Applications of Mesenchymal Stem Cells in Oral and Craniofacial Regeneration

Pasha Shakoori, DDS, MA, Quanzhou Zhang, PhD, Anh D. Le, DDS, PhD*

KEYWORDS

• Stem cells • Orofacial mesenchymal stem cells • Regenerative medicine • Tissue engineering

KEY POINTS

- The field of tissue engineering and regenerative medicine has been rapidly expanded through multidisciplinary integration of research and clinical practice in response to the unmet clinical needs for reconstruction of the dental, oral, and craniofacial structures.
- The significance of the various types of stem cells, specifically mesenchymal stem cells (MSCs) derived from the orofacial tissues, ranging from dental pulp stem cells (DPSCs) to periodontal ligament stem cells (PDLSCs) to mucosa/gingiva (gingiva-derived MSCs [GMSCs]) has been thoroughly investigated.
- Currently, there are several clinical trials aimed to further study the applications of oral and craniofacial stem cells in regeneration.

INTRODUCTION

Reconstruction of oral and craniofacial defects has been a challenging task for many clinicians. Since McGregor performed the first flap (temporalis) in the reconstruction of a postexcisional defect in the oral cavity in 1963,[1] many clinicians have attempted to modify surgical techniques in flap transfer to improve the functional outcomes. In many cases, however, complete restoration of the original anatomy and function is not possible regardless of the surgical technique used. This problem is further evident in the oral and craniofacial region considering the importance of functions, such as speech, mastication, appearance, and the effects of these deficiencies on general health, social acceptance, and self-esteem.[2]

Considering the limitations of reconstructive techniques, regenerative medicine and tissue engineering have been new avenues explored by scientists and clinicians to restore anatomy and function. In simplified terms, to regenerate tissue, a source of stem cells, a 3-D platform (scaffold), and a source of signaling molecules are needed.

The classic definition of a stem cell requires such cells to have 2 fundamental characteristics: self-renewal and potency. Allowing for self-renewal requires the capacity of a cell to divide without differentiation; potency specifies the capacity to differentiate into different cell types.

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Department of Oral and Maxillofacial Surgery/Pharmacology, University of Pennsylvania, School of Dental Medicine, 240 South 40th Street, Philadelphia, PA 19104-6030, USA
* Corresponding author.
E-mail address: Anh.Le@uphs.upenn.edu

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Table 1
Orofacial stem cells and clinical applications

MSCs	Markers	Animal Models	Studies	Disease Models
PDLSC	*STRO-1, CD146/MUC18*	Mouse	Seo et al,[22] 2004	
		Swine	Liu et al,[23] 2008	Periodontitis
		Swine	Ding et al,[24] 2010	Periodontitis
DPSC	*CD105*$^{+}$	Dog	Kerkis et al,[42] 2008	Muscular dystrophy
		Rat	Gandia et al,[43] 2008	Myocardial infarct
		Rabbit	Monteiro et al,[44] 2009	Cerebral ischemia
		Rabbit	Gomes et al,[45] 2010	Chemical-induced corneal injury
SHED	*Oct-4, Nanog, SSEA-3, SSEA-4, TRA-1-60, TRA-1-81*	Rat	Wang et al,[46] 2010	Parkinson disease
GMSC	*Oct-4, SSEA-4, STRO-1*	Mouse	Zhang et al,[33] 2009	Colitis
		Mouse	Zhang et al,[32] 2010	Wound healing
		Mouse	Su et al,[35] 2011	Contact hypersensitivity
		Rat	Wang, 2011[47]	Mandibular and calvarial defects
		Rat	Zhang et al,[48] 2013	Arthritis
SCAP	*STRO-1*	Swine	Sonoyama et al,[21] 2006	Tooth regeneration

There are 3 categories of stem cells: adult stem cells (ASCs), embryonic stem cells, and induced pluripotent stem cells (iPSCs). MSCs, which are found in many tissue sources, such as bone marrow and periosteum, are undifferentiated ASCs that are clonogenic and have the capacity to self-renew and differentiate into different cell lines. In vitro expansion of MSC results in cells that are fibroblast-like morphologically and can differentiate into osteoblasts, chondrocytes, adipocytes, and other cells.[3] Although embryonic stem cells are found only in the blastocyst stage of development, ASCs can be found in many adult tissues, in addition to bone marrow and periosteum, including the orofacial tissues (**Table 1**), such as teeth, dental pulp, supporting structures, and gingiva as well as fat, muscle, nervous tissues, skin, and others. iPSCs, a new source of pluripotent stem cells, can be derived from adult cells by introducing 4 pluripotency genes (Oct4, Sox2, cMyc, and Klf4), which are also called Yamanaka factors, named after Shinya Yamanaka, who was the first to generate iPSCs and later awarded the Nobel Prize in Physiology or Medicine in 2012 along with John B. Gurdon for this discovery.[3]

