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REVIEW

Dental stem cells and their promising role in neural regeneration: an update

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Abstract
Introduction Stem cell-based therapies are considered to be a promising treatment method for several clinical conditions such as Alzheimer's disease, Parkinson's disease, spinal cord injury, and many others. However, the ideal stem cell type for stem cell-based therapy remains to be elucidated.
Discussion Stem cells are present in a variety of tissues in the embryonic and adult human body. Both embryonic and adult stem cells have their advantages and disadvantages concerning the isolation method, ethical issues, or differentiation potential. The most described adult stem cell population is the mesenchymal stem cells due to their multi-lineage (trans)differentiation potential, high proliferative capacity, and promising therapeutic values. Recently, five different cell populations with mesenchymal stem cell characteristics were identified in dental tissues: dental pulp stem cells, stem cells from human exfoliated deciduous teeth, periodontal ligament stem cells, dental follicle precursor cells, and stem cells from apical papilla.
Conclusion Each dental stem cell population possesses specific characteristics and advantages which will be summarized in this review. Furthermore, the neural characteristics of dental pulp stem cells and their potential role in (peripheral) neural regeneration will be discussed.

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Keywords Dental stem cells · Neural characteristics · Tooth development · Stem cells

Introduction

In the last decade, cell-based therapies are emerging as a novel therapeutic option in a wide variety of neurological disorders such as Alzheimer's disease, Parkinson's disease, stroke, spinal cord injury, and peripheral nerve injury among others [1–4]. These neurodegenerative disorders are characterized by the loss or degeneration of neurons, leading to functional impairment. As treatment, therapies are based on delaying the deleterious effects from the loss of neurons or other neural cell types [5]. Neural stem cells are the most ideal cell source to be applied in stem cell-based therapies for neurological disorders, considering their self-renewal capacity and ability to differentiate into neural cell types such as neurons, astrocytes, and oligodendrocytes. However, neural stem cells are difficult to harvest from the adult brain, and therefore, other stem cell sources are needed. Several stem cell populations can be found within the adult human body. Among them are the mesenchymal stem cells (MSCs) which have been proven to be a multipotent stem cell population being able to differentiate into cells of adipogenic, chondrogenic, myogenic, and neurogenic lineages [6]. In addition, MSC secretes a broad range of bioactive molecules, such as growth factors, cytokines, and chemokines, which play an important biological role during injury [7]. Recently, MSC-like stem cell populations have been isolated from different dental tissues such as dental pulp, apical papilla, dental follicle, and periodontal ligament tissue [8–12]. The first section of this review gives a brief overview on stem cells in general. Next, the different stem cell populations present in dental tissues and their neural characteristics are discussed. The final section of the review focuses on the clinical application of dental (pulp) stem cells in neurological disorders.

Stem cells

Stem cells are defined as cells possessing the capacity of self-renewal and differentiation. This means that cells are able to give rise to two daughter cells with one being identical to the mother (self-renewal) and the other one being differentiated into a more specialized cell. Four types of stem cells have been established based on the ability and potency to differentiate into different cell types. (1) A fertilized egg can form an entire embryo including the extraembryonic tissues like the supporting trophoblast which is required for the survival of the developing embryo. These cells are termed *totipotent* stem cells. (2) *Pluripotent* stem cells give rise to germ cells and cells of mesoderm, endoderm, and ectoderm. These cells cannot form extraembryonic tissues and therefore cannot develop into a complete organism. (3) Postnatal or adult stem cells are termed *multipotent* stem cells and are capable of multi-lineage differentiation in cells of only one germ layer. (4) Cells which can only differentiate into one defined cell type are called *unipotent* or progenitor stem cells. These cells possess a limited self-renewal capacity, defining them still as stem cells [13].

Adult stem cells

During the adult life, stem cells are still present within various tissues and organs. These stem cells are able to self-renew and differentiate into cells of one germ layer. In addition, they are able to repopulate the tissue after damage and contribute to a natural turnover, meaning that they can provide a progeny even in the absence of injury [14]. Based on their differentiation capacity, adult stem cells are mostly referred to as multipotent stem cells. Several adult stem cell types can be distinguished, considering their presence within the body (hematopoietic stem cells, neural stem cells, mesenchymal stem cells…). Hematopoietic stem cells are present in bone marrow and can differentiate into all blood cells of the myeloid and lymphoid cell lineages. Neural stem cells can be isolated from the subventricular zone and from the subgranular zone of the hippocampal dentate gyrus. They are able to differentiate into the three cell types of the brain (neurons, astrocytes, and oligodendrocytes). MSC can be found in a variety of tissues and organs like bone marrow, adipose tissue, umbilical cord blood and stroma, placenta, amniotic membrane, synovium, lung, dental pulp tissue…. They are capable of differentiating into cells of the mesodermal lineage like adipocytes, chondrocytes, and osteoblasts.

Mesenchymal stem cells

Friedenstein et al. were the first to identify a cell population in the stromal fraction of rat bone marrow, which adhered to a plastic surface in vitro and was able to undergo osteogenic differentiation. This cell population was initially called fibroblast colony-forming cells but is now referred to as marrow stromal cells or MSC [15]. Bone marrow-derived MSC (BM-MSC) possesses the self-renewal capacity to form colonies in vitro and is capable of differentiating into multiple mesenchymal cell lineages in vitro and in vivo [6, 7]. However, they are limited to a growth potential of 30 to approximately 50 population doublings following ex vivo expansion [16, 17]. BM-MSC consists of a heterogeneous cell population with cells displaying a fibroblast-like or spindle-shaped morphology. After expansion, a more homogeneous cell population with a spindle-shaped morphology is derived. The precise identity of MSC remains a challenge due to the lack of a single definitive marker. Therefore, a panel of different cell surface antigens is used to identify MSC in a cell population. The cells should express associated markers CD29 (integrin β1), CD44 (hyaluronan receptor), CD73, CD105 (endoglin), the early bone marrow progenitor marker CD90 (Thy-1), and the extracellular matrix proteins vimentin, laminin, and fibronectin. MSC should lack marker expression of CD11b and CD14 (monocytes and macrophages), CD34 (primitive hematopoietic stem cells and endothelial cells), CD45 (leukocytes), CD79α or CD19 (B cells), and HLA-DR [18, 19]. Recently, it has been shown that MSC can undergo transdifferentiation towards cells of the neural lineage like astrocytes and neurons [20, 21]. Furthermore, after transplantation of BM-MSC into regions of central nervous injury, an improved functional recovery was observed in the injured rodent brain or spinal cord [22, 23].

