

REVIEW ARTICLE

Gene Therapy as a Management Tool in Dentistry

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ABSTRACT

Introduction: Gene therapy is an emerging field of biomedicine that has gained significant attention in dentistry too. Various research programs are being carried out to understand the cellular and molecular bases of every disease. Since most of the conventional therapeutic approaches are not so satisfactory in treating a disease completely, currently there is an increasing focus on gene therapy to treat a wide variety of inherited and acquired diseases. This new era of gene therapy can be accomplished in the medicine field primarily to replace or cure defective genes and treat a wide variety of gene disorders, whether the disease is due to single or multiple defective genes. It has a variety of applications in the field of dentistry like salivary gland disorders, autoimmune conditions, potentially malignant disorders, etc. The sites, such as minor salivary glands present in the labial and buccal mucosa and also mucosal keratinocytes are potential targets for gene therapy, since these structures are superficial and offer minimal hindrance to the gene therapy procedure. The present article discusses the basic principles of gene therapy, its applications in the field of dentistry, limitations, and disadvantages.

Keywords: Bone morphogenetic proteins, Deoxyribonucleic acid, Disease, Genes, Vector, Virus.

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INTRODUCTION

Researchers in medicine and dentistry are trying to eradicate diseases by changing the genes that are responsible for it. The process wherein the defective gene is cured or replaced by a new gene is known as gene therapy. Joshua Lederberg and Edward Tatum were the first persons who laid out the fundamental tenets for gene therapy.¹ Nowadays, it has been made possible to manipulate genes easily by incorporating the procedural advances in the field of molecular biological technology, such as

recombinant deoxyribonucleic acid (DNA) technology. A gene is defined as a smaller linear sequence of DNA that codes for a particular protein.² Genes are mainly the smallest functional units present on the DNA of the genetic system of the body that controls the function, growth, and development of an organism. The DNA of all the organisms possesses genes that are made of four bases: Adenine, guanine, cytosine, and thymine,³ whereas proteins are the large molecules as compared with genes, which perform various essential functions in the body. Genes basically perform two functions, i.e., determining the structure of the thousands of different proteins that are present in the human body and controlling where, when, and in what quantity each protein is made.⁴ Gene-related disorders are due to defective genes, where encoded proteins are unable to perform their function. The procedure of gene therapy is based upon the principle that an abnormal and defective piece of a gene can be replaced and repaired by means of curing the defective gene or incorporating a new gene. This procedure is called reverse mutation. The procedure uses a purified preparation of either a fraction or whole new gene in order to cure a disease. The procedure of gene therapy began in the 1980s with researchers trying gene therapy in bacteria. In humans, the first attempt to replace a defective gene was performed in 1990 for treating severe combined immunodeficiency.² However, the procedure was unsuccessful. Nowadays, management of various genetic diseases like diabetes mellitus, blood-related disorders, cystic fibrosis, cancer, heart diseases, autoimmune disorders, such as multiple sclerosis, etc., can be readily attempted by gene therapy.⁵ Gene therapy in recent days has several applications in dentistry, which includes bone repair, treatment of salivary gland diseases, autoimmune conditions, potentially malignant disorders, pain management, DNA vaccinations (periodontal diseases, caries), and autoimmune mucosal disorders.^{2,4,6}

According to the US Food and Drug administration, the basic principle of gene therapy is to replace a person's defective genes with new ones in order to cure a disease.⁷ The new gene inserted will modify the clinical course of the disease.

The procedure involved in gene therapy includes the following:

- Locating the gene of interest,

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- Acquiring a normal copy of gene (therapeutic gene) by restrictive endonuclease enzyme (cutting and splicing), and
- Finally cloning of therapeutic gene into a vector, which is a vehicle to deliver the gene of interest.²

Before insertion of a new gene, its safety and efficacy to potentially replace the defective gene are to be tested.⁵ There are several methods to either cure or replace a defective gene that includes³

- Defective gene regulation (the defective gene is partially turned off, so that it is not able to perform its functions)
- Defective gene is replaced by a normal gene through homologous recombination
- Insertion of a homologous normal gene into a non-specific location within the genome
- Reverse mutation is the correction of an abnormal gene through selective addition and subtraction of homologous base pairs, which restores the normal function of a gene.

