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Review Article

NUTRIGENOMICS: A NEW PARADIGM FOR REVEALING PERIODONTAL INTERRELATIONSHIPS

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ABSTRACT

Improved understanding of the mechanism behind periodontal tissue devastation, the potential protective role of nutrients and the advent of modern genomic measurement tools have led to an increased interest in the association between nutrition and periodontal disease. Nutrigenomics is an emerging field of science and technology revealing inter-relationships between nutrients and human genome using modern tools such as transcriptomics, metabolomics, epigenomics and proteomics. It implies that nutrition and genetics both play a significant role in the maintenance of human health as well as the development of lethal diseases. Nutrition may be important in redressing the balance between microbial challenge and the host response because it has been implicated in a number of inflammatory diseases and conditions, including type II diabetes mellitus, cardiovascular diseases, rheumatoid arthritis and inflammatory bowel disease, all of which have also been associated with periodontal diseases. Based on the pathology of periodontal disease, the assumption is that specific nutrients which can modulate immune and inflammatory responses could in turn modulate periodontal health. Antioxidant vitamins and trace elements which are known to be depleted during periods of inflammation can counteract reactive oxygen species damage to cellular tissues and modulate immune-cell function through the regulation of redox-regulated transcription factors and ultimately affect the production of cytokines and prostaglandins, thus leading to periodontal changes. Thus we now have the opportunity to study nutrient-gene interactions and how diet affects the inflammatory mechanisms underlying severe periodontitis.

Key words: Nutrigenomics, Metabolomics, Proteomics, Transcriptomics, Periodontitis.

INTRODUCTION

Periodontitis is defined as "an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms or groups of specific microorganisms, initiating progressive destruction of the periodontal ligament and alveolar bone with pocket development, recession, or both."[1] Moreover, periodontal disease has been associated as a risk factor for serious systemic diseases such as cardiovascular disease. Periodontal disease might add to the inflammatory burden of the individual and might increase the levels of cardiovascular risk based on serum C-reactive protein concentrations.[2,3]

Tooth loss has been associated with nutrient deficiency and changes in food predilection.Investigating the relation amongst nutrients and periodontal disease has been important to understand the potential role of dietary modification in the prevention and treatment of periodontal disease and the ultimate prevention of tooth loss through periodontal disease.[4] Improved understanding of the mechanism behind periodontal tissue destruction, the potential defensive role of nutrients and the advent of modern genomic measurement tools have led to an increased interest in the association between nutrition and periodontal disease.[5]

WHAT IS NUTRIGENOMICS?

Nutrigenomics is an emerging field of science and technology unrevealing inter-relationships between nutrients and human genome using

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modern tools such as transcriptomics, metabolomics, epigenomics and proteomics. It implies that nutrition and genetics both play a significant role in the maintenance of human health as well as the development of lethal diseases.[6]

Nutrigenomics aims to reveal the relationship between nutrition and the genome and to provide the scientific basis for improved public health through dietary means. It is extremely likely that interactions between genotype and diet are important in determining the risk of the most common complex diseases, including periodontal disease. Numerous nutritional genetic studies where the outcome measure was markers of disease threat, most notably cardiovascular disease and cancer provide proof of principle.[5]

It is well established that specific nutrients can modulate immune and inflammatory responses. Based on the pathology of periodontal disease the assumption is that these nutrients could modulate periodontal health. Researchers have found irrefutable evidence that macronutrients and micronutrients modulate pro-inflammatory and anti-inflammatory cascades, which influence a person's baseline inflammatory position. The functionality of nutrients in human biology extends beyond that of being fuels for energy production and cofactors in metabolism, to acting as molecular nods that are capable of modulating gene and protein expression at a molecular level. This review climaxes mechanisms whereby key macronutrients and micronutrients modulate inflammation.[7]

Recent studies concerning the interactions between nutrition and the genome have yielded hopeful results. They have revealed much about the ways in which individual genotypes modulate the responses to dietary factors and have provided rich mechanistic insights into how nutrients and other components of foods regulate gene expression as well as cell and tissue functions. Nutrigenomics shows a new way of working with nutrition and now, the knowledge of how food impedes with the genetic code and how the organism responds to these interferences and with the phenotype can be explained.[5]

The observed differences in the response of an individual to dietary modification can be attributed to differences in their genetic make-up, which emphasizes the importance of exploring the role of nutrient–gene interactions in the development of chronic diseases. Oral health scientists now have the opportunity to study nutrient–gene interactions and how diet affects the inflammatory mechanisms underlying severe periodontitis.

