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Potential Role of Stem Cells in Endodontic Regeneration: A Brief Review

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Abstract

Tissue engineering is a fast-growing scientific field connecting the principles of medicine, engineering, and biology to replace, restore, or regenerate tissues damaged or lost due to disease and/or trauma. The result of this approach relies on the essential interplay between stem cells, signaling molecules, and scaffolds; known as the classic tissue engineering triad. One component of this triad is Stem cells, which are defined as highly proliferative, unspecialized cells, which have the ability to differentiate into various other types of cells. After a long, extensive search in in vitro laboratory and in vivo preclinical animal experiments, the dental stem cells capable of regenerating the dentin-pulp complex were discovered. Consequently, the biological concept of 'regenerative endodontics' emerged and has highlighted the paradigm shift in the treatment of immature permanent teeth with necrotic pulps in clinical endodontics.

Regenerative endodontics was thus defined as biologically based procedures designed to physiologically replace damaged tooth structures, including dentin and root structures, as well as the pulp-dentin complex. The endogenous stem cells from an induced periapical bleeding and scaffolds using blood clot, platelet rich plasma or platelet-rich fibrin have been utilized in regenerative endodontics. The purpose of this article is to briefly review the role of stem cells in endodontics regeneration.

Keywords: *Tissue engineering, stem cells, Dental follicle precursor cells, Regenerative endodontics.*

Introduction

Tissue engineering has emerged as a major multidisciplinary field that seeks to surprise the benefits of life sciences with engineering principles to repair, regenerate, or enhance the function of defective tissues.1 The success of a tissue engineering approach depends on the appropriate selection of scaffolding material, stem cell type, and bioactive factors, known as the classic tissue engineering triad.1.2 (Figure 1). The stem cells are indispensable for tissue development and regeneration. Their unique properties include self-renewal and multilineage differentiation capacity.3

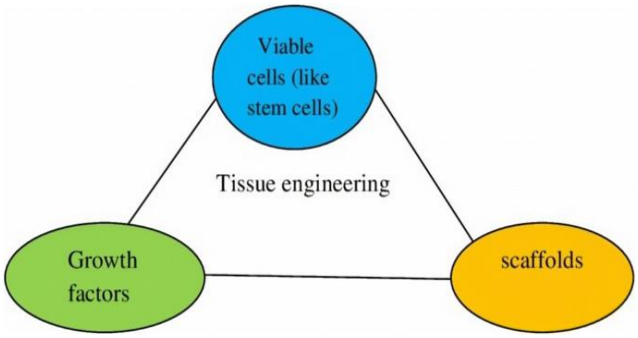

Figure 1: Tissue Engineering Triad

Interest in stem cells within the oral cavity started with the discovery of adult stem cells and their potential to regenerate numerous tissue types. Mesenchymal stem cells (MSCs) are promising adult stem cells with multipotent and self-renewing potential that are obtainable from various tissues and capable of regenerating a wide range of impaired tissues.[4]

Endodontists have been looking for biologically based treatment procedures, which could promote regeneration or repair of the dentin-pulp complex destroyed by infection or trauma for several decades. After a long, extensive search in in vitro laboratory and in vivo preclinical animal experiments, multipotent dental stem cells capable of differentiating into odontoblast-like cells, such as dental pulp stem cells,[2] stem cells from human exfoliated deciduous teeth[4], and stem cells from apical papilla[5], were discovered. Since then, the pulp biologists have tried to take advantage of these multipotent mesenchymal stem cells to regenerate the dentin-pulp complex.[6] Several preclinical animal studies have

demonstrated that it is possible to regenerate the dentin-pulp complex using dental pulp stem cells[7-10]. These preclinical animal studies established the basic concept of application of regenerative endodontics in clinical practice. This review article will provide a general overview on the role of stem cells in endodontics regeneration and readers are encouraged to more specific literature reviews for detailed discussion.

