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Research Progress of Odontogenic Stem Cells in the Field of Medicine

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Abstract

Dental stem cells have the characteristics of mesenchymal stem cells, which under certain appropriate conditions can differentiate into multiple cells such as osteocytes, chondrocytes, hepatocyte and neuronal like cells. DSCs are consisting of odontogenic stem cells mainly include dental pulp stem cells, periodontal ligament stem cells, stem cells from deciduous teeth, stem cells from apical papilla, as well as dental follicle progenitor cells. DSCs have been widely used in the field of preclinical research, including nervous system diseases, oral diseases, immune diseases, heart and lung diseases, etc. This review will focus on the clinical studies regarding DSCs in tissue regeneration.

Keywords: Odontogenic Stem cells; Translational research; Clinical trials; Tissue engineering

Introduction

With the rapid development of regenerative medicine, stem cell therapy has attracted wide attention as a new way to repair damaged cells, tissues and organs that cannot heal themselves, and its safety and efficacy have been confirmed in several studies around the world.

Odontogenic stem cells are kind of mesenchymal stem cells with self-renewal and multidirectional differentiation ability, which can differentiate towards osteoblasts, chondroblasts, odontoblasts, adipoblasts, neuroblasts and endothelial cells. Compared with mesenchymal stem cells derived from bone marrow, umbilical cord and adipose tissue, odontogenic stem cells have stronger proliferation and multiple differentiation, stronger proliferation and multiple differentiation, and advantages of easy access, small trauma and low immune rejection, and are one of the ideal stem cell sources for tissue regeneration [1,2].

The Type of Odontogenic Stem Cells

DPSCs

DPSCs Is the first identified dental pulp-derived DSCs, isolated by enzymatic digestion from the dental pulp of human third molars, and DPSCs showed a typical fibroblast-like morphology. Under different differentiation conditions, DPSCs can differentiate into odontoblasts, osteoblasts, adipocytes, nerve cells, and smooth muscle cells [3,4]. DPSCs Does not express specific biomarkers, but express BMMSCs markers such as Stromal cell antigen 1(STRO-1), CD146, and embryonic stem cell markers such as OCT4. Candidate markers for DPSCs include STRO-1, CD29, CD44, CD73, CD90, CD105, CD146, and CD166, as well as CD271 [5].

SHED

Miura et al. [6] confirmed that SHED isolated from detached deciduous teeth has strong plasticity and can differentiate into neuronal cells, adipocytes, osteoblasts, and odontoblasts. Compared with DPSCs, SHED is more accessible and less traumatic. Lindemann et al. [7] found that because the pulp cavity of lost deciduous teeth is more exposed than permanent teeth, cryoprotectant is more likely to absorb, so the feasibility of cryopreserved deciduous teeth is higher than that of permanent teeth. Therefore, detached deciduous teeth have better development prospects in tooth stem cell preservation than in permanent teeth.

PDLSCs

PDL is a special structure existing between the cementum and the alveolar bone, which is used to protect and support the dental tissue, through the continuous regeneration of MSCs produced by the dental capsule. PDL contains different types of cells that can differentiate into cementocytes

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and osteoblasts. Studies [8] confirmed that the isolated PDLSCs had a fibroblast-like morphology and exhibited clonal properties, with higher proliferation rate than DPSCs and expressed STRO-1 and CD146 as well as tendon-specific transcription factors [9]. PDLSCs With multidirectional differentiation potential, it can differentiate into osteoblasts, adipocytes, chondrocytes and chondrocytes under induction by appropriate media.

DFPCs

The sac originates from the ectoymal mesenchyme around unerupted teeth. DFPCs can regulate osteoclasts and osteoblasts during the eruption of teeth, and differentiate into the periodontal membrane [10]. DFPCs A fibroblast-like cells that can be isolated from the dental sac of human third molars and express various biomarkers, such as Notch1, STRO-1 and Nestin 10; DFPCs has multidirectional differentiation capacity into osteoblasts, adipogenic cells and nerve cells, which can be cultured for at least 15 generations; STRO-1 positive cells can differentiate into osteoblasts *in vitro*, which can form cementum *in vivo* [11]. DFPCs Dentogenic cell markers when stimulated by Bone Morphogenetic Protein 2 (BMP-2), BMP-7 and enamel matrix derivatives [12].

ABMSCs

Matsubara et al. [13] successfully isolated and cultured human ABMSCs, the cells formed fibrocyte-like morphology, had adhesion and colony growth, and expressed surface markers such as CD73, CD90, CD105 and STRO-1, but did not express the hematopoietic stem cell markers CD14, CD34 and CD45 [14,15]. ABMSCs can differentiate into osteoblasts, but also into chondrocytes and adipocytes. Bioceramics can be used as scaffold materials for ABMSCs attachment, proliferation, and migration for bone tissue engineering.

SCAPs

During the process of tooth development, the dental papilla develops into the dental pulp, and then promotes the tooth root development. The dental papillae are attached to the loose junction of the developing root. SCAPs early time period to express the mesenchymal surface marker CD24. SCAPs Under specific culture conditions, it can differentiate into osteoblasts, adipocytes, chondrocytes, and nerve cells. For tooth formation, SCAPs showed a higher proliferation rate than PDLSCs and is more easily isolated from human third molars [16].

