Potential application of dental stem cells in regenerative reconstruction of oral and maxillofacial tissues: a narrative review

Puhan He[1], Qunzhou Zhang[1], Faizan I. Motiwala[2], Rabie M. Shanti[1,3,4], Brian M. Chang[1,5], Anh D. Le[1,3]

[1]Department of Oral & Maxillofacial Surgery & Pharmacology, University of Pennsylvania School of Dental Medicine, Philadelphia, PA, USA; [2]University of Pennsylvania School of Dental Medicine, Philadelphia, PA, USA; [3]Department of Oral & Maxillofacial Surgery, Penn Medicine Hospital of the University of Pennsylvania, Philadelphia, PA, USA; [4]Department of Otorhinolaryngology-Head and Neck Surgery, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA; [5]Division of Restorative Sciences, University of Pennsylvania School of Dental Medicine, Philadelphia, PA, USA

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Correspondence to: Anh D. Le, DDS, PhD. Department of Oral & Maxillofacial Surgery, Penn Medicine Hospital of the University of Pennsylvania, Philadelphia; Department of Oral & Maxillofacial Surgery and Pharmacology, University of Pennsylvania School of Dental Medicine, 240 South 40th Street, Philadelphia, PA 19104, USA. Email: Anh.Le@pennmedicine.upenn.edu; Qunzhou Zhang, PhD. Department of Oral & Maxillofacial Surgery and Pharmacology, University of Pennsylvania School of Dental Medicine, 240 South 40th Street, Philadelphia, PA 19104, USA. Email: zqunzhou@upenn.edu.

Background and Objective: Oral and maxillofacial (OMF) defects caused by congenital conditions, injuries, ablative surgery for benign and malignant head & neck tumor, can often lead to OMF deformities and malfunctions in speech, mastication/chewing, and swallowing as well as have deleterious psychological effects and socioeconomic burdens to patients. Due to the unique complex 3D geometry of the head and neck region, reconstruction and rehabilitation of OMF defects remain a major challenge for OMF surgeons. The purpose of this narrative review is to update the information on the biological properties and functions of mesenchymal stem cells derived from various dental tissues (dental-MSCs) and their potential application in tissue engineering (TE) and regenerative reconstruction of OMF tissues.

Methods: A data-based search was performed by using PubMed database whereby articles published between 2000 and 2021 in English were included in the search with the following key words: dental stem cells, OMF reconstruction, OMF TE and regeneration.

Key Content and Findings: Currently, the advancement in stem cell biology, biomaterial science, and TE technology has demonstrated the significant potential application of stem cell-based therapy in regenerative reconstruction and rehabilitation of OMF defects. However, no stem cell-based product or device has been translated into clinical application to replace microsurgical free tissue transfer, the current mainstay of care in the reconstruction of OMF defects.

Conclusions: Currently, microsurgical free tissue transfer remains the gold standard mainstay of care for the reconstruction of OMF defects due to their abundant blood supply and flexibility for transplantation. However, several major challenges, such as the limited availability, the requirement of a second surgery, donor site morbidity, and the risk of free flap failure, have promoted the development of novel approaches. Due to the advancement in stem cell biology, biomaterial science, and TE technology, stem cell-based regenerative therapy is emerging as a promising therapeutic approach for a variety of diseases, including regenerative reconstruction and rehabilitation of OMF defects. In this narrative review, we update on the characteristics and biological functions of mesenchymal stem cells derived from various dental tissues (dental-MSCs) and their released cell-free products, extracellular vesicles (EVs). We also highlighted their potential application in TE and regenerative reconstruction of OMF defects in animal models and clinical studies and the potential challenges in this field.

Introduction

Reconstructive surgery is a growing aspect of oral and maxillofacial (OMF) surgery specialty. Among others, OMF surgeons are especially equipped to manage deformities and defects of the midface/maxilla, oromandibular region, and the temporomandibular joint (1-4). Defects in the head and neck may involve insult to multiple tissue types including bones, cartilage, muscle, skins, nerves and blood vessels. The complex anatomy and the presence of specialized organs such as the tongue, periodontium, and teeth (5-8) make reconstruction of this region especially challenging. OMF defects and deformities may be acquired, as a sequela of trauma and surgical resection due to neoplasm, infection or necrosis; or they may be congenital, as is in the case of cleft lips and palates (2). These defects result in facial disfigurement, speech impairment, mastication and swallowing difficulties, posing a significant psychological and economical burden to the patient and family (2,7,9-12). Reconstruction offers possibility of restoring function and cosmesis, and thereby improving overall quality of life (9,13,14).

In recent years, the development and advancement of state-of-the-art technologies and approaches, such as navigation, virtual surgical pre-planning (VSP), 3D printing technology, and microsurgical techniques have significantly advanced the field of OMF reconstruction (8,15). A successful reconstruction and functional rehabilitation of OMF defects rely on multiple factors, such as the type of defect, the health status of patients, and the treatment modality (13,15). Treatment modalities may include primary closure, healing by secondary intention, autografts, allograft, prosthesis and flaps. Locoregional flaps and vascularized soft-tissue and bone/composite free flaps are the mainstay of treatment for reconstruction of large OMF defects (16-20). However, donor site morbidity, and the inability to restore specialized tissue such as taste, sensory and periodontium pose challenges in reestablishing premorbid form and function (19). Therefore, further investigation on reconstruction surgery and functional rehabilitation techniques is requisite (13,15).

In the last decade, advancements in tissue engineering (TE), biomaterial science, and stem cell biology, have shed new light on the development of novel approaches for OMF reconstruction and functional rehabilitation (8). Regenerative medicine (RM) aims to use multiple approaches to replace or regenerate damaged cells, tissues and organs; or to stimulate the body's endogenous repair mechanisms (21). As an emerging field, RM integrates TE, material science, and stem cell biology to generate stem cell-based TE/RM products to meet the increasing clinical demand for tissue regeneration/reconstruction, including regenerative rehabilitation of OMF defects (22-24). This article reviews recent progress and potential towards the clinical application of stem cells, particularly, oral tissue-derived stem cells, in reconstructive surgery and regenerative rehabilitation in patients with OMF defects. We present the following article in accordance with the Narrative Review reporting checklist (available at https://fomm.amegroups.com/article/view/10.21037/fomm-21-10/rc).

Methods

In this narrative review, we searched the PubMed database using the following key words: dental stem cells, OMF reconstruction, OMF TE, oral craniofacial and maxillofacial tissue regeneration. The following MeSH terms were utilized to aid in the literature search as well: head and neck neoplasms, oral surgery, mesenchymal stem cells (MSCs), and TE. The published articles with full-text from Jan 2000 to Jan 2021 were included (*Table 1*) dental stem cells, OMF reconstruction, OMF tissue engineering and regeneration.

