

Future prospects of gene therapy in endodontics

Rachel Rosemary Maben*, Shruti Bhandary

Department of Conservative Dentistry and Endodontics, AJ Dental College and Hospital, Mangalore, Karnataka, India

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Abstract

Gene therapy represents a rapidly evolving field in regenerative medicine with promising applications in dentistry and endodontics. It involves the transfer of genetic material into cells to prevent, treat, or cure diseases. In endodontics, gene therapy offers potential solutions for pulpal regeneration, dentin repair, bone healing, pain control, prevention of dental caries, and even whole-tooth regeneration. With advances in molecular biology, stem cell therapy, tissue engineering, and biomaterial sciences, gene therapy is emerging as a futuristic therapeutic approach in conservative dentistry and endodontics. This review discusses the history, principles, delivery systems, applications, challenges, and future directions of gene therapy in endodontics.

Keywords: Gene therapy, endodontics, pulp regeneration, tissue engineering, dental stem cells, tooth regeneration

Introduction

Gene therapy is the transfer of genetic materials into target cells to achieve a therapeutic effect by replacing, modifying or regulating defective genes. Gene therapy is a rapidly advancing field of biomedical science that focuses on altering genetic material within cells to achieve therapeutic outcomes^[1, 2]. It is based on the understanding that many diseases arise from abnormalities in gene function, and by modifying or regulating these genes can help to restore normal cellular activity^[2]. Directly targeting the molecular basis of the disease, gene therapy offers a more precise and biologically oriented approach compared to conventional treatment methods^[3].

Over time, gene therapy has evolved from a theoretical concept to a practical strategy with applications in multiple areas of medicine^[3]. It generally involves introducing functional genes to compensate for defective ones, suppressing harmful gene activity, or editing genetic sequences to correct mutations^[4]. Depending on the method used, gene transfer can be performed directly within the body (*in vivo*) or through cells modified outside the body and later reintroduced (*ex vivo*)^[4]. A critical component of gene therapy is the use of delivery systems, known as vectors, which transport genetic material into target cells. These vectors may be viral or non-viral in origin, each offering distinct advantages in terms of efficiency, safety, and specificity^[5].

In dentistry, gene therapy has gained significant importance because oral tissues possess remarkable regenerative potential^[11]. Endodontics particularly benefits from regenerative approaches because the dental pulp contains stem cells capable of differentiation into odontoblast-like cells and other connective tissue elements^[12]. Gene therapy in endodontics aims to regulate cellular and molecular events responsible for tissue repair and regeneration^[11]. Unlike conventional therapies that mainly remove diseased tissue, gene-based approaches attempt to biologically restore

the normal structure and function of dental tissues^[11]. By delivering therapeutic genes into target cells, clinicians may stimulate stem cell differentiation, angiogenesis, dentin formation, bone healing, and immune modulation^[12].

Thus, gene therapy in endodontics aims to regenerate damaged pulp tissue, promote dentin formation, enhance periapical healing, reduce inflammation and pain, improve bone regeneration, prevent dental caries, and enable whole-tooth regeneration^[11, 12].

Recent advances such as CRISPR-Cas9-based genome editing have enabled precise and targeted modification of DNA sequences, further expanding the therapeutic potential of gene therapy^[6]. Despite its promising applications, gene therapy still faces challenges related to safety, long-term gene expression, and ethical considerations^[7]. Continuous advancements in molecular biology and biotechnology are improving the feasibility of gene therapy in medicine and dentistry^[8].

What are Genes?

Genes are the fundamental units of heredity composed of specific sequences of deoxyribonucleic acid (DNA) that carry information required for the synthesis of proteins and functional RNA molecules. They regulate cellular structure and function by directing protein synthesis involved in metabolism, growth, and differentiation. Each gene is located at a specific locus on a chromosome and contains coding (exons) and non-coding regions (introns) that regulate gene expression. Gene expression is influenced by both genetic and environmental factors. Mutations or alterations in genes can disrupt normal protein function, leading to diseases and developmental abnormalities. In dental tissues, genes regulate processes such as dentin formation, pulp healing, and mineralization. Understanding genes and their functions forms the basis for gene therapy aimed at restoring normal cellular activity.

