A “Living Medicine:” Engineered E. coli Shrink Tumors in Mice

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In a pair of NCI-funded studies, researchers have used an unconventional tool to successfully shrink tumors in mice: the bacterium E. coli. In one study, the researchers used the bacteria to teach immune cells how to find and attack cancer. In the other, they used it to deliver a protein that enhances a commonly used immunotherapy.

Unlike the strain of E. coli that causes food poisoning, the one the researchers worked with—called E. coli Nissle 1917—doesn’t cause illness. In fact, it has been used as a probiotic for more than a century, explained Nicholas Arpaia, Ph.D., an immunologist at Columbia University and lead researcher of the new studies.

In the first study, the researchers engineered E. coli to deliver small bits of tumor proteins to immune cells. Like giving a search-and-rescue dog an old T-shirt of a missing person, the bacteria show the immune cells what the tumor looks like so they can find and attack it. Treating mice with the bacteria educated immune cells and shrank tumors or eliminated them completely.

In the second study, the researchers engineered E. coli to deliver a protein to tumors called interferon gamma, which is critical for immunotherapies to work. In mice, combining an immunotherapy drug with the engineered bacteria kept tumor growth in check longer than either treatment on its own.

The studies were published in October in Nature and Science Immunology, respectively.

“These are early proof-of-concept studies that warrant future follow-up in human studies,” said Lillian Kuo, Ph.D., of NCI’s Division of Cancer Biology, which partially funded the studies.

Some of this research has come out of the now-completed Immuno-Oncology Translational Network, which was part of the Cancer Moonshot℠, Dr. Kuo added.

Using bacteria to make cancer therapies

Certain types of bacteria have a penchant for growing in the crowded, harsh conditions inside tumors. And because bacteria naturally grab the attention of immune cells, they can help trigger an immune response against cancer. Plus, it's relatively easy for scientists to alter bacterial genes, including making multiple genetic changes.

"The cool part is, with bacteria, you have a very large capacity to deliver many different types of therapeutics," said Tal Danino, Ph.D., a biomedical engineer at Columbia University and lead researcher of the new studies.

Together, these characteristics make bacteria an attractive choice for delivering cancer therapies directly to tumors, he said. Indeed, scientists are currently testing many kinds of bacteria-based cancer therapies in clinical studies.

Drs. Danino and Arpaia have previously designed several E. coli–based cancer therapies, including one that delivers modified versions of two immunotherapy drugs. Now they wanted to see if E. coli could be used to deliver other kinds of immunotherapy.

Engineered E. coli as a cancer treatment vaccine

For the first study, the researchers' goal was to make a cancer treatment vaccine—a treatment that teaches the immune system to find and attack cancer.

They engineered E. coli Nissle 1917 to make pieces of 19 abnormal proteins—also called neoantigens—that are found only in mouse colorectal cancer cells. Teaching immune cells to "see" these specific neoantigens not only helps them recognize tumors but also lowers the chances that immune cells will inadvertently damage healthy cells, the researchers explained.

They also made several changes to the bacteria that greatly boosted its capacity to make the tumor proteins and present them to different kinds of immune cells.

In mice with the same colorectal cancer used to identify the neoantigens, a single injection of the engineered bacteria greatly shrank tumors or eliminated them completely—whether the mice had one tumor or multiple metastatic tumors. Mice treated with the engineered bacteria also lived longer.

Various kinds of cancer-fighting immune cells were activated in and around tumors treated with the engineered bacteria. The treatment also tamped down the activity of immune cells that help tumors grow.

And, the researchers said, the approach can be adapted for other types of cancer. For example, the team also engineered bacteria to make tumor proteins from melanoma cells. Treating mice with those bacteria shrank melanoma tumors.

In each of the experiments, mice treated with engineered bacteria didn't lose weight, suggesting that the treatment didn't cause any major side effects.

Given these promising results, the researchers are interested in moving the treatment into human studies. Drs. Danino and Arpaia are involved in a start-up company that aims to develop bacteria-based cancer therapies.

But there are added challenges with human studies, such as personalizing the selection of neoantigens for each patient based on the proteins in their cancer cells, Dr. Danino said. And because the human immune system is more apt than the mouse immune system to react to certain bacteria, the bacteria may need additional genetic tweaks for safety, he continued.

Delivering interferon gamma to tumors

In the second study, the researchers engineered E. coli to deliver interferon gamma, a protein immune cells rely on to help them "see" and attack cancer.

Scientists have long been interested in combining interferon gamma with immunotherapies, particularly immune checkpoint inhibitors, which rev up cancer-killing immune cells.

But the challenge is that, when given as a pill or via an infusion, interferon gamma causes serious side effects. So, the researchers reasoned that delivering interferon gamma directly to tumors using E. coli Nissle 1917 might avoid some of the typical side effects.

They used a previously created strain of the bacteria that burst open and release their inner contents once they have grown to a sufficient number. In this case, each time the engineered bacteria reach the magic number, bacterial "guts" and interferon gamma—which are both giant red flags for immune cells—gush into the tumor.

A single injection of the engineered bacteria substantially slowed colorectal tumor growth in mice. But the tumors started growing again a few weeks after the treatment. However, when the researchers treated mice with the engineered bacteria plus an immune checkpoint inhibitor, tumor growth was kept in check for much longer. And, as hoped, no interferon gamma was detected in the blood of the mice.

The engineered bacteria also slowed the growth of colorectal tumors that were resistant to immune checkpoint inhibitors. That's noteworthy because although immune checkpoint inhibitors can lead to dramatic responses in some patients, these treatments can stop working if tumors figure out how to hide from T cells.

However, the engineered bacteria appeared to activate immune cells called NK cells, which can attack cancer cells that are hiding from T cells, Dr. Arpaia explained.

This shows that the engineered bacteria "can overcome resistance mechanisms [to checkpoint

inhibitors] through the activation of particular immune cell types," he said.

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