Review Article

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DENTAL STEM CELLS AND THEIR POTENTIAL ROLE IN REGENRATIVE DENTISTRY

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ABSTRACT:
In recent years, dentistry has begun to explore the potential application of stem cells and tissue engineering towards the repair and regeneration of dental structures. Mesenchymal stem cells were demonstrated in dental tissues, including dental pulp, periodontal ligament, dental papilla, and dental follicle. The multipotency, high proliferation rates, and accessibility make the dental stem cell an attractive source of mesenchymal stem cells for tissue regeneration. . This review discusses the perspectives in the field of stem cell-based regenerative dentistry addressing sources of stem cells identified in dental tissues; and new findings in the field of dental stem cell research and their potential use in regeneration.
Keywords: Dental stem cell, Tissue engineering, regeneration, stem cell

INTRODUCTION:

The discovery of dental stem cells and recent advances in cellular and molecular biology have led to the development of novel therapeutic strategies that aim at the regeneration of oral tissues that were injured by disease or trauma. Tissue engineering is a science based on fundamental principles that involves the identification of appropriate cells, the development of conducive scaffolds, and the understanding of the morphogenic signals required to induce cells to regenerate a tissue or organ.[1]

Dental Stem Cell: Dental Stem cells can be separated from the three groups of teeth as shown in figure no.1 they are:

(a) Deciduous Teeth: The healthy pulps of deciduous teeth are a rich source of viable stem cells. Scientific data sustains that separated stem cells from healthy pulp of deciduous teeth are extremely proliferative, still when the pulp is recovered in little quantities.

(b) Wisdom Teeth: The healthy pulp from wisdom teeth is a further exceptional source for workable stem cells. Entire or sectioned divisions of third molars containing healthy pulp can be recovered at the time of their exclusion. The pulp is often exposed if an impacted third molar needs to be sectioned for removal.

(c) Permanent teeth: Healthy pulp from all the permanent teeth is potential resource of stem cells. Bicuspids requiring to be removed for orthodontic suggestions are an example of this. Permanent teeth to be removed for orthodontic suggestions

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are an example of this. Permanent teeth to not to be included: endodontically-treated or non vital teeth, teeth with lively infections, teeth with rigorous periodontal disease and too much mobility, teeth with large restorations and deep caries, and teeth with calcified or sclerosed pulp chambers.[2,3]

Classification of dental stem cells.:

Stem cell possess a remarkable potential to proliferate and develop into many different cell types to form the desired tissue, these cells hold great promise for regenerative therapy

Teeth and supporting structures contain multiple lineage of stem cells including :

- SHED: from the dental pulp of exfoliated deciduous teeth termed stem cells from Human Exfoliated Deciduous teeth (SHED). [4,6,7,8]
- DPSC: Mesenchymal stem cells isolated from the dental pulp of permanent teeth , termed Dental Pulp Stem Cells (DPSC) [4,6]
- PDLSC :stem cells isolated from the periodontal ligament (PDLSC) [4,5]
- SCAP : Mesenchymal stem cells isolated from the apical end of developing tooth roots, termed Stem cells from the Apical Papilla (SCAP) [4]
- DFPC:stem cells isolated from dental follicle of developing tooth [4]

Classification of dental stem cell is shown in table no.1

More recently, another source of stem cell has been successfully generated from human somatic cells into a pluripotent stage, the induced pluripotent stem cells (iPS cells), allowing creation of patientand disease-specific stem cells.

Stem cells from Human Exfoliated Deciduous teeth (SHED)

Stem cells isolated from the pulp of human exfoliated deciduous teeth (SHED) have the capacity of inducing bone formation, generate dentin and differentiate into other nondental mesenchymal cell derivatives in vitro. They induced bone formation and produced dentin under in vivo conditions; and they were able to survive and migrate in murine brain after transplantation into immunocompromised animals.[8] 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 DPCSs, they are unable to regenerate complete dentin/pulp-like complexes *in vivo.* [7] With the osteoinductive potential, SHED can repair critical sized calvarial defects in mice with substantial bone formation.[5] SHEDs are capable of differentiation into odontoblast, adipocytes and neural cells.[9] Given their ability to produce and secrete neurotrophic factors, dental stem cells may also be beneficial for the treatment of neurodegenerative diseases and the repair of motor neurons following injury.[12-18]

