

Regenerative Endodontics

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ABSTRACT

Most of the teeth are saved each year by root canal therapy. Although current treatment options offer high levels of success for many conditions, an appropriate form of therapy might consist of regenerative approaches in which diseased or necrotic pulp tissues are removed and replaced with healthy pulp to revitalize teeth. Researchers are working for this objective. Regenerative endodontics is the formation and delivery of tissues to replace diseased, missing, and traumatized pulp. Regenerative endodontics provides direction of converting the nonvital tooth into vital once again. It focuses on replacing traumatized and pathological pulp with functional pulp tissue. Current regenerative methods successfully produce root development but still not able to reestablish real pulp tissue and give unpredictable results. There are several limitations that need to be addressed to improve the quality and efficiency of the treatment. The present review gives required details of regenerative endodontics and its objectives.

Keywords: Gene, Regenerative, Revascularization, Scaffolds, Stem cell.

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INTRODUCTION

A tooth is a biological organ which consists of multiple tissues including the enamel, dentin, cementum, and

pulp, encased in a biological socket constitute the periodontium, which includes the periodontal ligament (PDL), bone, and gingiva which continues as the oral mucous membrane. Dental caries is one of the most common problems in humans, second only to common cold and tooth loss is the most common human organ failure, affecting a vast majority of the population. Conventional dental treatment options range from simple restorations of decayed teeth, tooth devitalization and root canal treatment, extractions, and replacement by an implant supported prosthesis. Dental implants, despite being the treatment in vogue for a lost tooth, might not perform similar to a natural tooth would in relation to its surrounding tissues and its function. The treatment concepts that were once thought to be imaginative are today considered achievable. One of such success is regenerative therapy. Regenerative therapy provides many clinical dental benefits, including biological strategies to repair teeth and regrow lost teeth. Current concepts of regeneration of dental tissues can revolutionize the dental health provision. Research on large scale is being done worldwide to explore different aspects and feasibility of the regenerative therapy. Yildirim S et al regenerated a functional bioroot structure for artificial crown restoration by using allogeneic dental stem cells and Vc-induced cell sheet.¹ Researchers have done successfully functioning tooth in a mouse achieved through the transplantation of bioengineered tooth germ into the alveolar bone.² The ability of stem cells in the mouth of American alligators to regenerate teeth in humans is also under research.³ Presently, two methods exist in regenerative endodontics to treat nonvital infected teeth, first is the active pursuit of pulp dentin regeneration to implant or regrow pulp (tissue engineering technology), and second method in which new living tissue is expected to form from the tissue present in the teeth, allowing continued root development (revascularization).

Tissue engineering is an important aspect of regenerative endodontics.² The three important component for tissue engineering are: Stem cells to respond to growth factors, scaffold of extracellular matrix (ECM), and growth factors (signals for morphogenesis).

STEM CELLS/PROGENITOR CELLS

Stem cell biology has become an important component for the understanding of tissue regeneration, although much knowledge in this area has been from the *in vitro*

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studies. A stem cell is defined as a cell that has the ability to continuously divide and produce progeny cells that develop into various other types of cells or tissues.⁴ The stem cells are defined by having two major features, cells which are capable of self-renewal and when cells divide, some daughter cells give rise to cells that further become differentiated cells. Depending on the type of stem cells and their ability to become different tissues, the following categories of stem cells have been prepared:

- *Totipotent stem cells*: Each cell has the power of developing into an entire organism.
- *Pluripotent stem cells*: Cells from embryonic stem cells that when grown in the correct environment *in vivo* are capable of forming all types of tissues.
- *Multipotent stem cells*: Postnatal stem cells or commonly called adult stem cells that are capable of forming multiple lineages of cells. Dental stem cells come under this category.

SCAFFOLDS OR EXTRACELLULAR MATRIX

Stem cells must be maintained into a three-dimensional structure that can help cell organization and vascularization to form a better practical tissue engineering therapy. This can be done using a scaffold seeded with stem cells. A scaffold should have growth factors to aid stem cell proliferation and differentiation, leading to improved and faster tissue development. The scaffold may exert essential mechanical and biological functions needed by replacement tissue to achieve the goal of pulp tissue reconstruction. Different types of scaffold materials available are natural or synthetic and biodegradable or permanent.

Biological Requirements of a Scaffold

For better tissue development, a scaffold should have growth factors to help stem cell proliferation and differentiation.⁵ A scaffold should be more effective for transport of nutrients, oxygen, and waste. A high porosity and an adequate pore size are necessary to help cell seeding and diffusion throughout the whole structure of both cells and nutrients. The scaffold should be able to give structural integrity within the body and it should eventually break down, leaving the newly formed tissue that will take over the mechanical load. The rate at which degradation occurs has to match as much as possible with the rate of tissue formation.