Mesenchymal stem cells yield a great potential for stem cell-based regenerative therapies, based on their multilineage (trans)differentiation potential and their high proliferative capacity. The identification of the regenerative potential of mesenchymal stem cells has encouraged intense research during the last years.

Recently, various clinical studies are conducted using mesenchymal stem cells as transplants for treatment or to improve functional outcomes. For instance, the cardiac function of ischemic hearts was improved after intracardial transplantation of bone marrow MSC [24–26]. Furthermore, the infusion of allogenic whole bone marrow or bone marrow MSC in children, suffering from type III osteogenesis imperfecta, showed a promising phenotypic improvement with reduced fracture frequency and improved growth velocity [24–26]. Taken together, although clinical trials show promising results, there is still a long way to go before MSC can be used in the clinic as a standard treatment.

Tooth development

Tooth development is regulated by sequential and reciprocal interactions between the oral epithelium and the underlying

ecto-mesenchymal cells, both originating from migrating neural crest cells. These interactions result in the formation of an outer layer of enamel formed by ameloblasts, derived from the oral epithelium, and an inner layer of mineralized dentin synthesized by odontoblasts, which are derived from the dental papilla. The central chamber of the tooth contains a soft mucoid connective tissue called the dental pulp, also derived from the dental papilla, and is infiltrated by a network of blood vessels and nerve bundles [27, 28]. By close interactions and signals exchanged between epithelial and mesenchymal cells, a tooth will develop through a series of different stages (lamina stage, bud stage, cap stage, and bell stage) (Fig. 1).

Stem cells in dental tissues

Due to large drawbacks of obtaining BM-MSC including pain, morbidity, and low cell number upon harvest, alternative sources for MSC have been explored. During the last several years, various MSC-like cell types have been identified in dental tissues (see Table 1). The first type of dental stem cells was isolated from pulp tissue and was termed dental pulp stem cells (DPSCs) [8]. Subsequently, more dental stem cell populations were isolated and characterized: stem cells from human exfoliated deciduous teeth (SHED) [9], periodontal ligament stem cells (PDLSCs) [11], and stem cells from apical papilla (SCAP) [12, 29]. Recent studies have identified the fifth dental tissue-derived stem cell population referred to as dental follicle precursor cells (DFPCs) [10]. Dental tissues are specialized tissues that do not undergo continuous remodeling as shown in bony tissue; therefore, dental tissue-derived stem/progenitor cells may be more committed or restricted in their differentiation potency in comparison to BM-MSC. Additionally, dental mesenchyme is termed ecto-mesenchyme due to its earlier interaction with the neural crest. From this perspective, ecto-mesenchyme-derived dental stem cells may possess different characteristics [30].

Origin of different dental stem cells

As previously mentioned, oral tissues contain a rich source of dental stem cells: DPSC, SHED, PDLSC, SCAP, and DFPC. These stem cell populations can be isolated from different tissues of the oral and maxillofacial region. Furthermore, they are derived from different developmental stages.