Dental Pulp Stem Cells (DPSC) :

The first stem cells isolated from adult human dental pulp were termed dental pulp stem cells (DPSC).They were isolated from permanent third molars and exhibited high proliferation and high frequency of colony formation that produced calcified nodules.[10] DPSC cultures from impacted third molars at the stage of root development were able to differentiate into odontoblastlike cells with a very active migratory and mineralization. [10-16] In 2003 Dr. Songtao Shi, a Pedodontist discovered dental pulp stem cells by utilizing the primary teeth of his daughter & he named as stem cells from human exfoliated deciduous teeth. Many researchers have been done work on dental pulp, gazing for stem cells and they established that dental pulp was rich in different types of stem cells, like, adipocytes, chondrocytes, osteoblasts and mesenchymal stem cells. These mesenchymal stem cells are one of the most prospective stem cells which has wide therapeutic functions. Dental pulp stem cells can be found both in adults and children. Transplantation of Dental pulp stem cells into immune compromised might outcome in the formation of a dentin-like tissue, while bone marrow stem cells generated a tissue approaching that of lamellar bone. Pulpal wound healing and regeneration may be compromised with growing age .Healing depends on the strength and extent of the injury, presence of bacteria and host factors such as the level of native and systemic immunity. [2, 17]

Stem Cells from Apical Papilla (SCAP):

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 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. The higher proliferative potential of SCAP makes this population of cells suitable for cell-based regeneration and preferentially for forming roots. They are capable of forming odontoblast-like cells and produce dentin *in vivo* and are likely to be the cell source of primary odontoblasts for the root dentin formation. [10] This tissue may be benefited by its collateral circulation, which enables it to survive during the process of pulp necrosis. Perhaps, after endodontic disinfection, these cells give rise to primary odontoblasts to complete the root formation. The discovery of SCAP may also explain a clinical henomenon that was presented in a number of recent clinical case reports showing that apexogenesis can occur in infected immature permanent teeth with apical periodontitis or abscess [19] stem/progenitor cells were located in both dental pulp and the apical papilla, but they have somewhat different characteristics. [10] However, SCAPs have a greater capacity for dentin regeneration than DPSCs because the dental papilla contains a higher number of adult stem cells compared to the mature dental pulp.[5, 18]

Periodontal Ligament Stem Cells (PDLSC): The PDL has long been recognized to contain a population of progenitor cells and recently,studies identified a population of stem cells from human PDL capable of differentiating along mesenchymal cell lineages to produce cementoblast-like cells, adipocytes and connective tissue rich in collagen I. [5] These cells could be isolated as plastic-adherent, colony-forming cells, but display a low potential for osteogenic differentiation under in vitro conditions [5]PDL stem cells differentiate into cells or tissues very similar to the periodontium.[18] PDL stem cells (PDLSC) display cell surface marker characteristics and differentiation potential similar to bone marrow stromal stem cells and DPSC.[18] After PDLSC were transplanted into immunocompromised mice, cementum/PDL-like structures were formed Human PDLSC expanded *ex vivo* and seeded in threedimensional scaffolds (fibrin sponge, bovine-derived substitutes) were shown to generate bone.[20] These cells have also been shown to retain stem cell properties and tissue regeneration capacity. These findings suggest that this population of cells might be used to create a biological root that could be used in a similar way as a metal implant, by capping with an artificial dental crown.

Dental follicle precursor cells (DFPC):

The dental follicle, loose connective tissue that surrounds the developing tooth has long been considered a multipotent tissue, based on its ability to generate cementum, bone and PDL from the ectomesenchyme-derived fibrous tissue. Dental follicle precursor cells (DFPC) can be isolated and grown under defined tissue culture conditions, and recent characterization of these stem cells has increased their potential for use in tissue engineering applications, including periodontal and bone regeneration [16,20] DFPC form the PDL by differentiating into PDL fibroblasts that secrete collagen and interact with fibers on the surfaces of adjacent bone and cementum. Dental follicle progenitor cells isolated from human third molars are characterized by their rapid attachment in culture, and ability to form compact calcified nodules *in vitro.* [21] DFPC, in common with SCAP, represent cells from a developing tissue and might thus exhibit a greater plasticity than other dental stem cells. However, in the same way as for SCAP, further research needs to be carried out on the properties and potential uses of these cells.

