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# STEM CELLS: A NEWER APPROACH IN PERIODONTAL REGENERATION

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| **Dr. Benita Maria Regi** | Post graduate, Department of Periodontology, Rajarajeswari dental college and hospital, Bangalore. |
| **Dr. Savita S*** | Principal, Professor and Head of the Department, Department of Periodontology, Rajarajeswari dental college and hospital, Bangalore.*Corresponding Author. |

**ABSTRACT** Regeneration of tissues destroyed by periodontitis has long been an altruistic goal of periodontal therapy. Current regenerative procedures have limitations in attaining complete and predicable regeneration, especially in advanced periodontal defects. To date periodontal regeneration is considered to be biologically possible but clinically unpredictable. Stem cells are the novel entrant in periodontal regeneration. Recently, reports have begun to emerge demonstrating that populations of adult stem cells reside in the periodontal ligament of humans and other animals. This opens the way for new cell-based therapies for periodontal regeneration.

**KEYWORDS :** Stem Cells, Periodontal Regeneration, Tissue Engineering

## INTRODUCTION

Chronic periodontitis is a disease of the periodontium characterized by irreversible damage in connective tissue attachment and supporting alveolar bone. This destruction will lead to a functionally and aesthetically questionable dentition. Hence there has been an increased interest in the management of periodontal disease and as a result, improve the patient's quality of life. However current regenerative procedures have limitation in attaining complete and predictable regeneration especially in advanced periodontal defects[1-2].

Tissue engineering as proposed by Langer, et al. comprises of multiple progenitor cells, signalling molecules and conductive extracellular matrix scaffold, along with an adequate blood supply[3-4]. Scaffolds act as the extracellular matrix creating an environment suitable for cell proliferation and differentiation for a limited period of time. Hence scaffolds should fulfill certain requirements such as shape, pore size, rate of porosity to provide a viable extracellular matrix to the cells[5]. Signalling molecules also referred to as immunomodulatory polypeptides are essential to enhance cellular activities such as cell proliferation, differentiation, migration and apoptosis. Finally, progenitor cells or stem cells thriving within the scaffolds process the signals and carry out tissue regeneration[6].

According to Hynes, et al. the most critical component of tissue engineering is the choice of stem cell population[7]. Currently studies on stem cells have made an achievable progress as a potential application in regenerative periodontal therapy. amongst which mesenchymal stem cells are gaining considerable interest due to their unique properties[8-9]. Hence, we have focused on the scope of stem cells in periodontal regeneration.

## STEM CELLS

They are defined as clonogenic cells, which are capable of both self-renewal and multi-lineage differentiation[10]. 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

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

### Adult stem cells

The adult stem cells are basically undifferentiated cells found among differentiated cells in a tissue organ. They are also referred to as Mesenchymal Stem Cells (MSC). They have a characteristic feature of being able to proliferate and differentiate to yield the major specialized cell types of the tissue or organ.

### A) Bone Marrow derived Mesenchymal Stem Cells (BMMSC)

MSCs derived from the bone marrow are referred to as bone marrow derived mesenchymal stem cell (BMMSC). They have been incorporated in class III furcation defects in canine models resulting in successful results. 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.

### B) Dental MSCs:

These are found in various dental tissues. They are easier to harvest and associated with lesser patient related complications.

**1.Dental pulp stem cells (DPSCs)**:

In an investigation, Gronthos, et al. isolated from adult human dental pulp a clonogenic, rapidly proliferative population of cells which were found to be similar to BMSCs. Human derived DPSCs along with hydroxyapatite or beta tricalcium phosphate have been reported to be capable of forming bone and cementum. However, some authors are skeptical about the role of these cells in periodontal regeneration.

**2.Periodontal Ligament stem cell (PDLSC):**

Multipotent stem cells from human periodontal ligament were isolated for the first time by Seo, et al. He reported that PDLSCs exhibited some characteristic features similar to BMMSCs. The peculiar features were multipotency, clonogenic ability, high proliferation and expression of putative stem cell marker such as STRO-1 and perivascular cell marker CD 146 and it was concluded that periodontal ligament derived MSC are one of the most effective sources for periodontal regeneration.

