BRCA2 Protein Structure Found

MSKCC Investigators Determine the Function of Protein Linked to Breast and Ovarian Cancers

MSKCC structural biologist Nikola Pavletich and members of his laboratory have discovered the function of the protein BRCA2 (shown at left). Mutations in the *BRCA2* gene have been linked to hereditary breast and ovarian cancers.

Earlier studies suggested that BRCA2 was a tumor suppressor — a protective protein that prevents the development of cancer — but exactly how this protein does its job has not been understood until now. MSKCC scientists reported in September in the journal *Science* the atomic structure of a crucial part of the protein, discovering that BRCA2 binds directly to DNA and helps to repair genetic damage. Inability to correct genetic damage leads to unstable chromosomes and often to cancer.

"If BRCA2 is altered or missing, it leads to a dangerous accumulation of genetic errors," explained Dr. Pavletich, head of MSKCC's Laboratory of Structural Biology of Oncogenes and Tumor Suppressors and a Howard Hughes Medical Institute investigator. "By studying the normal function of BRCA2, we can understand how changes in the protein contribute to the development of cancer."

BRCA2 is an unusually large molecule, which has made it difficult for researchers to study. Dr. Pavletich's team, including postdoctoral researcher Haijuan Yang, the study's first author, worked for two years to crystallize the protein. (Biologists induce proteins to form crystals in order to study their three-dimensional structure.) "Tackling a protein of this size with conventional biochemical methods can be very intimidating," said Dr. Yang, who was a graduate student at the time. "But further computer analysis of the protein's amino acid sequence, using a program that we developed, suggested that a portion of the BRCA2 protein was likely to be the most important part and to contribute directly to its function in DNA repair."

The next step was to bombard the crystals with high-energy x-rays. Using x-ray crystallography, the x-ray diffraction patterns of the crystals were used to calculate a three-dimensional picture of the protein at the atomic level. This picture revealed that part of BRCA2 is similar in structure to other proteins that are known to bind DNA. The researchers then took the work a step further, showing that BRCA2 indeed binds to DNA in special regions that are commonly found in damaged DNA strands.

Nikola Pavletich and Haijuan Yang used x-ray crystallography to determine BRCA2's structure.

Dr. Pavletich's team then showed that BRCA2 participates in the repair of double-strand breaks. These breaks can lead to a particularly lethal type of damage: If both strands of the DNA double helix break at the same time, cells can permanently lose genetic information. The structure shows that BRCA2 binds the broken strands, enabling the recovery of lost information via a process called homologous recombination — in which the missing DNA is copied from another part of the cell.

"We are now a step closer to understanding this particular type of inherited breast and ovarian cancer," Dr. Pavletich said. However, it is not yet known why this genetic instability would lead to cancers specifically in the breast and ovary. Some scientists have suggested that certain tissues (such as the estrogen-rich tissues in those organs) may support the survival of genetically unstable cells better than others. In addition, DNA repair defects are more problematic in cells that divide frequently, because the defects are more likely to be passed on to the next generation of cells.

The other gene commonly linked to hereditary breast and ovarian cancers is called *BRCA1*. Although BRCA1 and BRCA2 have similar names and both are involved in DNA repair, there is no similarity in their protein sequences or structures, and the exact function of how the BRCA1 protein participates in DNA repair is not yet known.

Researchers from the University of Texas Health Science Center in San Antonio also contributed to the study, which was funded by the National Institutes of Health, the Howard Hughes Medical Institute, the DeWitt Wallace Foundation, the Samuel and May Rudin Foundation, and the Arthur and Rochelle Belfer Foundation. ☼