GENERAL PRINCIPLES OF GENE TRANSFER

The concept of gene therapy involves the introduction of exogenous genes into somatic cells that form the organs of the body to produce a desired therapeutic effect.

- The first step in the gene transfer procedure involves enzyme restriction endonucleases, which are used to selectively cleave a DNA fragment. For transfer of genetic material into the desired cells, a vector or vehicle is necessary. The vector is first isolated in its pure form and cleaved to allow insertion of the DNA fragment. At each cleaved ends of the vector, attachment with desired DNA fragments is being carried out to effectively close the molecule. This addition of vector with DNA fragments constitutes DNA chimera, which is based on recombinant DNA technology.
- The second step involves introduction of the vector into the desired cells, either intravenously or injected directly into a specific tissue in the body, which is later taken by the specific cells resulting in the production of a line of genetically homologous cells containing the DNA sequence introduced by the vector. The technique will result in production of clusters of cells with a specifically designed genetic make-up as necessary.^{1,3,4} Alternatively, if the patient's somatic cells have been removed from the body, they can be exposed to the vector in the laboratory. The cells with the desired vectors with attached DNA fragments are reintroduced into the patient-specific tissue. Vector mediates the delivery of restored gene into the patient's target cells. The genes will result in the formation of functional proteins which, in turn, carry out cellular functions effectively.^{3,4}

Requirements for Vector

- It should not be identified by immune system.
- It should be stable and easy to reproduce.
- It should have longevity of expression.
- It should have high efficiency (100% cells transfected).
- It should have high specificity and low toxicity.
- It should be able to protect and deliver DNA across the cell membrane into the nucleus.
- It should be able to transfer gene into the specific cells.
- It should be inexpensive.

However, no single vector type fulfills the above requirements. Hence, several vectors may be required for different clinical applications.

Types of Vector for Gene Therapy

Vectors used for gene therapy may be classified as either viral or nonviral. The most commonly used viruses as vectors are adenovirus, retro virus, and herpes simplex virus (HSV). Among these, adenovirus is commonly used, since the virus is cultured easily and has lower pathogenicity.² These viruses are attenuated to transfect genes, but they cannot replicate inside the cells and, hence, do not cause infection in the cells.⁷ This process of gene transfer mediated by viral vectors is called transduction.⁸

Adeno-associated virus (AAV) is a small virus incorporating only about half the amount of foreign DNA when compared with other viruses. This virus vector can readily transfer the functional gene at a specific site of chromosome 19.⁹ However, the major disadvantage of this vector is that it leads to the activation of recipient's immune pathways (innate and humoral) when applied *in vivo*.¹⁰

Retroviruses vector are able to infect only dividing cells. These vectors will lead to stable function as they transfer the foreign DNA into the host cell chromosomes permanently, thus leading to stable expression of germ cell lines. However, the genetic mutation may arise, if the transfer of genetic material is not controlled. These vectors require mitotic cell for transduction.¹¹ The HSV double-stranded viruses infect particular cells, such as neurons.^{9,12}

Nonviral vectors can further be classified into physical and chemical vectors. The transfer of genetic material by nonviral vectors is called as transfection.⁸ Physical vectors include electrophoration, microinjection, and use of ballistic particle.⁶ Chemical vectors include calcium particles, lipids, and protein complexes.

Electrophoration: In this method, the DNA is transferred into the desired cells through pores created by the passage of electric current.

Microinjection: In this method, DNA is introduced in a single cell.

Use of ballistic particles: Tungsten or gold particles are used over which the plasmid DNA is coated. The particles are then transferred into the tissue by means of an accelerated force generated by high-voltage electronic spark or helium discharge.

Calcium vectors: The ultra-low sized, highly mono-dispersed DNA-doped calcium phosphate nanoparticles protect from the external DNase environment and can be used safely to transfer the encapsulated DNA under *in vitro* and *in vivo* conditions.

Lipid vectors: In this type, a combination of plasmid DNA and liposome (an artificial lipid sphere with aqueous core) is inserted into the specific cell types, which later fuses with the cell membrane and results in availability of plasmid DNA into the cytoplasm.^{1,2}

Protein complex: The protein molecules in the form of cell surface receptors that are presents on the cell surface can act as DNA attachment site. Thus, attachment of the DNA ligands to these receptors will transfer DNA ligands into the cells.⁴

Nonviral vectors possess certain advantages, such as simple methods of DNA inoculation, large-scale production of vectors, and low host immunogenicity.