Stem Cells in General

A stem cell is commonly defined as a cell that has the ability to continuously divide and produce progeny cells that differentiate into various other types of cells or tissues. Duailibi *et al* in 2006 defined stem cells as "Quiescent cell populations present in low numbers in normal tissue, which exhibit the distinct characteristic of asymmetric cell division, resulting in the formation of two distinct daughter cells a new progenitor cell and other daughter cell capable of forming a differentiated tissue.[11]

Characteristics of stem cells[12,13]:

a) Totipotency: generate all types of cells, including germ cells.
b) Pluripotency: generate all types of cells except cells of the embryonic membrane.
c) Multipotency: differentiate into more than one mature cell.
d) Self-renewal: divide without differentiation and create everlasting supply.
e) Plasticity: mesenchymal stem cells (MSCs) have plasticity and can undergo differentiation.

Classification of stem cells5:

Stem cells are classified as below: (Table 1)

On the basis of origin	On the basis of source	On the basis of potency
Embryonic stem cells. (ESC) Somatic/ adult/ postnatal/ mesenchymal stem cells (MSC)	**Autologous:** obtained from the same individual **Allogenic:** obtained from donor of same species **Xenogenic:** obtained from donor of another species **Syngenic:** obtained from genetically identical organisms	**Totipotent:** can differentiate into all embryonic and extra embryonic cell types. **Pluripotent:** can differentiate into all types of cells except cells of the embryonic membrane. **Multipotent:** can differentiate into more than one mature cell **Unipotent:** can differentiate into only one type of cells.

The Stem Cells that are found in the pulp of permanent and deciduous teeth are adult multipotent mesenchymal stem Cells. The central region of the pulp contains large nerve trunks and blood vessels.

This area is lined peripherally by a specialized odontogenic area which has **three layers** (from innermost to outermost)[4,8,14].

- **Cell rich zone**; innermost pulp layer which contains fibroblasts and undifferentiated mesenchymal Stem Cells.
- **Cell free zone (zone of Weil)** which is rich in both capillaries and nerve networks. The nerve plexus of Rashkow is located in this zone.
- **Odontoblastic layer;** outermost layer which contains odontoblasts and lies next to the predentin and mature dentin.

Dental Stem Cells and Their Sources

Dental stem cells are mesenchymal stem cells (MSCs) capable of differentiating into at least three distinct cell lineages: osteo/odontogenic, adipogenic and neurogenic. They express various markers including those specific for MSC, embryonic stem cells and neural cells. Up to now, five different types of dental stem cells have been isolated from mature and immature teeth: dental pulp stem cells, stem cells from exfoliated deciduous teeth, periodontal ligament stem cells, stem cells from apical papilla and dental follicle progenitor cells. (Table 1)(Figure 2). All five sources have unique characteristics that may be used in dental tissue engineering including dental, enamel and periodontal tissue regeneration[14]. They could also be used as a promising tool in potential treatment of neurodegenerative, ischemic and immune diseases.

Table 1. Types of dental and Non-dental Stem Cells.

Types of Stem cells – Dental Origin	Types of stem cells - Non-Dental Origin
• Dental pulp stem cells (DPSCs) • Stem cells from exfoliated deciduous teeth (SHED) • Stem cells from apical papillae (SCAP) • Periodontal ligament stem cells (PDLSCs) • Dental follicle precursor cells (DFPCs)	• Stem Cells from Bone Marrow and Adipose Tissue • Induced Pluripotent Stem Cells (iPSCs).

A. Dental pulp stem cells (DPSCs):

The first human dental stem cells, named as dental pulp stem cells (DPSC), were isolated from adult human dental pulp by enzymatic digestion of the impacted third molar tooth pulp tissue14. DPSC show similar characteristics to BM stem cells (BMSC)15. Both populations express similar putative stem cell surface markers: CD44, CD106, CD146, 3G5 and Stro-1, bone-associated markers: alkaline phosphatase, osteocalcin and osteopontin15 and ESC markers: Oct4 and Nanog. Clonogenic cells with

high proliferation potential and long-term self-renewal16. They reside within niches in pulp chambers17 in a stable microenvironment, which depends on the interplay between growth factors, extracellular matrix proteins, receptor molecules, and stem cells18. Research has indicated that dental pulp stem cells have the ability to become odontoblast-like cells and generate ectopic dentin in the subcutaneous tissues of immunocompromised mice19,20. Furthermore, it was shown that DPSCs can differentiate into other non-dental cells, such as osteoblasts, odontoblast, chondrocytes, neuron cells, adipocyte, cardiomyocytes, and insulin-secreting Beta cells18.

