I J Pre Clin Dent Res 2014;1(4):93-99
October-December


International Journal of Preventive & Clinical Dental Research

# Dental Stem Cells & their role in Regenerative Therapies: A Systematic Review

**Abstract**

Stem cells have a capacity for self-renewal and capability of proliferation and differentiation to various cell lineages. They can be classified into embryonic stem cells (ESC) and non-embryonic stem cells (non-ESC). Mesenchymal stem cells (MSC) have shown promising results in several animal studies and clinical trials. ESCs also have a great potential but their use is still limited due to ethical and scientific considerations. The use of amniotic fluid derived cells, umbilical cord cells, fat and skin tissues and monocytes might be an adequate "ethically pure" alternative in future. Stem cells can be used to augment the body's own regenerative potential. This article reviews the role of dental stem cells in regenerative medicine.

**Key Words**

Stem cells; mesenchymal stem cells; clinical trials; tissue engineering; regenerative medicine

Manish Gupta,[1] Amit Mahajan,[2] Sunil D. Christopher,[3] Sumit Agarwal,[4] Nishant Singh,[5] Ankita Raj[6]

[1]Senior Lecturer, Department of Oral and Maxillofacial Surgery, Rama Dental College, Hospital and Research Centre, Kanpur, Uttar Pradesh, India
[2]Senior Lecturer, Department of Endodontics and Conservative Dentistry, Rama Dental College, Hospital and Research Centre, Kanpur, Uttar Pradesh, India
[3]Professor & Head, Department of Oral and Maxillofacial Surgery, Rama Dental College, Hospital and Research Centre, Kanpur, Uttar Pradesh, India
[4]Reader, Department of Oral and Maxillofacial Surgery, Rama Dental College, Hospital and Research Centre, Kanpur, Uttar Pradesh, India
[5]Reader, Department of Oral and Maxillofacial Surgery, Rama Dental College, Hospital and Research Centre, Kanpur, Uttar Pradesh, India
[6]Senior Lecturer, Department of Oral and Maxillofacial Surgery, Rama Dental College, Hospital and Research Centre, Kanpur, Uttar Pradesh, India

## INTRODUCTION

The science of tissue engineering and regenerative medicine has seen tremendous development especially in the field of stem cell research. Tissue engineering involves the development of functional tissue with the ability to replace missing or damaged tissue. This may be achieved either by transplanting cells seeded into a porous material or scaffold having open pores or by relying on ingrowth of cells into such a material, which in both cases develops into normal tissue [1]. Today stem cell biology is one of the most exciting fields of research with promising possibilities in all spheres of medical science. The term stem cell was proposed for scientific use by Russian histologist Alexander Maksimov in 1909. He was the first to suggest the existence of hematopoietic stem cells (HSC) with the morphological appearance of a lymphocyte, capable of migrating throughout the blood to micro ecological niches that would allow them to proliferate and differentiate.[2]

## CONCEPT OF STEM CELLS

Stem cells (SCs) are undifferentiated cells capable of self-renewal and differentiation into multiple functional cell types. These cells can widely be used in injury to promote repair and tissue regeneration.[3] All stem cells, regardless of their source, have three general properties, which make them different from other cells in the body:

a) **Are unspecialized/ undifferentiated**- one of the fundamental properties of a stem cell is that it does not have any tissue specific structures that allow it to perform specialized functions. However unspecialized stem cells can give rise to specialized cells, including heart muscle cells, blood cells or nerve cells.

b) **Can give rise to specialized cell types**- When unspecialized stem cells give rise to specialized cells, the process is called differentiation.
c) **Are capable of dividing and renewing themselves**- unlike muscle cells, blood cells or nerve cells, which normally do not replicate themselves, stem cells may replicate many times. If the resulting stem cells continue to be unspecialized, like the parent stem cells, the cells are said to be capable of long term self-renewal.

