized dentin (d'Aquino et al. 2008). hDPSCs are able to maintain and repair periodontal tissue, are characterized by a high proliferation rate (Nuti et al. 2016) and show plasticity in multi-lineage differentiation. Indeed, a number of in vitro studies have described the possibility to obtain osteoblasts-, chondrocytes-, adipocytes-, odontoblasts-, neural- and myocytes-like cells from hDPSCs (Bonaventura et al. 2018; Nuti et al. 2016; Sonoda et al. 2015).

hDPSCs are known to express mesenchymal- (CD13, CD29, CD44 and CD146) (Martens et al. 2012), staminal- (OCT3/4, NANOG and SSEA4) (Kerkis et al. 2006) and specific neuronal markers (βIII-tubulin, S100, Nestin, Synaptophysin) (Li et al. 2019; Martens et al. 2012). Recently, Niehage et al. (Niehage et al. 2016) identified new hDPSC surface proteins, such as tumor necrosis factor receptor superfamily proteins (CD40, CD120a, CD261, CD262, CD264 and CD266), some integrins (alpha-4, alpha-6 and alpha-10) and IL receptors (CD121a, CD130, CD213a1, CD217 and CDw210b).

Several soluble factors and cytokines secreted by hDPSCs, such as transforming growth factor beta (TGF-β), prostaglandin E2, interleukin-6 (IL-6) and IL-10, could be immunomodulator candidates for regulation of T lymphocyte function with a profound effect on clinical cell therapy (Demircan et al. 2011). For all these reasons, hDPSCs represent a rising candidate for tissue repair therapies (Sakai et al. 2012) and, in particular, for neuro-regeneration (Fig. 2).

Stem cells from human exfoliated deciduous teeth (SHED)

Miura et al. (Miura et al. 2003) were the first to isolate and characterize multipotent stem cells from exfoliated deciduous

