Nutrigenomics : A Revolution in Nutrition Science


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Abstract

The execution of the Human Genome Project has led to the development of a so far unexplored avenue in nutrition science – Nutrigenomics. There is a growing realization amongst scientists that an individual's health or disease status is not only a function of his or her genetic make up, but also of environmental factors, specifically food intake and nutrient exposure. The inception and progression of some common diseases such as obesity, cardiovascular disease and type 2 diabetes mellitus has been found to be very closely linked with diet and nutrient exposure. The basic concept of nutrigenomics is to modulate dietary constituents so as to control and regulate gene expression in the body. Nutrient regulation of gene expression can be studied in various ways. Transcriptomics, proteomics and metabolomics are the major approaches currently being used for this purpose. These hold great promise to increasing our knowledge of interactions between the diet and life processes, and may eventually lead to the development of novel functional foods to improve the health status of the general population. Also, an era of 'personalized nutrition' wherein each person's diet is designed based on his genetic make-up, now seems to be close at hand, thanks to this budding wonder-science.

Keywords: Nutrigenomics, Nutrigenetics, Transcritpomics, Proteomics, Metabolomics.

1. Introduction

In the past, nutrition, as a scientific discipline, focused mainly on epidemiology and physiology[1]. The health status of an individual was considered to be a function of his/her genetic make-up. However, in recent times, in light of the Human Genome Project and the rapid advances in molecular biology, it is becoming increasingly obvious that a person's health or disease status is not only a function of genetic background[2]. Food intake and nutrient exposure are key environmental factors involved in the pathogenesis and progression of common diet-related diseases like type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD) and obesity. There is now a growing recognition of the fact that nutrients can be potent dietary signals that influence the metabolic programming of cells and have an important role in the control of homeostasis[3].

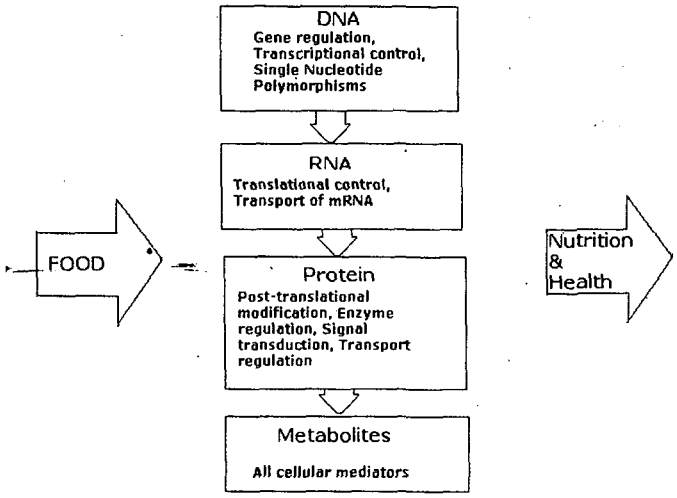

Figure 1: Health effects of food compounds are related to specific molecular interactions with the genome, transcriptome, proteome and metabolome. Adapted from Roche H.M.,[2].

Figure 1 illustrates that the key to understanding the full role of nutrition in health is based on multiple interactions between nutrition and the genome, at the level of DNA, RNA, proteins and metabolites[2]. The nature and duration of exposure to a nutrient is also significant. Therefore, complex experimental designs are required to provide a comprehensive understanding of nutritional genomics. The experimental models will have to investigate the effects of single nutrients initially, and then of the complex nutrient mixtures that are consumed daily as food. The models will have to account for synergistic and antagonistic effects/interactions between nutrient and non-nutrient components of food and also amongst different nutrients. Also, issues related to duration of dietary exposure need to be addressed, in order to determine the cumulative effect of nutrient exposure. Primarily, the healthy genotype/phenotype needs to be characterized so as to prove as a ground for comparison. In the long run, an in depth understanding of the nutrient-genome interaction will serve to generate data that can be used to design diets specific to a person based on his/her genetic make-up. The concept of 'personalized nutrition' does not seem too difficult to achieve, thanks to this new, fast-growing discipline.

2. Nutritional Genomics: Nutrigenomics and Nutrigenetics

The human genome and nutrition share a dynamic two-way interaction[4]. An individual's genetic background can determine nutrient status, metabolic response and predisposition to diet-related diseases. Also, nutrients can have a direct effect and interact with transcription factors to regulate gene expression. This dynamic cause-effect relationship between the genome and nutrients has led to two new sub-definitions, nutrigenomics and nutrigenetics[2]. Figure 2 illustrates the dynamic interaction between nutrition and the genome.

