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Dance Round

WE DANCE ROUND IN A RING AND SUPPOSE,
BUT THE SECRET SITS IN THE MIDDLE AND KNOWS.
ROBERT FROST

NUTRIGENOMICS: DNA-BASED INDIVIDUALIZED NUTRITION

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In the past decade, nutrition research has undergone an important shift from epidemiology and physiology to molecular biology, adipobiology and genetics, thus launching the science of nutrigenomics. To at molecular level study effects of nutrition on health and disease. The completion of several large genome projects has markedly altered the research agenda by drawing attention to the importance of genes in human nutrition. There has been a growing recognition that micronutrients and macronutrients can be potent dietary signals that influence the metabolic pathways of cells and have an important role in the control of energy, vascular and neuronal homeostasis. Accordingly, nutrition researchers have increasingly started to recognize that gene-environment interactions can be implicated in the pathogenesis of lifestyle-related diseases, particularly cardiometabolic diseases, fatty liver diseases, cancers, and Alzheimer' disease. An adiponutrigenomic insight into life expectancy is also outlined. Overall, the present Dance Round focuses on a mater of nationwide importance for Bulgaria, a country at the epicenter of today's global healthquake, the obesity and related diseases. ***Biomed Rev 2006; 17: 117-122.***

Key words: Disease prevention, food, genes, lifespan, nutrients

INTRODUCTION

Gene-environment interaction is behind the pathobiology of most widespread human diseases such as obesity and associated cardiometabolic diseases (atherosclerosis, hypertension, type 2 diabetes and metabolic syndrome). These are viewed as lifestyle-related disorders, and nutrition is among the environmental factors with the highest impact on human metabolic and vascular health. Whilst susceptibility to become *Homo obesus* (man the obese) is determined largely by ("thrifty") genes, the current obesity epidemic is significantly influenced by adverse lifestyle factors. Given our genetic background it is essentially infeasible for humans to self-regulate food intake under current

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obesigenic and atherogenic environment, especially in our country Bulgaria, an epicenter of global healthquake induced by stroke and myocardial infarction.

Here we *Dance Round (i)* nutrigenomics in disease prevention, particularly cardiometabolic diseases, and *(ii)* adiponutrigenomics of life expectancy, focusing on caloric restriction and its chemical mimetics, such as resveratrol.

THE SCIENCE OF NUTRIGENOMICS

Nutrigenomics (nutritional genomics) can be viewed as a nexus between health, molecular nutrition, and genes. Nutrigenomics covers a wide range of technologies concerned with elucidating how the genetic program operating in cells and tissues is potentially influenced by diet. There are three possible definitions for nutrigenomics: *(i) " ... the application of high throughput genomics tools in nutrition research"* (1), *(ii)* [nutrigenomics] *"... seeks to examine 'dietary signatures' in cells, tissues and organisms and to understand how nutrition influences homeostasis"* (1), and *(iii) "... the interface between the nutritional environment and cellular/genetic processes"* (2).

All of these draw certain parallels with other "-omics" sciences, particularly pharmacogenomics, but the comparison cannot be pushed too far; nutrigenomics faces complications that the other areas do not face, notably the length and the complexity of exposures. Nutrigenomics and other "-omics" sciences and technologies, such as transcriptomics, proteomics, metabolomics, and epigenomics, have added more complex functional analysis to the basic sequence information provided by the Human Genome Project (3).

Transcriptomics, for example, which uses microarrays, is a very valuable way of beginning to understand how nutritional exposure influences gene expression on a genomic scale (4). It is possible to group genes of interest for particular metabolic processes and capture information from all of these at once to see how the cell is functioning at any given time or under certain conditions. Such techniques are aided by the commercial development of chips orientated around particular metabolic or functional systems.

Proteomics uses protein separation usually on 2-D gels followed by quantification and identification often using mass spectrometric techniques to investigate differential protein expression again under different conditions or with different underlying pathology. The presence or absence of certain key proteins can give information about the early stages of disease (5).

