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PROMISING FUTURE OF STEM CELLS IN PERIODONTAL REGENERATION

Dental Science

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ABSTRACT

The periodontium is an unusually complex tissue comprised of two hard (cementum and bone) and two soft (gingiva and periodontal ligament) tissues To date, restoration of damaged or diseased periodontal tissues has relied almost entirely on the use of implantation of structural substitutes, often with little or no reparative potential. Due to issues such as the variability in safety, clinical effectiveness and stability over time of these agents, their use for periodontal regeneration has been questioned. Advances in stem cell biology and regenerative medicine have presented opportunities for tissue engineering and gene-based approaches in periodontal therapy. These new approaches offer interesting alternatives to existing therapies for the repair and regeneration of the periodontium. Here, we review current understanding of stem cells, their potential application in regenerative periodontal therapy, and discuss the challenges of translating stem cell research into clinical practice

INTRODUCTION

Periodontitis is one of the most widespread, bacteria-induced, chronic inflammatory diseases. It is considered a main cause of tooth loss and is associated with a number of systemic diseases in humans.[1]Thus, the negative impact of periodontitis on patients' quality of life indicates the need for more effective treatment of this condition.[2,3] Several procedures have been attempted to achieve periodontal regeneration, including root surface conditioning, bone graft placement, guided tissue regeneration and growth factor application. However, current regenerative procedures that are used either alone or in combination have limitations in attaining complete and predicable regeneration especially in advanced periodontal defects.[4] Recent advances in stem cell biology and regenerative medicine have presented opportunities for tissue engineering as well as gene-based approaches in periodontal therapy.[2]

The following discussion reviews our current understanding of stem cells and their potential application in regenerative periodontal therapy. Major progress in stem cell biology in the dental context is highlighted and the challenges in translating stem cell research into clinical practice are identified.

STEM CELLS AT A GLANCE:

Stem cells are the foundation cells for every organ and tissue in the body, including the periodontium.

A stem cell has two defining characteristics:[5]
(i) The ability for indefinite self-renewal to give rise to more stem cells; and
(ii) The ability to differentiate into a number of specialized daughter cells to perform specific function(s).

A stem cell can divide asymmetrically, in which case one of the two daughter cells retains the stem cell characteristics while the other is destined for specialization under specific conditions.[6]

Based on their origin, stem cells are categorized as:
i. Embryonic stem cells (ESCs)
ii. Postnatal stem cells/ somatic stem cells/Adult stem cells (ASCs)
a. Hemopoetic Stem Cells (HSCs)
b. Mesenchymal Stem Cells (MSCs).

Embryonic Stem Cells

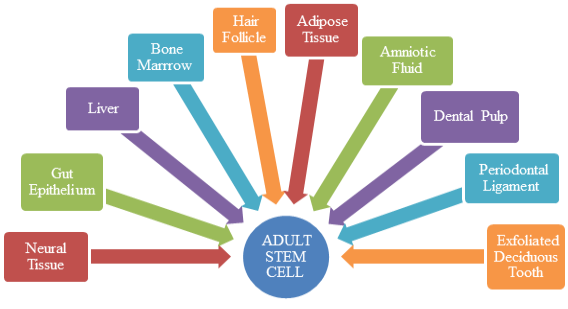
Human embryonic stem cells, derived from the inner cell mass of blastocysts, are pluripotent stem cells capable of differentiating into cells of all three germ layers of the adult body. Human embryonic stem cell lines are unique in that they can be maintained in an undifferentiated state in vitro for an indefinite period of time, while retaining their ability to differentiate into all types of specialized cells in the body.[8]

Adult Stem Cells

Adult, or tissue-specific, stem cells are found in the majority of fetal and adult tissues. Adult stem cells are thought to function in long-term tissue maintenance and/or repair by replacing cells that are either injured or lost. Adult stem cells have been used in pilot studies as potential cell-based therapy for various diseases. The following stem cell characteristics make them good candidates for cell-based therapy:[7]

a) Potential to be harvested from patients
b) High capacity of cell proliferation in culture
c) Ease of manipulation to replace existing nonfunctional genes via gene splicing methods
d) Ability to migrate to host target tissues (homing)
e) Ability to integrate into host tissues and interact with the surrounding tissues.