Discussion

MSCs

MSCs represent a population of multipotent postnatal

Table 1 The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	12/30/2020–2/1/2021
Databases and other sources searched	PubMed database
Search terms used (including MeSH and free text search terms and filters). Note: please use an independent supplement table to present detailed search strategy of one database as an example	Dental stem cells, oral and maxillofacial reconstruction, oral and maxillofacial tissue engineering and regeneration
Timeframe	2000–2021
Inclusion and exclusion criteria (study type, language restrictions etc.)	Articles written in English related to dental stem cells and oral and maxillofacial reconstruction were included. Any articles not written in English were excluded. No specific study type was excluded
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	The selection process was done by Dr. Qunzhou Zhang
Any additional considerations, if applicable	No additional considerations

stem cells with self-renewal and multipotent differentiation capabilities. The first isolated and most well characterized source of MSCs was from bone marrow (25). They are described as fibroblast-like in morphology and able to form adherent "colony-forming units-fibroblastic" (CFU-F) (26,27). Thereafter, the International Society of Cell & Gene Therapy (ISCT) defined human MSCs based on three minimal criteria,: (I) an adherent fibroblast-like appearance; (II) the expression of a panel of specific mesenchymal cell surface molecules such as CD73, CD90, and CD105, while lacking the expression of hematopoietic cell markers such as CD34, CD45, CD11b, CD14, CD19, and of human leukocyte antigen-D related (HLA-DR or HMC-II) surface molecules; (III) the potential to differentiate into trilineage of mesodermal cells, including osteocytes, adipocytes, and chondrocytes (28). In addition to bone marrow, a similar population of MSCs have been isolated and characterized from various types of connective tissues throughout the body, including but not limited to, adipose tissue (29), lung (30), skin (31), peripheral blood (32), synovial fluids (33), and skeletal muscle (34). MSCs have also been identified from placenta (35), umbilical cord (36) and more recently, orofacial and dental tissues as well (37,38). In the last two decades, numerous preclinical and clinical studies have demonstrated that endogenous MSCs play essential roles in tissue homeostasis and remodeling (39), while exogenous MSCs expanded *ex vivo* have been widely utilized in TE/RM. In addition to facilitating repair/regeneration of damaged tissue through its multipotency, MSCs have also been sourced for its immunomodulatory properties to treat inflammatory diseases such as graft-versus host disease,

multiple sclerosis, Crohn's disease, amyotrophic lateral sclerosis, among others (40-42).

New paradigm of MSC action: the secretome and extracellular vesicles (EVs)

Initially, it was thought that MSC-mediated regenerative therapeutic potentials are due to their multipotency as replacement cells to those injured/damaged cells. However, accumulating evidence indicates that clinical improvement can be achieved despite a limited number of MSCs engrafted and retained in the targeted tissues as well as the short survival time following their systemic or local transplantation. This suggests that MSC-mediated benefits might be due to their paracrine trophic effects (43). A growing body of evidence has demonstrated that MSCs exert their regenerative therapeutic effects mainly through their potent immunomodulatory/anti-inflammatory functions and pleiotropic effects mediated by their paracrine secretion of an array of soluble factors, such as cytokines, growth factors, hormones, miRNAs, and other bioactive small molecules. These factors have diverse biological functions, including but not limited to: (I) modulating both the local and systemic immune systems; (II) promoting angiogenesis; (III) promoting proliferation and survival of specific tissue resident cells; (IV) anti-apoptosis; (V) antioxidant effects, and so on (42-44). In 2019, ISCT accordingly added two more criteria to define MSCs, including their tissue of origin and related functional assays to determine their potential mechanism of action (MOA) (45).

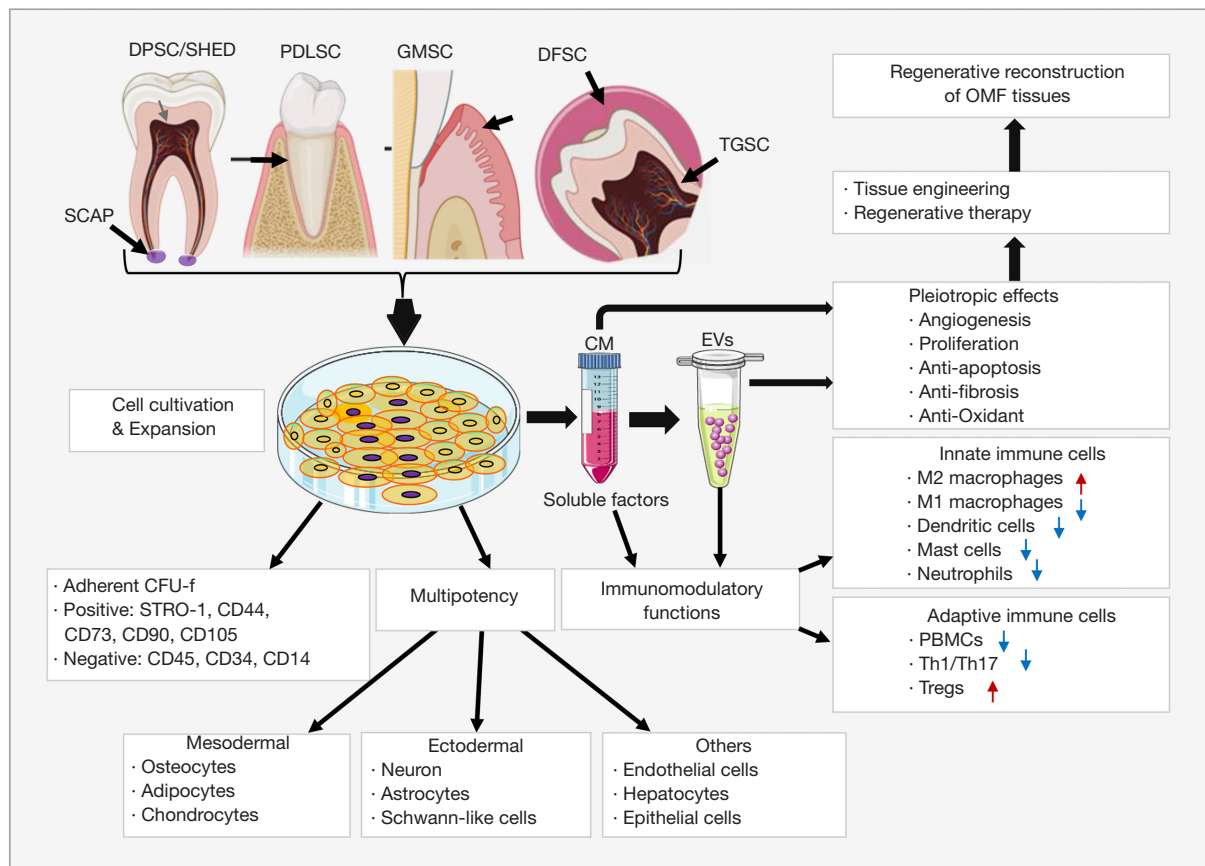EVs are nano-sized particles secreted by all types of cells,

