Medical Xpress

New insights into T cell exhaustion could improve cancer immunotherapies, study finds

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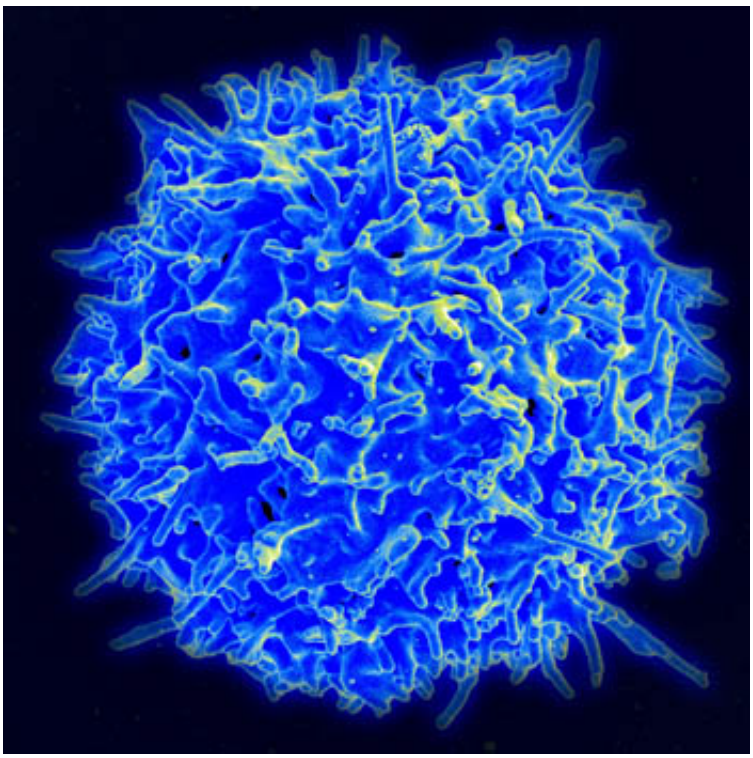

Scanning electron micrograph of human T lymphocyte or T cell. Credit: NIAID/NIH

Specially engineered immune cells called CAR T cells have proven themselves to be a powerful weapon against blood cancers, but against solid tumors they are much less effective, due in part to a process called

T-cell exhaustion. Now researchers at Penn Medicine have illuminated key molecular details of this exhaustion process that point to a specific strategy for overcoming it.

In the study, published Dec. 2 in *Cell*, the researchers developed a lab-dish model that allowed them to comprehensively study the exhaustion process in chimeric antigen receptor (CAR) T cells designed to attack pancreatic tumors. They observed that the T cell exhaustion process in the model closely resembled that seen in patients' T cells. The model also revealed new facets of the exhaustion process, including the role of two genetic regulators of exhaustion, ID3 and SOX4, whose silencing allowed CAR T cells to retain much of their effectiveness against the tumor cells.

"This brings us a step closer to next-generation CAR T cell therapies that will be much more effective against solid cancers," said co-senior author Carl June, MD, the Richard W. Vague Professor in Immunotherapy in the department of Pathology and Laboratory Medicine in the Perelman School of Medicine at the University of Pennsylvania and director of the Center for Cellular Immunotherapies at Penn's Abramson Cancer Center.

The other co-senior author of the study is Shelley L. Berger, PhD, the Daniel S. Och University Professor in the Department of Cell and Developmental Biology at Penn.

CAR T cells are natural infection- and cancer-fighting immune cells (more simply called T cells) that have been harvested from the blood of a patient and genetically reprogrammed. The reprogramming alters the patient's T cells so that they now recognize a marker (antigen) on cancer cells in that patient. The reprogrammed T cells are then multiplied using cell culture techniques and re-infused into the patient to attack the cancer. The technology, which June helped pioneer, has been approved

by the U.S. Food and Drug Administration since 2017 for treating certain lymphomas and leukemias—and in many cases has cured these cancers even when they were at advanced stages.

CAR T cells haven't been as effective against solid tumor-forming cancers, due to an important quirk of T cell biology known as T cell exhaustion, which is thought to have evolved as a way of keeping these powerful immune cells from causing too much collateral damage in the body. Exhaustion is triggered in T cells when they have been exposed for too long—on the order of weeks—to their target antigen, as they typically are in the case of solid tumors.

In the new study, the researchers developed a lab-dish model of T cell exhaustion to study it more closely, in the hope of revealing ways to reverse it They engineered CAR T cells against a cell marker called mesothelin, found on the surface of pancreatic and some other tumors, and kept the T cells exposed to mesothelin-expressing pancreatic tumor cells for four weeks.

The T cells responded by showing classic signs of exhaustion, but also signs that had not been evident in prior studies. These novel exhaustion phenomena included an identity change among some of the T cells, such that they partly reverted to an immune cell type, the NK cell, which has been considered a distant cousin of T cells. The scientists found signs of this same T cell to NK-cell transition among exhausted CAR T cells from cancer patients.

Perhaps most importantly, the scientists observed that CAR T cell exhaustion was accompanied by surges in the levels of two proteins, ID3 and SOX4, that work as master switches for large sets of genes in immune cells. Silencing these apparent T cell exhaustion switches allowed the exhausted CAR T cells to retain much of their tumor-killing effectiveness even after prolonged exposure to tumor cells.

The study therefore points to a specific strategy—inhibiting ID3 and/or SOX4—that might help CAR T cells work much better against solid tumors.

"These findings are exciting because of their potential clinical implications, but also because they essentially validate our new cell-based model's utility for exploring CAR T cell biology and continually improving this immunotherapy for the benefit of patients," said co-senior author Regina Young, PhD, director of research operations for the Center for Cellular Immunotherapies at Penn.

More information: Charly R. Good et al, An NK-like CAR T cell transition in CAR T cell dysfunction, *Cell* (2021). DOI: 10.1016/j.cell.2021.11.016

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