Regenerative Endodontic by Application Tissue Engineering for Dental Pulp Regeneration

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Abstract: ***The tooth is composed of distinct tissues including the outer mineralized enamel layer, the adjacent mineralized dentin layer, the dental pulp is composed of dental mesenchymal cells, nerves, blood vessels, and that has a vulnerable to infection and limited regeneration capacity. Entire pulp amputation followed by filling with an artificial material, cause non vital dental pulp and weakened tooth. Tissue engineering technology refers to combining biological approaches to regenerative medicine with engineering and materials science that has demonstrated promising result using stem cells associated with scaffold and morphogenic factors can use to regenerate pulp tissue.***

Keywords: regenerative endodontic, dental pulp, tissue engineering, pulp regeneration, stem cell

1. Introduction

The tooth is an organ, which is as important as other skeletal tissues such as, bone and cartilage. A tooth is a complex structure built by cells originated from both ectoderm and mesoderm, can form enamel, dentin, and pulp. Dental pulp is a soft connective tissue and its main functions are to produce dentin, and maintain the biological and physiological vitality of the dentin.[1,2]

Dental pulp is infiltrated by a network of blood vessels and nerve bundles emanating from the apical region. Damage to the dental pulp by mechanical, chemical, thermal, and microbial irritants activate various type inflammatory responses involving complex vascular, lymphatic, and local tissue reaction. The pulp reparative competence is observed when superficial carious lesions stimulate odontoblasts cell to increase their secretory activity. Nevertheless, when teeth suffer injuries, such as trauma, deep cavity preparation or severe caries lesion the odontoblasts may succumb, possibly leading the dental pulp to irreversible pulpitis or necrosis.[1,3]

Clinically, when pulp is diagnosed with irreversible pulpitis, in other words, no treatment can reverse the situation regardless of the amount of remaining normal pulp tissue, the entire pulp is amputated by pulpectomy. Partially removing the infected pulp, a procedure termed partial pulpectomy, has been proven to be ineffective as infection may still be left behind. The pulp space is then disinfected and replaced with a rubber-like material, such as guttapercha. Although the success rate of endodontic treatment is relatively high (78–98%), there are many problems associated with pulpless teeth have no sensation to irritations and lose a significant amount of tooth structure. Generally, conventional endodontic therapy is indicated in such situation and causes loss of a significant amount of dentin leaving as life-lasting sequelae a non-vital and weakened tooth. Regenerated pulp tissue should be functionally competent, for example, capable of forming dentin to repair lost structure.[1,3]

In order to avoid such problems and aiming at maintaining the tooth vital, new treatment strategies have been developed, based on tissue engineering principles. One novel approach to restore tooth structure is based on biology: regenerative endodontic procedures by application of tissue engineering. Tissue engineering is an emerging interdisciplinary science of design which aims at developing strategies for regeneration of damage organ and tissues, based on principles of engineering and life science and manufacture of new tissues to replace lost parts because of diseases. Tissue engineering is the field of functional restoration of tissue structure and physiology for impaired or damaged tissues because of cancer, diseases, and trauma.[3-5]

The field of science is grounded in the interplay of three essential components: scaffolds, responsive cell, and morphogens. Responsive cell are generally stem cells, scaffolds may serve as a 3-D framework for cells serving as an extracellular matrix for a finite period of time, and morphogens are proteins that induce cell signaling, influencing critical functions like cell division, matrix synthesis, and proliferation.[3,4]

2. Dental Pulp

Teeth are highly mineralized organs resulting from sequential and reciprocal interactions between the oral epithelium and the underlying cranial neural crest-derived mesenchyme. 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 incased in the mineralized dentin.[6,7]

Dental pulp, which is surrounded by three mineralized tissues (dentin, enamel, and cementum), consists of loosely connective tissue, pulp cells, odontoblasts, endothelial cells, mesenchymal cells, neural fibres, immune system cells, blood vessels, lymphatics, and the extracellular matrix. Dental pulp plays key roles in maintaining the function of healthy teeth and its main functions are to produce dentin and maintain the biological and physiological vitality of the dentin. Via the apical foramen of tooth, blood vessels supply nutrients to the tooth and remove waste products, and neural network warns for harmful stimuli as pain. Immune system cells including dendritic cells, macrophages, and T-lymphocytes, prevent entry of microorganisms and other foreign antigens. Pulp cells and odontoblasts repair dentin that has been lost due to tooth wear or dental caries, by depositing tertiary dentin on the pulp chamber surface as a protective physical barrier in order to block exogenous stimuli.[8-12]

