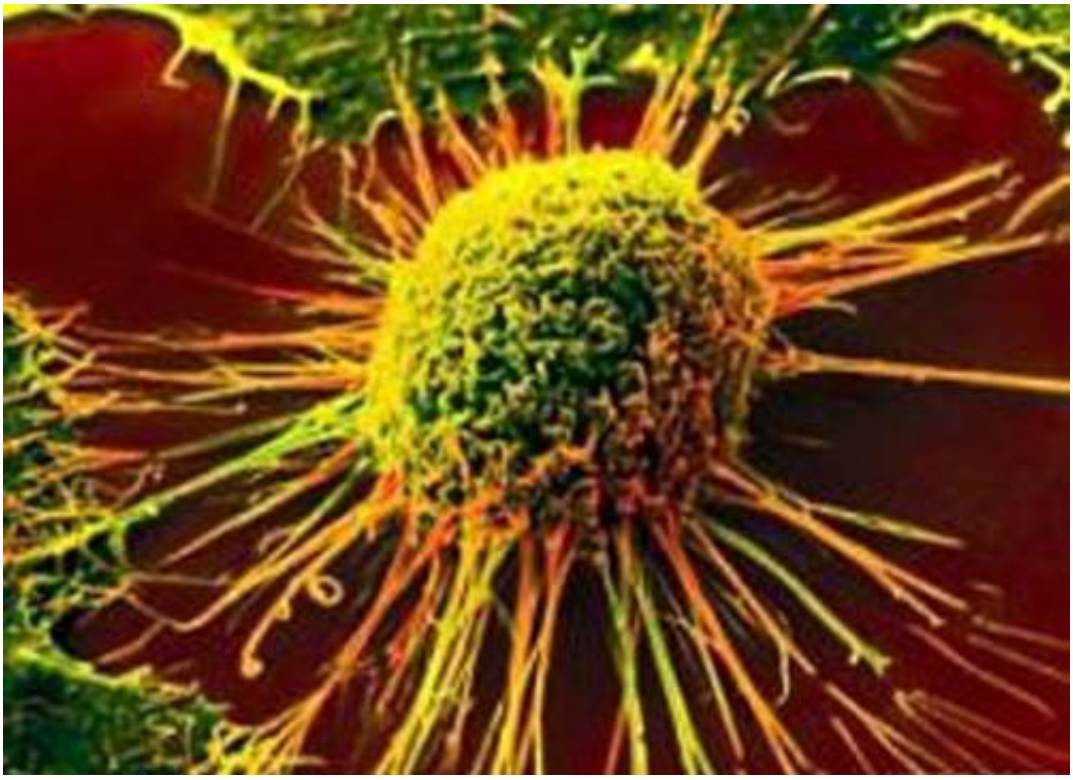
MedicalXpress

Researchers identify cancer cell defect driving resistance to CAR T cell therapy

January 30 2020



Some cancer cells refuse to die, even in the face of powerful cellular immunotherapies like CAR T cell therapy, and new research from the Abramson Cancer Center of the University of Pennsylvania is shedding light on why. In a new study, researchers describe how a death receptor pathway in the cancer cell itself plays a central role in determining its

response to CAR T cells. It's the first study to show that natural cancer features can influence response to CAR T cells, and that cancer cells can drive the development of CAR T cell dysfunction. The findings may provide guidance for future immunotherapies in patients whose blood cancers are resistant to CAR T therapy. The findings published today in *Cancer Discovery*, a journal of the American Association for Cancer Research.

CAR T cell therapy modifies patients' own immune T cells, which are collected and reprogrammed to potentially seek and destroy cancer cells. After being infused back into patients' bodies, these cells both multiply and attack, targeting cells that express a protein called CD19. In acute lymphoblastic leukemia (ALL), between 10 and 20 percent of patients have disease that is resistant to CAR T cells, but until now, researchers did not understand why.

"Most theories have centered around a defect in the T cells, but what we've shown here is that the problem originates in an important death signaling pathway in the cancer cell itself, which prevents the T cell from doing its job," said the study's co-senior author Marco Ruella, MD, an assistant professor of Hematology-Oncology in the Perelman School of Medicine at the University of Pennsylvania and a member of the Center for Cellular Immunotherapies in Penn's Abramson Cancer Center. Ruella's co-senior author is Saar Gill, MD, Ph.D., an assistant professor of Hematology-Oncology at Penn.

Researchers first performed a genome-wide CRISPR/Cas9-based screen of an ALL cell line known as Nalm6 to isolate pathways associated with resistance. CRISPR is a gene-editing tool that can effectively target specific stretches of genetic code, as well as modify DNA at precise locations for experiments and in some instances treatment. Cells were edited for loss of function of single genes and combined with CAR T cells for 24 hours to identify the pathway driving the primary resistance.

The team discovered that in ALL cells resisting CAR T attack, there was depletion of genes involved in activating the cell death pathway (FADD, BID, CASP8 and TNFRSF10B) and enrichment of genes required for resisting the cell death pathway (CFLAR, TRAF2 and BIRC2). When they tested this in animal models, the effect was even greater than what they had observed in vitro. The researchers were initially mystified by this discrepancy, prompting them to study the effect of the cancer on the T cells trying to kill it. This led them to the discovery that prolonged survival of cancer cells led to T cell dysfunction.

The team then explored the clinical relevance of these findings using pediatric patient samples from previous CAR T trials by analyzing the genes in leukemia cells and in T cells—pre- and post- infusion—from responders and non-responders. They found that the previously identified signaling pathways in cancer cells were directly associated with responses to CAR therapy in the patients from two clinical trials, further suggesting that death receptor signaling is a key regulator of primary resistance to CAR T cell therapy in ALL.

"We now know that resistance occurs in two phases: the cancer cells' initial resistance to death, followed by the cancer's ability to impair T cell function," said co-first author Nathan Singh, MD, MS, who led the work while he was a post-doctoral researcher with Carl June, MD, the Richard W. Vague Professor in Immunotherapy and director of the Center for Cellular Immunotherapies. Singh is now an assistant professor of Medicine at Washington University School of Medicine in St. Louis and a research member of Siteman Cancer Center. "Together, this leads to CAR T cell failure that allows the disease to progress."

Researchers say these findings suggest the use of heathy donor T cells for CAR T manufacturing may face the same barriers as cells used from the patient.

"This will also inform future research investigating new and improved CAR T cells that have the ability to overcome this resistance, along with therapies that target the defective signaling pathway in cancer cells," Gill said.

More information: Nathan Singh et al. Impaired death receptor signaling in leukemia causes antigen-independent resistance by inducing CAR T cell dysfunction *Cancer Discov* January 30 2020. DOI: 10.1158/2159-8290.CD-19-0813

Provided by Perelman School of Medicine at the University of Pennsylvania