Human stem cells can be divided into three main categories: embryonic, germinal and somatic (Fig. 1). Embryonic stem cells (ESCs) originate from the inner cell mass of the blastocyst. ESCs are omnipotent and have indefinite replicative life span, which is attributable to their telomerase expression.[4] Germinal stem cells (GSCs) are derived from primary germinal layers of embryo. They differentiate into progenitor cells to produce specific organ cells. Somatic/adult stem cells are progenitor cells as they are less totipotent i.e. less replicative life span than ESCs. They exist in mature tissues such as haematopoietic, neural, gastrointestinal and Mesenchymal tissues. The existence of stem cells within tooth was reported for the first time in 2000 when Songtao Shi group isolated cells with high proliferative potential for self-renewal from adult human dental pulp that are capable to develop into multiple cell lineages in vitro.[5] So far five different human dental-tissue-derived stem/progenitor cells have been isolated and characterized (Fig. 1).[6] These five sources are listed below:

**1. Dental Pulp Stem Cells (DPSCs)**

DPSCs were the first cells isolated from dental pulp of third molars (wisdom teeth) from adults (19-29 years of age). The pulp tissue was gently separated from the crown and root and degradation was performed using digestive enzymes (collagenase and dispase). After filtration and washing in growth medium single-cell suspensions were seeded into culture plates. Thus isolated cells are able to adhere to plastic and form fibroblast-like colonies, proliferate extensively, form odontoblasts and possess the capacity to differentiate in vitro into various cell types e.g. osteoblast, adipocytes or neural-like cells under stimulation in cultured medium.[7] The best known example of an adult stem cell is bone marrow stromal /stem cell (BMSCs), which is considered to be the gold standard in the assessment of in vitro differentiation of mesenchymal stem cells. Newly discovered type of progenitor and stem cells are compared with them. DPSCs occurred at an apparently higher frequency in comparison to the BMSCs. The proliferation analysis revealed that human DPSCs have faster population doubling time than BMSCs in vitro. Shi group studies demonstrated that DPSCs and BMSCs share a similar pattern of protein expression.[8] Access to the DPSCs collection site is relatively easy. As DPSCs can be extracted with high efficiency, exert extensive differentiation ability, and demonstrate interactivity with biomaterials DPSCs are considered ideal for tissue reconstruction.

**2. Apical Papilla Derived Stem Cells (APDCs) also called stem cells from apical papilla (SCAP)**

The physical and histological characteristic of the dental papilla located at the apex of developing human permanent teeth has recently been described and this tissue has been termed apical papilla. This tissue is loosely attached to the apex of the developing root and can be easily detached. A population of stem cells isolated from human teeth was found at the tooth root apex. These cells are called stem cells from apical papilla (SCAP) and have been demonstrated to differentiate and exhibit higher rates of proliferation in vitro than do DPSC. There is an apical cell-rich zone lying between the apical papilla and the pulp. Importantly, stem /progenitor cells were located in both dental pulp and the apical papilla, but they have somewhat different characteristics.[9] Mesenchymal cells within the dental papilla are responsible for production of dentin and pulp. First report about new class of cells with high proliferation activity and multilineage differentiation potential obtained from immature tip of the apical papilla of human developing third molars was published by Abe *et al*.[10] They are capable to form odontoblast-like cells and produce dentin in vivo and can serve as a cell source of primary odontoblasts for root dentin formation.[11]

**3. Periodontal Ligament Stem Cells (PDLSCs)**

The mesenchyme of the dental sac condenses to form the periodontal ligament (fiber). Periodontal ligament (PDL) is a tissue that connects cementum and alveolar bone to maintain and support teeth in situ. PDL perform supportive, sensory, nutritive, regenerative and homeostatic functions. The PDL has long been recognized to contain a population of progenitor cells. PDLSCs were first isolated by Seo et al, and were found to be capable of differentiating

