CAR T-Cell Therapy For Solid Tumors

By ACSH Staff — June 22, 2016

In recent clinical trials, Chimeric antigen receptor (CAR) T cell therapy, which edits a cancer patient's T cells to recognize their tumors, has dramatically improved the outcomes of blood cancer patients with advanced, otherwise untreatable forms of leukemia and lymphoma, but has yet to show the ability to treat solid tumors, the leading cause of cancer-related deaths, because they have targeted molecules found on the surface of both normal cells and cancer cells, resulting in serious side effects.

To overcome this hurdle, researchers in a new Immunity report [1] show they have genetically engineered human T cells to produce a CAR protein that recognizes a glycopeptide found on various cancer cells but not normal cells, and then demonstrated its effectiveness in mice with leukemia and pancreatic cancer.

It's proof-of-concept in mice, this type of therapy is still very new, and there are numerous factors that are involved at the tumor level that may limit treatment. In particular, more pre-clinical trials will be needed to determine the safety of this therapy in advanced mouse models that can more accurately predict safety in humans, and its efficacy specifically against metastatic cancer.

CAR T cell therapy involves engineering patients' own immune cells using the CRISPR/Cas9 system to recognize and attack their tumors. T cells are collected from the patient's blood and genetically engineered to express cell-surface proteins called CARs, which recognize specific molecules found on the surface of cancer cells. The modified T cells are then infused into the patient's bloodstream, where they target and kill cancer cells.

*MUC1 and Tn-MUC1 on normal and cancerous tissues. Section A) Confocal microscopy of normal human kidney immunostained for cell surface protein EpCAM (red) and normal MUC1. Normal MUC1 is found at the cellular surface in human kidney. Section B) Normal human kidney immunostained for EpCAM and Tn-MUC1 (green). Tn-MUC1 is found intracellular in normal MUC1-expressing tissues. Section C) Human breast cancer immunostained for EpCAM and Tn-MUC1. Tn-MUC1 is found at the cell membrane in cancer. Credit: Avery, Posey et al.*

The targeted immunotherapy occurred because they were able to find a marker on the tumor of a colleague with end-stage cancer - and it was on just about every other tumor they tested also. The cancer cell marker was a specific change in protein glycosylation, a unique pattern of sugars decorating a protein found on the cell surface. The researchers developed novel CAR T cells that express a monoclonal antibody called 5E5, which specifically recognizes a sugar modification--the Tn glycan on the mucin 1 (MUC1) protein--that is absent on normal cells but abundant specifically on cancer cells.

The 5E5 antibody recognized multiple types of cancer cells, including leukemia, ovarian, breast,
and pancreatic cancer cells, but not normal tissues. Injection of 5E5 CAR T cells into mice with leukemia or pancreatic cancer reduced tumor growth and increased survival. All six mice with pancreatic cancer were still alive at the end of the experiment, 113 days after treatment with 5E5 CAR T cells. Meanwhile, only one-third of those treated with CAR T cells that did not target Tn-MUC1 survived until the end of the experiment.

"This is the first approach using a patient's own immune cells that can specifically target this class of cancer-specific glycoantigens, and this has the great advantage of applicability to a broad range of cancers," says first author Avery Posey, an instructor at the Perelman School of Medicine of the University of Pennsylvania. "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."

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