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Review Article

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New Insights of Molecular Dentistry in Dental Management and Oral Biology

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Abstract

Evolution in dentistry, dental materials, genetics and disease management has been growing over the last few decades. Understanding the links between genetics and dental and oral diseases could result in better treatment option. This knowledge could also results in better control and prevention of diseases. This review demonstrates various links between genetic predisposition and effect on dental and oral tissues. It highlights the recent suggestions of up and down regulating different genes and their effect on dental and oral diseases. Further studies are needed to confirm those links and maybe a brighter future in the science of prevention will be reached.

Introduction

Human genome projects provide a broad picture about the genetic aspects of disease. It aims to create novel approaches in diagnoses, preventing and managing diseases. New knowledge has developed in our scientific understanding of the role of genetics for diagnosing diseases and for prevention and treatments. In the dental field, the hereditary factors involvement in caries, oral cancer and disease of the peridontium, malformation of the teeth, congenially missing teeth or other common oral disorders is becoming highly evident in dentistry, as are the collaboration of systematic genetic disease on oral health care.

Dentists should have knowledge to explain the genetic contribution and genetic factors to the patients. Additionally, dentists must familiarize themselves with the genetic that are helpful in diagnosing oral health diseases like orofacial anomalies. They should also familiarize themselves with the effect of such disorders on oral health care. The ultimate understanding of the dentist of these factors and the genetic oral susceptibility, risk factors of oral health and the lifestyle of each patient will lead the dentist to propose the effective prevention and treatment protocol for oral diseases.

Since the Human Genome Project innovation, it became of a great importance that the dentists carefully and adequately apply the genetic information in diagnosis and management of the dental and oral diseases. Knowing the molecular biology of periodontal structures, bony structure, salivary gland and development of the teeth will lead to advanced treatment strategies that will extremely vary from the current surgical based approaches in dentistry. We might eventually reach a conservative approach in treating dental and oral diseases.

Huge advancement has been made in the field of genetic approach for a range of utilization in dentistry since the introduction of gene therapy for dental management [1]. In dental gene therapy, the quality of life will improve. Molecular dentistry and the utilization of genes to manage and treat dental problems had been applied to different aspects in dentistry such as; orofacial pain, bone repair, cancer management, orthodontic tooth movement and regeneration and repair of the teeth. These aspects will be discussed below.

Orofacial Pain

Orofacial pain can be defined as the pain related to the head and neck area and can be correlated to the soft/hard tissues of the face. The pain impulses are perceived through the fifth cranial nerve/the trigeminal nerve and then transmitted to the central nervous system. The diagnosis and management of orofacial pain can be challenging to dentists as diagnosis is made by exclusion. It is difficult to know the origin and cause of the pain as well as the possibility of a referred pain from different sources such as; tempromandibular disorders (TMD), dental hard tissues, pulp inflammation, teeth hypersensitivity, oral soft tissues, salivary glands, neurological tissues, orthodontic tooth movement and vascular or psychogenic tissues [2]. The management of the pain may involve using of analgesics and sedatives medications [2,3].

Molecular biology and gene therapy is being studied as treatment of chronic pain by eliminating the use of drugs that have higher risk of systemic toxicity, addiction of opioid and other side effects [4]. To reduce pain, coding for anti-inflammatory peptides (anti-nociceptive proteins) that inhibits neurotransmission in the dorsal root ganglia can be achieved by either one of two ways. First, by induction of pia matter cells through the interdermal injection of adeno associated virus, modified adenovirus, or lipid encapsulated plasmids into the nerves of dorsal root ganglia. This will results in coding of interlukin-10 that induce pia matter production and hence pain reduction [5].

Second, by injecting a modified herpes virus into the nerves of the dorsal root ganglia through an intradermal route. The herpes virus has an ability to infect the nerves and hence it can signal for anti-inflammatory peptides. It can also inhibit the neural transmission and reduces the formation of nociceptive molecules hence reduction of pain [5].

However, until today, the utilization of genes in managing oro-facial pain is limited to animal. Gene therapy could raise hope in pain treatment by improving vector delivering systems in the future [6].

Bone Repair

Bone loss can occur due to trauma, reconstructive surgery, neoplasia, congenital defects or periodontal disease. Bone regeneration and remodeling strategies evolution through time has been of utmost importance in clinical research. Despite the fact that other dental hard tissues (such as enamel) cannot be regenerated, bone can be remodeled and have a good possibility to regenerate and repair [7].