TGPCs

TGPCs is a new stem cell population, formed in the middle and late stages of third molar tooth embryos, expressing MSCs related markers STRO-1, CDs and genes related to taxis expression (Nanog, OCT4, Sox 2, Klf 4 and c-Myc) [17]. TGPCs Similar to other MSCs, it can differentiate into adipocytes, osteoblasts, cementoblasts, chondrocytes as well as nerve cells. After hydroxyapatite/TGPCs co-implantation, osteoblasts appeared in the newly formed bone matrix, along with new bone formation. TGPCs it can differentiate into hepatocyte morphology, with hepatocyte phenotype and functional characteristics, and can be used for the treatment of liver diseases [17].

GMSCs

The gingiva is a special structure of the oral tissue, covering the alveolar ridge and retromolar region, and is a special component of the biochemical barrier and oral mucosa immunity. GMSCs easy to obtain from the gingival tissue of the mouth, and very little damage to the body. GMSCs Has cloning, self-renewal and multidirectional differentiation, and stem cell-like and immunomodulatory properties [18]. GMSCs expressed CDs, and OCT4, Sox2, Nanog, Nestin, SSEA-4 as well as STRO-1 were also positive. Gingival tissue exhibits nonscarring healing and rapid tissue reconstruction and regeneration capacity. GMSCs Has the ability to form connective tissue-like structures *in vivo*, and can form mineralized nodules, fat, cartilage-like matrix *in vitro* with different growth factors [19]. Other studies have shown that GMSCs still has the potential of osteogenesis after *in vitro* osteogenesis induction [20]. These attributes suggest the availability of GMSCs for tissue regeneration.

Application of Odontogenic Stem Cells in the Medical Field

Nervous system disease

Nervous diseases including central nervous system disease and peripheral nervous system disease, such as spinal cord injury, Alzheimer's Disease (AD), cerebral stroke, chronic cerebral ischemia, and sciatic nerve injury, bring great psychological burden and financial stress to patients, families and society, clinically, the combination of drug therapy and rehabilitation training; however, the curative effect is not good. The mature nervous system lacks the precursor cells necessary for regenerative nerve cells, so cell therapy based on Mesenchymal Stem Cells (MSC) brings new hope for the treatment of neurological diseases.

SHED was cultured under nerve-specific induction conditions to express not only neural stem cell-specific markers but also early and late neurons as well as the glial cell marker [21]. PDLSC is derived from periodontal membrane tissue and has the potential to differentiate into ectodermal (neurogenic), mesodermal (osteogenic and chondrogenic), and endodermal (pancreatic) cell lineage. DFSC is derived from dental vesicular follicles around unerupted teeth, and DFSC differentiated after neural induction can express late neuronal markers such as neurofilament protein to varying degrees. SCAP is present in the undeveloped periapical tissues of permanent teeth and expresses a variety of nerve growth and trophic factors, and *in vitro* experiments have proved that SCAP conditioned medium can promote neurite outgrowth [22].

DSC is used in CNS diseases: DSC transplantation can reduce the rate of apoptosis in SCI rats, and can differentiate into mature neurons to maintain neuronal survival, replace damaged cells by differentiation into oligodendrocytes, protect nerve fibers and myelin sheath, promote transactional axon regeneration, and promote nerve function recovery in SCI animals. Yang et al. [23] found that undifferentiated DPSC transplantation alleviated inflammatory response and promoted neurite regeneration by inhibiting the expression of Interleukin 1 (IL 1) and member of RAS homologous gene family A. Furthermore, DPSC can reduce the rate of hemorrhagic necrosis by reducing sulfonylurea receptor 1 expression.

SHED also promotes the recovery of motor function after SCI. Some scholars [24] have found that SHED transplantation 6 h after surgery, can protect neurons from early apoptosis, benefit the survival of more motor neurons at the ventral horn of the spinal cord, and this neuronal survival lasts until 6 weeks after the lesion; also, SHED can reduce astrocyte proliferation, blocking T lymphocyte infiltration into the spinal cord parenchyma, lower the proapoptotic factor Tumor Necrosis Factor-α (Expression of TNF-α), Keep mitochondrial constituent proteins in spinal cord tissue at normal levels; moreover, SHED transplantation prevents neuronal

excitatory amino acid transporter 3 and neuronal nitric oxide synthase overload, a protective effect against spinal nerve injury. In a study [25], used SHED polymer combined with SHED suspension in the rat total transverse spinal cord injury model, and the results found that the rat hindlimb function was significantly restored, and immunofluorescence staining showed myelin sheath and nerve fiber repair and regeneration. DPSC and SHED and human BMSCs (Bone marrow Mesenchymal Stem Cell) showed higher scores in DPSC and SHED groups, indicating that DSC is more neurorestorative than BMMSC [26].

