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Paradigm Shift: Biologic Solutions to Biological Problems

[1]Dr Subair Kayakool, Professor, Department of Periodontics, Mahe Institute of Dental Science and Hospital,Mahe, Puducherry, India-673310

[2]Dr Marjana Shukoor**,** Post Graduate Resident**,** Department of Periodontics, Mahe Institute of Dental Science and Hospital, Mahe, Puducherry, India-673310

[3]Dr Arjun Machingal Raveendran**,** Reader, Department of Periodontics, Mahe Institute of Dental Science and Hospital, Mahe, Puducherry, India-673310

[4]Dr Anil Melath, Professor and HOD**,** Department of Periodontics, Mahe Institute of Dental Science and Hospital, Mahe, Puducherry, India-673310

[5]Dr Jilu Jessy Abraham**,** Reader**,** Department of Periodontics,**,** Mahe Institute of Dental Science and Hospital,**,** Mahe, Puducherry, India-673310

Corresponding Author: Dr Marjana Shukoor, Post Graduate Resident**,** Department of Periodontics, Mahe Institute of Dental Science and Hospital, Mahe, Puducherry, India-673310**.**

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Abstract

Periodontal regeneration, aimed at restoring both the form and function of periodontal tissues, has evolved significantly since the introduction of guided tissue regeneration (GTR) by Melcher in the early stages of the field. Tissue engineering (TE) and regenerative medicine (RM) emerged as promising approaches, with the goal of achieving genuine tissue regeneration in a faster, less invasive, and higher-quality manner. The convergence of stem cells, scaffolds, and signaling molecules, along with advancements in scaffold design, 3D-printing, and gene therapy, holds great potential for advancing periodontal tissue engineering, paving the way for more effective and personalized regenerative solutions in clinical practice. This review explores the integration of signaling molecules, scaffolds, and gene therapy in current periodontal tissue engineering strategies.

Keywords: Tissue Engineering, Guided Tissue Regeneration, Regenerative Medicine.

Introduction

With the formation of alveolar bone and the establishment of a new connective attachment facilitated by collagen fibers arranged functionally on the developing cementum, periodontal regeneration aims for the complete restoration of both the height and functionality of periodontal tissues.[1] In 1993, Langer and colleagues proposed tissue engineering as a potential approach to replace missing periodontal tissues.[2]

The ultimate objective of tissue engineering is to expedite the healing process and, ideally, achieve genuine regeneration of a tissue's structure and function in a more dependable, faster, less invasive, and higher-quality manner compared to earlier passive procedures.[3,4]"

In the context of periodontal regeneration, TE/RM has evolved significantly over time beginning early on with the concept of guided tissue regeneration (GTR). The first to propose that the distinct cell types that initially repopulate the root surface after periodontal surgery will define the form of the new attachment and whether healing proceeds by repair or regeneration was Melcher[5].The biologicalrationale for the GTR treatment concept is based on the implementation of cell-occlusive barrier membranes to selectively exclude relatively rapid epithelial and fibroblastic down growth while promoting repopulation of defect sites with slower migrating cells from the periodontal ligament, bone, and cementum[6]. Based on the principles of GTR, guided bone regeneration (GBR) was created for the regeneration of osseous defects. Barrier membranes are used to mechanically prevent soft tissue ingrowth from the defect site to encourage repopulation with osteogenic progenitor cells. [7] GBR may be utilized for regeneration of critical size maxillofacial deficiencies, peri-implant bone defects, and also for post-extraction alveolar ridge augmentation.

Tissue Engineering

The major components of current tissue engineering-based treatment approaches include signaling molecules/growth factors, scaffolds, and cells with a particular focus on promoting osteogenesis, and angiogenesis, as well as controlling inflammation[8].It is important to note that these approaches can be used either alone or in combination with one another. Since the initial development of guided tissue regeneration (GTR) and guided bone regeneration (GBR), there have been significant advancements in the field, particularly regarding the integration of biologics, scaffolds, and gene therapy. These innovations aim to modulate the healing response effectively, ultimately enhancing regenerative outcomes[9].

