Review Article

Tissue engineering- An art and science of regeneration

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ABSTRACT

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. The association of biomaterials, stem cells, growth and differentiation factors has yielded the development of new treatment opportunities in the field of dentistry. The objective of using tissue engineering as therapeutic application has been to harness its ability to exploit selected and primed cells together with an appropriate mix of regulatory factors, to allow growth and specialization of cells and matrix. Tissue engineering in periodontology applies the principles of engineering and life sciences toward the development of biological techniques that can restore lost alveolar bone, periodontal ligament, and root cementum. 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.

Key Words: *Tissue engineering, stem cells, growth factors, periodontics, regeneration*

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. [1] 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. Additionally, mechanical devices or artificial prostheses may be subjected to wear upon long-term implantation, and could induce inflammatory response in the host. [2]

The use of synthetic restorative materials as substitutes for dental structures is a practice nearly as old as dentistry itself.[3] 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.

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, aswell 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.[4]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.[5]

On the other hand with the use of synthetic material replacements (e.g., dental implants) as part of a natural defense mechanism, the body has a tendency to encapsulate foreign materials in a thin, fibrous membrane. In case of dental implant, the fibrous capsule created by the immune response can potentially wall off the implant from its new environment and can prevent the implant from achieving true osseointegration, ultimately leading to failure.[6]

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."[7] 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 or improve tissue or organ function."[8]

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 regeneration by Nyman et al.[9] In the field of prosthetic and restorative dentistry the widespread application of this osteoconductive approach is osseointegration of dental implants by Branemark.

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 was with the discovery of bone morphogenetic proteins (BMPs).Urist first showed that new bone could be formed at nonmineralizing, or ectopic, sites after implantation of powdered bone (bone demineralized and ground into fine particles).[10] 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.

The third tissue engineering approach, cell transplantation, becomes very attractive in such situations. This approach involves direct transplantation ofcells grown in the laboratory. [11] 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.

The triad of tissue engineering

Tissue engineering is generally considered to consist of three key components: (i) stem/progenitor cells; (ii) a scaffold or extracellular matrix. (iii) Signaling molecules

In addition, growing tissues require an adequate vascular supply to ensure viability and an unencumbered physical space into which the growing tissue can expand.

Stem Cells

Stem cells are clonogenic cells capable of self-renewal and capable of generating differentiated progenies. These cells are responsible for normal tissue renewal as well as for healing and regeneration after injuries.[12]

Stem cells may be:

- Totipotent, i.e. early embryonic cells (one to three days from oocyte fertilization), which can give rise to all the embryonic tissues and placenta.
- Pluripotent, i.e. embryonic cells from blastocyst (4-14 days after oocyte fertilization), which can differentiate only into embryonic tissues belonging to the inner cell mass (ectoderm, mesoderm, and endoderm).
- 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).[13]

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.[14-16] Embryonic stem cells are derived from embryos that are 2 – 11 days old called blastocysts. Adult stem cells are multipotent stem cells, and depending upon their origin, they can be further classified into hemopoetic stem cells and mesenchymal stem cells. Friedenstein and colleagues first identified mesenchymal stem cells in aspirates of adult bone marrow.[17] Among the adults stem cells, bone marrow–derived stem cells or mesenchymal stem cells (MSCs) are adherent, proliferating, and capable of multilineage differentiation having the capability of differentiating into multiple tissue types, including bone, cartilage, muscle, tendon, etc., and hold great potential for autologous cell based therapy.[16]

In dentistry, the identification of mesenchymal stem cell-like populations has presented possibilities for the application of tissue engineering in the development of novel strategies for regenerative periodontal therapy. Seo et al. In year 1993 identified mesenchymal stem cells for the first time derived from adult periodontal ligament (PDL) known as PDL stem cells (PDLSCs). PDLSCs represent a novel population of multipotent stem cells, as shown by their capacity to develop into cementoblast like cells and adipocytes in

vitro and cementum/PDL like tissue in vivo. PDLSCs also demonstrate the capacity to form collagen fibers, similar to Sharpey's fibers, connecting to the cementum like tissue, suggesting the potential to regenerate PDL attachment.[18]

Scaffold / extracellular matrix

Scaffolds are temporary frameworks used to provide a three dimensional microenvironment where cells can proliferate, differentiate and generate the desired tissue.[19] A suitable bioactive three dimensional scaffold for the promotion of cellular proliferation and differentiation is critical in periodontal tissue engineering. The contemporary concept of scaffolding in tissue engineering is to mimic the functions of native extracellular matrix (ECM), at least partially.

