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Gene therapy in periodontics

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Abstract

Periodontal diseases are identified as infectious processes that need presence of bacteria and response of host and are also affected & modified by other local, environmental and genetic factors. Gene therapy is a part of modern molecular medicine. It holds a great assurance for the treatment of both acute and chronic diseases. Gene therapy is that the unique technique that uses gene to forestall or recover any diseases. The technique of gene therapy may allow doctors to treat a disorder by inserting a gene into patient’s cell rather than using drugs or surgery. There are many methods to replace or repair the genes targeted in gene therapy. Introduction of gene therapy in field of periodontics is playing an important role in control of periodontal disease. It is expected that gene therapy is offering many treatment approaches. Gene therapy and its application in field of periodontics is one of the recent advancements that is reviewed here.

Keywords: Dentistry; Gene therapy; Gene; Implantology; Periodontics; Regeneration

Introduction

Gene therapy is a part of modern molecular medicine and is holding great assurance for the treatment of both acute and chronic diseases. It has been named the medicine of

the future.[1] It is known because the ability of genetic improvement through the correction of altered (mutated) genes or site-specific modifications that focus on therapeutic treatment and holds a promising future for bridging the gap between the disciplines of medicine and clinical dentistry.[2] Gene therapy is that the unique technique that uses gene to forestall or recover any diseases. The technique of gene therapy may allow doctors to treat a disorder by inserting a gene into patient's cell rather than using drugs or surgery (Figure 1).

Some researchers and doctors are examining several approaches to gene therapy, including: i) replacing a mutated gene that causes disease with a healthy gene; ii) 'knocking out' or inactivating, a mutated gene that's functioning improperly; and iii) introducing new genes into the cells to shield from any diseases.[3] Periodontal regeneration has long been the ultimate goal in periodontal therapy. However, treating and re-establishing the diseased periodontium's original structure, properties, and performance constitute a major challenge.[4]

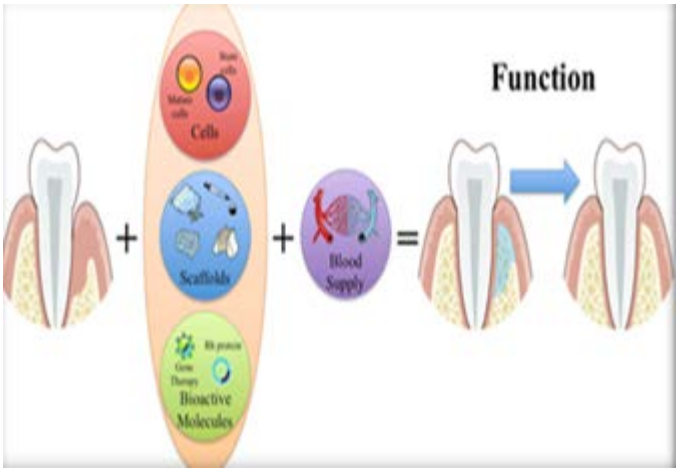

Figure 1: Periodontal Regeneration[5]

Fundamentals of gene therapy[6]

There are a range of various methods to replace or repair the genes targeted in gene therapy.

- A standard gene could also be inserted into a nonspecific location within the genome to replace a non-functional gene. This approach is most common.
- An abnormal gene can be swapped for a standard gene through homologous recombination.
- The abnormal gene can 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 specific gene might be altered.
- Spindle transfer is employed to exchange entire mitochondria that carry defective mitochondrial DNA.

Gene therapy strategies

Gene Augmentation Therapy (GAT)

Targeted Killing of Specific Cells

Targeted Inhibition of Gene Expression

Targeted Gene Mutation Correction

Types of gene therapy

Somatic Gene Therapy: Somatic gene therapy is defined as the correction of a defective or absent gene with its cloned functional equivalent.[7]

Germ Line Gene Therapy: Germ cells, i.e., sperm or eggs are modified by the introduction of functional genes, which are normally integrated into their genomes.[6]

Gene Therapy Approaches[8]

In Vivo Gene Therapy: A procedure in which a therapeutic gene is delivered through a vector directly into the target cells of patients to produce a therapeutic effect that averts or treats diseases.

