Scientists identify molecular link between metabolism and breast cancer

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(Medical Xpress)—A protein associated with conditions of metabolic imbalance, such as diabetes and obesity, may play a role in the development of aggressive forms of breast cancer, according to new findings by researchers at the National Cancer Institute (NCI), part of the National Institutes of Health, and their colleagues. Metabolic imbalance is often caused by elevated carbohydrate intake, which can lead to over-activating a molecule called C-terminal binding protein (CtBP). This over-activation, in turn, can increase the risk of breast cancer. Results of their work appeared in *Nature Communications*, Feb. 5, 2013.

"Modifying diet and maintaining a healthy diet, combined with developing pharmacological ways of lessening CtBP activity, may one day lead to a way to break the link between cancer and obesity," said Kevin Gardner, M.D., Ph.D., head of NCI's Transcription Regulation Section, Genetics Branch.

It has been known, primarily through population based studies, that there is a strong link between obesity and cancer. But the mechanism behind this link has been uncertain. A previous study conceived and carried out in Gardner's laboratory found that CtBP repressed expression of a gene associated with breast cancer (BRCA1) at an early age by sensing when the cell was in a high metabolic state that, in turn, led to processing large amounts of carbohydrates in the body.

This early study suggested that obesity and weight gain may contribute to

breast cancer by decreasing the level of the BRCA1 tumor suppressor gene expression in response to high carbohydrate intake. This explains, in part, why women who have hereditary mutations of BRCA1 also experience an increased risk of breast cancer if they gain weight.

Gardner's new study expands upon his past work. He analyzed prior gene expression studies to determine if gene pathways, repressed by CtBP, were diminished in breast cancer patients who suffered from more aggressive clinical outcomes. Gardner's team began first with the human breast cancer cells in the laboratory. They measured the association of CtBP and the genes it bound to in order to regulate expression. The researchers combined this approach with genome sequencing to confirm how, and where, CtBP bound to genes associated with breast cancer. Next, they integrated analyses with gene expression studies in cells in which they observed decreased the levels of CtBP by RNA interference (a process that inhibits gene expression), or by decreasing carbohydrate feeding of the cells.

The scientists found that, under conditions where they decreased the levels of CtBP, DNA repair increased and the cells developed stability and growth control. They determined that gene pathways targeted by CtBP were also disrupted in more aggressive breast cancers. Moreover, patients with high levels of CtBP in their tumors had shortened survival. And they showed that a small molecular inhibitor previously shown to bind to CtBP was able to reverse the gene-repressive effects of CtBP in breast cancer cells even under conditions of high carbohydrate feeding.

"Our new work suggests that targeting CtBP may provide a way of treating breast cancer and possibly preventing breast cancer," said Gardner. "Research should continue to focus on the link between obesity, CtBP and breast cancer. This will require more population-based studies and multi-disciplinary teams of scientist to investigate these links."

More information: Gardner K, et al. Genome-wide profiles of CtBP link metabolism with genome stability and epithelial reprogramming in breast cancer. *Nature Communications*. Feb. 5, 2013. DOI: 10.1038/ncomms2438

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