EDITORIAL

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Another piece in the BRCA1 puzzle

Every three minutes a woman in the United States is diagnosed with breast cancer. This is a daunting statistic—one that most women push to the back of their minds if they want to try to live a 'normal' life and not be paralyzed by this fear. But for those with a family history of the disease, that isn't an option.

While most breast cancer is sporadic, 5% of cases are genetically linked. Women that carry a mutation in one of the two known breast cancer susceptibility genes, *BRCA1* or *BRCA2,* have more than an 80% lifetime chance of developing the disease. They also have a greatly enhanced risk of developing ovarian cancer.

Cloning of the *BRCA* genes provided little insight into their function since they share no significant sequence similarity to molecules of known function or to each other. Extensive research from many different disciplines has identified a large number of interacting proteins as well as upstream and downstream targets; these include proteins involved in homologous recombination, DNA repair and cell cycle checkpoint control.

The first clue that the *BRCA* genes were involved in maintaining chromosomal integrity came from their connection with RAD51. RAD51 binds to single-stranded DNA (ssDNA) to form a nucleoprotein filament that invades and pairs with homologous sequences in double-stranded DNA (dsDNA) and thus is a critical player in initiating strand exchange. Upon DNA damage, the BRCA proteins appear to colocalize with RAD51 in foci that are thought to be sites of ongoing repair. Cell lines deficient in these proteins are sensitive to DNA-damaging agents that cause double-strand breaks. Together, these studies suggest that BRCA1, BRCA2 and RAD51 are essential for homology-dependent DNA repair.

Explaining more precisely how BRCA1 and BRCA2 function in the repair of double-strand breaks by homologous recombination is complicated by the size of these proteins (1,863 and 3,418 amino acids, respectively) and their many interaction partners. So researchers have asked whether the structures of parts of these proteins could provide some clues regarding their function.

The structures of an ~800-residue segment of BRCA2 bound to single-stranded DNA revealed domains that are also found in single-stranded (OB fold) and double-stranded (a helix-turn-helix motif) DNA-binding proteins. Given that BRCA2 interacts directly with RAD51 these structures suggest a number of ways in which BRCA2 could function in RAD51-mediated homologous recombination. For example, BRCA2 could recruit RAD51 to sites of double-strand breaks, affect the rate of RAD51 assembly onto ssDNA or affect the organization of RAD51 filaments.

While BRCA2 seems to play a direct role in homology-dependent DNA repair, the role of BRCA1 is less well understood. In part this is due to the many different molecules with which BRCA1 interacts, including tumor suppressors, DNA damage repair proteins, cell-cycle regulators and transcriptional activators and repressors. BRCA1 consists of an N-terminal RING finger domain that functions as an E3 ubiquitin ligase and two tandem C-terminal BRCT domains. The importance of the BRCT repeats is underscored by mapping of the majority of known cancer-causing BRCA1 mutations to these regions. Recent studies have shown that the BRCT repeats recognize phosphorylated proteins, such as the DNA helicase BACH1, and this interaction is essential for DNA damage-induced G2/M checkpoints.

Now, three groups have determined the structures of tandem BRCT repeats bound to phosphopeptides. Yi and colleagues (*Mol. Cell* **14**, 405-412, 2004) and Smerdon, Yaffe and coworkers (page 512 of this issue) determined the structure of BRCT repeats bound to a BACH1-derived phosphopeptide. Smerdon, Yaffe and colleagues further showed that a set of disease-related mutations disrupt BRCA1-phosphopeptide binding *in vitro* and *in vivo*. Glover and coworkers (page 519 of this issue) determined the structure of the BRCT repeat bound to a peptide containing the high affinity binding motif (pSer-X-X-Phe). These authors further examined the phosphopeptide binding properties of a large set of clinically derived BRCA1 BRCT variants and solved the structures of two mutant BRCT repeats. The results indicate that the peptide-binding surface of BRCA1 is essential for its tumor suppression function. All three groups identified a conserved pSer binding pocket on BRCT as well as a hydrophobic groove between the two BRCT repeats that recognizes the Phe. All of the structures explain why tandem, rather than single, BRCT repeats are required for phosphopeptide binding since residues from both repeats are important for peptide recognition.

While one can't argue that this isn't progress, all this information on how the *BRCA* genes function would be more satisfying if it also told us something about what goes wrong in sporadic breast cancers. But sporadic breast cancers are not associated with mutations in either gene. In fact, *BRCA1* and *BRCA2* are exceptional in this regard because tumor suppressor genes that are mutated in other inherited cancers (such as the genes encoding retinoblastoma, APC, p53 and VHL) are also typically inactivated in sporadic versions of the same cancers.

Complicating matters even further, both genes seem to function in large multiprotein complexes, and therefore defects in other components of these complexes might be important not only in the development of breast and ovarian cancer but other cancers as well.

For example, BRCA1 and BRCA2 participate in a network of interactions with the products of other cancer-associated genes, including those responsible for ataxia telangiectasia, Fanconi anemia, and Nijmegen breakage syndrome. These proteins recognize lesions that block or interfere with DNA replication during the S and G2 phases of the cell cycle, and so the type of cancer outcome may reflect the specific component of the larger BRCA-associated complex that is mutated.

Given the complexity of the problem it is no wonder that many researchers have had to take a reductionist approach. And while progress has been made by working on separate parts of what are likely to be multiple BRCA pathways, it is worth keeping in mind that to tackle such a diverse and complicated disease as cancer, the various parts are going to need to be woven into a whole at least at some point down the line. ■