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Review Article

Tissue Engineering in Periodontics – A Review

C.D. Dhalkari[1], Pallav Ganatra[2], Pawan Sawalakhe[2] and Abhishek Singh Nayyar*[3]

[1]Associate Professor, Department of Periodontology, GDC, Aurangabad, Maharashtra, India.
[2]Post-graduate Student, Department of Periodontology, GDC, Aurangabad, Maharashtra, India.
[3]Reader, Department of Oral Medicine and Radiology, Saraswati-Dhanwantari Dental College and Hospital and Post-Graduate Research Institute, Parbhani, Maharashtra, India.

***Corresponding Author**
Dr. Abhishek Singh Nayyar,
Reader cum Associate Professor,
Department of Oral Medicine and Radiology,
Saraswati-Dhanwantari Dental College and Hospital and Post-Graduate Research Institute,
Parbhani, Maharashtra, India
E-mail: singhabhishek.rims@gmail.com

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Abstract

Tissue engineering is a highly promising field of reconstructive biology that draws on recent advances in medicine, surgery, molecular and cellular biology, polymer chemistry, and physiology. 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. The authors reviewed controlled clinical trials which also included histological studies that evaluated the potential of tissue engineering as a clinical tool in regeneration. PubMed/MEDLINE databases were searched for studies up to and including June 2010 to identify appropriate articles. A comprehensive search was designed, and the articles were independently screened for eligibility. Articles with authentic controls and proper randomization and pertaining specifically to their role in periodontal regeneration were included. Studies demonstrated that periodontal regeneration with the use of combination of tissue engineered products with an osteoconductive matrix improve the beneficial effect of these materials by accelerating cellular in-growth and revascularization of the wound site. Studies have suggested the use of Platelet-derived growth factor alongwith beta tricalcium phosphate for regeneration of the periodontal attachment apparatus in combination with collagen membranes as an acceptable alternative to connective tissue graft for covering gingival recession defects. These studies concluded that growth factors promote true regeneration of the periodontal attachment apparatus and the use of combination protein therapeutics could provide more predictable, faster, and less invasive, less traumatic and efficient outcome for the patients.

1. Introduction

Today, the emergence of biological agents that stimulate a true regeneration of the tissues to their original form, are becoming the new horizon in periodontics. In the past, we had agents which facilitated healing but offered minimal osseoinductive effects such as demineralized freeze-dried bone allograft and platelet-rich plasma, which offered low levels of bone morphogenic proteins and low levels of platelet-derived growth factors, respectively.[1] However, the levels offered by these substances, in most cases, are too low to truly induce regeneration. Presently, there are two biologics commercially available, enamel matrix derivatives or Emdogain and recombinant human platelet-derived growth factors or GEN 21F (Osteohealth Co. Shirley, New York).[2] Enamel matrix derivative stimulates the regeneration of new cementum and periodontal ligament fibers on the root surface resulting in regeneration of a new attachment of the tooth with the adjacent bone and connective tissue. The recombinant platelet derived growth factors have been shown to induce osseous regeneration in periodontal defects when placed with tri-calcium phosphate as a carrier that is resorbed with the passage of time.[3] The true regeneration induced by these biologics should not be confused with the repair that may result from more traditional mechanical procedures such as root planing, curettage or flap surgery. No matter what device is used, curette, scalpel, laser, etc., the result is the same, a repair that may result in a significant improvement of the tissues, but not in a true regeneration of the tissues that is indistinguishable from the original. As the arena of tissue engineering continues to grow, not only will the list of biologics increase, but innovative delivery systems will be developed.[2]

1.1Definition

The application of the principles and methods of engineering and life sciences towards the fundamental understanding of structure/function relationships in normal and pathological mammalian tissues and the development of biological substitutes to restore, maintain or improve functions".[4]

1.2 What is tissue engineering? :

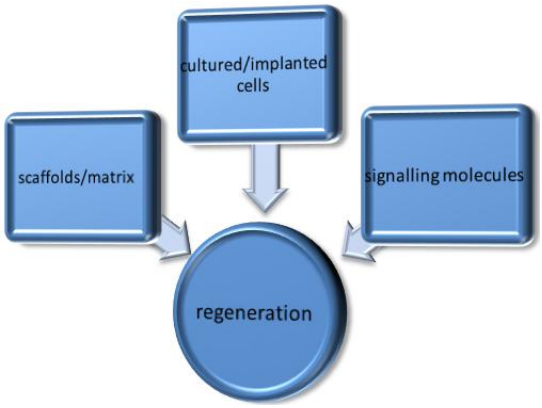
It is an interdisciplinary field which deals with the development and manipulation of laboratory grown molecules, cells, tissues, or organs to replace or support the function of defective or injured body parts".[4]

1.3 Necessity of tissue engineering:

- Most tissues cannot regenerate when injured or diseased;
- Even tissues that can regenerate spontaneously may not completely do so in cases of larger defects (e.g. bone); as also,
- Replacement of tissue with permanent implants is greatly limited.

