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Emerging role of Stem cells of dental origin in dentistry -A Review

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Abstract

In recent years, the greatest findings show that stem cells have been used to treat several diseases. Studies conducted with stem cells highly interest the scientific field due to their ability in stimulating tissue regeneration and, as a consequence, presenting many therapeutic perspectives. Such facts enable stem cells to be used in different dental procedures of which aim is to recover the quality of patients' oral health.

Stem cells are primordial cells that can differentiate and regenerate failing cells in different parts of the body such as heart, bones, muscles and nervous system. Till date, five major human dental stem cells have been isolated and characterized: Dental Pulp Stem Cells (DPSCs), stem cells from exfoliated deciduous teeth (SHED), periodontal ligament stem cells (PDLSCs), stem cells from apical papilla (SCAP), and dental follicle progenitor cells (DFPCs). These post-natal populations possesses mesenchymal stem cell (MSC) qualities, with the capability for multiline age differentiation potential and self-renewal. The dental stem cells are derived and isolated from specialized tissue with potent capacities to differentiate into osteogenic, neurogenic, chondrogenic, adipogenic, odontogenic cells.

For this review article we performed a search on PubMed, Medline Plus, Science Direct, google scholar, science direct etc for all English-language articles published in the last 10 years. We used the keywords were "adult stem cells", "dental stem cells, "dental stem cells banking", "stem cells from human exfoliated deciduous teeth (SHED)".

The aim of this review is to give outline of the stem cell types being investigated in the dental field including their tissue sources, properties, differentiation potential, and assessment of their advantages for tissue engineering.

Keywords: Adult stem cells, SHED, Mesenchymal stem cells, Dental stem cells, Dentistry.

Introduction

Stem cells are defined as clonogenic cells capable of both self- renewal and multiline age differentiation since they are thought to be undifferentiated cells with varying degrees of potency and plasticity.(1)

Mesenchymal stem cells (MSCs) are a potential source of adult stem cells (with mesodermal and neuroectodermal origin) for regenerative medicine as they are amazingly plastic and when expanded into colonies, retain their multiline age potential.

Medthodology

A systematic review of the literature was performed using various internet based search engines (PubMed, Medline Plus, Ebsco, Science Direct, Hinari). To limit our research to relevant articles, the search was filtered using terms review and original articles, published in the last 10 years and dental journals. Various keywords used for research were "adult stem cells", "dental stem cells, "dental stem cells banking", "stem cells from human exfoliated deciduous teeth (SHED)".

Adult stem cells, (MSCs) are a assorted split of pluripotent stromal cells that can be isolated from many different adult tissues and display the potential to give rise to cells of various lineages. Morphologically, MSCs may be either large and flat or elongated and fibroblast like.(2)

MSCs are able to differentiate into cells of mesodermal origin like adipocytes, chondrocytes or osteocytes.(3) The multipotent nature of MSCs is evident from the ability to differentiate along various lineages like osteoblasts, adipocytes, myelosupportivestroma, chondrocytes, and neuronal cells in response to specific stimuli.(2)

MSCs are also found within the dental pulp (DP), which is an extremely rich site for stem cell collection; due to its formation in a sealed compartment, it acts as ''sealed niche'' and thus it is possible to find a large number of stem cell there for colledtion.(4)

Dental stem cells are derived from the neural crest, and thus have a different origin from bone marrow-derived MSCs, which are derived from mesoderm.(5)

The first type of dental stem cell was isolated from the human pulp tissue and termed dental pulp stem cells (DPSCs).(6) Teeth, both primary and permanent teeth, the periodontal ligament, including the apical region of developing teeth and other tooth structures. **(Fig. 1)**

