# Introduction to the Thematic Minireview Series: Host-microbiome metabolic interplay

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**Long before the recent thrust of scientific research on the microbiome, the importance of its interface with the host was being acknowledged by practices such as probiotic supplementation, *e.g.* after a course of antibiotics, which has the unwanted side effect of depleting commensal bacteria. The shared metabolite capital between the host and the microbiome is extensive and tightly controlled. However, despite the influence of microbe-derived metabolites on many aspects of host physiology, behavior, and pathology, our understanding of this metabolic interface is still in its infancy and its therapeutic targeting is largely untapped. In this Thematic Minireview Series, JBC presents six exciting articles discussing a range of approaches for identifying microbial natural products, and elucidating their biosynthetic pathways and their physiological effects, which could potentially be leveraged for developing new therapeutics.**

Wilson, Zha, and Balskus (1) refer to the largely unknown trove of microbiome-derived natural products as "dark matter" and discuss approaches to unravel it. The sheer numbers of microorganisms that colonize humans (in the trillions), and collectively harbor 2 orders of magnitude more genes than the host, hint at the depth of the secondary metabolite trove. Computational mining of metagenomic sequence data is opening the doors to identifying biosynthetic gene clusters and the pathways that they encode. The review discusses alternative strategies that are in use for natural product discovery, each illustrated with success stories and a discussion of challenges. In addition to the better-studied gut microbiome, the nasal and skin microbiomes represent other environments of host-microbe metabolic interplay ripe for natural product mining.

Martinez, Leone, and Chang (2) focus on advances in identifying microbial metabolites linked to gastrointestinal and peripheral diseases. The human gut is estimated to host ~1000 bacterial species that exist within distinct micro-niches. 16S rRNA amplicon sequencing is being used to identify members of commensal microbial communities, while multi-omic techniques are helping to elucidate functional characteristics of their metabolism. The wealth of data being generated by metagenomic, meta-transcriptomic, and metabolomics studies contrasts with the bottlenecks in identifying and ascribing functions to small molecules. These multi-omic approaches are also revealing changes in microbial diversity, decreased abundance of commensals, and changes in metabolites (*e.g.* short-chain fatty acids) in some disease states.

The review by Brown and Hazen (3) discusses the challenges with using high-throughput approaches for cataloging microbially derived transcript and protein levels. They also emphasize the importance of (and challenges with) mapping the microbial metabolome under defined conditions. The metabolome holds the promise of furnishing disease biomarkers and identifying drug targets, as exemplified by the gut microbe-derived metabolite, trimethylamine *N*-oxide (TMAO),[2] which is causally linked to atherosclerosis and thrombotic vascular diseases. Nutrients in animal product-enriched Western diets drive the generation of the gut-derived metabolite, trimethylamine. The latter is acted upon by host flavin monooxygenases to produce TMAO. The promise of targeting bacterial trimethylamine lyase is discussed in this review.

Pellock and Redinbo (4) focus on the metabolic interface where the host appends glucuronic acid to endobiotics and xenobiotics and microbes remove it to retrieve carbon sources. This metabolic cycle involves host UDP-glucuronosyl transferase, which adds glucuronic acid, and microbial $\beta$-glucuronidases that remove it. The glucuronidation cycle can impact drug pharmacokinetics, influence local and systemic levels of endobiotics (*e.g.* bilirubin, thyroxine, and testosterone), and is associated with GI pathologies including colon cancer, Crohn's disease, and colitis. A therapeutically important consequence of this metabolic interplay is exemplified by the GI toxicity of SN-38, the active form of the colorectal and pancreatic cancer treatment prodrug, irinotecan. Liver metabolism leads to SN-38 glucuronide for excretion, which is countered by microbial retrieval of SN-38 in the gut. Rational targeting of microbial glucuronidase reduces dose-limiting GI toxicity of SN-38 and might be an effective strategy for increasing the tolerance and efficacy of other drugs whose metabolisms are influenced by the microbiome.

The review by Olsan, Byndloss, Faber, Rivera-Chávez, Tsolis, and Bäumler (5) highlights yet another dimension of the host-microbiome interface, *i.e.* how some gut microbes curtail colonization by others and how this balance in healthy individuals is disrupted upon antibiotic exposure. For instance, members of

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[2] The abbreviations used are: TMAO, trimethylamine *N*-oxide; GI, gastrointestinal.

the carbapenemase-producing Enterobacteriaceae family can expand during antibiotic therapy, which is a growing problem for nosocomial infections worldwide. Normally, the limited availability of host-derived electron acceptors, as well as the hypoxic conditions at crypt apexes, keeps the population of Enterobacteriaceae, which are facultative anaerobes, in check by Bacteriodia and Clostridia, which are strict anaerobes. However, an antibiotic-induced shift in colonic epithelial energy metabolism from microbiota-derived butyrate to glucose fermentation increases $O_2$ concentration and provides nitrate, a respiratory electron acceptor. These respiration-permissive conditions disrupt colonization resistance and fuel the post-antibiotic expansion of Enterobacteriaceae.

Krautkramer, Rey, and Denu (6) review eukaryotic chromatin regulation by host- and gut microbe-derived metabolites. They focus on methylation and acetylation, the two most common and well-studied posttranslational histone modifications, and on DNA methylation. One-carbon and central carbon metabolites signal host metabolic status to chromatin, affecting both histone and DNA modifications. Layered over this complex regulation governing deposition and removal of histone and DNA modifications is regulation by bioactive metabolites originating in the gut microbiota including butyrate, propionate, acetate, and short-chain fatty acids. The authors raise the intriguing possibility that changes in trans-generational epigenetic inheritance in response to dietary input might be modulated by microbiota-host interactions.

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