A.1 Immature Dental Pulp Stem Cells (IDPSC)

Recently, a subpopulation of DPSC has been described as human Immature Dental Pulp Stem Cells (IDPSC). IDPSC express ESC markers Oct-4, Nanog, SSEA-3, SSEA-4, TRA- 1-60 and TRA-1-81. It is assumed that these cells are precursors to the other two stem cell populations, known as DPSC and Stem cells from Human Exfoliated Deciduous teeth (SHED)19.

B. Stem cells from exfoliated deciduous teeth (SHED):

In 2003, Miura and coworkers isolated a population of multipotent stem cells from the remnant pulp of exfoliated deciduous teeth and showed for the first time that one naturally occurring exfoliated organ contains stem cells. These cells exhibit multipotential differentiation properties and increased cell-population doublings in comparison to DPSCs21. It has been also hypothesized that SHED cells have an extensive proliferation ability higher than DPSCs and MSCs derived from bone marrow, due to being a more immature population22. They can also be reprogrammed into iPSC. SHED were found to express ECS markers Oct4, Nanog, stage-specific embryonic antigens (SSEA-3, SSEA-4), and tumor recognition antigens (TRA-1-60 and TRA-1-81). Cultured SHED also express the cell surface molecules STRO-1 and CD146.

C. Stem cells from apical papillae (SCAP):

Apical papilla refers to the soft tissue at the apices of developing permanent teeth19. SCAP can only be isolated at a certain stage of tooth development, because during maturation and formation of the crown, dental papilla becomes the dental pulp. The apical portion of the dental papilla is loosely attached to the apex of the developing root and it is separated from the differentiated pulp tissue by a cell rich zone8. The dental papilla contains a higher number of ASC compared to the mature dental pulp. These cells located in the tooth root apex. According to the conducted scientific studies, it is believed that SCAP cells are involved in the formation of root dentin, as a source of primary odontoblast23, opposed to DPSCs, which take part in reparative dentin formation, providing replacement odontoblast24. It is hypothesized that a positive result of endodontic treatment of infected immature permanent tooth may be achieved due to the reservoir of SCAP in the apical papilla, and their ability to produce primary

odontoblasts involved in apexogenesis25, 26. SCAP, like other dental stem cells, express STRO-1 and CD146 but they also express CD24.

D. Periodontal ligament stem cells (PDLSCs):

These multipotent cells have the potential to develop into cementoblast-like cells, adipocytes, and chondrogenic cells.27,28 PDLSC show similar characteristic to DPSC and BMSC. PDLSC express the MSC-associated markers such as STRO-1 and CD146 and cementoblastic/osteoblastic markers: alkaline phosphatase, bone sialoprotein, osteocalcin and transforming growth factor-b receptor type I. A tendon-specific transcription factor, scleraxis, is expressed at higher levels in PDLSC than in BMMSC and DPSC. Therefore, using these cells in periodontal regeneration protocols is being considered29.

E. Dental follicle precursor cells (DFPCs):

Localized in a dental sac, also known as a dental follicle, a loose connective tissue that surrounds developing teeth, and also impacted teeth. Some studies have shown that DFPCs can transform into fibroblasts, osteoblasts, periodontal ligament, and cementoblasts30, thus these cells may be useful in regeneration therapies of periodontal tissues31.

Sources of Non-dental Stem Cells

1. Stem Cells from Bone Marrow and Adipose Tissue.

The availability and quality of dental pulp tissue sharply decline with age, nonodontogenic stem cells have been investigated as alternative sources among which stem cells harvested frombone marrow and adipose tissue showed greatest promise owing to their advantageous biological properties and partially shared gene expression profile of various growth factors, extracellular matrix (ECM) proteins, and transcriptional regulators32,33. Noticeably, autologous transplantation of adipose and bone marrow CD31− SP cells with SDF-1 yielded tissues that were morphologically identical to that derived by transplanted pulp CD31− SP cells and all three regenerated tissues possess functional properties similar to normal pulp34. Furthermore, connective tissue formation by nondental cells does notmean that it is functional. Additional evidence is needed to support the feasibility of using adipose and bone marrow tissue-derived stem cells in dentin/pulp regenerative therapies.