Tissue Engineering and Periodontium: As detailed above, tissue engineering is a contemporary area of applied biomedical research aimed at developing procedures and biomaterials for fabrication of new tissues to replace damaged tissues. The main requirements for producing an engineered tissue are the appropriate levels and sequencing of regulatory signals, the presence and numbers of responsive progenitor cells, an appropriate extracellular matrix or carrier construct, and an adequate blood supply to support and sustain healing till the desired outcome is achieved.[5] The periodontium could be considered a prime candidate for such procedures. It is important to overview how genomics, biomimetics, and proteomics will play pivotal roles in development of this fledgling field. Thus, an emerging paradigm of biological solutions for biological problems is appearing in both clinical dentistry and medicine. This allows diagnosis, treatment, therapeutics, and biomaterials to become biological and gene-based rather than being simply mechanical.[6]

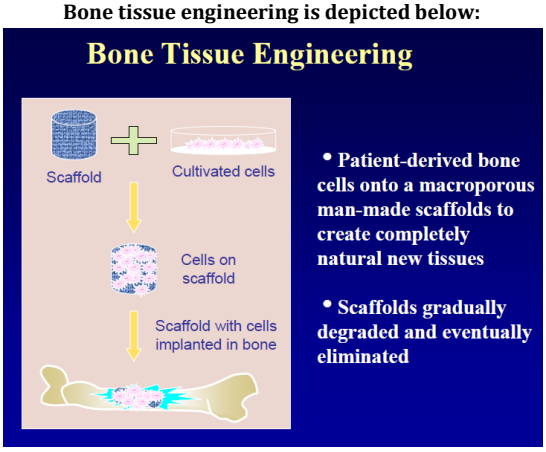
2. Tissue engineering in periodontics:[7]



Principles in tissue engineering: The principles and applications of cell delivery systems for periodontal regeneration are presented by Bartold *et al*. Successful tissue engineering requires an interplay between three components:

- The implanted and cultured cells that will create the new tissue;
- A biomaterial to act as a scaffold or matrix to hold the cells; and
- Biological signaling molecules that will instruct the cells to form the desired tissue type.

Bone tissue engineering is depicted below:



In tissue engineering, research is being carried out to recapitulate the developmental process as involved in cementogenesis, osteogenesis, and formation of periodontal ligament fibers leading to the regeneration of the damaged periodontium.[3] No current consideration of regeneration today would be complete without mentioning stem cells.[5]

3. Animal studies

Duailibi *et al*. did pioneering work on the successful bioengineering of pig and rat tooth tissues, including enamel, dentin, and pulp, from cultured tooth bud cells seeded onto biodegradable scaffolds implanted and grown in the omenta of adult rat hosts. These results significantly advance the practical application of tooth tissue engineering strategies by demonstrating that whole replacement of teeth may eventually be grown at the site of previously lost teeth. Nakahara *et al*. demonstrated improved regeneration of periodontal fenestration defects in dogs after implantation of collagen sponge scaffolds seeded with alkaline phosphatase positive periodontal ligament-derived cells, confirming their potential in dental tissue engineering.

4. Cells in dental tissue engineering (Odontoblasts, cementoblasts and osteoblasts):

The dental structure is a complex composition of differently specialized tissue and cell types consisting of dentin-producing odontoblasts, ameloblasts and periodontal structures such as cementum, periodontal ligament, gingiva, and alveolar bone. These structures are often affected by infectious diseases for example, periodontitis and caries, which if not treated adequately can result in early tooth loss. Tissue engineering holds the promise of, one day, offering the true replacement of lost tooth structures.[5]

5. Strategies to support healing:[8]

A number of strategies have been developed to support the healing process, such as:

- Inductive dental tissue engineering strategies that activate and stimulate endogenous cells by the incorporation of demineralized dentin fragments;
- Use of various extracellular matrix scaffolds (fibronectin, collagen, fibrin, hydroxyapatite, etc); and
- Addition of cytokines such as bone morphogenic proteins and transforming growth factor-b to support such regenerative procedures.[9]

Cells in tissue engineering:[5]

Hematopoietic stem cells can differentiate into virtually all the cell types of the blood cell lineage. The mesenchymal fibroblast-like cells were separated from Hematopoietic cells using their property of adherence to tissue culture plastic. Further, isolation of these pluripotent stem cells according to their specific surface markers increased their harvest efficiency and overall utility. Stem cells and progenitor cells contribute to various regenerative processes such as wound healing, angiogenesis and/or, healing of bone fractures. The local environment is thought to play an important and specific role in the commitment and differentiation of mesenchyme-derived stem cells. Unlike bone, dentin and cementum have no physiological turnover. Indeed, it has been indicated that these structures have only a limited reparative capacity to form tertiary dentin and new cementum, as seen after orthodontic tooth movement. Recently, however, stem cells have been identified and isolated from the periodontal ligament and dental pulp. Their cluster-forming and differentiation abilities, as well as their cell surface markers, were described by Gronthos and co-workers in 2005, and stem cells isolated from periodontal ligament were shown to form cementum-like mineralized structures in-vitro. Whether cementocytes and osteoblasts share the same ancestor cells is still uncertain. However, certain differences have been reported, including differing degrees of organization of mineralized cell products and

differences in their alkaline phosphatase activity. After transplantation in-vivo a dentin-like and dentin sialo-phosphoprotein-rich mineralization product has been observed.[10]