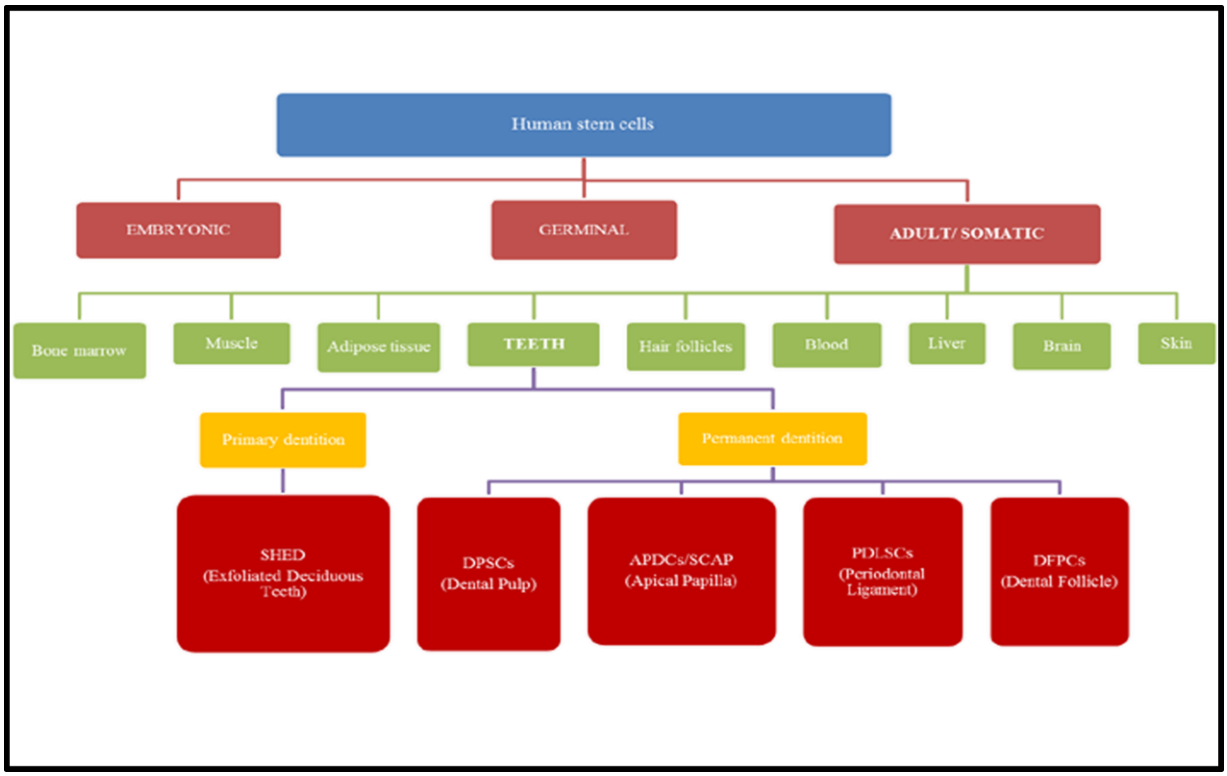


Fig. 1: Stem Cells In Dental Tissues

into cementoblast-like cells, adipocytes and collagen forming cells.[12]

**4. Dental Follicle Progenitor Cells (DFPCs)**

Dental follicles comprise the neural crest, which is derived from ectomesenchymal tissue surrounding the developing tooth germ. Human dental follicles play an important role in tooth eruption by regulating osteoclastogenesis and osteogenesis. After tooth eruption, the dental follicle differentiates into cells of the periodontium, including alveolar osteoblasts, the PDL, fibroblasts and cementoblasts. The pluripotency of DFSCs has also been demonstrated. Dental follicle cells can be easily isolated after wisdom tooth extraction. Third molar is very often extracted during orthodontic therapy or to avoid inflammation, so dental follicle, like other parts of third molars, is commonly discarded as medical waste. Thus third molars could be a practical cells source for potential therapeutic applications. The existence of progenitor/stem cells within dental follicle was reported for the first time in 2002 [13]. DFPCs can differentiate toward a cementoblast, osteoblast, periodontal ligament, adipogenic, osteogenic and neuronal lineage. Tsuchiya et al suggest that DFSCs potential for bone formation is similar to BMSCs.[14]