2. Induced Pluripotent Stem Cells (iPSCs).

The generating of induced pluripotent stem cells (iPSCs) is a groundbreaking work that revolutionizes the present scenario of regenerative medicine. Compared to other developmentally mature somatic cells that require additional reprogramming factors, oral-derived MSCs, DPSCs, SCAP, and SHED can be more easily reprogrammed into iPSCs at higher efficiencies and are therefore a more attractive

alternative source for iPSCs generation35. These interesting findings demonstrate much potential of iPSCs in future regenerative dentistry research.

Potential Applications of Stem Cells in Dentistry36

The regenerative potential of adult stem cells obtained from various sources, including dental tissues has been of interest for clinicians over the past years and most research is directed toward achieving the following:

• Repair and replacement of bone in craniofacial defects

• Periodontal regeneration

• Regeneration of damaged coronal dentin and pulp

• Regeneration of resorbed root, cervical or apical dentin, and repair perforations

• Whole tooth regeneration.

Objectives of Stem Cells Therapy in Endodontics37,38

The objectives of most researches on stem cells therapy are directed towards achieving the following:

1. Regeneration of pulp dentin complex

2. Regeneration of damaged coronal dentin

3. Regeneration of resorbed root, cervical or apical dentin and repair perforations

4. Whole tooth regeneration.

Role of stem cells in Regenerative Endodontic Therapy

Regenerative endodontics is defined as biologically based procedures designed to physiologically replace damaged tooth structures, including dentin and root structures, as well as the pulp-dentin complex. Owing to the recent advances in the field of biomedicine, tissue engineering, and material science, great progress has been achieved in the development of regenerative endodontics. We are now at a stage of paradigm shift in endodontic treatment from traditional restoration to complete replacement of the compromised dental pulp tissues.

The critical requirements for successful dentin/pulp regeneration are not confined to the morphogenesis of dentin/pulp like tissue but should also be accompanied with angiogenesis and neurogenesis. It must be noted that the deposited dentin like tissues on existing dentin structure are produced by the newly differentiated odontoblasts from the dentinal wall within the root canal space. Currently, potential

strategies dedicated to optimizing stem cell-mediated dentin/pulp regeneration are directed towards two main objectives: firstly, angiogenesis induction and, secondly, the promotion of tissue mineralization. The role of stem cells in endodontic therapy is given below.

Stem Cells in the Dental Pulp:

Both DPSC and SHED cells are originated from the dental pulp, they exhibit significant differences. For instance, during osteogenic differentiation, SHED present higher levels of alkaline phosphatase activity and osteocalcin production, and higher proliferative rate than DPSC539,40. SHED and DPSC cells are capable of regenerating dentin and pulplike tissues in vivo8,22,41. The main limitation is that the fraction of multipotent stem cells in the dental pulp is small39 and the location of these cells are not clearly known, but their phenotype is suggestive of their presence in perivascular niches15.

Stem Cells and Caries-Induced Dentinogenesis:

Dentinogenesis is a unique process, which involves the interaction between odontoblasts, endothelial cells, and nerves42. The dental pulp is a highly vascularized and innervated connective tissue responsible for maintaining the tooth vitality and able to respond to injuries. The odontoblasts, ecto-mesenchymal derived cells, are the first cells to respond to the injury caused by bacterial invasion during caries progression43. The endothelial cells and nerve cells located in the vicinity of the carious lesion modulate the odontoblastic response44,45,46. Primary odontoblasts are induced to secrete a dentin matrix that mineralizes as reactionary dentin in response to shallow caries47,48. This type of tertiary dentin protects the dental pulp from irritants and maintains dental pulp integrity.

