STRUCTURE WATCH

Three's a crowd

HtrA2/Omi — a mammalian mitochondrial serine protease — has an important role in apoptosis. It was identified because it binds to the inhibitor of apoptosis (IAP) proteins (see Review by Duckett on page 401 of this issue), and thereby promotes apoptosis by relieving IAP-mediated caspase inhibition. However, this is not the only way that HtrA2/Omi can promote apoptosis, as Shi and co-workers now report in *Nature Structural Biology*. They gained insights into the pro-apoptotic function of HtrA2/Omi by determining the crystal structure of the mature form of this protein at 2.0-Å resolution.

They found that mature HtrA2/Omi has two domains — a serine-protease domain and a carboxy-terminal PDZ domain — and that the functional protein is a pyramid-shaped homotrimer, which is formed by protease-domain interactions. The three amino-terminal IAP-binding sequences are located close together at the 'top' of the pyramid, and this crowding might adversely affect IAP binding. The PDZ domains are located at the pyramid base, where they restrict access to the protease-domain active sites.

When the authors investigated the functional significance of homotrimer formation and the IAP-binding sequence, they found that the former, but not the latter, was essential for a caspase-activating pro-apoptotic function of HtrA2/Omi. Homotrimer formation is important for the protease activity of HtrA2/Omi, and the authors speculate that the PDZ-domain crowding in the trimer stops them completely covering the protease-domain active sites, so that these sites can activate a caspase-dependent pathway in an IAP-independent manner. HtrA2/Omi might therefore induce cell death in several ways, and these studies have provided an important framework for understanding the mechanisms of HtrA2/Omi-mediated apoptosis.

REFERENCE Shi, Y. *et al.* Structural insights into the pro-apoptotic function of mitochondrial serine protease HtrA2/Omi. *Nature Struct. Biol.* **9**, 436–441 (2002)

A double life

Apoptosis-inducing factor (AIF) seems to have a double life. On the one hand it shows homology to prokaryotic oxidoreductases and can function as an electron transferase; on the other hand it is involved in a pathway of caspase-independent cell death. These two functions seem to be independent of one another, as inhibitors of redox function fail to inhibit the apoptogenic function of AIF. But would the structural analysis of AIF allow us to reconcile these two aspects of its personality? Would it provide insights into how AIF induces cell death? Unfortunately not, as the crystal structure of mouse AIF — reported by Alzari and colleagues in *Nature Structural Biology* — triggers even more speculation. Mouse AIF has an overall glutathione reductase-like fold, with classical FAD- and NADH-binding sites, but the carboxyl terminus folds in a way that is not seen in other oxidoreductases.

So, is the carboxyl terminus responsible for the apoptogenic activity of AIF? The report of an AIF homologue in *Dictyostelium discoideum*, which has apoptosis-inducing activity yet does not resemble mouse AIF — at the level of the primary sequence — in this carboxy-terminal region, argues against this hypothesis. So, even at a resolution of 2.0 Å, AIF remains a mystery.

REFERENCE Maté, M. J. *et al.* The crystal structure of the mouse apoptosis-inducing factor AIF. *Nature Struct. Biol.* **9**, 442–446 (2002)

DEVELOPMENT

Fight to survive

Shaping the growing wings of *Drosophila melanogaster* requires 'cell competition' — a process in which cells that proliferate too slowly, for whatever reason, are eliminated. A report in *Nature* now indicates that cells in the developing wing disc compete for the survival factor Decapentaplegic (Dpp) in order to escape death.

Cells with so-called *Minute* (*M*) mutations grow slowly as they are defective in producing ribosomal proteins, so they provide a useful tool for studying cell competition. In the wing disc, heterozygous *Minute* mutant ($M^{-/+}$) cells expand less when wild-type $M^{+/+}$ cells are present, which indicates that there is a control mechanism that compensates for the comparatively faster growth of $M^{+/+}$ cells by eliminating the $M^{-/+}$ cells.

But $M^{-/+}$ cells, although slow to proliferate, are still viable, so how are they eliminated? One possibility was that they underwent apoptosis, and TdT-mediated dUTP nick-end labelling (TUNEL) assays showed this to be true. As c-Jun amino-terminal kinase (JNK) is known to be involved in wing-cell apoptosis, the authors studied whether it could be responsible for specifying the demise of $M^{-/+}$ cells — and showed that this was the case.

The authors then made the connection that the product of a gene called *brinker* (*brk*) activates JNK, but is itself repressed by Dpp, a protein that promotes growth in *Drosophila* wings. So, might the absence of Dpp cause an increase in Brk, which could then induce JNK-mediated apoptosis? This is indeed what the authors found. If *brk* is expressed inappropriately in regions in which it is normally absent or present at low levels, cells are eliminated. Consistent with this, $M^{-/+}$ clones that express a *brk*-null allele are not eliminated — they continue to proliferate more slowly than $M^{+/+}$ cells.

Co-expression of baculovirus p35 protein, which inhibits apoptosis, allows *brk*-overexpressing cells to survive, as does repression of JNK activity. Among the issues that remain to be addressed is how ectopic *brk* expression activates JNK signalling and how the Dpp signal becomes limiting in slow-growing cells. But the model for cell competition that is proposed by the authors extends beyond slow-growers, and Dpp is probably just one of several factors that cells fight for to survive.

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References and links

ORIGINAL RESEARCH PAPER Moreno, E., Basler, K. & Morata, G. Cells compete for Decapentaplegic survival factor to prevent apoptosis in *Drosophila* wing development. *Nature* **416**, 755–759 (2002)

WEB SITE

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