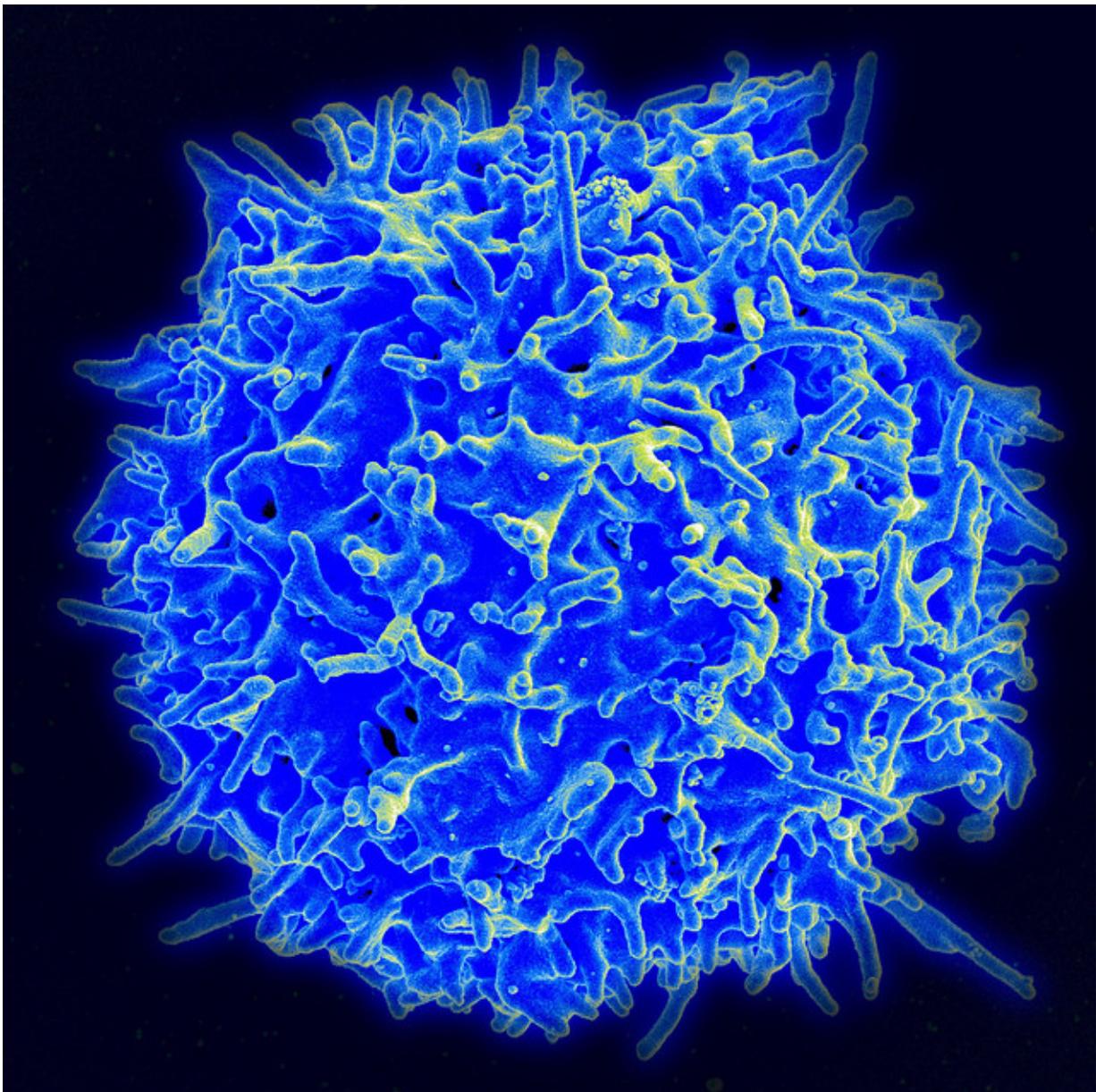


Study uncovers key parts of mechanism for activating T cells to fight cancer and other diseases

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Scanning electron micrograph of a human T lymphocyte (also called a T cell) from the immune system of a healthy donor. Credit: NIAID

In just a few years, CAR T-cell and other adoptive T-cell therapies have emerged as among the most promising forms of cancer immunotherapy. But even as these agents prove themselves against several forms of leukemia and lymphoma—and, potentially, certain solid tumors—basic questions remain about how they work.

In a study published online today by the journal *Immunity*, scientists at Dana-Farber Cancer Institute, Harvard Medical School, Vanderbilt University and colleagues at other institutions show how machinery within immune system T cells responds to outside signals and activates the cells to attack cancerous, infected, or otherwise diseased cells. The findings, based on 15 years of painstaking work to recreate and assemble key components of the signal-processing mechanism, may help researchers fine-tune T-cell therapies to the requirements of individual patients, the study authors say.

