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Gene–environment interplay: what do our genes say about dietary choices?

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The role of a healthy diet in disease prevention has been a topic of fundamental interest for millennia, and to improve the health and nutrition of its population, the US government has published the Dietary Guidelines for Americans (DGA) since 1980. Based on these guidelines, scientists have subsequently developed a DGA Adherence Index (DGAI) to better quantify the intake of a healthy diet (1). Meanwhile, healthy diets, the epigenetic diet, intermittent fasting, and various diet compositions are being increasingly studied in the context of aging and longevity in human and nonhuman species (2). When one considers how environmental factors affect gene expression, diet is of course a central factor that, through its interplay with the human genome, may modify the inflammation, metabolism, and composition of the body, which ultimately leads to various disease states.

In this issue of the Journal, a study by Lin et al. (3) entitled "Healthy diet is associated with gene expression in blood: the Framingham Heart Study" links gene expression with a quantitative measure of healthy diet (a recent version of the DGAI) in the Framingham Heart Study offspring and third-generation cohorts. In this retrospective study, the authors identified 19 genes whose expression was significantly associated with a healthy diet score. The genes identified played a role in lipolysis, thermogenesis, and glucose tolerance. The most significant gene was ARRDC3, which plays a role in regulating the cell-surface expression of adrenergic receptors and other G protein–coupled receptors. They then formulated a gene score reflective of the diet, which was associated with biological metrics and pathological processes such as an elevated BMI, type 2 diabetes, and metabolic syndrome. To test the validity of this score, they also conducted a prospective analysis, identifying individuals who developed diabetes and/or metabolic syndrome 6 years after the gene expression profiling. They found that the DGAI gene score was associated with incident diabetes, but not with metabolic syndrome. However, it is not clear whether the lack of a significant relationship between the gene score and incident metabolic syndrome was due to changes over time in diets, gene expression, or both. The study affords insight into the genomic-metabolic implications of a healthy diet, suggesting that eating a low-fat, high-fiber diet is associated with the expression of genes related to thermogenesis, lipolysis, and improved glucose tolerance. As such, this study provides an excellent example of the gene–environment interaction (4). In a prospective trial, Campbell and colleagues (5) found that weight loss was associated with changes in adipose tissue gene expression for 2 pathways, independent of the method utilized to achieve the weight loss. Prospective studies are needed to confirm whether dietary modifications over time may lead to changes in gene expression, which usually precede the progression or digression of disease phenotypes such as metabolic syndrome and/or diabetes.

The biological pathways identified in the Lin et al. (3) study also deserve special mention, in that 2 of the top 10 pathways involve infections by the Epstein Barr and measles viruses [Supplemental Table 3 in Lin et al. (3)]. In nonhuman studies, infection with certain strains of viruses has been shown to induce obesity by increasing lipogenesis and the insulin sensitivity of adipocytes, the so-called "infectobesity" (6). Future studies to investigate the relationships between viral and other infections and obesity-related outcomes should be considered, as both are representative of environmental factors, as well as potential therapeutic targets.

It is important to note that this study used a recall-based assessment of diet via a semiquantitative FFQ, and not a direct assessment of the macronutrient composition through metabolic measurements in blood or urine. Any measurement error in asking participants to recall their long-term diet with the FFQ is likely to be random with respect to their outcomes, since it was prospectively assessed prior to disease incidences. Such random errors may attenuate the effect estimates of diet–disease relationships towards the null, and the degree of this attenuation may depend on the magnitude of this variability. These interesting results need to be replicated in another population, with gender- and race-specific analyses, to understand whether the dietary environment affects distinct populations in a unique

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manner in their gene expression and subsequent biological mechanisms.

On a larger scale, diet and nutrition are multifactorial issues, with cultural and socioeconomic undertones. Diet is not just dictated by guidelines and individual choices, but also by availability and accessibility. Therefore, future studies that investigate the relationship of gene expression and a healthy diet in individuals exposed to a similar environmental milieu—for example, in accessibility, inducements, and the socioeconomic construct—are needed to understand the gene–environment interplay at the community level. These results can leverage genetic expression analyses to provide early biological footprints of an unhealthy diet environment, in order to facilitate the investigation of social factors that influence prevalences and outcomes of disease processes, such as food deserts and food swamps, without waiting for years of follow-up for disease processes to occur (7, 8). This methodology will enable the expedited formulation of policies that can facilitate changes to improve health and well-being.

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