A scaffold plays many roles in tissue regeneration process:[20]

• 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 the first Consensus Conference of the European Society for Biomaterials (ESB) in 1976, a biomaterial was defined as 'a nonviable material used in a medical device, intended to interact with biological systems'; however, the ESB's current definition is a 'material intended to interface with biological systems to evaluate, treat, augment or replace any tissue, organ or function of the body'. This subtle change in definition is indicative of how the field of biomaterials has evolved. Biomaterials have moved from merely interacting with the body to influencing biological processes toward the goal of tissue regeneration.[21]

Typically, three individual groups of biomaterials namely ceramics, synthetic polymers and natural polymers, are used in the fabrication of scaffolds for tissue engineering.

- Ceramic scaffolds- mainly for bone regeneration applications

Hydroxyapatite (HA) and tri-calcium phosphate (TCP) are the ceramic scaffolds. The interactions of osteogenic cells with ceramics are important for bone regeneration as ceramics are known to enhance osteoblast differentiation and proliferation.[22,23] However, their clinical applications for tissue engineering has been limited because of their brittleness, difficulty of shaping for implantation, and because new bone formed in a porous HA network cannot sustain the mechanical loading needed for remodeling.[24] In addition, although HA is a primary constituent of bone and might seem ideal as a bone graft substitute, problems also exist in that it is difficult to control its degradation rate.

- Synthetic polymers-

Polystyrene, poly-l-lactic acid (PLLA),polyglycolic acid (PGA) and poly-dl-lactic-co-glycolic acid (PLGA) are the synthetic polymers. They can be fabricated with a tailored architecture, and their degradation characteristics can be

controlled by varying the polymer itself or the composition of the individual polymer [25-27] .They have drawbacks like the risk of rejection due to reduced bioactivity. In addition, concerns exist about the degradation process of PLLA and PGA as they degrade by hydrolysis, producing carbon dioxide and therefore lowering the local pH which can result in cell and tissue necrosis [28].

- Natural or biologic materials-
  Collagen, various proteoglycans, alginate-based substrates and chitosan are the natural scaffolds. They are biologically active and typically promote excellent cell adhesion and growth. Furthermore, they are also biodegradable and so allow host cells, over time, to produce their own extracellular matrix and replace the degraded scaffold.

Table 1: Cell-delivery devices and scaffolds in periodontics [29]

NONRESORBABLE	EXPANDED POLYTETRA FLUOROETHYLENE (EPTFE) CERAMIC TITANIUM MESH
RESORBABLE	ALPHA-HYDROXYACIDS POLYGLYCOLIC ACID POLY(L-LACTIC ACID) COPOLYMERS OF POLY(LACTIC-CO-GLYCOLIC ACID) AMINO ACID-BASED POLYMERS COLLAGEN-LIKE PROTEINS ELASTIN-LIKE PROTEINS NATURAL PRODUCTS COLLAGEN HYALURONAN CHITOSAN GELATIN FIBRIN ALGINATE SYNTHETIC HYDROGELS POLY (ETHYLENE GLYCOL) POLY (ETHYLENE OXIDE) MATRIX EXTRACTS MATRIGEL

Table 2: Commercially available scaffold materials potentially available for oral tissue engineering application [30]

BIOMATERIAL	COMMERCIAL NAME
Allografts Demineralized freezedried bone allograft Freeze-dried bone allograft	 Distributed under various names by tissue banks Distributed under various names by tissue banks
Xenografts Anorganic bovine bone Hydroxyapatite	 Bio-Oss, OsteoGraf, Pep-Gen P-15
Alloplasts Tricalcium phosphate Hydroxyapatite Bioactive glass polymers Hard-tissue replacement polymer Coraline calcium carbonate	 Synthograft Periograf, Osteogen, ProOsteone PerioGlas, BioGran Bioplant Biocoral
Polymers and Collagens Collagen Poly(lactide-copolyglycolide) Methylcellulose Hyaluronic acid ester Chitosan	 Collaplug, Collacote, Gelfoam, Helistat HY
Enamel matrix derivative	Emdogain

Signalling molecules

Signaling molecules are proteins that may act locally or systemically to influence the growth and function of cells in various manners.[31] These molecules (cytokines) are biological mediators that regulate critical cellular activities including:

• Mitogenic (proliferative)

• Chemotactic (stimulate directed migration of cells)

• Angiogenic (stimulate the formation of new blood vessels).

