

## New Insight on the Role of Molecular Dentistry in the Perfection and Improvement of Clinical Dentistry

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### Abstract

Technological and scientific innovations have increased exponentially over the last decade. With the continuous advancement in new research techniques, researchers continually develop breakthrough therapies by understanding the cellular and molecular base of every disease. In the process of evolution, gene therapy and molecular dentistry are driving improvements in drug development. Gene therapy has opened doors to the era of evidence-based dentistry. Studies based on the interaction between genetic and dental disorders have given new understanding of the treatment options for oral diseases. Knowledge in molecular dentistry, transcriptomes, and proteomes can assist in better control and prevention of personalized orthodontics. This review portrays the links between genetic disposition and its significant impact in the field of dentistry.

**Keywords:** *Molecular Dentistry; Gene Therapy and Stem Cells*

### Introduction

Science is the knowledge of testable explanations and predictions. With scientific advancements in genetics, molecular biology and bioinformatics, the depth and breadth of every medical condition is researched to justify and establish best medical treatments to prevent and cure diseases [1]. One of the recent practices that create wonders in the clinical progress is the human genome projects [2]. They give a better understanding on the genetic aspects of every disease. Thanks to the novelty in genetic studies, that most of the disorders that have been pointed as the victim's error has now been identified as hereditary defects. Thousands of human genetic diseases have been identified so far with therapies and treatments being created with clinical efficacy. In the field of dentistry, hereditary factors are found to influence several oral disorders [3].

When genes are passed from parents to children, DNA changes within the gene also gets passed. Some of these changes may cause mistakes in protein instructions and may not work properly thereby causing genetic disorders. These genetic disorders may either be passed down dominantly or recessively. In the way of inheritance pattern a person may develop some disorders that may either have acute or chronic symptoms. This knowledge on genetic oral susceptibility, risk factors of oral health and effects of oral disorders can enlighten dentists to treat patients with appropriate diagnosis [4].

Genetic approach in dentistry has aided in the discovery of new treatments for a variety of diseases such as induction of new bone and cartilage tissue, artificial synthesis of saliva for patients with salivary gland disorders, autoimmune diseases, oral cancerous and precancerous condition, DNA vaccination etc. Researchers are trying to dig deeper into gene therapy to exterminate diseases by treating genes that are responsible for causing disorders [5]. The advances in genetics on dentistry, molecular biology of periodontal structures, biochemical developments in dental research and biomimetics in dentistry will pave way for enormous advanced treatment strategies of inherited dental and oral diseases [6,7]. This paper discuss briefly about these latest advances in the research and clinical practices of dentistry.

### Salivaomics

Salivaomics is the method of using saliva for diagnostic purposes. Progression in the field of molecular diagnosis has made physical examination easier without any pain or discomfort. Novel discoveries suggest clinically relevant information about a person can be obtained by his saliva. Researchers prove that oral fluid is also a source of biochemical data which may represent a significant reservoir of molecular and microbial information that correspond to the presence of disease in the body [8].

Biomarker in oral fluids is a huge leap in clinical science that unveils a large number of medically valuable analytics in saliva. Saliva contains bio-components which may be subjected to proximate and external factors. Monitoring the molecular compositions in saliva are inductive to both local and distant diseases. Detectable changes that arise in salivary proteome, transcriptome, mRNAs, miRNAs, metabolome, microbiome and epigenome may give evidence to a variety of diseases [9].

The patient's salivary transcriptomes are profiled using a microarray. It is then compared with the salivary-gland-specific gene expressions of a healthy person and the disease specific biomarkers are identified and validated to display the patient's periodontal status. Using the same technique researches are attempting to determine whether measurement of the inflammatory cytokines IL-1beta or TNF-alpha in saliva could be used as markers associated with clinical evidence of periodontal disease [5]. Though regeneration of lost periodontium has not yet been achieved till date it will become viable through advancement in therapeutic approaches in the near future.

### Dental pulp stem cell for bone defects and regeneration

By the beginning of the 21<sup>st</sup> century the use of mesenchymal stem cells (MSCs) for the treatment of diseases from muscular dystrophy to the regeneration of brain tissue has become a possibility. In the same way, after the discovery of dental pulp stem cells (DPSCs), several studies have developed in the field that promise alternative for regenerative therapies such as bone regeneration and periodontal ligament [10]. The multipotent DPSCs have the potential to differentiate into a variety of cell types including neural cells, adipocytes, odontoblasts, osteoblast and chondrocytes. Such stem cells have the ability to generate into dentin like tissue *In vitro* and *In vivo* studies. Most of the studies on animal models with human immature dental pulp stem cells (hDPSC) and scaffold technology have shown to repair local bone defects [11,12].

