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Research Article

TISSUE ENGINEERING- A NOVEL TECHNIQUE FOR PERIODONTAL REGENERATION

Pramod Waghmare[1] and *Ketaki Kanade[2]

[1]Department of Periodontology, Bharati Vidyapeeth Dental College and Hospital, Pune
[2]Bharati Vidyapeeth Dental College and Hospital, Pune

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ABSTRACT

Periodontal regeneration attributes to a complete recovery of the periodontal tissues in both height and function, that is, the formation of alveolar bone, a new connective attachment through collagen fibers functionally oriented on the newly formed cementum. Regeneration of the periodontal tissues is a complex phenomenon requiring interplay between various processes in a timely manner. Healing of the periodontal tissues is a complex phenomenon as it is permanently contaminated and is under a significant bacterial load. Added to this complexity are the occlusal forces on the tooth complex in the transverse and the axial planes which affect the stability of the healing wound. Complete regenerationis still considered a difficult and often resulted in incomplete regeneration. Tissue engineering has emerged as an alternative approach for the regeneration of periodontal tissues damaged by disease or trauma. This review article provides an insight into the principles and application of tissue engineering in treating periodontal diseases.

INTRODUCTION

The goal of periodontal treatment is to restore the periodontal attachment which includes restoration of cementum, periodontal ligament, and alveolar bone which are lost due to periodontal diseases or trauma. In the past decades, attempts have been made to explore various filler materials that can result in new clinical attachments, but have failed and showed healing by repair. Periodontal repair is a type of healing of a wound that attempts to restore the normal function and structure of the tissue and is considered as non-functional scarring. Periodontal regeneration attributes to the formation of alveolar bone, a new connective attachment through collagen fibers functionally oriented on the newly formed cementum. *(Illueca FM 2006)*

Tissue engineering was suggested as a technique for regenerating lost periodontal tissues by Langer and colleagues in 1993 *(Nakahara T 2006).* Tissue engineering is an interdisciplinary method that applies principles of engineering and the life sciences towards the development of biological substitutes that restore, maintain, and improve the function of damaged tissues and organs *(Abukawa H et al 2006).*The goal of tissue engineering is to promote healing, and ideally, true regeneration of a tissue's structure and function, more predictably, more quickly, less invasively, and more qualitatively than allowed by previous passive techniques. *(Lynch SE 2006, Mohammadi M 2007)*

Tissue engineering and Periodontium: It is a concept that uses applied biomedical research that aims at developing procedures and biomaterials which helps in regeneration of new tissues to replace the damaged tissues. The basic requirements for producing an engineered tissue are the appropriate levels of signaling molecules, the presence of responsive progenitor cells, an appropriate extracellular matrix, and an adequate blood supply for better healing till the desired outcome is achieved. *(Risbud MV 2005.)* The natural wound healing process usually results in tissue scarring or repair. With the use of tissue engineering, the wound healing process is manipulated so that tissue regeneration occurs.

The damaged tissues heal either by regeneration or repair and that depends upon two factors.

- The availability of cell types needed; and
- The presence or absence of cues or signals necessary to recruit and stimulate these cells.

Tissue engineering combines three key elements that bring upon regeneration.

1. Conductive scaffolds/Extracellular matrix.
2. Signalling molecules.

Corresponding author:* **Ketaki Kanade
BharatiVidyapeeth Dental College and Hospital, Pune

3. Stem/Progenitor cells.*(Kao RT 2000)*

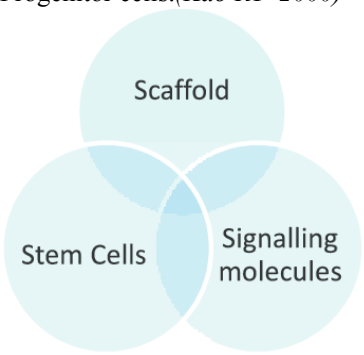

Figure 1 The Tissue Engineering Triad

Scaffolds

The scaffold provides a 3D substratum on to which the cells can proliferate, migrate, produce a matrix and form a functional tissue with a desired shape. An appropriate, bioactive three-dimensional scaffold is required for the promotion of cellular proliferation and differentiation. Scaffold plays a critical role in periodontal tissue engineering.

