Rama Univ. J. Dent Sci. 2018 March 5(1):1-8 ISSN No. 2394-417X (print), 2394-4188(online)

Review Article

Tissue Engineering - A Novel Approach for Periodontal Regeneration

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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. Tissue engineering is a novel and exciting field that aims to re-create functional, healthy tissues and organs in order to replace diseased, dying, or dead tissues. Tissue engineering and other cell based therapies have emerged as an alternative approach for the regeneration of several tissues damaged by disease or trauma, including the periodontium. This review article focuses on the basics about tissue engineering, its principles and strategies and how these principles can be applied in periodontics to provide us with successful results.

Keywords: Tissue engineering, scaffold, progenitor cells, signaling molecules, growth factors.

Introduction

The loss or failure of an organ or tissue is one of the most frequent, devastating, and costly problems in health care as the availability of compatible donors are severely limited. The currently used alternatives such as mechanical devices or artificial prostheses do not repair the tissue or organ function and are not intended to integrate into the host tissue. The use of synthetic restorative materials as substitutes for dental structures is a practice nearly as old as dentistry itself. To date, most of the procedures performed in dentistry are limited to the replacement of damaged tissues for biocompatible synthetic materials that may not present chemical, biological, or physical characteristics and behaviors similar to the host tissues. These discrepancies, together with the hostile environment of the oral cavity, result in relatively short-lived successful outcomes and frequent need for retreatment [1].The ultimate goal of periodontal therapy remains the predictable three dimensional repair of an intact and functional periodontal attachment that replicates its pre-disease structure. While periodontal treatment, aimed at removing the bacterial cause of the disease is generally very successful. However, the ability to predictably regenerate the damaged tissues still remains a major unmet objective for conventional treatment strategies [2].Current strategies used for treatment of lost tissues include the utilization of autogenous grafts, allografts, and synthetic materials (alloplasts). One of the major shortcomings with autografts, as well as allografts, is the fact that humans do not have significant stores of excess tissue for transplantation. Also donor site morbidity, anatomic and structural problems, and elevated levels of resorption during healing might occur. Whereas in case of allografts, there always exists the possibility of eliciting an immunologic response due to genetic differences, as well as inducing transmissible diseases [1]. Tissue engineering is a novel and exciting field that aims to re-create functional, healthy tissues and organs in order to replace diseased, dying, or dead tissues [3]. The oldest sign of something that resembles what we now know as "tissue engineering" comes from the Bible. "God turning one of man's ribs into a woman truly are the first example of growing human parts out of the body". Twentieth century gave us antibiotics, revolutionary imaging technologies and most important the silicon chip, which has shrunk the world for us and brought information to our finger tips or mouse tips! 21st century can be credited with biotechnology, genomics, and last but not the least, tissue engineering [4].

The term "tissue engineering" is used when primitive, embryonic or primordial cells are used to create totally or partially lost or damaged organs. However, the term has crept into clinical armory of periodontists and has attained certain halo and glamour even when used in mundane and prosaic situations like bone grafts in intra-bony defects. It has become a fancy to use the term and most books and tomes use this term in the most diluted terms. The gold standard to replace an individual's lost or damaged tissue is the same natural tissue. This

standard has led to concept of engineering or regenerating new tissue from pre-existing tissue. Tissue engineering is the relatively new, highly promising field of reconstructive biology that draws on the recent advances in medicine and surgery, molecular and cellular biology, polymer chemistry, and physiology [4].

The term tissue engineering was initially defined by the attendees of the first National Scientific Foundation (NSF) sponsored meeting in 1988 as "application of the principles and methods of engineering and life sciences toward fundamental understanding of structure function relationship In normal and pathological mammalian tissues and the development of biological substitutes for the repair or regeneration of tissue or organ function." In 1993, Langer and Vacanti summarized the early developments in this field and defined tissue engineering as "an interdisciplinary field" that applies the principles of engineering and life sciences toward the development of biological substitutes that restore, maintain/improve tissue or organ function [1].

This field builds on the interface between materials science and bio-compatibility, and integrates cells, natural or synthetic scaffolds, and specific signals to create new tissues. Tissue engineering is viewed as synonymous to "regenerative dentistry" because the goal of tissue engineering is to restore tissue function through the delivery of stem cells, bioactive molecules, or synthetic tissue constructs engineered in the laboratory [2].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 [5]. The requirements for tissue engineering are the appropriate levels and sequencing of regulatory signals, the presence and numbers of responsive progenitor cells, an appropriate extracellular matrix, carrier or scaffold and an adequate blood supply [6].

