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Review Article

Tooth Regeneration the Future of Dentistry- A Review

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Abstract

Tissue regeneration and engineering is the most challenging part of a tissue repair/regeneration program. The emergence of this branch in medicine has shed new light on the treatment of the patients with degenerative disorders. Regeneration of tooth structure is an upcoming field in dentistry which can lead to revolutionary changes in the approach of treatment of various conditions disease state of tooth. This article provides an overview of various modalities of tooth regeneration which may change the outlook of dentistry completely.

Keywords: Tooth Regeneration; Tissue Engineering; Enamel; Dentin; Pulp

Introduction

The word 'Regeneration' is defined as an act or the process of regenerating, or renewal or restoration of a body, bodily part, or biological system after injury or as a normal process [1].

Regenerative Medicine, aims to restore or establish the normal function of lost, diseased, damaged or ageing cells, tissues and organs using a range of approaches; including cell-based and gene-based therapies, tissue engineering and biomedical engineering [2]. Most of the treatment modalities are directed towards eliminating, controlling or alleviating symptoms and restore the damage or establish the normal function of tissues and organs [3].

Expanding the scope of regenerative medicine, researchers have also developed and applied regenerative procedures in oral soft and hard tissues [4].

Tooth Regeneration

A tooth is a complex dynamic biological organ which consists of multiple tissues including the enamel, dentin, cementum and pulp. Tooth loss is the most common organ failure. The only vascularized tissue of the tooth is the dental pulp that is encased in the mineralized dentin. Tooth regeneration represents a revolution in stomatology as a shift in the paradigm from repair to regeneration: repair is replacement by artificial materials whereas regeneration is by biological restoration. Tooth regeneration is an extension of the concepts in the broad field of regenerative medicine to restore a tissue defect to its original form and function by biological substitutes.

Current research efforts in whole tooth tissue engineering are focused on three areas [5]:

1. Molecular profiling of epithelial and mesenchymal PNDSC to define the genes whose coordinated expression confers on these cells the ability to adopt dental cell differentiation fates;
2. Defining methods of manipulating PNDSC via cell-cell and cell scaffold interactions to generate bioengineered tooth tissues of predetermined size and shape that exhibit similar physical and mechanical properties to those exhibited by naturally formed dental tissues; and
3. Promoting the formation of bioengineered tooth root structures, including cementum, periodontal ligament, and alveolar bone. Progress in each of these areas that will facilitate whole tooth tissue engineering efforts is described briefly.

Regeneration of teeth can be broadly divided into several areas as listed below. It is divided into following areas [6]:

- Regeneration or de novo formation of the entire, anatomically correct teeth.
- Regeneration of dental pulp.
- Regeneration of dentin based on biological approaches and potentially as biological fillers that may replace current synthetic materials for restorative dentistry.
- Regeneration of cementum as a part of periodontium regeneration or for loss of cementum and/or dentin resulting from trauma or orthodontic tooth movement.
- Regeneration of the periodontium including cementum, periodontal ligament and alveolar bone.
- Regeneration or synthesis of enamel-like structures that may be used as biological substitute for lost enamel.

Since a tooth is a biological organ, it is unavoidable that regeneration of various components of the tooth is highly inter-connected. Furthermore, successful regeneration of tooth components does not necessarily translate to regeneration of an entire tooth.

Two major cell types are involved in dental hard tissue formation: the mesenchyme-originated odontoblasts that are responsible for the production of dentin and the epithelium-derived ameloblasts that form the enamel. Odontoblasts are columnar post-mitotic cells that form a layer in contact with the dentin which is also responsible for dentin formation. Odontoblastic processes are formed at their distal part, penetrate the dentin and participate in the secretion of dentin matrix and minerals. The matrix is composed majority of collagen (90%) and non-collagenous proteins such as Dentin Sialophosphoprotein (DSPP) and Dentin Matrix Protein 1 (DMP-1). The deposition of apatite minerals on this matrix gives rise to the mature calcified dentin [5,7-10].

Making entire teeth with enamel and dentin structures *in vivo* is a reality and not a utopia. However, these bioengineered teeth have been produced in ectopic sites and are still missing some essential elements such as the complete root and periodontal tissues that allow correct anchoring into the alveolar bone [11]. Nakao., *et al.* (2007) proposed a mechanism for growing teeth in the mouse mandible [12]. In this study, epithelial and mesenchymal cells were sequentially seeded into a collagen gel drop and then implanted into the tooth cavity of adult mice. With this technique all dental structures such as odontoblasts, ameloblasts, dental pulp, blood vessels, crown, periodontal ligament, root and alveolar bone was observed. They concluded that, the implantation of tooth germs in the mandible allowed their development, maturation and eruption indicating that stem cells could be used in the future for the replacement of missing teeth in humans [13,14].

