Researchers develop basic computing elements for bacteria

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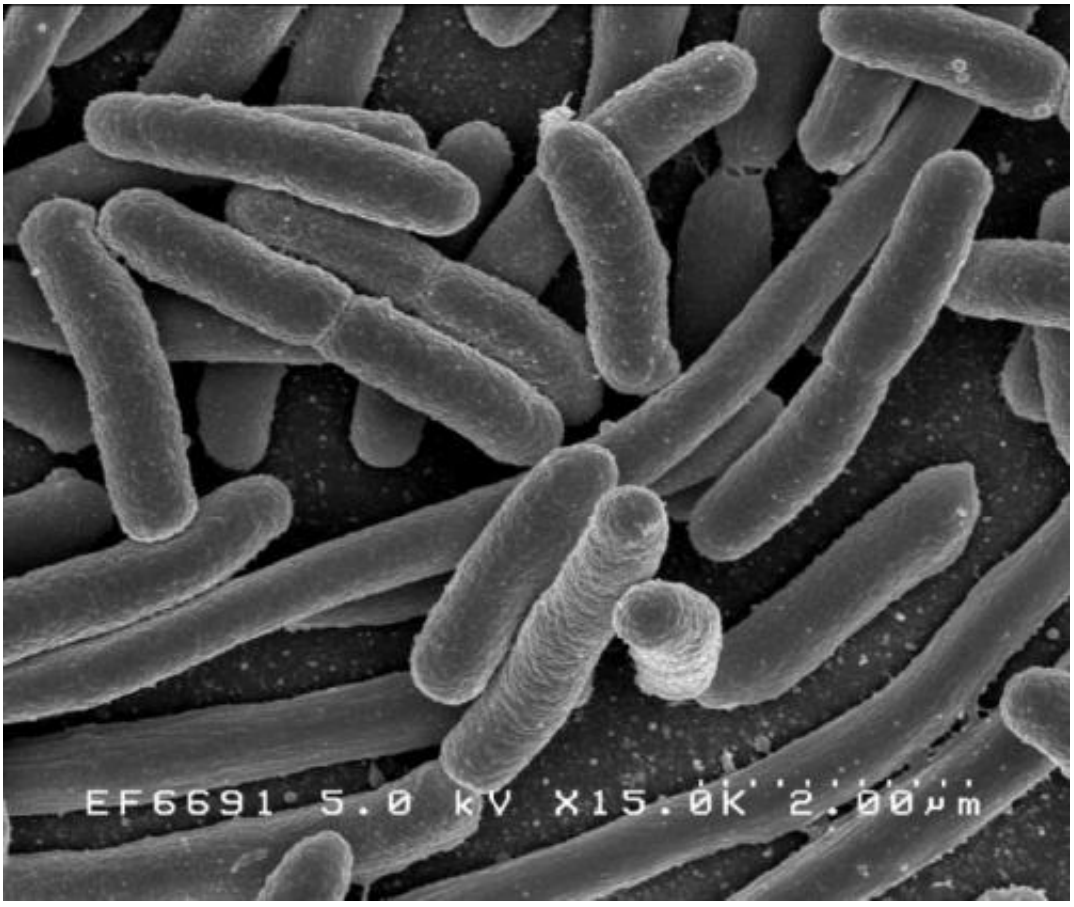

Escherichia coli. Credit: Rocky Mountain Laboratories, NIAID, NIH

The "friendly" bacteria inside our digestive systems are being given an upgrade, which may one day allow them to be programmed to detect and ultimately treat diseases such as colon cancer and immune disorders.

In a paper published today in the journal *Cell Systems*, researchers at MIT unveil a series of sensors, memory switches, and circuits that can be encoded in the common human gut bacterium *Bacteroides thetaiotaomicron*.

These basic computing elements will allow the bacteria to sense, memorize, and respond to signals in the gut, with future applications that might include the early detection and treatment of inflammatory bowel disease or colon cancer.

Researchers have previously built genetic circuits inside model organisms such as *E. coli*. However, such strains are only found at low levels within the human gut, according to Timothy Lu, an associate professor of biological engineering and of electrical engineering and computer science, who led the research alongside Christopher Voigt, a professor of biological engineering at MIT.

"We wanted to work with strains like *B. thetaiotaomicron* that are present in many people in abundant levels, and can stably colonize the gut for long periods of time," Lu says.

The team developed a series of genetic parts that can be used to precisely program gene expression within the bacteria. "Using these parts, we built four sensors that can be encoded in the bacterium's DNA that respond to a signal to switch genes on and off inside *B. thetaiotaomicron*," Voigt says.

These can be food additives, including sugars, which allow the bacteria to be controlled by the food that is eaten by the host, Voigt adds.

Bacterial "memory"

To sense and report on pathologies in the gut, including signs of bleeding

or inflammation, the bacteria will need to remember this information and report it externally. To enable them to do this, the researchers equipped *B. thetaiotaomicron* with a form of genetic memory. They used a class of proteins known as recombinases, which can record information into bacterial DNA by recognizing specific DNA addresses and inverting their direction.

The researchers also implemented a technology known as CRISPR interference, which can be used to control which genes are turned on or off in the bacterium. The researchers used it to modulate the ability of *B. thetaiotaomicron* to consume a specific nutrient and to resist being killed by an antimicrobial molecule.

The researchers demonstrated that their set of genetic tools and switches functioned within *B. thetaiotaomicron* colonizing the gut of mice. When the mice were fed food containing the right ingredients, they showed that the bacteria could remember what the mice ate.

Expanded toolkit

The researchers now plan to expand the application of their tools to different species of *Bacteroides*. That is because the microbial makeup of the gut varies from person to person, meaning that a particular species might be the dominant bacteria in one patient, but not in others.

"We aim to expand our genetic toolkit to a wide range of bacteria that are important commensal organisms in the human gut," Lu says.

The concept of using microbes to sense and respond to signs of disease could also be used elsewhere in the body, he adds.

In addition, more advanced genetic computing circuits could be built upon this genetic toolkit in *Bacteroides* to enhance their performance as

noninvasive diagnostics and therapeutics.

"For example, we want to have high sensitivity and specificity when diagnosing disease with engineered bacteria," Lu says. "To achieve this, we could engineer bacteria to detect multiple biomarkers, and only trigger a response when they are all present."

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