Metabolomics (or metabonomics) examines global patterns of metabolites present in the cell or in body fluids in response to specific dietary exposures. This requires powerful statistical tools (chemometric analysis) to investigate differences in the NMR spectra or analytes detected by HPLC or other separation techniques (6).

Epigenomics. Epigenetics is the study of modifications to the genome which are copied from one cell generation to the next but which do not involve changes to the primary sequence. These changes, mediated through modification of chromatin proteins such as histones and through the methylation of DNA, contribute to the regulation of transcription and provide a way for the genome to "learn from experience", regulating gene expression in response to dietary and other exposures and leading to altered cellular phenotypes associated, for example, with chronic disease or ageing (7).

All of these "-omics" sciences have been used to study in detail the molecular responses to food substances or the early stages of disease in common diet-related conditions (8,9). Nutrigenomics will promote an increased understanding of how nutrition influences metabolic, caloric and vascular homeosis, how this regulation is disturbed in the early phases of diet-related disease, and the extent to which individual sensitizing genotypes contribute to such diseases (10).

Who will be susceptible to disease and who will be responsive to dietary modification?

It is well known that there are differences in nutrient requirements which for several nutrients follow a normal distribution, with some individuals having very high requirements while others need much lower levels than average. At the heart of individual variation is the 0.1% of variation between the DNA sequences of any two individuals. Much of this variation is accounted for by single nucleotide polymorphisms (SNP), which are largely responsible for differences in complex characteristics such as the way in which we respond to our environment. These differences are likely to apply throughout life, from the early uterine environment right through to different ageing responses later in life. All of these technologies have so far been applied to cells in culture and to certain model organisms. The challenge will come in applying them to people, where problems both of study design and ethics will be encountered. In addition, with human beings, our means

of establishing accurate dietary exposures are imperfect and this is compounded by the need for observations over long time periods, by problems of access to the target tissues and their heterogeneity.

NUTRIGENOMICS' FIRST STEPS

Until recently, nutrition research concentrated on nutrient deficiencies and health impairment. The advent of genomics has created unprecedented opportunities for increasing our understanding of how nutrients modulate gene and protein expression and ultimately influence cellular and organismal metabolism. Eventually, nutrigenomics will lead to evidence-based dietary strategies for restoring health and fitness and for predicting and preventing lifestyle-related diseases (Figure).

Nutrigenomics seeks to provide a genetic understanding for how common dietary chemicals (i.e., nutrition) affects the balance between health and disease by altering the expression and/or structure of an individual's genetic makeup (11). The conceptual basis for this new branch of genomic research can best be summarized with the following five tenets (12): *(i)* common dietary chemicals act on the human genome, either directly or indirectly, to alter gene expression or structure, *(ii)* under certain circumstances and in some individuals, diet can be a serious risk factor for a number of diseases, *(iii)* some diet-regulated genes (and their normal, common variants) are likely to play a role in the onset, incidence, progression, and/or severity of chronic diseases, *(iv)* the degree to which diet influences the balance between healthy and disease states may depend on an individual's genetic makeup, and *(v)* dietary intervention based on knowledge of nutritional requirement, nutritional status, and genotype, that is, "individualized nutrition", can be used to prevent, mitigate or cure chronic disease.

Nutrigenomics refers to the prospective analysis of differences among nutrients with regard to the regulation of gene expression. In this context, nutrigenomics is a discovery science driven by the paradigms of molecular biology, enabled by microarray technology, and integrated on an informatics platform. In contrast, *nutrigenetics* refers to the retrospective analysis of genetic variations among individuals with regard to their clinical response to specific nutrients. In this context, nutrigenetics is an applied science driven by the paradigms of nutritional pharmacology in the context of genetic polymor-