BONE MARROW MESENCHYMAL STEM CELLS IN ORAL AND CRANIOFACIAL REGENERATION

Considering the nature and extent of structural defects in oral and maxillofacial region, many investigators have aimed to regenerate bone, cartilage, and fat using adult BMSCs. This advancement further resulted in attempts to create composite structures made of different tissue types. For instance, the condylar head of the temporomandibular joint complex contains a cartilaginous articular component housed over subchondral bone. In a study performed by Alhadlaq and colleagues,[4] the investigators induced rat BMSCs into osteogenic and chondrogenic cell lineages in vitro. The osteogenic and chondrogenic cells were further incorporated in polyethylene glycol–based hydrogel suspensions in 2 distinct and parallel hydrogel layers, which were sequentially photopolymerized in a human condylar mold. This cell-polymer solution resulted in the formation of cross-links in the mold that created the stratified organization of the bone and cartilage layers of the condylar head. This engineered condyle head was then transplanted into the dorsum of mice for 8 weeks and when harvested demonstrated stratified layers of bone and cartilage cells. The results of this study were further supported by the histologic and immunohistological studies and further expression profiles of these 2 distinct cell types. The results of this study can be considered primitive proof of the concept regarding the potential to use tissue engineering to create and replace composite structural components in the oral and maxillofacial region using adult BMSCs. Using a different approach, other researchers have used a gradient scaffold with incorporated bone morphogenetic protein 2 on the osteogenic side and transforming growth factor-β1 on the

chondrogenic side to repair composite osteochondral defects.[5]

MESENCHYMAL STEM CELLS DERIVED FROM OROFACIAL TISSUES

Compared with BMSCs isolated from long bones, BMSCs isolated from craniofacial bones show different characteristics and gene expression profile.[6] This difference is mostly attributed to most craniofacial bones arising from neural crest cells[7,8]; hence, many congenital bone diseases, such as Treacher-Collins syndrome,[9] craniofacial fibrous dysplasia,[10] and cherubism,[11] only affect the craniofacial bones, despite that the genes involved in causing the anomalies are expressed in other bones in the body as well. Notably, the craniofacial BMSCs proliferate faster, have increased levels of alkaline phosphatase, and form higher levels of compact bone compared with long bone BMSCs.[12,13] It has been proposed that the progenitor cells responsible for repair of craniofacial bony structures after injury reside in the craniofacial periosteum.[14] In addition to cells residing in the periosteum, craniofacial sutures contain specific MSCs called *Gli1+*, which are quiescent stem cells capable of regenerating dura and periosteum tissue once activated after sustaining injuries.[15] Identification of these cells might further clarify the mechanism of development of craniosynostosis considering that destruction of *Gli1+* cells in open cranial sutures results in premature closure of sutures.[15]

Mesenchymal Stem Cells Derived from Dental Pulps

Other efforts to identify new sources of MSCs have resulted in the isolation of stem cells from different orofacial regions. Postnatal human DPSCs have the potential to regenerate dentin/pulplike complexes and are hypothesized to be the progenitor cells activated when the pulp complex is in need of repair. Previously, studies had shown the odontogenic potential of dental pulp by showing mineralizing capacity using techniques such as cell-culture explants.[16–19] New studies show, however, that DPSCs show many specific similarities compared with BMSCs. These 2 populations of stem cells are both clonogenic, are highly proliferative, and have the capacity to regenerate tissue. The immune-histochemical analyses of human DPSCs and BMSCs in vitro have shown similar immunoreactivity profiles for both groups of cells. Furthermore, both groups of cells express endothelial and smooth muscle cell markers.[20] On the other hand, BMSCs are capable of forming lamellar bone when transplanted into mice, whereas transplanted DPSCs form odontoblast-like cells capable of forming dentin-like complexes under the same conditions.[7]

DPSCs have been used to create bioengineered dental root (bioroot complex) in swine (**Fig. 1**).[21] Investigators were able to create a bioengineered root complex in swine by using autologous DPSCs, scaffold constructs composed of tricalcium phosphate and hydroxyapatite, and appropriate growth factors with proper tissue conditions. A biological scaffold is a 3-D construct that can be impregnated with different growth factors, such as bone morphogenic protein, that provide the 3-D morphology required for the deposition of an extracellular matrix, which provides a better environment for cell adhesion and migration in regeneration. Such scaffolds can be created with materials that are incorporated into the engineered structure, such as hydroxyapatite or materials that resorb and only leave the newly generated structure. The created bioroot in this study was then harvested after 6 months and implanted in an extraction socket that was artificially created in the swine jaw bone and was later restored using a crown. This study illustrates the potential of creating a biological root complex using DPSCs under the appropriate conditions and use of the correct scaffolds.

