A protein converts immune cells to tumor killers

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Tumor cells are masters at evading detection. But new research from Rockefeller University shows how they can be exposed. By harnessing the immune system of patients with a rare neurological disorder, scientists have figured out how to transform immune cells that barely detect the presence of breast and ovarian tumors into ones that obliterate them.

The findings, which appear in this week's issue of the *Proceedings of the National Academy of Sciences*, not only bring researchers closer to a therapy for gynecological cancers, but also to the key that could unlock the general secrets of tumor immunity.

"It's a very romantic notion that the immune system recognizes tumors as foreign substances and kills them off," says first author Bianca Santomasso, a biomedical fellow. "Instead of using the slash, burn and poison approach of surgery, radiation therapy and chemotherapy, we are trying to harness naturally occurring tumor immunity from patients with paraneoplastic cerebellar degeneration to treat ovarian and breast cancer patients."

The research, led by Robert Darnell, a Howard Hughes Medical Institute investigator, head of Rockefeller's Laboratory of Molecular Neuro-oncology and Robert and Harriet Heilbrunn Professor in cancer biology, extends a hypothesis put forward by American and Australian scientists in 1957: Everybody develops tumors, but the immune system naturally kills off these cancerous cells day in and day out. The problem with this

hypothesis, though, was that there wasn't any way to test it since patients didn't show any symptoms, explains Darnell, who is also a senior attending physician at The Rockefeller University Hospital.

The rare neurodegenerative disease called paraneoplastic cerebellar degeneration (PCD) provided researchers with the opportunity to test this hypothesis. It is thought that patients get this disease when the immune system recognizes and attacks a protein that is expressed in tumor cells; these immune cells kill the tumor and protect the body from cancer, but then they go one step too far: They infiltrate the brain and kill a group of neurons that also express this protein, an antigen called cdr2. When these patients go to the doctor to check out their neurological symptoms, they are told that they also have gynecological tumors — often small ones that have not metastasized.

"These PCD patients had tumors for a while, but they never knew," says Darnell. "It is as if they developed an immune response to their own cancer."

Unlike most patients with ovarian and breast cancer, patients with PCD have immune cells circulating in their blood that specifically target the cdr2 protein as well as the molecular platform on which it docks. Although this protein resides within tumor cells (not on their surfaces), these immune cells, called CD8+ cytotoxic T cells, can still "see" cdr2 because a section of this protein docks onto a molecular platform that ships it to the cell's surface. Darnell and Santomasso's work, with help from a number of laboratory colleagues, was the first to identify which section, or peptide fragment, was naturally attached to this molecular platform — an important finding because this interaction determines how cytotoxic T cells target the cdr2-expressing cells. When the T cell's receptor binds to cdr2 and its platform, the immune cell releases substances that destroy the tumor.

In order to help breast and ovarian cancer patients, however, Santomasso and her colleagues needed to make the cancer patients' immune cells like those of PCD patients — cells that could kill tumors that harbor the cdr2 protein. First, they injected healthy mice with the cdr2 protein and determined that the peptide fragment that bound most strongly to the platform was also the one most strongly recognized by CD8+ cytotoxic T cells. From these potent cdr2-specific CD8+ cytotoxic T cells, they isolated the genes that code for the T cell receptor. When the team injected the T cell receptor genes to normal human immune cells, the cells were able to target cdr2-expressing human tumor cell lines and kill them.

"I was astonished," says Santomasso. "Human T cells can be transformed to specifically recognize antigens that are expressed in tumors and kill them. For breast and ovarian cancer patients, these findings hold great therapeutic promise."

Source: Rockefeller University