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Scientists transform cancer cells into weapons against cancer

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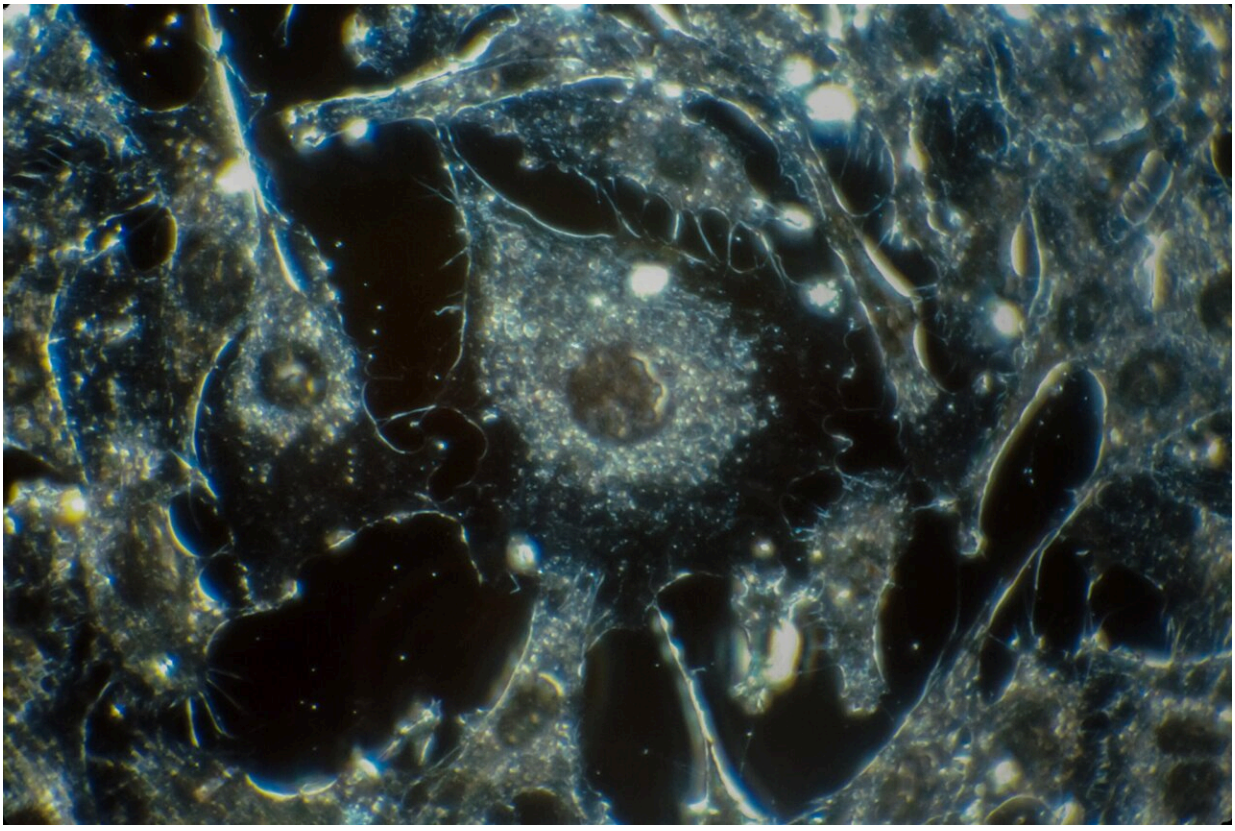

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Some cities fight gangs with ex-members who educate kids and starve gangs of new recruits. Stanford Medicine researchers have done something similar with cancer—altering cancer cells so that they teach

the body's immune system to fight the very cancer the cells came from.

"This approach could open up an entirely new therapeutic approach to treating cancer," said Ravi Majeti, MD, Ph.D., a professor of hematology and the study's senior author. The research was published March 1 in *Cancer Discovery*. The lead author is Miles Linde, Ph.D., a former Ph.D. student in immunology who is now at the Fred Hutchinson Cancer Institute in Seattle.

