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Review Article

Tissue engineering and its Impact on Dentistry: A review

[1]Komaldeep Kaur Sandhu, [2]Komaljot Kaur

[1,2]BDS (Intern), Sri Guru Ram Das Institute of Dental Sciences and Research, Amritsar, Punjab, India

ABSTRACT:
Tissue engineering is a novel and thrilling field that intends to restore functional, healthy tissue and organs in order to replace diseased, dying or dead tissues. Tissue engineering is an amalgamation of interaction between three key components namely, cells, scaffolds and signaling molecules. The focus of tissue engineering in dentistry is the regeneration of missing oral and maxillofacial tissues. It is an emerging field of source developing techniques for fabrication of new tissues for replacements based on principles of cells and developmental biology. The bonafide obstacle of tissue engineering in clinical treatment is the curtailment of surgical morbidity by application of biological signals or bioartificial components cultivated from patient's own cells, that can replace the lost body part or accomplish its repair without the need for autogenous tissue transfer. This article reviews basic concepts, applications and its future considerations in dentistry.
Key words: Biomaterials, Tissue engineering, stem cells, scaffolds

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Corresponding author: Komaldeep Kaur Sandhu, BDS (Intern), Sri Guru Ram Das Institute of Dental Sciences and Research, Amritsar, Punjab, India

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INTRODUCTION

Tissue loss occurring due to illness or disorder or congenital defects or acquired disease has lead to extensive healthcare problems universally. Current approach used for treatment of lost tissue involves the usage of autogenous grafts, alloplasts, allografts, and various other synthetic materials. Despite the favourable outcomes of these treatment approaches each one of them have some impediment. One of the major drawbacks of autograft, allograft is the fact that human body has depleted reservoir of excess tissue which is needed for transplantation. Another drawback includes anatomical and structural problems and donor site morbidity. This has lead to emergence of concept of tissue engineering as a promising regeneration system of lost tissue which restores functions and esthetic stimulation.[1]

Tissue engineering is a technique that makes use of specific biodegradable synthetic or natural scaffolds as well as advanced molecular techniques in order to replace tissue function.[1] Recent advances in biotechnology of morphogenetic factors and biomaterial have converged into evolving field of tissue engineering. Hence it's a budding interdisciplinary field which integrates biological components such as cells, any growth factors with emerging principles and synthetic materials and helps to restore, replace, maintain or improve tissue function. The biomaterials most commonly used are polymers of lactide and glycomers.[1] Today, tissue engineering in dentistry is utilization of biomodulation and incorporation of nanomaterials for reconstruction of oral and maxillofacial tissue. [2]

The terminology "tissue engineering" was first coined in the year 1987. The term "tissue engineering" is synonymously used with "Regenerative medicine". The molecular basis of regeneration is family of the bone morphogenetic proteins, isolated as a by-product of intense studies on the bone development cascade (Wozney,1992).[2]

Evidence based studies suggest that tissue engineering is indispensable in cases of any injury or diseases in which tissues cannot regrow. It is also vital in those cases in which tissues that can regenerate spontaneously; but are not able to do so as in cases of large defects (e g. bones). Tissue engineering is also crucial in cases where there are limitations of replacement of tissue with permanent implants.

Tissue engineering aims to create artificial tissue from biomaterials, specific cells and growth factors. The main target of tissue engineering is to assemble

functional construct that reinstate, sustain, or to remodel damaged tissue or whole organ.
This review will address the basic concepts of tissue engineering, strategies its applications pertinent to facial region and oral cavity, its limitations and future consideration.

CONCEPTS OF TISSUE ENGINEERING

There are three key components for tissue engineering-

1. Stem cells
2. Scaffolds
3. Signaling molecules/Growth factor

STEM CELLS

One of the core constituents of tissue engineering are stem cells. In multicellular organisms, stem cells are unspecialized and undifferentiated cells which are proficient to self replicate and continuously divide to augment various other types of cells or tissues. The ability for self renewal means that undifferentiated daughter cells are precisely same as mother cells and can further replicate many generations without losing their original characteristics.[2] This ability of stem cell to proliferate and differentiate as well as its capability to build structure through cells and bioscaffold interactions make it an imperative tool in tissue engineering.