Ex Vivo Gene Therapy: Cells are removed from a patient and they are maintained in culture to administer a therapeutic gene into the cells and then transfer into the patient.

Gene delivery

Non-viral gene delivery:

Mechanism (Figure 2)[9]

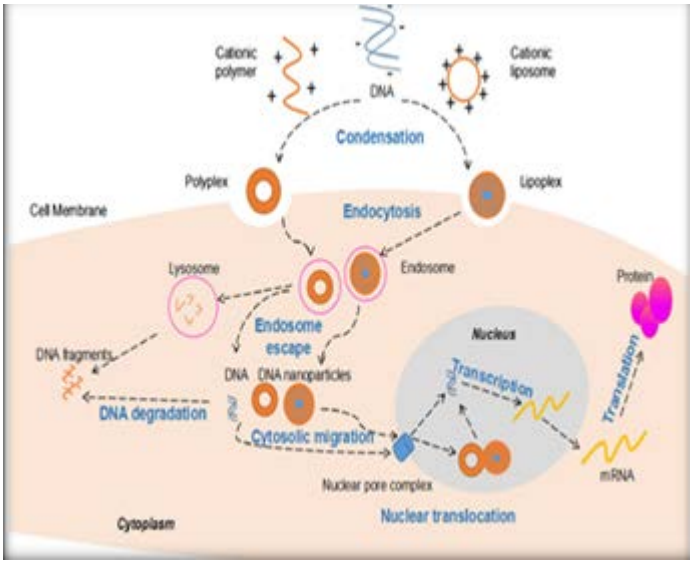

Figure 2: Mechanism

Physical methods

Electroporation: Electroporation is temporary destabilization of the cell membrane targeted tissue by insertion of a pair of electrodes into it so that DNA molecules in the surrounding media of the destabilized membrane would be ready to penetrate into cytoplasm and nucleoplasm of the cell.[10] (Figure 3)[11]

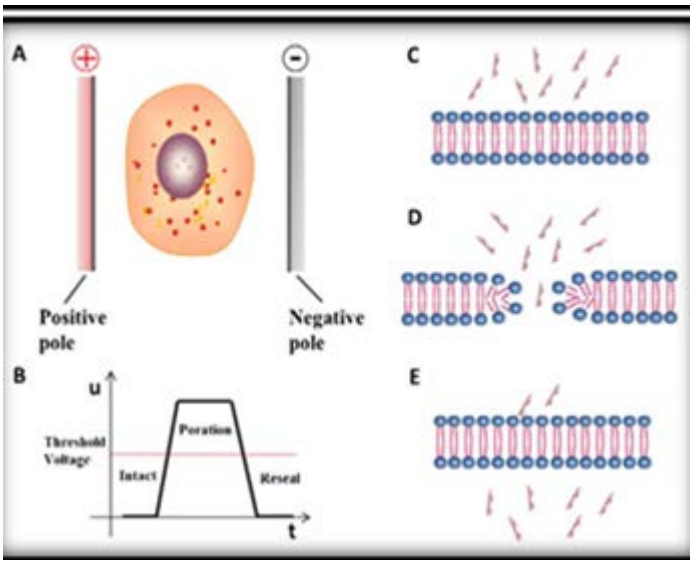

Figure 3: Electroporation

Ballistic DNA Injection (Figure 4)[12]: Delivering DNA coated heavy metal particles by crossing target tissue at a certain speed.[13]