Functions of a scaffold in tissue regeneration process: *(Spector M 2006)*

- It provides a framework to support cellular migration into the defect area from the surrounding tissues.
- It provides penetration of exogenous cells, growth factors, and genes.
- It may structurally reinforce the defect to maintain the shape of the defect.
- It serves as a barrier for the surrounding tissue that may impede the process of regeneration.
- A scaffold can serve as a matrix for exogenous and endogenous cell adhesion and thus can facilitate and regulate certain cellular processes, including mitosis, synthesis and migration.

Biomaterials used as scaffolds - Biomaterials used as scaffolds in tissue engineering are classified into two broad categories.

- Naturally derived.
- Synthetic.

Liao et al. (2010) in a study compared porous beta-tricalciumphosphate/chitosan composite scaffolds with pure chitosan scaffolds. Composite scaffolds showed higher proliferation rate of human periodontal ligament cells (HPLCs) and up-regulated the gene expression of bone sialoprotein and cementum attachment protein. In vivo, HPLCs in the composite scaffold not only proliferated, but also recruited vascular tissue in growth; thus, suggesting the benefit of using these composite scaffolds**.**

Table 1 Biomaterials used as scaffold(Um YJ 2008, Stavropoulos A 2010, Ballini A 2009, Lin HR 2004, Tabata M 2005, d'Aquino R 2009, Chan WD 2009, Lee YM 2000, Gunatillake PA 2003, Xu XL 2005 , Abukawa H2003, Kim S 2008, Laurencin CT 2003, Mohan 2008)

Naturally derived	Synthetic
Ceramic	Polyglycolic acid (PGA)
Hydroxyapatite (HA)	Polylacticacid (PLA)
Tri-calcium phosphate (TCP)	Poly (lactic-co-glycolic) acid (PLGA)
Hyaluronic acid	Polyphosphezene
Alginate	Nano calcium sulphate
Albumin	PLGA/HA matrices
Collagen	PLGA copolymer foam

Cells

Cell source is an important parameter to consider when applying tissue engineering strategies to restore lost tissues and functions.

Stem cells are immature progenitor cells that are capable of self-renewal and multi-lineage differentiation through a process of asymmetric mitosis that leads to two daughter cells, one identical to the stem cell (daughter stem cell) and one capable of differentiation into more mature cells (progenitor cells). *(Nadig RR 2009)*

Stem cellsmay be

1. Totipotent, i.e. early embryonic cells (one to three days from oocyte fertilization), which can give rise to all the embryonic tissues and placenta.
2. Pluripotent, i.e. embryonic cells from blastocystis (4-14 days after oocyte fertilization), which can differentiate only into embryonic tissues belonging to the inner cell mass (ectoderm, mesoderm, and endoderm).
3. Multipotent, i.e. embryonic cells from the 14th day onwards, which can give rise to tissues belonging to only one embryonic germ layer (ectoderm or mesoderm or endoderm). *(KramperaM et al 2007)*

Depending on the development stage of the tissues from which the stem cells are isolated, stem cells can be broadly divided into two categories: Adult stem cells and embryonic stem cells.(ShamblottMJ *et al* 1998, Thomson JA 1998, Pittenger MF 1999)

Table 2 Stem Cells Used For Periodontal Regeneration

1. Dental Pulp Stem Cells
2. Periodontal Ligament Stem Cells
3. Dental Follicle Stem Cells
4. Dental Epithelial Cells

Dental Pulp Stem Cells: In 2003, Shi and Gronthos isolated dental pulp stem cells through immunoselection. *(Risbud MV 2005)*. Odontoblasts possess its ability to form new functional odontoblast even after complete tooth development. It has the ability to form reparative dentin when exposed to deep caries and mild trauma or pulp capping. When third molar is extracted and it is cultured in suitable condition it has shown that Human dental pulp cells (odontoblastlike cells) produce dentin.*(BansalR 2015)*

