As the tumour cells had maintained a functional p53 pathway, might they also have avoided the aneuploidy that frequently characterizes tumour cells? A combination of multiplex fluorescence *in situ* hybridization and comparative genomic hybridization revealed that although the cells were normally diploid, two changes — on chromosomes 18 and 20 — were frequently observed.

Although these results leave us with some unanswered questions, they do provide a more physiological starting point for examining the mechanisms and consequences of transformation, and highlight some differences between the processes that occur in mouse and human cells.

Emma Greenwood

References and links

ORIGINAL RESEARCH PAPER Drayton, S. *et al.* Tumor suppressor $p16^{INK4a}$ determines sensitivity of human cells to transformation by cooperating cellular oncogenes. *Cancer Cell* **4**, 301–310 (2003)

WEB SITE

Gordon Peter's lab: http://science.cancerresearchuk.org/research/loc/london/lifch/petersg/

GLIOBLASTOMA

Cooperation is the key

The *RAS* and *AKT* oncogenes are frequently upregulated in glioblastomas, and experiments in glial progenitor cells indicate that they cooperate to induce glioblastoma formation. But what process do these two signalling pathways regulate? In the October issue of *Molecular Cell*, Eric Holland and colleagues show that, more than affecting transcription, these oncogenes cooperate to increase the translation of specific messenger RNAs that encode proteins important for cancer development.

Holland and colleagues used the RCAS/tv-a system to infect mouse glial progenitor cells with either constitutively active Kras, constitutively active Akt, or both. Kras activated Erk, which in turn activated the translation initiation factor eIF4E, whereas Akt activated TOR, which inhibits the eIF4E inhibitor 4E-BP and activates S6 ribosomal protein (S6RP) — also important in translation initiation. Interestingly, Kras increased the ability of Akt to inhibit 4E-BP and to activate S6RP, but the mechanism is unknown at present. The same pathways are activated in human glioblastoma cell lines, which confirms the relevance of this model.

So, these results confirm a causal link between the combined activity of Ras and Akt, and translation. They might act by differentially altering the translational efficiency of specific mRNAs, and the authors investigated this hypothesis by comparing total mRNA levels with that of polysomal mRNA when Ras or Akt were inhibited. Blocking either the Ras pathway with the Mek inhibitor U0126, or the Akt pathway with the PI3K inhibitor LY294002 and the TOR inhibitor rapamycin for two hours, had very little effect on total mRNA levels, as measured on a 12,488 gene array. Using a threefold change in levels as a cut-off, inhibiting the Ras pathway altered the expression of 12 genes and inhibiting the Akt pathway altered the expression of four genes. However, these genes were involved in cancer-relevant pathways, so should contribute to tumour development. By contrast, hundreds of mRNAs were lost from the polysome fraction when either Ras or Akt were inhibited for the same amount of time.

To obtain an unbiased profile of how Akt and Ras affect the generation of polysomal mRNA, the authors generated a normalized polysomal mRNA by comparing total and polysomal mRNA from seven different cell types — active Ras and Akt; active Ras; active Akt; active Ras and Akt with Ras pharmacologically inhibited; active Ras and Akt with Akt pharmacologically inhibited; and two controls. A refined analysis of these, using strict selection criteria, revealed that 219 mRNAs were associated more with polysomes when both Akt and Ras were activated. Less strict selection criteria resulted in 324 mRNAs and, together, these form a 'union set' of 426 mRNAs. Many of these encode components of signalling pathways and other biological functions that are known to be important in tumorigenesis.

A final question was whether the association with polysomes actually reflected a change in protein synthesis. A comparison of the hybridization values from the array analysis of total and polysomal mRNA with metabolic radiolabelling to determine the synthesis of candidate genes confirmed that it did in most cases.

So, it seems that Ras and Akt cooperate to alter the rate of synthesis of specific mRNAs, and their oncogenic effects could, largely, be through translation, rather than transcription.

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References and links

ORIGINAL RESEARCH PAPER Rajasekhar, V. K. *et al.* Oncogenic Ras and Akt signaling contribute to glioblastoma formation by differential recruitment of exisiting mRNAs to polysomes. *Mol. Cell* **12**, 889–901 (2003)

FURTHER READING Ruggero, D. & Pandolfi, P. P. Does the ribosome translate cancer? *Nature Rev. Cancer* **3**, 179–192 (2003)

WEB SITE

Eric Holland's lab: http://www.mskcc.org/prg/prg/bios/640.cfm