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Nutrigenomics: From molecular nutrition to prevention of disease

Ratna Trivedi[1]*, P.N.Patel[2], H.J.Jani[3], B.A.Trivedi[4]

[1]Department of Microbiology, Shree Ramkrishna Institute of Applied Sciences, M.T.B.College Campus, Athwalines, Surat, Gujarat, (INDIA)

[2]Department of Computer Application, Kalol Institute of Technology & Research Centre, Kalol National Highway, Kalol - 382 721, Gujarat, (INDIA)

[3]Department of Analytical Chemistry, Bhavnagar University, Bhavnagar, Gujarat, (INDIA)

[4]Department of Computer Application, Navagujarat College, Ashram Road, Ahmedabad, Gujarat, (INDIA)

E-mail : ppatel1487@gmail.com; drratnatrivedi@gmail.com; dev123@gmail.com

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ABSTRACT

Nutrition research concentrated on nutrient deficiencies and impairment of health. The advent of genomics-interpreted broadly as a suite of high throughput technologies for the generation, processing, and application of scientific information about the composition and functions of genomes-has created unprecedented opportunities for increasing our understanding of how nutrients modulate gene and protein expression and ultimately influence cellular and organismal metabolism. Nutritional genomics (nutrigenomics), the junction between health, diet, and genomics, can be seen as the combination of molecular nutrition and genomics. The diverse tissue and organ-specific effects of bioactive dietary components include gene-expression patterns (transcriptome); organization of the chromatin (epigenome); protein-expression patterns, including posttranslational modifications (proteome); as well as metabolite profiles (metabolome). Nutrigenomics will promote an increased understanding of how nutrition influences metabolic pathways and homeostatic control, 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. Eventually, nutrigenomics will lead to evidence-based dietary intervention strategies for restoring health and fitness and for preventing diet-related disease. In this review, we provide a brief overview of nutrigenomics from our point of view by describing current strategies, future opportunities, and challenges. © 2011 Trade Science Inc. - INDIA

KEYWORDS

Nutrition;
Nutrient deficiencies;
Genomics;
Nutrigenomics;
Epigenome;
Metabolome;
Transcriptome.

INTRODUCTION

Expectations of nutrigenomics[1-8] are extremely high, but progress is rather slow. The field of nutrigenomics faces the challenge of establishing a strong basic research foundation while simultaneously surmounting a number of technological hurdles. The coming years will likely require patience, realistic expectations, and strong

advocacy for the needed research funding. In addition, we must be innovative in our approaches to the complex problems that nutrigenomics presents. For example, a single nutrigenomics experiment can generate an enormous amount of data. We must quickly learn how to extract useful biological information from these data. Nutrigenomics must address management and storage of different types of data derived from the various technological platforms used development and application of new biostatistical algorithms, and inaccessibility of tissue samples from healthy volunteers.

Challenges of this scope and magnitude cannot be solved by one research group alone and will likely require collaboration among a number of different research teams. Furthermore, many of the genomics technologies are quite expensive. Not surprisingly, an increasing number of large national and international nutrigenomics research clusters are being formed to jointly address these and similar challenges. These clusters typically focus on specific aspects of nutrition research and disease prevention (TABLE 1) that can be approached with nutrigenomics research. For such a collaborative effort to be successful, there must be excellent communication among scientists from different disciplines (eg, nutrition, molecular biology, medicine, genomics, bioinformatics), and there must be a high level of compatibility of the genomics data produced in the various laboratories[9-11].

Several of these clusters or centers also involve collaboration between the food industry and academia. The food industry recognizes the need for nutrigenomics re- search as a basis for developing the concept of "personalized diets," for identifying molecular biomarkers or new bioactive food ingredients, and for validating the effectiveness of these bioactive ingredients as functional food components or nutraceuticals. An important aim of nutrigenomics research is to study genome-wide influences of nutrition, with specific focus on the role of metabolic stress in the genesis of the metabolic syndrome, the collection of phenotypes combining inflammation, metabolic stress, insulin resistance, and diabetes[12].