By DPSC into the hippocampus of the AD rat model, the expression of Biscortitin, neuron-specific nuclei, and neurofilament protein-200 increased, while the expression of Aβ decreased, and the cognitive and behavioral abilities significantly improved. DPSC can secrete growth factors and cytokines such as BDNF that participate in attenuate neurotoxicity, reduce the toxic effects of Aβ peptide, secrete degrading enzymes, and decrease the rate of apoptosis induced by Aβ peptide. Studies [27] have reported that because the conditioned medium contains growth factors and exosomes secreted by stem cells outside the cell, the conditioned medium of a variety of stem cells can effectively target tissue damage. Experiment [28] proved: SHED conditioned medium can provide a variety of nerve repair, such as nerve protection, axon extension, neurotransmitter, inhibit immune inflammation, regulate microglia, etc., and weakened the Aβ peptide induced inflammation, induce microglia, to anti-inflammatory M2 type macrophage-like polarization, will promote inflammatory microenvironment into anti-inflammatory microenvironment, thus conducive to the treatment of AD.

In vitro culture [29] shows that DPSC has the potential to differentiate into dopaminergic neuron-like cells. DPSC can protect dopaminergic neuron function and promote behavioral disorder recovery by down-regulating proinflammatory cytokines such as TNF-α, IL 1 α, IL 1 α, IL-6, TNF-β, IL-2, and IL-4. In an *in vitro* model of PD in co-culture of dopaminergic-like neurons with microglia [30] induced by inflammation, DPSC enhances neuro immunomodulatory activity by reducing DNA damage in dopaminergic neurons, inhibiting microglial proliferation, and reducing the production of reactive oxygen species and nitric oxide.

When DPSC was transplanted to the ischemic area of the middle cerebral artery, DPSC could migrate to the boundary of the ischemic area and express neural cells and neural stem cell markers, reducing infarct size and reducing cerebral edema [31]. Compared with BMMSC, intravenous graft DPSC can achieve similar functional recovery in rat model and significantly reduce infarct area; meanwhile, DPSC has high angiogenesis and neuronal differentiation, which can reduce the number of reactive neuroglial cells *in vivo*, protect the targeted migration of damaged astrocytes *in vitro* through autocrine/paracrine mechanism, and promote the angiogenic potential of DPSC angiogenesis. Tracking stem cell migration with PKH 26 staining, and comparing the therapeutic effect of DPSC and PDLSC on stroke, the results [32] found that PKH 26 fluorescent marker signal was more obvious in PDLSC group, and significantly promoted the recovery of neurological function. DPSC over expressing stem cell growth factor can regulate inflammation and blood-brain barrier permeability in the acute stage of stroke, enhance its neuroprotective effect, and prevent brain injury after ischemia/reperfusion.

DPSC has a high expression level of neurotrophins, which can significantly promote RGC survival and neurite regeneration when co-cultured with RGC, and DPSC transplantation causes more significant neuroprotection and axon regeneration compared than BMMSC. In an animal model of glaucoma [33], elevated intraocular pressure causes progressive loss of RGC, and intravitreally transplanted DPSC provides visual function for up to 35 d by protecting RGC and maintaining treatment. PDLSC transplanted rat optic nerve injury showed elevated positive expression of β-tubulin and growth-associated protein-43, suggesting a significant increase in the number of surviving RGC and regenerating axons. Co-culture of PDLSC and retinal explants *in vitro* [34], RSC survival and neurite regeneration in retinal explants could be enhanced by PDLSC through direct cell-cell interactions and increased BDNF secretion.

DSC for peripheral neurological disorders: DPSC can differentiate into Schwann cells *in vitro* and form myelinated nerve fibers and endophytic neurites after transplantation of these differentiated DPSC to the 15-mm sciatic nerve defect site in rats. Other studies [35] showed that the immuno selected STRO-1 ± c-Kit ± CD34+ DPSC could promote peripheral nerve regeneration and remyelination in the sciatic nerve injury model through differentiation into Schwann-cell precursors and secreting neurotrophic factors. Some scholars [36] will 10% GelMA hydrogel, recombinant human basic fibroblast growth factor and DPSC, and cellulose/soybean fiber composite membrane tube to repair rat sciatic nerve defect, 12 weeks after histology showed regenerative neurons, Schwann cells and myelinated nerve fibers, and the rat sciatic nerve function is restored, and almost all defect newly formed nerve tissue is derived from exogenous DPSC direct differentiation. After 4 weeks of DPSC transplantation into the skeletal muscle of diabetic nude mice, sensory disturbance, delayed nerve conduction velocity and decreased sciatic nerve blood flow were significantly improved, and DPSC transplanted to skeletal muscle was localized around the muscle bundle, producing new vascularization and neurotrophic factors.

Sasaki using a silicone tube containing DPSC to fix the facial nerve lesion area, Sasaki et al. [37] demonstrated that DPSC can promote facial nerve regeneration in both function and neuro electrophysiology. Application of immature DPSC immediately after facial nerve compression injury in rats could promote neuroprotection and remyelination after 2 weeks. Some scholars [38] used DPSC suspension in the rabbit model of buccal branch injury of the facial nerve, and found that the score of facial beard motor function was increased; they believe that it may be related to DPSC secretion and expression of BDNF and ciliary neurotrophic factor. Another study [39] showed that autologous nerve transplantation combined with SHED and polyglycolic acid catheter was used to repair rat facial nerve mandibular branch cut model, demonstrating facial nerve regeneration by evaluating composite muscle action potential and axon diameter, and SHED integrated and survived in nerve tissue within 6 weeks after transplantation, and differentiated into Schwann-like cells.

