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# Nutrition and Genomics

A rigorous understanding of how food components interact with the body and contribute to health is a key focal point of nutrition research. With relatively recent progress in the field of genetics, the interesting relationship between nutrients and genotype has become another important aspect of this field of study; sometimes coined "nutrigenomics," this relationship has been shown to have a large impact in modulating the effect that diet has on health. In particular, researchers desire to better understand the mechanism by which nutrients and genes influence each other to determine the physiological response individuals have to certain dietary patterns, and the disposition patients carries towards various chronic diseases, both which are heavily influenced by individual genetic variation. Though highly complex due to the high variability of genotypes between individuals and large number of factors at play, advancements in nutrient-gene research shows promising applications in health interventions. An overview of the work being done in this interdisciplinary field will be offered, covering details about how this research is being conducted, what insights have been uncovered thus far, and future implications in this exciting field of study.

Research examining the nutrient-gene interaction describes one of two closely related topics: nutrigenetics and nutrigenomics. Nutrigenetics studies the effects that inherited genes have on the body's metabolic response to food; that is, it seeks to understand how an individual's uptake and metabolism of nutrients are modulated by their genetics.[6] With this knowledge, it is understood that the physiologies of different individuals respond in varying ways to a given dietary pattern as a result of genetic variation.[2,10] These variations stem most

commonly from single nucleotide polymorphisms (SNPs)[4] that account for a majority of differences among individuals. On the other hand, nutrigenomics studies the effects of dietary intake on genetic function; that is, it seeks to understand how the foods one eats regulates gene expression.[4,10] Current research reveals that certain micronutrients play a pivotal role in the proper functioning of genes, serving as cofactors for important enzymes such as those involved in DNA synthesis and repair.[2] Dietary deficiencies in such micronutrients are thus linked to genome instability, resulting in negative health outcomes such as increased cancer risk.[5]

Nutrigenetic and nutrigenomic research can proceed through one of two methods. Researchers can either make hypotheses about how certain gene or protein expression patterns are affected by individual nutrient intake to study dietary effects; or they can take a "systems biology" approach, in which they attempt to define biomarker patterns characteristic of disease states and study how nutrients may change these biomarker levels, thus developing the ability to detect early signs of chronic disease and understand the influence of diet on diseases.[10] In both methods, researchers employ a set of analytical tools in order to examine the state of the body and the reciprocal nutrient-gene interactions to gain insight into the relationship between dietary patterns and health outcomes. These tools include epigenomics, transcriptomics, proteomics, and metabolomics.[1,4]

Epigenomics examines how nutrient intake induce epigenetic changes, thus affecting gene expression without changing one's DNA sequence through certain DNA modifications such as DNA methylation, chromatin packaging, and histone protein modification.[4,9] The process by which nutrients can induce genes to "turn on or off" is one possible link between nutrition and health status, given that gene expression has obvious implications on the physiology.[2] Capturing the profile of epigenetic effects each nutrient can induce is thus an

important aspect to understanding the nutrient-gene relationship. For example, it has been found micronutrients such as choline, folic acid, and certain B vitamins on DNA methylation that effectively reduces gene expression,[6] which can modulate risk of cancer depending on the genes affected.

Transcriptomics is another means by which gene expression is analyzed. Whereas epigenomics examines how the DNA itself has been structurally modified, transcriptomics examines the products of gene expression, particularly the profile of mRNA copies produced per gene to determine levels of expression.[1] This analytical tool is considered one of the most mature of the omic technologies used, having achieved a fair degree of development. Currently, researchers are able to determine gene expression levels for nearly all genes in a single experiment, allowing them to quickly glean the effect that intake of certain nutrients can have on the body's pattern of gene expression, with which they can make further hypotheses on health impacts.[1] Specific methods used to collect this data include real-time PCR and high-density microarray analysis.[10] Transcriptomics may also be used to define profiles for general health statuses of patients by looking at different mRNA biomarkers in the body to distinguish between patients in healthy, pre-disease, and disease states, which can offer useful information to guide their treatment. However, this tool is still faced with limitations that impede the progress of nutritional research. For example, the gene expression profile for one tissue sampled may not be representative of the pattern throughout the body, as certain nutrients may have a tissue-specific effect. Additionally, a rigorous understanding of health biomarkers in gene expression have yet to be established, making it difficult to identify patients in a pre-disease state using this information.[1]

Finally, the analytical tools of proteomics and metabolomics are used to assess additional important biomarkers in the body. Proteomics examines protein expression patterns and their post-translational modifications, while metabolomics analyzes the metabolite profile of the body.[1] These two tools are of particular interest for nutrition research because they can provide insight on the body's phenotypic responses to food intake. Analyzing this data could provide information such as how insulin levels, triglyceride levels, cytokines, etc. of different individuals change when given a dietary intervention, which can help determine its efficacy and distinguish for whom it would be beneficial. Thus, proteins and metabolites can effectively serve as biomarkers for both effects induced by nutrients, as well as markers for pre-disease and disease states. They are important to study independent of transcriptomics and gene expression because mRNA expression may not be proportionate to protein translation, as one mRNA copy can translate multiple proteins. Unfortunately, these tools are still relatively undeveloped; they are limited in their ability to capture all of the proteins and metabolites in a given sample, primarily due to limitations in the software needed to process the data.[1]