Periodontal Ligament Stem Cells: Periodontal ligament stem cells reside in the perivascular space of the periodontium and possess characteristics of mesenchymal stem cells and are a promising tool for periodontal regeneration. *(Brar GS 2012)*. Principle of guided tissue regeneration is based on this principle that periodontal ligament cell have the potential to give rise to various cells. *(Zhu W 2015)*. Multipotent progenitors from human PDL were shown to generate bone. These cells have also been shown to retain stem cell properties and tissue regeneration capacity even after recovery from solid-frozen human primary tissue. These findings suggest that cryopreserved PDLSCs from extracted teeth could prove useful for clinically relevant therapeutic applications in the future. *(NosratA 2014, Tatullo M 2015)*

Dental Follicle Stem Cells: These cells are considered as multipotent, based on their ability to generate cementum, bone and PDL from the ectomesenchyme derived fibrous tissue. Human dental follicle progenitor cells obtained from human third molars exhibit a characteristic ability to attach to tissue culture plastic. Dental follicle stem cells express side population stem cell markers and the demonstrated ability to differentiate into not only osteoblasts/cementoblasts but also adipocytes and neurons.

Dental Epithelial Stem Cells: Once enamel is formed and maturation stage is reached, oral ectoderm-derived ameloblasts are unable to proliferate or regenerate. However, continuously growing mouse incisors, and molars in some mammalian species, exhibit constantly replenishing populations of enamel organ tissue-derived stellate reticulum, stratum intermedium and surrounding outer enamel epithelial cells, providing a source of tissues to harvest for characterization of dental epithelial stem cells. *(Asatrian G 2015).* A specialized structure located at the apical region of the labial cervical loop in mouse incisors was characterized and named the 'apical bud' were suggested to act as stem cell containing compartments that could differentiate intoameloblasts through interaction with adjacent mesenchymal cells. *(Saito MT 2015)*

Signaling Molecules

Signaling molecules are proteins that may act locally or systemically to affect the growth and function of cells in various manners. The signaling molecules that have been studied largely are growth factors and morphogens which act by altering the cell phenotype i.e. they cause the differentiation of stem cells into bone forming cells. This process is known as osteoinduction.

These cytokines have pleotropic effects some of which include

- Mitogenic(proliferative);
- Chemotactic (stimulate directed migration of cells); and
- Angiogenic (stimulate new blood vessel formation) effects.*(Lynch SE 2006)*

Growth factors act on the external cell membrane receptors of a target cell, provide the signal to local mesenchymal and epithelial cells to migrate, divide, and increase matrix synthesis. The growth factor that has received the most attention in hard and soft tissue wound healing is platelet derived growth factor.

Table 3 Various growth factors and their actions

Insulin like growth factor-1	Cell proliferation, migration, differentiation and matrix synthesis
Transforming growth factor- beta 1	Proliferation of cementoblasts and PDL fibroblasts
Growth differentiation factor-5	Plays critical roles in tendon, skeletal, and ligament morphogenesis inhibits alkaline phosphatase activity in human periodontal ligament cells,
Periodontal ligament derived growth factor	Highly specific autocrine chemotactic agent for human periodontal ligament cells, which is1000 fold more potent than many known growth factors (IGF, PDGF, TGF)
Platelet-derived growth factor	Migration, proliferation and non-collagenous matrix synthesis of mesenchymal
Fibroblast growth factor-2	Proliferation and attachment of endothelial cells and periodontal ligament cells
BoneMorphogenicProteins (BMP)	Protein proliferation, differentiation of osteoblasts and differentiation of PDL cells into osteoblasts

Insulin like growth factor 1: Insulin like growth factor 1 is found in substantial levels in platelets and is released during clotting along with the other growth factors. It is a chemotactic agent for vascular endothelial cells that results in increases neovascularization. It promotes osteogenes is and cementogenesis. *Matsuda et al*. in 1992 demonstrated the mitogenic effects of insulin growth factor on periodontal ligament fibroblastic cells and concluded that a synergistic effect results from using a combination of platelet derived growth factor and insulin like growth factor 1.

