Gut bacteria from wild mice boost health in lab mice

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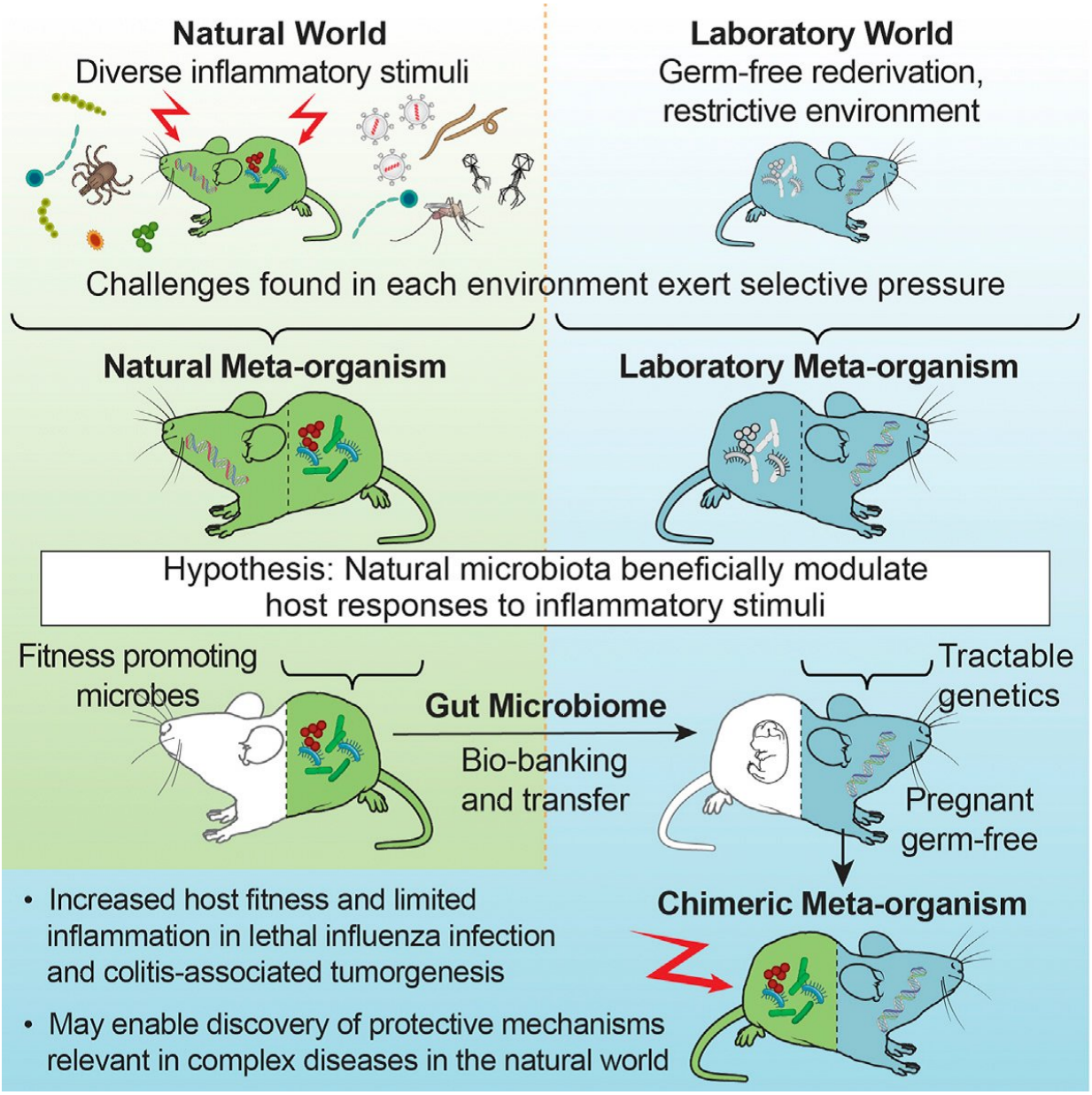

Visualization of the process of transferring gut microbiota from wild mice to laboratory mice. Credit: Rosshart et al.

