

The Potential For Nutrigenomics in Prevention of Metabolic Syndrome

J. David Gangemi,^a and Dana King^b

^aDepartment of Microbiology and Molecular Medicine, Clemson University, Clemson, SC 29634, USA, Fax: 1 864-656-3608; Tel: 1 864-656-3015; E-mail: gangemj@clemson.edu

^bFamily Care Medicine, Medical University of South Carolina, Charleston, SC 29412, USA, Tel: 1 843-792-5262; E-mail kingde@usc.edu

Received April 12, 2009

The relationship between diet and health has been recognized for millennia, but precisely “how” diet interacts with human physiology to elicit health or disease is only now beginning to be understood. The sequencing of the human genome as well as the development of new and innovative technologies in systems biology has allowed scientists to ask more probing questions into the relationship between diet and health at the most fundamental levels of biology. From this the “science of nutrigenomics” has emerged and it is now clear that certain dietary nutrients have the ability to interact with the human genome regulating gene function in positive and negative ways. Most importantly, the identification of specific nutrient chemicals that regulate genes is rapidly unfolding and the use of naturally occurring nutrient chemicals as pharmacological agents is becoming a reality. The net result is the development of new and innovative nutritional products for wellness and disease prevention.

Introduction

Dietary components provide the nutrient resources and energy needed for growth and repair of tissue throughout our lives. In adults, energy balance or homeostasis occurs when energy intake equals energy expenditure. Maintenance of this balance is required for a stable body weight. A chronic positive energy balance results in excess fat and obesity, which is linked to a constellation of health maladies, and is referred to as “metabolic syndrome”. This syndrome is associated with an increased risk of chronic diseases, including diabetes, cardiovascular disease, and stroke. Two hallmarks of metabolic syndrome are insulin resistance and increased markers of chronic inflammation.

Metabolic syndrome is characterized by a group of metabolic risk factors in a single person¹. They include:

- Central obesity (excessive fat tissue in and around the abdomen)
- Atherogenic dyslipidemia (blood fat disorders — mainly high triglycerides and low HDL cholesterol — that foster plaque buildups in artery walls)
- Insulin resistance or glucose intolerance (the body can't properly use insulin or blood sugar)
- Prothrombotic state (e.g., high fibrinogen or plasminogen activator inhibitor in the blood)
- Raised blood pressure (130/85 mmHg or higher)
- Proinflammatory state (e.g., elevated high-sensitivity C-reactive protein in the blood)

The underlying causes of this syndrome are overweight/obesity, physical inactivity and genetic factors. People with the metabolic syndrome are at increased risk of coronary heart disease, other diseases related to plaque buildups in artery walls

(e.g., stroke and peripheral vascular disease) and type 2 diabetes.

South Carolina has the dubious distinction of having one of the highest metabolic disease prevalence rates in the country². The occurrence of diseases related to this syndrome has resulted in a significant health-care burden and has prompted scientists from Clemson University, The University of SC and The Medical University of SC to join forces to seek solutions. In this regard an effort is now underway to form the SC Center of Economic Excellence in Molecular Nutrition where faculty from each university will collaborate to combine their individual strengths in plant breeding, nutrition, genomics, and gene regulation and function to develop prevention strategies. Motivation for this Center comes from long-held beliefs that chronic disease syndrome may one day be prevented through a better understanding and the mechanism through which specific nutrients are able to affect gene expression for human health.

Molecular Nutrition and Wellness

Molecular nutrition examines the interactions between nutrients and intracellular and extracellular molecules and is beginning to unravel the way nutrients affect cellular processes. This emerging field has been identified as one of the most exciting new frontiers in biomedical technology with the potential to dramatically improve human health and wellness worldwide³.

A component of molecular nutrition, nutrigenomics, or nutritional genomics, is a multidisciplinary science that combines information from genetics, nutrition, physiology, pathology, and molecular biology. The diet - nutrient interactions which occur in different individuals is complex and scientists are focusing on the polymorphisms which affect these interactions to help alleviate health disparities.

Dietary chemicals have been shown to alter gene expression in a number of ways⁴. For example, they may:

- act as ligands for transcription factor receptors
- be metabolized by primary or secondary metabolic pathways thereby altering concentrations of substrates or intermediates or
- alter signal transduction pathways

genes not believed to be associated with nutrient utilization. While more complex than yeast, the constellation of genes that make up the human genome respond in a similar fashion to dietary inputs⁵.

The science of nutrigenomics is multifaceted, but primarily looks at the molecular relationships between dietary intake and the response of genes, with the aim of extrapolating how gene expression affects human health^{3,4}. Nutrigenomics focuses on of the molecular relationships between dietary intake the effect of diet on the genome, epigenome, proteome, and metabolome. In understanding these effects, nutrigenomics attempts to define the relationship between specific nutrients and specific nutrient regimes (diets) on human health. Nutritional genomics, or nutrigenomics, is the study of how foods affect our genes and how individual genetic differences can affect the way we respond to nutrients (and other naturally occurring compounds) in the foods we eat.