WE ARE WHAT WE EAT: DIET MODIFYING GENE EXPRESSION

Efforts to unravel the etiology of disease often languish on the nature versus nurture debate. Recent advances suggest that neither nature nor nurture alone can explain the molecular processes that ultimately govern health. In most cases, the presence of a particular gene or mutation merely indicates a predisposition to a specific disease progression. Whether that genetic potential will manifest as a disease depends on elaborate interactions between the genome and environmental factors. Diet is disputably one of the most important environmental factors influencing health and disease. Although genes are critical for defining predilections, nutrition modifies the extent to which different genes are expressed and thereby modulates whether individuals fully express the promise established by their genetic background.

Associations between diet and disease have long been recognized through epidemiological studies. New genomic technologies, the so-called "-omics tools," are now elucidating the basis of these links. These technologies monitor the activity of multiple genes simultaneously at the level of RNA by transcriptomics, the level of the proteins by proteomics and ultimately the level of metabolites by metabolomics.[8]

The complement of proteins in a cell, and the quantities of each, can be very exceptionally controlled throughout the cell's life. As books in a library, the purpose of genes is to store information. Every single gene can be thought of as a book containing the information required to create a protein. In the same way that books may be taken off a shelf and read, genes are "read" or expressed to produce functional RNA and protein molecules in the cell. This transcription or "reading" of genes to produce RNA is the first stage of gene expression. The transcriptome is the whole set of RNA transcripts produced by the

genome at any one time. Contrasting the genome, the transcriptome is extremely dynamic. Most cells contain the same genome regardless of the type of cell, stage of progress or environmental conditions. On the contrary, the transcriptome varies considerably in these differing circumstances as a result of different patterns of gene expression. Transcriptomics, the learning of the transcriptome, is thus a global way of looking at gene expression in health, aging and disease.

While genes get a lot of attention, the proteins accomplish most life functions and even comprise the majority of cellular structures. Proteins are large, multifarious molecules made up of chains of amino acids. Chemical properties that differentiate the 20 different amino acids cause the protein chains to fold into specific three-dimensional structures that define their particular functions in the cell. The assemblage of all proteins in a cell is called its proteome. Again, contrasting the relatively static genome, but analogous to the transcriptome, the dynamic proteome changes from minute to minute in response to tens of thousands of intra and extra cellular environmental signals. A protein's chemistry and comportment are determined by the gene sequence and by the number and identities of other proteins produced in the same cell at the same time and with which it links and reacts. Studies to explore protein structure and activities, known as proteomics, will be the focus of much research for decades to come and will help further clarify the molecular basis of health and disease.

All genes and most proteins can be regarded as instruments for making up the biochemical composition and thereby the metabolic identity of an organism. Metabolomics is the learning of metabolite profiles in biological samples, mainly urine, saliva, and blood plasma. Metabolites are majorly the by-products of metabolism, which is the process of converting food energy to mechanical energy or heat. The number of varied metabolites in humans is unknown; estimates range from a low of 2,000 – 3,000 to a high of around 20,000, related to an estimated 25,000 genes and 100,000 proteins. The benefit of metabolomic analysis is that the biochemical consequences of mutations, variations in the environment and nutrition or treatment with drugs can be observed directly.

All of these "-omics tools" have been used to study in detail the molecular responses to food substances or the early stages of disease in common diet related situations. No single tool will provide all of the answers. Looking at the genome doesn't provide information about downstream function, and considering at the metabolome doesn't explain the underlying regulation. It's the combination of these tools that is important and will undoubtedly lead to a new understanding of health and disease.[9]

Nutrients can be thought of as dietary signals detected by cellular sensor systems that influence gene and protein expression and, subsequently, metabolite production. Recurring patterns of gene expression, protein expression and metabolite creation in response to particular nutrients or foods can be viewed as dietary signatures.Nutrigenomics studies these signatures to understand how nutrition influences health and disease. One potential outcome from nutrigenomics research is a more rational approach to food formulation. Based on a more wide-ranging understanding of the effects of diet on health, foods can be planned to modify expression profiles in affected animals to more closely reflect a healthy state.

Nutrigenomics explains how food chemicals affecting gene expression, while nutrigeneticsdeliberates SNPs-single nucleotide polymorphisms which define an individual's response to food according his/her own specific states of health and disease. In the nearby future people will prefer to a DNA analysis to have a guideline for avoiding disease and optimizing health disputes. How an individual reacts to a specific ingredient and how it can effects the genes variations can be explained well by nutrigenetics.[6] It recognizes an individual's hereditary predisposition to disease based on his or her genetic makeup. (Sanchez et al. 2008).