Transforming growth factor β: TGFβ is found in highest concentration in bone and platelets. TGF-β is a strong promoter of extracellular matrix production. It selectively stimulates periodontal ligament fibroblast proliferative activity. It stimulates type I collagen, fibronectin and osteocalcin biosynthesis, as well as bone matrix deposition and chemotaxis of osteoblast. On the other hand, TGF-β decreases synthesis of metalloproteinases and plasminogen activator, and also increases the synthesis of tissue inhibitor of metalloproteinases and plasminogen activator inhibitor, thus resulting in the decrease of connective tissue destruction. It actsas bone coupling factor linking bone resorptionto bone formation.

Growth differentiation factor-5: Growth differentiation factor-5 is a member of the transforming growth factor-beta superfamily. It plays critical roles in tendon, skeletal, and ligament morphogenesis. In vitro studies have shown that recombinant human growth ⁄ differentiation factor-5 inhibits alkaline phosphatase activity in human periodontal ligament cells. When delivered in a suitable carrier, recombinant human growth factors might allow regeneration of all periodontal tissues without the complications of ankylosis and rootresorption. (*DabraS 2012*)

Periodontal ligamentderived growth factor: *Nishimura et al*. in 1995 isolated a polypeptide factor from periodontal cells called periodontal ligament derived growth factor (PDLCTX). This peptide is highly specific autocrine chemotactic agent for human periodontal ligament cells, which is 1000 fold more potent than many known growth factors (IGF, PDGF, TGF). In addition, PDLCTX has no chemotactic effect on gingival fibroblast or epithelial cells thereby promising its utility for biological therapeutic regime needed for cell specific periodontal regeneration.*(SoodS 2012)*

Platelet-derived growth factor: *Ross et al*. in 1974 and *Kohler* and *Lipton* in 1974 suggested that the material released from platelets is the principal source of mitogenic activity present in serum, and it is one of the principal growth factors related to wound healing by growth of many cells. In vitro studies have demonstrated that platelet-derived growth factor enhances the proliferation and mitogenic activity of periodontal ligament-derived. It enhance bone and cementum formation. Lynch and co-workers demonstrated that platelet-derived growth factor-BB alone could significantly stimulate formation of new cementum and inserting collagenous fibers.

Fibroblast growth factor: Fibroblast growth factor is the member of heparin binding growth factor family. There are 7 forms of fibroblast growth factor. Besides its name activity exists beyond that of fibroblast and includes a wide variety of cell types such as smooth muscles, endothelial cells, chondrocytes and osteoblasts. It has a profound effect on

periodontal soft tissue and bone healing as it is mitogenic for fibroblasts, chondrocytes, osteoblasts, smooth muscle. FGF also stimulates DNA synthesis, angiogenesis, and cell replication.

Bone morphogenetic proteins: BMPs are bone growth factors synthesized and secreted by osteoblasts and incorporated into the organic matrix during bone formation. They are released during osteoclastic resorption and induce differentiation of mesenchymal cells into osteoblasts, stimulating osteogenesisin the remodeling and healing processes. Till now, 20 structurally related BMPs belonging to the TGF-β super family have been recognized. BMPs 2 and 7 are distinguished for their osteoinductive property, which are emerging as an alternative for filling of bone defects. However, the difficulty for their clinical use is that, because they are rapidly diffusible in biological media, to achieve maximum efficacy without the need for excessively high doses they should be associated with a carrier system that allows its continuous release in a rate compatible to that of new bone formation. In addition to undergoing controlled biodegradation, other essential requirements for a potential carrier are biocompatibility, reduced immunogenicity and no toxicity; ideally they should be osteoconductive, have mechanical stability and adequate porosity to allow infiltration of cells and support vascular ingrowth, and be sterile and user friendly.*(Cho Moon OL 1995)*

