Enhanced DNA-repair mechanism can cause breast cancer

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Although defects in the "breast cancer gene," BRCA1, have been known for years to increase the risk for breast cancer, exactly how it can lead to tumor growth has remained a mystery. In the October 15, 2007, issue of the journal *Cancer Research*, scientists from the University of Chicago and Kyoto University, Japan, suggest that a mechanism that normally repairs damaged DNA may function abnormally in BRCA1 carriers leading to one type of poor-prognosis breast cancer.

Their findings provide insight into how the normal BRCA1 gene suppresses the growth of tumors as well as the nature of the genetic instability that leads to cancer when BRCA1 is defective.

"If you take a normal, healthy cell and get rid of BRCA1, you end up with an unhealthy, slow-growing cell," said Douglas Bishop, PhD, associate professor of radiation and cellular oncology at Chicago and principal investigator of the study. "That's a bit of a paradox, because loss of BRCA1 also causes tumors and tumor formation is not normally associated with poor cell growth."

Bishop and colleagues found that the slow growth caused by loss of BRCA1 could be compensated for by increasing the amount of the DNA repair protein RAD51.

RAD51 is involved in homologous recombination, a method used by cells to repair damaged DNA. In homologous recombination, organisms heal broken chromosomes using an unbroken chromosome copy as a

template.

BRCA1 itself promotes DNA repair through recombination and the conventional view is that loss of BRCA1 causes tumors because DNA repair fails. The new work from Bishop and colleagues challenges this view.

"BRCA1-deficiency by itself would probably not cause a tumor," Bishop said, "but cells that manage to compensate for the BRCA1 defect in repair by ramping up RAD51 levels are likely to be less genetically stable than normal cells and therefore more prone to form tumors."

Using a public database, Bishop and colleagues examined genomic data from 117 primary breast tumors for evidence of elevated levels of RNAs for genes involved in homologous recombination. They found that the level of RNA for three genes -- RAD51 and two of its key accessory factors -- was significantly higher in BRCA1-deficient tumors compared with breast tumors that were not associated with BRCA1 mutations.

"High levels of RAD51 may help cells that lack BRCA1 overcome the defects in recombination caused by loss of BRCA1," Bishop said, "but the recombination that occurs in this situation may be abnormal and may actually cause mutations which in turn lead to the development of a tumor."

When the researchers took normal, healthy cells in culture and disabled the BRCA1 gene, the cells survived, but grew slowly and were unable to repair DNA damage normally. When Bishop and his coworkers increased the amount of RAD51 in these cells, however, the ability of cells to repair DNA damage was restored and the mutated cells grew more quickly.

In the future "it will be interesting to determine whether high levels of

RAD51 can predict tumor prognosis," said Bishop. "Its also possible that tumor cells with high levels of RAD51 are particularly dependent on that gene for survival and therefore sensitive to drugs that target RAD51"

Source: University of Chicago Medical Center

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