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Materials in periodontal regenerative therapy: An overview

Harshada T Zagade, Siddhartha A Varma *, Girish Suragimath and Sameer Zope

Department of Periodontology, School of Dental Sciences, Krishna Institute of Medical Sciences "Deemed to be University" Karad, Maharashtra.

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Abstract

Periodontal diseases refer to periodontal ligament injury affecting all the supporting structure and, if left untreated, results in loss of the tooth. Periodontal regenerative therapies aim towards healing all the damaged periodontal tissues by not only restoring structure but also the functions. This review provides information of all the currently-used as well as advanced biomaterials for periodontal regeneration. During this advancing research, various regenerative therapies of periodontal apparatus, such as guided tissue regeneration (GTR), enamel matrix derivative, bone grafts, growth factor delivery, and the combination of cells and growth factors with matrix-based scaffolds have been implemented to restore lost tooth-supporting tissues, including periodontal ligament, alveolar bone, and cementum. This review has stated about the recent progresses of periodontal regeneration by means of tissue-engineering.

Keywords: Barrier membrane; Gene therapy; Periodontal regeneration; Scaffold; Tissue engineering

1 Introduction

Periodontitis is the most common dental inflammatory disease associated with pathological conditions of gingiva and periodontium. The numerous bacterias such as gram positive and gram negative and their by-products forms integral component of plaque around the healthy gingiva and the periodontium. Periodontitis is defined as an inflammatory disease of supporting tissues of teeth caused by specific microorganisms or groups of specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with periodontal pocket formation, gingival recession or both [1]. Severity of this periodontal disease results in tooth loss, requiring periodontal therapy or regenerative therapy along with the oral health care and proper oral hygiene maintenance [2]. There are various treatment modalities in such cases that includes root coverage procedures, graft materials, barrier membranes, growth factors and gene therapy.

"To regenerate the lost periodontal structure" has been the ideal goal in periodontal regeneration. Re- establishment of the original form, shape, properties and functions of the periodontal ligament has been a challenge [3]. The primary goal of the periodontal therapy includes regeneration of periodontal structures and functions of soft tissues (Gingiva and Periodontal ligament) and hard tissues (Bone and Cementum) of periodontal apparatus. Different multidisciplinary methods such as bone grafting, distraction osteogenesis, allografts, bone-graft substitutes, guided bone regeneration and guided tissue regeneration are available in spite of which regeneration of periodontal defects remains as a challenge [4].

The periodontal wound healing comprises of two mechanism of healing that includes, the repair and the regeneration. The healing of tissues by the repair mechanism does not restore the architecture and function of periodontium

* Corresponding author: Siddhartha A Varma
Department of Periodontology, School of Dental Sciences, Krishna Institute of Medical Sciences "Deemed to be University" Karad, Maharashtra.

completely, while the regeneration leads to new tissue formation which is identical in structure as well as function compared to the original tissue [5]. Guided tissue regeneration is considered to be "gold standard" reconstructive approach in periodontal surgeries. Guided tissue regeneration is (GTR) "the method for the prevention of epithelial migration along the cemental wall of the pocket and maintaining space for clot stabilization" [1].

The periodontal regeneration using barrier membrane concept is based on several series of findings in the experiments on regenerative capacity of different periodontal tissues [6-7]. Epithelial exclusion and selective repopulation of the root surface by multipotential cells with the help of non-resorbable or resorbable occlusive membranes have become an accepted mode of PDL regeneration in periodontics [7].

1.1 Methodology

A computerized search of the PubMed, Google Scholar and ResearchGate databases using key words: Guided tissue regeneration* Periodontitis* and Periodontal regeneration* Materials Used for regeneration* in all fields was performed. The search consisted screening of original reports, review articles, and reference lists of recovered articles and hand searches of certain journals. All searches were focused on Periodontal regeneration and various biomaterials used for the regeneration.

1.2 Technique

Guided tissue regeneration is a surgical procedure where, full thickness mucoperiosteal flap is raised. Complete root debridement of affected teeth is done with through scaling and root planning. Later the GTR membrane is placed at the surgical site and held in place with sutures [8]. GTR membrane stabilization is performed with either of the techniques: 1. Periosteal suture 2. Fixation pins and/or screw. To attain the stability of membrane is critical regardless of the choice of membrane that is being used. Stabilization through use of fixation tacks and pins allows immobilization of the membrane and permits packing of the bone graft against membrane in case of guided bone regeneration. While stabilization with periosteal sutures, the suture used are resorbable material (thin suture, e.g., 6-0) and a relatively small needle (e.g., 10 to 13mm 3/8 circle). The suturing is started by stitching through the periosteum apically. Then the horizontal and vertical mattress sutures are placed to stabilize the membrane in case of guided bone regeneration. Closure of the mucoperiosteal flap should be done in two layers. The initial layer is closed using horizontal mattress sutures, placed 4 mm from the incision line, and single interrupted sutures are placed to close the edges of the flap. With this suturing technique, the flap are margins effectively approximated. Vertical incisions are closed using single interrupted sutures [9].

