Symposium Introduction: Nutrition and Gene Regulation

W. Allan Walker and George Blackburn

Harvard Medical School, Division of Nutrition, Boston MA 02215

Nutritional genomics is the study of nutrient-gene interactions and the effect these interactions have on health. It includes how diet affects the way genes are expressed, the effect of genes on how the body uses nutrients, and the effects of nutrients on molecular level processes in the body. It is an area of science that seeks to help people improve their health by studying how genes influence responses of genetically similar individuals or groups to foods. Knowledge of these interactions and variations can then be applied in the field of nutrigenetics to improve dietary guidelines for populations, or to tailor-make specific diets for individuals.

Dietary patterns are known to be strongly linked to 7 of the top 10 causes of sickness and death in North America, including heart disease, obesity, several cancers, and diabetes. A diet practiced by one individual may support his or her health and quality of life, yet the same diet practiced by another may lead to obesity and subsequent metabolic problems that compromise quality of life. The science of nutritional genomics should increase our understanding of diet-health-gene interactions, and provide a number of potential benefits for individuals, groups, and societies. These include improved individual health, greater consumer choice and control, an increased role for prevention in health management, greater social equity, and health care savings through the prevention and slowing of diseases. However, translating the flood of information from the mapping of the human genome into useful knowledge is a slow and painstaking process.

Dietary factors and related metabolic interactions have direct and indirect nutrient influence on specific gene regulation and expression. Research suggests that significant regulation appears to be at the level of transcription, with controlled modulation of messenger RNA levels. Data also indicate that nutritional factors, e.g., various vitamins regulated through dietary intake, can interact with other regulatory networks—such as tissue-specific, developmental, and hormonal factors, as well as dietary fat or carbohydrate—to regulate gene expression. Other studies have demonstrated regulation of apoprotein gene expression by sucrose-rich diet, nutritional regulation of gene expression in lipogenesis, and suppression of fatty acid synthase transcription by PUFA.

Sanderson suggests that changes in the intestinal lumen can alter the expression of molecules in the intestinal epithelium that direct the mucosal immune system, with the intestinal epithelium acting as a relay for transducing the information of the intestinal environment to the mucosal immune system. Data indicate that this mechanism has advantages over other forms of immune surveillance in the gut that require the breach of invading organisms. Such breaches can be manipulated by invading organisms such as the polio virus to enter the body. Sanderson et al. suggest that other mechanisms (e.g., enteral feeds used to treat Crohn's disease in children in the UK) can also alter the luminal environment radically enough to vary the signals from the intestinal epithelium to the mucosal immune system.

Girard reports that until recently, the regulation of gene expression in response to changes in nutritional environment was thought to be mediated primarily by hormones and/or the nervous system. However, the last decade has provided evidence that major (glucose, fatty acids, amino acids) or minor (e.g., iron, vitamin) nutrients, or their respective metabolites, regulate gene expression in a hormone-independent manner. Recent experiments indicate that regulation of gene transcription is not a simple PPAR-mediated process.

Rather, data show that a great diversity of fatty acid-sensor proteins and potential transcription factors are involved in fatty acid mediated gene expression. Sensors are known to relay the transcriptional effects of fatty acids, mediating them either directly, through their specific binding to various nuclear receptors (PPAR, LXR, HFN-4alpha), or indirectly, via modulations in the abundance of regulatory transcription factors (e.g., SREBP1-c, ChREBP). Each transcription factor makes a relative contribution to fatty acid-induced positive or negative gene expression.

Fatty acids control the expression genes encoding regulatory protein involved in their own metabolism via molecular mechanisms. Nonesterified fatty acids or their CoA derivatives seem to be the main signals involved in the transcriptional effect of long-chain fatty acids. Growing knowledge of the mechanisms by which fatty acids control specific gene expression may provide insight into the development of new therapeutic strategies for better management of whole body lipid metabolism and the control of blood levels of triglycerides and cholesterol, major risk factors for coronary heart disease.