Figure 1 Sources, properties, and biological functions of dental mesenchymal stem cells. Portions of this figure were made using templates from SMART SERVIER MEDICAL ART (https://smart.servier.com) and Biorender (https://biorender.com/). DPSC, dental pulp stem cells; SHED, stem cells from human exfoliated deciduous teeth; PDLSC, periodontal ligament stem cell; GMSC, gingiva-derived mesenchymal stem cell; SCAP, stem cells derived from apica papilla; DFSC, dental follicle stem cell; TGSC, tooth germ stem cell; OMF, oral and maxillofacial; CFU-f, colony forming unit-fibroblasts; CM, conditioned medium; EVs, extracellular vesicles; PBMC, peripheral blood mononuclear cell.

including MSCs, which play critical roles in intercellular communication through horizontal transfer of cargoes containing lipids, nucleic acids (DNA and RNA), proteins, and metabolites, etc. (46). Due to their biogenesis, size, and surface markers, EVs are generally classified into ectosomes and exosomes (47). Ectosomes, including microvesicles, microparticles, and large vesicles, are generated by the direct outward budding of the plasma membrane with a size ranged from ~50 to 1,000 nm in diameter, while exosomes are derived from endosomes with a size ranged from ~40 to 160 nm in diameter (~100 nm in average) (46). Accumulating evidence has shown that mesenchymal stem cell EVs (MSC-EVs) have pleiotropic effects on various biological processes of targeted cells, among which are immune responses, apoptosis, survival and proliferation, migration, lineage-specific differentiation, and angiogenesis (44,46,48). Numerous pre-clinical studies have shown that systemic or local administration of MSC-EVs display potent regenerative and therapeutic potentials for a variety of pathological conditions, thus supporting the notion that MSC-EVs could provide promising avenues to generate cell-free products applicable for TE and RM (44,48), including their application in OMF TE and regeneration (49).

MSCs derived from dental tissues

Of interest, a unique population of MSCs has also been isolated from various dental tissues (*Figure 1*). As early as in 2000, the first type of MSCs was isolated from human
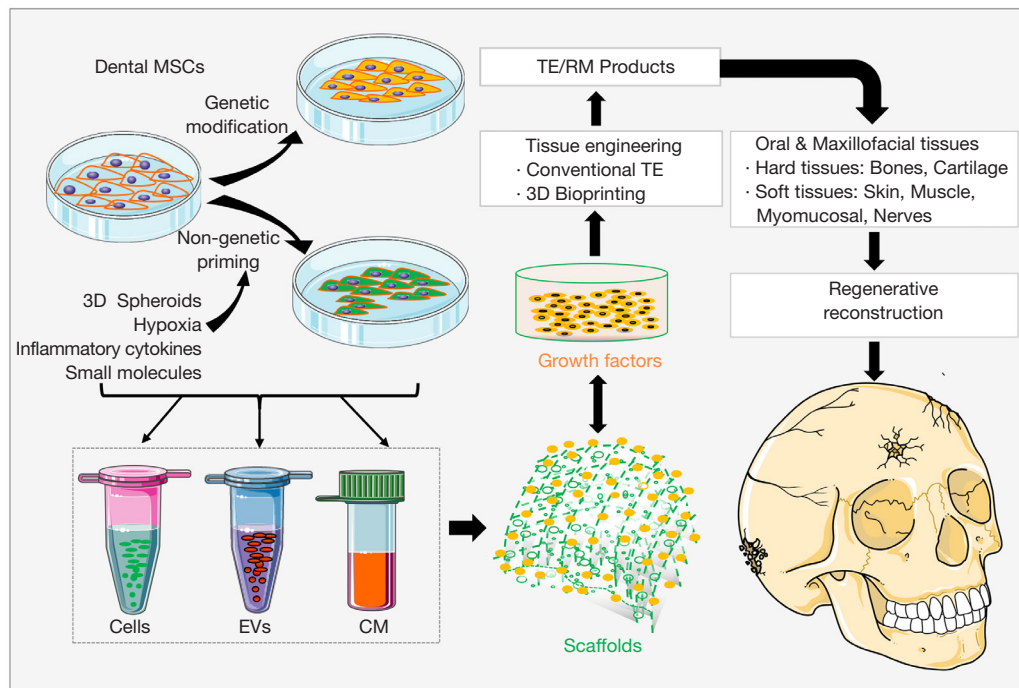
Figure 2 Potential application of dental MSCs and their cell-free products in tissue engineering and regenerative reconstruction of oral & maxillofacial tissue defects. Portions of this figure were made using templates from SMART SERVIER MEDICAL ART (https://smart.servier. com). MSC, mesenchymal stem cell; CM, conditioned medium; EVs, extracellular vesicles; TE/RM, tissue engineering/regenerative medicine.

dental pulp stem cells (DPSC) (50). Afterwards, MSCs have been isolated from other dental tissues, including exfoliated deciduous teeth (SHED) (51), periodontal ligament (PDLSC) (52), gingiva (GMSC) (53), apical papilla (SCAP) (54), dental follicle (DFSC) (55), and tooth germ stem cells (TGSC) (56). Similar to other sources of MSCs, such as BMSCs and ADSCs, these dental MSCs also possess potent self-renewal, multipotent differentiation, and immunomodulatory capacities (37,57,58) (*Figure 1*). During vertebrate embryonic development, most cranial/dental tissues are derived from neural crest (NC) (59,60). In recent years, studies have shown that a subpopulation of multipotent MSCs derived from human DPSCs (50,61), oral mucosa and gingiva (62-65), apical papilla (APSC) (66), DFSC (67), and PDLSC (68), are endowed with NC stem cell-like properties. Interestingly, as compared with mesoderm-derived MSCs, NC-derived MSC counterparts showed elevated differentiation potentials into neural cells and chondrocytes and enhanced immunomodulatory and anti-inflammatory effects both *in vitro* and *in vivo* (69). These studies suggest that dental tissues serve as important

reservoirs of adult NC-derived multipotent stem cells. Recently, several lines of evidence have also demonstrated the pleiotropic effects and regenerative and therapeutic potentials of EVs secreted by dental-MSCs (70-72) (*Figure 1*). Together, dental MSCs represent an easily accessible source of MSCs with great potential application in TE/RM, particularly, in OMF tissue regeneration (49).