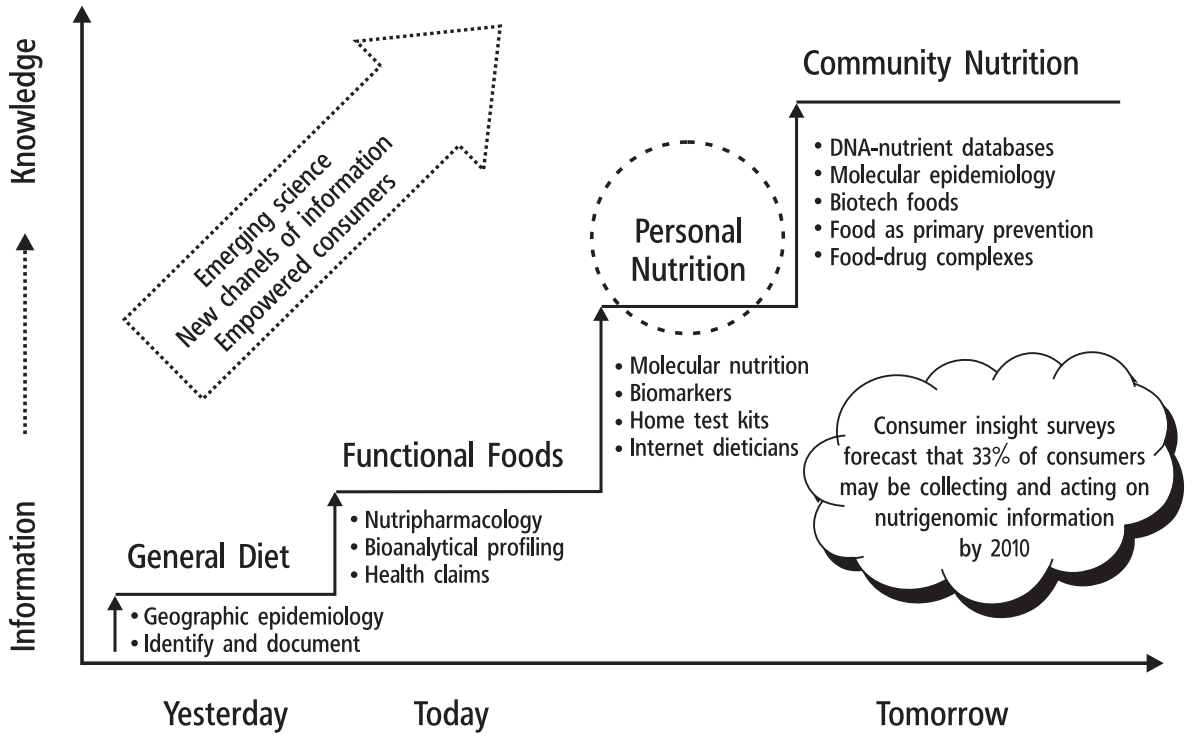

Figure 1. *"The Future of Nutritional Science". From the American Diatetic Association, 2003.*

phisms and clinical experience. Although the directionality of these distinctions is a useful interim construct, the distinctions are likely to erode and the concepts coalesce as the databases of the human genome and nutriome merge into a unifying paradigm of molecular nutrition (13).

NEW BIOMARKERS FOR DISEASES

The finding that several dietary compounds regulate gene expression has provided tools to help unravel molecular mechanisms behind lifestyle-related diseases. A major focus of nutrition research is on the prevention of chronic diseases including cardiometabolic and other obesity-linked diseases such as nonalcoholic steatohepatitis, polycystic ovary syndrome, obstructive sleep apnea syndrome, cancers (reviewed in 14-20) and also Alzheimer's disease (21,22). These disorders are partly mediated by chronic exposure to certain food components and therefore a critical part of the prevention strategy concerns changing food content and food habits (23).

