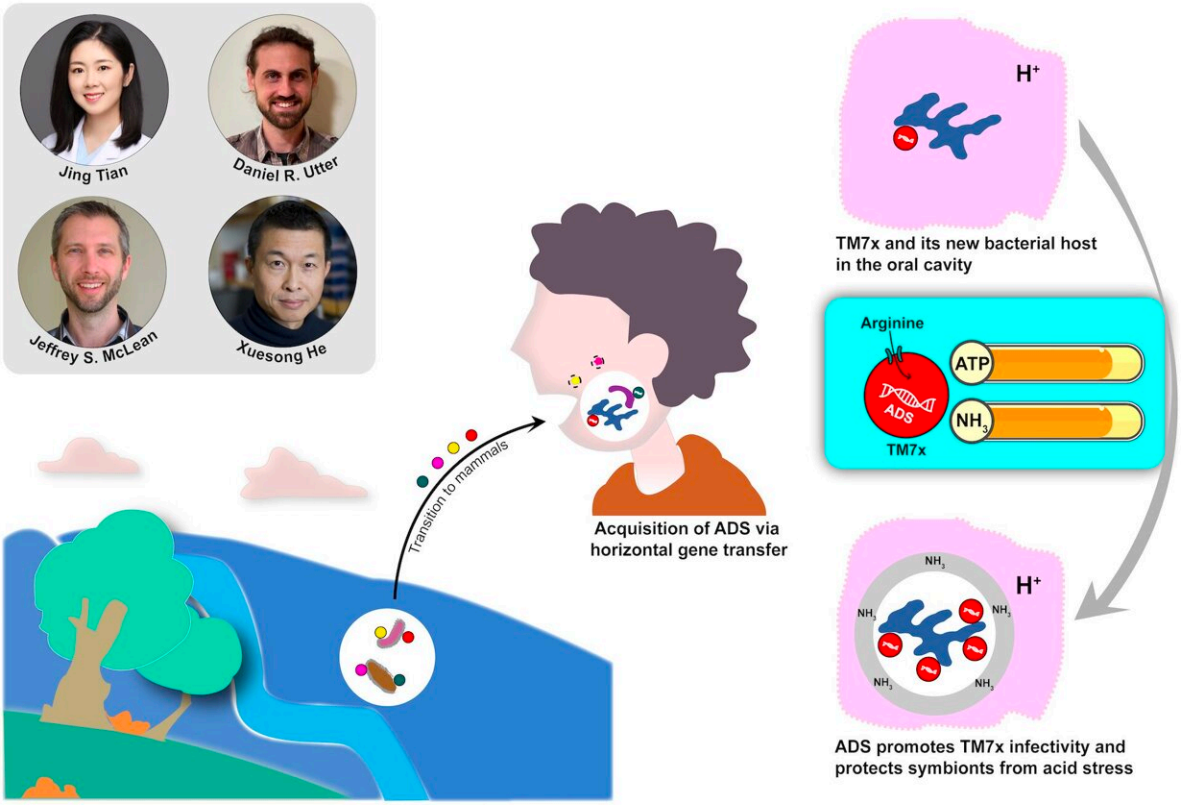
Researchers gain insights into how ultrasmall bacteria from the environment have adapted to live inside humans

January 3 2022



Researchers hypothesized that ultra-small bacteria called TM7 acquired the Arginine Deiminase System (ADS) as an evolutionary advantage to help them adapt and survive in the human oral cavity. To test this hypothesis, scientists developed a model system to experimentally investigate the function and impact of ADS on TM7x and its host bacterium. They found that ADS helped TM7x break down arginine, a process that produces the compounds Adenosine

triphosphate (ATP) and ammonia. The increased abundance of ATP and ammonia benefitted TM7x by increasing its infectivity, or ability to multiply. It also protected TM7x and its host bacterium from acid stress, a condition that microbes frequently encounter in the human oral cavity due to the acid created when bacteria feed on and metabolize dietary carbohydrates. Credit: Dr. Jing "Janet" Tian, Pediatric Dentist, Peking University Hospital of Stomatology, visiting scholar, The Forsyth Institute

The microbes that live inside our mouths, collectively known as the oral microbiome, impact our overall health in many ways that are not yet fully understood. Some bacteria cause inflammation, leading to periodontitis and other systemic diseases, such as cardiovascular disease and diabetes. Other oral organisms have been associated with certain types of cancer. Scientists are working to understand how these microbes interact with one another and our bodies to tease out their individual roles in health and disease.

