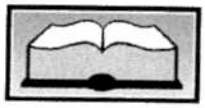
Review



Continuing Education Questionnaire, page 415
Meets Learning Need Codes 2000, 2010, 2050, and 4040

Nutrigenomics, Proteomics, Metabolomics, and the Practice of Dietetics

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ABSTRACT

The human genome is estimated to encode over 30,000 genes, and to be responsible for generating more than 100,000 functionally distinct proteins. Understanding the interrelationships among genes, gene products, and dietary habits is fundamental to identifying those who will benefit most from or be placed at risk by intervention strategies. Unraveling the multitude of nutrigenomic, proteomic, and metabolomic patterns that arise from the ingestion of foods or their bioactive food components will not be simple but is likely to provide insights into a tailored approach to diet and health. The use of new and innovative technologies, such as microarrays, RNA interference, and nanotechnologies, will provide needed insights into molecular targets for specific bioactive food components and how they harmonize to influence individual phenotypes. Undeniably, to understand the interaction of food components and gene products, there is a need for additional research in the "omics" of nutrition. It is incumbent upon dietetics professionals to recognize that an individual's response to dietary intervention will depend on his or her genetic background and that this information may be used to promote human health and disease prevention. The objectives of this review are to acquaint nutritional professionals with terms relating to "omics," to convey the state of the science to date, to envision the possibilities for future research and technology, and to recognize the implications for clinical practice.
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Nutrigenomics is the scientific study of the way specific genes and bioactive food components interact. It provides a basis for understanding how the health consequences of eating behaviors may vary across individuals. The concept of nutrigenomics builds on the premises that:

- diet and dietary components can alter the risk of disease development by modulating multiple processes involved with onset, incidence, progression, and/or severity;
- food components can act on the human genome, either directly or indirectly, to alter the expression of genes and gene products;
- diet could potentially compensate for or accentuate effects of genetic polymorphisms; and
- the consequences of a diet are dependent on the balance of health and disease states and on an individual's genetic background (1,2).

The study of nutrigenomics and/or associated changes in proteomics and metabolomics could ultimately identify molecular targets for nutritional preemption. This information is key to a personalized approach to nutrition, which will ultimately distinguish responders from nonresponders. The objectives of this review are to acquaint nutrition professionals with terms relating to "omics," to convey the state of the science to date, to envision the possibilities for future research and technology, and to recognize the implications for clinical practice. Figure 1 provides a glossary of terms used in this article.

Numerous dietary components can alter genetic and epigenetic events, and thereby influence health. In addition to the essential nutrients, such as calcium, zinc, selenium, folate, and vitamins C and E, there are a variety of classes of nonessential nutrients and bioactive components that seem to significantly influence health (Figure 2). These essential and nonessential bioactive food components are known to modify a number of cellular processes associated with health and disease prevention, including carcinogen metabolism, hormonal balance, cell signaling, cell cycle control, apoptosis, and angiogenesis (3). Often bioactive food components will modify several processes simultaneously. Thus, one of the real challenges is the identification of which process(es), either

