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**Finding harmful compounds in the human gut using a map of microbe-food-drug interactions**

*Abstract: ---*  We developed and tested a tool that can help researchers understand the role of microbial metabolism in the production of small molecules that play both helpful harmful roles in shaping human biology.

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 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 foods and drug derived compounds. The structure of a compound provides insight into what it does and what types of enzyme can metabolize it. For example, a key first step in identifying a new cancer drug may involve comparing the structural overlap between a known cancer drug and a large library of compounds. Compounds with structural similarity passing a cutoff are selected as candidates to validate with experiments. This process can significantly reduce the number of experiments done and help rank candidates. Of the thousands of compounds present in the human gut that vary structurally, many of these compounds have unknown functions. 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 overlap in structure a good way to systematically predict the metabolism of compounds by microbial enzymes or predict the function of a compound? We hypothesized that compound structure overlap is a significant predictor of functional overlap or shared processing by microbial enzymes.

Our approach to address this hypothesis involved the construction of a microbe-food-drug interaction network. We mined information on the structure of food and drug compounds, microbial enzymes that metabolize compounds and the toxicity of drug compounds. In the network compounds are linked based on a measure of stuructural similarity and toxicity similarity. Our measure of toxicity overlap between compounds primarily considers how many side effects two compounds share. Compounds were annotated with information about their medical uses. Enzymes were annotated with information on how many different microbial species carry them. We observed that compounds in the network with unknown functions cluster based on structural similarity, with compounds with known functions. This higlights opportunities for us to make predictions about the function and metabolism of these unknowns.

Next, we filtered the network for compounds that shared high structural and toxicity overlap. Among the compounds that met this criteria 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. We hypothesized 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 using mass spectrometry. We included controls to determine whether the conversion was due enzyme activity. 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.

There are opportunities to improve our approach by including additional relationships between compounds beyond structural similarity. Our approach is also limited to 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.