Review

Nutritional genomics

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Nutritional genomics is the science which study about the relationship between genome, nutrition, health and diseases. Principles of this science are based on the facts that the diet of a person interferes with the genetic makeup; thus by regulating the diet, certain diseases can be prevented or controlled. Dietary chemicals can affect gene expression directly or indirectly. A subset of genes regulated by diet must be involved in certain disease initiation, progression, and severity. Dietary intervention based on knowledge of nutritional requirement, nutritional status, and genotype can be used to prevent, mitigate, or cure chronic disease. It also studies about how individual differences in genes influence the body's response to diet. The study aims to harness the information contained in human genomes to achieve successful production and health.

Key words: Genomes, nutrition, diet, genes.

INTRODUCTION

Nutritional genomics is the science which study about the relationship between genome, nutrition, health and diseases. The term was coined by Della Penna in 1999 (Milner, 2004). The major practical translation of nutrition research to human and animal health consists of defining optimal dietary recommendations aimed to prevent disease and to promote optimal health. For this purpose, and based on the best scientific evidence available at the time, several dietary guidelines have been implemented to improve the health of the general population and of those at high risk for specific diseases. Nutritional genomics has the potential to assist scientists in interpreting the complex gene-nutrient interaction and the link between genetic abnormalities and disease, to analyze and integrate the vast data sets that these techniques and studies produce, and then to identify new bio markers. Nutritional genomics deals with how food interacts with our genes, proteins and metabolites, how genetic make-up interacts with diet, and how these interactions affect health and disease.

DISCUSSION

Nutritional genomics can be divided into two disciplines: (1) Nutrigenomics and (2) Nutrigenetics.

Nutrigenomics studies the effect of nutrients on health through alteration of genome, proteome, metabolome and the resulting changes in physiology. This is studied with genomics, proteomics, metabolomics and transcriptomics:

- Genomics: Genome is the total sum of the entire genetic makeup of an organism, and the study of the genome is known as Genomics.
- Transcriptomics: Transcriptome is the set of all RNA molecules produced in cells, and Transcriptomics is the study of messenger RNA molecules.
- Proteomics: Proteome is the entire set of proteins expressed by a genome and Proteomics is the study of the proteome.
- Metabolomics: Proteins are responsible for cell structure, growth, reproduction and coordination of these activities throughout the body, and the study of these processes and their metabolites is known as Metabolomics.

Nutrigenetics studies the effect of genetic variations on the interaction between diet and health with implications to susceptible subgroups. More specifically, it studies how individual differences in genes influence the body's response to diet and nutrition.

Principles of nutritional genomics

The conceptual basis for this new branch of genomic

research can best be summarized with the following five tenets:

1) Common dietary chemicals act on the human genome, either directly or indirectly, to alter gene expression or structure.
2) Under certain circumstances and in some individuals, diet can be a serious risk factor for a number of diseases.
3) Some diet-regulated genes are likely to play a role in the onset, incidence, progression, and/or severity of chronic diseases.
4) The degree to which diet influences the balance between health and disease states may depend on an individual's genetic makeup.
5) Dietary intervention based on knowledge of nutritional requirement, nutritional status, and genotype can aid in better understanding of the phenotype, and corrections can be made at an earlier time.

Alteration of gene expression or structure by common dietary chemicals

There is an association between food intake and the incidence and severity of chronic disease, but the concept that food contains bioactive chemicals is not apparent from the design of many molecular and genetic association studies or laboratory animal or cell culture experiments. The variety and concentrations of fatty acids, triglycerides, sterols, sterol esters, and tocopherols are likely to have many and diverse effects on physiology since dietary chemicals have several outcome upon entering a cell. Dietary chemicals can affect gene expression directly or indirectly. At the cellular level, nutrients may act as ligands for transcription factor receptors, and can be metabolized by primary or secondary metabolic pathways, thereby altering concentrations of substrates or intermediates; or they can positively or negatively affect signal pathways.

An example for dietary chemicals directly affecting signal transduction pathways is subsequently discussed. Green tea contains the polyphenol, 11-epigallocatechin-3-gallate (EGCG) (Sachinidis et al., 2000). EGCG inhibits tyrosine phosphorylation of Her-2/neu receptor and epidermal growth factor receptor, which, in turn, reduces signalling via the phosphatidylinositol 3-kinase (PI-3) 3 Akt kinase **3 NF-κB** pathway (Stefania et al., 2002). Activation of **the NF-κB** pathway is associated with some virulent forms of breast cancer. Platelet-derived growth factor receptor phosphorylation is also inhibited by EGCG and derivatives (Sakata et al., 2004). Thus green tea can prevent the occurrence of cancer to a certain extent.