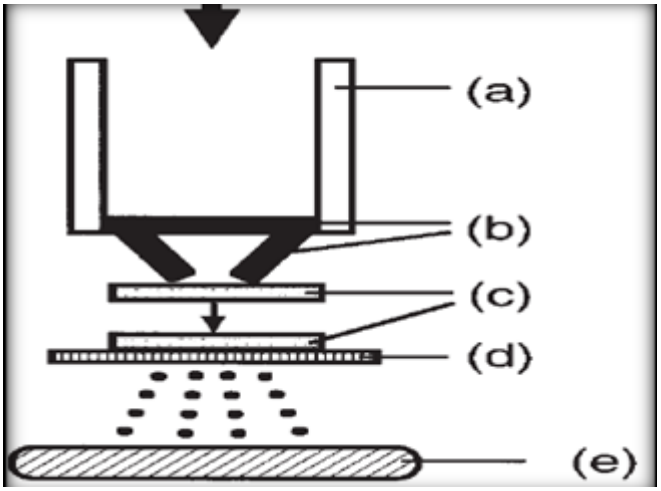

Figure 4: Ballistic DNA Injection[12]

Ultrasound: Ultrasound can make some nanomeric pores in membrane to facilitate intracellular delivery of DNA particles into cells of internal organs or tumours, therefore the size and concentration of plasmid DNA have great role in efficiency of the system

Hydrodynamic: Hydrodynamic is a very simple and highly efficient method for direct intracellular delivery of any water-soluble compounds and particles into internal organs.[10]

Magnetofection: Using strong high gradient external magnets, the complex is captured and held at the target. The genetic material is released by enzymatic cleavage of cross-linking molecule, charge interaction or degradation of the matrix.[13]

Chemical nonviral delivery systems

Cationic Lipids: The positively charged head group binds with negatively charged phosphate group in nucleic acids and form solitary compacted structure called lipoplexes.[13] the nanomeric complex between a cationic liposome or micelle and nucleic acids is called lipoplex.[10]

Cationic Liposomes: Liposomes are spherical vesicles made of phospholipids used to deliver drugs or genes.

They can range in size from 20 nm to a few microns. Liposomes offer several advantages for gene delivery:

• They are very cheap to produce and do not cause diseases

• Protection of the DNA from degradation, mainly because of nucleases

• They can transport large pieces of DNA

• They may be targeted to specific cells or tissues

Chitosan: Chitosan [b(1-4)2-amino-2-deoxy-D-glucose] is a biodegradable polysaccharide copolymer of N-acetyl-D-glucosamine and D-glucosamine obtained by the alkaline deacetylation of chitin.

Unique properties as carrier for gene therapy

Potentially safe and non-toxic, can be degraded into H2O and CO2 in the body and ensures its biosafety, biocompatible & does not elicit stimulation of the mucosa, cationic polyelectrolyte nature provides a strong electrostatic interaction with negatively charged DNA and protects the DNA from nuclease degradation, mucoadhesive property of chitosan potentially leads to a sustained interaction between the macromolecule being "delivered" and the membrane epithelia, promoting more efficient uptake, the ability to open intercellular tight junctions, facilitating its transport into the cells.

Poly (Ethylene Imine) (PEI): PEI is produced by the polymerization of aziridine and is used to deliver genetic material. The use of PEI for gene delivery is limited due to the relatively low transfection efficiency, short duration of gene expression, and elevated toxicity.

(E)Dendrimers:

Dendrimers bind to genetic material when peripheral groups, that are positively-charged at physiological pH, interact with the negatively-charged phosphate groups of the nucleic acid. The toxicity profile of dendrimers is good, although it depends on the number of terminal amino groups and positive charge density.

Poly-L-Lysine: Poly-L-lysine is a biodegradable peptide synthesized by polymerization on N-carboxy- anhydride of lysine. It has capacity to form nanometre size complexes with polynucleotides owing to the presence of proton able amine groups on the lysine moiety. The most commonly used poly-L-lysine has a polymerization degree of 90 to 450.

