The paradox “the more we know, the more we don’t know” has never been more true than in the case of research uncovering the genotypes that underlie human diseases. In recent years, unprecedented progress in genomic and molecular medicine has generated at least two new frontiers in science: the epigenetic basis for disease and the role of the gut microbiome in shaping human health. Although these new frontiers are contributing to a better understanding of human diseases, the common occurrence of two patients who, by every clinical measure, have identical pathologies with divergent outcomes continues to leave physicians and scientists without answers (2). Knowledge of individual differences in genetic codes (genotypes) may offer further insight in such a scenario, indicating an additional knowledge gap. The rapid expansion of biomedical knowledge in the postgenomic era is directly influencing the changing nature of research on dietary bioactives that may promote human health.

Genome Health: Lessons from Cancer Genomics Research

Research on cancer as a disease affecting humans began more than a century ago (1). By the end of the 20th century, Dulbecco (5) called for complete human genome sequencing as an essential tool for systematic discovery of the genes that drive cancer and other diseases. In response to this and other calls to action, the Human Genome Project (HGP) was launched in 1990, and a nearly complete sequence of the human genome was obtained by 2003 (11). Soon thereafter, a working group from the U.S. National Cancer Institute proposed a “human cancer genome project,” which became The Cancer Genome Atlas (TCGA) project.

One of the far-reaching outcomes of these initiatives has been the revelation of the critical role of epigenomic changes in the pathogenesis of cancer. Epigenomic changes may explain, at least partially, the proposed hallmark processes that occur in tumorigenesis and metastasis (10). As sequencing costs fall, it is predicted that utilization of genomic sequencing in diagnostics and clinical interventions will increase, which should favor the translation of pharmacogenomics and nutri-genomics principles and knowledge into routine clinical applications and patient care.

Nutrient–Gene Interactions, Epigenetics, and Disease

Although there are important general nutrition recommendations, it is now widely accepted that what constitutes optimal nutrition varies widely due not only to age, gender, and general health status, but also to an individual’s genetic and epigenetic background and potentially to their specific gut microbiota profile. It has been known for some time that genetic variation among individuals can differentially influence the effects of nutrients on metabolism; the newer piece to the puzzle is the epigenetic paradigm. Nutrients can differentially alter the activity of genes in individuals by turning them “on” or “off.” This process is independent of the DNA sequence, as has been determined by an array of identical-twin studies conducted over the past decade. These alterations, such as DNA
methylation or chromatin protein (histone) modifications, may be transient or quasi-permanent and even inherited. A myriad of laboratory animal and human studies have revealed that nutrition is an important epigenetic modifier. Moreover, altered epigenetics is associated with a variety of human disorders, such as cancer, obesity, diabetes, dyslipidemia, hypertension, and neurodegeneration. As a result, the importance of gene–nutrient interactions is noted in the “Bellagio Report on Healthy Agriculture, Healthy Nutrition, Healthy People” as being “fundamental to health” (15,17).

There are many bioactive molecules present in the diet that are capable of influencing epigenetics and that have been touted as potential chemopreventive agents. Examples include folate, B vitamins, retinoic acid, vitamin D3, resveratrol, genistein, epigallocatechin-3-gallate (ECGC), curcumin (8,18), and phenethyl isothiocyanate (13). It remains to be determined, however, whether the epigenetic influence of these agents can be achieved in humans as they have been observed in controlled cell culture and animal experiments. Also, it is important to determine the mechanistic and dose–response relationships of these dietary constituents and the window of time during the lifetime of an individual when they exert their maximum beneficial effects.

Although it is true that “we are what we eat but also what our parents and grandparents ate” (4), better biomarkers and assays are needed to assess variability in nutrition and metabolism in the population and its effects on epigenetics (3). To determine when and how it might be possible to intervene, data from intervention studies, not only association and observational studies, is required.

