HIGHLIGHTS

APOPTOSIS

Jaws of death

Vultures prefer their dinner already dead; sharks, on the other hand, will tend to kill it first. During apoptosis, removal of the corpses has long been thought to follow the vulture model — the phagocytes move in only once cells are dead or dying. But two reports in *Nature* suggest that the engulfment machinery acts in a more shark-like manner, and that it is actively involved in the process of killing.

Both groups studied cell death in the nematode *Caenorhabditis elegans*, which requires a handful of 'killer' genes — *ced-3*, *ced-4* and *egl-1* — plus two (partially redundant) pathways for engulfment. The first involves the CED-1 and CED-7 proteins, involved in recognizing corpses, along with CED-6, which is thought to transduce signals from CED-1. The second involves CED-2, CED-5, CED-10 and CED-12, proposed to be involved in forming cytoskeletal extensions around the dying cell.

Horvitz and colleagues started with a screen to identify new killer genes, looking for mutations that would enhance the defect in death caused by a *ced-3* partial-loss-of-function mutation (*ced-3(n2427)*). Surprisingly, they found that mutations in all of the engulfment genes — from both pathways — enhanced the cell death defects of *ced-3(n2427)*. Further investigation revealed that although engulfment genes are not needed for the initiation of cell death, they are required for efficient execution once cell killing has begun. The authors also showed that these genes act within the engulfing cell (rather than in the dying cell), and that they do not seem to work by inhibiting the protective function of anti-apoptotic genes such as *ced-9* (the worm *Bcl-2* homologue).

Hengartner and co-workers took a different approach, using four-dimensional-Nomarski time-lapse video microscopy to follow the kinetic and morphological changes that occur during cell death. But they came to the same conclusion, showing that cells with a weak mutation in *ced-3* can survive if phagocytosis is blocked by mutation of the engulfment genes.

These two studies show that cells can be rescued from the jaws of death by mutating the genes that control engulfment. These results not only highlight the importance of the engulfing cells, but also challenge the previously held assumption that activation of the *ced-3* killing activity represents a 'point of no return' beyond which cells cannot survive. Indeed, both groups propose that this previously unsuspected function of the engulfing cells could ensure that cells in which the *ced-3* killing signal has been switched on do not recover after the initial stages of death.

Alison Mitchell

References and links

ORIGINAL RESEARCH PAPERS Reddien, P. W., Cameron, S. & Horvitz, H. R. Phagocytosis promotes programmed cell death in *C. elegans*. *Nature* **412**, 198–202 (2001) | Hoeppner, D. J., Hengartner, M. O. & Schnabel, R. Engulfment genes cooperate with *ced-3* to promote cell death in *Caenorhabditis elegans*. *Nature* **412**, 202–206 (2001)

FURTHER READING Green, D. R. & Beere, H. M. Mostly dead. *Nature* **412**, 133–135 (2001)