**5. Stem Cells from Exfoliated Deciduous Teeth (SHED)**

At about 7 years of age, the process of replacement of 20 deciduous teeth for 32 permanent teeth begins. Unexpectedly, Miura et al. isolated a distinctive population of multipotent stem cells from the remnant pulp of exfoliated deciduous teeth.[15] These cells have the capacity of inducing bone formation, generate dentin and differentiate into other non dental mesenchymal cell derivatives in vitro. SHED exhibit higher proliferation rates, increased population doublings, in addition to osteoinductive capacity in vivo and an ability to form sphere-like clusters. However, unlike DPSCs, they are unable to regenerate complete dentin/pulp-like complexes in vivo.[16] With the osteoinductive potential, SHED can repair critical sized calvarial defects in mice with substantial bone formation.[17] Given their ability to produce and secrete neurotrophic factors, dental stem cells may also be beneficial for the treatment of neuro-degenerative diseases and the repair of motor neurons following injury. Because children naturally lose deciduous teeth, there are multiple opportunities to harvest this type of stem/progenitor cells in an almost painless and minimally invasive procedure. Thus, exfoliated teeth can be a unique resource for stem-cell transplantation in regenerative dentistry. Besides, in

the future, the possibility to bank these cells may provide sources for both allogenic and autologous cell replacement later when required.

## ROLE OF DENTAL STEM CELLS IN REGENERATIVE MEDICINE

### 1) DENTAL PULP REGENERATION

Efforts to induce tissue regeneration in the pulp space have been a long search. In 1962, Ostby proposed inducing haemorrhage and blood clot formation in the canal space of mature teeth in the hope of guiding the tissue repair in the canal. [18] However, the connective tissue that grew into the canal space was limited and the origin of this tissue remains unproved. Regenerative Endodontics represents a new treatment modality that focuses on reestablishment of pulp vitality and continued root development. This clinical procedure relies on the intracanal delivery of a blood clot (scaffold), growth factors (possibly from platelets and dentin), and stem cells.[19] These findings provide the biological basis for the participation of stem cells in the continued root development and regenerative response that follow this clinically performed procedure. As DPSC have the potent dentinogenic ability, they could be used for the vital pulp therapy. When DPSC are transplanted alone or in combination with BMP2 in the pulp cavity, these stem cells can significantly promote the repair and reconstruction of dentin-pulplike complex Prescott *et al*., placed the triad of DPSC, a collagen scaffold and DMP1 in the simulated perforation sites in dentin slices and then transplanted the recombination subcutaneously into the nude mice. After 6 weeks of incubation, well-organized pulplike tissue could be detected in the perforation site.[20] Cordeiro *et al.,* demonstrated that SHED/scaffold recombination prepared within human tooth slices also have the potential to form dental pulp-like structures.[21] The future development of regenerative endodontic procedures will require a comprehensive research program directed at each of these components and their application in the clinical practice.

### 2) BONE REGENERATION

Bone defects due to congenital and acquired causes such as trauma, surgery and tumors may lead to extensive bone loss and defects which require transplantation of bone tissue or substitutes to restore structural integrity and function. The current use of autologous cancellous bone grafting has its limitations especially in osteoporotic, paediatric and oncological patients and its harvest results in additional morbidity to the donor site, leading to pain, haematoma, or infection.[22] Allogenic bone has been used but this has minimal osteoinductive capacity, is possibly immunogenic, has a potential for disease transmission and is minimally replaced by new bone.[23] Most of the experimental and clinical evidence to date is supportive of the efficacy of MSCs in enhancing bone formation and healing of bone defects. Large animal models showed that the treatment of large bone defects with the application of MSCs on an osteoconductive carrier can be used successfully.[24] Kenji Ito *et al*., have studied osteogenic potential of effective bone engineering using DPSCs , bone marrow cells & periosteal cells for osseointegration of dental implants. Study concluded that DPSCs showed the highest osteogenic potential and may be useful cell source for tissue engineered bone around dental implants.[25] DPSCs showed differentiation profiles similar to those showed during bone differentiation and this event make them very interesting as a model to study osteogenesis and the relationship with scaffolds.[26] Such mesenchymal stem cells are extensively used in surgical repair/regeneration, as they instigate from neural crest and migrate, differentiate, participate in morphogenesis to give rise to structures of craniofacial region including muscle, ligament, cartilage, bone, periodontal membrane and teeth.[27]

