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Current And Future Trends in Periodontal Tissue Engineering and Bone Regeneration

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Abstract

Periodontal tissue engineering involves a multi-disciplinary approach towards regeneration of the periodontal ligament, cementum and alveolar bone surrounding teeth, whereas bone regeneration specifically applies to ridge reconstruction in preparation for future implant placement, sinus floor augmentation and regeneration of the peri-implant osseous defects.

Recently, various types of biomaterials have been prepared in the form of tissue engineering scaffold that facilitate the regeneration of damaged periodontal tissues.

Bone regeneration is often necessary to address various degrees and locations of bone defects. Irrespective of whether large defects of bone are caused by infection, trauma, tumor excision, and skeletal necrosis or by periodontitis, osteoporosis and insufficient implant bone, they all require treatments that involve bone regeneration.

The present narrative review discusses key advancements in PTEBR including latest and future trends in preclinical and clinical research, as well as the potential for clinical adaptability.

Keywords: Periodontal Tissue Engineering, Elements in Tissue Engineering, Signaling Molecules and Growth Factors

Introduction

The periodontium can be termed as an integrated, functional unit of multiple tissues that surrounds and supports the tooth, including but not limited to periodontal ligament (PDL), cementum (CM) and alveolar bone (AB). Periodontal tissues destruction are often due to chronic periodontal diseases, which can further lead to tooth loss. As a supportive treatment for periodontally diseased tooth, various biomaterials have been tried and tested, starting as a contact inhibition membrane in the guided tissue regeneration (GTR) that is the current gold standard in dental clinics. In recent times, various biomaterials have been prepared through tissue engineering scaffold to facilitate the regeneration process of damaged periodontal tissues. Starting from a physical substrate to support the healing process of a single type of periodontal tissue to multi-phase/bioactive scaffold system to guide an integrated regeneration of periodontium, technologies for scaffold fabrication have emerged and evolved in recent years.

Autologous bone graft regeneration procedure was long considered the gold standard for the treatment of bone defects in the clinic. However, the donor contribution is quite limited and the approach usually involves lots of complications. Additionally, this approach may carry the risk of disease transmission and bone integration of unsatisfactory standards. With advancements in technology, 3D-printed scaffolds have become popular over the past few decades because of their unique physical properties for tissue regeneration engineering and vascularized bone regeneration. One of the major aims of recent research and trials in periodontal tissue engineering and bone regeneration (PTEBR) is to develop therapeutic modalities that are capable of temporospatial recruitment and direction of host cells in a manner that promotes regeneration and healing.

This review covers the recent advancements, insights into tissue engineering, trends in growth factors for regenerative treatment and development of scaffolds designed for periodontal tissue and bone regeneration.

Insights Into Tissue Engineering

Regeneration of the lost periodontal tissues is the ultimate goal and objective of a successful periodontal therapy. A lot of techniques have been used to achieve this goal till date. Most recent advancements in this context is the concept of tissue engineering. Tissue engineering can be defined as the science of new tissues fabrication for replacement and regeneration of lost tissues or defined tissues[1]. This approach for regeneration of the lost tissues was initially proposed by Langer and Vacanti in 1993[2]. The primary aim of this specific therapy was to deliver biologically active elements that can get integrated into the host tissues and hence resulting in three-dimensional regeneration of the lost tissue which is structurally and functionally similar to the tissue that was lost.

In general, tissue engineering involves combining of living cells with a natural synthetic support or scaffold that is biodegradable in nature to build a three-dimensional living construct that is functionally, mechanically, structurally equal to or better than the tissue that is to be replaced[3].

Key Elements in Tissue Engineering

The Tissue Engineering Triad[4]

Scaffold (e.g., Collagen, Bone Mineral, Synthetics)

Cells (e.g., Fibroblasts, Osteoblasts, Chondrocytes)

Signaling Molecules (Growth Factors, Morphogens)

In order to achieve complete regeneration of the lost tissues, we need to have the progenitor cells which can differentiate into the desired cell types and thus achieving the desired structural components of extracellular matrix (ECM) and signaling the molecules which can initiate desired cellular activities, a scaffold which is able to carry these components in the active form and a conducive environment. Presently, there are two approaches used to regenerate tissues,

Ex vivo approach

In this technique, the tissue is created in a laboratory by culturing the cells. The process is carried on a scaffold, biodegradable in nature, in presence of the molecular factors that are required for growth and then it is transferred into the body. Various body organs have been developed with this technique.

In vivo approach

In this approach, all the components that are required for regeneration are placed within the tissue defect and an environment that is conducive to maximum regeneration has to be created to achieve favorable regeneration. For achieving any kind of tissue regeneration, some basic components are must, which participates at different levels guiding in the formation of the desired tissue. These can be called as the key elements of tissue engineering[3]. These include,

- Progenitor cells.
- Scaffold or supporting matrix.
- Signaling molecules.