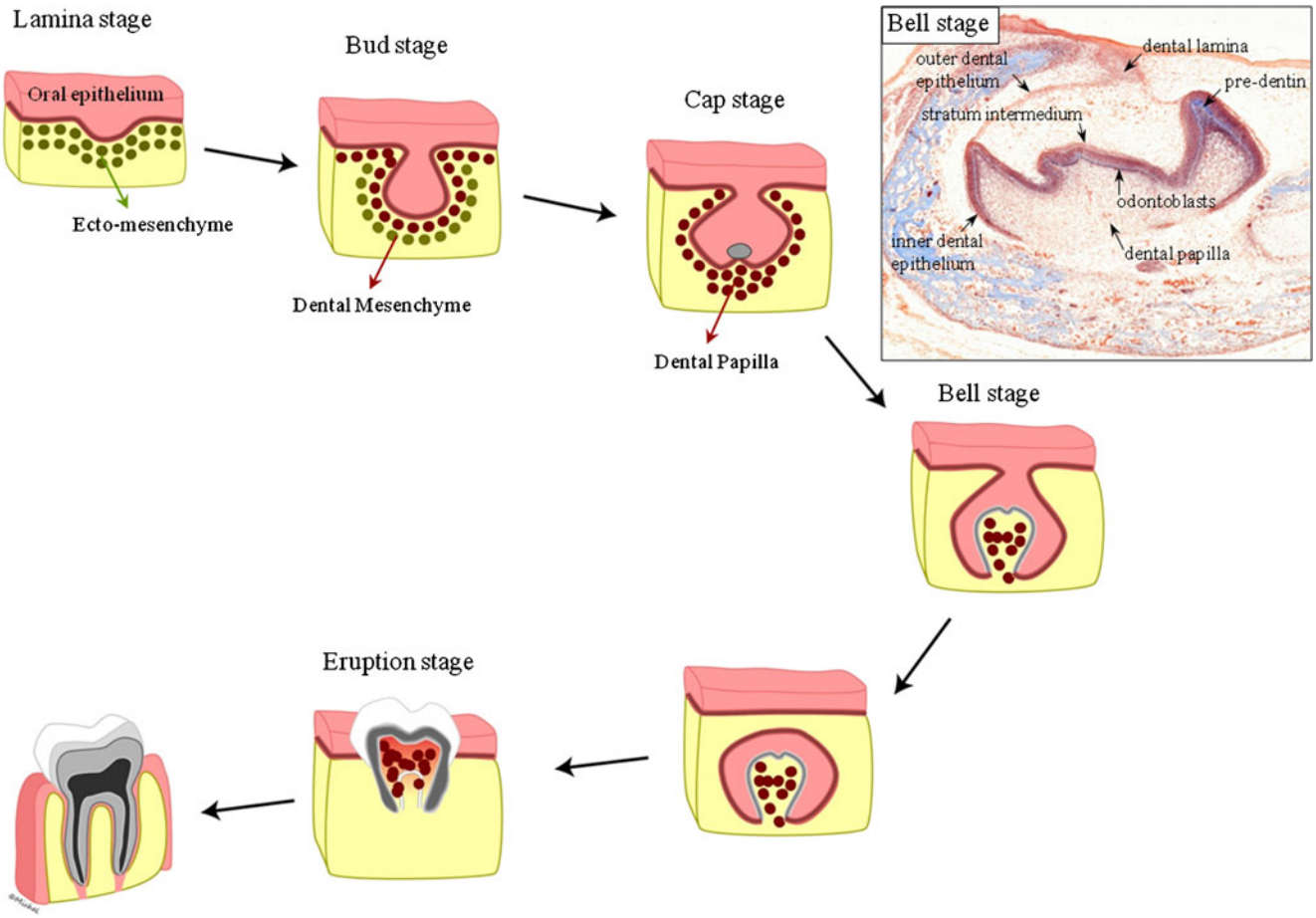

Fig. 1 Different stages during tooth development

Table 1 Overview differentiation potential of dental stem cells

	DPSC	SHED	PDLSC	DFPC	SCAP
Location	Permanent pulp tissue	Exfoliated deciduous pulp tissue	Periodontal ligament	Dental follicle of developing tooth	Apical papilla of developing root
Differentiation potential (in vitro)	Osteo-/odontogenic chondrogenic, adipogenic, myogenic, neurogenic, melanogenic, endothelial	Osteo-/odontogenic chondrogenic, adipogenic, myogenic neurogenic	Osteo-/odontogenic chondrogenic, adipogenic, myogenic, neurogenic, cementogenic	Osteo-/odontogenic, chondrogenic, adipogenic, neurogenic	Osteo-/odontogenic adipogenic, neurogenic
Differentiation potential (in vivo)	Ectopic dentin–pulp-like complex; secretion of neurotrophic factors; recruitment, proliferation, and maturation of endogenous neural cells; axon guidance; neuronal and glial differentiation	Ectopic dentin-like tissue; neuronal differentiation, incorporation in blood vessels	Cementum/periodontal ligament-like structure	Periodontal ligament-like structure	Dentin–pulp-like complex; vascularized pulp-like tissue

Dental pulp stem cells and SHED can be isolated from pulp tissue of impacted or erupted teeth as SHED can be found in primary teeth and DPSC in pulp tissue of secondary teeth. However, the study of Feng et al. reported that inside the pulp tissue, more than one stem cell population is present, depending on the environmental conditions [31]. Not only dental pulp tissue-derived stem cells but also pericyte-derived stem cells contribute to the differentiating stem cell population after damage has occurred to the dental tissue. Several research groups have shown that pericytes can differentiate into multiple cell types, in this way helping in tissue growth and/or repair [32–34]. In experiments using transgenic mice, Feng et al. found that during the late bud stage, pericytes migrate from capillary walls into the mesenchymal tissue condensing around the epithelial tooth bud. In the next stage of tooth development, the cap stage, pericytes are not only surrounding the vessels, but a few cells are also present inside the mesenchymal tissue, the dental papilla, that will form the pulp. The pericytes will remain quiescent until damage has occurred to the odontoblasts, stimulating the proliferation of pericytes. Consequently, this group states that two different stem cell populations exist inside the pulp tissue, pulp-derived stem cells, and pericyte-derived stem cells, contributing to the formation of most of the odontoblasts in growth and repair. This group also suggests that the amount of pericyte- and non-pericyte-derived stem cells, contributing to cell differentiation, depends on the extent of vascularity and kinetics of growth and tissue repair [31]. It must be noted that this research was performed on dental pulp tissue of the continuous growing incisor of mice which contain specialized cells at the cervical loop for continuous cell replacement due to the functional erosion of the tooth [35]. In addition, compared to molars, rodent incisors have no obvious crown or root, but a labial, enamel-covered surface and a lingual, enamel-free surface, respectively [35]. Several reports state that different stem cell niches are present within the dental pulp of continuous growing incisors in mice. The group of Janebodin et al. used a Wnt1-Cre/R26R-LacZ mice model to study the developmental origin of DPSCs [36]. They identified two regions in the dental pulp (sub-odontoblastic and perivascular region), containing neural crest derived-DPSC which were reported to be stem cells niches [34, 36, 37].

In human third molars, however, there are conflicting results about the number and location of stem cells niches. In the study of Martens et al., two distinct stem cell niches were observed in immature dental pulp tissue (third molars with root formation of <50 %) of human third molars: one niche at the perivascular zone and one niche at the cervical area towards the center of the pulp tissue and towards the apex. However, the presence of the niche at the cervical area of the tooth disappeared in adult dental pulp tissue (third molars with root formation of >50 %), leading to the presence of only one stem cells niche, namely, at the perivascular zone [38] which is confirmed by several other studies [34, 39, 40]. The group of Atari et al. isolated two distinct stem cell populations from the dental pulp of human third molars. Depending on the culture medium and the density at which the cells were seeded, dental pulp pluripotent stem cells or dental pulp mesenchymal stem cells could be isolated. These two populations coexisted in culture but differed in gene expression and differentiation potential [41]. However, they did not characterize the location of these two populations within the pulp tissue. If these two populations also exist in vivo, it needs to be determined by using, for instance, in situ immunohistochemistry. The group of Karbanova et al. [42] identified also multiple stem cell niches in impacted human third molars. By using a combination of different

markers (smooth muscle actin, CD146, Musashi-1, nestin, and neuro-glial 2), they found four alternative stem cells niches present within the dental pulp tissue containing distinct multipotent DPSC. Whether there are multiple stem cells niches present or which stem cell population(s) exist within the dental pulp tissue still needs to be further explored.

During the bud stage of tooth development, the dental follicle is formed and surrounds the developing pulp tissue. DFPC can be isolated from the dental follicle of impacted teeth. In the late bell stage, the dental follicle will differentiate into the supporting tissues of the tooth such as the periodontal ligament [43, 44]. SCAP can be isolated from the root apical papillae from impacted teeth as PDLSC can be isolated from the periodontal ligament of erupted teeth (Fig. 2). In addition, other stem cell populations can be found in the maxillofacial and oral region: BM-MSC, tooth germ progenitor cells, oral epithelial progenitor/stem cells, gingival-derived mesenchymal stem cells, periosteum-derived stem cells, and salivary gland-derived stem cells. These stem cell populations are nicely summarized in the review of Egusa et al. [45] and Chen et al. [45, 46].

Dental pulp stem cells

The possibility that dental pulp tissue might contain mesenchymal stem cells was first suggested by the observation that severe tooth damage penetrates both the enamel and dentin and into the pulp which stimulated a limited natural repair process. Consequently, new odontoblasts were formed, producing new dentin to repair the lesion [40, 47, 48]. DPSCs were for the first time isolated and characterized from dental pulp tissue by Gronthos et al. [8] in 2000. DPSCs are described as a high proliferative cell population possessing the self-renewal ability and multi-lineage differentiation potential [8, 49]. Furthermore, they can be induced to differentiate into odontoblast-like cells, characterized by polarized cell bodies and accumulation of mineralized nodules [50]. DPSCs display mesenchymal characteristics such as a fibroblast-like morphology, adherence to a plastic surface, and the ability to form colonies when cultured in vitro. A similar expression pattern of mesenchymal and hematopoietic surface markers is found in both DPSC and BM-MSC: a positive expression of the mesenchymal markers CD29, CD44, CD59, CD90, CD106, and CD146 and a negative expression for hematopoietic makers CD34, CD45, and CD11b [30, 51, 52]. Alge et al. also compared DPSC and BM-MSC regarding their proliferation rate, colony formation, clonogenic potential, and mineralization potential. They reported that DPSC have a higher proliferation rate, a greater clonogenic potential, and a higher number of stem/progenitor cells in the population and may have increased mineralization potential compared to BM-MSC [51].

