Study sheds new light on mechanism of breast cancer treatment resistance

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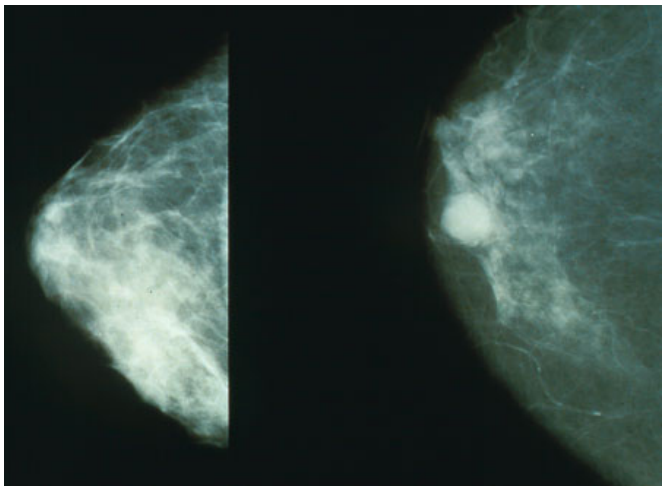

Mammograms showing a normal breast (left) and a breast with cancer (right). Credit: Public Domain

A study by researchers at Dana-Farber Cancer Institute has illuminated a specific mechanism by which estrogen receptor-positive (ER+) breast cancers can become resistant to standard therapies and metastasize.

The scientists say the mechanism explains why breast cancers with mutations in the ER gene itself—the target of drugs such as aromatase inhibitors and tamoxifen—become resistant to these therapies and are prone to become metastatic. Resistance to therapy for ER-positive breast cancer is a common cause of breast cancer mortality and a major unmet need.

Myles Brown, MD, director of the Center for Functional Cancer Epigenetics at Dana-Farber, and Rinath Jeselsohn, MD, of Dana-Farber's Susan F. Smith Center for Women's Cancers, led a research team reporting the findings in *Cancer Cell*.

A majority of women with breast cancer have tumors that are fueled by the hormone estrogen. Most are treated with therapies that prevent estrogen production or block the estrogen receptor in cancer cells to prevent binding by estrogen, with the goal of starving the tumor of estrogen and interrupting cancer growth.

Such endocrine therapies, including tamoxifen and aromatase inhibitor drugs, can prevent recurrence of early breast cancer, and can slow the progression of metastatic disease. However, in about one-third of patients with metastatic ER-positive breast cancer, treatment with endocrine therapies leads to the emergence of tumor cells that grow even in the absence of estrogen hormone , resulting in treatment-resistant disease that is often incurable.

In studying the molecular causes of resistance to endocrine therapies, scientists found DNA mutations in the estrogen receptor gene in a substantial number of patients with ER-positive breast cancer. In 2013, Jeselsohn and colleagues reported finding ER mutations in the tumors of women with metastatic ER-positive breast cancer. The scientists then created laboratory models of breast cancer to investigate how the mutations (which they estimate occur in about a third of women with metastatic ER-positive breast cancer) cause treatment resistance. In these experiments they found that the mutations caused the tumors to be resistant to the drugs tamoxifen and fulvestrant (another estrogen-blocker) and estrogen deprivation.

In the new report, however, the Dana-Farber scientists revealed another previously unknown effect of three of the mutations in the ER gene. That is, the mutations not only cause resistance to estrogen blockade, but also turn on genes that drive the breast tumors to metastasize to other organs. This kind of unexpected additional action of a mutated gene is termed "neomorphic."

"That tells us that even though the drug therapies are selecting tumors that can grow without estrogen, the mutations also confer a metastatic advantage to the tumor," explains Brown.

The researchers then used the CRISPR-Cas9 gene editing tool to launch a search to identify which genes are essential in cells with the ER mutations. Among the essential genes they found, CDK7 was of particular interest because it was a potential drug target. In fact, Dana-Farber colleague Nathanael Gray, PhD, and his team had previously developed an experimental CDK7 inhibitor called THZ1. Tests in cell culture and in animal models with transplanted breast tumors showed that the combination of THZ1 and the endocrine blocker fulvestrant slowed growth of tumors more strongly than either agent alone.

"These results support the potential of this combination as a therapeutic strategy to overcome endocrine resistance caused by the ER mutants," say the authors of the report.

Jeselsohn said that clinical CDK7 inhibitors are being developed, and that "we hope to test these drugs and develop a clinical trial for patients with ER-positive metastatic breast cancer."

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