Clinical Applications of Tissue Engineering For Periodontal Tissue Regeneration

Guided tissue regeneration

Nyman and *Karring* in 1982 were the first ones to have proposed the use of guided tissue regeneration for periodontal regeneration, which marked the evolution of periodontal regeneration technologies using tissue engineering. The placement of barrier membranes over the denuded root surface and the debrided periodontal defect has shown space provision, epithelial cell occlusion, and exclusion of gingival connective tissue from the root surface and selective repopulation of periodontal ligament cells.*(Peres JA 2011)*

Protein based approaches (Murakami S 2003, Nevins M 2003)

The use of growth and differentiation factors evolved tissue engineering to its next level and has been the most popular tissue engineering approach for regeneration of periodontal tissues.

Several growth factors have been used including

- Transforming growth factor β;
- Bone morphogenetic proteins (super family members);
- Basic fibroblast growth factor; and
- Platelet derived growth factor.

Enamel matrix derivative

The rationale for the clinical use of enamel matrix derivativeis the observation that enamel matrix proteins are deposited onto the surfaces of developing tooth roots before cementumformation.

Enamel Matrix Protein (EMPs) are commercially available as Emdogain which have been known to effect periodontal regeneration. Recent data from a systematic review indicates that biologically EMPs cause an increase in cell attachment of epithelial cells, gingival fibroblasts, and PDL fibroblasts. They increase the expression of transcription factors that are related to chondroblast and osteoblasts/cementoblast differentiation. Stimulation in the synthesis of total protein and extracellular matrix molecules has also been documented. Use of Enamel matrix derivative (EMD) and a demineralized freeze dried bone allograft (DFDBA) have been demonstrated to be osteopromotive in nature; thus, resulting in an additional increase in bone formation. The only concern with the use of EMD has been related to its application and its related viscous nature, which may not provide sufficient soft tissue/flap support; thus, potentially limiting the space available for the regeneration process*. (Gestrelius S 1997, Bosshardt DD 2008, Boyan BD 2000)*

Platelet rich plasma

Since physiologic concentrations of growth factors may not be sufficient to stimulate local bone formation, the use of exogenous growth factors to supplement endogenous biological mediators has been explored. Platelet rich plasma (PRP) is a volume of autologous plasma that contains a platelet concentration above baseline values. The development of PRP from autologous blood by simple, sterile (office based and Food and Drug Administration (FDA) cleared devices) by gradient density centrifugation produces a concentration of platelets with enhanced growth factors including PDGF, TGF-β, and insulin growth factor-1. It has been reported that PRP preparations may increase the concentrations of platelets up to 338%. PRP works through transmembrane receptors and intra cytoplasmic signaling pathways, as do all other growth factor preparations. PRP stimulates the proliferation of human osteogenic cells and periodontal ligament cells. Because PRP and all growth factor preparations work through normal regulated genes and are not autogenous, they are safe promoters of biologic healing and there is no risk of promoting neoplasia. *(Marx RE 2001, Okuda K 2003)*

Role of rhBMP-2 in periodontal regeneration

The identification and development of recombinant human bone morphogenetic protein-2 (rhBMP-2) has lead to the commercial availability for the first time of an osteoinductive autograft replacement (INFUSE® Bone Graft). rhBMP-2 is a homodimeric protein consisting of two BMP-2 protein subunits.

Studies provide an important insight that space provision appears critical to draw clinically significant benefits from a BMP construct.

