First in-depth profile of CAR T-cell signals suggests how to improve immunotherapy

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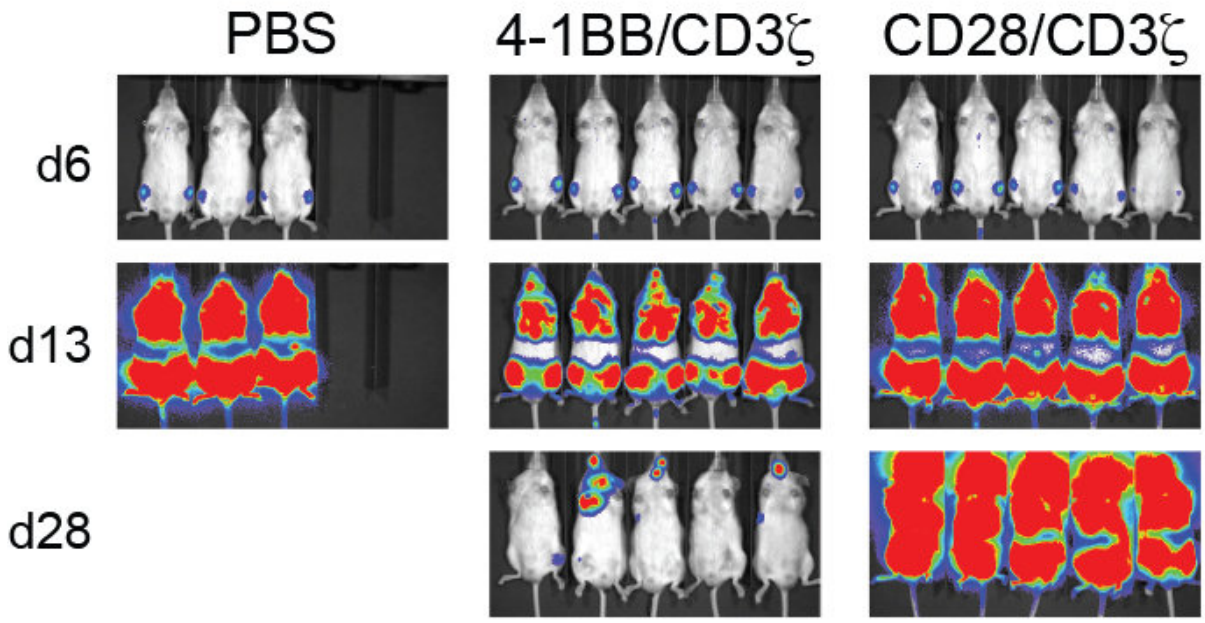

CAR-T cells with stronger signaling intensity were less effective against lymphoma cells in mice (right row, red) compared to CAR-T cells with less intense signaling (middle row). Credit: A.I. Salter et al., *Science Signaling* (2018)

CAR T-cell therapy, which reprograms immune cells to fight cancer, has shown great promise in people with some blood cancers who have not responded to other treatments. But until now, the underlying biological pathways enabling anti-cancer responses have not been thoroughly

examined.

Understanding these pathways is important for designing future generations of CAR T-cell therapies, including reducing side effects, preventing post-treatment relapse, and making them effective against more-common cancers, such as solid tumors.

In a study published Aug. 21 in *Science Signaling*, researchers at Fred Hutchinson Cancer Research Center compared T-cell signaling patterns in two different designs of CARs, short for "chimeric antigen receptors," using lab models. It's the first profiling of its kind to compare two common CAR designs that are used in the clinic.

"The immunotherapy field has had an explosion of interest in the past few years as an emerging new pillar of cancer treatment, and there's been a rush to test CAR T-cell therapies in the clinic," said Dr. Stanley Riddell, lead author of the paper and the scientific director of the Immunotherapy Integrated Research Center at Fred Hutch.

"When we began this study in 2014, we sought to understand the biology of CAR T-cell therapy. Now that we better understand how it works, we have new insights into how to improve this new medicine, which is critically important as the field moves toward designing CAR T-cell therapies for more types of cancers, including solid tumors," Riddell said.

CARs are synthetic receptors that are engineered into a type of immune cell called a T cell. The part of the CAR sticking out of the T cell recognizes cancer cells among healthy cells. The part of the CAR that's within the T cell has different components. Among them is a T-cell signaling unit called a costimulatory domain, which was of interest in the *Science Signaling* paper.

In their study, the researchers studied the differences between CARs built with the two most-commonly used costimulatory domains. Specifically, they examined how these two CAR designs—called CD28 and 4-1BB—signaled their T cells to mobilize against cancer, and how they affected T-cell behavior and effectiveness against human cancer cells in lab dishes and in mice.

"There's been plenty of interest in targeting the T cells to cancer, but little has been known about the instructions that CARs give to the T cells," said Alex Salter, first author and an M.D./Ph.D. student at Fred Hutch and the University of Washington. "I wanted to study how the CARs deliver instructions to T cells."

The researchers found that the same signaling pathways were initiated by both types of CARs but that the timing and intensity of the signal varied, with the CD28 CAR design showing faster and stronger activity and the 4-1BB CAR showing slower and milder activation. Further testing in a mouse model of lymphoma revealed that the 4-1BB CAR was more effective in clearing cancer cells.

The researchers also found:

- A signaling protein in T cells called Lck modulates the intensity of the T cell response in the CD28 CAR design, and the researchers could manipulate it to fine tune the response of the CD28 CAR.
- 4-1BB CAR T cells showed greater expression of genes associated with T-cell memory, suggesting that the 4-1BB CAR signaling may give rise to T cells that can live longer and maintain their anti-cancer effects.

"Our results suggest how different CAR designs could be used for different purposes," Salter said. "The faster, stronger response of the

CD28 CAR might benefit certain cancers whereas the slower, longer-lasting 4-1BB CAR could benefit others."

The comprehensive analysis of proteins involved in T-cell signaling was made possible by a method called mass spectrometry, of which co-author Dr. Amanda Paulovich of Fred Hutch is an expert. The *Science Signaling* paper is the first to use mass spec to measure how thousands of proteins are activated in clinically relevant T cells to carry out T-cell functions.

"We hope by developing a suite of targeted assays to phosphoproteins involved in T-cell signaling, we can help advance the immunotherapy field in developing more effective CAR T-cell therapies for patients," said Paulovich, a member of Fred Hutch's Clinical Research Division.

The researchers caution that their findings don't mean that one CAR is better than another as a treatment, but that the results do support clinical observations for how CARs work in patients and give insights on why some patients experience stronger side effects from CAR T and why some relapse following treatment.

The Fred Hutch team is now exploring how to design the next generations of CARs. For this work, researchers are harnessing multiple reaction monitoring mass spectrometry, a separate technique developed by Paulovich to more rapidly study next-generation CAR designs. These assays will complement other assays developed by her lab to quantify proteins that impact immune system function in tumors.

More information: "Phosphoproteomic analysis of chimeric antigen receptor signaling reveals kinetic and quantitative differences that affect cell function," *Science Signaling* (2018). stke.sciencemag.org/lookup/doi … 26/scisignal.aat6753

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