GTR technique is to prevent the apical growth of epithelium on the space over the denuded root surface by using GTR membrane, therefore enabling PDL cells and osteoblast to form PDL tissues and alveolar bone. There are various benefits of GTR treatments, includes greater clinical attainment level (CAL) gain, probing pocket depth (PPD) reduction and bone regeneration confirmed by clinical research. GTR has limitations for periodontal regeneration. Many aspects, such as systemic disease like diabetes, habits like smoking, poor oral hygiene, tooth anatomy and morphology, can affect the results of the GTR treatment [10].

1.3 GTR biomaterials

The barrier membranes should have properties like, biocompatibility, cell-occlusiveness, tissue integration, space maintenance, and clinical manageability [11]. Basically, GTR barrier membranes are classified as nonabsorbable and absorbable membranes. Non-absorbable membranes persist superior space maintenance ability compared to absorbable membranes. Gore-tex® was the first GTR barrier membrane, composed of polytetrafluoroethylene (PTFE) with high mechanical properties [12]. Further modifications such as titanium-reinforced PTFE membrane increased the compressive strength, giving better outcomes compared to the PTFE membrane [13]. The ultrathin (0.01 mm) titanium-reinforced PTFE membrane modification occupied smallest space, thus, providing more area for new tissue formation [14].

A second surgery is required in case of nonabsorbable barrier membranes, leading to an increased risk of infection, delayed wound healing, and impairing the regenerative outcomes. While absorbable membranes, they are gradually degraded in vivo thus, avoiding the drawback of second surgery after GTR procedure. Both natural and synthetic biomaterials are verified as absorbable GTR membranes. Usually, biomaterials of natural source origin have excellent biocompatibility with cellular binding sites, but have compromised mechanical strength [15]. In case of synthetic biomaterials, they have controlled degradation rates and mechanical properties, but lacks biological recognition (cellular binding motif). The degradation property of membranes can affect the ability of space maintaining thereby affecting new tissue formation. As a guideline, the degradation rate should be moderate: fast degradation rate leads to

premature mechanical loss while slow degradation rate prevents new tissue ingrowth. Absorbable membranes have a limitation of low mechanical strength compared to non- absorbable membranes.

2 Non-resorbable membranes

Non-resorbable membranes include expanded polytetrafluoraethylene (e-PTFE, Gore-Tex®), high-density polytetrafluoraethylene (d-PTFE), and titanium-reinforced high-density polytetrafluoraethylene (Ti-d-PTFE) membranes [16].

3 Resorbable Membranes Based on Natural Polymer

Natural polymers show good biocompatibility, safety, biodegradability, thus, it has been widely used as GTR and GBR materials.

3.1 Membrane Based on Collagen

Mostly types I and III Collagen membranes, have several superior properties such as good tissue integration, fast vascularization, biodegradation without foreign-body reaction, weak immunogenicity, osteoblastic adhesion, biocompatibility and capability of promoting wound healing, chemotactic action for fibroblasts and haemostatic property [17].

Enzymatic degradation by collagenases/proteases, and macrophage/polymorphonuclear leukocyte-derived enzymes and bacterial proteases aids in resorption of these collagen membranes. The resorption rate of collagen membranes shows variations ranging from 4 to 32 weeks [18,19].

It comprises of bilayer structure with a superficial compact smooth layer and an inner porous layer. When used for GBR, the porous and compact layers enable osteogenic cell migration to make bone ingrowth possible, and prevents the invasion of fibroblasts [20]. Degradation rate of monolayer Bio-Gide® and bilayer Bio-Gide® shows no difference. To reinforce the mechanical and biodegradable stability into collagen membrane, various chemical, physical, and biological cross-linking methods have been introduced to cross-link collagen.

Through cross-linking, the tensile strength of collagen is improved and their degradation time can be extended. Physical treatments such as de-hydrothermal treatment can be performed as an alternative to introduce cross-link efficiently [21,22].

