Applications of Gene Therapy in Dentistry: A Review Article

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Abstract

Gene therapy promises to possess a good prospect in bridging the gap between dental applications and medicine. The dynamic therapeutic modalities of gene therapy have been advancing rapidly. Conventional approaches are being revamped to be more comprehensive and pre-emptive, which could do away with the need for surgery and medicine altogether. The complementary base sequences known as genes convey the instructions required to manufacture proteins. The oral cavity is one of the most accessible locations for the therapeutic intervention of gene therapy for several oral tissues. In 1990, the first significant trial of gene therapy was overseen to alleviate adenosine deaminase deficiency. The notion of genetic engineering has become increasingly appealing as a reflection of its benefits over conventional treatment modalities. An example of how this technology may alter dentistry is the implementation of gene therapy for dental and oral ailments. The objective of this article is to examine the effects of gene therapy on the field of dentistry, periodontology and implantology. Furthermore, the therapeutic factors of disease therapy, minimal invasion, and appropriate outcome have indeed been taken into consideration.

Keywords
- gene therapy
- applications
- dentistry
- periodontology
- recent advances

Introduction

The future of gene therapy seems optimistic for bridging the gap between the realms of clinical dentistry and medicine. The goal of gene therapy is to generate functioning proteins by replacing the aberrant genes with their suitable analogs. Data suggest that underlying illnesses including malignancies, viral diseases, genetic abnormalities, and autoimmune disorders can be treated with gene therapy to prevent, mitigate, or perhaps cure them.[1] Researchers are striving to eradicate ailments at their very roots in research institutions all around the world. They are attempting to alter the genes that cause diseases rather than seeking for medications to treat ailments. Gene therapy is the approach used to do this. New gene-transfer technologies, methods, approaches, and perspectives have emerged over time. The term "gene therapy," that was initially used to refer to "genetic replacement treatment" in the early 1980s, has now outgrown its intended definition and is now used to allude to any process that involves some sort of gene transfer.[2] Furthermore, the heterogeneous origins of periodontal disease encompass microbial challenge and diverse host immune responses that are determined by genetic and environmental determinants.[3–5] In the first two steps in the process of gene therapy, human genetic code for the therapeutic is usually an attenuated carrier or vector, the protein is first cleaved and then put into its genome. The second stage involves introducing the modified vector to the intended human cells, which release the DNA sequence that is incorporated into a chromosome. The cells

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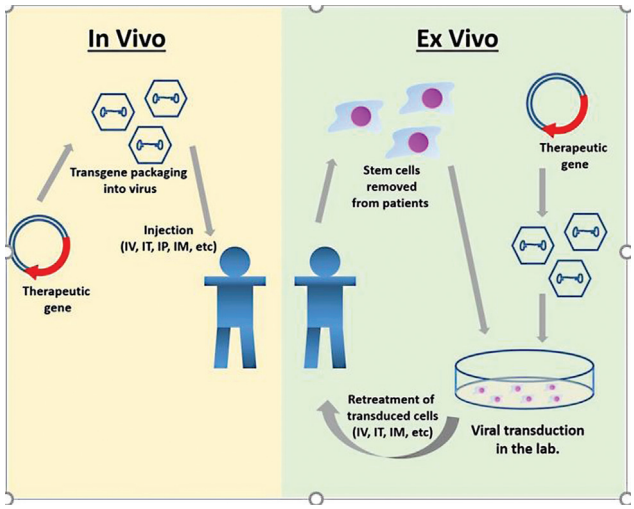

Fig. 1 In vivo and ex vivo gene transfer.

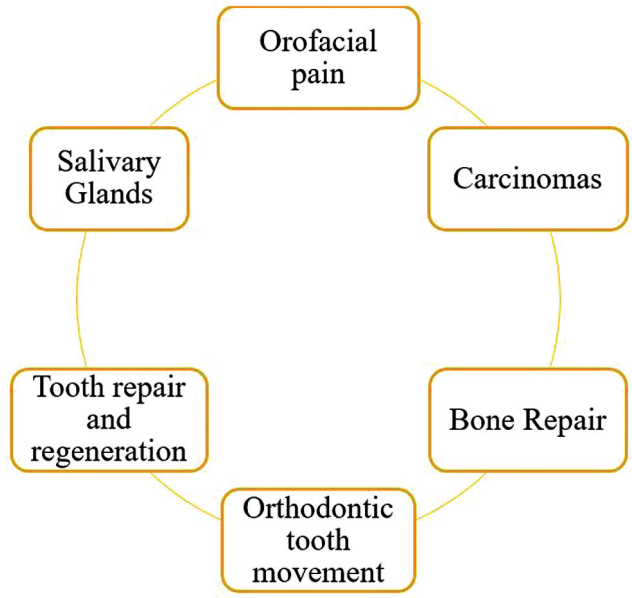

Fig. 2 Applications of gene therapy in dentistry.