The principle

Successful periodontal regeneration via tissue engineering approaches requires a number of important principles to be addressed; the engineered tissues have to have sufficient bio-mechanical strength, architectural properties and space-maintaining ability. The engineered tissue has to maintain space for in-growth of alveolar bone, but it also has to be exclusionary with respect to the epithelial tissues to prevent the formation of a long junctional epithelium. In addition, biological functions have to be appropriate to allow cellular recruitment and proliferation, vascularization and the delivery of the appropriate factors for regeneration [6].

Vascularization is an important part of any regeneration to avoid tissue necrosis. Using a tissue engineering construct of human periodontal ligament fibroblasts co-cultured with or without human umbilical vein endothelial cells that were found to form capillary-like structures when co-cultured with the human periodontal ligament fibroblasts. These cultures demonstrated longer survival, higher alkaline phosphatase activity and lower osteocalcin production than the human periodontal ligament fibroblast cultures alone. This is all consistent with a greater potential for regeneration and this approach may be beneficial in maintaining adequate vascularization for regeneration to be successful [6]. Recent advances in technology and bio-engineering have now opened the scope for the use of stem cells in these tissue engineering constructs. With the recognition of the presence of mesenchymal stem cells (MSCs) within periodontal ligament there has been considerable research carried out on the isolation, characterization and clinical utilization of these cells. Stem cells are divided into two broad categories: embryonic stem cells and adult stem cells. These are then further sub classified according to their origin and differentiation potential. Human embryonic stem cells, derived from the inner cell mass of blastocysts, are pluripotent cells capable of differentiating into cells of all three germ layers, ectoderm, mesoderm and endoderm. Human embryonic stem cells have two unique properties, i.e., (i) virtually unlimited proliferative potential in an undifferentiated state, and (ii) their pluripotency, which is the capability of differentiating into cells from all three germ layers mentioned above. However, human embryonic stem cell research has been associated with major ethical concerns [6]. Adult stem cells are found in the majority of fetal and adult tissues and are thought to play roles in long-term tissue maintenance and/or repair by replacing cells that are either injured or lost. They are generally multipotent stem cells that can form a limited number of cell types. Two common examples are hematopoietic and MSC. As the periodontlum is mesenchymal in origin, MSCs have been studied in periodontal regeneration research. In a recent study, bone marrow mesenchymal stromal cells on microcarrier gelatin beads were placed into surgically created rat periodontal defects with encouraging results being described for periodontal regeneration outcomes [6].

Strategies to engineer tissue

Currently, strategies employed to engineer tissue can be categorized into three major classes: conductive, inductive, and cell transplantation approaches. These approaches all typically utilize a material component, although with different goals. Conductive approaches utilize biomaterials in a passive manner to facilitate the growth or regenerative capacity of existing tissue. An example of this in the field of periodontics is the use of barrier membranes in guided tissue approach is osseo integration of dental implants by Branemark [1]. The second major tissue engineering strategy (induction) involves activating cells in close proximity to the defect site with specific biological signals. The origins of this mechanism were with the discovery of bone morphogenetic proteins (BMPs). Urist first showed that new bone could be formed at non-mineralizing, or ectopic, sites after implantation of powdered bone (bone de-mineralized and ground into fine particles). Contained within the powdered bone, were proteins (BMPs), which turned out to be the key elements for inducing bone formation. One limitation of inductive approaches is that the inductive factors for a particular tissue may not be known [1].

