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In this issue of *Gut Microbes*

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It is an amazing time to be a microbiologist. We have progressed from the study of microbes in monoculture to the study of microbes in mixed culture to the study of complex microbial communities in natural environments. Colony purification was an extremely powerful reductionist tool, but after decades of genetic analyses, many genes of model microbes still have no defined function. It is clear that many of these genes may be expressed, or may have phenotypes, only in the presence of other organisms. The early discovery of antibiotics was a step in this direction. The parallel discoveries of quorum sensing and biofilms led to the realization that individual cells of a species can cooperate with one another, in a coordinated multi-cellular fashion, to achieve common goals and to provide three dimensional structures to communities.[1-3] These findings were followed by numerous discoveries of chemical signaling between microbial species and even between kingdoms. Often neglected, the metabolic interactions between organisms are essential to microbial community structure and function.[4] Even the totality of these chemical signaling and metabolic interactions are probably just scratching the surface of the complexity with which microbes interact. The state of the "microbial interactions" field today seems similar to the state of "microbial pathogenesis" in the 1980s. At the time it was thought that pathogens, such as *Salmonella*, were simply "tougher" than organisms such as commensal *E. coli*. *Salmonella* could survive in hostile environments such as host immune cells because it was more resistant to digestive enzymes, acid, and oxidative stress than *E. coli*. It was later found that the mechanisms by which *Salmonella* evades host defenses are vastly more sophisticated, with secretion systems injecting more than 40 different proteins into host cells to manipulate cellular physiology in specific and elegant ways that are still far from understood. Although much less is known regarding microbial interactions, it is likely that they will turn out to be highly sophisticated as well. A striking example is the recent discovery that *P. aeruginosa* uses its Type 6 Secretion System (T6SS) to inhibit other bacteria only in response to attacks from other bacteria that also yield a T6SS, or even in response to mating attempts.[5,6]

In this issue of *Gut Microbes*, we focus on "microbial interactions" specifically within the gut. While this field is in its infancy, its importance is staggering. The development of a healthy microbial community is critical to the development of a healthy person. It seems like every day, more and more human diseases including inflammatory bowel disease (IBD), diabetes, obesity, cardiovascular disease, and allergies are suspected of originating with microbiota imbalances or dysbiosis.[7-12] There is even increasing evidence for a link between the gut microbiota and brain function, including autism spectrum disorder (ASD).[13] The microbiota is required for the nutrition of the host, the development of intestinal tissues, and the development of the host immune system.[9,11,14,15] The microbiota is also critically important for protecting the host from pathogens (often called colonization resistance [CR]). For instance, disruption of the mouse intestinal microbiota decreases the LD_{50} for *Salmonella* from 10^6 cfu to less than 10 cfu.[16-20] Partial restoration of resistance to *Salmonella* is achieved by inoculating the disrupted mice with a fecal suspension from untreated mice.[21] Clearly the host's normal microbiota plays a very important role in preventing pathogen colonization. Not surprisingly, gut communities are specifically adapted to the species, even the genotype, of the host.[22,23] For instance, mouse microbial communities are better than human communities at preventing *Salmonella* from inflaming the intestine.[15] A germ-free mouse can be inoculated with conventional mouse feces and become resistant to *Salmonella*-mediated inflammation within days. But germ-free mice inoculated with human feces do not become resistant.[15] Elucidating the mechanisms underlying phenomena such as these might one day lead to the rational design of novel probiotics and antibiotics, provide new insights into pathogen host ranges, and contribute to our understanding of the ecology of diseases and epidemics. This isn't just hype. Antibiotic-induced dysbiosis is the most clinically prevalent dysbiosis in the US healthcare system.[24-28] Broad-spectrum antibiotics can induce long-lasting effects on gut bacterial communities that ultimately result in gastrointestinal pathology.[29,30] Approximately 25% of cases of antibiotic-associated diarrhea are due to *Clostridium difficile*.[26,31] The spectrum of resulting disease can range from a state of asymptomatic carrier to pseudomembranous colitis and death.[27,28] In fact, what one might consider the ultimate probiotic, fecal transplantation, is remarkably successful at curing recurrent *C. difficile* infection.[32] A new industry will spring up if fecal transplantation proves successful in the treatment of obesity or ASD. The FDA held a public workshop in May 2013 to discuss the issues surrounding fecal transplantation, two of which are quality control and patient aversion. Both of these can be solved if combinations of isolated microbial species could be developed into effective probiotics.[33,34] One combination has already shown effectiveness in treating recurrent *C. difficile* infection and comes with the catchy name of "RePOOPulate".[35] This type of treatment will put more focus on researchers to determine the mechanism of action of probiotics and the mechanisms that

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allow these organisms to persist, or not, among disparate gut communities.[36,37]

Continuing on these themes, in this issue Vincent Young's group provides a review on the metabolic environment of the intestine and how disruptions of this environment facilitate infection by *Clostridium difficile*.[38] Bruce McClane's group provides a review on *Clostridium perfringens* and how it detects compounds produced by epithelial cells.[39] Zhongtang Yu's lab provides a comprehensive review on the microbiome of poultry, what factors are known to affect this microbiome and what affects the microbiome has on the host.[40] Jun Zhu's group provides a review on quorum sensing by *Vibrio cholerae* within the intestine,[41] and Dennis Kasper's lab provides a review on the host response to commensals, more specifically, on innate lymphocytes.[42]

Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.

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