Some of the most promising cancer treatments use the patient's own immune system to attack the cancer, often by taking the brakes off immune responses to cancer or by teaching the immune system to recognize and attack the cancer more vigorously. T cells, part of the immune system that learns to identify and attack new pathogens such as viruses, can be trained to recognize specific cancer antigens, which are proteins that generate an immune response.

For instance, in CAR T-cell therapy, T cells are taken from a patient, programmed to recognize a specific cancer antigen, then returned to the patient. But there are many cancer antigens, and physicians sometimes need to guess which ones will be most potent.

Like an immune response

A better approach would be to train T cells to recognize cancer via processes that more closely mimic the way things naturally occur in the body—like the way a vaccine teaches the immune system to recognize pathogens. T cells learn to recognize pathogens because special antigen presenting cells (APCs) gather pieces of the pathogen and show them to the T cells in a way that tells the T cells, "Here is what the pathogen looks like—go get it."

Something similar in cancer would be for APCs to gather up the many

antigens that characterize a cancer cell. That way, instead of T cells being programmed to attack one or a few antigens, they are trained to recognize many cancer antigens and are more likely to wage a multipronged attack on the cancer.

Now that researchers have become adept at transforming one kind of cell into another, Majeti and his colleagues had a hunch that if they turned cancer cells into a type of APC called macrophages, they would be naturally adept at teaching T cells what to attack.

"We hypothesized that maybe cancer cells reprogrammed into macrophage cells could stimulate T cells because those APCs carry all the antigens of the cancer cells they came from," said Majeti, who is also the RZ Cao Professor, director of the Institute for Stem Cell Biology and Regenerative Medicine and director of the Ludwig Center for Cancer Stem Cell Research and Medicine.

Ravi Majeti and his colleagues programmed mouse leukemia cells so that some of them could be induced to transform themselves into cells that attacked the cancer from which the cells were derived. Credit: Steve Fisch

Cell conversion

The study builds on prior research from the Majeti lab showing that cells taken from patients with a type of acute leukemia could be converted into non-leukemic macrophages with many of the properties of APCs.

In the current study, the researchers programmed mouse leukemia cells so that some of them could be induced to transform themselves into APCs. When they tested their cancer vaccine strategy on the mouse immune system, the mice successfully cleared the cancer.

"When we first saw the data showing clearance of the leukemia in the mice with working immune systems, we were blown away," Majeti said. "We couldn't believe it worked as well as it did."

Other experiments showed that the cells created from cancer cells were indeed acting as antigen-presenting cells that sensitized T cells to the cancer. "What's more, we showed that the immune system remembered what these cells taught them," Majeti said. "When we reintroduced cancer to these mice over 100 days after the initial tumor inoculation, they still had a strong immunological response that protected them."

"We wondered, If this works with leukemias, will it also work with solid tumors?" Majeti said. The team tested the same approach using mouse fibrosarcoma, breast cancer, and bone cancer. "The transformation of cancer cells from solid tumors was not as efficient, but we still observed positive results," Majeti said. With all three cancers, the creation of tumor-derived APCs led to significantly improved survival.

Lastly, the researchers returned to the original type of acute leukemia. When the human leukemia cell-derived APCs were exposed to human T cells from the same patient, they observed all the signs that would be expected if the APCs were indeed teaching the T cells how to attack the

leukemia.

"We showed that reprogrammed tumor cells could lead to a durable and systemic attack on the cancer in mice and a similar response with human patient immune cells," Majeti said. "In the future we might be able to take out tumor cells, transform them into APCs and give them back to patients as a therapeutic cancer vaccine."

"Ultimately, we might be able to inject RNA into patients and transform enough cells to activate the immune system against cancer without having to take cells out first," Majeti said. "That's science fiction at this point, but that's the direction we are interested in going."

More information: Miles H. Linde et al, Reprogramming Cancer into Antigen Presenting Cells as a Novel Immunotherapy, *Cancer Discovery* (2023). DOI: 10.1158/2159-8290.CD-21-0502

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