However, bone regeneration is not that easy as it involves regeneration and construction of complex specific three-dimensional bone structure. Yet, it would be helpful in the management of temporo-mandibular and other joint disorders, craniofacial anomalies and other bone anomalies, tooth loss, traumatic amputations and the consequences of tumor resection.

Broadly, in order to reach a successful bone regeneration, four crucial elements must be available; namely osteoinduction, differentiation of osteoblasts leading to production of the osteoid matrix, osteoconduction and mechanical stimulation. Gene therapy promotes the first three elements [8].

Gene therapy can enhance osteoblast differentiation and speed up the formation and secretion of osteoid matrix, facilitate osteoinduction via expression of growth factors and use an osteoconductive apparatus. Bone morphogenetic proteins (BMP-2, 4 and 7) are the only signaling molecules that are able to solitarily enhance de novo bone production at heterotopic and orthotopic sites. The osteo-inductive potential of BMPs makes them clinically worthy as another option to bone grafts [9]. Insertion of the BMP-2 genes directly to the osseous of the mandibular via a viral vector (adenoviral vector) is utilized in vivo to enhance healing of mandibular osseous defects [10].

Additionally, a variety of cells such as fibroblasts of human gingiva and fibroblasts from dental pulp, osteoblasts cells and myoblasts cells was utilized in vivo researches and an adenoviral vector was inserted in these cells so they were able to express the BMP-7 gene. They then differentiated into bone forming cells after being placed in a defect of osseous origin in vivo [10]. There is strong evidence that BMPs not only can work on osteoinduction but also they work in collaboration to enhance bone formation. Coordinated expression of BMPs 2, 3a, 4, 7 and 8 during fracture healing is important in both skeletal development and repair.

Platelet derived growth factor (PDGF) is effective in regeneration of hard and soft tissues. It can be used in tissue engineering of periodontal wound through the biological influence it has on cell migration, cell proliferation, formation of extra cellular matrix and is anti-apoptotic in nature.

PDGF activity is blocked by the growth arrest gene (gas gene). Gas gene signals the PDGF receptor; hence the PDGF activity is down regulated resulting in temporary biological activity and bioavailability of PDGF at the wound site. An in vivo PDGF-A gene was evolved recently at the University of Michigan. They transferred the gene via adenovirus vector (Ad-PDGF-A). The bioactive Ad-PDGF-AA protein released enhances sustained tyrosine phosphorylation and corrective down regulation of PDGF receptor, which is encoded by "growth arrest specific (gas) gene". This extends the effect of PDGF on cell signaling that is critical for cellular proliferation. The bone sialoprotein is a significant non-collagenous protein found in mineralized tissues and bone. Cbfa1 is a master gene in osteogenesis and is involved in bone sialoprotein gene expression, which implicated in cell differentiation and gene expression during bone repair and regeneration. By the in vivo delivery of a bone sialoprotein gene into an osseous defect, it has been shown to regenerate periodontal alveolar bone [11].

DNA Vaccination

Researchers in the dental field experimented the use of vaccination to eliminate dental caries and periodontal disease. In the past vaccination was through the administration of purified proteins of attenuated microbe. Nowadays there is a shift towards delivering DNA directly through plasmids. In animal models, the capability to produce an immune reaction to an antigen protein by insertion of plasmid DNA encoding the antigen has been successfully established. Until now, the development of DNA vaccination to be used in the oropharyngeal tissues is in the earliest stages. DNA vaccination will play a significant role in future strategies for preventing caries and periodontal diseases. Salivary gland immunization by utilizing plasmid DNA encoding the Porphyromonas gingivalis fimbrial gene enhance the production of fimbrial protein locally in the salivary gland with subsequent production of specific salivary immunoglobulin A and immunoglobulin G, antibodies and serum IgG antibodies. Also origination of antigen specific cytotoxic T lymphocytes can be reached leading in protection from P. gingivalis. Also any produced fimbrial protein in saliva can attach to pellicle components and also block the joining of P. gingivalis to the plaque. It has been stated that the plasmid pCIA-P encoding pac gene of S. mutans could enhance protective anti caries immune responses in rats by targeted salivary gland immunization. Future research plans must be performed in this filed for preventing periodontal diseases and dental caries [12].

