Genetic alterations in treatment-resistant metastatic breast cancer found to be distinct from those in primary tumors

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Drug-resistant, estrogen-fueled breast cancers that have spread beyond their initial site often have different genetic alterations than the original tumors, according to a large-scale tumor-tissue analysis led by Dana-Farber Cancer Institute scientists. The discovery of these differences, which may guide the search for new drug targets and influence the treatment patients receive if their cancer metastasizes, was presented today at the 2016 San Antonio Breast Cancer Symposium.

"In spite of tremendous advances in the treatment of estrogen receptor-positive breast cancer using therapies directed against the estrogen receptor [ER], patients frequently develop resistance to these therapies," said the senior investigator of the study Nikhil Wagle, M.D., deputy director of the Center for Cancer Precision Medicine at Dana-Farber and an associate member of the Broad Institute of MIT and Harvard. "These resistant tumors remain the most common cause of breast cancer death, yet mechanisms by which this resistance develops are poorly understood."

Unlike previous studies that have surveyed the genome of untreated breast cancers in their original location, the new research focused on metastatic tumor sample from patients with resistant disease, explained lead author of the study Ofir Cohen, PhD, a postdoctoral researcher and computational biologist at Dana-Farber and the Broad Institute. "Our current research is part of a growing effort by many researchers to start closing the gap by better understanding the genomic underpinning of the metastatic and resistance states."

In the study, Wagle, Cohen, and their colleagues analyzed treatment-resistant, ER-positive metastatic breast tumor samples from 130 patients treated at the Susan F. Smith Center for Women's Cancers at Dana-Farber. Pretreatment samples of primary tumors were analyzed from 34 of these patients. The investigators performed massively parallel sequencing (also known as "next-generation sequencing") on the entire exome (the genes encoding all of the proteins in the cancer cell) and transcriptome (all the genetic instructions for the production of cell proteins) of these breast cancer samples.

"We found the genomic landscape of drug-resistant, ER-positive metastatic breast cancer is significantly different from that of primary ER-positive breast cancer," Cohen said. "Moreover, we were able to identify multiple clinically relevant genomic and molecular alterations in the metastatic biopsies with implications for choice of next therapy, clinical trial eligibility, and novel drug targets."

Whole exome sequencing showed metastatic breast cancer samples to have more frequent alterations in the genes ESR1, ERBB2, PIK3CA, PTEN, RB1, AKT1, among others. Transcriptomic sequencing identified cell states that may cause tumors to become resistant to certain drugs.

"Genetic abnormalities that occur in both primary and metastatic tumors may be a signal of which tumors are likely to spread," Cohen said. "Abnormalities that are present primarily in metastatic tumor samples may provide clues to which drugs are likely to overcome or prevent resistance. These findings underscore the potential value of periodically monitoring the genomic make-up of tumors with technologies such as cell-free DNA from blood [liquid biopsies]."

When sequencing identified an abnormality in these tumors that could impact patients' treatment, the findings were sent to the clinicians and patients and

are being used for clinical decision-making, Wagle noted.

Researchers plan to integrate the functional and clinical findings of the study into a comprehensive "Resistance Atlas" for ER-positive metastatic breast cancer, which should help inform treatment decisions for individual patients and propel the development of new combination treatment strategies for the disease, Wagle said.

A limitation of the study is that because most of the samples were both metastatic and treatment-resistant, mutations involved in metastasis were interwoven with those involved in drug resistance. The investigators are using several functional assays to help untangle metastasis-driving events from resistance-conferring events, Cohen said.

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