Grains such as rice contain inositol hexaphosphate (InsP6), which inhibits TPA- or EGF induced cell transformation through its effects on PI-3 kinase. However, resveratrol, phenethyl isothiocyanate (PEITC), genistein, and retinoids (vitamin A and metabolites) also affect signal transduction pathways.

Diet as a risk factor for disease

The idea that adverse diet/genome interactions can cause disease is not new. The first example was the discovery of galactosemia by F. Goppart in 1917. Galactosemia is a rare recessive defect in galactose-1-phosphate uridyltransferase (GALT). The lack of GALT results in the accumulation of galactose in the blood, causing a number of health problems including mental retardation. Phenylketonuria (PKU), another recessive trait, was discovered in 1934 by Asbjørn Følling (Christ, In press). PKU is a defect in the enzyme phenylalanine hydroxylase that results in an accumulation of phenylalanine in the blood. The accumulation of high levels of phenylalanine can cause neurological damage. Both PKU and galactosemia can be screened in infants shortly after birth, and these diseases can be managed with low diets in phenylalanine and lactose, respectively.

Deficiency of vitamins B12, folic acid, B6, niacin, C, or E, or iron or zinc appears to mimic radiation in damaging DNA by causing single- and double-strand breaks, oxidative lesions, or both. Nutrient deficiencies are orders of magnitude more important than radiation because of constancy of exposure to milieu promoting DNA damage. Folate deficiency breaks chromosomes due to substantial incorporation of uracil in human DNA (4 million uracil/cell). Single-strand breaks in DNA are subsequently formed during base excision repair, with two nearby single-strand breaks on opposite DNA strands leading to chromosome fragmentation (Stover, 2004). Micronutrient deficiency may explain why the quarter of the US population that consume less than the recommended five portions a day of vegetables and fruits has approximately twice the rate for most types of cancer compared with the quarter with the highest intake. A number of other degenerative diseases of aging are also associated with low fruit and vegetable intake. Progress is also being made in determining specific mechanisms for the role of certain minerals (calcium, magnesium, manganese, copper, and selenium) and vitamins in heart disease from work done in humans and in cell culture systems.

Role of diet-regulated genes in chronic diseases

The progression from a healthy phenotype to a chronic disease phenotype must occur by changes in gene expression or by differences in activities of proteins and enzymes. Since dietary chemicals are regularly ingested and participate indirectly and directly in regulating gene expression, it follows that a subset of genes regulated by diet must be involved in disease initiation, progression, and severity. The clearest example of genotype-diet interactions in chronic disease is Type 2 diabetes, a

condition that frequently occurs in sedentary, obese individuals and certain minority groups. Once diagnosed with type 2 diabetes, some individuals can control symptoms by increasing physical activities and by reducing caloric intake, that is, expression of genomic information is changed by changing environmental (that is, dietary) variables. Other individuals are refractory to such environmental interventions and they require drug treatments. Many chronic diseases do not show the phenotypic plasticity seen in some type 2 diabetics, that is, symptoms are not reversible after some initiating event.

Individual's genetic makeup as key to the balance between health and disease states

All humans are 99.9% identical at the gene sequence level. The 0.1% variations in sequence, however, produce the differences in phenotypes (hair and skin color, height, weight, etc.) and an individual's susceptibility to disease or health. Alterations in phenotype result from differences in gene expression or altered macromolecular activities. A striking and simple example of how SNPs alter gene expression is a polymorphism that alters tolerance to dietary lactose. Adult mammals are typically lactose intolerant. A mutation occurred approximately 9,000 years ago in Northern Europeans that allowed expression of the lactase-phlorizin hydrolase gene (LCH locus) to continue into adulthood. Although there are 11 polymorphisms in this gene clustered into 4 (A, B, C, U) prevalent haplotypes (0.05%), a C13910T SNP located 14 kb upstream of the LCH (47) is highly associated with lactase persistence (lactose tolerance). This polymorphism is thought to alter regulatory protein-DNA interactions controlling expression of the gene. The A haplotype conferring lactose tolerance has an 86% frequency in the Northern European population, but has only 36% in Southern European populations (Jim and Raymond, 2004). The persistence of this variant in populations may confer selective advantages that include improved nutrition, prevention of dehydration, and improved calcium absorption.

