Can gut microbes impact chemotherapy? So far, the answer is 'yes'

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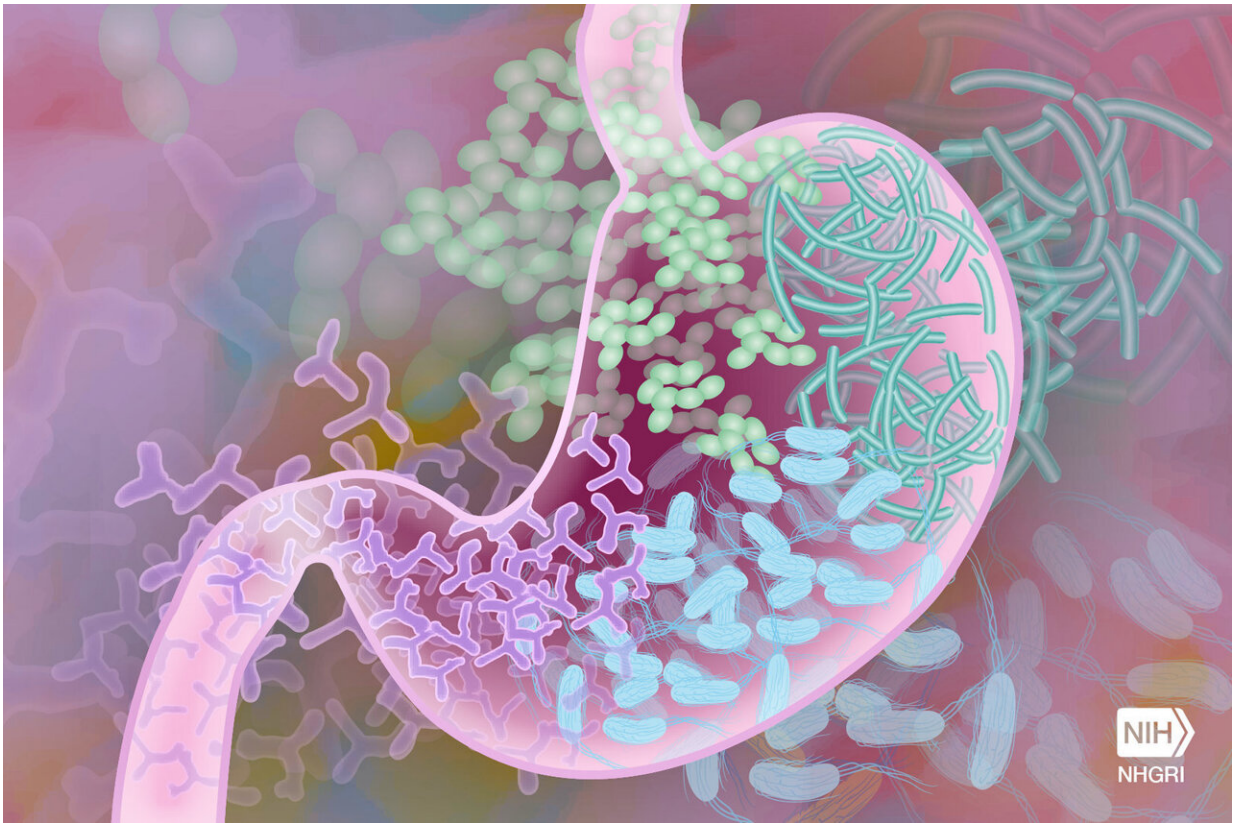

Illustration of bacteria in the human gut. Credit: Darryl Leja, National Human Genome Research Institute, National Institutes of Health

Bacteria in our guts play a significant role in how we digest what we eat, and what we eat includes oral medications we take. But the gut

microbiome's impact on drugs may be different from its impact on food because drugs are often intended to target a specific tissue or organ or process in the body.

Peter Turnbaugh, Ph.D., a professor of microbiology and immunology at UC San Francisco, began studying the impact by looking at how the microbiome impacts the cardiac drug digoxin. Now, his research group has applied this line of inquiry to better understand cancer chemotherapy .