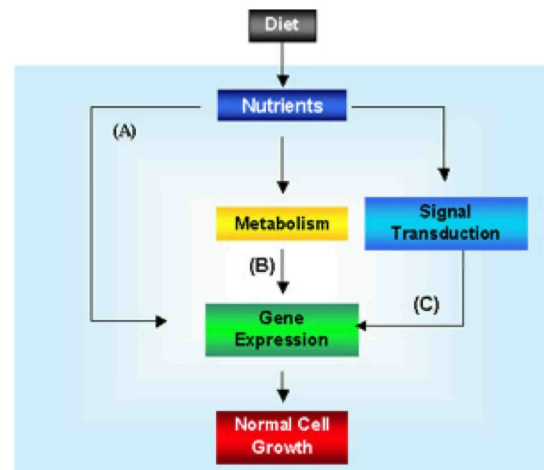
While somewhat controversial, nutrigenomics has been popularized with the idea of personalized nutrition based on genotype. While there is hope that nutrigenomics will ultimately enable such personalized dietary advice, the science is in its infancy and many more fundamental questions must be answered⁶.

Nutrigenomics and Disease Prevention

Throughout the 20th century, nutritional science focused on finding vitamins and minerals, defining their use and preventing the deficiency diseases that they caused. As the nutrition-related health problems of the developed world shifted to overnutrition, obesity and type 2 diabetes, the focus of modern medicine and of nutritional science changed accordingly.

In order to address the increasing incidence of these diet-related-diseases, the role of diet and nutrition has been and continues to be extensively studied. To prevent the development of disease,

nutrition research is investigating how nutrition can optimize and maintain cellular, tissue, organ and whole body homeostasis. This requires understanding how nutrients act at the gene, protein and metabolic levels. As a result, nutrition research has shifted from epidemiology and physiology to molecular biology and genetics⁶.



With this paradigm shift new data has emerged in support of dietary interventions in preventing, mitigating, or treating chronic disease, and certain cancers. The conceptual basis and scientific evidence to support dietary interventions can be found in the following observations:

- Under certain circumstances and in some individuals, diet can be a serious risk factor for a number of diseases.
- Common dietary chemicals can act on the human genome, either directly or indirectly, to alter gene expression or structure.
- The degree to which diet influences the balance between healthy and disease states may depend on an individual's genetic makeup.
- Some diet-regulated genes (and their normal, common variants) are likely to play a role in the onset, incidence, progression, and/or severity of chronic diseases.
- Dietary intervention based on knowledge of nutritional requirement, nutritional status, and genotype, have been used to prevent, mitigate or cure chronic disease.

The emergence and development of nutrigenomics has been possible due to powerful developments in genetic research. With these developments, biochemical disorders with a high nutritional relevance have been linked to a genetic

origin. Such disorders include a polymorphism in the gene for the hormone Leptin which results in gross obesity. While a few other genetic polymorphisms have been described, it is thought that many others result in minor deviations in nutritional biochemistry. The tools to study the physiological impact of these genetic polymorphisms are only now becoming available. Such tools include those that measure the transcriptome - DNA microarray, exon array, single nucleotide polymorphism arrays and genotyping^{5,6}.

The Promise of Nutrigenomics

In nutrigenomics, nutrients are seen as signals that communicate with specific cells in the body. These nutrients may be detected by a sensory system much like those associated with toll-like receptors on cell surfaces. Like the toll receptor, cellular signaling is induced through transcription factors which alter gene expression and protein/metabolite production in accordance with the level of nutrient present in the cell environment. As a result, it is believed that different diets will elicit different patterns of gene and protein expression and metabolite production. Nutrigenomics seeks to describe the patterns of these effects which have been referred to as *dietary signatures*⁶. Such dietary signatures can be examined in specific cells, tissues and organisms and in this way the manner by which nutrition influences homeostasis can be better understood. Genes which are affected by differing levels of nutrients are now being identified and their regulatory pathways are under investigation³. Through the identification of these genes and their regulatory pathways, scientists will soon have a better understanding of how nutrition influences metabolic pathways and homeostasis. Such an understanding will be essential in attempts to prevent the development of chronic diet related diseases such as obesity and type 2 diabetes. In this regard, finding markers of the early phase of diet related diseases for intervention with selected nutrients that could reverse or slow the disease process will expand the application of nutrigenomics. Thus, once a marker has been found and measured, the extent to which an individual is susceptible to disease development may be quantified and personalized dietary recommendations prescribed. Progress in this area will lead to the marketing and distribution of "science-based functional foods" that will keep people healthy according to their individual needs.

Chronic Disease Syndrome in SC

An estimated 79 million American adults (1 in 3) have cardiovascular disease (CVD), and millions more are at risk due to the presence of obesity, hypertension, and hyperlipidemia¹. CVD

accounts for 36.3% of U.S. mortality, or 1 out of every 2.8 deaths. SC is a leader in heart disease and in stroke among the U.S states; heart disease is the leading cause of death in SC, accounting for 10,000 deaths annually.² Further, in 2007, SC had the seventh worst obesity rate in the nation, with over 65% of all SC adults either overweight or obese. When examined across race/ethnicity in SC adults, a larger proportion of African-Americans in the state are overweight or obese (73.6%) as compared to Whites (63%)⁷. Recent research has established that inflammation plays a key role in the atherosclerotic process^{8,9}. Endothelial injury and plaque rupture are inflammatory processes that lead to thrombosis, myocardial infarction and stroke. Several proteins participate in the inflammatory processes that are useful for measurement. The most common and clinically useful measure is highly sensitive C-reactive protein (hsCRP), but several other markers have been investigated^{9,10}.