Allele: any one of a number of alternative forms of the same gene occupying a given position on a chromosome.
Angiogenesis: the formation and differentiation of blood vessels.
Apoptosis: a genetically determined process of cell self-destruction that is marked by the fragmentation of nuclear DNA; is activated either by the presence of a stimulus or by the removal of a stimulus or suppressing agent; is a normal physiological process eliminating DNA-damaged, superfluous, or unwanted cells; and, when halted (as by genetic mutation), may result in uncontrolled cell growth and tumor formation.
Bioactive food component: a compound occurring in food that brings about a physiological effect.
Chromatin: a complex of a nucleic acid with basic proteins (as histone) in eukaryotic cells that is usually dispersed in the interphase nucleus and condensed into chromosomes in mitosis and meiosis.
Codon: a sequence of three RNA or DNA nucleotides that specifies (codes for) either an amino acid or the termination of translation.
Deoxyribonucleic acid (DNA): the fundamental substance of which genes are composed; are localized especially in cell nuclei, and are constructed of a double helix held together by hydrogen bonds between purine and pyrimidine bases that project inward from two chains containing alternate links of deoxyribose and phosphate.
Down-regulation: a negative regulatory effect on a physiological process. At a molecular level, the regulatory sites include membrane receptors, genes, messenger RNA, and proteins.
Epigenesis: development involving gradual diversification and differentiation of an initially undifferentiated entity (as a zygote or spore).
Gene: the fundamental physical and functional unit of heredity, which carries information from one generation to the next; a segment of DNA, composed of a transcribed region and regulatory sequences that make transcription possible.
Genome: all the genetic material in the chromosomes of a particular organism; its size is generally given as its total number of base pairs.
Genotype: the genetic constitution of an organism, as distinguished from its physical appearance (its phenotype).
Haplotypes: a group of alleles of genes on a single chromosome that are closely enough linked to be inherited usually as a unit.
Histone: any of various simple water-soluble proteins that are rich in the basic amino acids lysine and arginine and are complexed with DNA in the nucleosomes of eukaryotic chromatin.
Ligand: a group, ion, or molecule coordinated to a central atom or molecule in a complex.
Metabolome: the whole set of metabolic entities and small pathway motifs in a cell, tissue, organ, organisms, and species.
Methylation: modification of a molecule by the addition of a methyl group.
Methylcytosine: a methylated pyrimidine base $C_5H_7N_3O$ found in the nucleic acids (as some DNAs and transfer RNAs) of some organisms.
Methyltransferase: any of several transferases that promote transfer of a methyl group from one compound to another.
Microarray: simply ordered sets of DNA molecules of known sequence. In the microarray technique, a probe sequence is immobilized on a surface, at a separation of a few micrometers so that it is possible to place many different probes on a small single chip surface of one square centimeter. Samples are usually labeled with a fluorescent dye that can be detected by a light scanner that detects color on the surface of the chip. Microarray analysis permits scientists to detect thousands of genes in a small sample simultaneously and to analyze the expression of those genes.
Nanotechnology: the interactions of cellular and molecular components and engineered materials—typically clusters of atoms, molecules, and molecular fragments—at the most elemental level of biology. Such nanoscale objects—typically, though not exclusively, with dimensions smaller than 100 nanometers—can be useful by themselves or as part of larger devices containing multiple nanoscale objects.
Nuclear receptor: one of the most abundant classes of transcriptional regulators in animals that regulate diverse functions, such as homeostasis, reproduction, development, or metabolism.
Nucleotide: subunit that polymerizes into nucleic acids (DNA or RNA); each nucleotide consists of a nitrogenous base, a sugar, and one to three phosphate groups.
Nutritional preemption: process of disease risk reduction via nutritional intervention approaches through a greater understanding of nutrigenomics, proteomics, and metabolomics.
Phenotype: the visible properties of an organism that are produced by the interaction of the genotype and the environment.
Polymorphism: existence of a gene in several allelic forms.
Proteome: set of proteins produced by a species.
Ribonucleic acid (RNA): a single-stranded nucleic acid similar to DNA, but having ribose sugar rather than deoxyribose sugar and uracil rather than thymine as one of the pyrimidine bases.
Ribosome: a complex organelle (composed of proteins plus ribosomal RNA) that catalyzes translation of messenger RNA into an amino acid sequence; made up of two nonidentical subunits each consisting of a different ribosomal RNA and a different set of proteins.
RNA interference: the mechanism by which double-stranded RNA specifically suppresses the expression of a gene bearing its complementary sequence.
S-adenosylmethionine (SAM): the active sulfonium form of methionine $C_{15}H_{22}N_6O_5S$ that acts as a methyl group donor in various biochemical transmethylation reactions (as the formation of epinephrine or creatine), that is formed when methionine reacts with adenosine triphosphate, and that is an intermediate in the formation of homocysteine.
Single Nucleotide Polymorphisms (SNPs): a variant DNA sequence in which the purine or pyrimidine base (as cytosine) of a single nucleotide has been replaced by another such base (as thymine); for a variation to be considered a SNP, it must occur in at least 1% of the population; SNPs make up about 90% of all human genetic variation and occur every 100 to 300 bases along the 3-billion-base human genome.
Transcription: the process whereby RNA is synthesized from a DNA template.
Transcriptome: the subset of genes transcribed in a given organism, the dynamic link between the genome, the proteome, and the cellular phenotype.
Transcriptomics: the study of the transcriptome, the complete set of RNA transcripts produced by the genome at any one time.
Translation: the process of protein synthesis whereby the primary structure of the protein is determined by the nucleotide sequence in messenger RNA.
Up-regulation: a positive regulatory effect on a physiological process. At a molecular level, the regulatory sites include membrane receptors, genes, messenger RNA, and proteins.

Figure 1. Glossary of terms related to nutrigenomics, proteomics, and metabolomics.

Nutrient group	Example
Phytochemicals	Carotenoids, flavonoids, indoles, isothiocyanates, allyl sulfur
Zoochemicals	Conjugated linoleic acid, n-3 fatty acids
Fungochemicals	β-glucans, lentinan, schizophyllan, and other compounds in mushrooms
Bacteriochemicals	Equol, butyrate, and other compounds formed from gastrointestinal flora fermentation

Figure 2. Some nonessential nutrients and bioactive components that can alter genetic and epigenetic events.

singly or in combination, are most important in bringing about a phenotypic change (Figure 3).

Although significant advances have been made in understanding the relationship between dietary factors and disease prevention, the identification of those who will or will not benefit from dietary intervention strategies remains a major obstacle to health promotion. The genetic revolution and the associated "omics" are providing new insights into a number of health issues, including the role of nutrition in disease prevention. Rapidly developing analytical and information technologies may allow for the identification and validation of molecular sites of action for bioactive food components and the discovery of how changes in these targets bring about phenotypic changes.

INTERINDIVIDUAL RESPONSE TO NUTRIENTS

Most genes have small sequence differences or polymorphisms that occur between individuals at about every 1,500 base pairs (4). Some of these polymorphisms may affect how well a protein works and how the protein interacts with other proteins or substrates. In 1999, several gene polymorphisms were identified as screening tools for predicting disease risk, including the HFE gene for hereditary hemochromatosis and the E4 allele of the APOE gene for cholesterol homeostasis and Alzheimer disease [reviewed by Motulsky (5)]. Although single nucleotide polymorphisms (SNPs) may hold true for some conditions, the phenotype predominately depends on a combination of genes and environmental and behavioral factors. Nevertheless, SNPs seem to be important in explaining some of the variation in response to food components. Scientists have identified over 3 million locations where single-base DNA differences or SNPs occur in humans and thus are potential sites for introducing variability (6). SNPs are the most common form of DNA sequence variation and are useful polymorphic markers for investigating genes. However, not all SNPs directly influence the quality and/or quantity of the gene product. As more information surfaces about the links between SNPs, dietary components, and phenotypes, it should become easier to predict those who might benefit most from dietary intervention. The simultaneous examination of multiple SNPs may offer special advantages in defining the biological response to food components or drugs because multiple genes are likely involved in determining physiological processes and their ultimate influence on a person's phenotype.