Nevertheless, researchers have been able to use these tools to glean information about how nutrients interact with the genome to affect our health. Researchers have examined their role as signaling molecules that alter the body's gene, protein, and metabolite expression patterns, which could theoretically be profiled and assigned to specific nutrients by the omics technology discussed to understand the exact effect each nutrient has.[1] This profile, called the "dietary signature,"[10] would provide clinicians with the ability to predict a nutrient's physiological effects, which could be utilized for dietary interventions. Nutrients generally carry out their signaling action through affecting transcription factors. They most frequently bind to a family of receptors known as nuclear receptors, which then interact directly with

DNA resulting in changes in expression patterns.[10] Through this process, these receptors can serve as nutrient detectors that elicit a specific response to a given nutrient consumed. One example found relates to the peroxisome proliferation activator receptor-a (PPARa), which binds to fatty acids resulting in a conformation change that causes the dissociation of repressor proteins and the recruitment of activators, thereby activating the genes with which this receptor interacts.[1]

These changes in expression lead to downstream effects that result in physiological changes. However, the exact physiological "signature" a nutrient may leave on the body can vary widely among different individuals, as it is modulated by their genotype. The genetic polymorphisms, which most commonly manifest as SNPs but can also stem from insertions, deletions, and repeats,[6] can affect how the body metabolizes various nutrients, which in turn affects their physiological response. For example, lipoprotein levels are widely recognized as viable biomarkers for coronary heart disease (CHD), and are typically treated first with dietary interventions. High-density lipoproteins (HDL), deemed "good" cholesterol, have a preventative role in heart disease by transporting cholesterol from tissues in the body to the liver for excretion. HDL is affected by intake levels of polyunsaturated fatty acids (PUFAs), but genetics determine both initial levels and how levels respond to dietary intake; while some individuals may see a large, beneficial increase in HDL given a certain therapeutic dietary intervention, others may see no change or even a decrease in HDL given the same diet.[11] In contrast, low-density lipoprotein (LDL), deemed "bad" cholesterol, deposits fat in tissue and blood vessels in the body, increasing risk for CHD. Dietary intake of nutrients like saturated fats and refined sugar are believed to raise LDL levels, but, similar to HDL, genetics can determine both initial levels and the individual's response to dietary patterns. These responses

may be linked through how the individual's gene expression patterns respond to intake of PUFAs.[10] Thus, genetics are a large factor in both one's predisposition to chronic diseases and in dictating what treatments are most effective. More specifically, some genetic variations can affect how well a nutrient binds to the transcription factors or other key components of the signaling pathway, which affects the biochemical reaction rate of transcription leading to either an up-regulation or down-regulation of related physiological effects.[10] With the current state of technology, this variation in response presents a challenge in understanding exactly how a nutrient may affect an individual given their genotypic variation; however, with further research, this knowledge may be utilized in customizing a dietary plan for patients.[11]

Nutrients also affect the proper functioning of DNA replication and repair processes, and thus play a role in maintaining genome stability and cancer risk. As much as 30% of one's risk for cancer can be attributed to diet alone.[6] In the current literature, researchers have identified certain micronutrients with a prominent role in proper DNA function, including (but not limited to) folic acid, calcium, magnesium, zinc, niacin, and vitamins B, C, D, and E.[4,5] Among other mechanisms, these nutrients often serve as cofactors or as part of the actual enzyme structure for enzymes involved in DNA synthesis and repair, preventing oxidative damage, and maintaining proper methylation of DNA.[2] Thus, deficiencies in such nutrients can cause damage to the genome due to inadequate enzymatic activity, the magnitude of which is equal to or greater than the effect of exposure to carcinogens and radiation that are well known for their damaging consequences.[2] This genomic instability can directly lead to increased risk for cancer by causing oncogenic mutations.

One case study of this aspect involves telomeres, which are caps at the ends of chromosomes that maintain the stability of the chromosome by preventing abnormal end-to-end

chromosome fusion during cell division. Telomere shortening, which occurs naturally with age, can lead to instability of the entire chromosome due to this end-to-end fusion, among other processes. These can lead to abnormal gene expression patterns and an increased risk for cancer. At a certain short telomere length, the cell may respond by engaging in apoptosis, or programmed cell death, that can lead to negative health effects. It has been found that deficiencies in folate and niacin are correlated with increased oxidative damage to these telomeres due to a lack of enzymatic activity involved in preventing or repairing such damage, which can increase the rate of telomere degradation.[2] Researchers also hypothesize that the role of folate in deoxythymidine triphosphate (dTTP) synthesis and incorporation into the DNA may also play a role. Insufficient folate can lead to reduced dTTP synthesis and thymine incorporation into the DNA, which can lead to increased uracil incorporation that leads to chromosome breakage, thus shortening telomere length in addition to the effects of oxidative stress and damage.[2]

