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Study uncovers mechanism used by BRCA1 to suppress tumors

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A new study by Georgetown University Medical Center researchers reveals how a well-known tumor suppressor gene may be functioning to stop cancer cell growth.

The findings, published online today in Oncogene, focus on the gene BRCA1, which is mutated in a majority of families who have hereditary breast and/or ovarian cancers, according to senior author Ronit I. Yarden, PhD, assistant professor in the Department of Human Science at the School of Nursing & Health Studies.

"There is a debate in the scientific community about whether BRCA1 enzymatic activity is important in tumor suppressor function," Yarden said. "My lab thinks it is."

Previous research by other investigators, according to Yarden, has shown that BRCA1 is an ubiquitin E3 ligase enzyme. When added to other proteins, ubiquitin has the ability to mark them for degradation and recycling.

Her laboratory worked to discover which proteins BRCA1 is targeting with ubiquitin and how that activity might help attenuate cell division in response to DNA damage – a function that is important for maintaining genomic integrity and suppressing tumor growth.

"Cells have surveillance mechanisms and check points that govern cell division," she said. "In order to conduct DNA repair in a timely fashion,

a cell must be stopped for awhile and then repaired. Once DNA is fixed, division can then begin again."

Yarden's lab discovered that BRCA1 targets two specific proteins cyclin B and Cdc25c, which are the "keeper genes" that regulate the G2/M checkpoint – the last checkpoint a cell has to go through before it divides.

"The paper shows that in response to DNA damage, BRCA1 is responsible for tagging these two proteins to stop the cells from dividing so repair can occur," Yarden said. "This work shows that BRCA1 enzymatic function is essential for maintaining genomic integrity and may explain BRCA1 role in tumor suppression."

"We identified a novel function," she said. "Although different substrates for BRCA1 were previously identified by other investigators, those didn't explain directly BRCA1's role in maintenance of genomic integrity. Our new targets are the first to directly link this ubiquitination function of BRCA1 to halting cell division that is important for maintenance of genomic integrity and stability, an important activity of tumor suppression."

Provided by Georgetown University Medical Center