Repairing bone defects and bone crack are the long standing goals in the research of mineralized tissue field. Research conducted at the University Of Michigan School Of Dentistry suggests that both orthotopic and ectopic bone formation can be achieved by transferring encoding bone morphogenetic proteins or BMPs through ex vivo methods. Also studies conducted by researchers at Hebrew University-Hadassah suggest that mesenchymal stem cells derived from bone marrow enhance the bone forming cells. Stem cells with BMPs also had the capacity to form new blood vessels as well as new bone. Research has also proven that delivering BMP-2 to tissues via adenoviral vector will heal defects in the mandible. Thus when the defective site is supplemented by therapeutic proteins such as BMP-2, 4 and 7, the reparative response is enhanced. There is also a clear possibility that varieties of BMP genes not only works on osteoinduction but also work collaboratively in skeletal development and repair [13].

Regeneration of bone structure is a complex process yet its usage in the management of craniofacial bone anomalies, tooth loss, temporomandibular joint disorders, other joint diseases, traumatic amputations and the consequences of tumor resection may be crucial [14,15].

### **Biomimetics in tooth growth**

Biomimetics is studying of biologically produced materials and biological mechanisms for the purpose of synthesizing similar materials without losing its functional and esthetic results. Some biomimetic products can be used in tooth agenesis to stimulate the regeneration of dental structures and lost dental tissue [16].

Tooth agenesis is the absence of one or more teeth due to developmental failure. The abnormal function of specific genes such as MSX1 and PAX9 which are cited as the main cause of tooth agenesis. Such patients may also suffer from malocclusion, periodontal damage, insufficient alveolar bone growth, reduced chewing ability, inarticulate pronunciation and other problems. While hundreds of genes such as, AXIN2, TGFA, IRF6 and FGFR1 are involved in teeth growth, several studies show that the failure of tooth bud development is mostly connected with defects in MSX1 and PAX9 gene [17]. Treatments for the missing teeth include orthodontic space closure, deciduous tooth maintenance, implant therapy and adhesive bridgework [18].

Using biomimetic dentistry and molecular biology, tooth growth can be achieved by adding necessary molecules to the oral cavity. With advancement in molecular biology and bioinformatics, it is assumed that in the coming years, the genetic etiology of tooth agenesis and the mutations associated with it will be understood which shall provide a way to effective treatment for tooth agenesis. Research on the regenerative property of the pulp-dentin can pave a way for laboratory tooth growth and surgical replacement with living and functional tooth. Though effective results are yet to be seen in humans, scientists in dental fields are working to identify the gene that initiates tooth growth to eliminate this disorder completely [19,20].

### **Vaccination for dental caries**

Dental caries is a major problem for health care providers. They are irreversible and occur on the surface of the teeth with Streptococcus mutants being the active participant in the disease [21]. The principal immunoglobulin isotype present in the external secretion around the infection is secretory IgA (SIgA). Immunization procedures against dental caries are mediated mainly by the induction of salivary SIgA antibodies [22]. Over a period of many years various modalities have been used to reduce the prevalence of dental caries but the advancements in molecular dentistry have led to the understanding that DNA vaccination will help cure hereditary caries and periodontal diseases. DNA vaccination is different from a conventional vaccination. It uses gene from a virus or bacteria to stimulate the immune system thereby preventing illness. The traditional administration of purified proteins or an attenuated microbe is shifted towards delivering DNA directly through plasmids. When plasmid DNA encoding the antigen was administered in an animal model, the plasma DNA encoding the *Porphyromonas gingivalis* fimbrial gene led to the production of fimbrial protein in its salivary gland tissue. Consequently, there was a production of specific salivary immunoglobulin A, immunoglobulin G antibodies and serum IgG antibodies. Furthermore, origination of antibodies, helper T cells and cytotoxic T-lymphocytes can be reached through DNA vaccination [23]. These approaches shall play a pivotal role in future strategies for preventing periodontal diseases and dental caries.

### **Restoration of salivary gland**

Salivary gland hypo-function may lead to several medical conditions like dental decay, bacterial infection, dry mouth (termed xerostomia) and swallowing dysfunction (dysphagia) [24]. The clinical treatment of xerostomia is palliative in nature. Thus gene therapy is currently examined as a potential treatment for the restoration of salivary gland. Improvisation in salivary gland function is triggered by the transfer of a new gene through retroductal cannulation of the affected major salivary gland. This leads to the production of a cellular

therapeutic protein or to the secretion of salivary amylase in blood stream. The genes used for salivary glands are genes-encoding hormones, an antimicrobial agent and membrane protein. Studies using a mice model have proved to be safe while preserving the secretory function. High efficacy was attained while using an AAV2/5 pseudotyped vector rather than a traditional AAV2 vector [12,25].

### Chronic orofacial pain management

Orofacial pain is a common phrase that covers any kind of pain felt around the mouth, neck and face. The underlying causes of orofacial pain may be anything from tooth ache, gum disease, sleep disorders, stress or tension or a serious pain related to temporomandibular disorders (TMD), masticatory musculoskeletal pain, cervical musculoskeletal pain, trigeminal neuropathic pain or neurovascular disorders [26]. These conditions have overlapping presentations that the source of the pain cannot be determined easily by the dentists. Due to several indicators, understanding and assessing the pain is quite a challenging process for the dentists. The cause of the chronic pain should be properly diagnosed to avoid any false treatment as this may become a threat to the patient's health [27].

