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INVITED MEDICAL REVIEW

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Stem cell-based tooth and periodontal regeneration

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Currently regeneration of tooth and periodontal damage still remains great challenge. Stem cell-based tissue engineering raised novel therapeutic strategies for tooth and periodontal repair. Stem cells for tooth and periodontal regeneration include dental pulp stem cells (DPSCs), periodontal ligament stem cells (PDLSCs), stem cells from the dental apical papilla (SCAPs), and stem cells from human exfoliated deciduous teeth (SHEDs), dental follicle stem cells (DFSCs), dental epithelial stem cells (DESCs), bone marrow mesenchymal stem cells (BMMSCs), adipose-derived stem cells (ADSCs), embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). To date, substantial advances have been made in stem cell-based tooth and periodontal regeneration, including dentin–pulp, whole tooth, bioroot and periodontal regeneration. Translational investigations have been performed such as dental stem cell banking and clinical trials. In this review, we present strategies for stem cell-based tissue engineering for tooth and periodontal repair, and the translational studies.

KEYWORDS
periodontal regeneration, stem cells, tooth regeneration

1 | INTRODUCTION

The tooth is a multistructure organ composed of the highly mineralized tissues of enamel, dentin, and cementum, as well as the soft connective tissues including dental pulp and the associated periodontium. The most common diseases associated with teeth and their supporting tissues are periodontal disease, caries, and traumatic injuries. Due to its complex structure and limited self-healing capability, it is necessary to introduce external interventions to promote the biological repair of damaged dental tissue. The current restorations for tooth loss are dentures, including removable, fixed dentures, and dental implants. Resin-based composites, inlays or onlays, and artificial crowns are used for partial restoration of hard tissue defects. Routine periodontal disease treatments include basic treatment, guided tissue regeneration (GTR), and guided bone regeneration (GBR). The outcomes of these methods are limited and associated with poor clinical predictability (Needleman, Worthington, Giedrys-Leeper, &

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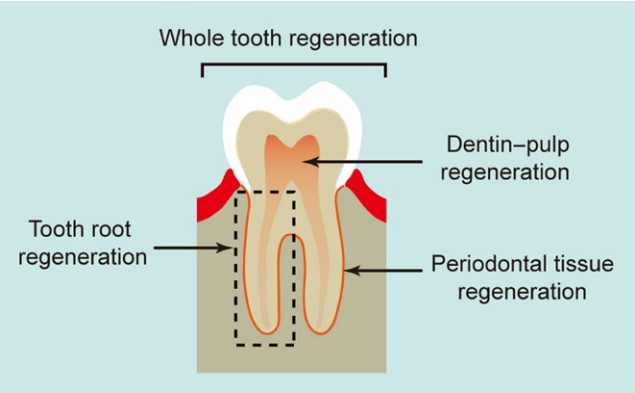

FIGURE 1 Stem cell-based tooth and periodontal regeneration. Current investigations of stem cell-based tooth and periodontal regeneration including dentin–pulp, tooth root, whole tooth, and periodontal tissue regeneration

Tucker, 2006). The concepts in restoring damage tissues have undergone significant change, from substitution to restoration or replacement, and finally regeneration. Since stem cell-based tissue engineering and regenerative medicine emerged two decades ago, these novel therapeutic strategies have been evaluated for their potential to replace, repair, maintain, and enhance tissue or organ function (Mao & Mooney, 2015). The strategy encompasses numerous elements, including biomaterials, stem cells, tissue-inducing substances, or biomimetic regenerative environments. Since craniofacial tissue engineering appeared in 1990s, substantial advances have been made in stem cell-based tissue engineering (Alsberg, Hill, & Mooney, 2001; Hollinger & Winn, 1999), especially in tooth and periodontal regeneration. Current investigations of stem cell-based tissue engineering for tooth and periodontal tissue include regeneration of dentin–pulp, tooth root, whole tooth, and periodontal tissue (Figure 1).

2 | STEM CELLS

The stem cells used for tooth and periodontal regeneration are both dental and non-dental mesenchymal stem cells (MSCs). The features of these stem cells have been identified and characterized (Huang, Gronthos, & Shi, 2009; Inanc & Elcin, 2011; Ullah, Subbarao, & Rho, 2015; Table 1). MSCs, which were first found in bone marrow, are multipotential stromal cells that can differentiate into a variety types of cells, such as osteoblasts, chondrocytes, myocytes, and adipocytes. Dental pulp stem cells (DPSCs), the first isolated MSCs from human teeth, have the potential to differentiate into odontoblasts, osteoblasts, chondrocytes, myocytes, and adipocytes, and neurocytes in vitro and in vivo (Gronthos, Mankani, Brahim, Robey, & Shi, 2000; Gronthos et al., 2002; Nuti, Corallo, Chan, Ferrari, & Gerami-Naini, 2016). MSCs were isolated from human exfoliated deciduous teeth (SHEDs) with similar osteo/odontogenic, chondrogenic, adipogenic, and neurogenic differentiation patterns as DPSCs, but with more proliferative activity than bone marrow MSCs or DPSCs (Martinez, Sasaki, Neves, & Da, 2016; Miura et al., 2003; Wang et al., 2010). Stem cells from the dental apical papilla (SCAPs) were reported in apical papillae of the developing tooth root apex, with the characteristics of highly proliferative, migratory, and regenerative potential, and are able to form dentin in vivo (Sonoyama et al., 2006, 2008). Periodontal ligament stem cells (PDLSCs) are able to differentiate into adipogenic and osteogenic cells, under defined culture conditions in vitro, and could mediate the regeneration of the periodontium in vivo (Seo et al., 2004). Stem cells from the dental follicle (DFSCs), which were first isolated from dental follicle of human third molar teeth, and reported as the progenitor cells or precursor cells (PCs) of cementoblasts, periodontal ligament cells, and osteoblasts, are able to differentiate into osteoblasts/cementoblasts, adipocytes, and neurons (Yao, Pan, Prpic, & Wise, 2008), and generate cementum and bone tissues in vivo (Morsczeck et al., 2005; Yokoi et al., 2007). Dental epithelial stem cells (DESCs), which were isolated from the developing third molar or epithelial rests of Malassez, were also studied for tooth and periodontal regeneration (Harada et al., 1999; Nam et al., 2011) and can generate enamel–dentin-like complex structures in vivo after being combined with dental mesenchymal cells (Honda, Shinohara, Hata, & Ueda, 2007).

The non-dental stem cells used for tooth and periodontal regeneration are primarily bone marrow mesenchymal stem cells (BMMSCs), adipose-derived stem cells (ADSCs), embryonic stem cells (ESCs), and induced pluripotent stem cells (iPSCs). BMMSCs were the first MSCs discovered and have shown a capacity for osteogenic, adipogenic, chondrogenic, and myogenic differentiation. For tooth and periodontal regeneration, BMMSCs can upregulate the expression of odontogenic genes and contribute to tooth regeneration after being recombined with embryonic oral epithelium (Ohazama, Modino, Miletich, & Sharpe, 2004). Moreover, c-Kit (+)-enriched BMMSCs can differentiate into ameloblast-like cells (Hu, Nadiri, et al., 2006; Hu, Unda, et al., 2006), as well as differentiate into periodontal tissue cells, and enhance periodontal regeneration (Hasegawa et al., 2006, Yang, Rossi, & Putnins, 2010).

