Some breast cancer tumors hijack patient epigenetic machinery to evade drug therapy

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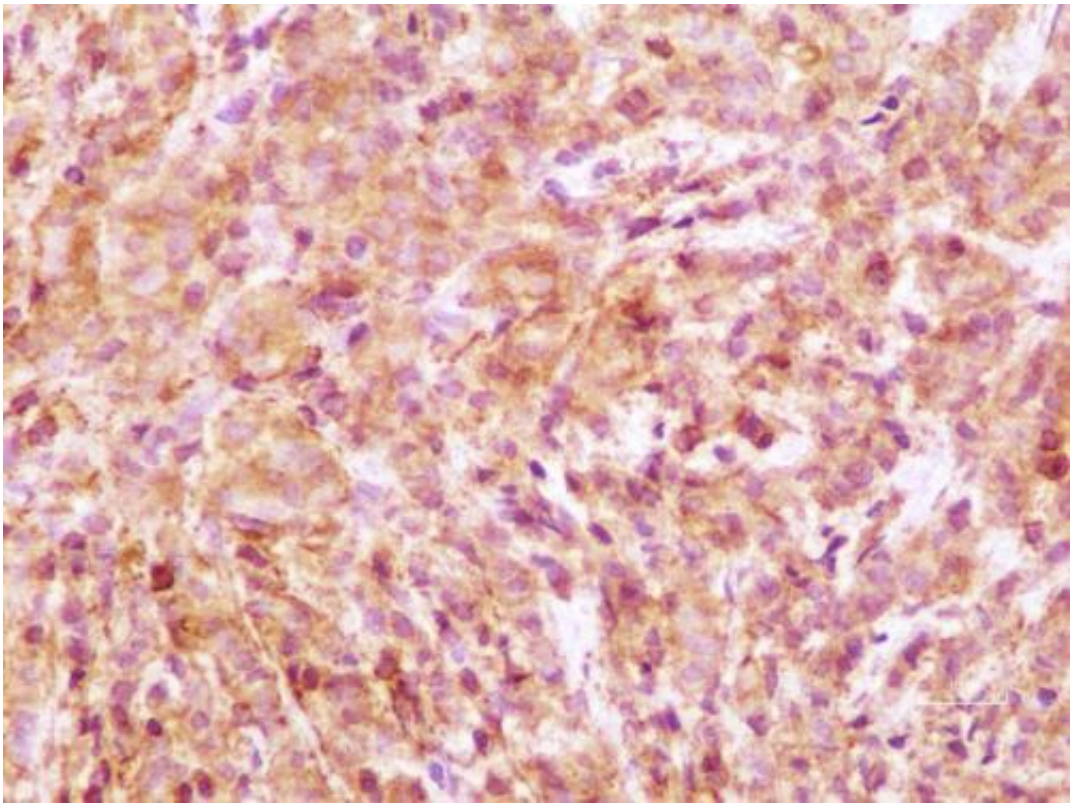

This image shows HOXC10 expression in a primary breast cancer tumor. Brown is HOXC10 and blue/purple is a counterstaining to show the cell, especially the nucleus of the cell. Credit: UPCI

A breast cancer therapy that blocks estrogen synthesis to activate cancer-killing genes sometimes loses its effectiveness because the cancer takes over epigenetic mechanisms, including permanent DNA modifications in

the patient's tumor, once again allowing tumor growth, according to an international team headed by the University of Pittsburgh Cancer Institute (UPCI).

The finding warrants research into adding drugs that could prevent the cancer from hijacking patients' repressive gene regulatory machinery, which might allow the original therapy to work long enough to eradicate the tumor, the researchers report in their National Institutes of Health-funded study, published in the current issue of *Science Translational Medicine*.

"Our discovery is particularly notable as we enter the era of personalized medicine," said senior author Steffi Oesterreich, Ph.D., professor in Pitt's Department of Pharmacology and Chemical Biology and at UPCI, a partner with UPMC CancerCenter, and director of education at the Women's Cancer Research Center. "Resistance to hormonal therapy is a major clinical problem in the treatment of most breast cancers. Through testing of a tumor's genetic and epigenetic make-up, we may be able to identify the patients most likely to develop such resistance and, in the future, create a treatment regimen tailored to giving each patient the best chance of beating their cancer."

Epigenetic translates to "above genetic" and is an emerging field of study that looks at how environmental factors—such as infections, pollutants, stress and, in this case, long-term exposure to drugs that block estrogen synthesis—could influence a person's DNA. Epigenetic changes do not alter the structure of the DNA, but they do change the way the DNA is modified, which subsequently determines the potential of gene regulation.

By performing a genome-wide screen in breast cancer cells, Dr. Oesterreich and her colleagues identified a gene called HOXC10 as one that the cancer seems to modify to allow continued tumor growth in

patients whose cancer becomes resistant to traditional therapies.

The hormone estrogen represses genes, such as HOXC10, that induce cell death and inhibit growth. About 70 percent of breast cancer tumors are positive for a protein called 'estrogen receptor alpha,' which prevents HOXC10 from killing the cancer. To overcome this, doctors put these patients on anti-estrogen therapy, including aromatase inhibitors.

Unfortunately, in some cases, the tumor uses different epigenetic mechanisms, independent of estrogen, to repress the HOXC10 gene. This allows the cancer to continue growing. When the tumor uses these mechanisms, it makes deeper modifications to the expression of the patient's DNA, permanently blocking the HOXC10 and other genes and making cancer treatment much more difficult.

"In some patients the tumors never respond to aromatase inhibitors and just keep growing. In other patients, using aromatase inhibitors to block estrogen synthesis and allow HOXC10 and other genes to destroy the cancer works in the short term," said Dr. Oesterreich. "But, eventually, we see the tumor start to gain ground again as the cancer permanently represses genes such as HOXC10. At that point, the aromatase inhibitor is no longer effective."

Dr. Oesterreich and her colleagues propose that future studies look at offering a combined therapy that, along with aromatase inhibitors, also introduces drugs that modify the epigenome to prevent or delay the cancer from repressing cancer-killing genes.

The researchers also note that more investigation is needed to fully understand all the mechanisms by which HOXC10 mediates cell proliferation and death, and the roles it may play in different types of tumors.

More information: "Epigenetic Reprogramming of HOXC10 in Endocrine-Resistant Breast Cancer," by T.N. Pathiraja et al. *Science Translational Medicine*, 2014.

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