Viewpoint

Mutations in DNA damage response genes and breast cancer susceptibility

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The risk of breast cancer is greatly increased in women who carry a mutation in one of the breast cancer susceptibility genes *BRCA1* or *2.* In the years since these genes were first isolated, evidence of their function in DNA damage responses and the DNA repair mechanism has accumulated. The DNA damage resulting from ionising and UV irradiation activates the ataxia-telangiectasia-mutated (ATM) and ataxia-telangiectasia- and RAD3-related (ATR) protein kinases, which in turn leads to the phosphorylation of BRCA proteins and other downstream targets such as CHEK2. It is known that the *BRCA1* and *2* and *CHEK2* gene products are cellular proteins that function to sense DNA damage, and to activate genes that both prevent cell cycle progression and initiate the DNA repair process. Several articles published over the last year have broadened our understanding of this pathway and its relevance to breast cancer risk and development.

BRCA1 and *2* mutations in women at increased risk of cancer are often predicted to lead to truncated proteins lacking the C-terminal region. Recently, the crystal structure of the functionally important BRCA1 C-terminal (BRCT) repeat region has been resolved by Williams and colleagues (*Nat Struct Biol* 2001, **8**:838-842). The data demonstrate that BRCT repeats within the protein are similar in structure, and pack together in a head to tail alignment. Interestingly, BRCA1 missense mutations that increase susceptibility to breast cancer cluster at the predicted interface between these repeats and destabilise the structure. This supports the functional importance of the BRCT repeat domain in cellular responses to DNA damage and breast cancer susceptibility. Another report by Chiba and Parvin has identified 4 distinct, multi-protein, BRCA1-containing, cellular complexes (*J Biol Chem* 2001, **276**:38549-38554). These include a complex with RAD50 (a molecule known to be involved in DNA damage response), a complex containing RNA Polymerase II, and a previously uncharacterised complex that forms in response to DNA replication inhibition, and contains the BRCA1-associated RING domain protein BARD1. Evidence continues to emerge of other links between DNA damage response genes, such as *BRCA1*, and DNA repair (for example, see article by Hartman and Ford, *Nat Genet* 2002, **32**:180-184). *BRCA1* can, it turns out, trigger global genome repair independently of p53, and also induce expression of the nucleotide excision repair genes *XPC*, *DDB2* and *GADD45*.

The search for gene mutations that explain why non-BRCA1/2 families can have high breast cancer penetrance has shown that other known proteins of the DNA damage response pathway are involved. Two papers report preliminary studies which showed that specific missense but not truncating mutations of the *ATM* gene have dominant negative effects on ATM function and segregate with breast cancer cases in some non-BRCA1/2 families with multiple cases of breast cancer (see Chenevix-Trench *et al*., *J Natl Cancer Inst* 2002 **94**:205-215 and Scott *et al*., *Proc Natl Acad Sci* 2002 **99**:925-930). Two other reports demonstrate that 1100delC, a specific CHEK2 truncating mutation, confers low penetrance susceptibility to breast cancer (see Meijers-Heijboer *et al*., *Nat Genet* 2002 **31**:55-59 and Vahteristo *et al*., *Am J Hum Genet* 2002 **71**:432-438). The evidence indicates that the 1100delC mutation contributes to familial clustering of breast cancer cases and, in particular, increases the rates of male breast cancer.

Finally, in a landmark publication earlier this year in *Nature*, van 't Veer and colleagues from the Netherlands Cancer Institute and Rosetta Inpharmatics suggested that breast cancer recurrence could be predicted by a gene expression signature involving as few as 70 genes (*Nature* 2002, **415**:530-536). The authors also analysed a group of tumours from germ-line *BRCA1* mutation carriers and established a molecular signature of 100 genes whose expression levels identifies this group as a distinct subset of breast cancers.

ATR = ataxia-telangiectasia- and RAD3-related; BRCT = BRCA1 C-terminal; BARD = BRCA1-associated RING domain.

These articles increase our knowledge of which genes function up- or down-stream of BRCA proteins and how mutations in these genes confer breast cancer susceptibility. This improved understanding may help us find novel strategies to prevent breast cancer through recognising those at risk. In addition, the finding that BRCA1 tumours have a specific molecular signature suggests that breast cancers caused by different germ-line gene mutations comprise separate subsets of tumours that can be targeted by specific therapies.

Articles selected from Faculty of 1000

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