History

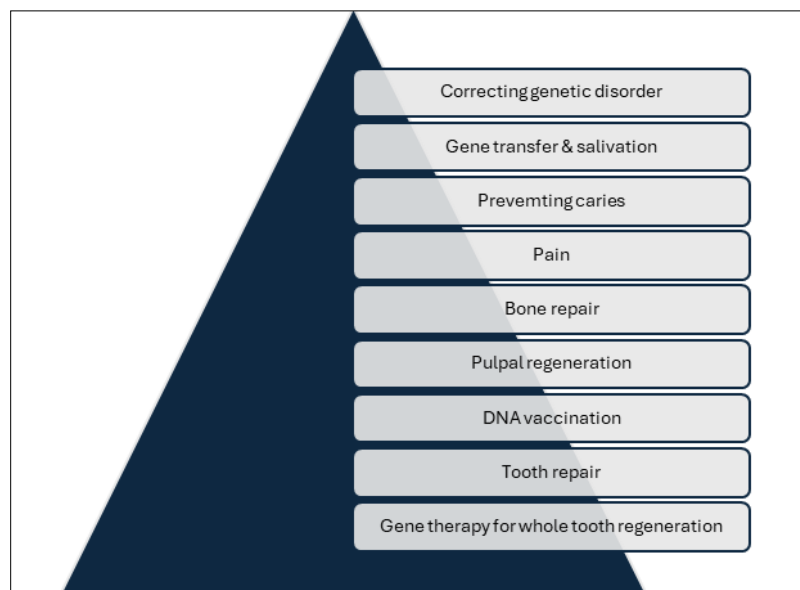
Year/Period	Historical Event	Significance
1953	Discovery of DNA double helix by Watson and Crick	Established the molecular basis of heredity and gene function
1970s	Development of recombinant DNA technology	Enabled manipulation and transfer of genes for therapeutic purposes
1980s	Emergence of gene therapy concept	Proposed correction of defective genes to treat diseases
1990	First successful human gene therapy trial for ADA-SCID	Demonstrated clinical feasibility of gene transfer
1996	Development of lentiviral vectors	Improved efficiency and stability of gene delivery
2000s	Expansion of gene therapy into dentistry	Applied in salivary gland repair, periodontal regeneration, and bone healing
2000s	Introduction of <i>in vivo</i> and <i>ex vivo</i> approaches	Enabled direct and cell-mediated gene delivery techniques
2012	Introduction of CRISPR-Cas9 technology	Allowed precise and targeted genome editing
2010s–Present	Development of non-viral and nanoparticle vectors	Improved safety and targeting efficiency in gene delivery
Present and Future	Integration with stem cells, tissue engineering, and 3D bioprinting	Enhanced regenerative dentistry and potential whole-tooth regeneration

Principles of Gene Therapy

Gene therapy is based on the introduction of therapeutic nucleic acids into target cells to achieve a desired biological effect [2]. The therapeutic strategy may involve gene augmentation, gene inhibition, or gene editing to restore normal cellular activity [3]. Efficient delivery of therapeutic genes is essential and is achieved using vectors, which may be viral or non-viral in nature [5]. Viral vectors provide high transduction efficiency, whereas non-viral vectors offer advantages such as reduced immunogenicity and improved biosafety [9]. Gene transfer can be carried out through

somatic gene therapy, which targets body cells without affecting future generations, or germline gene therapy, where genetic alterations are inherited by offspring. Based on the site of delivery, it may also be performed through *in vivo* or *ex vivo* techniques [4]. A major principle of gene therapy is selective and regulated gene expression to maximize therapeutic efficacy while minimizing adverse effects [3]. Recent advances in genome editing technologies have significantly improved the accuracy and specificity of targeted gene modification [6].

Applications



Correcting Genetic Disorder

Gene therapy has potential applications in the management of inherited craniofacial and dental abnormalities caused by defective genes [3]. Conditions such as amelogenesis imperfecta, dentinogenesis imperfecta, osteogenesis imperfecta, and ectodermal dysplasia are associated with mutations affecting tooth and bone development [3]. Conventional treatment mainly focuses on restorative rehabilitation, whereas gene therapy attempts to correct the underlying molecular defect. Therapeutic strategies involve replacement, suppression, or editing of abnormal genes responsible for defective enamel, dentin, or connective tissue formation [6]. Signaling pathways such as BMP, Wnt, and FGF are important regulators of odontogenesis and craniofacial morphogenesis [21]. Modern gene-editing

technologies including CRISPR-Cas9 may provide precise correction of defective genes in the future [6].

