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Dental Stem Cells: Sources, Clinical Implications and Challenges

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ABSTRACT

Background: Some cells possess unique property of self-renewal while maintaining undifferentiated state. These cells are capable to differentiate in to different cell types and generate complex tissue and organs. Human dental pulp tissue also demonstrates high growth potential and multipotency. These cells are designated as DPSCs (Dental Pulp Stem Cells). Multipotent stem cell population also include apical papilla, periodontal ligament and dental follicle progenitor cells, Stem cells from deciduous tooth. These cells can be genetically reprogrammed to induced Pluripotent cells for clinical interest. DPSCs are capable of forming ectopic dentin and associated pulp tissue and also found to be capable of differentiating in to adipocytes and neural like cells. This concise review article focuses mainly on stem cell types their potential therapeutic application and challenges for craniofacial tissue engineering.

Keywords: Dental pulp, dentistry, stem cells.

INTRODUCTION

Stem cells are undifferentiated embryonic or adult (post natal) stem cells that continuously divide. A fundamental property of stem cells is the ability to go through numerous cycles while maintaining undifferentiated state. Moreover, stem cells are capable to differentiate in to specialized cell types and generate various tissues and organs. (1, 2)

Embryonic stem cells are pluripotent cells with unlimited capacity to differentiate. But clinical feasibilities are limited due to ethical and legal issues. Tumorogenesis is also one of the common complications. (1, 3) Adult stem cells exists throughout the body in various tissues like bone marrow, neural tissue, skin ,ratina and dental pulp.(4)It can divide and create another cell like itself and even differentiated from itself. These cells show limited capacity for differentiation that is designated as multipotent compared with pluripotency of embryonic stem cells. However recent study revealed that adult stem cells have more plasticity than previously thought. They are comparatively easy to isolate, no ethical issues and no teratoma formation. These advantages make them useful in current day practice. (1, 3, 5)

Recently investigators have described methods to reprogram somatic cells of human by insertion of genes that reprogrammed somatic cells and converted them back to embryonic state. The resulting cells are designated as induced pluripotent stem cells. Latest reports have described successful attempts to develop pluripotent stem cells from human dental pulp recovered from deciduous tooth and third molars. This newly evolved concept may play a major role in future stem cell based therapy. (1, 6)

Sources of adult stem cells

1. Bone marrow
2. Adipose tissue
3. Stem cells from oral and maxillofacial structures

A. Dental pulp stem cells (DPSCs)
B.Stem cells from human exfoliated deciduous teeth (SHED)
C.Periodontal ligament (PDLSCs)

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D.Dental Follicle Progenitor cells (DFPSCs)
E.Stem cells from Apical Papilla (SCAP)

Bone marrow

The bone marrow is the most popular source of mesenchymal stem cells. It is known since decades that adult stem cells from bone marrow has been used to repair and/or replace diseased and/or damaged tissue. Bone-marrow-derived MSCs(mesenchymal stem Cells) have been described as colony-forming unit-fibroblasts (CFU-Fs) *in vitro* which were able to commit to osteogenic differentiation. Their capacity to form clonogenic colonies is characteristic of other somatic stem cells, such as hematopoietic stem cells, and defines their ability to undergo self-renewal. However, BMMSCs are limited to a growth potential of 30 to approximately 50 population-doublings (PDs) following *ex vivo* expansion. (7)

Bone marrow mesenchymal cells can differentiate in to osteogenic, chondrogenic, adipogenic, myogenic and neurogenic lineages. But the drawback of probable post operative pain and invasiveness of bone marrow derived stem cells propels the search for more accessible source of mesenchymal stem cells than those found in bone marrow. (1,5,8,9)

Adipose tissue

Adipose tissues are an abundant source of MSCs (Mesenchymal stem cells) and have been extensively studied in the field of regenerative medicine as a stem cell source. In experimental studies these cells have shown osteogenic differentiation and are expected to be an alternative source for bone regeneration in dentistry. Adipose derived stem cells can be readily harvested via lipectomy or from lipo aspirate from areas such as chin, abdomen, hips, buttocks and thigh with low donor site morbidity. (2)

Dental tissue

Because of higher proliferation capacity, abundant cell supply with minimal invasion dental pulp stem cells have received much attention as promising population of stem cells in the field of tissue engineering and regenerative medicine. Five different human dental stem cell populations have been identified and characterized as mesenchymal stem cells. (1, 5, 8)