TYPES OF STEM CELLS:

There are two types of stem cells:-

1. Embryonic stem cells/fetal stem cells
2. Adult stem cells / post natal stem cells

1. **Embryonic stem cells/ fetal stem cells**:- 4-5 days old blastocyst, contains embryonic stem cells, which are called pluripotent stem cells. Pluripotent stem cells form all cells of germ layers but do not make extra embryonic structures, such as placenta.[3]
2. **Adult stem cells/ post natal stem cells**:- These cells reside in mesenchymal tissues. Adult stem cells have been isolated from various tissues such as dental pulp, periodontal ligament, bone marrow, neural tissues, skin and retina, can also be obtained from the subject via a small tissue biopsy or aspirate, isolated and expanded into large quantities in vitro and transplanted back into the defect area. Although difficult to isolate, these cells have reduced probability to cause rejection.

Recently, the reprogrammed or induced Pluripotent Stem Cells (iPSCs) have been created artificially by genetic manipulation of adult stem cells.[1]

SCAFFOLDS

Biomaterial scaffold is one of the main elements in field of medicine, which work parallel to cells, environmental factors and signaling molecules, playing an important role in successful function tissue engineering.[4] Scaffold are the matrix that provide three-dimensional microenvironment which are favorable for cell growth, proliferation and differentiation at local site and provide mechanical support to tissue formation.
To determine the suitability of scaffold for use in tissue engineering; the following properties/ factors should be considered:-

1. **Biocompatibility**:- To provide adequate cell attachment, scaffold should be biocompatible with the host tissue, which will further help cells to function normally and successful migration to the site of injury or implant and finally enable proper proliferation of cells before new matrix establishment.
2. **Biodegradability**:- Scaffolds should degrade gradually so that it is replaced by regenerative tissues.[5]
3. **Mechanical properties**:- Preferably, each body tissue has its own mechanical stability and this is the key to select a suitable scaffold, therefore, mechanical properties are consistent with the anatomy of each tissue/organ.
4. **Structure**:-Scaffold must have structure that allows for efficient transport of nutrients and waste, growth factors and permits the inflow of oxygen to maintaining metabolic activities.
5. **Architecture**:-The architecture of scaffold should be such that it should possess sufficient mechanical resistance to withstand in vivo stresses.[1]
6. **Porosity**:- Scaffold must be porous enough to ensure cellular penetration and adequate diffusion of nutrients to cells within the construct and the extracellular matrix.[8]

SIGNALING MOLECULES/ GROWTH FACTORS

Cell signaling refers to a domain of complex system of communication which control cell activities and assembles all interactivities in a biochemical environment. [1] The fate of cell is influenced mainly by these signaling molecules.[1]
Examples of these signaling molecules are growth factors and cytokines. These growth factors are proteins which play a significant role in the regenerative process. They are normally released from cells and directly presented onto cell surface receptors through interactions with neighboring extracellular matrix. Binding of growth factors to particular cell membrane linked receptor activates various mechanism and pathways involved in tissue engineering, such as cell migration, survival adhesion, proliferation, growth and differentiation into desired cell type.
Any irregularity in the gene that codes for these proteins can cause numerous craniofacial skeletal dysostoses. The binding of growth factor to its receptor commences intracellular signaling that will lead to different events such as promotion, adhesion, migration. Hence, these molecules are recognized as

fairly important for tissue formation and may play an important role in regenerative medical approaches.[1]

STRATEGIES OF TISSUE ENGINEERING

1. **Cell injection therapy**
   As it is already known that formation of tissue results from action of cells; especially stem cells, to be precise, with its induction into the defect been suggested to regenerate tissues. However, its limitations include low engraftment and insufficient localization of the injected cells mainly in the areas having continuous movement. Moreover, another constraint is that inductive factor for particular tissue may not be known. Use of cell injection as a delivery vehicle to carry and deliver the material is done for appropriate localization and prevention of direct contact with immune system. Stem cells are the most triumphant cell for this technique.[2]
2. **Cell induction therapy**
   This technique involves activating cells in close proximity to defect site with specific biological signals.[5] The origin of this mechanism is rooted in the discovery of Bone morphogenic protein (BMP).[9] Urist first showed that new bone could be formed at non mineralizing or ectopic sites after demineralising and ground into fine particles.[6]Although this therapy was effective in regenerating some tissues, the development of an appropriate carrier to deliver these target sites limit its scope.[2]
3. **Cell seeded scaffolds**
   Combining all the previous attempts lead to emergence of another strategy to engineer tissue. This strategy depends on the isolation of appropriate cell population from a biopsy taken from the patient cell donor.[2] The potent immunomodulatory and anti inflammatory properties of human oral mucosa/ gingival delivered Mesenchymal Stem Cells (MSC) make them a very strong potential source for MSC based therapies for wound repair and wide range of inflammation related diseases.[2] Another alternative for this approach involves implantation of acellular scaffolds into the defect while body cells can populate the scaffold to form new tissue in situ.