Application of dental MSCs in TE and regeneration of OMF tissues

In 1997 Charles Vacanti stunned the world with his "Vacanti Mouse", a landmark in TE that Vacanti and his team successfully grew an ear on the back of a nude mouse following transplanation of a polymer-human chondrocyte construct (73). This fueled further advancement in TE demonstrating the potential to restore tissues with *ex vivo* fabricated constructs using different types of scaffold materials and living cells. Classically, TE relies on a "Regenerative Trinity" which involves the combination of scaffolds/biomaterials, living cells, and signaling/bioactive factors to engineer tissue constructs (21,22,24) (*Figure 2*).

In the last decade, significant progress has been made in the field of TE and regenerative reconstruction of oral and craniofacial tissues due to the advancement of biomaterial science, TE technology, and the understanding of stem cell biology (22-24). Herein, we focus on describing the potential application of dental MSCs in TE and regeneration of OMF tissues.

DPSCs and stem cells from human exfoliated deciduous teeth (SHED)

Human pulp stem cells include precursor cells isolated from dental pulp tissues of human extracted permanent teeth (DPSC) and SHED (74,75). As the first type of MSCs isolated from dental tissues (50), substantial progress has been made in understanding their biological properties. Their multipotency and immunomodulatory functions suggest their potential application in TE and regenerative therapy of a wide spectrum of pathological conditions (74,75). In fact, the application of DPSCs and SHEDs alone or in combination with different scaffolds in regeneration of oral and craniofacial tissues has been extensively explored in various rodent and large animal models as well as in some pilot clinical studies (*Table 2*).

In a rat mandibular ramus critical bone defect model, Zhang *et al*. showed that DPSC-seeded E1001(1k)/β-TCP scaffolds support the rapid regeneration of osteo-dentin-like mineralized jaw tissue, suggesting a promising new therapy for alveolar jaw bone repair and regeneration (80). Jahanbin *et al*. reported that transplantation SHED mixed with collagen matrix significantly enhanced new bone formation in a maxillary alveolar defect model in Wistar rats (82). Another study by Riccio *et al*. showed that silk fibroin/DPSC constructs exhibited strong regenerative capacity for correcting large cranial defects in rats (81). The potential of DPSC and SHED in cranial and maxillofacial bone regeneration have been further demonstrated in rabbit models (*Table 2*). Using a mandibular distraction model in New Zealand white rabbits, Alkaisi *et al*. showed that SHED can significantly enhance mandibular distraction osteogenesis (DO) (79). Most recently, Zhang *et al*. showed that transplantation of hDPSC/endothelial cells (HUVEC)-seeded E1001(1K)/β-TCP scaffolds significantly enhance bone formation in critical-sized alveolar bone defects in an *in vivo* rabbit mandible defect model (77). Gutiérrez-Quintero reported that transplantation of DPSCs seeded with hydroxyapatite matrix and polylactic polyglycolic acid (HA/PLGA) scaffolds also significantly augmented bone regeneration in bilateral mandibular critical-sized defects in rabbits (78). Implantation of DPSCs mixed with biodegradable poly[ethylene glycol]-diacrylate [PEGDA] hydrogels thiol-acrylate hydrogels also facilitated cranial bone regeneration in rabbits (76). Most recently, Ghavimi *et al*. reported that DPSCs mixed with nanofibrous asymmetric collagen/curcumin membrane containing aspirin-loaded PLGA nanoparticles can promote guided bone regeneration (GBR) in the defects created in both sides of the dog's jaw (83).

Critical-sized calvarial bone defect model in rodents is another popularly used model to evaluate the bone regenerative potentials of MSCs. Several studies have demonstrated the regenerative effects of DPSCs and SHEDs alone or in combination with different scaffolds on bone formation in critical-sized calvarial defects in mice (84-88) and rats (89-92). In addition, Wongsupa *et al*. reported that implantation of the bioengineered constructs of DPSCs in poly-ε-caprolactone (PCL)-biphasic calcium phosphate (BCP) scaffolds augment new bone formation in rabbit calvarial defects (93). In large animal models of dental implant surgeries, it has also been shown that DPSCs increases new bone formation and vertical bone height in experimental sheep (94) and dog (95) models. Most recently, Talaat *et al*. reported the potential use of DPSCs embedded in nanocellulose-chitosan thermosensitive hydrogel for cartilage regeneration (96).

In addition to the potential application of DPSCs and SHED in reconstruction of hard craniofacial and maxillofacial tissues, their use in reconstruction of soft OMF tissues, such as periodontal defects (97,99) and craniofacial nerves (100-102), has been suggested as well. For instance, Li *et al*. reported that autologous DPSCs derived from inflammatory dental pulps (DPSC-IPs) with β-TCP promote reconstruction of periodontal defects in minipig (97). Hu *et al*. reported that either direct DPSC injection or implantation of DPSC cell sheet significantly regenerated periodontal bone in swine even though DPSC sheet had more bone regeneration capacity compared with DPSC injection (98). In a pilot clinical studies with two patients with periodontal intrabony defects, the same group reported that DPSCs-IPs generated new bones to repair the periodontal defects 9 months after surgical reconstruction (99). For craniofacial nerve regeneration, implantation of DPSC-sheets and DPSCs infilled in PLGA artificial nerve conduits significantly promoted crush-injured and segmental defect models of rat facial nerves, respectively (100,101). The superior laryngeal nerve (SLN) plays an essential role in swallowing. A recent study showed that systemic