Dental pulp stem cells

Dental pulp-derived stem cells (DPSCs) are considered to be of great promise for use in tissue repair and regenerative medicine.To date, two types of adult stem cells have been identified in dental tissues.i.e. Epithelial stem cells and mesenchymal like stem cells. An adult epithelial stem cell niche has been demonstrated in cervical loop of developing rat tooth but not in humans (2).Mesenchymal stem cells have long been assumed to exist in dental tissues as some dental tissues such as PDL and dental pulp can regenerate by natural process even after trauma. Dental pulp stem cells can be isolated from fractured tooth requiring endodontic treatment, supernumerary tooth, permanent tooth requiring orthodontic extraction, anomalies such as odontoma and third molars. DPSCs can be easily collected even from discarded teeth with little ethical concerns and harvested in a minimally invasive and safe manner.

SHED Cells (Stem cells from human exfoliated deciduous tooth)

Living pulp remnant in exfoliated deciduous tooth is a good source of stem cells. These cells were 1st isolated and termed as SHED by Miura et al (10)SHED cells are highly proliferative stem cells capable of differentiating in to variety of cell types, including osteoblats,neural cells,adipocytes and odontoblasts(1).SHED cells have shown different gene expression profiles especially related to proliferation and extracellular matrix formation. SHED show higher proliferation rate than DPSCs and BMMSCs (1).SHED represents promising stem cell population as they are derived from non invasive source and naturally disposed with least ethical and legal issues. Because of higher proliferation capacity, abundant cell supply and painless stem cell collection with minimal invasion SHED could be desirable option as a potential source of stem cells for therapeutic implication.

PDLSCs (Periodontal ligament stem cells)

Periodontal ligament stem cells in humans were 1st identified in 2004 by Seo et al (11).These cells are capable to differentiate in to cementoblast like cells,

adipocytes, fibroblasts like cells, chondrocyte and connective tissue rich in collagen I in vitro and in vivo.Seo et al demonstrated the presence of clonegenic stem cells in enzymatically digested PDL and further showed that human PDLSCs transplanted in to immunodeficient rodent generated a cementum/PDL like structures that contributed periodontal tissue repair.(11) As PDL is under constant strain from the forces of mastication and PDLSCs likely to play role in maintaining PDL cell numbers. This explains why they are better than any other dental stem cell population at forming PDL like structure. (12)

DFPSCs

The dental follicle which forms at cap stage of tooth development is a loose vascular connective tissue consists of progenitors for PDL cells, cementoblasts and osteoblasts.DFPSCs were first isolated from the dental follicle of human third molars(13).As DFSCs come from developing tissue, it is considered that they might exhibit greater plasticity than other dental tissue stem cells (12, 13).These cells are able to differentiate in to cementoblast like cells, osteoblast like cells and fibroblast like cells in animal experiments (1).

SCAP cells (Stem cells from Apical Papilla)

SCAP cells were 1st isolated from human root apical papilla of extracted third molars. Sonoyana et al termed them SCAP cells and studied their biologic characteristics.(14)Dental papilla participate in root formation and later evolved to become pulp, during the course of tooth development dental papilla lies apical to dental pulp and epithelial diaphragm known as apical papilla. Postnatal root formation is a developmental process and apical papilla is essential for root development, therefore cells involved in it are more embryonic like. These cells are clonogenic and can undergo odontoblastic, osteogenic, adipogenic and neurogenic differentiation. (14, 15)

Clinical Application in orofacial region

1. Tooth regeneration (Enamel, Dentin, and Pulp)
2. Regeneration of PDL
3. Regeneration of craniofacial defect (Bone)
4. Soft tissue reconstruction

Tooth Regeneration

Many options are available for tooth replacement in current dental practice. Dental implant is one of the most popular and state of the art amongst them. Since these implants directly attach with bone without PDL (shock absorber), the forces of mastication are directly transferred to bone, which is the most common reason of implant failure. Therefore biological implant with natural anchoring fibrils, root, nerves and blood supply has become desirable option. However for the tooth regeneration epithelium and connective tissue cells must interact in concert. It is known that pulp cells differentiate in to odontoblasts and later form dentin but for the induction of odontogenic potential lies in the dental epithelium. No source of epithelial cells has been identified to date capable of inducing odontogenesis other than endogeneous dental epithelium of early stage embryo. Epithelial rests of Malassez(ERM) are the cells which can be induced in vitro to form enamel like tissue following recombination with dental pulp cells.(12)The cells which have capacity in vitro to form tooth are early embryonic neural crest derived ecto mesenchymal cells as they have already received inductive signals from the dental epithelium.(12) Nam et al isolated and characterized epithelial cell like cells from human deciduous dental pulp.(16) They possess epithelial markers and might play a role as an epithelial component for repair or regeneration of tooth enamel. Dental epithelium of early stage embryo, oral epithelium, salivary glands and gingiva also serve as source of epithelial stem cells in mice but more studies are necessary to determine their regenerative capacity in humans (17).Although essential for function, anatomical crown is less important as synthetic tooth crowns can be perfectly matched for size, shape and colour.Therefore for biological tooth replacement the ultimate goal is to form biological root (dentin and pulp).