A more recent strategy being used to draw associations between disease and genes and nutrients is the examination of haplotypes or haplotype blocks. A haplotype is the set of SNP alleles along a region of a chromosome. Haplotype analysis can be used to identify groups of SNPs linked together, and therefore may be useful in understanding the distribution of risk alleles in human populations and for tailoring prevention strategies to those at increased risk. Although theoretically there could be many haplotypes in a chromosome region, recent studies are finding only a few common haplotypes. For example, there are many SNPs in the human growth hormone secretagogue receptor (known as the GHSR or ghrelin receptor) that have an important role in the regulation of food intake and energy homeostasis (7). Baessler and colleagues (6) provide evidence showing that there is linkage and association between five SNPs and the two most common haplotypes with obesity in the general population. The development of common patterns, or haplotypes, of human genetic variation, as is occurring across populations in Africa, Asia, and the United States via the International HapMap Consortium, will be an invaluable resource for scientists searching for genes related to health and disease (8,9).

GENETIC RESPONSES TO INDIVIDUAL NUTRIENTS

The study of gene-nutrient interactions is an expanding area of science and one that is becoming increasingly documented in the literature. A complete discussion of the current understanding of nutrigenomics is beyond the scope of this review; however, critical concepts are highlighted through the use of examples. Some specific examples of the interrelationship between SNPs and specific food components are reviewed in this article. These examples show that some of the reported discrepancies in the response to disease outcome may arise from failing to account for interindividual genetic differences. For example, a polymorphism in the angiotensinogen gene may determine how an individual's blood pressure responds to dietary fiber. Angiotensinogen is a liver protein involved with increasing vascular tone and promoting sodium retention, and plasma levels correlate with blood pressure. A common protein polymorphism of the angiotensinogen gene encodes threonine (T) instead of methionine (M) at amino acid residue 235 (10). The interrelationship between polymorphisms in the angiotensinogen gene and the response to insoluble and soluble fiber intake was examined in a year-long crossover design study involving 40 normotensive subjects. Individuals with the angiotensinogen TT genotype had a decrease in blood pressure when provided a diet with increased amounts of insoluble fiber compared to increased amounts of soluble fiber were given (2.7 to 3.0 g/100 kcal of either insoluble or soluble fiber). In contrast, blood pressure in individuals with a TM or MM genotype was not significantly influenced by the type of fiber consumed (10). Thus, some of the reported discrepancies in the response of blood pressure to dietary fiber (11,12) may be related to interindividual genetic differences in response to different types of fiber.

Research over several decades supports a role for selenium in reducing cancer incidence when provided to an-

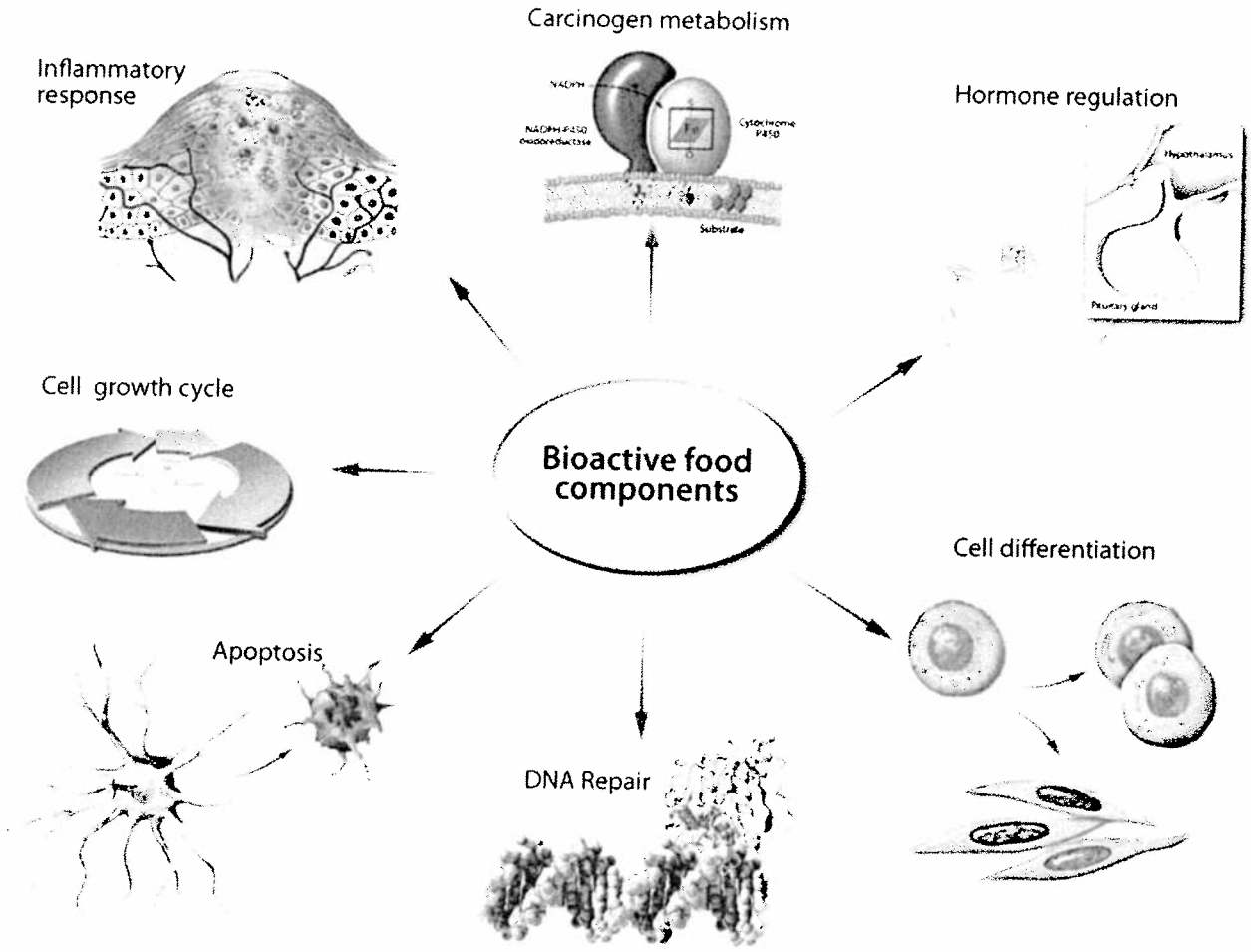

Figure 3. Bioactive food components can influence genetic and epigenetic events associated with a host of disease processes.