Promote angiogenesis

Odontogenic stem cells exist around the endothelial cells and can exert a role similar to pericytes, secreting blood through a paracrine effect. Tube growth factor, regulating the proliferation and differentiation of endothelial cells, and subsequently regulate angiogenesis [40]. The release of proangiogenic cytokines by odontogenic stem cells is a regulated by a delicate balance of several proangiogenic and antiangiogenic factors. Odontogenic stem cells can release pro-vascular growth factors, such as Vascular Endothelial

Growth Factor (VEGF), basic Fibroblast Growth Factor (bFGF), and Platelet-Derived Growth Factor (PDGF), et al. DPSCs can also release other proangiogenic factors including angiogenin, Angiopoietin (ANG), colony stimulating factor, dipeptidyl peptidase, endothelin 1, interleukin-8, insulin-like growth factor binding protein-3, monocyte chemoattractant protein-1 and urokinase plasminogen activator. To Human Umbilical Vein Endothelial Cells (HUVECs) Co-culture with DPSCs was capped in a peptide hydrogel PuraMatrix™ scaffold, in the absence of exogenous growth factors, DPSCs by promoting HUVECs, the migration and increasing VEGF expression promote the formation of early vascular network; root fragments of loaded cells and PuraMatrix™ scaffold were transplanted subcutaneously into the back of mice, vascularized dental pulp tissue formation can be observed.

We found that DPSCs exosomes can promote the proliferation of endothelial cells, enhance the migration ability of endothelial cells, induce endothelial cells to form a lumen, and promote angiogenic [41]. In addition, studies have shown that mesenchymal stem cells highly expressing Hypoxia-Inducing Factor-1α (HIF-1α) can secrete more exosomes and promote angiogenesis in endothelial cells. Mesenchymal stem cell exosomes can enhance their angiogenic capacity by loading the Jagged1 gene, which is pair-ischemic disease treatment has potential applications.

Zhang et al. [42] suggested that angiogenesis of tooth/C-induced by activation of classical Wnt/β-catenin signaling pathway. Recent studies have also shown that, Transforming Growth Factor β (TGFβ) inhibitor SB431542 enhances VEGF-A on shed deciduous tooth stem cells (Stem cells from Human Exfoliated Deciduous teeth, induction of SHEDs) to endothelial cell differentiation; SB-431542 inhibits SMAD 2 phosphorylation/3 and upregulates VEGF-A and Vascular Endothelial Cell Growth Factor Receptor 2 (VEGFR2), the combination of VEGF-A and SB-431542 enhanced SHEDs differentiation into endothelial cells.

Compared to DPSCs, PDLSCs has more potent angiogenic, osteogenic and neural differentiation properties. Endothelial cells obtained from the mouse periodontal membrane were more neovascular than endothelial cells in the dental pulp [43]. In addition to endothelial cells, smooth muscle cells are also important components of blood vessels. During vascular regeneration, SHEDs can induce differentiation into functional vascular smooth muscle cells through TGF-β1 stimulation, and this process is regulated through the ALK 5 signaling pathway.

Applications in bone tissue engineering

It has been reported that DPSC is able to differentiate into osteoblasts and produce bone-like tissue *in vivo*. However, in the study of Annibali et al. [44], using human DPSC failed to form new bone in a nude mouse model. Zhang et al. [45] found that in murine bone formation studies, there was no evidence of new bone formation in murine DPSC. Laino et al. [46] successfully used DPSC to form fresh autologous bone *in vitro*. After inserting fresh autologous bone into subcutaneous skin in mice for 4 weeks, it was successfully converted into lamellar bone. At the same time, DPSC can also be combined with chitosan and other scaffold materials [47,48]. DPSC and biomaterials have great potential [49] in future bone tissue engineering applications, but its impact on the differentiation mechanism of DPSC to osteoblasts remains to be further studied. Because DPSC has higher proliferation rate and better bone differentiation ability, while BMSCs have limited osteoblast differentiation rate and less calcified nodules, DPSC is the best ideal cell in bone formation research. However, the *in vitro* osteogenesis of DPSC is restrictive, and the selection of suitable scaffold materials to ensure that it can form a complete tissue rather than a monolayer enclosing the mineralized matrix is an important factor for the success of *in vitro* osteogenesis of DPSC.

In vitro, SHED showed higher proliferation, clone formation and doubling rates than bone marrow stromal stem cells (Bone Marrow Stromal Stem Cell, BMSSC), positive STRO-1 and CDl46 (MUCl 8) expression, also mainly around microvessels, with differentiation into neurons, adipocytes and odontoblasts, expressing mesenchymal and vascular related markers. The application of SHED in bone tissue engineering has been greatly developed in recent years [50]. SHED can proliferate and can differentiate into osteoblasts on chitosan/ Transforming Growth Factor (TGF)/-β1 scaffold/factor composite, which is of great significance for the future use of SHED/chitosan/ TGF-β1 scaffold in bone tissue engineering. In the mouse mandibular defect model [51], the investigators implanted three-dimensional polyhydrate hydro lactic acid scaffold composite SHED material into the damaged area, killed animals after 1 month, and found that they had no adverse effects on mice, and the osteogenic potential of SHED could be maintained throughout the experiment. This suggested that SHED composite scaffold could be used as a novel substitute for bone defects.

