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Tissue Engineering in Prosthodontics and Implant dentistry: From vision to reality, a review

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Abstract

The basic model for treating dental diseases is the removal of destructed tissues and replacing it with synthetic materials. Today, tissue engineering has made it clear that instead of using synthetic materials, we can utilize dental regenerations. Currently, there is tremendous expansion of tissue engineering in the form of cells, scaffolds, growth factors, controlled release carriers, engineering of biomaterials and in other different areas of basic and applied research. Recent advances in the field of prosthodontics and Implant dentistry promises significant changes in the more traditional areas of clinical dentistry. In this review we attempt to discuss the advances made since inception of tissue engineering, various modalities involved, its versatile application aspects, and future interventions required to translate it for clinical implementation.

Keywords: Dental implant, dental stem cells, tissue engineering

Introduction

The artificial generation of tissues, organs, or more complex living organisms is known to mankind as a dream or just a myth. During the last decades this vision has become feasible and has been recently introduced in the clinical medicine.

The term "**tissue engineering**" was up to the mid 1980's loosely applied in the literature, in cases of surgical manipulation of tissues and organs or in a broader sense when prosthetic devices or biomaterials were used. The term "tissue engineering" was introduced in medicine in 1987.[1]

Current reparative dental treatment which usually replaces a missing tooth with biocompatible or bioactive alloplastic material, was often accompanied by additional problems such as mechanical and biological failures. A more ideal solution would be to completely restore PDL onto implanted surface to fully replace the extracted tooth. This is the promise of tissue engineering, a field which aims to incorporate specific cell types into a suitable scaffold, together with appropriate signaling factors which when implanted will gradually regenerate ligamentous tissue on an implant surface that closely resembles the original periodontal tissue and restores its functionality.[2]

Need For Tissue Engineering

The basic model for treating dental diseases is the removal of destructed tissues and replacing it with synthetic materials. However, a few numbers of such materials have relatively the same physical and chemical properties of the natural tooth and often suffer from mechanical fracture. Moreover, the biocompatibility of most of such materials is the subject of much controversy.[3]

In prosthodontics and implant dentistry researches are going on with the alginate scaffolds encapsulating Mesenchymal cells(MSCs) , modifying the titanium surfaces which is the most common material used for dental implants to improve osseointegration and decrease the chances of failure . Also semi interpenetrating collagen composite hydrogels are gaining importance in the bone regeneration. Thus tissue engineering has become one of the most important aspects of dentistry.[4]

Tissue Engineering Components

- The cells,
- A scaffold, and
- The signaling molecules.

When these three components are transferred to the in vitro environment of tissue-engineered constructs, the extracellular matrix is replaced by the synthetic or natural scaffolds which are used to accommodate and arrange the cells in a three-dimensional fashion. The triad of cells, signals, and scaffolds thus makes up the “classic” tissue engineering triad.

However, beyond these three components, angiogenesis and vascularization play a very important role in cellular behavior and tissue repair, not only because blood supply is necessary for cell survival and development, but also because vessels provide a reservoir of undifferentiated perivascular cells that are recruited during tissue repair.[1]

Cells

The strategy of cell-based approaches is to obtain a small number of cells or a small tissue portion through a minimally invasive procedure and to expand these cells ex vivo to a volume that can be expected to form the desired amount and type of the tissue.

The functionality of these bio-hybrid constructs depends very much on survival and the performance of the implanted cells. Thus, besides the local conditions at the recipient site, both the initial cell source and the in vitro handling during cultivation of the constructs are important for successful its applications.[1]

Scaffolds

Tissue in the cranio-maxillofacial region is varied in composition, but in its simplest definition, it consists of a matrix and various cell types.[1]

The matrix represents a 3D structure or scaffold for cells, which provides them with a specific environment and architecture for a given functional purpose. The scaffold will act as a temporary matrix or template for cell proliferation, extracellular matrix deposition, bone regeneration, and remodeling until mature bony tissue is regenerated. During this process, the scaffold acts as a template for vascularization.[5]

In general, the materials that are used as scaffolds can be divided into **organic** and **inorganic** materials. Organic materials may originate from natural precursors such as collagen, chitosan, or silk or can be produced from synthetic polymers such as polyglycolic acid (PGA). Inorganic materials commonly consist of metals, alloys, or mineral compositions.