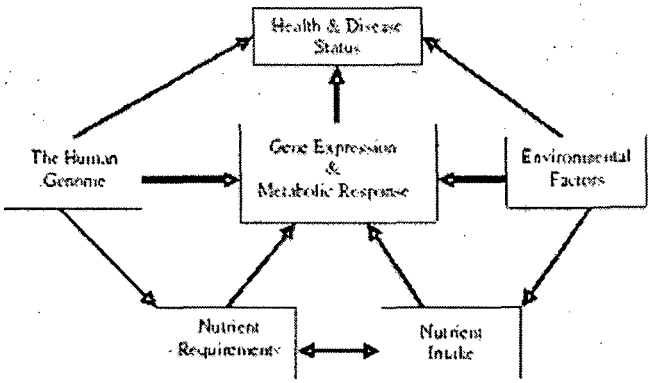

Figure 2: Two-way interaction between nutrition and the human genome. Adapted from Roche H.M. [2].

Nutrigenomics attempts to study the genome-wide influences of nutrition[1]. From a nutrigenomics perspective, nutrients are dietary signals that are detected by the cellular sensor systems that influence gene and protein expression and, subsequently, metabolite production. Also, nutrigenomics aims to identify the genes that influence the risk of diet related diseases, and to understand the mechanisms that underlie these genetic predispositions.

Nutrigenetics, on the other hand, seeks to explain how and to what extent nutrition-related traits and disorders are influenced by genetic variation[5]. In other words, it examines the effect of genetic variation on the interaction between diet and disease, or on nutrient requirements[1].

3. Measuring Nutrition-Responsive Genome Activity

The typical nutrigenomics experiment is based on several points such as the actual approach, the model system, the type of nutrition or diet and the appropriate technological methods[5]. The influence of nutrition on genome activity is usually studied in a comparative manner either by a direct or an indirect approach.

The direct approach involves making changes in the nutrients presented to a model system and then monitoring changes in gene expression. Most human intervention studies fall under this category. The indirect approach involves the study of nutrition-related traits and disorders such as obesity, T2DM and CVD. In such studies, gene expression is compared between subjects with and without the disorder. From the differences, the molecular pathways leading from health to disease under the influence of diet and lifestyle are deduced.

Many different model systems are available ranging from *in-vitro* cultured cells to animals and humans. Commonly used animal models are mouse, rats, pigs or the nematode worm *Caenorhabditis elegans*.

Many approaches and technologies are available for use in nutrigenomics experiments. Each approach studies gene expression on a different level and is being developed as a discipline in its own right. Some of the significant approaches are discussed here.

4. The 'Omics' Revolution in Nutritional Science

With the Human Genome Project (HGP) nearing completion, a new era in biological and medical sciences is beginning. This is often referred to as the 'omics' revolution. Established scientific disciplines such as toxicology, pharmacology and nutrition adopted techniques and knowledge from the HGP, thus leading to the genesis of toxicogenomics, pharmacogenomics and nutrigenomics respectively.

For performing a nutrigenomics experiment, it is necessary to measure the expression of many genes simultaneously under changing nutritional conditions. When genes are expressed, the genetic code of the DNA is transferred to mRNA in a process called transcription. After a complex pattern of processing, the mRNA is used to translate the coding information into the amino acid order of the corresponding amino acid protein. Thus, gene expression activity can be measured by determining the amount of mRNA or protein produced. These approaches for gene expression measurement fall into the areas of transcriptomics and proteomics respectively.

4.1 Transcriptomics

Transcriptome is a complete collection of gene transcripts (mRNA) in a cell or tissue at a given time[1]. Transcriptomics seeks to study the mRNA profile of a cell or tissue in order to assess gene expression. For instance, in the context of obesity, the study of all genes involved in storage of triglycerides in adipocytes would be required[5]. For this purpose, a simple experiment could be to isolate human adipocytes, incubate them in culture medium with and without added triglycerides, and compare the gene expression profiles from these two conditions. A transcriptomics approach would then necessitate isolation of RNA from the cells before and after exposure and comparison of RNA concentration on a gene to gene basis. This RNA profiling is very often done using DNA microarray technology. Thus gene expression can be efficiently measured using the transcriptomic profile of the cell and all genes involved in the storage of triglycerides in adipocytes can be studied.

