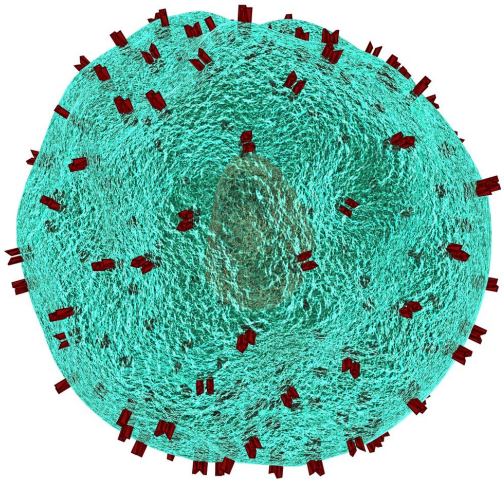
Targeting one type of immune cell with another slows cancer growth in preclinical studies

October 25 2022



Credit: CC0 Public Domain

A new approach to cancer immunotherapy that uses one type of immune cell to kill another—rather than directly attacking the cancer—provokes a robust anti-tumor immune response that shrinks ovarian, lung, and pancreatic tumors in preclinical disease models, according to researchers at the Icahn School of Medicine at Mount Sinai in New York. The findings were published in *Cancer Immunology Research*.

The study involved a twist on a type of therapy that uses immune cells known as CAR T cells. CAR T cells in current clinical use are engineered to recognize cancer cells directly and have successfully treated several blood cancers. But there have been challenges that prevent their effective use in many solid tumors.

Most solid tumors are heavily infiltrated by a different type of immune cell called macrophages. Macrophages help tumors grow by blocking the entry of T cells into tumor tissue, which prevents CAR T cells and the patient's own T cells from destroying the cancer cells.

To tackle this immune suppression at the source, the researchers engineered T cells to make a "chimeric antigen receptor" (CAR) that recognizes a molecule on the surface of macrophages. When these CAR T cells encountered a tumor macrophage, the CAR T cell became activated and killed the tumor macrophage.

Treatment of mice bearing ovarian, lung, and pancreatic tumors with these macrophage-targeting CAR T cells reduced the number of tumor macrophages, shrunk the tumors, and extended their survival.

The killing of tumor macrophages allowed the mouse's own T cells to access and kill the cancer cells. The investigators further demonstrated that this anti-tumor immunity was driven by release of the cytokine interferon-gamma—a molecule involved in the regulation of inflammatory responses—from the CAR T cells.

"Our initial goal was just to use the CAR T cells to kill the immunosuppressive macrophages, but we discovered they were also boosting tumor immunity by releasing this powerful immune-boosting molecule," said senior author Brian Brown, Ph.D., Director of the Icahn Genomics Institute and Associate Director of the Marc and Jennifer Lipschultz Precision Immunology Institute (PrIISM) at Icahn Mount Sinai. "It was a one-two punch from this single treatment."

Shifting the sights of CARs from cancer cells to tumor macrophages potentially addresses another key barrier to the successful elimination of solid tumors with CAR T cells. There are very few proteins found exclusively on cancer cells and not on healthy tissues that can be used to target cancer cells in solid tumors directly without damaging the healthy tissue.

The macrophages found in tumors that suppress immunity are very similar across different types of cancer and very different from macrophages in healthy tissues. This has led to an interest in macrophage-depleting agents for cancer therapy, but approaches developed to date have had limited success in clinical trials.

"Our molecular studies of human tumors have revealed macrophage subsets present in human tumors and not in normal tissues and are similar across tumors and across patients. So macrophage-targeting CAR T cells could be a broad way to target different types of solid tumors and improve immunotherapy," said Miriam Merad, MD, Ph.D., co-senior author of the study, and Director of PrIISM.

Next, the researchers are working on tumor macrophage-specific CAR and generating humanized versions of the genetic instructions, so that they can be introduced into cancer patients' own T cells.

More information: Alfonso R. Sánchez-Paulete et al, Targeting Macrophages with CAR T Cells Delays Solid Tumor Progression and Enhances Antitumor Immunity, *Cancer Immunology Research* (2022). DOI: 10.1158/2326-6066.CIR-21-1075

Provided by The Mount Sinai Hospital