**Nutrition, the Microbiome, and Health**

A recent intervention study evaluated the effects of a prebiotic fiber from wheat on various risk factors for cardiovascular diseases, together termed “metabolic syndrome,” which affects 34% of adults in the United States (14). Some starches and fibers resist digestion in the small intestine and are fermented in the colon, which harbors trillions of microbes. This live-in colony of microbes in the large intestine, which together can weigh several pounds and consists of hundreds of thousands of individual species, is fed every time a meal is consumed. Recent advances in genomics techniques (metagenomic approaches) have made it possible to study these microorganisms in detail. The next step will be to understand how these microorganisms vary among individuals and their mechanistic link to diet and disease.

There is evidence that the makeup of the inhabitants of the gut may explain why some individuals develop metabolic disorders or put on weight while others do not. Assessing a cause-and-effect relationship remains scientifically challenging, however. One study, organized through the European MetaHIT consortium, examined the bacterial genes present in the stool of nearly 300 Danish volunteers, both lean and obese, as well as markers of metabolic health. The team found that low microbial genetic diversity, which potentially correlates with low microbial species diversity, correlated with higher inflammation, greater insulin resistance, and other warning signs of metabolic diseases (12).

The question remains, what, if any, dietary modifications can improve microbial diversity in the gut and minimize disease risks, and do such modifications need to vary depending on an individual’s genetic/epigenetic makeup? Although the

An ad appeared here in the print version of the journal
hope is that specific answers to this question will be known in the future, for now research on the gut microbiome is still so new that ≈90% of the bacterial genes uncovered in the Danish and other similar studies remain uncharacterized. There is an entire universe in the gut, and we are just beginning to explore it.

**Dietary Bioactives and Whole Grains**

Consumption of plant-derived foods, particularly fruits, vegetables, and whole grain cereals, is encouraged, because they provide beneficial health effects due to the presence of a variety of biologically active dietary components, also referred to as bioactives. Although for many of these bioactives the exact nutritional benefits have not yet been fully defined, there is solid scientific evidence suggesting a role for them in disease prevention.

There also is growing evidence that whole grains, in particular, play an important role in the prevention of chronic diseases, which may be attributed to an array of bioactives, not only fiber content. Bioactive diversity is typically compromised during processing, which reduces the nutrient content of refined grain products. In epidemiological studies, increased whole grain intake has been associated with a reduced incidence of cardiovascular disease, obesity, diabetes, and certain cancers (6,7,19). Grains are more commonly consumed on a daily basis than vegetables and fruits. Therefore, the important role that whole grain consumption may play in disease prevention needs to be validated utilizing hypothesis-driven research, in addition to data from observational studies.

**Status of Personalized Dietary Guidelines**

It is now accepted that virtually all individuals have specific dietary requirements that are intimately linked to their genetic makeup, epigenetic status, and gut microbiome composition, as well as the surrounding environment. There is a consensus among biomedical professionals that personalized nutrition is the paradigm of the future (9,15,16). However, we do not yet have all the scientific data needed to devise and validate specific guidelines. In addition, as noted by Niculescu (15), assessing economic feasibility will be critical. From where we stand today, the road seems long and arduous, scientifically complex, and technically challenging and cannot be successfully navigated without integration and collaboration among a broad range of players: scientists, health providers, governments, consumer groups, for-profit groups, regulatory agencies, and political entities. However, the potential is huge, and the time may be right to act collectively.

**Acknowledgments**

Moul Dey is supported by National Institutes of Health grant R00AT4245, NIFA/SDAES grant 3AH360, and private food industry grant 3P2662.

**References**


Moul Dey is an associate professor in the Department of Health and Nutritional Sciences at South Dakota State University (SDSU), where she directs the nutrigenomics research program. Following doctoral training at the International Rice Research Institute and postdoctoral training at Cornell University, Moul joined Rutgers, The State University of New Jersey, as a member of the research faculty. Moul’s current research program at SDSU focuses on nutrient–gene interactions in the context of chronic human diseases and is funded by the National Institutes of Health, USDA grants through the South Dakota agriculture experiment station, and grants from private industry. Her work features a translational approach, combining efficacy and mechanistic studies in cell and animal models, as well as human studies. Moul serves on several editorial boards and as a peer reviewer for various journals. She has also served on panels for the National Institutes of Health, the US Department of Defense, and other organizations. Moul can be reached by e-mail at Moul.Dey@sdsstate.edu.