Disadvantages of nonviral vectors: The procedure can be used only with certain tissues and requires huge amount of DNA.³

Apart from viral vectors, stem cells may also be used in gene transfer. They are manipulated in the laboratory to possess the capability of accepting new genes, resulting in their functional change. Later, they are introduced into the desired tissues.^{4,5}

Types of Gene Therapy

- *Germ line gene therapy:* In this therapy, repair or replacement of defective gene is being carried out in germ cells. Modified gene would be transferred to next generations. Hence, cell change is permanent.
- *Somatic gene therapy:* Repair or replace defective gene in somatic cells. The change acquired is not permanent (limited to individual).

Types of Delivery

In vivo: Delivery of gene takes place in the body. During *in vivo* gene transfer, the foreign gene is injected into the patient by viral and nonviral methods.

Ex vivo: Delivery takes place outside the body and the cells are placed back in to the body. *Ex vivo* gene transfer involves a foreign gene inserted into the tissue cells cultivated in laboratory outside the body, and then the resulting genetically modified cells are transplanted back into the patient.

Requirement of Successful Gene Therapy

- Gene therapy should be able to transfer gene at the exact site of chromosomes of cells.
- Transferred gene should be active for desired duration as in case of an individual and be passed onto the next generations as in the cases of genetic diseases.
- There should be minimum side effects, which can be managed.
- Gene transfer at exact sites will result in exploring the genetic nature of the condition.
- Difficulties in gene therapy include⁹
- Procedural difficulty in transferring genes in sites like lung cells.
- The transferred genes may interfere with the functioning of other normal genes.
- Since there is a requirement of viruses as vectors, they may be recognized as pathogens by body's cells resulting in toxicity and exaggerated immune response.
- Adverse reactions are commonly encountered during gene therapy that requires viral vectors ranging from severe inflammatory processes and coagulopathies.^{10,13,14}
- Since multigene disorders require repair of different genes, they are generally difficult to manage by gene therapy.
- Gene therapy is expensive.

Applications in Dentistry

- *Bone repair:* Bone loss caused by trauma, neoplasia, reconstructive surgery, congenital defects, or periodontal disease is a major worldwide health problem. Therefore, successful repair and regeneration of the bone structures, such as alveolar bone, bone in temporomandibular area, and other joints will produce promising results in management of craniofacial conditions.^{15,16} Bone morphogenetic proteins (BMPs) play an important role during active bone formation in embryogenesis, growth of bony structures, and probably healing of fractured bone. Among these, BMPs 2, 4, and 7 can induce *de novo* bone formation both *in vitro* and at heterotopic sites. In the field of dentistry, these unique properties of BMPs are utilized in the reconstruction of lost bone by the methods transferring genes encoding BMPs.¹⁷ These BMPs are usually transferred to the action sites using adenovirus as vectors.^{2,5} In one study, *in vivo* transfer of mesenchymal stem cells expressing BMP-2 results in osteogenesis.⁶ Michigan research group has found nonosteogenic fibroblasts (gingiva, dental pulp) express BMP-7 gene after being infected with an adenoviral vector. The BMPs are agents well established in induction of both orthotopic and ectopic

bone formation. In addition to this, periodontal cells secrete transferring platelet-derived growth factor (PDGF) which, in turn, plays an important role in DNA synthesis. Therefore, delivery of PDGF by gene transfer stimulates gingival fibroblast, which lays down collagen and osteoblasts (new alveolar bone formation and regeneration of bone around implants).¹⁸

This is based on periodontal therapy.

Bone sialoprotein (BSP) is a major noncollagenous protein in bone and other mineralized tissues. The transfer of BSP gene by gene therapy procedures to an osseous defect is known to regenerate alveolar bone.⁴ Various studies have shown the positive role of BSP gene in regenerating alveolar bone around teeth and implant-supported prosthesis.¹⁸

Ex vivo Gene Transfer for Bone Repair: The advantage of an *ex vivo* gene transfer approach is that specific cells like bone marrow cells or stem cells can be selected as the cellular delivery vehicle for specific clinical problems. In *ex vivo* gene transfer, patient's stem cells are extracted from the tissue. The gene transfer procedures are carried out in laboratory settings and extracted cells are reimplanted into their respective anatomic site. The cells that have received the most interest as a cellular delivery vehicle are mesenchymal stem cells, muscle-derived stem cells, adipose-derived stem cells, buffy coat cells from bone marrow or blood, and skin fibroblast.^{4,6}

