IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 15, Issue 1 Ver. III (Jan. 2016), PP 62-68
www.iosrjournals.org

Stem Cells in Dentistry: A Boon to Oral & Maxillofacial Surgery

[1]Saba Majid, [2]Dr. Ramesh Ram Fry, [3]Dr. Samta Goyal,
[4]Dr. Jatinder Pal Singh Chawla,

[1)] BDS Student, M.M. College of Dental Sciences & Research, MMU, Mullana, Ambala, Haryana, INDIA
[2)] Professor, Department of oral and maxillofacial surgery, M.M. College of Dental Sciences & Research, MMU, Mullana, Ambala, Haryana, INDIA
[3)] Professor, Department of oral and maxillofacial surgery, Saraswati Dental College, Lucknow, Uttar Pradesh, INDIA.
[4)] Post Graduate Student, Department of oral and maxillofacial surgery, M.M. College of Dental Sciences & Research, MMU, Mullana, Ambala, Haryana, INDIA

Abstract:
Objectives: *Here, a brief overview of the state-of-the-science in dentistry, oromaxillofacial diseases especially oral cancers is given and discussion of possible implications of the stem cell hypothesis to the treatment and management part is focussed.*
Material and Methods: *The authors used ''PUBMED'' to find relevant literature written in English and published from the discovery of stem cells until today. A combination of keywords was used as the search terms e.g., "stem cells", ''tissue engineering'', ''approaches'', ''strategies'' ''dentistry'', ''regenerative dentistry'', ''oral surgery'', ''oral & maxillofacial surgery'', ''craniofacial stem cells'' and ''head & neck cancer stem cells".*
Results: *Stem cells have self-renewal abilities and are capable of differentiating into multiple cell lineages; hence a promising candidate for cell-based tissue engineering. Adult Stem cells derived from bone marrow (BMSCs) are most commonly used for bone regeneration purposes. Stem cells can be useful in the regeneration of bone and to correct large craniofacial defects due to cyst enucleation, tumor resection, and trauma. The closure of a bone defect is commonly carried out with the transfer of tissue, which have disadvantages like, not able to restore the unique function of the lost part, donor site morbidity, accompanied by scarring, infection and loss of function. Stem cells in oromaxillofacial region can replace this technique by having no such disadvantage.*
Conclusions: *The future dentistry will be more of regenerative based, where patients own cells can be used to treat diseases. Stem cell therapy has got a paramount role as a future treatment modality in dentistry. Stem cells should be differentiated to the appropriate cell types before they can be used clinically, otherwise it might lead to deleterious effects. Future tissues like tissue engineered bone grafts, engineered joints and cranial sutures can be developed with stem cell therapy. A team of professionals including stem cell biologists, molecular biologists, geneticists and clinicians with knowledge of oral and maxillofacial disorders is needed to develop the field of craniofacial tissue engineering.*
Keywords: *Bone progenitors Mesenchymal stem cells Oral & Maxillofacial Surgery Regenerative dentistry Stem cell(s) Tissue Engineering*

I. Introduction

A stem cell is defined as an unspecialized cell that can continuously produce unaltered daughters and has the ability to generate cells with different and more restricted properties. Stem cells can divide either symmetrically or asymmetrically. Asymmetric divisions keep the number of stem cells unaltered and are responsible for the generation of cells with different properties. These cells can either multiply (progenitors or transit amplifying cells) or be committed to terminal differentiation. Progenitors and transit amplifying cells have a limited lifespan and therefore can only reconstitute a tissue for a short period of time when transplanted. In contrast, stem cells are self-renewing and thus can generate any tissue for a lifetime. This is a key property for a successful therapy.

Sources of stem cells in dentistry

There are two primary sources of stem cells: adult stem cells and embryonic stem (ES) cells. In addition to these stem cells, which are naturally present in the human body, induced pluripotent stem (iPS) cells have been recently generated artificially via genetic manipulation of somatic cells [1]. ES cells and iPS cells are collectively referred to as pluripotent stem cells because they can develop into all types of cells from all three germinal layers. In contrast, most adult stem cells are multipotent, i.e., they can only differentiate into a limited

number of cell types. Following are the different types of stem cells under consideration for applications in dentistry in terms of their clinical availability.

a) Adult stem cells

Adult stem cells are also called somatic stem cells or postnatal stem cells, and they are found in many tissues and organs. Although very few of these cells are present in adult tissues, they undergo self-renewal and differentiation to maintain healthy tissues and repair injured tissues. Recent stem cell studies in the dental field have identified many adult stem cell sources in the oral and maxillofacial region. Many types of adult stem cells reside in several mesenchymal tissues, and these cells are collectively referred to as mesenchymal stem cells or multi-potent mesenchymal stromal cells (MSCs).