T cells, whose surfaces are dotted with structures known as T-cell antigen receptors (TCRs), patrol the body for signs of infection or other disease. As they keep watch, their TCRs lock onto bits of proteins, called antigens, displayed on protein structures decorating the surface of other cells in the human body. The antigens reveal whether a cell is normal or diseased. If a cell is diseased, these "protein bit flags" are recognized as "foreign" and, the T cell switches on, or activates, to kill the diseased cell. In CAR T-cell therapy, billions of a patient's T cells are removed and engineered to produce a structure called a chimeric antigen receptor, or CAR, that recognizes and latches on to a cancer cell. The

resulting CAR T cells—essentially, high-performance versions of ordinary T cells—are then infused into the patient, where they take up the battle against tumor cells. Other TCR immunotherapies use genetically engineered T cells employing natural TCRs rather than chimeric receptors to target specific tumor cell antigens, also called neoantigens. Of note, in every healthy human being there are billions of distinct T cells each bearing unique TCRs and collectively capable of recognizing the myriad antigens that identify [diseased cells](#).

"While CAR T cells, and T cells in general, are often effective in identifying and killing tumor [cells](#), the precise mechanism by which the TCR works hasn't been clear," says the study's lead author, Kristine Brazin, Ph.D., of Dana-Farber and Harvard Medical School. "How is the signal, which originates when the receptor links to a tumor antigen, transmitted through the cell membrane into the cell interior leading to cell activation?"

Answering that question involved a deep dive into the intricacies of the TCR. Far from being a rigid, seamless object, the receptor consists of eight distinct subunits which can move as the TCR operates, even dissociating one subunit pair from one another in a highly choreographed manner.

The most prominent features of the TCR are two long components, dubbed α and β , which are unique to each individual T cell and extend like pincers from the cell membrane to snare a particular cell antigen. Beside α and β , there are six other CD3 subunits common to all TCRs involved in signaling the T cell that the specific pincer has detected antigen. Scientists have had a clear picture of the portions of the TCR that rise from the surface of the cell but knew little about the portions that anchor the receptor in the T-cell membrane.

Brazin and her colleagues focused on the α region of the TCR. Using

nuclear magnetic resonance technology, they determined the structure of the section of TCR α implanted in the membrane. Here a surprise was in store.

"The assumption had been that this region, known as the transmembrane segment, was always straight," Brazin relates. "We found, however, that it is sometimes bent in an L-shaped formation."

When configured like an L, the segment remains largely within the cell membrane. When, like a flexible straw, it straightens up, one end pokes into the cell interior.

"We wanted to understand why this segment is sometimes embedded so shallowly in the membrane—in an L shape," Brazin relates. "We tried to make it straight."

To do that, she and her colleagues made mutant versions of two protein residues that cling to the sides of the transmembrane segment. Mutating one of those residues, called Arg251, caused the segment to become slightly more embedded in the membrane. Mutating the other, Lys256, made it become much more deeply immersed. Other residues were found to regulate the interconversion between bent and straight forms, with the latter jutting further through the cell membrane.

It was on the surface of the cell, however, that this bending and unbending made the biggest difference. When the transmembrane segment is in full L-shape, it presses tightly against the CD3 subunits at its side. When it unbends a little—as when Arg 251 was mutated—that tightness relaxes a bit, and the T cell enters an early stage of activation. When it becomes more fully immersed in the cell membrane, the gap with CD3 widens further and the T cell enters a later stage of activation, ready to attack [tumor cells](#).

"The looser the connection between the transmembrane segment and CD3 subunits, the higher the state of T cell activation," Brazin remarks. "Our findings suggest that the mechanical force of the TCR's interaction with antigens during T cell movement initiates T cell activation by weakening the connection between the transmembrane segment and CD3."

The finding suggests that small-molecule drugs or genetic engineering approaches that widen or narrow the space between the transmembrane segment and CD3 could be used to tune the strength of T-cell attack on cancers or other non-malignant diseases, as needed for individual patients, the researchers say.

"This study represents a success of multidisciplinary basic science, explaining how bioforces involving antigen recognition initiate TCR signaling through the T-[cell membrane](#) with potential for future translational impact," says the study's senior author, Ellis Reinherz, MD, Chief of the Laboratory of Immunobiology and Professor of Medicine in the Department of Medical Oncology at Dana-Farber and Harvard Medical School. "A special scientist such as Kristine Brazin with tireless persistence, focus and intellect was required to solve this mystery over more than a decade of research effort," he added.

More information: Kristine N. Brazin et al, The T Cell Antigen Receptor α Transmembrane Domain Coordinates Triggering through Regulation of Bilayer Immersion and CD3 Subunit Associations, *Immunity* (2018). [DOI: 10.1016/j.immuni.2018.09.007](https://doi.org/10.1016/j.immuni.2018.09.007)

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