Mesenchymal Stem Cells Derived from Periodontal Ligaments

Periodontal ligament tissues have also shown to house PDLSCs. Once cultured in appropriate conditions, PDLSCs are capable of differentiating into cementoblast-like cells, adipocytes, and cells with the capacity to form collagen.[22]

Autologous transplantation of PDLSCs in a miniature porcine model of periodontitis has been shown effective in treating periodontal disease, resulting in regeneration of periodontal tissue in a surgically created periodontal defect (see **Fig. 1**).[23] Moreover, considering the limitations in using autologous cells, especially in older population of patients, allogeneic PDLSCs have been used to treat bone and periodontal defects.[24] Periodontal disease, in addition to compromising oral and dental tissue, has been associated with a variety of systemic conditions, such as cardiovascular disease and diabetes,[25] and the application of these cells in treating periodontitis could have a significant impact in improving oral and systemic health in the general population and result in a reduction of health care costs.

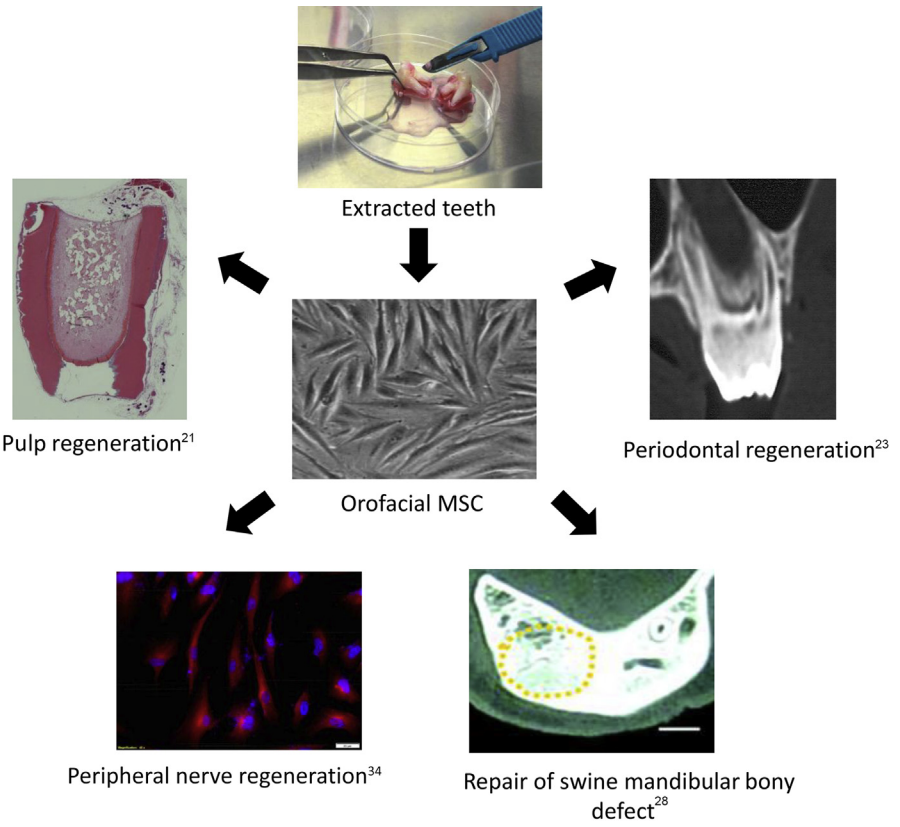

Fig. 1. Regeneration of the dental, oral, and craniofacial tissues using orofacial MSCs. (*From* Refs.[21,23,28,34]; with permission.)