Dental Stem Cells in regeneration : Dental Stem Cells in regeneration is shown in figure no.2. Extracted teeth are traditionally thought to be medical waste. Historically, the therapeutic potential of dental stem cells was not well understood, and there were no appropriate storage methods for potential donor teeth or dental stem cells.Many types of dental stem cells have now been identified from human teeth and surrounding tissues. Unlike embryonic stem cells, which involve the destruction of human embryos,dental stem cells are accessible and available and, most importantly, there are few if any ethical considerations. With advances in tissue engineering, dental stem cells have shown their potential in regenerating odontoblasts [15] ,dentin pulp-like structure, and dentin.[23] Furthermore, dental SCs can differentiate into adipocytes [7] and neurons[24] and promote the proliferation and differentiation of endogenous neural cells. It is also possible that myocardial infarction [25-30] and liver dysfunction [26] could be treated with dental SCs in the near future. Thus, the therapeutic capability and clinical benefits of dental SCs are not limited to dental use but can also be used for regenerative medicine. [34–38] However, the absence of appropriate preservation methods for teeth and/or dental stem cells remains a significant limitation. Because of the opportunity to preserve dental stem cells for medical applications, the term “tooth bank” was first raised in 1966. [39] With the rapid development of advanced cryopreservation technology, the first commercial tooth bank was established as a venture company at National Hiroshima University in Japan in 2004. By systematic organization, an increasing number of teeth have been cryopreserved for future generative medicine.[40-45]

CONCLUSION :

Stem cells of dental origin have multiple applications nevertheless there are certain limitations as well. The oncogenic potential of these cells is still to be determined in long-term clinical studies. Moreover, the research is mainly confi ned to animal models and their extensive clinical application is yet to be tested. Other major limitations are the difficulty to identify, isolate, purify and grow these cells consistently in labs. Immune rejection is also one of the issues, which require a thorough consideration; nevertheless use of autologous cells can overcome this. Lastly, stem/progenitor cells are comparatively less potent than embryonic stem cells. Teeth-like structures cannot replace actual teeth, thus a considerable research research and development efforts is required to advance the dental regenerative therapeutics. Researchers still need to grow blood and nerve supply of teeth to make them fully functional. Although not currently available, these approaches may one day be used as biological alternatives to the synthetic materials currently used. Like other powerful technologies, dental stem cell research poses challenges as well as risks. If we are to realize the benefits, meet the challenges, and avoid the risks, stem cell research must be conducted under effective, accountable systems of socialresponsible oversight and control, at both the national and international levels.

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TABLE:

Type of dental stem cell	Location	Proliferation rate	Heterogeneity	Multipotentialy	Tissue repair
SHED	Exfoliated deciduous tooth pulp	High	Yes	Odontoblast, osteoblast, chondrocyte, myocyte, neurocyte, adipocyte, iPS	Bone regeneration, neuroregeneration, tubular dentin
DPSC	Permanent tooth pulp	Moderate	Yes	Odontoblast, osteoblast, chondrocyte, myocyte, neurocyte, adipocyte, corneal epithelial cell, melanoma cell, iPS	Bone regeneration, neuroregeneration, myogenic regeneration, dentinpulp regeneration
SCAP	Apical papilla of developing root	High	Yes	Odontoblast, osteoblast, neurocyte, adipocyte, iPS	Bone regeneration, neuroregeneration, dentin-pulp regeneration, root formation
PDLSC	Periodontal ligament	High	Yes	Odontoblast, osteoblast, chondrocyte, cementoblast, neurocyte	Bone regeneration, root formation, periodontal regeneration
DFPC	Dental follicle of developing tooth	High	Yes	Odontoblast, osteoblast, neurocyte	Bone regeneration, periodontal regeneration

DPSC = dental pulp stem cells;

SCAP = stem cells from the apical papila;

SHED = stem cells from the pulp of human exfoliated deciduous teeth;

PDLSC = periodontal ligament stem cells;

DFPC = dental follicle precursor cells.