This present review provides an overview ofperiodontal tissue engineering aboutsignalling molecules/growth factors, scaffolds, as well as gene and cell therapy [Figure 1]. Three essential components are included in the tissue engineering approach to bone and periodontal regeneration to speed up regeneration. [10]

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

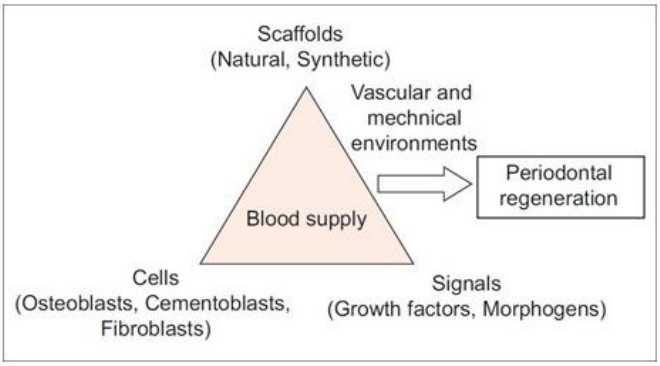

Figure 1: The tissue engineering triad [11]

Cells

Asymmetric mitosis produces two daughter cells from stem cells: a daughter stem cell that is identical to the parent stem cell and a progenitor cell that can differentiate into more mature cells. Stem cells are immature progenitor cells capable of self-renewal and multi-lineage differentiation.[12]To date, a variety of stem cells, including mesenchymal, embryonic, and induced pluripotent stem cells, have been reported to promote regeneration of damaged tissues [13].

Types of stem cells for tissue regeneration

- 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 blastocystis (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 ,mesoderm or endoderm).[14]

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.[15–17]

- Embryonic stem cells are derived from embryos that are 2 – 11 days old called blastocysts. They are totipotent cells. Due to ethical concerns and the risk of tumorigenicity and teratoma formation, its use has been restricted to the research field.
- Adult stem cells are multipotent stem cells, and depending upon their origin, they can be further classified into hematopoietic stem cells and mesenchymal stem cells. Friedenstein and colleagues first identified mesenchymal stem cells in aspirates of adult bone marrow.[18] Among the adult stem cells, bone marrow–derived stem cells or mesenchymal stem cells (MSCs) are adherent, proliferating, and capable of multi-lineage 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.[17]

Cell Source for Progenitor Cells

Periodontal ligament-derived cells: The multipotential properties of periodontal ligament-derived cells make them desirable sources for the regeneration of periodontal tissues, which include bone, cement, and periodontal ligament.[19]

Periodontal ligament-derived mesenchymal stromal cells: Seo et al. isolated a population of multipotent stem cells in human periodontal ligament and indicated that periodontal ligament-derived mesenchymal stromal cells exhibited some characteristics similar to those of mesenchymal stromal cells, such as multipotency, clonogenic ability, high proliferation and the expression of the putative stem cell marker STRO-1, as well as the perivascular cell marker CD146.[20]

Periosteal cells: The cultured periosteum expresses genes relevant to periodontal tissue and is capable of differentiating into an osteoblastic lineage. Yamamiya et al. showed cultured periosteum combined with platelet-rich plasma and hydroxyapatite induced clinical improvements in human infrabony defects.[21]

Gingival epithelium and fibroblast: Gingival epithelial sheets derived from human gingival tissues were developed and applied clinically as a treatment for chronic desquamative gingivitis.[22]. Mohammadi et al. applied autologous gingival fibroblasts for patients with insufficient attached gingiva and showed an increase in the width of keratinized tissue.[23]

Bone marrow-derived mesenchymal stem cells: Kawaguchi et al., demonstrated that autotransplantation of bone marrow-derived mesenchymal stem cells induced periodontal regeneration in experimental class III furcation defects in dogs.[24]

Scaffold or Supporting Matrices

Tissues are composed of two components: cells and their surrounding extracellular matrix (ECM), which is known to play an important role in cell proliferation and differentiation. The ECM's primary job is to support cell development and provide cells with necessary nutrients[25]. ECM has been reported to create a framework for cell growth and to efficiently provide the nutrients or growth factors needed for cells [26]. It is difficult to naturally repair a large-size tissue defect by supplying cells to the injured sites, since not only the cells but also the ECM are lost. Therefore, to promote tissue regeneration, it is necessary to make an artificial ECM environment for transplanted cells, and biomaterials are useful substitutes for ECM, and are also useful in cell therapy. For cell penetration into the biomaterial scaffold and the delivery of oxygen and nutrients to the cells, the scaffold should be porous. In addition, the scaffold should be biodegradable for proper replacement of damaged tissues with the transplanted cells [27].

