TUMOUR REGRESSION

# RAS, the magician

Spontaneous disappearance is, unfortunately, a rare event in oncology, but neuroblastomas are more likely to play this trick than other tumours. What makes them regress? Paradoxically, the overexpression of two oncogenes — *HRAS* and *TRKA* — has been associated with a good prognosis, but the mechanism of regression has remained a mystery. Possibilities include apoptosis and differentiation, but Chifumi Kitanaka and colleagues now bring a third possibility onto the scene: non-apoptotic cell death.

Japan has a population-screening programme for neuroblastoma in infants, which permits the detection of neuroblastomas that might otherwise spontaneously regress. The authors first compared tumour samples from mass-screened patients with clinically detected tumours from older children who had advanced-stage neuroblastomas. Patches of HRAS staining occurred more frequently in mass-screened tumours than in clinically detected tumours, and these patches frequently colocalized with areas of degenerating cells. However, these regions did not stain for two classical apoptotic markers — active caspase-3 or fragmented 3′ DNA ends (TUNEL assay). Instead, staining with the periodic-acid–Schiff reagent and electron-microscopic analysis hinted that the cells might be eating themselves (autophagy).

The authors then turned to neuroblastoma cell lines to determine whether *HRAS* expression could kill these cells by a non-apoptotic mechansism. Expression of either wild-type *HRAS* or *RAS*V12, a constitutively active HRAS mutant, caused the cells to round up and fragment, whereas expression of an inactive *HRAS* mutant had no effect. Furthermore, the degenerating cells looked quite different from those that were induced to apoptose by staurosporine or serum withdrawal. Again, no DNA fragmentation was apparent in TUNEL assays, and electron microscopy revealed increased numbers of lysosomes, characteristic of autophagic degeneration.

Is caspase activation required for this peculiar form of HRAS-mediated cell death? Caspase inhibitors did not prevent HRAS-induced cell death, but did block staurosporine-mediated apoptosis. Furthermore, poly(ADP-ribosyl) transferase (PARP), which is invariably attacked by active caspases, was not fragmented in *RAS*-expressing neuroblastoma cells. Finally, overexpression of the anti-apoptotic protein BCL-$X_L$ did not block HRAS-mediated cell death, but did prevent staurosporine-mediated death. Active HRAS, then, can kill cells by a mechanism that is distinct from apoptosis.

Expression of both *HRAS* and the gene for the nerve growth factor (NGF) receptor TRKA is a better indicator of good prognosis than either gene alone, so the authors wanted to know whether TRKA could augment HRAS-mediated cell death. NGF increased the proportion of HRAS-mediated cell degeneration, but only when *TRKA* was overexpressed.

Can we learn some magic tricks from this study? If there are other ways to activate this apparently autophagic pathway, perhaps one day we'll be able to make neuroblastomas — and maybe other tumours, too — disappear even if they don't express favourable markers.

*Cath Brooksbank*

## References and links

**ORIGINAL RESEARCH PAPER** Kitanaka, C. *et al.* Increased Ras expression and caspase-independent neuroblastoma cell death: possible mechanism of spontaneous neuroblastoma regression. *J. Natl Cancer Inst.* **94**, 358–368 (2002)

**FURTHER READING** Reynolds, C. P. Ras and seppuku in neuroblastoma. *J. Natl Cancer Inst.* **94**, 319–321 (2002)

**WEB SITE**

The Neuroblastoma Hope Foundation:
http://www.acor.org/diseases/cns/nblastoma/

# TRIAL WATCH

## Mammography moves on

A new analysis of data from four Swedish randomized controlled trials might finally bring an end to the debate surrounding the benefits of mammography screening. In the 16 March issue of *The Lancet*, Lennarth Nystrom and colleagues report that mammography screening for breast tumours does lead to a statistically significant reduction in cancer mortality in women aged 55 years or over. The study is an updated analysis of the large Swedish clinical trials that have been at the centre of that controversy. In a study published in 2001, Ole Olsen and Peter Gotzsche raised concern that mammography randomized trials — including the Swedish trials — were flawed, and did not provide reliable evidence to support the benefit of this screening procedure. Nystrom *et al.* therefore extended their analysis, performing a long-term follow-up study of the outcomes of 247,000 women over almost 16 years. They also determined the age-specific and trial-specific effects of mammography on breast cancer mortality, and re-examined their earlier data in light of Olsen and Gotzsche's critiques of their randomization procedures. In comparing the relative risks for breast cancer death (and death from all causes) between women who received mammography screening and controls, the authors reported 584 breast cancer deaths among the 1,688,440 women in control groups, but only 511 breast cancer deaths in 1,864,770 women who were invited for mammography screening. This represents a statistically significant overall reduction in breast cancer mortality of 21%. The reduction was greatest (33%) in the age group 60–69 years at entry to the trials. Nystrom *et al.* also report statistically significant effects in the age groups 55–59, 60–64 and 65–69 years, but only a small relative risk reduction (5%) in women aged 50–54 years. So, the benefits of mammography increase with age.

In an editorial accompanying the research, Karen Gelmon claims that the study shows "real but modest" benefits for screening, and states that the new analysis "reassures us that the Swedish data are believable". Hopefully, the research will settle the debate among scientists and statisticians over the value of mammograms, and lend credence to the US government's recent recommendation that women older than 40 have the tests every 1–2 years.

**ORIGINAL RESEARCH PAPER** Nystrom, L. *et al.* Long-term effects of mammography screening: updated overview of the Swedish randomised trials. *Lancet* **359**, 909–919 (2002)

**FURTHER READING** Olson, O. & Gotzsche, P. C. Cochrane review on screening for breast cancer with mammography. *Lancet* **358**, 1340–1342 (2001) | Gelmon, K. A. & Olivotto, I. The mammography screening debate: time to move on. *Lancet* **359**, 904–905 (2002)

**WEB SITE**

NCI statement on mammography screening:
http://newscenter.cancer.gov/pressreleases/mammstatement31jan02.html