Key function of mutation in hereditary breast and ovarian cancer gene discovered

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It is widely known that mutations in the breast cancer susceptibility 1 (BRCA1) gene significantly increase the chance of developing breast and ovarian cancers, but the mechanisms at play are not fully understood. Now, researchers at Virginia Commonwealth University Massey Cancer Center have shown that certain BRCA1 mutations result in excessive, uncontrolled DNA repair, which challenges the prior assumption that mutations in BRCA1 only contribute to breast cancer through a reduction in function.

Recently published in the journal Aging, the study led by Kristoffer Valerie, Ph.D., discovered that certain BRCA1 mutations affecting the BRCA1 C-terminal (BRCT) binding site resulted in excessive DNA repair, or hyper-recombination, which may contribute to the development of breast and ovarian cancers. The BRCT domain is a protein binding site typically found on DNA repair proteins like BRCA1 that are responsible for maintaining genomic stability and facilitating DNA repair. This study has implications for the treatment, diagnosis and development of therapies for patients with breast and ovarian cancer.

"Our findings suggest that caution should be exercised when targeting BRCA1 for breast and ovarian cancer therapies," says Valerie, co-leader of the Radiation Biology and Oncology program and a professor in the Department of Radiation Oncology at VCU Massey Cancer Center. "We need to better understand the biological mechanisms that lead to the development of breast and ovarian cancer before we attempt to attack it through targeted therapies aimed at causing DNA damage."

When DNA damage occurs, various forms of BASC (BRCA1-associated genome surveillance complex) bind to the BRCT domain on BRCA1. BASC is a protein complex that in part binds to the BRCT domain and serves as a "docking site" for other proteins and enzymes to come in, effectively repair the DNA damage and leave when repair is completed. However, certain BRCT mutants unable to bind to BASC disrupt the delicate DNA repair process. Previously, it was assumed this meant that BRCA1 was unable to assist with the repair process and, thus, recombination did not occur.

Valerie and his colleagues showed through experiments with cultured breast cancer cells and tissue samples from breast cancer patients that BRCT mutants increased ubiquination of BASC, which, in turn, increased recombination several-fold over normal levels. Ubiquitin is a small protein in all living organisms that "marks" other proteins for degradation or, as more recently discovered, the participation in specific cellular processes such as recombination. The researchers proposed that the hyper-recombination resulting from increased ubiquination of the BASC might result in improperly repaired DNA and increased genomic instability, which could lead to the development and aggressive progression of breast and ovarian cancers.

"Our results point to ubiquitination as a potential therapeutic target," says Valerie. "By disrupting ubiquitination we may be able to prevent hyper-recombination and stop the growth of cancer cells with these BRCT mutations. This might sensitize the cancer cells to radiation therapy while having little effect on cells with normal BRCA1 function."

The researchers hope to continue studying the role of BRCA1 in DNA double-strand break repair in order to determine whether the mutations they examined are important for the onset of cancer and whether targeted therapies can be developed.

More information: The full manuscript of this study is available online at: www.impactaging.com/papers/v3/n5/abs/100325a.html

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