SYSTEMIC DISEASES MODIFIED BY DIET

Physiological processes such as absorption, transportation, biotransformation, up taking mechanism, storing mechanism and excretion, and cellular mechanisms of action affect the biological effects of nutrients and food bioactive. These processes involve different genes which can change their functional and physiological response

to different nutritional compounds. Diet and gene interactionelucidates genes affecting different homeostatic pathways (Garcia-Bailo et al., 2009). New food products has been manufactured on the genetic basis considering food been liked or disliked which escort to the development of new food products according to the ethical rules of society, which may lessen the risk of chronic diseases(Corbin and Zeisel, 2012) According to various research studies nutrients is also having the abilities of altering the genetic expression at gene regulation level, signal transduction or by changing chromatin structure or changing protein function. Diet can cause epigenetic variations for example methylation of DNA or it may affect the genes expression at genes level. Molecular signatures also express the genes profile considering specific nutrients. (vanOmmen et al., 2010).[6]

Recently it has been suggested that nutrition may be important in redressing the balance between microbial challenge and the host response because it has been implicated in a number of inflammatory diseases and conditions, including type 2 diabetes mellitus, cardiovascular disease, rheumatoid arthritis and also inflammatory bowel disease, all of which have also been associated with periodontal disease.[10] Diets high in saturated fats and sugars and low in fruit, vegetables and fiber are common risk factors associated with these chronic diseases.[11] Numerous nutritional genetic studies where the outcome measure was markers of disease risk, especially cardiovascular disease and cancer. Lower risk of prostate and breast cancers in areas such as Asia, where there is a habitual high intake of soy and isoflavone, are well documented.[12] Recent genome-wide association studies have identified a genetic-susceptibility locus for type 2 diabetes comprising a nonsynonymous single nucleotide polymorphism (C / T; rs13266634) in a beta cell-specific zinc-transporter gene. This zinctransporter gene (SLC30A8, coding for ZnT8) may be important in insulin storage and release.[13]

A number of genetic variations have been shown to increase the susceptibility to micronutrient associated diseases, like type 2 diabetes mellitus, obesity, cardiovascular diseases and certain autoimmune diseases. The vitamin D3 receptor (VDR) gene, for example, encodes the nuclear hormone receptor for vitamin D3. It fits in place to the family of transcriptional regulatory factors. Targets of this receptor are mainly involved in mineral metabolism though the receptor regulates a variety of other metabolic pathways, such as those associated in the immune response and cancer. Polymorphism of the VDR gene has been related to bone mineral density, and also numerous chronic diseases such as cancer – mainly breast cancer, prostate cancer and malignant melanoma – type 2 diabetes mellitus, Parkinson's disease, lung diseases, gastrointestinal disease, multiple sclerosis and periodontal disease.[14]

SYSTEMIC DISEASES REGULATING PERIODONTAL HEALTH

A direct link between periodontal disease and nutrition has been established recently through a number of cross-sectional studies. Results from a prospective, observational study carried out over 14 years revealed that men with a high consumption of wholegrain were 23% less likely to develop periodontitis than were those who had the lowest consumption of wholegrain.[15] Three separate analyses of the US Third National Health and Nutrition Examination Survey (NHANES III) produced statistically significant associations between periodontitis and markers of increased body mass, leading the authors to conclude that obesity could be a potential risk factor for periodontal disease, especially in younger subjects.[5] It is well established that specific nutrients can modulate immune and inflammatory responses.[16]

Based on the pathology of periodontal disease the assumption is that these nutrients could modulate periodontal health. Increased production of reactive oxygen species raises requirements for the antioxidant nutrients involved in defense. Antioxidant vitamins (vitamins A, C and E) and trace elements (selenium, copper and zinc), known to be depleted during periods of inflammation , can counteract reactive oxygen species damage to cellular tissues and modulate immune-cell function through the regulation of redox-regulated transcription factors and ultimately affect the production of cytokines and prostaglandins. Moreover, selenium has further important redox functions, with selenium-dependent glutathione enzymes being involved in the reduction of damaging lipid and phospholipid hydroperoxides

to harmless products. A rodent model of zinc deficiency has shown an increased susceptibility to periodontal disease progression, as revealed by increased plaque and higher gingival index measurements. These vitamins and trace elements are also known to play a pivotal role in maintaining epithelial tissue integrity and structure, which is also relevant to periodontal health.[17]