Blood vessels and nerve bundles enter the dental pulp through the apical foramen and provide nutrition and a responsive sensory nervous system, react to infection, and form reactionary dentin, thus maintaining pulp homeostasis. The dental pulp has several vital functions such as protection from infections by immunological surveillance, rapid reparative dentin formation to guard against noxious external stimuli, and maintenance of tensile strength to prevent tooth fractures.[4,9,13]

The dental pulp is also able to reinitiate dentinogenesis to protect itself from external injury and insult. The pulp-healing processes are complex and dependent on the extent of injury, among many other factors. With mild injury, healing involves a simple up-regulation of dentinogenic events by existing primary odontoblasts (reactionary dentinogenesis). However, with greater tissue injury, more complex defense and healing responses occur, with recruitment of stem/progenitor cells, their differentiation to odontoblast-like cells, and subsequent up-regulation of secretory activity. Many of the molecular and cellular processes involved in this healing events.[14]

3. Dental Pulp Regeneration

It is generally accepted that dental pulp plays important roles in maintaining tooth. When damage to dental pulp is reversible, pulp wound healing can proceed, whereas irreversible damage induces pathological changes in dental pulp, eventually requiring its removal. Development of regeneration therapy for the dentin-pulp complex is important to overcome limitations with presently available therapies.[11,15]

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.[6]

Vascularization and innervation are the other two characteristics of the pulp. The regenerated blood vessels should have a connection with periapical or bone marrow tissues around the teeth, which could receive a regular blood flow from circulation and supply nutrient to the regenerated tissue and dentin. More importantly, the regenerated tissue should be innervated, so that the teeth are be able to sense hot/cold stimulation and pain during infection. Pulp tissue regeneration may present an ideal alternative treatment to traditional root canal therapy. The present concept of pulp tissue regeneration includes two possible approaches. The first is revascularization; where a new pulp tissue is expected to grow into the root canals from the remaining tissues exist apically in the root canal. The second includes the replacement of the diseased pulp with a healthy tissue that is able to revitalize the tooth and restore dentin formation process.[13,16]

Over the past century, endodontic therapy has shown a high rate of success in retention of teeth; however, this is not always possible. Many teeth remain unrestorable due to several reasons, and vital pulp therapy procedures are not always predictable, often resulting in the need for eventual endodontic therapy. Although the endodontic therapy is effective in combating infection and have clinical success rates can exceed 90%, it does not restore lost dental pulp tissue and the vitality of the tooth, and instead are extracted.
Regenerative endodontic methods have the potential for regenerating both pulp and dentine tissues and therefore may offer an alternative method to save teeth that may have compromised structural integrity.[10,17]

In view of the increasing demand for maintaining pulp vitality and the high cost of endodontic treatments being performed every day, there has been increasing interest in investigating new methods for tissue replacement. Tissue engineering involves the development of functional tissue with the ability to replace missing or damaged tissue. This may be achieved either by transplanting cells seeded into a porous material or scaffold having open pores or by relying on ingrowth of cells into such a material, which in both cases develops into normal Tissue.[17,18]

Regenerated pulp tissue in a tooth should be:[19]

1. Vascularized
   Vascularization may be difficult for teeth that the apical canal opening for blood vessel entrance is small (< 1mm). The size of apical opening would affect the ingrowth of blood vessels into the engineered pulp tissue. The larger the opening, the more likely the angiogenesis can occur.
2. Containing similar cell density and architecture of the extracellular matrix to those of natural pulp.
   As along as good blood supply can be achieved, optimal cell density and the laid down of good quality extracellular matrix should occur. New odontoblast like cells will form against the existing dentinal wall that has been chemically disinfected as evidenced by our recent report.

3. Capable of giving rise to new odontoblasts lining against the existing dentin surface and produce new dentin.
4. Innervated
   With respect to innervation, it is likely that regenerated pulp contains ingrown nerve fibers from and adjacent natural tissues.

