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Study identifies new genetic signatures of breast cancer drug resistance

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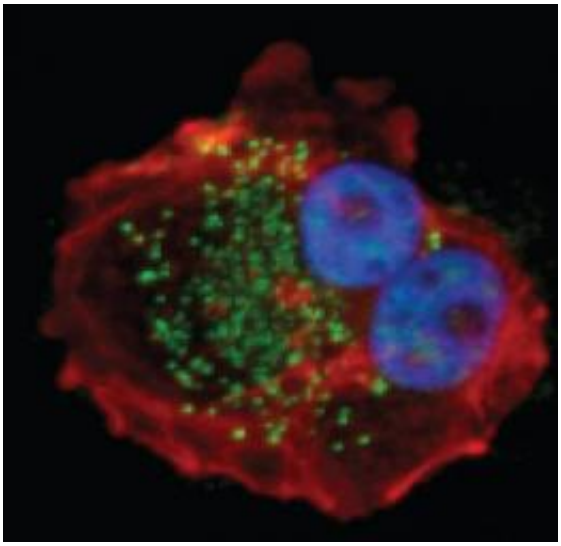

A protein called HSPB8 was identified in the screen. HSPB8 appears to confer resistance by the surprising mechanism of blocking autophagy, a process where cells escape death by consuming proteins inside the cell. Immunofluorescence images show that after silencing HSPB8 in all drug resistant subclones, the characteristic redistribution of anti-MAP LC3 into punctuate green structures appear, indicating active autophagy. Credit: Laura Gonzalez, Biodesign Institute at Arizona State University

A new study conducted by Josh LaBaer's research team in the Biodesign Institute at Arizona State University has pinpointed more than 30 breast cancer gene targets -- including several novel genes -- that are involved in drug resistance to a leading chemotherapy treatment.

The results of the study may one day aid in the treatment of the one in ten U.S. women who will develop breast cancer, by empowering physicians with a more personalized approach to therapy as well as a new tool for the early screening of those that may ultimately become resistant to chemotherapy.

Drugs like tamoxifen have been part of the standard treatment regimen for many breast cancer patients and saved countless lives. Unfortunately, a very serious therapeutic problem can occur when the drug loses its potency over time as women develop a resistance to the drug treatment, and tumors reemerge. Tamoxifen is an effective treatment for the 60 percent of women who are clinically diagnosed as ER+ (estrogen receptor positive), blocking hormones needed for tumor growth.

"The management of breast cancer is complicated, depending on the stage, size of tumor, and other things, but almost all ER+ women end up on tamoxifen, and it is still considered the first line of adjuvant chemotherapy ---along with resection and local radiation---used in both the early treatment of breast cancer and in late stages of the disease," said LaBaer, who holds the Virginia G. Piper Chair in Personalized Medicine at ASU and is director of the Center for Personalized Diagnostics at the Biodesign Institute. "We wanted to use a model where we could use our high-throughput technology to identify genes that encourage drug resistance to ultimately identify a signature that predicts which women will do well on a particular drug."

Using a well-established cell model for breast cancer along with the LaBaer lab's extensive collection of fully sequenced human genes, the team performed the largest genetic screen of its kind---testing the ability of 500 regulatory proteins, called kinases, that have been implicated in tumor growth and drug resistance.

"Kinases turn out to be a key drug target and we wanted to take

advantage of the large number of kinase genes available in the lab," said postdoctoral researcher Laura Gonzalez, who conducted and was lead author of the study, published in the early online edition of the *Proceedings of the National Academy of Sciences*. "This was the largest high-throughput screen of its kind, and it was critical to design our study in a way that we could correlate our cell studies with patients in the clinic."

Dr. Joshua LaBaer's Biodesign Institute team used a well-established cell model for breast cancer along with the extensive collection of fully sequenced human genes, the team performed the largest genetic screen of its kind -- testing the ability of 500 regulatory proteins, called kinases, that have been implicated in tumor growth and drug resistance. Credit: Biodesign Institute, Arizona State University

By comparing gene expression patterns in cells that were sensitive (greater than 90 percent death) or resistant in response to tamoxifen, the group identified a suite of genes that failed to respond to the drug. Encouragingly, these genes were found only in the resistant cells. Furthermore, the team correlated their cell studies back to the clinic, finding a drug resistance signature that predicted the early relapse of breast cancer for women taking tamoxifen in two different clinical

cohorts.

The team identified more than 30 kinases that repeated allowed the sensitive cells to grow in the presence of drug. Several were already known, but many were novel.

One of these, an atypical kinase called HSPB8, represents an entirely new mechanism for drug resistance. HSPB8 appears to confer resistance by the surprising mechanism of blocking autophagy, a process where cells escape death by consuming proteins inside the cell. This may suggest an important role for autophagy in developing resistance to tamoxifen.

"Women who had elevated levels of HSBP8 in one of our clinical cohorts, did worse on tamoxifen than women who did not," said LaBaer. "One gene alone in that cohort predicted outcome, which is very interesting. Relatively little is known about HSBP8 and so we have a gene with new territory to study."

Next, the team will investigate the role of several of the other genes identified in the study, in the hopes of contributing toward society's understanding of the underlying mechanisms of tamoxifen resistance in breast cancer. "We will continue to use this approach as a model of what happens in women, and looking from the perspective of what genes encourage resistance. If you can find these, you can identify drugs that inhibit them," said LaBaer.

Provided by Arizona State University