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.

Growth factors

Growth factors are naturally occurring proteins that regulate various aspects of cell growth and development. [32, 33] During wound healing, these growth factors modulate cell proliferation, differentiation migration, extracellular matrix formation and other cellular functions. In periodontal regeneration, much of the focus has been on platelet-derived growth factor and basic fibroblast growth factor-2.

Morphogens or differentiation factors: bone morphogenetic proteins

Bone morphogenetic proteins are a group of regulatory glycoproteins that are members of the transforming growth factor-beta superfamily. These molecules primarily stimulate differentiation of mesenchymal stem cells into chondroblasts and osteoblasts. In the field of periodontal regeneration, BMPs of interest are bone morphogenetic protein-2 (OP-2), bone morphogenetic protein-3 (osteogenin) and bone morphogenetic protein-7 (OP-1). [34]

Platelet derived growth factor

Platelet-derived growth factor (PDGF) was discovered by Lynch and coworkers in the late 1980s.[35] Moon et al. applied PDGF-BB to promote migration and proliferation of periodontal ligament fibroblasts and demonstrated that PDGF has the capacity to stimulate bone formation and periodontal regeneration in vivo .Thus it holds promise as an important adjuvant to periodontal surgery.[36]

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. [37] Han and Amar demonstrated that in vitro IGF-I substantially enhanced cell survival in periodontal ligament fibroblast by the upregulation of antiapoptic molecules and downregulation of proapoptotic molecules.[38]

Transforming growth factor

The two best characterized polypeptides from this group of growth factors are transforming growth factor family (TGF) α and TGF-β.Three forms of TGF-β have been identified namely TGF-β1, TGF-β2, and TGF-β3. 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, TGFα, and EGF and fibroblast growth factor (FGF)possibly by altering their cellular response or by inducing their expression.[39]

Oates et al. compared the mitogenic activity of TGF-β with interleukin1 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.[40]

Fibroblast growth factor

Fibroblast growth factors are the members of heparin binding growth factor family. The two most thoroughly characterized forms are: Basic FGF (bFGF) and acidic FGF (aFGF).They promote proliferation and attachment of endothelial cells and PDL cells in wound healing process. FGF-2 is known to attract epithelial cells more effectively than FGF-1.[41]

Takayama *et al*. examined the efficiency of topical application of FGF2 with periodontal regeneration in the bony defects by surgically creating furcation class II bone

defects in nonhuman primates and concluded that a topical application of FGF-2 can enhance considerable periodontal regeneration. [42]

Enamel matrix derivative (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 TGF β and BMP to stimulate bone formation. Enamel matrix derivative stimulates angiogenesis directly by stimulating endothelial cell proliferation and chemotaxis, and stimulates vascular endothelial cell growth factor production by periodontal ligament cells.[43] When applied to root surfaces, the proteins are absorbed into the hydroxyapatite and collagen fibers of the root surface, where they induce cementum formation followedby periodontal regeneration.

Platelet rich plasma

Platelet rich plasma (PRP) is an autologous concentration of platelets, containing a number of important growth factors such as PDGF, TGFβ, IGF, EGF, and VEGF. This mixture of growth factors in platelet rich plasma putatively stimulates the proliferation of fibroblasts and periodontal ligament cells, extracellular matrix formation and neovascularization. Additionally, platelet-rich plasma may suppress cytokine release and limit inflammation, thereby promoting tissue regeneration.[44] 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.

Table 3: Effect of various growth factors and BMPs in periodontal regeneration [30]

Growth factor	Fibroblast proliferation	Osteoblast proliferation	Mesenchymal cell differentiation	Vascularization	Extracellular matrix synthesis
EGFs	+ +	-	+ +	+	-
FGFs	+ +	+ +	-	+ +	-
PDGFs	+ +	+ +	-	+ (indirect effect)	-
IGFs	+	+ +	-	-	+ +
TGF-β	+ or -	+ or -	-	+ (indirect effect)	+ +
BMPs	-	+ or-	+ +	+ + (indirect effect)	+ or -

++ = Greatly increased, + = Increased, – = No or negative effect, EGF = Epidermal growth factor, FGF = Fibroblast growth factor, PDGF = Platelet derived growth factor, IGF = Insulin like rowth factor, TGF = Transforming growth factor, BMP = Bone morphogenetic proteins

