Finally, abnormalities in the cell cycle have been observed in degenerating neurons, so the authors examined cell-cycle control in the *Hq* mice. A series of experiments showed that granule and retinal cells from *Hq* mice re-enter the cell cycle aberrantly, before they die by apoptosis, supporting the idea of a link between cell-cycle re-entry and oxidative stress.

How do these results square with AIF's known function as a pro-apoptotic molecule? The authors propose that AIF normally acts, either indirectly or directly, as a free-radical scavenger in the mitochondrial membrane — it prevents oxidative stress by mopping up H_2O_2 in particular. Under conditions that induce apoptosis, however, AIF translocates to the cytoplasm and nucleus, where it promotes chromatin condensation and other features of apoptosis. As well as shedding light on the functions of AIF, then, this study has pinpointed the first *in vivo* model for studying how oxidative stress might affect cell-cycle re-entry and apoptosis.

Alison Mitchell

References and links

ORIGINAL RESEARCH PAPER Klein, J. A. *et al.* The harlequin mouse mutation downregulates apoptosis-inducing factor. *Nature* **419**, 367–374 (2002)

DNA REPLICATION

Ku calls time

Not all genes are created equal when it comes to replication — whereas some genes are replicated early during S phase, others are not replicated until much later. The factors that control this difference are not well understood, but a report by Donaldson and colleagues in *Genes & Development* now describes one way of controlling replication timing at telomeric regions. Interestingly, though, the protein involved is probably more familiar to those who study DNA repair.

Replication timing is known to be influenced by several factors, including a gene's position on the chromosome or in the nucleus — those genes that are nearest to the nuclear periphery (and in yeast cells to the telomeres, which localize to the nuclear periphery) tend to replicate later.

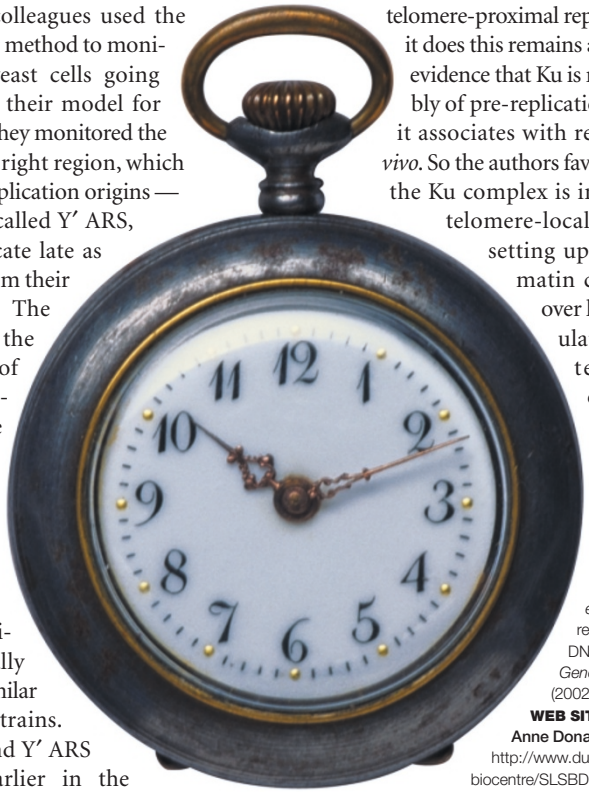
Armed with this knowledge, Donaldson and colleagues wondered whether Ku — which acts at eukaryotic telomeres — might be involved in replication timing. The Ku heterodimer consists of two subunits (known as yku70 and yku80 in yeast), and it is important in the repair of double-stranded DNA breaks. In yeast, these proteins are required for the localization of telomeres to the nuclear periphery, and they are also involved in the recruitment of silencing (Sir) proteins to telomeres.

Donaldson and colleagues used the dense isotope transfer method to monitor replication in yeast cells going through S phase. As their model for telomere replication, they monitored the yeast chromosome V right region, which contains two active replication origins — *ARS501* and the so-called Y′ ARS, both of which replicate late as might be expected from their telomeric positions. The authors also studied the replication time of internally located origins at some distance from the telomeres.

Replication was then compared at the various origins in wild-type and *Ku* deletion yeast strains. In a *yku70* strain, replication at the internally located origins was similar to that in wild-type strains. However, *ARS501* and Y′ ARS replicated much earlier in the mutant than in the wild-type strain. The authors also observed some 'escape replication' (whereby origins replicate before they are released from the block that is used for synchronization) of *ARS501* and Y′ ARS — a phenomenon that has previously been reported for very early-replicating sequences. The authors found similar results at other telomeres, as well as in a *yku70yku80* deletion strain.

As Ku is involved in recruiting the Sir3 protein to telomeres, one possible explanation is that, when Ku is deleted, the localization — and hence function — of Sir3 is disrupted. So the authors tested the effects of deleting *sir3* in their system. The Y′ ARS was replicated earlier in the *sir3* deletion strain than in wild-type yeast. However, *ARS501* was barely affected, indicating that the effect of deleting Ku is not simply to disrupt the recruitment of Sir3 to telomeres.

The conclusion, then, is that Ku has a specific function in determining the activation time of telomere-proximal replication origins. How it does this remains a mystery. There is no evidence that Ku is needed for the assembly of pre-replication complexes or that it associates with replication origins *in vivo*. So the authors favour a model in which the Ku complex is involved, through its telomere-localization function, in setting up a specialized chromatin context that can act over large distances to regulate the time at which telomere-proximal origins fire. And time will tell if they're right.



Alison Mitchell

References and links

ORIGINAL RESEARCH PAPER Cosgrove, A. J. *et al.* Ku complex controls the replication time of DNA in telomere regions. *Genes Dev.* **16**, 2485–2490 (2002)

WEB SITE

Anne Donaldson's laboratory: http://www.dundee.ac.uk/biocentre/SLSBDIV3add.htm

© 2002 Nature Publishing Group