Review Article

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A REVIEW ON DENTAL STEM CELLS AND TISSUE ENGINEERING: CONNECTING THE LINK

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ABSTRACT

The regeneration potential of human tissue is very limited. With time and continuous research, science has reached a new level where we are almost capable of regenerating lost tissue. Adult stem cells are multipotent and can be induced experimentally to differentiate into various cell lineages. Hence, such cells play a role in achieving the promise of tissue regeneration. As of now, tests and trials are happening worldwide, but this advancement is still to be implemented in everyday practice. This article is our attempt to bring together all the relevant facts about stem cells, their use in tissue engineering and its application; through reviewing the key articles published so far on this topic so as to gather all the needful information about this utterly vast and complex matter. This review will also update the existing and current stem cells application in engineering tissue structures and its future prospects in the field of dentistry.

Keywords: Stem cells; Tissue engineering; Tissue Regeneration; Dental

INTRODUCTION

The regeneration of lost tissues has been of interest to mankind for many years; however, the subject of regenerative dentistry has gained great momentum only in the recent past. The various clinical trials on stem cells that are being conducted along with the increasing knowledge of regeneration of oral tissues are likely to pave a way for great advancements in the field of tissue engineering. The majority of structures in the oral cavity including the teeth are derived from mesenchymal cells (MCs). Development of any such structure includes migration of MCs from the neural crest, differentiation and subsequent participation in morphogenesis. Almost all craniofacial structures, such as bone, cartilage, ligaments, cranial structures, musculature, tendons, the periodontium, and the teeth develop by this process.¹ After birth, mesenchymal cells are referred to as the mesenchymal stem cells (MSCs). In the adults, MSCs maintain the physiological tissue turnover time and in the event of injury or disease, these cells differentiate to launch the event of tissue regeneration.² New approaches in tissue engineering are being developed to reconstruct and restore the function of the damaged or diseased organ or tissue. The term “tissue engineering” was coined in 1993 by Langer and Vacanti³ to describe the process by which tissues and organs are regenerated by cell transplantation with or without a scaffold. Stem cells are defined by their capacity to produce daughter cells with different and more restricting properties. In human postnatal dental tissue, five different sources of mesenchymal stem cells (MSCs) are known which include the dental pulp, periodontal ligament, exfoliated deciduous teeth, dental follicle and root apical papilla.⁴⁻⁸

Multipotency is a unique property of such cells to form multiple cell types. The stem cells, under suitable conditions, have wide differentiation potential with the capability to develop into almost any cell in the body.⁹

Adult stem cells derived from dental tissue

Stem cells have been derived from different parts of erupting, existing or exfoliated deciduous as well as permanent teeth. All these cells have been believed to share a common lineage of being derived from the neural crest.

Figure 1: Different sources of the human dental tissue-derived mesenchymal stem cells

DFPCs: dental follicle progenitor cells; ABMSCs: alveolar bone derived mesenchymal stem cells; GMSCs: gingival mesenchymal stem cells; DPSCs: dental pulp stem cells; SCAP: stem cells from the apical papilla; PDLSCs: periodontal ligament stem cells; SHED: stem cells from human exfoliated deciduous teeth; TGPCs: tooth germ progenitor cells. (Adapted from Chalisserry *et al*¹⁰)

Dental pulp stem cells Putative stem cells from the tooth pulp have been identified.¹¹ They were isolated for the first time ever in the year 2000 by Gronthos *et al.*¹² The possibility that tooth pulp might contain stem cells was first suggested by the observation that severe tooth damage that penetrates both enamel and dentin and into the pulp stimulates a natural repair process, by which new odontoblasts are formed, which produce new dentin to repair the lesion.¹³ Further characterizations revealed that Dental Pulp Stem Cells (DPSCs) were also capable of differentiating into other mesenchymal cells *in vitro* such as odontoblast, adipocyte, chondrocyte and osteoblast.¹⁴ DPSCs can be isolated both from permanent as well deciduous dentition, followed by *in vitro* expansion, and then applied for various tissue engineering purposes such as repair of bone defects.¹⁵