MORPHOGENS (SIGNALING MOLECULES)/GROWTH FACTORS

Growth factors are biological modulators that are able to help cell proliferation and differentiation.⁵ Growth factors are ECM molecules, which are involved in signaling and

regulating dentogenic process during tooth development. Application of these exogenous signaling factors has been recommended for regenerative therapies whereas a number of challenges in the methods of delivery should be addressed before they are to be used in regular clinical practice. Britto LR et al pioneered the use of human cloned bioactive osteogenic protein-1 with a carrier matrix of purified bovine type I collagen powder, moistened with sterile saline, for starting reparative dentin formation in monkeys.⁶ Some of the naturally occurring and commercially available osteogenically active growth factors are named as: Bone morphogenic/morphogenetic protein, platelet-derived growth factor, insulin-like growth factor, fibroblast growth factor, transforming growth factor-beta, dentin sialoprotein, dentin phosphoprotein, and enamel matrix derivative.

GENE THERAPY

Genes can initiate a natural biological process by expressing a molecule involved in regenerative response for the tissue of interest.⁷ Accurate delivery and efficient transfer of genes into target tissue cells, prompt assessment of gene expression at required times and appropriate levels, and/or minimization of undesirable systemic toxicity are important prerequisites for successful gene therapy. Either viral or nonviral vectors are used to promote the cellular uptake and expression of genes. Viral vectors are genetically changed to eliminate their disease causing ability. The viruses can replicate genes of interest together with their own genome, through the use of host cell genetic process. Ultrasound mediated gene delivery is successful both *in vivo* and *in vitro* but electroporation method is successful only *in vitro*. This may be because of the deficiency of erythrocytes in the plasma clot due to thermal changes during electroporation *in vivo*. In the *in vivo* method, the gene is delivered systematically into the bloodstream or locally to target tissues by injection or inhalation. In this method, the healing potential of pulp tissue is increased by genes inducing dentin directly applied on the exposed amputated dental pulp. The *ex vivo* method involves genetic manipulation of cells, which are then transplanted to the regeneration site. The *ex vivo* gene therapy stimulates reparative dentin formation rapidly in comparison to *in vivo* gene therapy.⁸ From these available data, there are certain challenges to the gene therapy: Need for formation of isolation, identification, and expansion protocol of pulp stem cells. Appropriate and efficient gene delivery system needs to be optimized. Potential health hazards exist with the use of gene therapy. These arise from the use of the gene transfer system, rather than the genes expressed.⁹

REVASCULARIZATION

Basically, body tissue consists of two components: Cells and the surrounding environment. Revascularization approach in young permanent infected teeth with immature root apex and apical periodontitis was first initiated in 1971,¹⁰ however, it was not successful due to drawbacks in technologies, material, and instruments available in those times. However, with the currently available technologies, several case reports^{11,12} have shown revascularization of necrotic root canal systems by disinfection followed by establishing bleeding into the canal system via over instrumentation. The revascularization method assumes that the root canal space has been disinfected and that the formation of blood clot forms a matrix (e.g., fibrin) that traps cells capable of initiating new tissue formation. It is different from apexification because not only the apex is closed, however, the canal walls are thicker also. It is also different from apexogenesis which also completes successfully a closed apex and thicker dentinal walls, but by the use of remaining vital root pulp. All the studies show continued thickening of the dentinal walls and subsequent apical closure. The root length is increased by the growth of the cementum. Connective tissue similar to PDL was also seen in the canal space.¹³ The success of root canal revascularization is due to the following facts: First, the immature avulsed tooth has an open apex, short root, and intact but necrotic pulp tissue. Hence, the new tissue has easy access to the root canal system and a relatively short distance for proliferation to reach the coronal pulp horn. The ischemically necrotic pulp works as a scaffold into which the new tissue grows. Thus, the competition between proliferation of new tissue and infection of the pulp space favors the new tissue. Second, minimum instrumentation preserves viable pulp tissue which helps in further development of open apex root. Third, young patients have more healing capacity and greater stem cell regenerative potential.

CONCLUSION

Regenerative endodontic strategies have the power to save lots of teeth which have compromised structural integrity. Each of the regenerative techniques has advantages and disadvantages, and a few of the techniques

are hypothetical, or at an early stage of development. As regenerative endodontics has unique direction, the success of the field depends on the final introduction of such therapies into clinical practice at large. In future, we can observe which of the multiple approaches in regenerative endodontics will withstand the test of clinical usage.

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