Stem Cells and Pulp Angiogenesis:

Vascular endothelial growth factor (VEGF) is a potent inducer of endothelial cell differentiation and survival, and it is the most effective angiogenic factor49. Vascular endothelial growth factor is strongly expressed by odontoblasts and in the subodontoblastic layer in vivo50,51,52. Vascular endothelial growth factor also plays a critical role on the control of vascular permeability during physiological and pathological events49. Vascular endothelial growth factor is potently expressed in dental pulp tissues of teeth undergoing caries-induced pulpitis, by immunohistochemical studies52.

Application of stem cells in regenerative endodontics:

Pulp Implantation: In pulp implantation, replacement pulp tissue is transplanted into clean and shaped root canal systems. The source of pulp tissue may be a purified pulp stem cell line that is disease or pathogen-free or is created from cells taken from a biopsy, that has been grown in the laboratory. The advantage of this system it is relatively easy to grow cells on the filters in the laboratory. The potential

problem associated with the implantation of sheets of cultured pulp tissue is that specialized procedures may be required to ensure that the cells properly adhere to the root canal wall38,53.

Pulp Revascularization:

Pulp necrosis of an immature tooth as a result of caries or trauma could arrest further development of the root, leaving the tooth with thin root canal walls and blunderbuss apices. Regeneration of the pulpal tissue of an infected immature tooth might take place if suitable environment is possible with absence of intrapulpal infection. The pulpal space might become repopulated with mesenchymal cells arising from dental papilla or apical periodontium54. Many case reports have suggested the revascularisation of necrotic root canals by disinfection followed by establishment of bleeding in to the canal system by means of over instrumentation55,56. The common advantages of such type of revascularisations are, firstly, it is technically simple and can be done using available instruments and intra canal medicaments without expensive biotechnology. Secondly, the regeneration of root canal system by using the patient's own blood cells avoids the possibility of immune rejection and transmission of pathogens from the replacement of pulp with a engineered tissue construct38,53.

Whole Tooth Regeneration

Ikeda et al, 2009 reported a successful fully functioning tooth replacement in an adult mouse achieved through the transplantation of bioengineered tooth germ into the alveolar bone in the lost tooth region57. Tooth-like tissues have been generated by the seeding of different cell types on biodegradable scaffolds. A common methodology is to harvest cells, expand and differentiate cells in vitro, seed cells onto scaffolds, and implant them in vivo, in some cases, the scaffolds are re-implanted into an extracted tooth socket or the jaw. This technology was proposed as a model for future organ replacement therapies. A possible risk of some stem cell treatments may be the development of tumors or cancers. For example, when cells are grown in culture (a process called expansion), the cells may lose the normal mechanisms that control growth or may lose the ability to specialize into the cell types you need. Also, embryonic stem cells will need to be directed into more mature cell types or they may form tumors called teratomas. Other possible risks include infection, tissue rejection, complications arising from the medical procedure itself and many unforeseen risks.

Conclusion

Stem cells are critical for the physiology of the dental pulp and for the response of this tissue to injury. These developments provide a peak into the wider aspect of future of regenerative endodontics in retaining the natural dentition which is the prime goal of endodontics. The discovery and understanding of dental pulp stem cells have provided us a better insight into the healing potential of the immature teeth. The use of stem cells in regenerative endodontics is one of the most exciting developments in the field of dentistry especially endodontics. Endodontists are at the fore front in this cutting-edge technology by continuous improvement of knowledge in the fields of pulp biology and tissue engineering. Therefore, endodontist should recognize the potential of the emerging field of regenerative endodontics and the possibility of obtaining stem cells during conventional dental treatments that can be banked for autologous therapeutic use in the future.

References

1. Langer, R. & Vacanti, J. P. Tissue engineering. Science 1993; 260, 920–926.

2. Parveen, S.; Krishnakumar, K.; Sahoo, S.K. New era in health care: Tissue engineering. J. Stem Cells Regen. Med. 2006, 1, 8–24

3. Zhang, Z., Gupte, M. J. & Ma, P. X. Biomaterials and stem cells for tissue engineering. Expert. Opin. Biol. Ther. 13, 2013; 527–540.