Salivary Gland Modification

Salivary glands are considered excellent targets for gene therapy because of their accessibility, vascularity, and protein-secretory capacity [2]. Gene transfer to salivary glands can be used to manage xerostomia, especially in patients who develop salivary gland dysfunction after radiation therapy for head and neck cancers [15]. Aquaporin-1 gene transfer has shown improvement in salivary flow and glandular function in experimental and clinical studies [1, 5]. Gene therapy may also stimulate production of antimicrobial proteins, growth factors, and buffering agents that protect oral tissues against infection

and demineralization^[2]. Genetically modified salivary glands may function as biological factories capable of secreting therapeutic proteins into saliva or systemic circulation. This approach has potential applications not only in dentistry but also in systemic disease management.

Preventing Dental Caries

Gene therapy may provide long-term biological prevention of dental caries by targeting both microbial and host-related factors^[17]. Dental caries is a multifactorial disease involving bacterial biofilm formation, acid production, and enamel demineralization. Molecular approaches aim to alter cariogenic bacteria such as *Streptococcus mutans* to reduce acidogenicity and virulence^[17]. Replacement therapy using genetically modified non-cariogenic bacterial strains may help prevent recolonization by pathogenic microorganisms^[17]. Gene transfer systems can also increase production of antimicrobial peptides such as defensins, lactoferrin, and lysozyme within saliva. DNA vaccines targeting bacterial adhesion proteins and glucosyltransferase enzymes may stimulate mucosal immunity and reduce bacterial attachment to tooth surfaces. Future strategies may additionally enhance enamel resistance through regulation of mineralization-related genes and promotion of remineralization processes.

Pain

Gene therapy offers a biologically based method for long-term control of pulpal and orofacial pain^[3]. Conventional analgesics provide temporary relief and may produce systemic adverse effects with repeated use^[3]. Gene therapy attempts to regulate pain pathways by modifying neural transmission and suppressing inflammatory mediators^[7]. Therapeutic genes encoding anti-inflammatory cytokines, endogenous opioids, endorphins, and enkephalins can provide prolonged analgesic effects^[7]. Gene transfer may also reduce neurogenic inflammation and chronic neuropathic pain by modulating trigeminal nerve activity and sodium channel expression. Viral and non-viral vectors can be used for localized delivery into affected tissues, thereby minimizing systemic toxicity. This approach may improve postoperative comfort following endodontic treatment and reduce dependence on systemic medications.

Bone Repair

Gene therapy has shown promising results in regeneration of bone associated with periapical lesions, osseous defects, traumatic injuries, and surgical procedures. Therapeutic genes stimulate osteoblast differentiation, angiogenesis, and mineralized tissue formation^[18]. Bone morphogenetic proteins are among the most extensively studied molecules because of their ability to induce osteogenesis^[18]. Other important growth factors include PDGF, VEGF, IGF, and TGF- β , which enhance cellular proliferation and vascularization^[18]. Gene-activated matrices and stem cell-loaded scaffolds help improve localized bone repair and accelerate healing. In endodontics, enhanced bone regeneration is beneficial following periapical surgery, cystic lesion management, and repair of large inflammatory defects. Controlled gene expression may improve both the speed and quality of regenerated bone while reducing postoperative complications.

Pulpal Regeneration

Pulpal regeneration is one of the most significant applications of gene therapy in regenerative endodontics^[1].

^[1]. Conventional root canal treatment removes infected pulp tissue but cannot restore the biological vitality of the tooth^[1]. Gene therapy aims to regenerate healthy pulp tissue capable of performing sensory, nutritive, immune, and reparative functions^[1, 2]. Therapeutic genes stimulate stem cell proliferation, angiogenesis, extracellular matrix formation, and differentiation of odontoblast-like cells^[1, 2]. Growth factors such as BMPs, VEGF, TGF- β , PDGF, and FGF play important roles in regeneration of the dentin-pulp complex^[1, 2]. Dental pulp stem cells, stem cells from apical papilla, and mesenchymal stem cells are commonly used in regenerative procedures^[10,20]. Scaffold systems such as hydrogels, collagen matrices, and nanofibers provide structural support for cell growth and vascularization^[16]. Successful pulpal regeneration may lead to continued root development, apical closure, increased dentinal wall thickness, and restoration of tooth vitality.