A wide range of synthetic and organic materials have been produced for biomaterials. Particularly beneficial for tissue engineering are biodegradable polymers including collagen, gelatin, fibrin, hyaluronic acid, and poly(lactic-co-glycolic acid) [28]. The combination of these scaffolds and stem cells was used for skin wound healing [29].

The major roles for supporting matrices are [30]

1. It acts as a framework, preserving the defect's shape. To prevent the surrounding tissue from collapsing into the wound site, it offers physical support for the healing area.
2. It serves as a 3D substratum for cellular adhesion, migration, proliferation, and production of extracellular matrix.
3. It serves as a barrier to restrict cellular migration selectively.
4. It might operate as a means of delivering growth elements.

Signaling molecules

Proteins known as signaling molecules can have a variety of local or systemic effects on how cells develop and function. Growth factors and morphogens, which function by changing the cell phenotype, or by inducing the differentiation of stem cells into bone-forming cells, or osteoinduction, are the two types of signaling molecules that have drawn the most interest.[3]

Summary of commercially available and commonly studied biologic agents;[31]

Abbreviation	EMD	PDGF-BB	FGF-2	BMP-2 and -7
Factor	Enamel Matrix Derivative	Platelet-Derived Growth Factor-BB	Fibroblast Growth Factor-2	Bone Morphogenic Protein-2 and 7
Endogenous sources	Hertwig's epithelial root sheath	BB isoform: osteoblasts, macrophages & endothelial cells. Only AB isoform is derived from platelets and is found in blood.	Macrophages & endothelial cells	Osteoblasts & bone matrix

Abbreviation	EMD	PDGF-BB	FGF-2	BMP-2 and -7
Action	Believed to play a role in cementogenesis.	↑ chemotaxis of PMNs & monocytes, ↑ endothelial cell chemotaxis, proliferation & differentiation, ↑ fibroblast proliferation & ECM synthesis	↑ fibroblast proliferation & ECM synthesis ↑ endothelial cell chemotaxis, proliferation & differentiation ↑ mesenchymal progenitor cell migration	BMP-2: ↑ mesenchymal osteoprogenitor cell migration BMP-7: ↑ osteoblast and chondroblast differentiation
FDA approval (Labelled usage)	Yes (intrabony, class 2 furcation defects & gingival recession coverage)	Yes (intrabony defects, furcations, gingival recession)	No	BMP-2: Yes (sinus augmentation, socket preservation) BMP-7: No for dental usage; approved for spinal fusion & long bone non-union treatment
Preclinical and clinical evidence for other usages	Clinical evidence for treatment of peri-implantitis-associated defects	Clinical evidence for GBR and peri-implantitis-associated defects	Clinical evidence for intrabony defects; pre-clinical evidence for peri-implant defects	Clinical evidence for GBR and pre-clinical evidence for peri-implantitis-associated defects
Commercial products	Emdogain (Straumann)	GEM 21S (Lynch Biologics)	None yet	BMP-2: Infuse Bone Graft (Medtronic) BMP-7: Osigraft (Stryker Biotech)

Insulin-like growth factor

A potent chemotactic agent for vascular endothelial cells, insulin-like growth factor (IGF) promotes enhanced neovascularization. It also stimulates the mitosis of many cells in vitro such as fibroblasts, osteocytes, and chondrocytes[19]. IGF-I is known as somatomedin C and IGF-II has been called multiplication-stimulating activity. Insulin-like growth

factor-I is found in substantial levels in platelets and is released during clotting along with the other growth factors.IGF-II is the most abundant growth factor in the bone and it also promotes parameters of bone formation but is not as potent as IGF1. [32]

Transforming growth factor family

The two best-characterized polypeptides from this group of growth factors are the Transforming growth factor family (TGF)-α and TGF-β. TGF-β appears to be a major regulator of cell replication and differentiation. TGF-β is encoded by three different genes 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. [33]

Advancements

Advancements in scaffold

One of the major tenets of tissue engineering is that biologics, including cells, proteins, and genes, can be delivered via a degradable scaffold to promote regeneration. In general, scaffolds must fulfill four fundamental requirements: (1) form: able to match the geometry of complex 3D defects; (2) function: must transiently support functional and biomechanical demands during healing; (3) formation: should enhance regeneration; and (4) fixation: must readily interface and integrate with the surrounding tissues[34].