The extracellular matrix in dentistry: Many extracellular matrix proteins are involved in tooth development. Type IV collagen, fibronectin, laminin, and nidogen are all expressed in the basement membrane of the murine tooth germ layer, with tenascin, laminin, and fibronectin also getting expressed in the odontoblastic layer. Taba *et al* studied the effects of fibronectin on ameloblast cells in-vitro, demonstrating that it accelerated ameloblast differentiation. The interactions between various types of extracellular matrix, dental pulp, fibroblasts, and ameloblasts have been studied for decades, but the exact mechanisms of each interaction are not yet determined. Fibronectin and laminin are also believed to affect dental pulp cells during tooth development, influencing cell adhesion and tissue architecture via integrin binding. Zhu *et al* showed that b1 integrins played a role in dental pulp cell adhesion to laminin but not fibronectin, using monoclonal antibody blocking studies. Fibronectin and laminin have also been shown to enhance gingival cell attachment to the surfaces of dental implants. Reelin, a large extracellular matrix glycoprotein, has been associated with human odontoblasts in-vivo and in-vitro. Osteoadherin, a small leucine-rich proteoglycan, is synthesized by osteoblasts and ameloblasts. It has also been reported in the alveolar bone, predentin, and enamel matrices of rat and mouse teeth.[11] Another matrix protein, fibrodentin, is thought to be essential for initiation of reparative dentin during wound healing.[12] Dental tissue engineering has been primarily utilized in treating periodontitis, a chronic inflammatory disease, resulting in the permanent destruction of alveolar bone and gingival recession. Several studies have investigated combinations of scaffolds and stem cells to regenerate the periodontium and secure teeth. Sculean *et al*. reported that the application of bovine derived xenograft and bioresorbable collagen in patients with periodontal defects resulted in a significant improvement, with reduction of periodontal probing depth and clinical attachment levels observed 1 year post-treatment follow-ups. Dentin regeneration, especially in vital pulp therapy, is another potential area for tissue engineering applications. The extracellular matrix plays an essential role in odontoblast differentiation and guides dentin repair. However, the ability of the matrix to regenerate may be compromised in the damaged area, requiring a replacement matrix to encourage cell migration and differentiation. Synthetic scaffolds, such as alginate hydrogels, have been used in dentin generation.

6. Drawbacks:[9]

Failure;
Foreign body reaction;
Failure to grow/remodel;
Disease transmission;
Immune reactions against implanted scaffolds; and
Harvest site morbidity.

Tissue engineering strategies for the future generation in dental implants:[13]

The replacement of lost teeth with endosseous dental implants is an effective and acceptable treatment modality. This requires special considerations, and to be successful, implants must integrate with the surrounding hard tissues prior to prosthetic rehabilitation. This is defined as osseointegration and is the direct association of osseous tissue with inert alloplastic biomaterial surface Ca-P coating. Emerging technologies eliciting titanium fluoride-mediated mineral precipitation and manipulation of implant micro- and nano-topographies are areas to improve not only the osteoconductivity but potentially the inductability of dental and orthopedic joint implants. The recently developed biomimetic coating approach has advantages over the conventional plasma-spraying technique in coating porous metallic implant surfaces and polymeric tissue engineering scaffolds. Biomimetic Ca-P coating is an ideal carrier of therapeutic and bioactive agents, such as osteoinductive proteins, growth factors and antibiotics. The incorporation of amelogenins in the Ca-P coatings may lead to the invention of a new generation of biomaterials with improved mechanical and biological properties required for bone and tooth regeneration. Manipulation of the surface topographies will allow for the development of site directed tissue engineering strategies. Tissue engineering techniques for regenerating periodontal defects will become the new basis for regeneration of the alveolar bone and the placement of dental implants. Chemical and biomimetic strategies are also increasingly being developed to design improved surface chemistry of implants.[6]

7. Conclusion

Many advances have been made over the past decades in the reconstruction of complex periodontal and alveolar bone wounds. Developments in polymeric and ceramic scaffolding systems for cell, protein and gene delivery have undergone significant growth. The targeting of signaling molecules or growth factors (via proteins or genes) to the periodontium has led to significant new knowledge generation using bioactive molecules that promote cell proliferation, differentiation, matrix biosynthesis, and angiogenesis. However, a major challenge that has been overlooked has been the modulation of the exuberant host response to microbial contamination that plagues the periodontal wound environment. Further advancements in the field will continue to rely heavily on multidisciplinary approaches combining engineering, dentistry, medicine and infectious disease specialists in repairing the complex periodontal wound environment. The advent of viable tissue engineering will have an effect on the therapeutic options available to oral health specialists. What may be concluded from the current status of periodontal regeneration is that, as many investigators have previously stated, there is not going to be one magic solution that can be used to treat all periodontal patients, but rather a combination of different approaches that can be adjusted to fit the specific need of the individual patients.

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