Study uses genetic approach to manipulate microbes in gut

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We are what we eat, but who are "we"? New, high-powered genomic analytical techniques have established that as many as 1,000 different single-celled species coexist in relative harmony in every healthy human gut.

"For each human cell in your body there are 10 microbial cells, most of them living in the gut and helping us digest things we can't digest on our own," said Justin Sonnenburg, PhD, assistant professor of microbiology and immunology at the Stanford University School of Medicine. "In turn, what you eat is proving to be one of the major determinants of the components of your 'inner self' — that community of bacteria living in your intestine."

Each individual's microbial ecosystem is different in its relative composition, with potential implications for our health. Disorders such as inflammatory bowel disease, colorectal cancer and even obesity have been linked to skewed intestinal microbe distributions.

Scientists hope that someday they will be able to manipulate microbial populations in the gut as a way of remedying disease and enhancing health. One step toward this goal would be taking "genomic censuses" to categorize and count the interacting components of each individual's bacterial community and characterize how they respond to interventions, such as changes in diet. That's no small task, because the aggregate gene count of the micro-organisms dwelling in a typical human gut outnumbers our own by a hundredfold — millions of them, versus the

20,000 human genes that have been identified.

In an animal study to be published June 25 in *Cell,* Sonnenburg and his colleagues showed that zeroing in on just a small set of bacterial genes, while ignoring the vast majority, allowed them to predict how bugs would respond to a diet change. The results highlight the potential of the burgeoning new field of prebiotics, which (in contrast to probiotics — the seeding of food with healthful bacterial organisms) involves adding substances to the diet in an effort to shift the mix of bugs in our gut in a healthy direction.

In conducting the study, the researchers used a vastly simplified model of the internal mammalian microbial ecosystem to prove that they could predict, by looking at a mere handful of microbial genes, how a shift in diet can alter the microbial composition of the gut. Sonnenburg's team introduced two distinct species of bacteria, both known to abound in the human digestive tract, into mice that had been raised in a sterile environment and so lack the normally resident microbes — also known as "germ-free" mice. Then they fed the mice a diet rich in a particular complex carbohydrate that one bacterial species seemed genetically better equipped to digest, based on the presence of a small set of genes in its genome. As predicted, that bacterial species became predominant in the mice's intestines.

These results set the stage for scaling up germ-free mice into living laboratories into which scientists can introduce, one by one, steadily increasing numbers of bacteria found in the human intestine, eventually enabling a sophisticated understanding of the astonishingly complex microbial superorganism that dwells inside each of us.

The complex carbohydrate the Stanford researchers added to the mice's diet was inulin, which is found in certain bulbous plants — onions, garlic, Jerusalem artichokes — and has gained wide use as a prebiotic

supplement (for instance, in yogurt or in powdered form) by people who believe it encourages the proliferation of healthful "good" bacteria. We humans can't digest inulin on our own, but some bacteria are equipped with genes that encode enzymes capable of sawing through the chemical links joining this substance's constituent sugar molecules.

"Think of these enzymes as a unique set of utensils that allow them to eat this food we can't cut," said Sonnenburg. The byproducts of bacterial metabolism are often valuable nutrients for humans — a win-win situation.

Previous genomic analyses had determined that only one of the two bacterial species the investigators introduced to the germ-free mice featured, among its 5,000 or so genes, a roughly 10-gene assemblage that permits the breakdown of inulin.

The researchers used a standard laboratory technique to precisely assess changes in each of the two species' relative abundance before and after dietary inulin supplementation. "Within one or two weeks, there was a significant change in the composition of the mice's gut communities," said Erica Sonnenburg, PhD, senior research scientist in Justin Sonnenburg's lab and first author of the study. As predicted, the ratio of inulin-digesting to non-digesting species shifted in favor of the former in the inulin-fed mice.

Both Erica and Justin Sonnenburg (they're married) warned that it will be a while before the results in this simple experimental system — two competing bacterial species — can be extrapolated to the nearly-1,000-species jungle that is the real, human gut-dwelling microbial community. But the Sonnenburg lab has already embarked on increasing the complexity of their experimental system by increasing the number of human-associated bacteria into germ-free mice that have been "humanized" so that their intestines contain a microbial community

similar to that of the human gut.

"We've now got germ-free mice to which we've introduced batches of bacteria representative of an entire human gut community in all its complexity," said Erica Sonnenburg. "We're looking to see if the bugs that we think should do better actually do better in this more competitive environment."

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