January 30, 2020

Microbiology

Gut microbes transform the food and the drugs we ingest

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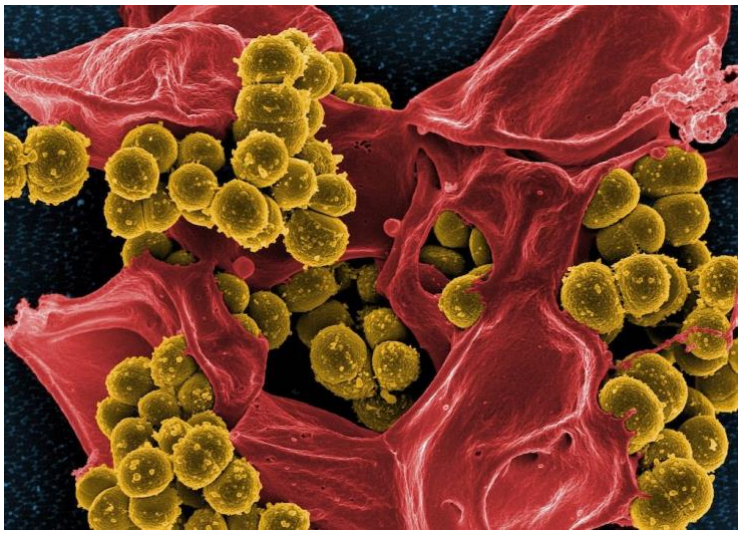
This Break was edited by Giacomo Rossetti, *Scientific Editor* - TheScienceBreaker

ABSTRACT

We developed and tested a tool that can help researchers understand the role of gut microbesin the production of small molecules that play both helpful and harmful roles in shaping human biology.



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Microbes in the human gut play essential roles in maintaing human health. Gut microbes carry out many of these roles using a large toolkit of enzymes that can metabolize and transform larger, complex compounds into smaller compounds. Microbial enzymes breakdown many compounds from the human diet - that human enzymes are unable to process - into products that provide energy, train our immune system or are essential vitamins. Some microbial enzymes can also cause harm if they alter foods or drugs in a way that makes them toxic or prevents them from carrying out a beneficial function. We have limited information about which microbial enzymes interact with which foods and drugs, or how these interactions affect human health.

One way to study the interactions between microbial enzymes and compounds derived from foods and drugs is to focus on the structure or shape of such compounds. The structure of a compound provides insight into what it does and what types of enzyme can transform it . Compounds with structural similarity are selected as candidates to validate with further experiments. Of the thousands of compounds present in the human gut many of these compounds have unknown functions. Hence we asked the following questions: what is the diversity of stuctures of known food and drug products that are present in human gut? How many of these compounds are linked to enzymes? And, is structure similarity a good way to predict the function of a compound? We hypothesized that compound structure overlap is a significant predictor of the

function of gut compounds that are procecessed by specific microbial enzymes.

Our approach to address this hypothesis involved the construction of a microbe-food-drug interaction network based on: 1)the structure of food and drug compounds; 2)microbial enzymes that transform the compounds and 3) the toxicity of drug compounds. The results is that in such a network, the compounds are linked based on a measure of stuructural similarity and toxicity similarity. We observed that compounds with unknown functions are very similar to compounds with known functions in the network. This higlights opportunities for us to make predictions about the function and metabolism of these unknown compounds.

Next, we filtered the network for compounds that shared high structural and toxicity overlap. Among the compounds that met this criteria there were an ovarian cancer drug called altretamine and an environmental contaminant called melamine. Both compounds are known to cause damage to the kideney and diarrhea. Melamine was previously found to be converted by microbial enzymes into a compound that is harmful; but, the gut microbiota is not known to play a role in the metabolism of altretamine or its toxicity.

It is hypothesized that altretamine toxicity is caused by its conversion into toxic metabolites. And we thought that the gut microbiota metabolizes altretamine and may therefore play a role in its toxicity. Human stool contrains a diverse community of bacteria that can serve as an imperfect proxy of the microbial community living in the human gut. We incubated human stool samples with altreatamine and quantified the levels altretamine and metabolites formed over time. We found that a key predicted metabolite formed in the fecal samples.

We used this tool to identify a previously unknown role of gut microbiota in the metabolism and potentially the toxicity of a cancer drug. Beyond drug metabolism, there are many important aspects of human biology that will benefit from a greater understanding of how the gut microbiota processes compounds such as drugs taken for medical use.

There are opportunities to improve our approach by including additional relationships between compounds beyond structural similarity. Our approach is also limited to microbial enzymes present in a publically available database called KEGG. As we learn more about microbial enzymes, we can update and improve the network. This network is a powerful tool to guide mechanistic investigations into diet-drug-microbiota interactions.