Table 2 Application of DPSC/SHED in OMF tissue regeneration

Cell type	Scaffolds/other factors	Model	Object	References
DPSC	thiol-acrylate hydrogels (Poly[ethylene glycol]-diacrylate [PEGDA] hydrogels)	Cranium defect	Rabbit	Aghali A et al. 2020, (76)
DPSC	E1001(1k)-βTCP	Mandible defect	Rabbit	Zhang W et al. 2020, (77)
	Hydroxyapatite matrix and polylactic polyglycolic acid (HA/PLGA)	Mandibular defect	Rabbit	Gutiérrez-Quintero JG et al. 2020, (78)
SHED		Mandibular distraction, 6-weeks	Rabbit	Alkaisi A et al. 2013, (79)
DPSC	E1001(1k)/β-TCP	Mandibular ramus critical bone defect, 6-weeks	Rat	Zhang W et al. 2016, (80)
DPSC	Silk fibroin scaffolds	Cranial bone defects	Rat	Riccio M et al. 2012, (81)
SHED	Collagen matrix	Maxillary alveolar defects, 2-months	Rat	Jahanbin A et al. 2016, (82)
DPSC	Aspirin-loaded PLGA nanoparticles	Alveolar bone defect, 28 days	Dog	Ghavimi MA et al. 2020, (83)
DPSC-EVs	PLGA and PEG, controlled release of DPSC-EVs	Calvarial defect	Mice	Swanson WB et al. 2020, (84)
DPSC sheets	4-(4-methoxyphenyl)pyrido [40,30:4,5]thieno[2,3-b]pyridine-2-carboxamide (TH)	Calvarial defect	Mice	Fujii Y et al. 2018, (85)
DPSC	T-mDPSCs	Calvarial defect, 3-months	Mice	Collignon AM et al. 2019, (86)
SHED	FGF2 primed SHED	Calvarial defect	Mice	Novais A et al. 2019, (87)
SHED		Calvarial defect, 12-weeks	Mice	Nakajima K et al. 2018, (88)
DPSC	β-TCP	Calvarial defects; 12-weeks	Rat	Annibali S et al. 2014, (89)
DPSC	hyaluronic-based hydrogel scaffold	Calvarial defect, 8-weeks	Rat	Petridis X et al. 2015, (90)
DPSC	HA/TCP	Calvarial defect	Rat	Asutay F et al. 2015, (91)
DPSC	Collagen gel scaffolds	Calvarial defect	Rat	Chamieh F et al. 2016, (92)
DPSC	PCL-BCP	Calvarial defect	Rabbit	Wongsupa N et al. 2017, (93)
DPSC	Particulate DBBG	Dental implant	sheep	Çolpak HA et al. 2019, (94)
DPSC		Dental implants, 8-weeks	Dogs	Ito K et al. 2011, (95)
DPSC	β-GP to CS	Cartilage, 14 days	Rat	Talaat W et al. 2020, (96)
DPSC	β-TCP	Periodontal defect, 3-months	Minipig	Li Y et al. 2019, (97)
DPSC	Cell sheet	Periodontal defect, 12-weeks	Minipig	Hu J et al. 2016, (98)
Autologous DPSC	β-TCP	Periodontal defect, 9-months	Human, 2 patients	Li Y et al. 2016, (99)
DPSC	DPSC sheet	Facial nerve, crush-injury	Rat	Ahmed MN et al. 2020, (100)
DPSC	PLGA artificial nerve conduits	Facial nerve, 2-months	Rat	Sasaki R et al. 2011, (101)
SHED-CM	Conditioned medium	Superior laryngeal nerve lesion	Rat	Tsuruta T et al. 2018, (102)

DPSC, dental pulp stem cells; SHED, stem cells from human exfoliated deciduous teeth; OMF, oral and maxillofacial; PLGA, poly(lactic-co-glycolic acid); PEG, poly(ethylene glycol); EV, extracellular vesicle; β-TCP, β-tricalcium phosphate; PCL, poly-ε-caprolactone; BCP, biphasic calcium phosphate; DBBG, deproteinized bovine bone graft; GP, glycerophosphate; CS, chitosan.

Table 3 Application of PDLSCs in OMF tissue regeneration

Cell type	Scaffolds/other factors	Model	Object	References
PDLSC	Cell sheet	Periodontal defect	CB17/lcr-scid/scid	Raju R et al. 2020, (103)
PDLSC	Bio-Gide® membrane	Periodontal defect	Rats	Liu J et al. 2019, (104)
PDLSC-CM	Conditioned medium	Periodontal defect model	Rat	Nagata M et al. 2017, (105)
PDLSC	Gelfoam®	Periodontal fenestration defects	Rats	Han J et al. 2014, (106)
PDLSC	Titanium implants	Dental implant	Rat	Lin Y et al. 2011, (107)
DFSC/PDLSC	Cell sheets	Periodontal defect	Canine	Guo S et al. 2017, (108)
PDLSC	Collagen powder	Periodontal furcation defects	Minipigs	Basan T et al. 2017, (109)
PDLSC		Periodontitis	Dog	Park JY et al. 2011, (110)
PDLSC	Cell sheet	Periodontal defect	Human	Iwata T et al. 2018, (111)
PDLSC	Bio-Oss	Maxillary sinus floor augmentations	Dog	Yu BH et al. 2014, (112)
PDLSC	RGD tripeptide	Calvarial defects	Mice	Moshaverinia A et al. 2014, (113)
PDLSC-CM	Conditioned medium	Calvarial defect	Mice	Ogisu K et al. 2020, (114)
PDLSC	HA-ECM	Calvarial defects	Rat	Tour G et al. 2012, (115)
PDLSC	HGCCS	Calvarial defect	Rat	Ge S et al. 2012, (116)
PDLSC	Collagen membrane (Bio-Guide)	Calvarial defect	Rabbit	Kadkhoda Z et al. 2016, (117)

PDLSC, periodontal ligament stem cell; OMF, oral and maxillofacial; CM, conditioned medium; DFSC, dental follicle stem cell; RGD, arginine-glycine-aspartic acid; HA-ECM, hydroxyapatite-incorporated extracellular matrix; HGCCS, nanohydroxyapatite-coated genipin-chitosan conjunction scaffold.

administration of SHED-conditioned media (SHED-CM) could promote axonal regeneration and functional recovery of injured SLN (102). Altogether, these compelling findings have elucidated the potential application of DPSCs and SHED in TE and regenerative reconstruction of cranio-maxillofacial defects.

PDLSC

Since the initial isolation of PDLSCs (52), a number of studies have extensively investigated their extraordinary biological properties and regenerative potentials. Of particular significance is the application of PDLSCs cell sheets alone or in combination with scaffolds in rodent periodontal defect models (*Table 3*) (103-106) to regenerate the periodontium, a complex composed of root cementum, alveolar bone, gingiva, and periodontal ligament (PDL) (118). For instance, transplantation of PDLSCs combined with Bio-Gide® collagen membrane or GelFoam significantly increased bone volume and average thickness of bone trabecular bone in a rat periodontal defect model, with

enhanced regeneration of cementum-like structure and formation of collagen fiber formation (104,106). Nagata *et al*. reported that directly local application of PDLSC-derived conditioned medium (CM) could also enhance rat periodontal regeneration by reducing TNF-α production thereby suppressing the inflammatory responses (105). Lin *et al*. reported that transplantation of PDLSCs with dental implants can organize periodontal tissues at the site of previously lost teeth in rats (107). In periodontal defect models of large animals, such as canines (108,110) and minipigs (109), transplantation of PDLSC sheets or PDLSCs combined with collagen powder over surgically created periodontal defect sites promote periodontal regeneration even under an inflammatory microenvironment (108). In the advanced periodontitis model in dog, where a circumferential defect involving the alveolar bone, periodontal ligament and cementum was surgically created, autologous PDLSCs showed the best regenerative capacity for these structures as well as peripheral nerve and blood vessel (110). Furthermore,