imals in nontoxic amounts. Likewise, some epidemiological studies suggest that selenium may help prevent cancer in humans. Selenium supplementation has been linked with a reduced incidence of liver, colon, prostate, and lung cancer in humans (13). However, all individuals may not respond equally. Genetic variability may determine how a person responds to selenium supplementation. Glutathione peroxidase is a selenium-dependent enzyme that acts as an antioxidant enzyme. A polymorphism at codon 198 of human glutathione peroxidase results in a substitution of leucine for proline, and has been associated with an increased risk of lung cancer. Why this occurs is not yet known, but may relate to the amount of selenium needed to optimize enzyme activity (14). In a study nested within the α-Tocopherol, β-Carotene Cancer Prevention Study cohort, individuals with one copy of the allele for leucine (proline/leucine) were at an 80% greater risk for lung cancer, and individuals with two copies of the allele for leucine (leucine/leucine) were at a 130% greater risk compared with those with the proline genotype (proline/proline) (15). Similar findings were reported for breast, head and neck, bladder, and skin cancer (14,16,17). The efficacy of selenium use in humans with the different glutathione peroxidase alleles is unknown. However, in a breast cancer model in which breast cancer cells were transfected with glutathione peroxidase containing either the leucine or the proline coding allele, the leucine-coding allele was less responsive to increased activity as a result of selenium supplementation as compared with the proline-containing allele (14). It is possible that this correlation reflects the reduced ability to use and metabolize selenium because glutathione peroxidase activity did not vary. Such information suggests that we may be able to use information about some polymorphisms as surrogate markers to identify the need for increased or decreased amounts of essential nutrients, as suggested by Ames and colleagues (2).

The response to other dietary components, such as caffeine, may also depend on SNPs. A study investigating the role of caffeine as a risk factor for bone loss in elderly women found that those with a variant of the vitamin D receptor (tt genotype) and who had caffeine intakes greater than 300 mg/day had significantly higher rates of bone loss than did women with the TT genotype (18). Because abstinence from caffeine-containing beverages may not represent a popular alternative, additional re-

search is needed to identify other interventional strategies, such as modifying calcium and/or vitamin D intake for individuals with the tt genotype.

Many of the known effects of vitamin D are likely mediated through a genomic pathway by way of the vitamin D receptor (VDR). VDR is expressed in many normal tissues and solid epithelial tumors. Polymorphisms in the VDR gene may influence the expression or function of the VDR protein. Several VDR polymorphisms, including *Fok*1, *Bsm*I, and *poly-A* polymorphisms, may affect the response to various dietary components and possibly disease risk (19-21). The *Fok*1 VDR polymorphism, with the FF genotype, may be particularly important in determining the effect of dietary calcium on colon cancer risk. Although dietary calcium or fat did not influence colon cancer risk in those with the FF genotype, a decrease in the intake of dietary calcium or fat was linked to increased colon cancer risk with multiple copies of the f allele (ff>Ff). Overall, individuals possessing the ff genotype were at a 2.5-fold increased risk of colon cancer when low-calcium and low-fat diets were consumed (22). In another study investigating energy balance and VDR genotype, individuals who were least physically active and had the ff VDR genotype were at greater risk of colon cancer (23). Furthermore, two VDR polymorphisms, *Bsm*I and *poly-A*, have been evaluated for their association with diet and colorectal cancer risk. High levels of dietary calcium and vitamin D reduced the risk of rectal cancer and provided support for a weak protective effect for the SS *(poly-A)* and BB *(Bsm*I*)* VDR genotypes. This study found that the risk associated with VDR genotypes depends on the level of dietary calcium and vitamin D intake and the tumor site (21).

Diet and genotype may also affect mortality in genetically altered models of cancer susceptibility. Using a mouse model for familial adenomatous polyposis, a common genetic alteration in colon cancer, Yang and colleagues showed that providing a Western-style diet (high in fat and phosphate and low in calcium and vitamin D), compared with an ideal semipurified diet, decreased survival (24). This effect is magnified when the p21 gene, which is an important regulator of the cell cycle, was inactivated (25). However, without controlling for both the genotype and these differences in dietary patterns, differences between the groups would not be discernible.

MORE IS NOT ALWAYS BETTER

Increased intake of some dietary components may not improve health. Undeniably, high energy intake resulting in obesity is a major public health concern and is associated with several chronic diseases (26). Gene-nutrient imbalances may explain the morbidity and mortality complications that are linked to obesity (Figure 4). The prevalence of obesity has increased dramatically in the United States since the 1980s and is increasing at an alarming rate throughout the world. Both postmenopausal breast and prostate cancer deaths significantly correlate with body mass index (27). It is estimated that current patterns of overweight and obesity in the United States could account for 14% of all deaths from cancer in men and 20% of those in women (27). It has been estimated that about 90,000 deaths per year from cancer might be avoided if the adult population could maintain a body mass index of less than 25 throughout life (27).

