

New pathway provides more clues about BRCA1 role in breast cancer

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A breast cancer gene's newly discovered role in repairing damaged DNA may help explain why women who inherit a mutated copy of the gene are at increased risk for developing both breast and ovarian cancer.

The discovery also could lead to more effective therapies for women with and without mutated copies of the BRCA1 gene, according to a study led by Duke University Medical Center researchers.

“Since it was discovered in 1994, BRCA1 and its role in preventing and causing cancer has been intensely studied, and our research represents an important piece of the puzzle,” said Craig Bennett, Ph.D., a researcher in Duke’s Department of Surgery and lead investigator on this study. “This study has identified an important mechanism by which BRCA1 comes into play when DNA -- the basis for all cell function -- is damaged. We have shown that this theory holds up not just in scientific models but in human breast cancer cells as well.”

The findings appear in the January 16, 2008 online edition of the journal PLoS ONE. The study was funded by the United States Department of Defense, the National Institutes of Health and the Italian Association for Research on Cancer.

The researchers first looked at yeast to demonstrate that a molecular pathway that is particularly susceptible to BRCA1 influence is also crucial to normal cell function.

“The BRCA1 pathway we discovered is directly involved with the critical process of transcription, in which RNA acts as a messenger between DNA and the making of proteins,” Bennett said.

DNA damage is a normal result of exposure to environmental agents, such as carcinogens, and the response to this damage can be influenced by other normal human processes such as aging and hormonal changes, Bennett said. It's what happens to RNA transcription after damage occurs in DNA that is BRCA1-dependent.

“We found that BRCA1 acts together with transcription to detect DNA damage and to signal the cell to repair itself,” Bennett said. “When BRCA1 does not function correctly, as when it is mutated, DNA damage remains un-repaired and cancer can occur.”

The researchers applied their findings in yeast to human breast cancer cells, with the same results.

“The fact that we were able to duplicate our results in human breast cancer cells is hugely important,” said Bennett. “Yeast is a wonderful model organism that has been used to make significant discoveries in many areas of science and medicine, including Parkinson’s and Alzheimer’s diseases, but the ability to replicate results in human cells is key.”

Bennett said the discovery will lay the groundwork for further investigation of the role of BRCA1 and possibly lead to new therapeutic strategies targeting the genes or protein products within this pathway.

Women who have inherited a BRCA1 mutation have up to an 80 percent risk of developing breast cancer in their lifetime, and they are also at risk for developing the disease at much younger ages than women without the mutation, according to the American Cancer Society. Their

risk for developing ovarian cancer is about 40 to 50 percent, compared to just over one percent for the general population. The mutation is most often found in women with Eastern European Jewish origin, but can be found in women of any race.

“Someday we hope that this research will lead to the development of more effective ways to treat both the women who have inherited a mutated copy of the BRCA1 gene and those who have not,” Bennett said.

Source: Duke University Medical Center

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