Editorial Overview: Insights into Molecular Mechanisms of Microbiota

Symbiotic partnerships between animal or plant hosts and microbes are omnipresent in nature and are essential for many aspects of biology. These relationships vary from relatively "simple", consisting of a host and just one or a few microbial partners, to remarkably complex. Examples of the latter include the rich assemblages of microorganisms that colonize various regions of the human alimentary tract such as the mouth and colon, encompassing hundreds or thousands of co-resident microbial species and strains. In such ecosystems, microbial members engage in a myriad of interactions with each other, including forms of competition, cooperation, and exchange of DNA, as well as interactions with their host. These and other activities impact host biology in ways that are frequently beneficial but, in other cases, that promote disease, either directly or indirectly [1]. Understanding the molecular mechanisms that underlie these processes has been a goal for decades, but while recent technological advances have greatly expanded our descriptive view of these ecosystems, our knowledge of underlying functions and mechanisms has lagged. Technical capabilities and conceptual insights offer promise that these deficiencies can soon be remedied. This topic is the focus of this Special Issue.

Interest in the taxonomic composition and functional potential of plant and animal microbiotas is now rampant! As an example, PubMed searches for two common terms (microbiota and microbiome) that are often used to denote host-associated microbial communities respectively return over 1600 and 2600 articles published in the first half of 2014 alone, in contrast to 754 and 785 articles from all of the year 2009. Much of this fervor has been fueled by technological advances, most notably in DNA sequencing, informatics, and other "-omics" approaches, combined with large-scale projects aimed at characterizing host-associated microbial communities that are important to human health. For example, endeavors such as the Human Microbiome Project sponsored by the National Institutes of Health [2] and the Metagenomics of the Human Intestinal Tract program sponsored by the European Commission [3] have yielded an immense amount of information about the microbial taxa that dwell in and on the human body, their genomic content, and compositional dynamics over time or between subjects. Many smaller projects have similarly probed the microbiotas of other animals, ranging from termites and other insects [4] to domesticated or wild non-human mammals [5,6]. As a result, we have an unprecedented, deep, yet mostly descriptive view of the taxonomic, genetic, and compositional dynamics of many "healthy" or "normal" host-microbial ecosystems. We also have similar views of human microbial ecosystems during many unhealthy or diseased states, such as inflammatory bowel disease [7], colon cancer [8,9], obesity [10,11], bacterial vaginosis [12], atopic dermatitis [13], rheumatoid arthritis [14], and autism spectrum disorder [15], to name just a handful. In virtually all of these latter examples, microbiota causality is still uncertain and mechanistic details remain obscure.

Given our current depth of descriptive insight into the taxonomic and metagenomic content of host-associated microbial communities—and the likelihood that the technologies that have enabled these advances will continue to become increasingly accessible, powerful, and utilized—there exists an urgent need for corresponding functional insight into the mechanisms that govern these systems. Such functional insight may very well represent the rate-limiting step in transforming our current view of complex host-microbial systems into a more precise working knowledge that can be leveraged to preserve or manipulate their effects or design drugs to subvert deleterious outcomes. Indeed, the classical approach to understanding processes such as microbial pathogenesis has relied on harnessing molecular genetics, biochemistry, and other tools, combined frequently with use of relevant models that predict key features of the natural system. This is a time-consuming path demonstrated by the decades required to generate a substantial mechanistic understanding of how even a single organism causes disease. When multiplied by the hundreds or thousands of relevant microorganisms that may inhabit a single host and their complex set of interactions, this becomes a truly daunting task. Therefore, to move forward with such functional and mechanistic studies on a large scale, we need to think in new and different ways about how to apply classical approaches to these systems. Innovative thinking that challenges current paradigms will be needed to expand throughput and enable mechanistic elucidation at the community level. Such endeavors necessitate diverse biological

and *in silico* model systems with complementary strengths. They also require interdisciplinary approaches involving microbiology, informatics and mathematics, biochemistry, genomics, immunology, ecology, and engineering and a bevy of other specific fields that offer tools to better understand these systems, in combination with clinical insight and measurements. Finally, the importance of continuous and creative dialogue between the experts in these fields cannot be overestimated.

The seven review and perspective articles included in this Special Issue address a variety of topics surrounding the needs outlined above. The first article describes recent advances in using tractable insect systems to model symbiotic host-microbe interactions from nutrient exchange to immunity, the principles of which can often be extrapolated to more complex systems (Douglas, pp. 3830-3837). The remaining articles focus on various aspects of the complex microbial ecosystem that exists within the human gut. They deal with topics ranging from the environmental factors (e.g., chemical variations in dietary polysaccharides) that influence the membership and physiology of the gut microbiota (Hamaker and Tuncil, pp. 3838-3850; Martens *et al.*, pp. 3851-3865) to approaches for intentional manipulation and restoration of this ecosystem in the face of perturbations such as antibiotic use (Gibson *et al.*, pp. 3866-3876), which render it susceptible to pathogen invasion. Important and emerging facets of gut microbiota physiology, such as the ability of its members to transform the pharmaceuticals we use (Redinbo *et al.*, pp. 3877-3891) or the impact of under-appreciated forces, such as viruses, to shape this ecosystem, are also considered (Abeles and Pride, pp. 3892-3906). Finally, use of mathematical models to harness the immense amount of sequence-based data from the gut microbiota into a predictive model of ecosystem function is discussed (Bucci and Xavier, pp. 3907-3916).

Collectively, the articles in this Special Issue offer a glimpse into a much larger field that is expanding and evolving very rapidly. The diversity of ideas and approaches presented in the accompanying articles provides a window into an exciting future involving the elucidation of mechanisms underlying microbiota-host associations. The involvement of the microbiota in all facets of human biology, directly or indirectly, combined with microbiota plasticity, suggests important avenues for preventing and treating a wide range of diseases. However, the compositional distinctness of each human's microbiota and its dynamic nature over time together pose a daunting challenge for the emerging paradigm of precision medicine. Mechanism-based insight offers the hope of distilling common functional attributes and interactions that transcend species identity and provides a path forward to help make sense of the exceptional complexity.

Due to the ubiquity of complex microbial communities across our planet, the principles that emerge from the study of host-associated microbiotas will have broad implications for a variety of issues beyond human health, ranging from biofuels to bioremediation to conservation. Given the necessity of broad foundational knowledge at this early stage of inquiry, this field will prosper from diverse approaches and experimental models dedicated to reveal how interactions between molecules explain the behavior of the host-associated microbiotas for which we have obtained such deep, sequence-based information. Scalable experimental systems such as the use of germfree animals—to which increasingly complex communities can be assembled from individually characterized "microbial parts" [16] or *in vitro* assays of microbiota-associated functional activities—offer substantial opportunities that have yet to be pushed close to their limits (e.g., simultaneous colonization with dozens or hundreds of fully sequenced and characterized strains or high-throughput measurements of biochemical transformations by complex mixed culture collections). It remains to be seen if such "bottom up" approaches, which are well suited for building layers of increasing functional understanding, can ultimately connect with and explain the dynamics that are observed in native microbial communities. Given the unexpected complexity that has been revealed by many studies so far, including those summarized in this Issue, the future for this field is bright. As new and fundamental biological principles emerge, we should enjoy both better health and a better appreciation of the interactions that are central to our dependence on the microbes that surround and inhabit us.

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