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Journal of Nutritional Biochemistry Special Issue: nutritional modulation of the gut microbiome in gastrointestinal and metabolic disease

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Introduction

The goal of this *Journal of Nutritional Biochemistry* Microbiome Special Issue is to highlight some of the latest gut microbiota research that establishes connections between dietary-induced changes in the gut microbiota and how microbiota-diet interactions influence health and disease. To date, much research related to dietary-mediated alterations in the gut ecosystem has demonstrated associations between changes in the microbial profile with certain dietary conditions or disease states without clearly establishing a causative link. While identifying the causal role of gut microbes remains challenging, it is important to focus on physiologically relevant implications for the host. Here, we have attempted to bring together work that aims to demonstrate causation between dietary-mediated changes in gut microbiota membership and function, and specifically how these changes contribute to, prevent disturbances to or restore both local and systemic disease processes. While in many cases causation still remains elusive, the studies outlined here employ tools that move the needle, including the use of preclinical models, providing evidence of diet-induced shifts in microbial function and careful study design using human subjects, which together provide a framework for the research community to build upon. In total, we have selected 21 articles in this Special Issue which feature a link between diet, the gut microbiota and disease states including metabolic diseases, jaundice, inflammatory bowel disease and other important host processes including the gut–brain axis, as well as growth and development.

Functional foods and gut microbiota

The microbiome plays an extensive role in maintaining normal host physiology. As reviewed by Mukherjee et al. [1], the microbiome drives immune development and homeostasis and is crucial in protecting against gastrointestinal infectious diseases, including bacterial and viral

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infections, mediated not only by community membership but also by their functions. Gut microbes serve as an extension to the hosts' digestive and metabolic capacity by harboring diverse sets of nonmammalian genes. In doing so, the gut microbiome digests and modifies otherwise indigestible compounds, such as fibers and polyphenols, thereby equipping the host with important functional molecules such as short-chain fatty acids (SCFAs) and aromatic metabolites, respectively. In this issue, several authors present reviews or primary work showing microbiota community changes and interactions with plant or microbe-derived compounds, including β-glucans, aromatic metabolites and polysaccharides. Jayachandran et al. [2] review the microbe-mediated impact of β-glucans, a form of soluble fiber derived from yeast or functional foods, on restoration of glucose homeostasis, immune function and cancer prevention in both preclinical and clinical settings. Using a preclinical mouse model of colitis, Ren et al. [3] reveal that dietary incorporation of polysaccharides derived from the fungus *Hericium erinaceus* prevents colitis-associated gut dysbiosis, resulting in less severe disease. The capacity of dietary supplementation with specific polysaccharide sources can change not only the microbial community membership but also function. Using in vivo and in vitro approaches, Li et al. [4] identified that enriching the murine diet with barley leaf resulted in increased microbial production of SCFAs and aromatic metabolites. In the context of functional foods in humans, Kaczmarek et al. [5] demonstrate that simple short-term addition of cooked broccoli to the human diet can shift the gut microbiota community membership using a controlled, randomized crossover study where healthy subjects serve as their own control. Similarly, Berding et al. [6] demonstrate that, in adolescent humans, both stability of microbial membership and capacity to produce volatile fatty acids are influenced by dietary intake patterns over time as well as diet composition (i.e., refined carbohydrates vs. complex grain sources). Notably, it is critical in human studies that subjects serve as their own control to account for interindividual variation observed in gut microbiota composition as performed in the studies presented herein [5–7].

Three studies in this Special Issue focus on determining the impact of polyphenols derived from cranberries, grapes or blueberries in direct or indirect modulation of the gut microbial community membership. Rodríguez-Morató et al. [7] performed a nicely controlled randomized double-blind crossover dietary intervention in which healthy adults consuming an animal-based diet supplemented with 30 g cranberries for 5 days displayed a decrease in carcinogenic bile acids such as deoxycholic acid and an increase butyric and acetic acid in stool compared to consuming the animal-based diet alone. Associated changes were found in gut microbiota structure such as an increase in Bacteroidetes and decrease in Firmicutes with cranberry supplementation. However, changes in host outcomes including trimethylamine (TMA), trimethylamine-N-oxide (TMAO) and cytokine levels in the blood were not significantly impacted in this study. Using animal models, Zhang et al. [8] and Jiao et al. [9] not only demonstrate changes in community composition with grapes and blueberries, respectively, but also explore the functional significance of these changes to the host, particularly in the context of metabolic diseases, including diabetes and obesity.

The implication of microbial interactions with polyphenols extends beyond production of metabolites. For instance, work by Ho et al. [10] revealed that bioactive phenolic acids from dietary flavanols can impact alpha synuclein folding in the brain, a key component in

diseases such as Parkinson's disease, using a combination of humanized germ-free mice and *Drosophila*. Together, these studies highlight the direct and indirect impact of microbe-derived products or functional foods on shaping the gut microbiota as well as how these changes influence host health both within and beyond the intestine.

