IN THE NEWS

Detection technology

Mammography is an important screening method that detects breast cancer at an early stage. However, conventional X-rays can only identify lumps that are 10–12 mm across, because the similar densities of normal and cancer cells mean that only a large collection of tumour cells can be detected. Now, a new technology could allow lesions to be found when they are less than half that size.

Scientists at University College London, UK, led by Robert Speller, discovered that X-rays scatter in a unique way on contact with tumour cells, but not normal cells. The team developed a device to measure this effect — diffraction enhanced breast imaging (DEBI) — and initial results on normal tissue and tumour biopsies have been promising. Robert Speller told *New Scientist* magazine that "we should be able to pick up something from 4 mm in diameter".

The device works by scanning the breast in the normal way, but it includes a second detector that measures the scatter. "The team now needs to work out how to build the extra detector and analysis electronics into existing mammography systems" (*Health-news.co.uk*, 20 February 2003).

Although this is a potential breakthrough that could improve breast cancer detection, further research is needed. "Andy Hanby, a breast pathologist from Leeds University, said the method needed to be put through clinical trials before its ability to detect smaller tumours is confirmed" (*Health-news.co.uk*), and Clara MacKay, at the UK charity Breast Cancer Care said that "these kinds of advances in early detection raise issues about appropriate management of such early lesions" (*BBC News*).

Emma Greenwood

TUMOUR SUPPRESSORS

Ever-decreasing effects

Knockout and conditional mouse models allow investigators to compare phenotypic differences when gene expression is either 'on' or 'off', but mutations that occur in real life could generate expression levels that fall between these two extremes. In the March issue of *Nature Genetics*, Greg Hannon, Scott Lowe and colleagues use RNA interference (RNAi) to generate a series of p53 hypomorphs, and show that the level of p53 markedly affects the level of disease.

The authors generated three retroviral vectors that each contained a distinct short hairpin RNA to target the *Trp53* gene. When transfected into cultured cells, these constructs — p53-A, -B and -C — had differential effects on p53 protein expression, which corresponded to differences in the ability of mouse embryonic fibroblasts (MEFs) to form colonies in a colony-formation assay. Following expression of p53-A, which had the least effect on protein levels, only a few colonies were able to grow, whereas p53-C significantly decreased protein expression and many more colonies grew.

So, do these RNAi constructs also affect the tumorigenic capacity of cells? Haematopoietic stem cells were infected with viruses produced from these constructs and were transplanted into Eμ-*Myc* mice, which develop B-cell lymphomas at 4–6 months. All mice developed palpable lymph nodes within 3–5 weeks, indicative of lymph-node hyperplasia, but only those with p53-B and p53-C developed B-cell lymphomas and showed a decrease in survival, compared with control Eμ-*Myc* mice.

Further analysis showed that p53-B recipients developed smaller and less-malignant tumours than p53-C recipients. The tumours of p53-B recipients still had a high rate of apoptosis, a low mitotic index and did not significantly infiltrate into the lung and liver, whereas the p53-C recipients had low levels of apoptosis, a high mitotic index and a large amount of infiltration. Interestingly, the tumours produced in both of these recipients were not genomically unstable, unlike those that are found in *Trp53*$^{-/-}$ mice. These results confirm how important the apoptotic function of p53 is for tumour suppression.

In Eμ-*Myc* mice that are heterozygous for *Trp53*, all tumours that develop show loss of heterozygosity at the *Trp53* locus. Might expression of the RNAi constructs relieve this selection pressure? One of two tumours that developed in p53-B recipients and four of four tumours that developed in p53-C recipients had not lost the second wild-type *Trp53* allele, indicating that loss of heterozygosity is not required for tumour development in the presence of the RNAi constructs.

So, as well as producing null phenotypes, RNAi can generate intermediate phenotypes that can help dissect protein function. This protocol also has interesting therapeutic implications, as it shows that stable RNAi can suppress the deleterious function of genes in stem cells *ex vivo*, and that these retain their function *in vivo*.

Emma Greenwood

References and links

ORIGINAL RESEARCH PAPER Hemann, M. T. *et al.* An epi-allelic series of p53 hypomorphs created by stable RNAi produces distinct tumor phenotypes *in vivo*. *Nature Genet.* **33**, 396–400 (2003)

WEB SITES

Greg Hannon's lab: http://www.cshl.org/public/SCIENCE/hannon.html
Scott Lowe's lab: http://www.cshl.org/public/SCIENCE/lowe.html