In the third tissue engineering approach, cell transplantation, becomes very attractive in such situations. This approach involves direct transplantation of cells grown in the laboratory. Here tissue biopsy from the patient is taken to the laboratory and multiplied several million fold. Principles of cell biology must be employed in order to grow these cells and sustain their function. Engineers manufacture the biodegradable polymer matrices and the tissue growth bioreactor in which the tissue will grow. Once the cells have been expanded to an appropriate number, they are placed (seeded) onto the polymer scaffold. The tissue is then allowed further growth in the bioreactor until time of transplantation. After transplantation, the engineered tissue may continue to grow until completely developed.[1]

The tissue engineering approach to bone and periodontal regeneration combines three key elements to enhance regeneration.[Fig.1]

1. Progenitor cells
2. Scaffold or supporting matrix
3. Signaling molecules

Progenitor 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 capable of self-renewal and multi-lineage differentiation through process regeneration by Nyman et. al. ln the field of asymmetric mitosis that leads to two daughter cells, one identical to the

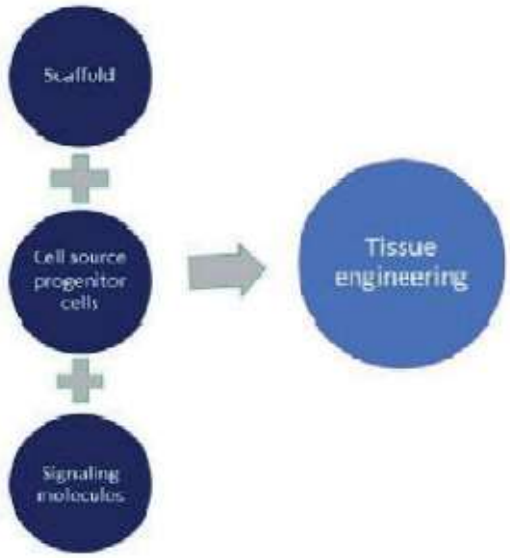

Figure 1: Tissue engineering key elements

stem cell (daughter stem cell) and one capable of differentiation into more mature cells (progenitor cells) [5].

Stem cells may be: [5]

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).

Dental Stem cells [7]

Dental stem cells (DSCs) are MSC-like populations with self-renewal capacity and multi-differentiation potential. Dental pulp stem cells (DPSCs) were the first isolated and characterized DSCs. Later, other types of DSCs were discovered: Stem cells from

human exfoliated deciduous teeth (SHED), periodontal ligament stem cells (PDLSCs), dental follicle precursor cells (DFPCs) and stem cells from apical papilla (SCAP). These five types of DSCs have an amazing multi-potency of differentiation such as osteogenic, odontogenic, dentinogenic, cementogenic, adipogenic, chondrogenic, myogenic and neurogenic. Further, DSCs seem to maintain multipotent properties after short- and long-term cryopreservation. DPSCs represent a diverse population, with individual isolated clones demonstrating differences in proliferative rates and their abilities to differentiate down specific lineages. According to a recent study, this proliferative and regenerative heterogeneity is related to contrasting telomere lengths and CD271 expression between DPSCs populations. Besides, it has been compared the DPSC5 kinetics of third molar with premolar teeth and found that DPSCs from third molar teeth proliferated much faster [7]. Nakamura et al compared the "sternness" of SHED with DPSCs and bone marrow-derived mesenchymal stem cells (BMMSCs) and noticed that SHED revealed higher proliferation rate than that of DPSCs and BMMSCs, and higher expression of genes of cell proliferation and extracellular matrix elements [7].

1. Scaffold

The scaffold provides a 3D substratum on to which, the cells can proliferate and migrate, produce a matrix and form a functional tissue with a desired shape. A suitable bioactive three-dimensional scaffold for the promotion of cellular proliferation and differentiation is critical in periodontal tissue engineering [5].

A scaffold plays many roles in tissue regeneration process: [5]

• It serves as a framework to support cellular migration into the defect from surrounding tissues.
• It serves as a delivery vehicle for exogenous cells, growth factors, and genes.
• It may structurally reinforce the defect to maintain the shape of the defect.
• It serves as a barrier to prevent infiltration of surrounding tissue that may impede the process of regeneration.
• Before its absorption, a scaffold can serve as a matrix for exogenous and endogenous cell adhesion and thus facilitates and regulates certain cellular processes, including mitosis, synthesis and migration.

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

• Synthetically derived.
• Naturally derived.

Ceramics: Natural and synthetic HA (hydroxyl apatite) and beta tri-calcium phosphate (TCP) arc osteoconductive, biocompatible, and do not stimulate immunological reaction. TCP is a naturally occurring material comprising of calcium and phosphorous and is used as a ceramic bone substitute [3].

