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NIH Animal Model Uncovers a Role of BRCA1-Associated Breast Tumor Formation

A team of researchers at the National Institutes of Health (NIH) has uncovered the role of two key genes implicated in the development of inherited forms of breast cancer. In the May issue of *Nature Genetics*, Xiaoling Xu, Chu-xia Deng, and colleagues from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) unveil a model of tumor formation that holds great potential for studying breast cancer in women.

The animal model reveals new detail about how mutations in BRCA1 and another gene, called p53, work in tandem to accelerate tumor formation and growth. "This model may speed the process of future research on breast cancer and its treatment," says Xu, lead author of the study. Researchers at the National Human Genome Research Institute and the National Cancer Institute also contributed to the project.

Scientists have known that mutations of BRCA1 are involved in the development of these cancers but had not been able to identify specifically how alterations in BRCA1 affected the timing and process of tumor development. "We knew from previous work

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that the role of BRCA1 in tumor formation was not straightforward," says Deng, a co-author of the study.

Recent work by the same team established that BRCA1 plays a critical role in controlling when cells divide and how genetic material is duplicated. In the *Nature Genetics* study, the researchers showed that mutations in BRCA1 create an environment in which genes such as p53 mutate more readily. "Loss of BRCA1 creates the condition for p53 to mutate," says Lothar Hennighausen, a mammary gland expert and NIDDK co-author of the study. "P53 is believed to be the gatekeeper. Then when you lose p53, the tumor grows," he adds. Half of human tumors have mutated p53 genes.

Studying the relationship of mutations in BRCA1 and p53 was a complex process that took over three years. First, to uncover the function of BRCA1, the researchers bred mice to contain mutations in BRCA1 genes in mammary gland tissues only, and only at specific points in development. BRCA1 genes in these mice were unaltered in other cell tissues.

To accomplish this specific "knock-out" of genes, NIDDK's Kay-Uwe Wagner, the second author of the study, applied a technique that uses specially developed genes to act like molecular scissors that can recognize, target, and cut out critical segments of genetic material. The study of the resulting knockout mice allowed the NIDDK researchers to build an accurate model of the mechanism by which BRCA1 mutations lead to tumorigenesis.

When BRCA1 alone was deleted from mammary glands, 5 of 23 of the experimental mice developed tumors over one year. The tumors showed rearrangements of chromosomes where p53 is located. To focus on the role of p53, the researchers then introduced a copy of a mutated p53 gene into the mice. When the researchers introduced altered p53, 8 of 11 mice formed tumors, a 90 percent increase. Tumors also grew faster—in 6 months instead of twelve—when the two mutations were present.

"We now have direct genetic evidence that p53 is involved in BRCA1-associated tumorigenesis," says Xu, "but it is probably not the only mutation involved. There may be some others, perhaps some that activate oncogenes—the cancer genes that promote uncontrolled cell growth."

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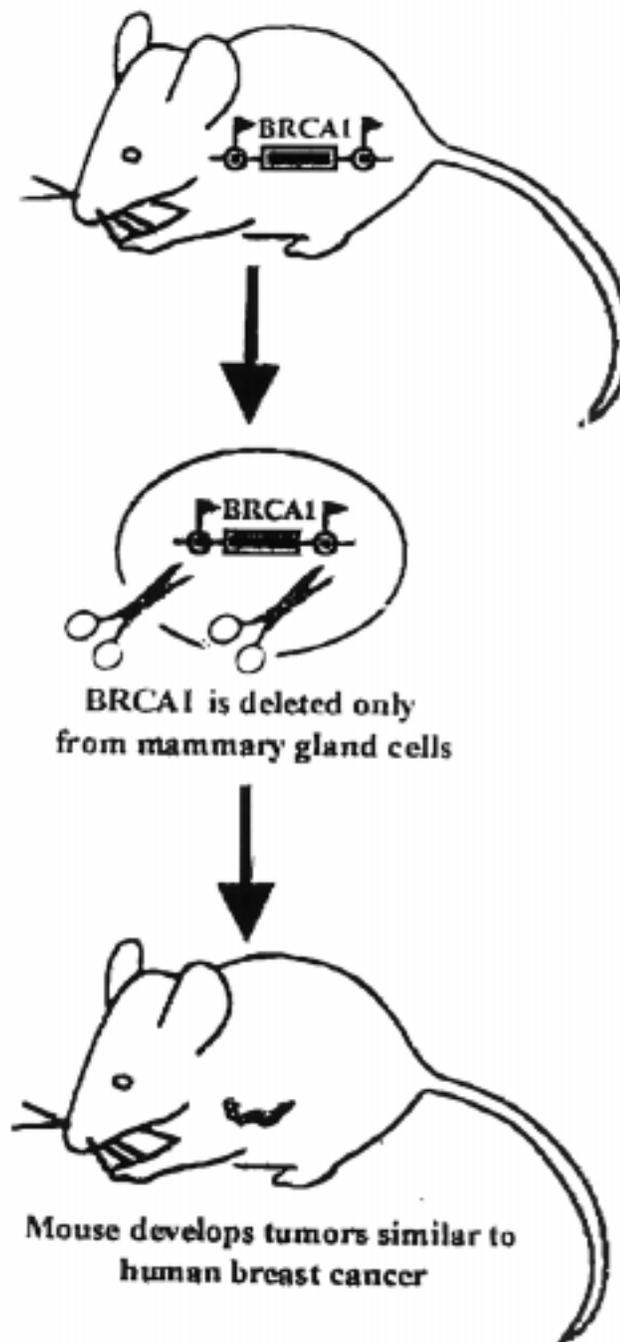
"Animal models are vital to our understanding of human disease. This model is the first that shows cancer development similar to the development of breast cancer in women. It will be an important tool for future work on tumors and their progression," says NIDDK Scientific Director Allen Spiegel, M.D.

The researchers believe that this model provides a route for testing drugs to prevent tumor formation in humans, as well as to test the role of environmental agents, such as radiation or environmental estrogens in tumor growth.

An estimated 175,000 women will be diagnosed with breast cancer in 1999; about 43,000 will die. Mutations in the BRCA1 gene are found in 90 percent of women who have inherited both breast and ovarian cancer, and in about 50 percent of women with inherited breast cancer alone.

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Radio Editors: A one-minute audio report with actualities is available at 1-800-MED-DIAL (1-800-633-3425) on Thursday April 29 at 5:00 p.m. EDT.



NIDDK researchers developed a genetically engineered mouse that allowed them to study the formation of cancer in breast tissue. In the mouse, the breast cancer gene BRCA1 was flagged for deletion in every cell of the body. The researchers targeted molecular scissors to cut out the gene only from mammary gland cells; BRCA1 remained unaltered in all other cells of the body. The mice with the deleted BRCA1 cells developed breast cancer. When another gene, p53, was also deleted, mice developed more breast tumors at a very rapid rate.