Adipose-derived stem cells are stem cells derived from adipose tissues and are, thus, abundant and have been widely used for regenerative medicine. Transplanting ADSCs in periodontal tissue defects can promote cementum and organize periodontal ligament fibers and periodontal vessel regeneration (Lemaitre et al., 2017; Tobita, Uysal, Ogawa, Hyakusoku, & Mizuno, 2008). The gene expression patterns of ADSCs are similar to DPSCs, and transplanting ADSCs into adult rabbit extraction sockets can regenerate dentin, periodontal ligament, and alveolar bone structure (Hung et al., 2011).

Embryonic stem cells are pluripotent stem cells derived from the undifferentiated inner cell mass of the blastocyst and can differentiate into almost all cell lineages including endoderm, mesoderm, and ectoderm (Evans & Kaufman, 1981). ESCs can differentiate odontogenic and periodontal cell lineages in conditioned culture medium or if cocultured with PDLSCs or embryonic oral epithelium cells, indicating their potential for tooth and periodontal regeneration (Inanc et al., 2009; Ning et al., 2010).

Induced pluripotent stem cells (iPSCs) were firstly discovered in 2006 and then raised substantial interest in regenerative medicine (Takahashi & Yamanaka, 2006). Recently, dental cells including DPSCs, SHEDs, PDLSCs, and SCAPs have been successfully reprogrammed into iPS cells (Wada et al., 2011; Yan et al., 2010). In addition, iPS cells reprogrammed from non-dental cells, can also result in alveolar bone formation, cementum, and periodontal

TABLE 1 Comparison of stem cell features between dental and other stem cells (Huang et al., 2009; Inanc & Elcin, 2011; Ullah et al., 2015)

Stem cell types		Population doubling	Multipotential differentiation	De novo tissue formation	Application in tooth and periodontal regeneration
Dental stem cell	DPSCs	60–120	Osteo/Dentinogenic Adipogenic Chondrogenic Myogenic Neurogenic	Dentin–pulp-like tissue Bone-like tissue Blood vessel Neuronal tissue	Dentin–pulp Tooth root Periodontal tissue regeneration
	SHEDs	>140	Osteo/Dentinogenic Adipogenic Chondrogenic Myogenic Neurogenic	Dentin–pulp-like tissue Bone-like tissue Blood vessel Neuronal tissue	Dentin–pulp Tooth root Periodontal tissue regeneration
	SCAPs	>70	Osteo/Dentinogenic Adipogenic Neurogenic	Dentin–pulp-like tissue Blood vessel	Dentin–pulp Tooth root regeneration
	PDLSCs	ND	Osteo/Cementogenic Adipogenic Chondrogenic Neurogenic	Cementum-like tissue PDL-like tissue	Periodontal tissue regeneration
	DFSCs	ND	Cementogenic Odontogenic Adipogenic Chondrogenic	PDL-like tissue Cementum-like tissue	Tooth root Periodontal tissue regeneration
Non-dental stem cell	BMMSCs	30–50	Osteogenic Odontogenic Adipogenic Chondrogenic Myogenic Neurogenic	Bone-like tissue Cartilage Muscle Neuronal tissue Tooth-like tissue	Whole tooth Periodontal tissue regeneration
	ADSCs	30–50	Osteogenic Adipogenic Chondrogenic Myogenic Neurogenic	Bone-like tissue Cartilage Blood vessel Adipose tissue	Periodontal tissue regeneration
	ESCs	ND	Almost all cell lineage including endodermal, mesodermal, and ectodermal	Bone-like tissue Cartilage Myocardium Blood vessel Adipose tissue Neuronal tissue	Whole tooth Periodontal tissue regeneration
	iPSCs	ND	Almost all cell lineage including endodermal, mesodermal, and ectodermal.	Bone-like tissue Cartilage Myocardium Blood vessel Adipose tissue Neuronal tissue	Whole tooth Periodontal tissue regeneration

ND, not determined; DPSCs, dental pulp stem cells; SHEDs, stem cells from human exfoliated deciduous teeth; SCAPs, stem cells from the dental apical papilla; PDLSCs, periodontal ligament stem cells; DFSCs, dental follicle stem cells; BMMSCs, bone marrow mesenchymal stem cells; ADSCs, adipose-derived stem cells; ESCs, embryonic stem cells; iPSCs, induced pluripotent stem cells.

ligament (PDL) regeneration in mice, and demonstrated the ability of iPSCs to contribute to periodontal regeneration (Duan et al., 2011). Tooth formation depends on multiple cell populations, such as dental epithelium, dental mesenchyme, and neural crest-like cells; iPSCs could differentiate into these cells that promote tooth regeneration (Cai et al., 2013; Wen et al., 2012). In addition, iPSCs can differentiate into mesenchymal stem cells and osteoprogenitor cells, which have potential for dental tissue regeneration (Hynes et al., 2015).

3 | THE DENTIN–PULP REGENERATION

Dental pulp is a complex organized tissue with various types of cells and structures, providing nutrition, sensation, and defense against the various pathogens; additionally, it produces dentin and maintains the biological and physiological vitality of the dentin. Pulpitis, which is one of the most common diseases related to pulp, usually

