Female urinary tract lactobaccilli can kill pathogenic bacteria

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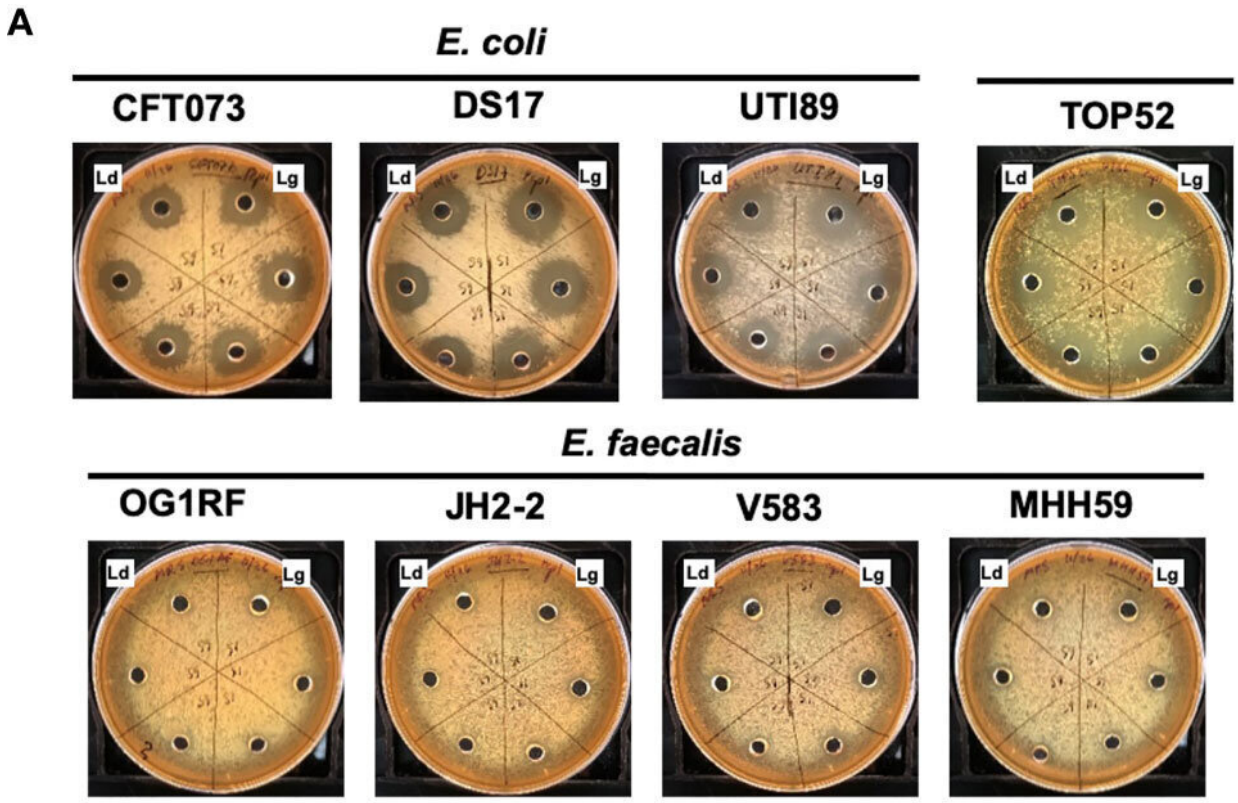

Urinary lactobacilli L. gasseri 5006-2 and L. delbrueckii 5010-2 inhibit a broad range of uropathogens. Representative images of well-diffusion inhibition assays using E. coli, K. pneumoniae, and E. faecalis (A), and zone of inhibition sizes of one-day old (dark blue) or two-day old (light blue) cultures of L. gasseri 5006-2 [Lg, (B)] and L. delbrueckii 5010-2 [Ld, (C)] against 8 pathogenic strains (Table 2). Error bars indicate standard deviation of three biological replicates, *p Frontiers in Cellular and Infection Microbiology (2022). DOI: 10.3389/fcimb.2022.870603

Lactobacilli that live in the human female urinary tract's microbiome are competitive and kill nearby pathogenic bacteria, according to the first study of its kind by a team led by microbiologist Dr. Tanya Sysoeva of The University of Alabama in Huntsville (UAH). The study was recently published in *Frontiers in Cellular and Infection Microbiology*.

Greater understanding of the processes involved could lead to new therapies that encourage the "good" bacteria to battle the "bad," as a preventative or a treatment for urinary tract infections (UTIs).

"Our group is primarily focusing on trying to find alternatives to traditional antibiotic therapy because we know the antimicrobials are failing more and more often," says Dr. Sysoeva, an assistant professor of biological sciences at UAH, a part of the University of Alabama System, and director of the Sysoeva Lab. "Pathogens are notorious about picking up resistances."

A well-understood urinary microbiome could also prove helpful in general disease diagnostics. "The hope is that in the future we can not only 'pee on a stick' to check for pregnancy or infection, but we ambitiously envision that we will be able to detect other diseases, perhaps due to better understanding of how the urinary microbiome reacts to our health changes and conditions," she says.

The in vitro laboratory research utilized a repository of bacteria isolated from healthy and diseased post-menopausal women that had previously been collected by Dr. Sysoeva and Dr. Nazema Siddiqui, an associate professor of obstetrics and gynecology at Duke University.