- *Pain management:* Eliminating pain is a major part of dental practice. The pain pathways have been successfully manipulated with gene therapy in order to alleviate pain symptoms, particularly in pain that occurs in superficial structures. Gene transfer may be particularly useful for managing chronic pain. Several studies in animal models have shown that viral-mediated transfer of genes encoding opiate peptides to peripheral and central neurons can lead to antinociceptive effects. Pain management using gene therapy utilizes the continuous release of short-lived bioactive peptides around dorsal horn of spinal cord, which modifies pain pathways. Intrathecal injection of vectors derived from adenovirus, AAV or lipid-encapsulated plasmids coding interleukin-10, transducing neurons of the dorsal root ganglia by injection of HSV-based vectors into the skin, and injecting vector virus carrying the gene for an endogenous opioid have been tried to control chronic pain arising in the oral structures and temporomandibular joints.
- *DNA vaccination:* Scientists have tried to use classical vaccination technology to eradicate dental caries or periodontal diseases, thus far achieving mixed success. Various researches have been carried out to modify immune responses to a particular antigen by administration of plasmid DNA encoding the antigen.

The DNA vaccines have also been tried in the field of dentistry, particularly for preventing periodontal conditions and dental caries. The gene therapy utilizes injection of plasmid DNA as vector encoding the antigen, such as *Porphyromonas gingivalis* into the salivary gland tissue, leading to the production of specific salivary immunoglobulin (Ig)A, IgG, and antigen-specific cytotoxic T lymphocytes providing resistance against future antigenic exposure and dental caries. There is inhibition in plaque formation as *P. gingivalis* will no longer be available for attachment with biofilm on tooth surfaces. In another study, the gene therapy utilizing plasmid pCIA-P vector encoding pac gene of *S. mutans* showed resistance to caries in rats by targeted salivary gland immunization.^{4,6}

- *Keratinocyte:* The cells presents in the skin and oral mucosa are the keratinocytes. These cells are vulnerable to many gene disorders, such as autoimmune conditions. These cells are easily accessible and can be monitored easily. The use of skin keratinocytes is particularly important during burns in skin and oral mucosa, wherein the lost keratinocytes can be replaced by gene therapy. This procedure can also be applied during skin graft procedures. The replaced keratinocytes later exhibit normal epithelial morphology and function. Various researches have demonstrated the ability of human keratinocytes to synthesize and secrete biologically active recombinant proteins, such as growth hormone, apolipoprotein E, and the coagulation factor IX. Gene therapy can be used to treat keratinocyte disorders and dermatologic disorders like ichthyosis and epidermolysis bullosa.^{2,4,6}
- *Salivary glands:* The main function of salivary glands is to produce saliva and large amounts of enzymes and proteins performing various functions in the oral cavity. The procedure where entry into the salivary gland is made through its duct system is called intraductal cannulation. In this procedure, the main duct is cannulated and the site is used for gene transfers through vectors by a retrograde injection. Aim is to provide gene therapy to patients suffering from irreversible salivary gland dysfunction resulting from either irradiation for head and neck cancers or Sjögren's syndrome by augmenting salivary secretions. This is facilitated by transferring genes that encode secretory proteins into salivary glands. The proteins are subsequently secreted in an exocrine manner. This site can also be used for gene therapy for systemic autoimmune disorders, such as Sjögren's and Mikulicz syndrome.^{2,4,6} A study showed that gene therapy using interleukin-27 ameliorates Sjögren's syndrome-like autoimmune exocrinopathy.¹⁹

- *Oral cancer*: Oral cancer can occur on exposure to a wide variety of bacterial and chemical agents. The general principle in cancer treatment is the exposure of cancer cells to a modified gene product resulting in cancer cell death. It can be achieved by^{1,2,20}
- Gene addition therapy
- Gene excision therapy
- Downregulation of the gene expression that stimulates tumor growth
- Immunotherapy, i.e., enhancement of body's natural immunity to fight antigens
- Suicide gene therapy, i.e., introduction of genes that exert the chemotherapeutic effect of the drugs used in chemotherapy only to the cancer cells and offers maximum protection to normal cells.
- Introduction of genes to inhibit tumor angiogenesis
- Cancer vaccination

