malignant component disappeared completely — so OCT-3/4 does seem to be required for tumour maintenance, which makes it an interesting therapeutic target.

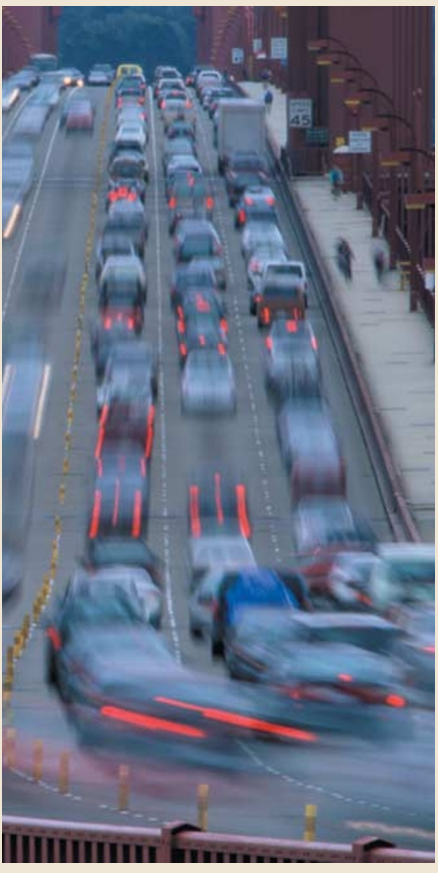
To confirm its function as an oncogene, the authors next transfected Swiss 3T3 fibroblasts with *OCT-3/4* or *RAS*. Interestingly, *OCT-3/4* transfected cells had a similar ability to grow in the absence of anchorage — a hallmark of cancer cells — as *RAS*-transfected cells, and they formed more invasive tumours than *RAS*-transfected cells when injected into immunodeficient mice.

So, *OCT-3/4* seems to act as a dose-dependent oncogene and determines the specific cell fate of arising tumours. What is left to be determined is the mechanism by which this transcription factor acts.

Emma Greenwood

References and links

ORIGINAL RESEARCH PAPER Gidekel, S. *et al.* Oct-3/4 is a dose-dependent oncogenic fate determinant. *Cancer Cell* **4**, 361–370 (2003)



BREAST CANCER

EMSY forges a link

One of the recent puzzles in cancer research has been why the breast and ovarian cancer susceptibility genes *BRCA1* and *BRCA2* do not seem to be involved in sporadic cancer. Expression of *BRCA1* is occasionally lost because of promoter hypermethylation, but the same has not been found for *BRCA2*. The discovery of the BRCA2-interacting protein EMSY, by Tony Kouzarides and colleagues, might now allow part of this puzzle to be solved. It is thought to provide the link between *BRCA2* and sporadic cancer.

EMSY was identified in a yeast two-hybrid screen with the amino terminus of BRCA2 and the interaction was confirmed using purified proteins. The activities of BRCA2 include transcriptional activation, DNA repair and chromatin remodelling, and EMSY is implicated in all of these. It can repress the ability of BRCA2 to activate transcription of a reporter construct; it localizes to sites of DNA damage after γ-irradiation; and it interacts with chromatin-remodelling proteins.

The potential involvement in chromatin remodelling was discovered after *EMSY* was cloned. The sequence was novel, but contained an 80-amino-acid domain — named EMSY N-terminal domain (ENT) — that was found in nine *Arabidopsis* proteins. These proteins also contained a new Royal-family domain, designated Agenet, that can recognize lysine-methylated histones, which explains the link with chromatin remodelling.

As EMSY does not possess such a domain, might it, instead, interact with other proteins that do contain Royal-family domains? In two-hybrid screens with the N terminus of EMSY, over 80% of the interacting clones contained a Royal-family domain. The authors showed that two of these, HP1β and BS69, could also interact *in vivo*. So, it is likely that one of the functions of EMSY is in chromatin regulation.

But what about the connection with cancer? *EMSY* maps to chromosome 11q13.4-5, which is frequently amplified in sporadic breast cancer. Four different amplicons are found within this region and the authors used fluorescence *in situ* hybridization (FISH) to show that *EMSY* was amplified in 5/28 (18%) breast cancer cell lines and in 1/5 samples from newly diagnosed patients. The degree of amplification correlated with the expression level of *EMSY* and the authors showed that *EMSY* could be amplified independently from other genes in the region.

To investigate the significance of this amplification, the authors next looked at how it affects prognosis by comparing expression in tissue samples from patients with sporadic breast cancer with their outcome. *EMSY* was shown to be amplified in 70/551 (13%) cases and the median disease-specific survival for node-negative breast cancer was 6.4 years with the amplification, but 14 years without. So, *EMSY* amplification correlates with a poorer prognosis, specifically for node-negative breast cancer.

As *BRCA2* mutation increases susceptibility to ovarian cancer, as well as to breast cancer, the authors investigated whether *EMSY* was amplified in sporadic ovarian cancer. They found amplification in 17% of high-grade carcinomas, but none in low-grade tumours.

So, the BRCA2 pathway might be involved in sporadic breast and ovarian cancer after all. Although this is yet to be confirmed, the fact that EMSY and BRCA2 have overlapping functions and cause the same pathologies is encouraging. As EMSY inhibits the transcriptional activation function of BRCA2, it is certainly possible that *BRCA2* deletion and *EMSY* amplification have similar effects.

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References and links

ORIGINAL RESEARCH PAPER Hughes-Davies, L. *et al. EMSY* links the BRCA2 pathway to sporadic breast and ovarian cancer. *Cell* **115**, 523–535 (2003)

WEB SITE

Tony Kouzarides' lab:
http://www.welc.cam.ac.uk/groups/kouzarides.html