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REVIEW ARTICLE

A review on the applications of tissue engineering in branches of dentistry

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Abstract

Background: The major focus of dentistry has been primarily on the modification and improvement of synthetic material properties, but the emergence of dental tissue engineering has led to an evolution in the framework of the main products, such as restorative materials and implants. **Aim:** The aim of the present study is to assess the applications of tissue engineering in different fields of dentistry. To this end, a review was made on articles, which are available in Medline using keywords, such as dental stem cell, teeth tissue engineering, regenerative dentistry, oral surgery, periodontal regeneration, and regenerative endodontics. Papers were mostly searched from 2000 onward. **Conclusion:** According to the results, we could predict that although there are serious problems in dental tissue engineering, this technique could gain numerous applications in dentistry, sooner, or later. **Clinical Significance:** By embracing such a modern technology, the biomaterials science would undoubtedly face a dramatic historical transition.

Keywords: Dental stem cells, oral surgery, periodontal regeneration, regenerative dentistry, regenerative endodontics, teeth tissue engineering

Introduction

The basic model for treating dental diseases is the removal of destructed tissues and replacing that 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 a mechanical fracture. Moreover, the biocompatibility of most of such materials is the subject of much controversy. Today, tissue engineering has made it clear that instead of using synthetic materials, we can utilize dental regeneration.[1] In fact, using this realm of study, in addition to atraumatic care and a treatment with greater longevity, we could replace the tissues, which are destroyed as a result of cancer and periodontal diseases or were absent congenitally.[2] In dentistry, we are looking forward to totally regenerate tissues such as alveolar bone, periodontal ligament, enamel, dentin, and even the whole tooth. Obviously, the first step is to be fully acquainted with the biology and embryonic development of desired tissues.[3]

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.[4] Tissue engineering comprises three major components of biologic tissues, that is, adult stem cells, growth factors, and extracellular matrix scaffolds.[5]

In general, 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.[6] In tooth, in addition to the isolation of dental pulp stem cells (DPSCs), other sources of stem cells are also mentioned, which are human exfoliated deciduous teeth (SHEDs), apical papilla (SCAP), and DPSCs.[7-10] Recent studies have shown that the stem cells of other tissues, such as bone marrow, fat tissue, and endometrium are also able to differentiate odontoblasts or tooth-forming cells.[11-13] Such cells brought hope to the future of regenerative medicine, especially regenerative dentistry.[14] In addition to the stem cells, scaffolds and messenger molecules are 2 other key components of tissue engineering. Scaffolds, which are currently divided into 2 groups of natural and synthetic, are in fact playing the role of extracellular matrix and acting as a carrier for growth factors and depends on the type of tissue to be regenerated there are considerable difference among these factors.[15,16]

In the present study, concerning the specialized branches of dentistry, the application of tissue engineering was reviewed in different fields of dentistry.

Periodontology

Periodontitis is an inflammatory disease which clinically causes the loss of a number of tissues, such as periodontal ligament and alveolar bone.[17] Surgery, grafts, growth factors, and membranes have been the common treatments for this disease, so far. Recently, a population of stem cells was identified in periodontal ligament.[18,19] Such cells, named periodontal ligament stem cells, were able to distinguish osteoblasts and cementoblasts *in vitro* condition and were also capable to convert to cementum and ligament tissue *in vivo* condition.[14,20] These cells were also detected in periodontal ligament of laboratory mice and sheep and their functionality were also assessed in neural cells.[20,21] Further, studies indicated that freezing has no impact on these cells, so banking them is counted as a clinical necessity.[22] 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.[22] 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.[23] It is reported recently that the stem cells of root apical papilla area in combination with ligament stem cells, can form periodontal structures.[10] Several studies have assessed the possibility of using tissue engineering in treating periodontal diseases.[24] One of the other applicable methods of tissue engineering in periodontology is use of gene therapy.[25] Within this method, the stem cells were transfected by adenoviruses containing growth factor and placed in the lesion area.[26] Numerous studies have reported the application of gene therapy in the regeneration of periodontal.[27-29]

Certainly, having a general information of the cellular and molecular trend of the periodontal tissues is necessary for successful regeneration of periodontal using the tissue engineering. Further, the favorable mechanism of cell proliferation and their transfer to the scaffold, differentiation-inducing conditions, and gene mutation probability should be studied in long-term period.

Endodontics

Every year, millions of teeth are survived by endodontic treatments. Although modern therapies could guarantee a high rate of success in most of the cases, an ideal treatment would be based on regenerative approach, which after removing the necrotic pulp could replace the tooth with a fresh pulp and survive the tissue. Regenerative endodontics means generating tissue to replace the damaged pulp or necrotic tissue. Dental pulp tissue contains stem cells, which can differentiate odontobalsts in response to various growth factors. There are several methods for pulp regeneration.[30] One of these methods is direct injection of stem cells into the disinfected channel, after opening of *in vivo* apex. One of the major problems of this method is how to find a source of stem cells capable of differentiating various types of cells existing in a pulp (fibroblast, odontoblast, endothelial cells). Furthermore, to prevent from cell movement toward other tissues use of scaffold seems necessary. Cordeiro *et al.* by direct injection of scaffolds containing teeth (SHED) stem cells and endothelial cells into the root channel managed to form a structure similar to dental pulp.[31]

The other method is called *ex vivo*. In this method, the stem cells are grown and differentiated on the scaffold in the presence of required signals, then will be implanted in the root channel. Each technique has some pros and cons, which should be defined through clinical research studies and basic sciences.

