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An Attempt to Involve Genetics: To Evolve Periodontics.

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Review Article

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ABSTRACT

Periodontal disease is found with high prevalence and variability with few individuals experiencing severe destruction. As host susceptibility may be defined in terms of genetic variation, now the focus is been to quantify genetic risks, identify specific genetic variants and correct genetic defect. Gene therapy is a technology by which genes or small DNA or RNA molecules are delivered to human cells, tissues or organs to correct a genetic defect or to provide new therapeutic functions for the ultimate purpose of preventing or treating diseases. This review article briefs about fundamentals of gene therapy, various modes of administration and its future implications in field of Periodontics.

INTRODUCTION

Traditionally, Periodontitis was thought to be strictly environmental in origin [1]. These diseases are defined by signs and symptoms of gingival inflammation and periodontal tissue destruction [2]. Current understanding includes the role of host genes in the etiology and pathogenesis of periodontal diseases which is critically important to the determination of patient risk for periodontal tissue breakdown. Periodontal therapy includes systemic adjuncts to local treatment and special precautions in patient management. Gene therapy a part of recent technology is still in infancy stage and more theoretical in nature.

Gene therapy is a field of biomedicine. There have been tremendous advances in gene therapy relevant to dentistry since 1995 [3]. However, in the field of periodontics gene therapy has not been applied with success primarily because the technology of gene therapy is still far from perfect and certainly has its own substantial problems. At present, gene therapy modalities for periodontal regeneration are at clinical trial levels in animal models. However, research is underway for using gene therapy approaches to alter host responses and specific periodontal pathogens. The understanding of basic principles and advances in gene therapy is essential to have an insight into the prospects and advances of this new field in periodontics.

What are genes?

Genes are specific sequences of bases that encode instructions on how to make proteins. Genes are carried on chromosomes and are the basic physical and functional units of heredity [4].

What is gene therapy?

Gene therapy is a technology by which genes or small DNA or RNA molecules are delivered to human cells, tissues or organs to correct a genetic defect or to provide new therapeutic functions for the

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ultimate purpose of preventing or treating diseases. The most comprehensive description of gene therapy is use of recombinant genetic material under different forms or pharmaceutical, as a therapeutic agent [5].

How does gene therapy function? [5].

The delivery of genes (gene transfer) can take place directly into the patient's body (in vivo gene therapy), or in cells which are treated outside the body and then reimplanted or re-infused into the patient (ex vivo gene therapy).

In in vivo gene therapy, a therapeutic gene is administered to a specific tissue or organ for a defined application. The administration can take the form of particles derived from disabled viruses (viral vectors), artificial particles (synthetic vectors), or "naked" DNA. The route of administration can be intravenous, intramuscular, by inhalation, or by direct injection into the target organ.

In ex vivo gene therapy, the cells come either from the same patient (autologous treatment) or from a donor (allogeneic treatment). Gene transfer is carried out in culture by many different techniques, again involving viral or non-viral vectors. Due to limitations in growing, manipulating, and re-administering cells from many tissues and organs, ex vivo gene transfer is today essentially limited to blood, skin and liver cells, to cells of the immune system, or to tumour-derived cells used as cancer vaccines.

Because non-viral alternatives do not have the drawbacks of undesired host immune reactions or potential tumorigenesis, they are likely to be given more consideration in the future.

Viral vectors:

- Retrovirus – a class of viruses that can create double stranded DNA copies of their RNA genomes.
- Adenoviruses- a class of viruses with double stranded DNA genomes.
- Adeno-associated viruses – A class of small, single stranded DNA viruses that can insert their genetic material at a specific site on chromosome
- Herpes simplex viruses- a class of double stranded viruses that can infect a particular cell type i.e. neurons.
- Lenti viruses

Non-viral vectors:

- Plasmids
- DNA polymer complexes.

Implications of gene therapy in periodontics [6]

Gene therapy has been used as a mode of tissue engineering in periodontics. The tissue engineering approach reconstructs the natural target tissue by combining 3 elements namely scaffold, signalling molecules and cells.

Three basic approaches in tissue engineering are:

- Protein based approach- In this approach growth and differentiation factors are used for regenerating periodontal tissues.
- Cell based approach- In this approach mesenchymal stem cell is used for reconstruction.
- Gene delivery approach- It involves 2 basic modalities
    - In vivo gene delivery- In this approach, gene constructs such as plasmid or a viral particles are entrapped physically in a scaffold. When scaffold is implanted into the tissue defect, host cells migrate into implant with the help of gene constructs and start producing proteins.
    - Ex vivo gene delivery- In this approach cultured cells are transfected using non-viral delivery systems or transduced using viral methods with gene constructs in vitro and than they are transplanted into the tissue defect.