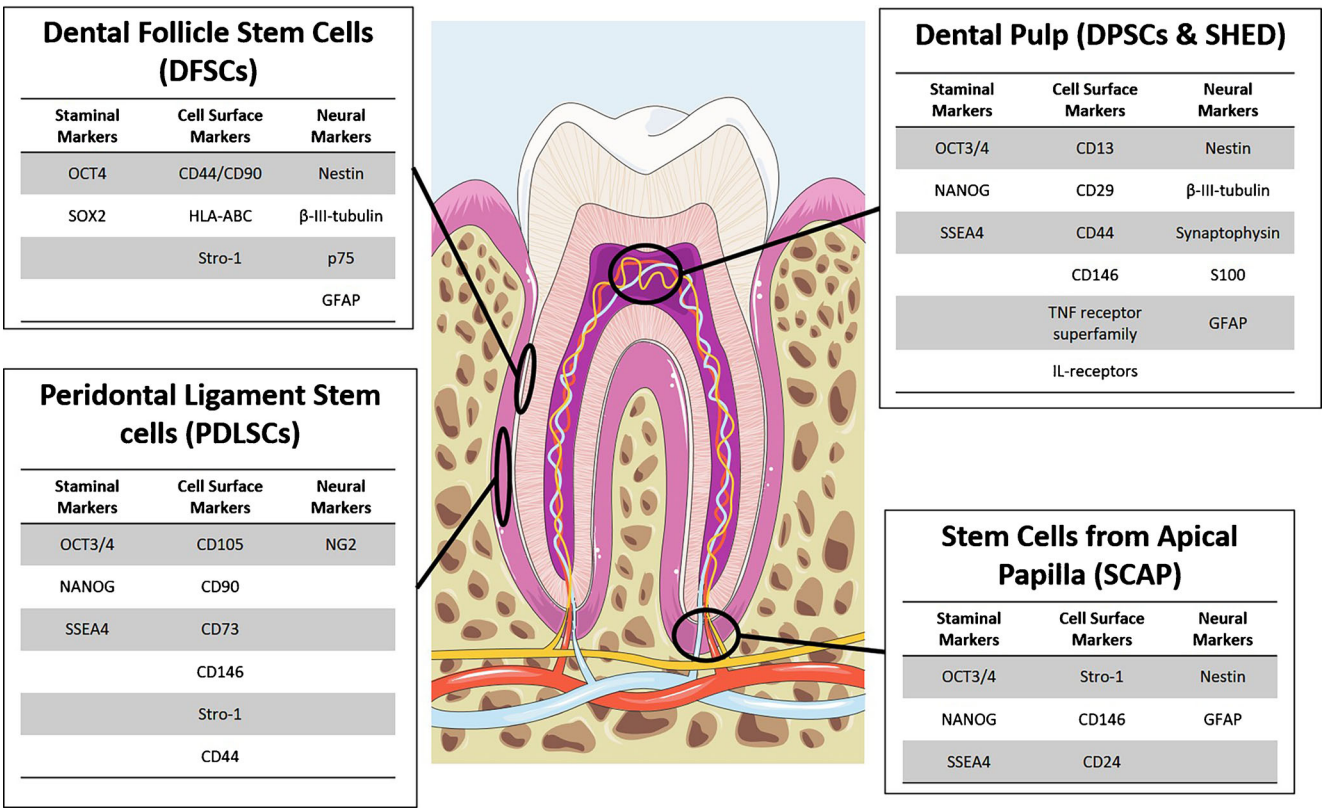


Fig. 1 Anatomical niches of dental mesenchymal stem cells mostly used in neuro-regenerative approaches. Classification and neurogenic induction properties are based on the expression on their cell surface of neuronal markers (this figure was realized with elements from Servier Medical Art: www.servier.fr/servier-medical-art)

teeth (SHED) within dental pulp tissue. These particular MSCs express Stro-1 and CD146; two early mesenchymal markers also present in cell surfaces of BM-MSCs and DPSCs (Fig. 1). In vitro studies showed that SHEDs are able to differentiate into cells of osteogenic, adipogenic, myogenic and chondrogenic lineages (Bakopoulou et al. 2011a; Kerkis et al. 2006; Miura et al. 2003; Wang et al. 2010).

SHED are able to express some neural progenitor markers, such as nestin and the glial marker glial fibrillary acidic protein (GFAP) at both the mRNA and protein levels (Miura et al. 2003). In vitro neural differentiation studies have also demonstrated that this cell population differentiates into neural cells that are able to survive for more than 10 days when transplanted into an adult rodent brain, leading to an overexpression of neural markers, such as neurofilament (Miura et al. 2003). Wang et al. (Wang et al. 2010) described that SHED are able to form in vitro neural-like spheres in a medium optimized for neural stem cells and to further differentiate into dopaminergic neurons. When differentiated into dopaminergic neurons and transplantated in a rat animal model of Parkinson's disease, these cells partially improve motor dysfunctions (Gnanasegaran et al. 2016). A recent study reported that SHED therapy reduces neuronal loss over time (do Couto Nicola et al. 2017). In addition, recent reports demonstrated that SHED-conditioned media may afford significant therapeutic improvements for treating autoimmune diseases, such as multiple sclerosis (Shimojima et al. 2016).

Periodontal ligament stem cells (PDLSCs) and stem cells from apical papilla (SCAP)

Two other cell types included in the oral cavity are the periodontal ligament stem cells (PDLSCs) and the apical papilla stem cells (SCAP), a specialized soft connective tissue that physically sustain teeth structure by linking roots and alveolar bone (Beertsen et al. 1997) (Fig. 1). PDLSCs, deriving from the neural crest (Fortino et al. 2014), exhibit immunosuppressive properties that are mediated by soluble factor release (Wada et al. 2009) and are able to maintain their MSC characteristics after in vivo transplantation, which highlights their possible use in cell therapy and neurogenesis (Bueno et al. 2019; Lei et al. 2014). SCAPs have been described by Sonoyama et al. (Sonoyama et al. 2006; Sonoyama et al. 2008) as a lineage with a higher rate of proliferation and a propensity to osteo/odontogenic differentiation (as demonstrated by the expression of CD24 on the cell surface) (Bakopoulou et al. 2011b; Liu et al. 2015). However, several studies have reported the adipogenic and neurogenic differentiation capacity of SCAP (Abe et al. 2007; De Almeida et al. 2014; Sonoyama et al. 2006; Sonoyama et al. 2008). In fact, under standard culture conditions, SCAP physiologically express neural markers (nestin, βIII-tubulin and GFAP) and, after stimulation, produce additional neural markers such as NeuN, medium chain neurofilaments, neuron-specific enolase and glial markers CNPase (Sonoyama et al. 2008). Furthermore, it has been demonstrated that SCAP, seeded onto a synthetic scaffold, when transplanted into immunocompromised mice, produce regeneration of vascularized pulp-like tissue and the formation of dentin-like mineral structures (Huang et al. 2009).