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.[32] 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.[33]

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.[34] Moreover, the significance of endothelial cells and Vascular endothelial growth factor is confirmed in angiogenic.[35]

It is noteworthy that the success of regenerative endodontics treatments depends on the capability of scholars in creating a technique which allows the dentist to generate a pulp functional tissue in the disinfected and transformed channel.

Oral and Maxillofacial Surgery

The application of tissue engineering in oral surgery includes several branches, which studied in different articles.[36,37]

Tissue engineering of temporomandibular joint

Temporomandibular joint is a complicated system, which could be interrupted due to trauma or inflammation. Common available treatments usually cause the formation of oscar fibrocartilage tissue, which lacks the mechanical properties of natural cartilage tissue. Tissue engineering of this joint calls for regeneration of 2 components of bone and cartilage. Cartilage generation, however, is more difficult than bone regeneration, in that in most studies although stem cells differentiation is to chondrocytes, the regenerate tissue is not like the natural tissue, structurally and functionally. Many growth factors were identified in this way, which could contribute to the joint regeneration.[38]

According to studies conducted in 2004 and 2005 based on detailed computer images, a scaffold was designed of polylactic acid and hydroxyapatite (PLLA/HA), in which the chondrocyte cells were differentiated and the gingival fibroblasts cells, which under the influence of Ad.BMP7 were transferred to the scaffold. The scaffold was then implanted subcutaneously in the body of a laboratory mouse with no immune system. 4 weeks after, the bone and cartilage structures were observable with certain interface.[39] This study indicated that the tissue engineering of temporomandibular joint is possible though serious challenges lie in this method.

Tissue engineering of skin and oral mucosa

Regeneration of skin and oral mucosa in patients, who lost a part of their tissues due to burn, major surgeries, or trauma is the matter of the utmost significance. Previously, initial treatments were skin grafts, but gradually the use of cultured epithelial layers from small biopsies become increasingly common. Skin is the first engineered tissue, which is confirmed by the FDA for clinical applications. All FDA-certified regenerated skill products are composed of Foreskin neonatal-based cells. These cells are capable of proliferation and could be the generator of 80,000 meters of final skin product.[40]

Like skin, oral mucosa is formed of stratified squamous epithelium, which covers the lamina propria. At present, multilayer cultivation of gingival keratinocytes has resulted in some relative success and could be applied for biocompatibility tests and studies of oral biology.[41] Commercial products, such as skin Ethic's gingival epithelium and Keratinized EpiOral squamous epithelial products are currently in stock.

Tissue engineering of salivary glands

Losing the function of salivary glands is reported following the adverse effect of medicines, radiotherapy, and autoimmune diseases, such as Sjogren's syndrome. Decreased saliva, which is known as gastrostomia, is often associated with caries, mucosal infections, and dysphasia. Salivary glands are composed of four certain types of epithelial cells (acini, ducts, basal, and myoeptithelial) and discovering a cell able to differentiate to these cells is a great challenge for tissue engineering. The epithelial cells of salivary gland ducts, which were cultivated on PLLA scaffold, were used in the initial studies.[42] However, it was gradually revealed that these cells are not efficient in tight junctions and therefore cannot stimulate the unilateral movement of liquid saliva.[43] Currently, the progenitor epithelial cells of salivary glands are detected and could be used in tissue engineering. The stem cells from mouse bone marrow could also differentiate to acini cells and express the alpha amylase.[44]

At present, gene therapy is used as a clinical trial for regeneration and stimulation of salivary tissues in patients with head and neck cancer, who have radiotherapy.[45]

Implant therapy

Today, the use of implant as a standard method of dentistry is fully accepted. The success of dental implants depends on their placement in a bone with sufficient density and volume. One of the major problems in implant surgery is that in most of the cases, surgeons are faced with considerable erosion of alveolar bone, where it is needed to increase the bone length. Techniques which are currently evaluated in different studies, include use of different kinds of membranes, xenografts, and HA.[46]

Use of bone tissue engineering in bone defections is one of the alternative methods for grafts.[47] Several studies have used ceramic and fibrin scaffolds for bone formation. Due to their slow rate of erosion as well as low plasticity, porous ceramics have shown favorable results.[48] However, due to hemostatic property, angiogenic ability, faster healing, and bone formation process, as well as osteoconductive property, fibrin is a suitable material. This element is a combination of fibrinogen and thrombin, and in terms of biocompatibility, biodegradation, and appropriate cell band is approved.[49] Moreover, platelet-rich plasma is realized as one of the effective growth factors in bone tissue engineering.[50] Use of hydrogels for covering implants would make the culture of osteoblasts in implants and their better osteointegration possible.