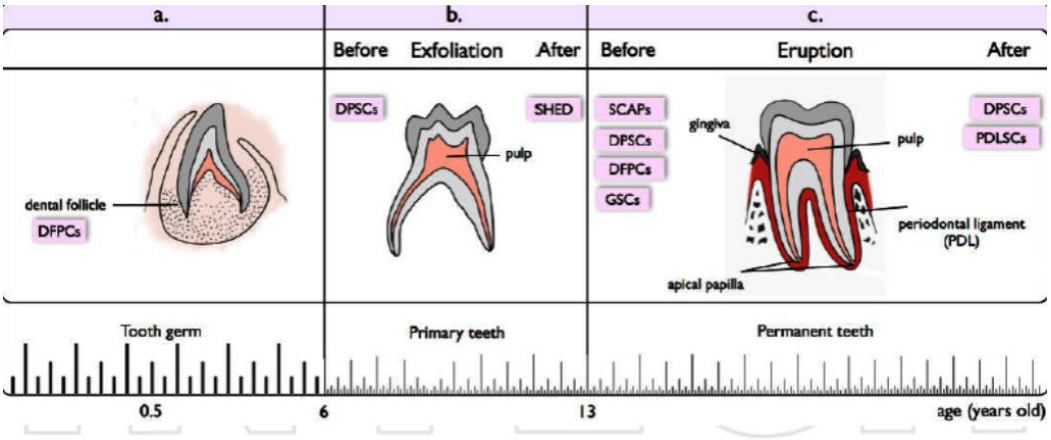

Fig. 1: Dental stem cells at different anatomical locations and stages during human lifetime in a.) tooth germ, b.) primary teeth, c.) permanent teeth. (Ref: Dental-related Stem Cells and Their Potential in Regenerative Medicine, Razieh Karamzadeh and Mohamadreza Baghaban Eslaminejad. Department of Stem Cell and Developmental Biology Iran. http://dx.doi.org/10.5772/55927)

The factors which make dental stem cells unique are:

- They are plenty and easy to collect; dental stem cells can be collected from baby teeth and wisdom teeth which would or else be discarded.
- Dental stem cells are highly proliferative, grows better in culture than any other types of adult stem cells.
- Dental stem cells are reported to be more immature than other sources of mesenchymal stem cells (MSCs), thus offers greater differentiation potential.
- Dental stem cells are not the subject of the same ethical concerns as embryonic stem cells as they adult stem cells.

Advantages Dental Stem Cell

The advantages of stem cells from oral and maxillofacial region is that:

1. Have high plasticity.
2. Can be cryopreserved for longer period; thus ideal for stem cell banking.
3. Shows good interaction with scaffold and growth factors; hence are good source for tissue engineering.
4. Aautologous stem cell source is the best option as stem cells transplantations from other sources can cause pathogen transmission and in addition need immunosuppression, Dental pulp stem cells can be better source due to easy surgical access, very low morbidity of the anatomical site after the collection of the pulp.[7]

The dental stem cells can be recovered from the following:**(Fig. 2)**

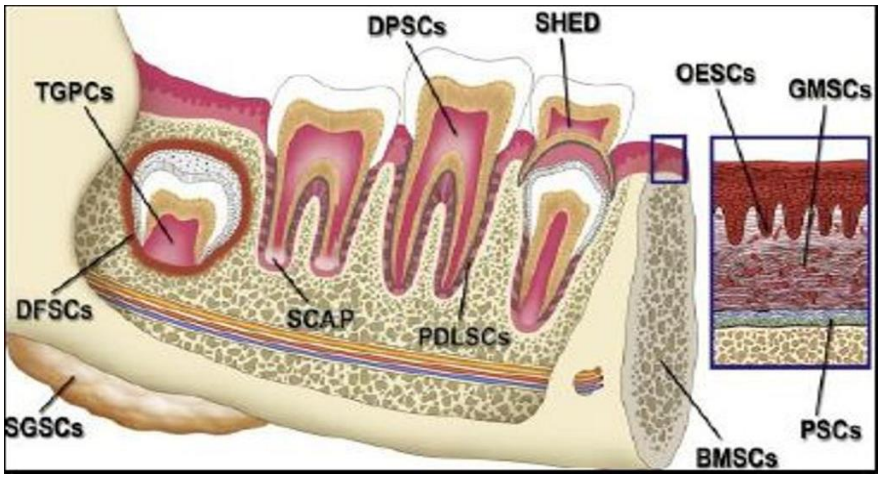

Fig. 2: **Sources of various dental stem cells(Ref: Hiroshi Egusa et al .Stem cells in dentistry – Part I: Stem cell sources. Journal of Prosthodontic Research Volume 56, Issue 3, July 2012, Pages 151–165**