Growth factors

Growth factors are proteins produced by cells that act as signaling molecules on an appropriate cell to carry out the desired function. These proteins activate the cellular communications network and influence functions, such as

cell proliferation, matrix deposition, and differentiation of tissues.[1]

Applications In Prosthodontic

In prosthodontics, the applications of tissue engineering are related to the following aspects.

Surface Coated Titanium

Despite its remarkable success as a bone tissue implant-material, decades of experience in Ti implantation have highlighted some aspects that need to be improved. [6]

Surface modifications intend to improve the interactions of Ti based implants with surrounding biological media and to overcome some of the limitations associated with Ti. Particularly, major challenges in the field are issues such as osseointegration capability, prevention of bacterial colonization, and reduction in implant rejection (which may be related to the biofilm formation).[7]

Certain topographic characteristics of Ti implants, such as porosity or roughness, directly affect the progression of the cell adhesion, proliferation, and differentiation. Additionally, increased surface area promotes cell attachment and augments biomechanical interlocking between bone and an implant. For decades, surface topography modification was based on machining processes, with turned implants being the most commercially successful design. Since then, several physical and chemical techniques capable of modifying the Ti surface topography, such as Ti plasma spraying, grift-blasting, acid etching, or plasma electrolytic oxidation, have been applied to Ti implants in order to enhance its surface features. These techniques modify surface roughness and induce the formation of a Ti oxide layer, thereby improving tissue response.(fig.1)[6]

The biological rationale behind the use of ceramic coatings relies on their biocompatibility and on ability to improve the bone healing process. In general, ceramic coatings are considered osteoconductive; they improve the osseointegration of the implanted materials by mimicking the natural process of the bone healing. To this end, calcium release from ceramic coatings allows for the deposition of a biocompatible thin layer of biological apatite (carbonated hydroxyapatite), which facilitates host cells to adhere and differentiate, yielding proper osseointegration of the implanted material. Ceramic coatings can be organic or inorganic.[7]

Organic surface modifications involve the immobilization of different polymers and molecules such as synthetic polymers, polysaccharides, proteins, or peptides onto biomaterial surfaces to target cell response at the tissue−implant interface. Many different biologically functional molecules can be immobilized onto titanium surfaces to enhance bone regeneration at the interface of the implant devices. In contrast to inorganic calcium phosphate coatings, biomolecule surface modification utilizes purely organic components of bone to affect the tissue response.[8]

Hydrophilic biostable polymers such as poly vinyl alcohol (PVA), polymethacrylic acid (PMA), or polyethylene glycol (PEG) are frequently used as coatings for metallic implants, offering a soft interface that, in some cases, inhibits bacterial adhesion on Ti based materials.

In terms of surface topography, some synthetic polymeric coatings could be tailored in order to achieve a semiordered nanoscale surface. Such nanotexturing may serve to improve the cell response, as was reported for the polymethyl methacrylate (PMMA) polymer, which showed superior mesenchymal stem cell differentiation, and enhanced the induction of TGFB-1 expression.

Naturally occurring coatings are a subset of bioactive materials that can be grouped into three categories: **polysaccharides, Extracellular matrix (ECM) proteins, and peptides**. This increasing interest stems from their

inherent low toxicity, their biodegradability, low cost, and renewability. In addition, natural coatings have shown specific advantages in bone tissue engineering, through the activation of specific biological signaling pathways, induction of cell adhesion, and modification of bone remodeling.

Ultimately, every application and target tissue requires specific optimization of the type of coating and type and load of active molecules. Thus, coatings to be developed in the future may require the incorporation of natural components present in bone, such as ECM proteins or other biological factors, to bring its characteristics closer to that of the natural bone tissue.[7]

Implants

One essential aspect in the performance of an implant is the mechanical and biological behavior of its interface with the bone. A stable and resistant interface between the biomaterial surface and its surrounding tissue is a vital prerequisite both for immediate implant loading, and for the long-term success of such implants.[9]

To date, major “disconnect” exists between the principles of periodontal regeneration and oral implant osseointegration . That entity is the presence of a periodontal ligament (PDL) to allow for a more dynamic role beyond the functionally ankylosed or the osseointegrated oral implant.[10]