Table 1.Dental Stem cell types [5-16]

FIGURES:

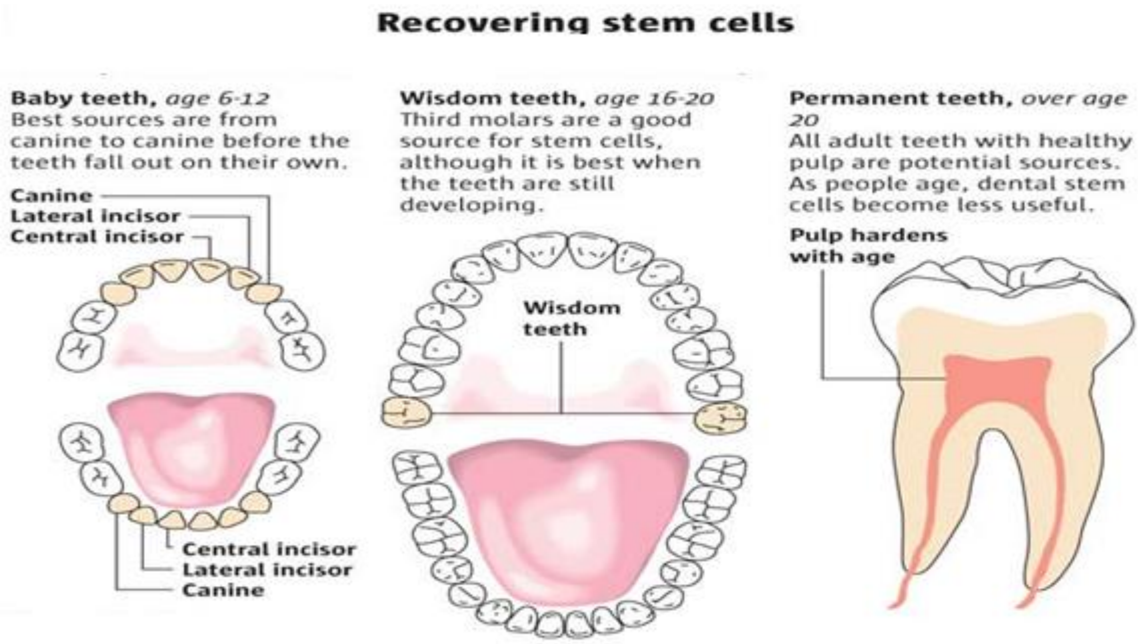

Figure 1: Recovering Stem Cell

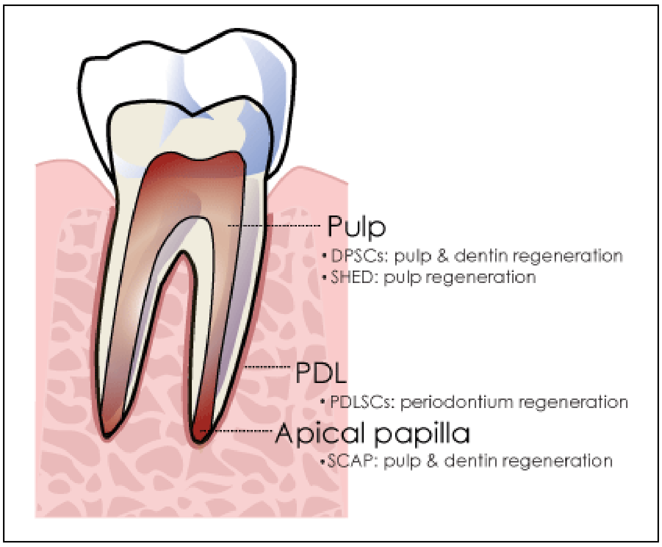

Figure 2 : Dental Stem Cells in regeneration