DPSCs are ectodermal-derived stem cells, originating from migrating neural crest cells and possess mesenchymal stem cell properties [53–56]. They are multipotential cells being able to differentiate in vitro into cells of the odontogenic, adipogenic, osteogenic, chondrogenic, myogenic, melanogenic, and neurogenic lineages under the appropriate culture conditions [8, 57–63]. In vivo studies reported the formation of an ectopic pulp–dentin-like tissue complex when transplanted with a hydroxyapatite/tricalcium phosphate (HA/TCP) carrier into immunocompromised mice. A vascularized pulp-like tissue was formed surrounded by a layer of odontoblast-like cells expressing dentin sialophosphoprotein (DSPP), which produced dentin-containing dentinal tubules similar to those in natural dentin. DPSC could also produce bone when implanted subcutaneously in immunocompromised mice with HA/TCP as a carrier [8, 64]. Huang et al. showed that also a dentin–

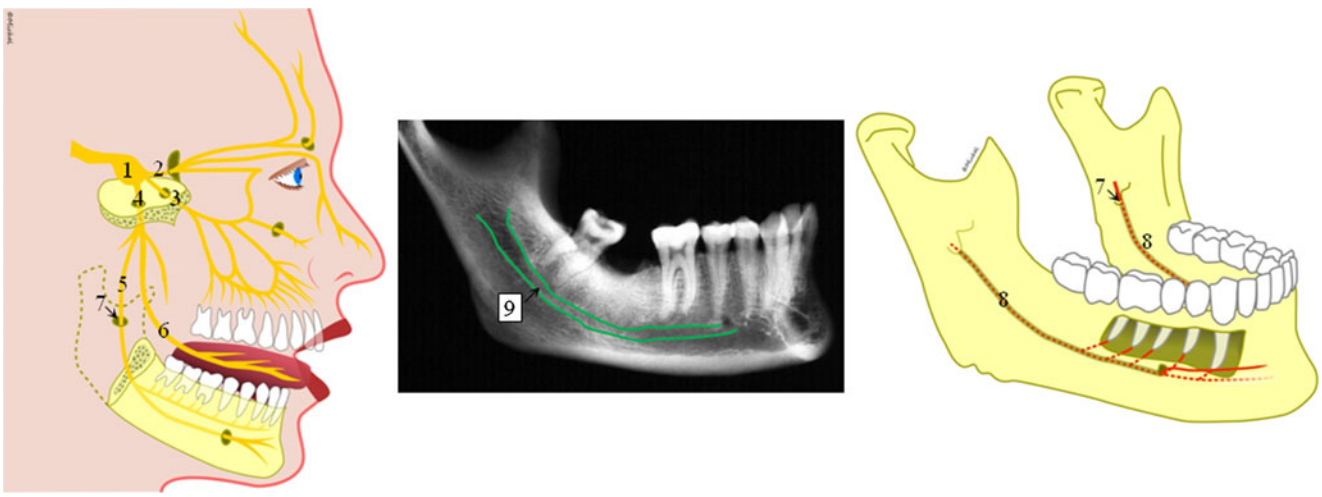

Fig. 2 Anatomical image of inferior alveolar nerve and its canal. *1* Trigeminal ganglion, *2* ophthalmic nerve, *3* maxillary nerve, *4* mandibular nerve, *5* inferior alveolar nerve, *6* lingual nerve, *7* mandibular foramen, *8* inferior alveolar nerve in mandibular canal, *9* mandibular canal

pulp-like complex with a good vascularity could be regenerated in an emptied root canal space by DPSC [65].

Moreover, Marchionni et al. were able to differentiate the DPSC into endothelial-like cells. Incubation of DPSC with vascular endothelial growth factor (VEGF) resulted in an increased expression of several blood vessel markers such as FLT-1, KDR, ICAM-1, and von Willebrand factor. When cultured on a fibrin mesh, VEGF-induced DPSCs displayed endothelial features such as a focal organization into capillary-like structure [66]. However, the endothelial differentiation potential of DPSC in vivo is still under debate. Although DPSCs were able in vivo to induce host neovascularization in two different animal models (rat acute myocardial infarction and mouse hind limb ischemia), DPSCs were only found in the proximity of the newly formed capillaries but were not incorporated into the blood vessel wall. Therefore, no in vivo endothelial differentiation was reported [67, 68]. In addition, DPSC can express neural markers, produce and secrete neurotrophic factors, induce axon guidance, and differentiate into functionally active neurons, suggesting their potential as cellular therapy for neuronal disorders [58, 59, 69–73]. This topic will be further discussed in "Neural characteristics of dental stem cells" and "Dental stem cells as treatment for peripheral nerve injury," respectively.

Several studies have demonstrated that DPSCs retain their stem cell properties following cryopreservation. DPSC cultures can be established from extracted human third molars with a high efficiency, even after the whole tooth is cryopreserved [74–76]. Given that extracted human teeth are routinely discarded as medical waste, cryopreservation of DPSC, dental pulp tissue, or even of a whole tooth yields great advantages for tissue engineering and regenerative medicine. Therefore, DPSC should be used for cell banking.

Based on the multi-lineage differentiation potential of DPSC, their ease of isolation, and cryopreservation properties, DPSC can be an ideal stem cell population for future stem cell-based therapies.

Stem cells from human exfoliated deciduous teeth

Miura et al. were the first to isolate and characterize a multipotent stem cell population within dental pulp tissue derived from exfoliated deciduous teeth (SHED) [9]. Compared to DPSC, SHED possess a higher proliferation rate, increased cell population doublings, sphere-like cluster formation, osteo-inductive capacity in vivo, and failure to reconstitute a complete dentin–pulp-like complex. SHED were found to express the cell surface molecules Stro-1 and CD146, two early mesenchymal markers present in BM-MSC and DPSC. In vitro studies showed that SHED were able to differentiate into cells of osteogenic, adipogenic, neurogenic, myogenic and chondrogenic lineages [9, 77–79]. Furthermore, when SHED were subcutaneously transplanted in immunocompromised mice, they formed ectopic dentin-like tissue, but they were unable to regenerate a dentin–pulp-like complex. SHED did not differentiate into osteoblasts but induced new bone formation by forming an osteo-inductive template to recruit murine host osteogenic cells. These data suggest that deciduous teeth may not only provide guidance for the eruption of permanents teeth, as generally assumed, but may also be involved in inducing bone formation during the eruption of permanent teeth [9]. A recent study of Sakai et al. used the combination of in vitro and in vivo approaches to investigate the potential of SHED to differentiate into functional odontoblasts and angiogenic endothelium. They showed that SHED were capable of differentiating into functional blood vessels that connected with the host vasculature. Furthermore, the mineralized tissue generated by SHED in the pulp chamber of the tooth slice/scaffolds had morphological features of dentin, including the presence of dentinal tubules and predentin, which distinguish it from osteoid tissue [80].