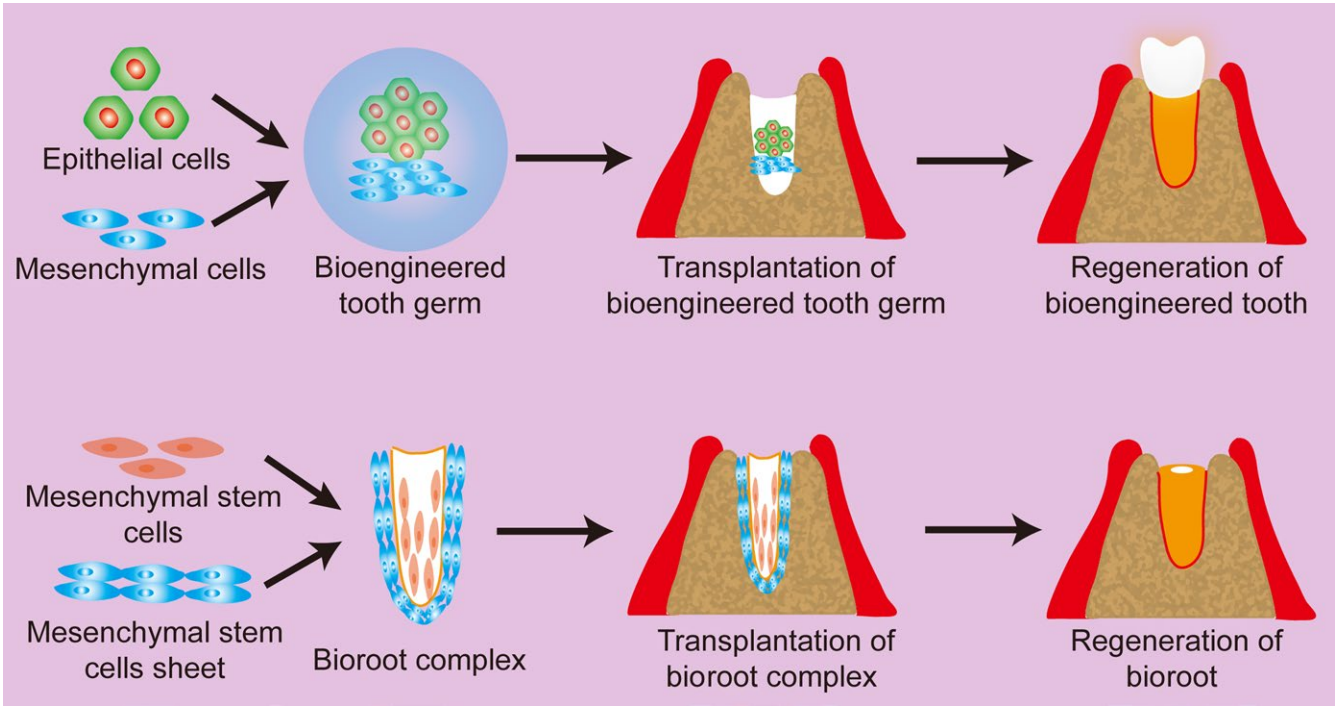

FIGURE 2 Regenerative strategy of whole tooth and bioroot. Fully functional teeth can be regenerated in vivo by transplanting bioengineered tooth germs reconstituted from epithelial and mesenchymal cells via the organ germ method. The functional regeneration of bioroot in vivo by transplanting bioroot complex reconstituted from scaffold, mesenchymal stem cells, and mesenchymal stem cells sheets

caused by dental trauma and caries. Due to the complex structure, small volume, and insufficient blood supply of dental pulp, it is difficult to eradicate the infection and initiate self-healing in pulpitis. The traditional therapy for pulpitis is root canal therapy, by removing the inflamed pulp and replacing it with inorganic material. However, this treatment usually leads to tooth fragility and fracture (Ricketts, 2001). As a result, keeping or regenerating vital pulps is a better choice. There are primarily two approaches for dental pulp regeneration: pulp revascularization; and scaffold and/or stem cell-based pulp regeneration. Dental pulp revascularization usually depends on inducing host cells from the apical region to migrate into the root canal and differentiate into a vascularized pulp tissue. The root canal space should be disinfected, and the resulting blood clots induce cell migration and initiate pulp tissue formation. Another approach is scaffold and/or stem cell-based pulp regeneration. Since Mooney and colleagues' first study of pulp tissue engineering (Mooney, Powell, Piana, & Rutherford, 1996), numerous studies have been made in a variety of animal models to achieve complete pulp regeneration.

3.1 | Cell-transplanted approach for dentin–pulp regeneration

Dental pulp stem cells can form dentin-like structures when transplanted in combination with hydroxyapatite/tricalcium phosphate (HA/TCP) in immunocompromised mice (Gronthos et al., 2000). Dentin–pulp tissue has been regenerated using different kinds of stem cells such as SHEDs and SCAPs (Cordeiro et al., 2008; Huang, Al-Habib, & Gauthier, 2013) combined with scaffolds. Not only the ectopic dentin–pulp tissue, but also pulp-like tissue can be regenerated de novo in emptied root canal space by SCAPs and DPSCs (Huang et al., 2010). Preclinical studies about dentin–pulp regeneration in large animal models have also been performed. Porcine deciduous pulp stem/progenitor cells transplanted with a beta-tricalcium phosphate (β-TCP) scaffold could mediate dentin–pulp regeneration in swine (Zheng et al., 2012). A combination of dental pulp cells and platelet-rich plasma could increase dentin–pulp regeneration within the root canals of miniature dogs (Zhu et al., 2013).

3.2 | Cell homing approach for dentin–pulp regeneration

Unlike the cell transplant approach, the basis of a cell homing approach is encouraging the recruitment of endogenous cells, including stem/progenitor cells to repair or regenerate tissue (Laird, von Andrian, & Wagers, 2008; Lee et al., 2010). Cell homing induced by a series of molecules (vascular endothelial growth factor, platelet-derived growth factor, or basic fibroblast growth factor combined with nerve growth factor and bone morphogenic protein 7 [BMP7]) is sufficient for the regeneration of dental-pulp-like tissue in endodontically treated human teeth (Kim, Lee, Kim, & Mao, 2010; Kim, Xin, et al., 2010). A cell homing approach eliminates the cell isolation, culture, and transplantation and would be an optional therapy for dental dentin–pulp regeneration (Huang & Garcia-Godoy, 2014; Kim et al., 2013).

4 | WHOLE TOOTH REGENERATION

Tooth loss is one of the most common diseases and can be caused by periodontal disease, caries, or trauma. Currently, dental implants are considered as the best clinical method for restoring tooth function and have achieved long-term success. With the advance of biomedical science, regenerative medicine has become a promising therapeutic strategy to heal or replace damaged tissues and organs. Thus, it is not surprising that the concept of tooth regeneration is of considerable interest to researchers.

4.1 | Epithelial–mesenchymal-based whole tooth regeneration

The principle of epithelial–mesenchymal interactions is used to guide the tooth regeneration as tooth regeneration strategy (Figure 2). According to the cell reconstruction way, epithelial–mesenchymal-based tooth regeneration could be divided into two categories, scaffold dependent, and independent.

4.1.1 | Scaffold independent epithelial–mesenchymal-based tooth regeneration

Dissociation–reassociation experiments showed that dental epithelial histogenesis and crown morphogenesis can be controlled by dental mesenchyme (Hu et al., 2005). A two-step implantation–transplantation strategy was proposed for a clinically feasible approach of tooth regeneration: an initial temporary ectopic implantation under the skin of the host allows further development of the crown as well as the formation of root tissues, the periodontium and surrounding bone; then, this material might be transplanted as a whole to the host site (maxilla or mandible; Hu, Nadiri, et al., 2006; Hu, Unda, et al., 2006). This strategy was also known as the cell aggregation method. The dental epithelial and mesenchymal tissues from embryonic tooth germs were isolated by using stereomicroscopic guidance, and dissociating such tissues with surgical and enzymatic treatments to obtain single stem cells. These were then used to reconstitute bioengineered tooth germs without scaffolds (Purnell, 2008). The bioengineered tooth germ was transplanted into a tooth loss region directly and then would develop into a functioning mature tooth (Ikeda et al., 2009). Alternatively, the bioengineered tooth germ was cultured into a bioengineered tooth unit, which contained a mature tooth, periodontal ligament, and alveolar bone, and then transplanted into a tooth loss region (Oshima et al., 2011). Recently, iPSCs were used for whole tooth regeneration. When combined with integration-free human urine-induced pluripotent stem cells (ifhU-iPSCs)-derived epithelial sheets, mouse dental mesenchyme stem cells, and transplanted into mouse subrenal capsules for 3 weeks, a tooth could be regenerated (Cai et al., 2013).