- **Bone marrow–derived mesenchymal stem cells**: Bone marrow transplants were the first successful stem cell therapies but due to ethical concerns presently peripheral blood stem cell collection is being used in place of bone marrow aspiration.
- Gingival stem cells
- Periodontal ligament - Periodontal ligament stem cells(PDLSC)
- Dental follicle precursor stem cell.
- Stem cells from pulpal origin.

Subsequently, following types of populations were identified:

- Permanent teeth - Dental pulp stem cells (DPSC): derived from third molar.
- Deciduous teeth - Stem cells from human-exfoliated deciduous teeth (SHED): stem cells are present within pulp of deciduous teeth.
- Stem Cells from apical papilla (SCAP).
- Dental follicle progenitor cells (DFPC).
- Stem cells from human natal dental pulp8(hNDP).

Types of Stem Cells Explored in the Dental Field

Bone Marrow Stromal Stem Cells (BMSSCs): Bone marrow is a store house of stem cells so, in addition to hematopoietic stem cells (HSCs), the bone marrow contains bone marrow stromal stem cells (BMSSCs) giving rise rise to non-hematopoietic tissues. BMSSCs are bone marrow cell populations that were the first mesenchymal stem cells to be isolated exploiting their property to adhere to tissue culture plastics.[9]

BMSSCs have been isolated and characterized from the extra[10] as well as the intra- oral[11] bone marrow. They are capable of forming colony forming unit-fibroblasts (CFU-Fs) in vitro[10] and can express Oct-4, Nanog, STRO-1, CD73, CD90, CD105, CD146 and gives negative impression for CD14, CD34, CD45 and HLA-DR12They possesses multiple mesenchymal lineages differentiation potential that including osteoblasts, adipocytes, chondrocytes, muscle cells, tenocytes, or nerve cells.[13]

Alveolar Bone proper-derived Stem Cells: The alveolar bone proper PDL is embryonically derived from the dental follicle. Recently, the minimally invasive scheme for isolation of alveolar bone margin-derived stem cells was introduced;[14] which was found to be conservative alternative to many previously described isolation techniques for adult stem/progenitor cells from the dental pulp or periodontal ligament as well as the intra-[15] and extra-oral[16]bone marrow.

The isolated cells showed plasticity and colony formation, and positive expression for the surface markers CD73, CD90, CD105, STRO-1, and CD146/MUC18, and possess negative expression of the hematopoietic markers CD14, CD34, and CD45. The cells could be differentiated into osteoblastic, adipocytic, and chondroblastic lineages and established a high expression of ALP, type I, III, and V collagens.[15,16]

Further studies are needed to verify the regenerative potential of these cells as well as to compare them with other stem cell populations.

Gingival Stem Cells: Gingiva forms a key component of the periodontium; gingiva's most distinguished characteristics is its outstanding regenerative and wound healing capacity with a fast reconstitution of tissue design, with little evidence of scarring.[17] The multiple functions of gingival fibroblasts, their range in sensitivity to growth factors and in their ability to produce specific extracellular matrix proteins during healing, verified that gingival connective tissue fibroblasts constitute a heterogeneous cells population.[18]

The isolated gingival stem cells expressed positively for CD73, CD90, and CD105 and lacked expression for CD14, CD34, and CD45. They possesses multiline age differentiation capacity into adipocytes, osteocytes, and chondrocytes.[19] Gingival margin-derived stem cells possess immunomodulatory properties that can exploited experimentally in the therapy of inflammatory destructive diseases including arthritis and colitis through inhibiting the proliferation of T-lymphocytes and promoting the proliferation of regulatory T cells.[22]

In a recent study it was found that gingival stem cells possess a remarkable periodontal regenerative potential when used in conjunction with collagen and demineralized bovine cancellous bone matrices**.**[23]