### 3) CARDIAC REPAIR

Regardless of the recent advances in prevention and treatment of myocardial infarction (MI), it remains one of the major causes of mortality worldwide. In this perspective, cardiomyocytic differentiation of DPSCs has been studied by various researchers. It was found that DPSCs can help cardiac repair after myocardial infarction. In an experimental model of acute myocardial infarction, the left coronary artery was ligated in nude rats. Then DPSCs were transplanted to the border of the infarction zone. Four weeks after transplantation, evidence of cardiac repair was noted with improved cardiac function, increase in the number of vessels and a reduction in infarct size. The cardiac repair occurred in the absence of any evidence of DPSCs differentiation into cardiac or smooth muscle cells. This suggests that DPSCs induced cardiac repair due to its secretion of different growth factors and cytokines such as vascular endothelial growth factor, insulin-like growth factor- 1 and -2 and stem cell factor, which helped in inducing angiogensis and cardiac regeneration at the infarction zone.[28]

Therefore, it seems that DPSCs have the potential to be used as a novel and alternative source for treatment of not only dental but also some other ischemic diseases.

**4) NEURAL REGENERATION**

Several studies have shown that DPSCs are competent of provoking long term regeneration of nerves in damaged spinal cord. Apel *et al*., potentially investigated the neuro‑protective effect of DPSCs *in vitro* models of Alzheimer's and Parkinson's disease.[29] They also obtained DPSCs from adult rat incisors by systematic isolation and were added to the neuron cultures two days prior to the neurotoxin treatment. It was also revealed that DPSCs expressed a neuronal phenotype and produced the neurotropic factors like NGF (nerve growth factor), GDNF (Glial cell derived neurotrophic factor), BDNF (Brain derived neurotrophic factor) and BMP2. Also, DPSCs protected primary neurons and helped in the cell viability.[30] In an experiment the DPSCs were transplanted into rats with completely severed spinal cords. It was demonstrated that DPSCs promoted the regeneration of transacted axons by directly inhibiting multiple axon growth inhibitors and by prevention of apoptosis of neurons, astrocytes and oligodendrocytes. The DPSCs also differentiated into mature oligodendrocytes to replace cells that were lost. Later on Almeida *et al*., supported the fact on the basis of their study where they explored the outcomes of human dental pulp stem cells in a mouse model with compressive spinal cord injury.[31]

**5) IMPLICATIONS FOR CANCER TREATMENT**

At present, the cancer treatment is targeted at its proliferation potential and its ability to metastasise, and hence the majority of treatments are targeted at rapidly dividing cells and at molecular targets that represent the bulk of the tumour. This may explain the failure of treatments to eradicate the disease or the recurrence of the cancer. Although current treatments can shrink the size of the tumour, these effects are transient and usually do not improve patient's survival outcomes.[32] For tumours in which the cancer stem cells play role, three possibilities exist. First, the mutation of normal stem cells or progenitor cells into cancer stem cells can lead to the development of the primary tumour. Second, during chemotherapy, most of the primary tumour cells may be destroyed but if cancer stem cells are not eradicated, they become refractory cancer stem cells and may lead to recurrence of tumour. Third, the cancer stem cells may emigrate to distal sites from the primary tumour and cause metastasis.[33] Theoretically, identification of the cancer stem cells may allow the development of treatment modalities that target the cancer stem cells rather than rapidly dividing cells in the cancer. This may cure the cancer as the remaining cells in the cancer growth have limited proliferative capability. Although the idea of the therapies focused on the cancer stem cells may look exciting, targeting the cancer stem cells may not be easy. The cancer stem cells are relatively quiescent compared to other cancer cells and do not appear to have the hyper-proliferation signals activated such as tyrosine kinase. These make the cancer stem cells resistant to the toxicity of the anti-cancer drugs, which traditionally target the rapidly dividing cells. Much of the research is now focused on targeting the essential genes or pathways crucial for the cancer development through the cancer stem cells, with any possible therapies targeted against TICs. Thus, the concept of the cancer stem cells has opened new areas of research in carcinogenesis and future treatment options.

