Study suggests using excess stress to kill therapy resistant breast cancer

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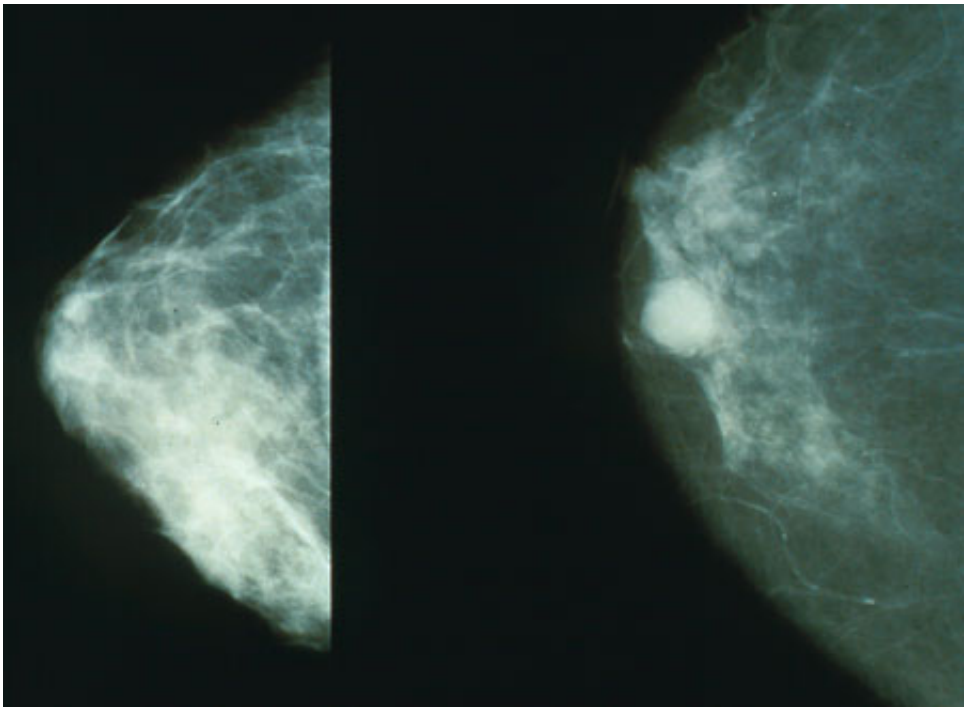

Mammograms showing a normal breast (left) and a breast with cancer (right). Credit: Public Domain

Maxing out the inherently stressed nature of treatment-resistant breast cancer cells thwarts their adaptive ability to evolve genetic workarounds to treatment, a new study suggests.

Scientists from Cincinnati Children's Hospital Medical Center report their results May 26 in *Science Signaling*.

"We present an alternative generic strategy for cancer treatment, which is removing cancer cells' defenses against their own intrinsic stress," said Kakajan Komurov, PhD, lead author and a researcher at the Cancer and Blood Disease Institute at Cincinnati Children's. "We leverage the fact that tumor progression essentially is an evolutionary process. Our findings highlight the feasibility of maximizing cell stress by inhibiting adaptive pathways to cause cell death."

Most research into targeted cancer therapy focuses on oncogenes - genes known to cause cancer. Because many cancers adapt and evade therapies, and some oncogenes are hard to target, different treatment strategies are needed. Komurov and his colleagues experiment with targeting the non-oncogene vulnerabilities of cancer - a potential new strategy gaining traction in the cancer research community.

The scientists focused their study on an especially hard-to-treat form of breast cancer driven by the HER2-mTOR molecular pathway. Standard treatment for this cancer is combination chemotherapy, including an agent that specifically targets the HER2 gene. The conventional therapy offers limited clinical benefit, with over half of cases resulting in treatment resistance and disease progression, according to Komurov.

In their current study, researchers used in vitro experimentation of human breast cancer cell lines and extensive computer analysis of genomic data from The Cancer Genome Atlas and International Cancer Genome Consortium.

The team searched for non-oncogenic vulnerabilities in breast cancers that overexpress a gene called ERBB2, which encodes HER2. Looking at tumor progression as an evolutionary process, the authors searched specifically for genes with profiles suggesting some form of adaptive selection. They found that cancers over expressing ERBB2 have increased expression of genes that regulate proteins in what turns out to

be an important survival mechanism for HER2 cancer cells - the endoplasmic reticulum associated degradation pathway, or ERAD.

The endoplasmic reticulum is an internal component of cells critical to the structure of proteins. It helps ensure the string-like strands of proteins fold accurately to assume correct form and function. As a result of chemotherapy, genetic instability and other biologic factors, proteins become misfolded in cancer cells and cause a condition called proteotoxic burden and stress. The ERAD pathway helps the cancer cells cope with the misfolded proteins and proteotoxic stress.

Study data show that HER2-positive breast cancer cells become addicted to the ERAD pathway. Consequently, instead of the cancer cells being sensitive to chemotherapy and dying off, ERAD allows the cancer cells to survive. This finding prompted researchers to theorize that inhibiting ERAD might be part of a therapeutic strategy.

The researchers also looked for other "stress-related" pathways that act downstream of ERAD to augment therapeutic inhibition of ERAD. They identified the IRE1-JNK pathway as a potential suppressor of HER2-positive breast cancer. IRE1, which resides in the endoplasmic reticulum of cells, has been implicated in stress-related cell death through its ability to activate an enzyme called JNK. When stress in the endoplasmic reticulum occurs, JNK instructs cells to enter programmed cell death, or apoptosis.

The researchers then tested a combination treatment in HER2-positive breast cancer cells. It involved genetically deleting or pharmacologically inhibiting ERAD. They also promoted the function of JNK by pharmacologically blocking phosphatases that inhibit JNK's function. The combination therapy was effective at selectively killing the HER2-positive breast cancer cells, according to the authors.

Komurov said the researchers are now testing the experimental treatment regimen in mouse models of HER2-postive breast cancer to verify the computer and cell data. The researchers also plan to begin testing an experimental cancer drug entering Phase 1 clinical trials that blocks a component of the ERAD pathway known VCP/ATPase.

"Another very valuable follow up would be to scan for and identify markers among all cancers that could benefit from the general therapeutic approach we have proposed in the current study," added Komurov, who is in the Division of Experimental Hematology and Cancer Biology at Cincinnati Children's.

Provided by Cincinnati Children's Hospital Medical Center