Bacteria on Drugs: is your microbiome metabolizing your medications?

preview for “Zimmermann et al. (2019) Mapping human microbiome drug metabolism by gut bacteria and their genes. Nature” and “Chankhamjon et al. (2019). Systematic mapping of drug metabolism by the human gut microbiome. bioRxiv.”

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Introduction

Humans vary in their responses to medical treatment, but the sources of this variation are only beginning to be elucidated. Genetic tests are now routinely used to customize the dosage of thiopurine chemotherapy in leukemia, and to determine whether HIV patients should be treated with the antiretroviral abclavavir[1]. Beyond human genetic factors, the microbiome also contributes to treatment outcomes by modulating immune responses, affecting the activity of human metabolic enzymes, and directly modifying xenobiotics[2]. This raises the possibility that pre-, pro-, and anti-biotics can be used to manipulate the microbiome and thereby improve responses to pharmaceutical therapies.

The human microbiome encodes 150-fold more genes than the human genome, making it difficult to study and predict which drugs are modified by microbial metabolism. So far, most studies have tackled this challenge one drug at a time. For instance, the chemotherapeutic irinotecan is modified by bacterial glucuronidases to generate a toxic product, and irinotecan side-effects can be alleviated by treatment with a glucuronidase inhibitor[3]. Two recent studies from the Goodman (Yale University School of Medicine) and Donia (Princeton University) labs greatly expanded our knowledge of drug-bacteria interactions by using high-throughput methodologies to discover hundreds of microbiome-mediated pharmacological transformations[4,5].

Results

Zimmerman et al. systematically analyzed the interaction between human gut bacteria and drugs, and they identify the metabolized version of the drugs and the bacterial genes responsible. Zimmerman and colleagues first conducted an in-vitro analysis where they examined pairwise interactions of 271 chemically diverse drugs with 76 bacterial species that represent major phyla in human microbiota by LC-MS. The authors used targeted metabolomics to monitor drug levels and then used untargeted metabolomics to find microbially synthesized metabolites. The targeted metabolomics found that levels of 176 drugs had decreased by at least 20% over the course of a 12-hour incubation with at least one of the tested bacterial strains. Untargeted metabolomics revealed over 600 new metabolites created by bacteria, many through previously known mechanisms like deacetylation and hydrogeneration. Not all drugs with metabolizable chemical structure underwent a microbial transformation, however, suggesting structural specificity.

The authors t then identified bacterial genes responsible for drug metabolization, focusing on the *Bacteroides thetaiotaomicron*. They tested a gain-of-function(g-o-f) library, consisting of 2-8 kb fragments of *B. thetaiotaomicron* genome expressed in *E. coli*, against the 46 drugs it metabolizes. This

allowed them to characterize a gene-drug-metabolite network, in which some genes catalyze very specific transformations, while others act promiscuously on multiple drugs. For instance, the product of gene bt4096 can metabolize 18 drugs into 41 metabolites. The authors further expanded their g-o-f approach, identifying 13 additional drug metabolism genes from the *Bacteroides dorei* and *Collinsella aerofaciens* genomes. Taken together, Zimmerman and colleagues found a way to study the effect of microbial gene products on drugs.

Since Zimmerman *et al.* performed their experiments using bacterial monocultures, it was unclear which of these chemical transformations would occur at appreciable levels in the species-rich environment of the human gut. This concern was partially addressed by a parallel study by Chankhamjon et al., which examined drug metabolism by a complex community of gut bacteria isolated from a healthy human donor. These authors first optimized conditions to culture the microbiota *ex vivo* while maintaining maximum species diversity, and then incubated this polymicrobial culture with a panel of 575 drugs. Of the 438 drugs compatible with their analysis pipeline, 13% were subject to bacterial metabolism, showing that the human microbiome can contribute to the pharmacokinetics of many more drugs than was previously appreciated. Some drugs are even sequentially metabolized by multiple members of the microbiota. Chankhamjon et al. also found that bacterial metabolism of structurally related drugs can cause very different physiological consequences. For instance, bacterial metabolism of doxifluridine forms a cytotoxic product, while bacterial metabolism of trifluridine results in drug inactivation. Together, these two studies show that bacteria within the human microbiome can catalyze a wide variety of pharmacological transformations, and the methods developed by these groups will facilitate further in-depth analysis of the bacterial contribution to pharmacokinetics.

Perspectives

Through these two studies, the Donia and Goodman labs identified a wide variety of pharmacological agents that can be metabolized by the human microbiome. For several of these drugs, they also identified the bacterial gene(s) responsible for the transformation, and the resulting metabolic product(s). Future studies may reveal how differences in microbiota composition affect drug metabolism, and whether this explains differences in clinical outcomes. These findings also raise the possibility of improving patient responses to treatment by manipulating their microbiome. Furthermore, these studies provide a blueprint for examining microbially mediated drug metabolism that can be used during the development and characterization of new drugs.

The authors found that steroids, as well as drugs containing ester, lactone, amide, nitro, and azo functional groups are particularly susceptible to bacterial metabolism. Further study is required to identify the exact chemical structures of the resulting metabolites, and whether any of these metabolites retain therapeutic efficacy or exhibit toxicity. It will also be interesting to examine whether chronic treatment with these pharmaceuticals affects the extent to which they are microbially metabolized, either through changes to the activity of specific metabolic enzymes, or changes to the composition of the microbial community. Overall, these two studies represent a significant step forward in our understanding of how bacterial metabolism affects pharmaceutical treatment.

References

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