Probiotics evolve inside mice, a path that could affect humans, too

By Shraddha Chakradhar @scchak

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Pop an aspirin, and you know the drug will be metabolized in a few hours and whatever doesn’t go into the bloodstream will be out of you shortly thereafter. But the same can’t be said for probiotics, so-called good bacteria that are ingested or otherwise consumed for health benefits.

Because they’re living organisms, the bacteria are likely to go on reproducing and responding to their new environment in the human gut. And a new study¹ suggests that probiotics might behave in ways that we perhaps didn’t anticipate.

“It’s the first time that we’ve systematically asked the specific question: Do these bugs evolve during the course of treatment?” said Gautam Dantas, a researcher at Washington University in St. Louis and senior author of the study, published Tuesday in Cell & Host Microbe. Dantas and his colleagues believe the answer is yes.

The team looked at E. coli Nissle, or EcN, which is sold as a probiotic in Europe and Canada and touted as being protective against severe gastrointestinal issues. “We want to establish the safety [of these
probiotics] and part of it is knowing their propensity to pick up genes or mutate. That’s a big question out there,” said Ilana Brito, a microbiome scientist at Cornell University, who was not involved in the study.

The researchers isolated microbes from the guts of eight healthy people, broke up the bacterial DNA, and created a vast library of 15 million fragments of DNA. These DNA fragments were then mixed in with EcN and the resulting combinations, along with unmodified EcN, were transplanted into four different kinds of animals: mice with no pre-existing gut microbiome; mice with a small set of gut bacteria; mice with a normal microbiome; and mice that had a normal microbiome but were treated with antibiotics to slightly reduce the diversity of the gut microbiota.

The mice were also exposed to different diets, including a typical mouse diet, which is high in fiber, and a Western diet (high fat, high sugar, low fiber).

Five weeks after the transfers to the mice, the scientists noticed that the bacteria in mice with the lowest microbial diversity — mice with no pre-existing microbiota or a limited set of microbiota — underwent the biggest evolutionary changes. In one type of change, the bacteria acquired a new ability to process certain sugars. Other bacterial species would typically take on the task, but without these other bugs, EcN likely took on the job itself.

Some of the bacteria also evolved to eat into the protective mucus layer that lines the small intestine, which Dantas said could spell trouble down the road.

“Maybe that’s not a problem, but as EcN compromises that particular barrier now, you might imagine that a pathogen coming through might take advantage of that,” he said.

The findings of the study, “shouldn’t surprise anybody,” said Bernat Olle, CEO of microbiome therapeutics company Vedanta Biosciences, who wasn’t involved with the study. “Whether you give [bacteria] as fecal transplant or defined therapies, they will constantly respond to the environment.” Olle, who said that his company is interested in better understanding the changes that beneficial bacteria undergo once they’re given to humans, also cautioned against extrapolating too much from findings in mice. “These kinds of findings are going to be very system-specific and unlikely to be the same in humans,” he said.

Despite this, the findings are likely to have important takeaways for drug developers. “If you plan to design a probiotic therapy, you probably want to know the paths that it takes in the gut,” said Nathan Crook, the study’s lead author and a former postdoc in Dantas’ lab, who is now at North Carolina State University. “So does it evolve in a way that is beneficial for your therapy or benign or actively detrimental?”

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Probiotics studies often don’t disclose safety data or risks, report finds.
Although the Food and Drug Administration monitors off-the-shelf probiotics found in grocery and health stores as supplements, the agency has not yet approved any probiotic for any condition. Many companies are trying to prove therapeutic benefit from having people ingest beneficial bacteria either in their purest form or in the form of fecal transplants for a range of diseases including C. difficile infection and inflammatory bowel disease.

Ultimately, Dantas said, the study is intended to demonstrate “long-term consequences from short-term actions,” such as modifying diet or the gut bacterial makeup, with the added caveat that these probiotic treatments are intended to be taken temporarily.

“We shouldn’t be scared of evolution. I think we should embrace it,” he said, adding, “What’s bad is the unknown. Having information in hand now allows you to be more judicious about how you use these probiotics later.”

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