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Stem Cells: Future Arena of Regeneration

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Review Article

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Abstract: Periodontal ligament stem cells (PDLSCs), which reside in the perivascular space of the periodontium, possess characteristics of mesenchymal stem cells and are a promising tool for periodontal regeneration, as they can be harvested with considerable ease and are associated with minimal donor morbidity. Hence this review deals in detail with the various characteristics of MSCs, which support their capability to differentiate into periodontal cells, and the extent to which they have been utilized in periodontal regeneration.
Keyword: Mesenchymal stem cells, periodontal regeneration, periodontal ligament stem cells

INTRODUCTION

Regenerative periodontal therapy is designed to restore the structure and function of the periodontium, thereby, promoting the formation of new cementum, alveolar bone and functionally oriented periodontal ligament (PDL) [1]. With tissue regeneration, damaged periodontal tissues can be repaired via application of stem cells, growth factors, or an extracellular matrix scaffold. The concept that stem cells may reside in the periodontal tissues was first proposed almost 20 years ago by Melcher. The most compelling evidence that these cells are present within the periodontal tissues has been provided by the in vivo and histological studies of McCulloch and coworkers [2-5].

To date, several types of stem cells have been investigated for periodontal regeneration, which comprise mesenchymal stem cells (MSCs), embryonic stem cells (ESCs), and induced pluripotent stem cells (iPSCs) [6]. Mesenchymal stem cells are emerging as a promising therapeutic approach of cell-based therapy for a wide range of diseases.

Stem Cells

Primitive cells with very high potential and infinite ability of self-renewal and differentiation into other cell types [7]. According to their origin and differentiation potential, stem cells are classified as:

- Embryonic stem cells
- Adult stem cells
- Induced pluripotent stem cells

Embryonic stem cells are derived from the inner cell mass of blastocyst stage of embryonic developments, prior to implantation in the uterine wall. They are pluripotent stem cells, which imply that they are capable of giving rise to cells of all three germ layers. Hence the ideal source for periodontal regeneration [8]. However, their use in clinical therapy has been hampered by ethical concerns [9]. Another important disadvantage is that, their implantation in the human body has been associated with the occurrence of rare cancers [8].

The *adult stem cells* are basically undifferentiated cells found among differentiated cells in a tissue organ, also referred to as Mesenchymal Stem Cells (MSCs). They have the ability to proliferate and differentiate to yield the major specialized cell types of the tissue or organ. Also, they adhere to plastic and have specific surface antigens (CD105, CD73, and CD90) [10].

MSCs derived from the bone marrow are referred to as *bone marrow derived mesenchymal stem cell* (BMMSC) and have been the most studied amongst mesenchymal stem cells [11-13]. They have been shown to form the supporting structures of the tooth suggesting it to be an excellent source for periodontal regeneration [14].

BMMSCs were incorporated in class III furcation defect in canine models and found them present even after 1 month, suggesting that they ultimately form various periodontal cells needed for

regeneration [15]. Also, Yamada, *et al*. [16] managed to successfully carry out periodontal regeneration using autologous BMMSCs and platelet-rich plasma.

Since harvesting BMMSCs is associated with certain limitations such as pain, morbidity and decreased number of cells obtained, therefore alternate sources for obtaining MSCs to carry out periodontal regeneration have been sought.

Findings of Lin et al provide the first evidence that stem cells participate in the healing of regenerating periodontal defects in humans and offer support for the use of stem-cell based tissue engineering in regenerative periodontal therapy. Gomez et al demonstrated the use of human periodontal ligament cell sheet technique which can be applied for regeneration of periodontal ligament–cementum complex in clinical settings [17].

The various dental MSCs that has been found till date to be useful in periodontal regeneration as illustrated in Figure 1 [10].