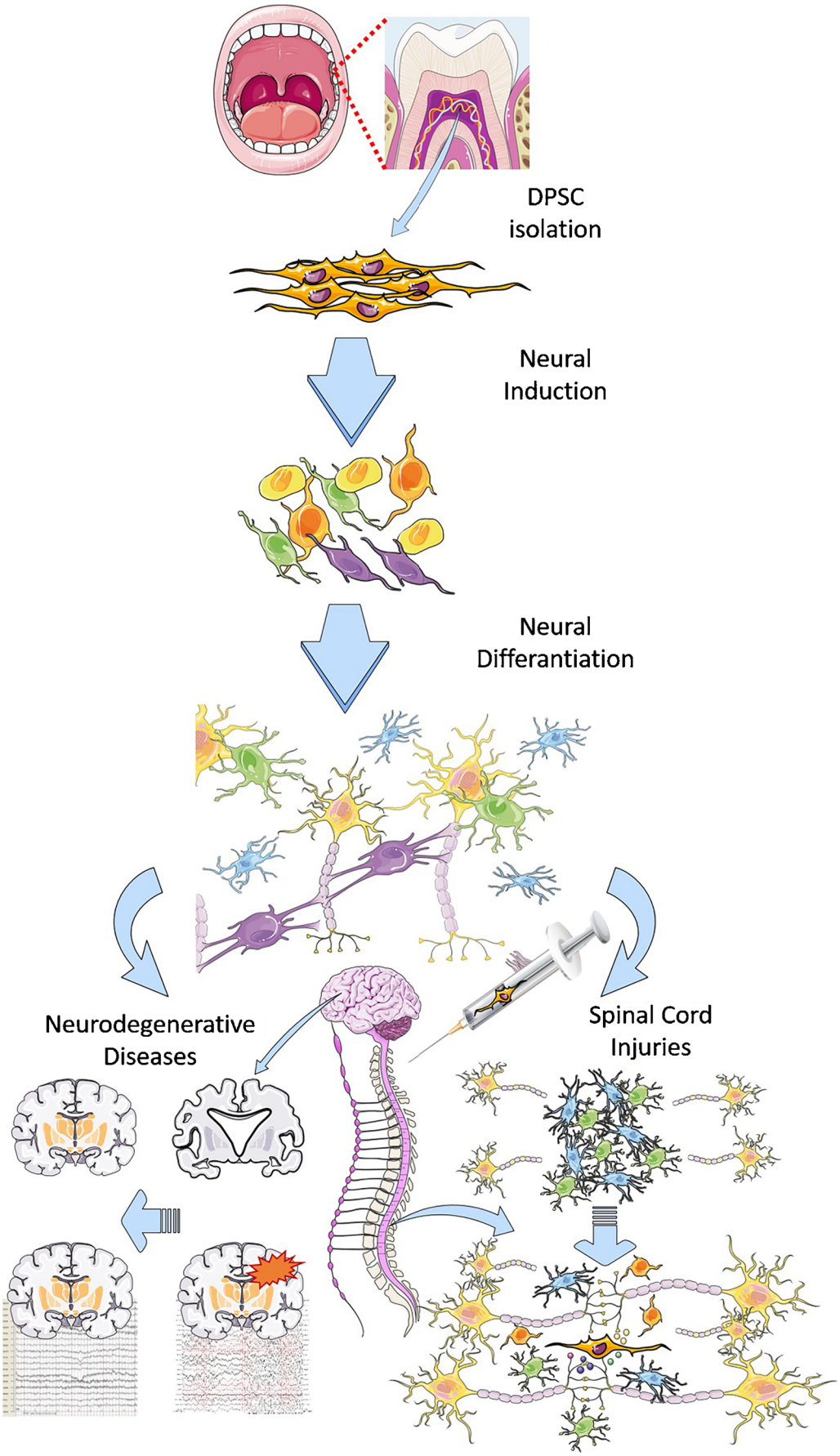
Dental follicle stem cells (DFSCs)

