IN BRIEF

NUCLEAR TRANSPORT

Binding of the Mex67p/Mtr2p heterodimer to FXFG, GLFG, and FG repeat nucleoporins is essential for nuclear mRNA export.

Strässer, K., Bassler, J. & Hurt, E.
J. Cell Biol. **150**, 695–706 (2000)

Messenger RNA export through the nuclear pore involves a number of nucleoporins and the Mex67p/Mtr2p complex, but its mechanism is not well understood. Hurt and colleagues show that Mex67p and Mtr2p bind as a heterodimer to RNA and also to several conserved nucleoporin motifs. They propose that transport through the pore is directed by sequential interactions with first the Nup82 and then the Nup116 complex. This mechanism resembles that used by importin family members to transport proteins through the nuclear pore.

CELL POLARITY

CHE-14, a protein with a sterol-sensing domain, is required for apical sorting in *C. elegans* ectodermal epithelial cells.

Michaux, G. et al.
Curr. Biol. **10**, 1098–1107 (2000)

It's a mystery how trafficking of proteins to the apical or basolateral membranes of polarized cells is controlled, but evidence implicates proteins containing sterol-sensing domains. Here, Michaux and colleagues characterize CHE-14, a new member of the Patched family of sterol-sensing proteins, in *Caenorhabditis elegans*. CHE-14 is most closely related to Dispatched, a *Drosophila* protein with 12 putative transmembrane domains that is involved in releasing the secreted signalling molecule Hedgehog from cells. CHE-14 mutants accumulate vesicles at the apical membranes of epithelial cells, and CHE-14 tagged with green fluorescent protein rescues the mutant phenotype and localizes to apical membranes. Deletion of the predicted extracellular loops and transmembrane domains, including the sterol-sensing domain, abolishes its ability to rescue the secretion phenotype, whereas the predicted cytoplasmic loops seem dispensable. The authors propose a model in which CHE-14 and its close relative Dispatched are required for exocytosis, whereas Patched and the Niemann–Pick C protein — another sterol-sensing protein — are required for endocytosis.

ANGIOGENESIS

Genes expressed in human tumor endothelium.

St. Croix, B. et al.
Science **289**, 1197–1202 (2000)

To survive and grow, tumours need their own supply of blood. They produce factors to stimulate the formation of new blood vessels, but does the endothelial lining of these vessels differ from that in vessels from healthy tissues? This paper indicates that they do — and dramatically so. The authors compare gene-expression profiles in endothelium derived from normal and tumour tissue, and find that of the 170 transcripts predominantly expressed in the endothelium, 79 are differentially expressed.

APOPTOSIS

DIABLO is double trouble

Scientific announcements are a bit like catching a bus — a long wait, and then two arrive at once. This was the case back in July, when the groups of Xiaodong Wang in Dallas and David Vaux in Melbourne independently described a new mammalian protein that promotes apoptosis. Its activity has now been further characterized, as Wang and colleagues report in *Nature*.

The protein in question — named Smac by Wang's group and DIABLO by Vaux and colleagues — promotes apoptosis by binding to and antagonizing members of the IAP (inhibitor of apoptosis protein) family. These IAPs have an anti-apoptotic activity because they bind and inhibit caspases, the key effectors of cell death.

In *Drosophila*, the activity of IAPs is countered by the imaginatively named Reaper, Hid and Grim proteins — hence the search for mammalian functional homologues. And, as described in the two initial reports, Smac/DIABLO fits the bill. It promotes apoptosis by binding to the IAPs, and prevents them from sequestering caspases.

But how does it do this? Wang and colleagues now provide clues with the crystal structure of Smac/DIABLO at a resolution of 2.2 Å. The structure reveals that Smac/DIABLO forms a homodimer in solution, so the authors first asked whether this is the functional form. They engineered missense mutations to perturb dimer formation, and found that the interaction of monomers with an IAP (XIAP) was indeed disrupted (although not abolished).

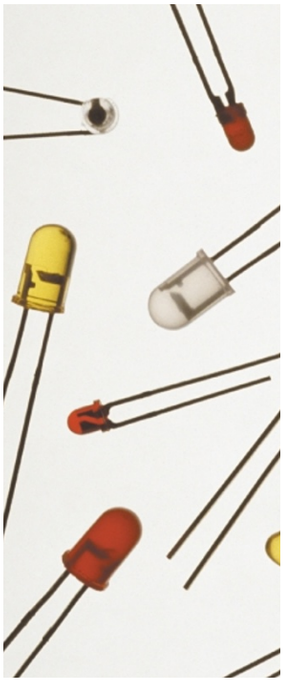
At least one function of Smac/DIABLO is to stimulate the cleavage of procaspase 3 from an inactive procaspase precursor to the mature form, caspase 3. Wang and co-workers reconstituted this function *in vitro* using purified recombinant components (including XIAP), then asked whether Smac/DIABLO might also promote the catalytic activity of mature caspase 3. They found that it could, and conclude that Smac/DIABLO triggers apoptosis through at least two mechanisms — it induces the proteolytic activation of procaspase 3, and also promotes the enzymatic activity of mature caspase 3.

TELOMERES

Caps and cancer

Telomerase is activated in many human cancers, and the possibility of targeting tumours with telomerase inhibitors is attractive. But a study in September's *Nature Genetics* shows that *Terc*$^{-/-}$ mice, which lack functional telomerase, are especially sensitive to ionizing radiation. The scientific implication is that functionally intact telomeres and the response to ionizing radiation are somehow linked; the clinical one is that it may not be wise to treat cancer patients with both telomerase inhibitors and ionizing radiation.

Alison Mitchell



References and links

ORIGINAL RESEARCH PAPER Wong, K.-K. *et al*. Telomere dysfunction impairs DNA repair and enhances sensitivity to ionizing radiation. *Nature Genet.* **26**, 85–88 (2000)
FURTHER READING González-Suárez, E., Samper, E., Flores, J. M. & Blasco, M. A. Telomerase-deficient mice with short telomeres are resistant to skin tumorigenesis. *Nature Genet.* **26**, 114–117 (2000)
REVIEW Lundblad, V. DNA ends: maintenance of chromosome termini versus repair of double strand breaks. *Mutat. Res.* **451**, 227–240 (2000)