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Triple-negative breast cancer target for drug development identified

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Often deadly "triple-negative" breast cancers might be effectively treated in many cases with a drug that targets a previously unknown vulnerability in the tumors, according to a UC San Francisco researcher who described her discovery in a study published online October 3, 2013 in the journal *Cancer Cell*.

UCSF researcher Luika Timmerman, PhD, an investigator in the UCSF Helen Diller Family Comprehensive Cancer Center, found that many cell lines obtained from triple-negative breast cancer are especially dependent on cystine, one of the 20 amino acids that are the building blocks of proteins that all cells need. Timmerman used an FDA-approved drug to inhibit activity of a transporter protein that ferries cystine into triple-negative breast cancer cells, and found that it significantly inhibited their growth in culture and when the cancer cells were transplanted into mice.

Roughly one in six women with breast cancer have triple-negative breast cancer, and only about three out of four with this type survive five years or more. These tumors sometimes grow aggressively, advancing from being undetectable to becoming difficult-to-treat between regular screening mammography exams, for instance.

Drugs now are available that effectively target the estrogen and HER2 receptor proteins, which are found in many breast tumors, and these drugs spare most normal cells in the body. However, triple-negative breast cancers are difficult to treat effectively because they do not make

either of these receptors. To treat patients with triple-negative breast cancer, physicians instead use older chemotherapies that produce side effects in normal tissues, thus limiting the doses that patients can receive.

Timmerman found that she could significantly slow growth of triple-negative tumors using an FDA-approved anti-inflammatory drug called sulfasalazine to block a specific cystine transporter called xCT. While sulfasalazine itself would not be appropriate for treating cancer, Timmerman said, it could serve as a "lead compound" that could be used to develop drugs that specifically target xCT on tumor cells.

"This study of human tumors in mice and of breast cancer cell lines demonstrates the potential of targeting not only this cystine transporter, but also other metabolic abnormalities in cancer," Timmerman said.

Timmerman has spent several years studying the abnormal metabolic behavior of cancer cells, which can differ substantially from the metabolism of normal cells. "Different cancers seem to acquire different metabolic abnormalities that might in some cases give them a growth or survival advantage," she said.

"One of the strengths of this study was the large number of different cell lines I was able to test. When I saw similar results in many samples, I felt I was looking at a fundamental metabolic behavior that we could exploit to specifically target triple-negative tumors that overexpress the xCT cystine transporter, a significant group of previously untargettable tumors."

Timmerman initially focused on investigating the metabolism of the amino acid glutamine among different breast cancer-derived cell lines because glutamine metabolism was long known to be perturbed in cancer. She matched genetic "microarray" data that tracks gene activity

to functional differences among tumors and tumor cell lines in culture.

But she also measured amino acids and other molecules in cell culture to detect metabolic changes. When she did so, she noticed that cystine and glutamate levels are frequently correlated in triple-negative cancers. A series of experiments led to the discovery that the cystine transporter xCT was abundant and active on many triple-negative tumors and tumor cell lines. Timmerman then tested sulfasalazine on tumors grown in mice and in tumor cell lines and found that blocking xCT activity strongly retarded the growth of triple-negative tumors.

"We have identified a compelling therapeutic target commonly expressed by breast tumors of poorest prognosis, and a lead compound for rapid, effective drug development," Timmerman said.

Provided by University of California, San Francisco