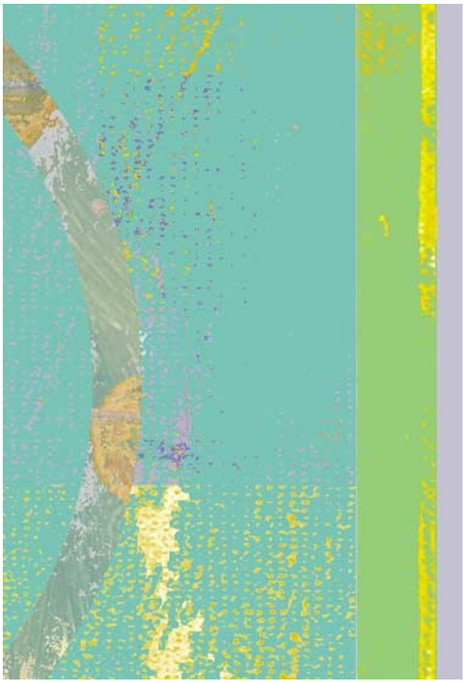

As *XIST* is required for X-chromosome inactivation, Ganesan *et al.* investigated whether loss of *BRCA1* influences the pattern of histone H3 methylation on lysine 9 (H3mK9), which is associated with transcriptional silencing. In female cells, there is a large amount of H3mK9 staining on Xi, but this is absent from HCC1937 cells. Similarly, H3mK9 immunofluorescence analysis on frozen sections of sporadic and *BRCA1*-deficient breast cancers indicates that BRCA1 is required for focal staining of H3mK9, and hence gene silencing.

But is loss of *BRCA1* expression sufficient to reactivate previously silenced genes? This was tested in a female mouse cell line in which one X chromosome carried a non-functional copy of *Xist* and the other, inactivated, X chromosome carried a silenced copy that was tagged with GFP. RNAi of *Brca1* resulted in the reactivation of *Xist*–GFP in a subset of these cells.

The loss of *BRCA1* in women might therefore reactivate genes that are normally silent on the Xi. The upregulation of a set of X-chromosomal genes in *BRCA1*-deficient ovarian cancers lends support to the importance of this phenomenon in promoting tumorigenesis, but the establishment of a firm link remains a future goal.

Emma Greenwood

References and links

ORIGINAL RESEARCH PAPER Ganesan, S. *et al. BRCA1* supports XIST RNA concentration on the inactive X chromosome. *Cell* **111**, 393–405 (2002)

WEB SITE

David Livingston's lab: http://www.hms.harvard.edu/dms/bbs/fac/livingston.html

Does this study tell us anything about BRCA2's role in cancer?

The authors show that several point mutations in *BRCA2*, which have previously been linked to cancer, impair the ability of BRCA2 to bind RAD51. RAD51 would therefore be unable to repair damaged DNA, which could explain the development of cancer. The importance of this interaction also means that the BRCA2–RAD51 interface could be a target for the development of small-molecule inhibitors as potential anticancer drugs.

Alison Mitchell
***Editor,* Nature Reviews Molecular Cell Biology**

References and links

ORIGINAL RESEARCH PAPER Pellegrini, L. *et al*. Insights into DNA recombination from the structure of a RAD51–BRCA2 complex. *Nature* 10 Nov 2002 (doi:10.1038/nature01230).

WEB SITE

Ashok Venkitaraman's lab: http://www.hutchison-mrc.cam.ac.uk/Venkitaraman.html

IN BRIEF

THERAPEUTICS

Synthetic small inhibiting RNAs: efficient tools to inactivate oncogenic mutations and restore p53 pathways.

Martinez, L. A. *et al. Proc. Natl Acad. Sci. USA* **99**, 14849–14854 (2002)

RNA interference is increasingly used to aid research by allowing the generation of functional knockouts. But can this technique be translated into the clinic to treat patients with cancer? Martinez *et al.* have constructed short interfering RNAs that can differentiate between wild-type and point-mutated p53. So, the mutant p53 — in tumours that express wild-type and mutant protein — could be selectively deleted, forming the basis of tailored therapy.

DIAGNOSTICS

Serum proteomic patterns for detection of prostate cancer.

Petricoin, E. F. *et al*. *J. Natl Cancer Inst.* **94**, 1576–1578 (2002)

At present, to confirm whether men with increased levels of prostate-specific antigen have prostate cancer or not, a biopsy sample must be taken. Petricoin *et al*. developed a bioinformatics algorithm that allowed discrimination between patients with prostate cancer and those with benign or no disease. The serum proteomic pattern correctly predicted 95% of patients known to have prostate cancer and 78% of patients with benign conditions.

IMMUNOTHERAPY

Dual-specific T cells combine proliferation and anti-tumor activity.

Kershaw, M. H., Westwood, J. A. & Hwu, P. *Nature Biotechnol*. **20**, 1221–1227 (2002)

Antitumour immunity requires T-cell activation, but tumour antigens are generally poor immunogens. To expand tumour-reactive T cells *in vivo*, Kershaw *et al*. generated dual-specific T cells that could respond not only to an immunogen, but could also recognize folate-binding protein (FBP) — an antigen associated with ovarian cancer. Mouse dual-specific T cells responded to both allogeneic antigen and FBP-expressing tumour cells *in vitro*, and expanded in response to immunization with allogeneic cells *in vivo*. Human dual-specific T cells were also generated.

THERAPEUTICS

Inhibitors of Ras/Raf-1 interaction identified by two-hybrid screening revert Ras-dependent transformation phenotypes in human cancer cells.

Kato-Stankiewicz, J. *et al. Proc. Natl Acad. Sci. USA* **99**, 14398–14403 (2002)

The signalling cascade that acts through RAS and RAF is activated in a significant number of tumours, so inhibiting their association is a viable therapeutic strategy. Small-molecule compounds that inhibit this interaction were identified using a two-hybrid approach. These prevented activation of the mitogen-activated protein kinase pathway and caused reversion of several *RAS*-transformed phenotypes, such as influencing morphology, invasiveness and anchorage-independent growth in a number of cell types.