**6) STEM CELL THERAPY FOR DIABETES**

Diabetes is one of the most common chronic degenerative endocrinal diseases which can although be managed clinically with the use of insulin injections, but still it remains an incurable and inconvenient disorder. In the long term it is associated with a number of clinical complications, and there is a desire to see new methodologies to replace defective cells and provide a lasting normality without the need for drug treatment. Significant steps have been made toward the use of stem cell technologies to generate b cells as a potential therapy for patients suffering from diabetes. Embryonic and adult stem cells have been used for the production of insulin producing cells derived from amniotic fluid, bone marrow and adipose tissue.[34] Chen et al. showed that insulin producing cells (IPCs) can be derived from monoclonal and polyclonal DPSCs. Furthermore, when subjected to same IPCs producing protocol, they demonstrated that the insulin yield of polyclonal and clonal DPSCs was higher than that of BMSCs.[35]

**CONCLUSION**

Stem cell therapy is emerging as a revolutionary treatment modality to treat diseases and injury, with wide-ranging medical benefits. There are several

potential aspects of using stem cells in reparative and reconstructive of tissues. Recent studies show that stem cells of dental origin (particularly SHED) appear to have the ability to develop into more types of body tissue than other types of stem cells. This difference opens the door for further more therapeutic applications. . While the promise of the immense scope and magnitude that stem cell therapies will have upon the population will only be fully realized in the future, Dental professionals have realized that the critical time to act is now. But at the same time there are also some safety issues inherent in stem cell therapy. Like any other new technology, it is completely unknown what the long-term effects of such interference with nature could be. Based on the accumulated laboratory and clinical evidence, a road map to establish ''stem-cell-based regenerative medicine'' should thus be presented by authorized organizations as a solid consensus toward the future of dentistry.

**REFERENCES**


1. Atala A, Lanza RP. Methods of tissue engineering. San Diego, CA: Academic Press; 1st Edition, 2002.
2. Ramalho‐Santos M, Willenbring H. On the origin of the term "stem cell". Cell Stem Cell. 2007;1(1):35‐8.
3. Potten CS, Loeffler M. Stem cells: attributes, cycles, spirals, pitfalls and uncertainties. Lessons for and from the crypt. Development. 1990;110:1001-20.
4. Soltysova A, Altanerova V, Altaner C: Cancer stem cells. Neoplasma. 2005:52:435-440.
5. Gronthos S, Mankani M, Brahim J, Robey PG, Shi S. Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. Proc Natl Acad Sci. 2000;97:13625-13630.
6. Witkowska-Zimny M. Dental Tissue as a Source of Stem Cells: Perspectives for Teeth Regeneration. J Bioengineer & Biomedical Sci. 2011;S2:006.
7. Gronthos S, Brahim J, Li W, Fisher LW, Cherman N, *et al*. Stem cell properties of human dental pulp stem cells. J Dent Res. 2002;81:531-535.
8. Gronthos S, Mankani M, Brahim J, Robey PG, Shi S. Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. Proc Natl Acad Sci. 2000;97:13625-13630.
9. Sonoyama W, Liu Y, Yamaza T, Tuan RS, Wang S, Shi S, *et al*. Characterization of the Apical papilla and its residing stem cells from human immature permanent teeth: a pilot Study. J Endod. 2008;34:166-171.
10. Abe S, Yamaguchi S, Watanabe A, Hamada K, Amagasa T. Hard tissue regeneration capacity of apical pulp derived cells (APDCs) from human tooth with immature apex. Biochem Biophys Res Commun. 2008;371:90-93.
11. Sonoyama W, Liu Y, Yamaza T, Tuan RS, Wang S, *et al*. Characterization of the apical papilla and its residing stem cells from human immature permanent teeth: a pilot study. J Endod. 2008;34:166-171.
12. Seo BM, Miura M, Gronthos S, Bartold PM, Batouli S, Brahim J, *et al*. Investigation of multipotent postnatal stem cells from human periodontal ligament. Lancet 2004;364:149-155.
13. Handa K, Saito M, Yamauchi M, Kiyono T, Sato S *et al*. Cementum matrix formation in vivo by cultured dental follicle cells. Bone. 2008;31:606-611.
14. Tsuchiya S, Ohshima S, Yamakoshi Y, Simmer JP, Honda MJ. Osteogenic differentiation capacity of porcine dental follicle progenitor cells. Connect Tissue Res. 2010;51:197-207.
15. Miura M, Gronthos S, Zhao M, Lu B, Fisher LW, *et al*. SHED: stem cells from human exfoliated deciduous teeth. Proc Nat lAcad Sci USA. 2003;100:5807-5812.
16. Bawane SS. Dental Pulp Stem Cells: A Promising Tool for Tissue Regeneration. IOSR Journal of Dental and Medical Sciences. 2013;12(2):40-45.
17. Seo BM, Sonoyama W, Yamaza T, Coppe C, Kikuiri T, Akiyama K, *et al*. SHED repair critical-size calvarial defects in mice. Oral Dis. 2008;14:428-434.
18. Nygaard-Ostby B, Hjortdal O. Tissue formation in the root canal following pulp removal. Scand J Dent Res. 1971;79:333-349.
19. Lovelace TW, Henry MA, Hargreaves KM, Diogenes A. Evaluation of the delivery of mesenchymal stem cells into the root canal space of necrotic immature teeth after clinical regenerative endodontic procedure. J Endod. 2010;37:133-138.
20. Prescott RS, Alsanea R, Fayad MI, Johnson BR, Wenckus CS, Hao J, *et al*. In vivo generation of dental pulp-like tissue by using dental pulp stem cells, a collagen scaffold, and

