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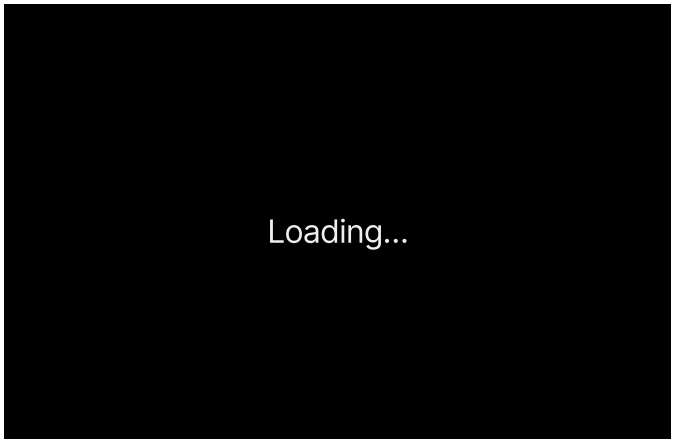
Programming probiotics for early detection of liver cancer

Scientists at the University of California, San Diego and the Massachusetts Institute of Technology (MIT) have described a new method for detecting liver cancer metastases in mice. The approach uses over-the-counter probiotics genetically programmed to produce signals easily detectable in urine when liver cancer metastases are present. The results of the new study, published in the May 27 issue of Science Translational Medicine, indicate that genetically-programmed probiotics may be useful for detecting liver cancer metastases early-on in the progression of the disease.

Liver cancer metastases are difficult to detect with conventional imaging, and new methods are needed that can detect the metastases in a timely matter. The metastatic spread of cancer is ultimately responsible for 90 percent of all cancer-related deaths, and liver metastases are particularly challenging for clinicians due in part to their small size and multiplicity. If metastases are detected early, patients have a much higher chance of survival.

By using probiotics as a platform for early detection of liver metastases in mice, the researchers took advantage of the fact that certain bacteria are able to pass from the gastrointestinal tract directly into the liver – and the fact that certain bacteria are drawn to tumors.



Over the last 100 years or so, scientists have become increasingly aware of bacteria in environments previously thought to be sterile, such as tumors, indicating that bacteria are part of normal human physiology.

“It was discovered in the early 1900s that certain bacteria selectively colonize tumors,” said Arthur Prindle, one of two first-authors on the study, who performed this research as a bioengineering Ph.D. student at UC San Diego. “No one knows for sure, but this could be due to the lack of immune surveillance

and availability of nutrients inside the tumor – the bacteria can grow freely without the interference of the immune system."

Armed with this knowledge, the researchers set out to develop a simple method for detecting liver metastases using a mouse model for liver cancer and the probiotic bacterium E. coli Nissle 1917 (EcN). First, they needed to test the idea that a probiotic taken orally would colonize metastases, something that was only previously demonstrated when bacteria were injected directly into the bloodstream.

"EcN is a safe and widely used probiotic," said Prindle. "In fact, we were able to order it from Amazon and engineer it to express the genes we wanted. Next, we needed to see how it would behave in our mouse model."

This meant shipping off their probiotic to the study's other first author, Tal Danino and senior author and MIT professor Sangeeta Bhatia from the Koch Institute for Integrative Cancer Research at MIT. When Danino received the bacteria, the cells had been engineered by the team at UC San Diego to contain a circular piece of DNA called a plasmid, which expressed a gene that caused the bacteria to generate a luminescent signal from the bacterium's natural production of enzymes.

"Because the bacteria were giving off light, we were able to see that they were localizing to the metastases as we had hoped," said Danino, who earned his Ph.D. in bioengineering at UC San Diego before moving on to MIT. "However, the signal is difficult to detect inside a mouse, and even more so within a human. We needed to come up with another way the bacteria could report the presence of a tumor."

To do that, the group engineered the bacteria to overexpress a LacZ reporter.

LacZ is a gene that encodes the protein beta-galactosidase, an enzyme that causes bacteria to appear blue when grown on a medium that contains its substrate. When inside an animal, the product of the enzymatic activity is excreted in urine and causes it to change color; if liver metastases were present, the urine of the mice turned red.

The researchers also added gene cassettes that would ensure the bacteria that colonized the tumor contained their plasmid – one such set of genes contained a toxin that would kill the bacteria if they mutated so as to lose the plasmid. Another caused the plasmid to move to opposite ends of the bacterial cell during DNA replication, which ensured that each daughter cell would receive a copy.

Possible impact

UC San Diego bioengineering and biological sciences professor and the other senior author on the work, Jeff Hasty, expects the new method will enable the detection of liver cancer at an earlier stage, increasing the chances that it will be treated successfully.

"There are multiple reasons to use probiotics in the early detection of cancer," said Hasty. "First, probiotic bacteria are susceptible to antibiotics, which enables their rapid removal from a

patient's system once they've done their job. Second, probiotics will do what they do best – grow. That means that patients only need to be given enough probiotic bacteria to ensure that one bacterium arrives at its target location."
The study followed these mice for over a year after oral delivery and found no deleterious health effects.

MEDIA CONTACT

Deborah Jude, 858-534-8390, djude@ucsd.edu