A pharmaceutical approach to prevention of CVD inherently exposes millions of people without disease to the risk of adverse effects and interactions of multiple medications (aspirin—ulcers, bleeding; statins—liver dysfunction/myopathy; fenfluramine and phentermine—valvular heart disease and pulmonary hypertension). A more appealing approach is to identify, test, and use natural phytochemicals with anti-inflammatory and antioxidant activity and few side effects, to not only prevent CVD but promote general wellbeing.

Dietary Interventions to Reduce Chronic Disease Syndrome in SC

One of the most promising candidates currently under investigation in South Carolina is the common table grape. Animal, laboratory, and epidemiologic data indicate that higher intake of polyphenol-rich grapes have anti-inflammatory and potent antioxidant effects that may reduce the risk of CVD and other chronic disease states such as hypertension. These beneficial effects have been attributed to the bioactive constituents resveratrol and flavonoids such as anthocyanins^{11,12}. Recent evidence shows that red wine derived from table grapes (*Vitis vinifera*) may lower the risk of CVD¹³⁻¹⁵. Before proceeding with clinical studies of grape concentrates in clinical populations, the potential bioactive phytochemicals in grapes need to be more fully identified. The molecular mechanisms underlying the effect of grape phytochemicals in CVD prevention are yet to be elucidated, but alterations in cell signaling pathways leading to inflammation are a distinct possibility. Phase I and II trials need to be conducted in a carefully chosen target population with increased inflammation and oxidative stress (overweight/obese but otherwise healthy adults,¹⁶⁻¹⁸ to

determine the maximum tolerable dose, adverse effects and effective dose ranges of grape products.

In contrast to table grapes, research on muscadine (*Vitis rotundifolia*), a native and valuable fruit crop in Southeastern US, including SC and GA, is under-developed. Muscadine is classified under the genus *Vitis* with other grape species, but further classified to a separate subgenus, *Muscadinia*, due to genetic and botanical differences between muscadine and other grapes. Muscadines are well adapted to warm and humid climate in the Southeastern US in which other grapes do not thrive. Muscadines have a higher total phenolic content compared to table grapes and small fruits¹⁹. Recent evidence shows that photochemical constituents of muscadines are distinct and differ from other grapes by having unique phenolic compounds, such as ellagic acid and other anthocyanins in appreciable amounts²⁰⁻²². Anthocyanins are present as 3,5-diglucosides in the muscadine as opposed to 3-glucosides in other grapes, and glycosylation has been shown to be a major determinant of bioavailability^{22,23}. Major phenolics reported in muscadine skins are ellagic acid, myricetin, quercetin, and kaempferol while for the muscadine seeds are gallic acid, catechin, and epicatechin²⁰; most of the polyphenols are concentrated in the seed and skin. Therefore, muscadine seed and skin polyphenols may have different bioactivity, as compared to those of other grapes, due to the presence of unique polyphenols. These unique constituents may act as a source of novel compounds for targeted intervention in the inflammatory pathways. Clinical studies now underway at the Medical University of SC will focus on chemically defined constituents from muscadine seed and skin extracts to determine which ones have the greatest impact on inflammatory markers in patients with metabolic syndrome. Once identified, these extracts will be evaluated in larger trials in and out of SC to evaluate the long-term effects on prevention and/or delay in onset of the diseases associated with metabolic syndrome.

While it appears that certain classes of polyphenols, e.g. anthocyanins, in muscadines contain the bioactives needed for reducing inflammation, the cellular mechanism by which these substances impact disease are complex involving a highly evolved cellular circuitry in which gene expression, either directly or indirectly induced, results in physiologic change. With the recent advancements in systems biology (genomics, proteomics, and metabolomics) we may soon be able to dissect and control cellular circuits, which are regulated by polyphenols. Certainly our ability to control expression of nuclear factor-kappaB and inflammatory cytokines such as TNF-alpha and Il-6 appear to be likely candidates for initial investigations.

Conclusions

The science of nutrigenomics continue to generate much interest and activity with the expectation that many of the disparities in wellness can be prevented, but much remains to be done, and this science is still in its infancy. The promise of nutritional genomics in personalized medicine and health is based on an understanding of our nutritional needs, nutritional and health status, and our genotype. Nutrigenomics could have significant impacts on society – from medicine to agricultural and dietary practices to social and public policies – and its applications are likely to compare to those arising from the human genome project. Chronic diseases (and some types of cancer) may be preventable, or at least delayed, by balanced, sensible diets. Knowledge gained from comparing diet/gene interactions in different populations may provide information needed to address the larger problem of global malnutrition and disease.

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