

WEB WATCH

SCOP means structure

• <http://scop.mrc-lmb.cam.ac.uk/scop/>

In Russian, the word scop (скон) can mean a 'pile' or 'accumulation'. In English, however, it stands for something completely different — the 'structural classification of proteins', a widely used database for the investigation of protein structures and sequences.

The SCOP database was officially launched in 1995 by Alexey Murzin, Steven Brenner, Tim Hubbard and Cyrus Chothia at the MRC Laboratory of Molecular Biology in Cambridge, UK. The database now has mirror sites around the world for faster local access, and has recently been updated (version 1.61, November 2002).

When SCOP was launched, its aims were to provide "a detailed and comprehensive description of ... structural and evolutionary relationships", as well as providing "links to co-ordinates, images of the structure, interactive viewers, sequence data and literature references". This it now does, and much more.

The site has extensive linking through to entries in the Protein Data Bank, and is searchable at several different levels (structural similarity, keywords). The curators point out that the database is of use to experimental structural biologists (for exploring the 'structure space' near their protein of interest) and theoreticians (who can browse the various protein folds), as well as to molecular biologists, who can use the classifications in the database to locate proteins of interest.

On the down-side, the site is uninspiring in design and the amount of information is a little overwhelming for the first-time user. But there's a clear 'help' page explaining the features and layout of the site. And with so much functionality available, who needs much in the way of form?

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APOPTOSIS

Another fragment in the death puzzle

The activation of apoptotic cascades triggers a series of events, one of which is the condensation and fragmentation of chromosomal DNA. In mammals, at least three proteins have been implicated in this process — DFF40/CAD, the apoptosis-inducing factor (AIF) and a mitochondrial endonuclease termed endonuclease G (EndoG). How do these proteins work, and are their pro-apoptotic functions conserved in other species? These are the questions tackled by Ding Xue and colleagues, who report their results in *Science*.

The authors started by cloning *wah-1*, which is the *Caenorhabditis elegans* homologue of AIF. They then examined the effects of inhibiting the expression of *wah-1* using RNA-mediated interference (RNAi) and found that, in *wah-1*(RNAi)-treated worms, the appearance of embryonic cell corpses during normal development was delayed. This phenotype is similar to that observed in *cps-6* mutant worms (CPS-6 is the worm orthologue of mammalian EndoG), and so indicates a role for WAH-1 in the progression of apoptosis. However, a *cps-6* mutation did not enhance the *wah-1*(RNAi) phenotype, indicating that WAH-1 and CPS-6 might function in the same pathway.

Xue and co-workers next used TUNEL assays to show that, like AIF, WAH-1 induces chromosome fragmentation. And, using a WAH-1–green fluorescent protein (GFP) fusion protein, they showed that WAH-1 localizes to the mitochondria. So how is WAH-1 activated? The release of apoptogenic factors from mitochondria in response to pro-apoptotic stimuli is triggered by so-called 'BH3-domain-only' proteins. In worms, the most upstream cell-death activator is also a BH3-domain protein, EGL-1. The authors asked whether global expression of *egl-1* could release WAH-1 from the mitochondria, and they found that it could — the punctate mitochondrial staining pattern of WAH-1–GFP became more uniformly spread throughout the cell, and more GFP fluorescence was seen in nuclei,

indicating the release of this protein from the mitochondria to mediate chromosome fragmentation.

These results indicate that the mitochondrial cell-death pathway is indeed conserved in worms, but what about the mechanism of AIF-mediated DNA degradation? Hints that WAH-1 and CPS-6 act in the same pathway led Xue and colleagues to examine whether these two proteins interact directly. GST-fusion-protein pulldown experiments confirmed that they interact *in vitro*, and the authors further showed that they act synergistically to induce cell killing. They monitored this *in vitro* by looking at the cleavage of DNA at various concentrations, and found that cleavage occurred at lower concentrations of protein when the two proteins were incubated together than when either protein was used alone. *In vivo*, the ectopic expression of *wah-1* or *cps-6* alone in touch-receptor neurons led to the death of 5–8% or 15–23% of the neurons, respectively. When *cps-6* and *wah-1* were expressed together, however, 53–75% of the neurons were killed.

These results, say the authors, indicate that "EndoG and AIF ... define a single conserved DNA-degradation pathway initiated from the mitochondria". However, there are some differences between the worm and human pathways. For example, whereas AIF acts in a caspase-independent manner, WAH-1 requires functional CED-3 (the worm caspase homologue) for full activity. Moreover, unlike AIF, WAH-1 does not bind FAD and does not seem to have an oxidoreductase activity. These data fit in well, then, but the puzzle is still far from solved.

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 **References and links**

ORIGINAL RESEARCH PAPER Wang, X. *et al.* Mechanisms of AIF-mediated apoptotic DNA degradation in *Caenorhabditis elegans*. *Science* **298**, 1587–1592 (2002)

FURTHER READING Cande, C. *et al.* Apoptosis-inducing factor (AIF): key to the conserved caspase-independent pathways of cell death? *J. Cell Sci.* **115**, 4727–4734 (2002)