Polymers: Polymers include synthetic polyesters, such as polylactic acid, polyglycolic acid, natural polymers like collagen fibrin, albumin, hyaluronic acid, cellulose, chitosan, polyhydroxyalkanoates, alginate, agarose and polyamino acids etc [3].

Synthetic polyesters: PGA (polyglycolic acid) is a polymer of glycolic acid. PLA (polylactic acid) is the polymer of lactic acid. Co polymers of PGA have been used for many types of biomaterials, including sutures (vicryl). PLGA (polylacticcoglycolic acid) is a copolymer of PGA and PLA. Due to its biocompatibility, controlled structural and mechanical properties, tailored degradation rates, and its potential as growth factor delivery vehicles, it has been considered as the prime candidate for use in regenerative medicine and dentistry [3].

Natural polymers

Chitosan: It is a biodegradable natural carbohydrate biopolymer that has been shown to improve wound healing and improve bone formation. It is nontoxic and non-immunogenic, and has such structural characteristics that make it possible to be used as a bone substitute and as a scaffold for cell attachment [3].

Collagen: Collagen can be processed to make collagen foam, collagen fiber and collagen membrane which have favorable properties that can be used for scaffold in tissue engineering.' Liao *et. al.,* in a study compared porous beta tri-calcium phosphate/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 [5].

2. Signalling molecules

Signaling molecules arc proteins that may act locally or systemically to affect the growth and function of cells in various manners. The two types of signaling molecules that have received the greatest attention are growth factors and morphogens that act by altering the cell phenotype i.e. by causing the differentiation of stem cells into bone forming cells a

process commonly 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.

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.

Platelet-derived growth factor

Platelet-derived growth factor (PDGF) is the natural wound healing hormone. It is naturally produced by the body at sites of soft tissue and bone injury. It was discovered by Lynch and coworkers in the late 1980s. While PDGF secreted from platelets play an important role in initial wound healing, its subsequent secretion from macrophages continues the events of wound healing through up-regulation of other growth factors and cells that ultimately promote fibroblastic and osteoblastic functions. Moon *et. al.* applied PDGF-BB to promote migration and proliferation of periodontal ligament fibroblasts. They demonstrated that PDGF has the capacity to stimulate bone formation and periodontal regeneration *in vivo* and indicate that it holds promise as an important adjuvant to periodontal surgery [5].

Insulin like growth factor

Insulin like growth factor (IGF) is a potent chemotactic agent for vascular endothelial cells resulting in increased neovascularization. It also stimulates mitosis of many cells *in vitro* such as fibroblasts, osteocytes, and chondrocytes. Insulin like growth factor-I is found in substantial levels in platelets and is released during clotting along with the other growth factors. Han and Amar demonstrated that *in vitro* IGF-l substantially enhanced cell survival in periodontal ligament fibroblasts compared to gingival fibroblasts by the up-regulation of anti-apoptotic molecules and down regulation of pro-apoptotic molecules [5].

Transforming growth factor family

The two best characterized polypeptides from this group of growth factors are Transforming Growth Factor family, TGF-α and TGF-β. TGF-β appears to be a major regulator of cell replication and differentiation. Three forms of TGF-β have been identified namely TGF-β1, TGF-β2, and TGF-β3. TGF-β isoforms have multiple regulatory roles in the synthesis, maintenance and turnover of the extracellular matrix. TGF-β is chemotactic for fibroblasts and cementoblasts, and promotes fibroblast accumulation and fibrosis in the healing process. It can also modulate other growth factors such as PDGF, TGF-α, Epidermal growth factor (EGF) and fibroblast growth factor (FGF) possibly by altering their cellular response or by inducing their expression. Oates *et. al.* compared the mitogenic activity of TGF-β with interleukin and PDGF in fibroblast cells derived from periodontal ligament explants. TGF-β was relatively a weak mitogen for Periodontal (PDL) cells compared to PDGF, suggesting that TGF-β may indirectly stimulate DNA synthesis.[5] Whether TGF-β1 directly enhances periodontal regeneration, is still controversial (Tatakis *et. al.,* 2000); however, it has been reported that TGF-β1 induced endochondral bone formation (Serra *et. al*., 1999). Another study suggested that TGF-β3 in Matrigelmatrix (BD Biosciences, San Jose, CA) in combination with minced muscle tissue significantly enhanced the periodontal regeneration in class Ill furcation defects in P. ursinus (Ripamonti *et. al.*, 2009) [8].