Salati notes that regulation of the activity of enzymes involved in lipogenesis is key to understanding how a cell...
adapts to dietary energy in the form of carbohydrate versus energy in the form of triacylglycerol. Changes in the activity of these enzymes are largely caused by changes in the rates at which their proteins are synthesized, with dietary nutrients signaling these changes via alteration of hormone concentrations or their own unique signal transduction pathways.

**Bioactive food components and molecular targets**

Milner reports mounting evidence pointing to dietary habits as an important determinant of cancer risk and tumor behavior. At the same time, he notes inconsistencies in the literature that are probably due to variable abilities of bioactive constituents to reach or affect critical molecular targets. Data indicate that fluctuations in the foods consumed not only influence the intake of particular bioactive components, but may also alter metabolism, and potentially influence the sites of action of both essential and nonessential nutrients.

Gene polymorphisms are increasingly recognized as another factor that can alter the response to dietary components (nutrigenetic effect) by influencing the absorption, metabolism, or sites of action. In addition, variation in the ability of food components to increase or depress gene expression (nutrigenomic effect) may account for some observed inconsistencies in response to dietary change. A host of food components known to influence phosphorylation and other posttranslational events make it is likely that these, and other proteomic modifications, account for at least part of the response and variation reported in the literature.

The term *nutritional genomics* has been used to describe work at the interface of plant biochemistry, genomics, and human nutrition. Genetic changes arising as a result of single point mutations, rearrangements, or copy number involving either deletions or additions likely influence the response to various dietary components. The basis for nutrigenomics arises from rather compelling evidence that a variety of nutrients interact with specific molecular targets. Invariably, studies reveal that a host of messages are modified by the presence or absence of a food component.

Proteomic techniques are being developed and refined to assist in the identification of the proteome, which is defined as all of the proteins present in a particular cell at a particular moment. The importance of these types of investigations stems from the fact that gene expression does not always correlate with protein expression, and the influence of food components may be either translational or posttranslational rather than at the transcriptional level.

Proteomic-based studies, although technically challenging, complement genomic studies and are essential in any comprehensive research strategy aimed at examining the molecular processes and factors involved in modulating disease risk. The use of current proteomic tools will not only advance the field of nutritional sciences, but will make the discipline more valuable for its involvement in disease prevention including cancer.

Metabolomic science derives from the fact that responses to a bioactive food component cannot be considered to occur in isolation, but must be evaluated in the context of an entire diet. Metabolomics involves the systematic estimation of metabolomes, i.e., the characterization of all metabolites and small molecular weight compounds occurring in an organism. Several methods, including principal component analysis and clustering, are being examined to analyze metabolomic data. Metabolomic subsets, such as the lipid and amino acid metabolome, already suggest that some very useful information can be obtained from metabolomic analyses.

**Fatty acid binding proteins**

Hotamisligil’s research indicates that fatty acid binding proteins (FABPs) are members of a family of proteins highly conserved with the task of protecting the delicate lipid balance of a cell. However, when faced with metabolic or inflammatory stress, they fail, turning the cytosol into an inhospitable environment with less than ideal outcomes. Recent studies focus on how FABP’s direct lipid traffic and simultaneously control metabolic and inflammatory pathways under the pressures of the metabolic syndrome.

Under normal physiologic conditions, mice do not have a compromised phenotype when FABPs are deleted, but they benefit enormously when faced with systemic stresses, particularly of metabolic and inflammatory origin. Evidence suggests an evolutionary role for the existence of this protein. For survival of the most successful organism, efficiency in metabolic and immune responses is crucial to resist starvation as well as infection. Evolutionary selection has clearly preserved the FABP from yeast to humans, indicating that the close link between the inflammatory and metabolic responses underlies the conservation of FABP function.

