A breast cancer drug, susceptible to resistance, can be restored to effectiveness, researchers demonstrate

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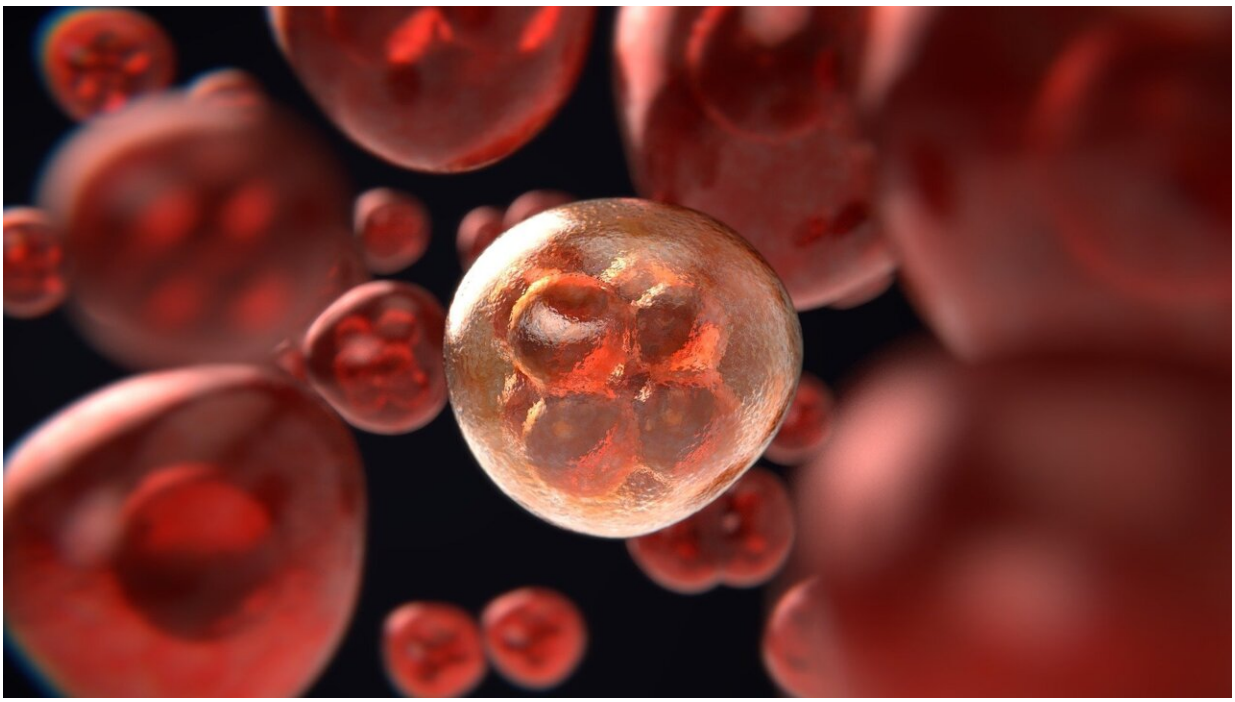

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In a new paper published in *Cancer Research*, researchers at MUSC Hollings Cancer Center have shown that targeting a protein called TACC3 (transforming acidic coiled-coil containing protein 3) can restore the effectiveness of the breast cancer drug T-DM1 if the cancer

cells have developed resistance.

T-DM1, known by the brand name Kadcyla, is approved to treat women with HER2-positive breast cancer. It was first approved in 2013 for metastatic HER2-positive breast cancer. Its use was later expanded to treat early-stage HER2-positive breast cancer if cancer cells remained after surgery and pre-surgery chemotherapy.

"T-DM1 has been the first and one of the most successful antibody drug conjugates (ADCs) used for breast cancer, but resistance is a major problem," explained Hollings researcher Ozgur Sahin, Ph.D., professor and SmartState Endowed Chair in Lipidomics and Drug Discovery in the Department of Biochemistry and Molecular Biology.

An antibody drug conjugate combines an antibody with a chemotherapy drug—a "payload" delivered directly to the cancer cell.

Although the drug has been in use for 10 years, this new research out of the Sahin Lab shows for the first time a previously unrealized mechanism that causes it to work.

"This is the first study showing that T-DM1 induces immunogenic cell death (ICD) and that in resistance, this immunogenic cell death is gone—lost. By targeting TACC3, we can bring it back and make the drug work again," Sahin said.

"Notably, this really opens a new avenue for studying different ADC drugs with different payloads in the context of immunogenic cell death induction."

ICD is a type of cell death that triggers a response from the immune system—when ICD is activated, the dying cancer cell releases danger-associated molecular patterns, or DAMPs. This helps the infiltration of

dendritic cells and T-cells. Activated immune cells pick up on the presence of DAMPs and go to work attacking remaining cancer cells.

Some, but not all, chemotherapy drugs induce ICD.

T-DM1 activates the spindle assembly checkpoint (SAC) in cells, a critical checkpoint in cell division, whose purpose is to ensure that one copy of each chromosome is properly attached and lined up on opposite sides in preparation for division into two identical daughter cells. While T-DM1 can activate SAC in sensitive cells, leading to ICD, this checkpoint is lost in T-DM1-resistant cells.

TACC3 also gets involved in cell division, particularly cancer cell division. There's an abundance of TACC3 in cancer cells, and high levels of this protein are associated with worse outcomes.

In their experiments, the researchers found that when cancer cells become resistant to T-DM1, there are high levels of TACC3 that inhibit the spindle assembly checkpoint process. T-DM1 can't kickstart the spindle assembly checkpoint, and the DAMPs are never released, so the immune cells never spring into action.

Inhibiting TACC3, the researchers found, lets T-DM1 get on with its job.

The co-first authors of the paper, Emre Gedik, Ph.D., and Ozge Saatci, Ph.D., noted that the proposed combination of T-DM1 and TACC3 inhibitors aids in reviving immunogenic cell death in T-DM1-resistant tumors that was otherwise lost so that the anti-cancer immune cells can sneak in.

"These findings represent a key advancement in overcoming drug resistance in HER2-positive breast cancer," Gedik and Saatci wrote.

Sahin noted that the assistance of Shikhar Mehrotra, Ph.D., was invaluable. Mehrotra's research centers on targeting T-cell signaling.

Their combined research points to new possibilities.

"Our data encourages testing the combination of TACC3 inhibitors with other ADCs beyond T-DM1, or even with immune checkpoint blockers, to achieve superior and durable responses," the researchers wrote.

More information: Mustafa Emre Gedik et al, Targeting TACC3 induces immunogenic cell death and enhances T-DM1 response in HER2-positive breast cancer, *Cancer Research* (2024). DOI: 10.1158/0008-5472.CAN-23-2812 aacrjournals.org/cancerres/art … genic-cell-death-and

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