Scientists show how BRCA1 cancer gene mutations harm breast cells

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(Medical Xpress) -- Working with human breast cells, researchers at the Johns Hopkins Kimmel Cancer Center have shown how the inactivation of a single copy of the breast cancer gene BRCA1 leaves breast cells vulnerable to cancer by reducing their ability to repair DNA damage, causing genetic instability. An inherited mutation in BRCA1 is the leading risk factor for hereditary breast cancer, prompting preventive mastectomies or close monitoring. The new findings may aid development of drugs to prevent hereditary breast cancer and tools to identify women who benefit most from prophylactic treatments.

Precisely how BRCA1 inactivation raises cancer risk has remained something of a puzzle. BRCA1 is considered a "tumor suppressor" gene, and typically the loss of one copy of such genes is not enough to cause cancer. That's because humans inherit two copies of each gene (one from each parent), and the second copy works well enough to keep cells healthy – just as a car can safely stop after losing the front brakes since the rear brakes are still intact. Cancer apparently develops in such cases only after the second copy is inactivated in a cell, perhaps by some random mutation during cell division, resulting in the "second hit" – causing uncontrolled cell growth as if the cell lost its "brakes."

Mouse models of BRCA-related cancers have shown that "hits" to genes such as TP53 occur before the second "hit" to the remaining functional copy of BRCA. "In theory, this process would take a long time, and BRCA-related breast cancers occur at an early age," according to Ben Ho Park, M.D., Ph.D., associate professor of oncology at the Johns

Hopkins Kimmel Cancer Center.

Park discusses breast cancer genomics research at Johns Hopkins:

For the study, reported in the *Proceedings of the National Academy of Sciences* Oct. 25, Park and his team at Johns Hopkins took advantage of new technology to introduce a single copy of a typical BRCA1 mutation into normal breast cells.

The leading hypothesis has been that the original inactivation of a single copy of BRCA1 causes further DNA mutations to accumulate more quickly than normal – a condition called "genomic instability." The protein coded by BRCA1 is involved in repairing major DNA breaks, so it would make sense that its inactivation could weaken a cell's resistance to DNA mutations, says Park.

But the consequence of losing a single copy of BRCA1 was not easy to model or study, he adds. Previous efforts to create mice with single-copy BRCA1 mutations had uncertain results because the mice failed to show the pattern of human cancers. Researchers also have found it difficult to create human cell lines in which the only flaw is a single mutated copy of BRCA1.

To test the idea, Park's team first selected cell lines derived from non-cancerous human breast epithelial cells – where BRCA1 breast cancers originate. They then used an advanced gene-targeting technique to create new cell lines that have a typical cancer-linked BRCA1 mutation in only one copy of the gene.

Park's team then ran tests on the two cell types – the ones that had the BRCA1 mutation, and the original cells that had two healthy copies of BRCA1 – and compared their DNA repair activity. They were able to show that cells with BRCA1 mutations were less efficient at conducting

the type of DNA repair known to involve the BRCA1 protein. The BRCA1-mutated cells were more likely to die when exposed to a DNA-damaging chemotherapy drug or radiation. BRCA1-mutated cells allowed to divide for several weeks also were more likely to lose other genes, including genes often mutated in breast tumors. Tests on non-cancerous breast cells taken from women with BRCA1 mutations showed similar genetic losses.

"What this shows is that having only a single working copy of BRCA1 really does bring about changes in a cell that would be expected to give rise to cancer," Park says.

Park plans additional experiments on their new cell models of BRCA1-mutations. "We hope to use this new system to introduce other known BRCA1 mutations, to get a better idea of the relative cancer risk each individual mutation represents, because right now there are few good ways to do that," he says. "In the future, we hope to further define risk so that family members with one type of BRCA1 mutation may be advised to get preventive treatment or surgery, and those with other BRCA1 mutations could rely on careful screening."

The new cell models also may be useful in determining the susceptibility of various BRCA1 mutations to drugs, he adds. Anti-cancer drugs known as PARP inhibitors are currently in clinical trials against tumors with BRCA1-mutations.

Women born with a mutated copy of BRCA1 have been shown to have lifetime risks of breast cancer between 50 and 90 percent, a wide range. They also have high, but variable, risks of ovarian and other cancers.

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