How important is the gut microbiome? It may depend on your genetics

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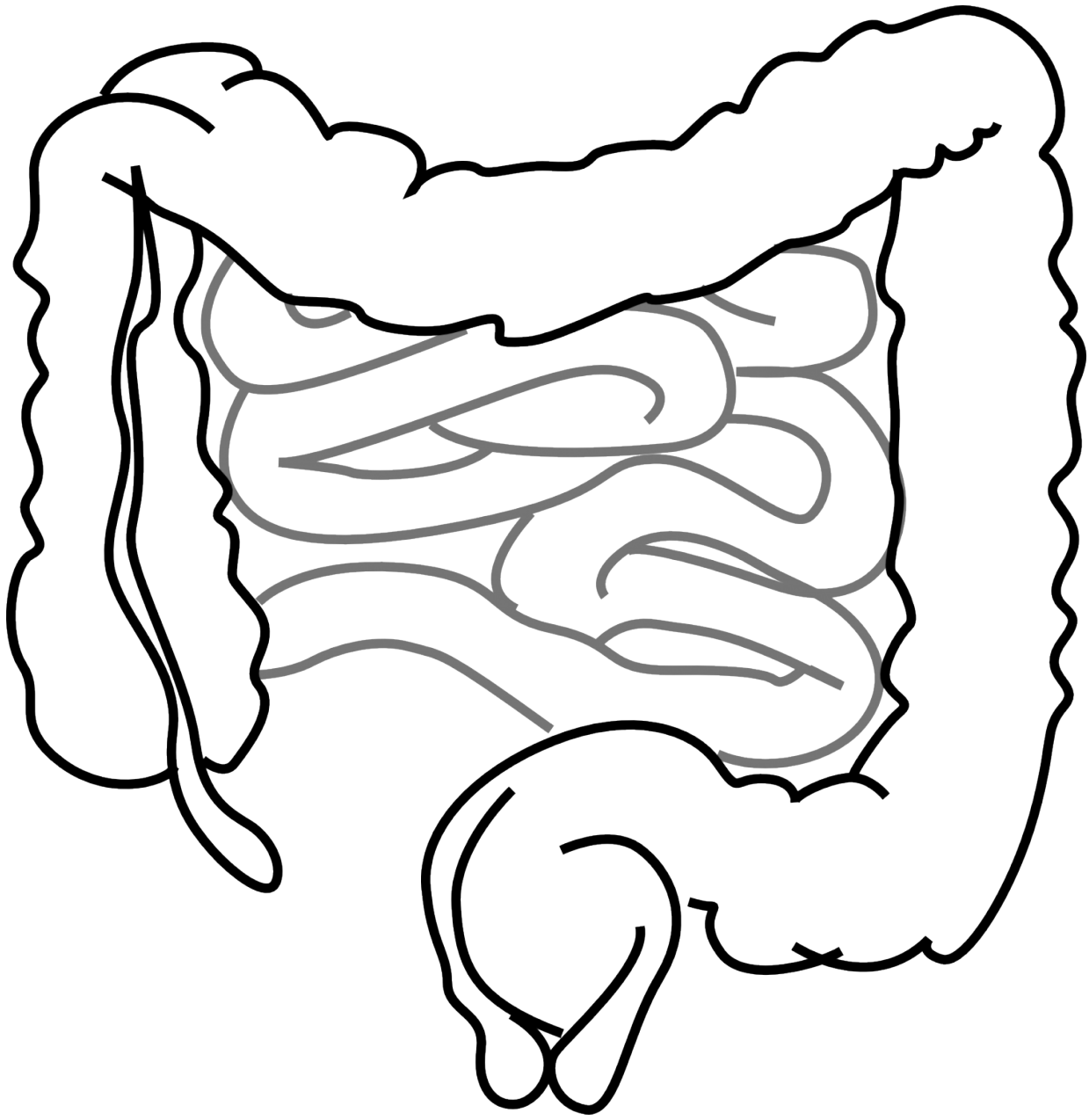

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Our gut microbiomes—the bacteria that live in our digestive tract—play major roles in our health. Scientists around the world are studying therapies that manipulate the microbiome, including probiotics (such as live bacterial cultures in yogurt), prebiotics (edible fibers meant to promote beneficial bacteria), antibiotics and transplants of microbes from healthy people.

