Researchers use skin-colonizing bacteria to create a topical cancer therapy in mice

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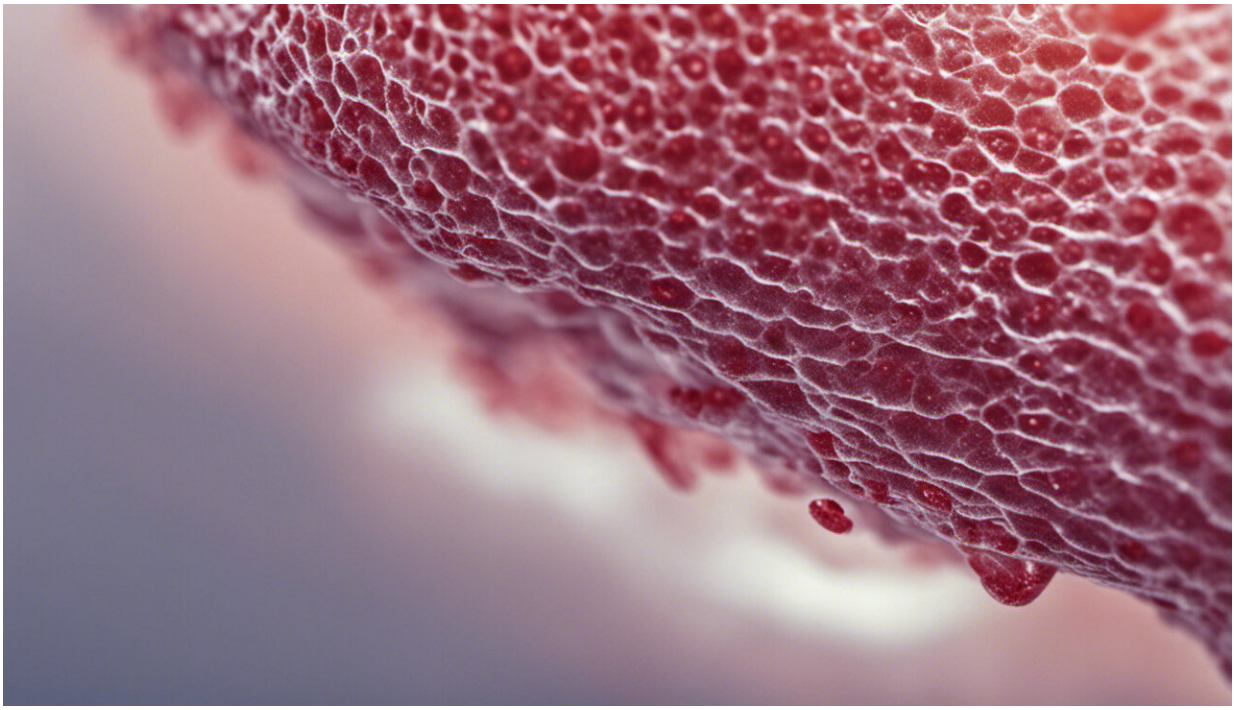

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While studying a type of bacteria that lives on the healthy skin of every human being, researchers from Stanford Medicine and a colleague may have stumbled on a powerful new way to fight cancer.

After genetically engineering the bacteria, called Staphylococcus

epidermidis, to produce a tumor antigen (a protein unique to the tumor that's capable of stimulating the immune system), they applied the live bacteria onto the fur of mice with cancer. The resulting immune response was strong enough to kill even an aggressive type of metastatic skin cancer, without causing inflammation.

"It seemed almost like magic," said Michael Fischbach, Ph.D., an associate professor of bioengineering. "These mice had very aggressive tumors growing on their flank, and we gave them a gentle treatment where we simply took a swab of bacteria and rubbed it on the fur of their heads."

Their research was published online April 13 in *Science*. Fischbach is the senior author, and Yiyin Erin Chen, MD, Ph.D., a former postdoctoral scholar at Stanford Medicine, now an assistant professor of biology at the Massachusetts Institute of Technology, is the lead author.

Skin colonizers

Millions of bacteria, fungi and viruses live on the surface of healthy skin. These friendly colonists play a crucial role in maintaining the skin barrier and preventing infection, but there are many unknowns about how the skin microbiota interacts with the host immune system. For instance, unique among colonizing bacteria, staph epidermidis triggers the production of potent immune cells called CD8 T cells—the "killer" cells responsible for battling severe infections or cancer.

The researchers showed that by inserting a tumor antigen into staph epidermidis, they could trick the mouse's immune system into producing CD8 T cells targeting the chosen antigen. These cells traveled throughout the mice and rapidly proliferated when they encountered a matching tumor, drastically slowing tumor growth or extinguishing the tumors altogether.

"Watching those tumors disappear—especially at a site distant from where we applied the bacteria—was shocking," Fischbach said. "It took us a while to believe it was happening."

