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REVIEW ARTICLE

Tissue engineering, an emerging field in dentistry - A review

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Abstract

The branch of tissue engineering has emerged as a new scientific field which enlightened many new approaches to the vital pulp therapy. The main objective of this field is to regenerate the tooth-tissue structure as well as the function with the help of interactions between the three key elements, i.e. stem cells, scaffolds, and morphogens. In this technique, various principles of biology, medicine, and engineering are combined for regeneration and/or repair of a damaged tissue or organ. This review article gives an insight into the basic concepts of tissue engineering and strategies so far studied. Furthermore, this article focuses on the key elements which are used in tissue engineering and the clinical approaches that can be applied in dentistry.

Introduction

Many factors such as disease, traumatic injuries, and birth abnormalities can cause tissue loss, which is a significant health problem all over the world. When the craniofacial region is involved, it causes major physiological as well as psychological effects on the patients. Recreation or reorganizing the cranial and maxillofacial region up to the functional as well as esthetic requirement is thereby desired in the affected patients.[1]

The present review mainly describes the research efforts concentrated in the methodology for orofacial reconstruction by making the use of stem cells, morphogens, scaffolds, and medical devices to a better denotative tissue engineering approach and the principle strategies of tissue engineering. This article also addressed the future potential and the significant advancements in this field.

What is the Need for Tissue Engineering?

Tissue engineering promises to produce better organs for transplantation. Using this technique along with the genetic therapy, it might be possible to rectify many incurable defects of the genes. A major aim of the tissue engineering is to construct transplantable vital tissue *in vitro*.

Artificial tissues can bring a revolution in the healthcare facility by providing the soft and hard tissues on demand.

Components of Tissue Engineering

Basically, three key elements are used in the tissue engineering, which includes stem cells, scaffolds, and morphogens. A new component "bioreactors" are currently added in the field of tissue engineering, which significantly enhanced the biosynthetic activity in a wide range of various types of cells.

Stem cells

Stem cells are the unspecialized, immature cells having the potential to differentiate and develop into various cell lineages. According to the conventional definition, these cells, through "self-renewal," can renew themselves indefinitely[2] and they may vary according to the type of cells that they can produce and their location in the body. The recent studies have revealed that there is a rich source of stem cells in oral tissues and these are easily accessible to the dentists. Stem cells have unique abilities and are specifically important for the development of the innovative technologies for the various strategies of tissue engineering[3] to replace or regenerate diseased, damaged or missing tissues, and even organs by design of the extracellular environment and *in vitro* cell manipulation.

- Embryonic stem cell: These are pluripotent stem cells, which are derived from embryos (blastocysts), i.e., they have the capacity to form all tissues.

- Adult stem cells (multipotent cells): These are undifferentiated cells that typically generate the cell types of the tissue in which they reside. For example, mesenchymal stem cells.

Sources of Stem Cells in Dentistry

1. Dental pulp stem cells
2. Stem cells from exfoliated deciduous teeth
3. Stem cells from apical papilla
4. Periodontal ligament stem cells
5. Mesenchymal stem cells from gingiva
6. Progenitor cells from oral mucosal lamina propria
7. Dental follicle stem cells
8. Tooth germ progenitor cells
9. Oral epithelial progenitor/stem cells
10. Periosteum-derived stem cells
11. Salivary gland-derived stem cells.

Morphogens

Morphogens are the proteins that induce the cell signaling and influence the critical functions such as cell division, proliferation, and matrix synthesis.

They are extracellularly secreted, and during the epithelial-mesenchymal interactions, they signal the governing morphogenesis.

The morphogenetic signaling networks include the five major classes of evolutionarily conserved genes such as follows:
a. Bone morphogenetic proteins;
b. Fibroblast growth factors;
c. Wingless- and int-related proteins;
d. Hedgehog proteins;
e. Tumor necrotic factor.

Scaffolds

Scaffolds are the materials that have been engineered to generate desirable cellular interactions which will play a crucial role in the formation of new functional tissues for various medical purposes.

The scaffold provides a three-dimensional (3-D) microenvironment physicochemically and biologically for cellular growth, differentiation, adhesion, and migration. They are responsible for the transportation of oxygen, nutrition, and waste products.

It also acts as a carrier for morphogens in the cell therapy.

Scaffolds and carrier systems have used three types of biomaterials:
1. Natural (or biological) materials,
2. Ceramic or glass materials, and
3. Polymeric materials.

Many other materials which can be used as scaffolds are as follows:
- Fibronectin
- Collagen
- Synthetic extracellular matrix
- Alginate hydrogel
- MTA powder
- Fibrous titanium mesh and
- Biodegradable porous calcium phosphate.

Bioreactors

The "bioreactor" is a system in which the conditions are closely controlled to induce or permit certain behavior in living cells or tissues.

The primary objectives of these systems are to achieve the spatial uniformity in the cell distributions on 3-D scaffolds and to maintain the desired concentrations of nutrients and gases in the culture medium as well as to expose the developing tissue to appropriate physical stimuli.

Strategies of Tissue Engineering

Strategies employed to engineer tissue can be categorized into three major classes:
1. Cell conduction therapy
2. Cell induction therapy
3. Cell transplantation.

The strategies depend on utilizing one or more key elements, for example, cells, matrix, and growth factors to guide tissue regeneration.[3-7]
1. The conductive approach makes the use of a membrane as a barrier which will inhibit connective tissue cells that can interfere with the regenerative process, while enables the host cells which are desired to populate at the regeneration site.
2. The inductive approach makes use of a biodegradable polymer scaffold. These will act as a vehicle for delivering genes and growth factors to the host site and can be released at a controlled rate.
3. The cell transplantation strategy makes use of similar vehicle for the delivery of transplant cell site.

