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Future Strategies of Gene Therapy for Preventing Periodontal Diseases

Gaurav G Durge*
School of Dental Sciences, Karad, Malkapur, Maharashtra, India

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ABSTRACT

In periodontics, gene therapy has been used as a technique for tissue engineering. The tissue engineering approach can assist in the restoration of injured periodontium, including cementum, gingiva, periodontal ligament, and bone, by combining four components: scaffold, signalling molecules, cells, and blood supply. Since almost 50 years ago, the idea of transferring genes to tissues for clinical purposes has been addressed. Recombinant DNA technology has exponentially improved our ability to alter a cell's genetic code, which has advanced this objective. The initial idea that gene therapy should only be taken into account for a selectively few major organs as a means of treating life-threatening illnesses that are resistant to conventional treatment has changed. Several non-life-threatening illnesses that have a negative impact on a patient's quality of life lack viable therapies. Morbidity has been made possible by the absence of effective treatments, providing a justification for broadening the application of gene therapy. In the last few years, gene therapy has made impressive advancements. Gene therapy will have a major and widespread impact on fields dependent on biological research, even while significant issues prevent its frequent clinical usage. This review's objective is to assess the advancements made in addressing gene transfer strategies for treating various dental-related illnesses and issues.

Keywords: Gene therapy, Periodontics, Tissue engineering, Cementum, Recombinant DNA technology, Dental practice.

I. INTRODUCTION

The endeavour to alter the genome of a living organism for the treatment or curing of diseases as well as, controversially, for eugenics began with the discovery of the molecular basis of genes[1]. Beginning in the 1990s, genetic engineering research mainly concentrated on two methods of targeting genes: homologous recombination (HR) and conditional targeting. Human sickness might be treated by HR. Double-strand breaks (DSBs) can improve HR effectiveness. Site-specific DSBs can be produced by nuclease enzymes like as Zinc Finger Nucleases

(ZFNs), Transcription Activator-like Nucleases (TALENs), and designer mega nucleases[2].

Inflammatory and destructive reactions range widely in periodontal disorders, which are assumed to have a complex aetiology. Periodontitis has been linked to a number of genetic risk factors. Significant advancements in the management of periodontal disease and the reconstruction of the dentoalveolar apparatus have been made since the introduction of gene therapy in dentistry. Biomedicine includes the field of gene therapy[3]. The genetic change of cells for therapeutic purposes is a broad definition of gene therapy. Genes are certain base sequences found in chromosomes that function as the fundamental building block of inheritance. The genetic makeup of each person varies, and genetic alterations are what cause individuals to differ from one another. Serious diseases can be brought on by certain alterations, usually in a single gene[4].

➢ Areas of Impact on Dentistry

Bone Repair

There are many different inflammatory and destructive periodontal diseases. One of the most clinically significant long-term objectives of research in the field of mineralized tissue is the development of efficient treatments for bone regeneration. A significant global health issue is bone loss brought on by trauma, neoplasia, reconstructive surgery, congenital abnormalities, or periodontal disease[5]. The selection of the three-dimensional shape and the type of tissue generated during the regeneration of these bone structures presents far more difficulties. Nonetheless, it would be extremely helpful for treating traumatic amputations, the effects of tumour excision, tooth loss, temporomandibular and other joint problems, and craniofacial and other bone deformities[6].

Gene Therapeutics to Salivary Gland

Salivary gland loss results from a number of clinical disorders, including Sjögren's syndrome and radiation treatment for head and neck cancer (SS). So, until the invention of gene therapy, the development of a revolutionary treatment to repair or regenerate injured salivary gland tissue was eagerly anticipated. Excellent target locations for gene transfer include the salivary glands. Furthermore, they are enclosed, which is anticipated to reduce the unfavourable access of given vectors and transgenes to other organs[7]. They are capable of synthesizing enormous amounts of proteins. The numerous branches and trunk-like architectural arrangement of the salivary gland explains how a minimally invasive approach can transport a gene to the apical pole of each glandular cell. Gene delivery vectors—viral or nonviral—are injected retrograde ly into the canulated main duct opening in the oral cavity[8].

Ex vivo Gene Transfer for Bone Repair

The benefit of using ex vivo gene transfer is that the surgeon can choose particular cells (such as bone marrow cells or stem cells) to act as the cellular delivery system for particular clinical issues. Ex vivo techniques also have a high cell transduction effectiveness[9]. It is feasible to remove patient cells, infect them for a little time, and then reimplant the transduced cells at the proper anatomic place. Mesenchymal stem cells, muscle-derived stem cells, adipose-derived stem cells, buffy coat cells from bone marrow or blood, and skin fibroblasts are the cells that have attracted the most interest as a cellular delivery vehicle[10].

