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Plant-based foods and the microbiome in the preservation of health and prevention of disease

Stephen JD O'Keefe

Division of Gastroenterology, University of Pittsburgh, Pittsburgh, PA, USA; and African Microbiome Institute, University of Stellenbosch, Stellenbosch, South Africa

Epidemiological surveys backed up by dietary intervention studies and mechanistic investigations in experimental animals have demonstrated that high-fiber, plant-based diets can prevent many diseases common in industrialized societies (1). A common cause hypothesis has been proposed through the effect that these diets have on the composition and metabolic activity of the colonic microbiota. Colonic microbial fermentation of plant residues results in health-promoting and cancer-suppressing metabolites. Fiber is metabolized to SCFAs, which have profound anti-inflammatory, antiproliferative, and antineoplastic properties (1). However, specialized colonic microbes also break down plant cell walls and release "phytochemicals" such as the polyphenols, anthocyanins, phenolics, and flavins, all of which also have anti-inflammatory, antioxidant, and antineoplastic properties (2). These actions amplify those of SCFAs on the colonic epithelium and at distant sites following absorption. Studies have shown that fecal slurries are more potent in suppressing cancer cell growth compared with mixtures of the contained SCFAs alone (3, 4). Meanwhile, recent advances in high-throughput sequencing techniques to identify differences in human and microbial genes, followed by mass spectrometric separation and characterization of their nutritional needs and metabolite products, have delivered massive volumes of "big data." All this information is useless unless it can be integrated by advanced computer modeling, opening up the whole new field of systems biology, in which, for the first time, we are gaining glimpses into how life functions.

The article by Lampe et al. (5) in this edition of the Journal exemplifies these exciting developments, wherein observations of nutrient metabolism are linked with data from the microbiome, the metabolome, the human genome, the exfoliome, the transcriptome, and the inflammasome. In an elegant randomized controlled crossover study among 42 healthy volunteers, the authors tested the effect of a 50-mg phytochemical supplement on the fecal microbiome, the fecal exfoliome (exfoliated host intestinal cells), and the expression of host colonic mucosal genes. The chosen supplement was flaxseed lignan, a cross-linked phenolic polymer, with the active ingredient being 7 secoisolariciresinol diglycoside (SDG). The main dietary sources are seeds, cereals, fruit, berries, nuts, and vegetables. SDG is released from plant residues in the colon and converted stepwise by specialized gut bacteria to the more biologically active enterolignans, enterodiol and enterolactone (ENL) (6). Lignans are phytoestrogens and exhibit both estrogenic and antiestrogenic activities in humans depending on host estradiol balances (7). There is evidence that they reduce the risk of several diseases—including breast, prostate, and colorectal cancer, cardiovascular diseases (CVD), and type 2 diabetes—by their phytoestrogen properties (7–11). There is also evidence that SDG metabolites protect against CVD and the metabolic syndrome by reducing lipid and glucose concentrations, lowering blood pressure, and decreasing oxidative stress and inflammation (12). Flax lignans may also reduce cancer risk by preventing precancerous cellular changes and by reducing angiogenesis and metastasis. In particular, they may reduce the risk of breast cancer and help prevent its advance through their effect on sex hormone activity and growth factor-associated angiogenesis (13). Most of these effects are remarkably similar to those of fiber fermentation products, especially butyrate. It seems unlikely that a single nutrient on its own can have such pleotropic effects, and it has been suggested that ENL, like butyrate, may be a biomarker of a healthy lifestyle (14).

Nutritional supplementation is a deeply controversial field. The belief that if a small amount of a supplement is good, a large amount is better was debased by the experience with vitamin A, glutamine, and antioxidant studies in which unphysiological additions to the diet were shown to worsen outcome (15, 16). The situation is different, however, with fiber supplementation, in which one is replacing something that is lost with commercial processing of foods. All the evidence points to a physiological need for ~50 g fiber per day, which is the amount contained in the traditional African diet and associated with the prevention of westernized diseases (17–20). This is approximately twice the USDA recommended intake of 25 g/d for women and 38 g/d for men, which was based on the quantity needed to prevent CVDs, and 3 times the current intakes in westernized populations. The same argument can be used for lignan supplementation. In Lampe et al.'s (5) study, 50-mg supplements were given, which is 50

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Address correspondence to SJDO (e-mail: sjokeefe@pitt.edu).

Abbreviations used: CVD, cardiovascular disease; ENL, enterolactone; SDG, 7 secoisolariciresinol diglycoside.

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times the current intakes in the United States and Europe (21, 22). Despite these high concentrations, there were only modest effects on the microbiota and host intestinal gene expression, even after making allowance for ENL excreter status. However, important differences might have been missed by the relatively small sample size and low quantities of RNA extracted from the fecal exfoliome. Host mucosal gene expression for anti-inflammatory mediators transforming growth factor-β and IL-10 receptors were shown to be higher in high ENL excreters, whereas exfoliome pro-inflammatory NF-κB and nitric oxide synthase 2 gene expression and genes involved in the peroxisome proliferator-activated receptor-γ network were lower. The microbiome changes were also small, with the relative abundance of only 1 genus, *Alistipes*, remaining significantly associated with ENL after controlling for a false detection rate < 0.1.

The differences in gene expression between host mucosal epithelial cells and host exfoliome detected by Lampe et al. (5) are of greatest interest. In a way, it is a pity they did not mirror each other. If this had been the case, the collection of fecal exfoliome could have been proposed as a noninvasive alternative to endoscopic mucosal biopsy. The current scientific literature is brimming with studies describing differences in the microbiome composition and diversity, leading to descriptions of states of "dysbiosis" and "disease-related signatures" without measuring their impact on colonic mucosal health or disease. However, as the authors note, the exfoliome contains cells not just from the colon but also from the small intestine (e.g., neuroendocrine and Tuft cells). Cells from the stomach and pancreas were absent, presumably because of autodigestion. Thus, measurement of both mucosal and exfoliated epithelial cells opens up the possibility of gaining further simultaneous information on how the intervention or disease is affecting the small intestine, which is even less commonly biopsied than the colon. This approach was used by Chapkin's group (23) in an earlier study of the fecal exfoliome of a mouse model of nonsteroidal anti-inflammatory drug enteropathy. In this study, they compared the fecal exfoliome to colonic and small intestinal mucosa transcriptome and demonstrated that the exfoliome closely resembled that of the transcriptome of the small intestine.

There are still numerous barriers to surmount before we can fuse the results of simultaneous multiomic studies in humans to better understand the interactions between the hundreds of nutritional components that make up our food, the trillions of microbes that reside in our gut, the copious metabolites they produce, and the way they interact to influence body health and disease. However, progress is being made, as exemplified by Lampe et al.'s (5) study, and it is reasonable to predict that this approach will lead us closer to defining the ideal dietary requirements to not only extend our life span but also optimize the quality of life in the years we gain.

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