were deficient in p53 alone, and this indicated that p63 and p73 might act with p53 — or in a parallel pathway — to induce apoptosis after DNA damage. The authors confirmed these results in an *in vivo* system — the developing nervous system of day-13.5 mouse embryos, in which p53 has been shown to be important for γ-irradiation-induced apoptosis.

Although other mechanisms of p53-dependent apoptosis have been proposed, there is a general consensus that p53 acts in this process by the initiation of downstream target genes. So, Jacks and colleagues studied the induction of p53 target genes in MEFs that lacked the various p53 family members. The induction of some targets, such as *Cdkn1a* (which encodes p21) and *Mdm2*, was no different in wild-type cells than in cells that lacked p63, p73 or p63/p73. But other genes — *Bax* and *Perp*, for example — were not expressed in MEFs that lacked p63 and p73. Notably, Bax and Perp are linked to apoptotic responses.

The authors had shown that both p53 and p63 are enriched in the nuclei of MEFs after DNA damage, so they tested whether these proteins can bind the promoters of p53 target genes. Both proteins associated with the *Cdkn1a*, *Mdm2*, *Bax* and *Perp* promoters in wild-type MEFs. However, in cells that lacked p63 and p73, p53 could no longer associate with the *Bax* or *Perp* promoters in response to DNA damage. Moreover, in p53-deficient MEFs, p63 was found specifically at the *Bax* and *Perp* promoters.

These results indicate a model in which p63 and p73 regulate the ability of p53 to bind at certain promoters after its induction in response to DNA damage. And, as the authors speculate, they might "portend a greater role for these proteins in tumour suppression and chemosensitivity".

Alison Mitchell
Editor, Nature Reviews Molecular Cell Biology

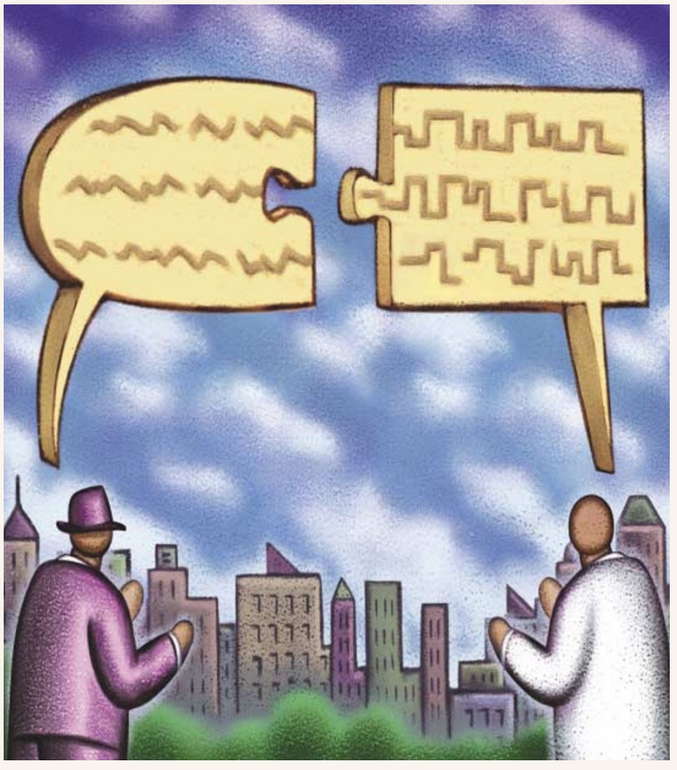
References and links

ORIGINAL RESEARCH PAPER Flores, E. R. *et al*. p63 and p73 are required for p53-dependent apoptosis in response to DNA damage. *Nature* **416**, 560–564 (2002)

FURTHER READING Yang, A. & McKeon, F. p63 and p73: p53 mimics, menaces and more. *Nature Rev. Mol. Cell Biol*. **1**, 199–207 (2000)

WEB SITE

Tyler Jacks' lab: http://web.mit.edu/biology/www/facultyareas/facresearch/jacks.shtml



IN BRIEF

TUMOUR SUPPRESSORS

HLTF gene silencing in human colon cancer.

Moinova, R. *et al. Proc. Natl Acad. Sci. USA* **99**, 4562–4567 (2002)

Expression of helicase-like transcription factor (*HLTF*) — a member of the SWI/SNF family of chromatin-remodelling enzymes, which have been shown to be disrupted in cancer — is lost in ~30% of colon cancer cell lines. This loss is accompanied by promoter methylation, and is restored following addition of 5-azacytidine, a demethylating agent. Interestingly, the *HLTF* promoter is not methylated in breast or lung cancer, so *HLTF* might specifically suppress colon cancer. Consistent with this, its transfection into *HLTF*-deficient cell lines suppresses colony growth.

P53 REGULATION

Deubiquitination of p53 by HAUSP is an important pathway for p53 stabilization.

Li, M. *et al. Nature* **416**, 648–653 (2002)

To function as a tumour suppressor, p53 must first be freed from the clutches of MDM2, a ubiquitin ligase that targets p53 for degradation. Li *et al.* have used mass spectrometry to identify p53-interacting proteins, and have discovered herpesvirus-associated ubiquitin-specific protease (HAUSP). HAUSP can deubiquitylate — and therefore stabilize — p53, even in the presence of MDM2. Accumulation of p53 results in growth arrest and apoptosis. HAUSP might therefore act as a tumour suppressor, by stabilizing p53.

MOUSE MODELS

Nf2 gene inactivation in arachnoidal cells is rate limiting for meningioma development in the mouse.

Kalamarides, M. *et al. Genes Dev.* **16**, 1060–1065 (2002)

Tumours of the membranes that cover the brain, known as meningiomas, are a common affliction of people with neurofibromatosis type 2, which is caused by inactivation of the *NF2* gene. However, *Nf2*$^{-/-}$ mice don't develop meningiomas. Michel Kalamarides and colleagues have developed the first genetically modified mouse model of meningioma by knocking out *Nf2* in a small number of meningeal cells.

THERAPEUTICS

ErbB2 is essential in the prevention of dilated cardiomyopathy.

Crone, S. *et al*. *Nature Med*. **8**, 459–465 (2002)

Herceptin (trastuzumab) — a humanized monoclonal antibody specific for the extracellular domain of the receptor tyrosine kinase ERBB2 — is used to treat breast cancers that overexpress *ERBB2*. Some patients who take this drug, however, experience cardiac dysfunction. To investigate the role of ErbB2 in the adult heart, mice with a ventricular-restricted deletion of *ErbB2* were generated. These mice developed many features of dilated cardiomyopathy, indicating that ErbB2 function is required for normal cardiomyocyte function. Strategies to prevent cardiac dysfunction must therefore be developed for patients who take Herceptin.