with the new genetic design eventually produce the requisite therapeutic proteins as soon as the gene is "switched on" at the appropriate region.[1,6,7] Somatic and germ line gene therapies are the two principal phases of gene therapy, respectively.[8] Depending on the vector's delivery method, gene transfer can be achieved by either of two methods: ex vivo gene transfer, which involves injecting the genetically engineered vector into cultured tissue cells prior to actually transferring the altered tissues into the body, or in vivo gene transfer, which involves directly injecting genetically engineered vectors into the patient[7,9] (►**Fig. 1**).

Applications in Dentistry

The significant development has been made innumerable applications of gene therapy in dentistry.[10] This is shown in ►**Fig. 2**.

Salivary Glands

A major salivary gland's primary excretory ducts are retroductally cannulated as part of a gene therapy for salivary glands. This may lead to the synthesis of a protein that is therapeutic for cells[11,12] or can cause secretions to enter the circulation or saliva.[13,14] A wide range of genes, including those producing hormones,[15,16] an antibacterial agent,[17] membrane proteins,[18,19] transcription factors,[20] protease inhibitors,[21] a protein-regulating apoptosis,[22] and numerous nonmammal "reporter proteins," are applied for salivary glands.[23–25]

Sjogren's syndrome (SS) is an autoimmune disorder. It is basically characterized by dry eyes and dry mouth. The syndrome frequently coexist with other immune system disorder including lupus and rheumatoid arthritis. Given this circumstance, a broad paradigm for creating innovative protein and more recently gene-based treatments for several autoimmune illnesses, including SS, has evolved. This method that we employ, which involves a biological component that boosts Th2 activities and inhibits Th1 cells, is probably effective for treatment.[26] Interleukin-10 or vasoactive intestinal peptide, for example, are forms of anti-inflammatory cytokines whose transfer might result in a reduction in the production of proinflammatory cytokines, protecting salivary glycoproteins (SGs) and maintaining their secretory function.[27]

Bone Repair

Bones have a good potential for regeneration and healing and can be amended, in contrast to other dental hard tissues (such enamel and dentin).[28,29] Ex vivo techniques have been employed in dentistry to transfer the genes that code for bone morphogenetic proteins.[30,31] Bone morphogenetic proteins are recognized inducers of ectopic and orthotopic bone development. Bone fractures and traumas frequently heal without leaving scars. But bone healing and remodeling might be difficult in circumstances with pathological fractures or significant bone deformities.[32–35] The robust mitogen known as platelet-derived growth factor (PDGF) is yet another that is crucial for wound healing. The biological effects of PDGF are antiapoptotic in nature and affect cell migration, proliferation, and the production of extracellular matrix. The growth arrest gene halts its activity (gas gene). The development of the bioactive PDGF gene has enabled us to circumvent the growth arrest gene's inhibitory effects, which are crucial for wound healing.[36] In conjunction to the *CBFA1* gene, which is vital in cell differentiation and bone sialoprotein gene expression during bone repair and regeneration, the bone sialoprotein is a significant noncollagenous protein implicated in bone healing.[37]

Carcinomas

Cancers of the oral cavity, paranasal sinuses, larynx, pharynx, and head and neck skin are all covered by the category of squamous cell carcinoma of the head and neck (SCCHN). It is deemed to be the sixth most prevalent cancer in the world.[32] In preclinical and clinical trials for squamous cell carcinoma,

a unique gene therapy strategy that preferentially multiplies within tumor cells and lyses them has been thoroughly investigated. For the therapy of malignancies lacking p53 activity, ONYX-015 (d11520), an E1B 55kD gene-deleted adenovirus, has been created.[38] Patients with recurrent/refractory squamous cell carcinoma can safely administer ONYX-015 through intratumoral injection. However, when this particular type of gene therapy was administered alone, there was very limited evidence of antitumor efficacy.[39,40] There were significant objective responses, including a high percentage of complete responses, in a phase II study of intratumoral ONYX-015 injection with cisplatin and 5-fluorouracil in patients with recurrent SCCHN. In contrast to all noninjected tumors treated with chemotherapy alone, none of the responsive tumors had progressed by 6 months. Tumor-selective viral replication and necrosis induction were seen in tumor samples taken after therapy, but there was no obvious link between the presence of p53 mutations in the tumor and the clinical outcome.[41] These findings corroborate the paucity of a bystander interaction and illustrate the significance of creating systemic administration agents.