(i) Introduction to MSCs

In cell culture, MSCs can be identified and isolated based on their adherence to tissue-culture-treated plastic. MSCs are among the most promising adult stem cells for clinical applications; they were originally found in the bone marrow, but similar subsets of MSCs have also been isolated from many other adult tissues, including skin, adipose tissue and various dental tissues [2,3]. In 2006, the International Society for Cellular Therapy (ISCT) proposed minimal criteria to define human multipotent MSCs; notably, the ISCT termed MSCs as mesenchymal stromal cells, regardless of the tissue from which they are isolated [4]. According to the ISCT criteria, MSCs must be adherent to tissue-culture-treated plastic when maintained in standard culture conditions. Finally, MSCs must be able to differentiate to osteoblasts, adipocytes and chondroblasts in vitro [5].

(ii) Bone marrow-derived MSCs (BMSCs)

Adult bone marrow contains rare multipotent progenitor cells that are generally termed BMSCs. Despite their heterogeneity, BMSCs possess a high replicative capacity and have the capacity to differentiate into various connective tissues cell types. In addition, BMSCs robustly form bone in vivo, which makes them an appropriate stem cell source for bone regeneration therapy [6].

- **BMSCs from the iliac crest**

BMSCs from the iliac crest have been extensively studied and demonstrated to differentiate along osteogenic, chondrogenic, adipogenic, myogenic or non-mesenchymal neurogenic lineages [7]. The bone marrow of the iliac crest is the most documented cell source for MSCs in regenerative medicine, possibly because it is routinely collected for bone marrow transplantation for leukemia treatment. Because of their great potential for bone regeneration [6], BMSCs from the human iliac crest may be applicable to bone tissue engineering irrespective of the age of the patient [8].

- **BMSCs from orofacial bones.**

Although the iliac crest has served as the primary source of BMSCs to date, human BMSCs can also be isolated from orofacial (maxilla and mandible) bone marrow aspirates obtained during dental surgical procedures such as dental implant treatment, wisdom tooth extraction, extirpation of cysts and orthodontic osteotomy. Orofacial bone-derived BMSCs can be obtained not only from younger patients but also from relatively aged individuals, and the age of the donor seems to have little effect on the BMSC gene expression pattern [9].

Indeed, it is well documented that the orofacial BMSCs are phenotypically and functionally different from iliac crest BMSCs. Igarashi et al.2007 reported that orofacial BMSCs have a discrete differentiation potential with distinct expression patterns for several MSC marker genes compared with tibia-, femur-derived BMSCs[10]. These properties of orofacial BMSCs may provide an advantage for orofacial bone regeneration.

(iii) Dental tissue-derived stem cells

To date, two types of adult stem cells have been characterized in dental tissues, i.e., epithelial stem cells and MSC-like cells. An adult epithelial stem cell niche in teeth was first demonstrated by Harada H et al.,1999 via organ culture of the apical end of the mouse incisor[11]. The niche is located in the cervical loop of the tooth apex and possibly contains dental epithelial stem cells, which can notably differentiate into enamel-producing ameloblast. Although the epithelial stem cell niche is useful for analyses of the fate decision of stem cells in tooth development, no information is available for dental epithelial stem cells in humans. This niche may be specific to rodents because their incisors differ from all human teeth in that they erupt continuously throughout the life of the animal.

MSC-like cells have also been identified in the ‘‘developing’’ dental tissues, such as the dental follicle, dental mesenchyme and apical papilla. The dental follicle, which is a dental sac that contains the developing tooth and differentiates into the periodontal ligament, contains dental follicle stem cells (DFSCs) with the ability

to regenerate periodontal tissues [12]. Stem cells from the apical papilla (SCAP) were found in the papilla tissue in the apical part of the roots of developing teeth [13]. Compared with DPSCs, SCAP demonstrate better proliferation in vitro and better regeneration of the dentin matrix when transplanted in immunocompromised mice. These findings suggest that ''developing'' dental tissues may provide a better source for immature stem cells than ''developed'' dental tissues. However, these cells are heterogeneous with various differentiation states, as they include true ''stem'' cells, progenitor cells and possibly fibroblasts [14,15]. Therefore, it is necessary to effectively classify and purify these cells to prevent unexpected clinical results.

