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EDITORIAL

Gut microbial metabolites in health and disease

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Each of us harbors a complex microbial community in our intestines with which we co-exist throughout our life. While this community can be a source of infection, most of the time its members remain contained by the gut barrier; nevertheless the commensal microbiota plays an important role in health, including mediating many of the effects of diet. Interactions between microbial cells and their components and the gut-associated immune system have been the focus of much research effort. Increasingly, however, research is revealing the critical role played by microbial metabolism in the gut in influencing health outcomes. We know that the collective biochemical abilities of the gut microbiota are many times greater than those of the human host; furthermore, since most microbial metabolites can diffuse readily and be taken up by the gut mucosa, their potential for bioactivity is considerable. The purpose of this Special Issue is to highlight a number of important linkages between products of microbial metabolism and human physiology that have been documented recently.

Much of the energy that drives microbial growth in the large intestine comes from dietary carbohydrates (fiber, resistant starch) that remain undigested in the upper GI tract. The main products of microbial fermentation of these substrates are the short chain fatty acids (SCFA) acetate, propionate and butyrate, whose diverse effects on human health are increasingly recognized. In this issue Morrison & Preston[1] provide a timely overview of recent developments, which include SCFA signaling interactions via free fatty acid receptors and impacts on the immune system. The relationship to obesity and type 2 diabetes is particularly intriguing, but still unresolved. While absorption of microbially-produced SCFA provides the human body with 'extra' energy from dietary components that our own enzymes cannot digest, recent evidence shows that SCFA may also help to promote satiety. SCFA also arise from the fermentation of proteins in the gut, but the chemical diversity of amino acids results in many other products that have their own distinctive biological activities. For example, the aromatic amino acids tryptophan is fermented to yield indole, a compound that acts as a signaling molecule. The work of Whitfield-Cargile et al. reported here,[2] shows that in a mouse model, indole may help to alleviate some of the negative consequences of the non-steroidal anti-inflammatory drug indomethacin.

Microbial activity has a profound influence on the availability and bioactivity of many compounds that we consume in our diets. Plant-based foods are a rich source of polyphenolic molecules that have diverse and complex effects upon mammalian metabolism. Braune & Blaut[3] provide a highly informative review of the role of human colonic bacteria in the metabolism of flavonoids of dietary origin. Most flavonoids exist in the plant as glycosides, are released in the gut by microbial action, and then subject to specific microbially-mediated transformations that produce an even wider variety of molecules. The potential for inter-individual variation in the physiological effects of these plant-derived compounds due to variation in the gut microbiota is therefore considerable.

Gut bacteria also transform compounds that are produced by the body, sometimes with adverse consequences. The important topic of bile salt metabolism is introduced by Ridlon et al.[4] who provide an overview of the complex interplay between synthesis and conjugation by the host, and de-conjugation together with conversion of primary to secondary bile salts by

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gut bacteria. More specifically, in a second article, Ridlon et al.[5] propose mechanisms by which microbial metabolism of taurocholate (whose formation is favored by diets high in animal protein) may promote colorectal cancer, through sulfide formation from taurine and via the tumor-promoting activity of the secondary bile acid deoxycholate.

A fundamental factor underlying the metabolism of anaerobic communities is the fate of hydrogen. Consumption of hydrogen within the community to produce methane, acetate or sulfide has consequences both for the host and for microbial metabolism. Wolf et al.[6] report that hydrogenase genes are present in 70% of human colonic bacteria whose genomes are available from the Human Microbiome Project. Interestingly their metagenome analysis emphasizes the importance of group A3 [FeFe] hydrogenases implicated in flavin-based electron bifurcation reactions, both in Firmicutes and Bacteroidetes.

In conclusion, the combination of gut microbiology with new genomic and metabolomics data, as illustrated by the articles in this Issue, promises to uncover many more important linkages between microbial metabolites and health in the future. This knowledge will provide better understanding of the impacts of diet and inter-individual variation and should reveal new avenues for disease prevention.

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