Gene Therapy for Orthodontic Tooth Movement

The remodelling of alveolar bone, which is regulated by osteoclasts and osteoblasts, is necessary for tooth mobility. They come from two main sources: hemopoietic cells and stromal cells (osteoblasts) (osteoclasts). Interaction with cells from the osteoblastic lineage is necessary for the development of mature bone resorbing osteoclasts from hematopoietic progenitors. Hence, it is believed that periodontal ligament cells or osteoblastic cells are

required to support osteoclastogenesis[11]. The receptor activator of NF-kappa B (RANK) ligand, often known as RANKL, is the substance that facilitates this interaction. RANK, the receptor for RANKL, is expressed by osteoclastic precursors. Osteoprotegerin (OPG), which is made by osteoblastic cells or periodontal ligament cells and functions as a dummy receptor for RANKL to inhibit RANKL-RANK interaction, is a ligand for RANKL as well. Hence, excessive OPG expression can prevent the development of osteoclasts. Gene therapy using OPG and RANKL was employed in two exquisite investigations by Kanzaki et al. to both speed up and slow down orthodontic tooth movement in a rat model. After 21 days, a local RANKL gene transfer to the periodontal tissue enhanced the movement of orthodontic teeth by almost 150% without causing any systemic consequences. "Local RANKL gene transfer might be a beneficial technique not only for shortening orthodontic treatment, but also for shifting ankylosed teeth where teeth fused to the surrounding bone," the authors wrote in their conclusion. In contrast, after 21 days of forceful application, local OPG gene transfer reduced tooth mobility by around 50%. Similar techniques could be utilised by orthodontists in 40 years to speed up therapy and enhance outcomes[12].

Gene Therapy to Grow New Teeth

Dental experts want to be able to create teeth in a lab so that patients who have lost their natural teeth can have them implanted. These teeth wouldn't have nerves or blood vessels, but they would be constructed of the same materials as human teeth. To do this, scientists need to identify the genes that construct the 25 main proteins that make up tooth structures. Several other genes may also be involved in telling the body when, how, and where to create a certain tooth[13-14]. As many as 10% of all genes may be involved in some way in tooth development. The master gene PAX 9—essential for tooth development—was discovered at the Baylor College of Medicine. In the future, it is hoped that we will be able to bioengineer human teeth as replacements[15].

➢ Approaches for Gene Therapy

- ✓ A normal gene may be inserted into a nonspecific location within the genome to replace a nonfunctional gene. This approach is most common.
- ✓ An abnormal gene could be swapped for a normal gene through homologous recombination.
- ✓ The abnormal gene could be repaired through selective reverse mutation, which returns the gene to its normal function.
- ✓ The regulation (the degree to which a gene is turned on or off) of a particular gene could be altered.
- ✓ Spindle transfer is used to replace entire mitochondria that carry defective mitochondrial DNA[16].

➢ Implications of Gene Therapy in Periodontics

Since 1995, gene therapy has made enormous strides that are important to dentistry. It has even been widely researched within the subject of periodontics. Nowadays, tissue engineering and genetic principles are being used for periodontal rehabilitation. By combining four components—the framework, signalling molecules, blood supply, and cells—the tissue engineering approach reconstructs the native target tissue[17].

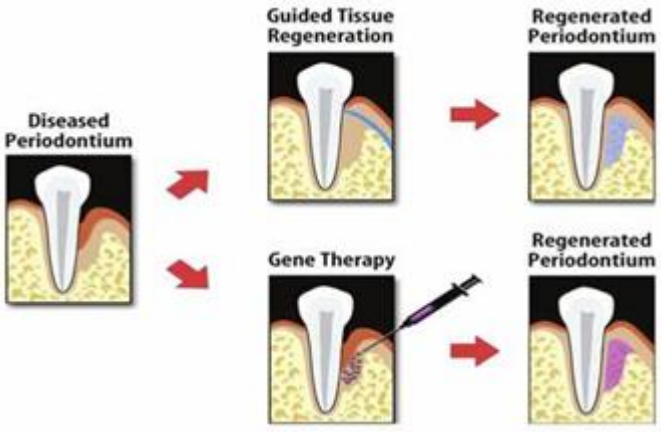

Fig 1: Gene Therapy in Periodontics

➢ **Designer Drug Therapy in Treating Periodontal Disease**

Designer medication therapies that target one or both areas of the genes can be created if it is understood which genes are required for normal development. Because they would only effect the gene flaw that has been clearly detected through genetic research, these designer drugs would be safer than the medications we use today[18].

