New CAR T cell therapy using double target aimed at solid tumors

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Chimeric antigen receptors (CARs), engineered from a patient's own immune cells, have been successful for treating blood cancers, but using CARs for solid tumors has been limited by side effects to normal tissues containing the protein targeted by the engineered cells.

Now, in this month's issue of *Immunity*, a research team from the Perelman School of Medicine at the University of Pennsylvania describes how an antibody that recognizes the combination of a known cancer-associated surface protein and a cancer-associated carbohydrate can be applied as a CAR-based therapy for a wide range of solid tumors. The team demonstrated the new CARs' effectiveness in mouse models of pancreatic cancer.

"We engineered T cells to target a cancer-associated surface protein with shortened carbohydrate molecules," said first author Avery Posey, PhD, an instructor in Pathology and Laboratory Medicine. "Future cancer immunotherapies combining the targeting of cancer-specific carbohydrates and cancer proteins may lead to the development of incredibly effective and safe new therapies for patients. These engineered cells will be able to increase cancer specificity of this immunotherapy and decrease the potential for toxicity in patients."

In general, CAR T cell therapy involves collecting T cells from a patient's blood through a process similar to dialysis and engineering them to express cell-surface proteins that recognize specific molecules on the surface of cancer cells. The modified T cells are then given back to the patient to target and kill those cancer cells.

Posey, along with co-senior authors Laura Johnson, PhD, director of the Solid Tumor Immunotherapy Laboratory in the Center for Cellular Immunotherapies, and Carl June, MD, the Richard W. Vague Professor in Immunotherapy and director of the Center for Cellular Immunotherapies, and colleagues from the University of Copenhagen and University of Chicago, developed CAR T cells that express an antibody that specifically recognizes truncated carbohydrate molecules on a mucin 1 (MUC1) protein, which is absent on normal cells but abundant on cancer cells of many types of solid tumors and leukemias.

When these CAR T cells were injected into mice with leukemia or pancreatic cancer, the tumors shrank, and were even eliminated in most animals, resulting in increased survival. The mice with pancreatic cancer were still alive 113 days after treatment with the CAR T cells; however, only one-third of the animals treated with CAR T cells that did not target the MUCI proteins with the truncated carbohydrate survived until the end of the experiment. Importantly, the CAR T cells could not damage normal human cells or cells without the abnormal carbohydrate.

In addition, demonstrating through high-powered microscopy that normal cells express the immature, cancer-related version of the MUC1 protein only inside the cell while cancer cells shuttle the abnormal protein to the cell surface, was helpful to show why these CAR T cells can only recognize the cancer-specific protein on tumors.

These findings suggest that targeting abnormal, cancer-specific carbohydrates on proteins found in normal tissues and solid tumors could become a new immunotherapy for solid cancers. This combined tumor targeting may lead to future development of safe and effective therapies for patients.

Posey is currently collaborating with University of Copenhagen colleague and co-author Catharina Steentoft, PhD to develop new therapies of this class. "Our study demonstrated safety and efficacy of this novel approach of cancer targeting,"

Johnson said. "We are continuing to evaluate the safety of this therapy in additional models. Once the new models are complete, we plan to move this therapy into a phase I clinical trial for patients with solid tumors."

More information: Immunity, Pingen et al: "Host inflammatory response to mosquito bites enhances severity of arbovirus infection." www.cell.com/immunity/fulltext … 1074-7613(16)30205-9 , DOI: 10.1016/j.immuni.2016.05.014

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