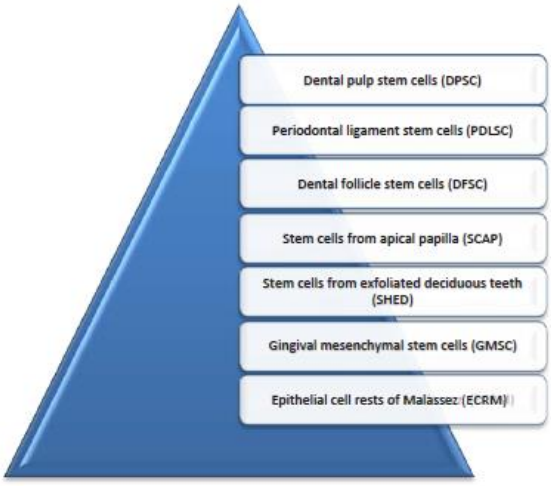

Fig-1/ Table-1: Different dental mesenchymal stem cells

MSCs	Pioneer/ Source	Properties
Dental Pulp stem cells (DPSC)	Gronthos and collaborators, 2000 isolated DPSC from Dental pulp.	1. Higher proliferation rate 2. Greater capacity to form mineral nodules, so more apt for regeneration of mineralized tissues than BMSCs. 3. Ability to differentiate into osteoblast, smooth muscle cells, adipocyte-like cells, neuron, dentin, dentin-pulp-like complex and endothelial like cells [18, 19].
Periodontal ligament stem cells (PDLSC)	Neural crest cell origin Seo et al isolated PDLSC first	1.Higher proliferation rate 2. Less mineralized nodules when compared to BMSCs. 3.Ability to differentiate into osteoblasts, cementoblasts, adipocytes, chondrocytes and Endothelial like cells. 4. In vivo experiments confirmed the ability to form periodontal ligament and cementum-like Tissue [20].
Dental follicle stem cells (DFSC)	Dental follicle	1. Differentiate into osteoblast, adipocyte, chondrocyte and neuronal cells. 2.Presents differences on proliferation and mineralization patterns which suggests that they could Commit in distinct lineages [21].
Stem cells from Apical Papilla (SCAP)	Apical Papilla at root apex of developing tooth.	1. Differentiates into osteoblastic, odontoblastic, adipocyte - like and neuron-like cells under specific induction [22]. 2. A cDNA microarray profiled comparative analysis between SCAP and DPSCs concluded that genes such as CD24 and survivin were highly expressed in SCAPS.
Stem cells from exfoliated deciduous teeth (SHED)	Remnant pulp of Exfoliated Deciduous Teeth,2003	1. Higher proliferative rate, when compared to BMSCs and DPSCs [23,24]. 2. Higher capability to differentiate in osteoblast and adipocyte-like cells when Compared to DPSCs in vitro [24]. 3. Also differentiates into odontoblast, neural cells [24,25].
Gingival mesenchymal stem cells (GMSC)	Gingival connective tissue	1. Differentiate into osteogenic, chondrogenic and adipogenic lineages. 2. Presents an immunomodulatory capacity [26].

Since periodontal regeneration is essentially a re-enactment of the development process including morphogenesis, cytodifferentiation, extracellular matrix production and mineralization, such processes support the concept that some mesenchymal stem cells remain within the periodontal ligament and are responsible for tissue homeostasis, serving as a source of renewable progenitor cells generating cementoblasts, osteoblasts and fibroblasts throughout adult life [Fig.2] [27].

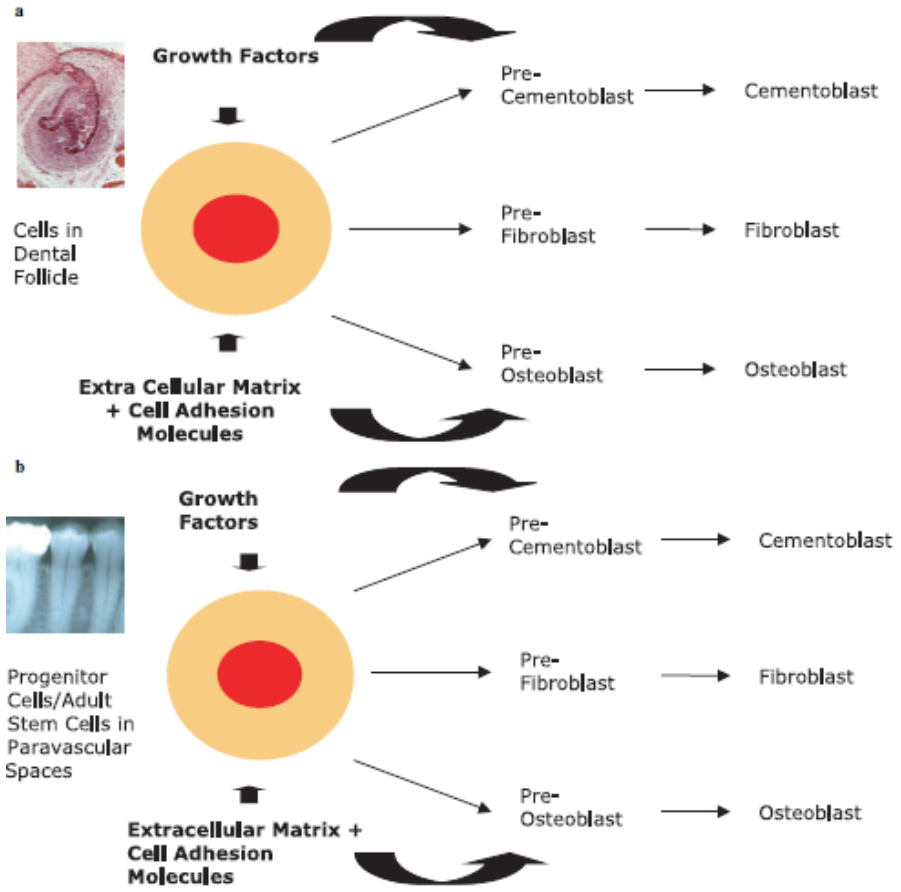

Fig-2: Role of periodontal stem cells in (a) periodontal development and (b) periodontal regeneration

Future Directions

BMSSCs express a variety of growth factors and cytokines that may control proliferation and differentiation of the host-derived cellular components of the hematopoietic system or microenvironmental compartment that they encounter. Improvements in the quality of transplanted stem cells and design of delivery vehicles are considered to be critical for the overall success of BMSSC-mediated bone regeneration.

CONCLUSION

Dental MSCs is a promising tool for periodontal regeneration. They have been found with similar characteristics as embryonic stem cells and other MSCs. Also, they are in many cases harvested from dental tissues which are to be discarded. Harvesting these cells is associated with minimal donor morbidity.

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