Stem cells from human exfoliated deciduous teeth (SHED)

Stem cells isolated from the pulp of human exfoliated deciduous teeth have the capacity to induce bone formation, generate dentine and differentiate into other non-dental mesenchymal cell derivatives *in vitro*.¹⁶ Studies using SHED as a tool in dental pulp tissue engineering *in vivo*, where the infected pulp was removed and replaced with stem cells, have revealed that the resultant tissue has architecture and cellularity closely resembling that of dental pulp, a tissue important for tooth vitality.¹⁷ SHED have been considered to be one of the best cell source candidates for the reconstruction of alveolar cleft owing to less surgical as well as psychological invasions in nature during the sampling and transplantation of these the cells.¹⁸

Figure 2: Dental pulp engineered using SHED (adapted from Cordeiro *et al*¹⁹)

Figure 3: Normal pulp from an extracted control tooth (adapted from Cordeiro *et al*¹⁹)

Periodontal ligament stem cells

The Periodontal ligament is a fibrous connective tissue that contains specialized cells locked between the bone like cementum and the inner wall of the alveolar bone socket. The PDL has long been recognized to contain a population of progenitor cells.²⁰ Recent studies have identified a population of stem cells from the human periodontal ligament capable of differentiating along-with mesenchymal cell to produce tissue rich in collagen.²¹ The periodontal ligament stem cells can easily differentiate into

osteogenic and adaptogenic cells *in vitro*, thus aiding in periodontal regeneration *in vivo*.²² Direct transplantations of the periodontal ligament stem cells into the area of periodontal defect has been stated to result in periodontal regeneration.²²

Figure 4: Periodontal ligaments attached to the root surface of an extracted third molar (adapted from Seo *et al*²⁰)

Figure 5: Single colony formed from the cell clusters derived from periodontal ligaments (adapted from Seo *et al*²⁰)

Root apical stem cells

A unique population of dental stem cells known as stem cells from the root apical papilla is located at the tip of growing tooth roots. The apical papilla tissue is only present during root development before the tooth erupts into the oral cavity. Such stem cells have the capacity to differentiate into odontoblast and adipocytes. Most human tissue from early in their development are not clinically available for stem cell isolation; however, because roots develop postnatal, stem cells from root apices are accessible in dental clinical practice from extracted wisdom teeth.²³ Since apical papilla acts as the precursor of radicular pulp, it has been speculated that the root apical stem cells are similar to the stem cells found in the dental papilla, though *in vitro* comparison studies show certain differences.¹⁴

Figure 6: Isolated apical papilla from extracted third molar (adapted from Sonoyama *et al*⁸)

Dental follicle stem cells

The dental follicle is a loose ectomesenchyme derived connective tissue sac surrounding the enamel organ and dental papilla of the developing tooth germ before eruption. It is believed to contain the progenitor for cement oblast, PDL and osteoblast. 24

Oral mucosa derived stem cells

These stem cells comprise of either gingiva or oral epithelial stem cells. The oral epithelial stem cells are unipotent, further differentiating into epithelial cells *in vivo*. However, *in vitro* studies report the development of stratified oral mucosal graft that can be utilized in oral grafting procedures. Gingival stem cells, on the other hand, are multi-potent, abundant and easy to isolate, which renders their use in clinical practice quite viable. 25

Human periosteum derived stem cells

These stem cells have the capacity to give rise to chondrogenic, odontogenic, myogenic, as well as adaptogenic cells and are thus used in case of large orofacial defects as they produce cortical bone. 25

Stem cells derived from salivary glands

These cells not only have the capacity to give rise to ductal and acinar cells but retain the potential to produce amylase and mucin as well. They can be highly beneficial to patients undergoing therapy which leads to decreased salivary gland function. 25

