Pushing T cells down 'memory lane' may improve cancer therapy

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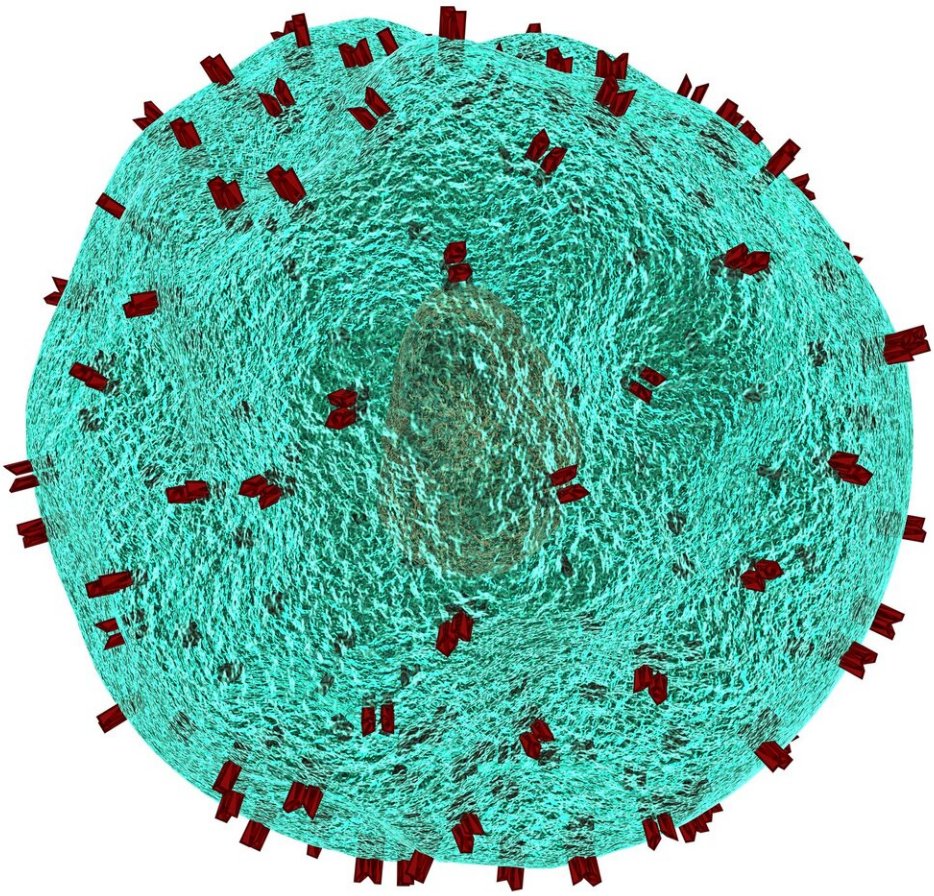

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Scientists at St. Jude Children's Research Hospital identified a molecular mechanism that in a preclinical study unlocked the promise of CAR T-cell therapy for treatment of solid tumors. The results were published today in the journal *Nature*.

"Our work extends from the basic biology of T lymphocytes to a possible application in the clinic, with an exploration of deep molecular mechanisms along the way," said co-corresponding author Doug Green, Ph.D., St. Jude Department of Immunology chair. "We found that just like many of us, if you are an activated T cell, things that happen early in your life can impact your later development. We identified that an interaction between the protein c-Myc and the complex cBAF early in T-cell activation influences cell fate trajectory."

Chimeric antigen receptor (CAR) T cells are a type of immunotherapy that modifies a patient's immune cells to target cancer cells. This type of therapy has had remarkable success in treating children and adults with leukemia and lymphoma, particularly in relapsed patients. However, CAR T cells have not had the same success against solid tumors, with problems involving persistence and function.

Currently too many CAR T cells become effector cells, those that directly kill infected or cancerous cells. Too few become memory cells that persist and create more T cells over the long term. The researchers believed that if they created more memory cells, they could improve CAR T-cell therapy.

"Effector cells do a job and then die," Green said. "Memory cells stick around and can generate effector cells (while maintaining the memory

cell pool) and therefore they can launch continued attacks. So, we think that memory cells likely do a better job of getting rid of tumors."

A molecular mystery

The researchers needed to find what guides T cells to become effector or memory types and then use that knowledge to modify the process. The process begins when a T cell is activated by an antigen, such as a piece of virus or cancer-related molecule. That parental T cell divides into two daughter cells, which can become effector or memory cells.

Green's group recently showed that the distribution of the protein c-Myc in a parental T cell can be important for this process. Researchers knew that a daughter cell with more c-Myc becomes an effector cell. In this study, the team found that the protein complex cBAF (canonical Brg1/Brg-associated factor) interacted with c-Myc. Daughter cells with high cBAF and c-Myc concentrations became effector T cells.

cBAF binds certain regions of chromatin, proteins on DNA. The finding suggests it may guide cell fate, what type of T cell they become, by controlling expression of effector cell related genes.

The distribution of cBAF occurs in the first activated T cell that begins the adaptive immune response; therefore, the researchers realized that cell fate is decided early in the immune response.

A fortuitous finding and collaboration

While Dr. Green's group was studying T cell divisions, co-corresponding author Hongbo Chi, Ph.D., St. Jude Department of Immunology, was studying how a T cell becomes a memory cell. Chi's laboratory used the genetic screening tool CRISPR to knockout genes and observe the

impact on T-cell fate.

"T cells represent a cornerstone for cancer immunotherapy," Chi said. "There is a continuing interest in improving T-cell function for better cancer treatment. As such, my lab is interested in identifying metabolic drivers in T-cell memory responses. Given the crosstalk between metabolic and epigenetic pathways, we did an in vivo CRISPR screen of epigenetic regulators of T-cell memory. That led us to cBAF."

"We were looking at what happens to components of the cBAF complex in activated T cells," Green said. "At the same time, the Chi lab had been fishing in a pond filled with molecules that might influence the cell fate to generate effector versus memory T cells. When we compared notes, we realized that our independent findings were telling us something interesting, so we joined forces."

The groups worked together to confirm that targeting multiple parts of the cBAF complex affects memory T-cell generation. The researchers also found the exact locations in the genome where cBAF components bind and found that cBAF promoted the expression of genes associated with effector cell function.

Together against tumors

The collaborators used the molecular information they discovered to increase CAR T-cell efficacy. They applied a cBAF inhibitor during CAR T-cell activation to generate more memory T cells. In a preclinical model, the inhibitor-treated T cells controlled tumor growth better than untreated cells. The treated cells also survived longer and in larger numbers. The researchers replicated the promising results in multiple solid tumor types. The study is one of the first to show that CAR T cells can be modified transiently to more effectively kill solid tumors.

"cBAF factors are a potential target to boost CAR-T therapeutic effects against cancer," Chi said, "but our work also demonstrates that by better understanding basic immunobiology and T cell function, we can develop better therapeutics for cancer and other diseases."

More information: Douglas Green, Components of the cBAF complex and c-Myc cooperate in early fate decisions of CD8+ T cells, *Nature* (2022). DOI: 10.1038/s41586-022-04849-0. www.nature.com/articles/s41586-022-04849-0

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