Not only the osteo/odontogenic differentiation capacity of SHED is investigated during the last several years, but also the neurogenic induction of SHED has gained much attention. Previous investigations into the neural potential of SHED have shown that under non-neuronal induction conditions, these cells expressed the neural progenitor marker, nestin, and the glial marker, glial fibrillary acidic protein (GFAP), at both the mRNA and protein levels. In vitro neural differentiation studies of SHED demonstrated that this cell population was able to differentiate into neural cells based on cellular morphology and the expression of early neuronal markers. Furthermore, it was shown that SHED can survive for more than 10 days when transplanted into the adult rodent brain and expressed neural markers such as neurofilament M [9]. The study of Wang et al. indicated that SHED were able form neural-like spheres in a medium optimized for neural stem cells in vitro and were able to further differentiate into a cell population that contained specific dopaminergic neurons. Moreover, SHED and SHED-derived spheres survived and differentiated into dopaminergic neurons after transplantation in a rat animal model of Parkinson's disease, partially improving the behavioral impairment [79]. Taken together, SHED probably represent a cell population of more immature multipotent stem cells than DPSC.

Periodontal ligament stem cells

The periodontal ligament is a specialized soft connective tissue derived from the dental follicle and also originates from neural crest cells. The periodontal ligament connects the cementum (a thin layer of mineralized tissue covering the roots of the teeth) to the alveolar bone and functions primarily to sustain and help constrain teeth within the jaw. The periodontal ligament does not only have an important role in

supporting teeth but also contributes to tooth nutrition, homeostasis, and repair of damaged tissues [27]. It has been shown that the periodontal ligament contains a stem cell population, PDLSCs, which have the potential to form periodontal structures such as the cementum and periodontal ligament and were able to differentiate in vitro into osteoblasts, cementoblasts, adipocytes, and chondrocytes [11, 81, 82]. Moreover, PDLSCs were able to differentiate into spontaneously contracting myotubes, neurofilament-positive neuron-like cells, GFAP-positive astrocyte-like cells, and 2′,3′-cyclic nucleotide-3′-phosphodiesterase (CNP)-positive oligodendrocyte-like cells [83]. When transplanted into immunocompromised rodents, PDLSC showed the capacity to form collagen fibers, similar to Sharpey's fibers, connecting to the cementum-like tissue generating a cementum/periodontal ligament-like structure. PDLSC contributed in this way to periodontal tissue repair, suggesting the potential to regenerate periodontal ligament attachment [11]. This correlates with the fact that PDLSC had a high expression of scleraxis, a specific transcription factor associated with tendon cells. Upon implantation into the tooth socket of the mandible of a minipig, PDLSC transplanted with HA/TCP as a carrier formed an artificial bioroot encircled with periodontal ligament tissue [29, 84]. PDLSCs have thus the potential for forming periodontal structures, especially including the cementum and periodontal ligament.

Dental follicle precursor cells

Dental follicle is an ecto-mesenchymal tissue that surrounds the enamel organ and the dental papilla of the developing tooth germ prior to eruption. This tissue contains progenitor cells that form the periodontium, cementum, alveolar bone, and periodontal ligament. Dental follicle cells shape the periodontal ligament by differentiating into periodontal ligament fibroblasts that secrete collagen and interact with fibers on the surfaces of adjacent bone and cementum. Precursor cells (DFPC) have been isolated from human dental follicles of impacted third molars using enzymatic digestion of dental follicle tissue and express the stem cell markers Notch1, Stro-1, and nestin. DFPCs have the ability to differentiate into osteoblasts/cementoblasts, chondrocytes, adipocytes, and neuron-like cells when grown under the appropriate culture conditions in vitro [10, 85, 86]. In addition, immortalized DFPCs were transplanted into immunocompromised mice and were able to recreate a new periodontal ligament-like structure after 4 weeks [87]. Human DFPCs were transplanted in immunocompromised mice in combination with hydroxyapatite powder to investigate the developmental potential in vivo. Transplants generated a structure compromised of fibrous or rigid tissue, which showed an increased human specific osteocalcin and bone sialoprotein expression and a decreased collagen type I expression indicating the osteogenic differentiation of DFPC. However, there was no dentin, cementum, or bone formation observed in the transplants in vivo [10]. Moreover, in vivo studies are necessary to elucidate the differentiation potential and the application of DFPC for hard tissue regeneration.

Stem cells from apical papilla

In developing teeth, root formation starts as the epithelial cells from the cervical loop proliferate apically and influence the differentiation of odontoblasts from undifferentiated mesenchymal cells and cementoblasts from follicle mesenchyme. It has been known that the dental papilla contributes to tooth formation and eventually converts to pulp tissue. As the root continues to develop, the location of the dental papilla becomes apical to the pulp tissue [27, 88]. The group of Sonoyama et al. discovered a potentially new type of stem cells in the apical papilla of human immature permanent teeth [12, 29]. SCAP appear to be a different population of stem cells from DPSC. SCAP possess a higher proliferation rate and are more committed to osteo/odontogenic differentiation. Furthermore, SCAP express mesenchymal stem cell markers similar to DPSC and the additional cell surface marker CD24 which is downregulated in response to osteogenic stimulation. CD24 expression is found in SCAP cultures, but not in DPSC or BM-MSC cultures. Despite that SCAP express many osteo/dentinogenic markers, they express lower levels of dentin DSPP, matrix extracellular phosphoglycoprotein, transforming growth factor β receptor, fibroblast growth factor receptor, and CD146 compared to DPSC [89]. Several studies also report the adipogenic and neurogenic differentiation capacity of SCAP [12, 29, 90]. In addition, under standard culture conditions, SCAP already express some neural markers (nestin, β-III tubulin, and GFAP) which decreased after neurogenic induction. After stimulation, additional neural markers were expressed, including NeuN, neurofilament M, neuron-specific enolase, and glial markers CNP [12, 90]. In vivo studies indicate that SCAP are also capable of forming a dentin–pulp-like complex after transplantation into immunocompromised mice in an HA/TCP carrier [12, 29]. Furthermore, SCAP, seeded onto a synthetic scaffold and placed into a human root segment, were transplanted into immunocompromised mice to investigate the regeneration capacity in an emptied root canal space. The regeneration of vascularized pulp-like tissue and the formation of dentin-like mineral structures depositing onto the existing dentinal wall in the root canal space was observed [65]. The study of Sonoyama et al. showed that SCAP could also be used in combination with PDLSC to form a bioroot. Using a minipig model, autologous SCAP and PDLSC were loaded onto HA/TCP and Gelfoam scaffolds, respectively, and implanted into tooth sockets of the lower jaw. Periodontal ligament tissue encircled the bioroot and appeared to have a natural