4.1.2 | Scaffold-dependent epithelial–mesenchymal-based tooth regeneration

To regenerate a tooth, the most important is reconstructing the epithelial–mesenchymal complex and mimicking the reciprocal epithelial–mesenchymal interactions that occur during the tooth's developmental process (Ikeda & Tsuji, 2008). Porcine third molar tooth buds were dissociated into single-cell suspensions and seeded them onto biodegradable polymers, and tooth-like tissue were generated after transplantation into rat hosts (Young et al., 2002). Also, rat tooth bud cells were isolated and seeded on polyglycolic acid (PGA) or polylactide co-glycolide copolymer (PLGA) scaffolds, and the results have shown potential to generate tooth-like tissues (Duailibi et al., 2004). A three-dimensional bioengineered incisor tooth germ culture method has been established by a three-dimensional collagen gel (Nakao et al., 2007).

4.2 | Stem cell-based whole tooth regeneration

Due to the limited sources of autologous tooth germ cells, or potential immunorejection of xenogenic tooth germ cells, epithelial–mesenchymal-based tooth regenerations are of limited application. Thus, the concept of stem cell-based tooth regeneration has emerged. This strategy of tooth regeneration depends on the multipotential differentiation of stem cells, rather than epithelial–mesenchymal interactions. A tooth-shaped scaffold constructed by poly-ε-caprolactone (PCL) and hydroxyapatite (HA), and combined with stromal-derived factor-1 and BMP7, was able to generate a whole tooth-like structure by recruiting endogenous cells (Kim, Lee, Kim, & Mao, 2010; Kim, Xin, et al., 2010).

5 | THE BIOROOT REGENERATION

Although great progress has been made in whole tooth regeneration, there are still some obstacles, such as uncontrolled morphology and tooth eruption. The tooth root provides a stable anchor for a natural or postsupported crown. Compared to whole tooth regeneration, regenerating the root may be more feasible in the near future. A bioroot was regenerated by implanting preshaped root-like scaffolds combined with mesenchymal stem cells into the alveolar bone to form a functional root, having root-like structure, similar biomechanical properties and elements to natural teeth, periodontal ligament-like tissue and dentin-like matrix structure, and is capable of supporting post-crown prostheses (Figure 2). In the first attempt, a root shape of HA/TCP as a carrier covered with autologous SCAPs was used for dentin regeneration, and autologous PDLSCs used for periodontal ligament regeneration, in miniature pigs. A root/periodontal complex formed and the concept of a bioroot was verified (Sonoyama et al., 2006). A subsequent study transplanted a root shape HA/TCP scaffold containing allogeneic dental pulp stem cells and covered by a vitamin C-induced allogeneic periodontal ligament stem cell sheet, into the jaw bones of miniature pigs. Functional bioroot regeneration was also achieved (Wei et al., 2013). Compared to a dental implant, a bioroot is superior in biomechanical properties, such as compressive strength, modulus of elasticity, and torsional force, that is, all more similar to the properties of the natural tooth root (Gao et al., 2016). In addition, treated dentin matrix (TDM) could be a biological scaffold for

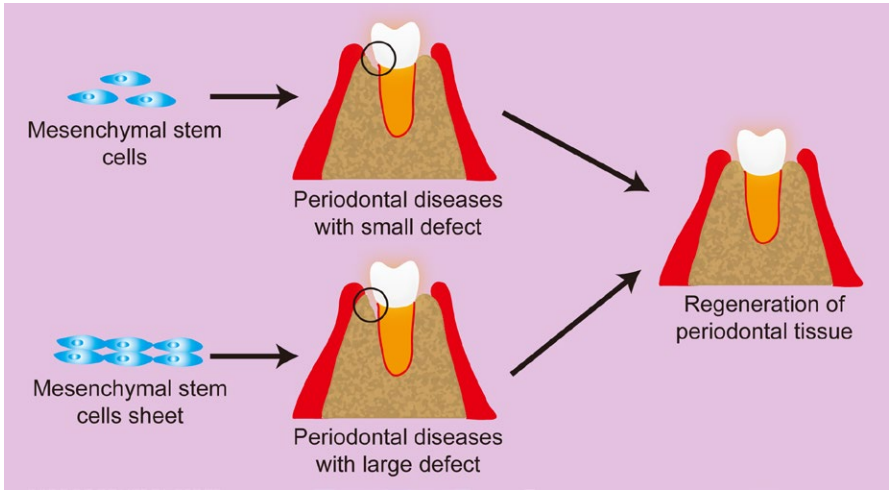

FIGURE 3 Regenerative strategy of periodontal tissue. Periodontal tissue can be regenerated in periodontal diseases with bone defects by injection of mesenchymal stem cells or transplantation of mesenchymal stem cells sheets

TABLE 2 Clinical trials of stem cell-based tooth and periodontal regeneration

	Study	Conditions	Intervention	NIH clinical trial registration number
1	Revitalization of Immature Permanent Teeth With Necrotic Pulps Using SHED Cells	Dental pulp necrosis; permanent incisor avulsed by trauma	Scaffold-free SHED-derived pellet	NCT01814436
2	Feasibility of the Preparation of an Advanced Therapy Medicinal Product for Dental Pulp Regeneration	Dental pulp regeneration	Teeth avulsion	NCT02842515
3	Clinical Trials of Regeneration for Periodontal Tissue	Adult periodontitis	Surgical operation of cell transplantation	NCT00221130
4	Periodontal Tissue Regeneration Using Autologous Periodontal Ligament Stem Cells	Periodontal pocket	Cell therapy	NCT01357785
5	Periodontal Ligament Stem Cell Implantation in the Treatment of Periodontitis	Chronic periodontitis	Cell sheet pellets and cell sheet fragment	NCT01082822
6	Periodontal Regeneration of Chronic Periodontal Disease Patients Receiving allogeneic Stem Cells Injection Therapy	Periodontal diseases	DPSC injection	NCT02523651
7	Autologous Alveolar Bone Marrow Mesenchymal Stem Cells for the Reconstruction of Infrabony Periodontal Defects	Chronic periodontitis	BMMSCs/fibrin glue/collagen fleece	NCT02449005

dentinogenesis and tooth root construction (Luo et al., 2015; Yang et al., 2012).

6 | PERIODONTAL TISSUE REGENERATION

Periodontitis is a chronic infectious disease of the soft and hard tissues supporting the teeth and is a major cause of tooth loss in adults (Pihlstrom, Michalowicz, & Johnson, 2005). Mesenchymal stem cells derived from inflamed periodontal ligaments exhibit impaired immunomodulation (Liu et al., 2012). Conventional periodontal therapy involves debridement of the root surface to induce healing, guided tissue regeneration (Needleman et al., 2006), and bone graft placement. Indeed, the traditional treatment for periodontitis is associated with a relatively high degree of variability in clinical outcome (Aichelmann-Reidy & Reynolds, 2008), and the curative effect remains unsatisfactory. The advances in regenerative medicine have made it possible for periodontal regeneration based on MSC-mediated tissue engineering (Bartold, McCulloch, Narayanan, & Pitaru, 2000). Among all the mesenchymal stem cells, PDLSCs are the main candidate stem cells in periodontal regeneration. Transplanting PDLSCs directly into periodontal defect areas resulted in periodontal regeneration (Bartold, Shi, & Gronthos, 2006). When transplanted into surgically created periodontal defect areas in miniature pigs, autologous and allogeneic PDLSCs also were capable of regenerating periodontal tissues (Ding, Liu, et al., 2010; Ding, Wang, et al., 2010; Liu et al., 2008), indicating PDLSC-mediated tissue engineering could be a useful treatment for periodontitis. The potential mechanism has also been clarified and is largely dependent on the immunomodulatory properties of PDLSCs. These cells possess low immunogenicity and remarkable

immunosuppression via secreting prostaglandin E2 (PGE2), leading to PGE2-induced T-cell anergy (Ding, Liu, et al., 2010; Ding, Wang, et al., 2010). In addition, PDLSCs suppressed B-cell activation through cell-to-cell contact mostly mediated by programmed cell death protein 1 (PD1) and programmed cell death 1 ligand 1 (PDL1; Liu et al., 2013).