It is known that biologic root formation requires dentin –pulp complex formation. Although DPSCs demonstrate multilineage potential, they maintain their original properties as dental pulp cells and are capable to form dentin –pulp complex. Many studies showed tubular dentin formation upon implantation of stem cells with scaffold and reparative dentin formation on amputed pulp in mice. But they failed to reveal dentinal tubules in dentin like tissue in humans. Regeneration of tooth

pulp is much sought goal in regenerative dentistry as current endodontic practice of replacing infected pulp by inorganic materials results in a non vital and weak tooth. Recent studies showed positive results of de novo regeneration of dental pulp in emptied root canal space using dental stem cells in mice. Angiogenesis and neurogenesis are critical for pulp regeneration. Iohara K et al showed CD 31/CD 146 positive cells in permanent and deciduous pulp tissue with high angiogenic and neurogenic potential. (18)

Regeneration of Periodontal ligament (PDL) and Bone

Human tissues are different in term of regenerative properties. Stem cells are a promising tool for hard tissue regeneration, thanks to their particular characteristics of proliferation, differentiation and plasticity.

Teeth are complex organs made up of two specialized hard tissue, enamel and dentin, which is attached to bone through specialized ligament-periodontal ligament.Irreservible loss of connective tissue attachment and supportive bone occurs because of periodontitis.PDL has long been recognized to contain a population of progenitor cells, which are capable to differentiate in to mesenchymal cell lineages to produce cementoblast like cell,adipocytes and collagen I in vitro and vivo(12).In a study by Egusa H et al PDLSCs have demonstrated the ability to regenerate periodontal tissues in experimental animal models(3).Even SHED cells and BMSCs are also reported to induce the formation of a bone like matrix with lamellar structure(3).Atari M et al compared the osetogenic capacity of DPPSCs and DPMSc isolated from the same donors and cultivated in similar osteogenic medium. New bone tissue formed by DPPSCs was in perfect continuity with the trabecular host bone structure compared to DPMSc(19).In cases where there is insufficient bone for implants, such as tooth loss as a consequence of bone loss that occurs in post menopausal osteoporosis and other systemic conditions,implants have to be preceded by bone grafts.(12)

Soft tissue reconstruction

Soft tissue reconstruction to correct large craniofacial defect has become essential part of current day esthetic practice. It is known since long that various flap and graft are used to reconstruct the compromised tissue, but it often leads to donor site morbidity. Adipose tissue derived stem cells exposed to proper medium and shaped in appropriate scaffold can be used to reconstruct soft tissue defect (2,4,5) .Although it seems that several different types of cells reside in dental pulp tissue, adipocytes are not the normal cellular component in dental pulp. However it is reported now that a more potent adipogenic inductive culture medium can induce DPSCs form adipocytes (4).

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, polymer and materials scientists, mechanical engineers and clinicians with knowledge of oral and maxillofacial disorders is needed to develop the field of craniofacial tissue engineering(20)

CONCLUSION

Dental stem cells have many advantages over other stem cell source in the field of regenerative medicine. Results to date suggest that various dental tissues are rich source of adult mesenchymal stem cells for a wide range of clinical applications. However further studies are necessary to establish evidenced based practices for awareness of dentists and patients regarding importance and use of stem cells in cell based regenerative therapies.

In Furtherance

Dental caries is common public health problem resulting in pulp and later tooth loss. Dental pulp provides nutrient and oxygen supply, innervations, reactionary dentin formation and immune response. Therefore, human dental pulp cells with highly angiogenic and neurogenic potential are critical for pulp regeneration. DPSCs can also serve as potential source for treatment of cerebral and limb ischemia.

Regeneration of dentine, odontoblasts, dental pulp, bone, cartilage, muscle, hair follicle, cornea, neural cells, melanocytes and endothelial cells from DPSCs have been reported. Clinical trials to evaluate the properties of DPSCs have not been widely reported

but their potentiality to differentiate in to neural and muscular cells suggests they may have wider clinical implication.