(iv) Oral mucosa-derived stem cells

The oral mucosa is composed of stratified squamous epithelium and underlying connective tissue consisting of the lamina propria, which is a zone of well-vascularized tissue, and the submucosa, which may contain minor salivary glands, adipose tissue, neurovascular bundles and lymphatic tissues depending on the site [16]. To date, two different types of human adult stem cells have been identified in the oral mucosa. One is the oral epithelial progenitor/stem cells, which are a subpopulation of small oral keratinocytes (smaller than 40 mm) [17]. Although these cells seem to be unipotential stem cells, i.e., they can only develop into epithelial cells, they possess clonogenicity and the ability to regenerate a highly stratified and well-organized oral mucosal graft ex vivo, which suggests that they may be useful for intra-oral grafting [18].

The inherent stemness of gingival cells may therefore partly explain the high reprogramming efficiency of gingiva-derived fibroblastic cell populations during iPS cell generation [19]. The multipotency of GMSCs/OMSCs and their ease of isolation, clinical abundance and rapid ex vivo expansion provide a great advantage as a stem cell source for potential clinical applications.

(v) Periosteum-derived stem/progenitor cells

The periosteum is a specialized connective tissue that covers the outer surface of bone tissue. The osteogenic capacity of the periosteum of long bones, and the periosteum membrane was found to form a mineralized extracellular matrix under the appropriate in vitro conditions. De Bari et al.,2006 demonstrated that single-cell-derived clonal populations of adult human periosteal cells possess mesenchymal multipotency, as they differentiate to osteoblast, chondrocyte, adipocyte and skeletal myocyte lineages in vitro and in vivo. Therefore expanded periosteum-derived cells could be useful for functional tissue engineering, especially for bone regeneration [20].

Periosteal grafts have been shown to induce cortical bone formation, whereas bone marrow grafting induced cancellous bone formation with a bone marrow-like structure in a rat calvarial defect model [21], which implies that the source of the transplanted cells can influence the structural properties of the regenerated bone. The robust osteogenic potential of periosteum-derived cells has inspired dentists to use the periosteum for orofacial bone regeneration. Therefore, the periosteum is a source of stem/progenitor cells for bone regeneration, particularly for large defects.

(vi) Salivary gland-derived stem cells

Patients afflicted with head and neck cancer who receive radiotherapy suffer from an irreversible impairment of salivary gland function that result in xerostomia and a compromised quality of life. Therefore, stem cells in the adult salivary gland are expected to be useful for autologous transplantation therapy in the context of tissue engineered-salivary glands or direct cell therapy. Lombaert et al., 2008 reported that an in vitro floating sphere culture method could be used to isolate a specific population of cells expressing stem cell markers from dissociated mouse submandibular glands [22]. These cell populations could differentiate into salivary gland duct cells as well as mucin- and amylase-producing acinar cells in vitro. These reports suggest that the salivary gland is a promising stem cell source for future therapies targeting irradiated head and neck cancer patients. However, primary cultures of dispersed cells will always contain a number of cells with different origins, such as parenchymal cells, stromal cells and blood vessel cells, which makes it difficult to select salivary gland stem cells. Indeed, Gorjup et al., 2009 isolated primitive MSC-like cells from the human salivary gland, but possibly from stromal tissue, which expressed embryonic and adult stem cell markers and could be guided to differentiate into adipogenic, osteogenic and chondrogenic cells [23]. To obtain a genuine stem cell population that can be considered to be a true stem cell for the salivary gland, it is necessary to select cells carrying a specific marker or labelled with induced reporter proteins.

(vii) Adipose tissue-derived stem cells (ASCs)

Adipose tissue is an abundant source of MSCs and has been extensively studied in the field of regenerative medicine as a stem cell source. Adipose-derived MSCs can be readily harvested via lipectomy or from lipoaspirate from areas such as the chin, upper arms, abdomen, hips, buttocks and thighs in large numbers with low donor-site morbidity [24], as liposuction is one of the most common cosmetic procedures. Pieri et al.,

2010 demonstrated that the transplantation of autologous ASCs with an inorganic bovine bone scaffold (Bio-Oss1) enhanced new bone formation and implant osseointegration following vertical bone augmentation of the calvarial bone of rabbits, which suggests that ASCs may be useful for vertical alveolar bone augmentation for implant treatment [25].