- rhBMP2 has been combined with ACS atellocollagensponge (ACS).
- rhBMP2 has also been used in a DFDBA as fibrin clot carrier.
- rhBMP2 and calcium phosphate cement matrix.

Hanisch O Tatakis reported that rhBMP-2/ACS at 1.5 mg/cc, INFUSE® Bone Graft, induced significant bone formation suitable for implant placement. Tissue engineering using PRP or recombinant protein therapeutics is a clinical reality in periodontal, cranio maxillofacial, and orthopedics indications**.**

(McKay WF 2007, Sigurdsson TJ 2001, Seeherman H 2006,. Hanisch O 1997)

Dental surgeons at long last have access to pure recombinant tissue growth factors, allowing us to progress from previously passive therapies to new active treatments, thereby enhancing the opportunity for regeneration of bone and other tissues and providing more predictable, faster, less invasive, less traumatic, and efficient outcome for the patient.

Cell based approaches

Cell transplantation using autologous cells is expected to play a central clinical role in the future. Dental cell seeding attempts have attempted to regenerate the periodontal tissues since 1990s. Attempts have been made to create the target tissue in the laboratory by culturing and proliferating mesenchymalcells together with scaffolds, before transplanting them into the body.

Typical cell harvesting methods using enzymatic dispersion might destroy critical cell surface proteins such as ion channels, while growth factor receptors and cell to cell junctions remain intact. *Okano et al*. in 1990 developed temperature responsive culture dishes (commercially available under the name of Up Cell TM, Cell SeedInc., Tokyo, Japan) by grafting a polymer poly N isopropylacylamide (PIPAAm) onto tissue culture graded polystyrene dishes by irradiation with an electron beam. Cells generally adhere to hydrophobic surfaces, but not to hydrophilic surfaces. Attemparatures lower than 32°C, PIPA Amis fully hydrated. This dish allowed intact cells with preserved extracellular matrix proteins and normal cell functions to be harvested with just low temperature treatment. This has evolved into a novel strategy called "Cell sheet engineering" which produces tissues without a specific scaffold. Transplanted cell sheets can be grafted to the recipient tissues without suturing.

Akizuki et al. in 2005 investigated periodontal healing after the application of periodontal ligament cell sheet in beagle dogs. These results demonstrated that, in the experimental group, periodontal tissue healing with the formation of bone, periodontal ligament and cementumoccurred in three out of the five defects.

Hasegawa et al. in 2005 assessed the ability of periodontal ligament cell sheets toregenerate the periodontal ligament tissue and demonstrated its usefulness in periodontaltissue regeneration. *Flores et al.* in 2008 evaluated whether human PDL cell sheet could reconstruct periodontal tissue and found that transplanted PDL cell sheet cultured with osteogenic differentiation medium induced periodontal tissue regeneration containing an obvious cementum layer and Sharpey's fiber.

Huang and Zhang (2010) have set forward a hypothesis of transplanting PDL cell obtained from the periodontium of autogenous extracted teeth, such as the third molar and premolar for orthodontic purposes sheets when cultured using the cell sheet engineering approach into the implant beds before inserting the implants.

Gene delivery based approaches

Studiesontissue engineeringhave investigated various gene delivery techniques. These techniques involve a gene encoding atherapeutic protein being introduced into the cells which can then express the target protein. This technique avoids the problems associated with the protein delivery method by maintaining constant protein levels at the site of the defect.*(Nakahara T 2006)*

CONCLUSION

The regeneration of the periodontiumis known to be challenging to the clinicians. Thus, the development of new therapies tissue engineered scaffolds opened a new era of the periodontal regeneration. In the near future along with conventional therapy these newer approaches will be useful for regenerating lost tissues and may become key in regenerating oral function disrupted by periodontal disease. The regeneration of the periodontiumis known to be challenging to the clinicians. Thus, the development of new therapies based on cells and/or tissuee engineered scaffolds opened a new era of the periodontal regeneration.

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