Recently, the therapeutically viable approaches for tooth regeneration by contrasting cell transplantation and cell homing approaches. Tooth regeneration by cell transplantation is a meritorious approach. However, there are hurdles in the translation of cell-delivery-based tooth regeneration into therapeutics. The most important one of these difficulties is inaccessibility of autologous embryonic tooth germ cells for human applications. Xenogenic embryonic tooth germ cells (from non-human species) may elicit immunorejection and tooth dysmorphogenesis [15]. Autologous postnatal tooth germ cells (e.g. third molars) or autologous dental pulp stem cells are of limited availability and remain uncertain as a cell source to regenerated an entire tooth. Regardless of cell source, cell- delivery approaches for tooth regeneration, similar to cell-based therapies for other tissues, encounter translational barriers [5,16].

Tooth regeneration by cell transplantation

Tooth bud cells and bone marrow osteoprogenitor cells in collagen, PLGA or silk-protein scaffolds induced putative tooth-like tissues, alveolar bone and periodontal ligament. Embryonic oral epithelium and adult mesenchyme together upregulate odontogenesis genes upon mutual induction, and yielded dental structures upon transplantation into adult renal capsules or jaw bone [17].

Autologous embryonic tooth germ cells are inaccessible for human applications. Xenogenic embryonic tooth germ cells (from non- human species) may elicit immunorejection and tooth dysmorphogenesis. According to Yildirim Sibel., *et al.* autologous postnatal tooth germ cells (e.g. third molars) or autologous dental pulp stem cells are of limited availability. Regardless of cell source, cell delivery for tooth regeneration, similar to cell-based therapies for other tissues, encounters translational barriers. Similar to tooth regeneration, existing effort in dental pulp regeneration has focused on cell transplantation. Several reports have documented regeneration of dental pulp-like tissue *in vitro* or ectopically by transplantation of dental pulp stem cells. Deciduous and adult dental pulp stem cells seeded in a self-assembling peptide-amphiphile hydrogel showed distinctive behavior: greater proliferative rate for deciduous cells but greater osteogenic differentiation potential for adult cells. Delivery of collagen scaffolds with dental pulp stem cells and dentin matrix protein-1 in dentin slices in mice led to ectopic formation of pulp-like tissue. Pulpectomy, the most common endodontic treatment, involves extirpation of dental pulp, and therefore leaves no dental pulp stem cells in the same tooth for pulp regeneration. For a patient who requires endodontic treatment in a given tooth but has intact dentition otherwise, no healthy tooth is to be sacrificed for isolation of dental pulp stem cells. Even in patients whose autologous dental pulp stem cells can be harvested, e.g. from extracted wisdom teeth, clinical therapy of dental pulp regeneration is difficult to develop due to excessive costs including cell isolation, handling, storage, and shipping, ex vivo manipulation, immune rejection (for allogeneic cells), not to mention liabilities of potential contamination, pathogen transmission and tumorigenesis that may be associated with cell transplantation. Two-dimensional CT or MR images can be reconstructed to yield high resolution 3D shape and dimensions of the patient's tooth to be extracted. The fabricated 3D tooth scaffold can be sterilized and shipped to the clinic within 2 - 3 days. Upon tooth extraction, the dentist implants the biomaterial tooth scaffold. In our report, a bio-root was regenerated within 2 months. The advantage of this approach is that no stem cells need to be harvested or ex vivo manipulated [5].

Tooth regeneration by cell homing

As an initial attempt to regenerate teeth, anatomically shaped and dimensioned scaffold from biomaterials is fabricated, using our previously reported approach. In a study conducted by Dissanayaka, Waruna Lakmal., *et al*. scaffolds with the shape of the human mandibular first molar were fabricated via 3D layer-by-layer apposition. The composite consisted of 80% (m/m) polycaprolactone (PCL) and 20% (m/m) of hydroxyapatite (HA) (Sigma, St. Louis, MO). PCL-HA was co-molten at 120°C and dispensed through a 27-gauge metal nozzle to create repeating 3D microstrands (200 μm wall thickness) and interconnecting microchannels (diameter- 200 μm). All scaffolds were then sterilized in ethylene oxide for 24h. A blended cocktail of stromal derived factor 1 (SDF1) (100 $ng \cdot mL^{-1}$) and bone morphogenetic protein 7 (BMP7) (100 $ng \cdot mL^{-1}$) was adsorbed in 2 mg·mL-1 neutralized type collagen solution (all from R and D, Minneapolis, MN). SDF1 was selected for its effects to bind to CXCR4 receptors of multiple cell lineages including mesenchymal stem/progenitor cells. BMP7