Tissue engineering approaches for periodontal regeneration

Tissue-engineering approaches for periodontal regeneration are nondefinitively subdivided into three principal therapeutic strategies. [31, 45,46]

- cell-based therapy—implantation of freshly isolated or cultured cells, which can be

autologous or allogenic cell suspensions or cell-sheets that are injected and/or transplanted to periodontal defect sites. Akizuki et al. 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 cementum occurred in three out of the five defects. [47] Hasegawa et al. assessed the ability of periodontal ligament cell sheets to regenerate the periodontal ligament tissue and demonstrated its usefulness in periodontal tissue regeneration.[48]

Flores et al. 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 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. [49, 50, 51]

- in vitro approaches—implantation of tissues assembled in vitro from cells, scaffolds, and biomolecules (for example, growth factors, growth factor encoding genes, completely lyophilized cell fractions, peptides, and polysaccharides).
- in vivo approaches—in situ tissue regeneration by implantation of different types of matrices (such as hydrogels and microspheres/beads) in combination with cells and/or biomolecules, or a scaffold containing biomolecules implanted directly into the defects that stimulates the body's own cells to promote local tissue regeneration.

Applications of tissue engineering in periodontics

Guided Tissue Regeneration (GTR)- The biological principle of using cell occlusive barriers was described by Melcher (1976).[47] Nyman and Karring, in 1982 were the first to have proposed the use of guided tissue regeneration for periodontal regeneration, which marked the evolution of periodontal regeneration technologies using tissue engineering. GTR consists of placing barriers of different types to cover the bone and periodontal ligament (PDL), thus temporarily separating them from the gingival epithelium. This provides space and a favorable niche to guide the right type of cells (PDL cells, cementoblasts, and osteoblasts) to attach at the root surface, and tries to exclude undesirable cells (epithelial cells) from attaching to the root surface.

Guided Bone Regeneration (GBR) - GBR involves the use of membranes to guide the formation of bony tissue by separating the underlying bone from the overlying connective tissue and by creating a space into which the desirable bone cells can migrate. [47] This is usually done before placement of the implant for bone augmentation.

Bone Grafts- Bone grafts aim to restore the height of the alveolar bone around a previously diseased tooth; thus, the principles and techniques from bone regeneration have been directly transferred to periodontal therapy with or without modifications.[52] Currently the gold standard material for bone defect repair is

autografts; however, donor site morbidity and limited supply prevent the wide application of this method. Allografts and xenografts are widely available but face issues such as immune rejection and potential transmission of infectious diseases. In view of the limitations inherent with conventional bone graft strategies, tissue engineering represents a promising approach for bone repair and regeneration. Advances in tissue engineering have led to innovative scaffold designs, complemented by progress in the understanding of cell-based therapies and bioactive growth factor delivery.

Recent Advances in Tissue Engineering

Gene therapy

- Refers to the treatment of a disease by means of a genetic manipulation.
- Genetic information is transferred to the target cells, which enables them to synthesize a protein of interest to treat disease.
- Gene transfer is accomplished through the use of viral [retroviruses, adenoviruses (Ad) and adeno-associated viruses (AAV)] and non-viral vectors (plasmids and DNA polymer complexes.[53]
- Gene vectors can be introduced directly to the target site (in vivo technique), or selected cell can be harvested, expanded, genetically transduced, and then reimplanted (ex vivo technique).[53]
- The application of growth factors or soluble forms of cytokine receptors by gene transfer provides a greater sustainability and bioavailability of growth factors within periodontal wounds.[54]

PDGF has demonstrated strong potential in promoting gingival, alveolar bone and cementum regeneration in a variety of wound healing models. When periodontal defects were treated with adenovirus encoding PDGF-B, strong evidence of bone and cementum regeneration beyond that of control vectors, consisting of nearly fourfold increases in bridging bone and six fold increases in tooth-lining cemental repair was seen.[55]

Limitations of gene therapy

- Short lived nature of gene therapy
- Immune response of the patient
- Problems with viral vectors like patient toxicity, and immune and inflammatory responses
- Limitations of sufficient quantity of the engineered gene that can be delivered
- Extreme cost
- Ethical restrictions

Recombinant Protein Therapeutics

With advances in recombinant technology, the development and commercialization of pure recombinant human growth factor matrix combination has been developed. Combination products which represent the next generation of tissue engineering therapeutics, have gained increasing attention from clinicians and researchers as a strategy to optimize tissue regeneration. Proteins may now be synthesized, concentrated, purified, and packaged in large sterile quantities under tightly controlled and regulated conditions. Providing growth modulating molecules in a highly concentrated pure and consistent form and the ability to combine highly concentrated forms of individual signaling proteins with conductive matrices is important in order to increase the predictability of regenerative procedures.

