Pathways that Can Repair Brca1 Cancer Gene Mutation Clarified in Mice

April 1 2010

(PhysOrg.com) -- In a new study in mice, scientists have compensated for mutations in the Brca1 gene that can lead to cancer by deleting a second gene, which then lessens the probability of cancer. Mice Brca1-associated mammary tumors have significant similarities to human BRCA1- associated (BReast CAncer 1, early onset) breast cancer in regard to tumor aggressiveness, high incidence, mutations and genetic instability. The study, led by scientists at National Cancer Institute (NCI), part of the National Institutes of Health, and their colleagues, appeared online April 1, 2010 and in print April 16, 2010, in the journal *Cell*.

In humans, mutations in the BRCA1 gene increase the risk of breast, ovarian, and other cancers by impairing an important pathway for the repair of damaged DNA. Lead investigator Andre Nussenzweig, Ph.D., head of the Molecular Recombination Section of NCI's Experimental Immunology Branch, and his colleagues found that when a gene known as 53BP1 was also defective, the formation of the mammary tumors that normally develop in Brca1 mutant mice was suppressed. Moreover, they found that inactivation of 53BP1 restored the DNA repair function that is lost when Brac1is mutated.

The protein produced by the Brca1 gene participates in an important DNA repair pathway called homologous recombination (HR). This pathway is used to repair a type of DNA damage called replication-associated chromosome breaks, which develop spontaneously when cells divide. When HR is defective, whether through Brca1 mutations or

mutations in other genes whose products are involved in this pathway, cells must rely on alternative DNA repair pathways. These other pathways are more error-prone, or mutagenic, than HR, and they can lead to the formation of abnormal and unstable chromosome structures. The resulting genomic instability increases the risk of tumor development.

Women who carry a harmful mutation in the BRCA1 gene have up to an 85 percent lifetime risk of developing breast cancer, and up to a 40 percent lifetime risk of developing ovarian cancer. To date, there are no effective or targeted therapies that overcome the breast cancer susceptibility caused by mutations in BRCA1. "Promoting HR by using drugs that inhibit toxic pathways for DNA repair could greatly reduce the development of breast and ovarian cancer in women with BRCA1 mutations," said Nussenzweig.

The team used a strain of mice, originally developed by NIH researchers, that have a defective Brca1 gene. These mice frequently develop mammary tumors, which are similar to human breast cancers. Nussenzweig and colleagues found when the mice also were lacking the function of a protein called 53BP1, mammary tumor formation was largely suppressed.

To investigate the molecular basis by which the loss of 53BP1 suppressed Brca1-associated mammary tumor formation, the researchers undertook a series of experiments using mouse cells grown in culture. These experiments showed that it was possible to restore HR to Brca1-deficient cells by inactivation of the gene 53BP1.

Further analysis led to a model in which both Brca1 and 53BP1 are capable of binding to replication-associated chromosome breaks. According to this model, when both proteins are present, Brca1 displaces 53BP1, the HR machinery has full access to the breaks, and HR

proceeds. In Brca1-deficient cells, the binding of 53BP1 to the site of DNA damage interferes with the activity of HR proteins. Consequently, the damage is instead repaired by an alternative mutagenic pathway that promotes cancer. When 53BP1 is absent, Brca1 is not needed to displace it. Therefore, HR can take place normally when both proteins are missing.

"Our results show that the choice of pathway used to repair DNA damage determines whether the repair is error-free or error-prone. This opens the possibility of using drugs to inhibit mutagenic DNA repair pathways and promote error-free DNA repair," said Nussenzweig.

The study also suggests that BRCA1-deficient tumors may become resistant to chemotherapy by acquiring additional mutations in certain DNA repair proteins, but that such resistance may one day be overcome by drugs developed to affect pathway choice, according the researchers.

More information: Nussenzweig A, et al. 53BP1 Inhibits Homologous Recombination in Brca1-Deficient Cells by Blocking Resection of DNA Breaks. *Cell*, April 16, 2010. DOI 10.1016/j.cell.2010.03.012

Provided by National Institutes of Health

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