BRCA1 mutation linked to breast cancer stem cells

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A new study may explain why women with a mutation in the BRCA1 gene face up to an 85 percent lifetime risk of breast cancer. Researchers from the University of Michigan Comprehensive Cancer Center found that BRCA1 plays a role in regulating breast stem cells, the small number of cells that might develop into cancers.

The study, in mice and in human breast cancer cells, found that BRCA1 is involved in the stem cells differentiating into other breast tissue cells. When BRCA1 is missing, the stem cells accumulate unregulated and develop into cancer.

“Our data suggest that an important reason women with BRCA1 mutations get breast cancer is that BRCA1 is directly involved in the regulation of normal breast stem cells. In these women, loss of BRCA1 function results in the proliferation of breast stem cells. Since we believe that breast cancer may originate in these cells, this explains why these women have such a high incidence of breast cancer,” said senior study author Max S. Wicha, M.D., Distinguished Professor of Oncology and director of the U-M Comprehensive Cancer Center.

The study, published online this week in the Proceedings of the National Academy of Sciences, provides strong support for the hypothesis that a small number of cells, called cancer stem cells, are responsible for fueling a tumor’s growth. Wicha’s lab was part of the team that first identified stem cells in human breast cancer in 2003.

BRCA1 is one of two genes, that when mutated confers a high risk of breast and ovarian cancer. Previous research has shown that BRCA1 is involved in DNA repair, but it has been unclear why women with this gene mutation have such a high risk of breast cancer, up to 85 percent lifetime risk compared to 16 percent in the general population.

The cancers which develop in these women are generally a more aggressive form called “triple negative type,” because they do not express hormones or proteins, including estrogen, that can be targeted with therapies. In the current study using both mice and human breast cells, researchers found that BRCA1 regulated the development of the estrogen-receptor-negative stem cells into estrogen-receptor-positive cells. When BRCA1 is missing, genetically unstable stem cells accumulate and then may develop into breast cancers.

Researchers detected clusters of expanded stem cells in breast tissue isolated from women carrying BRCA1 mutations, and found that women with these expanded stem cells had a particularly high chance of developing breast cancer.

“If larger studies confirm these findings, it could potentially lead to a test to identify BRCA1 carriers at particularly high risk of developing breast cancer. This might help them and their physicians make a more informed decision about preventative measures such as prophylactic mastectomy,” Wicha says.

BRCA1 mutations are the most common cause of hereditary breast cancer, which account for approximately 10 percent of the 180,000 breast cancers diagnosed in the United States this year. For information about breast cancer, call the U-M Cancer AnswerLine at 800-865-1125. To learn more about cancer stem cells, visit www.mcancer.org.

In addition to Wicha, study authors were U-M research investigator

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The University of Michigan has filed for patents covering these and related technologies, and, through its Office of Technology Transfer, is currently looking for commercialization partners to help bring the technology to market. Much of the work is being commercialized through OncoMed, a University of Michigan startup company in which Max Wicha and other U-M inventors hold a financial interest.

Source: University of Michigan Health System