The dream of bioengineered organs will come true with the multidisciplinary approaches of clinicians and scientists.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Sedgly CM, Botero TM. Dental stem cells and their sources. Dent.Clin N Am 2012; 56,549-561.

2.Yalvac ME, Ramazanoglu M, Rizvanov AA, Shahin F, Bayrak OF, Salli V et al. Isolation and characterization of stem cells derived from human third molar tooth germs of young adults; implications in neovascularization, osteo-,adipo- and neurogenesis. The Pharmacogenomics Journal 2009;1-9.

3.Egusa H, Sonoyama W, Nishimura M, Afsuta I, Akiyama K, Stem cells in dentistry: Part I Stem cell sources.J of Prosthodontic Research 2012;56(3),151-165.

4. S. GronthosJ. Brahim, W Li, Fisher LW, Cherman N, Boyde A et al. Stem cell properties of Human Dental Pulp stem cells.J Dent Res 2002;81(8),531-535.

5. Sunil PM, Manikandhan R, Muthu MS, Abrahum S. Stem cell therapy in oral and maxillofacial region: An overview.2012; 16(1), 58-63.

6. Takahashi K, Yamanka S.Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 2006; 126,663-76.

7.Huang GT, Gronthos S, Shi S. Mesenchymal stem cells derived from dental tissues vs those from other sources, their biology and role in regenerative medicine. J Dent Res. 2009 Sep; 88(9): 792–806.

8. Kawashima N. Characterization of dental pulp stem cells: A new horizon for tissue regeneration. Archives of Oral Biol., 2012 ;(57), 1439-1458.

9. Brar GS, Toor RSS. Dental stem cells: Dentinogenic, osteogenic and neurogenic differentiation and its clinical cell based therapies. Indian J of Dental Research 2013; 23(3), 393-397.

10. Miura M, Gronthos S, Zhao M, Lu B, Fisher LW, Robey PG et al. SHED: Stem cells from human exfoliated deciduous teeth. Proc Natl Acad Sci USA 2003;100:5807-12.

11. *Seo BM, Miura M*, *Gronthos S*, Bartold PM, Batouli S, Brahim J, et al. (2004). Investigation of multipotent postnatal stem cells from human periodontal ligament.Lancet 2004:364:149-55.

12. *Volponi AA, Pang Y*, & Sharpe PT. Stem cell-based biological tooth repair and regeneration. Trends in Cell Biol. 2010:20(12):715-722.

13. *Morsczeck C*, *Gotz W*, Schierholz J, Zeilhofer F, Kühn U, Möhl C, Sippel C, Hoffmann KH (2005) Isolation of precursor cells (PCs) from human dental follicle of wisdom teeth.Matrix Biol 2005;24:155-165.

14. Sonoyama W, Liu Y, Yamaza T. Characterization of the apical papilla and its residing stem cells from human immature permanent teeth: A pilot study. J Endod. 2008; 34:166-71.

15. Huang GT, Sonoyama W, Liu Y et al. The hidden treasure in apical papilla: the potential role in pulp/dentin regeneration and bio root engineering. J Endod 2008;34:645-51.

16. *Nam H*, *Lee G*. Identification of novel epithelial *stem cell*-like cells in human deciduous dental pulp. Biochem Biophys Res Commun.2009 ;14,386(1), 135-9.

17. Linares AI, Vico RM, Borrego ES, Fernandez AM, Reina ES, Mendoza AM.Stem cells in current pediatric dentistry practice. Archives of Oral Biol 2013; 58(3), 227-238.

18. K. Iohara, M. Nakashima, M. Ito, M. Ishikawa, A. Nakasima, and A. Akamine Dentin Regeneration by Dental Pulp Stem Cell Therapy with Recombinant Human Bone Morphogenetic Protein 2.J Dent Res 2004; 83: 590-595,

19. Atari M, Ballé-Serrano J, Gil-Recio C, Giner-Delgado C, Martínez-Sarrà E, García-Fernández DA

et al. The enhancement of osteogenesis through the use of dental pulp pluripotent stem cells in 3D. Bone. 2012 Apr; 50(4):930-41

20. Mao JJ, Giannobile WV, Helms JA, Hollister SJ, Krebsbach PH, Longaker MT, et al. Craniofacial tissue engineering by stem cells. J Dent Res. 2006;85:966–79.