The most common source of adult stem cells is the bone marrow, which contains hematopoietic stem cells and bone marrow stromal cells or mesenchymal stromal/stem cells.[2]



Mesenchymal stem cells:

- Were initially identified in rodent marrow as colony-forming unit fibroblasts capable of forming bone, cartilage and fat, as well as reconstituting the hematopoietic microenvironment.

- Phenotypically, mesenchymal stem cells can express the characteristics of endothelial, perivascular, neural, bone or muscle cells, and also express a range of surface markers.

- Also been shown to form cementum, periodontal ligament and alveolar bone in vivo after implantation into periodontal defects in beagle dogs, suggesting that bone marrow may be a useful source of mesenchymal stem cells for periodontal regeneration.

Stem Cells in Dental and Periodontal Tissues

- The first human dental stem cells were isolated from dental pulp tissue of extracted third-molar teeth and were characterized relative to bone marrow mesenchymal stem cells, were found to be highly proliferative, clonogenic cells capable of differentiating into odontoblast-like cells and forming dentin / pulp-like complex when implanted into immunocompromised mice.[9]

- Periodontal ligament stem cells were first isolated in 2004 and have been shown to give rise to adherent clonogenic clusters resembling fibroblasts. They are capable of developing into adipocytes, osteoblast-like cells and cementoblast-like cells in vitro as well as producing cementum -like and periodontal ligament-like tissues in vivo.[10]

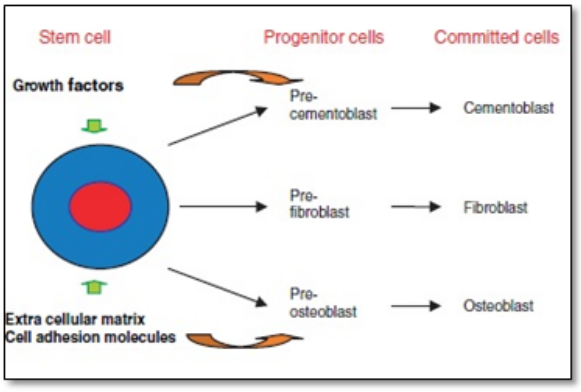


Figure 1: *Differentiation of adult mesenchymal stem cells and progenitor cells into periodontal cells*

Periodontal ligament stem cells also express an array of cementoblast and osteoblast markers as well as the STRO-1 and CD146 antigens, which are found on dental pulp stem cells and bone marrow mesenchymal stem cells. These findings indicate that periodontal ligament stem cells have properties similar to those of dental pulp stem cells and bone marrow mesenchymal stem cells, and this may represent another mesenchymal stem cell-like population.[11]

POTENTIAL APPLICATION OF STEM CELLS IN DENTISTRY[7]

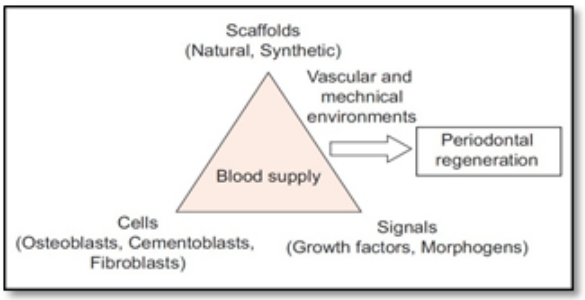
The regenerative potential of adult stem cells obtained from various sources including dental tissues has been of interest for clinicians over the past years and most research is directed toward achieving the following:

Regeneration of damaged coronal dentin and pulp Regeneration of resorbed root, cervical or apical dentin, and repair perforations Periodontal regeneration Repair and replacement of bone in craniofacial defects Whole tooth regeneration.

Potential Application of Stem Cells in Periodontal Regeneration Stem cells have been used extensively in many medical disciplines for the repair and / or regeneration of defective tissues and organs In dentistry, the identification of mesenchymal stem cell-like populations from both dental and non-dental tissues has presented exciting possibilities for the application of tissue engineering as well as gene based therapies. These techniques have the potential to lead to the development of novel strategies for regenerative periodontal therapy.[2]

Periodontal Tissue Engineering

Tissue engineering is a contemporary area of science based on the principles of cell biology, developmental biology and biomaterials science to develop new procedures and biomaterials to replace lost or damaged tissues.



This approach may overcome a major shortcoming associated with conventional regenerative e procedures because the recruitment of progenitor cells and growth factors is negated and healing can be enhanced.

Tissue-engineering strategies have been applied to reconstruct damaged periodontal apparatus, either by reiteration of tooth development based on epithelial– mesenchymal tissue recombination or by seeding of cells on biomaterial scaffolds.

