Applications of Mesenchymal Stem Cells in Oral and Craniofacial Regeneration

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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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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