A low percentage of STRO-1 positive cells was found in SCAP, and a higher percentage of STRO-1 positive cells in osteogenic or odontoblasts cultured alone. In addition, SHED was positive for several neural markers by immunohistochemical staining, such as β-tubulin, Neuronal core antigen (NeuN), Nestin, glial fibrillary acidic protein (Glial Fibrillary Acidic Protein, GFAP), neuro microfilament M, and neuron-specific enolase (Neuron Specific Enolase, NSE). That is, SCAP is similar to DPSC and SHED and may originate from neural crest cells, or from neural crest-related cells [52].

PDLSC is widely used in bone tissue engineering. Yamada et al. [53] showed that canine PDLSC was able to repair jaw defects below 10 mm in diameter and form more vessels during bone repair. Studies [54,55] have shown that PDLSC has greater osteogenic potential compared to gingival MSCs. However, the study of Yang et al. [56] showed that gingival MSCs have better osteogenic potential than PDLSC under inflammatory conditions. It has been shown that the hydroxyapatite scaffold deposited by the Extracellular Matrix (ECM) can significantly enhance the osteogenic differentiation potential of PDLSC *in vitro* [57]. Based on this, Ge et al. [58] inoculated PDLSC on nano-hydroxyapatite-chitosan scaffold and Genipin-chitosan scaffold respectively to evaluate their bone repair ability *in vivo*, and found that the activity and alkaline phosphatase activity of PDLSC inoculated on nano-hydroxyapatite-chitosan scaffold were better; meanwhile, the bone-related markers bone sialolin, ostemodulin and osteocalcin were significantly upregulated.

Application in myocardial regeneration

Due to the potential of odontogenic stem cells for multidirectional differentiation, some investigators have tried to use DPSCs to treat myocardial infarction. Gandia et al. [59] used coronary artery ligation to create an acute myocardial infarction model in nude mice and injected DPSCs into the myocardium. Four weeks later, they found significantly improved myocardial function, reduced infarct area and increased neovascularization in nude mice. Xin et al. [60] suggested that differentiation of odontogenic stem cells into cardiomyocytes is

primarily through regulation of P13 kinase/Akt signaling channels, therefore, odontogenic stem cells could be used as a stem cell source for cardiomyocyte regeneration. Yamaguchi et al. [61] found that SHED conditioned medium could effectively reduce the myocardial damage caused by myocardial ischemia and reperfusion, reduce cell apoptosis and infarct area, and downregulate the levels of various types of inflammatory factors, such as TNF α, IL 6 and IL β. The study further found that the SHED conditioned medium contained higher concentrations of hepatocyte growth factor (Hepatocyte Growth Factor, HGF) compared with the conditioned media of MSCs and adipose stem cells. When the hepatocyte growth factor was removed, *in vitro* inflammation and apoptosis decreased. This suggests that SHED suppresses inflammation and apoptosis through secreted hepatocyte growth factors, thus creating a favorable microenvironment for odontogenic stem cells to repair myocardial infarction. Di Scipio et al. [62] found that DPSCs can migrate to the myocardial injury area to make contact with cardiomyocytes, probably through the cellular interaction mediated by gap junction protein 43, neurocalcin and Willebrand factor; meanwhile, the stromal cell-derived factor 1 (Stromal Cell Derived Factor 1, SDF 1), fibrous growth factor 2 (Fibroblast Growth Factor 2, FGF 2) and the hepatocyte growth factor are involved in the DPSCs migration process. At present, the molecular biological mechanisms related with the treatment of odontogenic stem cells for myocardial infarction have not been fully elucidated. However, due to the low immunogenicity of odontogenic stem cells, as a potential cell source of allogeneic transplantation, and safe and convenient materials, better than myocardial stem cells and bone marrow mesenchymal stem cells, it is believed that the future odontogenic stem cells will receive more and more attention in the field of myocardial regeneration.

Application in ocular diseases

DSCs, as an autologous stem cell, have been used in the treatment of corneal blindness. The cornea has a similar embryonic origin to DPSCs, and after induction of differentiation *in vitro*, DPSCs expresses the molecular properties of keratinocytes, keratins, and keratin sulfate proteoglycans at the gene and protein levels [63], and generates tissue-engineered corneal tissue structures that do not cause cell rejection *in vivo* [64]. This finding demonstrates the value of DPSCs therapeutics in the field of cell or tissue engineering [65].

And scholars research [66], the optic nerve damage, mice in the body transplantation DPSCs, promoted the neurotrophic factor-mediated retinal ganglion survival and axon regeneration Gomes will pulp stem cell transplanted into resection rabbit cornea burn model, 3 months found corneal transparency improved, and a small amount of neovascularization. Mead et al. [67] transplanted DPSCs and BMMSCs into intravitreal animals of rats with optic nerve injury, and the survival rate of retinal ganglion cells in the DPSCs treatment group was higher than that in the BMSCs group after 20 days. In addition, Syed Picard et al. [64] found DPSCs *in vitro* under certain conditions can be differentiated into corneal stromal cells, and in the body can form tissue engineering cornea, matrix tissue, considering odontogenic stem cells relative to corneal stem cells, can be more easily isolated and low immunogenicity, the future odontogenic stem cells have great potential to achieve clinical individualized treatment of corneal disease. Recent studies [68] have found that DPSCs can differentiate into retinal ganglion cells under three-dimensional culture conditions.

