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Sci. STKE, Vol. 2003, Issue 190, pp. tw256, 8 July 2003.
[DOI: 10.1126/stke.2003.190.tw256]

APOPTOSIS:
A DNA Nuclease "Double Agent"

There is an arsenal of factors that survey DNA, repairing damage and, in some cases, also aiding replication. But when programmed cell death is initiated, DNA becomes fragmented and eventually degraded by mechanisms that are not fully understood. Parrish *et al.* have now identified an enzyme that appears to function in these two opposing events. In mammals and *Caenorhabditis elegans*, a nuclease called EndoG (CPS-6 in the worm) has been implicated in apoptotic DNA destruction. The enzyme resides in mitochondria but relocates to the nucleus where it appears to further resolve DNA breaks that have already been initiated. Worms lacking functional CPS-6 display delayed cell death and accumulation of TUNEL (terminal deoxyribonucleotidyl transferase-mediated dUTP-biotin nick end labeling)-reactive DNA breaks during development. Through a genome-wide functional screen based on RNA interference, the authors have identified a cell death-related nuclease called CRN-1 as a cofactor for CPS-6 in directing this conserved DNA degradation pathway. Ironically, CRN-1 is a homolog of mammalian flap endonuclease-1 (FEN-1), a DNA replication and repair factor. The study shows that *CRN-1* is ubiquitously expressed in nuclei throughout development, and larva with reduced *CRN-1* expression showed the same phenotype as the *CPS-6* mutant. Recombinant CRN-1 also associated with radiolabeled CPS-6, and both enzymes acted cooperatively in vitro--each enhanced the other's nuclease activity. In addition to the known endo- and exonuclease activities of FEN-1, CRN-1 further displayed another endonuclease activity that cleaves double-stranded DNA with a single-stranded gap. The authors propose that CPS-6 and CRN-1 are part of the overall apoptotic DNA degradation machinery that generates DNA nicks, gaps, and fragments. Association with CPS-6 in the nuclease could cause CRN-1 to switch from operating in DNA replication and repair to destroying its genome.

J. Z. Parrish, C. Yang, B. Shen, D. Xue, CRN-1, a *Caenorhabditis elegans* FEN-1 homologue, cooperates with CPS-6/EndoG to promote apoptotic DNA degradation. *EMBO J.* **22**, 3451-3460 (2003). [Abstract] [Full Text]

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- Jay Z. Parrish, Chonglin Yang, Binghui Shen, and Ding Xue
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  EMBO J. 22 (13) : 3451-3460. [Abstract] [Full Text] [PDF]