Over years, many strategies have been developed to enhance integration of implants through surface modifications and coatings to improve mechanical, physical, and chemical characteristics, yet the lack of PDL attachment renders implant treatment underprovided. Tissue engineering has opened a new era in periodontal regeneration, and more so in treatment with dental implants. New technologies that use guided proliferation of PDL purified stem cells appear to promote periodontal regeneration around dental implants, which is a major goal for optimizing implant therapy providing the patient with a biological dynamic implant rather than an ankylosed inert tooth substitute (Fig. 2). These newer implants are known as Ligaplants.[9&11]

The ligaplants system mimics the placement of natural tooth roots in alveolar bone. They become firmly integrated into the bone without interlocking and without direct bone contacts, despite the initial fitting being loose in order to spare the PDL cell cushion. Thus, the surgical procedure for ligaplants seems to be easy. It also induces the formation of new bone even when placed in sites which are associated with large periodontal defects, precluding the need for bone grafting as well as eliminating other problems such as gingival recession and bone defects of the missing tooth site. Therefore, these implants could be placed where periodontal bony defects are present.[12]

Growth factors

Transforming growth factor-β (TGF-β) was reported to increase PDL cell-surface proteoglycan genes such as syndecan-2 and β glycan, and promote the synthesis of DNA, fibronectin, osteonectin, and connective tissue growth factor (CTGF). Also, it had an essential role in PDL fibroblastic differentiation from stem or progenitor cells, and in maintaining PDL apparatus under physiological conditions.

Platelet-derived growth factor (PDGF) stimulated the proliferation, migration, and matrix synthesis of cultured periodontal cells, including gingival and PDL fibroblasts, cementoblasts, and osteoblastic cells. The PDGF family is composed of five

isoforms: PDGF-AA, -BB, PDGF-CC and -DD in addition to PDGF AB. PDGF-BB is most effective in PDL cell mitogenesis and matrix biosynthesis.[9]

Three-dimensional hollow root form scaffold made of biodegradable DL-lactide-co-glycolide (PLG) with 80%

porosity was seeded with cultured bone marrow stem cells and it was inserted around a titanium implant fixture in a goat animal model. The scaffold acted as a delivery vehicle for the cells, and the geometric form of the scaffold allowed for distribution of the masticatory load along the viscoelastic nature of the scaffold wall and its interconnected pores. After 10 days, remnants of the scaffold could not be identified and were replaced by periodontal-like tissue around the implants.

Delivery of PDL cells via non-woven polyglycolic acid (PGA) mesh is a viable approach in promoting periodontal tissue regeneration, and provides the possibility of PDL regeneration on the dental implants. Human periodontal ligament cells were seeded and cultured onto PGA 3D scaffolds, in which human periodontal ligament cells adhered well to scaffolds and exhibited excellent matrix secretion ability under light.[9]

This approach offers the potential for clinical implementation of customized periodontal scaffolds that may enable regeneration of multi-tissue interfaces which are required for dental implant applications.

A sodium titanate surface was considered as a potential alternative to the sandblasting surface modification that might provide a promising environment for the PDL ligament anchored implants.

Dental implant treatment modality is a worldwide demand, and the development of a PDL attachment around dental implants is now an available option to improve the biological performance of the dental implants and prolong the life of the prosthesis. Tissue engineering concepts, together with isolation of periodontal stem cells from extracted third molars, open up a new era of dental treatment.[8]

The concept of depending on PDL stem cells separated from the surface of extracted teeth relies on the fact that PDL cells are capable of conserving elements of original gene expression patterns during growth in vitro, which allow them to restore their original tissue after the implantation. Several challenges must be considered that arise from the multipotency of PDLSCs and their potential to differentiate in all three types of cell population of the periodontal tissues (i.e. cementoblasts, fibroblasts, and osteoblasts).

An ideal situation would be to completely restoring PDL onto the implanted surface to fully replace the extracted tooth. This is the promise of tissue engineering, a field which aims to incorporate specific cell types into a suitable scaffold, together with appropriate signaling factors which when implanted will gradually regenerate ligamentous tissue on an implant surface that closely resembles the original periodontal tissue and restores the functionality.[9]

Composite and Polymers

The scientific challenge in tissue engineering encompasses understanding the cells themselves, their mass transport requirements and physiologic environment, in addition with the development of optimal scaffold materials that are usually porous and biodegradable and act as temporary 3D templates for cell adhesion, proliferation, migration and ultimately, the formation of new tissue.