3.2 Membrane Based on Chitosan

Since, past 20 years, chitosan, has driven attention as candidate material for GTR and GBR procedure due to its low cost, superior biocompatibility, flexibility in hydrated environments, non-antigenicity, appropriate degradation rate, haemostatic activity, antimicrobial and wound healing potential [23-26]. Chitosan membranes usually persist for 16-20 weeks at the site [27]. It was reported that chitosan nanoparticles act synergistically with chlorhexidine mouthwash for periapical guided tissue regeneration [28]. These results suggest that antibacterial property of chitosan can be improved in periapical regenerative procedures.

3.3 Membrane Based on Gelatin

Gelatin, a soluble protein obtained from partially denatured collagen, has established virtuous attention owing to its availability, easy handling and cost efficiency [29]. But it shows deprived mechanical properties and fast degradation.

3.4 Membrane Based on Silk Fibroin (SF)

Silk fibroin (SF), a natural protein that can be obtained from silk worms (e.g., Bombyx mori) or spiders, has various important properties such as, good biocompatibility, good oxygen and water vapor permeability, and biodegradability [30]. The degradation rate of biopolymer membranes depends on concentration of fibroin. These usually degrade after 1 month of operation [31]. The tensile strength of the wet SF membrane was higher when compared with the tensile strength of the wet EDC-cross-linked collagen and PTFE membranes.

4 Resorbable Membranes Based on Synthetic Polymer

Currently, most of the resorbable synthetic polymer membranes available in the market are based on copolymers and aliphatic polyesters, such as poly (lactic acid) (PLA), poly (glycolic acid) (PGA), poly(ε-caprolactone) (PCL), poly (hydroxyl valeric acid), and poly (hydroxyl butyric acid). The shortcomings such as inflammatory foreign-body reactions are seen with their degradation products [32].

4.1 Polylactic Acid (PLA) and Polylactic acid/Polyglycolic Acid Copolymer (PLGA)

Polylactic acid (PLA) is most common and important polymer. For example, Guidor® Matrix Barrier (Sunstar Americas, Inc. near Chicago, IL, USA). It is the first and most broadly studied alloplastic matrix and barrier technology. Two polymers such as, poly-D, L-lactide (PDLLA) and poly-L-lactide (PLLA) blend together to form homogenous bi-layered membrane. These Barrier membranes can maintain its barrier function for a minimum time period of six weeks, while it is progressively resorbed in 13 months [33].

Even though PLA- and PLGA-based membranes are non-cytotoxic and biodegradable, they tend to release oligomers and acid by-products during degradation process, that may trigger inflammation reactions and foreign body response in vivo [34], and thus further studies are being carried out to improvise in its properties.

4.2 Polyethylene Glycol (PEG)

One of the most important biodegradable material with cell-occlusive property is Polyethylene glycol (PEG), and biocompatible polymer, is a candidate for GBR and GTR procedures [35-37].

5 Resorbable Membranes Based on Polymer Composite

5.1 Polymer Blends

Polymer membranes have several crucial principles for GBR and GTR success, single polymer cannot meet all the principles. Thus, it is an efficient solution to blend two or more polymers to overcome their respective limitations and show more positive synergistic effects.

5.2 Blends of Natural Polymer

Chitosan is natural polymer. Protein polymers shows better bioactivity than chitosan polymers, also its mechanical properties are poor. For example, gelatin has free carboxyl groups on its backbone, and it can easily blend with chitosan to form a network by hydrogen bonding. A central chitosan layer sandwiched by two collagen membranes containing 20 wt % Hydroxyappatite, A tri-layered membrane was fabricated [38]. Results stated that such gelatin/chitosan or collagen/chitosan membranes are better choice for guided tissue and bone regeneration as it holds sufficient mechanical and structural properties. These properties function as a barrier membrane, and also lead to proteins promoted osteogenic differentiation.

5.3 Blends of Synthetic Polymers

Synthetic Polymers, weak mechanical strength, makes it difficult to maintain the shape of a PLGA scaffold during various in vitro and in vivo experiments. Therefore, PLGA can be blended with other polymers, for example, PCL/PLGA composite scaffolds were formed by mixing PCL and PLGA in the same ratio. The Compressive strength and modulus of this newly manufactured membrane were much higher than that of pure PLGA scaffolds [39].

5.4 Blends of Natural Polymer and Synthetic Polymer:

Natural polymers have much better biocompatibility or bioactive properties, for example gelatin. It consists of many integrin-binding sites for cell adhesion and differentiation [40,41]. When natural polymers are blended with synthetic polymers, it combines both the advantageous properties of natural and synthetic polymers [42].