DFSCs were isolated for the first time in 2005 from dental follicles, an ecto-mesenchymal-derived connective tissue (Morsczeck et al. 2005; Zeichner-David et al. 2003). Several studies have demonstrated that hDFSCs have the capacity to differentiate into multiple cell lineages such as osteoblastic, adipogenic and neurogenic lineages (Yao et al. 2008). In addition, since they can be easily obtained during various surgical procedures, hDFSCs represent a good alternative source of MSC suitable for regenerative purposes in cell therapy.

Regenerative effects of DPSCs in neurodegenerative conditions

Despite the fact that BMSCs are the most used MSCs for treating a large range of diseases, they possess several disadvantages linked to bone marrow isolation and lower proliferation rates (Huang et al. 2008; Stenderup et al. 2003). Dental stem cells show MSC-like properties and possess neural characteristics thanks to their origin from the neural crest, their neural marker expression and their ability to secrete neurotrophic factors (Király et al. 2011; Nosrat et al. 2001, 2004). In particular, different studies have confirmed the enormous potential of DPSCs as sources of neuro-regenerative factors. For example, the use of new technologies made possible the differentiation of DPSCs into retinal ganglion-like cells in a three-dimensional network resembling the natural environment of retinal cells. These studies proposed DPSCs as candidates for glaucoma treatment and retinal degenerative diseases (Bray et al. 2014; Roozafzoon et al. 2015).

A specific interest regards the capacity of DPSC to differentiate into oligodendrocytes using a medium enriched in Olig2 factor. Surprisingly, DPSC-derived oligodendrocytes significantly increased the in vivo myelination of peripheral nerves, suggesting the potential use of DPSCs in the cure of myelin-related diseases (Askari et al. 2014). Furthermore, recent discoveries on new factors that induce oligodendrocytes proliferation (Alvarez-Saavedra et al. 2016) extend the possibilities of using DPSCs as a source of myelin. Finally, a recent study reported that DPSC transplantation exerts a neurotrophic effect onto Schwann cells, contributing to peripheral nerve regeneration (Yamamoto et al. 2016). DPSCs can also be used as a source of neurotrophic factors, Aβ-degrading enzyme


DPSC
isolation
Neural
Induction
Neural
Differantiation
Neurodegenerative
Diseases
Spinal Cord
Injuries

◀ **Fig. 2** Neuro-regeneration through DPSCs. DPSCs can be easily isolated from adult deciduous teeth. Given their neurogenic induction properties, DPSCs can be in vitro differentiated into mature neurons or different glial cells, such as Schwann cells or oligodendrocytes. These cells can be implanted into CNS to revert neurodegeneration by replacing dead neurons, promoting myelination, or secreting anti-inflammatory chemokines and neurotrophic factors (this figure was realized with elements from Servier Medical Art: www.servier.fr/servier-medical-art)

(such as neprisilyn–NEP) and antiapoptotic factors, rendering DPSCs as promising candidates for secretome-based therapy in neurodegenerative diseases (Gnanasegaran et al. 2017; Mita et al. 2015; Wang et al. 2017).

All together, these results indicate that hDPSCs may promote regeneration of damaged neuron cells in disease models and serve as a useful cell source for the treatment of neurodegenerative diseases (Ullah et al. 2017; Yang et al. 2017) (Fig. 2).

Clinical development of DPSCs in neuro-regeneration

The most promising clinical applications of DPSCs involve the correction of metabolic diseases and treatment of liver diseases with high mortality rates, such as cirrhosis and hepatocellular carcinoma (Ishkitiev et al. 2010; Ohkoshi et al. 2017). Furthermore, DPSCs have become the preferred alternative to harvesting stem cells during hepatic transplantation (Lei et al. 2014). When DPSCs are cultured on hydrogels, they can spontaneously differentiate into both odontogenic and osteogenic phenotypes (Ishkitiev et al. 2010).

