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TISSUE ENGINEERING : A SOOTHSAYER IN DENTAL REGENERATION REVOLUTION

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ABSTRACT:

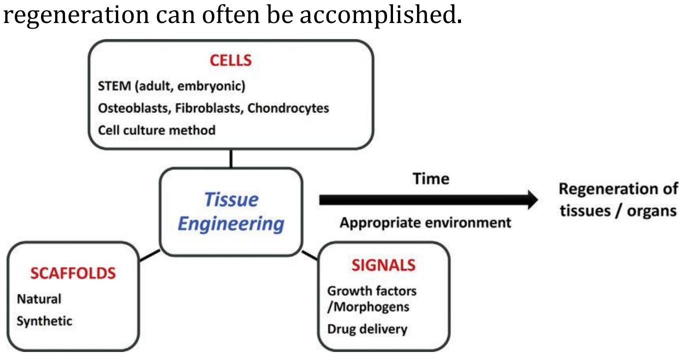
Tissue engineering envelops a fast developing multidisciplinary field. Both from a medical and dental social point of view, there is great need to safeguard tissues and organs to overcome the shortage of donor organs and to reduce the health care cost. Tissue engineering is an interdisciplinary field that combines the principles of engineering, material and biological sciences toward the development of therapeutic strategies and biological substitutes that restore, maintain, replace or improve biological functions. The association of biomaterials, stem cells, growth and differentiation factors have yielded the development of new treatment opportunities in most of the biomedical areas, including Dentistry. The objective of this paper is to present the principles underlying tissue engineering and the current scenario, the challenges and the perspectives of this area in Dentistry.

KEYWORDS:

DENTAL STEM CELLS, ORAL SURGERY, PERIODONTAL REGENERATION, REGENERATIVE DENTISTRY, REGENERATIVE ENDODONTICS, TEETH TISSUE ENGINEERING.

INTRODUCTION

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. Langer et al. defined the tissue engineering as an interdisciplinary field of study, which employs the principles of engineering and life science to develop the biological components, which need to be healed or improved. [1] Tissue engineering comprises three major components of biologic tissues, that is, adult stem cells, growth factors, and extracellular matrix scaffolds. 2 This concept is often represented as a triangle, indicating that by combining the three key elements tissue regeneration can often be accomplished.



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 ultimate goal of periodontal therapy is to completely restore the periodontal attachment including cementum, periodontal ligament, and alveolar bone lost due to periodontal disease or trauma. In the past few decades, many attempts have been made to unravel the "magic filler" material that could result in new clinical and histological attachment, but have only culminated in healing by repair.

Periodontal repair refers to healing that does not allow the original morphological nor functional restoration of the tissue, considered as non-functional scarring. Periodontal regeneration attributes to a complete recovery of the periodontal tissues in both height and function, that is, the formation of alveolar bone, a new connective attachment through collagen fibers functionally oriented on the newly formed cementum.[3] Regeneration of the periodontal tissues is a complex phenomenon requiring interplay between various processes in a timely manner.

STEM CELLS

Stem cells are those clonogenic cells capable of spontaneous division and distinction from various cell lines. Stem cells are classified into 2 groups of embryonic and adult cells. Adult stem cells are responsible for restoration and reconstruction of different tissues.[4] Stem cells are immature progenitor cells capable of self renewal and multi-lineage differentiation through a process of asymmetric mitosis that leads to two daughter cells, one identical to the stem cell (daughter stem cell) and one capable of differentiation into more mature cells (progenitor cells).[5]

STEM CELLS MAY BE:

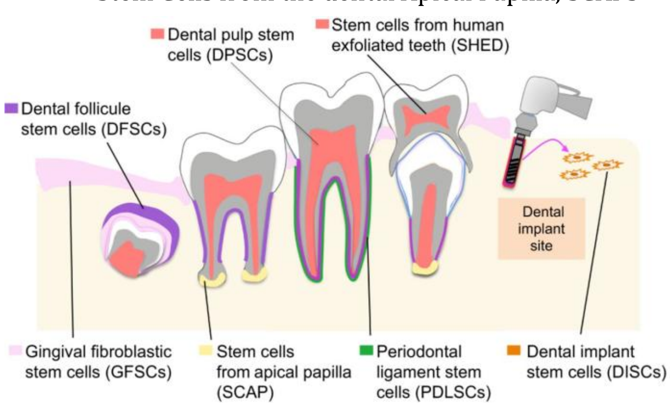
1. Totipotent, i.e. early embryonic cells (one to three days from oocyte fertilization), which can give rise to all the embryonic tissues and placenta.
2. Pluripotent, i.e. embryonic cells from blastocystis (4-14 days after oocyte fertilization), which can differentiate only into embryonic tissues belonging to the inner cell mass (ectoderm, mesoderm, and endoderm).
3. Multipotent, i.e. embryonic cells from the 14 day onwards, which can give rise to tissue belonging to only one embryonic germ layer (ectoderm or mesoderm or endoderm).[6]

Stem cells are classified into 2 groups of embryonic and adult cells.[7] 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 tumorogenicity 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 hemopoetic stem cells and mesenchymal stem cells. Friedenstein and colleagues first identified mesenchymal stem cells in aspirates of adult bone marrow. [8]Adult stem cells are responsible for restoration and reconstruction of different tissues.