To date, only three recombinant growth factor products have been widely used

• rh PDGF BB (gel).[56]
• rhPDGFBB (with β tricalcium phosphate).[57]
• rh BMP□2 (with type I collagen sponge).[58]

The mitogenic responsiveness of periodontal cells to local application of PDGF-BB was confirmed in a dog model by Wang and Castelli. Its levels were raised in cases of periodontitis, but not in diabetic cases; thus, suggesting that PDGFBB driven repair process is suppressed under diabetic conditions. [59]

Studies have also suggested that the use of rh PDGF+ β TCP and a collagen membrane may represent an acceptable alternative to connective tissue graft for covering gingival recession defects.[57]

The identification and development of recombinant human bone morphogenetic protein -2 (rhBMP2) has led to the commercial availability for the first time of an osteoinductive autograft replacement (INFUSE Bone Graft).

- rhBMP 2 has been combined with ACSatellocollagen sponge (ACS).[60]
- rhBMP2 has also been used in a DFDBA/fibrin clot carrier.[61]
- rhBMP2 and calcium phosphate cement matrix.[62]

Challenges in Tissue Engineering

1. Periodontium being a complex structure, more than one tissue should be reconstructed namely alveolar bone, periodontal ligament, root cementum and gingiva. Hence needs the 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. Although many carrier systems have been tested, none of them appears to be ideal.

Conclusion

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.

References

1. Pollock JM, Vacanti JP. Tissue engineering. Semin Pediatr Surg 1996;5(3):191-196.
2. Maguire JK, Cosca MF, Lynch MH. Foreign body reaction to polymeric debris following total hip arthroplasty. Clin Orthop 1987;216:213–223.
3. Majumdar SK. History of dentistry: an overview. Bull Indian Inst Hist Med Hyderabad 2002;32:31–42.
4. Damien JC, Parson JR. Bone graft and bone graft substitutes:a review of current technology and applications. J Appl Biomaterials 1991;2:187-208.
5. Buck BE, Malinin TI. Bone transplantation and human immunodeficiency syndrome (AIDS).Clin Orthop 1989;240:129-36.
6. Branemark R, Branemark PI, Bjorn Rydevik, Robert R Myers. Osseointegration in skeletal reconstruction and rehabilitation: a review. J of rehab research & deve 2001;38(2):175-181.
7. RM Nerem. Tissue engineering. Ann Biomed Eng 1991;19:529-545.