Immortalization and neural differentiation of DPSCs are now a reality. Recent studies (Urraca et al. 2015) have demonstrated that DPSCs transplanted in vivo present even more stable characteristics than the cells differentiated in vitro (Lei et al. 2014). These findings make dental tissue-derived stem cells an excellent pre-clinical model in cell therapy and tissue engineering studies.

The efficacy of DPSCs in pre-clinical studies is based on two different mechanisms: neuro-regeneration and neuroprotection (Mita et al. 2015). DPSCs showed remarkable tissue regenerative capability after spinal cord injury through their immunomodulatory, differentiation and protection capacity (do Couto Nicola et al. 2017; Yang et al. 2017). Additional progress in their clinical neuro-regeneration application is represented by the ability of DPSCs to repair peripheral nerve injury (Ullah et al. 2017).

Currently, the gold standard treatment for peripheral nerve injury is nerve grafting but this technique has several disadvantages, such as donor site morbidity (Sultan et al. 2019). Independent studies have demonstrated that DPSCs ameliorate peripheral nerve injuries, such as sciatic nerve injury (Kolar et al. 2017; Yamamoto et al. 2016) and multiple sclerosis (Shimojima et al. 2016). More recently, DPSCs significantly ameliorated the motor defects in a cerebellar ataxia animal model (Aliaghaei et al. 2019).

Dental mesenchymal stem cells (DPSCs) and spinal cord injury

Spinal cord injury (SCI) is characterized by the loss of neuronal cells as a consequence of a physical trauma, due to inflammatory responses triggered by the mechanical trauma (Ahmed et al. 2016; Crowe et al. 1997; Schwab and Bartholdi 1996; Thuret et al. 2006). DMSC-based therapies have shown promising results in SCI treatment (Wang et al. 2017). DPSC can be differentiated into Schwann-like glial cells, becoming able to secrete neurotrophic factors (NTF) and promote survival and neurite outgrowth (Choo et al. 2008). However, many difficulties still exist in the use of DMSCs for SCI regeneration, such as the low rate of cell engraftment and survival after transplantation. In order to overcome these issues, engineered 3D scaffolds have been proposed for DMSCs delivery after SCI, which may provide a surrounding environment conferring a mechanical support to promote cell adhesion, migration and in vivo differentiation (Mead et al. 2017). In this regard, different in vivo studies have highlighted the significant impact of DMSCs as a promising strategy for neuronal repair, functional recovery and tissue regeneration after SCI. A preliminary study in animal models of SCI demonstrated the therapeutic potential of DPSCs through a paracrine-mediated mechanism that promotes axon regeneration and survival of endogenous neurons and glia within and around the lesion site (Martens et al. 2014). Transplanted neural induced SHED in a rat SCI site is known to improve locomotion (Taghipour et al. 2011). Some authors administered neural-differentiated DPSCs combined with a chitosan scaffold into a chronic contusive SCI rat model (Zhang et al. 2016). In this DPSC-/chitosan scaffold-treated group, a greater amount of BDNF, GDNF, b-NGF and NT3 was found in the site of lesion and was responsible for hind limb locomotor recovery. Recently, a thermosensitive heparin-poloxamer (HP) hydrogel containing DPSCs and bFGF was used as an optimal combination of scaffold, cell and growth factors for neuronal regeneration as well as functional recovery after SCI (Luo et al. 2018).

Conclusion

Since DPSCs are widely available and easily accessible, they represent an alternative to traditional therapies in the management of neurological disorders, including SCI. DPSCs hold several advantages over BM-MSCs, such as less invasive isolation and superior *ex vivo* proliferation. However, several aspects of these stem cells still need to be fully investigated, such as their differentiation potential into the cells of interest, their ability to produce and secrete neurotrophic factors, their homing properties and their immune response modulatory abilities.

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Compliance with ethical statements

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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