Molecular conversations

Chemical biologists are uniquely positioned to uncover and precisely manipulate the molecular basis of interactions between microbiomes and their hosts.

Rich microbiomes composed of diverse bacteria, fungi and viruses can be found living in close physical relationships with animal and plant hosts. These microbes constantly interact with each other and with their hosts, through communication that is fundamentally driven by biomolecules, as each side of this partnership produces compounds that shape the other in both cooperation and competition. In this themed issue, we present a collection of Review articles that explore these microbiome–host relations and the effects of their disruption at the molecular level.

Perhaps the most obvious benefit that healthy microbiomes supply for their hosts is the prevention of colonization by exogenous, potentially pathogenic species. Native microbiota, with an established presence in their ecological niche, are able to out-compete invaders for available space and resources. However, microbiota may also play more sophisticated roles in promoting host innate immunity by anticipating incoming invaders associated with the host's feeding through, for example, circadian clock–driven production of antimicrobial peptides.

Although mammals and other animals can exert some degree of control over their microbiome composition through their diet, plants take the ability to shape their microbiomes to another level through the production of numerous bioactive natural products of their own. Weng et al. discuss how plants can produce toxic compounds that ward off pathogens and herbivores, as well as metabolites that specifically attract desired microbiome residents, such as flavonoids that attract beneficial symbiotic fungi, or volatile (*E*)-β-caryophyllene that recruits entomopathogenic nematodes.

In humans, *Escherichia coli* is one of the most well-known residents of the gut microbiota. Although modern science has co-opted *E. coli* as a workhorse laboratory strain for the heterologous production of useful biomolecules, the 'wild-type' strains found in the gut naturally produce their own bioactive metabolites. As described by Gatsios et al., these natural products can have a profound effect on their host and the rest of the gut microbiome, such as microcins' preventing colonization by other bacteria, or colibactin's DNA-alkylating activity, which has been linked to gastric cancer. However, unlike *E. coli*, most members of the human microbiota are unculturable in the laboratory or are present at low levels within the host, which makes their unique metabolites impossible to detect directly and their genomes difficult to assemble. The discovery of new microbiome-linked metabolites will benefit from the development of sophisticated bioinformatics methods such as MetaBGC that are capable of handling highly fragmented meta-genomic data.

The molecules produced by microbiomes affect their host both locally and in remote organ systems. The 'gut–brain axis', in which metabolites found in the human brain originate from gut bacteria, is a particularly striking example of the distal effects of microbiome metabolites. For example, taurine, short-chain fatty acids and γ-aminobutyric acid are just a few of the known gut microbiome–produced compounds that have neurological and behavioral effects in the host, in whom disruption of healthy gut–brain axis signaling can lead to motor defects and other manifestations. Chaudhari et al. explore how these links between the human microbiome and diverse diseases are being established by progressing from correlative relationships between altered microbiome content and disease state, to identifying strain- and molecule-specific causal relationships.

Microbiome composition has also been found to correlate with resistance to age-related diseases including diabetes and infection, as reviewed by Zhou et al. Levels of microbiome-derived short-chain fatty acids, particularly butyrate, tend to decrease with age, whereas their supplementation has a protective effect in colitis, diabetes and other diseases. Long-lived people tend to harbor distinct microbiomes enriched for species that produce unique secondary bile acids such as lithocholic acid derivatives that may offer protective advantages against pathogenic infection. Another class of bacterially derived secondary bile acids, deoxycholic acid derivatives, confer anti-diabetic effects through antagonism of the farnesoid X receptor, as also discussed by Chaudhari et al.

Bile acid biosynthesis provides a good example of the potentially complicated interplay between host and commensal microbes. Primary bile acids are produced in the mammalian liver and then modified by gut bacteria through either conversion into secondary bile acids or hydrolysis by bile salt hydrolases. This type of intertwined pathway in which metabolites are handed back and forth between host and microbiota is also seen in the case of the atherosclerosis-linked metabolite trimethylamine-N-oxide (TMAO). Gut bacteria metabolize choline from high-fat diets into trimethylamine (TMA), which the liver converts into TMAO. In this case, the host diet leads to defects in mitochondrial bioenergetics, which confer a fitness advantage on *E. coli* harboring the CutC enzyme that enables conversion of choline to TMA.

Detailed molecular-level understanding of the effects that microbiomes and their hosts have on each other enables the design and implementation of more-precise medical and environmental interventions. Knowledge of the enzymes involved in the biosynthesis of microbiome-derived molecules can enable drug design, as in the case of bile salt hydrolase inhibitors that alter conjugated bile acid profiles. The careful construction of synthetic microbiome communities provides the opportunity for optimizing the efficacy of fecal microbiota transplantation, such as precisely combining strains designed to increase butyrate levels. Synthetic biology tools and protein engineering can also be used for the development of effective probiotic strains specifically targeted to relevant molecular signals, as in the case of a recently developed yeast strain that intercepts extracellular ATP that would promote inflammatory bowel disease.

The examples of microbiome-based chemical communication described in this issue and in the literature are certainly only a fraction of the inter-species relationships waiting to be discovered in and on the bodies of animal and plant hosts. Chemical biology provides the tools and perspectives for the discovery of new microbiome-linked compounds, elucidation of the molecular basis of their inter-species effects, and then the use of this knowledge to manipulate these interactions effectively for the benefit of humans. ❐

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