Periodontal Ligament Stem Cells (PDLSCs): The periodontium, is a highly specialized and complex connective tissues of the human body, that is derived from the dental follicle and the neural crest cells. The PDL harbors a varied population of progenitor cells,[22] thought to be responsible for maintaining tissue homeostasis and to play a crucial role in periodontal regeneration. Human PDLSCs have been successfully isolated by many researchers from the root of extracted teeth.[23]

PDLSCs expresses positively for the stem cell markers like STRO-1 and CD146/MUC18.[24] PDLSCs also expressed mature mineralized tissue markers like ALP, type I and III collagens, osteonectin, osteopontin, osteocalcin, BSP and high levels of scleraxis, a tendon-specific transcription factor associated with tendon cells, PDLSCs are multipotent, thus have capability to differentiate into adipocytes, cementoblast like cells, osteoblasts, and collagen forming cells.[24] The characteristic feature of PDLSCs to produce cementum and PDL-like tissue.[24]

Dental Pulp Stem Cells (DPSCs): The identification and isolation of an odontogenic progenitor population in adult dental pulp were first reported by Gronthos and co-workers in 2000 by desirable quality of their clonogenic abilities, rapid proliferative rates, and

capacity to form mineralized tissues both in vivo and in vitro.[25]

Pulp cells expressed bone markers like osteoblasts such as bone sialoprotein, alkaline phosphatase, type I collagen, and osteocalcin. There is a great potential for isolation of a large number of DPSCs from a single tooth that could be used for dentinal repair of a number of teeth. In a chemically defined culture medium, DPSCs can be differentiated into smooth and skeletal muscle cells, neurons, and cartilage and bone cells.[26]

The most striking feature of DPSCs is their ability to regenerate a dentin-pulp-like complex that is composed of mineralized matrix with tubules lined with odontoblasts, and fibrous tissue containing blood vessels in an arrangement similar to the dentin-pulp complex found in normal human teeth.

It is well known that on pulpal injury, reparative/tertiary dentine forms as a protective barrier for the pulpal chamber.[27] This natural regenerative potential of the dentin/pulp complex points to the possibility that dental pulp may contain stem cells or progenitors responsible for its regeneration/repair. DPSCs from CFU-F and could produce dentine-pulp like structures.[28]

DPSCs possess a self-renewal capability and multi lineage differentiation potential into chondrocytes, adipocytes, odontoblasts, and neural-like cells under appropriate induction conditions.[29]

Advantages of DPSCs

1. They are more prone to form neurons than other stem cells; hence can be a good adjunct for the treatment of neurological disorders.
2. There are fewer ethical consideration than those which cover other stem cells.
3. They are more easily isolated than other stem cells, such as MSCs from the bone marrow and NSCs from cadavers.

DPSCs, are thought to arise from two different sources: ectomesenchyme of the neural crest or ectoderm of the dental lamina and hence possess two different cell lines.[30] The Stem Cells that are found in the pulp of deciduous and permanent teeth are adult multipotent mesenchymal stem cells.

Eligibility criteria for harnessing stem cells of pulpal origin from tooth

A healthy pulp contains viable stem cells; thus for a pulp to be considered healthy, the tooth must have:

- An intact blood supply
- Be free of infection, deep caries, and any other pathologies.

Stem cells are diffusely spread throughout the cellular zone adjacent to the nerve and blood vessels within the pulp and; hence are not concentrated within any particular area of a healthy pulp.[31]

To recover DPSC's stem cells teeth can be divided into four distinct tooth groups:

a. Deciduous Teeth: The healthy pulps of deciduous teeth are a rich source of viable stem cells. Scientific data supported that stem cells isolated from healthy pulp of deciduous teeth are highly proliferative, even when the pulp is recovered in small quantities.