Applications in Dentistry [Figure 1]

The development and function of orofacial structures are very specific and unique.[8] Apart from the specific developmental and functional characteristics of oral tissues, they also have a limited and variable regenerative capacities.[9]

Tissue engineering is expanding extensively to develop a completely functional bio-engineered tooth.[10]

Various advancements have been going on to reach a destination where it will be a reality to develop a fully functional bioengineered tooth. This section of the article covers the attempts of tissue engineering for soft tissue replacement such as skin, mucosa, muscles, and salivary glands and hard tissues such as temporomandibular joints (TMJ) and bone.[11,12]
1. Dentin-pulp complex - the secretion of transforming growth factor as well as stimulation of the differentiation of pulp progenitor cells into odontoblast-like cells plays a crucial role in angiogenesis, progenitor cells recruitment, differentiation of the cell, and finally mineralization of the injured area.[13]

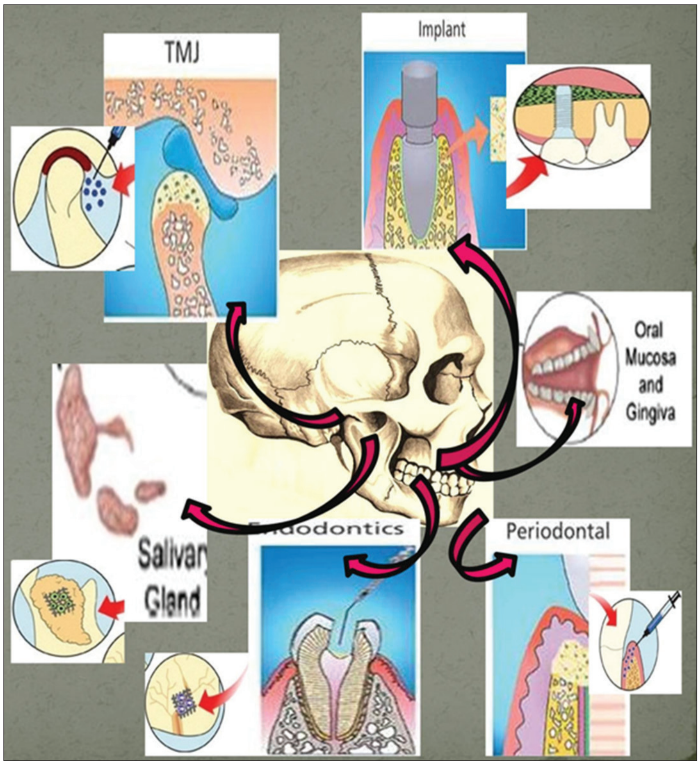

Figure 1: Application in dentistry

Stem cell therapy has also been attempted for the regeneration of the dentine-pulp complex because dental tissues are a rich source of stem cells.[14-16]

2. Periodontium - the advancement in the branch of tissue engineering utilizes cytokines and growth factors to regenerate periodontium.[17,18]

Guided tissue/bone regeneration membrane utilizes occlusive membranes to keep the space of defect patent. It also selectively encourages the appropriate cells for the regeneration of lost tissues and for the support of newly formed tissues.[19]

3. Bioengineered teeth - tooth development, also called as odontogenesis, is a complex process which involves a series of reciprocal interactions between epithelium and mesenchyme and the coordination between the crown and the root development and its associated periodontium. Accordingly, the cells have been dissociated from the epithelium and mesenchymal tissues of pre- or post-natal tooth germ and were used to restructure a "bioengineered tooth germ" *in vitro*. The attempts have been made to produce a whole tooth by transplanting a bioengineered tooth germ in an organ culture or into the oral environment.[20]
4. Skin, facial muscles, oral mucosa, and salivary glands - tissue engineering has made tremendous advancement in the regeneration of the skin, and currently, several skin substitute products (epidermal, dermal, or composite) are commercially available now. Same protocol as that of the skin has been followed for the bioengineering of the oral mucosa.[21]

The muscle fiber composition and muscle anatomy are unique when compared to other skeletal muscles. To get a 3-D scaffold that fulfils the demands of elasticity, stability and biocompatibility are the main hindrance for the clinical application of tissue-engineered muscle. Therefore, tissue engineering holds a promise to treat the patients with partial tongue resection and facial paralysis in the future.[22]

Impaired salivary glands can be biologically substituted by the help of tissue engineering. However, the key issue is to culture the highly differentiated human salivary gland cells as and difficult to expand them *in vitro*.

5. Bone and TMJ - encouraging results have been shown radiographically as well as histologically by the application of fleeces of the autogenic periosteal cells-seeded polymer for the augmentation of the maxillary sinus floor before insertion of the implant. Injectable composites could be used for stem cell-based bone engineering in case of irregular defects.

TMJ treatment is one of the most difficult tasks because of its limited vascular supply and therefore limited self-repair capacity. For regeneration of the unique articular cartilage, injectable smart hydrogels could be employed to transfer the cells along with the cell therapy.[23]

Conclusion and Outlook

Tissue engineering is providing a new era for therapeutic medicine. It is advancing and extensively extending to involve various tissues of our body.

Tissue engineering was just an idea three decades ago, but today it has become a potential therapy for several conditions. To develop a more regenerative breakthrough and leading to off-the-shelf bio-products for replacing various lost tissues and organs, a detailed knowledge of stem cell biology as well as understanding of embryonic development is required.[24,25]

Oral tissues regeneration *per se* requires recapitulation of the biological development of several tissues and interfaces and undoubtedly is very challenging.

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