Viral Vectors

Retrovirus (Figure 5)[14]

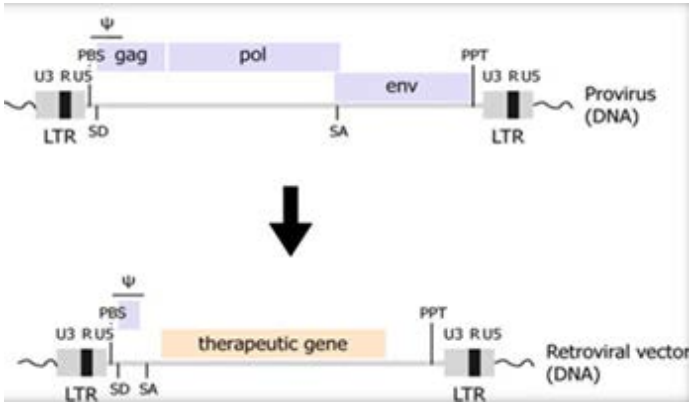

Figure 5: Structure of retroviral vectors[14]

Lentivirus (Figure 6)[15]

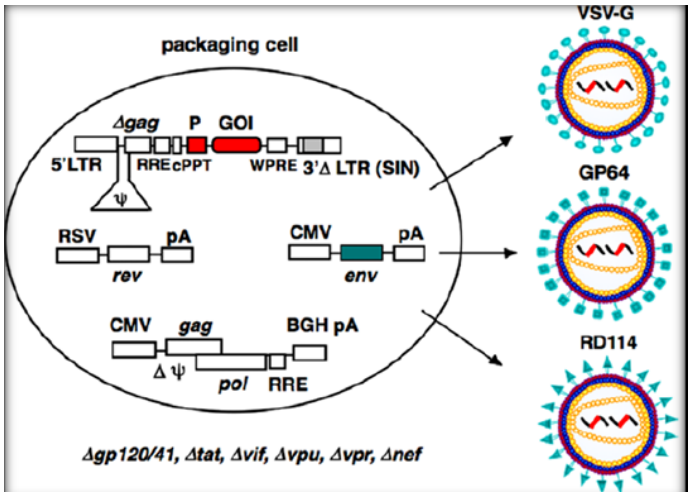

Figure 6: Lentiviral vector production[15]

(C)Adenovirus

(D)Adeno-Associated Vectors

(E)Herpes Simplex Virus

Technical difficulties[6,16]

1. Difficulty in delivering of gene: It is not easy or predictable to deliver successful gene in gene therapy even for single gene disorder
2. Short-lived nature of gene therap
3. Activation of immune response: Viral vector can be recognized as antigen and leads to activation of immune respons
4. Chance of inducing a tumour (insertion mutagenesis): If the DNA is integrated in the wrong place in the genome, it can induce disease
5. Safety of vector: Viruses, the carrier of choice in most gene therapy studies, present a variety of potential problems to the patient toxicity, immune and inflammatory responses and gene control and targeting issues
6. Difficulty to treat multigene disorder
7. Expensive

Gene therapy in clinical medicine

Alzheimer's disease: Tiny particles called exosomes, which are released by cells, to administer drugs into the brains of mice. Exosomes could be used to carry gene therapy to particular genes in the brain. One among these genes is BACE1, produces a protein associated with Alzheimer's disease.

Cystic fibrosis: In therapy, treatment targets the cause of cystic fibrosis instead of just treating the symptoms. Gene therapy for cystic fibrosis began in 1990, when scientists successfully corrected faulty cystic fibrosis transmembrane conductance regulator (CFTR) genes.

Diabetic Neuropathy: Gene therapy shows promise in treating diabetic polyneuropathy, a disorder that commonly affects diabetics who've had the disease for several years. Researchers in Boston found that intramuscular injections of vascular endothelial growth factor (VEGF) gene may help patients with diabetic polyneuropathy.