Application in oral diseases

Restoration and regeneration of dentine/pulp tissue: Recent studies [69] have reported that DPSC, SHED and SCAP all have some multidirectional differentiation potential, including the formation of the dentine/pulp-like complex. At present, there are several main methods for repair and regeneration.

(1) Dental-derived stem cells are directly implanted into the dental pulp cavity. Iohara et al. [69] introduced the *BMP-2* gene to the DPSC by electroporation technology and then implanted into the autologous pulp, and found that the DPSC transplanted into the pulp injury model in canine teeth formed restorative dentin. Their transplantation of DPSC or DPSC+*BMP-2* into the pulp cavity of canine teeth could significantly promote the restoration and regeneration of the dentin/pulp complex. Gotlieb et al. [70] study reported that regeneration of pulp tissue with tooth-derived stem cells could replace traditional root canal treatment.

(2) Dental-derived stem cells combined with stents are implanted into the dental pulp cavity. The above method of directly inserting stem cells into the pulp cavity is difficult to succeed. The key problem is that the blood supply from the apical foramen cannot meet the survival needs of stem cells and the limited self-healing and regeneration of the pulp tissue itself. Iohara et al. [71] reported that transplantation of CD105+ cell subsets isolated from DPSC into live hounds could regenerate dental pulp. They combined CD105+ dental pulp stem cells with a collagen scaffold into the lower part of the root canal. The cytokine SDF-1 and zinc phosphate adhesive powder were added to the upper part of the root canal and filled with photosensitive plastic. After 90 days later, the new pulp tissue grew to the contact interface between the enamel dentin and the adhesive powder, and the similar normal dental pulp cells, new capillaries and nerve synapses grew from the apical foramen into the new pulp. Therefore, according to Iohara et al. [71], the CD105+ subset of DPSC has a more important clinical application potential for the regeneration and restoration of human dental pulp tissue.

(3) The tooth-derived stem cells and stent materials were first implanted into the animal, and then removed and implanted into the human dental pulp cavity. Huang et al. [72] reported that DPSC or SCAP were implanted onto a polymer scaffold and transplanted subcutaneously in mice. After a certain period of time, the stent containing the dental source stem cells was removed and then implanted into the human root tube. They found that new blood vessels grew into the human pulp tissue and formed a dentin-like tissue that grew on the inner wall of the root canal. However, this layer of regenerated dentin-like tissue is different from natural, such as edententine tubules and abnormal dentin cell morphology.

(4) Dental-derived stem cells and stent materials were implanted on human tooth tissue blocks and then implanted into the animal. Prescott et al. [73] placed the combination of DPSC, collagen scaffold and DMP-1 at the artificial perforation of dentine and then implanted nude mice for subcutaneous growth. After 6 weeks of growth in nude mice, good dentin/pulp complex generation occurred at the perforation. Cordeiro et al. [74] implanted SHED on a biological stent and then implanted it into human dental tablets. It was found that there was similar physiological pulp tissue formation. Transmission electron microscopy and immunohistochemistry experiments showed that the transplanted SHED can differentiate into dentinal cells and vascular endothelial cells. Sakai et al. [75] found by dental tablet model (tooth slice model) that new dentin was formed on the

artificial pulp regenerated with polylactic acid (Poly-L-Lactic Acid, PLLA) stent and DPSC.

For the restoration and regeneration of periodontal tissues: He et al. [76] performed earlier studies on periodontal regeneration. Subsequently, Yen et al. [77] performed a study of "whole tooth regeneration". Periodontal tissue mainly includes four tissues, namely, epithelium, cementum, alveolar bone and periodontal membrane. Its regeneration requires four components: Cells, signaling molecules, blood vessels and stent materials to form a complete periodontal tissue. Different combinations of stem cell types can be used as a source of stem cells for periodontal tissue repair and regeneration.

(1) Periodontal stem cell alone is used for periodontal tissue repair. Since PDLSC and PDLP can derive the periodontal membrane and can differentiate into osteoblast, cementum blast and fibroblasts, PDLSC and PDLP are preferred for periodontal tissue repair. Other stem cells include bone marrow mesenchymal stem cells (Bone Marrow Mesenchymal Stem Cell, BM-MSC), adipose stem cells (Adipose-Derived Stem Cell, ADSC) and embryonic stem cells (Embryonic Stem Cell, ESC). Dangaria et al. [78] comparative study of dental pulp stem cells, periodontal stem cells and dental follicular stem cells found that periodontal membrane stem cells produced and expressed the highest periostin (periostin) and tendinin (scleraxis). Periodontal membrane stem cells can form new periodontal membrane on the surface of natural root after 3 weeks of culture. If the root is implanted into the alveolar bone, a new periodontal membrane can be formed and stabilized with the alveolar position. In addition, other stem cells can be cultured with Periodontal Membrane (PDL) cells to obtain the characteristics of PDLSC, and then used for regeneration and repair of periodontal tissue [74].

