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Newly engineered CAR T cells can better discriminate between cancer and normal cells

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A new development in engineering chimeric antigen receptor (CAR) T cells, called affinity tuning, can make the CAR T cells spare normal cells and better recognize and attack cancer cells, which may help lower the toxicity associated with this type of immunotherapy when used against solid tumors, according to a preclinical study.

Many solid cancers have high levels of certain proteins such as ErbB2 and EGFR, which make them suitable targets for anticancer therapies. However, such proteins are also present at low levels in normal cells. Because of this, CAR T cells that are developed to target one of these proteins on tumor cells also recognize and attack normal cells that have the protein, causing severe toxicity. Zhao and colleagues are working to address this challenge.

To develop CAR T cells that can distinguish between cancer and normal cells, Zhao and colleagues first constructed a panel of CARs with the scFvs using sequences from mutated 4D5 antibodies that had varying affinities to ErbB2, a protein present at high levels in some solid tumors, including breast cancer. Next, they incorporated different scFvs into the CAR backbone or "construct," such that they resulted in a range of CAR T cells—from those that had high affinity to ErbB2 to those that had low affinity to ErbB2. The newly engineered CAR T cells varied in their affinity to ErbB2 by three orders of magnitude.

The researchers then conducted a series of experiments to test the functionality of the affinity-tuned CAR T cells and found that high-

affinity CAR T cells did not discriminate tumor cells from normal cells and attacked all of them, whereas low-affinity CAR T cells were sensitive to tumor cells that had high levels of ErbB2 and not to normal cells that had low levels of the protein.

Next, they tested the engineered CAR T cells in mice that bore human cells with high levels of ErbB2 on one side of their bodies and human cells with normal levels of ErbB2 on the other side of their bodies. Here again, low-affinity CAR T cells selectively eliminated cells that had high levels of ErbB2 but had no effect on cells that had normal levels of the protein.

In order to prove that this technology can be extended to other solid tumor targets, the researchers developed low-affinity CAR T cells targeting EGFR, a protein present in high levels in some lung and colon cancers, among others, and preliminary preclinical results showed that these CAR T cells were able to discriminate between cancer cells and normal cells.

In an interview, Zhao said, "CAR T-cell therapies are very promising for leukemias, with high response rates, but adapting this treatment approach to solid tumors has been a great challenge. One of the reasons for this is the lack of good targets.

"I and my colleagues at the laboratory of Carl June, MD, director of the University of Pennsylvania's Center for Cellular Immunotherapies, have been working for the past three years to optimize a system to fine-tune the affinity of single chain variable fragments (scFv)—the part of the CAR T cell that recognizes the tumor target—such that they are able to discriminate tumors that have high levels of a protein from normal tissues that have low levels of the same protein," Zhao explained.

"Unlike the common expectation that lowering the affinity of CAR T

cells might also lower their efficacy, we have shown that lowering the affinity in fact does the opposite—lower-affinity CAR T cells displayed more potent reactivity to tumor cells expressing high levels of the target than did higher-affinity CAR T cells," Zhao said.

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