The totally synthetic biodegradable polymer or inorganic bioactive phase composites are particularly attractive as tissue engineering scaffolds due to the flexibility in tailoring structural properties, bioactive behavior and biodegradation kinetics. Significant developments have been made in extending existing polymer processing methods to the manufacturing of these synthetic polymeric matrix composites incorporating inorganic bioactive phases, as opposed to the inclusion of biomolecules or growth factors such as bone morphogenic proteins (BMPs) and VEGF.[13]

Synthetic biodegradable polymers are widely considered materials for the development of tissue engineering scaffolds. Numerous other bio-resorbable materials are being suggested for use as scaffolds, including naturally occurring and totally synthetic polymers, bioactive porous ceramics produced by foaming methods such as sol-gel, rapid prototyping and replicating techniques.[14] Moreover, composites based on biodegradable polymer matrices with the addition of inorganic bioactive phases such as hydroxyapatite (HA) or bioactive glass, in the form of particles or fibers, are increasingly being considered for use as bone tissue engineering scaffolds due to their improved physical, biologic and mechanical properties, and in particular the capacity they offer in tailoring their structure and degradation rate to the specific need at the site of the implant.

Bioactive ceramics, such as HA, tricalcium phosphate and certain compositions of silicate and phosphate glasses (bioactive glasses) and glass ceramics (e.g., apatite–wollastonite) react with physiologic fluids and through cellular activity to form tenacious bonds to hard (and in some cases) soft tissue. A characteristic of many bioactive materials is the formation of a biologically active HA layer in the presence of body fluids in vitro or in vivo. The materials with the highest levels of bioactivity develop a silica gel layer that promotes HA formation. Thus, HA formation on material surfaces upon immersion in acellular simulated body fluid is considered a qualitative measure of bioactivity. Bioactive glasses (e.g., 45S5 Bioglass®) with compositions in the system SiO2Na2O-CaO-P2O5, having less than 55% SiO2, exhibit high bioactivity index (class A), and bond to both soft and hard connective tissues.[13]

It has recently been found that reactions on bioactive glass surfaces release critical concentrations of soluble Si, Ca, P and Na ions, which induce intracellular and extracellular responses. For example, a synchronized sequence of genes is activated in osteoblasts that undergo cell division and synthesize an extracellular matrix, which mineralizes to become the bone.

In recent investigations, 45S5 Bioglass has also been shown to increase secretion of vascular endothelial growth factor in vitro and to enhance vascularization in vivo, suggesting scaffolds containing controlled concentrations of Bioglass may stimulate neovascularization, which is beneficial to large tissue engineered constructs. The excellent properties of bioactive glasses and their long history of applications in biomedical implants has recently prompted extensive research regarding their use in tissue engineering and regeneration strategies , mainly in the form of powder aggregates and porous substrates (foam scaffolds) .[13]

Indeed, further research emphasis should be placed into the incorporation and appropriate delivery of these factors alone, or in combination with the bioactive inorganic phases. For example, the possibility of incorporating bone-acting drugs or growth factors into composites formed by biodegradable polymers and bioactive glasses or HA inclusions are starting to be explored.[15]

Conclusion

Tissue engineering-based approaches certainly have the potential to achieve success in above mentioned arena and the future research drive seems to be diverting from a metal-based implant to a more biological, cell-based one. Thus, the absolute minimum requirement for tooth regeneration of this type is the successful formation of a heterogeneous and dynamic array of tissues including roots, the periodontal ligament, nerve and vascular tissues, as well as the most essential dentine-pulp complex. Perhaps the least important anatomical structures are the mineralised tissues of the crown as current synthetic tooth

crowns function more than adequately, as well as being matched for the size, shape, colour and occlusion.[16]

Regenerating oral tissues, in particular, is challenging and requires recapitulation of the biological development of several tissues and interfaces. The progress in this field is taking several routes including; cell biology, the development of the novel scaffolds/fabrication methods/characterization techniques.

In prosthodontics, the studies about the applications of tissue engineering are not extensive yet. Further studies and research should be promoted related to implant dentistry and scaffold materials as it is one of the emerging fields in dentistry.[4&17]

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