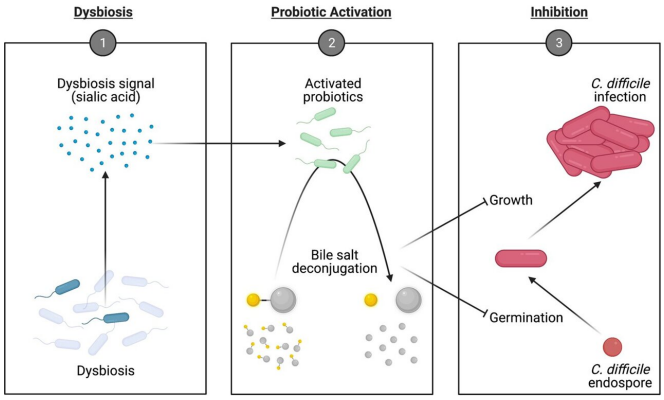
Scientists engineer probiotic to prevent infection of large intestine

4 August 2022



Schematic of the engineered probiotics against CDI. Probiotics were engineered to restore intestinal bile salt metabolism in response to antibiotic-induced microbiome dysbiosis in order to inhibit the germination and growth of C. difficile. Credit: *Nature Communications* (2022). DOI: 10.1038/s41467-022-31334-z

Scientists from the Yong Loo Lin School of Medicine, National University of Singapore (NUS Medicine) have created a probiotic to restore bile salt metabolism, found in the gastrointestinal tract, to counter the onset and effects of Clostridium difficile infection (CDI).

CDI is the infection of the large intestine or colon that leads to infectious diarrhea, caused by an infectious bacterium known as Clostridium. Most cases of CDI have been observed to occur in those who have been taking antibiotics or just finished their course of antibiotics.

The administration of antibiotics in the treatment of CDI causes an imbalanced gut microbiome, known as dysbiosis, which can disrupt other microbiome processes such as bile salt metabolism. The dysregulation of bile salt metabolism can activate dormant Clostridioides difficile spores, leading to CDI, causing severe diarrhea and colitis—inflammation of the large intestine, or a reinfection of CDI.

A team of researchers, led by Associate Professor Matthew Chang, from the Synthetic Biology Translational Research Program at NUS Medicine and NUS Synthetic Biology for Clinical and Technological Innovation (SynCTI), engineered a probiotic that can detect the occurrence of antibiotic-induced microbiome imbalance and express an enzyme that can regulate the bile salt metabolism upon detection. This probiotic contains a genetic circuit that comprises a genetically encoded sensor, amplifier and actuator.

The team used an E. coli probiotic strain as the host because of its proven safety record in humans and its gram-negative nature makes it compatible with the current CDI therapy that uses antibiotics targeting gram-positive bacteria. The sensor in this probiotic, detects the presence of sialic acid, a gut metabolite that is indicative of microbiome imbalance. The actuator produces an enzyme that can regulate the bile salt metabolism, activated by the sensor, and it reduces the germination of the Clostridioides difficile spores that causes CDI, when induced by the sialic acid sensor. The team also included an amplifier in the probiotic which amplifies the activation by the sensor and increases the production of the enzyme, reducing the germination of the Clostridioides difficile spores by 98%. Experiments showed that the probiotic significantly reduced CDI in laboratory models, as demonstrated by a 100% survival rate and improved clinical outcomes.

Assoc Prof Chang is encouraged by this advancement that sheds more light on the gut environment and how it can be manipulated to create less invasive treatment strategies. He says, "This scientific innovation gives a better understanding on how we can control the microenvironment in the body, without needing to exert direct lethality to kill the Clostridioides difficile

bacterium, give additional drugs, or use invasive methods to rid the infection. Our perspectives have shifted towards studying how we can come up an antimicrobial strategy to complement and assist the natural biological processes in the body to help limit the onset of infection. This is useful when considering the development or improvement of future therapeutics for CDI."

The paper was published in *Nature Communications* in July 2022.

More information: Elvin Koh et al, Engineering probiotics to inhibit Clostridioides difficile infection by dynamic regulation of intestinal metabolism, *Nature Communications* (2022). DOI: 10.1038/s41467-022-31334-z

Provided by National University of Singapore