Genetic differences in the immune system shape the microbiome

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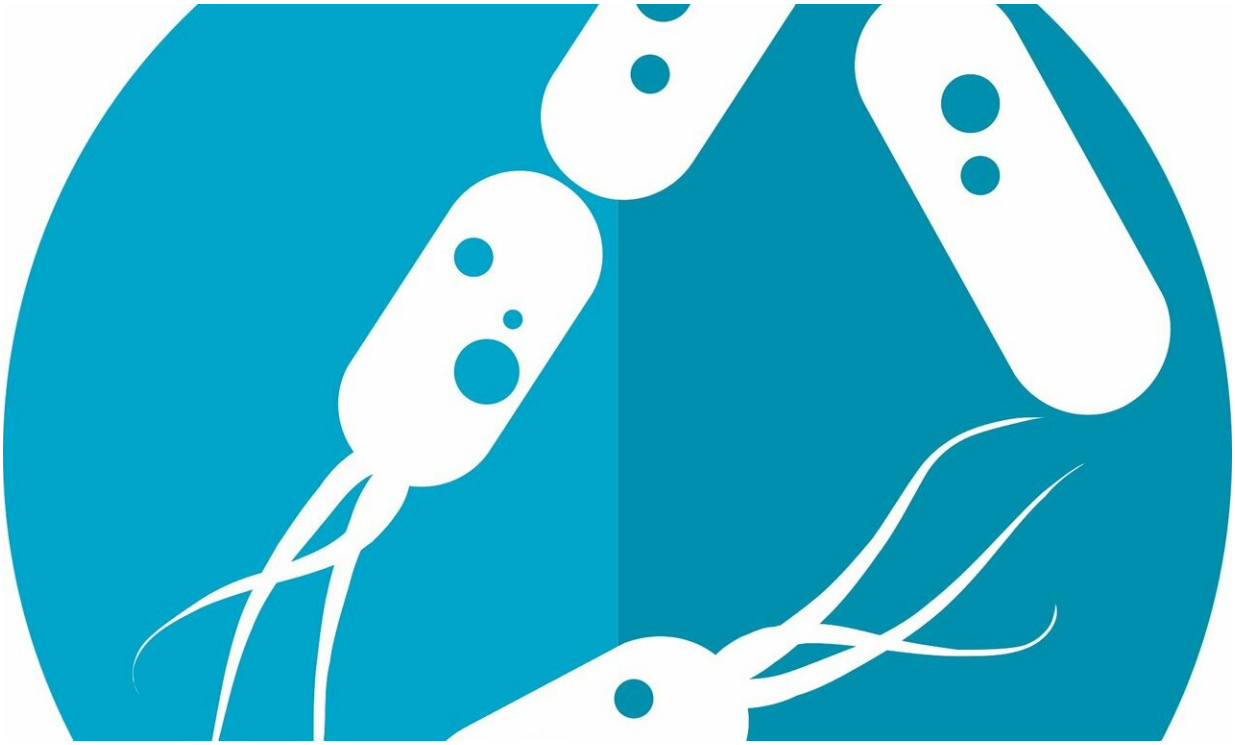

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Genetic differences in the immune system shape the collections of bacteria that colonize the digestive system, according to new research by scientists at the University of Chicago.

In carefully controlled experiments using germ-free mice populated with

microbes from conventionally raised mice, the researchers showed that while the makeup of the microbial input largely determined the resulting microbiome of the recipients, genetic differences between strains of mice played a role as well.

"When the input is standardized, you can compare mice of different genetic strains and see what these genetics do to the microbiome in recipient mice," said microbiome researcher Alexander Chervonsky, MD, Ph.D., a senior author of the new study, published in *Cell Reports*. "This approach allowed us to tell whether there was a genetic influence, and indeed there is. So, the next question was what mechanisms are involved?"

One of the challenges facing microbiome researchers is that it can be difficult to compare the results of experiments due to "batch effects" or "legacy effects." When scientists transfer microbes from one mouse to another, the result is largely determined by the microbiome of the source animal, what kind of food they eat, where they live, etc. So even if researchers in two different labs use the exact same breed of mice with the same genetic backgrounds, they will see two different pictures when they analyze the microbiome of the recipients. "Input defines the output," Chervonsky said.

To overcome these effects, Chervonsky and microbiologist Tatyana Golovkina, Ph.D., co-senior author of the new study, carefully limited their experiments to make an apples-to-apples comparison. They transferred microbes from one conventionally raised mouse to many genetically identical mice from UChicago's gnotobiotic (germ-free) mouse facility. These mice are specially bred so they don't have any bacteria in their bodies or digestive tracts from birth to provide a blank slate to see what happens when they're colonized with bacteria.

Chervonsky and Golovkina repeated these steps many times, transferring

microbes from one source mouse to many recipients, some with similar genetic backgrounds and some with slight differences in their immune systems. They then worked with pathologist Aly A. Khan, Ph.D., and Dionysios Antonopoulos, Ph.D., a microbiologist from Argonne National Laboratory, to analyze the genome sequences of the resulting microbiomes in the recipient mice and their offspring and compare the effects of different immune system genes.

Animals have two primary types of immunity: innate, or inborn, immunity that uses standard, hardwired mechanisms to fend off pathogens, and adaptive immunity that "learns" as it encounters different pathogens and uses T cells and B cells to target their unique receptors. Some of the mice Chervonsky and Golovkina used in their experiments were congenic, or genetically the same except for differences in part of the genome called the major histocompatibility locus (MHC), which determines adaptive immunity.

When they looked into how these different immune mechanisms shaped the microbiomes of the recipient mice, the researchers saw that while adaptive immunity had some effect on certain strains of bacteria, overall the effects were not dramatic. In some cases, bacteria even took advantage of the adaptive immune response to thrive. Instead, the majority of the differences they saw could be attributed to innate polymorphic genes, or different variations of genes in the MHC.

"Manipulation of the adaptive system leads to some changes, but to our surprise, they were not dramatic," Chervonsky said. "The vast majority of the mechanisms that determine differences in the outcome are those which are polymorphic but not part of the adaptive immune response."

Golovkina said she hopes this work will set an example for how to standardize microbiome studies. The gnotobiotic facility is a key component of ongoing research on the immune system, genetics and the

microbiome under the umbrella of the Duchossois Family Institute at UChicago. Using standard tools like germ-free mice to carefully control the conditions of experiments, researchers can build upon previous work instead of conducting one-off, standalone experiments.

"There are standards in many different types of research, but they're almost non-existent in microbiome research," Golovkina said. "We're trying to set up a standard of analysis for these questions about how to compare differences in microbial composition."

More information: "Polymorphic immune mechanisms regulate commensal repertoire," *Cell Reports* (2019). DOI: 10.1016/j.celrep.2019.09.010

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