Researchers identify potential approaches to modify the vaginal microbiome

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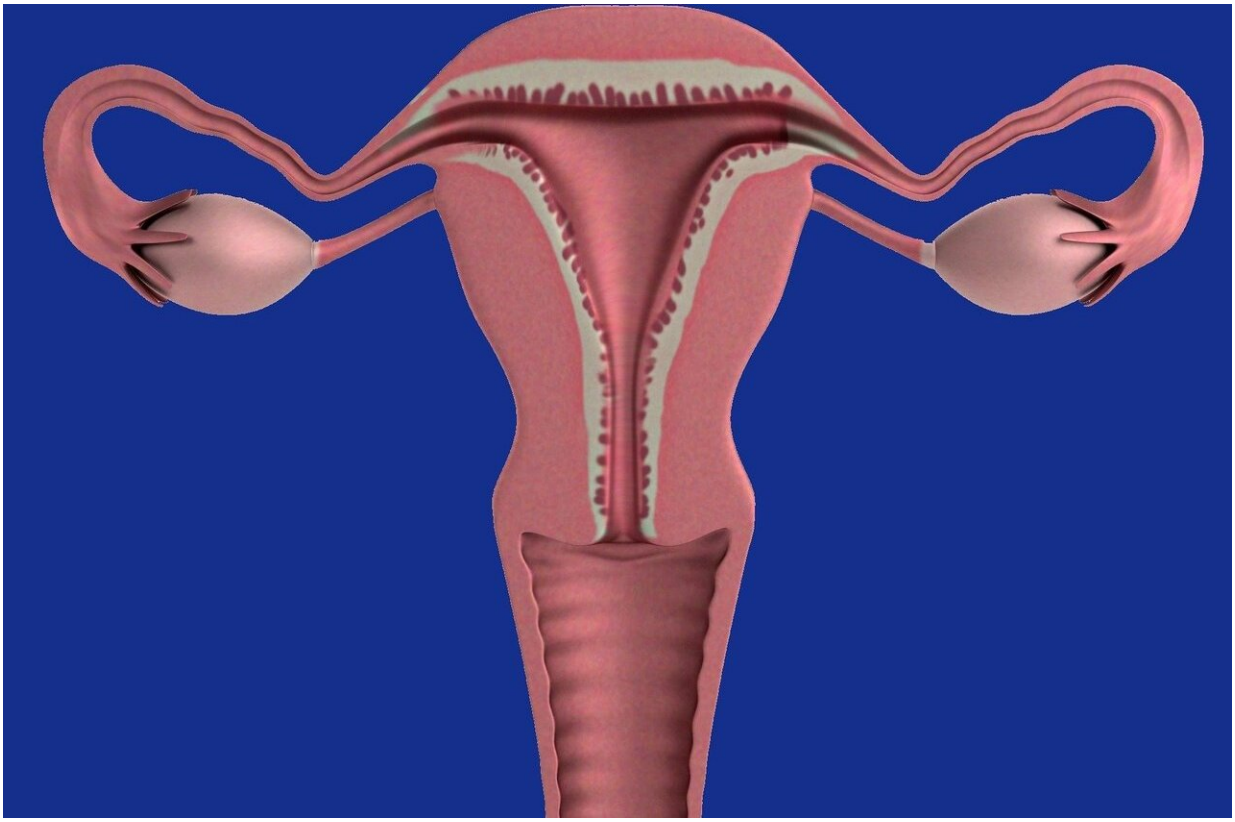

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The female genital tract is naturally colonized by mixed communities of bacteria, known as the vaginal microbiome. When these communities are dominated by species such as Lactobacillus crispatus, they provide

important protective functions in genital health. But overgrowth of certain other bacterial species is linked to a condition known as bacterial vaginosis (BV). BV affects nearly 30% of women around the world, carrying increased risk for sexually transmitted diseases, HIV, and—in pregnant individuals—premature birth. Unfortunately, current antibiotic-based treatments for BV are poorly effective with high rates of recurrence.

One reason for BV recurrence may be that treatment often causes the microbiome to become dominated by a species called Lactobacillus iners instead of by L. crispatus. In a paper published this week in *Nature Microbiology*, researchers at the Ragon Institute of Massachusetts General Hospital (MGH), Massachursetts Institute of Technology (MIT) and Harvard and colleagues show that L. iners has unique nutritional requirements that distinguish it from L. crispatus, potentially allowing it to be targeted using novel therapeutic strategies.

"L. iners is the most abundant and common vaginal bacterial species worldwide, but it is poorly studied because scientists have had difficulty growing it in lab under conditions used to culture species like L. crispatus," explains Seth Bloom, MD, Ph.D., an Instructor in the Infectious Diseases division at Massachusetts General Hospital and Harvard Medical School, who was lead author on the study. Bloom and colleagues found that adding the amino acid cysteine to standard Lactobacillus culture media allowed them to grow L. iners strains from samples collected from U.S. and South African women.

Surprisingly, when the researchers analyzed a novel collection of more than 1,200 vaginal Lactobacillus genomes from more than 300 women across four continents, they found that none of the species were able to make their own cysteine. This finding was confirmed in experiments conducted with Ben Woolston, Ph.D., and Emily Balskus, Ph.D., at the Harvard Department of Chemistry and Chemical Biology. The team

therefore hypothesized that all vaginal Lactobacillus species require external cysteine sources. They measured cysteine concentrations in vaginal fluid samples from South African women with high rates of BV, finding that higher vaginal cysteine levels were linked to Lactobacillus-dominant microbiomes while BV was associated with low cysteine levels.

"The results suggested all vaginal lactobacilli acquire cysteine from their environment, but L. iners's ability to do so was more limited than other species," says Bloom. "Indeed, when we looked at the genomes, we saw that all species except L. iners had multiple systems that are predicted to transport cysteine or its oxidized form, cystine." The team therefore tested effects of compounds known to inhibit cystine uptake, finding that cystine uptake inhibitors selectively blocked growth of L. iners in the lab, but not other Lactobacillus species.

"These findings were exciting because they suggested a way to improve BV treatment by blocking L. iners growth in favor of more health-associated species like L. crispatus," explains co-author Nomfuneko Mafunda, an MPH candidate at the Harvard T.H. Chan School of Public Health who contributed to this study while working as a technician at the Ragon Institute. To test this idea, Bloom and Mafunda constructed mixed bacterial communities including L. iners, L. crispatus, and various BV-associated bacteria in the laboratory. They then treated the communities with an antibiotic commonly used for BV therapy, with a cystine uptake inhibitor, or a combination of the two. Their results showed that the combination allowed L. crispatus to outcompete other species more effectively than the antibiotic alone.

The researchers believe these results suggest a path to better therapies. "One reason it's been difficult to develop effective BV treatments is that we haven't had the correct tools to study the vaginal microbiome in the lab," says Doug Kwon, MD, Ph.D., Ragon core member and senior

author on the study. "Here, developing the right tool to cultivate L. iners in the lab immediately translated into an important finding that will hopefully lead to improved therapies for BV."

The team emphasizes that several important questions remain. It isn't yet clear how L. iners takes up cysteine from its environment, and more potent versions of the inhibitors may need to be developed before the strategy can be used to treat patients. Even so, the study is a promising step forward for this common but difficult-to-treat condition.

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