was selected for its effects on dental pulp cells, fibroblasts and osteoblasts in SDF1- and BMP7-loaded collagen solution was infused in scaffold's microchannels by micropippeting, and cross linked at 37 for 1h. Control scaffolds were infused with the same collagen gel but without growth factor delivery. Recently it was studied that alginate scaffold can also be used for tooth regeneration.

The anatomy of bioengineered tooth crowns closely resembles that of naturally formed tooth crowns, bioengineered tooth root structures are relatively undeveloped [18]. The presence of Hertwig's epithelial root sheath structures in bioengineered teeth, rudimentary tooth root structures that precede the formation of mineralized tooth root tissues, suggests that tooth root development is initiated but does not continue to develop into functional tooth roots containing cementum, periodontal ligament, and alveolar bone, as found in naturally formed teeth. There are several plausible explanations as to why functional tooth roots have not developed in the bioengineered tooth tissues analyzed to date. One is that the bioengineered dental implants were not allowed to develop for long enough. It is possible that if the implants were allowed to grow for longer periods of time, more developed tooth root tissues would form [5].

Using successful techniques of bioengineering neonatal intestine and stomach, immature tooth bud tissue enriched in dental progenitor cells were studied by Yelick Pamela C and Joseph P Vacanti, to seed biodegradable scaffolds that then were implanted in a host animal to provide sufficient revascularization of bioengineered tissues [15,19-21]. When the implants were harvested and analyzed after 25 to 30 weeks of growth, in many instances, the dissociated tooth bud cells had reorganized into what appeared to be small, anatomically correct tooth crowns with rudimentary tooth root structures. Molecular and cellular analyses of bioengineered tooth tissues generated from pig and rat tooth bud cells demonstrated that developing bioengineered tooth crowns express the same genes and proteins found in naturally formed teeth. The demonstration that a tissue engineering approach could be used to regenerate dental tissues is promising, suggesting that clinically relevant therapies based on this approach could be used to repair or regenerate dental tissues and whole teeth. The current task is how to perfect tooth tissue engineering techniques, such that bioengineered dental tissues and whole teeth are integrated physically and functionally with pre-existing dental tissues. Ideally, bioengineered dentin and enamel used to repair defects in pre-existing teeth can be integrated seamlessly with pre-existing naturally formed dentin and enamel crystals, eliminating the presence of interface sites susceptible to refracturing. Bioengineered whole teeth would be modelled to occlude with opposing and adjacent teeth properly and anchored to underlying alveolar bone via periodontal ligament tissue to transmit mechanical signals properly, allowing for orthodontic treatments as required. Biologic tooth substitutes would exhibit proper proprioception, facilitating the life of the implant and adjacent and opposing teeth [15].

Tooth loss or absence is a common and frequent situation that can result from numerous pathologies such as periodontal and carious diseases, fractures, injuries or even genetic alterations. In most cases this loss is not critical, but for aesthetical, psychological and medical reasons (e.g. genetic aberrations) replacement of the missing teeth is important. Recent efforts made in the field of biomaterials have led to the development of dental implants composed of biocompatible materials such as titanium that can be inserted in the maxillary and/or mandibular bone to replace the missing teeth. However, implants are still not completely satisfactory and their successful use greatly depends on their osteointegration. The quantity and quality of the bone, as well as its interaction with the surface of the implant are some crucial parameters that can influence the achievement of the operation. Although innovative materials and techniques (e.g. surface treatment) have been used for the improvement of implant osteointegration, the metal/bone interface does not ensure complete integration of the implant, thus reducing its performance and long-term stability [5,15].

Conclusion

With the advancement of the tissue engineering field, its introduction in the field of dentistry can look forward to the development of the oral tissues and regeneration of whole tooth. Tooth regeneration can change the entire outlook of dental treatments which can lead to new innovations in this era of dentistry. Current regenerative technology has progressed remarkably, and many patients can be benefitted by the contributions of the tooth regenerative therapy for dental disorders. In the dental field, recent studies of stem-cell biology have led to the identification of candidate cell sources based on tooth organogenesis for tooth tissue regeneration and tooth replacement therapy.

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