4. Tissue Engineering

The regeneration of the pulp-dentin complex has been a great challenge to both scientists and clinicians. To restore the damaged tissue or organs, it is critical to understand the developmental process behind the tissue engineering and regenerative medicine.[20,21]

Tissue engineering is a multidisciplinary approach and merging the principles of engineering and bioscience aiming to develop biological substances for the restoration, conservation and/or improvement of the tissue function to regenerate functional tooth-tissue structure based on the interplay of three basic key elements: stem cells, morphogens and scaffolds. Various approaches have been considered in tissue engineering and regenerative medicine, but currently the most common is to use a biodegradable scaffold in the shape of the new tissue that is seeded with either stem cells.[22,23]

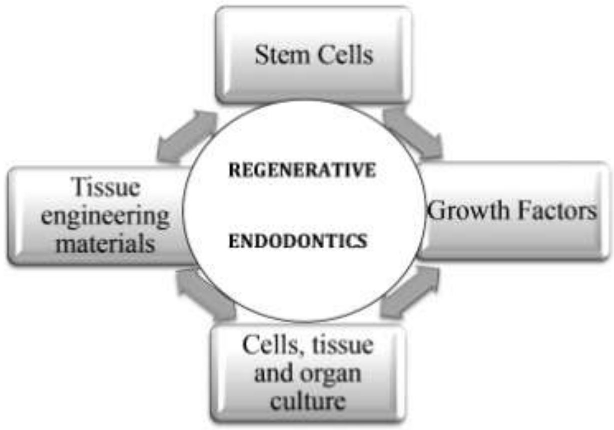

Figure 1: Regenerative Endodontics[5]

The applications are based on the ability of the cells to proliferate and differentiate as well as on the construction of structures through cell and bio scaffold interactions. Traditionally, three elements, namely (i) stem cells, (ii) scaffolds, and (iii) signaling molecules (e.g., growth factors), were used to achieve pulp regeneration. In the process of pulp regeneration, stem cells were first isolated and manipulated *in vitro*. Then, the cells were loaded onto scaffolds incorporated with signaling molecules and transplanted into the root canal of *ex vivo* tooth slides or *in situ* canine tooth.[13,18]

Until now, both stem cell transplantation and cell homing strategies have been applied in pulp regeneration. In the strategy of cell transplantation, stem cells should first be isolated, expanded, seeded into the scaffold, and finally transplanted. Cell homing is aimed to achieve tissue repair/regeneration through recruiting of endogenous cells to injured tissue via signaling molecules. Compared with stem cell transplantation, cell homing strategies do not need to isolate and manipulate stem cells *in vitro*.[13]

The ultimate goal for tissue engineering and regenerative medicine is to develop therapies to restore lost, damaged, or aging tissues using engineered or regenerated products derived from either donor or autologous cells. The aim of regenerative medicine is to simulate natural processes *in vitro* in order to recreate a tissue or an organ. Pulp tissue regeneration may present an ideal alternative treatment.[8,16,22,23]

4.1 Stem Cell

Stem cells play essential roles in tissue engineering for organ development and tissue repair. Stem cells are unspecialized cells / undifferentiated cells, with the ability to divide and give rise to identical, capable of renewing themselves, and under certain physiologic or experimental conditions, they can be addressed to more specialized committed lineages.[8,20,23]

Under specific condition, they can differentiate to various cell types that comprise the human body. Therefore, the stem cells are capable of developing to mature cells, with distinctive figures and specific functions, such as neural and muscle cells.

According to their potency, stem cells are classified into totipotent (generate all differentiated cells in an organism e.g., fertilised egg), pluripotent (form the three germ layers; ectoderm, endoderm and mesoderm e.g., embryonic stem cells), multipotent (differentiate into several cell lines but with more restricted number of phenotypes e.g., mesenchymal stem cells), oligopotent (differentiate into a few cell types e.g., myeloid stem cells) and unipotent cells (i.e., differentiate into one cell type e.g., skin stem cells).[18,24] According to their origin, stem cells are divided in two groups:[8,20,22,18,24]

1) Embryonic stem cells (ES)
Embrionic Stem cells are derived from the inner cell mass of early embryos, called blastocysts. ES cells derived from the blastocyst have the ability to differentiate into multipotent stem / progenitor cells, including epithelial, mesenchymal, and other tissue specific.

There are four primary sources for embryonic stem cells:[5]
- Existing stem cell lines
- Aborted or miscarried embryos
- Unused In vitro fertilized embryos
- Cloned embryos

The sourcing of embryonic stem cells is controversial and is surrounded by ethical and legal issues, which reduces the attractiveness of these cells for developing new therapies. Embrionic stem cells are capable of dividing and renewing themselves for long periods without differentiating, whereas most somatic or adult stem cells cannot.[5,22]

2) Adult stem cells (AS)
Adult stem cell are derived from adult tissue, some multipotent AS cells however remain in the developed tissue and have the ability to regenerate and/or repair injuries, for example mesenchymal stem cells (MSCs) derived from bone marrow, dental pulp, adipose tissue, dermis and umbilical cord. Oral stem cells mainly include dental pulp stem cells (DPSCs), stem cells from exfoliated deciduous teeth (SHED), stemcells from apical papilla (SCAP), periodontal ligament stem cells (PDLSCs), mesenchymal stemcells from gingiva (GMSCs), and progenitor cells from oral mucosal lamina propria (OMLP-PCs).

