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NUTRIGENOMICS

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Nutritional genomics, or nutrigenomics, is a promising multidisciplinary field that focuses on studying the interactions between nutritional factors, genetic factors and health outcomes. Its goal is to achieve more efficient individual dietary intervention strategies aimed at preventing disease, improving quality of life and achieving healthy aging. Scientific progress in nutrition, medical and food sciences is having an increasingly profound impact on consumer's approach to nutrition. There is a growing awareness that many chronic diseases are caused by unbalanced diet. In addition to disease prevention, the role of food as an agent for improving health has been proposed and a new class of food, so called functional food, has come into being. This term is used to indicate a food that contains some health-promoting components and not only traditional nutrients. From this point of view we could argue that many nutritional products belong to the family of functional food replete with bioactive peptides, antioxidants, probiotic bacteria, highly absorbable calcium, conjugated linoleic acid and other biologically active components.

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Knowledge gained from comparing diet/gene interactions in different populations may provide information needed to address the larger problem of global malnutrition and disease.

Key word: genetic effects, food, disease

INTRODUCTION

The science of nutrigenomics continues to evolve, it will reveal not only which foods can have a direct impact on our genes, but also the mechanisms as to how and why. The ultimate goal is to be able to prevent, and potentially even treat, disease through targeted nutrition.

Regulation of gene expression is actually adaptive mechanism for survival. Organisms can sense the absence or presence of metabolites and respond to nutrient deficiency or excess by increasing or decreasing production of cellular proteins necessary for a myriad of functions. GILLES (2003) demonstrated that certain flavonoids found in citrus peel enhanced expression of a gene involved in the human body's natural defense against cancer. The current research and potential for nutrigenomics have been highlighted in numerous recent articles (GILLES, 2003, KAUWELL, 2005).

Genetic effects of food

Components found in food interact with biochemical pathways at the molecular level. DANNENBERG and REIDENBERG (1994) suggested that dietary fats act as drugs. They detailed the pharmacological effects associated with numerous fatty acids that are part of our daily diet, including modification of blood pressure, cholesterol levels, risk of carcinogenesis, and levels of pre-inflammatory chemicals. While most measurements of the impact of food on human biochemistry utilize quantification of biomarkers, evidence is mounting that, in many cases, modulation of gene expression by bioactive is an important mechanism of action.

Folic acid was identified in early research as an important regulator of gene expression. Folate provides the precursors for purine and thymidylate syntheses and for methylation of DNA, and therefore plays a direct role in regulation of gene expression. Undermethylation of DNA – a prerequisite for proliferation of cancer cells/has been detected in humans fed a folate/deficient diet.

Nutrient/gene/disease interactions have been documented for several common food substances. Vitamins (tocopherol, biotin), minerals (zinc), and phytochemicals (flavones, catechin) have all been demonstrated to alter gene expression in human cells in culture. Cells in culture offer the opportunity to explain the mechanism by which food substances can alter gene expression. Several methods have been identified whereby nutrients interfere with gene expression. These include direct involvement in DNA synthesis (biotin metabolites), DNA methylation (folic acid), and alteration of mRNA stability (vitamin D).

Table 1. Genetic effects of nutrients

Nutrient	Gene impact	Deficient diet - Disease potential
Folic acid	DNA methylation	Cancer
Fatty acids	Bind to transcription factors	Obesity
Vitamin D	mRNA stability	Kidney disease
Flavones	Increase mRNA synthesis	Cancer
Theaflavins	Decrease mRNA synthesis	Arthritis

A key mechanism of action involving nitrient-gene interactions is the ability and necessity of some nutrients to act as ligands and bind with transcription factors. Transcription factors bind to specific DNA sequences in the promoter region specific genes, thereby either enhancing or suppressing gene expression. Binding of a nutrient to a transcription factor will affect the ability of a transcription factor to bind to DNA. For example, peroxisome proliferation – activated receptors (PPARs), a family of steroidal, nuclear transcription factors, affect expression of genes associated with fatty acid metabolism, energy balance, and tumorigenesis (KLIEWER et al., 2001). In an intricate, multi-step process, fatty acids (omega-3 and omega – 6 fatty acids) bind to the PPAR, which then in turn binds to another transcription factor called retinoid X receptor (RXR) that is activated only when vitamin A derivatives (from carrots) bind (OUAMRANE et al., 2003). Gene expression results from the fatty acid / PPAR-reinoid /RXR complex that directly binds to the DNA.