Laboratory mice that are given the gut bacteria of wild mice can survive a deadly flu virus infection and fight colorectal cancer dramatically better than laboratory mice with their own gut bacteria, researchers report October 19 in the journal *Cell*.

The immunological benefits from the wild mice's gut bacteria may, in part, explain a persistent problem in disease research: Why disease experiments in lab mice, such as vaccine studies, turn out very differently in humans or other animals.

"We think that by restoring the natural 'microbial identity' of laboratory mice, we will improve the modeling of complex diseases of free-living mammals, which includes humans and their diseases," said Barbara Rehermann, M.D., senior author of the paper. Rehermann is chief of the Immunology Section, Liver Diseases Branch, of the NIH's National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

"By being so different, natural microbiota will help us to discover protective mechanisms that are relevant in the natural world and absent in the laboratory," said Stephan Rosshart, M.D., first author of the paper and NIDDK postdoctoral fellow.

Mammals—humans included—depend on their microbiota, the collection of microorganisms they host in and on their bodies. Evolution shapes each animal's microbiota, favoring populations of microorganisms that help the animal survive their environment and diseases they encounter. But laboratory mice aren't random house mice plucked from a field or basement.

Laboratory mice are carefully bred, fed, and raised in tightly controlled conditions so that each mouse has predictable traits and genetics. This is a great advantage in basic biology research, but creating that predictability means that a controlled environment, and not the survival pressures of the outside world, shaped the microbiotas of laboratory mice.

"We hypothesized that this might explain why laboratory mice, while paramount for understanding basic biological phenomena, are limited in their predictive utility for modeling complex diseases of humans and other free-living mammals," said Rosshart.

So, the researchers tried to give laboratory mice back what they have lost: a naturally co-evolved wild mouse gut microbiota. The researchers trapped more than 800 wild mice from eight locations across Maryland and the District of Columbia to find healthy, suitable candidates for a gut microbiota donation.

They then tested and compared the gut microbiomes (collective genomes of the gut microbiota) of the wild mice (Mus musculus domesticus) and a common strain of laboratory mice, called C57BL/6, from multiple sources. The researchers confirmed that C57BL/6 mice had distinct gut microbiomes from wild mice.

Researchers then introduced (engrafted) the microbiota of wild mice to pregnant, germ-free C57BL/6 mice. Germ-free mice are raised in a sterile environment and don't have microbiomes of their own. For a control group comparison, the researchers also engrafted microbiota from regular C57BL/6 mice into a separate group of pregnant, germ-free mice. Four generations later, the mice still carried either the wild microbiomes or the control laboratory microbiomes passed down from their foremothers.

When exposed to a high dose of influenza virus, 92 percent of the laboratory mice with wild microbiomes survived, whereas only 17 percent of laboratory mice and mice in the control group survived. In other experiments, the laboratory mice with wild microbiomes had better outcomes in the face of induced colorectal tumors, whereas the other mice had a greater number of tumors and more severe disease. The beneficial effects of the wild microbiota were associated with reduced inflammation in both models.

The researchers note that more work and evaluation is needed for definitive results, and they hope to improve and expand upon the method of using natural microbiomes in laboratory mice.

"We are planning to create a complete microbiological fingerprint of natural microbiota and its potential trans-kingdom interaction by describing all components of the microbiome—for example, viruses and fungi—in parallel and at various body sites," Rehermann said.

More information: *Cell*, Rosshart et al.: "Wild Mouse Gut Microbiota Promotes Host Fitness and Improves Disease Resistance." www.cell.com/cell/fulltext/S0092-8674(17)31065-6 , DOI: 10.1016/j.cell.2017.09.016

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