"Suicide" Gene Therapy

"Suicide" gene therapy entails inserting a gene that permits a prodrug to transform into an active cytotoxic drug into a cell. Herpes simplex virus thymidine kinase is the method that has been investigated the most (HSV-TK). This gene produces a viral enzyme that converts ganciclovir into a monophosphate form, which intracellular enzymes then further phosphorylate into an active triphosphate substance that stops DNA synthesis.[42]

Orofacial Pain

Orofacial discomfort is pain experienced in the face, head, and neck's soft and hard tissues region. Because of their intricacy and the unclear processes behind their etiology and pathogenesis, many orofacial pain syndromes, especially those that are chronic, may be particularly challenging to identify and treat.[43–48] They range from those with a clearly identifiable cause (such as trigeminal postherpetic neuralgia and posttraumatic trigeminal neuropathic pain) to those that may be idiopathic (such as burning mouth syndrome, persistent idiopathic facial pain, and persistent idiopathic dentoalveolar pain), as well as those that manifest as a symptom of a known chronic disorder or disease. Moreover, if the acute disease is not adequately treated in a timely and suitable manner, ~20% of acute pains might develop into a chronic pain state.[49–53] Analgesics[54–56] and sedatives[57] are typically used in pain treatment. Gene therapy is being researched to effectively facilitate chronic pain effectively by reducing the consumption of medications that pose the threat of systemic toxicity, opioid addiction, and other detrimental consequences.[58] At the moment, gene therapy is mostly used in animal models to treat pain. Recently, it was shown that expressing the human preproenkephalin gene via a herpes simplex vector reduced trigeminal pain in a mouse model.[59] In the future, enhanced vector gene systems may make gene therapy more effective in treating pain syndromes including trigeminal neuralgia and temporomandibular joint diseases.[60,61]

Tooth Repair and Regeneration

Known for decades as an organ with strong reparative and regeneration capabilities is the pulp. Dental pulp cells have the ability to terminally develop into cells that mimic odontoblasts to generate reparative dentine. The enhanced odontogenic differentiation capacity of pulp cells transfected with growth/differentiation factor 11 has been observed in tests of gene therapeutic approaches.[62] It has also been researched how to stimulate the differentiation of pulp cells into odontoblast-like cells using the synthetic glucocorticoid dexamethasone and growth factors (GFs) such as BMP2.[63,64] When given directly to the exposed tooth pulp during in vivo gene therapy, genes that stimulate dentine development improve the ability of tissues such as the dentine pulp complex to recuperate.[65] Dental pulp stem cells may also offer a novel alternative cell population for heart,[66] bone,[67,68] muscle,[69] brain,[70] and tooth repair and/or regeneration,[71–73] pertaining to in vivo empirical evidences in animals. Notably, a patient underwent the first clinical application for dental pulp stem cell-assisted alveolar bone restoration last year with success.[74]

Orthodontic Tooth Movement

Alveolar corticotomy surgery is an adjunctive treatment that can cut the length of orthodontic treatment in half.[75,76] Alternative treatments must be considered, nevertheless, because of the short-accelerated mobility time and the high morbidity rates associated with this type of surgery. Bone resorption and apposition are two biological processes that are intimately related to tooth movement (TM). The ratio of the receptor activator of nuclear factor-kB (RANKL) to the osteoprotegerin (OPG) is intimately related to the biomolecular pathways of osteoclast activation (OPG).[77] Corticotomy-assisted malocclusion treatment has been demonstrated empirically to reduce TM phases due to the enhanced pace of bone remodeling caused by the so-called regional acceleratory phenomenon.[78,79] Taking into account all the information, we hypothesize that sustained overexpression of RANKL will not only increase osteoclastogenesis and bone resorption and selectively activate osteoclast but will also cause tooth movement (TM) under force to accelerate over time rather than just at the start of therapy, in contrast to the corticotomy procedure. It was proposed that local RANKL gene transfer would be a helpful strategy for shifting ankylosed teeth as well as for shortening orthodontic therapy. Local OPG gene transfer, in contrast to RANKL, reduced tooth displacement after 21 days of force application by around 50%. As a result of shorter treatment times and better outcomes, orthodontic therapy will undergo a paradigm change.[80] Additionally, gene therapy has demonstrated potential outcomes in reducing orthodontic TM discomfort. Future gene therapy therapeutic solutions that may be administered to manage the discomfort associated with orthodontic TM may be developed as a consequence of more study.[56]