One of the other effective methods for controlled release of the growth factors is the use of drug delivery systems by various microspheres.[51] By covering the implant surface, the polylactic microspheres, which contain growth factors such as transforming growth factor-beta or insulin-like growth factor-I, could yield successful results in increasing osteointegration.

Cleft palate

Cleft lip and palate is a common congenital disease, which is seen in almost one or 2 babies per 1000 birth. The current approach for treating cleft lip and palate is surgery and bone grafts, which have some limitations.[52] By regenerating bone as well as soft tissues using the stem cells, scaffolds, and growth factors, tissue engineering could be accepted as an alternative treatment. Currently, more studies are concentrated on the identification of molecular messaging system, which causes such disease and several growth factors were detected in this way, the most important of which is Wnt pathway.[53]

Since cleft lip and palate is a congenital defect, children are our target patients.Hence, we should study more precisely how to use tissue engineering and control it in children.

Restorative

The aim of restorative dentistry is to regenerate those dental structures which are lost due to decays. These structures include tooth enamel and dentin, which are currently replaced by composites, amalgams, or porcelain. The subject of replacing such damaged tissues with natural ones came up recently.[54]

Many animal studies are carried out for dentin regeneration, so far and they were effective. In the study of Iohara *et al.*, the transplantation of a pulp exposed with stem cells of dental pulp has led to dentin regeneration and the formation of a dentin bridge.[55] Use of different kinds of stem cells, including buds, milk teeth, permanent tooth pulp, and bone marrow could help dentin generation.[14]

Regenerating enamel by tissue engineering is much harder than regenerating dentin, in that the ameloblastoma cells, which compose the enamel, will destroy after tooth growth. Therefore, in contrast to dentin, the damaged enamel is not able to repair itself. It is specified recently that under certain conditions, some of oral epithelial cells are able to differentiate to ameloblastoma cells. Harada *et al.* carried out a research on anterior teeth of mouse and by observing the permanent germination of these teeth and frequent generation of enamel during the lifetime of this animal, were managed to identify the epithelial stem cells in cervical area of these teeth.[56] Further, the molecular messaging pathway, which causes the differentiation of stem cells to ameloblastoma, was also detected, which is called Notch pathway. The identification of this pathway could be helpful in inducing different stem cells to ameloblastoma. According to a study conducted in 2007 by Honda *et al.*,[57] enamel organ epithelial cells were isolated from the third molar of guinea pig and placed on collagen sponge along with dental pulp cells. 4 weeks after, the enamel and dentin structures were established. Moreover, within another study, Hu *et al*. could differentiate the stem cells of bone marrow to ameloblastoma.[58] According to this study, a combination of stem cells of bone marrow, epithelial dental embryonic cells, and dental mesenchyme was used.

Prosthodontics

Today, the missing teeth are replaced with denture or, in the best way possible, with implant. Although these are known as successful treatment, they have several shortcomings. One of the long-term objectives of this paper is complete restoration of maxillofacial tissues. This phenomenon calls for differentiation of several tissues such as enamel, dentin, pulp, cementum, and the formation of periodontal ligament using various messaging molecules.

According to Young *et al.*, the implant of isolated cellular suspension from third molar dental follicle of guinea pig into the omentum of mouse lacking the immune system has led to the formation a tooth-like tissue with all dental structures.[59] However, this tissue was unfortunately not similar to a fully evolved adult tooth. A similar study was conducted using the stem cells of bone marrow and oral epithelium cells of mouse embryos, which brought about the same results.[11]

The regeneration of a whole tooth is recently based on two approaches: Tooth formation *ex vivo*, tooth formation *in vivo*. Based on the latter approach, the planted stem cells on a scaffold can be transplanted in the body and transformed to dental structures.[60] At present, there are numerous problems to the complete regeneration of dental structure. Identifying an appropriate source of epithelial and mesenchyme stem cells is one of the problems, which can differentiate to all dental structures. The other problem is the germination of implanted tooth, in that the dental follicle which play an important role in teeth germination, is absent in these conditions. The type of connection of implanted tooth with vessels and nerves of the apical area is another problem. Finally, the immune responses to the implanted tooth have not assessed accurately, so far and are highly questioned.[61]

Many questions are posed concerning the best cellular source for dental tissue engineering, which should be answered before their clinical application.[62] Defining the best scaffold among different types of natural and synthetic ones as well as the growth factor is a challenging task. Moreover, the possibility of rejection of cellular implants and scaffolds by the immune system and tumorigenesis of cells is also existed. Evaluating the compatibility of biological properties (like aging) of implanted tissue with the surrounding tissues is among the upcoming issues.

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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