8. Langer R, Vacanti JP. Tissue engineering. Science 1993;260:920–926.
9. Nyman S, Lindhe J, Karring T, Rylander H. New attachment following surgical treatment of human periodontal disease. J Clin Periodontol 1982;9:290–296.
10. Urist MR. Bone formation by autoinduction. Science 1965;150(698):893-899.
11. Krebsbach PH, Kuznetsov SA, Bianco P, Gerhon Robey P. Bone marrow stromal cells: characterization and clinical application. Crit Rev in Oral Biol Med 1999;10(2):165-181.
12. Van der Kooy D, Weiss S. Why stem cells? Science 2000;287:1439–1441.
13. Krampera M, Franchini M, Pizzolo G, Aprili G. Mesenchymal stem cells: From biology to clinical use. Blood Transfus 2007;5:120-129.
14. Shamblott MJ, Axelman J, Wang S, Bugg EM, Littlefield JW, Donovan PJ, et al. Derivation of pluripotent stem cells from cultured human primordial germ cells. Proc Natl Acad Sci USA 1998;95:13726-13731.
15. Thomson JA, Itskovitz Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, et al. Embryonic stem cell lines derived from human blastocysts. Science 1998;282:1145-1147.
16. Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, et al. Multilineage potential of adult human mesenchymal stem cells. Science 1999;284:143-147.
17. Friedenstein AJ. Precursor cells of mechanocytes. Int Rev Cytol1976;47:327-359.
18. Seo BM, Miura M, Gronthos S, Bartold PM, Batouli S, Brahim J, et al. Investigation of multipotent postnatal stem cells from human periodontal ligament. Lancet 2004;364:149-155.
19. Kemppainen JM, Hollister SJ. Tailoring the mechanical properties of 3D-designed poly (glycerol sebacate) scaffolds for cartilage applications. J Biomed Mater Res A 2010;94:9–18.
20. Spector M. Basic principles of scaffolds in tissue engineering. In: Lynch SE, Marx RE, Nevins M, Lynch LA, editors. Tissue engineering: Applications in Oral and Maxillofacial Surgery and Periodontics. 2nd ed. Chicago: Quintessence Publishing; 2006.p.26-32.
21. Fergal JO Brien. Biomaterials and scaffolds for tissue engineering materials today 2011; 14(3):88-95.
22. Hench LL. Bioceramics, a clinical success. J Am Ceram Soc 1998;81:1705-1728.
23. Ambrosio AM, Sahota JS, Khan Y, Laurencin CT. A novel amorphous calcium phosphate polymer ceramic for bone repair: I. Synthesis and characterization. J Biomed Mater Res 2001;58:295-301.
24. Wang M. Developing bioactive composite materials for tissue replacement Biomaterials 2003;24:2133-2151.
25. Lu Lichun, Zhu Xun, Valenzuela, Richard G. Biodegradable Polymer Scaffolds for Cartilage Tissue Engineering. Biomaterials 2000;21:1837-1845.
26. SH Oh, SG Kang, ES Kim. Fabrication and characterization of hydrophilic poly (lactic-co-glycolic acid)/poly (vinyl alcohol) blend cell scaffolds by melt-molding particulate-leaching method, Biomaterials 2003;24:4011-4021.
27. Rowlands AS, Lim SA, Martin D, Cooper-White JJ. Polyurethane/poly (lactic/glycolic) acid composite scaffolds fabricated by thermally induced phase separation. Biomaterials 2007; 28:2109-2121.
28. Liu, H, Slamovich EB, Webster TJ. Less harmful acidic degradation of poly (lactic-co-glycolic acid) bone tissue engineering scaffolds through titania nanoparticle addition. Int J Nanomedicine 2006;1:541-545.

29. Bartold P, Xiano Yin, Lingstaadas SP, Paine ML, Snead ML. Principles and applications of cell delivery systems for periodontal regeneration. Periodontology 2000 2006;41:123–135.
30. Kao RT, Murakami S, Ross Bierne O. The use of biologic mediators and tissue engineering in dentistry. Periodontology 2000 2009;50:127–153.
31. Bartold P, Mcculloch CA, Narayanan AS, Pitaru S. Tissue engineering: A new paradigm for periodontal regeneration based on molecular and cell biology. Periodontol 2000 2000;24:253-269.
32. Lind M. Growth factors: possible new clinical tools. A review. Acta Orthop Scand 1996;67: 407–421.
33. The American Academy of Periodontology. The potential role of growth and differentiation factors in periodontal regeneration. J Periodontol 1996;67:545–551.
34. Massague J. TGF-b signal transduction. Ann Rev Biochem 1998;67:753–791.
35. Lynch SE, de Castilla GR, Williams RC, Kiritsy CP, Howell TH, Reddy MS, et al. The effects of short term application of a combination of platelet derived and insulin growth factors on periodontal wound healing. J Periodontol 1991;62:458-467.
36. Cho Moon OL, Wen Langhin AA, Genco Robert J. Platelet derived growth factor – modulated guided tissue regenerative therapy. J Periodontol 1995;66:522-530.
37. Bennett NT, Schultz GS. Growth factors and wound healing: Biochemical properties of growth factors and their receptors. Am J Surg 1993;165:728-737.
38. Han X, Amar S. IGF-I signalling enhances cell survival in PDL fibroblasts vs gingival fibroblasts. J Dent Res 2003;82:454-459.
39. Hollinger J, Buck D, Bruder SP. Biology of bone healing: Its impact on clinical therapy. In: Lynch, Samuel E, Genco Robert, Marx Robert, editors. Tissue Engineering: Applications in Maxillofacial Surgery and Periodontics. 1st ed. Chicago: Quintessence Publishing; 1999.p.17-53.
40. Oates TW, Rouse CA, Cochran DL. Mitogenic effects of growth factors of human periodontal ligament cells in vitro. J Periodontol 1993;64:142-148.
41. Raja S, Byakod G, Pudakalkatti P. Growth factors in periodontal regeneration. Int J Dent Hygiene 2009;7:82-89.
42. Takayama S, Murakami S, Shimabukuro Y, Kitamura M, Okada A. Periodontal regeneration by FGF-2 (bFGF) in primate models. J Dent Res 2001;80:2075-2079.
43. Schlueter SR, Carnes DL Jr, Cochran D. In vitro effects of enamel matrix derivative on microvascular cells. J Periodontol 2007;78:141–151.
44. El-Sharkawy H, Kantarci A, Deady J, Hasturk H, Liu H, Alshahat, et al. Platelet-rich plasma: Growth factors and pro- and anti-inflammatory properties. J Periodontol 2007;78:661–669.
45. Douglass GL. Periodontics—tissue engineering and the future. J Calif Dent Assoc 2005; 33:203-204.
46. Kao RT, Conte G, Nishimine D, Dault S. Tissue engineering for periodontal regeneration. J Calif Dent Assoc 2005;33:205-215.
47. Akizuki T, Oda S, Komaki M, Tsuchioka H, Kawakatsu N, Kikuchi A, et al. Application of periodontal ligament cell sheet for periodontal regeneration: A pilot study in beagle dogs. J Periodont Res 2005;40:245-251.
48. Hasegawa M, Yamato M, Kikuchi A, Okano T, Ishikawa I. Human periodontal ligament cell sheets can regenerate periodontal ligament tissue in an athymic rat model. Tissue Eng 2005;11:469-498.
49. Flores MG, Yashiro R, Washio K, Yamato M, Okano T, Ishikawa I. Periodontal ligament