Gene therapy in dentistry

Gene therapy for bone repair : Gene therapy may represent an ideal approach towards augmenting bone regeneration as it enhances the first three conditions needed for bone regeneration: Via expression of growth factors gene therapy can enhance osteo-induction, induce osteoblast differentiation and facilitate the production of osteoid matrix and utilize an osteoconductive apparatus. In the case of bone regeneration, transient expression is also a desirable benefit and is readily available with existing gene transfer techniques. Thus, gene therapy in bone regeneration has the unique ability to deliver gene products at elevated levels for an extended duration to precise anatomic locations.[17]

Gene therapy for salivary gland disorders: Salivary glandular tissue lends itself well to gene therapy since it is easily accessible via retrograde instillation of medicines through the salivary ducts and is anatomically encapsulated from adjacent structures, thereby reducing concerns associated with viral vector transduction.[17]

- Gene Therapy for Irradiation-induced Hyposalivation: An adenovirus-mediated water channel (aquaporin-1, AQP1) gene transfer into irradiated submandibular glands showed increased saliva flow in a rat model. Gene transfer can also be utilized to augment salivary secretions by transferring genes that encode secretory proteins into salivary glands
- **Gene Therapy for Sjogren's Syndrome Impaired Salivary Gland Function**: Potential target genes in gene therapy for SS-damaged hyposalivation include inflammatory mediators, cytokine inhibitors, apoptotic molecules, cell-cell interaction or intracellular molecules
- **Gene Transfer to Salivary Glands**: It was shown that rat salivary glands, after being administered the rAd5 vector

encoding human alfa-1 antitrypsin (hA1AT), were able to secrete the transgene protein into the bloodstreams.

Gene therapy for chronic pain management: The utilization of gene transfer technology offers a potentially new approach to manipulate specific, localized biochemical pathways involved in pain generation. The utilization of gene transfer in place of drug delivery to achieve the continual release of short-lived bioactive peptides in or near the spinal dorsal horn underlies the foremost common strategies for gene therapy of pain.

Gene therapy for DNA vaccinations: In the last decade, gene transfer research has led to a novel way to achieve vaccination: Directly delivering DNA in a plasmid vs the traditional administration of a purified protein or an attenuated microbe. DNA vaccines consist of a eukaryotic expression vector containing a target gene of interest.[17]

Gene therapy for implant osseointegration: Adenovirus-vectors encoding human Platelet Derived Growth Factor-β (PDGF-β) have been used to accelerate bone fill and improve bone density thereby improving implant osseointegration. Recently, calcium phosphate nano-particles have been used as a non-viral vector to transduce PDGF-gene plasmids to human fibroblasts.[18]

Gene therapy to keratinocytes: Epidermal and oral keratinocytes are potential vehicles for gene therapy. Several features of these tissues can be utilized to achieve delivery of therapeutic gene products for local or systemic delivery. These qualities include:

(1) The presence of stem cells

(2) The cell-, strata- and site-specific regulation of keratinocyte gene expression

(3) Tissue accessibility

(4) Secretory capacity.

Gene therapy for orthodontic tooth movement: Local RANKL gene transfer to the periodontal tissue accelerated orthodontic tooth movement by approximately 150% after 21 days, without eliciting any systemic effects.[17]

Gene therapy in periodontics

(a)Periodontal Tissue Regeneration

Platelet derived growth factor: PDGF-BB is most effective on PDL cell mitogenesis and matrix biosynthesis.[19] Recombinant human PDGF-BB in a synthetic scaffold matrix (beta-tricalcium phosphate) promotes long-term stable clinical and radiographic improvements for patients with localized periodontal defects. Most recently, analysis of the release of this growth factor by nano-sized calcium phosphate particles is showing promising results in terms of biocompatibility and efficient transfection into fibroblasts.[5]

Bone morphogenetic proteins: After the treatment with recombinant BMP – 2 many studies have shown a significant improvement of alveolar bone regeneration in the periodontal defects and rh-BMP 2 also improved the regeneration of cementum and insertion of periodontal ligament fibres.[16] BMP-7 promotes proliferation, differentiation, and mineralized nodule formation, especially in cemento blasts by inducing PCPE1 and BMP1 responsible for processing of type I collagen. It also downregulates BMP-4, although it upregulates DMP-1, probably more through the IGF-II than the IGF-I pathway.[5] After BMP-12 treatment, results showed less bone and more functionally oriented PDL between the new bone and new cementum.[19]

