IN THE NEWS

Age discrimination

Many of the body's tissues are constantly renewed. In fact, the average age of cells in a human adult body might be only 7–10 years, according to stem cell biologists from the Karolinska Institute in Stockholm, Sweden.

Jonas Frisén and colleagues have developed a new technique for measuring the age of cells, and published their first findings in *Cell*.

The Frisén team hypothesized that the dramatic increase in atmospheric radioactive carbon 14 (^{14}C) as a result of nuclear testing during the Cold War in the early 1960s and the exponential decline after 1963 might provide a modern-day 'carbon dating' equivalent.

As DNA does not exchange carbon after it is generated, the amount of ^{14}C in a cell's DNA reflects the amount of atmospheric ^{14}C at the time of its birth.

Looking at tissue samples from deceased adult subjects that had been exposed to a changing ^{14}C environment, Frisén and colleagues concluded that cells from the cerebral cortex were as old as the subjects themselves. "The reason these cells live so long is probably that they need to be wired in a very stable way," said Frisén (news@nature.com, 14 July 2005).

However, all other tissues they studied were considerably younger — the average age of cells in the intestine is ~10 years and in skeletal muscle ~15 years.

So, if the body is capable of regenerating most of its tissues, why do we age? "The notion that stem cells themselves age and become less capable of generating progeny is gaining increasing support," according to Frisén (*The New York Times*, 2 August 2005). And he is hopeful that the new carbon dating technique might shed light on this theory.

Arianne Heinrichs

CELL CYCLE

Checking the damage

The transcriptional activation of target genes after cellular stress by the tumour suppressor p53 can cause cell-cycle arrest or apoptosis. But the regulation of this process is proving increasingly complex. Now, Irena Dornreiter and colleagues have identified an isoform of human p53 that has an essential role in the intra-S-phase checkpoint that ensures accurate DNA replication.

The Dornreiter team identified an alternatively spliced p53 transcript in human and monkey (but not rodent) cells that lacked 198 nucleotides between exons 7, 8 and 9, which they named Δp53. At the protein level, immunoblot analysis and mass spectrometry confirmed that a truncated form of p53 correlated with the alternatively spliced Δp53 cDNA and lacked the core domain of the normal protein. This Δp53 isoform could form homodimers and homotetramers but could not heterodimerize with full-length p53, suggesting that it might have an alternative function.

Full-length p53 induces the transcription of cell-cycle regulatory genes such as *p21*, *14-3-3σ* and *GADD45*, as well as pro-apoptotic genes such as *MDM2*, *BAX* and *PIG3*. However, overexpression studies and chromatin immunoprecipitation (ChIP) analysis showed that the Δp53 isoform only regulates transcription of the cell-cycle genes and not the pro-apoptotic genes. Damage-induced p53 activation in S-phase cells causes cell-cycle arrest, but is thought to avoid the premature activation of the p53-mediated apoptotic pathway by an unknown cell-cycle-specific mechanism. So, as Δp53 does not activate the pro-apoptotic genes, the authors proposed that it might be responsible for the transcriptional activation of p53 targets during S phase.

Subsequent experiments showed that, after irradiation, the *p21* promoter binds to full-length p53 exclusively during the G1 and G2 phases of the cell cycle, and that it specifically associates with Δp53 only during S phase. This suggests that the transcriptional activities of p53 and Δp53 are independent of each other. This was confirmed by studying irradiation-induced p21 production. For the first 10 hours after irradiation, p21 production was mediated by Δp53, but full-length p53 did not begin to regulate p21 production until 8 hours had passed. So the transcriptional activities of p53 and Δp53 are independent and temporally separated.

The intra-S-phase checkpoint is controlled by the activation of ataxia telangiectasia and RAD3-related protein (ATR), which signals through checkpoint kinase-1 (CHK1), CDC25A and cyclin-E–cyclin-dependent-kinase-2 (CDK2) to transiently inhibit DNA replication. The CDC25–cyclin-E–CDK2 pathway is initiated rapidly, but only prevents DNA replication for ~2 hours. However, after ultraviolet light (UV) damage, S phase is delayed for ~6 hours. So could Δp53 be responsible for this continued inhibition of DNA replication?

The authors suggest that this is indeed the case: Δp53 is activated

ORGANELLE BIOGENESIS

Where did I come from?

How do peroxisomes form in eukaryotic cells? A definitive answer to this question has been elusive, with some believing that, similar to the Golgi, peroxisomes are derived from the endoplasmic reticulum (ER) and others believing that, similar to mitochondria, they are autonomous entities. However, Tabak and colleagues now resolve this issue in *Cell* by showing that peroxisomes come from the ER.

The authors worked in *Saccharomyces cerevisiae* and created a system that allowed the real-time imaging of peroxisome biogenesis. They focused on peroxin-3 (Pex3), an integral membrane protein that is essential for the biogenesis of these organelles. They made a yeast strain that could be induced to express endogenous levels of fluorescently labelled Pex3 (Pex3–YFP) by putting the gene encoding this construct under the control of a galactose-inducible promoter and exposing cells to galactose for a limited time. In the absence of galactose, Pex3 and peroxisomes were absent from these cells.