Utilizing Molecular Biology in Tooth Formation

This protocol followed is in form of adding molecules to enhance de novo tooth initiation in the oral cavity. The presence of endogenous dental cells can be activated or repressed by gene-delivery strategies to form a tooth accompanied with gene manipulated tooth regeneration. One gene named PAX 9 was found and identified as a master gene, it plays a critical role in tooth development.

Growing teeth in the laboratory then transplant them surgically into the alveolar bone of patients might be a possibility in the future. However, these teeth would lack the nerve supply and the blood supply, but they could be made using same structures as human teeth. This challenging growth can be achieved only if researched discovered the 25 proteins making up the tooth plus the genes signaling the body on how to form teeth.

It was assumed that 10% of the total number of genes was involved in the process of tooth formation. We hope that in the future, the

scientist could bioengineer the natural teeth for subsequent use clinically in surgical replacement of the lost teeth [13].

Cancer Management

Squamous cell carcinoma affecting the head and neck area is considered the sixth most common cancer worldwide. It refers to oral cavity cancer, cancer of larynx and pharynx and paranasal sinuses. Due to the anatomical location of the head and neck region and due to the critical surgical approaches in these areas, gene and molecular management is considered an attraction for researches and a hope for the oromaxillofacial surgeons. This will lead to insertion of vectors directly to the diseased site with only a minimum risk of systemic toxicity [14].

Several approaches have been developed for cancer gene therapy such as; the insertion of genes with antiangiogenic properties in a different tumor cells and this can be referred to antiangiogenic therapy. Enhancing immune responses through the transfer of immune accessory molecules, cytokines, or tumor antigens is another approach. Selective killing of tumor cells by using oncolytic virus therapy can be also used in cancer management. Suicide gene therapy to stop cancer cells with a gene construct to convert a prod rug into an active drug that is toxic for target cells. And lastly, the insertion of tumor suppressor genes, such as p53 in cancer cells or what is known as gene replacement therapy [15]. Replacing a mutated p53 gene with a normal wild-type p53 gene is a potential strategy to head and neck cancer management. However, this protocol is limited by the lack of mutated p53 in few tumors and additionally by the current limitations of vector strategies in transferring the gene.

These strategies may converge and can usually be used in combination to amplify potential therapeutic effects. Nowadays, the use of vectors based on retroviruses or adenoviruses became more frequent.

The first step squamous cell cancer of head and neck believed to be inactivation of p16, it is thought that 80-90% of the cases had inactive p16. Therefore replacement therapy can be achieved using p16. Loss of p16 expression is secondary to allelic loss of the 9p21 locus and mutation and/or hypermethylation of the gene [16].

Orthodontic Tooth Movement

The main principle of tooth movement relies on the resorption and apposition of bone using osteoclasts and osteoblasts consequently. In a rat model, gene therapy using osteoprotegerin (OPG) and RANKL was utilized to facilitate orthodontics tooth movement. Local RANKL gene transfer to the periodontal tissue enhances and facilitates orthodontic tooth movement by approximately 150% after 21 days, without producing any systemic effects. Therefore, problems like ankylosis or prolonged orthodontic treatment can be solved by gene therapy. Local OPG gene transfer blocks tooth movement by about 50% after 21 days of forced application. In future similar protocols may be utilized by orthodontists to minimize and shorten treatment time and improve results [10].

Salivary Gland Gene Therapy

The application of gene therapy on salivary gland management may involve transfer of a new gene via retroductal cannulation to the main excretory ducts of major salivary glands. This can lead to the secretion of a cellular therapeutic protein or to production of either in bloodstream or in the saliva. Human kallikrein was first identified in rat plasma after salivary glands transduction. This study showed that gene therapy of salivary glands might exceed the treatment of salivary glands to involve major systemic pathologies such as haemophilia or diabetes, radiation damage to salivary glands and autoimmune Disorders [10].

The Future of Molecular and Genetic Implications in Dentistry

The use of dental genetic and molecular techniques might develop in the future. The focus will be on targeting genetics to regenerate dental tissues rather than repair those using dental materials. This can be achieved by investigating the specific genes involved in evolution and maintenance of dental and surrounding tissues.

An example of this would be the regeneration of pulpal tissue rather than removal of it followed by regeneration of dentin and enamel.

Furthermore, research could be directed towards prevention and resistance of dental diseases including caries and periodontal diseases. Any maybe one day will have a nation who is caries and periodontal disease free.

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