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Study links deficiency of cellular housekeeping gene with aggressive forms of breast cancer

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UT Southwestern Medical Center scientists have identified a strong link between the most aggressive type of breast cancer and a gene that regulates the body's natural cellular recycling process, called autophagy.

Based on analysis of two large breast cancer databases, reduced activity of an autophagy gene, beclin 1, was related to both a higher incidence of triple-negative breast cancer and a poorer prognosis for breast cancer patients.

The study, published in the online journal *EBioMedicine*, is the first to document a correlation between beclin 1 and triple-negative human breast cancer and validates research in mouse models.

"We have potentially identified a new pathway to be targeted in the most aggressive, difficult-to-treat form of breast cancer," said Dr. Beth Levine, Director of the Center for Autophagy Research and a Howard Hughes Medical Institute Investigator at UT Southwestern. "These data suggest that decreased beclin 1 activity contributes to breast cancer and poor survival outcomes. As a result, therapies that increase beclin 1 activity in breast cancer may be beneficial."

Triple-negative breast cancer - which accounts for 10 to 20 percent of breast cancer - is called such because the cancer's cells lack estrogen and progesterone receptors and also do not have an excess of the human

growth factor receptor 2 (HER2) protein on their surfaces. Chemotherapy, the standard treatment, has been limited in its effectiveness against triple-negative breast cancer.

"With low beclin 1 expression, you have up to a 35-fold higher risk of having triple-negative breast cancer. That's really strong," said Dr. Levine, who holds the Charles Cameron Sprague Distinguished Chair in Biomedical Science and is co-senior author of the study with Dr. Yang Xie, Associate Professor of Clinical Science.

UT Southwestern researchers analyzed 3,057 breast cancer cases for levels of expression of beclin 1 and BRCA1, a nearby gene that is associated with inherited breast cancer. The data came from The Cancer Genome Project in the United States (1,067 cases) and the Molecular Taxonomy of Breast Cancer International Symposium in the United Kingdom and Canada (1,992 cases).

"We know that about 35 percent of all breast cancers are missing copies of both the beclin 1 and BRCA1 genes," said Dr. Levine. "To find out which of the two genes is important, we looked at the levels of expressions of both genes and how they related to different clinical features of breast cancer. Strong associations were seen between low expression of beclin 1, but not BRCA1, and adverse clinical features."

Along with the 35-fold higher risk of having triple-negative breast cancer, the findings showed low levels of beclin 1 activity also correlated with worse outcomes.

"Patients with breast cancer and low beclin 1 expression had a 67 percent increase in the risk of dying from breast cancer compared with patients who had higher levels of beclin 1 expression," Dr. Xie said.

Increasing beclin 1 activity could, therefore, become a new therapy for

breast cancer patients, especially those with the triple-negative type. Several approved drugs that happen to increase beclin 1 activity are already used for other types of cancer. They included four classes of drugs: inhibitors of either beclin 1/BCL-2 binding, protein kinase B (AKT), epidermal growth factor receptor (EGFR), or HER2.

"Our study mandates the need for further research to see whether agents that upregulate beclin 1 could save more lives of breast cancer patients," Dr. Levine said.

Dr. Levine's research team studies genes involved in the autophagy process and their roles in cancer, aging, infections, and neurodegenerative diseases, while Dr. Xie's UT Southwestern lab focuses on improving cancer treatments through statistical and computational analysis of biological and clinical data.

Provided by UT Southwestern Medical Center

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