Gene therapy and molecular biology is being studied to overcome the challenges of pharmacotherapy and the complexity of chronic pain. Use of gene therapy enhances the expression of anti-pro-inflammatory cytokines that links to both neuropathic pain and opioid analgesic tolerance development. A carrier called vector which is a virus that is genetically altered to carry normal human DNA, is introduced into the nerves of dorsal root ganglia of the patient. Since the vector is targeted at a very specific area even a single dosage provides long term pain relief [28]. Factually 70% of gene therapy has used modified virus such as retroviruses, lentiviruses, adenoviruses, herpes simplex virus (HSV) and adeno-associated viruses (AAVs) as vectors to deliver genes [29-31].

There is also another method of pain reduction using non-viral options for gene delivery [32]. The therapeutic DNA is directly introduced into the target cells or by creating an artificial lipid encapsulated plasmid that is injected into the root ganglia. Compared to viral vectors the non-viral vectors are easy to produce and can deliver large genetic sequence. Though gene therapy is limited to animal studies, it has emerged as a next generation tool to achieve treatment for pain using vector delivery systems [33].

### Oral malignant tumor management

Tumor cell implicates impaired cell cycle progression, largely due to mutations and the over expression of cell-cycle regulators [34]. Oral Squamous Cell Carcinoma is one of the malignant tumors of the oral cavity. It represents 95% of all tumors affecting the head and neck area. Oral cancer that occurs mostly to patients above the age of 50 is associated with genetic mutations that results due to the consumption of alcohol, tobacco chewing, betel quid etc. Since this malignant disorder occurs in the cells that control cell growth, it results in uncontrolled proliferation of cells. Standard therapies do not usually hinder the spreading of these tumor cells. Due to its anatomical location, and the critical treatment results, gene therapy was introduced into this treatment [35,36].

Cancer gene therapy has several approaches that involve gene addition therapy, antisense RNA therapy, immunotherapy and suicide gene therapy. In gene addition therapy a wild-type p53 gene is injected to the patient replacing the mutated p53 gene, with an adenoviral vector. Ad-p53 is confirmed to be safe and well tolerated. Many other studies are underway using Ad-p53 to patients with oral squamous cell carcinoma to determine its role as surgical adjuvant and in combination with DNA- damaging agents [37,38].

Systemic administration of EGFR antisense RNA inhibits the tumor growth in xenograft models. Immunotherapy approach involves either boosting the immunogenic potential of the tumor cells or augmenting the patient's immune response to a tumor. Suicide gene therapy involves introduction of a gene into a cell that enables a prodrug to be activated into an active cytotoxic drug. Herpes simplex virus-thymidine kinase (HSV-TK) via adenovirus vector combined with ganciclovir administration is the most extensively used approach. Collectively the therapies involved in tumor management can be termed under corrective gene therapy, cytoreductive gene therapy, immunomodulatory gene therapy. Gene therapy thus has a pervasive and significant impact in areas related to oral malignant tumors [39,40].

### Orthodontic tooth movements

Orthodontic tooth movement results from forces delivered on teeth during bone remodeling. The remodeling of periodontal ligament and alveolar bone due to mechanical stress affects the orthodontic tooth movement [41]. Periodontal ligament and alveolar bone is controlled by osteoclasts and osteoblasts. Hemopoietic cells are the source for the formation of osteoclasts and stromal cells create osteoblasts. For osteoclasts to mature it has to interact with osteoblastic lineage [42]. The molecules that take part in this interaction are the receptor activator of the nuclear factor kappa B (RANK) and receptor activator of nuclear factor kappa-B ligand (RANKL). During the interaction RANKL signaling is inhibited by Osteoprotegerin (OPG), a soluble receptor produced by osteoblasts. Due to the inhibition of RANKL by OPG the process of bone resorption gets jammed. Significant studies made on a rat models, using gene therapy with OPG and RANKL. An obvious accelerated orthodontic tooth movement was achieved through these mediators. It was observed that transfer of the RANKL gene to the periodontal-tissue activated osteoclastogenesis and accelerated the amount of the tooth movement. Therefore, treatment duration can be shortened and results can be enhanced using this process [43,44].

### Conclusion

It can be stated that modern dentistry is evolving with revolutionary techniques in patient treatment and disease prevention. Growing trends in molecular study will enhance the prevention of the two important diseases, tooth decay and periodontal diseases, that every dentists encounter. Biomimetics may open windows to bone substitutes, remineralization of tooth surface and biofilm destruction. There may be considerable growth in the field of personalized dental medicine regenerative dentistry by the analysis of genomic information. Advancements in Genetic engineering techniques will enable the development of pulpal tissue inside non vital the root canals to grow and fulfill the chamber triggering epithelial cells to form dentin and enamel, thus implementing the biologic restoration of teeth. Furthermore, nanotechnology and stem cell therapies will gain more importance in the coming years, taking dentistry to a different dimension.

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