Stem cell banking

Several dental stem cell banks have offered to harvest and store stem cells that may potentially enable the use of the stem cell for therapy in the future for treatment of disease and regenerative therapy. Dental pulp stem cells can be collected and isolated from patients at any age, preferably from young adults. 9 Though it is still in its early years, the tooth stem cell banking is growing rapidly. Various countries such as USA, Japan, Norway and China have established tooth stem cell banks. In India, tooth banks such as “Stemade” and “Storeyourcells” are involved in banking dental stem cells. 10

Scaffold

Scaffolds are porous, degradable structures fabricated from either natural material such as collagen or fibrin or synthetic polymers. The principle for the design of tissue engineering scaffolds remains clear. The scaffold should mimic the structure and biologic function of the native extracellular matrix as much as possible both in terms of chemical and physical structure. The main aim of tissue engineering is the regeneration of tissue or organ that can be put to use.

Tissue engineering

Tissue engineering is an emerging biotechnological area which combines various aspects of medicine, cell, molecular biology and engineering for the purpose of regenerating, repairing or replacing diseased tissue. 26 Tissue engineering is emerging as a significant potential alternative or complimentary solution to Tissue and Organ failure as a result of injury, or other type of damage, whereby tissue and organ failure is addressed by implanting natural, synthetic or semi synthetic tissue and organ

mimic that are either fully functional or that grows into required functionality. 27 The young but growing field of tissue engineering is truly a multidisciplinary one, where living cells are harvested using stem cells, grown in the laboratory and stimulated to form specific tissues that mimic the complex structures and physiological behavior of natural tissue.

Applications of tissue engineering

Tissue Engineering in Orthopedics

Musculoskeletal disorders have become one of the major health concerns because of aging and increased occurrence of sports related injury. Among other things, engineering of bone, cartilage and ligament has been the prime focus of tissue engineers. Autogenous grafts and allogeneous grafts have been used for many years, but various problems such as failure of complete resorption of autologous bone, difficulty in shaping the bone graft to fill the defect and lack of sufficient parent material greatly limit their potential as bone substitutes. 28,29

Tissue Engineering in Skin

Skin is the body's largest organ and the body's first line of defense against disease causing organism. Human Cadaver skin has been commonly used as a temporary covering, but insufficient supply, epidermal sloughing, immune reaction and disease transmission are the major limitation in this case. Autologous graft is also quite popular but though it provides timely wound coverage, it may lead to painful donor sites which are slow to heal and be unsuccessful due to underlying deficiencies. Tissue engineering is expected to have a great impact on wound repair. Skin is a difficult organ to transplant because of its strong immune defense system. 30,31

Cardiovascular tissue engineering

Vascular grafting is a common surgical procedure for advanced cardiac disease, but it has significant limitations and complications. Arterial conduits have restricted dimensions and are limited in supply while venous conduits have various degenerative alterations that can lead to aneurysm formation during high pressure arterial circulation. Allografts are problematic because of the high rate of rejection. 32

Treatment of heart ailment is also difficult because heart lacks the ability to regenerate, as it lacks the population of proliferating cells. There are also no stem cells and injury to the myocardium results in an irreversible loss of cells. Cardiovascular tissue engineering is focusing on the development of blood vessels, heart valves and myocardium. Tissue engineering may also be used to improve the function of native tissue, such as congestive heart failure. 33

Dental Tissue Engineering

Through Dental tissue engineering the hopes is to regenerate dento alveolar tissue including alveolar bone, periodontal ligament, dentin, enamel and perhaps a whole new tooth. 34,35 Recent isolation of stem cells from the human periodontal ligament represents potential therapeutically viable tissue forming cells for its regeneration. Though regeneration of whole new organs like teeth are certainly more demanding but by understanding the genetic control of the key process that form teeth in the embryo, the development of the teeth could be recreated in the mouth of a patient.