The nuclear receptors, peroxisome proliferator-activated receptors (PPARs), for example, are ligand-activated receptors that regulate the expression of genes involved in the storage and metabolism of fats. Three subtypes have been identified and include alpha, gamma, and delta. The nuclear receptor peroxisome proliferator-activated receptor-gamma (PPAR gamma) is recognized for its involvement in regulating insulin resistance and blood pressure. In individuals with a specific polymorphism in the PPAR gamma (Pro12Ala), a low polyunsaturated-to-saturated fat ratio is associated with an increase in body mass index and fasting insulin concentrations. When the dietary ratio of polyunsaturated (P) to saturated (S) fats is high, the opposite is true (28). Their data suggest that when the dietary P:S ratio is low, the body mass index in Ala carriers is greater than that in Pro homozygotes, but when the dietary ratio is high, the opposite is seen. The interaction between type of dietary fat and PPAR gamma genotype emphasizes the complexity found in examining gene-nutrient interactions and that ratios of nutrients may be important. As more information surfaces about diet-gene interactions, we should be in a better position to explain the large heterogeneity in findings that has plagued clinical nutrition.

RESPONSES TO COMBINATIONS OF FOODS

Evidence exists showing that important interactions occur by combining foods or food components. For example, the combination of soy and tea as part of a complete diet appears more effective than either alone in inhibiting prostate cancer growth and metastasis in a mouse model of human prostate cancer (29,30). Similar results were observed in levels of prostate-specific antigen, a marker used to diagnose prostate cancer. Soy, combined with black or green tea, has been reported to synergistically reduce serum prostate-specific antigen concentrations in men (29). Considerable insight into food-food interactions is needed to understand how to use diet to bring about phenotypic change.

NUTRITIONAL EPIGENETICS

Epigenetic events can be modified by bioactive food components and are another critical factor in establishing which gene functions are selectively activated. A variety of regulatory proteins including DNA methyltransferases, methyl-cytosine guanine dinucleotide binding proteins, histone-modifying enzymes, chromatin remodeling factors, and their multimolecular complexes are involved in the overall epigenetic process (31). Because epigenetic events can be changed, they offer another explanation for how environmental factors, such as diet, can influence biological processes and phenotypes. The degree of methylation can be determined by the availability of methyl donors, methyl transferase activity, and potentially demethylation activity (31). Hypomethylation, or decreased DNA methylation, patterns are a

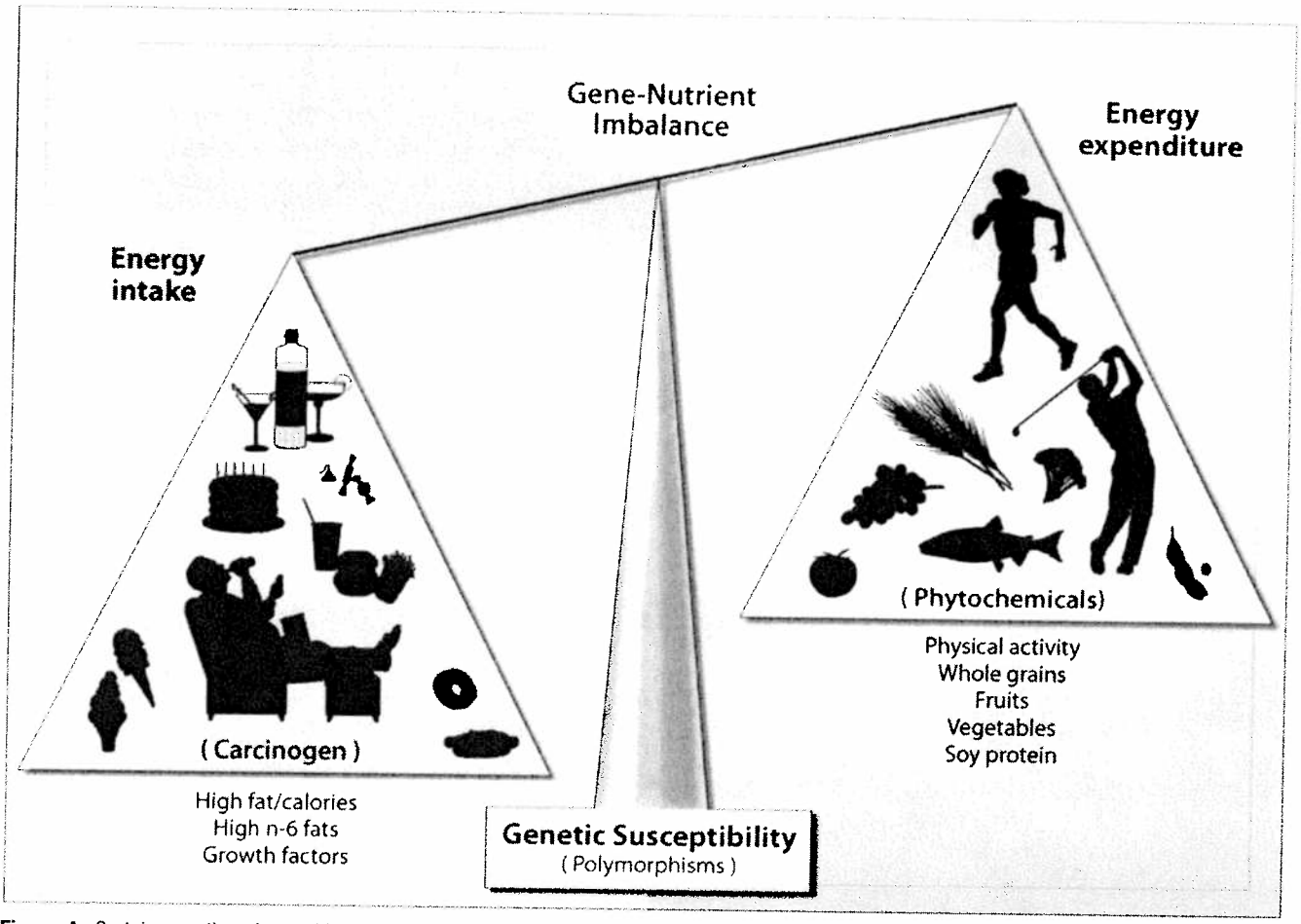

Figure 4. Certain genetic polymorphisms can shift the balance of energy intake and energy expenditure and thereby influence bioenergetics and obesity. Higher energy intakes, a low polyunsaturated-to-saturated fat ratio, insulin resistance, and a sedentary lifestyle leading to obesity are risk factors for chronic diseases, such as heart disease, diabetes, and cancer, depicted when the scale is sloping downward. The right side of the scale portrays lifestyle including physical activity and a diet rich in whole grains, fruits, vegetables, and soy protein, which are associated with less risk for obesity and chronic disease. Gene-nutrient imbalances may explain the morbidity and mortality associated with obesity.