(2) The combination of two dental-derived stem cells for the repair of periodontal tissue. SCAP and PDLSC were combined with scaffold material for restoration and regeneration of periodontal tissue. Recent studies include the following methods: First, the stem cells are directly implanted into the defect area. Seo et al. [79] caused a periodontal surgical defect in the immunosuppressed rat mandibular molar region, then human PDLSC implantation, and found that 2 of the 6 samples had visible PDLSC integration into the periodontal membrane and a small amount of PDLSC attached to the surface of the alveolar bone and teeth. These findings suggest that PDLSC has a role in promoting periodontal regeneration. Second, the stem cells were first cultured, expanded and directional differentiated *in vitro*, and then used for periodontal defect repair. Yamada et al. [80] used autologous Bone Marrow Mesenchymal Stem Cells (BMMSC) after *in vitro* culture and directed differentiation, mixed with platelet-rich plasma to repair periodontal defects, and found that the repair effect was significantly improved. Kawaguchi et al. [81] expanded with autologous MSCs *in vitro* and then transplanted into the periodontal defect area of an animal model, which found that the defect was completely repaired after 4 weeks. Although BMMSC is not dental stem cells, BMMSC and dental stem cells are both Mesenchymal Stem Cells (MSC), so they have similar functions. Third, stem cell transplantation is combined with conventional periodontal surgery. Especially when performing deep cleansing and root surface leveling (Scaling and Root Plannin, SRP), stem cell transplantation is usually combined with traditional periodontitis treatment to achieve better treatment results [73,82].

(3) Stem cells are combined with cell growth factors and auxiliary materials to repair the periodontal tissue. Currently, the commonly used cell growth factors are TGF-β, bF GF, BMP, IGF-1, PDGF, BMP-2, and Emdogain. The application of these cytokines makes dental stem cells function better in a similar native microenvironment. Some researchers used PDLSC, PDGF and BMP, and found that all three components of periodontal tissue could get regenerative repair. The stem cell SCAP and PDLSC were placed on a scaffold consisting of granular Hydroxyapatite/Tricalcium Phosphate (HA/TCP) and then implanted for the formation of root/periodontal tissue complex. In addition, the combination of polyglycolic acid (Polyglycolic Acid, PLGA) stent material and PDLSC for periodontal repair also achieved obvious effect [83]. The initial manufacturing process of the stent is complex, the shape of the stent is quite different from the periodontal defect, and the state of the small holes of the finished stent cannot be controlled. The recent development of 3D rapid forming (Rapid Prototyping, RP) and nanotechnology can overcome the above defects and form a 3D personalized scaffold within a few hours, opening up a new method to repair periodontal tissue defects combined with stem cells and stent materials.

For dental tissue regeneration: Current dental implantation lacks the appearance and periodontal membrane of natural root, so the regeneration of natural root or whole tooth is an urgent problem to be solved clinically. Some researchers have tried non-odontogenic stem cells to conduct exploratory studies for the regeneration of teeth. Ohazama et al. [84] combined the embryonic tooth epithelium with the adult bone marrow stromal cells and then implanted it into the animal kidney sac, which was found to form the tooth-like structures. Further studies showed that the embryonic oral epithelium synthesized from neural stem cells (Neural Stem Cell, NSC), Embryonic Stem Cells (ESC) and adult Bone Marrow Mesenchymal Stem Cells (BM-MSC) was implanted into the adult jaw and animal kidney sac, which was found to have tooth like structure and bone regeneration. Ferro et al. [85] also successfully transdifferentiated Adipose-Derived Stem Cells (ADSC) into 3D tooth bud-like organs and phenotypes *in vitro*. These studies have an important guiding role in the reconstruction of teeth with odontogenic stem cells [78].

(1) Crown regeneration Yan et al. [86] DPSC and adult rat root tip tooth bud cells (apical bud cells), after implantation *in vivo* form a typical crown like structure, including ameloblasts layer, enamel, dentin, early dentin and dentin cell layer, but the method based on DPSC, has failed to observe the formation of the root. Human enamel develops from the epithelial tissue of the teeth [86], and dental epithelial stem cells (that is, those that can express enamel protein) are still being explored. Normal teeth, and the epithelial stem cells, which grow into the teeth, have disappeared. Only in animals, such as the cervical ring of mouse incisors. Nagano et al. [87] reported that odontoblasts were able to express tooth enamel protein, bringing hope for the synthesis of tooth enamel with non-ameloblasts.

(2) Root regeneration Sonoyama et al. [88] use SCAP and PDLSC, combined with HA or TCP stent materials, respectively, and then implanted into the alveolar socket of the pig mandible. After 3 months, the biological tooth root is formed, which can be used for piling and crown for tooth restoration. This root is composed of dentin produced by SCAP, surrounded by a periodontal membrane, and forms a natural association with the alveolar bone. However, the disadvantage is that the residual HA in the dentin, which reduces the strength of the root, and its histocompatibility remains to be long-term research. Guo et al. [89] collected rat tooth capsule stem cells (DFSC) after 9 months of subculture, inoculated on the dentinal matrix scaffold, and then implanted into the rat alveolar socket,

with the formation of root-like tissue 4 weeks later. But the same DFSC implantation into the skull does not form the root. This result indicates that the DFSC scaffold requires the microenvironment of the alveolar socket to regenerate the root.