4. Capparè, P.; Tetè, G.; Sberna, M.T.; Panina-Bordignon, P. The Emerging Role of Stem Cells in Regenerative Dentistry. Curr. Gene Ther. 2020, 20, 259–268.

5. Rao, M.S. Stem Sense: A Proposal for the Classification of Stem Cells. Stem Cells Dev. 2004, 13, 452–455.

6. Marion, N. W. & Mao, J. J. Mesenchymal stem cells and tissue engineering. Methods Enzymol. 420, 339–361 (2006).

7. Corderio, M.M.; Dong, Z.; Kaneko, T.; Zhang, Z.; Miyazawa, M.; Shi, S.; Smith, A.J.; Nör, J.E. Dental pulp engineering with stem cells from exfoliated deciduous teeth. J. Endod. 2008, 34, 962–969.

8. Huang, G.T.; Yamaza, T.; Shea, L.D.; Djouad, F.; Kuhn, N.Z.; Tuan, R.S.; Shi, S. Stem/progenitor cell-mediated de novo regeneration of dental pulp with newly deposited continuous layer of dentin in an in vivo model. Tissue Eng. Part A 2010, 16, 605–615.

9. Iohara, K.; Imabayashi, K.; Ishizaka, R.;Watanabe, A.; Nabekura, J.; Ito, M.; Matsushita, K.; Nakamura, H.; Nakashima, M. Complete pulp regeneration after pulpectomy by transplantation of CD105+ stem cells with stromal cell-derived factor-1. Tissue Eng. Part A 2011, 17, 1911–1920.

10. Kim, J.Y.; Xin, X.; Moioli, E.K.; Chung, J.; Lee, C.H.; Chen, M.; Fu, S.Y.; Koch, P.D.; Mao, J.J. Regeneration of dentin-pulp-like tissue by chemotaxis-induced cell homing. Tissue Eng. Part A 2010, 16, 3023–3031.

11. Duailibi et al . Bioengineered Dental Tissues Grown in the Rat Jaw. J Dent Res. 2008 August ; 87(8): 745–750.

12. Sita Rama Kumar et al. Stem cells in endodontic therapy. Int J Med Res Health Sci. 2014;3(4):977-983

13. Rita Chandki, M.Kala, Priyank Banthia, Ruchi Banthia: From stem to roots: Tissue engineering in endodontics. J ClinExp Dent 2012; 4(1):66-71.

14. Gronthos, S.; Mankani, M.; Brahim, J.; Gehron Robey, P.; Shi, S. Postnatal human dental pulp stem cells (DPCs) in vitro and in vivo. Proc. Natl. Acad. Sci. USA 2000, 97, 13625–13630.

15. Shi, S.; Gronthos, S. Perivascular Niche of Postnatal Mesenchymal Stem Cells in Human Bone Marrow and Dental Pulp. J. Bone Miner. Res. 2003, 18, 696–704.

16. Gong, T.; Heng, B.C.; Lo, E.C.M.; Zhang, C. Current Advance and Future Prospects of Tissue Engineering Approach to Dentin/Pulp Regenerative Therapy. Stem Cells Int. 2016, 2016, 1–1317.

17. Ledesma-Martínez, E.; Mendoza-Núñez, V.M.; Santiago-Osorio, E. Mesenchymal Stem Cells Derived from Dental Pulp: A Review. Stem Cells Int. 2016, 2016, 1–12.

18. Potdar, P.D. Human dental pulp stem cells: Applications in future regenerative medicine. World J. Stem Cells 2015, 7, 839–851.

19. Sonoyama, W.; Liu, Y.; Yamaza, T.; Tuan, R.S.; Wang, S.; Shi, S.; Huang, G.T.-J. Characterization of the Apical Papilla and Its Residing Stem Cells from Human Immature Permanent Teeth: A Pilot Study. J. Endod. 2008, 34, 166 171.

20. Kim, S.; Shin, S.-J.; Song, Y.; Kim, E. In Vivo Experiments with Dental Pulp Stem Cells for Pulp-Dentin Complex Regeneration. Mediat. Inflamm. 2015, 2015, 1–6.