Diet, gut microbiota and host metabolism

It is now well established that the gut microbiome influences host metabolism, including development of diseases associated with metabolic syndrome, liver and digestive organ function, and peripheral energy metabolism. Three reviews are included in the Special Issue that outline the current state of knowledge of how gut microbes impact three diseases that make up metabolic syndrome, including obesity, type 2 diabetes (T2D) and nonalcoholic fatty liver disease (NAFLD) which are rapidly becoming urgent public health epidemics in westernized societies. Rong et al. [11] first review how the gut microbiota influences adipose homeostasis and peripheral energy metabolism in the context of obesity and glucose tolerance, while Sharma and Tripathi [12] outline the current understanding of how diet-induced gut microbes impact T2D in both human and preclinical models. Altamirano-Barrera and colleagues review the mechanisms of how gut microbes broadly influence pathology of liver diseases including NAFLD [13].

The prenatal and newborn period is also profoundly influenced by microbial-derived metabolites *in utero* and postnatal microbial colonization of the gut, where microbial signatures may have early and lasting metabolic consequences for the host. Usman et al. [14] performed studies to show that the SCFA sodium acetate could prevent disruptions to glucose metabolism and improve fetal outcomes mediated through maternal hepatic oxidative pathways in a pregnant rat model of excessive late gestational androgen exposure. Sane et al. [15] provide evidence that gut microbes induced by dietary supplementation with human milk influence risk of onset and progression of T2D using the nonobese diabetic mouse model.

While the gut microbiota shares an ecosystem with the host intestine, the liver serves as the first extraintestinal metabolic organ exposed to microbial metabolites and small molecules, which can profoundly impact liver homeostasis. Work by Zhou et al. [16] reveals how early-life microbial communities and dysbiosis may influence serum bilirubin and risk of jaundice. In adult mice, Moreira et al. [17] explore how the diabetes drug liraglutide directly modulates the gut microbiota and alters NAFLD development using both a genetically susceptible and a high-fat-diet-induced obesity model. This important work highlights how commonly prescribed drugs may have important implications for health through both microbial and host xenobiotic metabolism, an area that is woefully underexplored but of fundamental importance. Finally, the impact of caloric restriction on gut microbiota membership and function was explored by Kok et al. [18], in a murine model, underscoring the crucial role for gut microbes for energy extraction from the diet throughout the lifespan. This work showed increased representation of potentially beneficial microbiota within the gut microbial community, which correlates with changes in host gene expression profiles and circulating metabolome of both microbe- and host-derived metabolites.

Gut microbiota and the brain

Beyond the work performed by Ho et al. [10] revealing a role for gut microbes in alpha-synuclein folding, this Special Issue also includes additional intriguing work tying gut microbes to the gut–brain axis. Lombardi et al. [19] provide an overview of how nutritional components interact with the gut microbiota to influence risk of neuroimmune inflammation and disease. Morshedi et al. [20] explored the emerging role for psychobiotic effects in the gut and brain of diabetic animals. This work demonstrates that probiotic vs. prebiotic vs. combinatorial administration of a single bacteria with or without fermentable fiber in a chemically induced T2D rat model results in improved glucose homeostasis, resolution of local antioxidant markers in the amygdala and improved behavioral outcomes. Similarly, Chen et al. [21] showed that combinatory dietary supplementation with the Chinese traditional medicine plant Puerariae Lobatae Radix and herb Chuanxiong Rhizoma could prevent cerebral ischemic stroke-induced remodeling of the gut microbiota, restore gut–brain barriers and improve host outcomes in a murine model. Together, this collection of work reveals that pre/probiotics and diet-induced gut microbiota can influence the central nervous system, providing a potential novel modality to treat systemic diseases, which requires further investigation to identify mechanisms of action.

Conclusion

This diverse collection of work strongly demonstrates that diet remains one of the major environmental factors that drive gut microbiota membership and function. While focus on the microbiome has exploded over the last decade, our understanding of how functional foods shape microbial community function remains limited. In this issue, the authors employed diverse approaches, including *in vitro* tools, metabolomics measurements, preclinical models and human intervention trials; the authors of these featured publications demonstrate that the gut microbiota can directly and indirectly influence host health and disease. In particular, study design is critical to the sound interpretation of how diet-induced changes to gut microbiota membership and function impact these host outcomes. The studies outlined here employ preclinical models, providing evidence of diet-induced shifts in microbiome function and resultant host responses, as well as careful study design using human subjects, which provides a framework for the research community to build upon. We hope that the readership of the *Journal of Nutritional Biochemistry* enjoys this intriguing and thought-provoking collection of work focused on the nutritional modulation of the gut microbiome in health and disease.

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