➢ **Impact In Dentistry**

In infectious diseases

By directly modifying the expression of a gene or the activity of its products, gene therapy tries to prevent the reproduction of an infectious agent by stimulating a targeted immune response or secreting inhibitory substances in vivo. Moreover, it can be applied to stop the extracellular dissemination of the infectious agent. Even today, substantial research is being done on HIV infection (US Gov NCT04378244, 2020)[19]. A research utilising DeltaRex-G gene therapy for COVID-19(CORONA) symptoms was registered with clinical trials gov. in the USA on May 7, 2020. According to reports, it won't start recruiting volunteers until July 9, 2020[20].

In Tooth and Periodontal Regeneration

Sonoyama, Liu, Yamaza, et al. (2006) used stem cells derived from the root apical papilla of human teeth to demonstrate functional tooth regeneration in a small pig model. They were successful in creating a root-periodontal combination that could hold a replacement crown. A recombinant plasmid was successfully used by Tan, Zhao, Gong, et al. (2009) to produce bioactive basic fibroblast growth factor, which supported canine periodontal regeneration[21]. PDGFB gene in vivo transfer promoted periodontal tissue regeneration in a rat model, particularly in the cementum and alveolar bone. Dental pulp stem cells, periodontal ligament stem cells, dental apical papilla stem cells, and stem cells from human exfoliated deciduous teeth dental follicle or epithelium or adipose tissue have all been shown to help with the regeneration of dentin-pulp, the entire tooth or its root, or even the regeneration of periodontium when used in stem cell-based tissue engineering[22].

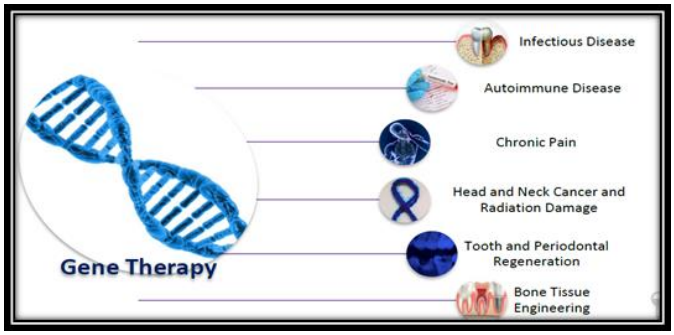

Fig 2: Applications of gene therapy in dentistry

➢ **Periodontal Tissue Engineering**

By providing signalling molecules, cells, and scaffold/matrix to periodontal abnormalities, tissue engineering aims to regenerate the functional tissue that requires a succession of crucial processes occurring during periodontal tissue creation and growth[23].

Protein-based Therapeutics

Periodontal regeneration can be hastened by using biological mediators such growth factors from recombinant technology and a partially purified protein combination from growing teeth. The short half-life and instability of these proteins, which necessitate numerous delivery dosages, are significant downsides. Newer safe methods of periodontal regeneration by cell-based approach have emerged as a result of limitations such limited control over dose administration, loss of bioactivity, non-targeted delivery, and/or lack of availability[24].

Cell-based Therapeutics

Allogeneic and xenogeneic cells, which are heterogeneous, are powerful triggers of immunogenic reactions when they are used for tissue engineering, whereas autologous cells seem to be the best suitable source of cells for tissue engineering. Although six different types of stem cells have been found in

humans, they have primarily been divided into adult stem cells and embryonic stem (ES) cells[25].

Embryonic Stem Cells

When compared to multipotent or unipotent cells, the advantage of ES cells is that they have a higher potential for differentiation. The stem cells display alkaline phosphatase, stage-specific embryonic antigens 3 and 4, and proteins TRA-1-81 and TRA-1-60[26].

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[27].

➢ Target Genes For Periodontal Tissue Engineering

Bone morphogenetic proteins (BMPs) and members of the transforming growth factor-beta (TGF-) family are both peptides. The TGF-1 induces cementoblast growth, bone matrix apposition, and bone cell replication. 18 When it comes to cementogenesis and the construction of the periodontal ligament (PDL), the BMP-3 and BMP-7 (also known as osteogenic protein-1) are crucial components. Platelet-derived growth factor (PDGF), combined with increases in the rate of bone matrix apposition and bone collagen synthesis, stimulates DNA synthesis and cell replication in osteoblasts[28]. Insulin-like growth factor-1 stimulates human PDL fibroblast proliferation in a dose- and time-dependent manner, and together with PDGF-BB and TGF-, these factors help to promote the regeneration of periodontal soft and hard tissues[29].

