Researchers identify protein that controls CAR T cell longevity

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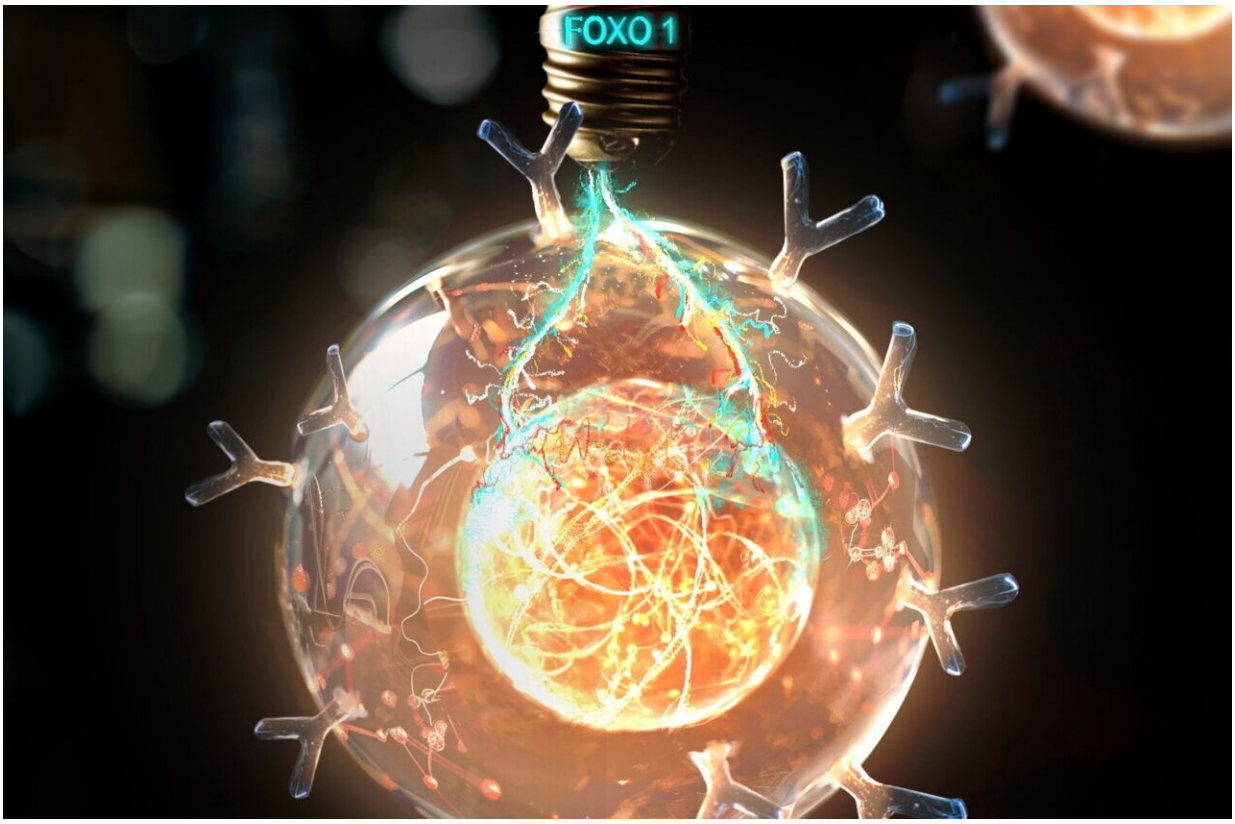

Like a lightbulb, CAR T cells designed to kill cancer often burn out due to exhaustion and poor persistence. Doan et al. discovered that a transcription factor called FOXO1 is responsible for keeping the CAR T lightbulb energized by activating genes which counteract exhaustion, promote persistence, and enhance CAR T cell antitumor activity. (Artwork by Gerardo Sotillo). Credit:

Gerardo Sotillo, Stanford Medicine

CAR T cell therapy has revolutionized the way certain types of cancer are treated, and the longer those CAR T cells live in a patient's body, the more effectively they respond to cancer. Now, in a new study, researchers at Children's Hospital of Philadelphia (CHOP) and Stanford Medicine have found that a protein called FOXO1 improves the survival and function of CAR T cells, which may lead to more effective CAR T cell therapies and could potentially expand its use in difficult-to-treat cancers. The findings were published online in *Nature*.

T cells are a type of immune cell that recognize and kill pathogens in order to protect the host. Cancer is often able to evade the body's immune system, but as a result of CAR T cell therapy, a patient's own T cells can be reprogrammed to recognize and kill these cancer cells, which has led to FDA-approved treatments for certain types of lymphomas and leukemias.

However, fewer than 50% of patients who receive CAR T cell therapy remain cured after a year. One of the reasons for this is that CAR T cells often don't survive long enough in patients to completely eradicate their cancer. Prior research has demonstrated that patients who are cured through CAR T cell therapy often have CAR T cells that live longer and can more successfully fight cancerous cells.

To determine what helps CAR T cells live longer, researchers wanted to understand the underlying biology behind memory T cells, which are a type of natural T cell whose purpose is to persist and retain function. One protein of interest, FOXO1, which activates genes associated with T

cell memory, has previously been studied in mice but remains under-researched in human T cells or CAR T cells.

"By studying factors that drive memory in T cells, like FOXO1, we can enhance our understanding of why CAR T cells persist and work more effectively in some patients compared to others," said senior study author Evan Weber, Ph.D., an Assistant Professor of Pediatrics at the University of Pennsylvania Perelman School of Medicine and cell and gene therapy researcher within the CHOP Center for Childhood Cancer Research (CCCR) and the Center for Cellular and Molecular Therapeutics (CCMT).

To learn more about the role of FOXO1 in human CAR T cells, the researchers in this study used CRISPR to delete FOXO1. They found that in the absence of FOXO1, human CAR T cells lose their ability to form a healthy memory cell or protect against cancer in an animal model , supporting the notion that FOXO1 controls memory and antitumor activity.

Researchers then applied methods to force CAR T cells to overexpress FOXO1, which turned on memory genes and enhanced their ability to persist and fight cancer in animal models. In contrast, when the researchers overexpressed a different memory-promoting factor, there was no improvement in CAR T cell activity, suggesting that FOXO1 plays a more unique role in promoting T cell longevity.

Importantly, researchers also found evidence that FOXO1 activity in patient samples correlates with persistence and long-term disease control, thereby implicating FOXO1 in clinical CAR T cell responses.

"These findings may help improve the design of CAR T cell therapies and potentially benefit a wider range of patients," Weber said.

"We are now collaborating with labs at CHOP to analyze CAR T cells from patients with exceptional persistence to identify other proteins like FOXO1 that could be leveraged to improve durability and therapeutic efficacy."

More information: Evan Weber, FOXO1 is a master regulator of memory programming in CAR T cells, *Nature* (2024). DOI: 10.1038/s41586-024-07300-8.
www.nature.com/articles/s41586-024-07300-8

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