"We wanted to know if the microbiome matters in the metabolism of anti-cancer drugs that are critical for treating colon cancer and other types of cancers," said Turnbaugh. "So far, it looks like the answer is yes."

How does the gut microbiome impact cancer treatment?

The concept of the bacteria in our gut interacting with medications dates back at least 50 years. Researchers have known that sometimes bacteria can metabolize drugs in ways that alter their effects on the body. In terms of cancer, seminal studies from Matthew Redinbo at the University of North Carolina have shown that gut bacteria can re-activate the chemotherapy drug irinotecan after it's been inactivated by the host, leading to side effects that limit the dose that can be administered to patients.

However, the broader role of the microbiome in other types of cancer chemotherapy remains unclear, in part due to methodological limitations. Over the past decade or so, advances in DNA sequencing, coupled with approaches to manipulating the microbiome in test tubes and in animal models, have helped set the stage to better understand

exactly how the microbiome exerts an impact on drug activity.

What's an example that you've seen in your studies?

My lab recently published a study looking at how the microbiome effects metabolism of chemotherapy drugs called fluoropyrimidines (FPDs), which are frequently used to treat colon cancer. This work was led by a former postdoc Peter Spanogiannopoulos and a talented MD/Ph.D. student, Than Kyaw, with help from collaborators in the UCSF Helen Diller Family Comprehensive Cancer Center, among others. We suspected that bacteria living in the gut can intercept and inactivate some of the drug before it's able to get to the tumor.

We knew going in that these FPD drugs are metabolized in the liver by a specific enzyme. We discovered that multiple types of bacteria in the gut, including E. coli and other common gut bacterial species, produce very similar enzymes, and those bacterial enzymes were breaking down the drug, turning a substance that would be actively killing cancer cells into an inactive metabolite.

On the flip side, we also found that the oral version of the drug, which needs to be metabolized before it becomes active, can also be activated by that very same strain of E. coli. So, here you have the same bacterial strain that can contribute to both activation and inactivation of this drug.

Wow, there's a lot of complexity here. How many different bacteria and genes are in most people's guts?

One of the things that's fun—and daunting—about the microbiome is that each of us has a very different microbiome. We may all have E. coli in our gut, but we might have different strains of it. And those

differences between strains for some bacteria can result in really big differences in the genes that are found in their genome. So, just knowing the name of the bacteria doesn't always tell you what it can do.

The genetic diversity in the human gut microbiome is orders of magnitude greater than what we see in the human genome. To give you a sense of the numbers, think about this: The average bacterial strain has between 3,000 and 5,000 genes. In contrast, the whole human genome is between 20,000 and 30,000 genes. So, you only need about 10 species of bacteria to have more genes than the human genome. And most people have hundreds of different species living in their digestive tract. So, the numbers get pretty big.

Do you imagine that in the future a cancer patient will have their microbiome sequenced before they have cancer treatment?

The idea of sequencing the genome of the cancer cells themselves has been incredibly successful. Now, doctors can look at the DNA of the primary tumor, figure out what the mutations are, and tailor their treatment plan to genetic insights about the tumor.

The reason this works is that we've got all this prior literature from people studying how mammalian cells divide and how the cell cycle works. On the microbiome side, we're much more limited right now due to our lack of genetic insights into most human-associated bacteria. We can readily sequence the microbiome, but the challenge we face now is figuring out the right genetic markers to be looking at. We have a signal-to-noise issue where there are millions of different genes that you can measure, and now we need to identify, in an unbiased and systematic way, which ones are telling us something informative and are the ones we want to track.

Right now, we're still in the phase of figuring out how and why the microbiome matters for drugs across multiple disease areas, including cancer. My hope is that research like our recent study will motivate others to help untangle how all this works, and, eventually, take on the complicated studies in humans that get us to the ultimate question, which is: How can you use the microbiome to improve precision medicine?

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