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# Intestinal bacteria drive obesity and metabolic disease in immune-altered mice

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Increased appetite and insulin resistance can be transferred from one mouse to another via intestinal bacteria, according to research being published online this week by *Science* magazine.

The finding strengthens the case that intestinal bacteria can contribute to human obesity and metabolic disease, since previous research has shown that intestinal bacterial populations differ between obese and lean humans.

"It has been assumed that the obesity epidemic in the developed world is driven by an increasingly sedentary lifestyle and the abundance of low-cost high-calorie foods," says senior author Andrew Gewirtz, PhD, associate professor of pathology and laboratory medicine at Emory University School of Medicine. "However, our results suggest that excess caloric consumption is not only a result of undisciplined eating but that intestinal bacteria contribute to changes in appetite and metabolism."

The first author of the paper is Emory faculty member Matam Vijay-Kumar, PhD, who has been studying a mouse strain with an altered immune system. These mice were engineered to lack a gene, Toll-like receptor 5 (TLR5), which helps cells sense the presence of bacteria. TLR5 recognizes flagellin, the main component of the apparatus (flagella) that many bacteria use to propel themselves.

The study began with Emory researcher Jesse Aitken's unexpected observation that TLR5-deficient mice are about 20 percent heavier than

regular mice and have elevated triglycerides, cholesterol and blood pressure. They also have mildly elevated blood sugar and increased production of insulin, Vijay-Kumar and Gewirtz found. TLR5-deficient mice tended to consume about 10 percent more food than their regular relatives. When their food was restricted they lost weight but still had a decreased response to insulin (i.e. insulin resistance). When fed a high-fat diet, TLR5-deficient mice gained more weight than regular mice and, moreover, developed full-blown diabetes and fatty liver disease. In short, TLR5-deficient mice exhibit "metabolic syndrome," a cluster of disorders that in humans increases the risk of developing heart disease and diabetes.

Previous research has shown that TLR5 plays a prominent role in controlling bacteria in the intestine. Under certain conditions, many TLR5-deficient mice develop colitis, an inflammatory bowel disease, while the majority of the mice have chronic low-level inflammation.

"The intestine is like a complex community, with good and bad actors," Gewirtz says. "We can think of TLR5 as being like a neighborhood police officer who can distinguish law-abiding residents from potential trouble makers. Take away TLR5, and the safety of the community deteriorates."

Treating TLR5-deficient mice with strong antibiotics, enough to kill most of the bacteria in the intestine, reduces their metabolic abnormalities. This led Gewirtz's team to analyze the composition of the intestinal bacteria of TLR5-deficient mice, collaborating with Ruth Ley at Cornell University.

Ley's earlier research on mice and humans shows that obesity results in more bacteria of the Firmicutes family and less of the Bacteroidetes, which increases the intestine's ability to harvest calories from food. In contrast, TLR5-deficient mice had normal proportions of Firmicutes and

Bacteroidetes but differed in the bacterial species that comprised these families.

Importantly, Gewirtz and his team found that transfer of the intestinal bacteria from TLR5-deficient mice to regular mice transferred many of the characteristics of metabolic syndrome including increased appetite, obesity, elevated blood sugar, and insulin resistance.

Humans' intestinal bacterial populations are thought to be acquired at birth from family members and are relatively stable, but they can be influenced by diet and antibiotics.

"Previous research has suggested that bacteria can influence how well energy is absorbed from food, but these findings demonstrate that intestinal bacteria can actually influence appetite," Gewirtz says.

Noting that insulin is known to dampen appetite, he adds: "Even in the absence of colitis, the TLR5-deficient mice seem to have low-level inflammation. We're not yet sure if this inflammation leads to alterations in intestinal bacteria or vice versa, but this shows that once the microbial community changes, it can transfer metabolic abnormalities to other mice. This suggests that it's possible to 'inherit' metabolic syndrome through the environment, rather than genetically. Do obese children get that way because of bad parenting? Maybe bacteria that increase appetite are playing a part."

Gewirtz says his team plans future investigations into variations in the TLR5 gene in humans, and additional studies of what's different about the bacteria in TLR5-deficient mice and how they might influence appetite and metabolism.

**More information:** M. Vijay-Kumar et al. Altered Gut Microbiota in Toll-Like Receptor-5 (TLR5) Deficient Mice Results in Metabolic

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Provided by Emory University