- Harvest Zone: The harvest zone for stem cells is from deciduous canine to canine; as deciduous molars may have their pulp chambers obliterated by the erupting permanent bicuspids by the time they become loose.
- Deciduous tooth that has more than a third of the root structure left intact and has just started to loosen, and is not being extracted for reasons such as infection or associations with pathology possess high number of viable stem cells. **(Fig. 3)**

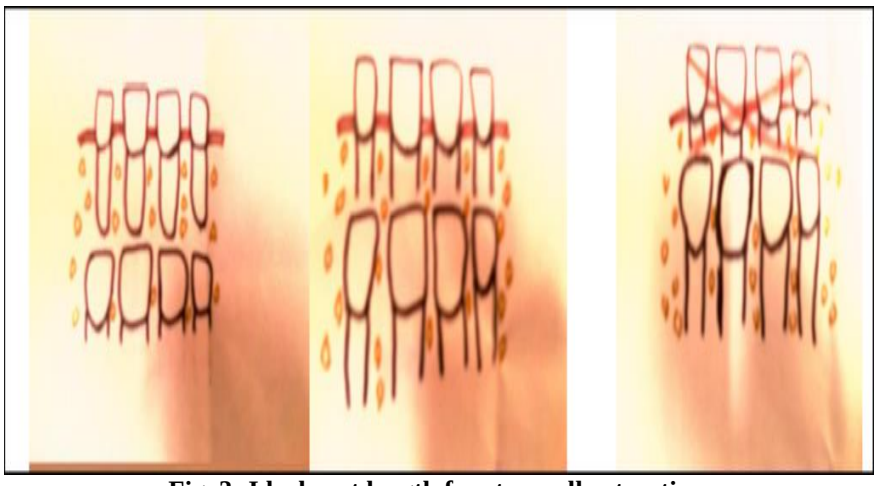

Fig. 3: Ideal root length for stem cell extraction

b. Wisdom Teeth:

- Developing third molars have a larger volume of pulp tissue than teeth that are mature with their roots completely formed; therefore the best to recover these teeth during the developmental stage (between 16-20 years of age), when the stem cells are very active in the formation of the root and supporting root structures.

c. Permanent teeth:

- All permanent teeth with healthy pulp are potential sources of stem cells.
- Bicuspids needing to be removed for orthodontic indications are an example of this.
- Age. As individual ages cells proliferation potential are diminished; therefore stem cells should be extracted from the earlier age.

d. Supernumerary teeth: Supernumerary or mesiodens are another ideal source for dental stem cells.

Stem Cells from Human Exfoliated Deciduous Teeth (SHEDs): Stem Cells from Human Exfoliated Deciduous Teeth (SHEDs) was found in the exfoliated human primary teeth, recently by Miura et al, in 2003.[32] SHED's can be isolated and expanded ex vivo, therefore deciduous teeth may be an ideal resource of stem cells to repair damaged tooth structures, induce bone regeneration, and probably to treat neural tissue injury or degenerative diseases.

SHED expressed neuronal and glial cell markers, which relates to the neural crest-cell origin of the dental pulp.[33] Neural crest cells play a pivotal role in embryonic development, giving rise to a variety of cell types such as neural cells, pigment cells, smooth muscle, craniofacial cartilage, and bone . Dental pulp cells demonstrated the ability to produce neurotrophic factors and therefore motor neurons are able to survive even after spinal cord injury.[34]

SHEDs expressed positively for surface markers like CD146/MUC18 and STRO-1 similar to other MSCs[35] and a variety of osteoblastic and odontoblastic markers including Runx2, ALP, matrix phosphoglycoprotein, bone sialoprotein (BSP), and DSPP. They also exhibits the embryonic stem cell markers Nanog, Oct4, stage-specific embryonic antigens (SSEA-3, SSEA-4), and tumor recognition antigens (TRA-1-60 and TRA-1-81).[36] SHEDs showed adipogenic, neurogenic, myogenic as well as chondrogenic differentiation potential similar to other stem cell populations.[32,36]**(Fig. 4)**