Vascular endothelial growth factor: Blocking VEGF leads to a decrease in trabecular bone formation at the growth plate secondary to suppression of blood vessel invasion and impairment of cartilage resorption. VEGF is able to promote ossification by either inducing neovascularization or by directly affecting bone cells. can stimulate ossification through the two pathways of

endochondral ossification and intramembranous ossification.[16]

Transforming growth factor beta: TGF-β1 seems to play an important role in inducing fibroblastic differentiation of PDL stem/progenitor cells and in maintaining the PDL apparatus under physiological conditions[16]

Transcription factors and regulators: Runt-related transcription factor 2 (Runx2), Osterix (Osx), and LIM domain mineralization protein (LMP), may hold promise in periodontal tissue engineering, especially in alveolar bone augmentation. Runx2 is a master transcription activator of osteoblast differentiation. Osx is a zinc-finger-containing transcription factor that works downstream of Runx2 in osteoblast differentiation. LMP-1 is an intracellular protein that is highly upregulated at the early stage of osteoblast differentiation.[16]

Bone sialoprotein: Cbfa1 is a "master-gene" in osteogenesis and is involved in BSP gene expression which controls the cell differentiation during bone repair and regeneration.[16] By the in vivo delivery of a BSP-gene into an osseous defect, it has been shown to regenerate periodontal alveolar bone.[20]

NTF-hydrogel therapy: NTF-hydrogel therapy is a novel, innovative method of regenerating bone.[20] NTFs have been immobilized in hydrogels, microspheres, electro-spun nanofibers and combined systems, which serve as depots for sustained local release of protein NTF-hydrogel therapy is a novel, innovative method of regenerating bone.[16]

Angiogenic factors for periodontal repair: Basic fibroblast growth factor (bFGF or FGF-2) has been demonstrated to have potent angiogenic activity and potential to induce the growth of immature PDL cells. Enamel Matrix Derived protein (EMD) has angiogenic effects both in vitro and in vivo. First, PDL cells secrete growth factors, including TGF-β1, IL-6, and PDGF-AB after exposure to EMD. TGF-β1 and PDGF-AB have been shown to accelerate the rate of healing in periodontal wounds by specifically stimulating the proliferation of PDL cells. Second, it has been demonstrated that EMD can modulate the bacterial growth of putative periodontal pathogens.[17]

Anti-apoptosis gene: The Bcl2 family of proteins are considered as gatekeepers to the apoptotic response and comprises proapoptotic and antiapoptotic members. It is used in regulation of tissue dynamics and is specifically thought to induce apoptosis in terminally differentiated cells, including inflammatory cells.[16,20]

DNA Devices: This gene delivery technology employs proprietary formulations incorporating intact DNA into polymers capable of being used as coatings on implantable devices such as periodontal implants creating a new class of site-specific gene therapy products.[20]

Gene Therapy in Implantology

Park., et al. in 2015 evaluated ex vivo BMP 2 gene delivery using canine periodontal ligament stem cells for regeneration of per-impactites defects. Lutz., et al. in 2008 evaluated rate of bone formation and osseointegration after topical gene delivery with a liposomal vector system carrying BMP 2cDNA in combination with collagen carrier in freshly created peri implant bone defects.[16]

Future strategies of gene therapy:

Genetic approach to biofilm antibiotic resistance:

One of the best-known of these biofilm-specific properties is the development of antibiotic resistance that can be up to 1,000-fold greater than planktonic cells.[21] Study by Mah., et al. identified gene ndv B encoding for glycosyltransferase required for the synthesis of periplasmic glucans in wild form of Pseudomonas

aeruginosa RA14 strain. This remarkably protected them from the effects of antibiotics biocides, and disinfectant.[16]

