Nutrigenomics, Metabolic Correction and Disease: The Restoration of Metabolism as a Regenerative Medicine Perspective

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ABSTRACT

Nutrigenomics is the study of the effects of food and food constituents on gene expression. The study of nutrigenomics may have a major impact in the development of tailor-made food, supplements and beverage products in the near future. The "genetic nutritioneering" concept summarizes the information on how diet, supplements, lifestyle and environmental factors influence gene expression. In order to overcome their particular genetic pre-disposition that can lead to serious diseases, people may be able to choose customized diets, supplements and make lifestyle modifications, which would optimize their metabolic status. Nutrient intake for each person varies according to their unique genetic make-up and individual lifestyle choices. Therefore, it may be possible to "correct" physiological disruptions by implementing "Metabolic Correction" principles. To completely accomplish these goals of optimal health, new international alliances and policies need to be developed and implemented and more sound, evidence-based research needs to be conducted.

Keywords: Nutrigenomics; Epigenetics; Metabolic correction; Disease

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INTRODUCTION

Epigenetics refers to inherited variation to the DNA that regulates chromosome architecture and modifies gene expression without alterations to the underlying DNA sequence.[1] Nutrigenomics is the study of the effects of food and food constituents on gene expression. It entails how DNA is transcribed into messenger RNA (mRNA) and then translated into proteins; providing a foundation for the understanding of the biological activity of food components.[1] Nutrigenomics has also been defined by the influence of genetic variation on nutrition by investigating how gene expression or single-nucleotide polymorphisms affect a nutrient's absorption, metabolism, elimination and/or biological effects. In this manner, nutrigenomics may help to establish a scientific approach to optimizing nutrition, with respect to a subject's genotype. Nutrigenomics provides us the toolbox to understand more precisely how nutrition works. Nutrigenomics is also defined as how food and ingested nutrients may influence the genome,[2] while nutrigenetics is defined as how a person's genetic make-up affects a response to diet.[3]

By determining the mechanism of nutrient effects at a genetic level, nutrigenomics may be able to delineate the relationship between specific nutrients or diets and its effect on human health. Nutrigenomics has also been connected with the idea of personalized nutrition based on genotypes and falls into the broader field of personalized medicine.[4] While there is a hope that nutrigenomics will ultimately enable such personalized dietary advice, its contribution to public health can be even larger. Numerous others have previously described a similar concept, whereby the diet can impact gene expression.[5–12]

DIET ALTERS EXPRESSION OF GENETIC INFORMATION

It has been shown that nutritional factors have a major influence on gene expression (genomics and transcriptomics), protein synthesis (proteomics), and metabolism (metabolomics). Changes to mRNA and expression profiling and the corresponding proteins regulate the transport of certain nutrients and metabolites. As a result, a new patient-centered health care approach may focus upon nutrition and other modifiable lifestyle factors to achieve optimal gene expression, and therefore improved optimal health (see Figure 1).

Sub-groups within a heterogeneous population may act differently from a single dietary intervention, which supports the concept of biochemical individuality.[5] An example of this is the use of folic acid in a population lacking the methylene tetrahydrofolate reductase (MTHFR) gene, this population in order to benefit from this supplement would need the activated form of folic acid. Another important concept is genetotrophic disease[6] which is a disease that results from the suboptimal consumption of nutrients necessary to meet the genetically determined biochemical requirements of the individual. One of the main functions of micronutrients (vitamins and minerals) is to enhance enzyme efficiency. Vitamins are co-factors for enzymes, and enzymes are proteins and proteins may be transformed due to genetic changes and this affects their function. The formation of an active cofactor requires active enzymes, moreover to have enzymes functioning at their maximal capacity; sufficient active cofactors must be present.[7]

An example of biochemical individuality is the genetic polymorphisms associated with folate metabolism. The activation of di-hydrofolic acid to 5-methyl-tetrahydrofolate (active form of folate) requires MTHFR. If MTHFR is defective (mutated), the activation of folate is diminished. If insufficient activated folate is formed, further enzymes needing this cofactor will have a decreased activity. This problem is observed in homocysteinemia.

