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Scientists dig into breast cancer origins

Special to the Enterprise
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UC Davis scientists have made groundbreaking pro-gress in understanding the genetic origins of breast cancer by successfully purifying a protein linked to the disease.

The results of the study are published online today in the journals Nature and Nature Structural and Molecular Biology.

Two teams of UC Davis researchers purified, for the first time, the breast cancer susceptibility gene BRCA2 and used it to study the oncogene's role in DNA repair. Their work opens new possibilities for understanding, diagnosing and treating breast cancer.

BRCA2 is known to be involved in repairing damaged DNA, but exactly how it works with other molecules to repair DNA has been unclear, said UCD microbiology professor Stephen Kowalczykowski, the senior author of the Nature paper.

"Having the purified protein makes possible far more detailed studies of how it works," Kowalczykowski said.

Kowalczykowski's group purified the protein from human cells. Another group, led by UCD microbiology professor Wolf-Dietrich Heyer, used genetic engineering techniques to manufacture the human protein in yeast.

The work of Heyer's group is published in Nature Structural and Molecular Biology.

The two approaches are complementary, Heyer said, and the two teams have been talking and cooperating throughout the experiments.

Experiments with the BRCA2 protein confirm that it plays a role in repairing damaged DNA. It acts as a mediator, helping another protein, RAD51, to associate with a single strand of DNA and stimulate its activity.

One BRCA2 molecule can bind up to six molecules of RAD51.

The RAD51/DNA complex then looks for the matching strand of DNA from the other chromosome to make an exact repair. If the BRCA2/RAD51 DNA repair system is not working, the cell resorts to other, more error-prone methods.

DNA is constantly suffering damage, even if you avoid exposure to carcinogens, and if that damage is not repaired, errors start to accumulate, Kowalczykowski said.

Those errors eventually can lead to cancer, he said.

The BRCA2 gene was discovered in 1994. Mutations in BRCA2 are associated with about half of all cases of familial breast and ovarian cancer (cases where the propensity to develop cancer seems to be hereditary) and are the basis for genetic tests.

But purifying the protein made by the gene has proved difficult.

"It's very large, it does not express well, and it degrades easily," Kowalczykowski said.

After testing many different cell lines, Ryan Jensen, a post-doctoral researcher in Kowalczykowski's lab, succeeded in introducing a BRCA2 gene into a human cell line and producing it as a whole protein. Jensen and another postdoctoral researcher, Aura Carreira, tested the purified protein for its function in repairing damaged DNA.

Jie Liu, a postdoctoral researcher in Heyer's lab, found that a much smaller protein called DSS1 stimulated BRCA2 to assemble functional RAD51/DNA complexes. Together with Liu, staff research associate Tammy Doty and UC Davis undergraduate student Bryan Gibson, now a doctoral student at Cornell University, purified the human BRCA2 and DSS1 proteins from yeast.

One application of the purified protein is to make antibodies to BRCA2 that could be used in test kits as a supplement to existing genetic tests, Kowalczykowski said.

A more exciting possibility, he said, is to use the system to screen for drugs that activate or inhibit the interaction between BRCA2, RAD51 and DNA. Many cancer treatments

work by creating breaks in DNA, and a drug that selectively shuts down a specific DNA repair pathway — making it harder for cancer cells to recover — could make the cells more vulnerable to treatment.

That strategy is already being exploited by a new class of drugs called PARP inhibitors, currently in clinical trials. PARP inhibitors target an alternate DNA repair pathway that cells use when the BRCA2 repair pathway is not available.

The BRCA2 protein also can be used to study how different mutations affect the gene's function.

"We're just starting to scratch the surface and understand more of the mechanisms and interaction with other factors," Kowalczykowski said.

The work was supported by grants from the National Institutes of Health, the U.S. Department of Defense Breast Cancer Research Program, the Susan G. Komen Breast Cancer Foundation and the UC Davis Cancer Center.

Jensen was supported by a fellowship from the American Cancer Society; Carreira was supported by a fellowship from the Spanish Ministry of Education and Science, and Liu by a fellowship from the Tobacco-Related Disease Research Program.

— UC Davis Health System