Scientists identify genes that disrupt response to breast cancer treatment

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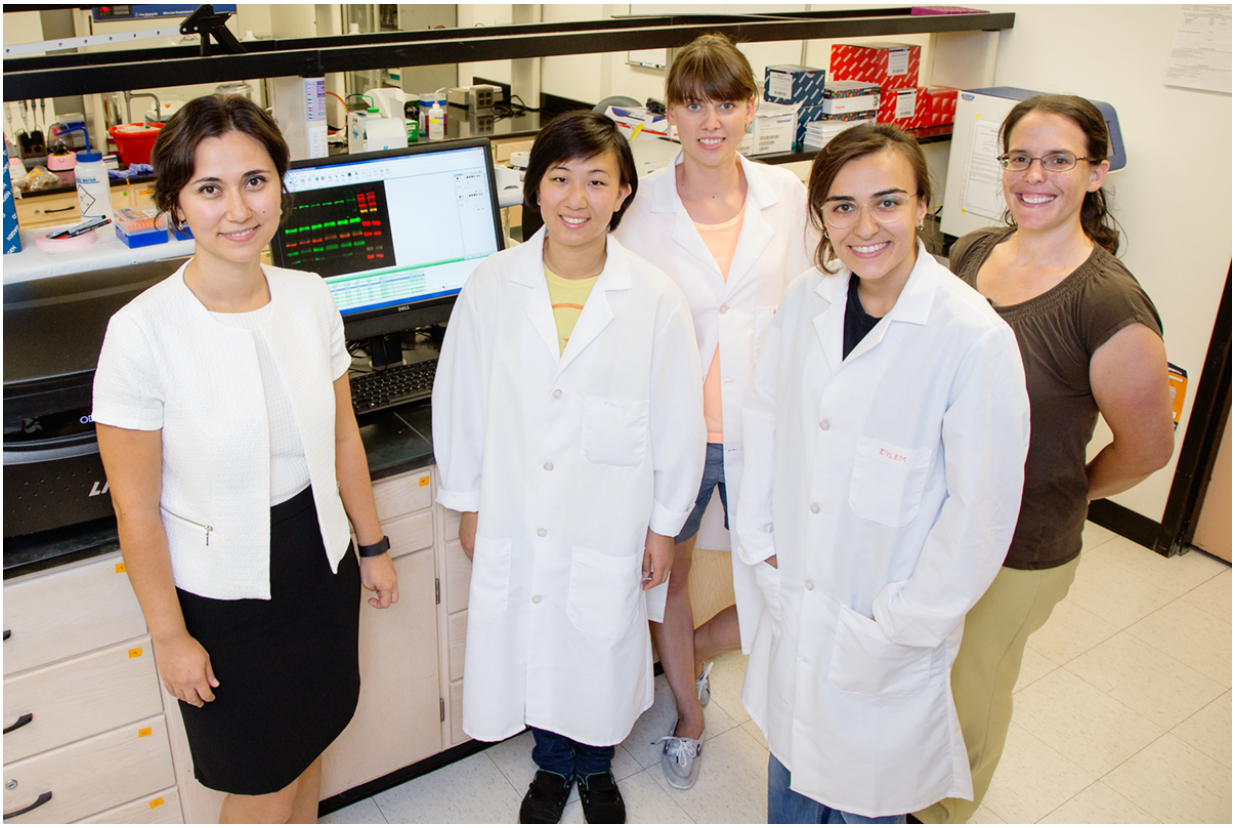

In breakthrough research on breast cancer, a team at the University of Illinois discovered that higher levels of the nuclear transport gene XPO1 indicate when a patient is likely to be resistant to the popular drug tamoxifen. The team, from left, food science and human nutrition professor Zeynep Madak-Erdogan; graduate students Karen Chen, Kinga Wrobel and Eylem Kulkoyluoglu; and epidemiology professor Rebecca Smith. Credit: L. Brian Stauffer

Scientists may have unlocked the genetic code that determines why many patients with estrogen receptor-positive breast cancer fail to respond to the widely used drug tamoxifen.

Patients who have higher levels of several nuclear transport genes - particularly the protein XPO1 - are more likely to be resistant to tamoxifen, resulting in the development of incurable metastatic cancer, according to a new study led by researcher Zeynep Madak-Erdogan at the University of Illinois.