nearly universal finding in cancer. These patterns are accompanied by site-specific hypermethylation DNA patterns. Chronic administration of methionine- and choline-deficient diets resulted in global hypomethylation of hepatic DNA and spontaneous tumor formation in rats (32). Several dietary factors may influence the supply of methyl groups available for the formation of S-adenosylmethionine. Furthermore, dietary factors may modify the use of methyl groups by processes including shifts in DNA methyltransferase activity. A third plausible mechanism may relate to shifts in DNA demethylation activity caused by food components, although this process is not well understood. Finally, DNA methylation patterns may influence the response to bioactive food components and thereby account for differences in response in normal and neoplastic cells (Figure 5).

Studies show that DNA methylation is dependent on bioactive food components ranging from alcohol to zinc (3,31-34) (Figure 6). The role of maternal dietary methyl donor supplementation in mice on DNA methylation and methylation-dependent epigenetic phenotypes in the offspring has been investigated in the agouti mouse model. Supplementation of choline, betaine, folic acid, vitamin B-12, methionine, and zinc to the maternal diet led to an increase in the level of DNA methylation in the agouti gene and a change in the color pattern of the hair coat. This phenotypic change has recently been shown to coincide with a lower susceptibility to obesity, diabetes, and cancer (34,35). This study suggests that in utero exposure to dietary factors may not only influence embryonic development but also have long-term health implications as well.

The discovery that the coat color and disease susceptibility in mice can be affected by the diets of their mothers provides rather compelling evidence that nutrition can alter epigenomic expression (35). These data suggest that environmental factors, such as diet, are key regulators in DNA methylation and histone regulation modifications. These processes can control gene expression (31,36). Epigenetic changes may regulate cell cycle control, DNA damage, apoptosis, invasion, imprinting, and aging.

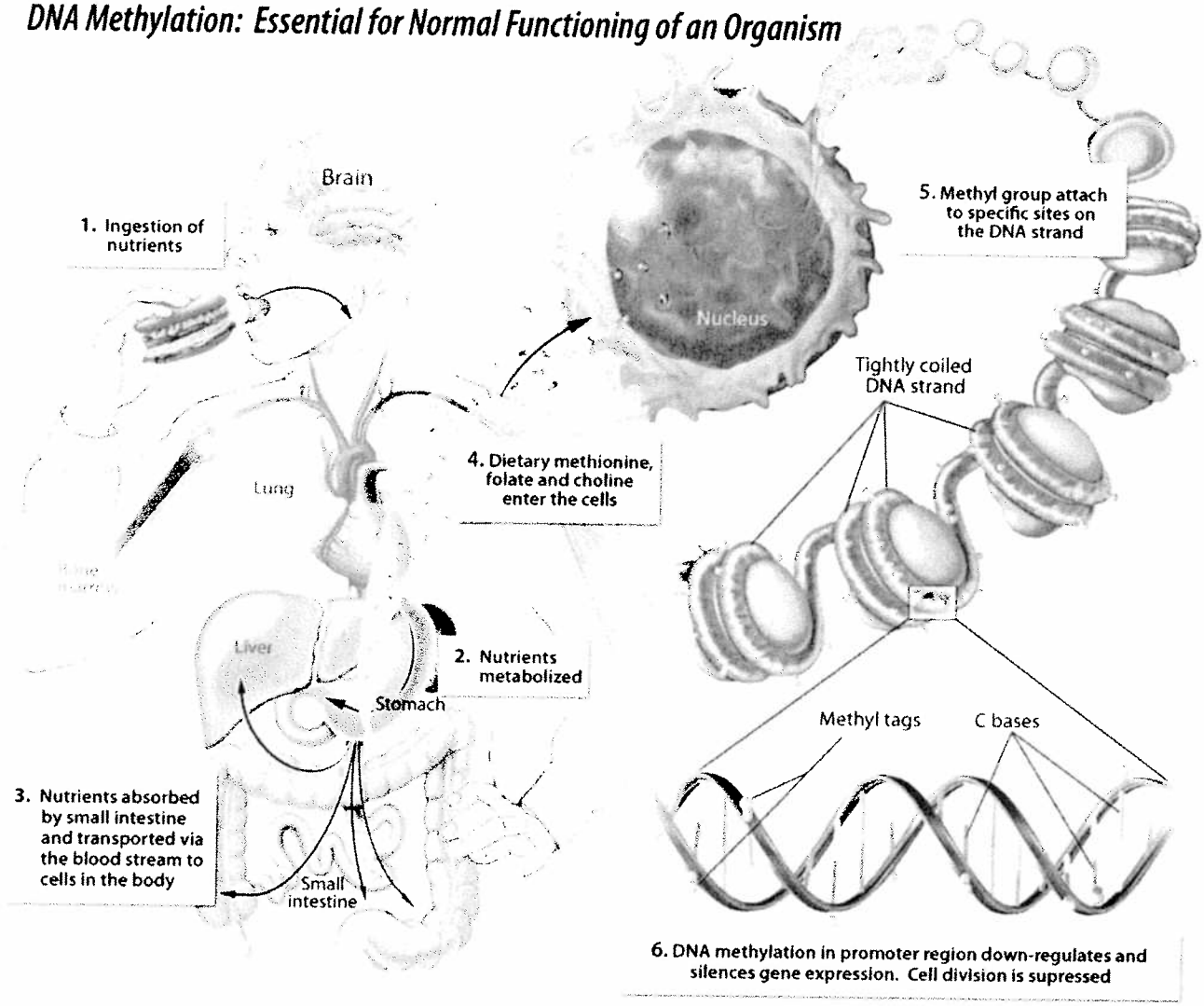

Figure 5. Dietary factors and the regulation of DNA methylation.