Discovering natural dietary ligands that regulate important metabolic pathways have recently been identified for several new members of the nuclear receptor superfamily, including peroxisome proliferator-activated receptors (PPARs), liver X receptors, farnesoid X receptor, constitutive androstane receptor, and pregnane X receptor (24). All of these receptors are relatively promiscuous, recognizing both endogenous and exogenous ligands that often share little or no structural similarity. Therefore these receptors are potential mediators of nutrients and other natural products that have beneficial effects. Several nuclear receptors bind substances in the diet or metabolites of dietary substances. This makes nuclear receptors a fascinating link between nutrition, genomics, endocrinology and molecular biology. For instance, n-3 polyunsaturated fatty acids, including linoleic acid, linolenic acid, and the fish oils docosahexaenoic acid and eicosapentaenoic acid, have all been shown to bind and activate PPARγ and PPARδ, though their affinity is higher for PPARα. Saturated and monounsaturated fatty acids, including palmitic, oleic, and arachidonic acids, also bind for PPARα with greater affinity than either activate PPARγ and PPARδ (25). Further, the emerging studies on nutrient-induced gene expression for other obesity-related molecules such as adipokines (15-20) frame a novel target of nutritional genomics, namely adiponutrigenomics.

ADIPONUTRIGENOMICS OF LIFESPAN: YES, *SIR!*

Recent data may join adipobiology (15-20) and nutritional genomics, including xenohormesis (26,27), in the processes of ageing and lifespan (28-32). Encoraging results obtained until now include (26-30): *(i)* yeast, worms, flies, rodents or humans kept on caloric restriction diet enjoy healthy longevity (26-30), *(ii)* treatment with resveratrol, a xenohormetic molecule of polyphenol nature, extends lifespan of treated animals *via* stimulation of the actvity of nicotinamide adenine dinucleotide (NAD)+ deacetylases, e.g. adipose-specific, inner mitochondrial membrane protein, sirtuin 3 (SIRT3, named after the gene *Sir,* silent information regulator) (31,32 for Alzheimer's disease treatment), *(iii)* caloric restriction-induced increase in lifespan is accompanied by elevated brain levels of brain-derived neurotrophic factor (BDNF) (33; 34-36 for both BDNF and nerve growth factor, NGF), *(v)* n-3 polyunsaturated fatty acids increase circulating levels of adiponectin (37), an "anti-kine" (38), that is, adipokine with antiobesity, anti-inflammatory, anti-diabetic and anti-atherogenic effects (reviewed in 15,18), and, noteworthy, *(v)* resveratrol mimics caloric restriction's effects, thus promising a (charming) chance for *Homo besus* to enjoy both weight loss and pleasure of eating (and drinking).

In perspective, various nutraceuticals such as Pycnogenol (39) as well as functional foods may be pursued for their possible impact on the biology of NGF, BDNF, adiponectin and other metabotrophic factors including sirtuins (26-32,34-36); such an (adipo)nutrigenomic approach may also be applied to an age-related phenomenon recently dubbed inflammageing (40,41).

CONCLSUION

Food components may have fundamental influences on health and disease that can further be explained by studying nutrient-induced gene, protein and metabolite expressions. This may help to better understand nutrition's impact on energy, metabolic and vascular homeostasis and thus developing better strategies for the prediction, prevention and treatment of, at least, lifestyle-related diseases. In the coming years, we may indeed identify the mechanisms driving the connection between diet and the outward manifestation of genes, the "nutritional" phenotype.

Dietary advice is traditionally based on observations at the level of large populations. However, advice that is good for the majority of people can be bad for a minority with different genetic background. There are estimates that dietary guidelines designed for entire populations give recommendations that

might only work for two people out of three. Hence, potential benefits of nutrigenomics research may include an improved individual health, greater consumer choice and control, greater disease prevention and related health care system savings. On top of this, nutrigenomics promises to enable people to reduce risks of developing diet-related diseases, and may be able to treat existing conditions. It is likely that adjustments to diets over a long time will strongly reduce the risks of a large number of diseases. In effect, genetic passport may help launching once's individualized "diaeteticon" (42). It is not only CR (*caloric restriction*) but, more importantly, escaping from any CR (*creativity restriction*) that may indeed help achieving that goal.

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