**3.Stem cells from apical papilla (SCAP):**

Apical papilla is the soft tissue present at the apices of developing roots of permanent teeth. It is responsible for the formation of the radicular pulp hence SCAP resemble DPSCs however, they are comparatively more immature hence superior for tissue regeneration. They are isolated from tips of developing roots, hence can be harvested easily during extraction of impacted third molars.

**4.Dental Follicle Stem Cells (DFSC):**

Dental follicle is an ectomesenchyme derived loose connective tissue sac surrounding the developing tooth bud from which arises the alveolar bone, cementum and periodontal ligament. DFSCs are relatively easy to harvest as can be procured from the follicles of unerupted third molars. Wnt5a proteins have been found to play an important role in stimulating and regulating the role of DFSCs in forming non-mineralizing PDL and mineralized alveolar bone and cementum.

**5.Stem cells from Human Exfoliated Deciduous teeth (SHED):**

They have a higher proliferation rate as compared to BMMSC and PDLSC, also result in increased bone formation. SHED instead of directly forming the specific cells, create a special template for recruiting host cells, resulting in inducing the new tissue formation.

### 6.Gingival Mesenchymal stem cells (GMSC):

Oral MSCs derived from human gingiva (GMSCs) also have been considered as a promising alternative cell source for periodontal regeneration. In addition to physical characteristics of gingival fibroblasts they exhibit adherence to plastic and multilineage differentiation potential. In a canine model with class III furcation defects, the transplanted GMSCs significantly enhanced the regeneration of the damaged periodontal tissue, including the alveolar bone, cementum, and functional periodontal ligament[11].

### Induced Pluripotent stem cells

Apart from the MSCs, experiments have been carried out to test whether somatic cells can be induced to transform into pluripotent stem cells. Cells obtained from oral epithelium or other dental sources can be easily transformed to the desired cell type using the required transcription factors. These stem cells have drawn considerable attention since they are very similar to embryonic stem cells, hence considerable potential in periodontal regeneration.

## CURRENT TREATMENT APPROACHES

### 1.Cell Sheet Engineering:

Although stem cells may be a promising source of periodontal regeneration, for better results they need to be transferred to the target site with appropriate scaffold and the correct signalling molecules for them to differentiate into the desired tissues.

Conventionally, tissue engineering involved the incorporation of cells, growth factors and scaffold separately into the defect. Over the years, researchers attempted at culturing cells in vitro under ideal conditions resulting in formation of cell sheets which were separated from the substratum by enzymatic treatment and placed at the target site. This however was found to impair cell functions, since the proteolytic enzymes used hydrolyse various membrane associated proteins resulting in damage to the cell membrane. Pioneering work carried out by Okano, et al. in the field of cell sheet engineering helped in overcoming this issue and making it a viable mode of periodontal regeneration.

Okano, et al. incorporated a temperature responsive polymer poly(N-isopropylacrylamide) (PIPAAm) in the culture dishes to detach the cell sheets. Since this polymer is hydrophilic at temperatures greater than 32°C and hydrophobic when temperature is reduced below 32°C, also cells adhere to hydrophobic surfaces, therefore it is a useful aid in detaching the cells from the culture dishes. Cell sheet engineering with the help of temperature responsive dishes can act as an effective means for periodontal regeneration. These temperature responsive cell sheets can be grafted to recipient site without suturing. Cell sheet engineering has been extensively applied for periodontal regeneration by researchers in vitro and in animal studies[11].

### 2.Gene and cell-based therapy

The inherent proliferative and pluripotent capabilities of stem cells may offer treatment of human diseases, including periodontitis, by repairing, replacing or regenerating damaged tissues. Stem cells may act as suitable vehicles for the delivery of therapeutic genes in gene therapy, and as therapeutic agents per se in cell-based therapy. Gene therapy is a new approach for the treatment of human diseases. It relies on genetic engineering, which involves molecular techniques to introduce, suppress or manipulate specific genes, thereby directing an individual's own cells to produce a therapeutic agent. 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 topical application (e.g., short duration of action) can be overcome.