APPLICATIONS OF TISSUE ENGINEERING

BONE

Bone regeneration is one of the most comprehensively investigated application of tissue engineering. Restoration of bony defect in case of craniofacial region remains a salient challenge. In order to overcome the snag of current bone graft material, amalgamation of progenitor cells or seeding of osteogenically differentiated cells is the basic concept of bone tissue engineering. Use of scaffold in optimal and refining manner is another dominant aspect for bone tissue engineering. In case of cell based construct, lining osteogenic cells are carried on scaffolds to the bone defect site in order to allow development of 3-dimentional tissue structure. Despite the significant amount of advancement in tissue engineering, there are still some limitations. The significant stress and strain in craniofacial bones, mostly due to strong muscles of mastication, are significant challenges to any engineered construct. Some of the clinical cases in which surgical medication is required are distraction osteogenesis, Guided Tissue Regeneration (GTR), bone regeneration and reconstruction of oral and maxillofacial bone defects. Current strategies aimed at replacing bony defects involve utilization of various types of autografts, allografts, biosynthetic materials. Limited availability need for additional surgical site, disease transmission and immunorejection remain a significant hurdle to their implementation.[7]

CARTILAGE

Destruction of cartilage is associated with injury, trauma and a number of diseases such as degenerative articular cartilage destruction of TMJ. Paucity of inductive molecules and limited ability of cartilagenous tissue to regenerate have developed fascination among researchers and manufacturers in developing cell transplantation approach to engineering the cartilage. Chondrocytes from numerous locations in the body can be obtained, cultured in vivo and implanted.[9]

ENAMEL REGENERATION

Being the hardest tissue in the body, enamel is highly organized dental tissue which covers the outermost layer of tooth crown. Ameloblasts, the enamel forming cells are specialized epithelial cells which differentiate from inner cells of enamel organ. In order to reinstate the enamel defects caused due to trauma or carrier, artificial materials were manufactured to resemble its hardness. Unfortunately, most of the current materials do not possess same mechanical, physical and esthetic properties of lost tissues. Despite the urgent need for tooth enamel regeneration, enamel tissue engineering is facing many difficulties.[8]

DENTIN PULP REGENERTAION

Regeneration of dentine pulp complexes have been explored through segregation and analysis of regenerative abilities of stem cells. Since dental tissues are substantial source of stem cells, hence new therapeutic possibilities may be feasible. Cell free scaffolds such as emdogain gel or blend of emdogain and platelet rich plasma also stimulate the regeneration of dentine pulp complex. The ability of Dental Pulp Stem cells and Periodontal Ligament Stem cells to produce pulp-dentine like complexes in vivo suggests potential application involving stem cells, growth factors and scaffolds for apexification and apexogenesis.[9]The conventional strategic approach for engineering the dentine-pulp complexes involves the use of injectable hydrogels and cell therapy due to size and confinement of pulp within root canal. In the past decade, regenerative endodontic has gained much attention as it offers alternative approach for treatment of endodontically involved teeth by filling the canal with vital tissues instead of artificial materials.[10]

PERIODONTAL REGENERATON

Periodontitis is a ubiquitous condition of inflammation that is responsible for wrecking of tooth supportive connective tissue such as alveolar bone, gingiva and ultimately leads to tooth loss. Regeneration of the tooth supporting structure that is cementum- periodontal ligament- bone interface and structure are very demanding and require coaction of all cellular and molecular events involved in regeneration of these complexes tissue. Guided Tissue Regeneration and Guided Bone Regeneration (GBR) are routine practice approaches that utilize occlusion membrane to maintain the defective space, selectively encourage the appropriate cells to regenerate the local tissues and support newly formed tissues.[2] GTR and GBR periodontal membranes are now being developed by combining natural and synthetic polymer using method such as film casting, dynamic filtration and electrospinning. Another method to accomplish periodontal regeneration is by the use of platelet rich plasma (PRP). In addition, PDL stem cells (PDLSc) from extracted teeth have recently been cultured, expanded and differentiated to achieve efficient dental tissue regeneration.

