

APOPTOSIS

Divide or die

Cell proliferation and cell death might seem like opposing functions, but oncogenes such as *E1A* and *MYC* are able to initiate both. Apoptosis is thought to be a safety mechanism, and is induced when the oncogenic signal to proliferate is recognized as excessive, and hence likely to cause tumorigenesis. The mechanisms by which oncogenes induce cell death have not been clearly established. Zaher Nahle, Scott Lowe and colleagues have investigated this phenomenon using *E1A*, and have found that the E2F transcription factor, which promotes replication and hence proliferation, has a key role in coordinating these processes.

The authors first investigated whether overexpression of *E1A* in mouse embryo fibroblasts (MEFs) and normal diploid human fibroblasts (IMR90 cells) affected the protein levels of caspases — the effectors of cell death — and found that both initiator and effector caspases were upregulated by 5–15-fold. A similar increase was observed in cells deficient for either ARF or p53, so *E1A* must upregulate caspases through a p53-independent pathway.

One of the key targets of *E1A* is retinoblastoma (RB), and *E1A* mutants that are unable to inactivate RB do not upregulate caspases. Similarly, *RB*^{-/-} MEFs expressed higher levels of caspases than wild-type cells. Introduction of wild-type RB, but not a tumour-derived mutant that can not bind E2F, into RB-deficient cells represses this caspase expression, and implicates the E2F family of proteins in this apoptotic pathway. In fact, expression of E2F1 is sufficient to induce this caspase induction.

So are caspases transcriptional targets of E2F1, or is the induction indirect? Northern blots showed that caspase mRNA was increased by 5–15-fold (similar to the protein levels) when either *E1A* or E2F1 was expressed in IMR90 cells. Caspase mRNA levels also increase as cells enter S phase, which coincides with the activity of E2F1 and the levels of cyclin A mRNA — a known E2F1 target. Analysis of caspase promoters provided further support that E2F could transcriptionally activate caspases, as several contain E2F1-binding sites, and chromatin immunoprecipitation experiments confirmed this — E2F1 precipitates from *E1A*-expressing cells that contained sequences from the caspase-7 promoter. The caspase-7 promoter was also able to drive transcription of the luciferase reporter gene — expression increased by almost 18-fold — when E2F1 was expressed.

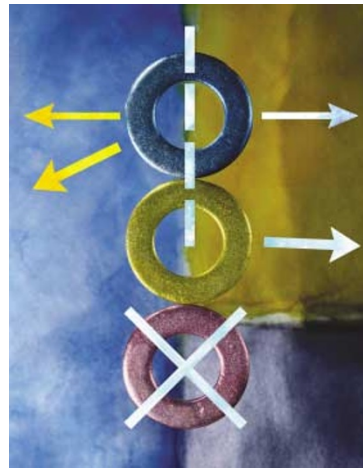
But what is the physiological role of this caspase induction? It is not sufficient to induce apoptosis and, instead, seems to sensitize cells to apoptotic stimuli, such as serum withdrawal and adriamycin treatment. E2F1 is also known to activate cytochrome *c* release — a downstream event in the apoptotic pathway — by a p53-dependent pathway. The requirement for p53 in inducing apoptosis could be recapitulated, at least in part, by either introducing BAX — a proapoptotic protein that facilitates cytochrome *c* release — to *TP53*^{-/-} *BAX*^{-/-} cells expressing *E2F*, or by directly microinjecting cytochrome *c* into *TP53*^{-/-} *RB*^{-/-} cells. Under these conditions, caspase induction by E2F1 is able to enhance apoptosis, underscoring the cooperation of the p53-dependent and -independent pathways in inducing apoptosis.

So, the *E1A* oncogene coordinates division and death by using the same machinery — E2F — to initiate both processes. Whether other oncogenes operate in the same way remains to be determined.

Emma Greenwood, Senior Editor, Nature Reviews Cancer

References and links

ORIGINAL RESEARCH PAPER Nahle, Z. *et al.* Direct coupling of the cell cycle and cell death machinery by E2F. *Nature Cell Biol.* **4**, 859–864 (2002)



IN BRIEF

CELL SIGNALLING

A novel Epac-specific cAMP analogue demonstrates independent regulation of Rap1 and ERK.

Enserink, J. M. *et al.* *Nature Cell Biol.* **4**, 901–906 (2002)

Protein kinase A (PKA) is required for the cyclic AMP-induced activation of the extracellular signal-regulated kinase (ERK), but not for the cAMP-induced activation of the small GTPase Rap1 through the guanine nucleotide-exchange factors Epac1 and Epac2. Using a cAMP analogue as a tool to distinguish between PKA- and Epac-mediated effects, the authors found that the cAMP-induced regulation of ERK and the activation of Rap1 are independent processes.

NUCLEAR TRANSPORT

Karyopherins in nuclear pore biogenesis: a role for Kap121p in the assembly of Nup53p into nuclear pore complexes.

Lusk, C. P. *et al.* *J. Cell Biol.* **159**, 267–278 (2002)

Karyopherins — also known as importins or exportins, depending on the direction of transport — mediate nuclear transport through the nuclear pore complex (NPC). Karyopherin Kap121 interacts specifically with nucleoporin Nup53, and Lusk *et al.* now show that Kap121 targets Nup53 to the NPC. Nup53 is subsequently released from Kap121 by Nup170, which allows Kap121 to continue its movement through the NPC.

TELOMERES

A bulged stem tethers Est1p to telomerase RNA in budding yeast.

Seto, A. G. *et al.* *Genes Dev.* **16**, 2800–2812 (2002)

The RNA subunit of telomerase functions as the template for telomeric DNA synthesis, but it is not clear whether the RNA subunit has other functions. Here, Seto *et al.* report the identification of a conserved RNA bulged stem that is essential for telomerase function *in vivo* and that interacts with the telomerase regulatory protein Est1, which recruits or activates telomerase at the telomere.

GENE EXPRESSION

The SR protein SRp38 represses splicing in M phase cells.

Shin, C. & Manley, J. L. *Cell* **111**, 407–417 (2002)

SR proteins function in both constitutive and alternative pre-mRNA splicing. Shin and Manley now report the identification of an unusual member of the family — SRp38. Unlike other SR proteins that induce splicing, SRp38 acts as a splicing repressor that is activated by dephosphorylation during M phase. In mitotic cells splicing is inhibited by SRp38, which implies that cell-cycle-specific dephosphorylation of SRp38 is involved in gene silencing during mitosis.