This goal is rather ambitious, but is based on the idea that nutrition should focus primarily on health and disease prevention and be complementary to pharmacological therapy, which targets the pathophysiological

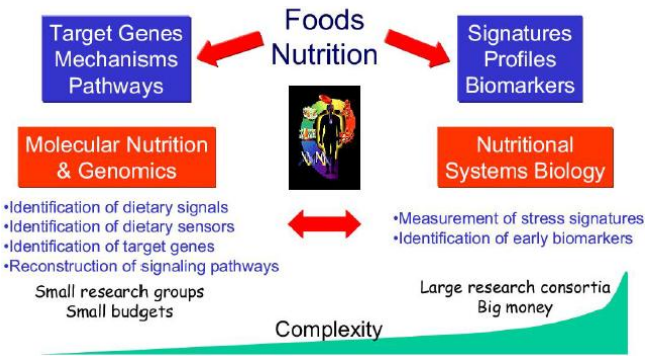

Figure 1 : Two strategies for nutrigenomics

aspects of disease. To realize this goal, new genomics-based phenotypical biomarkers are needed that allow early detection of the onset of disease or, ideally, the predisease state of the metabolic syndrome, a condition referred to as metabolic stress.

To approach this complex condition, molecular utrition research on organ-specific dietary response patterns using transgenic and knock-out mouse models is combined with genomic technologies. From a molecular standpoint, nutrients are considered to be "signaling mol- ecules" that, through Appropriate cellular sensing mechanisms, result in translation of these dietary signals into changes in gene, protein, and metabolite expression[8]. Such an approach allows insight into the mechanisms of nutrition at the molecular level (ie, what happens in our cells and organs when we eat, when we do not eat, or when we eat too much).

Nutrigenomics: How to get simple answers for a complex science?

An important challenge in nutrition research is the complexity and variability of nutrition and foods. The body has to handle a large number of different nutrients and other food components and nutrient concentrations can be high (micromolar to millimolar) without reaching toxic levels. Each nutrient can also have numerous targets with different affinities and specificities. This situation contrasts starkly with pharmacology, where single agents are used at low concentrations and act with a relatively high affinity and selectivity for a very limited number of biological targets. The challenge of nutrigenomics research is to break down the important but complex research problems into small feasible projects that can be handled by normal-sized research groups (Figure 1). One possibility is to switch from the

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TABLE 1 : Overview of selected international nutrigenomics consortia and networks

Consortium	Country	Focus	Web site
Center of excellence for nutritional genomics	United states	Personalized diet:diet-gene interactions	www.nutrigenomics.ucdavis.edu
Dutch nutrigenomics consortium	The Netherlands	Metabolic syndrome:early biomarkers	www.nutrigenomics.nvngc
Network of excellence in nutrigenomics (NUGO)	Europe (European community)	Establishment of a european nutrigenomics research network (research, training, standardization)	www.nugo.org
Centre of excellence in nutrigenomics	New Zealand	Crohn's disease; new food bioactivity	www.nutrigenomics.org.nz
Functional food genomics	Japan	Biomarkers and bioactivity food ingredients	
Nutrigenomics network	Germany	Complex diseases: diet-gene interaction	www.nutrigenomik.de

most complex system, the human being, to simpler or more easily accessible organisms, such as yeast and *Caenorhabditis elegans*, which can serve as model systems. These organisms have sophisticated genetics as well as sequenced genomes, and researchers have made important discoveries in nutrigenomics using these model systems. Even the fruit fly *Drosophila* is an attractive model organism for conducting nutrigenomics research[2] because it has adipose-like tissues and a lipid transport system, which makes it acloser model to humans with respect to obesity and associated diseases than many other model organisms. Another possible strategy is to use methods that are well established in medical or pharmacological research but are rather new to nutrition research. For example, analogous to pharmacology, nutrients or dietary metabolites can be viewed as signaling molecules that are recognized by specialized cellular-sensing mechanisms[8]. The information that allows nutrients to activate specific signaling pathways is contained within their molecular structure. Minor changes in structure (eg, saturated vs unsaturated fatty acids or cholesterol vs plant sterols) can have a profound influence on which sensor pathways are activated. The challenge ahead is to further identify the molecular pathways that are influenced by individual nutrients and to determine the downstream effects of this regulation. Nutrigenomics can greatly assist in this identification because it allows the genome-wide characterization of nutritional target genes. With this type of information, researchers can comprehensively understand how nutrients act and explain how diet has such an impressive effect on health and disease, which is now widely acknowledged. Ultimately, nutrigenomics research will lead to development of evidence-based healthful food and lifestyle advice and dietary interventions for contemporary humans.