6 Resorbable Membranes Containing Functional Materials

6.1 Polymer Membranes Loaded with Antibacterial Agents:

Recently membranes have been loaded with antibiotics. Membranes are designed with antibiotic content for local drug release to overcome the disadvantages of conventional systemic drug administration. For example, metronidazole (MNA)-loaded polymeric membrane. It showed a significant progress on the periodontal and bone regeneration following GTR and GBR procedures [43].

Commonly, antibiotics were directly blended with membranes, this resulted in a higher outburst and short time period of drug release that could not effectively prevent bacterial infections. Hence, it is necessary to develop novel GTR and GBR membranes with slow and controlled release of antibacterial agents, especially in patients with a predisposition to complications like smokers, patients with diabetes mellitus, and so on [44].

6.2 Polymer Membranes Loaded with Growth Factors

Another method such as introducing Growth factors in the membrane was performed. Growth factors are critical signaling molecules that perform the actions by binding cells through specific transmembrane receptors on the target cells. These signals to the specific cells may achieve tissue regeneration by providing control, on growth factor delivery [45]. 3-D printing method was used to manufacture GBR membrane loaded with rhBMP-2, these membranes were programmed for sustained release of rhBMP-2 up to 28 days; in a in-vivo experiment, these rhBMP-2 loaded membrane induced higher new bone formation and led to almost entire healing of 8 mm calvarial defects within eight weeks [46].

7 Oral Tissue Engineering and Regeneration materials:

Tissue engineering is a concept interlinked with regenerative medicine but it differs in its goal regarding the engineering and manufacturing of replacement tissue, but both regenerative medicine and tissue engineering considered as a single field of interest. The aim of tissue engineering is to regenerate lost tissue or organ with its original integrity and function using patients own cells with various other technique other than grafting procedures. It can be used for construction of various tissue defects with specific cells having potential to regenerate the same [47].

Tissue engineering is based on following three important components as shown in figure1.

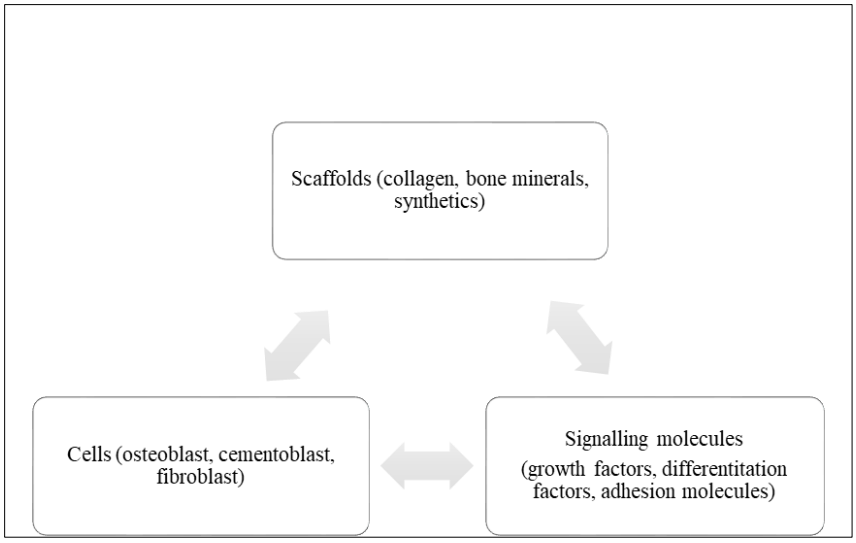

Figure 1 Three important components of tissue engineering

Tissue engineering is considered as future tend in regeneration which includes various advances such as multiphasic scaffold, 3D printed constructs, hydrogels.

7.1 Cells

Cells included in the tissue engineering are pleuripotent stem cells such as CD34+ marrow cells, CFU cells, pre-osteoblasts, endosteal /periosteal osteoblasts. These cells communicate in the environment with the help of signalling molecules or the growth factors on a three-dimensional (3D) structure. Figure 2.