relationship with the surrounding bone, 3 months after implantation. Although newly formed bioroots showed a lower compressive strength than that of natural swine root dentin, they seemed capable of supporting porcelain crown and resulted in normal functions [29].

The discovery of SCAP may also explain a clinical phenomenon, apexogenesis that can occur in infected immature permanent teeth with apical periodontitis or abscess. It is likely that stem cells residing in the apical papilla survived the infection due to their proximity to the periapical tissues. This tissue may be benefited by its collateral circulation, which enables it to survive during the process of pulp necrosis. After endodontic disinfection, SCAP might, under the influence of the survived Hertwig's epithelial root sheaths, give rise to primary odontoblasts to complete root formation [12, 91, 92]. SCAP are derived from a developing tissue that may represent a population of early stem/progenitor cells which can be a superior cell source for tissue regeneration.

Clinical application of dental stem cells in neural regeneration

Neural differentiation of stem cells is of great interest for (autologous) stem cell-based therapies. The differentiation potential of BM-MSC into neuron-like cells has been described in in vitro culture conditions [93–98]. As described above, dental stem cells contain MSC-like properties and possess neural characteristics such as neural marker expression and the production and secretion of neurotrophic factors [38, 71, 73, 99]. In addition, they originate from the neural crest and are able to be differentiated into neuron-like cells [59, 69]. Overall, dental stem cells can be good candidates for stem cell-based therapies. However, before using dental stem cells as transplant in neural regeneration studies, several aspects of these stem cells needs to be fully investigated such as their differentiation potential into the cells of interest, their ability to produce and secrete (neuro)trophic factors, homing, and modulation of the immune response. The following sections focus on the immunomodulatory capacity, the neural characteristics and neural differentiation potential of dental stem cells, followed by the application of using dental stem cells as treatment in facial or inferior alveolar nerve injury.

Immunomodulatory characteristics of dental stem cells

Several studies report the immunomodulatory and anti-inflammatory capacities of MSC [100, 101]. By suppressing T cell activation and secreting soluble factors, MSCs could mediate the immune response and consequently provide a more optimal environment for tissue regeneration [100, 101]. Therefore, MSCs are seen as promising candidates for stem cell-based therapy in several clinical conditions such as cell transplantation in immune-mediated disorders. Recently, stem cells derived from dental tissues are found to possess similar immunomodulatory characteristics in vitro based on the production of soluble factors, such as TGF-beta and HGF, and on the absence of MHC class II molecules. Several studies indicate that dental stem cells are able to suppress the activation and proliferation of T cells and the proliferation of peripheral blood mononuclear cells [102–105]. In addition, a recent study of Yamaza et al. in 2010 reported the successful use of SHED in systemic lupus erythematosus (SLE) in mice. SHED did not only reduce the level of Th17 cells in the peripheral blood, they were also capable of recovering trabecular bone and inhibiting osteoclast activity, thereby improving SLE disorders in mice [106]. Although in vitro studies show promising results, studies using animal models are necessary to further explore and elucidate the immunomodulatory and anti-inflammatory capacities of these stem cells in vivo before they can be applied as stem cell-based therapy in clinical conditions.

Neural characteristics of dental stem cells

Several studies confirm the neural characteristics of DPSC, such as the expression of neural markers, the production and secretion of neurotrophic factors, and the possible (trans)differentiation into functionally active neurons [58, 59, 69–72]. Since DPSC are a neural crest-derived stem cell population, they might express certain neural markers in an undifferentiated state. It has been reported that naïve DPSC already express nestin, neurofilament, vimentin, S100, and β-III tubulin [38, 78, 107]. However, the expression of neural markers in undifferentiated DPSC is dependent on the serum levels used during culture time [42]. When growth media with low serum levels (2 %) were used, the expression level of nestin was increased, compared to culture conditions with high serum levels (10 %). In addition, no expression of β-III tubulin and S100 could be detected in undifferentiated DPSC when using low serum conditions. Therefore, the morphological changes and/or neural marker expression after neural differentiation are not the only characteristic that needs to be addressed in neural differentiation studies. The functionality of the differentiated cells is of even importance. The neuronal differentiation potential of DPSC is widely explored during the last several years [8, 42, 58, 59, 69, 78, 107, 108]. Several protocols are described to induce neuronal differentiation such as (1) transplantation of DPSC into injured rodent brain, (2) chemical and cytokine induction by using a mixture of neuronal inducing agents, or (3) the generation of neurospheres [58, 68–70, 108, 109]. To determine the success of neuronal differentiation, several criteria must be fulfilled as follows: (1) a neuronal morphology, it is a polarized cell with a single axon

and multiple dendrites; (2) the expression of neural markers such as NeuN, β-III tubulin, neurofilament, and MAP2; (3) the coexistence of voltage-gated sodium and potassium channels and being able to generate action potentials; and (4) the presence of synapses, neurotransmitters, and neurotransmitter receptors to communicate between neurons [93]. The neuronal differentiation of DPSC includes the addition of media for epigenetic reprogramming and neural induction followed by a neuronal maturation step. Different media are described in the literature for the induction of neural differentiation leading to the following different results: (1) achieving only a reversible differentiation followed by either dedifferentiation or massive cell death, (2) obtaining an incomplete neuronal differentiation, and (3) acquiring fully functional neuron-like cells with voltage-gated sodium and voltage-gated potassium channels [59, 69, 110]. The study of Kiraly et al. is the first to describe DPSC that are fully differentiated into functional neuron-like cells expressing neuronal markers NeuN, NSE, and neurofilament and displaying voltage-gated sodium and potassium channels which are necessary to generate action potentials [59]. Furthermore, they injected neuronally predifferentiated DPSC into the brain cortex of an animal model of traumatic brain injury and demonstrated that engrafted DPSC-derived neuronally predifferentiated cells integrated into the host brain and showed neuronal properties as expressing neuron-specific markers and exhibiting voltage-dependent sodium and potassium channels [58]. However, these studies did not describe the presence of synapses or the generation of action potentials, which are additional criteria for fully functional neurons.