However, combining tamoxifen with the drug selinexor, which inhibits the activity of XPO1, enhances patients' sensitivity to tamoxifen and prevents breast tumors from recurring, the researchers reported in a paper published online by the journal *Molecular Endocrinology*.

The researchers also identified a "signature" of 13 nuclear transport genes, including XPO1, which provides clinicians with a biomarker to predict which patients are likely to be endocrine resistant and choose alternative treatments that may achieve better outcomes for these patients, said Madak-Erdogan, a professor of food science and human nutrition.

Estrogen receptor-positive breast cancer accounts for about 70 percent of all clinical cases of breast cancer. In these forms of the disease, the nuclei in patients' breast cells overproduce a protein that binds with and grows in response to estrogen. Tamoxifen, an endocrine therapy that has been widely used since the 1970s, blocks this binding process, constraining the growth and dissemination of the cancer cells.

However, up to one-third of patients with hormone-responsive breast cancer don't respond efficiently or eventually stop responding to tamoxifen, conditions known as endocrine resistance.

While tamoxifen is still very effective compared with other endocrine-targeting agents, determining which patients will respond effectively to the drug has perplexed physicians and researchers for some time, Madak-Erdogan said.

The current study built upon prior research at Illinois that identified the hormone ERa as the agent that activates and regulates the kinase ERK5, a protein that relays signals from outside cells to their nuclei, triggering either increased cell proliferation or metastasis. Madak-Erdogan was a co-author on that study, which was led by Swanlund Professor of Molecular and Integrative Physiology Benita S. Katzenellenbogen and co-written by then-undergraduate students Rosa Ventrella and Luke Petry.

Based upon those findings, Madak-Erdogan and her co-authors on the current study hypothesized that nuclear transport genes, particularly XPO1, might be involved in exporting ERK5 from cells' nuclei, promoting invasive, aggressive tumors.

The scientists conducted a multiphase, mixed-methods study, which included meta-analyses of genetic data on breast tumors, monitoring gene expression in laboratory cultures of human breast cancer cells and experiments using mice that developed estrogen receptor-positive breast cell tumors.

In analyzing data on genes that were differentially expressed in ERa-positive and ERa-negative tumors, the researchers ultimately identified 13 genes that were over-expressed in the most aggressive, difficult-to-treat types of breast tumors.

"When we looked into the gene signature further, we found that if a patient had higher expression of XPO1, their survival time was less, they had metastases earlier on and endocrine-resistant tumor cells proliferated more rapidly when treated with tamoxifen," Madak-Erdogan said.

In the laboratory, the researchers mimicked endocrine resistance by growing tamoxifen-responsive breast cancer cells from 33 patients in a tamoxifen solution for 100 weeks. When they examined the activity of ERK5 at three intervals, they found that transportation of ERK5 to cells' nuclei increasingly diminished as endocrine resistance progressed.

Hypothesizing that a combination treatment might help restore endocrine sensitivity, the researchers treated tamoxifen-resistant breast cancer cells in mice with both increasing doses of the XPO1 inhibitor selinexor and tamoxifen.

"When we treated those tamoxifen-resistant tumors with the inhibitor for XPO1 in combination with tamoxifen, we were able to completely block tumor progression," Madak-Erdogan said. "Even weeks after the treatment was done, we didn't see any tumor recurrence."

"If we use this combination - targeting the estrogen receptors with tamoxifen, and XPO1 with the inhibitor selinexor - we can delay the development of endocrine resistance, effectively killing the tumor cells and at the same time reducing the dose of tamoxifen that's needed," said Madak-Erdogan, who also holds an appointment in the Division of Nutritional Sciences.

Selinexor, which is already in clinical trials for treating leukemia and therapy-resistant prostate cancer, is tolerated well, and patients experience very mild side effects that wear off as therapy continues, Madak-Erdogan said.

More information: Kinga Wrobel et al, ERα-XPO1 crosstalk controls tamoxifen sensitivity in tumors by altering ERK5 cellular localization, *Molecular Endocrinology* (2016). DOI: 10.1210/me.2016-1101