Progenitor Cells

Most of the current literature, research on periodontal regeneration has discussed the periodontal ligament-derived cells for their potential ability to differentiate into various different types of cells required for regeneration of lost tissues. However, the other sources which include periodontal ligament-derived mesenchymal stromal cells, bone marrow-derived mesenchymal stem cells (BMMSCs), periosteal cells, adipose-derived stem cells (ADSCs), gingival fibroblasts and ES/iPS cells have also been investigated recently[5].

Scaffold Or Supporting Matrix

Scaffolds can be termed as natural or synthetic materials that are used to carry biologically active molecules to the site of regeneration. Tissue engineering scaffolds can be fabricated using several natural and synthetic polymers[6]. The primary requirements for a scaffold are,

- It should be inherently biocompatible.
- It must be biodegradable, and highly cell-adhesive.
- It should have a mechanically stable, porous and three-dimensional structure.
- It should have a predictable and simple manufacturing process.

Naturally derived scaffold materials[7]

- Fibrin
- Collagen
- Chitosan
- Alginate
- Hyaluronic acid

Synthetically derived scaffold materials[7]

These are biodegradable in nature, synthetic polymers to carry bioactive molecules.

Signaling Molecules and Growth Factors

The signaling molecules play a vital role in various biological processes. They are secreted by various cells in response to stimulus and they act on the same, neighboring and distant cells

to bring specific effects. The knowledge of signaling molecules involved in regeneration process is primarily derived from wound healing. The application of growth factors and bone morphogenetic proteins (BMP's) has

thus shown to enhance the periodontal regeneration. Growth factors play a vital role during growth and development. They enhance the regeneration via stimulating synthesis of ECM by cells such as fibroblasts, osteoblasts[8] etc.

Promising results from numerous clinical and pre-clinical trials has led to the subsequent introduction of various growth factors available in the commercial market for the purposes of periodontal, soft and hard tissue regeneration, peri-implant.

This section aims to provide the reader an insight into various growth factors and signaling molecules in periodontal and peri-implant tissue engineering-based treatment approaches.

Growth factors are basically polypeptide molecules released by cells in the inflamed area that regulate events associated with wound healing. These are naturally occurring proteins that regulate various aspects of cell growth and development, acting systemically or locally." Growth factor" is a general term to denote a group or class of polypeptide hormones that can stimulate a wide variety of cellular events such as proliferation, differentiation and production of extracellular matrix proteins[8].

Rationale For Using Growth Factors In Periodontal Regeneration

When injury occurs, in initial stage, a "well-orchestrated" Well-cell and cell-ECM interaction is initiated which activates the healing process. A complex activity of various molecules including growth factors and cytokines begins in the inflamed areas initiating remodeling of ECM. Several tissue repair studies conducted on animals provide concrete evidence that key growth factors involved in wound healing include EGF, TGF-a and ß, PDGF, acidic and basic FGF.

Types of Signaling Molecules/ Growth Factors Include / Biochemical Mediators

Bone morphogenic Proteins, Fibroblast growth factor, Epidermal growth factor, Cementum derived growth factor, Parathyroid derived growth factor and Insulin-like growth factor, Platelet derived growth factor, Transforming growth factor.

Bone Morphogenic Proteins

As of now, currently fourteen BMPs have been identified, with BMP-2, 4, 5, 6, 7, and 9 showing osteoinductive potential. Of these, BMP-2 and -7 have been most extensively studied for periodontal tissue engineering purpose. BMPs are a group of proteins that are responsible for guiding the differentiation of mesenchymal cells into the bone and bone marrow cells, and have been demonstrated in preclinical studies to stimulate chemotaxis mechanism, survival and also osteogenic differentiation of the bone marrow mesenchymal stem cells (BMSCs)[9,10].

Although the use of BMPs in periodontal regeneration related procedures has shown successful results in the treatment of furcation and intrabony defects, complications such as root resorption and ankylosis have also been reported. As a result, BMPs in recent times are indicated mostly for implant site preparation, during ridge preservation and sinus floor augmentation procedures[11,12].

Current Strategies for Periodontal Regeneration

Current techniques to achieve periodontal regeneration are based on using a scaffold matrix which may or may not carry biologically active molecules in the periodontal defect (bone grafts or hard tissue replacement polymer) or creating a three-dimensional area which is secured by a membrane and thus allow proliferation of the cells

from PDL to facilitate the regeneration process (guided tissue regeneration).

Presently, research is also being done to incorporate various biologically active molecules (BMP's and growth factors) in scaffolds which are placed within the periodontal defect to achieve maximum regeneration. The scaffolds used so far in periodontal research are bone grafts, synthetic polyesters such as polylactic acid, polyglycolic acid.

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