Fibroblast growth factor family

Fibroblast growth factors are the members of heparin binding growth factor family. The two most thoroughly characterized forms are: Basic Fibroblast growth factor (bFGF) and acidic Fibroblast growth factor (aFGF). Both aFGF and bFGF are single chain proteins that are proteolytically derived from different precursor molecules to generate biologically active proteins of 15,000 molecular weight. They promote proliferation and attachment of endothelial cells and PDL cells in wound healing process. FGF-21s known to attract epithelial cells more effectively than FGF-1.[5] The use of bFGF, a growth factor that is already utilized clinically for wound healing in patients with intractable skin ulcers, has been investigated for bone formation and periodontal regeneration. Its efficacy on periodontal regeneration was demonstrated in beagles and nonhuman primates (Murakami et al., 1999, 2003; Takayama *et. al.,* 2001). A multicenter, randomized clinical trial was performed using a 3% hydroxypropyl cellulose carrier (Kitamura et al., 2008, 2011); the results showed that bFGF was safe and effective for periodontal regeneration.[8] Kitamura *et. al.* did a recent randomized clinical trial trying to evaluate the therapeutic response to varying doses of FGF-2

(bFGF). They demonstrated a significant increase in the alveolar bone height on using 0.3% FGF-2.[5] Takayama *et. al.* examined the efficiency of topical application of FGF-2 with periodontal regeneration in the bony defects by surgically creating furcation class II bone defects in non-human primates and concluded that a topical application of FGF-2 can enhance considerable periodontal regeneration [5].

Hepatocyte growth factor

Hepatocyte growth factor (HGF) is a secreted, heparin sulfate glycosaminoglycan-binding protein. HGF has been shown to have mitogenic effects on osteoblasts; thus, participating in the bone remodeling process. Yamada *et. al.* cultured fibroblasts in a culture medium containing HGF and concluded that they produced good cell proliferation and vascular endothelial growth factor (VEGF) release. The results suggest that it may provide a new tool for the treatment of gingival recession. [5].

Bone morphogenetic proteins

Bone morphogenetic proteins (BMPs) are the members of transforming growth factor β (TGF-β) superfamily, which play a crucial role in cell growth and differentiation. They are a group of related proteins that are known to possess the unique ability to induce cartilage and bone formation. They trigger cellular effects by way of heterotetrameric seri ne/threonine kinase receptors and intracellular signalling proteins known as “small mothers against decapentaplegic” (Smads). BMPs, like PDGF, play a role in the blood vessel formation. They play an important role in the angiogenetic activity by up-regulating the angiogenetic peptides like VEGF, may bind to endothelial cells and stimulate the migration and promote blood vessel formation.SBMP2 in particular has been thoroughly studied for periodontal regeneration [8].

The hallmark property of BMP is the differentiation factor. BMP will differentiate an undifferentiated mesenchymal cell into an osteoblast. In contrast, PDGF is a chemotactic and mitogenic factor for osteoblast like precursors [5].

Other members of the BMP family, such as BMP-7 /OP-i (Giannobile *et. al.*, 1998; Ripamonti *et. al.*, 2001), BMP-12/GDF-7 (Wikesjo *et. al.*, 2004), BMP-4/ GDF-5 (Kwon *et. al.*, 2010; Lee *et. al.*, 2010), have also been investigated in large animal models, and their efficacies for periodontal regeneration were observed in all studies. A recent study compared the carriers, b-TCP and ACS, for BMP-14/GDF-5 delivery in a canine periodontal defect model (Kim *et. al.*, 2013). The authors observed that b-TCP was superior for new bone formation [8].

Ribonucleic acid mediated silencing [2]