The mesenchymal stem cells are multipotent cells that can proliferate and differentiate into a range of cell types comprising various tissues, such as osteoblasts, neuroblasts, cartilage, endothelial, muscle and adipose cells.

Due to their properties, stem cells have the potency to become an important tool of tissue engineering and regenerative medicine. Stem cells are often categorized according to their source as:[5,18]

1) Autologus postnatal stem cells
   The most practical clinical application of a stem cell therapy would be to use a patient's own donor cells. These cells are obtained from the same individual to whom they will be implanted.
2) Allogenic postnatal stem cells
   These cells are obtained from the donor of same species.
3) Xenogenic cells
   These are isolated from individuals of another species.

Table 1: Type of stem cell[25]

Stem Cell Type	*Cell Plasticity*	*Source of Stem Cell*
Totipotent	Each cell can develop in to a new individual	Cells from early (1 -3 days) embryos
Pluripotent	Cells can form any (over 200) cell types	Some cell of blastocyst (5-14days)
Multipotent	Cells differentiated, but can form a number of other tissue	Fetal tissue, cord blood and post natal stem cell including dental pulp stem cell

4.2 Scaffold for Tissue Regeneration

To create a more practical endodontic tissue engineering therapy, stem cells must be organized into three dimensional structures that can support cell organization and vascularization. The scaffold provides a three-dimensional environment for cells to attach and grow, therefore mimicking the in vivo condition. Additionally, these synthetic matrices can be fabricated such that it may form any desired shape and carry needed growth factors to guide the process of cell differentiation and tissue formation.[5,19]

Scaffolds are an innovative approach in bioengineering technology, with their main objective being to form a three-dimensional housing in a measured morphology for the desired cells to be seeded. It is important to select appropriate scaffolds for successful tissue regeneration. It is well known that essential properties of scaffolds are mechanical properties such as porous three dimension structure, and mechanical strength, as well as biological properties such as biocompatibility and biodegradation.[15,23]
The role of a scaffold is to provide support for delivering cells and/or growth factors to the proposed site of tissue regeneration, provide an environment that allows the implanted cells to proliferate, differentiate, and form the desired tissue or organ. The porous material to serve as the matrix to facilitate the regeneration must have certain pore characteristics, chemical compositions, and mechanical properties. In tissue engineering, the selection of a suitable scaffold is critical. Scaffolds can be identified as biocompatible structures that support cells growth and provide a suitable environment for tissue formation.[5,16,22]

Toward these goals, there are important features to consider in scaffold selection, including the physical and mechanical aspects of the material, its biocompatibility, and its degradation timeline. These physical aspects of a 3D scaffold include the porosity (pore volume fraction of the scaffold), pore size (pore diameter), pore structure (shape), and all aspects that can influence how well the cells adhere to the material. Good scaffolds should allow cell attachment, proliferation, migration, differentiation, and provide mechanical support for the extracellular matrix generation. Ideally, scaffolds must be biodegradable as a native tissue and should degrade in a controlled manner which is consistent with the formation of the new tissue.[16,22]

In regenerative therapy, scaffolds were used clinically and showed a capability to generate tissues with analogous cellular formation. The scaffold materials can be classified as:[5,16,23]
1) Biodegradable or Permanent
2) Natural or Synthetic (artificial)

Natural
Natural scaffolds are usually more biocompatible and have the advantages of providing specific cell interactions. However, they have the shortcomings of difficulty in obtaining in large amounts, the large batch to batch variations, limited design ability and the lack of good mechanical properties. In contrast, synthetic-derived scaffolds have good reproducible mechanical properties and controlled degradation time, but they lack the presence of cellular signals required for tissue engineering.

Natural scaffold derivatives of the extracellular matrix, protein materials such as collagen or fibrin, and polysaccharide materials, like chitosan or glycosaminoglycan (GAGS).

The biological properties of natural extracellular matrix (ECM) actively contribute in regeneration processes of damaged tissues. This makes ECM attractive as scaffolds for tissue engineering. Some examples of natural ECM scaffolds are Fibrin, collagen, hyaluronic acid (HYA) sponge, amniotic membrane (AM), and many types of polysaccharides.