Intake of n-3 polyunsaturated fatty acids, predominantly found in oily fish, increase the tissue concentrations of eicosapentaenoic acid and docosahexaenoic acid, which are known to downregulate inflammation. Studies of n-3 fatty acids in rodent models have demonstrated decreased levels of the major inflammatory mediator's prostaglandin E2, prostaglandin F2 alpha, leukotriene B4 and platelet activating factor in gingival tissue, which are known to contribute to bone destruction in periodontal disease. Further analyses of these fatty acids suggest that n-3 polyunsaturated fatty acid metabolites may act as signals to prevent neutrophil-mediated tissue damage. A recent longitudinal study of periodontal disease markers in elderly patients revealed that those who consumed the lowest level of n-3 fatty acids (stratified for eicosapentaenoic acid and docosahexaenoic acid) had higher incidences of periodontal disease, suggesting an inverse relationship between dietary n- 3 fatty acid intake and the progression of periodontal disease in older people.[18]

MECHANISMS REVEALING NUTRITIONAL MODULATION OF PERIODONTAL INFLAMMATION

Periodontitis is initiated by the plaque biofilm,[19] but most tissue destruction results from an abnormal inflammatory immune response in patients predisposed to the condition.[20] The response is characterized by hyperinflammation, which fails to eradicate the causative pathogens and generates prolonged release of neutrophil proteolytic enzymes, proinflammatory mediators and reactive oxygen species (ROS), which in turn destroy the periodontal attachment.[21] The etiology of an inflated inflammatory immune response is complex, but several common features of hyperinflammation underlie the major chronic diseases of humans.[22-24]

Researchers have found irrefutable evidence that macronutrients and micronutrients modulate proinflammatory and anti-inflammatory cascades, which influence a person's baseline inflammatory status. The functionality of nutrients in human biology extends beyond that of being fuels for energy production and cofactors in metabolism, to acting as molecular signals that are capable of modulating gene and protein expression at a molecular level. These review highpoints mechanisms whereby key macronutrients and micronutrients modulate inflammation.[25]

Diets high in complex carbohydrates are generally healthy, whereas those rich in refined carbohydrates can be major causes of chronic inflammation.[25,26]Elevated glucoseand lipid levels generate ROS at a rate that exceeds endogenous antioxidant defenses, and oxidative stress results. Investigators have noted that this "postprandial dysmetabolism" plays a role in the genesis of inflammation.Multiple elevations in glucose eventually lead to chronic inflammatory pathologies.[26-28]

Diet-induced hyperlipidemia induces oxidative stress and downstream inflammation,[29] and lipoproteins formed by liver hepatocytes can be converted to free fatty acids within the circulation and taken up by adipocytes, thus acting as a basis of proinflammatoryadipokines. Furthermore, in states of oxidative stress, lipid peroxidation (a chain reaction induced by ROS attack on the polyunsaturated fatty acid [PUFA] side-chains of lipid membranes) arises, [21]lowdensity lipoproteins are oxidized (oxLDL) and the oxLDLs bind to a group of pattern recognition receptors called "toll-like receptors" (TLR-2/4) on inflammatory cell membranes, triggering NF-κB activation via the protein-kinase-C enzyme and other related pathways. NF-κB transcribes several proinflammatory cytokines.[29]

Researchers have demonstrated antioxidant depletion in periodontitis locally in the periodontium[30] and within plasma, where investigators established an inverse relationship between reduced concentrations of plasma total antioxidants and vitamin C and increased prevalence of periodontitis.[31] Intervention studies involving patients with periodontitis and demonstrable vitamin deficiencies, however, are scarce. Therefore, the basis for individual vitamin supplements as therapeutics in the absence of frank deficiency is flawed because of the potential

for in vivo vitamin-radical formation; the need for cooperative antioxidant cascades to be augmented and the need for only subtle increases in antioxidant status necessary to down regulate pro inflammatory gene transcription.[21] Intervention studies performed in the 1980s (reviewed by Chapple and Matthews) using individual vitamin supplements investigated only patients who did not have vitamin deficiency, who were in worthy periodontal health or both. A latest study ofpatients with metabolic syndrome provided early indications of the potential of antioxidants found naturally in foods to reduce periodontal inflammation(at clinical and biomarker levels) in patients with disease.[32]Additionally, researchers have proposed reduced glutathione (GSH), the key intracellular antioxidant redox-regulator of NF-κB, as a novel approach to downregulation of hyperinflammatory events.[33] GSH levels appear depleted in periodontitis[34] and methods of enhancing intracellular GSH may prove beneficial.