The ribonucleic acid (RNA) mediated silencing process is defined as RNAi, a discovery for which Fire and Mellow received the 2006 Nobel Prize. It is based on the principle of RNA interference (RNAi), a novel mechanism of action whereby the expression of certain genes detrimental to the tissue regeneration process is silenced by RNAs. RNAi works through small RNAs of approximately 20 to 30 nucleotides that guide the degradation of complementary or semi complementary molecules of messenger RNAs (post-transcriptional gene silencing) or interfere with the expression of certain genes at the promoter level (transcriptional gene silencing). Artificially, transcribed short hairpin RNAs (shRNAs) can be introduced into the cell by plasmid transfection or viral transduction, or small linear RNAs (siRNA) can be directly transfected into the cells. In the cytoplasm, the shRNAs or siRNA participate in endogenous posttranscriptiona I gene silencing. The synthetic RNAs are recognized and processed by an endo-ribonuclease named Dicer and incorporated into the RNA induced silencing complex. Then, silencing occurs through the AGO2-mediated cleavage of target messenger RNAs. Most RNA based therapeutics currently under investigation uses siRNAs because they are safe and cost effective. They can be introduced into the cells without the aid of viruses and can be chemically synthesized. The first siRNA based therapeutic tested in human clinical trials was the VEGF targeted RNA for the treatment of macular degeneration of the retina. Tumor necrosis factor-a targeted siRNA can suppress osteolysis induced by metal particles in a murine calvaria model, opening the way to the application of RNAi in orthopaedic and dental implant therapy. In terms of bone regeneration, Gazzerro and colleagues have demonstrated that down regulation of Gremlin by RNAi in ST-2 stromal and MC3T3 osteoblastic cells increases the BMP-2 stimulatory effect on alkaline phosphatase activity and on Smad 1/5/8 phosphorylation, enhances osteocalcin and Runx-2 expression, and increases Wnt signaling, with the potential to increase bone formation *in vivo.* Taken together, these studies prove that RNAi, when adequately used, can foster tissue regeneration. The use of RNA based therapeutics for tissue regeneration is still in its early stages. Nevertheless, RNAi promises to be an effective therapeutic tool and may be successful in periodontal regeneration [2].

Implantation of live cells

Effective augmentation techniques to treat more challenging esthetic concerns, such as open interproximal spaces and other severe oral soft tissue deficiencies, though, are not currently available but cell-based therapies may change this. Enumerated below are some of the examples enlightening the use of live cell based therapy in the field of periodontics [2].

Platelet Rich Plasma (PRP)

PRP is an autologous concentration of platelets, containing a number of important growth factors such as PGDF, TGF-, IGF, EGF and VEGF. Additionally PRP also contains proteins (i.e. fibrin, fibronectin, vitronectin) known to act as cell adhesion molecules for osteoconduction and as a matrix for bone, connective tissue and epithelial migration. An average increase of 338% in platelet count is seen during processing which helps in healing process[9]. Although ineffective for periodontal regeneration, platelet rich plasma is used to stabilise graft materials for implant site augumentation and appears to enhance early soft tissue healing [10].

Enamel Matrix Derivatives (EMD)

EMD is an acidic extract containing hydrophobic protein assembly of amelogenins which has the capacity to induce regeneration of all periodontal tissues. This is obtained from developing porcine teeth and found to contain TGFβ, &BMP to stimulate bone formation. Enamcl matrix proteins is composed of a number of proteins, such as amelogenin (exists in several different sizes), amelin (ameloblastin/ sheathlin), enamelin, tuft proteins and proteases. Amelogenin being the most abundant component constitutes more than 90% of the matrix [9].

Gene Therapy

One of the major limitations associated with the use of growth and differentiation factors are their short biological half-lives. Gene therapy can be used for extended local delivery of these factors. Recently, gene delivery of platelet derived growth factor was accomplished by the successful transfer of the growth factor gene into the cementoblast and other periodontal cell types. Gene therapy studies utilizing bone morphogenic proteins have also been performed [10].

The major drawbacks of tissue engineering include failure of the tissue to sustain growth and eventually undergo necrosis; foreign body reaction to the implanted materials to initiate regenerative procedures and provide scaffolds; failure to grow/remodel; disease transmission; immune reactions against implanted scaffolds; and harvest site morbidity [11].

Future Directions

Tissue engineering is emerging as a vibrant industry with a huge potential market. In future, periodontal therapies will involves nano-science and moldless manufacturing technology commonly known as rapid prototyping (RP) or solid free form fabrication (SFF). These innovations will make it possible to fabricate complex scaffolds that mimic the different structure and physiologic functions of natural fibro-osseous tissues, including those, such as periodontium, which consists of hard and soft tissues. It may also be possible to produce patient specific cell scaffold constructs with optimal distribution of cells and high vascular permeability [9]. The recently developed bio-mimetic coating approach in implants has advantages over the conventional plasma-spraying technique in coating porous metallic implant surfaces and polymeric tissue engineering scaffolds. Bio-mimetic Ca-P coating is an ideal carrier of therapeutic and bioactive agents, such as osteoinductive proteins, growth factors and antibiotics. Tissue engineering techniques for regenerating periodontal defects will become the new basis for regeneration of the alveolar bone and the placement of dental implants. Chemical and biomimetic strategies are also increasingly being developed to design improved surface chemistry of implants [11].

