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Oncology

Purification of BRCA2 protein allows understanding of its role in DNA repair

By Laura Dean
26 August 2010
Nature 2010; Advance online publication

MedWire News: By purifying the breast cancer type 2 (BRCA2) protein, researchers have established that it enhances the functions of the RecA homolog, E. coli protein (RAD51), which is essential for recombinational repair of DNA breaks.

Until now, the large size of BRCA2 (3418 amino acids, produced by the breast cancer susceptibility gene *BRCA2*), the difficulty in driving high-level expression, insufficient solubility, and its propensity to degrade, have precluded its isolation, and hampered fuller understanding of its functions, explain Stephen Kowalczykowski and colleagues, from the University of California in Davis, USA.

However, as reported in the journal Nature, Kowalczykowski's group has successfully purified the protein from human cells, which enabled them to study its role in DNA repair.

They found that BRCA2 binds RAD51 and potentiates recombinational DNA repair by promoting assembly of RAD51 onto single-stranded DNA (ssDNA). An essential function of RAD51 in DNA repair is its capacity to homologously pair and exchange DNA strands.

BRCA2 acts by targeting RAD51 to ssDNA rather than double-stranded DNA, say the researchers. This enables RAD51 to displace replication protein-A (RPA) from ssDNA and stabilize RAD51-ssDNA filaments by blocking ATP hydrolysis.

The RAD51/DNA complex then looks for the complementary DNA strand to make an exact repair.

Of note, BRCA2 does not anneal ssDNA complexed with RPA, implying it does not directly function in repair processes that involve ssDNA annealing, write Kowalczykowski and co-authors.

Another group, led by Wolf-Dietrich Heyer, also from the University of California in Davis, used genetic engineering techniques to manufacture the human BRCA2 protein in yeast.

They found that a much smaller protein called DSS1 stimulated BRCA2 to assemble functional RAD51/DNA complexes.

That work, along with a third study on the same topic, by Stephen West (Cancer Research UK, South Mimms, Hertfordshire) and colleagues, is published in *Nature Structural and Molecular Biology.*

These findings help to explain why DNA repair would be severely disrupted in cells lacking functional BRCA2, remark Kowalczykowski *et al*.

They conclude: "The ability to purify full-length human BRCA2, a protein directly responsible for genetically predisposing individuals to substantially high risks for cancer, should open a whole new venue for understanding this very large and complex protein."

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