Hung et al., 2011 demonstrated that ASCs implants were able to grow self-assembled new teeth containing dentin, periodontal ligament and alveolar bone in adult rabbit extraction sockets with a high success rate [26]. Further studies on the isolation, characterization and application of ASCs to enhance their efficacy for bone and periodontal regeneration will provide a definitive protocol for the use of waste fat tissues in future clinical applications.

b) Pluripotent stem cells

Pluripotency is defined as the capacity of individual cells to generate all lineages of the mature organism in response to signals from the embryo or cell culture environment [27]. Because of their intrinsic pluripotency and unlimited self-renewal, dental applications of pluripotent stem cells are expected to primarily involve basic research on developmental biology, drug testing and regenerative therapies. Therefore, the differentiation of pluripotent cells towards clinically useful oral lineages is primary focus in dental research.

(i) ES cells

ES cells are produced by culturing cells collected from the undifferentiated inner cell mass of the blastocyst, which represents an early stage of embryonic development after fertilization (Thomson JA et al., 1998). This embryonic origin is the major reason that ethical and moral questions are associated with the use of human ES cells [29]. ES cells are expected to provide an in vitro model system and transplantation substrate for animal models to study the controlled differentiation of pluripotent stem cells into specific lineages of oral tissues and organs, such as mucosa, alveolar bone, periodontal tissues and teeth [30]. These approaches can be useful to obtain a better understanding of oral developmental biology and may lead to future strategies in regenerative dentistry that meet clinical needs.

(ii) iPS cells

In 2006, Dr. Shinya Yamanaka discovered that normal mouse adult skin fibroblasts can be reprogrammed to an embryonic state by introducing four genetic factors (Oct3/4, Sox2, Klf4 and c-Myc), and the resulting cells were termed iPS cells [31]. Just a year after the mouse study was reported, the findings were replicated in human skin cells [32], which opened the door to generate a patient-specific ES cell equivalent from autologous somatic cells. This technology is expected to revolutionize medicine because of the capacity of iPS cells to develop into all tissues/organs and thereby support the emerging field of ‘‘personalized medicine’’, which uses a patient’s own cells to provide biologically compatible therapies and individually tailored treatments.

These iPS cells may be of particular importance for developing innovative technologies to regenerate missing jaw bones, periodontal tissues, salivary glands and lost teeth [33].

II. Engineered orofacial tissues

Orofacial structures are very unique in their development and function. Orofacial bones, for example, are derived from both neural crest and paraxial mesoderm; the skeletal bones however derived from mesoderm. Furthermore, orofacial bones undergo significant stress and strain produced from different muscles of mastication and respond differently to growth factors and mechanical stimuli [34]. Furthermore, oro-facial tissues have limited and variable capacity for regeneration. Unlike alveolar bones, cementum has a very slow regenerative capacity. Unlike enamel, dentine can regenerate. As it is encased in dentine and has limited apical blood supply, the pulp has a limited capacity for regeneration [35].

(i) Dentine-pulp complex

The regeneration of the dentine-pulp complex, obtained with pulp capping materials (e.g., calcium hydroxide, mineral trioxide aggregates, Biodentine), has been correlated with the stimulation of differentiation of the pulp progenitor cells into odontoblast-like cells [36] or secretion of TGF-b1 which plays a key role in angiogenesis, recruitment of progenitor cells, cell differentiation and finally mineralisation of the injured area. Stem cell therapy has been attempted for regeneration of the dentine-pulp complex. Dental tissues are a very rich source of stem cells. Examples of these tissues include e.g., pulp, apical papilla, human retained or exofoliated deciduous teeth, oral mucosa and gingiva. Growth factors [e.g., fibroblast growth factor basic (FGF), transforming growth factor b1 (TGF-b1) and endothelial growth factor (EGF)] have been also included within the scaffolds to modulate the function of stem cells [37].

(ii) Periodontium

Tissue regeneration of the periodontium is no longer considered solely as an experimental approach, and significant progress has been made these past 10–15 years with respect to the development of biodegradable scaffold materials. Today's concepts of matrix-and scaffold-based tissue engineering involve the combination of a scaffold with cells and/or biomolecules that promote the repair and/or regeneration of such tissues. More recently, regenerative therapies have considered whole tissue architecture, the ultimate goal aimed at the creation of scaffolds that create a temporary 3D matrix upon which cells and tissues can grow exclusively in vitro and/or in vivo. The advances made by targeting particular families of growth factors and other signalling molecules at both the protein and gene levels has led to promising results.