Table 4 Application of GMSCs in oral & craniofacial tissue regeneration

Cell type	Scaffolds/other factors	Model	Object	References
GMSC-CM	Conditioned medium	Periodontal defects	Rats	Qiu J *et al.* 2020, (122)
GMSC-EV	TNF-α pre-conditioned	Periodontal	Mice	Nakao Y *et al.* 2020, (123)
GMSC		Class III furcation defects	Dog	Yu X *et al.* 2013, (124)
GMSC	IL-1Ra HA-sECM	Periodontal defects	Minipig	Fawzy El-Sayed KM *et al.* 2015, (125)
GMSC	IV injection	Mandibular bone	Mice	Xu QC *et al.* 2014, (126)
GMSC	Alginate-based adhesive, photocrosslinkable, and osteoconductive hydrogel biomaterial (AdhHG)	Rat peri-implantitis model	Rat	Hasani-Sadrabadi MM *et al.* 2020, (127)
GMSCs	Hydrogel scaffold PuraMatrix™	Maxillary alveolar defect	Nude rats	Kandalam U *et al.* 2020, (128)
GMSC	Type I collagen	Mandibular defect Calvarial defect	Rat	Wang F *et al.* 2011, (129)
GMSCs	Bio-Oss®/SB431542	Maxillary bone defects	minipigs	Shi A *et al.* 2019, (130)
GMSC-EV	PLA 3D printing	Calvarial defect	Rat	Pizzicannella J *et al.* 2019, (131)
GMSC-EV	(3D) engineered scaffolds (PLA)	Calvarial defect	Rat	Diomede F *et al.* 2018, (132)
GMSC		Palatal wound	Mice	Su Y *et al.* 2018, (133)
Fetal GMSCs		Gingival defects	Rat	Li J *et al.* 2018, (134)
GMSC-EV	SIS-ECM	Tongue defects	Rat	Zhang Y *et al.* 2019, (135)
GMSC	SIS-ECM	Tongue defects	Rat	Xu Q *et al.* 2017, (136)
GMSC	3D spheroid, 3D bioprinting	Facial nerve	Rat	Zhang Q *et al.* 2018, (137)
GMSC-NCC	AxoGuard nerve conduits	Facial nerve	Rat	Zhang Q *et al.* 2018, (138)

GMSC, gingiva-derived mesenchymal stem cell; CM, conditioned medium; EV, extracellular vesicle; HA-sECM, hyaluronic acid synthetic extracellular matrix; PLA, polylactic acid; SIS-ECM, small intestinal submucosa extracellular matrix.

a single-arm and single-institute clinical study has demonstrated the safety and efficacy of autologous PDLSC sheets in 10 cases of patients with periodontitis at 6-months following transplantation, with sustained therapeutic effects for a mean follow-up period of 55±19 months and no serious adverse events observed (111).

In addition to the potent periodontal regenerative properties, preclinical studies using rodents and large animal models have shown that PDLSCs can induce craniofacial bone regeneration in rodent and large animal models (*Table 3*). In a dog model of bilateral maxillary sinus floor augmentation, Yu *et al.* showed that seeding of PDLSCs or BMMSCs onto Bio-Oss can promote bone formation and mineralization and maintain the maximum volume of the augmented maxillary sinus (112). Meanwhile, several studies have shown that transplantation of PDLSC CM or various PDLSC-seeded scaffolds can significantly enhance bone repair/regeneration in calvarial defects in

mice (113,114), rat (115,116), and rabbit (117). These compelling findings have demonstrated that PDLSCs have potentials in the regeneration/reconstruction of oral maxillofacial tissues, particularly, lost/damaged support tissue in the periodontium complex, including the alveolar bone, periodontal ligament, and cementum (119).

Gingiva and oral mucosa-derived MSCs (GMSCs and OMSCs)

GMSCs represent another population of adult dental stem cells isolated from the lamina propria of gingival tissues (53). Similar to other sources of MSCs, GMSCs possess multipotent differentiation and potent immunomodulatory/anti-inflammatory capacities, making them an easily accessible source of MSCs for TE and regenerative therapy of various craniofacial and non-craniofacial disorders (120,121) (*Table 4*). Several lines of evidence have shown that transplantation of GMSC-

derived CM, exosomes or GMSC-seeded scaffolds can stimulate periodontal repair/regeneration in periodontal defect models in rats (122,123), dogs (124), and minipigs (125). For instance, Yu *et al*. reported that transplanted GMSCs significantly enhanced the regeneration of the damaged periodontal tissue, including the alveolar bone, cementum and periodontal ligament (PDL) in Class III furcation defects of dogs. They found that GMSCs were able to differentiate into osteoblasts, cementoblasts, and PDL fibroblasts *in vivo* (124). These findings indicate that GMSCs represent a novel cell source for periodontal tissue. Fawzy El-Sayed *et al*. reported that GMSCs in conjunction with IL-1Ra-loaded HA-sECM significantly enhance periodontal regeneration in a minipig model (125).

In addition to the periodontal regenerative capacity, several preclinical studies have shown that GMSCs also have the potential to promote craniofacial bone regeneration in rodents (126-129) and minipigs (130). Most recently, a study has shown that GMSCs effectively delivered by a bioinspired adhesive hydrogel with tunable mechanical properties and biodegradability, can aggregate, form hydroxyapatite microparticles, and significantly promote craniofacial bone regeneration in rats (127). In a critical-sized maxillary alveolar defect model in nude rats, combination of predifferentiated osteogenic GMSCs, self-assembling hydrogel PuraMatrix™ (PM), and low doses of BMP2 accelerated alveolar bone regeneration when compared to cells or material alone. Predifferentiated osteogenic GMSCS are GMSCs induced with osteogenic medium resulting in increased expression of osteogenic surface markers such as CD10, CD92, and CD140b (128). An early study showed that implantation of GMSCs seeded on type I collagen gel significantly facilitate repair/regeneration of the mandibular and calvarial defects at 2 months in rats postsurgical reconstruction (129). Most recently, Shi *et al*. reported that treatment with a TGF-β signaling inhibitor, SB431542, increased the osteogenic differentiation potential of GMSCs and transplantation of autologous pig GMSCs pretreated with SB431542 significantly induce bone regeneration in critical-sized maxillofacial bone defects of minipigs (130).