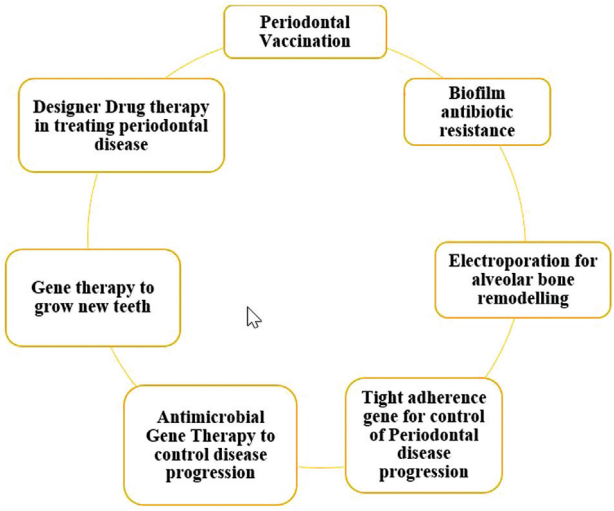

Fig. 3 Applications of gene therapy in Periodontics.

Applications of Gene Therapy in Periodontics ►Fig. 3

Periodontal Vaccination

When a mouse's salivary gland is subjected to plasmid DNA encoding the *Porphyromonas gingivalis* fimbrial gene, the salivary gland produces fimbrial protein locally in the salivary gland tissue that further leads to the production of specific serum and salivary immunoglobulin G (IgG) and immunoglobulin A antibodies. The *P. gingivalis* that was generated might be negated, prohibiting it from aiding to the growth of plaque (►**Fig. 3**).

Furthermore, investigators have discovered in rats that vaccination with genetically manipulated *Streptococcus gordonii* vectors expressing *P. gingivalis* is fimbrial antigen is effective at preventing *P. gingivalis*-associated periodontitis.[81]

Hemagglutinin, an integral to maintaining of P. gingivalis' lethality, has been detected, cloned, and amplified in *Escherichia coli*. In Fischer rats infected with *P. gingivalis*, the subcutaneous administration of recombinant hemagglutinin B (rHag B) culminated in serum IgG antibody and the synthesis of interleukin-2 (IL-2), IL-10, and IL-4, which offered protection against *P. gingivalis*-induced bone loss.[82]

Biofilm Antibiotic Resistance

According to research, bacteria which form biofilms are up to 1,000 times more resistant to antibiotics than their natural counterparts, making them challenging to regulate.

Recently, Mah et al revealed the *Pseudomonas* aeruginosa RA14 strain gene *ndvB*,[82] which expresses for the glycosyltransferase requisite for the biosynthesis of periplasmic glucans.

Electroporation for Alveolar Bone Remodeling

When confronted to elements involving mechanical strain and inflammation, periodontal tissue aggressively revamps by synthesizing a wide range of chemicals. Predictable alveolar redevelopment has really been demonstrated utilizing in vivo transfer of the *LacZ* gene (containing code for a multitude of remodeling molecules) into periodontal ligament (PDL) and leveraging plasmid DNA as a vector combined with transient transfection (electric impulse) to transfer the gene into cell.[83]

Tight Adherence Gene for Control of Periodontal Disease Progression

A significant first component in the establishment of localized aggressive periodontitis is the invasion of target tissue by a periodontal pathogen such as *Actinobacillus actinomycetemcomitans*. *Actinobacillus actinomycetemcomitans* has been revealed to require a "tight adherence" in to attach and be virulent. Researchers have isolated a mutant strain defective in the "tight adherence gene" that could really predictably influence the progression of periodontal disease by inhibiting *A. actinomycetemcomitans* recruitment and pathogenesis.[84]

Antimicrobial Gene Therapy to Control Disease Progression

Transfecting host cells with an antimicrobial peptide or protein-encoding gene is one technique for strengthening the host defense mechanism against infection.

So, according to the research, there was a robust antimicrobial activity that augmented host antimicrobial defenses when host cells were invaded in vivo with the defensin-2 (*HBD-2*) gene utilizing retroviral vector.[85]

F. Designer Drug therapy in treating periodontal disease[85]

If the genes required for normal development are determined, "designer therapeutic interventions" that tackle one or both components of the gene can be devised. As they would only alter the gene abnormality that has been clearly recognized via genetic research, these designer therapies would be safer than the pharmaceuticals we use today.

