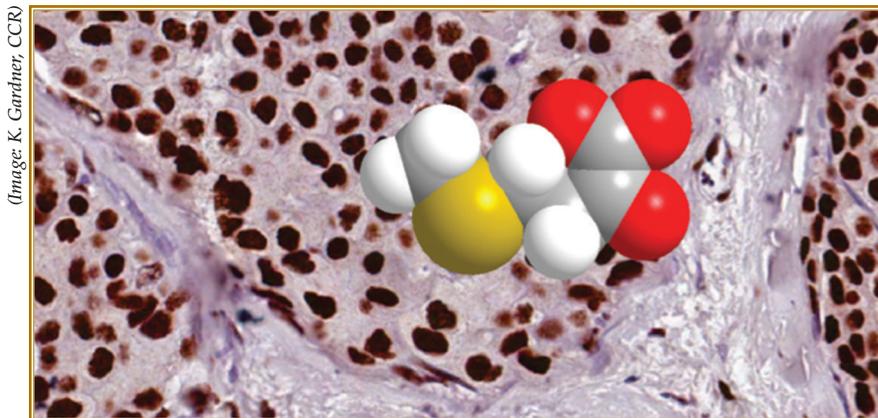


Newly Identified Mechanism Links Obesity_{with} Breast Cancer



(Image: K. Gardner, CCR)

CtBP expression in breast cancer with model of a molecule that can inhibit CtBP activity

Mounting evidence points to obesity as a risk factor for a variety of cancers. Now a new study by CCR scientists shows that excessive carbohydrate metabolism activates a protein that suppresses *BRCA1* and many other genes involved in DNA repair. The protein, called c-terminal binding protein (CtBP), links breast cancer with obesity, diabetes, and other conditions associated with metabolic imbalance, according to a study led by Kevin Gardner, M.D., Ph.D., a Senior Investigator in the Genetics Branch. The findings appeared recently in *Nature Communications*.

Dividing cells rely on the energy provided by carbohydrate metabolism. Through carbohydrate metabolism, the energy contained in sugars such as glucose gets transferred to a high energy intermediate known as NADH, which then gets converted into a substance called ATP that fuels cellular activity.

In previous research, Gardner and colleagues had revealed that NADH, CtBP, and *BRCA1* work in interconnected ways. Specifically, NADH activates CtBP, which itself

represses *BRCA1* activity. During carbohydrate metabolism, normal cells produce limited amounts of NADH, while cancer cells generate excess NADH. This results in constant CtBP activation, *BRCA1* repression, and limited DNA repair.

Based on those findings, Gardner speculated that high glucose levels encountered in obesity and diabetes also fuel excess NADH generation and boost cancer risk. “We projected that this could be the link between excessive weight gain and breast cancer,” Gardner said. During the study, Gardner also investigated if CtBP regulates other DNA repair genes in addition to *BRCA1*.

To investigate, Gardner’s research team used chromatin immunoprecipitation combined with DNA sequencing (ChIP-seq) to determine how many genes CtBP interacts with in breast cancer cell lines. That research provided evidence that CtBP functions as a master regulator for a suite of DNA repair genes. “We identified more than 1,800 gene targets for CtBP, many of which are involved in DNA repair and some of which are linked to hereditary breast cancer,” Gardner

said. Then the team silenced CtBP with RNA interference and found that *BRCA1*’s expression—and also that of CtBP’s other targets—rose in response, resulting in more efficient DNA repair.

Gardner’s research also showed that elevated glucose levels—similar to those detected in the cells of diabetic patients—result in higher CtBP activity compared to low glucose levels. Cells exposed to high glucose levels were also less able to repair DNA, but Gardner’s team showed it was possible to reverse this effect with small molecules that inhibit CtBP activation.

Then the researchers studied CtBP levels in tumor samples obtained from breast cancer patients. The results showed that differential expression of CtBP-targeted genes predicts poor clinical outcomes, while high CtBP levels in patient tumors predict shorter median survival. “Our data suggests that losing weight improves DNA repair and genome stability in patients who have cancer,” Gardner added. “Similarly, obesity activates CtBP and may contribute to more aggressive malignancies.”

The Gardner team plans to investigate CtBP’s role in a variety of other cancers. An additional goal is to identify new drugs that target CtBP and limit its tumor-promoting effects in obese patients.

For more information about Dr. Gardner’s research, please visit his CCR Web site at <http://ccr.cancer.gov/staff/staff.asp?name=gardner>.