cell sheet promotes periodontal regeneration in athymic rats. J ClinPeriodontol 2008;35:1066-1072.
50. Huang SY, Zhang DS. Periodontal ligament cell sheet engineering: A new possible strategy to promote periodontal regeneration of dental implants. Dent Hypothesis 2010;1:23-30.
51. Melcher AH. On the repair potential of periodontal tissue. J Periodontol 1976;47:256-260.
52. Hanes PJ. Bone replacement grafts for the treatment of periodontal intrabony defects. Oral Maxillo fac Surg Clin North Am 2007;19:499-512.
53. Ramseier CA, Abramson ZR, Jin Q, Giannobile WV. Gene therapeutics for periodontal regenerative medicine. Dent Clin N Am 2006;50:245–263.
54. Jin QM, Anusaksathien O, Webb SA, Rutherford RB, Giannobile WV. Gene therapy of bone morphogenetic protein for periodontal tissue engineering. J Periodontol 2003;74:202–213.
55. Jin Q, Anusaksathien O, Webb SA, Printz MA, Giannobile WV. Engineering of tooth-supporting structures by delivery of PDGF gene therapy vectors. Mol Ther 2004;9:519–526.
56. Huang JS, Huang SS, Deuel TF. Human platelet derived growth factor. Radioimmunoassay and discovery of a specific plasma binding protein. J Cell Biol 1983;97:383-388.
57. McGuire MK, Scheyer ET. Comparison of recombinant human platelet derived growth factor bb plus beta tricalcium phosphate and a collagen membrane to subepithelial connective tissue grafting for the treatment of recession defects: A case series. Int J Periodontol Rest Dent 2006;26:127-3.
58. Selvig KA, Sorensen RG, Wozney JM, Wikesjo UM. Bone repair following recombinant human bone morphogenic protein-2 stimulated periodontal regeneration. J Periodontol 2002;73:1020-1029.
59. Giannobile WV. Periodontal tissue engineering by growth factors. Bone 1996;19(1):23-37.
60. McKay WF, Peckham SM, Badura JM. A comprehensive clinical review of recombinant human bone morphogenetic protein-2 (INFUSE® Bone Graft). Int Orthop 2007;31:729-734.
61. Sigurdsson TJ, Nguyen S, Wikesjo UM. Alveolar ridge augmentation with rh BMP-2 and bone to implant contact in induced bone. Int J Periodontics Restorative Dent 2001;21:461-463.
62. Seeherman H, Li R, Bouxsein M, Kim H, Li JX, Smith Adaline EA, et al. rhBMP-2/Calcium phosphate matrix accelerates osteotomy site healing in a nonhuman primate model at multiple treatment times and concentrations. J Bone Joint Surg Am 2006;88:144-160.

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