4.2 Proteomics

The proteome of a cell or tissue represents the complete collection of proteins present in it at a given time. Proteomics is the study of proteomes which attempts to determine their role inside cells and the molecules with which they interact[1]. Although techniques exist to monitor the activity of every gene at the mRNA production level, a lot of research is focusing on gene expression at the level of proteins[5]. This is mainly because post-translational modification and alternative RNA processing enable one gene to produce several proteins differing in physico chemical and functional characteristics. Thus the protein profile of a cell can change even without an alteration in mRNA levels. With reference to the experiment discussed above,

a proteomics approach would involve assessing the changes in gene expression by isolating and subsequently separating proteins in the adipocytes. Various techniques such as two dimensional gel electrophoresis, 2D differential gel electrophoresis (2D-DIGE), ELISA or mass spectrometry in combination with knowledge of the sequence genome can be used. Recently, protein microarray technology has been launched which provides a promising alternative to these procedures.

The difference between the protein profile of cells exposed to triglycerides and those not exposed to the triglycerides would serve as a measure of gene expression in the two sets. Therefore, proteomics provides the researcher with a picture of the gene expression in the experimental cells, which takes into account the fact that a single gene may be responsible for the production of multiple proteins.

4.3 Metabolomics

Metabolomics utilizes analytical chemistry technologies such as NMR spectroscopy and mass spectroscopy to capture complete data on the low molecular weight metabolites, nutrients and other compounds in various human biofluids, which represent the metabolome[3]. Therefore, metabolomics can be regarded as the large scale analysis of multiple metabolite concentrations under changing nutritional conditions[3]. Metabolomics can be specially suited to assess exposure to nutrients for measuring compliancy during a dietary intervention or for determining the bioavailability of nutrients.

The growing importance of metabolomics in nutrition research can be accounted for by a number of reasons[6]. Firstly, many metabolites are part of our nutrition or are derived from food compounds. This establishes a very strong link with diet. Secondly, the metabolome can be regarded as the functional readout of transcriptomic and proteomic changes. Thirdly, different body fluids are readily available from human studies and nutrition research. Besides, many disease targets for nutrition research are directly related to the metabolome. Thus metabolomics represents a holistic approach in nutrigenomics research wherein the complete set of metabolites in body fluids is considered as a representation of gene expression.

5. Recent Developments: Some Success Stories

Numerous studies have been performed till date in nutrigenomics. In many cases, specific nutritional factors, which affect the expression of some genes involved in disease, have been isolated. Some examples of successful nutrigenomics studies are discussed below.

5.1 Neural-Tube Defects: The Folic Acid Connection

In the decades after World War II, it was observed in many western countries that the incidences of spina bifida (a birth defect caused by incomplete closure of one or more vertebral arches of the spine, resulting in malformation of the spinal cord[7]) decreased gradually[5]. A large epidemiological study identified folic acid or folate as the active component and pre-conceptional folic acid consumption was advised as a general preventive measure. At the same time, it became clear that, regarding the risk for a child with spina bifida, the women in the population can be divided into three groups:

a. those who are not at risk even with a low folate intake,
b. those who are at risk with low dietary folate but can be helped by increased folate intake, and
c. those who are at risk despite extra folate intake.

The cause for this variation in risk is presumably genetic predisposition. A nutrigenomics study led to the detection of 667 C ⟶ T and 1298 A ⟶ C alleles in the gene for 5,10-methylenetetrahydrofolate reductase as risk factors. However, not all of the relative risk of the folate responsive women can be explained by these alleles. Therefore the search for genetic variation in other genes continues. New candidate genes may be provided by a nutrigenomics search for folate responsive genes.

5.2 SREBPs: Control of Cholesterol Synthesis

Lipid homeostasis in vertebrate cells is regulated by a family of membrane bound transcription factors designated as sterol regulatory element-binding proteins (SREBPs)[8]. SREBPs directly activate the expression of more than 30 genes involved in the synthesis and uptake of cholesterol, fatty acids, triglycerides and phospholipids, as well as the NADPH cofactor required to synthesize these molecules. In the liver, three SREBPs regulate the production of lipids for export into the plasma as lipoproteins and into the bile as micelles.

SREBPs are activated through proteolytic processing. The three proteins required for this purpose have been identified using somatic cell genetics[9]. One is an escort protein designated SREBP cleavage-activating protein (SCAP)[8]. When the cholesterol content of the cells rises, SCAP senses the excess cholesterol, changing its conformation in such a way that the SCAP/SREBP complex is no longer incorporated into the endoplasmic reticulum. In this way, the transcription of SREBP target genes ceases. This mechanism is the molecular basis of cholesterol feedback inhibition of gene expression. It can thus be exploited in a nutrigenomics experiment to modulate the risk for CVD which arises from cholesterol imbalance.