Alcohol	Arsenic
Betaine	Choline
Coumestrol	Equol
Fiber	Folate
Genistein	Methionine
Selenium	Polyphenols
Vitamin A	Vitamin B-6
Vitamin B-12	Zinc

Figure 6. Dietary factors known to influence DNA methylation.

TRANSCRIPTOMICS AND MICROARRAY TECHNOLOGIES

DNA modification alone will not give the entire picture of the impact of how various dietary factors may contribute to a person's phenotype. The regulation of the rate of transcription of genes (transcriptomics) by food components represents another intriguing site for regulation of an individual's phenotype (Figure 7). A host of essential nutrients and other bioactive food components can serve as important regulators of gene expression patterns. Vitamins, minerals, various phytochemicals, and macronutrients can modify gene transcription and translation, which can alter biological responses such as metabolism, cell growth, and differentiation, all of which are important in the disease process. The development of microarray technology is providing nutritional scientists with a powerful tool for examining potential sites of action of food components and their interactions with various cellular processes. Genome-wide monitoring of gene expression using DNA microarrays allows the simultaneous assessment of the transcription of tens of thousands of genes and of their relative expression between normal cells and diseased cells or before and after exposure to different dietary components. Microarray technology pro-

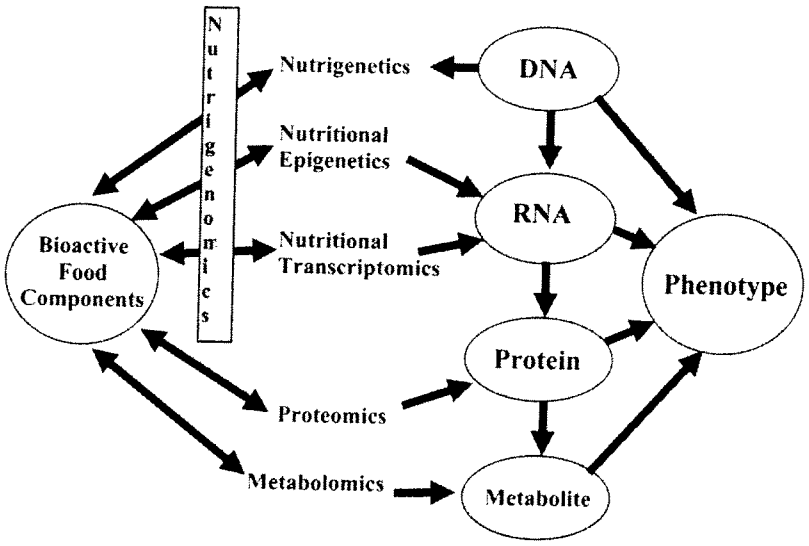

Figure 7. Using the "omics" of nutrition to identify how dietary factors contribute to establishing a phenotype.

vides the tools to elucidate gene expression changes that occur in diseased compared with normal cells. This information should assist in the discovery of new biomarkers for disease diagnosis and prognosis prediction and of new therapeutic tools. The use of a molecular approach to health and disease should help to introduce individualized medicine and to determine appropriate clinical strategies, including those associated with nutritional preemption.

To prevent transcriptomics from becoming purely descriptive, a greater understanding will be needed about how food components regulate genes (37). For this purpose a variety of mice models, particularly knockouts, have been used to identify specific sites of action of bioactive food components. For example, use of knockout mice has assisted in identifying the nuclear factor E2 p45-related factor 2 (Nrf2) and the Kelch domain-containing partner Keap1 as the complex that is modified by sulforaphane (38). Gene expression profiles from wild-type and Nrf2-deficient mice fed sulforaphane have shown several novel downstream events and thus more clues about the true biological response to this food component. For example, in addition to an inability to upregulate glutathione s-transferase, nicotinamide adenine dinucleotide phosphate:quinone reductase, gamma-glutamylcysteine synthetase, and epoxide hydrolase, a block in Nrf2 also is involved with the regulation of xenobiotic metabolizing enzymes, antioxidants, and biosynthetic enzymes of the glutathione and glucuronidation conjugation pathways. Similar studies with PPAR alpha-null mice have shown its role in regulating various sites of lipid metabolism (39).

Because microarray technologies only give a point-in-time comparison, overinterpretation is a real possibility. It has long been recognized that adaptive processes occur after the ingestion of foods or components in a number of metabolic pathways. Thus, the quantity and duration of exposure are critical dimensions to consider when evaluating microarray information. Molecular studies have already shown that specific events in cell cycle progression that are modified by energy restriction can rather quickly be reversed by refeeding (40). Again, the ability of the body to adapt will dictate the frequency by which interventions will be needed to bring about a desired effect. Another challenge with microarray analysis is how to analyze the massive amounts of data that are generated. Because of the number of genes whose expression can be modified by dietary components, a hierarchical cluster analysis is often used, which may minimize the significance of a particular gene in explaining the overall response. Although most studies use a 50% change in gene expression patterns as a cut point for statistical significance, a shift in mRNA expression in much lower amounts may have physiological significance. As advances in bioinformatics occur, the importance of changes in mRNA expression should help with predicting disease risk and identifying those individuals who would benefit from dietary change.