Various mesenchymal stem cell populations exist in the tooth. According to their position in the tooth they can be grouped as[9]:

- Dental Pulp Stem Cells, DPSCs
- Stem cells from Human Exfoliated Deciduous teeth, SHEDs
- PerioDontal Ligament Stem Cells, PDLSCs
- Dental Follicle Stem Cells, DFSCs
- Stem Cells from the dental Apical Papilla, SCAPs



SCAFFOLDS-

The scaffold provides a 3D substratum on to which the cells can proliferate and migrate, produce a matrix and form a functional tissue with a desired shape. A suitable bioactive three-dimensional scaffold for the promotion of cellular proliferation and differentiation is critical in periodontal tissue engineering.

A scaffold plays many roles in tissue regeneration process[10]

- It serves as a framework to support cellular migration into the defect from surrounding tissues.
- It serves as a delivery vehicle for exogenous cells, growth factors, and genes.
- It may structurally reinforce the defect to maintain the shape of the defect.
- It serves as a barrier to prevent infiltration of surrounding tissue that may impede the process of regeneration.

Before its absorption, a scaffold can serve as a matrix for exogenous and endogenous cell adhesion and thus facilitates and regulates certain cellular processes, including mitosis, synthesis and migration.

Scaffold	Properties	Advantages	Disadvantages
(1) Chitosan	Chitosan, the fully/partially deacetylated form of chitin. Its wide variety of application ranging from skin, cartilage, bone and vascular grafts to substrates, mammalian cell culture. Fibrin a complex network formed by polymerization of fibrinogen in the presence of the enzyme thrombin.	Biologically renewable. Biodegradable, Biocompatible. Non-antigenic. Non-toxic. Biofunctional. Bioadhesive materials	Inducing rapid bone regeneration at initial stages. Bone formation after implanting these matrices occurs over a long period. Rapid degradation in vivo.
(2)Fibrin	Fibroin is a fibrous protein constituting the core of silk, while sericin is a glue-like protein surrounding fibroin	Induce improved cellular interaction. High biocompatibility	Difficult to maintain structural integrity.
(3) Silk fibroin	Derived from collagen Insoluble in water	Biocompatibility, Slow degradability , Excellent mechanical properties	Spider silk production very less
(4) Gelatin	Component of natural extra cellular matrix(ECM) Component of natural ECM.	Biodegradability and biocompatibility in physiological environment, Low antigenicity[7]	poor mechanical properties. Brittle
(5) Collagen	Role in natural Wound healing	Biocompatible. Good cell recognition	Poor mechanical properties
(6) Hyaluronic acid	Originates from seaweed. Structurally similar to natural glycosaminoglycan	Biocompatible. Easily functionalized	Poor mechanical properties
(7) Alginate		Good cell recognition Biocompatible. Simple gelation methods	Poor mechanical properties

Scaffolds are temporary frameworks used to provide a three-dimensional microenvironment where cells can proliferate, differentiate and generate the desired tissue.[11]

The design of the ideal scaffold for each tissue to be formed is a challenging task. Ideally, a scaffold must allow cell attachment and migration, permit the localized and sustained delivery of growth factors, and enable the influx of oxygen to maintain the high metabolic demands of cells engaged in tissue regeneration.

Scaffolds are usually made from ceramics, natural or synthetic polymers, or composites from these materials . The choice of scaffold material depends on the desired outcome thus physical (e.g. rheological behavior, mechanical properties, surface roughness and porosity) as well as chemical characteristics (e.g. mode, velocity and products of degradation) must be considered.

CELL SIGNALLING / GROWTH FACTORS

Signaling molecules are proteins that may act locally or systemically to affect the growth and function of cells in various manners. The two types of signaling molecules that have received the greatest attention are growth factors and morphogens that act by altering the cell phenotype i.e. by causing the differentiation of stem cells into bone forming cells - a process commonly known as osteoinduction.

Growth factors act on the external cell membrane receptors of a target cell, provide the signal to local mesenchymal and epithelial cells to migrate, divide, and increase matrix synthesis. The growth factor that has received the most attention in hard and soft tissue wound healing is platelet derived growth factor.