(iii) Bioengineered teeth

Tooth development, odontogenesis, is a complex process involving a series of reciprocal epithelial–mesenchymal interactions and coordination between the crown and the root with its associated periodontium [38]. Accordingly, cells dissociated from epithelium and mesenchymal tissues of prenatal or postnatal tooth germ were used to reconstitute a ''bioengineered tooth germ'' in vitro. Transplantation of bioengineered tooth germ into the oral environment or an organ culture has been then attempted to produce a whole tooth [39]. Using prenatal tooth germ cells showed higher tendency for tooth formation with proper crown shape than postnatal tooth germ cells [40]. Again, the effect of the source and age of tooth bud on the innate regenerative capacity of the isolated cells as well as the effect of scaffolds on cell behaviour required more investigations.

(iv) Skin, oral mucosa, facial muscles and salivary glands

Tissue engineering made extensive progress in the area of skin regeneration and recently several skin substitute products (epidermal, dermal or composite) are now commercially available. The pioneering work started by the observation of entire keratinising colonies from in vitro cultured epidermal keratinocytes. The formation of keratinocytes sheets was then followed using autogenic or allogenic epidermal cells. The keratinocytes sheet has the ability for renewal throughout the patient's lifetime and can undergo organisation and differentiation after grafting.

Due to the similarity between skin and oral mucosa, the development of engineered oral mucosa followed the same protocol i.e., started with the development of epithelial sheet, then composite oral mucosal equivalents either by seeding oral keratinocytes on three-dimensional cell seeded scaffold. Furthermore, both skin and mucosal substitutes can be used interchangeably. Recently, the tissue engineered oral mucosa has been further improved for either intraoral or extraoral use [41].

Various tissue engineering strategies have been currently researched for regeneration of facial muscles. Implantation of myoblasts seeded collagen constructs was also effective in promoting volume preservation and/or tongue reconstruction. Injection of platelet-rich plasma, growth factors and stem cell-based strategy has been also employed. The use of these biological therapies however requires a standardised, safe use in the clinic and careful understanding of the mechanisms involved in the survival, proliferation and differentiation of stem cells and in muscle regeneration as a whole [42].

Treatment of salivary glands' hypofunction following irradiation in head and neck area is only limited to the administration of saliva substitutes and sialogogues that require frequent administration. Tissue engineering provides a biological substitute to impaired salivary glands. The main challenge however is to culture the human salivary gland cells as they are highly differentiated and difficult to expand in vitro. Selective functionalisation of degradable scaffold with chitosan and/or laminin provide chemical signals that support proliferation of epithelial cells and promoted the apicobasal polarity, required for directional secretion by secretary cells [43].

(v) Bone and temporomandibular joints

Application of autogenic periosteal cells-seeded polymer fleeces to augment the floor of the maxillary sinus before implants insertion showed encouraging results from both radiographical and histological examinations [44]. For irregular defects, injectable composites could be useful for stem cell-based bone engineering. Autogenic growth factors-rich plasma in combination with inorganic bone (Bio-Oss1) has been also employed clinically in sinus floor elevation; this treatment was effective in forming new vascularised bone [45].

Temporomandibular joint (TMJ) is one of the most difficult tissues to treat due to the limited blood supply and hence limited capacity for self-repair. The articular cartilage of TMJ has a surface layer of fibrocartilaginous and deep layer of hyaline-like hypertrophic zone with a thin intermediate proliferative zone. For regeneration of this unique cartilage, cell therapy comes first and injectable smart hydrogels could be employed to transfer cells [46]. As known, the autogenic cells are the gold standard cell source used for tissue regeneration, but it would be very difficult to harvest cells from the diseased TMJ.

Regarding the TMJ disc, acellular porcine-derived ECM was effective as inductive template for reconstruction of TMJ disc when implanted in vivo for 6 months and it has been assumed that this bioscaffold represents an off-the-shelf solution for engineering of TMJ disc [47]. Regarding the cellular component, adipose stem cells (ADSCs) could be a potential cell source for TMJ engineering. The approaches employed to overcome the challenge of TMJ engineering have been varied from cell injection therapy to the use of synthetic or natural scaffolds as well as relying to some extent on biological modulators; each with varying degree of success.