In the case of retinoids from carrots and fatty acids from salmon, they bind to specific genes via a PPAR complex, resulting in, for example, reduction of fatty acid synthesis and increase in fatty acid oxidation. The list of genes regulated by fatty acids is extensive (PEGORIER et al., 2004). It includes genes involved in fatty acid transport, oxidation of fatty acids, desaturation of fatty acids, glycolysis, lipogenesis, and lipoprotein metabolism.

An important area for identification of bioactives is inflammation, which leads to an accelerated development of a multitude of chronic diseases. Naturally occurring nutraceuticals, specifically antioxidant bioactives, such as plant phenols, vitamins, carotenoids, and terpenoids, have been shown to have significant beneficial effects for health promotion by reducing the process of sustained inflammation that accompanies chronic disease.

Both enzyme and non-enzyme components of antioxidant protection are present in each organism, tissue and cell and they represent our genetically determined potential for defense from oxidative stress. Our defense system may be supplemented and enhanced by appropriate, healthy diet which included intake of the nutritive components that contain natural antioxidants. This type of nutrition is generally accepted trend in the world, since previous practice has suggested the possibility that this kind of nutrition may reduce the risk of carcinogenesis, chronic heart diseases, nerve diseases, etc.. Namely, quality food must contain necessary quantity of important and active components in order to supply the organism with necessary and increased quantities of the organic substance, vitamins and microelements. Antioxidative properties are highly important food quality parameters. This involves control of the level of high molecular (enzymatic) and low molecular (vitamins A,C,E etc.) components of the antioxidant defense system in the food products during the manufacturing process, preparation and distribution to consumers, as well as possibility of additional enrichment with the above-mentioned components. The argument that healthy food represents an important component of the preventive medicine is supported by the increasing number of experimental and clinical studies indicating that spontaneous miscarriages, as well as birth of children with inborn defects, are frequently the consequence of lack of certain antioxidant dietary components (HASLER, 2000; FANG et al., 2002). We are obviously coming closer to the Hippocrates words said in the 4th century BC.: ***Let food be thy medicine and medicine be thy food.***

The above assertion is supported by conclusions presented by YUNG et al (2006). Namely, they have presented in detail roles of proteins, lipids, vitamins, minerals and phytochemical antioxidants in maintenance of oxidoreductive balance, which is a key factor in preservation of the homeostasis of the organism in general.. They have finally concluded that recent knowledge in the field of free radical biology represents a base for practical application of antioxidants for improvement of human health and prevention of the cardiovascular diseases. Having in mind the fact that quality food among other properties must have antioxidant properties necessary for maintenance of the general homeostasis of the organism, it becomes clear that healthy food has an important place in modern medicine, primarily as a means of prevention. Maintenance of the good antioxidative status during infant growth and development is crucial, since it enables one of the essential prerequisites for appropriate cell differentiation and proliferation to be fulfilled. Formation and maturation of all systems, particularly the immune and neuroendocrine systems are to the certain extent correlated with the existing antioxidative status of the organism. Having in mind the above fact, the nature took care to supply human milk, in addition to low molecular antioxidative components, with high molecular enzyme components, cytosolic and mitochondrial SOD, which in the natural lipoprotein milieu express significant physiological activity (KIYOSAWA et al. 1993, KASAPOVIĆ et al. 2005). Complex conformational structure of the above-mentioned enzyme molecules and their natural lipoprotein coating enable preservation of the structure and function of the enzyme molecule. In addition to the human milk, SOD is also present in cow’s milk (FILIPOVIĆ et al. 2005). Statistical analysis evidenced that even in case of absence of significant difference between the cow’s milk samples related to protein concentration, the difference in specific SOD activity still exists. The sample containing the highest SOD activity, which makes it as quality as the human milk, is recommended as a staring material for baby formulas.