Another approach for inducing neuronal differentiation is the generation of neurospheres wherein DPSCs are cultured in specialized culture conditions such as the appropriate nonadherence culture plates and culture medium supplemented with growth factors to induce neuronal differentiation. Also, this method of neuronal differentiation led to the expression of neural markers nestin, β-III tubulin, S100, MAP2, and CD81, a transmembrane protein present in neural progenitor cells [109, 111]. The electrophysiological properties and in vivo application of cells being differentiated via this approach remain to be elucidated.

Differentiating stem cells into the cell type of interest is not the only goal when investigating the neural regeneration capacity of stem cells. The ability to produce and secrete (neuro)trophic factors is of even importance. Secreted neurotrophic factors can bind to specific membrane receptors triggering the activation of signaling pathways that coordinates cellular functions. For instance, they can induce the differentiation of endogenous stem cells into the cell types needed at the place of injury or elicit the secretion of neurotrophic factors by the endogenous cells, resulting in a better tissue regeneration process. Several studies demonstrated that DPSCs were not only able to differentiate into functionally active neurons, but they were also capable of secreting many neurotrophic growth factors such as brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), fibroblast growth factor (FGF), glial cell-derived growth factor (GDNF), nerve growth factor (NGF), and VEGF. These factors are important in promoting neuronal rescue and survival, neurite outgrowth, and guidance in vitro and in vivo [69–72] and in stimulating neurogenesis after transplantation in the hippocampus [108].

The neuroprotective effect of DPSC in the central nervous system and central nervous disorders such as spinal cord injury, Alzheimer's disease, and Parkinson's disease have been described in several studies. The production of BDNF, GDNF, and NGF by DPSC have been found, both in vitro and in vivo, to promote the survival of sensory and dopaminergic neurons, to favor the rescue of motor neurons in an animal model of spinal cord injury, and to promote the survival and sprouting of neurons from trigeminal and sympathetic ganglia [71, 72, 112]. In addition, DPSC grafted into the hippocampus of immune-suppressed mice stimulated neural cell proliferation, shown by a significant increase in proliferating cells at the site of the graft and also caused the recruitment of endogenous neural cells to the site of engraftment. It was stated that the proliferation, differentiation, maturation, and recruitment of endogenous neural cells was caused by altering the microenvironment in the brain through an increased production of neurotrophic factors CNTF, VEGF, NGF, and beta-FGF by the engrafted DPSC [108]. In a recent study, DPSCs were transplanted into the cerebrospinal fluid of rats in which cortical lesion was induced. Those cells migrated as single cells into a variety of brain regions and were detected in the injured cortex expressing neuron-specific markers. This showed that DPSC-derived cells integrated into the host brain may serve as useful sources of neurogenesis and gliogenesis in vivo, especially when the brain is injured [59]. The spontaneous differentiation potential of DPSC strongly suggests their possible applications in regenerative medicine.

In 2011, the study of de Almeida et al. showed that after transplanting human DPSC (hDPSC) into the epicenter of a spinal cord lesion (compression injury) in mice, an overall better tissue organization, larger areas of white matter preservation, release of neurotrophic factors, and a significantly better functional outcome were obtained. Due to the local release of neurotrophic factors like BDNF, NGF-beta, NT-3, and NT-4 by hDPSC, animals treated with hDPSC had better results regarding to white matter preservation and functional testing. They hypothesized that the secretion of neurotrophic factors may have led to a stimulation of collateral sprouting. By forming a bridge over the lesion, new synaptic contacts were formed enhancing the functional outcome. In addition, 8 weeks after transplantation, they found surviving cells which expressed the Schwann cell and astrocytes markers

S100 and GFAP. This differentiation of hDPSC into a glial cell type contributed to the regeneration of the damaged axons in the compressed lesion [113]. Furthermore, the group of Sakai et al. also obtained positive results when transplanting DPSC and SHED into a rat model of spinal cord injury [4]. Transplanted DPSC or SHED significantly improved the recovery of the hind limb locomotor function, and engrafted SHED suppressed the apoptosis of neurons, astrocytes, and oligodendrocytes, resulting in the preservation of neurofilaments and myelin sheaths in the region surrounding the epicenter of the lesion. In contrast to the group of Almeida, they performed a complete transection of the spinal cord instead of a compression lesion. In addition, cells were transplanted immediately after surgical transection which is impractical for most human cases of spinal cord injury. Contusion or compression models of spinal cord injury would provide experimental conditions that are closer to the clinical human cases of spinal cord injury [4, 113]. Therefore, further investigation is necessary to explore the beneficial effects of dental stem cell transplants in contusion or compression models of spinal cord injury. Whether transplanted cells improve the functional recovery via the secretion of neurotrophic factors, via cell replacement, or via both mechanisms remains to be elucidated. Taken together, DPSC yields a great potential as cellular therapy for neurological disorders based on their neural crest origin and their neural characteristics in vitro and in vivo.

A recent study by Struys et al. indicated that DPSC can be successfully labeled with superparamagnetic iron oxide particles (SPIO) in order to allow visualization using in vitro and in vivo MRI [114]. SPIO-labeled DPSCs were stereotactically engrafted into the brain of immune-deficient mice, and 2-weeks after injection, the transplanted cells could be detected by means of MRI. Since SPIO labeling had also no effect on the differentiation potential of DPSC, this technique is a very promising tool for future noninvasive monitoring of cell therapy in neuronal disease models and clinical studies. Furthermore, in this study, no signs of tumorigenecity or teratoma formation were observed during the studied time course of 4 weeks, which indicated that DPSC provided a harmless approach for cell replacement therapies.