✓ Sonic Hedgehog

A regulator protein of embryonic osteogenesis and the healing of bone fractures is also encoded by the sonic hedgehog gene, and it is present during embryogenesis. This protein may have important impacts on periodontal bone regeneration[30].

✓ Wingless

It is still entirely unknown how wingless affects the homeostasis and regeneration of periodontal tissues. Its function in periodontal regeneration has to be confirmed by additional research[31].

➢ Delivery Approaches and Strategies

For the direct supply of growth factors, various methods and tactics have been used: Gene delivery methods using an in vivo technique, noncovalent immobilisation, and covalent immobilisation manipulating the cells that are already present in the host's body naturally; ex vivo approach: manipulating cells that have been removed from the host's body before being given back to the host[32].

Gene Delivery for Host Modulation of Periodontal Disease

AAV was used in gene therapy to deliver the tumour necrosis factor receptor-immunoglobulin Fc (TNFR: Fc) fusion gene to experimental Porphyromonas gingivalis-lipopolysaccharide-mediated bone loss. This treatment prevented P. gingivalis-lipopolysaccharide-mediated bone loss and sustained therapeutic levels of serum TNFR protein for about three months[33].

➢ Applications of gene therapy in dentistry

The significant development has been made innumerable applications of gene therapy in dentistry[34].

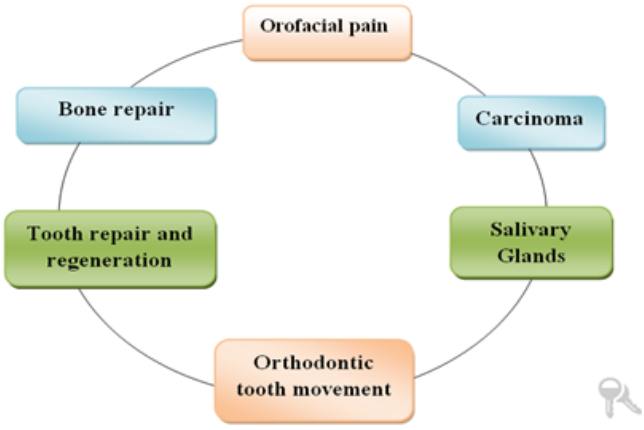

Fig 3: Applications of gene therapy in dentistry

Salivary Glands

As part of salivary gland gene therapy, the principal excretory ducts of a large salivary gland are retroductally cannulated. The creation of a protein that is therapeutic for cells or the entry of secretions into the bloodstream or saliva may result from this. Salivary glands use a vast variety of genes, including those that make hormones, an antibiotic substance, membrane proteins, transcription factors, protease inhibitors, a protein that controls apoptosis, and various nonmammal "reporter proteins." An autoimmune condition is known as Sjogren's syndrome (SS). Basically, it is identified by dry mouth and eyes. Lupus and rheumatoid arthritis are two immune system disorders that frequently occur with the condition. This situation has led to the evolution of a broad paradigm for developing novel protein- and more recently gene-based therapeutics for a number of autoimmune diseases, including SS[35].

Bone Repair

In contrast to other dental hard tissues, bones have a good capacity for regeneration and healing as well as being amendable (such enamel and dentin). The genes that encode bone morphogenetic proteins have been transferred using ex vivo methods in dentistry. Either orthotopic or ectopic bone growth is known to be induced by bone morphogenetic proteins. Traumas and bone fractures usually recover without leaving any visible scars[37]. However when there are pathological fractures or substantial bone abnormalities, bone healing and remodelling may be challenging. Another powerful mitogen that is essential for wound healing is platelet-derived growth factor (PDGF). PDGF has biological actions that are antiapoptotic in nature and have an impact on cell migration, proliferation, and extracellular matrix synthesis. The action is stopped by the growth arrest gene (gas gene). We have been able to avoid the growth arrest gene's inhibitory effects, which are essential for wound healing, through the development of the bioactive PDGF gene[36].

Carcinomas

Squamous cell carcinoma of the head and neck includes cancers of the oral cavity, paranasal sinuses, larynx, pharynx, and head and neck skin (SCCHN). It is ranked as the sixth most common cancer worldwide. A novel gene therapy approach that preferentially multiplies within tumour cells and lyses them has been comprehensively examined in preclinical and clinical studies for squamous cell carcinoma. An E1B 55kD gene-deleted adenovirus called ONYX-015 (d11520) was developed for the treatment of cancers lacking p53 function. By intratumoral injection, ONYX-015 can be safely administered to patients with recurrent/refractory squamous cell carcinoma. Unfortunately, there was very little proof of antitumor activity when this specific form of gene therapy was used alone[37].