Multiphasic scaffolds are defined based on variations in architectural characteristics (such as porosity and pore organization) and chemical composition throughout a construct. They are often designed to resemble the structural organization as well as the cellular and biochemical composition of native tissues[35]. Considering the complex structure of the periodontium and the interactions between multiple soft and hard tissues, Ivanovski et al.[36] summarized key considerations in the design of multiphasic scaffolds for periodontal tissue engineering: (1) the compartmentalization of bone and periodontal attachment tissue formation that is integrated over time; (2) the promotion of cementum formation on the root surface; and (3formations of periodontal ligament fibers with the proper orientation for insertion into newly formed bone and cement.

3D-printing

Over the past two decades, much effort has been applied towards creating porous constructs from the traditional freeze-casting and gas-foaming methods to the emerging wide variety of 3D-printing technologies that can be used to create ordered porosity and user-defined shapes [37]. Several 3D-printing techniques, such as 3D wax printing and fused deposition modeling, have been investigated to facilitate morphogenesis of the periodontal tissue complex. In 2014, Lee et al.[38] printed seamless scaffolds with region-specific microstructures consisting of three phases. It was shown that multiphasic scaffolds yielded aligned PDL-like collagen fibers that were inserted into bone-like tissue as well as putative cementum matrix protein-positive tissues. These conventional 3D-printing methods utilize fiber diameters between 100-200 μm and are thus incapable of fabricating high-resolution architectures down to the size of single cells (10-20 μm). In 2020, Bartnikowski et al.[39] developed an accurate and reproducible workflow for the fabrication of highly porous custom 3D-printed scaffolds for large-volume alveolar bone regeneration.

In conclusion, further research on 3D printing must consider the specific needs for regenerating the periodontal complex, including the demand for high-resolution structures with optimum porosity and adaptable forms [40].

Gene therapy

To replicate the natural regenerative differentiation potential for tissue regeneration, growth factors must trigger the appropriate and precise cellular signals for host cell populations to follow [41]. Short half-lives and diffusion from the site of intended action are inherent properties of topical growth factor application, which typically occur in a single high-dose bolus[42]. This can lead to a burst release over a short time frame, which can interfere with the bioactivity of other growth factors[43,44]. Gene therapy helps to overcome these constraints by facilitating prolonged growth factor production and secretion. Controlling stem cell differentiation with gene therapy offers an additional strategy for making cells produce and secrete growth factors [44], and allows cell-mediated production of proteins with authentic post-translational modifications and increased biological activity[45].

Vectors used in gene therapy include plasmids, adenoviruses (Ad), lentiviruses, retroviruses, adeno-associated viruses (AAVs), and baculoviruses, each of which have their pros and cons [46]. Dunn et al.[47]implemented delivery of Ad-BMP-7 using a collagen matrix in a preclinical model to treat peri-implant osseous defects and reported that gene delivery began on day 1 and reached peak expression on day four. Gene treatment of dental implant fixtures with Ad-BMP-7 resulted in enhanced alveolar bone defect fill, coronal new bone formation, and new bone-to-implant contact.Clinical trials are needed to assess the safety and efficacy of gene therapy for periodontal tissue engineering and bone regeneration purposes in humans - to the best of our knowledge, these studies have not yet been conducted.[31]

Conclusion

In conclusion, further research on 3D printing must consider the specific needs for regenerating the periodontal complex, including the demand for high-resolution structures with optimum porosity and adaptable forms [40]. Gene therapy To replicate natural regenerative differentiation potential for tissue regeneration, growth factors must trigger the appropriate and precise cellular signals for host cell populations to follow [41].

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Treating dental implant fixtures with Ad-BMP-7 gene therapy led to improved filling of alveolar bone defects, increased formation of new bone at the crown of the

implant, and enhanced bone-to-implant contact. However, it's important to note that clinical trials are necessary to evaluate the safety and effectiveness of gene therapy to regenerate periodontal tissue and bone in humans. As far as our current knowledge goes, such trials have not been conducted yet.In conclusion, a deeper understanding of the molecular and cellular mechanisms responsible for the development of each component of periodontal tissue is essential to fully grasp the rationale behind regeneration therapies.Although growth factors have considerable potential in this regard, they are limited by their extremely wide range of activity and lack some tissue specificity. Therefore, it is necessary to keep researching regional elements that might be unique to the periodontal tissues' growth (and regeneration). Continued efforts should be undertaken to investigate ways to achieve genuine regeneration of all periodontal connective tissues (cementum, ligament, and bone) to a level commensurate with health and, as a result, restore the dentition's original form and function with an improved tooth.

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