Functional characteristics of antitumor T cells change w increasing time after therapeutic transfer

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Scientists have characterized how the functionality of genetically engineered T cells administered therapeutically to patients with melanoma changed over time. The data, which are published in *Cancer Discovery*, a journal of the American Association for Cancer Research, highlight the need for new strategies to sustain antitumor T cell functionality to increase the effectiveness of this immunotherapeutic approach.

Early clinical research has indicated that cell-based immunotherapies for cancer, in particular melanoma, have potential because patients treated with antitumor T cells frequently have an initial tumor response; however, those responses are often transient.

"The cell-based immunotherapy we utilized was that of genetically engineered T cells," said James R. Heath, Ph.D., Elizabeth W. Gilloon Professor of Chemistry at the California Institute of Technology in Pasadena, Calif. "This approach is the most widely applicable way to generate large numbers of highly functional antitumor T cells."

Different T cell functions are associated with distinct proteins. Heath and colleagues took a closer look at how genetically engineered T cells functioned or failed after being transferred into patients. To do this, they used a recently developed, multiplexed technology that gave them a high-resolution view of which function-associated proteins individual cells expressed.

The researchers analyzed T cells isolated from blood samples taken from three patients with melanoma at several time points after treatment with genetically engineered antimelanoma T cells. Each of the patients from whom samples were taken had exhibited a different level of response to the immunotherapy.

The most highly functioning genetically engineered antimelanoma T cells made up about 10 percent of the total population of transferred T cells.

"However, they dominated the immune response," Heath said. "In other words, 10 percent of the cells are putting out 100 times more protein than the other cells."

Although these highly functioning genetically engineered T cells had high tumor-killing capabilities when a patient first received them, those capabilities disappeared within two to three weeks.

"The genetically engineered T cells did recover their high functional capacity, but those functions no longer included tumor-killing," Heath said. "However, there was another population of T cells that emerged at around one month that did exhibit tumor-killing characteristics."

These new T cells appeared to be a byproduct, through a process known as epitope spreading, of the original genetically engineered, tumor-killing T cells the patient received, Heath explained. The researchers also discovered one potential cause for the transient response to T cell therapy. Results showed that as the patient's own immune system recovered, after its initial depletion prior to therapy, those recovering T cells appeared to inhibit the antitumor immune response.