Acknowledgments

Funding resources not required.

Conflicts of Interest statement

1. Source of funding - no
2. Paid consult to sponsor – not applicable
3. Study investigator funded by sponsor – no
4. Patient data and pictures- undisclosed

There are no conflicts of interest.

Conflicts of Interest:- None declared

References

[1]. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, Yamanaka S. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 2007;131(5):861–72. [Medline: 18035408]

[2]. Ding DC, Shyu WC, Lin SZ. Mesenchymal stem cells. Cell Transplant 2011;20(1):5-14. [Medline: 21396235] [doi: 10.3727/096368910X].

[3]. Fernandes KJ, McKenzie IA, Mill P, Smith KM, Akhavan M, Barnabé-Heider F, Biernaskie J, Junek A, Kobayashi NR, Toma JG et al. A dermal niche for multipotent adult skin-derived precursor cells. Nat Cell Biol. 2004;6(11):1082–93. [Medline:15517002]

[4]. Horwitz EM, Le Blanc K, Dominici M, Mueller I, Slaper-Cortenbach I, Marini FC, Deans RJ, Krause DS, Keating A. Clarification of the nomenclature for MSC: the International Society for Cellular Therapy position statement. Cytotherapy 2005;7(5):393–5. [Medline:16236628]

[5]. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, Deans R, Keating A, Prockop Dj, Horwitz E. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 2006;8(4):315–7. [Medline:16923606]

[6]. Derubeis AR, Cancedda R. Bone marrow stromal cells (BMSCs) in bone engineering: limitations and recent advances. Ann Biomed Eng. 2004;32(1):160–5. [Medline:14964731]

[7]. Egusa H, Schweizer FE, Wang CC, Matsuka Y, Nishimura I. Neuronal differentiation of bone marrow-derived stromal stem cells involves suppression of discordant phenotypes through gene silencing. J Biol Chem. 2005;280(25):23691–7. [Medline: 15855172]

[8]. Mendes SC, Tibbe JM, Veenhof M, Bakker K, Both S, Platenburg PP, Oner FC, de Bruijn JD, van Blitterswijk CA.. Bone tissue-engineered implants using human bone marrow stromal cells: effect of culture conditions and donor age. Tissue Eng. 2002;8(6):911–20. [Medline: 12542937]

[9]. Han J, Okada H, Takai H, Nakayama Y, Maeda T, Ogata Y. Collection and culture of alveolar bone marrow multipotent mesenchymal stromal cells from older individuals. J Cell Biochem. 2009;107(6):1198–204. [doi: 10.1002/jcb.22224].

[10]. Igarashi A, Segoshi K, Sakai Y, Pan H, Kanawa M, Higashi Y, Sugiyama M, Nakamura K, Kurihara H, Yamaguchi S et al. Selection of common markers for bone marrow stromal cells from various bones using real-time RT-PCR: effects of passage number and donor age. Tissue Eng. 2007;13(10):2405–17. [Medline: 17596118]

[11]. Harada H , Kettunen P , Jung HS , Mustonen T , Wang YA , Thesleff I. Localization of putative stem cells in dental epithelium and their association with Notch and FGF signalling. J Cell Biol. 04 October 1999; 147 (1): 105-20. [Medline:10508859]

[12]. Park BW, Kang EJ, Byun JH, Son MG, Kim HJ, Hah YS, Kim TH, Mohana Kumar B, Ock SA, Rho GJ. In vitro and in vivo osteogenesis of human mesenchymal stem cells derived from skin, bone marrow and dental follicle tissues. Differentiation 2012;83(5):249–59. [Medline:22469856] [doi: 10.1016/j.diff.2012.02.008]

[13]. Huang GT, Sonoyama W, Liu Y, Liu H, Wang S, Shi S. The hidden treasure in apical papilla: the potential role in pulp/dentin regeneration and bioroot engineering. J Endod. 2008;34(6):645–51. [Medline:18498881] [doi: 10.1016/j.joen.2008.03.001]

[14]. Miura, M., Gronthos, S., Zhao, M., Lu, B., Fisher, L.W., Robey, P.G., et al. SHED: stem cells from human exfoliated deciduous teeth. Proc Natl Acad Sci USA 2003;100,5807–12. [Medline:12716973]

[15]. Gronthos, S., Brahim, J., Li, W., Fisher, L.W., Cherman, N., Boyde, A., et al. Stem cell properties of human dental pulp stem cells. J Dent Res. 2002;81,531–5. [Medline: 12147742]

[16]. Garant PR. Oral mucosa. In: Dickson A, editor. Oral cells and tissues. Illinois: Quintessence; 2003: 81–122.