Different people have different rates of biochemical reactions and this is determined by their unique genetic makeup. This is the central dogma of the biochemical individuality concept and of the Metabolic Correction model. Many current nutritional studies are performed in a way that even though they are controlled, they may not differentiate between sub-groups.

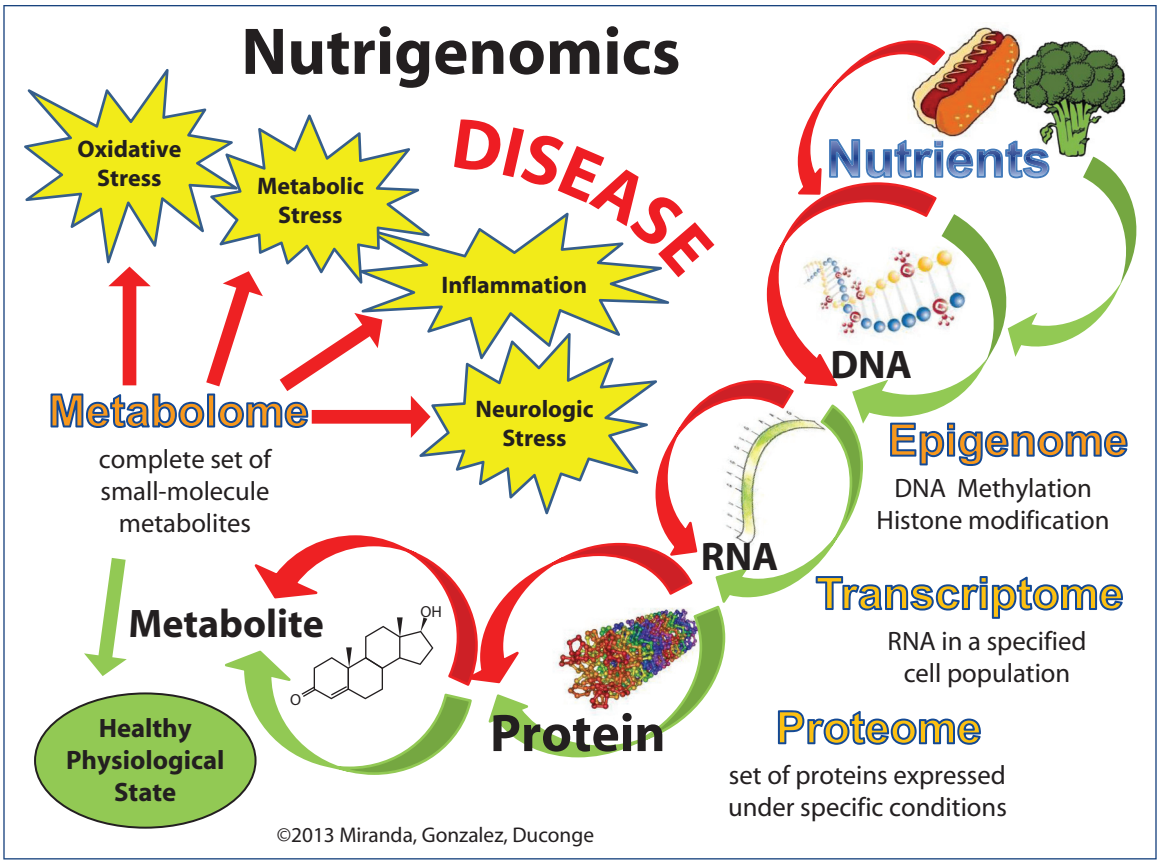

Figure 1: Illustrates the concept of Nutrigenomics as the effects of the balance of nutrients on gene expression leading the body to different biochemical routes and endpoints. Through its sequential effect on the epigenome, transcriptome, proteome, metabolome which can produce either a healthy physiological state or a fundamental metabolic disruption (biochemical imbalance) such as excessive inflammation, oxidation, neurologic stress and metabolic stress. Epigenome chemical changes to the DNA and histone proteins; these changes can be passed down to an organism's offspring. Transcriptome is the set of all RNA molecules produced. Proteome is the entire set of proteins expressed at a given time under defined conditions. Metabolome refers to the complete set of small-molecule metabolites (such as metabolic intermediates, hormones and other signaling molecules, and secondary metabolites).