DISCUSSION

It is clear that there is a need of clinical studies for such treatment, vast patient flow and an obvious consideration for financial resources. Dental stem cells are viable source of mesenchymal stem cells, which have multiple clinical utilizations. The efficiency and quality of tissue repair using dental stem cells, in relation to the cost involved will remain a matter of concern. The molecular basis of this phenomenon needs to be investigated because it might provide a paradigm for increasing stem cell numbers in cultures of other cell type.³⁶ Promises of tissue engineering are great, but there exist major challenges that must be met for this new field to reach its potential application. Although clinical trials have been conducted and tooth stem cell banking has been established, the beneficial aspects for patients need to be taken into consideration. A critical challenge in tissue engineering is to regenerate tissue that grow or remodel in concert with the changing needs of the human body. Another principal requirement for tissue engineered *in vitro* is the sufficient supply of oxygen and nutrients. A solution to this may be the use of engineered scaffolds.³⁷

CONCLUSION

Taken together, these recent findings clearly indicate the role of dental and periodontal structures in stem cell studies. Also, our review of recent studies on tissue engineering is clear indicative of the use of dental stem cells in tissue engineering. The identification of several types of epithelial and mesenchymal stem cells in the tooth and the knowledge of molecules involved in stem cell fate is a significant achievement. However, many problems remain to be addressed before considering the clinical use of these technologies.