[17]. Izumi K, Tobita T, Feinberg SE. Isolation of human oral keratinocyte progenitor/stem cells. J Dent Res. 2007;86(4):341–6. [Medline: 17384029]

[18]. Izumi K, Feinberg SE, Terashi H, Marcelo CL. Evaluation of transplanted tissue-engineered oral mucosa equivalents in severe combined immunodeficient mice. Tissue Eng. 2003;9(1):163–74. [Medline:12625965]

[19]. Egusa, H., Okita, K., Kayashima, H., Yu, G., Fukuyasu, S., Saeki, M., et al. Gingival fibroblasts as a promising source of induced pluripotent stem cells. PLoS One 5, 2010;e12743. [doi: 10.1371/journal.pone.0012743]

[20]. De Bari C, Dell'Accio F, Vanlauwe J, Eyckmans J, Khan IM, Archer CW, Jones EA, McGonagle D, Mitsiadis TA, Pitzalis C et al.. Mesenchymal multipotency of adult human periosteal cells demonstrated by single-cell lineage analysis. Arthritis Rheum. 2006;54(4):1209–21. [Medline:16575900]

[21]. Ueno T, Honda K, Hirata A, Kagawa T, Kanou M, Shirasu N, Sawaki M, Yamachika E, Mizukawa N, Sugahara T. Histological comparison of bone induced from autogenously grafted periosteum with bone induced from autogenously grafted bone marrow in the rat calvarial defect model. Acta Histochem. 2008;110(3):217–23. [Medline: 18082248]

[22]. Lombaert IM, Brunsting JF, Wierenga PK, Faber H, Stokman MA, Kok T, Visser WH, Kampinga HH, Haan G, Coppes RP. Rescue of salivary gland function after stem cell transplantation in irradiated glands. PLoS One 2008;3(4):e2063. [doi: 10.1371/journal.pone.0002063]

[23]. Gorjup, E., Danner, S., Rotter, N., Habermann, J., Brassat, U., Brummendorf, T.H., et al. Glandular tissue from human pancreas and salivary gland yields similar stem cell populations. Eur J Cell Biol. 2009;88,409–21.

[24]. Mizuno H, Tobita M, Uysal AC. Concise review: adipose-derived stem cells as a novel tool for future regenerative medicine. Stem Cells 2012;30(5):804–10. [Medline:22415904] [doi: 10.1002/stem.1076]

[25]. Pieri F, Lucarelli E, Corinaldesi G, Aldini NN, Fini M, Parrilli A, Dozza B, Donati D, Marchetti C. Dose-dependent effect of adipose-derived adult stem cells on vertical bone regeneration in rabbit calvarium. Biomaterials 2010;31(13):3527–35. [Medline: 20170950] [doi: 10.1016/j.biomaterials.2010.01.066].

[26]. Hung CN, Mar K, Chang HC, Chiang YL, Hu HY, Lai CC, Chu RM, Ma CM. A comparison between adipose tissue and dental pulp as sources of MSCs for tooth regeneration. Biomaterials 2011;32(29):6995–7005. [Medline:21696818] [doi: 10.1016/j.biomaterials.2011.05.086]

[27]. Wray J, Kalkan T, Smith AG. The ground state of pluripotency. Biochem Soc Trans. 2010;38(4):1027–32. [Medline: 20658998] [doi: 10.1042/BST0381027]

[28]. Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, Jones JM. Embryonic stem cell lines derived from human blastocysts. Science 1998;282(5391):1145–7. [Medline: 9804556]

[29]. Wobus AM, Boheler KR. Embryonic stem cells: prospects for develop- mental biology and cell therapy. Physiol Rev. 2005.;85(2):635–78. [Medline:15788707]

[30]. Kang HK, Roh S, Lee G, Hong SD, Kang H, Min BM. Osteogenic potential of embryonic stem cells in tooth sockets. Int J Mol Med. 2008;21:539–44.

[31]. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 2006;126(4):663–76. [Medline:16904174].

[32]. Takahashi, K., Tanabe, K., Ohnuki, M., Narita, M., Ichisaka, T., Tomoda, K., et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 2007;131(5),861–72. [Medline:18035408]

[33]. Egusa H. iPS cells in dentistry. Clin Calcium 2012;22(1):67–73.