In spite of their bone regenerative potentials, several lines of evidence have shown that transplantation of GMSCs can facilitate oral and craniofacial soft tissue repair/regeneration, such as palatal wound (70,133), gingival (134), and tongue myomucosal defects (135,136), and facial nerve injuries (137,138). For instance, Li *et al*. recently reported that transplantation of GMSCs from human fetal gingival tissue remarkably promotes repair/regeneration of gingival defects in a rat model (134). Using a critical-sized tongue defect model in rats, Xu (136) and Zhang (135) *et al*. reported that implantation of GMSC-loaded porcine small intestine submucosal extracellular matrix (SIS-ECM) membrane remarkably facilitated regeneration of tongue muscles and taste buds possibly by promoting endogenous muscle stem cell activation and suppressing fibrosis. Recently, Zhang *et al*. reported that implantation of 3D bio-printed scaffold free nerve structures with 3D-spheroids of GMSCs as the only cellular "bio-ink" (137) or implantation of collagen nerve conduits loaded with GMSC-induced NC stem-like cells (138) robustly promote axonal regeneration and functional recovery of transected facial nerves in rats. Altogether, these studies have underscored the potential application of GMSCs in TE and regenerative reconstruction of OMF tissue defects.

Dental follicle progenitor cells (DFPCs)
DFSCs represent a population of stem cells that contributes to the development of the periodontal ligament, cementum, and alveolar bone proper (139). Several preclinical studies have demonstrated the oral and craniofacial regenerative potentials of DFSCs in rodents (140-143) and large animal models (108,141,144) (*Table 5*). A recent study showed that transplantation of DFSC cell sheets or DFSCs in combination with treated dentin matrix (TDM) induced periodontal-like tissue formation in dogs (141). In a canine periodontal defect model, Guo *et al*. reported that implantation of DFSC cell sheets robustly promoted the complete periodontal regeneration, including periodontal ligament-cementum complex and alveolar bone formation (108). In an early study, Zuolin *et al*. reported that transplantation of DFSC-beta-tricalcium phosphate ceramic (beta-TCP) complex promote the restoration of periodontal defects in beagle dogs (144). In addition, the regenerative potential of DFSCs on bone formation has also been demonstrated in alveolar and cranial bone defect models in rats (141-143). For example, implantation of DFSC-polycaprolactone (PCL) scaffold constructs significantly enhanced bone regeneration in critical-size skull defects in rats (142). In an alveolar bone defect model in rats, Nie *et al*. reported that implantation of bio-implants composed of Ad-BMP9-transfected rat DFSCs and coralline hydroxyapatite (CHA) scaffolds remarkably enhance alveolar bone regeneration (143). These findings

Table 5 The potential application of DFSCs and SCAP in OMF tissue regeneration

Cell Type	Scaffolds/other factors	Model	Object	References
DFSC-CM	Conditioned medium	Pulpitis	Rat	Hong H *et al.* 2020, (140)
DFSC	HA/β-TCP particles/cell sheets/treated dentin matrix	Calvarial defect/periodontal defect	Rat/dog	Yang H *et al.* 2019, (141)
DFSC/PDLSC	Cell sheets	Periodontal defect	Canine	Guo S *et al.* 2017, (108)
DFSC	β-TCP	Periodontal defects	Dog	Zuolin J *et al.* 2010, (144)
DFSC	Polycaprolactone scaffold	Cranial/skull defects	Rat	Rezai-Rad M *et al.* 2015, (142)
DFSC	Coralline hydroxyapatite	Alveolar bone defect	Rat	Nie L *et al.* 2017, (143)
SCAP	3D-printed hydroxyapatite scaffolds	Pulp	Nude mice	Hilkens P *et al.* 2017, (145)
SCAP-Exo		Dentinogenesis	Nude mice	Zhuang X *et al.* 2020, (146)
SCAP		Periodontitis	Minipig	Li G *et al.* 2018, (147)
SCAP	SFRP2 expressing	Periodontitis	Minipig	Li G *et al.* 2020, (148)

DFSC, dental follicle stem cell; SCAP, stem cells derived from apica papilla; OMF, oral and maxillofacial; CM, conditioned medium; PDLSC, periodontal ligament stem cell; HA, hydroxyapatite; β-TCP, β-tricalcium phosphate.

have demonstrated the potential application of DFSCs in regenerative reconstruction of OMF tissues.

SCAP

SCAP represent a unique subpopulation of dental stem cells from immature permanent teeth (54) and have been shown to be another type of dental MSCs with potential application in regenerative endodontic procedures and TE/RM in general (149,150) (*Table 5*). When 3D-printed hydroxyapatite scaffolds containing DPSCs and/or SCAPs were subcutaneously transplanted into immunocompromised mice, vascularized pulp-like tissue as well as mineralized tissue formed at 12-weeks post-transplantation, demonstrating angiogenic and regenerative potential (145). Li *et al.* recently reported that local injection of SCAPs promote periodontal complex regeneration in the swine periodontitis model (147,148). Altogether, these findings support the potential application of SCAPs in regenerative reconstruction of OMF tissues.

Application of dental MSC-EVs in OMF tissue regeneration

MSC-EVs serve a myriad of biological functions and possess immense therapeutic potential (44,48). Accumulating evidence has shown the potential use of dental MSC-derived EVs as cell-free agents in TE and regenerative therapy in the dental and craniofacial reconstruction (151,152) (*Figure 2*). Administration of CM derived from different types of dental-MSCs displayed potent regenerative/therapeutic potentials in oral and craniofacial defect models. For instance, SHED-CM has been shown to induce rat superior laryngeal nerve (SLN) regeneration (102). PDLSC-CM could stimulate bone regeneration in calvarial defects of mice (114) and periodontal regeneration in rats (105). GMSC-CM and DFSC-CM significantly promote rat periodontal (122) and pulp-dentin (140) regeneration, respectively. Additionally, it has been shown that GMSC-EVs loaded with a poly-(lactide) (3D-PLA) facilitated calvarial bone regeneration in rats (153).