Synthetic

Synthetic biodegradable polymers, such as polyglycolic acid (PGA), polylactic acid (PLA) and poly-lactic-coglycolide, have been initially approved by the Food and Drug Administration (FDA) as drug delivery systems. Their biocompatibility and a broad range of reproducibility make them attractive for tissue engineering studies. Polymers scaffold shape, porosity, mechanical properties, pores diameter, and degradation time can be successfully controlled in the preparation techniques.

Table 2: Possible scaffolds for dental pulp regeneration[16,23]

Classification	*Scaffold*
Synthetic polymers	PGA PLA PLLA PLGA OPLA PGA/PLLA
Bioactive ceramics	HA β-TCP BCP
Bioactive Glass	Silicate bioactive glass Borate and borosilicate glass
Naturally derived scaff old	Fibrin Collagen HYA sponge Amniotic membrane Polysaccharides (chitin, chitosan, cellulose, alginate, agar, pectins, dextran and glycosaminoglycans)

Sacffold/ matrix can play several roles during the process of regeneration in vivo:[5]

1) It can structurally reinforce the detective site so as to maintain the shape of the defect and prevent distortion of surrounding tissue.
2) The matrix can serve as a barrier to the in growth of surrounding tissue that may impede the process of regeneration. The concept of guided tissue regeneration is based in part on the prevention of overlying gingival tissue from collapsing into the periodontal defect.
3) The matrix can serve as a scaffold for migration and proliferation of cells in vivo or for cells seeded in vitro.
4) The matrix can serve as an insoluble regulator of cell function through interaction, with certain integrins and other cell receptors.

To achieve the goal of pulp tissue reconstruction, scaffolds must meet some requirements:[5]

1) Biodegradability is essential, since scaffolds need to be absorbed by the surrounding tissues without the necessity of surgical removal.
2) A high porosity and an adequate pore size are necessary to facilitate cell seeding and diffusion throughout the whole structure of both cells and nutrients.
3) The rate at which the degradation occurs has to coincide as much as possible with the rate of tissue formation; this means while the cells are fabricating their own natural matrix structure around themselves, the scaffold is able to provide structural integrity within the body, and it will eventually break down, leaving the newly- formed tissue that will take over the mechanical load.

4.3 Morphogen

It is well known that growth factors, stem cells, and scaffolds, are essential for tissue engineering to regenerate tissues. During regeneration processes, stem cells differentiate into specific cells for tissue defects, growth factors induce proliferation and differentiation of stem cells, and scaffolds with properties of extracellular matrix temporally support structures for cell growth, differentiation, and tissue formation.[1,11]

Growth factor are proteins that bind to receptors on the cell surface and induce cellular proliferation or differentiation. Many growth factor are quite versatile, stimulating cellular division in numerous cell types, while others are more cell specific. Growth factor are extracellularly secreted signals governing morphogenesis or organogenesis. They regulate the division or specialization of stem cells to the desirable cell type and mediated key cellular event in tissue regeneration including cell proliferation, chemotaxis, differentiation, and matrix synthesis. [25-27]

A variety of growth factors have successfully been used for dentin-pulp complex regeneration, including Transforming Growth Factors (TGFs), Bone Morphogenic Proteins (BMPs), Platelet Derived Growth Factor (PDGF), Insulin Like Growth Factor (IGF), Fibroblast Growth Factors (FGFs). Therapeutic intervention with recombinant growth factors also provides possibilities for control of cell activity during repair. Harnessing both endogenous and exogenous sources of growth factors can provide exciting opportunities for novel biological approaches to dental tissue repair and the blueprint for the regeneration of the tooth. These approaches offer significant potential for improved clinical management of dental disease and maintenance of tooth vitality.[5,26]

5. Conclusion

Pulp regeneration will be used as the basis for tissue engineering to radically alter restorative dentistry and the prognosis of restored teeth. One novel approach to restore tooth structure is based on biology: regenerative endodontic procedures by application of tissue engineering. Pulp tissue regeneration may present an ideal alternative treatment.

Tissue engineering is a multidisciplinary approach and merging the principles of engineering and bioscience aiming to develop biological substances for the restoration, conservation and/or improvement of the tissue function to regenerate functional tooth-tissue structure based on the interplay of three basic key elements: stem cells, morphogens and scaffolds. The ultimate goal for tissue engineering and regenerative medicine is to develop therapies to restore lost, damaged, or aging tissues using engineered or regenerated products.

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