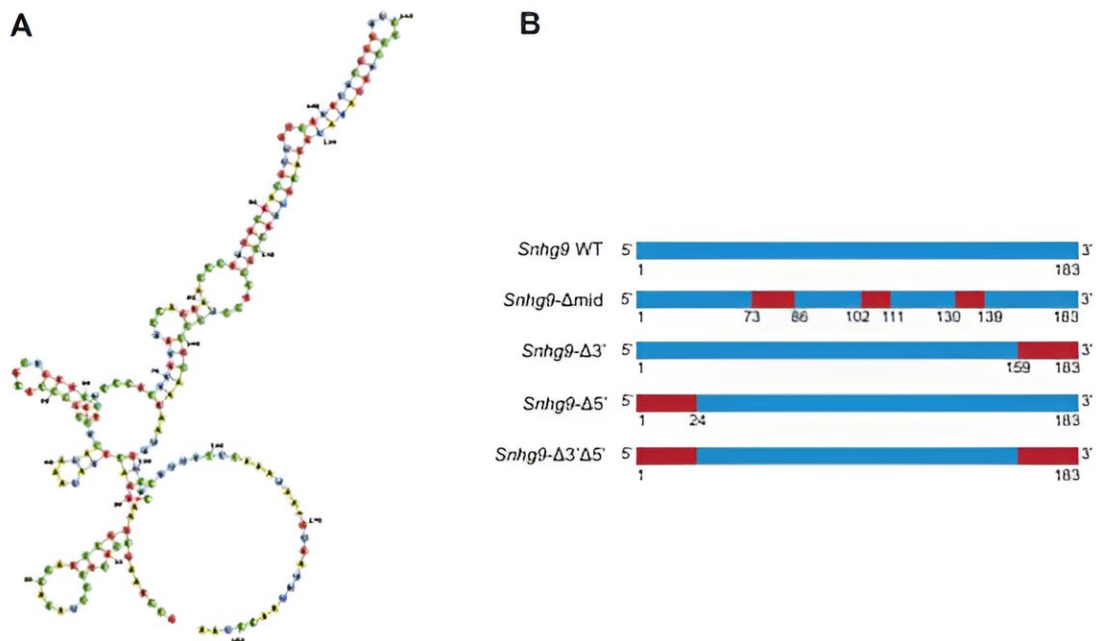


Intestinal bacteria release molecular 'brake' on weight gain, study finds

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Secondary structure of long non-coding RNA *Snhg9*. (A) Secondary structure of *Snhg9* RNA predicted by RNAfold (49) with nucleotide positions indicated. (B) Locations of nucleotide deletions analyzed in Fig. 2E. Credit: *Science* (2023). DOI: 10.1126/science.ade0522

Bacteria that live in the intestines inhibit a molecule that limits the amount of fat absorbed, increasing weight gain in mice fed a high-sugar,

high-fat diet, researchers from UT Southwestern Medical Center report. The findings, published in *Science*, could eventually lead to new ways to combat obesity, diabetes, and malnutrition—health problems that plague hundreds of millions worldwide.

"We know that there are big differences in the composition of the [gut microbiome](#) between lean and [obese mice](#), as well as lean and obese people. The question we've been grappling with is, does our microbiome cause metabolic changes that promote obesity, and if so, what are the molecular causes? This study paints part of that picture," said Lora Hooper, Ph.D., Professor and Chair of Immunology, Professor of Microbiology, a member of the Center for the Genetics of Host Defense at UT Southwestern, and a Howard Hughes Medical Institute Investigator. Dr. Hooper co-led the study with Yuhao Wang, Ph.D., a former UTSW graduate student and postdoctoral researcher in the Hooper lab who is now a faculty member at Zhejiang University in Hangzhou, China.

Researchers have long known that "germ-free" [mice](#), which have no gut microbiome and are maintained in sterile colonies, tend to be leaner than mice with gut microbes, especially when fed a Western-style high-sugar, [high-fat diet](#). Searching for reasons why, Drs. Hooper and Wang and their colleagues used RNA sequencing to compare [gene expression](#) in the small intestines of [germ-free mice](#) and "conventional" counterparts with typical gut bacteria.

The team homed in on a gene called *Snhg9*, which produces a long, noncoding RNA whose function was unknown. A series of experiments showed that the RNA molecule produced by *Snhg9* binds to a protein called CCAR2, setting off a molecular cascade that prevents dietary fats from being absorbed by the cells that line the intestine. Additional investigation showed that the intestinal cells that produced this RNA decreased its synthesis when they were alerted to the presence of gut

microbes through a feedback loop governed by the immune system.

In germ-free mice and mice genetically altered to produce extra Snhg9 RNA, the process kicked off by this molecule protected them from becoming obese, even on a Western-style diet. Additional tests showed these animals weren't absorbing as much dietary fat as wild-type mice. However, mice genetically altered to lack Snhg9 gained excess weight on the high-sugar, high-fat diet, even when their gut microbes were killed off with antibiotics.

Together, the findings—which follow a [2017 paper](#) led by Drs. Hooper and Wang that identified a molecular "accelerator" for lipid absorption and metabolism—help solve the mystery of how the microbiome regulates metabolism in host organisms. The discovery could eventually lead to ways to manipulate this interaction to prevent or treat metabolic diseases. For example, Dr. Hooper said, researchers may eventually be able to treat malnutrition by inhibiting Snhg9 or treat obesity by mimicking Snhg9 function with pharmaceuticals.

More information: Yuhao Wang et al, The gut microbiota reprograms intestinal lipid metabolism through long noncoding RNA Snhg9, *Science* (2023). [DOI: 10.1126/science.ade0522](https://doi.org/10.1126/science.ade0522)

Provided by UT Southwestern Medical Center

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