[34]. Herring SW, Ochareon P. Bone – special problems of the craniofacial region. Orthodontics and Craniofacial Research 2005;8(3):174–82. [Medline:16022719]

[35]. Huang GT. Pulp and dentin tissue engineering and regeneration: current progress. Regenerative Medicine 2009;4(5):697–707. [doi: 10.2217/rme.09.45]

[36]. Tecles O, Laurent P, Aubut V, About I. Human tooth culture: a study model for reparative dentinogenesis and direct pulp capping materials biocompatibility. Journal of Biomedical Materials Research Part B: Applied Biomaterials 2008;85(1):180–7. [doi: 10.1002/jbm.b.30933].

[37]. Mathieu S, Jeanneau C, Sheibat-Othman N, Kalaji N, Fessi H, About I. Usefulness of controlled release of growth factors in investigating the early events of dentin-pulp regeneration. Journal of Endodontics 2013;39(2):228–35. [doi: 10.1016/j.joen.2012.11.007].

[38]. Hu, B., Nadiri, A., Kuchler-Bopp, S., Perrin-Schmitt, F., Peters, H., Lesot, H. Tissue engineering of tooth crown, root, and periodontium. Tissue Engineering 2006;12,2069–75. [Medline: 16968149].

[39]. Ikeda E, Morita R, Nakao K, Ishida K, Nakamura T, Takano-Yamamoto T, Ogawa M, Mizuno M, Kasugai S, Tsuji T. Fully functional bioengineered tooth replacement as an organ replacement therapy. Proceedings of the National Academy of Sciences of the United States of America. 2009;106(32):13475–80. [Medline:2720406] [doi: 10.1073/pnas.0902944106].

[40]. Honda MJ, Fong H, Iwatsuki S, Sumita Y, Sarikaya M. Tooth-forming potential in embryonic and postnatal tooth bud cells. Medical Molecular Morphology 2008;41(4):183–92. [doi: 10.1007/s00795-008-0416-9].

[41]. Patterson JM, Bullock AJ, MacNeil S, Chapple CR. Methods to reduce the contraction of tissue-engineered buccal mucosa for use in substitution urethroplasty. European Urology 2011;60,856–61. [Medline:21803482] [doi: 10.1016/j.eururo.2011.07.045]

[42]. Longo UG, Loppini M, Berton A, Spiezia F, Maffulli N, Denaro V.. Tissue engineered strategies for skeletal muscle injury. Stem Cells International 2012:1–9. [Medline:3216349] [doi:10.1155/2012/175038].

[43]. Cantara SI, Soscia DA, Sequeira SJ, Jean-Gilles RP, Castracane J, Larsen M. Selective functionalization of nanofiber scaffolds to regulate salivary gland epithelial cell proliferation and polarity. Biomaterials 2012;33(33):8372–82. [Medline: 3491572] [doi: 10.1016/j.biomaterials.2012.08.021].

[44]. Schmelzeisen R, Schimming R, Sittinger M. Making bone: implant insertion into tissue-engineered bone for maxillary sinus floor augmentation-a preliminary report. Journal of Cranio-Maxillo-Facial Surgery 2003;31(1):34–9. [Medline: 12553924].

[45]. Anitua E, Prado, Orive G. Bilateral sinus elevation evaluating plasma rich in growth factors technology: a report of five cases. Clinical Implant Dentistry and Related Research 2012;14(1):51–60. [Medline: 20626759] [doi: 10.1111/j.1708-8208.2009.00233.x].

[46]. Vinatier C, Gauthier O, Fatimi A, Merceron C, Masson M, Moreau A, Moreau F, Fellah B, Weiss P, Guicheux J. An injectable cellulose-based hydrogel for the transfer of autologous nasal chondrocytes in articular cartilage defects. Biotechnology and Bioengineering 2009;102(4):1259–67. [doi: 10.1002/bit.22137].

[47]. Brown BN, Chung WL, Almarza AJ, Pavlick MD, Reppas SN, Ochs MW, Russell AJ, Badylak SF. Inductive, scaffold-based, regenerative medicine approach to reconstruction of the temporomandibular joint disk. Journal of Oral and Maxillofacial Surgery 2012;70(11):2656–68. [doi: http://dx.doi.org/10.1016/j.joms.2011.12.030].