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Gene Enhanced Tissue Engineering [4]

The general strategy of tissue engineering is to supplement the regenerative site with a therapeutic protein-like growth factor. However the problem with the delivery of growth factor is its short life (a few hours). This is due to proteolytic breakdown and receptor mediated exocytosis and solubility of the delivery vehicle. To overcome this problem, gene therapy has been developed which provides long-term exposure (at least two weeks) of the growth factor to the periodontal wound.

Clinical trials using gene therapy [4,7,8,10]

Sr no	Author	Study	Results
1	Jin QM et al	Different cell types such as non-osteogenic fibroblast (from human gingiva and dental pulp), oral keratinocytes, myoblasts, as well as osteoblasts were infected with adenoviral vector	These cells differentiated into bone forming cells when placed into the osseous defect *in vivo*.
2	Chen GP et al	In vivo PDGF-A gene transfer through adenovirus vector (Ad-PDGF-A).	Bioactive Ad-PDGFAA protein released induces sustained tyrosine phosphorylation and corrective down regulation of PDGF receptor which is encoded by "growth arrest specific (gas) gene" was seen this extends the effect of PDGF on cell signaling which is critical for cellular proliferation.
3	Diego S.	Bcl2 gene (antiapoptosis gene) in conjunction with gene activated matrix technology (GAM) was introduced into a highly localized tissue injury site .	Improvement in the clinical outcome of the tissue injury by means of tissue repair and/or tissue regeneration was observed.
4	Mellon C.	NTF gene (non-viral non- immunogenic gene) was injected together with a synthetic, non-immunogenic hydrogel made from hyaluronic acid into the site of bone loss	It induced neighboring cells to produce new bone tissue.
5	Chang P C et al	Alveolar ridge defects were created in rats and were treated at the time of titanium implant installation with a collagen matrix containing an adenoviral vector encoding PDGF-B, Ad encoding luciferase (Ad-Luc; or recombinant human PDGF-BB protein (rhPDGF-BB, 0.3 mg ml(-1)	Bone repair was accelerated by Ad-PDGF-B and rhPDGF-BB delivery compared with Ad-Luc, with the high dose of Ad-PDGF-B more effective than the low dose.
6.	Dunn et al	In vivo gene delivery of Ad/BMP-7 in a collagen gel carrier	Successful regeneration of alveolar bone defects around dental implants was promoted.

Future Strategies of Gene Therapy in Preventing Periodontal Diseases [4]

Gene Therapeutics-Periodontal Vaccination

In the last decade gene transfer research has led to a novel way to achieve a vaccination like

- 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 production of secreted IgA which could neutralize P. gingivalis and limit its ability to participate in plaque formation. Similarly, secreted fimbrillin in saliva could bind to pellicle components blocking the attachment of P. gingivalis.
- Scientists have also demonstrated the efficacy of immunization with genetically engineered Streptococci gordoni vectors expressing P. gingivalis fimbrial antigen as vaccine against P. gingivalis associated periodontitis in rats.
- The gene hemagglutinin, which is an important virulence factor of P. gingivalis, has been identified, cloned, and expressed in Escherichia coli. The recombinant hemagglutinin B (rHag B) when injected subcutaneously in Fischer rats gave protection against P.gingivalis induced bone loss.

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Genetic Approach to Biofilm Antibiotic Resistance

Using a genetic approach researchers have isolated ndvB mutant of Pseudomonas aeuroginosa, still capable of forming biofilm but lacking the characteristic of periplasmic glucans, thereby, rendering microbial communities in biofilm more susceptible to conventional antibiotic therapy.

An In vivo Gene Transfer by Electroporation for Alveolar Remodelling

Predictable alveolar bone remodelling has been found after, in vivo transfer of LacZ gene into the periodontium and using plasmid DNA as a vector along with electroporation (electric impulse) for driving the gene into cell.

Tight Adherence Gene for the Control of Periodontal Disease Progression

Development of mutant strains of "tight adherence gene" of Actinobacillus actinomycetemcomitans required for its adherence and virulence, limits colonization and pathogenesis of Actinobacillus actinomycetemcomitans.

Antimicrobial Gene Therapy to Control Disease Progression

Researchers have shown when host cells were infected in vivo with defensin-2 (HBD-2) gene via retroviral vector; there was a potent antimicrobial activity which enhanced host antimicrobial defence.

CONCLUSION

Conventional periodontal therapy consists of patient education, oral hygiene importance, scaling and root planing and regular patient recalls, it may or may not include periodontal surgery. Aggressive and atypical forms of periodontitis clearly show the host immune response playing a significant role.

Gene therapy has the potential to treat diseases such as cystic fibrosis, cancers, heart diseases and human immunodeficiency virus infection. However, to date, no clinical trial of gene therapy has resulted in the development of a commercially available treatment. Unsettled issues in gene therapy include effectiveness of delivery, longevity of the therapy and safety of procedures. Gene therapy as a part of treatment modality for periodontal tissues is yet at an emerging level. Further research and more clinical trials would help understand the role of gene therapy better and make Periodontics more predictable.

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