WEB WATCH

Getting to the core

- http://research.nhgri.nih.gov/bic/

The breast information core (BIC) is an international collaborative effort whose main goal is to facilitate the detection and characterization of breast cancer susceptibility genes, and, particularly, to share and coordinate non-published information between like-minded researchers. The group has a steering committee (headed by David Goldgar of the International Association of Cancer Research) and has a general meeting every year, which is apparently announced via a newsletter, although there is no link to one or to details of the meetings on the web site.

To view any information, you must register, and with that completed you can click onto the BIC database — the core of the site — and see the mutations data for *BRCA1* and *BRCA2*, which were last updated in August 2002. The databases can be searched by clicking on the exons themselves, or by using a form to search the genes. These data have also been summarized in several different ways for easier digestion — you can view graphs of missense or frameshift mutations, view a table of single-nucleotide substitutions, or a bar graph of insertions and deletions. Importantly, there is also a mutation submission form where you can submit your findings — these data are examined and edited by the steering committee to maintain the quality of the data.

So, although extra sections such as published laboratory methods (which consists of just two papers published in 1997) and a discussion forum (the link did not work) are not that useful at present, the core of the site is comprehensive and well worth a visit for *BRCA* researchers.

Ezzie Hutchinson

TUMOUR SUPPRESSORS

Women only

Women-only nights can be fun, but other events that occur exclusively to women are not so great. Why, for example, should only women who inherit a mutation in the *BRCA1* tumour suppressor be prone to breast cancer? Shridar Ganesan *et al.* have shown, in the 1 November issue of *Cell*, that BRCA1 might be involved in X inactivation. Perhaps this could explain this female-specific phenomenon.

BRCA1 was known to localize to the unpaired X chromosome in pachytene spermatocytes, and Ganesan *et al.* confirmed this by showing that BRCA1 colocalized with a component of the XY body. The XY body shows similarities to the inactive X (Xi) chromosome in female somatic cells — both are heterochromatic, silenced and are coated with the non-coding *XIST* RNA — so does Xi also localize BRCA1?

Immunofluorescence of BRCA1 and fluorescent *in situ* hybridization (FISH) of *XIST*, carried out on female human cell lines, revealed that BRCA1 and *XIST* could colocalize to a nuclear structure — FISH of an X-chromosome probe confirmed that this was one of the X chromosomes. Chromatin immunoprecipitation analysis — using antibodies to BRCA1 or its binding partner BARD1 — followed by reverse-transcriptase polymerase chain reaction (RT-PCR) of *XIST* confirmed this interaction.

The next step was to investigate what happened in *BRCA1*-deficient cells. Frozen sections from sporadic breast and ovarian cancers were examined, and although the majority had nuclear BRCA1 and focal *XIST* (as opposed to diffuse) staining, those from *BRCA1*-deficient women did not. The HCC1937 human breast cancer cell line — which contains a germline mutation in one *BRCA1* allele and has lost the wild-type allele — also lacked focal *XIST* staining. This could be restored by ectopic expression of wild-type *BRCA1*, but not of cancer-associated *BRCA1* mutants. Similarly, RNA interference (RNAi) of *BRCA1* in wild-type cells decreased focal staining of *XIST*.

So how does BRCA1 regulate *XIST* — through its localization, synthesis or stability? The authors carried out RT-PCR of *XIST* in HCC1937 cells that were transfected with either a vector control or with wild-type *BRCA1*, to distinguish between these alternatives. The levels of *XIST* RNA were equivalent in both transfected lines, indicating that BRCA1 can influence *XIST* localization, but not its synthesis or stability.

DNA REPAIR

Molecular mimicry

Germline mutations in the *BRCA2* gene cause increased susceptibility to breast and ovarian cancers, so much work is being done to understand the cellular role of BRCA2. It is known to interact with — and modulate the function of — RAD51, a protein that is involved in recombinational DNA repair. But what does this interaction mean at a functional level?

Reporting in *Nature*, Tom Blundell, Ashok Venkitaraman and colleagues now reveal the structural basis for the BRCA2-dependent regulation of RAD51. They describe the 1.7-Å crystal structure of a complex between BRC repeat 4 (BRC4) of BRCA2 and the RecA-homology domain of RAD51, and show that the BRC repeat mimics a conserved motif found in RAD51, so enabling BRCA2 to control the activity of RAD51.

When mammalian cells are exposed to DNA damage, RAD51 oligomerizes on damaged DNA ends to form a nucleoprotein filament that is essential for subsequent steps in recombinational DNA repair. To work out how this happens, the authors compared the BRC4–RAD51 structure with that of the bacterial RAD51 homologue, RecA, which also forms a helical filament. They discovered that a conserved sequence motif in BRC4 structurally mimics a seven-amino-acid sequence that is found at the interface between subunits in the RecA filament. They then used this information to show that RAD51 oligomerizes through a similar motif. This motif is conserved in RecA-like molecules from bacteria to humans, highlighting a common structural mechanism for the formation of such nucleoprotein filaments.

BRCA2 binds to RAD51 through six of its eight so-called BRC repeats (BRC1–8). From the structure of the BRC4–RAD51 complex, the authors show that these BRC repeats mimic the structure of the natural RAD51 motif that forms the interface between RAD51 subunits in the nucleoprotein filament. So BRCA2 copies a structure in RAD51 to control the oligomerization state of RAD51.