CELL CYCLE

Two's company

It's not always the case that you can't have too much of a good thing. For example, although two centrosomes are essential for assembly of the bipolar spindle during mitosis, more than that can lead to genome instability. It's important, then, that centrosomes are duplicated only once per cell cycle. But how is this regulated?

In January's *Nature Cell Biology*, Steven Reed and co-workers propose a model for duplication of the spindle pole body (SPB; the yeast equivalent of the centrosome). Based on the premise that DNA replication — which also must occur only once per cell cycle — is coordinated with cell-cycle progression, the authors asked whether cyclin/CDK activities might activate duplication of the SPB and inhibit reduplication until completion of the cycle.

According to Reed and colleagues' model, the three G1 cyclins (Clns 1, 2 and 3) in budding yeast are involved in controlling SPB duplication. Subsequent maturation, an essential step that must be completed before SPBs can reduplicate, is directed either by the two S-phase B cyclins, Clb5 and Clb6, or by one of four mitotic B cyclins (Clbs 1, 2, 3 and 4). Finally, the four mitotic B cyclins can block SPB reduplication until mitosis has been completed or under checkpoint-arrest conditions. It seems that a fine balance between the positive and negative effects of cell-cycle proteins does, indeed, regulate SPB duplication.

Alison Mitchell

References and links

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APOPTOSIS

Bax to Bak

There's a fine line between life and death — a tightrope walked by the Bcl-2 family of pro- and anti-apoptotic proteins. Tip the balance too far one way and, as discussed in two new papers, the cell slides helplessly to its death.

Members of the Bcl-2 family fall into three subfamilies. On one side of the death equation are the anti-apoptotic proteins Bcl-2 and Bcl-x_L; on the other side are the pro-apoptotic members, including the Bax subfamily (Bax and Bak) and the 'BH3-only' proteins (such as Bid and Bad). But how do the interactions between these various proteins control apoptosis?

Reporting in *Cell*, Nico Tjandra and colleagues discuss the regulation of Bax. They have used NMR to solve its solution structure — a structure, say the authors, that is strikingly similar to that of Bcl-x_L. Both contain nine α-helices, with the first eight (α1–α8) occupying almost identical positions despite low sequence similarity. But whereas Bcl-x_L (right-hand figure) contains a hydrophobic pocket that can accommodate another protein (here, the Bak BH3 peptide; yellow), in Bax this pocket is occupied by its own α9 helix (green). How, then, does Bax interact with other members of the Bcl-2 family?

The authors believe that the answer lies in a conformational change. Early during apoptosis, Bax translocates from the cytosol to the mitochondria. Here it inserts into the outer mitochondrial membrane (OMM), where it is involved in the release of cytochrome *c* and apoptosis. The authors propose that a conformational change, which allows Bax to insert into the OMM, also disengages the α9 helix from the hydrophobic pocket. This would expose the pocket, allowing it to bind other proteins.

One candidate that might slip into this pocket is Bid — the subject of a report in *Genes and Development* by Stanley Korsmeyer and colleagues. They have studied tBid, a truncated, physiologically active form of Bid, which is involved in the release of cytochrome *c* from mitochondria. It could do this either by forming a pore through which cytochrome *c* can escape across the OMM, or by activating another mitochrondrial protein with the same net effect.

Korsmeyer and co-workers favour the second possibility. They show that, for apoptosis to occur, tBid's BH3 domain (which is required for dimerization) must be present on the cytoplasmic face of the mitochondria. This indicates that tBid acts by binding other proteins, and the authors reveal at least one of its partners to be Bak. Not only do Bak and tBid interact physically, but this association is required for the release of cytochrome *c*. Finally, on binding tBid, Bak undergoes a conformational change and forms oligomers — indicating, speculate the authors, the possible formation of a cytochrome *c* -permeant pore.

The mitochondrial preparation used by Korsmeyer and colleagues did not contain abundant Bax, and the authors are now repeating these experiments in cells that contain both Bax and Bak. Indeed, the idea that Bid acts as a death ligand fits well with the proposed opening of Bax's hydrophobic pocket to accommodate other members of the Bcl-2 family. However, the functions of Bcl-2 family members in apoptosis remain controversial, and it's likely to be some time before all of their molecular balancing acts are revealed.

Alison Mitchell

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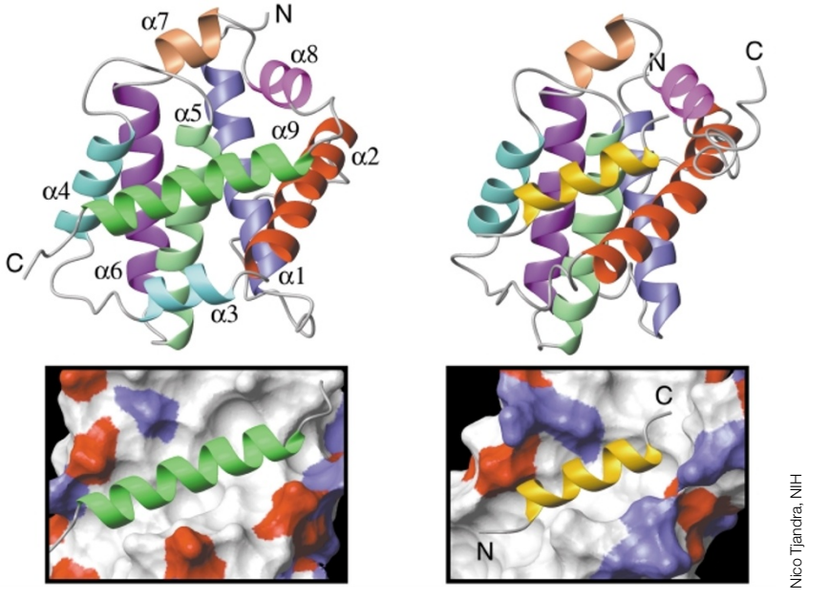

Nico Tjandra, NIH

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