"As microbiologists, we are very curious to see whether the microbes that are residents in our bladders can resist invasion of the 'bad guys,'

pathogenic bacteria or uropathogens," says Dr. Sysoeva. "As a scientific community, we know a lot about the uropathogens because they were characterized for decades. But very little is known about those 'residential,' or so-called commensal bacteria."

Since most female urinary tract microbiomes have been shown to be dominated by lactobacilli, a type of lactic acid-forming bacteria, Dr. Sysoeva's team chose to focus on them.

"This killing by lactobacilli will even work if the uropathogens have multiple antibiotic resistances," Dr. Sysoeva says. "It is very exciting to realize that the human bladder is, or can be, colonized by those lactobacilli and possibly be protected from the infection."

The human microbiome is a collection of all microorganisms living in and on the human body, she says.

"It is thought that, in our bodies, for each one of our cells we have one or more microbial cells. Therefore, microbes are bringing a lot of genes and functionality to our organism, not just infectious disease."

Many different rooms

While it's called the human microbiome, it is actually a collection of different microbiomes.

"One can think of it as a house with many different rooms," Dr. Sysoeva says. "It is because our body has such different spaces—think of your skin properties versus, let's say, your gut."

Even within the gastrointestinal tract, the conditions in the oral cavity, stomach or intestines are drastically different and involve different nutrients, oxygen and acidity, she says.

"Therefore, each part will have different microbes and hence their unique microbiome, like the oral microbiome, stomach microbiome and colon microbiome," says Dr. Sysoeva. "The latter is what most likely we would call a gut microbiome that we've heard so much about."

The human urinary tract is populated by a very low biomass but a diverse community of microbes that are mainly bacteria, she says.

"We call them the commensal urinary microbiome or urobiome for short. The composition of this urobiome is highly variable between people and even in one individual over time, but the composition seems to associate with urinary and general health."

Dr. Sysoeva's recent research has uncovered new questions.

"While it is promising in terms of thinking of how we can use our microbiome to prevent and maybe to treat the urinary infections, we see that our assays in the laboratory might not explain everything," she says.

"For example, we see that lactobacilli isolated from women with recurrent UTIs are also capable of inhibiting the pathogens in test tube laboratory conditions," Dr. Sysoeva says. "We also found that in some patients the 'good lactobacilli' are coexisting with pathogens. As these are initial studies, we do not know why it is so."

It's possible that, since samples were collected in the absence of active infection, the lactobacilli are keeping the pathogens in check or that there are other factors at play, she says. Maybe the lactobacilli inhibit the pathogens in the test tube but they're not in range of each other in the bladder, or the bladder's condition doesn't allow them to do so because it affects their metabolism.

"It is the very first study of these interactions and the microbiome is a

complex community of microbes that interacts with our cells and our immune system, and that changes with the conditions such as diet or drugs," Dr. Sysoeva says. "We observe that healthy patients tend to be colonized by certain types of lactobacilli but not others, and that the mechanisms of how microbes compete or kill each other vary."

Observations that urinary lactobacilli are very diverse are "super important because when we are looking for some 'good probiotic' for urinary health or for even a treatment in the form of these 'good bugs,' we need to pick the right strains," she says. "We cannot just tell people to eat yogurt or a random lactobacilli-containing probiotic."

Future investigations

Further research is needed to investigate which lactobacilli will be able to colonize the bladder and which best resist pathogenic invasions.

"Who will be a good protector?" Dr. Sysoeva asks.

To answer that, the researchers have expanded testing to include more varieties of urinary bacteria, not just lactobacilli.

"We plan to test isolates from patients from different age groups, test more complex interactions and determine how host cells affect those interactions," says Dr. Sysoeva. "There is a long way ahead of us but I hope it will lead to targeted therapeutics that we can test in clinical trials and alleviate suffering for recurrent UTI patients, or help those with antibiotic resistant infections, which we cannot treat otherwise."

With aging, both sexes become increasingly susceptible to UTIs, and future research will require similar studies for men, Dr. Sysoeva says.

A goal is to understand development of the urinary microbiome

throughout the lifespan, as well as its differences between the sexes and in various metabolic and disease conditions. Under a new grant and in collaboration with Dr. Maryellen Kelly, an assistant researcher professor at the Duke University School of Nursing, and Dr. Lisa Karstens, an assistant professor at Oregon Health and Science University, the microbiome in children will be explored using novel sequencing methods.

Dr. Sysoeva recently submitted two large grant proposals in collaboration with Dr. Siddiqui and Dr. Maria Hadjifrangiskou, an associate professor in the Departments of Molecular Pathogenesis and Urological Surgery at Vanderbilt University and colleagues.

"In both we are aiming to bring our urinary lactobacilli into an animal model, in this case into mice, to test the protective effects and their mechanisms in vivo (in a living organism)," Dr. Sysoeva says. "It will be exciting to expand into this realm with access to the germ-free mice facilities, clinical researchers specializing on pelvic floor disorders and experts in uropathogens."

More information: James A. Johnson et al, Commensal Urinary Lactobacilli Inhibit Major Uropathogens In Vitro With Heterogeneity at Species and Strain Level, *Frontiers in Cellular and Infection Microbiology* (2022). DOI: 10.3389/fcimb.2022.870603

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