Why tumors evade immunotherapy

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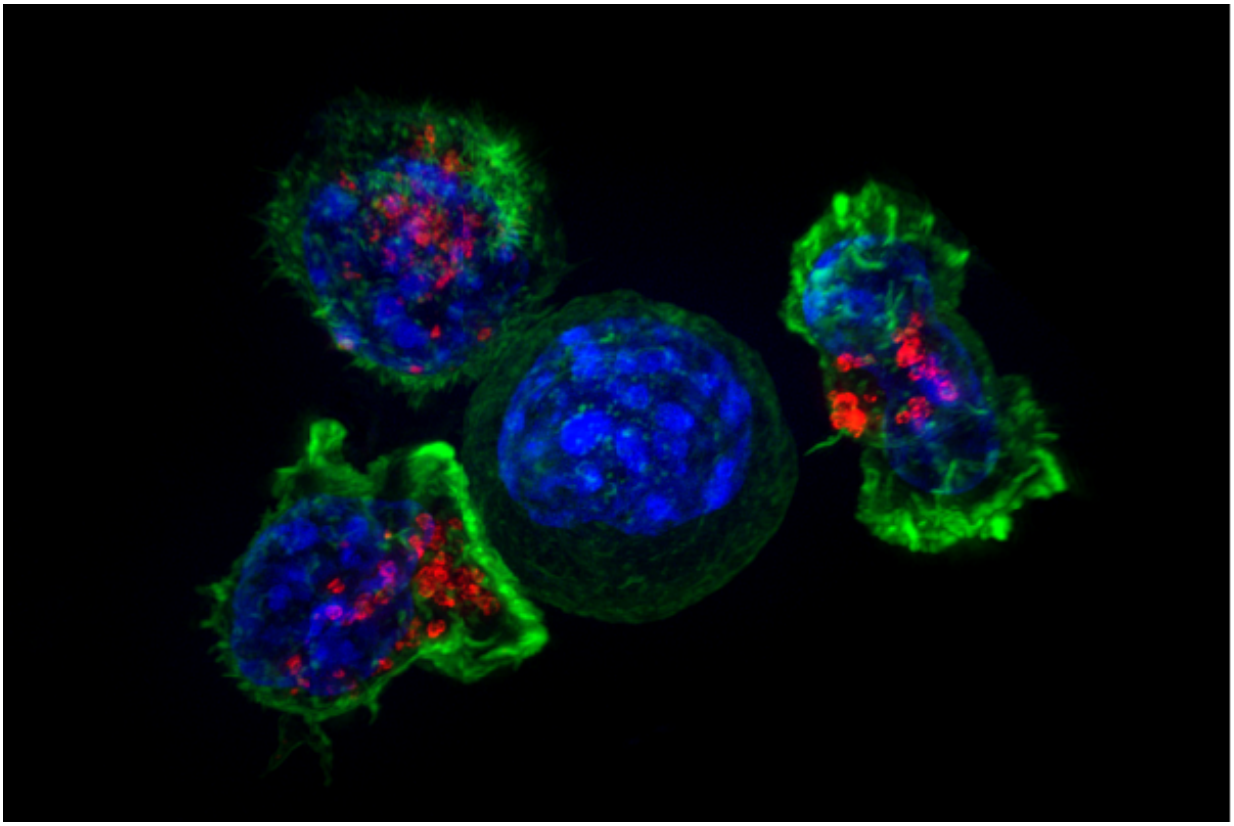

Credit: Max Delbrück Center for Molecular Medicine in the Helmholtz Association

Immunotherapy is a new and highly promising form of treatment for cancer. In many patients, however, tumors recur after immunotherapy. In the latest issue of the *Journal of Experimental Medicine*, the members of a research team from the Max Delbrück Center for Molecular

Medicine (MDC) in the Helmholtz Association, the Berlin Institute of Health (BIH), and Charité – Universitätsmedizin Berlin explain why some tumors recur and how this can be prevented. The findings will aid the selection of suitable targets for immunotherapy.

One form of immunotherapy for cancer is T-cell receptor gene therapy. It involves removing T-cells (a type of immune cell) from the blood and altering them in the test tube to enable them to target cancer cells. The cells are then re-introduced into the patient's bloodstream, where they find and destroy the tumor cells. In clinical trials, this procedure has proved effective for some types of cancer, but it has often been found that new tumors recurred after treatment.

"The tumors are not recognized by the T-cells," explains biologist Dr. Ana Textor. The postdoc researcher in the team headed by Prof. Thomas Blankenstein at the MDC and the Charité is the lead author of the current study. "We want to find out how to reduce the frequency with which the cancer recurs after treatment," says Dr. Textor.

T-cells kill cells bearing certain molecules on their surface

To achieve this, Textor focused on a particular molecule on the cell surface, the epitope. Epitopes are at the heart of the immune response. They are produced inside the cell by specialized enzymes, which split and trim proteins into short fragments and send them to the cell surface as epitopes.In cancer, proteins are pathologically altered through mutation; they too appear on the cell surface, in this case as "neo-epitopes."A cell with a neo-epitope can be recognized by T-cells, which then destroy the cell.

Some epitopes escape the modified T-cells

Successful T-cell receptor gene therapy involves training T-cells with the help of a suitable neo-epitope. T-cells are modified to recognize the neo-epitope and thus recognize and destroy the tumor.

In their experiments, the researchers trained two different types of T-cell, each of which recognized one of two epitopes that are characteristic of tumors. One of the T-cell types permanently destroyed the tumors in a mouse model. After treatment with the other T-cell type, initial tumor regression was followed by recurrence.

Epitopes are produced in the cell in different ways

The researchers found that when the tumor recurred, the epitopes were no longer present on the cell surface in sufficient quantity.This was because the epitopes in these cancer cells were no longer correctly trimmed enzymatically – in this case by the enzyme ERAAP.ERAAP is not being properly activated until the cell is stimulated by the signal molecule interferon gamma.The tumor cells, however, were insensitive to interferon gamma and could no longer be recognized by the T-cells because they were no longer producing the epitope.

By contrast, the epitopes on the cells of the successfully treated tumor did not require processing by ERAAP and were therefore also not dependent on stimulation by interferon gamma.

The new findings thus represent an important step towards the more successful application of T-cell receptor gene therapy, as Textor explains: "Epitopes that do not need processing by the enzyme ERAAP are therefore likely to be a better choice for immunotherapy."

More information: Ana Textor et al, Preventing tumor escape by targeting a post-proteasomal trimming independent epitope, *The Journal*

of Experimental Medicine (2016). DOI: 10.1084/jem.20160636