The mystery of the T cells that do nothing

Fischbach and his team didn't start out trying to fight cancer. They wanted to answer a much more basic question: Why would a host organism waste energy making T cells designed to attack helpful colonizing bacteria? Especially as these T cells are "antigen-specific," meaning each T cell has a homing receptor that matches a single fragment of the bacterium that activated it.

Even stranger, the CD8 T cells induced by naturally occurring staph epidermidis don't cause inflammation; in fact, they appear to do nothing at all. Most scientists thought colonist-induced T cells must be fundamentally different from regular T cells, Fischbach said, because instead of traveling throughout the body to hunt for their target, they seemed to stay right below the skin surface, somehow programmed to keep the peace between bacteria and host.

To test whether these colonist-induced CD8 T cells could behave like regular killer T cells, the researchers engineered a strain of staph epidermidis to produce a different antigen—one that would generate T cells specific for a commonly studied tumor model in mice.

They genetically grafted a small fragment of DNA encoding part of a protein called ovalbumin onto the surface of staph epidermidis. They chose ovalbumin because it's been engineered into many commonly studied mouse tumor lines, including a type of aggressive melanoma, and therefore can act as a tumor antigen in multiple types of cancer.

The power of tumor-specific T cells

Next, the scientists applied the genetically engineered bacteria to healthy mice. Because staph epidermidis is an efficient skin colonizer, they didn't need to clean or shave the animals' fur, but simply rubbed the bacteria on their heads. As expected, colonization didn't cause any inflammation or infection.

As controls, other mice were treated with either no bacteria, wild-type staph epidermidis (not expressing the ovalbumin peptide) or heat-killed ovalbumin-expressing staph epidermidis, which couldn't colonize the skin because it was dead.

Six days later, the scientists injected the mice with melanoma tumor cells expressing ovalbumin. While all three types of control mice rapidly developed skin tumors, those that had been treated with live, genetically engineered staph epidermidis grew tumors much more slowly and, in many cases, didn't grow tumors at all.

When the researchers went looking for an explanation, they found ovalbumin-specific CD8 T cells in the draining lymph nodes of the skin, in the spleen and in the slowly growing tumors—meaning, Fischbach said, T cells generated by colonizing bacteria must carry the same immune potential as regular killer T cells.

"I honestly hadn't expected it to work," Chen said. "Every other type of tumor vaccine research involves radiation, chemotherapy or surgery, but we barely did anything to these mice. The T cells did the work for us."

15 out of 16 tumors disappeared

To find out whether their method could treat established melanoma, the

researchers tried injecting cancer cells up to two weeks before colonization with the genetically engineered staph epidermidis.

Even when melanoma had metastasized to the lungs, treatment with the bacteria drastically shrank the size of tumors or eliminated them, significantly improving survival times for the mice. The method also worked when the researchers used naturally occurring melanoma antigens, rather than ovalbumin.

When the researchers combined the new treatment with a second type of immunotherapy designed to bolster T cell activity, called "checkpoint blockade," the benefit was even more pronounced: 15 out of 16 established tumors disappeared. When the mice were re-injected with more cancer cells 30 days later, tumors still didn't grow.

"This appears to be evidence of a memory immune response," Fischbach said, "similar to what happens after a vaccine."

The researchers now believe that the host organism produces these T cells to essentially vaccinate itself against the colonists, protecting against inevitable cuts and scrapes that could allow bacteria to breach the skin barrier.

"In these experiments, we've basically tricked the host into thinking that the tumor is bacterially infected," Fischbach said, "and then the host is going after that tumor aggressively."

The scientists also swapped out the melanoma antigen for a prostate tumor antigen and tested their method in a mouse model of prostate cancer. Again, the therapy dramatically slowed tumor growth, suggesting that genetically engineered skin-colonizing bacteria can generate a potent immune response against more than just skin cancer.

Translating the therapy to humans

The researchers are quick to point out that cancer therapies developed in mice don't always work in humans. But Fischbach says there are reasons to be hopeful. First, a previous study led by co-author Yasmine Belkaid, Ph.D., chief of the metaorganism immune section at the National Institutes of Health, showed that staph epidermidis induces the same type of CD8 T cell response in primates as it does in mice. Secondly, while staph epidermidis usually disappears from mouse skin within a few weeks, most humans are permanently colonized with some strain of the bacteria.

"Human skin is the natural home for staph epidermidis," Fischbach said. "In humans, the bug will colonize more efficiently, potentially leading to a constantly renewing supply of tumor-specific T cells."

Other forms of cancer immunotherapy require collecting T cells from a patient, engineering them in the lab to produce a tumor-specific antigen, then injecting them back into the same individual, often with severe side effects.

"We've discovered that the host is vaccinating itself, day in and day out, against organisms that live at barrier surfaces," Fischbach said. "If we can direct even a bit of this immune attention toward specific cancers—or potentially infectious diseases—we will have a very effective, low-cost therapy that can simply be applied to the skin."

More information: Y. Erin Chen et al, Engineered skin bacteria induce antitumor T cell responses against melanoma, *Science* (2023). DOI: 10.1126/science.abp9563

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