Dental stem cells as treatment for peripheral nerve injury

Although DPSCs are extensively investigated for their role in central nervous disorders, only one report is available describing the potential role of DPSC in peripheral nerve injury [115]. In this study, degradable polyglycolic acid (PLGA)–collagen tubes were filled with DPSC and transplanted into a rat model of facial nerve injury. The

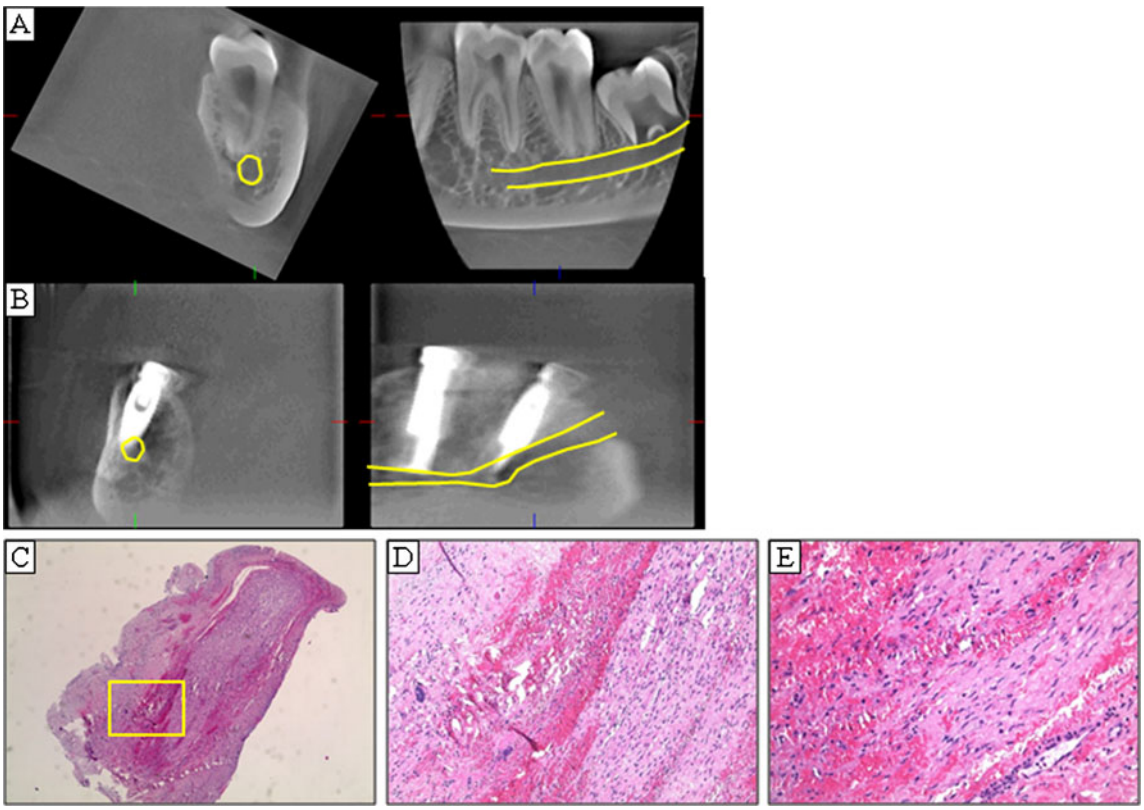

Fig. 3 Mandibular canal and injured IAN. Cone beam CT images of the mandibular canal (**a**, **b**, *yellow circle*) and histological image of inferior alveolar nerve injury displaying necrosis (**c**–**e**) (in courtesy of Prof. Dr. R. Jacobs and Prof. Dr. C. Politis)

PLGA tubes served as a nerve guide until reconnection was established, and the tubes were resorbed after reconnection of the nerve stumps. In addition, axonal regeneration of the facial nerve was promoted after transplantation of DPSC-containing PLGA tubes. Although these results are promising, further studies are needed to determine whether PLGA tubes are the ideal nerve guides, and whether large gap lesions (more than 15 cm) can be regenerated using dental stem cells as a cell source.

Another possible application of DPSC in peripheral nerve injury is the transplantation of cells into the lesion of the inferior alveolar nerve. The inferior alveolar nerve (IAN) is a branch of the mandibular nerve that contains sensory fibers. It enters the mandibular foramen, runs in the mandibular canal, and supplies the mandibular teeth with sensory branches (Fig. 2). The mandibular canal is located under the lower molars and runs in close relationship with the roots of teeth above. In some cases, this distance is very near, and caution must be taken when performing extraction of the lower (third) molar. Parts of the root often extend around or in the canal so that the inner contents of the mandibular canal, the IAN, can be damaged after extraction of the tooth, leading to necrosis of the injured nerve (Fig. 3).

Extraction of the lower third molar is one of the common performed procedures in dental or oral and maxillofacial surgery. The majority of the patients shows no post-extraction complications and fully recovers. However, 0.5 % to approximately 8 % of the patients suffer from neurological problems including neuralgia or impaired sensibility not only in the area of the IAN but also in the entire area of the trigeminal nerve [116, 117]. Injury to the IAN can cause a variety of symptoms like altered sensation, pain, reduces the quality of life, and is associated to psychological problems. Other causes for IAN injury are osteotomy, placement of dental implants, injection of local analgesics, and facial traumas [118–120].

Because the IAN lies within the body of the mandible, repair of the nerve after injury is a complex and difficult procedure. Several surgical techniques have been developed during the last several years including anastomosis of the nerve ends with nerve or vein grafts, but the overall clinical results were not as good as expected [121]. To achieve optimal peripheral nerve regeneration, the following conditions need to be provided: increase of the neural capability to induce axonal outgrowth, to prevent loss of basal lamina and denervation changes in Schwann cells, and finally, to impede inhibitory effects of extracellular matrix [122]. Cellular-based therapies might be a promising alternative as treatment for peripheral nerve injury since the current classical techniques have disappointing results. Schwann cells could be an interesting cell source considering that they play an important role during the regeneration of peripheral nerves. Denervated Schwann cells proliferate and promote the regeneration of axons following nerve injury [123]. However, the major drawback of using Schwann cells is the loss and sacrifice of another peripheral nerve for harvesting Schwann cells. In addition, Schwann cells have a slow and time-consuming grow capacity in vitro, leading to the need of an alternative cell source with Schwann cell characteristics [124, 125]. Several in vitro and in vivo studies report the differentiation of mesenchymal stem cells to support peripheral nerve regeneration. Differentiated MSCs were shown to express Schwann cell markers and supported neurite outgrowth in vitro. In addition, several in vivo studies provided histological evidence of an improved axonal outgrowth, but there are few studies examining functional outcomes, and these studies had inconsistent findings [122, 124, 126–132]. Taken into account that DPSC are a neural crest-derived cell population and that they possess mesenchymal and neural characteristics, DPSC can be an optimal alternative cell source for regeneration studies of peripheral nerve injury.

Conclusion

Stem cell-based therapies gained increasingly interest during the last several years as a potential treatment for neurological diseases or injuries. Promising results are already available with using dental stem cells in various in vitro and animal models of neuronal disorders. The neural crest-derived origin of DPSC gives the cells a predisposition for neural differentiation, and together with their neural characteristics, such as secretion and production of neurotrophic factors, DPSC can be the appropriate candidates for future studies in investigating their regenerative potential and possible therapeutic role in central and peripheral nervous diseases and injuries.

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

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