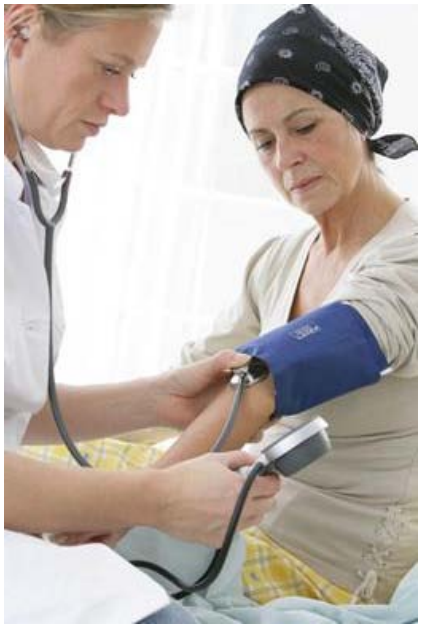
Published online 22 August 2010 | Nature | doi:10.1038/news.2010.422

News

Breast cancer protein is finally purified

Isolation of BRCA2 could help understanding of cancer risk and aid drug screening.

Alla Katsnelson



The purified BRCA2 protein will help scientists unravel how mutations in the gene encoding it cause cancer.CHASSENET / SCIENCE PHOTO LIBRARY

After a decade and a half of effort, biochemists have succeeded in isolating a pure extract of the tumour suppressor protein BRCA2 from human cells. The feat, achieved independently by three labs, expands what is known about how the protein keeps tumours in check. It also opens the door to studying how mutations in the BRCA2 sequence cause cancer and to search for compounds that could block this destructive process. The findings are published online today in Nature[1] and Nature Structural & Molecular Biology[2,3].

BRCA2 — breast cancer type 2 susceptibility protein — has a dubious claim to fame: some mutations in the gene coding for the protein lead to a dramatic increase in the chances that a person will develop breast, ovarian and other types of cancer.

The BRCA2 gene was discovered in 1994. In tandem with other tumour suppressor proteins, including the related protein BRCA1, BRCA2 repairs damage to DNA that can occur as cells divide. Without it, strands of DNA are prone to break, causing mistakes in how genes are read and turned into protein. Researchers have isolated pure fractions of proteins that interact with BRCA2, but until now have had no success in doing the same for BRCA2 itself, instead deriving clues about its function by studying similar proteins in worms or bacteria or fragments of the human version.

A major difficulty is the size of the protein — BRCA2 clocks in at 3,418 amino acids. "That is really huge," says Wolf-Dietrich Heyer, a biochemist at the University of California, Davis, and lead author on one of the papers[2]. "I'm not aware of any other proteins that size that have been purified to homogeneity."

On top of that, says Stephen Kowalczykowski, also a biochemist at the University of California, Davis, and lead author of another of the papers[1], BRCA2 is extremely unstable on its own, and commonly exists in complexes with other proteins. "People have got it partially purified, but the question has always been contamination," he says. "You really need to get it squeaky clean, and that has been the major stumbling block."

The fixer

Kowalczykowski and his group added a maltose-binding protein tag to one end of the BRCA2 protein, which helps to increase its solubility and promote proper protein folding, hence stabilizing it. This allowed the researchers to then fish out BRCA2 in pure form from cultured human epithelial kidney cells. Ryan Jensen, a postdoc in Kowalczykowski's lab and the first author on the Nature paper[1], spent four years simply optimizing the purification process, Kowalczykowski says.

> “The significance is enormous.”

Heyer and his team used a slightly different approach, expressing the protein in yeast[2]. In a third study[3], led by Stephen West, a geneticist at Cancer Research UK in London, researchers inserted the BRCA2 gene into cultured human epithelial cancer cells as part of a bacterial construct. Both teams added tags to their proteins to help purify them.

With the protein in hand, scientists can now "do all types of mechanistic experiments" that have so far eluded researchers, says Patrick Sung, a biochemist at Yale University in New Haven, who was not involved in the work. "The significance is enormous," he says, "not only in understanding how BRCA2 works, but also in providing a framework for working with other proteins known to interact with it."

