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REVIEW ARTICLE

# Gene Therapy in Periodontal Tissue Engineering

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## ABSTRACT

An elaborate system of signaling molecules regulates the cellular and molecular events of periodontal healing, the primary strategy for which is functional periodontal compartment regeneration and replication of components of the natural cellular microenvironment by providing an artificial extracellular matrix and by delivering growth factors. A new, so-called gene delivery method works by converting cells into protein- producing factories, thereby bypassing the dilemma. Gene therapy can channel the cellular signals in a controlled and very systematic manner, to provide encoded proteins at every stage of tissue regeneration. The aim of this review is to highlight the applications of gene delivery and tissue engineering in periodontal regeneration.


**Keywords**: Gene therapy, Periodontal regeneration, Stem cells, Tissue engineering, Vectors.

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## INTRODUCTION

The cellular and molecular events of periodontal healing are coordinated and regulated by an elaborate system of signaling molecules, pointing to a primary strategy for functional periodontal compartment regeneration to replicate components of the natural cellular microenvironment by providing an artificial extracellular matrix and by delivering growth factors. However, the localized delivery of growth factors requires a large amount of protein to stimulate significant effects *in vivo*, even with optimal carriers. This increases the risk of side effects. This problem can be circumvented by use of gene delivery method, where therapeutic agents to be delivered are deoxyribonucleic acid (DNA) plasmids that include the gene-encoding desired growth factors instead of recombinant proteins. Gene therapy in periodontology is currently in its budding stages. A safe and effective delivery platform needs significant and serious efforts in order to clarify how gene delivery may mimic the critical aspects of natural biological processes occurring in periodontal development and repair.[1] Thus, a current challenge faced by clinicians is the complete regeneration of the periodontal tissues, paying way to novel treatments that utilize gene-based approaches. This current review enlightens the clinicians with the application of gene-based therapeutics in periodontal tissue regeneration.

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## PERIODONTAL TISSUE ENGINEERING

The goal of tissue engineering lies in regenerating the functional tissue that needs a series of key events occurring during periodontal tissue formation and growth, by means of delivering signaling molecules, cells, and scaffold/matrix to periodontal defects.[2-4]

### Protein-based Therapeutics

Biological mediators, such as partially purified protein mixture from developing teeth and growth factors from recombinant technology can be used to accelerate periodontal regeneration. However, there are major drawbacks, which are the short half-life and the instability of these proteins, resulting in multiple delivery dosages.[5] Limitations like limited control over dose administration, loss of bioactivity, non targeted delivery, and/or lack of availability have led to newer safe modes of periodontal regeneration through cell-based approach.

### Cell-based Therapeutics

Autologous cells appear to be the most appropriate source of cells for tissue engineering, whereas allogeneic and xenogeneic cells being heterogeneous are potent agents for immunogenic reactions when they are utilized for tissue engineering.[3]

Although six types of stem cells have been isolated in humans, they have been categorized mainly into embryonic stem (ES) cells and adult stem cells.[6]

### Embryonic Stem Cells

The ES cells have an advantage of having greater differentiation potential when compared with multipotent or unipotent cells. Alkaline phosphatase, stage-specific embryonic antigens 3 and 4, and proteins TRA-1-81 and TRA-1-60 are exhibited by the stem cells.[7]

### Adult Stem Cells

Tissues, such as skin, hematopoietic system, bone, and liver have the capacity to repair and renew, indicating

presence of stem or progenitor cells.[8] Adult stem cells appear more mature with a finite life span and only multipotent differentiation capacity when compared with ES cells.[9] Hematopoietic stem cells were the first adult stem cells that were isolated from bone marrow.[10] Apart from hematopoietic cells, adult non hematopoietic stem cells also reside in the bone marrow microenvironment.[11]

### Gene Delivery-based Therapeutics

Gene delivery-based therapeutics is based on transferring of genetic materials to alter specific genes in individual cells to produce a therapeutic effect.[12]

## VECTORS FOR GENE DELIVERY

Gene delivery vectors are divided into two groups: Viral and nonviral vectors.[13]

### Viral Vectors

- *Adenoviral vectors*: These possess a characteristic feature of (a) infecting a variety of cell types (b) being purified at high titers and (c) result in a high level of gene expression.[14] Disadvantages include the inability to express the gene for a long term and also result in inducing host immunogenic response.
- *Retroviral and lentiviral vectors*: These have the advantage over adenoviral vectors due to their low-grade immunogenicity and expressing genes for a long term.[15]
- *Adeno-associated viral (AAV) vectors*: Adeno-associated viral are known for their superior safety feature due to their nonimmunogenic nature and are thought to be useful in periodontal regeneration.[16] They express and deliver gene throughout life in both dividing and nondividing cells.