Previous studies mainly combined the stem cells with a scaffold for periodontal regeneration, for example, collagen, fibrin, hydrogel, gelatin. However, major concerns are the complicated transplantation process and the potential for host rejection. Recently, non-scaffold tissue engineering has been of increasing interest to researchers. There are primarily two non-scaffold strategies, cell injection and cell sheets (Figure 3).

Cell injection has been the common treatment in stem cell-based tissue engineering (Kinnaird et al., 2004). Local injection of DPSCs or PDLSCs has also been shown effective for treating periodontal diseases (Baik, Park, Lee, & Chung, 2014). Periodontal regeneration was observed in a rat periodontitis model after local injection of a BMMSC suspension (Du, Shan, Ma, Wang, & Fan, 2014).

Cell sheet engineering has been developed as a unique, scaffold-free method of cell processing by culturing in ascorbic acid (Wei et al., 2012; Du et al., 2014) or utilizing temperature-responsive cell culture vessels (Owaki, Shimizu, Yamato, & Okano, 2014). Cell sheets can maintain extracellular matrix and cell–cell junctions, which would be degraded by proteolytic enzymes such as trypsin and/or dispase, and has shown positive outcomes in treating many diseases (Nishida et al., 2004; Ohashi et al., 2007; Owaki et al., 2014). Transplantation of periodontal ligament cell (PDL) cell sheets in an athymic rat mesial dehiscence model led to identifiable periodontal ligament-like tissues that included an acellular cementum-like layer and fibrils anchoring into this layer (Hasegawa, Yamato, Kikuchi, Okano, & Ishikawa, 2005). Periodontal ligament cell sheets were used for periodontal regeneration in studies of dogs (Akizuki et al., 2005; Iwata et al., 2009). Besides PDLSCs (Ding, Liu, et al., 2010; Ding, Wang, et al., 2010; Liu et al., 2008), DPSCs (Hu et al., 2016; Khorsand et al., 2013), SHEDs (Fu, Jin, Ma, Fan, & Wang, 2014), BMMSCs (Du et al., 2014), ADSCs also have the potential for periodontal regeneration (Tobita & Mizuno, 2013).

7 | TRANSLATIONAL STUDIES IN STEM CELL-BASED TOOTH AND PERIODONTAL REGENERATION

7.1 | Tooth stem cell banking

Compared to other stem cells' banking, tooth stem cell banking is just at the initial stage, but is catching up quickly. Cryopreservation does not affect the biological and immunological properties of SCAPs, supporting the feasibility of SCAP cryopreservation in nitrogen (Ding, Liu, et al., 2010; Ding, Wang, et al., 2010). In the USA, there are several companies or institutions (BioEden, StemSave, The Tooth Bank, National Dental Pulp Laboratory, Store-A-Tooth) involved in banking tooth stem cells. In Japan, Hiroshima University established a tooth bank named "Three Brackets," and Nagoya University also developed a tooth bank in 2007. Taipei Medical University (TMU) in collaboration with Hiroshima University also opened a similar tooth bank. In Norway, the Norwegian Tooth Bank was set up for collecting exfoliated primary teeth from children (Arora, Arora, & Munshi, 2009). In India, tooth banks (Stemade and Storeyourcells) have also been established for dental stem cell banking. In China, tooth stem cell banking has been established for years in Beijing and dental stem cell products, such as human dental pulp mesenchymal stem cell injection, are now being used in routine clinical practice.

7.2 | Human studies and clinical trials

Periodontal regeneration was achieved in human studies using PDLSCs, BMMSCs, and cells derived from gingiva or periosteum (Monsarrat et al., 2014). In addition, several clinical trials have been registered for dental pulp and periodontal regeneration (Table 2). A clinical trial was conducted for revitalization of immature permanent teeth with necrotic pulps using autologous SHEDs, which is currently recruiting participants (NIH clinical trial registration number: NCT01814436). Another clinical trial was directed at transplanting autologous DPSCs for dental pulp regeneration (NIH clinical trial registration number: NCT02842515). This study is now finished, but the outcome is still unpublished. Additional clinical trials are targeted for periodontal regeneration. There were two trials for periodontal regeneration using PDLSCs, one for the safety and efficacy of autologous PDLSCs for the regeneration of deep periodontal infrabony defects in 35 patients (NIH clinical trial registration number: NCT01357785), and another for safety and efficacy of periodontal regeneration by allogeneic PDLSC cell sheet in 80 patients (NIH clinical trial registration number: NCT01082822). No clinical safety problems were found during these clinical trials. However, no statistically significant differences between the group treated with PDLSC sheets and the control group were seen (Chen et al., 2016). In addition, two trials are currently recruiting patients. One aims to study local periodontal regeneration of chronic periodontal disease patients receiving allogeneic human DPSCs via injection therapy (NIH clinical trial registration number: NCT02523651). Another is a randomized trial, focusing on the safety and efficacy of regenerative treatment of infrabony periodontal defects using autologous BMMSCs combined with collagen scaffolds enriched with fibrin glue (NIH clinical trial registration number: NCT02449005).

8 | SUMMARY

Several kinds of stem cells have been isolated from human adult teeth and have been used for tooth and periodontal regeneration. Non-dental stem cells, like BMMSCs, ADSCs, and iPSCs, have also been used for these studies. Different strategies were investigated for tooth and periodontal regeneration, such as epithelial–mesenchymal-based whole tooth regeneration or cell homing strategies, bioroot regeneration, cell injection, or cell sheet-based periodontal regeneration. However, the fates and functions of stem cells after transplantation

need to be clarified. Although tooth stem cell banking and clinical trials have been organized, their beneficial results for patients need to be determined. With improved efficacy of tooth and periodontal regeneration, stem cell-based tooth and periodontal regeneration may become widely used for clinical applications in the future.

CONFLICT OF INTEREST

The authors declare no competing financial interests.

AUTHOR CONTRIBUTIONS

L Hu and Y Liu contributed to the writing and figure design. SL Wang contributed to review design and editing and critically revised the manuscript.

REFERENCES

Aichelmann-Reidy, M. E., & Reynolds, M. A. (2008). Predictability of clinical outcomes following regenerative therapy in intrabony defects. *Journal of Periodontology*, *79*, 387–393.

Akizuki, T., Oda, S., Komaki, M., Tsuchioka, H., Kawakatsu, N., Kikuchi, A., … Ishikawa, I. (2005). Application of periodontal ligament cell sheet for periodontal regeneration: A pilot study in beagle dogs. *Journal of Periodontal Research*, *40*, 245–251.

Alsberg, E., Hill, E. E., & Mooney, D. J. (2001). Craniofacial tissue engineering. *Critical Reviews in Oral Biology and Medicine*, *12*, 64–75.