Cytokine/Growth factor	General role
VEGF	Stimulation and regulation of angiogenesis and vasculogenesis
bFGF	Stimulation of the proliferation of multiple cell types
IGF-1	Stimulation of the proliferation and growth of multiple cell types
SDF1	Chemotactic factor for monocytes, lymphocytes, megakaryocytes and hematopoietic cells
TGFβ	Regulation of cell proliferation and differentiation
IL-6	Mediator of inflammation and acute phase reaction

PLATELET-DERIVED GROWTH FACTOR-

PDGF secreted from platelets play an important role in initial wound healing, its subsequent secretion from macrophages continues the events of wound healing through up-regulation of other growth factors and cells that ultimately promote fibroblastic and osteoblastic functions.[12]

INSULIN LIKE GROWTH FACTOR-

Insulin like growth factor (IGF) is a potent chemotactic agent for vascular endothelial cells resulting in increased neovascularization. It also stimulates mitosis of many cells *in vitro* such as fibroblasts, osteocytes, and chondrocytes.[13] Insulin like growth factor-I is found in substantial levels in platelets and is released during clotting along with the other growth factors.

TRANSFORMING GROWTH FACTOR FAMILY-

TGF-β is chemotactic for fibroblasts and cementoblasts, and promotes fibroblast accumulation and fibrosis in the healing process. It can also modulate other growth factors such as PDGF, TGF-α, and EGF and fibroblast growth factor (FGF) possibly by altering their cellular response or by inducing their expression.[14]

FIBROBLAST GROWTH FACTOR FAMILY-

Fibroblast growth factors are the members of heparin binding growth factor family. The two most thoroughly characterized forms are: Basic FGF (bFGF) and acidic FGF (aFGF). They promote proliferation and attachment of endothelial cells and PDL cells in wound healing process. FGF-2 is known to attract epithelial cells more effectively than FGF-1.[15]

Concerning the specialized branches of dentistry, the application of tissue engineering was reviewed in different fields of dentistry.

PERIODONTOLOGY

One of the applications of tissue engineering in periodontal regeneration is the use of stem cells and signals on scaffolds and their implantation of the lesion area. Studies revealed that by implanting a ceramic scaffold containing mice periodontal ligament cells, a periodontal cementum, and ligament is formed. Moreover, the transplantation of bone marrow stem cells in class III lesion area of a dog has led to the regeneration of ligament, cementum, and alveolar bone. It is reported recently that the stem cells of root apical papilla area in combination with ligament stem cells, can form periodontal structures. [16] Several studies have assessed the possibility of using tissue engineering in treating periodontal disease. [17]One of the other applicable methods of tissue engineering in periodontology is use of gene therapy. Within this method, the stem cells were transfected by adenoviruses containing growth factor and placed in the lesion area.[18] Numerous studies have reported the application of gene therapy in the regeneration of periodontal.

ENDODONTICS

In dental pulp tissue engineering, soft scaffolding, such as hydrogels, can be used instead of natural and synthetic polymer scaffolds. Such scaffolds are in syringe type and are injectable in the root channel.[19]One of the other probable applications of stem cells in endodontics is in apexogenesis and apexification. Immature permanent teeth are usually rich sources of stem cells and blood vessels, which could be used in cells for apexogenesis.[20]

Regeneration of pulp vessels and nerve is one of the basic problems of dental pulp tissue engineering. The pulp is a tissue full of nerves, which enters the pulp through the apical hole along with blood vessels. These nerves have numerous roles and their regeneration is extremely vital in pulp. Recently, it is specified that some member of Bone morphogenetic protein family contribute to neurogenesis.[21] Moreover, the significance of endothelial cells and Vascular endothelial growth factor is confirmed in angiogenic.

CHALLENGE

Although, tissue engineering in a primitive form has already been applied in the middle ages and a significant amount of research is performed dealing with this topic, an effective and predictable clinical approach is not crystallized yet. In dentistry, bone substitutes and membranes are used for the regeneration of lost support tissues, but specific tissue engineered products of the clinical efficacy and superiority has been proven are not available. Although, there is continuous progress and development, it can be expected that a reliable application for small as well as large tissue defects has to wait for another 5–10 years. The regeneration of a complete new tooth will take a much longer space of time and is still utopian and perhaps a non-realistic ambition. For scientists, tissue engineering offers a huge challenge: all efforts of last-decade have evidently shown that it has indeed been feasible to regenerate tissues. In view of this, the longterm goal in dentistry remains the regeneration of all relevant dental tissues with as top on the pie the regeneration of a whole tooth. This aim is feasible under the condition of the availability of sufficient research funding and establishment of dedicated research programs.

CONCLUSION

Although such as the tissue engineering of other body organs dental tissue engineering is also faced with considerable challenges, by the advancement of research studies on stem cells, it seems that the reconstructed tissues by tissue engineering could supersede the current synthetic materials in the near future. What is more important in this regard is the need to update information in dentistry community and to add this subject to the training topics. We hope to become self-sufficient in such modern sciences, including tissue engineering, in the future.

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