MedicalXpress

Prior chemotherapies may impair ability to develop effective CAR T-cells

March 19 2018

Pediatric patients with solid tumors may have poor quality T cells compared to patients with leukemia, and certain chemotherapies were detrimental to the T cells and their potential to become CAR T cells, according to data presented during a media preview for the AACR Annual Meeting 2018, April 14-18, in Chicago, Illinois.

"The FDA approval of tisagenlecleucel (Kymriah), a CD19-targeted chimeric antigen receptor T-cell therapy (CART), was a landmark moment for childhood cancer therapy," said David M. Barrett, MD, Ph.D., assistant professor of pediatrics at Children's Hospital of Philadelphia. "This therapy takes a patient's own immune cells, called T cells, and modifies them in the lab to wake them up and recognize that patient's leukemia.

"In several of the patients with leukemia we first attempted to treat, we noticed the T cells looked exhausted when we first collected them and they either did not survive the lab process to turn them into CAR T cells or did not have enough energy left to work in the patient as a result," he added.

In order to modify T cells into CAR T cells, the T cells from the patient must be healthy enough to survive in the lab and then have enough energy left once returned to the patient to kill their cancer, Barrett explained. "This is important because these children did not have any other therapies that could potentially cure their cancer and we didn't even get to try in some of them because their T cells were too poor in

quality."

Barrett and colleagues wanted to understand why some children have poor quality T cells. "We were interested in learning what made good starting material for CAR manufacture, rather than repeating prior work on learning what a good CAR T cell looks like after it has been made."

The team found that T cells that use glutamine and fatty acid pathways as fuel sources had great CAR T-cell potential while those that depended on glycolysis, another fuel source, were poorly suited to the process of CAR T manufacture.

The researchers collected peripheral blood samples from 157 pediatric patients with acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia, non-Hodgkin lymphoma, Hodgkin lymphoma, neuroblastoma, osteosarcoma, rhabdomyosarcoma, Wilms tumor, or Ewing sarcoma, at diagnosis and after each cycle of chemotherapy.

The researchers found that the CAR T-cell potential of the T cells was very poor in all tumor types except ALL and Wilms tumor in the pre-chemotherapy samples, and noticed a decline in CAR T-cell potential with cumulative chemotherapy in all cancer types. They found that the T cells with poor CAR T-cell potential were biased toward using glycolysis as their fuel source instead of using fatty acids.

They also found that certain types of chemotherapy were especially harmful to the "spare respiratory capacity" (SRC) of T cells. "SRC is a measure of the energy reserve of a cell, and is based on how many mitochondria are present and how healthy they are," said Barrett. Mitochondria are the energy generators of a cell. Having a poor energy reserve means the T cell will die before it has finished killing a patient's cancer or may not even work at all, he said.

"We have gotten CAR T cells to work for leukemias but not yet been very successful in solid tumors. There are a number of potential reasons for this, but our data suggest poor T-cell starting material may be a key first problem," Barrett noted.

"The T cells from solid tumor patients may need different manufacturing protocols to be successful," he added.

The researchers conducted preliminary experiments and demonstrated that it is possible to force the T cells to use fatty acids, the preferred source of fuel, to restore the SRC in chemotherapy-exposed T cells. "These early results give us hope we can exploit this during manufacturing of CAR T cells to make highly active products we otherwise would not have from standard manufacturing approaches," Barrett said.

A limitation of the study is that the researchers did not make CAR T cells from these patients, but used a surrogate small-scale procedure that correlates with CAR T-cell performance. "We have not yet fully validated the metabolic pathways via complete metabolite analysis, though this is underway," Barrett said.

Provided by American Association for Cancer Research