Data suggest the concept of a biological role for FABPs as a potential central regulator of common pathways controlling metabolic and inflammatory signaling under physiological and pathologic conditions. For many signaling systems acutely activated, such as during inflammation, regulatory mechanisms have evolved to amplify and/or attenuate the response. For example, inflammatory stress increases lipolysis in the adipocyte and fatty acid synthesis by the liver, while decreasing oxidation of fatty acids by the liver, heart, and muscle, thereby flooding the system with excess fatty acids.

While FABPs appear necessary to evoke a strong inflammatory response, too strong a response can be overwhelming and damaging. Data suggest that FABPs may be master regulators, necessary to fine-tune the balance between the availability of metabolic resources, a robust inflammatory response, and its resolution. Further understanding of the mechanism of action, and eventual modulation of FABP activity, might lead to opportunities to regulate lipid-sensitive pathways. Based on the limited expression pattern of FABPs, interference with the protein’s ability to orchestrate lipid signals may provide clinicians with pharmaceutical specificity in a highly cell-type-restricted manner. In time, the true nature of FABPs will yield to scientific inquiry, paving the way for the development of therapeutic options for a broad range of pathologies, including obesity, insulin resistance, type 2 diabetes, atherosclerosis, and perhaps other inflammatory conditions such as arthritis, asthma, or Alzheimer’s disease.

**Cancer prevention**

Genetically engineered mouse strains with over expressed or inactivated cancer-related genes have recently been developed. These provide investigators with powerful tools for studying carcinogenesis and for testing preventive strategies that can offset increased genetic susceptibility to cancer in humans due to specific genetic lesions. Hursting reports work on the development of relevant animal models for cancer prevention research that aims to: 1) characterize the molecular mechanisms that underlie effective modulators of cancer risk; 2) capitalize on mechanistic information to develop effective combination regimens; and 3) develop surrogate endpoint biomarkers that can be translated to human studies.

Research to date has focused on preventing cancer by dietary interventions, particularly obesity prevention/energy...
balance modulation, in mice deficient in the p53 tumor suppressor gene, the most frequently altered gene in human cancer. Given the impact of obesity on cancer development, and the paucity of mechanistic data on this association, studies of energy balance and cancer are essential. Hursting also proposes to capitalize on the availability of new tools (e.g., genetically-engineered mice, gene expression microarrays, and proteomics) to identify additional targets that can be modulated.

Hursting is currently comparing and combining caloric restriction and exercise in p53-deficient mouse models, as well as in other tumor models. They are also investigating the role of IGF-1, other hormones, and body composition in the energy balance and cancer relationship. Together, findings clearly demonstrate that the increased susceptibility to cancer as a result of a genetic lesion, such as loss of p53 tumor suppressor function, can be offset, at least in part, by preventive approaches.

Halperin reports that the composition of diets critically influences the expression of many genes. Long chain ω-3 PUFA are of particular interest since they represent one dietary component that appears to have a significant impact on the expression of specific genes. The molecular mechanism of the anti-cancer activity of ω-3 PUFA includes the partial depletion of ER Ca++ stores, which inhibits translation initiation and preferentially downregulates the synthesis and expression of oncogenes and growth-promoting proteins that block the progression of the cell cycle in G1. Long chain ω-3 PUFA also induce the expression of pro-apoptotic proteins through gene-specific regulation mediated by transcription factors.

Halperin notes that perhaps the most important aspect of his research is the generation of tools that allow assessment of whether the anti-cancer effect demonstrated in vitro and in animal models also operates in human subjects. He expects accreditation of the translation initiation machinery as the effector of the anti-cancer properties of ω-3 PUFA in humans to foster clinical trials to test their therapeutic and preventive effect in human cancers. Furthermore, since the expression of other genes involved in the pathogenesis of several diseases may also be highly regulated at the level of translation, it is conceivable that ω-3 PUFA may help treat and perhaps reduce the risk of some chronic pathological conditions that burden the human population.