PUFAs of the omega-3 form (ω-3PUFAs) found in fish oils lower postprandial triglyceride levels[35] and confer anti-inflammatory and cardiovascular protective effects.[36] ω-3PUFAs also inhibit lipid mediators of inflammation (such as prostaglandin E2, arachidonic acid, 5-lipoxygenase and cyclo-oxygenase), modulate lymphokine production and upsurge antioxidant capacity,[37-39] and are reported to decrease osteoclast activity.[40]Kesavalu and colleagues[41] demonstrated that rats infected with *Porphyromonasgingivalis* and fed a diet rich in ω-3 PUFAs for 22 weeks experienced less bone loss than did control rats fed a diet rich in n-6 PUFAs. Gene expression echelons of IL-1β and TNFα declined, and those of interferon-γ and intracellular antioxidant enzymes increased.[42]One mode of action of PUFAs includes the downregulation of proinflammatory gene expression via the nuclear peroxisome proliferator–activated receptors (PPARs) others include inflammation-resolving mediators derived from ω-3 PUFAs (resolvins).[43]

Thus nutrigenomic studies have highlighted theimportance of variations in gene structure (forinstance, at the transcription factor binding site) on differential responses of patients to specificnutrients.

MICRO NUTRITIONAL APPROACHES TO PERIODONTAL THERAPY: DO WE KNOW ENOUGH?

Periodontitis is associated with low serum/plasma micronutrient levels that may result from dietary and/or life-style factors as well as nutrigenetic characteristics. Primary evidence suggests beneficial results from nutritional interventions; supporting the contention that daily intake of certain nutrients should be at the higher end of recommended daily allowances. For inhibition and management of periodontitis daily nutrition should include sufficient antioxidants, vitamin D, and calcium. Insufficient antioxidant levels may be managed by higher intake of vegetables, berries, and fruits (e.g. kiwi fruit), or by phytonutrient supplementation. Antioxidant micronutrient deficiencies can be met by a higher intake of vegetables, fruits, and berries.[44]

The majority of patients are not antioxidant vitamin deficient and monovitamin supplements may be associated with toxicity effects. Current evidence shows some benefit in reducing gingival inflammation from vitamin C supplementation, provided UL are not exceeded. The most appropriate sources of vitamin C are natural fruits such as kiwi fruit.[45]The most appropriate sources of polyphenolicflavenoids and carotenoids are from natural fruit/vegetable/ berry intake or the use of whole fruit, vegetable, and berry concentrates. An initial intervention study with a powdered capsular form of the latter phytonutrients showed promise as an adjunctive approach to standard periodontal therapy in improving pocket depth reductions.[46]

The observed differences in the response of an individual to dietary modification can be attributed to differences in their genetic make-up, which emphasizes the importance of exploring the role of nutrient–gene interactions in the development of chronic diseases. Oral health scientists now have the opportunity to study nutrient–gene interactions and how diet affects the inflammatory mechanisms underlying severe periodontitis.

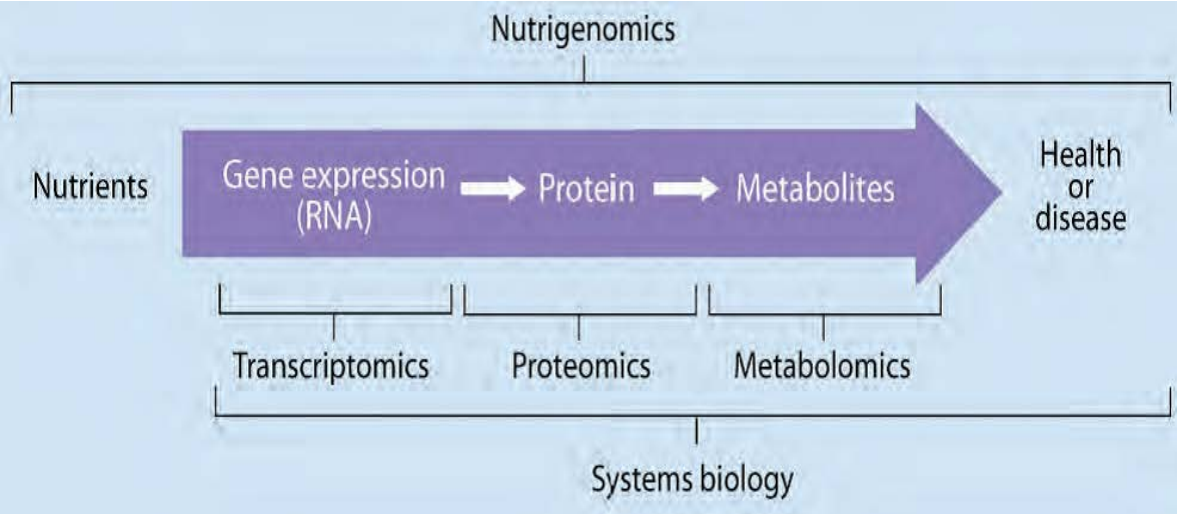

Figure 1:

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