Dietary constituents have been shown to alter gene expression in a number of ways. For example: 1) Acting as ligands for transcription factor receptors; 2) By being metabolized in primary or secondary metabolic pathways thereby altering concentrations of substrates or intermediates; 3) By altering signal transduction pathways.[13]

To understand nutrition's potential to maintain health and prevent disease may lie in the study of epigenetics, which is defined as the study of heritable changes in gene expression that do not involve a modification in the underlying DNA sequence.[14] Although epigenetics does not result in changes to the nucleotide sequence, it does comprise molecular modification of DNA and histones (i.e., proteins that package DNA in human cells), like DNA methylation and histone deacetylation. Since information flows in both directions (i.e., from DNA to proteins and from proteins to DNA), gene expression can also be activated or deactivated by signals from the environment. Dietary factors, such as the daily intake of folate, can be considered as an environmental stimulus with the potential to affect gene activation through, for instance, a change in the DNA methylation status.[15] Accordingly, genes alone do not determine biological fate; it is the response to environmental stimuli that actually determines the gene expression that accounts for such outcomes. Most epigenetic

changes occur at specific times in an individual's life and, unlike germline mutations, they are potentially reversible.[14]

On the other hand, the methylation of mRNA plays a key role in energy homeostasis, the process by which the body maintains a complex biochemical dynamic equilibrium, which is postulated as a new pathway in the regulatory process that contributes to obesity and type 2 diabetes.[16] Indeed, the reversible modification of N6-methyladenosine in mRNA is prevalent throughout the mammal kingdom. Evidence strongly indicates that this reversible, post-transcriptional modification has major roles in mRNA metabolism and might represent another area of biological regulation in the form of "RNA epigenetics".[16]

While excess caloric intake increases biomarkers of advanced aging and chronic diseases,[17] caloric restriction (CR) is one of the most studied ways to extend life span.[18] One of the most robust evidence on the effects of CR is a 20 year study with Rhesus monkeys where a modest CR resulted in a three-fold reduction in the risk of age-related disease.[19] CR triggers changes in gene expression that improve biomarkers of youth and health, such as metabolic rate, insulin sensitivity, cardiac health and cognition.[20] CR significantly inhibits the expression of nuclear factor-kappa B (NF-kB). NF-kB is a gene regulator that controls the level of many physiological molecules such as pro-inflammatory cytokines, free radicals and cholesterol which are associated with age-related health deterioration.[21–25]

Among the inflammatory cytokines and other inflammation mediators inhibited by suppressing gene expression are interleukins and tumor necrosis factor (TNF) and cyclooxygenase-2 (COX-2). These mediators have been implicated as a risk factor of cancer, atherosclerosis, and chronic inflammation.[26–29]

A dietary regimen to achieve the benefits of CR might be difficult for most individuals, but inhibition of NF-kB and other cytokines may also be achieved with the use of some nutrients such as resveratrol, pterostilbene, quercetin, grape seed extract and vitamin D.[30–35] It has been proposed that the use of these compounds could be important in the prevention and management of many conditions where inflammatory cytokines play a key pathophysiologic role.

One important mechanism of CR produced-glucose control is by activation of gene regulators called *peroxisome proliferator-activated receptors* (PPARs), which are responsible for fat and carbohydrate metabolism and maintain mitochondrial function.[36] PPARs are nuclear receptors whose stimulation has been associated with several physiologic pathways related to the regulation of intestinal inflammation.[37] Resveratrol[38] and pterostilbene[36] up-regulate the production and activity of PPAR, inducing cellular processes that sustain an improved metabolic profile. Grape seed extract regulates a different group of PPARs that controls fat storage. Grape seed extract induces fat metabolism while inhibiting the development of new fat cells.[39, 40]

GENETIC NUTRITIONEERING

"Genetic nutritioneering" can be summarized as the impact of nutrition on genetic expression and its subsequent effect on health.[41] Genetic nutritioneering synthesizes the information on how diet, lifestyle and environment influences gene expression. Genetic inheritance is merely a template of the genetic expression. Three important influences can modify how genes are expressed. First, what genes are turned on; second, how the messages in genes are transcribed; and third, what are the post-translational effects in the cells by this gene expression. All these influences can be modified by nutrition and lifestyle. It is thought that disease results when nutritional and lifestyle factors alter the expression of genes in such a way as to produce a phenotype of disease.[9]