Leptin

In his keynote address, Friedman discussed the role of leptin as a central mediator in a negative feedback loop regulating energy homeostasis. He noted that although elucidation of leptin’s role enables a more detailed view of the biology underlying energy homeostasis, most obese individuals are leptin resistant. According to Friedman, the development of effective treatment for obesity and the metabolic syndrome will require more complete understanding of the molecular components of the leptin pathway.

Friedman and Cohen’s recent review of studies on the identification of one such component, stearoyl-CoA desaturase-1 (SCD-1), suggests that leptin’s metabolic effects are, to a large extent, mediated by repression of this gene. The specific mechanism by which leptin represses SCD-1 is currently unknown, but it could involve both transcriptional and post-translational modulation. Moreover, SCD-1 appears to be a critical metabolic control point partitioning fats towards storage when activity is high, and towards oxidation when activity is low.

Greater insight into the role of SCD-1 in other aspects of the metabolic syndrome, such as diabetes and atherosclerosis, will require further study. Research is also necessary to determine whether the absence of SCD-1 confers any adverse health risks. Data indicate that increased fatty acid oxidation may raise the levels of toxic free radicals, which could predispose to cancer or reduced longevity. While a mouse model algorithm has found SCD-1 to be the most potently leptin-regulated gene, other genes identified as being either specifically repressed or induced by leptin may also have critical physiological roles. According to Friedman, future work will determine whether inhibition of SCD-1 could be a therapeutic target in the treatment of obesity, hepatic steatosis, and other components of the metabolic syndrome.

Mantzoros reported on the role of leptin in the regulation of several neuroendocrine axes, such as the hypothalamic-pituitary-gonadal and the hypothalamic-pituitary-thyroid axes in human, and its potential pathophysiological role in eating disorders. Recent discoveries indicate that leptin levels above a certain threshold are required to activate the hypothalamic-pituitary-gonadal and hypothalamic-pituitary-thyroid axes in men, whereas the hypothalamic-pituitary-adrenal, renin-aldosterone, and growth hormone-IGF-1 axes may be largely independent of circulating leptin levels in humans.

Leptin is a hormone that communicates information on the body’s fat stores/energy reserves to the brain, thus maintaining normal function of several neuroendocrine axes. Several conditions, including eating disorders such as anorexia nervosa and bulimia nervosa, are associated with altered serum levels of leptin as well as abnormalities in neuroendocrine functions. According to Mantzoros, recently completed intervention studies propose that leptin acts as a “master hormone” in regulating neuroendocrine function in normal healthy volunteers. These studies have already provided the basis for a better understanding of the mechanisms underlying the hormonal abnormalities of subjects with eating disorders, and may lead to the development of new therapeutic strategies for these conditions.

Summary

This symposium provided an overview of research in the field of nutritional genomics, including developments in nutrigenomics, proteomics, and metabolomics. Speakers reviewed nutrient-gene-health processes that have the potential to help prevent many diseases, and greatly affect our optimal nutrition and health. Humans differ in their metabolic regulation, and the optimal diet for one person is not necessarily the optimal one for another. Determining which diet is best for each individual will require personalized assessment.

Progress towards the goal of individualized diets and health care will make diagnostic use of single biomarkers of diseases inadequate for accurate surveillance and intervention in problems of metabolic regulation in healthy individuals. At a 2003 symposium on next-generation nutritional assessment, Bruce German (1) noted that measuring entire metabolic pathways is the ultimate scientific goal, and that modern analytic techniques are in a position to deliver such capabilities. His challenge to us at that time was to build the metabolic knowledge to understand metabolism as a whole, and provide guidance to individuals to change their diets and lifestyles to affect metabolism in a net positive direction (2). This symposium shows impressive advances in that direction, with the promise of accelerating progress as our knowledge base in nutritional genomics continues to grow.

LITERATURE CITED