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Study highlights new drug, molecular insight into triple negative breast cancers

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Most breast cancers are treated by blocking their addictions, for example depriving estrogen-fueled tumors of estrogen. But what about breast cancers without these hormonal addictions? In so-called "triple negative" tumors the cancer's addiction remains a mystery, making this subtype difficult to treat. However, a University of Colorado Cancer Center study presented today at the American Association for Cancer Research (AACR) Annual Meeting 2014 showcased a new drug active against triple-negative breast cancer, and through analysis of the drug's mechanism of action, offers increased understanding of the biology of this very aggressive form of breast cancer.

"We developed the compound AMPI-109 in collaboration with Dr. Rahul Ray, a synthetic organic chemist at the Boston University School of Medicine, and showed its effectiveness in preliminary studies of renal and prostate cancers. But it seemed initially as if the drug was inactive against breast cancer," says James R. Lambert, PhD, investigator at the CU Cancer Center and assistant research professor at the CU School of Medicine.

However, the initial test of AMPI-109 had been performed against only one form of breast cancer and this disease is notoriously heterogeneous. Despite initial negative results, the group decided to investigate the drug's efficacy against a panel of all known breast cancer subtypes. Strikingly, Lambert and colleagues found the drug was especially effective in specifically one subtype: triple-negative breast cancer, in which the drug blocked the growth of cells by greater than 50 percent.

"This was exciting," Lambert says, "not only did we have a drug that potentially targeted triple-negative breast cancer, but we had a biochemical tool that could be used to dissect the molecular underpinnings of the disease. "

To begin to investigate the molecular mechanism of AMPI-109 action in triple negative breast cancer, the group performed a genome-wide functional genetic screen, individually turning off every gene in the cell while exposing the cells to the drug. Identification of the silenced genes in cells that survived drug treatment would show which genes are essential for the drug's cell-killing effect.

"The number one candidate gene from that experiment, performed in collaboration with Dr. Christopher Porter, assistant professor at the CU School of Medicine, was the gene PTP4A3, a gene already implicated as an oncogene in colorectal and liver cancer," Lambert says. He suggests the current study is the first description of PTP4A3 as a potential oncogene in the context of triple-negative breast cancer.

Further work by the lab's graduate student, Hamid Gari, used computer modeling to explore the potential interaction of the PTP4A3 protein with the drug AMPI-109. Sure enough, Gari's modeling, in addition to biochemical experiments, showed that AMPI-109 binds to the catalytic site of the PTP4A3 protein and impairs its ability to function, offering the first evidence that this newly discovered triple-negative breast cancer oncogene may be targetable with AMPI-109.

"But we also wanted to study the effects of blocking PTP4A3 function in the cell," says Gari. When the group directly knocked down expression of the PTP4A3 gene in triple-negative breast cancer cells, they saw a 48 percent reduction in cell growth and a drastic reduction in the cancer cells' ability to migrate, a characteristic cancer cells often acquire in order to spread throughout the body, or metastasize.

"Not only do our data identify PTP4A3 as a potential oncogene in triple negative breast cancer, but it also offers the first reported evidence that AMPI-109 prevents the growth and migratory capability of triple negative breast cancers by targeting PTP4A3. Additionally, this has important clinical implications because we may be able to use PTP4A3 protein levels as a predictive marker to determine which patients may best respond to treatment with AMPI-109," said Gari.

"If PTP4A3 is an oncogenic driver of triple negative breast cancer, and if our drug inhibits it by this mechanism, this could have strong clinical importance for the population of the people with this disease, for whom treatment has been especially challenging," Lambert says.

Provided by University of Colorado Denver