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Research on immune-cell therapy could strengthen promising melanoma treatment

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A new study of genetically modified immune cells by scientists from UCLA and the California Institute of Technology could help improve a promising treatment for melanoma, an often fatal form of skin cancer.

The research, which appears March 21 in the advance online edition of the journal *Cancer Discovery*, was led by James Heath, a member of UCLA's Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research and UCLA's Jonsson Comprehensive Cancer Center. Heath is a professor of molecular and medical pharmacology at UCLA and also holds the Elizabeth W. Gilloon Chair in Chemistry at Caltech.

The melanoma treatment uses T cells—immune cells that play a major role in fighting infection—taken from patients with melanoma. The cells are then genetically modified in the laboratory so that when they are reintroduced into a patient's bloodstream, they specifically attack melanoma tumors. In early clinical trials, this treatment was shown to shrink tumors dramatically in many patients, but the positive effects were often short-lived.

The UCLA and Caltech researchers found that after the engineered T cells were returned to patients, their efficacy faded within two to three weeks. Surprisingly, however, once the engineered cells were no longer effective, a new group of non-engineered T cells arose that had a similar tumor-killing effect that lasted even longer, the scientists discovered.

Using newly developed nanotechnology chips to perform multidimensional and multiplexed immune-monitoring assays, the researchers were able to examine at high resolution single engineered T cells taken at different times from patients undergoing the therapy, each of whom had a different level of response to the treatment.

"The engineered T cells did not recover their tumor-killing effect," Heath said, "but after one month, another group of T cells appeared that did have tumor-killing effects for another 90 days. Those were not the genetically engineered T cells, and they appeared to be a byproduct of a process called 'antigen spreading' by the original engineered cells. After 90 days, those cells lost their tumor-killing ability as well."

Antigen spreading is a process by which a T cell that has been engineered to attack a particular tumor expands its immune response to other T cells in the body, which then attack the same tumor but are focused on different antigens. (Antigens are substances that trigger a response by the body's immune system.) Scientists may be able to use this process, Heath stressed, to improve T cell–based treatments for melanoma.

"Our results have led us to possible ways to improve the T cell therapy to extend its positive effect," Heath said. "We need to incorporate strategies that maintain the functional properties of the engineered T cells used for therapy. This might include modifying how we grow the T cells in the laboratory to make their tumor-killing effect last longer or make them resistant to the effects of the patient's T cells as they recover from pretreatment chemotherapy conditioning and possibly increase the antigen spreading of anti-tumor T cells."

UCLA professor of medicine Dr. Antoni Ribas was one of Heath's key collaborators on the research.

"One of the possible approaches to resolve the problem identified by this study is to use engineered blood stem cells—instead of the peripheral blood used in the original trials—with this therapy in the hope that the engineered blood stem cells will provide a renewable source of engineered T cells," said Ribas, a member of UCLA's Broad Stem Cell Research Center and Jonsson Cancer Center.

Caltech's Chao Ma, the study's first author, said the findings and the use of the new nanotechnology assay process hold promise for treatments of other disease as well.

"This study points to the value of these single-cell functional analyses for probing the successes and failures of a sophisticated immunotherapy," he said. "I am excited to see its use as a monitoring tool to understand a spectrum of other cellular immunotherapies in the near future."

Provided by University of California, Los Angeles

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