A small but significant percentage of the *Slp65*$^{-/-}$ mice developed solid tumours, mostly close to the scapula, and splenomegaly; all these tumours consisted solely of pre-B cells expressing pre-BCRs. The authors propose that the increased proliferation of mutant pre-B cells seen in culture causes this increase in tumours. But they also suggest that, as the proportion of tumours is small, increased expression of pre-BCRs is not sufficient for tumorigenesis; secondary mutations are required, and are given greater opportunity to occur. Whether proliferating pre-B cells are prone to such mutations is a question for the future.

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References and links

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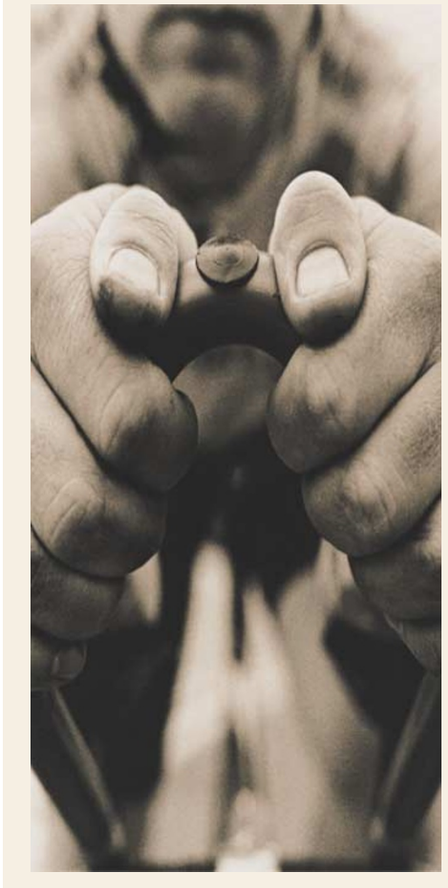

TRANSFORMATION

Telomerase — the third element?

Unlike mouse cells, primary human cells are refractory to oncogenic transformation — transformation requires a specific combination of three genetic elements (the *HRAS-V12* oncogene, the SV40 early region and the catalytic subunit of telomerase (*TERT*)) as opposed to a combination of two oncogenes in mouse cells. But what characteristic might explain this difference? The relative ease of immortalization of mouse cells — because they have longer telomeres and express telomerase — is one possibility, and a requirement for telomere maintenance and immortality in human cells is supported by the fact that *TERT* is the third element. However, in the November issue of *Cancer Cell*, Yvette Seger *et al.* investigate this premise, and show that TERT does not have to be one of the three elements.

Expression of *HRAS-V12* alone causes irreversible growth arrest, and adenovirus *E1A* is one of the few oncogenes that can rescue this phenotype; in fact, expression of *HRAS-V12* and *E1A* is sufficient for transformation of mouse cells, so the authors investigated whether this oncogenic combination could also transform primary human fibroblasts — BJ cells. They first investigated whether cells expressing *HRAS-V12* and *E1A* showed anchorage-independent growth — a characteristic of transformation — and found that they did. Co-expression of *HRAS-V12* with *E1A* deletion mutants confirmed that E1A must maintain the ability to interact with p300, p400 and the retinoblastoma (RB) family. Interestingly, despite showing characteristics of transformation, these cells are not able to form tumours when injected into immunocompromised mice. So, what other element might be required for this function?

The SV40 early region is known to abrogate both the RB and p53 pathways, so the authors investigated whether expression of the oncogene *MDM2*, which inhibits p53, could confer tumorigenic potential on the *HRAS-V12*- and *E1A*-expressing BJ cells. Triple-infected cells (BJ/ERM cells) were injected into immunocompromised mice and were able to generate tumours with a similar latency to human cancer cell lines.

So, can transformation really occur in the absence of telomerase activity or an alternative telomere-maintenance strategy? Telomerase activity could not be detected using the TRAP assay in the BJ/ERM cells, and they also do not seem to be immortal — they undergo 'crisis' and adopt a senescent phenotype after prolonged culture. Similarly, the tumours that are formed from these cells do not generally express *TERT*, as shown by reverse-transcriptase polymerase chain reaction, and do not have telomerase activity, as shown by the TRAP assay. On explantation into culture, BJ/ERM tumour cells undergo crisis, which is indicative of a lack of telomere maintenance, and telomeric fluorescence *in situ* hybridization revealed that the telomeres continued to be eroded during tumour growth, confirming that telomeres were not maintained by the alternative (ALT) recombination-based mechanism.

Karyotypic analysis of chromosomes from explanted BJ/ERM tumour cells reveals many chromosomal abnormalities, which are characteristic of the end-to-end chromosome fusions that occur as telomeres shorten. This type of chromosomal instability could accelerate the tumorigenic process.

So, unlike previous transformation protocols, this one does not require telomerase activity or immortalization, demonstrating that immortality is not an obligate characteristic of a cancer cell.

Emma Greenwood

References and links

ORIGINAL RESEARCH PAPER Seger, Y. R. *et al.* Transformation of normal human cells in the absence of telomerase activation. *Cancer Cell* **2**, 401–413 (2002)

WEB SITE

Greg Hannon's lab: http://www.cshl.org/gradschool/hannon_html