### Nonviral Vectors

These consist of naked DNA alone or in conjunction with a carrier. They are superior when compared with viral vectors due to their non immunogenicity, low toxicity, and less likely of being introduced into the host cell genome.[17]

## DELIVERY APPROACHES AND STRATEGIES

Different approaches and strategies for direct delivery of growth factors have been employed: Noncovalent immobilization; covalent immobilization; gene delivery approaches – *in vivo* approach: Manipulating the cells residing naturally within the individual's body; *ex vivo* approach: Manipulating the cells obtained from individual's body and subsequently returning it to the host.[5]

## TARGET GENES FOR PERIODONTAL TISSUE ENGINEERING

Transforming growth factor-beta (TGF-β) family members and bone morphogenetic proteins (BMPs) belong to the same peptide superfamily. The TGF-1 stimulates bone cell replication and apposition of bone matrix and activates proliferation in cementoblasts.[18] The BMP-3 and BMP-7 (i.e., osteogenic protein-1) play an important role in the assembly of periodontal ligament (PDL) and in cementogenesis.[19] The DNA synthesis and cell replication in osteoblasts is stimulated by platelet-derived growth factor (PDGF) [20] along with increases in the rate of bone matrix apposition and bone collagen synthesis.[21] Human PDL fibroblast proliferates in response to insulin-like growth factor-1 in a dose- and time-dependent manner [22] and along with PDGF-BB and TGF-β induce periodontal soft and hard tissues regeneration.[23]

### Sonic Hedgehog

The sonic hedgehog gene also encodes a regulator protein of embryonic osteogenesis and the repair of bone fractures, which may also have significant effects on periodontal bone regeneration and is found during embryogenesis.[4]

### Wingless

The role of wingless in homeostasis and regeneration of periodontal tissues remains largely unknown. Future studies are required to substantiate its role in periodontal regeneration.[12]

## GENE DELIVERY SYSTEMS/DEVICES

### Microparticulate Systems

The function of particulate systems was considered as a mode to protect DNA during tissue regeneration and provide adequate control over release rate. Hence, much attention has been focused on Food and Drug Administration-approved poly (lactic-co-glycolic acid) (PLGA), for the encapsulation of genes.[24] Other materials used are natural chitosan[25] and gelatin.[26]

### Polymeric Hydrogel Systems

Commonly used hydrogels are poly (ethylene glycol), polylactic acid (PLA), polyglycolic acid, PLGA, and copolymers poly (epsilon-caprolactone)–poly (ethylene oxide)–poly (epsilon-caprolactone).[27]

### Implantable Scaffolds

Currently used scaffolds include (i) porous collagen/chitosan scaffold, (ii) gelatin sponge system, (iii) biodegradable PLA barrier device (Atrisorb), (iv) space-providing

macroporous expanded polytetrafluoroethylene device, and (v) hydroxyapatite-based biomimetic matrix.[28]

### Gene Delivery for Host Modulation of Periodontal Disease

Gene therapy using AAV to deliver the tumor necrosis factor receptor-immunoglobulin Fc (TNFR: Fc) fusion gene to experimental *Porphyromonas gingivalis*–lipopolysaccharide-mediated bone loss resulted in sustained therapeutic levels of serum TNFR protein for ≥3 months, and inhibition of *P. gingivalis*–lipopolysaccharide-mediated bone loss.

## CONCLUSION

Genetically modified cell therapy is considered to be the recent advance in periodontal regeneration. Moving from tissue repair to regeneration is a dream that requires extensive interdisciplinary collaborative approaches.

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