In recent years, surmounting evidence has implicated the regenerative/therapeutic potentials of EVs released by different types of dental-MSCs (*Table 5*). Swanson *et al.* reported that application of DPSC-EVs with a controlled-release by PLGA and poly(ethylene glycol) (PEG) remarkably increase calvarial bone regeneration in mice (84). DPSC-EVs promote dentin-pulp regeneration following injection into the exposed pulp tissue of rat incisors (154). In a minipig model of pulp injury, Wen *et al.* reported that treatment with DPSC-EVs mixed with treated dentin matrix (TDM) proteins significantly promote pulp-dentin complex repair/regeneration (155). Regarding the regenerative/therapeutic potential of GMSC-EVs in OMF defects, Kou *et al.* showed that local

injection of GMSC-EVs significantly facilitated palatal wound healing in mice (70). Most recently, it has been reported that EVs from TNF-α-preconditioned GMSCs displayed potent regenerative/therapeutic potentials in periodontal regeneration of mice (123). In a critical-sized tongue defect model in rats, Zhang *et al*. showed that transplantation of SIS-ECM loaded with GMSC-EVs significantly promoted taste bud regeneration (135). Furthermore, implantation of GMSC-EVs loaded with 3D printing biomaterial, poly(lactide) (3D-PLA), display bone regenerative capacity in calvarial defects in rats (131,132). In a nude mice model, subcutaneous transplantation of BMSCs mixed with SCAP-Exo showed significantly increased ectopic formation of dentine-pulp like structures, suggesting the specific dentinogenetic potential of SCAP-EVs (146). Lastly, Shi *et al*. has recently reported that application of hydrogel loaded with EVs derived from LPS-preconditioned DFSCs remarkably prevented bone loss and engendered new bone formation in experimental rat periodontitis model (156). Taken together, these results demonstrate compelling evidence for the use of CM and/ or purified EVs derived from dental-MSCs as alternative cell-free products for TE and regenerative reconstruction of OMF tissue defects.

Challenges of MSC-based regenerative therapies

Despite a favorable safety profile and numerous studies demonstrating its effectiveness in preclinical studies, in general, there has been limited success of application of MSCs and MSC-EVs in humans (41,42). The cause of this translational barrier is due to multiple intrinsic and extrinsic factors that can contribute to the heterogeneity in the potency of MSC products. These factors include differences in donors (e.g., their age, health status, tissue origins), the methods for MSC preparation (e.g., the isolation, *ex vivo* culture/expansion, and storage) and administration (e.g., the route, dosage, frequency, and the carrier/vehicle) as well as the health/disease status of the recipients (42). In term of MSC-based TE, the difference in the type of biomaterials or scaffolds, TE technologies, small molecules and/growth factors may also significantly affect the potency and clinical outcomes of MSC-based TE products (157). Even though a general safety profile has been well recognized for MSC-based therapy, there

are still some related potential risks, side effects or complications, such as acute/immediate responses to MSC administration, infection, thrombotic/embolic (158), and ectopic calcification (159), heterotopic ossification (160), or tumor-like tissue mass formation (161). Therefore, more rigorous studies are warranted to evaluate the therapeutic potency as well as potential short-term and long-term complications related to MSC-based regenerative therapy, including MSC-based reconstruction and rehabilitation of OMF defects.

Summary

Significant progress has been made in TE and MSC-based regenerative therapy across many fields of medicine, including oral & maxillofacial reconstruction and facial cosmetics (22,23). To date, there have been over 1,200 registered and 300 completed clinical trials using MSCs to treat a large spectrum of pathological conditions (https://www.clinicaltrials.gov/) (42), including MSCs used in the management of craniofacial injuries or abnormalities (https://www.clinicaltrials.gov). In addition, MSC-derived EVs, a cell-free product, implemented in many preclinical models of diseases, have demonstrated therapeutic capacity in the regeneration of OMF tissues (*Table 6*). Of note, however, MSCs and MSC-EV products when applied to humans do not show the same therapeutic effect. This is largely attributed to the heterogeneity in the potency and property of MSCs owing to differing intrinsic factors, such as the tissue source and donor characteristics, as well as extrinsic factors, such as methods and technologies involved in tissue harvesting, cell isolation/expansion, TE, and product storage/administration (42). It is thus essential to establish standard operating procedures (SOP) for all the steps in the production of dental MSCs, MSC-EVs, or MSC-based TE constructs with cGMP qualities (15). Generation of MSC-EVs presents additional technical and biological challenges (162,163). Specifically, cell isolation methods significantly affect the purity and yield of EVs (164), while the source and status of cells affect the production and cargo components of MSC-EVs (162,163). To advance the clinical application of MSC-EVs in OMF tissue regeneration and reconstruction, it is critical to experimentally optimize their production in future studies.

Table 6 Potential application of dental-MSC-derived EVs in OMF tissue regeneration

Cell type	Scaffolds/other factors	Model	Object	References
SHED-CM	Conditioned medium	Superior laryngeal nerve lesion	Rat	Tsuruta T *et al.* 2018, (102)
PDLSC-CM	Conditioned medium	Periodontal defect model	Rat	Nagata M *et al.* 2017, (105)
PDLSC-CM	Conditioned medium	Calvarial defect	Mice	Ogisu K *et al.* 2020, (114)
DFSC-CM	Conditioned medium	Pulpitis	Rat	Hong H *et al.* 2020, (140)
GMSC-CM	Conditioned medium	Periodontal defects	Rat	Qiu J *et al.* 2020, (122)
GMSC-CM	a poly-(lactide) (3D-PLA)	Calvarial defect	Rat	Diomede F *et al.* 2018, (153)
DPSC-EV		Odontogenesis/Pulp	Rat	Zheng J *et al.* 2020, (154)
DPSC-EV	Treated dentin matrix	Pulp-dentin complex	Minipig	Wen B *et al.* 2020, (155)
DPSC-EV	PLGA and PEG, controlled release of DPSC-EVs	Calvarial defect	Mice	Swanson WB *et al.* 2020, (84)
GMSC-EV		Palatal wound	Mice	Kou X *et al.* 2018, (70)
GMSC-EV	SIS-ECM	Tongue defects	Rat	Zhang Y *et al.* 2019, (135)
GMSC-EV	TNF-α pre-conditioned	Periodontal	Mice	Nakao Y *et al.* 2020, (123)
GMSC-EV	PLA 3D printing	Calvarial defect	Rat	Pizzicannella J *et al.* 2019, (131)
GMSC-EV	(3D) engineered scaffolds (PLA)	Calvarial defect	Rat	Diomede F *et al.* 2018, (132)
DFSC-EV	LPS pre-conditioned/hydrogel	Periodontal	Rat	Shi W *et al.* 2020, (156)
SCAP-EV		Dentinogenesis	Mice	Zhuang X *et al.* 2020, (146)

SHED, stem cells from human exfoliated deciduous teeth; MSC, mesenchymal stem cell; EV, extracellular vesicle; OMF, oral and maxillofacial; CM, conditioned medium; PLGA, Poly(lactic-co-glycolic acid); PEG, poly(ethylene glycol); SIS-ECM, small intestinal submucosa extracellular matrix; LPS, lipopolysaccharide.

Footnote

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