The basic aim in gene therapy of cancer is introduction of new genes in the cancerous cells either to replace mutated genes or causing killing of cancerous cells without any toxicity to surrounding normal cells. However, there is possibility of exaggerated immune response on exposure to viral antigens when used as a vector. Adeno-associated viruses have been successfully used for a longer time as a vector for gene therapy in head and neck cancers. These viral vectors are less immunogenic than other viral vectors. Mutations in p53 tumor suppressor gene occur in over 50% of human cancers. Therefore, replacement of a mutated p53 gene with a wild-type (normal) p53 gene can be successfully applied as a potential treatment approach in head and neck cancers. Another tumor suppressor gene that could be replaced in head and neck cancer therapy is p16, since in squamous cell carcinoma of head and neck region, 80 to 90% of cases show p16 inactivation, which is believed to be the first steps in head and neck cancer carcinogenesis. Therefore, replacement of lost p16 gene may produce promising results. The p27 is another gene concerned with the inactivation of cell cycle of tumor cells, inducing apoptosis, and, hence, suppression of tumor growth occurs.²⁰

Another treatment modality that can be applied in cancer treatment is gene-directed enzyme-prodrug therapy in which a recombinant viral vector is generated, which encodes a harmless prodrug-activating enzyme, such as nitroreductase, thymidine kinase, or cytosine deaminase and is injected into the desired site. When the molecule reaches its desired site, the enzyme causes conversion of prodrug into a highly toxic cytotoxic drug. One example is thymidine kinase gene of HSV transforms ganciclovir into ganciclovir phosphate. The activated drug is able to leech out of the virus-11 infected cells to kill surrounding noninfected cells, creating a bystander effect in cancer resulting in oncolysis.

The NF- κ B activity suppression through gene therapy. NF- κ B molecules are thought to be associated with the progression and metastasis of various cancers, including oral squamous cell carcinoma. Therefore, its inhibition may be a useful adjuvant treatment in oral cancer therapy.²⁰ Various studies are being carried out to demonstrate the role of multiple genes to target complex multiple pathways in carcinogenesis.²¹

Orthodontic Tooth Movement: Tooth movement occurs due to the remodeling of PDL and alveolar bone occurring in response to orthodontic force. Gene therapy with osteoprotegerin (OPG) and RANKL has been used to inhibit and accelerate orthodontic tooth movement in a rat model. According to one study, local OPG gene transfer inhibited tooth movement by about 50% after 21 days of forced application,⁶ whereas local RANKL gene transfer to the periodontal tissue accelerated orthodontic tooth movement by approximately 150% after 21 days, without any systemic effects. Therefore, the selective gene transfer in orthodontic treatment can be applied to reduce the duration of the treatment.

Role of Dentists in Gene Therapy

A main advantage for dentists in gene therapy studies is the readily accessible oral tissues. The application of gene transfer is not only limited to oral structures, but can readily be modified by the course of many systemic conditions. There is a promising future of the oral physicians in the field of gene therapy. Dentists with necessary experience in gene therapy could routinely be called as "gene therapists." Since oral cavity is easily accessible, structures like salivary glands and oral keratinocytes are excellent target sites for gene transfer as in cases of autoimmune disorders and salivary gland dysfunction. In addition, gene therapy in cancers has shown excellent results. Therefore, dental surgeons can be the best-fitting professionals to administer gene therapy in the oral cavity, which bears minor salivary glands and keratinocytes, as well as extension of the procedures into the field of orthodontics, oral surgery, and oncology.

CONCLUSION AND FUTURE PROSPECTIVE

Gene therapy essentially consists of introducing specific genetic material into target cells without producing toxic effects to the surrounding tissue. However, there is a lack of an efficient nontoxic gene delivery system, which remains a major hindrance to the successful gene transfer to the desired site. Gene therapy possesses excellent potential in the treatment of various dental diseases including head and neck cancers. Since the beginning of dentistry, rapid advances have been done in therapeutic approaches for diseases. But still there

are many nonlife-threatening conditions, for which there are no effective treatments. The future of gene therapy is promising and excellent. The scope of gene therapy has been extended to reduce the mortality and morbidity rates associated with conventional therapeutic approaches.

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