DNA Vaccination

DNA vaccination is an emerging application of gene therapy aimed at prevention of oral infectious diseases^[17]. DNA vaccines involve introduction of plasmid DNA encoding specific microbial antigens into host cells, leading to stimulation of humoral and cellular immune responses^[17]. In dentistry, DNA vaccines are mainly being investigated against cariogenic bacteria and periodontal pathogens. Vaccines targeting *Streptococcus mutans* surface proteins and glucosyltransferase enzymes may reduce bacterial colonization, plaque formation, and acid production^[17]. DNA vaccines offer advantages such as long-lasting immunity, safety, and ease of production compared with conventional vaccines. Mucosal vaccine delivery systems through oral, nasal, or salivary routes are also being explored for improved patient acceptance and localized immune protection.

Tooth Repair

Gene therapy can significantly improve reparative dentinogenesis and healing of damaged dental tissues^[1, 1]. Following trauma, caries, or restorative procedures, odontoblasts and pulp cells attempt to repair injured dentin through formation of tertiary dentin^[1, 2]. Therapeutic genes encoding BMPs, TGF- β , and other growth factors stimulate odontoblast differentiation, extracellular matrix secretion, and mineralization^[1, 2]. Gene-mediated repair strategies may improve outcomes of procedures such as direct pulp capping, pulpotomy, apexogenesis, and regenerative pulp therapy. Stem cell recruitment, angiogenesis, and scaffold-based delivery systems further support regeneration of the dentin-pulp complex^[16]. Controlled release of bioactive molecules within the pulp chamber may enhance healing while preserving pulp vitality and normal tooth function.

Whole Tooth Regeneration

Whole-tooth regeneration is one of the most advanced applications of gene therapy in dentistry^{[1, 3], [1, 4]}. The objective is to bioengineer a fully functional natural tooth using stem cells, growth factors, scaffolds, and genetic regulation^[1, 3]. This approach attempts to recreate the epithelial-mesenchymal interactions that occur during normal tooth development^[1, 4]. Important signaling pathways involved include BMP, Wnt, Sonic hedgehog, Notch, and FGF pathways^[21].

Experimental studies have demonstrated formation of tooth-like structures with enamel, dentin, pulp tissue, periodontal ligament, and alveolar bone integration in animal models^[1, 4]. Bioengineered teeth have also shown eruption potential and functional response to mechanical forces. Future developments in stem cell biology, tissue engineering, and gene editing may eventually allow patient-specific biological tooth replacement^[21].

Challenges

Although gene therapy shows promising results in regenerative endodontics, several challenges still limit its routine clinical application^[7]. Viral vectors provide high gene transfer efficiency but may cause immune reactions, toxicity, insertional mutagenesis, and possible tumor formation^[7]. Non-viral vectors are safer but often demonstrate lower transfection efficiency and shorter duration of gene expression^[9]. Achieving controlled and targeted gene delivery within the complex root canal environment remains another major challenge^[1, 11]. Maintenance of stem cell survival, vascularization, and tissue integration within regenerated pulp tissue also remains difficult. High treatment cost, ethical concerns, and lack of long-term clinical trials further restrict widespread clinical use. Problems related to scaffold design, microbial contamination, and predictable regeneration continue to affect treatment outcomes.

Future Directions

Future research in gene therapy mainly focuses on developing safer, more effective, and clinically predictable regenerative approaches^[6]. CRISPR-Cas9 technology may allow precise correction of defective genes and improve treatment specificity. Nanotechnology-based delivery systems and smart biomaterials may enhance targeted gene transfer and reduce immune reactions^[19]. Advances in stem cell engineering, scaffold fabrication, and 3D bioprinting are expected to improve regeneration of pulp, dentin, and bone tissues^[19]. Personalized regenerative therapies based on individual genetic profiles may also become possible in the future. Whole-tooth regeneration using stem cells and molecular signaling pathways may eventually replace conventional prosthetic rehabilitation and dental implants^[13,21].

Conclusion

Gene therapy represents a rapidly advancing field in regenerative endodontics and dentistry. It offers promising applications in pulpal regeneration, bone repair, pain management, prevention of dental caries, salivary gland modification, tooth repair, and whole-tooth regeneration. Integration of stem cell therapy, growth factors, scaffolds, and gene delivery systems has significantly improved the potential for biologically based dental treatment.

Although several biological, technical, and ethical challenges still remain, continuous advances in molecular biology, tissue engineering, and gene editing technologies are improving the safety and effectiveness of regenerative therapies. With further research and clinical development, gene therapy may become an important component of future endodontic practice and transform the management of dental diseases

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