METABOLIC OPTIMIZATION

The field of nutrigenomics is focused on the need for biomarkers that capture health improvements, rather than health deterioration.[42] This is an interesting concept since so far nutrition has used classic biomarkers from biomedical areas, such

as LDL-cholesterol and inflammatory markers to describe health status. However, these markers do not necessarily reflect health accurately. In order to optimize health, these biomedical markers may not be as valuable as once thought. This is because their focus is largely on whether health is deteriorating, rather than improving. In other words, functional health assessments would be potentially more important than tests for markers or for diagnosis of disease. Functional health assessments such as the rational use of reliable testing of blood nutrients, inflammatory mediators, metabolic intermediaries and many others will be increasingly important tools to improve assessment and therapeutic success. Therefore, using this concept may lead to better outcomes.

We need to understand the role of nutrients in metabolism to use this knowledge to control disease and increase wellness. These processes permit organisms to grow, reproduce, maintain their structures and react to their environments. Metabolism can be divided into two categories: catabolism, which breaks down molecules and anabolism that uses energy to construct functional and structural molecules. The biochemical reactions of metabolism are structured into different metabolic pathways, in which one substance is transformed by a sequence of enzymes. These are crucial to metabolism because they allow cells to drive thermodynamically (energy consuming) unfavorable reactions by coupling them to favorable ones.

Metabolism involves a vast array of chemical reactions; of particular importance are those involved in the transfer of functional groups. When a methyl group, for example, is added to a particular molecule, it may change its activity. DNA methylation is of particular interest as there is substantial amount of evidence that suggest that it has important therapeutic applications in cancer.[43] This simple chemical reaction allows cells to use metabolic intermediates to carry chemical groups between different reactions. These group transfer intermediates are called cofactors or coenzymes. Each transfer reaction is facilitated by a particular coenzyme. These coenzymes are continuously being made, consumed and then recycled. These coenzymes and cofactors need vitamins and minerals as part of their structure to function.

Each vitamin is typically used in multiple reactions and therefore has multiple functions. Most vitamins function as part of coenzymes that help act as catalysts and substrates in metabolism. Nevertheless, in human physiology vitamins have diverse biochemical roles such as hormones (vitamin D), antioxidants (vitamin E), mediators of cell signaling, regulators of cell and tissue growth, and as promoters of differentiation (vitamin A). Water soluble vitamins are phosphorylated or are coupled to nucleotides when used in biochemical pathways of the cell. Another function of coenzymes is to transport chemical groups between enzymes, for example folic acid carries different forms of carbon group (methyl, formyl, and methylene) into the cell.

Dietary minerals are the chemical elements required by living organisms present in common organic molecules, excluding carbon, hydrogen, nitrogen and oxygen. There are seventeen required minerals (essential minerals) to support cell structure and function in human biochemical processes. There are two kinds of minerals: macro-minerals and trace minerals. The macro-mineral group includes calcium, phosphorus, magnesium, sodium, potassium, chloride and sulfur. The trace minerals include chloride, iodine, iron, copper, selenium, zinc and others. Most nutritionists and dieticians believe that the requirements for minerals are met simply with a conventional balanced diet, however this may ignore biochemical individuality. The optimum intake of micronutrients for each person will vary according to age, genetic constitution, diseases, and exposure to stress and toxins. The failure to apply the concept of biochemical individuality may negatively impact an individual's efforts to reach metabolic optimization. Conversely, it has been proposed that a metabolic tune up could produce a marked increase in health in certain individuals.[44]

METABOLIC CORRECTION

The "Metabolic Correction" principle provides the mechanistic explanation of the bio-utilization of nutrients for preventive and therapeutic purposes against disease.[12, 45] Metabolic Correction

is a functional concept of cellular biochemistry to achieve metabolic or physiological optimization. Impaired or incomplete cellular biochemical reactions are repaired with the Metabolic Correction principle.[12, 45]

Approximately 50 different human genetic diseases are caused due to a reduced binding affinity (Km) of a polymorphic enzyme for its coenzyme.[46] In a number of cases this can be improved by providing high doses of the appropriate coenzyme, which may often be the B vitamins.[7, 45, 46] Many polymorphisms also result in a lowered affinity of the enzyme for the coenzyme.[46] This Km concept explains why it could be a good part of health promotion to include a multiple vitamin mineral supplement in one's daily routine.