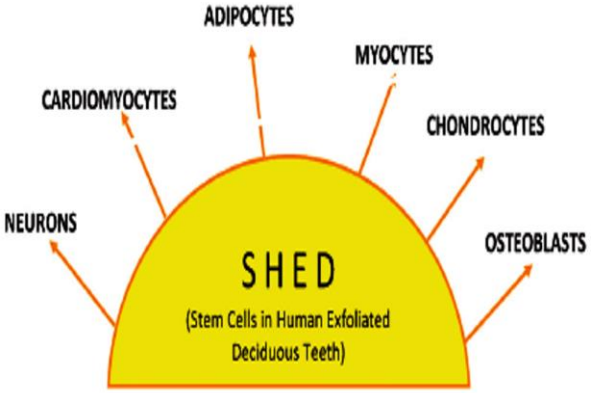

Fig. 4: SHED-derived mesenchymal stem cells

Regarding their osteogenic potential, Miura et al.[32] stated that SHEDs could not be differentiated directly into osteoblasts, but had distinctive osteoinductive abilities, inducing new bone formation by recruiting host osteogenic cells. Studies show that SHEDs might be promising source of stem cells for tooth structure repair and bone regeneration.[36]

Dental Follicle Stem Cells (DFSCs): The dental follicle is a mesenchymal component that surrounds the tooth germ during development in its socket prior to eruption and through complex interactions cementum, PDL, and alveolar bone are formed. Dental follicle stem cells (DFSCs) were initially isolated from follicles of human impacted third molars that scheduled for extraction.[37]

Ectomesenchymal cells present in the dental follicles are derived from the neural crest. DFSCs can differentiate into mesenchymal derived cells like cementoblasts, adipocytes and chondrocytes.[38] DFSC's expresses positively for the stem cell markers STRO-1, Notch-1, and nestin.[39] DFSC cell lines were found to be varied and consists of three main lineages: a highly undifferentiated, periodontal ligament type lineage, a cementoblastic, and an osteoblastic lineage.[40]

Stem cells from the apical papilla (SCAP): Stem cells from the apical papilla (SCAP)were first described in 2008.[41] Dental papilla is basically embryonic tissue that is responsible for the formation of dental pulp and the crown. SCAPs can only be isolated at certain specific stages of the development of tooth. Dental papilla contain higher number of adult stem cells than mature dental pulp, therefore SCAPs have a greater potential for regenerating dentin than DPSCs.[42] Study by Sonoyama W. et al. demonstrated formation of dental connective tissue is induced by a combination of SCAPs and PDLSCs.[42]

SCAP showed similar osteo/dentinogenic with lower adipogenic differentiation potential when compared to DPSCs and BMMSCs. SCAP also expressed a higher proliferation rate and mineralization potential when compared to DPSCs.[43] SCAP expressed positively for STRO-1, CD146 and CD34 and negatively for CD45. SCAP also expressed

multiple dentinogenic markers including ALP, bone sialo phosphoprotein, osteocalcin[43] and the growth factors TGF betaRI and FGFR1.[42] SCAP express lower levels of DSP, matrix extracellular phosphoglycoprotein (MEPE), transforming growth factor b receptor II (TGFbRII), FGFR3, Flt-1 (VEGF receptor 1), Flg (FGFR1), and melanoma. associated glycoprotein (MUC18) when compared to DPSCs, 40. Upon stimulation with a neurogenic medium, SCAP expressed neurogenic markers as nestin and neurofilament M.[42]

Conclusion

1. Dental pulp is a remarkable site of stem cells;
2. Collecting stem cells from dental pulp is a noninvasive practice that can be performed in the adult during life and in the young after surgical extraction of wisdom teeth, or exfoliating deciduous tooth having sufficient root a common surgical practice;
3. Tissue sacrifice is very low when collecting dental stem cells hence no ethical concerns;
4. Dental pulp is ideal for tissue engineering and for clinical use in several pathologies requiring tissue growth and repair.
5. Bone marrow is considered the site of first choice for hematopoietic stem cell collection, dental pulp is considered as one of the major sites for mesenchymal cell collection.
6. Finally concluding authors suggests need for more work with dental stem cells to be considered as a future perspective for treatment of various dental as well as medical disorders.

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