

Gut microbiome may make chemo drug toxic to patients

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Libusha Kelly, Ph.D. Credit: Albert Einstein College of Medicine

Albert Einstein College of Medicine researchers report that the composition of people's gut bacteria may explain why some of them suffer life-threatening reactions after taking a key drug for treating

metastatic colorectal cancer. The findings, described online today in *npj Biofilms and Microbiomes*, a Nature research journal, could help predict which patients will suffer side effects and prevent complications in susceptible patients.

"We've known for some time that people's genetic makeup can affect how they respond to a medication," says study leader Libusha Kelly, Ph.D., assistant professor of systems & computational biology and of microbiology & immunology at Einstein. "Now, it's becoming clear that variations in one's gut microbiome—the population of bacteria and other microbes that live in the digestive tract—can also influence the effects of treatment."

Irinotecan is one of three first-line chemotherapy drugs used to treat colorectal cancer that has spread, or metastasized, to other parts of the body. However, up to 40 percent of [patients](#) who receive irinotecan experience severe diarrhea that requires hospitalization and can lead to death. "As you can imagine, such patients are already quite ill, so giving them a treatment that causes intestinal problems can be very dangerous," says Dr. Kelly. "At the same time, irinotecan is an important weapon against this type of cancer."

Irinotecan is administered intravenously in an [inactive form](#). Liver enzymes metabolize the drug into its active, toxic form that kills cancer cells. Later, other liver enzymes convert the drug back into its inactive form, which enters the intestine via bile for elimination. But some people harbor digestive-tract bacteria that use part of inactivated irinotecan as a food source by digesting the drug with enzymes called beta-glucuronidases. Unfortunately, this enzyme action metabolizes and reactivates irinotecan into its toxic form, which causes serious side effects by damaging the intestinal lining.

To minimize irinotecan-related toxicity, doctors have tried using oral

antibiotics to kill bacteria that make the enzymes. But antibiotics kill protective gut microbes as well, including those that counteract disease-causing bacteria. A 2010 study in *Science* involving mice found that drugs that selectively target *E. coli* beta-glucuronidases can reduce irinotecan's toxicity.

In the current study, Dr. Kelly and her colleagues investigated whether the composition of a person's microbiome influenced whether irinotecan would be reactivated or not. The researchers collected [fecal samples](#) from 20 healthy individuals and treated the samples with inactivated irinotecan. Then using metabolomics (the study of the unique chemical fingerprints that cellular processes leave behind), the researchers grouped the fecal samples according to whether they could metabolize, or reactivate, the drug. Four of the 20 individuals were found to be "high metabolizers" and the remaining 16 were "low metabolizers."

Fecal samples in the two groups were then analyzed for differences in the composition of their microbiomes, with a focus on the presence of beta-glucuronidases. The researchers found that the microbiomes of high metabolizers contained significantly higher levels of three previously unreported types of beta-glucuronidases compared to low metabolizers.

"We hypothesize that people who are high metabolizers would be at increased risk for side effects if given irinotecan, but that will require examining the microbiomes of cancer patients—something we are now doing," says Dr. Kelly.

The findings suggest that analyzing the composition of patients' microbiomes before giving irinotecan might predict whether patients will suffer side effects from the drug. In addition, as suggested by the 2010 mouse study, it might be possible to prevent adverse reactions by using drugs that inhibit specific beta-glucuronidases.

"Another intriguing idea is to give patients prebiotics," says Dr. Kelly. "Beta-glucuronidases have an appetite for the carbohydrates found in the inactive form of irinotecan. If we feed patients another source of carbohydrates when we administer [irinotecan](#), perhaps we could prevent those enzymes from metabolizing the drug."

Beta-glucuronidases in the gut might also interact with commonly used drugs including ibuprofen and other [nonsteroidal anti-inflammatory drugs](#), morphine, and tamoxifen. "In these cases, the issue for patients may not be diarrhea," says Dr. Kelly. "Instead, if [gut bacteria](#) reactivate those drugs, then patients might be exposed to higher-than-intended doses. Our study provides a broad framework for understanding such [drug-microbiome](#) interactions."

More information: "Human microbiome signatures of differential colorectal cancer drug metabolism" *npj Biofilms and Microbiomes*, 2017.

Provided by Albert Einstein College of Medicine

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