Gene Therapy to Grow New Teeth

Dental research is hoping to be able to fabricate teeth in a laboratory so that individuals who have misplaced their tooth structure can have them implanted. These teeth would not even have nerves or blood vessels, but they would be composed of the same components as human teeth. To achieve this, researchers must determine the genes that generate the 25 regulatory proteins that help compensate the tooth structure. Nevertheless, there may also be numerous of other genes instructing the body where, when, and when to develop a specific tooth.[85]

Gene Therapy to Promote Oral Implant Osseointegration

There is immense potential for periodontal regenerative medicine in the use of osteogenic GFs, such as PDGF, to replenish tooth-supporting and peri-implant alveolar bone in preclinical studies models[86–90] and in early human trials.[91,92] The drug fragility at the administering site is one rationale why the consequences of these interventions are constrained in terms of regeneration and dependability.

So, using gene therapy to modulate osteogenic GF release and bioavailability affords prospects for tissue engineering of osseous defects.[93] Our team has recently seen the possibility of utilizing genetic recombination to rejuvenate the cementum and alveolar bone around teeth, together with the alveolar bone associated with dental implant fixtures.[36,94]

These investigations have already shown that the use of genome editing for bone regeneration does have a significant amount of potential.

As contrary to continuous PDGF administration in vitro, gene transfer has been demonstrated to boost gingival fibroblast, PDL, and tooth-lining cell (cementoblast) mitogenesis and proliferation. Furthermore, PDGF has also shown remarkable results in fostering bone repair surrounding teeth and dental treatment. This application's key goal is to assess novel PDGF gene transfer regenerative medicine methodologies in animal models with the long-term intent of human use.[95,96]

Recent Advances of Gene Therapy

To convey genes more accurately and effectively for combatting maladies that are not amenable to treatment with a single stimulus-responsive gene carrier, numerous multiple stimulus-responsive nanocarriers have been developed.[97] Systems that adapt to multiple stimuli make use of multiple stimulus responses. For illustrate, two polymeric micelles featuring sulfonamide-functionalized poly(N-isopropylacrylamide) substrates were used to generate pH/temperature sympathetic nanocarriers.[98] Both sulfadimethoxine surface-functionalized and sulfamethazine surface-functionalized micelles exhibited higher intracellular uptake when activated with a proof-of-concept antiproliferative drug under mildly acidic conditions (pH 6.8) at temperatures well above their lower critical solution temperatures. Both forms of microemulsions could be employed as an intracellular pH and temperature-responsive medicament or gene delivery system.

Future Directions in Periodontal Regeneration

The domain of periodontal care is severely affected by tissue engineering. Bioengineering attempts to devise a therapeutic system to support periodontal repair are integrating cell and gene therapy to accelerate and steer periodontal wound closure into a more predictable regenerative trajectory. However, there are still several challenges. Numerous emerging systems with the potential to augment tissue-healing biology have been highlighted in the content of this assessment. How to improve the utilization of cells and genes delivered to a passive or compliant environment where there is context for the kind of cell desired, but in which certain molecular signals are given to stimulate normal cell function, remains a major challenge today. Identifying cell sources and clinically relevant cell numbers, integrating multiple cells into existing tissue matrices, and striving to achieve bioactivity of tissue equivalents using an expanded repertoire of biomaterials are all obstacles to overcome that the field of tissue engineering still needs to transcend. The practical and regulatory requirements to deploy these technologies in the health care setting continue to pose major challenges to the domains of cell and gene transfer.

Conclusion

Despite the enormous interest in this area, there have been no dentine repair clinical studies and only a limited number of periodontal disease therapy clinical applications. Cell-based bioengineering and material sciences must specify the prerequisites for producing reliable, repeatable goods that are inspected for efficacy and safety. In-depth research is being done on gene therapy for a variety of biomedical and dental uses. Gene therapy is anticipated to be a very helpful tool for the management of oral illnesses and improving the prognosis and quality of life in light of the exponential growth in instances of oral squamous cell carcinoma and periodontal disorders. The positive results of recent human clinical studies have given physicians confidence that gene therapy may soon advance to practical applications. Future clinical orthodontics will benefit from this sort of biological research because, like other biomedical disciplines, it must adapt to new developments in biological applications to improve clinical outcomes and treatment effectiveness. Finding solutions to these problems that prevent gene therapy from becoming a common therapeutic option should be the focus of research. In the near future, it is anticipated that this will be able to get over the challenges posed by gene therapy's clinical uses. With more study and advancements, dentists will take on a new role as "gene therapists," excelling at treating mouth cancer and mending alveolar bone abnormalities in clinical settings.

Conflict of Interest
None declared.

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