Challenges with Tissue Engineering [9]

1. Structural and functional complexity of the Periodontium needs right combination and dosage of growth factors for successful regeneration.
2. Sustained storage and delivery of growth factors with a suitable carrier system is needed for long term and profound effect and promising regeneration of periodontal tissues.

Conclusion

The regeneration of the periodontium is known to be challenging to the clinicians. Thus, the development of new therapies tissue engineered scaffolds opened a new era of the periodontal regeneration. Tissue engineering has provided us a new therapeutic alternative for the management of periodontal defects. To date, many cellular and molecular mechanisms involved in the repair and regeneration of periodontal tissues have been identified, and advances in the fields of molecular biology, human genetics, and stem cell biology have set the stage for

significant discoveries that will pave the way for the development of new tissue-engineering procedures needed for the predictable regeneration of periodontal tissues. 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. Further advancements in the field will continue to rely heavily on multidisciplinary approaches combining engineering, dentistry, medicine and infectious disease specialists in repairing the complex periodontal wound environment. The advent of viable tissue engineering will have an effect on the therapeutic options available to oral health specialists. In addition to the classical issues to be faced in every engineering discipline, TE requires special efforts to be pointed on the needs of living organisms. Either when designing models for *in vitro* biological studies or grafts for *in vivo* regeneration, it should be taken into accounts the complexity of tissue architecture. For instance, the implementation into 3D cultures of vascularization networks that facilitate a constant turnover of oxygen and nutrients is under extensive studies.

References

[1] Chandran N, Suchetha A, Mundinamane DB, Sapna N, Sravani K, Phadke PV. Tissue engineering- An art and science of regeneration. Int J Med and Dent Sci 2015. 4(2) :932-945.

[2] Dabra S, Chhina K, Soni N, and Bhatnagar R. Tissue engineering in periodontal regeneration: A brief review. Dent Res i 2012 Nov-Dec; 9(6): 671—680.

[3] Deka N.Tissue engineering periodontal regeneration. Int 2015, 1(4): 71-74.

[4] Chugh applications Arora N. Tissue engineering in periodontics: Alternate god. J

[5] Pandit N, Malik R, and Philips D. Tissue engineering: A new vista in periodontal regeneration. J Indian SocPeriodontol. 2011 Oct-Dec; 15(4): 328—337.

[6] Bartold PM, Gronthos 5, lvanovski 5, Fisher A, Hutmacher DW. Tissue engineered periodontal products. J Periodont Res 2016; 51: 1—15.

[7] Botelho J,Cavacas M.A, Machado V &Mendes J.J (2017) Dental stem cells: recent progresses in tissue engineering and regenerative medicine, Annals of Medicine, 49:8, 644-651.

[8] Iwata T, Yamato M, Ishikawa' I, Ando T, AND Okano T. Tissue Engineering in Periodontal Tissue. Anat Rec, 297:16—25, 2014.

[9] Antush Mittal, Shoyab Khan, Kanteshwari I. K. "Tissue Engineering in Periodontics : A Review".NJDSR 2012;Vol.1

[10] Siddhartha VA, Sarthak B, Rashmi G, Shilpa S, Uzma B. Tissue Engineering in Periodontics. Annals Dent Res 2012; 2 (1): 1-7.

[11] Dhalkari C.D, Ganatra P. Sawalakhe P. Nayyar A.S. TISSUE ENGINEERING IN PERIODONTICS-A REVIEW. International Journal of Therapeutic Applicatlons2ol5; Volume 28: 1-5.

How to cite this article: Tissue engineering - A Novel Approach for Periodontal Regeneration. Gupta I, Gupta R, Gupta N, Ranjan P, Amranath J, Mishra S.; Rama Univ. J. Dent. Sci. 2018 March; 5(1):1-8. Sources of support: NIL Conflict of Interest: None Declared.