Further advancement in the understanding of this nutrient-gene relationship can open up opportunities for promising clinical applications of this knowledge in the future. One prominent application is the possibility of providing personalized diet plans to patients based on their genotype, which can be utilized to determine their nutrient requirements, predisposition to disease, and physiological response to specific nutrients.[10] While promising, this intervention involves a complex application of different information sources. First, researchers must understand and create a defined physiological profile of biomarkers in the body that distinguish healthy, pre-disease, and disease states. Through the use of multiple omics analytical tools, a clinician could integrate information about transcript, protein, and metabolite patterns in the body to create such a profile, though creating such criteria is difficult given the amount of

variability in these patterns within healthy individuals and within patients with chronic diseases.[1] After gaining an ability to assess these physiological states, clinicians then need a rigorous understanding of how each nutrient alters biomarker levels, and how an individual's genotypic variant modulates the effect that these nutrients have. With these pieces of knowledge, it may then be possible to prescribe a personalized, optimal diet to an individual based on their genetics to help them achieve a healthy physiological state as characterized by the defined pattern of biomarkers.

Unfortunately, the implementation of this intervention method is hindered by many limitations that face nutrition research, especially given the added level of complexity contributed by genetics. One obstacle hindering the progress in research needed to develop such an intervention is the small effect that nutrient intake has on gene expression patterns and other physiological parameters. While available omics technologies could theoretically assess the expression profile in the body before and after nutrient intake, very sensitive technology is needed to precisely detect these changes.[1] Similarly, omics technologies currently require a rather large sample of tissue to perform analyses that presents an obstacle for data collection. Transcriptomics can more readily be used because the RNA examined can be amplified, reducing the amount of tissue needed. However, there is no technology currently available to amplify metabolites and protein, which limits their use.[4] Finally, researchers do not yet understand what expression patterns distinguish a healthy, pre-disease, and disease state given the variability of profiles within each state, as previously discussed.

Even with highly sensitive equipment, reliably identifying the effect a nutrient has on the body is difficult given the huge variability in individual response and the large number of hard-to-control physiological factors that can modulate this response. Currently, researchers do

not have a good understanding of precisely how SNPs in the genome modulate the change in gene expression in response to a given nutrient, limiting their ability to predict an individual's response. Moreover, this knowledge will be very difficult to develop with current research methods because factors such as age, sex, environment, and health or disease state also affect phenotypic response to a nutrient and are difficult to distinguish. Certain metabolic responses may also be tissue-specific, adding yet another level of complexity given that data is often collected from only one tissue sample.[1] Finally, epigenetics can also play a role in modulating one's response to nutrient intake, and currently it is very difficult to separate whether a change in gene expression is caused by the genome, epigenetic modifications, or possibly an interaction between the two. Finally, researchers have yet to make significant progress on how nutrients might interact with one another to also modulate gene expression patterns, which may also have a significant impact and is important to consider given that a personalized diet intervention involves food consisting of many different nutrients, not single nutrients in isolation. Given this interplay of different, difficult to control factors and parse out causal mechanisms, nutrition research that can help predict individual response to food is progressing at a very slow rate, requiring specific and narrow research questions that further knowledge by very slight increments.[1]

Should the knowledge required to implement a personalized diet program be acquired, the clinical application of this revolutionary intervention may still be complicated by a lack of consumer acceptance and widespread use due to a number of issues. There has been discussion over privacy issues, as personalized technology would require patients to share a large amount of health information which may make some patients wary or uneasy.[12] The involvement of genetics in a food context also can evoke negative sentiments about genetic modification of

foods, which many consumers reject on the basis of seeming unnatural, an apparently important aspect about food consumption given the popular movement in organic food consumption. Similar sentiments could be associated with a genetic-based personalized food plan. Finally and most prominently, consumers often make food purchases based on food preference, cost, and convenience; health often ranks low in the food decision-making process. Even if the technology were available and accepted, this factor may prevent widespread implementation on a public health scale because it can be very difficult to persuade consumers to change their dietary consumption patterns.[12] Perhaps, though, patients who have a particular health issue for which they are prescribed a personalized diet plan may more readily adopt this intervention, and could pave the way for more widespread acceptance.

Overall, the incorporation of genetics into nutrition research is still in its infancy; researchers still have much to learn regarding the relationship of how individual genetic variability affects physiological response to nutrient intake. While omics technology is being developed to acquire such knowledge, its current state is rather limited in the information it can provide. Coupled with the sheer complexity of the nutrient-gene interaction due to the interplay of many complex factors, the application of nutrigenomics technology such as personalized dietary interventions still lies far in the future. However, this technology shows promise as an effective way to optimize health on a personal level; hopefully, in the coming years meaningful progress can be made to advance this field.

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