Joslin Diabetes Center investigators now are shedding light on how the success of such microbiome treatments may be affected by genetics of the individual or animal being treated.

In work published online today by the *Journal of Clinical Investigation*, a team of Joslin researchers reported on experiments among three genetically different strains of mice (two closely related and one more distant). They discovered that giving the mice antibiotics produced very different effects on their gut microbiomes, as well as on their insulin sensitivity, tissue inflammation and related metabolic functions such as blood glucose, depending on the genetic background of the mouse.

"The potential implication of our research is that genetic background will make a big difference in response to changing the gut microbiome, not just in mice, but also in humans where such treatments are being used for gastrointestinal and metabolic diseases," says C. Ronald Kahn, Joslin's chief academic officer and professor of medicine at Harvard Medical School.

"Our research suggests that some people are more genetically susceptible to the impact of the microbiome than others, and treatments that change

the microbiome will make a big difference in some but not in others," says Kahn, who is senior author on the paper. "So understanding these genetic factors could play an important role in predicting the future usefulness of microbiome therapies for obesity and metabolic disease."

Among the three strains of mice that were studied, one strain is prone to diabetes and obesity, a second is prone to obesity but not diabetes, and a third is not prone to either condition. The mice were placed on high-fat diets, which raise the chances of developing the two conditions. Next, they were given one of two types of antibiotics commonly used in medicine, one that is absorbed into the bloodstream and one that is not, each of which had a different effect on the microbiome.

The researchers discovered that in the mice prone both to obesity and diabetes, treatment with either antibiotic not only changed the gut microbiomes but improved metabolism for the mice—lowering blood glucose, reducing tissue inflammation and increasing insulin signaling. But in the other two types of mice, changes in the microbiome did not bring these positive changes in metabolism.

Many of the metabolic changes in the mice prone both to obesity and diabetes could be duplicated by transferring gut microbes from mice treated with antibiotics to mice lacking normal gut microbes. That finding supports the hypothesis that the antibiotic effects on the microbiome, rather than other biological mechanisms, drive the metabolic changes, Kahn says.

Starting to probe the variations in metabolism between mice, the researchers found that one big factor was how the mice responded to changes in bile acid metabolism. Bile acids are molecules secreted by the liver into the gut, where they aid in the absorption of fats, Kahn explains. Additionally, bacteria in the gut chemically modify bile acids into forms that are reabsorbed into the bloodstream and help to respond to

inflammation.

The impact of antibiotics on bile acid metabolism varied across the three strains of mice, which partly explains why the different strains displayed different responses in tissue inflammation, insulin signaling and other metabolic functions. "So we showed, using these animal models, a link between the changing microbiome and changing inflammation, which contributes to insulin resistance," Kahn says.

The Joslin researchers are following up with more detailed study of how bile acids and other metabolites (small molecules) are involved in control of metabolism.

"Bile acids are just the tip of the iceberg," Kahn says. "In on-going research, we've identified hundreds of human metabolites that change a lot in response to both diet and antibiotics. We're trying to track down exactly what these metabolites are, how they might influence insulin sensitivity, and which will be important regulators of blood glucose or weight gain, the two factors we really want to improve in patients at risk for type 2 diabetes."

The team also will look at how these modified metabolites might affect clinical behaviors ranging from eating behaviors to depression and anxiety, he says.

When these mechanisms are better understood, researchers will be better able to predict which patients will respond best to microbiome treatments, Kahn says. "If we can identify those people who are most likely to benefit from changing the microbiome, we might find a big effect among them," he suggests.

More information: Shiho Fujisaka et al. Antibiotic effects on gut microbiota and metabolism are host dependent, *Journal of Clinical*

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