Arora, V., Arora, P., & Munshi, A. K. (2009). Banking stem cells from human exfoliated deciduous teeth (SHED): Saving for the future. *Journal of Clinical Pediatric Dentistry*, *33*, 289–294.

Baik, H. S., Park, J., Lee, K. J., & Chung, C. (2014). Local application of periodontal ligament stromal cells promotes soft tissue regeneration. *Oral Diseases*, *20*, 574–581.

Bartold, P. M., McCulloch, C. A., Narayanan, A. S., & Pitaru, S. (2000). Tissue engineering: A new paradigm for periodontal regeneration based on molecular and cell biology. *Periodontology 2000*, *24*, 253–269.

Bartold, P. M., Shi, S., & Gronthos, S. (2006). Stem cells and periodontal regeneration. *Periodontology 2000*, *40*, 164–172.

Cai, J., Zhang, Y., Liu, P., Chen, S., Wu, X., Sun, Y., … Pei, D. (2013). Generation of tooth-like structures from integration-free human urine induced pluripotent stem cells. *Cell Regeneration*, *2*, *6*.

Chen, F. M., Gao, L. N., Tian, B. M., Zhang, X. Y., Zhang, Y. J., Dong, G. Y., … Jin, Y. (2016). Treatment of periodontal intrabony defects using autologous periodontal ligament stem cells: A randomized clinical trial. *Stem Cell Research & Therapy*, *7*, 33.

Cordeiro, M. M., Dong, Z., Kaneko, T., Zhang, Z., Miyazawa, M., Shi, S., … Nor, J. E. (2008). Dental pulp tissue engineering with stem cells from exfoliated deciduous teeth. *Journal of Endodontics*, *34*, 962–969.

Ding, G., Liu, Y., Wang, W., Wei, F., Liu, D., Fan, Z., … Wang, S. (2010). Allogeneic periodontal ligament stem cell therapy for periodontitis in swine. *Stem Cells*, *28*, 1829–1838.

Ding, G., Wang, W., Liu, Y., An, Y., Zhang, C., Shi, S., & Wang, S. (2010). Effect of cryopreservation on biological and immunological properties of stem cells from apical papilla. *Journal of Cellular Physiology*, *223*, 415–422.

Du, J., Shan, Z., Ma, P., Wang, S., & Fan, Z. (2014). Allogeneic bone marrow mesenchymal stem cell transplantation for periodontal regeneration. *Journal of Dental Research*, *93*, 183–188.

Duailibi, M. T., Duailibi, S. E., Young, C. S., Bartlett, J. D., Vacanti, J. P., & Yelick, P. C. (2004). Bioengineered teeth from cultured rat tooth bud cells. *Journal of Dental Research*, *83*, 523–528.

Duan, X., Tu, Q., Zhang, J., Ye, J., Sommer, C., Mostoslavsky, G., … Chen, J. (2011). Application of induced pluripotent stem (iPS) cells in periodontal tissue regeneration. *Journal of Cellular Physiology*, *226*, 150–157.

Evans, M. J., & Kaufman, M. H. (1981). Establishment in culture of pluripotential cells from mouse embryos. *Nature*, *292*, 154–156.

Fu, X., Jin, L., Ma, P., Fan, Z., & Wang, S. (2014). Allogeneic stem cells from deciduous teeth in treatment for periodontitis in miniature swine. *Journal of Periodontology*, *85*, 845–851.

Gao, Z. H., Hu, L., Liu, G. L., Wei, F. L., Liu, Y., Liu, Z. H., … Wang, S. L. (2016). Bio-root and implant-based restoration as a tooth replacement alternative. *Journal of Dental Research*, *95*, 642–649.

Gronthos, S., Brahim, J., Li, W., Fisher, L. W., Cherman, N., Boyde, A., … Shi, S. (2002). Stem cell properties of human dental pulp stem cells. *Journal of Dental Research*, *81*, 531–535.

Gronthos, S., Mankani, M., Brahim, J., Robey, P. G., & Shi, S. (2000). Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. *Proceedings of the National Academy of Sciences of the USA*, *97*, 13625–13630.

Harada, H., Kettunen, P., Jung, H. S., Mustonen, T., Wang, Y. A., & Thesleff, I. (1999). Localization of putative stem cells in dental epithelium and their association with Notch and FGF signaling. *Journal of Cell Biology*, *147*, 105–120.

Hasegawa, M., Yamato, M., Kikuchi, A., Okano, T., & Ishikawa, I. (2005). Human periodontal ligament cell sheets can regenerate periodontal ligament tissue in an athymic rat model. *Tissue Engineering*, *11*, 469–478.

Hasegawa, N., Kawaguchi, H., Hirachi, A., Takeda, K., Mizuno, N., Nishimura, M., … Kurihara, H. (2006). Behavior of transplanted bone marrow-derived mesenchymal stem cells in periodontal defects. *Journal of Periodontology*, *77*, 1003–1007.

Hollinger, J. O., & Winn, S. R. (1999). Tissue engineering of bone in the craniofacial complex. *Annals of the New York Academy of Sciences*, *875*, 379–385.

Honda, M. J., Shinohara, Y., Hata, K. I., & Ueda, M. (2007). Subcultured odontogenic epithelial cells in combination with dental mesenchymal cells produce enamel-dentin-like complex structures. *Cell Transplantation*, *16*, 833–847.

Hu, J., Cao, Y., Xie, Y., Wang, H., Fan, Z., Wang, J., … Wang, S. (2016). Periodontal regeneration in swine after cell injection and cell sheet transplantation of human dental pulp stem cells following good manufacturing practice. *Stem Cell Research & Therapy*, *7*, 130.

Hu, B., Nadiri, A., Bopp-Kuchler, S., Perrin-Schmitt, F., Wang, S., & Lesot, H. (2005). Dental epithelial histo-morphogenesis in the mouse: Positional information versus cell history. *Archives of Oral Biology*, *50*, 131–136.

Hu, B., Nadiri, A., Kuchler-Bopp, S., Perrin-Schmitt, F., Peters, H., & Lesot, H. (2006). Tissue engineering of tooth crown, root, and periodontium. *Tissue Engineering*, *12*, 2069–2075.

Hu, B., Unda, F., Bopp-Kuchler, S., Jimenez, L., Wang, X. J., Haikel, Y., … Lesot, H. (2006). Bone marrow cells can give rise to ameloblast-like cells. *Journal of Dental Research*, *85*, 416–421.

Huang, G. T., Al-Habib, M., & Gauthier, P. (2013). Challenges of stem cell-based pulp and dentin regeneration: A clinical perspective. *Endodontic Topics*, *28*, 51–60.

Huang, G. T., & Garcia-Godoy, F. (2014). Missing concepts in de novo pulp regeneration. *Journal of Dental Research*, *93*, 717–724.

Huang, G. T., Gronthos, S., & Shi, S. (2009). Mesenchymal stem cells derived from dental tissues vs. those from other sources: Their biology and role in regenerative medicine. *Journal of Dental Research*, *88*, 792–806.

Huang, G. T., Yamaza, T., Shea, L. D., Djouad, F., Kuhn, N. Z., Tuan, R. S., & Shi, S. (2010). Stem/progenitor cell-mediated de novo regeneration of dental pulp with newly deposited continuous layer of dentin in an in vivo model. *Tissue Engineering Part A*, *16*, 605–615.