The technique of cell transplantation, within three-dimensional matrices, to regenerate the periodontium has been extensively studied.

Snyder EY *et al.* [12]	Swine stem cells from the apical papilla were combined with periodontal ligament stem cells to regenerate root and periodontal structure in minipigs.
Kawaguchi H *et al.* [13]	Autologous bone marrow mesenchymal stem cells and adipose-derived stem cells can regenerate alveolar bone and periodontal ligament-like structures after transplantation in
Trubiani O *et al.* [11]	Dental stem cells were to achieve periodontal regeneration both in vitro and in vivo. In these studies, progenitor cells were seeded directly onto biomaterial scaffolds (e.g. polyglycolic acid, calcium phosphate material, collagen sponges) followed by transplantation into periodontal defects in animal models.
Gomez *et al.* [14]	Demonstrated the use of human periodontal ligament cell sheet technique which can be applied for regeneration of periodontal ligament-cementum complex in clinical settings.
Mizuno *et al.* [15]	Attempted to regenerate periodontal tissue defects by grafting autologous cultured membrane derived from the periosteum.
Yamada *et al.* [16]	Reported a novel approach to periodontal regeneration with mesenchymal stem cells and platelet-rich plasma (PRP).
Lin *et al.* [17]	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.

An ideal source of stem cells for periodontal regeneration should be:[18]

- Nonimmunogenic,
- Highly proliferative,
- Easy to harvest,
- Resilient to prolonged processing and
- Able to differentiate into desired cell types.

Human-induced pluripotent stem cells can be derived from a dental source (e.g. gingival fibroblasts of the patient) and then differentiated into a variety of autologous cell types (including dental stem cells and

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dental epithelium) for in vivo administration.

Stem Cell-Mediated Gene Therapy

In the context of periodontal regeneration, gene therapy seeks to optimize the delivery of agents, such as growth factors; to periodontal defects so that the limitations associated with the efficacy of topical application of these factors (e.g. a short duration of action) can be overcome. Two potential strategies for delivering therapeutic Trans genes into human recipients are:[18]

(i) The direct infusion of the gene of interest using viral or nonviral vectors in vivo; and
(ii) The introduction of the gene into delivery cells (often a stem cell) outside the body ex vivo followed by transfer of the delivery cells back into the body.

The inherent proliferative and pluripotent capabilities of stem cells may offer lifelong opportunities for treatment by repairing, replacing or regenerating the damaged tissues. The use of such technology with dental stem cells may offer an alternative to conventional methods as a result of their ability to provide a renewable source of growth factor release for regeneration. However, much work is still needed to optimize the number of cells that are virally transduced and to maximize the duration and extent of gene expression. Further research is also needed to address the potential risks of viral recombination and immune responses towards viral antigens, which may ultimately determine the success of gene-transfer techniques in periodontal regeneration.[19]

CHALLENGES IN BRINGING STEM CELL-BASED RESEARCH TO PRACTICE

Many challenges remain in bringing stem cell research to clinical practice in humans, and it is important to overcome these challenges to fulfill our goal of treating periodontal diseases with stem cell-based therapy.

Furthermore, these challenges can be categorized into following:

Biological Challenges	Technical Challenges	Clinical Challenges
The molecular pathways that underlie stem cell self-renewal and differentiation are largely unknown	The technical challenges in stem cell therapy are associated with cell manipulations, scaffold materials and delivery systems.	Immune rejection after administration, oncogenic properties of stem cells and functional integration of transplanted tissues into the host.

CONCLUSION

Stem cells derived from all sources hold immense medical promises. Stem cell therapies have virtually unlimited medical and dental applications. While there are several barriers that need to be broken down before this novel therapy can be translated from lab to clinics, it is certain that the future is going to be exciting for all of us. In particular, a thorough understanding of the underlying processes in periodontal development, as well as the mechanisms behind stem cell self-renewal and differentiation, will be required. Refinement of current laboratory techniques to facilitate handling of stem cells and their translation to a clinical setting will be equally critical in advancing the field. Studies on both embryonic cells and adult stem cells should continue as part of a collective effort to expand our knowledge on how cells function and what fails in the disease process. It is this combined and solid knowledge base that will underpin future treatment modalities and ultimately make stem cell-based tissue engineering and gene therapy a realistic alternative in periodontal regeneration.

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