SALIVARY GLAND REGENERATION

The production and secretion of saliva is extremely crucial to preservation of oral health and function. In developmental or acquired disorders like sjogren's syndrome, salivary gland neoplasm, etc, the loss of salivary gland parenchyma and incompetence to generate saliva remarkably influence quality of life of person. Remedy of salivary gland hypofunction also known as xerostomia following radiation in head and neck is only restricted to delivering of salivary substitutes and sialogogues that necessitates periodic administration .Tissue engineering provides biological substitutes to impaired salivary gland. The utilization of 2- dimensional scaffold is nevertheless, still a feasible option to engineer salivary gland. Gene therapy is another budding approach for salivary regeneration in which prevailing non secretory duct epithelial cells change into secretory cells capable of fluid movement. Baum et al. initiated via cell transplantation approach, the development of an artificial salivary gland substitute composed of polymers tube line by epithelial cell.[11]

BIOENGINEERED TOOTH

The foremost objective of contemporary restorative dentistry is to functionally and esthetically reinstate the diseased or lost tooth structure. Loss of tooth structure due to decay or trauma is most frequently replaced with utilization of restorative materials. Despite of the fact that these traditional restorative materials have proven to be highly efficacious in preservation of teeth; however, they still have some deterrents such as short life span and thus eventually require replacement. Therefore, regeneration of lost tooth structure would have noticeable advantages.

Tooth regeneration is an adjunct of current development in tissue engineering.[12] Use of dental implants are among the most progressive alternative for replacing lost and missing tooth but they depend on direct integration of bone within the implant structure. With recent advances in stem cell biology and tissue engineering, biological tooth may become an alternative for replacing the missing teeth.[13]

Recent studies are mainly focused on making use of stem cell technology to evolve regionally pertinent induced pluripotent stem cells lines for use in orofacial region. This can eventually lead to evolution of economically viable therapies and pitch in towards progressive oral health. Key challenges in this field include convolution of oral tissues, limited availability of autologous tooth, loss of remodeling ability in enamel and dentin and cost effectiveness of these procedure.

REGENERATION OF SKIN OR ORAL MUCOSA

The most victorious application of tissue engineering is the development of skin equivalents. In the oral cavity, the obligation for soft tissue restoration is more frequently linked to lost gingival tissues and less often to lost oral mucosa and skin in case of disfigured tissue. Numerous techniques have evolved over the past years in order to regain the esthetics of gingival and oral tissues. These include pedicle flaps, epithelised/ non epithelised soft tissue autografts or bilaminar technique. The body does not discard these grafts since they are autologous.[2]

The engineering and transplantation of oral mucosa and gingiva can be potentially vital as a new technique in periodontal graft surgery and in the management of recession of gingiva as well.

LIMITATIONS AND FUTURE CONSIDERATIONS

Tissue engineering represents one of most exhilarating advances in regenerative medicine. The potential to fabricate new tissues and organs from patient's own cells has switched treatments and prognosis for innumerable patients. However, major challenges lie not only on the scientific aspect but also in the application of technology. A major issue is the host of therapies. Other drawbacks include foreign body reaction, disease transmission, donor site morbidity and failure to grow or remodel. Another key dispute lies in ethical concerns regarding engineered tissue.

Further studies are imperative to augment cell viability, boost total cell density, optimize bioactive molecule dose, control its delivery site and comprehend the kinetics of biofactor. Studies are essential to design scaffolds with chemical composition, pore/size that allows cells to sustain their optimum tissue forming potential. Reconstruction of complex tissue defect made up of multiple cell types has not been attempted yet and will likely to be introduced in near future.

Recently, engineering of dental pulp and dentin with pulp derived stem cells has made substantial advancement. Using tooth as an autologous cell source and its potential utilization of anogenic stem cells both require further research to determine ultimate benefit to the patient. More research should also be aimed at matter of how to attain swift revascularization of the tissue engineered construct to optimize the survival of tissue engineered graft.[11]

Regeneration of tissues by tissue engineering is an inexorable therapy and unabating synergistic attempts among research scientists and dental professionals are needed to pool assets to accelerate its growth.

CONCLUSION

Dental practice has inevitably been influenced by novel technologies, be it the evolution of modern restorative material or tissue engineering. Many advances have been made over the past decade in tissue engineering; that have provided a substantial incentive for biomedical community to render these findings into clinical application.

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