IN THE NEWS

Man's best friend

The long-held view that dogs can detect cancer in their owners is now scientifically proven. Research published in the *British Medical Journal* (25 September 2004) indicates that canines can distinguish urine from patients with bladder cancer from urine from individuals without cancer with a 41% success rate, well above the 14% expected by chance alone.

The study, carried out by Dr Carolyn Willis and colleagues at the Amersham Hospital, UK, recruited dogs from the nearby Hearing Dogs for Deaf People facility. "Dogs can be trained to detect some odour characteristics for bladder cancer", said Willis (*Reuters*, 24 September 2004). On nine different occasions, the dogs were exposed to seven samples and would then lie down next to the 'positive' one. "The principal aim is to use the dogs to help us find specific markers for cancer", Willis concludes; "it's a bit like naming the ingredients of a soup", commented one of the dog trainers, Claire Guest (http://news.bbc.co.uk, 23 September 2004).

Professor David Neal, from Cancer Research UK, said "many cancer patients do have abnormal proteins in their blood and urine" (http://news.bbc.co.uk, 23 September 2004). Although it is unlikely that dogs will be used to diagnose cancer, Neal felt that this research might help to develop other detection methods.

Not all the dogs performed well though. Toddy, the mongrel, "was working at a rate of no better than chance really", said his trainer Andrew Cook, "but we still love him" (http://edition.cnn.com/, 23 September 2004).

Nicola McCarthy

OVARIAN CANCER

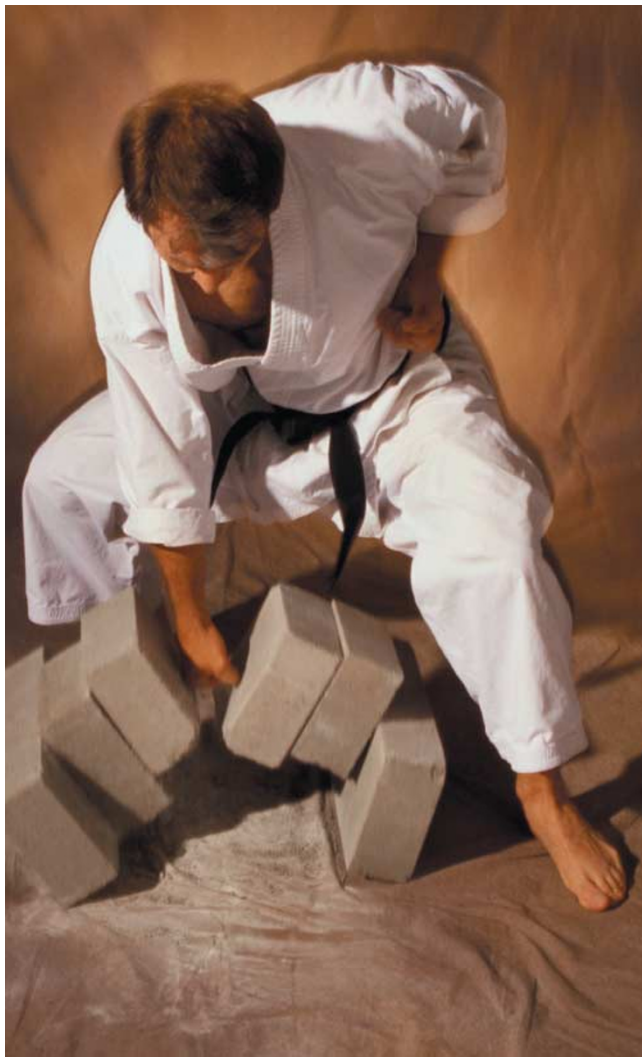
Controlled aggression

Little is known about the molecular and genetic events that underlie the highly aggressive nature of ovarian cancers. Using comparative genomic hybridization (CGH) to identify amplified regions of tumour DNA samples, Gordon Mills and colleagues have identified the small GTPase RAB25 as an important mediator of ovarian tumour growth and progression.

Chromosome 1q has been previously shown to be frequently amplified in ovarian and breast cancers, but no one has identified the specific genetic elements in this region that might underlie tumour initiation or progression. Using CGH analysis, Mills and colleagues identified a 1.1 megabase region located at chromosome 1q22 that was amplified in 28 of 52 (54%) of advanced serous epithelial ovarian cancers. In examining DNA samples of patients with ovarian cancer, they observed that after surgery and chemotherapy patients with increased copy numbers of this region either failed to enter a disease-free state or experienced a much shorter disease-free survival, compared with other patients with ovarian cancer.

Chromosome 1q22 contains 34 genes, so which of these might be associated with disease progression? By analysing microarray data and mRNA expression levels of these genes, the authors observed that only the *RAB25* mRNA levels were markedly increased in most (89%) ovarian tumour samples. Similar findings were confirmed in an independent data set. The increase in *RAB25* expression was more commonly detected in late-stage (stage III and IV) than in early-stage tumours, and overexpression was associated with decreased time of patient survival. The gene was also found to be upregulated in about 50% of breast tumour samples, compared with normal tissue, and had been previously reported to be upregulated in prostate and bladder tumours.

Is *RAB25* upregulation sufficient to promote tumour growth or progression? Mills and colleagues overexpressed the gene in ovarian and breast cancer cell lines, and showed that it protected cells from apoptosis and anoikis induction. These cell-survival-promoting effects were mediated through activation of the phosphaditylinositol 3-kinase (PI3K) signalling pathway, indicated by the presence of phosphorylated AKT, leading to reduced expression of pro-apoptotic BCL2 family members. Inhibition of *RAB25* expression by RNA interference reversed this effect, causing cells to undergo apoptosis. *RAB25* is a well-known regulator of vesicle trafficking and cytoskeletal organization, but further studies are required to determine how it might interact with this anti-apoptotic PI3K signalling pathway.



What are the effects of RAB25 on *in vivo* tumour growth? Overexpression of RAB25 in ovarian cancer cell lines caused larger, more aggressive tumours to form when cells were injected into nude mice. The gene was not able to transform non-tumorigenic ovarian epithelial cells, however, indicating that it is required for progression, but not initiation, of ovarian and possibly breast cancer.

Kristine Novak

References and links

ORIGINAL RESEARCH PAPER Cheng, K. W. *et al*. The RAB25 small GTPase determines aggressiveness of ovarian and breast cancers. *Nature Med.* 24 Oct 2004 (doi:10.1038/nm1125)

FURTHER READING Schaner, M. E. Gene expression patterns in ovarian carcinomas. *Mol. Biol. Cell* **14**, 4376–4386 (2003)

WEB SITE

Gordon Mills' lab:
http://www2.mdanderson.org/depts/molether/staff/mills_gordon.html