21. Miura, M.; Gronthos, S.; Zhao, M.; Lu, B.; Fisher, L.W.; Robey, P.G.; Shi, S. SHED: Stem cells from human exfoliated deciduous teeth. Proc. Natl. Acad. Sci. USA 2003, 100, 5807–5812.

22. Nakamura, S.; Yamada, Y.; Katagiri, W.; Sugito, T.; Ito, K.; Ueda, M. Stem Cell Proliferation Pathways Comparison between Human Exfoliated Deciduous Teeth and Dental Pulp Stem Cells by Gene Expression Profile from Promising Dental Pulp. J. Endod. 2009, 35, 1536–1542

23. Kaushik, S.N.; Kim, B.;Walma, A.M.C.; Choi, S.C.;Wu, H.; Mao, J.J.; Jun, H.-W.; Cheon, K. Biomimetic microenvironments for regenerative endodontics. Biomater. Res. 2016, 20, 1–12.

24. Bakopoulou, A.; Leyhausen, G.; Volk, J.; Tsiftsoglou, A.; Garefis, P.; Koidis, P.; Geurtsen, W. Comparative analysis of in vitro osteo/odontogenic differentiation potential of human dental pulp stem cells (DPSCs) and stem cells from the apical papilla (SCAP). Arch. Oral Biol. 2011, 56, 709–721.

25. Chueh, L.-H.; Huang, G.T.-J. Immature Teeth with Periradicular Periodontitis or Abscess Undergoing Apexogenesis: A Paradigm Shift. J. Endod. 2006, 32, 1205–1213.

26. Banchs, F.; Trope, M. Revascularization of Immature Permanent Teeth with Apical Periodontitis: New Treatment Protocol? J. Endod. 2004, 30, 196–200.

27. Nagatomo, K.; Komaki, M.; Sekiya, I.; Sakaguchi, Y.; Noguchi, K.; Oda, S.; Muneta, T.; Ishikawa, I. Stem cell properties of human periodontal ligament cells. J. Periodontal Res. 2006, 41, 303–310.

28. Seo, B.-M.; Miura, M.; Gronthos, S.; Bartold, P.M.; Batouli, S.; Brahim, J.; Young, M.; Robey, P.G.; Wang, C.Y.; Shi, S. Investigation of multipotent postnatal stem cells from human periodontal ligament. Lancet 2004, 364, 149–155.

29. Hasegawa, M.; Yamato, M.; Kikuchi, A.; Okano, T.; Ishikawa, I. Human Periodontal Ligament Cell Sheets Can Regenerate Periodontal Ligament Tissue in an Athymic Rat Model. Tissue Eng. 2005, 11, 469–478.

30. Bojic, S.; Volarevic, V.; Ljujic, B.; Stojkovic, M. Dental stem cells—Characteristics and potential. Histol. Histopathol. 2014, 29, 699–706.

31. Kémoun, P.; Laurencin-Dalicieux, S.; Rue, J.; Farges, J.-C.; Gennero, I.; Conte-Auriol, F.; Briand-Mesange, F.; Gadelorge, M.; Arzate, H.; Narayanan, A.S.; et al. Human dental follicle cells acquire cementoblast features under stimulation by BMP-2/-7 and enamel matrix derivatives (EMD) in vitro. Cell Tissue Res. 2007, 329, 283–294.

32. C.-N.Hung, K.Mar, H.-C. Chang et al., “A comparison between adipose tissue and dental pulp as sources of MSCs for tooth regeneration,” Biomaterials, vol. 32, no. 29, pp. 6995–7005, 2011.

33. S. Shi, P. G. Robey, and S. Gronthos, “Comparison of human dental pulp and bone marrow stromal stem cells by cDNA microarray analysis,” Bone, vol. 29, no. 6, pp. 532–539, 2001.

34. R. Ishizaka, K. Iohara, M. Murakami, O. Fukuta, and M. Nakashima, “Regeneration of dental pulp following pulpectomy by fractionated stem/progenitor cells from bone marrow and adipose tissue,” Biomaterials, vol. 33, no. 7, pp. 2109–2118, 2012.