Orofacial Pain

Orofacial discomfort is pain felt in the soft and hard tissues of the face, head, and neck. Certain orofacial pain disorders, especially those that are chronic, may be particularly difficult to identify and treat due to their complexity and the unclear processes underlying their aetiology and pathophysiology. They include both those with a known cause (such as trigeminal postherpetic neuralgia and posttraumatic trigeminal neuropathic pain) and those that may be idiopathic (such as burning mouth syndrome, persistent idiopathic facial pain, and persistent idiopathic dentoalveolar pain) [38]. They also include those that appear as a symptom of a known chronic disorder or disease. Also, 20% of acute pains may turn into a chronic pain state if the acute disease is not appropriately treated in a timely and appropriate manner. Pain management often involves the use of analgesics and sedatives. By lowering the use of drugs that carry the risk of systemic toxicity, opioid addiction, and other negative effects, gene therapy is being studied as a potential treatment for chronic pain[39].

Orthodontic Tooth Movement

An add-on procedure called alveolar corticotomy surgery can reduce the duration of orthodontic therapy in half. However, due to the short accelerated mobility time and high morbidity rates associated with this type of surgery, alternative treatments must be taken into account. Tooth mobility is closely correlated with the physiologic processes of bone resorption and apposition (TM). The biomolecular processes of osteoclast activation are closely related to the ratio of the osteoprotegerin (OPG) to the receptor activator of nuclear factor-kB (RANKL) (OPG). While the so-called regional acceleratory effect speeds up bone remodelling, corticotomy-assisted malocclusion therapy has been empirically shown to minimise TM phases. In light of the available data, we hypothesise that sustained overexpression of RANKL, in contrast to corticotomy surgery, will cause tooth movement (TM) under force to accelerate over time as opposed to just at the beginning of therapy. This will increase osteoclastogenesis and bone resorption as well as specifically activate osteoclasts. Local RANKL gene transfer was suggested as a useful method for shortening orthodontic treatment and shifting ankylosed teeth. In contrast to RANKL, local OPG gene transfer significantly decreased tooth displacement after 21 days of force application by around 50%. Orthodontic therapy will see a paradigm shift as a result of quicker treatment periods and greater results. Gene therapy has also shown promise in easing the discomfort associated with orthodontic TM. Further research could lead to the development of future gene therapy therapeutic options that could be used to treat the discomfort related to orthodontic Procedures[40].

- **Present Concerns and Future Trends**

A rate-limiting factor in gene therapy research is off-target effects. Because they may enter at places other than those for planned therapy, viral vectors are prone to unexpected outcomes. This may interfere with crucial genes and cause undesirable mutations. The well-known instance of Jesse Gelsinger serves as a sombre reminder of the risks involved in the practise of molecular medicine. The use of a viral vector to treat the patient's hereditary ornithine transcarbylamase deficiency resulted in severe immunological rejection and the patient's eventual death. Three years later, malignant T-cell proliferation caused by the insertion of a retroviral vector gene near the LMO2 proto-oncogene promoter was seen in two of the youngest patients being treated in a trial for severe combined immunodeficiency[41].

We have gone a long way from 1967, when MW Nirenberg first questioned if the world was prepared for the difficulties of gene surgery, to the approval of the first gene therapy product Glybera 45 years later. Gene therapy is a potential new approach to treating disease today. A lot of research is already being done to enhance the effectiveness and safety of this innovative medicine. Over 2597 gene therapy trials were underway in 38 countries as of November 2017, with the majority of them targeting cancer and heritable monogenic illnesses (Gin, Amaya, Alexander, et al., 2017). Due to its potential to eradicate disease from the DNA upstream, gene therapy is extremely likely to become a common treatment option in the future[42].

II. CONCLUSION

The most recent development in periodontal regeneration is thought to be the use of genetically modified cells in therapy. The goal of transitioning from tissue repair to regeneration calls for comprehensive interdisciplinary cooperation methods. Scientists are working to stop diseases at their very roots in research institutions all around the world. The majority of traditional medical treatments don't work as well as they should. They are attempting to alter the genes that cause the diseases rather than using medications to treat illness and diseases. Genes are particular nucleotide sequences that include instructions for making proteins. When these genes

are changed and their encoded proteins are unable to perform their intended tasks, genetic disease results. The future of gene therapy in periodontics looks bright. In periodontics, gene therapy has been applied as a technique for tissue engineering. The tissue engineering approach can assist in the restoration of injured periodontium, including cementum, gingival, periodontal ligament, and bone, by combining four components: scaffold, signalling molecules, cells, and blood supply.

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