TELOMERASE

ALternative pathways?

Are telomerase and ALT two equivalent pathways to immortality? This is the question that Robert Weinberg and colleagues have addressed in a report in the 1 October issue of *Proceedings of the National Academy of Sciences*.

Both pathways result in the addition of telomeric sequence onto the ends of chromosomes, preventing crisis and allowing cells to proliferate indefinitely. But ALT seems to occur less frequently than might be expected.

Cells that have been immortalized with TERT — the catalytic component of telomerase — can be converted from a non-tumorigenic to a tumorigenic state by the addition of the HRAS-V12 oncoprotein; is the same true for cells that have been immortalized by ALT? The GM847 cell line lacks telomerase activity, and maintains its long

telomeres using ALT; however, the addition of HRAS-V12 did not produce cells that were able to induce tumour formation when injected into immunodeficient mice. This ability was restored when TERT was also introduced.

So does telomerase replace ALT as the mechanism by which cells maintain their telomeres? GM847 cells that have been transfected with HRAS-V12 and TERT still have AA-PML bodies — a marker for ALT cells — that contain the characteristic proteins TRF2 and PML, indicating that ALT remains active even when TERT is expressed.

Interestingly, the ability of telomerase to elongate telomeres is not even required for the tumorigenic phenotype, as TERT that is tagged at its carboxyl terminus with HA — which has *in vitro* telomerase activity, but can not elongate telomeres *in vivo* — is still able to confer tumorigenic potential when transfected into GM847 cells with HRAS-V12.

So what additional role does TERT perform in these cells? In normal tissue-culture conditions, the growth

TUMORIGENESIS

Clockwork

The daily oscillations of biological processes, known as circadian rhythms, are regulated by genetically controlled endogenous clocks. Disruptions in circadian rhythms have been associated with cancer — people and animals with irregular sleep–wake cycles are more susceptible to certain cancers, and the efficacy and toxicity of some chemotherapy agents correlate with the timing of drug delivery. A recent study by Fu *et al.* reported that mice with targeted disruption in a circadian control gene develop tumours, providing the opportunity to study the molecular basis of this relationship.

So far, eight core circadian genes have been identified. Among these are the *Per1*, 2 and 3 genes, which encode non-DNA-binding nuclear factors. The expression of these genes oscillates over the 24-hour circadian period. Mice with a homozygous mutation in *Per2* (*mPer2^{m/m}*) have been previously reported to be deficient in circadian clock function. In the 4 October issue of *Cell*, Fu *et al.* report

that these mice have neoplastic phenotypes, such as salivary-gland hyperplasia and teratoma formation, reduced levels of thymic apoptosis in response to γ -radiation and increased susceptibility to cancer.

So *Per2* seems to have a role in regulating cell proliferation and apoptosis, but what is its function? The authors examined mRNA levels of genes that are associated with cell-cycle regulation and tumour suppression in the *mPer2^{m/m}* mice, to see if their expression patterns were disrupted. The first gene they investigated was the transcription factor *c-Myc* — an oncogene that regulates both apoptosis and proliferation, and is also known to control the expression of several circadian genes. The authors found that the expression pattern of *c-Myc* is itself regulated by circadian genes, and that its expression pattern was disrupted in *mPer2^{m/m}* mice. Expression of several *c-Myc*-target genes, including *Ccnd1* (which encodes cyclin D1) and *Gadd45a*, were also found to be under

circadian control, so were also altered in the mutant mice. Mutations in *Per2* had no effect on the expression of *c-Myc*-target genes that were not regulated by the circadian cycle, such as *Cdk4* and *Trp53* (which encodes p53).

Fu *et al.* propose that loss of *mPer2* function leads to disrupted regulation of a number of circadian rhythm genes, such as *c-Myc*, which are involved in growth regulation. Deregulation of *c-Myc* has been associated with DNA damage, defective cell-cycle arrest and tumour development, and is likely to be a culprit in the tumours that form in *mPer2^{m/m}* mice. Aberrant control of circadian rhythms might prove to be another hallmark of tumour development, but it will be important to determine whether mutations in circadian genes also contribute to cancer development in humans.

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References and links

ORIGINAL RESEARCH PAPER Fu, L. *et al.* The circadian gene *Period2* plays an important role in tumor suppression and DNA damage response *in vivo*. *Cell* **111**, 41–50 (2002)

FURTHER READING Zheng, B. *et al.* Non-redundant roles of *mPer1* and *mPer2* genes in maintaining the mammalian circadian clock. *Cell* **105**, 683–694 (2001)

WEB SITE

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