5.3 PUFAs and Gene Expression

Fats are essential macronutrients in the diet which play many roles in the body. Due to its high energy density, fat is the ideal storage form of excess energy[10]. At the cellular level, fatty acids form an essential part of the phospholipid bilayer of membranes. Fatty acids serve as precursors to the signaling molecules such as steroids and prostaglandins. Apart from these established roles of fatty acids, it is becoming clear that polyunsaturated fatty acids (PUFAs) can specifically and rapidly cause changes in cellular metabolism, differentiation and growth through alterations in gene expression patterns[11].

n-3 and n-6 PUFAs have been known to confer various health benefits including increased insulin signaling, enhanced immune response, decreased plasma lipid levels and decreased incidence of lung disease and coronary heart disease[10]. Also, consumption of PUFAs is beneficial in certain cancers such as breast, prostrate and colorectal.

The role of PUFAs in the regulation of mammalian gene expression has been well characterized. In a study, it was seen that supplementation of a fat-free diet with either saturated fatty acids

or cholesterol had no effect, but supplementation with linoleic acid caused a number of changes. Enzyme activities of fatty acid synthase, malic enzyme and glucose-6-phosphate dehydrogenase (G6PD) were decreased demonstrating rapid, direct and specific regulation of enzymes of lipid metabolism by a particular fatty acid. There are numerous other examples of PUFA regulation of gene expression. These can be used as targets in nutrigenomics studies.

5.4 Conjugated Linoleic Acids and Obesity

A recent study shows that a subgroup of fatty acids known as conjugated linoleic acids (CLAs), and in particular the *cis-9,trans-*11 CLA isomer may have the potential to improve lipid metabolism and insulin sensitivity within the context of obesity[4]. This effect has been ascribed to differential SREBP-1c gene expression, a key regulatory transcription factor involved in lipogenesis and glucose metabolism. The study thus represents an avenue for altering the fatty acid composition in the diet so as to control the occurrence of obesity and T2DM as a consequence of obesity.

6. Benefits from Nutrigenomics

Considering the specificity and significance of information required for and obtained from nutrigenomics, it is conceivable that the benefits from this new scientific discipline would be manifold. Some of the major benefits with respect to nutrition related disorders are given below[5].

1. **New biomarkers for nutrition related diseases**
   Some genes which are up- or down- regulated during disease progression can be used as biomarkers for different stages of disease. They can be incorporated into diagnostic protocols for determining the right moment for disease stage specific nutritional intervention or therapy.
2. **Biomarkers to monitor the efficacy of nutritional intervention**
   Comparative studies before, during and after an intervention will reveal genes and expression profiles indicative of the progress and the success of treatment by nutrition.
3. **Genes and molecular pathways as targets for prevention**
   Knowledge about the genes, the molecular pathways that they are a part of and their specific role in the pathogenesis will bring forth novel strategies for prevention of disease or disease progress.
4. **Knowledge-based functional foods**
   A pathogenic gene expression profile can be normalized using mixtures of specific nutrients as nutraceuticals. Because nutrition can be employed in a natural way, it will be much more acceptable to the public than the remedies for actual prevention of the disease.

7. Future Perspectives

As a science, nutrigenomics is still in stages of infancy. There are relatively few convincing studies in the area, and the discipline as such is not very well defined[1]. However, high expectations are already being placed on nutrigenomics. In these euphoric pioneering times for the discipline, the potential barriers to its success need to be recognized. Food is typically a complex and variable mixture of nutrients and other components. Besides, nutrients are weak signaling factors and must be considered in the context of chronic exposure. Single Nucleotide Polymorphisms (SNPs) can be focused on as targets for nutrigenetics research. Monogenic disorders like familial hypercholesterolemia can be studied very effectively using specific SNPs that are known to be responsible for these[12]. Nutrigenomics researchers must also deal with the challenge of understanding polygenic die-related diseases[1]. Finally, the research should be such that genome-scale questions can be addressed rather than limited specific hypothesis. All these factors will be pivotal in the progress and utility of this 'miracle science'. Nutritional systems biology, a science that exploits all available data generated by genomics technology in a complete description of a biological system, will prove a very important tool in nutrigenomics research in the near future[6].

Nutrigenomics research has been taken up by numerous scientists all over the world. As a result, an enormous set of data is being generated in the field. One major issue is, therefore, the streamlining of data acquisition, data handling and data analysis in order to assure high quality and comparability of data obtained at different sites[5]. The European Community has financed a Network of Excellence with the acronym 'NuGO' (www.nugo.org) to start a major effort in this area. The co-ordination of research at various locations is sought through this network.

The challenges before this growing science are many, but it is expected that these will be overcome in future using the various approaches mentioned and using advanced bioinformatics tools for data handling and processing. Nutrigenomics, with its enormous potential in the field of nutrition, could become our stepping stone to a world where each person receives specialized treatment for his diseases. In other words, nutrigenomics can pave the way for an era of personalized nutrition.

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