REFERENCES

1. J.J. Mao *et al.* Craniofacial Tissue Engineering by Stem Cells. *J Dent Res* 2006; 85(11): 966-979.
2. Caplan AI. Mesenchymal stem cells. *J Orthop Res* 1991; 9: 641-650.
3. Langer R, Vacanti JP. Tissue engineering. *Science* 1993; 260(5110): 920-926. DOI: 10.1126/science.8493529.
4. Gronthos S, Mankani M, Brahimi J, Robey P, Shi S. Postnatal human dental pulp stem cells *in vitro* and *in vivo*. *Proc Natl Acad Sci USA* 2000; 97: 13625-13630.
5. Seo BM, Miura M, Gronthos S, Brahimi J, Young M, Robey PG, Wang CY, Shi S. Investigation of multipotent postnatal stem cells from human periodontal ligament. *Lancet* 2004; 364: 149-155.
6. Miura M, Gronthos S, Zhao M, Lu B, Fisher LW, Robey PG, Shi S. SHED: Stem cells from human exfoliated deciduous teeth. *Proc Natl Acad Sci USA*. 2003; 100: 5807-5812.
7. Yao S, Pan F, Prpic V, Wise GE. Differentiation of stem cells in the dental follicle. *J Dent Res* 2008; 87: 767-771.
8. Sonoyama W, Liu Y, Yamaza T, Tuan RS, Wang Shi, Huang GT. Characterization of the apical papilla and its residing stem cells from human immature permanent teeth: a pilot study. *J Endod* 2008; 34: 166-171.
9. Archana Bhat, Anh D Le. Craniofacial Tissue Regeneration: Where are we? *CDA Journal* 2009; 37: 799-803.
10. Chalisserry EP, Nam SY, Park SH, Anil S. Therapeutic potential of dental stem cells. *J Tissue Eng*. 2017; 8: 204173141770253.
11. Gronthos S. Post natal human dental pulp stem cells (DPSCs) *in vitro* and *in vivo*. *Proc Natl Acad Sci* 2002; 81: 531-535.
12. Gronthos S, Mankani M, Brahimi J, *et al.* Postnatal human dental pulp stem cells (DPSCs) *in vitro* and *in vivo*. *Proc Natl Acad Sci* 2000; 97(25): 13625-13630.
13. Smith A J, Lesot H. Induction and regulation of crown dentinogenesis: embryonic event as a template for dental tissue repair? *Crit. Rev. Oral Biol. Med* 2001; 12: 425-437.
14. Graziano A. Dental pulp stem cells: A promising tool for bone regeneration. *Stem Cell Rev* 2008; 4: 21-26.
15. Huang GJ, 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; 88(9): 792-806.
16. Miura M. SHED: stem cells from human exfoliated deciduous teeth. *Proc. Natl. Acad. Sci USA*; 2003. p. 75-81.
17. Cordeiro MM. Dental pulp tissue engineering with stem cells from exfoliated deciduous teeth. *J Endod* 2008; 34: 791-796.
18. K. Nakajima *et al.* Biochemical and Biophysical Research Communications 2018; 497: 876-882.
19. Cordeiro MM, Dong Z, Kaneko T, Zhang Z, Miyazawa M, Shi S, *et al.* Dental Pulp Tissue Engineering with Stem Cells from Exfoliated Deciduous Teeth. *J Endod* 2008; 34(8): 962-9. Available from: <http://dx.doi.org/10.1016/j.joen.2008.04.009>
20. Seo BM. Investigation of multipotent postnatal stem cells from human periodontal ligament. *Lancet* 2004; 364: 41-49.
21. Seo B. M., Miura M., Gronthos S., Bartold P. M., Batouli S., Brahimi J., Shi S. Investigation of multipotent postnatal stem cells from human periodontal ligament. *Lancet* 2004; 364: 149-155.
22. Bartold P. M., McCulloch C. A., Narayanan A. S. and Pitaru S. Tissue engineering: A new paradigm for periodontal regeneration based on molecular and cell biology. *Periodontology* 2000; 24: 253-269.
23. Sonoyama W, Liu Y, Fang D, *et al.* Mesenchymal stem cell-mediated functional tooth regeneration in swine. *PLoS One* 2006; 1(1): e79.
24. Handa K. Progenitor cells from dental follicle are able to form cementum matrix *in vivo*. *Connect tissue Res* 2002; 43: 406-408
25. Majid S, Fry RR, Goyal S, Chawla JPS. Stem cells in dentistry: A boon to oral and maxillofacial surgery. *IOSR-JDMS* 2016; 15(1): 62-68.
26. Gronthos S, Mrozik K, Shi S, Bartold PM. Ovine periodontal ligament stem cells: isolation, characterization and differentiation potential. *Calcif Tissue Int* 2006; 79(5): 310-317.
27. Perissidis A. Tissue Engineering. *Nat biotechnol* 1999; 17: 508-510.
28. Laurencin CT, Ambrosia AM, Borden MD, Cooper JA. Tissue Engineering: orthopedic applications. *Annu Rev Biomed Eng* 1999; 1: 19-46.
29. Landis WJ, Jacquet R, Hillyer J, Zhang J, Siperko L, Chubinskaya S, Asamura S, Isogai N. The potential of tissue engineering in orthopedics. *Ortho Clin North Am* 2005; 36: 97-104.
30. Philips T. Chronic cutaneous ulcers; etiology and epidemiology. *J Invest Dermatol* 1994; 102: 38S-41S.
31. Falang V. Chronic wounds: Pathophysiological and experimental considerations. *J invest Dermatol* 1993; 100: 721-725.
32. Niklason LE, Gao J, Abbott WM, Hirschi KK, Houser S, Marini R, Langer R. Functional arteries grown *in vitro*: Science 1999; 284: 489-493.

33. Dorfman J, Duong M, Zibaitis A, Pelletier MP, Shum-Tim D, Li C, Chiu RC. Myocardial tissue engineering with autologous myoblast implantation: J Thorac Cardiovasc Surg 1998; 116: 744-751.
34. Kaigler D, Mooney D. Tissue engineering's impact on dentistry: J Dent Educ 2001; 65: 456- 462.
35. Thesleff I, Tummers M. Stem cells and tissue engineering: prospects for regenerating tissues in dental practice. Med Princ Pract 2003; 12 (suppl 1): 43–50.
36. Ana Angelova Volponi, Yvonne Pang, Paul T Sharpe. Stem cell based biological tooth repair and regeneration 2010; 20-206(12-6): 715-722.
37. Parveen S, Krishnakumar K, Sahoo SK. New Era in Health Care: Tissue Engineering; 2006. JSRM.1.1.e1-e-19

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