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APOPTOSIS

Which way will the Dicer roll?

> DCR-1 can fragment DNA by switching from being an RNase to a DNase

A defining characteristic of apoptosis is chromosomal DNA degradation by deoxyribonuclease (DNase)-mediated fragmentation. In mammals, these DNases include DNA fragmentation factor 40 kDa (DFF40) and its chaperone and inhibitor, DFF45. During apoptosis, caspases cleave DFF45, releasing DFF40 to cleave DNA. In *Caenorhabditis elegans*, however, no homologues of DFF40 and DFF45 have been identified, and it is unclear how apoptotic DNA degradation is initiated. Nakagawa *et al.* now reveal that in *C. elegans*, this process is mediated by the RNase Dicer 1 (DCR-1).

The nuclease CPS-6 (CED-3 protease suppressor 6) is involved in apoptotic DNA degradation, and CPS-6-mutant worms accumulate TUNEL-stained nuclei owing to a defect in resolving 3′ hydroxyl DNA breaks (which are labelled by TUNEL). The authors carried out RNA interference (RNAi)-mediated knockdown of nucleases in CPS-6-mutant worms and found that DCR-1 knockdown reduced the number of TUNEL-stained cells. DCR-1-deletion mutants showed a strong reduction of TUNEL-stained cells and contained fewer apoptotic cells, suggesting that DCR-1 is required to generate TUNEL-reactive DNA breaks in apoptotic cells and promote apoptosis upstream of CPS-6 and other nucleases.

DCR-1 processes double-stranded RNA (dsRNA) to generate small RNAs that are involved in gene silencing. Worms defective for other RNAi components do not show the same apoptotic phenotypes as DCR-1 mutants. So how does DCR-1 mediate the processing of DNA in apoptosis? Because apoptotic DNA degradation occurs downstream of caspases, the authors investigated whether DCR-1 is a direct substrate of the caspase cell death protein 3 (CED-3; a caspase 8 homologue) and found that it is. Interestingly, cleavage of DCR-1 by CED-3 occurs in one of the two RNaseIII domains in DCR-1 (which are required for binding and cleaving dsRNA), destroying the ability of DCR-1 to process dsRNA. The CED-3-mediated cleavage of DCR-1 generates a carboxy-terminal product that retains the other RNaseIII domain. Unlike full length DCR-1, truncated DCR-1 can generate 3′ hydroxyl DNA breaks, suggesting that DCR-1 undergoes a protease-mediated conversion from an RNase to a DNase.

Finally, as truncated DCR-1 can rescue the cell death defect of DCR-1 mutants, but expression of a *dcr-1* transgene lacking a CED-3 cleavage site cannot, truncated DCR-1 is sufficient to mediate the pro-apoptotic function of DCR-1. DCR-1-deletion mutants also exhibit aberrant vulva anatomy owing to defective microRNA production, which is rescued by expression of DCR-1 that cannot undergo CED-3-mediated cleavage, but not by expression of truncated DCR-1. DCR-1 therefore has independent functions in RNAi and apoptotic DNA fragmentation.

Thus, unexpectedly, in addition to processing small RNAs, DCR-1 can fragment DNA by switching from being an RNase to a DNase. It will be interesting to see whether this conversion occurs in the regulation of other nucleases and in mammals.

Debbie Walker

ORIGINAL RESEARCH PAPER Nakagawa, A. *et al.* Caspase-dependent conversion of Dicer ribonuclease into a death-promoting deoxyribonuclease. *Science* **328**, 327–334 (2010)
FURTHER READING Degterev, A. & Yuan, J. Expansion and evolution of cell death programmes. *Nature Rev. Mol. Cell Biol.* **9**, 378–390 (2008)