Hung, C. N., Mar, K., Chang, H. C., Chiang, Y. L., Hu, H. Y., Lai, C. C., … Ma, C. M. (2011). A comparison between adipose tissue and dental pulp as sources of MSCs for tooth regeneration. *Biomaterials*, *32*, 6995–7005.

Hynes, K., Menichanin, D., Bright, R., Ivanovski, S., Hutmacher, D. W., Gronthos, S., & Bartold, P. M. (2015). Induced pluripotent stem cells:

A new frontier for stem cells in dentistry. *Journal of Dental Research*, *94*, 1508–1515.

Ikeda, E., Morita, R., Nakao, K., Ishida, K., Nakamura, T., Takano-Yamamoto, T., … Tsuji, T. (2009). Fully functional bioengineered tooth replacement as an organ replacement therapy. *Proceedings of the National Academy of Sciences of the USA*, *106*, 13475–13480.

Ikeda, E., & Tsuji, T. (2008). Growing bioengineered teeth from single cells: Potential for dental regenerative medicine. *Expert Opinion on Biological Therapy*, *8*, 735–744.

Inanc, B., & Elcin, Y. M. (2011). Stem cells in tooth tissue regeneration–challenges and limitations. *Stem Cell Reviews*, *7*, 683–692.

Inanç, B., Elçin, A. E., & Elçin, Y. M. (2009). In vitro differentiation and attachment of human embryonic stem cells on periodontal tooth root surfaces. *Tissue Engineering Part A*, *15*, 3427–3435.

Iwata, T., Yamato, M., Tsuchioka, H., Takagi, R., Mukobata, S., Washio, K., … Ishikawa, I. (2009). Periodontal regeneration with multi-layered periodontal ligament-derived cell sheets in a canine model. *Biomaterials*, *30*, 2716–2723.

Khorsand, A., Eslaminejad, M. B., Arabsolghar, M., Paknejad, M., Ghaedi, B., Rokn, A. R., … Jahangir, S. (2013). Autologous dental pulp stem cells in regeneration of defect created in canine periodontal tissue. *Journal of Oral Implantology*, *39*, 433–443.

Kim, K., Lee, C. H., Kim, B. K., & Mao, J. J. (2010). Anatomically shaped tooth and periodontal regeneration by cell homing. *Journal of Dental Research*, *89*, 842–847.

Kim, J. Y., Xin, X., Moioli, E. K., Chung, J., Lee, C. H., Chen, M., … Mao, J. J. (2010). Regeneration of dental-pulp-like tissue by chemotaxis-induced cell homing. *Tissue Engineering Part A*, *16*, 3023–3031.

Kim, S. G., Zheng, Y., Zhou, J., Chen, M., Embree, M. C., Song, K., … Mao, J. J. (2013). Dentin and dental pulp regeneration by the patient's endogenous cells. *Endodontic Topics*, *28*, 106–117.

Kinnaird, T., Stabile, E., Burnett, M. S., Shou, M., Lee, C. W., Barr, S., … Epstein, S. E. (2004). Local delivery of marrow-derived stromal cells augments collateral perfusion through paracrine mechanisms. *Circulation*, *109*, 1543–1549.

Laird, D. J., von Andrian, U. H., & Wagers, A. J. (2008). Stem cell trafficking in tissue development, growth, and disease. *Cell*, *132*, 612–630.

Lee, C. H., Cook, J. L., Mendelson, A., Moioli, E. K., Yao, H., & Mao, J. J. (2010). Regeneration of the articular surface of the rabbit synovial joint by cell homing: A proof of concept study. *Lancet*, *376*, 440–448.

Lemaitre, M., Monsarrat, P., Blasco-Baque, V., Loubieres, P., Burcelin, R., Casteilla, L., … Kemoun, P. (2017). Periodontal tissue regeneration using syngeneic adipose-derived stromal cells in a mouse model. *Stem Cells Translational Medicine*, *6*, 656–665.

Liu, O., Xu, J., Ding, G., Liu, D., Fan, Z., Zhang, C., … Wang, S. (2013). Periodontal ligament stem cells regulate B lymphocyte function via programmed cell death protein 1. *Stem Cells*, *31*, 1371–1382.

Liu, D., Xu, J., Liu, O., Fan, Z., Liu, Y., Wang, F., … Wang, S. (2012). Mesenchymal stem cells derived from inflamed periodontal ligaments exhibit impaired immunomodulation. *Journal of Clinical Periodontology*, *39*, 1174–1182.

Liu, Y., Zheng, Y., Ding, G., Fang, D., Zhang, C., Bartold, P. M., … Wang, S. (2008). Periodontal ligament stem cell-mediated treatment for periodontitis in miniature swine. *Stem Cells*, *26*, 1065–1073.

Luo, X., Yang, B., Sheng, L., Chen, J., Li, H., Xie, L., … Tian, W. (2015). CAD based design sensitivity analysis and shape optimization of scaffolds for bio-root regeneration in swine. *Biomaterials*, *57*, 59–72.

Mao, A. S., & Mooney, D. J. (2015). Regenerative medicine: Current therapies and future directions. *Proceedings of the National Academy of Sciences of the USA*, *112*, 14452–14459.

Martinez, S. D., Sasaki, R. T., Neves, A. D., & Da, S. M. (2016). Stem cells from human exfoliated deciduous teeth: A growing literature. *Cells Tissues Organs*, *202*, 269–280.

Miura, M., Gronthos, S., Zhao, M., Lu, B., Fisher, L. W., Robey, P. G., & Shi, S. (2003). SHED: Stem cells from human exfoliated deciduous teeth. *Proceedings of the National Academy of Sciences of the USA*, *100*, 5807–5812.

Monsarrat, P., Vergnes, J. N., Nabet, C., Sixou, M., Snead, M. L., Planat-Benard, V., … Kemoun, P. (2014). Concise review: Mesenchymal stromal cells used for periodontal regeneration: A systematic review. *Stem Cells Translational Medicine*, *3*, 768–774.

Mooney, D. J., Powell, C., Piana, J., & Rutherford, B. (1996). Engineering dental pulp-like tissue in vitro. *Biotechnology Progress*, *12*, 865–868.

Morsczeck, C., Gotz, W., Schierholz, J., Zeilhofer, F., Kuhn, U., Mohl, C., … Hoffmann, K. H. (2005). Isolation of precursor cells (PCs) from human dental follicle of wisdom teeth. *Matrix Biology*, *24*, 155–165.

Nakao, K., Morita, R., Saji, Y., Ishida, K., Tomita, Y., Ogawa, M., … Tsuji, T. (2007). The development of a bioengineered organ germ method. *Nature Methods*, *4*, 227–230.

Nam, H., Kim, J., Park, J., Park, J. C., Kim, J. W., Seo, B. M., … Lee, G. (2011). Expression profile of the stem cell markers in human Hertwig's epithelial root sheath/Epithelial rests of Malassez cells. *Molecules and Cells*, *31*, 355–360.

Needleman, I. G., Worthington, H. V., Giedrys-Leeper, E., & Tucker, R. J. (2006). Guided tissue regeneration for periodontal infra-bony defects. *Cochrane Database Systematic Review*, CD001724.