Gene therapeutics-periodontal vaccination: In the last decade gene transfer research has led to a novel way to achieve a vaccination. A salivary gland of a mouse when immunized using plasmid DNA encoding the Porphyromonas gingivalis (P. gingivalis) fimbrial gene produces fimbrial protein locally in the salivary gland tissue resulting in the subsequent production of specific salivary immunoglobulins A, or IgA and immunoglobulin G, or IgG, antibodies and serum IgG antibodies. This secreted IgA could neutralize P. gingivalis and limit ability to participate in plaque formation. Similarly, secreted fimbrillin in saliva could bind to pellicle components blocking the attachment of P. gingivalis.[21] Scientists have also demonstrated the efficacy of immunization with genetically engineered Streptococci gordoni vectors expressing P. Gingivalis is fimbrial antigen as vaccine against P. gingivalis associated periodontitis in rats.[22] The recombinant hemagglutinin B (rHag B) when injected subcutaneously in Fischer rats infected with P. gingivalis showed serum IgG antibody and interleukin-2 (IL-2), IL-10, and the IL-4 production which gave protection against P. gingivalis induced bone loss.[6] Currently, Hag A and B have been more extensively characterized than Hag C or D. Furthermore, there has been a great deal of interest in the potential utilization of Hag B in vaccine development.[21]

An in vivo gene transfer by electroporation for alveolar remodelling: Using an in vivo transfer of LacZ gene (gene encoding for various re-modelling molecules) into the periodontium and using plasmid DNA as a vector along with electroporation (electric impulse) for driving the gene into cell, has shown predictable alveolar bone remodelling.[6]

Antimicrobial Gene Therapy To Control Disease Progression: One way to enhance host defense mechanism against infection is by transfecting host cells with an antimicrobial peptide/protein encoding gene. Researchers have shown when host cells were infected in vivo with β defensin-2 (HBD-2) gene via retroviral vector; there was a potent antimicrobial activity which enhanced host antimicrobial defences.[16]

Designer drug therapy in treating periodontal disease: If genes necessary for normal development are known, then "designer drug therapies" aimed at one area of the gene or the other can be developed. These designer drugs will be safer than today's medicines because they would only affect the defect in a gene clearly identified through genetic research.

Tight adherence gene for the control of periodontal disease progression: Researchers have developed mutant strains lacking the "tight adherence gene" which could predictably control periodontal disease progression by limiting colonization and pathogenesis of Actinobacillus actinomycetemcomitans.[20]

Future Perspectives

Major advances have been made over the past decade in the reconstruction of complex periodontal and alveolar bone wounds that have resulted from disease or injury. Utilization of exosomes as carriers for gene therapy have also been studied. Designer drugs are going to be safer than today's medicines because they will only affect the defect in a gene clearly identified through genetic research. Further advancements within the field will still rely highly on multidisciplinary approaches that combine engineering, dentistry, medicine, and infectious disease specialists in repairing the complex periodontal wound environment.[16] Unprecedented levels of control over nucleic acid delivery, modulation of the immune system, and precise manipulation of the human genome –

technologies not imaginable ten years ago – will certainly unlock new areas of medicine over the next ten years.[23]

Conclusion

Today's improvements in technology coupled with the changing pattern of diseases have stimulated research on genetics. Gene therapy has a promising role in the field of periodontics but it does encompass serious ethical issue to be dealt with. There are still lots of research and details of mechanisms to be understood to include these practically in day-to-day treatment modalities.[23]

