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A chink in the armor of breast cancer cells

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Working with human breast cancer cells, a team of scientists from Ann & Robert H. Lurie Children's Hospital of Chicago have successfully turned off a misbehaving protein that fuels the growth of a particularly aggressive, drug-resistant form of the disease known as triple-negative breast cancer.

In a set of lab experiments, the team managed to neutralize the protein, called Nodal, a growth factor already known for its role in early embryonic development.

A description of the work is published in the March 23 issue of the journal *Cell Cycle*.

The team's work demonstrates that in addition to its role in promoting embryonic growth, Nodal also appears to play a role in instigating malignant cell changes that culminate in the development of triple-negative breast cancer.

The findings, researchers say, reveal a key player in the development of a disease that has long mystified scientists.

The so-called triple-negative breast cancer is not caused by any of three hormones and growth factors known to drive the development of other forms of disease. Thus, triple-negative breast cancer does not respond to traditional therapies that "starve" cancer cells of their fuel. As a result, patients diagnosed with this disease are treated with more toxic forms of chemotherapy, rather than with precision-targeted treatments that spare

healthy cells and tissues.

If reaffirmed in further experiments, the results can pave the way to much-needed new therapies for a form of the disease that accounts for 20 percent of all breast cancers.

"While clearly preliminary, our results reveal a pivotal catalyst in the development of a disease for which we lack precision-targeted, effective treatments," says study author Thomas Bodenstine, Ph.D. "Our results also indicate one possible way to improve the accuracy and efficacy of current treatments by delivering an antibody that can neutralize the influential tumor-promoting effects of this gene."

Building on earlier observations that the protein Nodal is found in higher levels in many aggressive forms of cancer, the team homed in on human breast cancer cells obtained from patients with the triple-negative form of the disease. The scientists pre-treated cancer cells with doxorubicin, a commonly used breast-cancer drug, then added an antibody known to disable, or inactivate, Nodal.

Cancer cells treated with combination therapy were weaker and died off faster than breast cancer cells that received only standard drug treatment, the researchers found.

To understand why that was, researchers used a form of protein analysis to track minute shifts in proteins inside the cancer cells. The proteins of cancer cells treated with the dual therapy, the research team found, were less capable of repairing themselves. In other words, the researchers say, adding the antibody somehow made the cells weaker, less capable of repair and survival and thus rendered them more vulnerable to the effects of the standard chemotherapy drug.

"The antibody appears to create vulnerability in the cells' armor,

exposing them to the effects of the standard drug," says Mary J.C. Hendrix, Ph.D., principal investigator on the study.

"The new study establishes several key findings with great potential for future clinical application that can also help pave the way to less toxic chemotherapy treatments," writes Danny Welch, Ph.D., in an accompanying editorial by a team of breast-cancer specialists not involved in the research. Welch is professor and chair of the Department of Cancer Biology at the University of Kansas.

Bodenstine, now an assistant professor of biochemistry at Midwestern University, completed the work while completing a post-doctoral research fellowship at the Hendrix Lab at the Stanley Manne Children's Research Institute.

Hendrix, formerly president and chief scientific officer of Stanley Manne Children's Research Institute, is now president of Shepherd University in Shepherdstown, West Virginia.

Provided by Ann & Robert H. Lurie Children's Hospital of Chicago