Among the diverse bacterial species living within our mouths is a group belonging to the Candidate Phyla Radiation (CPR). These bugs are especially mysterious because they are ultra-small, adopt a unique symbiotic lifestyle with their host bacteria, and most have yet to be cultured by scientists and studied in the lab. The only bacteria within the CPR to be examined in-depth are a group called TM7, which were cultivated for the first time by Forsyth Institute researcher Dr. Xuesong He in 2014.

In an important step toward better understanding these elusive bacteria, Dr. He and his collaborator, Dr. Jeffrey S. McLean at the University of Washington, have developed a new model system using the first isolated human oral TM7 strain, TM7x, and its host bacterium, Actinomyces odontolyticus. Researchers used the model system to experimentally study these tiny bacteria, testing a hypothesis for how TM7 adapted to

live inside humans, and providing empirical data to confirm previous genomic studies. Their findings were published today in the journal *Proceedings of the National Academy of Sciences (PNAS)*.

Scientists have found TM7 in many different environments, including soil, groundwater, and the bodies of other mammals. Studies have shown that while maintaining a remarkably similar genome overall, the TM7 found in human mouths are unique from those in other environments because they have acquired a gene cluster encoding the arginine deiminase system, or ADS.

"This was intriguing to us since there seem to be very few genomic changes that occurred in this group of tiny bacteria with already small genomes as they transitioned from the environment to mammals," said Dr. McLean.

Researchers hypothesized that TM7 acquired ADS as an evolutionary advantage to help them adapt and survive in the human oral cavity. To test this hypothesis, Dr. Jing "Janet" Tian, first author of the study, used the model system to experimentally investigate the function and impact of ADS on TM7x and its host bacterium. She found that ADS helped TM7x break down arginine, a process that produces the compounds Adenosine triphosphate (ATP) and ammonia. The increased abundance of ATP and ammonia benefitted TM7x by increasing its infectivity, or ability to multiply. It also protected TM7x and its host bacterium from acid stress, a condition that microbes frequently encounter in the human oral cavity due to the acid created when bacteria feed on and metabolize dietary carbohydrates.

Ultimately, the experiment showed TM7x were able to survive in the experimental environment for longer than they could without the addition of arginine, thanks to ADS.

"Most of the current studies on CPR bacteria are based on a culture-independent genomic approach. Using this TM7 bacterial model system, we are able to directly test a hypothesis generated from genome analysis, which helps move the CPR research field from genome-focused studies toward hypothesis-driven studies to better understand their biology," said Dr. He.

"The production of ammonia through TM7-encoded ADS raises the pH level in the human oral microenvironment, which poses an intriguing question about the role of TM7 in the development of dental caries," said Dr. Tian, a Pediatric Dentist at Peking University Hospital of Stomatology and visiting scholar at Forsyth. In a previous study of dental caries in children, Dr. Tian found that the abundance of TM7 increased significantly after treatment of the caries. "We think this indicates that TM7 may be more associated with a caries-free state, and we are planning to do more research in this area," Dr. Tian said.

This study also adds to a growing body of evidence that TM7 bacteria may play a more protective role in oral health than researchers initially thought. For example, abundance of TM7 is found to increase drastically in the mouths of patients with periodontal disease, which led scientists to assume the bacteria contributed to the disease. But a recent study by led by Dr. Batbileg Bor at Forsyth showed the opposite effect—TM7 decreased periodontal inflammation and bone loss in a mouse model.

"We are still in the early stages of understanding how each of the many different types of these ultrasmall parasitic bacteria, which we basically just uncovered within humans, are impacting health and disease," said Dr. McLean.

"That's why it's so important to have a bacterial model system to not only achieve better understanding of the unique lifestyle of TM7, but experimentally test whether the hypotheses based on genomic studies or

clinical observation actually stands," Dr. He said. "Now, we have a manipulatable model system for TM7, which is truly a major advantage."

More information: Earlier study: Otari Chipashvili et al, Episymbiotic Saccharibacteria suppresses gingival inflammation and bone loss in mice through host bacterial modulation, *Cell Host & Microbe* (2021). DOI: 10.1016/j.chom.2021.09.009

Acquisition of the arginine deiminase system benefits epiparasitic Saccharibacteria and their host bacteria in a mammalian niche environment, *Proceedings of the National Academy of Sciences* (2022). DOI: 10.1073/pnas.2114909119.

Provided by Forsyth Institute