Quantifying host-microbiota interactions

Modeling the microbiome increases understanding of its role in drug metabolism

By Maria Zimmermann-Kogadeeva

The human microbiota is a complex microbial community living on and in our bodies. Its impact on a host's health is immense, affecting digestion (1), the immune system (2), behavior (3), metabolic diseases (4), and responses to drugs (5–7). Rapid advances in experimental and computational methods have moved the human microbiome field from identifying associations between microbiota composition and host health to unraveling the underlying molecular mechanisms (8–10). However, exactly how much the microbiota contributes to host health is a very difficult question to answer.

By focusing on mechanistic and quantitative questions about the microbiome's contributions to host metabolism, I leverage my background in applied mathematics and systems biology to develop computational models describing host-microbiota interactions. Good models require good data from controlled experiments—a challenging proposition in complex host-microbiota systems. As a postdoc, I joined Andy Goodman's lab at Yale University and found myself in a perfect position to collect such data.

By combining bacterial genetics with gnotobiotic mouse models, I learned how to modify the microbiome of germ-free, sterile mice. In the Goodman lab, we used these mice to study the contribution of microbiota to host metabolism of a number of pharmaceutical drugs. We found that this was also a good system to quantify host-microbiota interactions in vivo, because the compounds we used can be introduced into the system in a controlled way.

We first focused on brivudine, an antiviral compound that can be converted into a potentially toxic metabolite, bromovinyluracil (BVU), by either a host or its microbiome (11). To identify bacteria capable of converting brivudine to BVU, we incubated individual bacterial species with the drug in vitro. One of the most potent brivudine metabolizers was Bacteroides thetaiotaomicron, a common gut bacterium with a genetic deletion library readily available. By incubating this library with the drug, we identified one bacterial mutant that had lost the capacity to convert brivudine to BVU. We then colonized germ-free mice with either the wild-type or mutant B. thetaiotaomicron, which provided us with a controllable host-microbiome system and two mouse groups that were identical, save for a single bacterial gene.

When we administered brivudine to these two groups, the observed outcome was somewhat puzzling. Although drug levels in the intestine were much higher in mice colonized with the mutant bacterium, serum levels were comparable between the two mouse groups. The metabolite levels showed the opposite pattern: no difference (and very low levels) in the intestine but much higher metabolite levels in the sera of mice colonized with the wild-type bacterium (see the figure). These data could potentially be explained by bacterial conversion of the drug in the intestine and the rapid metabolite absorption into the serum.

To test this explanation, we started with a simple kinetic model with two equations describing host drug metabolism in the liver and bacterial drug metabolism in the intestine. Once solved, this equation system showed that the difference between the amounts of metabolite absorbed into the sera of each of the two mouse groups was determined by the amount of BVU produced by microbes in the gut. This controlled experimental setup allowed us to quantify that the bacterial contribution to the toxic drug metabolite in vivo was about 70% (12) (see the figure).

We expanded the model to describe drug metabolism processes in eight different tissues and in enterohepatic circulation (when the drug metabolized in the liver is secreted back into the small intestine via bile). We then demonstrated that our approach can be generalized to estimate the bacterial community's contribution to drug metabolism.
Experimental and computational approaches that quantify host and microbial contributions to drug metabolism

Oral drugs are administered to gnotobiotic mice that differ in a single microbial drug-metabolizing enzyme (GN\textsuperscript{MUT}, mutant; GN\textsuperscript{WT}, wild type); drug and drug metabolite kinetics are then quantified across tissues. A microbiome-host pharmacokinetic model developed from these measurements accurately predicts serum metabolite exposure and untangles host and microbiome contributions to drug metabolism.

Contribution to drug metabolism even if the metabolizing species remain unknown by using data from germ-free mice and mice harboring a complex microbial community. We also showed that microbial contribution to the drug metabolite far exceeds the host for sorivudine, an antiviral drug with different host and microbiome metabolism rates, and for clonazepam, an anxiolytic and anticonvulsant drug converted to multiple metabolites (12).

Quantifying the metabolic host-microbiome interaction allows us to study, explain, and predict the system’s behavior in different conditions. By analyzing how drug and metabolite profiles change when model parameters are varied, we found that the similarity of drug serum profiles between germ-free and colonized mice can be explained by the fast and microbiota-independent drug absorption from the small intestine. Our model further suggests that even for rapidly absorbed drugs, microbiome contributions to a host’s metabolism can be substantial under certain conditions (e.g., a high microbiome to host ratio of drug metabolism or extensive enterohepatic circulation of the drug and its metabolites) (13). Such computational models enable us to investigate host-microbiota interactions in silico, guide experimental design, and help reduce the number of experiments needed to confirm model predictions.

To systematically investigate microbial capacity to metabolize drugs, we next conducted a high-throughput in vitro screen. We found that microbiota contribution to drug metabolism might even be more widespread than we anticipated—two-thirds (176 out of 271) of the human-targeted drugs we examined were metabolized by at least one of the 76 tested bacteria (14).

Although follow-up studies are required to test these microbiota-drug interactions in vivo, our findings emphasize that the microbiota should be considered when developing new drugs, stratifying patients, and choosing the most efficient treatment strategies. In the future, I believe that computational models combined with quantitative experimental data will allow us to measure host-microbiome interactions beyond drug metabolism and to better understand, predict, and control the effect of the microbiome on our health in everyday life.

REFERENCES AND NOTES
Quantifying host-microbiota interactions
Maria Zimmermann-Kogadeeva

Science 373 (6551), 173.
DOI: 10.1126/science.abi9357

ARTICLE TOOLS  http://science.sciencemag.org/content/373/6551/173.2

REFERENCES  This article cites 14 articles, 3 of which you can access for free
http://science.sciencemag.org/content/373/6551/173.2#BIBL

permissions  http://www.sciencemag.org/help/reprints-and-permissions

Use of this article is subject to the Terms of Service