Signatures of health and disease

A major focus of nutrition research is on prevention of chronic diseases, such as cardiovascular disease, metabolic syndrome, and cancer. These disorders are partly mediated by chronic exposure to certain food components and, therefore, a critical part of the prevention strategy concerns changing food habits. Causal relationships between those bioactive dietary components and prevention or outcome of a disease can only be assessed by long-term intervention trials, which are time-consuming and costly. Other conventional nutrition intervention studies use biomarkers like disturbed lipid profiles (eg, cholesterol, triglycerides), increased blood pressure, or reduced insulin sensitivity as predictors of diseases, such as cardiovascular disease or metabolic syndrome. These biomarkers are mainly single proteins or metabolites or certain body functions that can be used as indicators for pathophysiological changes that can ultimately lead to a variety of chronic diseases, depending on the individual genotype. A complete biomarker profile will be more characteristic for the health status of an individual than single markers. The ability to assess these so-called "signatures" of health and disease hold the promise of a more complete phenotyping of humans and the ability to monitor health status using a noninvasive tool. Biomarker profiles can be determined on a genomics-transcriptome, proteome, and metabolome level, all having their own specific advantages as markers of body health status.

From genotype to phenotypev

Most chronic diseases, such as cardiovascular disease, metabolic syndrome, and cancer are multifactorial disorders caused by multiple genetic and environmental factors. Multigenic or polygenic diseases are

caused by a combination of genetic variations in multiple susceptibility genes. Different combinations of gene variants can lead to a similar disease phenotype, further complicating the picture. Moreover, several modulator effects of dietary components on the phenotype by a genetic variation have been described and are referred to as gene-nutrient effects[33]. Investigation of combinations of genetic variants and the effect of nutrients in relation to a disease requires large study populations of patients and controls. The known gene variants and the modulator effects of nutrients in relation to a disease have recently been discussed in an excellent review by Ordovas and Corella[9]. Most genetic variations, such as single-nucleotide polymorphisms (SNP), insertions, or repeats have been found by sequencing genes coding for enzymes or transporters related to the disease of interest.

With sequencing of the whole human genome, knowledge about genetic variations has increased, and microarrays containing around 500,000 SNPs (500 K-arrays) are already available. These chips can be used in association studies to identify new candidate loci for a disease[10]. Nutrition research has until now focused mainly on no more than a few SNP simultaneously and on the opportunity to abolish possible harmful consequences of the SNP by nutrition intervention. Research into these so-called nutrient gene interactions with genome-wide SNP arrays are complicated by multiple genes, dietary components, and gene-nutrient interactions[11]. Before technologies such as this can be applied in nutrition research, they first have to be proven and validated in disease association research studies.

Can a bioinformatician make sense of your microarray experiment?

Another limitation in nutrition research is the relatively small effect of dietary interventions on physiological parameters. Similarly, effects of nutrition on gene-expression patterns are also hard to detect. Consequently, a suitable study approach is required along with the need to develop state-of-the-art sensitive microarray analysis systems. Although a major technological advance, microarray technology has strengths and limitations that must be factored into the research design. A robust research hypothesis and study design will help to ensure the research question is adequately addressed by the experimental design (avoiding the so-called "fishing experiments"). Important factors that can influence gene expression in humans as well as in animals are age, sex, nutritional status, and other possibly unknown (patho)- physiological parameters. In addition, these methods work best when genotype variation is minimal, which is feasible in animal studies with inbred strains but not with human beings. The most easily obtained information in human intervention trials is race and family history. Once a transcriptomics study is performed, RNA quality and quantity should be verified and subsequent labeling and hybridization of RNA should preferably be conducted by the same technician and within the same microarray experiment. In order to enhance accuracy, pooling of samples is not desirable, but increasing the number of biological replicates will decrease the false-positive rate and result in reliable data[11].

Future perspectives

Will nutrigenomics stay exciting enough over the next several years to sustain development of an extensive research foundation? We are sure this will be the case because it is widely appreciated that further developments in nutrition and food development are impossible without exploring the mechanisms underlying nutrition. Will it then be possible from nutrigenomics research to develop food and beverage products that can help prevent or reduce onset and impact of complex diseases, such as type 2 diabetes, cardiovascular disease, and some forms of cancers? Can food products be tailored to promote the health and well-being of groups in the population identified on the basis of their individual genomes? The potential is there and exciting new developments are unfolding. However, it is important to re-evaluate expectations on a regular basis. What can we achieve within the scope of the expertise and techniques we have available now and in the near future? In the coming years, we have to put all our efforts into gaining a thorough understanding of how nutrients interact with the human genome at a molecular level. To be able to use genetic blueprints or genotypes in dietary prevention of disease, we must first identify the mechanisms driving the connection between diet and the outward manifestation of our genes, our phenotype.

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