Another new technology is RNA interference, which can be used to stop the expression of a particular gene. This technology has been used to investigate which genes are involved in explaining the actions of bioactive food components and characteristics of diseases and conditions (41). By using RNA interference, investigators systematically disrupted expression of all of the genes in the worm model system *Caenorhabditis elegans* to determine which gene inactivation decreased body fat and which increased fat storage. This allowed for the identification of a core set of fat regulatory genes and pathway-specific fat regulators (42). Likewise, this technology has been used to identify sites of action of isothiocyanate compounds, such as sulforaphane, that arise from broccoli and other related foods (43). As transcriptomic information becomes available, it should be possible to identify targets for treating obesity and other unhealthful conditions with foods or their components.

THE OTHER "OMICS" OF NUTRITION

Dietary components can also modify the translation of RNA to proteins and the posttranslational events, which

can affect protein activity. Just as the genome is the entire set of genes, the proteome is the set of proteins produced by a species. However, unlike the genome, the proteome is dynamic and varies according to the cell type and the functional state of the cell. Although the genomic response to bioactive food components may have limited influence, it could have marked effects on the proteome. One of the frontiers in nutrition and disease prevention research is the development of pioneering technologies for proteomic analysis. Proteomics can be used to identify abnormal protein structures and show how they affect biology and respond to diet. It allows one to determine whether and how bioactive food components influence three-dimensional proteins. In an animal model, the impact of dietary fish oil, conjugated linoleic acid, or elaidic acid on lipoprotein metabolism and insulin levels was investigated using proteomics (44). Fish oil supplementation was found to lower plasma and liver cholesterol and triglycerides, plasma free fatty acids, and glucose, but to increase plasma insulin. Providing conjugated linoleic acid lowered plasma cholesterol, but increased plasma and liver triglycerides, plasma beta-hydroxybutyrate, and insulin. Elaidic acid was observed to lower plasma and liver cholesterol. Proteomic techniques identified significant regulation of 65 cytosolic and 8-membrane proteins, many of which were related to lipid and glucose metabolism and to oxidative stress. The combination of proteomics and physiologic measurements provided important insights into the possible mechanisms by which these dietary fatty acids regulated lipid metabolism (ie, altering protein levels of long-chain acyl-coenzyme A thioester hydrolase and adipophilin in the liver) (44).

As with transcriptomics, proteomic analysis provides a point-in-time snapshot in relation to dietary interventions. To assess the impact of diet, multiple exposures and varying durations will be needed to predict who might respond to dietary change.

One of the newest "omics" in nutrition is metabolomics, which refers to the dose and temporal changes in cellular small-molecular-weight compounds in response to dietary treatments. For example, one study used a metabolomic approach to evaluate all of the biochemical changes occurring after dietary intervention in humans. In this study, plasma profiles of healthy premenopausal women were analyzed before and after consumption of 60 g soy (45). Despite the presence of substantial intersubject variability, the metabolomic analysis enabled the identification of plasma components related to the dietary intervention. Soy intervention changed the plasma lipoprotein, amino acid, and carbohydrate profiles, suggesting soy-induced alterations in fat, protein, and carbohydrate metabolism. It is possible that these types of studies will allow for the identification of individuals, based on their metabolic abilities, who would benefit from a variety of foods and/or food patterns. As information in this area emerges, dietetics professionals will be provided with additional tools to make personalized nutrition recommendations.

The metabolic response will also depend on the quantity and timing of exposure to bioactive food components. For example, timing seems to be crucial in determining whether genistein, the primary isoflavone in soy, is protective against cancer. In a rat chemical carcinogenesis model, limiting the exposure of dietary genistein to the prenatal or adult periods of life does not predispose or protect against mammary cancer. In contrast, exposure to dietary genistein during the prepubertal and prepubertal plus adult periods protects against chemically induced mammary cancer in this model (46). The mechanisms of these differential effects may stem from mammary gland differentiation (46). An epidemiological report using the Shanghai Center Registry, a case-controlled study, showed an inverse relationship between soy food intake by adolescent girls (13 to 15 years old) and breast cancer incidence later in life (47). It may be that the consumption of soy during the prepubertal period, compared with other stages in the life cycle, may be more efficacious against mammary cancer development. Again, metabolomics may provide important subtle clues that are critical for health promotion.

CONCLUSIONS

The "omics" and associated technology will surely provide a greater understanding of the environmental and behavioral factors that influence phenotype and its relationship to health and wellness. Nutritional strategies for health in the future will require greater attention to a personalized approach that builds on nutritional preemption for desired outcomes. The use of such an approach may allow for prevention measures to block or suppress the initiation, promotion, and progression of pathways that lead to a lethal phenotype. Although nutritional preemption has been the foundation for understanding the essential nature of nutrient deficiencies and the complications related to deficiencies, it has not been embraced as an overall strategy for how all bioactive food components may influence disease risk.

Although we should never lose the public health messages for health promotion, it is clear that not all individuals respond identically to a diet or to dietary components. Eventually, the integration of nutrition and genomics may lead to the enhanced use of personalized diets to prevent or delay the onset of disease and to optimize and maintain human health. Although unprecedented opportunities exist for the expanded use of foods and bioactive food components to achieve genetic potential, increase productivity, and decrease risk of disease, the science to make such decisions has not reached a level of confidence to achieve personalized nutrition recommendations. The success of nutritional preemption approaches will depend on the ability to identify and validate nutrigenetic, nutritional epigenetic, proteomic, and metabolomic biomarkers to determine cause, effect, and susceptibility to disease. In addition, the success of this approach will depend on the ability to communicate effectively to the health care community and consumers the value of genomic information for developing a personalized nutrition plan and to do so within a bioethical framework.

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