Every physiological component must be considered in order to perform at peak efficiency. Although not formally recognized in the literature, the term "Metabolic Optimization" describes a systematic approach to training and nutrition. Metabolic processes can be viewed as links in a chain. The strength of the entire chain can be compromised by only one weak link.

Metabolic Optimization is hypothesized to result in faster recovery, greater strength, more endurance, higher lactate tolerance, an increased Vo_2 Max, a reduction in injuries and illnesses, better performances and more energy.[47, 48] The lack in USA of patients who present recognized deficiency diseases such as pellagra, rickets, scurvy, acute night-blindness or beriberi has probably led to a false sense of security and the belief that almost everyone gets enough vitamins from food. However, a significant portion of the American population does not even reach the Recommended Daily Allowance (RDA) of some critical nutrients from their diet.[49] A state of subclinical deficiency or dietary insufficiency seems prevalent and may have serious health consequences. Supplementation with specific nutrients has been estimated to be cost effective in preventing diseases.[50] Food alone may not provide sufficient micronutrients for preventing deficiency or insufficiency.[51] Many older adults do not consume sufficient amounts of numerous necessary nutrients from foods alone. Supplements compensate, but only an estimated half of this population uses them daily.[50]

When one component in the metabolic micronutrient network is inadequate, repercussions are experienced in a sequenced biochemical pathway that can lead to the disease state. For example, many diseases may result from mitochondrial damage. These include cancer, accelerated aging and Alzheimer's disease.[52–56] Many of the carriers of identified human genetic diseases due to defective enzymes can be improved or ameliorated by providing high doses of the B-vitamin component of the corresponding needed coenzyme. Raising the levels of the coenzyme may partially restore enzymatic activity, to near normal function.[9, 44]

CONCLUSION

We cannot change our genes, but we may have some control over their expression. We may be capable of modifying what they make and the power to turn them on or off, through proper nutrition, supplementation and healthy lifestyle. In general, diet, environment, lifestyle and exposure to toxic substances all work together in modifying the way one's individual genes are expressed. The particular conditions to which genes are exposed determine our biological fate of health or disease.

A statistical genetic risk to a disease or condition does not mean that an individual will express the disease or condition. What is ultimately relevant is the interaction between the genes and the environment. Thus, people should be encouraged to select a diet and supplements that are appropriate for their particular genetic pre-disposition.

Scientific formulations capable of multifunctional synergy with the ability to support healthy genomics, proteomics, and metabolomics should be an area of focus. This approach can produce a partnership with healthcare professionals that will allow individuals to optimize their health regardless of their underlying genetics. We need to understand the mechanisms by which nutrients in food and supplements can alter health. From that knowledge, better/healthier choices can be developed by food manufacturers about how to prepare and what to put into their products. The study of nutrigenomics may have a major impact on

the development of customized food, supplements and beverage products in the future.

There are a number of economic implications to the development of nutrigenomics: 1) To prevent diseases is economical, since prevention is less expensive than treatment; 2) To lessen the cost of healthcare is imperative, since healthcare or better yet disease-care cost is too high and continues to increase; 3) To educate the public in this new health paradigm, so they can start taking better care of themselves; 4) To make science accessible, in all terms, especially economically; so that medication, supplementation and Metabolic Correction costs can be lower.

There are several significant social and public health implications of such an approach. Many more trials are required, including the need for high-quality human trials that utilize the concept of biochemical individuality. Then we will be able to repeat what the wise father of medicine, Hippocrates, said thousands of years ago: "Let medicine be your food and food be your medicine".

DISCLOSURE OF INTERESTS

Dr. Gonzalez and Dr. Miranda-Massari have a patent 14/096,048 pending. The authors have no other interests to disclose.

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