35. X. Yan, H. Qin, C. Qu, R. S. Tuan, S. Shi, and G. T.-J. Huang, “iPS cells reprogrammed from human

mesenchymal like stem/progenitor cells of dental tissue origin," Stem Cells and Development, vol. 19, no. 4, pp. 469–480, 2010.

36. Saraswathi Gopal, Arathy Manohar L. Stem cell therapy: A newhope for dentist.Journal of Clinical and Diagnostic Research 2012; 6(1): 142-44.

37. Murray PE, Garcia-Godoy F, Hargreaves KM. Regenerative endodontics: a review of current status and a call for action. J Endod 2007;33(4):377-90.

38. Harikumar, Kavitha A, Jayaprada J, Shetty SR. Regenerative Endodontics. Ind J Dent Adv 2010;2(2):203-209.

39. Balic A, Aguila HL, Caimano MJ. Characterization of stem and progenitor cells in the dental pulp of erupted and unerupted murine molars. Bone 2010; 46:1639–51.

40. Koyama N, Okubo Y, Nakao K, et al. Evaluation of pluripotency in human dental pulp cells. J Oral Maxillofac Surg 2009; 67:501–506.

41. Sakai VT, Zhang Z, Dong Z. SHED differentiate into functional odontoblast and endothelium. J Dent Res 2010; 89:791–96.

42. Linde A, Goldberg M. Dentinogenesis. Crit Rev Oral Biol Med 1993; 5:679–728.

43. Ruch JV, Lesot H, Bègue-Kirn C. Odontoblast differentiation. Int J Dev Biol 1995; 39:51–68.

44. Takahashi K. Pulpal vascular changes in inflammation. Proc Finn Dent Soc. 1992; 88(S1): 381–85.

45. Avery, JK. Cox, CF.Chiego, DJ. Structural and physiologic aspects of dentin innervation. In: Linde, A., editor. Dentin and Dentinogenesis. CRC Press; Boca Raton: 1984;1:19-46.

46. Kramer IR. The vascular architecture of the human dental pulp. Arch Oral Biol 1960; 2:177–89.

47. Linde A, Lundgren T. From serum to the mineral phase. The role of the odontoblast in calcium transport and mineral formation. Int J Dev Biol 1995; 39:213–22.

48. Smith AJ, Cassidy N, Perry H. Reactionary dentinogenesis. Int J Dev Biol 1995; 39:273–280.

49. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med 2003; 9:669– 76.

50. Nor JE, Christensen J, Mooney DJ, et al. Vascular endothelial growth factor (VEGF)-mediated

angiogenesis is associated with enhanced endothelial cell survival and induction of Bcl-2 expression. Am J Pathol 1999; 154:375–84.

51. Botero TM, Son JS, Vodopyanov D. MAPKsignaling is required for LPS-induced VEGF in pulp stem cells. J Dent Res 2010; 89:264–69.

52. Guven G, Altun C, Günhan O. Co-expression of cyclooxygenase-2 and vascular endothelial growth factor in inflamed human pulp: an immune histo chemical study. J Endod 2007; 33:18–20

53. T. Nivethithan and Manish Ranjan M. Stem cells in regenerative endodontics. International Journal of Pharmaceutical Sciences and Research, 2017; Vol. 8(5): 1972-1977.

54. Ding RY, Cheung GS, Chen J, Yin XZ, Wang QQ, Zhang CF. Pulp revascularization of immature teeth with apical periodontitis: a clinical study. J Endod 2009;35(5):745-9.

56. Iwaya S, Ikawa M, Kubota M. Revascularization of an immature permanent tooth with apical periodontitis and sinus tract. Dent Traumatol 2001; 17: 185–187.

57. Ikeda E, Morita R, Nakao K, Ishida K, Nakamura T, Takano-Yamamoto T et al. Fully functional bioengineered tooth replacement as an organ replacement therapy. Proc Natl Acad Sci USA 2009;106(32):13475-80.