dentin matrix protein 1 after subcutaneous transplantation in mice. J Endod. 2008;34:421-426.
21. 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;34:962-969.
22. 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;88:792-806.
23. Enneking WF, Campanacci DA. Retrieved human allografts: a clinicopathological study. J Bone Joint Surg Am. 2001;83(7):971-86.
24. Goshima J, Goldberg VM, Caplan AI. The osteogenic potential of culture-expanded rat marrow mesenchymal cells assayed in vivo in calcium phosphate ceramic blocks. Clin Orthop. 1991;262:298-311.
25. Kenji Ito. Osteogenic potential of effective bone engineering using dental pulp stem cells, bone marrow stem cells and periosteal cells for osseointegration of dental implants. Int J of Oral & Maxillofac implants. 2011;26(5):947-954.
26. 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.
27. Graziano A, d'Aquino R, Laino G, Proto A, Giuliano MT, Pirozzi G. CD34 + stem cells produce bone nodules in vivo. Cell Prolif. 2008;41:1‑11.
28. D'aquino R, De Rosa A, Laino G, Caruso F, Guida L, Rullo R, Checchi V, *et al*. Human dental pulp stem cells: from biology to clinical applications. J Exp Zool. 2008;310.
29. Apel C, Forlenza OV, de Paula VJ, Talib LL, Denecke B, Eduardo CP, *et al*. The neuroprotective effect of dental pulp cells in models of Alzheimer's and Parkinson's disease. J Neural Transm. 2009;116:71‑8.
30. Zhang W, Walboomers XF, van Kuppevelt TH, Daamen WF, Bian Z, Jansen JA. The performance of human dental pulp stem cells on different three‑dimensional scaffold materials. Biomaterials. 2006;27:5658‑68.
31. de Almeida FM, Marques SA, Ramalho Bdos RS, Rodrigues RF, Cadilhe DV, Furtado D, *et al*. Human dental pulp cells: A new source of cell therapy in a mouse model of compressive spinal cord injury. J Neurotrauma. 2011;28:1939‑49.
32. Reya T, Morrison SJ, Clarke MF, Weissman IL: Stem cells, cancer, and cancer stem cells. Nature. 2001;414:105-111.
33. Jordan CT, Guzman ML, Noble M. Cancer stem cells. N Engl J Med. 2006;355:1253-1261.
34. Lumelsky N, Blondel O, Laeng P, Velasco I, Ravin R, McKay R. Differentiation of embryonic stem cells to insulin‑secreting structures similar to pancreatic islets. Science. 2001;292:1389‑94.
35. Chen M, Lee CH, Li A, Huang M, Shen T, Yang R, *et al*. Insulin producing cells (IPCS) from dental pulp stem/progenitor cells.