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Mutations linked to breast cancer treatment resistance

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Researchers at the University of Michigan Comprehensive Cancer Center have identified a type of mutation that develops after breast cancer patients take anti-estrogen therapies. The mutations explain one reason why patients often become resistant to this therapy.

The study appears online in *Nature Genetics*.

The discovery stems from a program at the U-M Comprehensive Cancer Center called Mi-ONCOSEQ in which patients with advanced cancer have their DNA and RNA sequenced to identify all types of genetic mutations that could play a role in the cancer. Researchers use the findings to help direct therapies they think will work best. But they also use the data to find new genetic links. The detailed analysis means that researchers can identify anomalies among a small number of patients.

In this case, they looked at 11 patients with metastatic breast cancer that was classified as estrogen receptor positive, meaning the cancer is influenced by the hormone estrogen. This is the most common type of breast cancer.

The analysis found that six patients had mutations in the estrogen receptor. All of them had been treated with an aromatase inhibitor, a type of drug that blocks estrogen production.

What's more, the researchers found that the mutations were not present before the patients started their treatment, which means it was the

therapy itself that caused the mutations to develop or be selected.

"This is the tumor's way of evading hormonal therapy. These mutations activate the estrogen receptor when there is no estrogen – as is the case when a patient takes an aromatase inhibitor. It's essentially an on-switch for the estrogen receptor," says
lead study author, Dan Robinson, Ph.D., research assistant professor of pathology at the U-M Medical School.

This on-switch essentially circumvents the effects of the aromatase inhibitor, preventing estrogen receptor signaling from being shut down. That's when patients become resistant to the therapy, which leaves them with few other treatment options. Some 40,000 people will die from breast cancer this year in the United States, with the majority having estrogen receptor positive tumors.

"We've been trying for a long time to understand why people become resistant to anti-hormone therapy. This finding sheds an entirely new light onto the problem. Now, we can look at how these estrogen receptors function and begin to develop drugs to shut down or attack this mutation," says study co-author Anne F. Schott, M.D., associate professor of internal medicine at the U-M Medical School.

The researchers also suggest that blood tests could be used to monitor patients and detect these mutations to potentially shift treatment before resistance develops. It's not yet known how frequently these mutations in the estrogen receptor occur. Currently, no treatment exists to target the mutations.

"Precision medicine approaches will allow us to understand how targeted therapies are working, but another important challenge is to understand the mechanisms by which tumors become resistant to these treatments so that we can prevent the resistance or develop strategies to overcome it,"

says senior study author Arul Chinnaiyan, M.D., Ph.D., director of the Michigan Center for Translational Pathology and S.P. Hicks Professor of Pathology at the U-M Medical School.

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