Cancer cells found to repair their own membranes after attack by T cells

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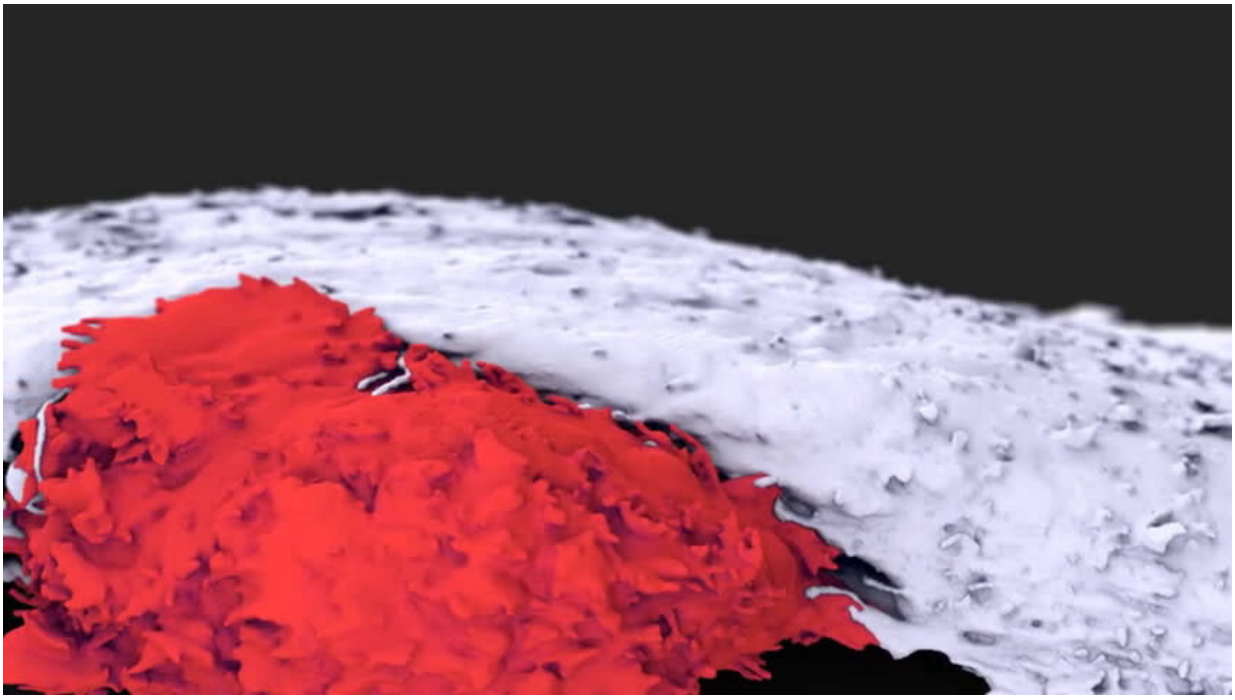

Credit: *Science* (2022). DOI: 10.1126/science.abl3855

A team of researchers from Genentech, Inc., the Howard Hughes Medical Institute and the Peter MacCallum Cancer Center, has found that cancerous tumor cells are able to survive attacks by repairing holes in their membranes caused by a protein released from T cells. In their paper published in the journal *Science*, the group describes how they used high resolution imaging to learn more about what happens when T

cells, known as cytotoxic T lymphocytes (CTLs), attack cancerous tumor cells. Norma Andrews, with University of Maryland, College Park, has published a Perspectives piece in the same journal issue outlining the work done by the team.

Prior research has shown that the way CTLs kill cells infected by a virus or bacteria, and sometimes those that are cancerous, is by glomming onto the cell and then releasing two protein toxins: perforin and granzyme. The first, perforin, eats holes through the cell's membrane. The second then enters the cell through the holes and sets off apoptosis, which is normal programmed cell death. In this new effort, the researchers have learned how cancer cells respond to such an attack.

Using high resolution imaging and a strategy that allowed them to separate cells during early permeabilization, researchers were able to watch as a CTL attached itself to a tumor cell and then set off its attack. They observed that the perforin ate holes through the membrane as intended and then granzymes began to enter the cell. But they also saw something else: The cancer cell began emitting a type of protein called endosomal sorting complexes required for transport (ESCRT), which prior research has shown is produced by cells as a means for repairing membrane damage. This blocked the entrance of more granzymes, which stopped the apoptosis, allowing the cancer cell to remain alive.

The researchers then tried two different ways (using CRISPR to disable a gene involved in production of ESCRT and engineering cells to over-express an enzyme involved in the process) to stop the cancer cells from emitting ESCRT, and found that both ways reduced the ability of the cell to survive an attack by CTLs.

More information: Alex T. Ritter et al, ESCRT-mediated membrane repair protects tumor-derived cells against T cell attack, *Science* (2022). DOI: 10.1126/science.abl3855

Norma W. Andrews, Resisting attack by repairing the damage, *Science* (2022). DOI: 10.1126/science.abp8641