Mesenchymal Stem Cells Derived from Developing Teeth

Vascularized tissues of dental pulp in addition to dentin have been regenerated using 2 other sources of stem cells from the oral cavity: stem cells from apical papilla (SCAP) and stem cells from human exfoliated deciduous teeth (SHED).[24–27] SCAP and other types of pulp stem cells have potentials for pulp/dentin regeneration, and the combination of SCAP and PDLSCs for bioroot engineering has been reported by Sonoyama and colleagues[21] (see **Fig. 1**). Orofacial MSCs have also shown the potential and capacity to regenerate bone in larger defects. SHED-mediated jaw bone regeneration in miniature swine[28] demonstrated the potential of stem cell applications in regeneration of large defects in larger animal models, which could lead to the conduction of human clinical trials aiming to regenerate and repair mandibular bony defects (see **Fig. 1**). For instance, investigators have used MSC implantation in treatment of osteonecrosis of the jaw in swine.[29]

Sinus augmentation and repair of alveolar bone defects have been major tasks in oral and maxillofacial rehabilitation. Harvest of bone and tissues from distant sites have been associated with limitations and problems, such as donor site morbidity.[30] Therefore, it is crucial to use new sources of cells and tissues to reduce donor site morbidity and challenges faced when harvesting tissue from distant sites. Cells and tissues harvested from maxillary tuberosities previously showed expansion and differentiation potential when used in maxillary sinus augmentation procedures.[31]

Mesenchymal Stem Cells Derived from Gingival Tissues

A subpopulation of MSCs has also been isolated from human gingival tissues (GMSCs), which not only possess stem cell properties but also exhibit potent immunomodulatory and anti-inflammatory effects in tissue.[32,33] GMSCs can be differentiated into adipocytes, osteocytes, chondrocytes, and different lineages of neural cells, such as neuronal and Schwann cells.[33] Most recently, studies have shown that GMSCs can be directly induced into neural progenitor-like cells by using nongenetic

approaches. GMSC-derived induced neural progenitor cells show enhanced therapeutic effects on repair/regeneration of injured rat sciatic nerves (see **Fig. 1**).[34] Investigators have also shown that GMSCs are capable of inducing M2 polarization of tissue macrophages.[32] In the presence of GMSCs, macrophages exhibit M2-like macrophage phenotypes characterized by an increased expression of mannose receptors and anti-inflammatory cytokine interleukin 10, while showing decreased expression of proinflammatory cytokine, tumor necrosis factor-α.[32] Additionally, GMSCs are capable of suppressing the activation and function of inflammatory Th-1 and Th-17 cells and promoting the generation of anti-inflammatory regulatory T cells.[32–36] The constellation of effects of GMSCs on both T cells and macrophages results in their application in the therapy for various inflammation-related disease models in rodents, including colitis, contact-allergic dermatitis, oral mucositis, and skin wound healing.[32–36]

CLINICAL TRIALS

Although investigators have attempted to use such cells and technologies to regenerate different tissue types, currently the regenerative modalities using stem cells are not standard therapies approved by major regulatory bodies, such as the Food and Drug Administration. Many such studies are in the stage of animal models or human clinical trials to receive approvals for applications in human subjects.

A review of literature regarding the application of adult MSCs used in maxillary sinus augmentation showed that in the period 2004 to 2011, only 4 randomized controlled trials with numbers of patients ranging from 5 to 26 investigated the efficacy of cell-based methods.[37] A systematic review with meta-analysis of the application of MSCs in maxillary sinus augmentation identified a total of 39 studies (21 human and 18 animal studies) from 2004 to 2014 and demonstrated significant variation in study design, results, and follow-up outcomes.[38] A recent randomized controlled trial (phase 1/phase 2) investigated the total bone and the quality of bone regenerated in maxillary sinus bony defects using autologous cells enriched with $CD90^+$ stem cells and $CD14^+$ monocytes in 30 human participants.[39] In addition to using stem cells to engineer bone, the investigators installed oral implants in the regenerated bone and functionally loaded the implants with prosthetic teeth. Although the radiographic analysis of the regenerated bone did not show a difference in the total bone regenerated between the study and control groups, the bone regenerated using cell-based methods had a higher density. Moreover, the bone core biopsies revealed that stem cell therapy benefited patients with severe defects the most considering the bone volume fraction.[39]

FUTURE PERSPECTIVES

MSCs harvested from oral and craniofacial regions offer easier accessibility with potentially reduced donor site morbidity compared with other grafting sources. These cells have a great potential in differentiation to other cell types and aid in the regeneration of tissues composed of different cell types in the oral and craniofacial region. Before using these cells in human subjects, however, studies need to assess the safety of cell-based therapies, regenerative and differentiation efficacy, and the controlled expansion of these cells in the body. Currently, there are several clinical trials aimed to further study the applications of oral and craniofacial stem cells in regeneration. For instance, the applications of autologous PDLSCs in treating periodontal regeneration and treatment of periodontal disease[40] and the use of SHED cells in the revitalization of immature permanent teeth with necrotic pulp[41] are 2 examples of such trials. Such clinical trials play a pivotal role in shedding light on the potentials of stem cells in tissue engineering and repair of major oral and craniofacial defects with restoring both structure and function.

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