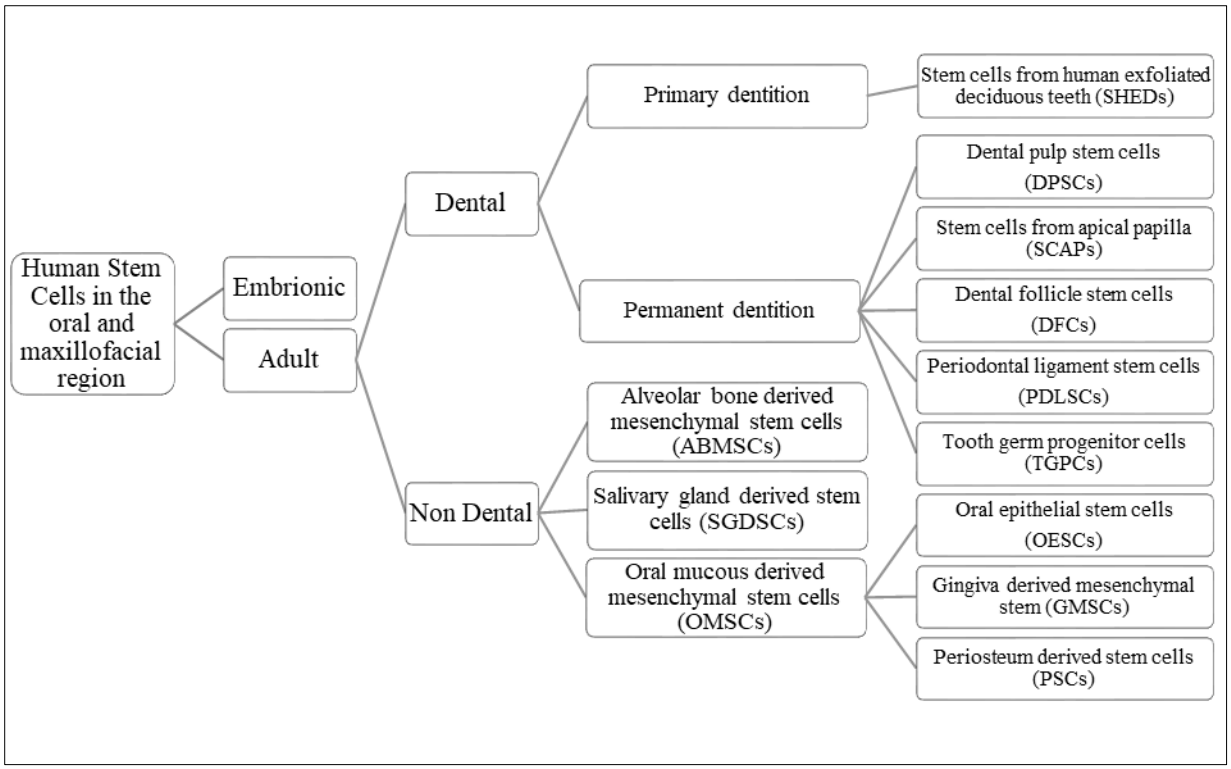

Figure 2 Types of human stem cells (SCs) in the oral and maxillofacial region

7.2 Scaffolds

Scaffolds forms desirable cellular interactions provides matrix or lattice network for the cells in the environment to migrate and commences their activities [48].

These scaffold materials should follow some properties such as: Mimicking the stem cell niche to alter the regulation of stem cells; Cell—scaffold interplay and scaffold designing; Honeycomb microarray film application for PDL cell sheet engineering; Possible induction of cementogenesis by modulation of the extracellular ionic microenvironment using bioactive ceramic scaffolds; Application of nanofabricated hydroxyapatite for bone tissue engineering [49].

7.3 Growth factors

A growth factors are naturally produced substance in human body with ability to stimulate cell proliferation, wound healing, and rarely cellular differentiation. The careful controlled coordinated expression of various growth factors directs specific cells to proliferate, undergo clonal amplification of progenitor cells, and ultimately produce and release ECM for related tissue regeneration.

8 Gene therapy

The short half-life of topically administered Growth Factors (GFs) in vivo, ranges usually from several hours to several days thus, researchers have tried to increase protein activity using gene delivery approach. This approach includes conversion of cells into protein-producing factories which can be achieved by delivering plasmid DNA that encodes the GF(s) of interest into cells/tissues either directly or via gene delivery vehicles or vectors. This method has seemed as a capable strategy for the modulation of the host response generated by periodontal microbe and regeneration of periodontium during disease progression. Gene therapy helps in signaling the available cells to differentiate into a phenotype that are more favorable to the regenerative process [50].

9 Conclusion

This review has focused on various available biomaterials for the periodontal regeneration. These Biomaterials in periodontal regeneration include inorganic materials, polymeric materials and composites. Inorganic biomaterials are substitutes used for bone and cementum regeneration due to their similar composition and mechanical property, while the polymeric biomaterials are used for PDL regeneration. Thus, the combination of various inorganic and polymeric materials is used fabricate biomimetic matrix / lattice for bone and cementum regeneration. The currently regenerative options for intra-bony defects are very few while there is no effective regenerative techniques specifically for horizontal bone augmentation. The future trends in periodontal regeneration are focussed on stem cell therapy, cell sheet engineering, growth factors and may become key in regenerating oral PDL tissues disturbed by periodontal disease.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest.

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