Two major strategies for delivering therapeutic transgenes into human recipients are:

(1) direct infusion of the gene of interest using viral or non-viral vectors in vivo; and
(2) introduction of 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 use of both in vivo and ex vivo gene delivery strategies via adenoviral (Ad) vectors encoding growth promoting molecules such as platelet-derived growth factor (PDGF) and bone morphogenetic protein-7 (BMP-7) has been investigated for its potential in periodontal regeneration by Giannobile and colleagues. The introduction of transgenes into dental stem cells may offer an alternative to conventional methods because stem cells have the potential to provide a sustained source of growth factors for regeneration[9].

However, much work is still needed to optimize the number of cells that are virally transduced to express specific genes, in order to maximize the duration and extent of gene expression, and ultimately to determine the success of gene transfer techniques in periodontal regeneration. Further research is also needed to address potential risks of viral recombination and immune responses towards viral antigens which could potentially hinder the progress of gene therapy in treating periodontal diseases.

## LIMITATIONS

| Biological | Technical | Clinical |
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| Molecular pathways responsible for stem cell proliferation and differentiation are unknown | Culture mediums are not well developed enough to mimic in vivo conditions to ensure safe and consistent stem cell proliferation and differentiation.<br>Stem cell line production for human trials could be hampered by the use of xenogenic products in culture mediums as they could be a potential source of pathogens.<br>Mesenchymal stem cells have a limited life span unlike embryonic stem cells which are immortal<br>An ideal biocompatible scaffold and transport mechanism is still under research. | Integration of the human stem cell derivatives with the recipient tissue and their ability to carry out the desired functions in humans is still under speculation |

## CONCLUSION

Stem Cells are currently the focus of research as these cells can be harvested with considerable ease and are associated with minimal donor morbidity. Research into the use of stem cells for tissue regeneration has the potential to significantly influence periodontal treatment strategies and lead to complete restoration of the lost tissues to their original architecture and function.

## REFERENCES


1. Pejcic A, Kojovic D, Mirkovic D, Minic. Stem cells for periodontal regeneration. BJMG 16/1 (2013) 7-12
2. Sander l, Karring t. Healing of periodontal lesions in monkeys following the guided tissue regeneration procedure. A histological study. J clin Periodontol. 1995; 22(4):332-337
3. Langer R, Vacanti JP. Tissue engineering. Science. 1993 May 14;260(5110):920-6
5. Srisuwan T, Tilkorn DJ, Wilson JL, Morrison WA, Messer HM, Thompson EW, Abberton KM. Molecular aspects of tissue engineering in the dental field. Periodontol 2000.2006;41: 88-108
6. Graziano A, d'Aquino R, Cusella-De Angelis MG, De Francesco F, Giordano A, Laino G, Piattelli A, Traini T, De Rosa A, Papaccio G. Scaffold's surface geometry significantly affects human stem cell bone tissue engineering. 1J Cell Physiol. 2008 Jan;214(1):166-72
7. Nör JE. Tooth regeneration in operative dentistry. 1Oper Dent. 2006 Nov-Dec;31(6):633-42
8. Hynes K, Menicanin D, Gronthos S, Bartold PM. Clinical utility of stem cells for periodontal regeneration. Periodontol 2000. 2012;59(1):203-27
9. Lin NH, Gronthos S, Bartold PM. Stem cells and periodontal regeneration. Aust Dent J. 2008 53(2):108-121.
10. Han J, Menicanin D, Gronthos S, Bartold PM. Stem cells, tissue engineering and periodontal regeneration. Aust Dent J. 2014; 59(1):117-30.
11. Thomas GV, Thomas NG, John S, Ittycheriya PG. The scope of stem cells in periodontal regeneration. J Dent Oral Disord Ther 3(2): 1-9.