

Gene implicated in progression and relapse of deadly breast cancer

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Scientists from Weill Cornell Medical College and Houston Methodist have found that a gene previously unassociated with breast cancer plays a pivotal role in the growth and progression of the triple negative form of the disease, a particularly deadly strain that often has few treatment options. Their research, published in this week's *Nature*, suggests that targeting the gene may be a new approach to treating the disease.

About 42,000 new cases of triple negative breast cancer (TNBC) are diagnosed in the United States each year, about 20 percent of all breast cancer diagnoses. Patients typically relapse within one to three years of being treated.

Senior author Dr. Laurie H. Glimcher, the Stephen and Suzanne Weiss Dean of Weill Cornell Medical College, wanted to know whether the gene – already understood from her prior work to be a critical regulator of immune and metabolic functions – was important to cancer's ability to adapt and thrive in the oxygen- and nutrient-deprived environments inside of tumors. Using cells taken from patients' tumors and transplanted into mice, Dr. Glimcher's team found that the gene, XBP1, is especially active in triple negative breast cancer, particularly in the progression of malignant cells and their resurgence after treatment.

"Patients with the triple negative form of breast cancer are those who most desperately need new approaches to treat their disease," said Dr. Glimcher, who is also a professor of medicine at Weill Cornell. "This pathway was activated in about two-thirds of patients with this type of

breast cancer. Now that we better understand how this gene helps tumors proliferate and then return after a patient's initial treatment, we believe we can develop more effective therapies to shrink their growth and delay relapse."

The group, which included investigators from nine institutions, examined several types of breast cancer cell lines. They found that XBP1 was particularly active in basal-like [breast cancer cells](#) cultivated in the lab and in triple negative breast [cancer cells](#) from patients. When they suppressed the activity of the gene in laboratory cell cultures and animal models, however, the researchers were able to dramatically reduce the size of tumors and the likelihood of relapse, especially when these approaches were used in conjunction with the chemotherapy drugs doxorubicin or paclitaxel. The finding suggests that XBP1 controls behaviors associated with tumor-initiating cells that have been implicated as the originators of tumors in a number of cancers, including that of the breast, supporting the hypothesis that combination therapy could be an effective treatment for triple negative breast cancer.

The scientists also found that interactions between XBP1 and another transcriptional regulator, HIF1-alpha, spurs the cancer-driving proteins. Silencing XBP1 in the TNBC cell lines reduced the tumor cells' growth and other behaviors typical of metastasis.

"This starts to demonstrate how cancer cells co-opt the endoplasmic reticulum stress response pathway to allow tumors to grow and survive when they are deprived of nutrients and oxygen," said lead author Dr. Xi Chen, a postdoctoral associate at Weill Cornell, referring to the process by which healthy cells maintain their function. "It shows the interaction between two critical pathways to make the [cells](#) better able to deal with a hostile microenvironment, and in that way offers new strategies to target triple negative [breast cancer](#)."

Scientists still need to study how those strategies would help women with the disease.

"Obviously we need to know now whether what our group saw in models is what we'll see in patients," said coauthor Dr. Jenny Chang, professor of medicine at Weill Cornell and director of the Houston Methodist Cancer Center. "We are very excited about the prospect of moving this research forward as soon as possible for the benefit of patients."

More information: [www.nature.com/nature/journal/...
ull/nature13119.html](http://www.nature.com/nature/journal/full/nature13119.html)

Provided by Weill Cornell Medical College

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