References

1. Lundstrom K, Boulikas T. Viral and non-viral vectors in gene therapy: technology development and clinical trials. Technology in cancer research & treatment. 2003 Oct;2(5):471-85.
2. Gonçalves GA, de MA PR. Gene therapy: advances, challenges and perspectives. Einstein (Sao Paulo) 15 (3): 369–375.
3. Sung YK, Kim SW. Recent advances in the development of gene delivery systems. Biomaterials research. 2019 Dec;23(1):1-7.
4. Lin NH, Gronthos S, Mark Bartold P. Stem cells and future periodontal regeneration. Periodontology 2000. 2009 Oct;51(1):239-51.
5. Padial-Molina M, Rios HF. Stem cells, scaffolds and gene therapy for periodontal engineering. Current Oral Health Reports. 2014 Mar 1;1(1):16-25.
6. Chatterjee A, Singh N, Saluja M. Gene therapy in periodontics. J Indian Soc Periodontol. 2013;17(2):156–61.
7. Kinnon C, Levinsky RJ. Somatic gene therapy for genetic disease. Archives of disease in childhood. 1990 Jan;65(1):72.
8. Chung HJ, Lee HS, Kim HJ, Hong ST. The Mechanical Agitation Method of Gene Transfer for Ex-Vivo Gene Therapy. Non-Viral Gene Therapy. 2011 Nov 7:91.
9. Wu P, Chen H, Jin R, Weng T, Ho JK, You C, Zhang L, Wang X, Han C. Non-viral gene delivery systems for tissue repair and regeneration. Journal of translational medicine. 2018 Dec;16(1):1-20.
10. Nayerossadat N, Maedeh T, Ali PA. Viral and nonviral delivery systems for gene delivery. Advanced biomedical research. 2012;1.
11. Du X, Wang J, Zhou Q, Zhang L, Wang S, Zhang Z, Yao C. Advanced physical techniques for gene delivery based on membrane perforation. Drug delivery. 2018 Jan 1;25(1):1516-25.
12. Kuriyama S, Mitoro A, Tsujinoue H, Nakatani T, Yoshiji H, Tsujimoto T, Yamazaki M, Fukui H. Particle-mediated gene transfer into murine livers using a newly developed gene gun. Gene therapy. 2000 Jul;7(13):1132-6.
13. Ramamoorth M, Narvekar A. Non-viral vectors in gene therapy-an overview. Journal of clinical and diagnostic research: JCDR. 2015 Jan;9(1):GE01.
14. Giacca M. Methods for gene delivery. In Gene therapy 2010 (pp. 47-137). Springer, Milano.
15. Mátrai J, Chuah MKL, VandenDriessche T. Lentiviral Vectors. In: A Guide to Human Gene Therapy. WORLD SCIENTIFIC; 2010. p. 53–67.
16. Thomas SJ, Pr A, Abraham S, Reejaol. Current Concepts and Future Aspects of Gene Therapy in Periodontics. Acta Scientific Dental Sciences. 2018;20(7):118–126.
17. Prabhakar AR, Paul JM, Basappa N. Gene therapy and its implications in dentistry. International journal of clinical pediatric dentistry. 2011 May;4(2):85.
18. Swamy DF, Dessai SSR, Barretto ES, Dsouza KM. Gene therapy applications in dentistry: A review. J

Clin Diagn Res [Internet]. 2017; Available from: http://dx.doi.org/10.7860/jcdr/2017/28150.10703

19. Sood S, Gupta S, Mahendra A. Gene therapy with growth factors for periodontal tissue engineering–A review. Medicina oral, patologia oral y cirugia bucal. 2012 Mar;17(2):e301.
20. Karthikeyan BV, Pradeep AR. Gene therapy in periodontics: a review and future implications. J Contemp Dent Pract. 2006 Jul 1;7(3):83-91.
21. Mahale S, Dani N, Ansari SS, Kale T. Gene therapy and its implications in Periodontics. Journal of Indian Society of Periodontology. 2009 Jan;13(1):1.
22. Katz J, Black KP, Michalek SM. Host responses to recombinant hemagglutinin B of Porphyromonas gingivalis in an experimental rat model. Infection and immunity. 1999 Sep 1;67(9):4352-9.
23. Bulaklak K, Gersbach CA. The once and future gene therapy. Nature Communications. 2020 Nov 16;11(1):1-4.