The three studies examined the interaction of the full-length BRCA2 protein with other proteins, primarily one called RAD51, which repairs DNA by assembling around breaks in the strands, and forming filaments through which nucleotides (components of DNA) are pulled in to fix the DNA gaps. By studying the interaction between BRCA2 and RAD51, all three teams confirmed that BRCA2 helps RAD51 to initiate filament growth.

Biochemistry boon

For the most part, the studies confirmed ideas about BRCA2 function. "But we also uncovered some aspects of protein function that you couldn't have known unless you did the biochemistry," Kowalczykowski says.

For example, BRCA2 had been thought to assist in fixing one particular form of DNA damage, but by studying its interactions with DNA proteins, Kowalczykowski and his team concluded that it has a wider role. "The properties of BRCA2 place it as a being a general mediator of DNA break repair," he says.

"I don't think there were major surprises" in the groups' findings, says Sung. "The major accomplishment comes from the fact that people have been working on this for so long."

The ability to purify BRCA2 should allow structural biologists to solve the structure of the protein, which could provide more information about its function. "In principle the procedures are there for someone to do this," says Kowalczykowski, but so far, he says, the yields of the techniques used by the three groups are too small.

More immediately, says Sung, the work provides "a system to look at tumour-associated mutations" in BRCA2 — researchers can introduce mutations into the BRCA2 sequence, and then purify the resultant protein to understand the effects of the mutations on the protein's function.

Additionally, says Kowalczykowski, "having a protein and knowing how it behaves means you can use chemical biology screening tools" to look for chemical compounds, and eventually drugs, that can stop mutant versions from wreaking havoc in cells.

References

1. Jensen, R. B., Carreira, A. & Kowalczykowski, S. C. Nature advance online publication doi:10.1038/nature09399 (2010).
2. Liu, J., Doty, T., Gibson, B. & Heyer, W.-D. Nature Struct. Molec. Biol. advance online publication doi:10.1038/nsmb.1904 (2010).
3. Thorslund, T. *et al.* Nature Struct. Molec. Biol. advance online publication doi:10.1038/nsmb.1905 (2010).

Comments

If you find something abusive or inappropriate or which does not otherwise comply with our Terms or Community Guidelines, please select the relevant 'Report this comment' link.

Comments on this thread are vetted after posting.

There are currently no comments.

Add your own comment

This is a public forum. Please keep to our Community Guidelines. You can be controversial, but please don't get personal or offensive and do keep it brief. Remember our threads are for feedback and discussion - not for publishing papers, press releases or advertisements.

You need to be registered with Nature to leave a comment. Please log in or register as a new user. You will be re-directed back to this

page.

- Log in / register
- **comments** on this story
- **Stories by subject**
  - Cell and molecular biology
  - Biotechnology
  - Health and medicine
  - Genetics
- **Stories by keywords**
  - BRCA2
  - Breast cancer
  - Ovarian cancer
  - DNA repair
- **This article elsewhere**
  - Blogs linking to this article
  - Add to Connotea
  - Add to Digg
  - Add to Furl
  - Add to Newsvine
  - Add to Del.icio.us
  - Add to Twitter

Recent activity

most recent stories

- Australia's electorate sends climate-change message
  23 August 2010
- Breast cancer protein is finally purified
  22 August 2010
- Solar System older than previously thought
  22 August 2010
- Pakistan faces long-term damage to irrigation system
  20 August 2010
- Extent of lingering Gulf oil plume revealed
  19 August 2010

commented stories

- Physicists get political over Higgs 27 comments 04 August 2010
- A solar salamander 14 comments 30 July 2010
- An easy way to boost a paper's citations 13 comments 13 August 2010
- Pakistan's floods: is the worst still to come? 10 comments 13 August 2010
- News briefing: 30 July–5 August 2010 9 comments 04 August 2010

Related stories

- Breast cancer gene patents judged invalid30 March 2010
- Translational research: Talking up translation27 January 2010
- Lawsuit rekindles gene-patent debate26 January 2010
- Gene-testing firms face legal battle25 June 2008
- Genes alone raise breast-cancer risk24 October 2003

nature jobs

- Nature
- ISSN: 0028-0836
- EISSN: 1476-4687