(3) Whole tooth regeneration human tooth formation depends on the interaction between the otogenic epithelium and the odontogenic mesenchyme. However, once the process of enamel formation is completed and the teeth emerges, the odontogenic epithelial cells will then apoptosis and disappear. So many studies have combined odontogenic stem cells with tooth germ cells. Ikeda et al. [90] reported that dental epithelial cells were isolated from the cup stage of mouse tooth development, and they were combined with DPSC on collagen gel *in vitro*, and the tooth embryos formed were implanted into the mouse jaw. The results showed that the biosynthetic tooth was well combined with alveolar bone and had the function of natural teeth. At present, there are four main sources of cells for total tooth regeneration: (1) tissue cells of tooth embryos, including the whole tooth embryo or some tooth embryos or isolated cells; (2) adult tissue cells such as dental pulp and gingival cells and (3) odontogenic and non-dental stem cells including Bone Marrow Mesenchymal Stem Cells (BM-MSC) and Adipose Stem Cells (ADSC); (4) Induced Pluripotent Stem Cells (iPSC cells produced by autologous tissue cells through somatic cell reprogramming (Induced Pluripotent Stem Cell, iPSC). The above four cells can be used alone or in combination to induce whole tooth regeneration. The experimental methods of whole tooth regeneration include: (1) the tooth embryo tissue or cells are implanted into a certain part of the living body, such as chicken all allele chorio, kidney capsule or subcutaneous, etc., after the tooth crown is formed, the graft is implanted into the jaw to produce teeth. (2) The isolated cells are first cultured, induced and expanded *in vitro*, and then implanted into living alveolar bone or other sites to produce whole tooth adult dental-derived stem cells belong to a type of Mesenchymal Stem Cells (MSC), but do not include odontogenic epithelial cells. Therefore, odontogenic stem cells are used to reconstruct whole teeth and lack odontogenic epithelial cells. With the recent development of induced Pluripotent Stem Cells (iPSC) technology, tooth-derived stem cells bring hope for whole tooth regeneration. The brief process of biological tooth regeneration using iPSC include: *in vitro* isolation and amplification of autologous DPSC, introduction of four reprogramming genes (OCT 4, Sox 2, KLf 4 and c-Myc) into somatic cells such as DPSC to form iPSC and induce iPSC differentiation into odontogenic epithelial cells, and implantation of odontogenic epithelial cells with autologous DPSC, allowing them to continue growth and regenerate whole tooth [91-93]. As there are still many problems in biological tooth regeneration, such as the limited source of human dental epithelial cells, the only cell source of undifferentiated mature wisdom teeth and impacted teeth, using iPSC technology for tooth regeneration will be an important research direction.

Study on the injury repair of skull bone, jaw bone and facial bone

D'aquino et al. [94] successfully cultured bone tissue fragments with DPSC, which were implanted into animals to produce plate bone with vascular supply. They also reported the results of clinical studies with DPSC for mandibular defects. They first extracted the patient's maxillary wisdom teeth, isolated and cultured the autologous DPSC, and then implanted it into a gelatin carrier to produce the DPSC complex. Then bilateral mandibular wisdom teeth were removed, DPSC complex was placed on one side and the other for control. It was found those 60 days after surgery, the cortical bone of the second molar on the experimental side reached the junction between the enamel and the bone. At 3 months after surgery, the expression of newborn bone tissue, cytokines, BMP-2, and Vascular Endothelial Growth Factor (VEGF) was significantly higher on the experimental side than on the contralateral side. One year after surgery, the experimental side fully stabilized ossification, achieving the purpose of bone regeneration of the second molar [94]. In addition, Sonoyama et al. [88] reported that SHED repaired large areas of skull defect in animals. Riccio et al. [95] also reported that the application of human DPSC with filament protein scaffold repaired the large defects of rat parietal bone. However, some studies have reported the repair of craniofacial defects with non-odontogenic stem cells such as ADSC or BM-MSC, and some studies have reported ADSC or BM-MSC combining BMP-2 cytokines and scaffold for skull defect repair [96,97].

Conclusions and Outlook

Dental-Derived Stem Cells (DSC) is mesenchymal stem cells derived from teeth and periodontal tissues, which have similar morphological and functional characteristics with bone marrow mesenchymal stem cells. Because DSC has the characteristics of convenient materials, strong proliferation ability and osteogenic differentiation, it has important application value for tooth, pulp damage, periodontal disease tissue damage repair and whole tooth regeneration. At the same time, because of its differentiation into nerve cells, myocardial cells and other cells, it has become an important source of cells to repair nerve damage and neurodegenerative diseases, myocardial infarction and diabetes.

At present, most of the research on dental-derived stem cells is in the stage of *in vitro* culture identification, multi-directional differentiation and animal experiments. The future research will aim at the clinical transformation and application of dental-derived stem cells, and carry out in-depth research in many aspects.

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