One of the most important protein- containing foodstuffs is milk, as well as its various products (WONG et al. 1996). Milk is a polyphasic secretion of the mammalian gland, containing 3.3% protein, 3.9% fat, 5.0% lactose and 0.7% minerals (WONG et al. 1996 SWAISGOOD 1986). The most abundant milk proteins are phosphoproteins caseins, composed of α-,β-, and κ-casein fractions, which comprise approximately 80% of total protein content (SWAISGOOD 1986). Milk caseins are predominantly organized as micelles, with the dispersion range size from 20 to 600 nm, mutually held by calcium phosphate bridges (SCHMIDT, 1986; DALGLEISH, 1988; DALGLEISH and LOW, 1988; DALGLEISH and LOW, 1989; LAW 1996). About two thirds of the milk calcium and one half of the milk phosphate are bound in micelles in the colloidal form. The soluble milk protein fraction comprises β-lactoglobulin, α-lactalbumin, serum albumin, lactoferrin, immunoglobulins, and β-microglobulin (WONG, 1996; SWAISGOOD, 1986). Several of milk proteins are suggested to have a role in its antioxidant activity: *e.g.* lactoferrin, which binds prooxidative iron ions (LANDMARK-MANSSON and AKESSON, 2000), and caseins in a free form (TAYLOR and RICHARDSON, 1980). However, cow milk also contains well-known antioxidant enzyme Cu/Zn - dismutase (Cu/Zn-SOD) and also traces of Mn-superoxide dismutase (Mn-SOD) (LANDMARK- MANSSON and AKESSON, 2000; HICKS. 1980), both of which were previously thoroughly characterized in some bovine cells (McCORD and FRIDOVICH, 1969; EVANS et al.,1974; ABERNETHY, 1974). These enzymes perform dismutation of superoxide anion to hydrogen peroxide, and are consequently thought to be the first line in the mammalian antioxidative defense system (LANDMARK- MANSSON and AKESSON, 2000).

This term is used to indicate a functional food that containes some health-promoting components, such as antioxidants, and not only traditional nutrients. From this point of view, we showed that the high antioxidant content of the initial raw milk, as well as the technology of its processing are of great importance for the preservation of SOD activity in the final foodstuff product. Thus, the obtained data of specific SOD activity in full milk and milk fractions may be of practical significance when choosing the starting milk samples for further processing (RADOJČIĆ et al., 2002).

Further research on individual differences in genetic profiles and nutrient requirements will help establish nutrigenetics as an essential discipline for nutrition and dietetics practice.

CONCLUSION

Nutrigenomics revitalized the field by showing that nutrients can interact with the genome and modify subsequent gene expression, which has provided a great impetus for nutrigenetic research and nutraceuticals development based on nutrigenetics. The conceptual basis for this new branch of genomic research can best be summarized by the following five principles of nutrigenomics:

i) under certain circumstances and in some individuals, diet can be a serious risk factor for a number of diseases;

ii) common dietary components can act on the human genome, either directly or indirectly, to alter gene expression or structure;

iii) the degree to which diet influences the balance between healthy and disease states may depend on an individual's genetic makeup;

iv) some diet-regulated genes are likely to play a role in the onset, incidence, progression, and/or severity of chronic diseases;

v) dietary intervention based on knowledge of nutritional requirement, nutritional status, and genotype ("personalized nutrition") can be used to prevent, mitigate or cure chronic disease.

This review shows the potential application of nutrigenomics information toward the development of a clinically tested product providing opportunities for nutraceutical and functional food industries.

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NUTRIGENOMIKA

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I z v o d

Nutrigenomika je nauka koja izučava efekte bioaktivnih komponenti hrane na ekspresiju gena. Zahvaljujući genetskoj različitosti naša biotransformacija i kapacitet detoksikacije , kao i podložnost bolestima, značajno variraju od osobe do osobe. Moguće je, ako je potrebno, menjati ekspresiju gena promenom načina ishrane, što dovodi do aktiviranja gena, koji sprečavaju razvoj različitih patoloških procesa. Sve je više podataka koju ukazuju da su mnoge hronične bolesti uzrokovane neusklađenom ishranom.

Pravilna ishrana podrazumeva korišćenje hrane, koja deluje na različitim fiziološkim nivoima organizma u smislu promocije zdravlja, pa se takva vrsta hrane naziva ***funkcionalna*** hrana. Ova vrste hrane pored uobičajenih hranljivih sastojaka sadrži i funkcionalne komponente, kao što su bioaktivni peptidi, antioksidanti, prebiotici, probiotici i dr.

Ovakav način ishrane je opšti svetski trend, jer je dosadašnja praksa pokazala da funkcionalna hrana može smanjiti rizik od geneze kancera, hroničnih srčanih obolenja, nervnih obolenja i dr. Antioksidativne komponente su veoma važno svojstvo funkcionalne hrane. U prilog tvrdnji da funkcionalna hrana predstavlja bitnu komponentu preventivne medicine govori sve veći broj eksperimentalnih i kliničkih studija. Nutrigenomika i trend personalizacije ishrane razvija se vrlo dinamično, a rezultati ovih istraživanja daju značajne podatke, koji ukazuju na neophodnost primene nutrigenomskog testa.

Dakle, sekvenciranje genoma otvorilo je potpuno novo poglavlje u razumevanju interakcije zdravlja i ishrane, pre svega, personalizovane ishrane kao saveznika zdravlja.

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