Dietary intervention based on individualized nutrition

Dietary intervention based on knowledge of nutritional requirement, nutritional status, and genotype (individualized nutrition) can be used to prevent, mitigate, or cure chronic disease. This assertion is obvious for nutritional deficiencies such as scurvy and beriberi or the potential harm from dietary phenylalanine for phenylketonurics. On the other hand, some diseases cannot be controlled by dietary intervention. Glucose-6-phosphate dehydrogenase A44G (DNA: C131GP) uses NADP as a cofactor. Defects in this gene are involved in favism and hemolytic anemia (Frank and Maj, 2005). Increased dietary intake of nicotinic acid or nicotinamide might increase NADPH coenzyme concentrations enough to alter the equilibrium of GPDH 43 GPDH _ NADPH. NAD is a cofactor for aldehyde dehydrogenase (ALDH), an enzyme involved in alcohol intolerance and linked to Alzheimer and cancer. A cSNP causes E487K, which increases the Km 150-fold. This variant could not be treated with diet because the NAD substrate concentration could not be increased sufficiently to overcome the increased Km.

Nutritional genomics and cancer

Many bioactive components from the plant kingdom that have been shown to influence cancer pathways in experimental models include folate from green leafy vegetables, selenium from grains and nuts, diallyl disulfide and other organosulphur compounds from garlic, lycopene from tomato products, genistein and other isoflavones from soy products, epigallocatechin-3-gallate and other polyphenols in tea, and isothiocyanates and indole-3-carbinol from cruciferous vegetables.

Four distinct mechanisms are intricately related to cancer: DNA methylation, histone modifications, microRNAs as well as other non-coding regulatory RNA, and the emerging evidence concerning chromatin remodeling factors. Abnormal DNA methylation patterns are virtually a universal finding in cancer, as changes in DNA methylation have been observed in many cancer tissues, specifically colon, stomach, uterine cervix, prostate, thyroid, and breast tissues. A common observation in cancer cells is global DNA hypomethylation which is associated with chromosomal instability.

In utero or neonatal exposure to bisphenol A (BPA) shows that a high-production volume chemical used in the manufacturing of polycarbonate plastic is associated with higher body weight, increased breast and prostate cancer, and altered reproductive function (Ross, 2007). A study carried out in this regard showed that maternal exposure to this endocrine active compound shifted the coat color distribution of Avy mouse offspring to yellow by decreasing CpG methylation in the agouti locus. Moreover, maternal nutritional supplementation of the BPA diet with either methyl donors or genistein resulted in a control coat color distribution and negated the DNA hypomethylating effect of BPA. Thus, early developmental exposure to a xenobiotic chemical such as BPA can change offspring phenotype by stably altering the epigenome, an effect that can be counteracted by maternal dietary supplements. These types of studies also suggest that *in utero* exposure to dietary components may not only influence embryonic development but may also have profound and long-term health consequences.

Another example for the impact of diet on epigenetics concerns histone modification. Recent investigations suggest that several dietary factors, including butyrate (formed in the colon from the fermentation of dietary fiber), diallyl disulfide (present in garlic and other *Allium* vegetables), and sulforaphane (found in cruciferous vegetables) have the ability to inhibit type I and II Histone deacetylases HDAC enzymes. These dietary compounds have been associated with cancer prevention in various preclinical and clinical studies. The inhibition of HDAC activity by these dietary constituents may be associated with their cancer protective effects as they have been shown to inhibit cell proliferation and stimulate apoptosis in a manner similar to other HDAC inhibitors.

An interesting example that highlights fruits and vegetables, which contain several dietary components, concerns manganese superoxide dismutase (MnSOD), which is a mitochondrial enzyme that plays a key role in the detoxification of reactive oxygen species. A polymorphism (a valine to alanine substitution) in the mitochondrial targeting sequence, thought to alter transport of the enzyme into mitochondria, has been associated with increased risk for breast cancer. This association has been found to be more pronounced among women with low intake of fruits and vegetables (Li et al., 2005).

CONCLUSION

In summary, nutritional genomics will be the driving force of future nutritional research, in that it has the potential to change dietary disease prevention and therapy and can have a major impact on animal and human health. However, the complexity of the goals set for nutritional genomics is tremendous and their accomplishment will require breaking many of the modes of traditional research and seeking integration of multiple disciplines and laboratories working coordinately. Despite the difficulties described, preliminary evidence strongly suggests that the concept will work and that by using behavioral tools founded on nutrition, it will be possible to harness the information contained in human genomes to achieve successful production and health.

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