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Trigger for Key Breast Cancer Protein Identified

In breast cancer research, the gene *BRCA1* has received the lion's share of attention because mutations in that gene are responsible for about three percent of all cases of breast cancer. Researchers from the Howard Hughes Medical Institute (HHMI) at Baylor College of Medicine have identified a protein that triggers the mouse version of the BRCA1 protein to initiate the repair of damaged DNA. They say that mutations in the human gene that produces this trigger protein are likely to be responsible for more instances of breast cancer than *BRCA1* mutations.

The discovery of the trigger protein, which is made by a gene called *ATM*, suggests that malfunctions in *Brc1* and *ATM* combined may account for nearly ten percent of all breast cancers. Both *Brc1* and *ATM* are part of the cell's machinery for repairing genetic damage caused by radiation.

"We have now established a pathway that connects two major tumor suppressors involved in breast cancer."

— Stephen J. Elledge

The discovery of *ATM*'s role in triggering *Brc1* was reported in the November 5, 1999, issue of *Science* by HHMI investigator Stephen Elledge and his colleagues in the biochemistry department at Baylor College of Medicine. Co-authors of the paper are David Cortez, Yi Wang and Jun Qin.

The *ATM* gene, which stands for "ataxia telangiectasia mutated," is named for the genetic disease in which people with two malfunctioning copies of the gene lose brain cells and control over muscles, have high cancer rates and increased sensitivity to radiation. The *ATM* protein is a "kinase," a type of enzyme that activates other proteins by adding a phosphate to them in a process called phosphorylation.

In their experiments, Elledge and his colleagues found that normal cells pulsed with gamma radiation contained phosphorylated *Brc1*; while irradiated cells from ataxia telangiectasia (AT) patients who do not have functional *ATM* genes did not. When the scientists inserted a functioning *ATM* gene into the cells of AT patients, the *Brc1* protein did show

phosphorylation.

Detailed studies of the *Brcal* protein revealed that there are many sites on the molecule where phosphorylation can occur. When the scientists mutated the protein and blocked many of those sites, they found that the ATM protein could no longer control the *Brcal* protein.

"We believe that these studies show that ATM is the sensor and the instructor for *Brcal*," said Elledge. "It tells *Brcal* that there is a chromosome break due to radiation, and *Brcal* is involved in orchestrating the repair process to fix the damage.

"Thus, we have now established a pathway that connects two major tumor suppressors involved in breast cancer."

Elledge emphasized that ATM and *Brcal* are both middlemen in the DNA repair process and that further research will likely reveal that there are many more genes involved in the DNA repair pathway that may be important in breast cancer.

"Studies in yeast have shown that there are many other genes in this pathway," said Elledge. "We don't know all of the human genes yet, and it may be that we will end up with just one major pathway that accounts for a significant portion of all breast cancers."

ATM mutations may account for significantly more cases of breast cancer than the one to three percent attributed to *Brcal* mutations, Elledge said.

"This work may provide a molecular explanation for other studies indicating that women who are heterozygous for *ATM* that is, they had one mutant form of the gene had a three- to four-fold higher predisposition to breast cancer."

Elledge and his colleagues also point out that studies in mice have shown that one mutant *ATM* gene rendered the animals more sensitive to genetic damage from radiation. Given that many women also possess one mutant *ATM* gene, the researchers write in the journal *Science* that their results "may have relevance to the issue of the relative benefits of broad x-ray screening for the early detection of breast cancer, a question to be resolved only by epidemiological studies."

According to Elledge, past studies also suggest that *ATM* is not a rare mutation. "If the published numbers are correct, there are one million women who are heterozygous for *ATM*, which means that it could actually account for a greater percentage of breast cancer than *Brcal*," Elledge said.