Ning, F., Guo, Y., Tang, J., Zhou, J., Zhang, H., Lu, W., … Jin, Y. (2010). Differentiation of mouse embryonic stem cells into dental epithelial-like cells induced by ameloblasts serum-free conditioned medium. *Biochemical and Biophysical Research Communications*, *394*, 342–347.

Nishida, K., Yamato, M., Hayashida, Y., Watanabe, K., Yamamoto, K., Adachi, E., … Tano, Y. (2004). Corneal reconstruction with tissue-engineered cell sheets composed of autologous oral mucosal epithelium. *New England Journal of Medicine*, *351*, 1187–1196.

Nuti, N., Corallo, C., Chan, B. M., Ferrari, M., & Gerami-Naini, B. (2016). Multipotent differentiation of human dental pulp stem cells: A literature review. *Stem Cell Reviews*, *12*, 511–523.

Ohashi, K., Yokoyama, T., Yamato, M., Kuge, H., Kanehiro, H., Tsutsumi, M., … Nakajima, Y. (2007). Engineering functional two- and three-dimensional liver systems in vivo using hepatic tissue sheets. *Nature Medicine*, *13*, 880–885.

Ohazama, A., Modino, S. A., Miletich, I., & Sharpe, P. T. (2004). Stem-cell-based tissue engineering of murine teeth. *Journal of Dental Research*, *83*, 518–522.

Oshima, M., Mizuno, M., Imamura, A., Ogawa, M., Yasukawa, M., Yamazaki, H., … Tsuji, T. (2011). Functional tooth regeneration using a bioengineered tooth unit as a mature organ replacement regenerative therapy. *PLoS ONE*, *6*, e21531.

Owaki, T., Shimizu, T., Yamato, M., & Okano, T. (2014). Cell sheet engineering for regenerative medicine: Current challenges and strategies. *Biotechnology Journal*, *9*, 904–914.

Pihlstrom, B. L., Michalowicz, B. S., & Johnson, N. W. (2005). Periodontal diseases. *Lancet*, *366*, 1809–1820.

Purnell, B. (2008). New release: The complete guide to organ repair. Introduction. *Science*, *322*, 1489.

Ricketts, D. (2001). Management of the deep carious lesion and the vital pulp dentine complex. *British Dental Journal*, *191*, 606–610.

Seo, B. M., Miura, M., Gronthos, S., Bartold, P. M., Batouli, S., Brahim, J., … Shi, S. (2004). Investigation of multipotent postnatal stem cells from human periodontal ligament. *Lancet*, *364*, 149–155.

Sonoyama, W., Liu, Y., Fang, D., Yamaza, T., Seo, B. M., Zhang, C., … Shi, S. (2006). Mesenchymal stem cell-mediated functional tooth regeneration in swine. *PLoS ONE*, *1*, e79.

Sonoyama, W., Liu, Y., Yamaza, T., Tuan, R. S., Wang, S., Shi, S., & Huang, G. T. (2008). Characterization of the apical papilla and its residing stem cells from human immature permanent teeth: A pilot study. *Journal of Endodontics*, *34*, 166–171.

Takahashi, K., & Yamanaka, S. (2006). Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell*, *126*, 663–676.

Tobita, M., & Mizuno, H. (2013). Adipose-derived stem cells and periodontal tissue engineering. *International Journal of Oral and Maxillofacial Implants*, *28*, e487–e493.

Tobita, M., Uysal, A. C., Ogawa, R., Hyakusoku, H., & Mizuno, H. (2008). Periodontal tissue regeneration with adipose-derived stem cells. *Tissue Engineering Part A*, *14*, 945–953.

Ullah, I., Subbarao, R. B., & Rho, G. J. (2015). Human mesenchymal stem cells – current trends and future prospective. *Bioscience Reports*, *35*, e00191.

Wada, N., Wang, B., Lin, N. H., Laslett, A. L., Gronthos, S., & Bartold, P. M. (2011). Induced pluripotent stem cell lines derived from human gingival fibroblasts and periodontal ligament fibroblasts. *Journal of Periodontal Research*, *46*, 438–447.

Wang, J., Wang, X., Sun, Z., Wang, X., Yang, H., Shi, S., & Wang, S. (2010). Stem cells from human-exfoliated deciduous teeth can differentiate into dopaminergic neuron-like cells. *Stem Cells and Development*, *19*, 1375–1383.

Wei, F., Qu, C., Song, T., Ding, G., Fan, Z., Liu, D., … Wang, S. (2012). Vitamin C treatment promotes mesenchymal stem cell sheet formation and tissue regeneration by elevating telomerase activity. *Journal of Cellular Physiology*, *227*, 3216–3224.

Wei, F., Song, T., Ding, G., Xu, J., Liu, Y., Liu, D., … Wang, S. (2013). Functional tooth restoration by allogeneic mesenchymal stem cell-based bio-root regeneration in swine. *Stem Cells and Development*, *22*, 1752–1762.

Wen, Y., Wang, F., Zhang, W., Li, Y., Yu, M., Nan, X., … Pei, X. (2012). Application of induced pluripotent stem cells in generation of a tissue-engineered tooth-like structure. *Tissue Engineering Part A*, *18*, 1677–1685.

Yan, X., Qin, H., Qu, C., Tuan, R. S., Shi, S., & Huang, G. T. (2010). iPS cells reprogrammed from human mesenchymal-like stem/progenitor cells of dental tissue origin. *Stem Cells and Development*, *19*, 469–480.

Yang, B., Chen, G., Li, J., Zou, Q., Xie, D., Chen, Y., … Tian, W. (2012). Tooth root regeneration using dental follicle cell sheets in combination with a dentin matrix – based scaffold. *Biomaterials*, *33*, 2449–2461.

Yang, Y., Rossi, F. M., & Putnins, E. E. (2010). Periodontal regeneration using engineered bone marrow mesenchymal stromal cells. *Biomaterials*, *31*, 8574–8582.

Yao, S., Pan, F., Prpic, V., & Wise, G. E. (2008). Differentiation of stem cells in the dental follicle. *Journal of Dental Research*, *87*, 767–771.

Yokoi, T., Saito, M., Kiyono, T., Iseki, S., Kosaka, K., Nishida, E., … Teranaka, T. (2007). Establishment of immortalized dental follicle cells for generating periodontal ligament in vivo. *Cell and Tissue Research*, *327*, 301–311.

Young, C. S., Terada, S., Vacanti, J. P., Honda, M., Bartlett, J. D., & Yelick, P. C. (2002). Tissue engineering of complex tooth structures on biodegradable polymer scaffolds. *Journal of Dental Research*, *81*, 695–700.

Zheng, Y., Wang, X. Y., Wang, Y. M., Liu, X. Y., Zhang, C. M., Hou, B. X., & Wang, S. L. (2012). Dentin regeneration using deciduous pulp stem/progenitor cells. *Journal of Dental Research*, *91*, 676–682.

Zhu, W., Zhu, X., Huang, G. T., Cheung, G. S., Dissanayaka, W. L., & Zhang, C. (2013). Regeneration of dental pulp tissue in immature teeth with apical periodontitis using platelet-rich plasma and dental pulp cells. *International Endodontic Journal*, *46*, 962–970.

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