Researchers identify critical metabolic alterations in triple-negative breast cancer cells

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Researchers at Fox Chase Cancer Center have identified a host of small molecules critical to metabolism in cells of triple-negative breast cancer—one of the least understood groups of breast cancer. These molecules, called metabolites, include key players in energy regulation and lipid synthesis. They could help pave the way for helping researchers differentiate among different forms of the disease and ultimately point to new targets for treatment.

Jeffrey Peterson, PhD, a cancer biologist at Fox Chase, led the new studies, which also included researchers from Berlin-based Metanomics Health GmbH, a company specializing in metabolic profiling. Peterson will present the new findings at the AACR Annual Meeting 2013.

"There's tremendous excitement in the cancer field for the possibility of manipulating metabolism for therapeutic benefit," Peterson says.

Patients with triple-negative breast cancer constitute about 15 to 20 percent of all breast cancer cases, though incidence is disproportionately higher among young and African-American women. In triple-negative breast cancer, tumor cells lack receptors for two hormones—progesterone and estrogen—and a protein called HER2/neu. This type of cancer is notoriously difficult to treat and does not respond to some of the most effective treatments available for other types of breast cancer, like trastuzumab, which interferes with the HER2 receptor

in HER2+ breast cancer, or endocrine therapies like tamoxifen.

Triple-negative breast cancer is not one well-defined disease. It's a large group of diseases that all lack the three receptors but may differ from each other in critical ways, from individual molecules all the way up to clinical prognosis and treatment options. Peterson says that cataloging the small molecules involved in cellular metabolism may help researchers differentiate among these different cancers lacking the three receptors.

"One of our hopes is to understand how this heterogeneous disease can be classified into subtypes," says Peterson. "We'd like to be able to define each subtype and a biomarker for each of those subtypes, based on the specific metabolites altered in that subtype."

Like healthy cells, tumor cells take food from the blood and turn it into energy, but their metabolic processes differ from those of healthy cells. In recent years scientists have begun to try to find ways to exploit these differences to selectively kill cancer cells, with the ultimate goal of developing new therapies. Peterson and his colleagues used cutting edge technology, including liquid chromatography-mass spectrometry, to survey the amounts of a wide range of metabolites in cells from nine widely-used cell lines of triple-negative breast cancer. They also zoomed in to study particular, targeted metabolites more closely. Broad metabolic profiling is new technology, and Peterson and his colleagues are among the first teams of researchers to apply it to the study of triple-negative disease.

They looked at both the metabolic "footprints" and "fingerprints" of the cells. The metabolic "footprint" includes the metabolites that go in to a cell from the surrounding media—or come out the other end of the process. The metabolic "fingerprint" shows all the molecules that work inside the cell during metabolic processes.

"We basically remove all the cells from the media, and then extract all of their small metabolites(less than 1500 dalton) and analyze those," Peterson says.

He says this catalog of metabolites from these cell lines is a good first step toward using metabolic markers to better understand the disease. Since triple-negative breast cancer is heterogeneous, the next step, he says, is to replicate the study in other cell lines and validate potential biomarkers.

This study grew out of another ongoing project by Peterson and his team. He was the lead author on a paper, published in the journal Nature Biotechnology in 2011, introducing a new technique to study the action of kinases—which are a class of enzymes that control cellular metabolism. Once that tool was developed, he decided to apply it to the poorly understood triple-negative breast cancer. In another study he's presenting at the AACR Annual Meeting 2013, Peterson and colleagues show how this technique can be used to identify small molecules that block the kinases important to the growth of triple-negative disease.

"Those small molecules may be the starting point for new therapies," he says. Ultimately, he says, he'd like to combine the metabolite and kinase studies to develop targeted therapies that stymy the metabolism of cancer cells.

Provided by Fox Chase Cancer Center