The Caspase Homolog *csp-1* Promotes Programmed Cell Death in a Subset of Cells that Die During Development

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Programmed cell death plays critical roles in metazoan development and in the removal of damaged, virus-infected or cancerous cells. 131 somatic cells die by programmed cell death during the development of the *C. elegans* hermaphrodite. Most of these deaths require the caspase CED-3, a cysteine protease that presumably promotes death via the proteolysis of downstream substrates. However, a small but detectable number of cells die in animals that completely lack *ced-3* activity, indicating the existence of a *ced-3*-independent death program. In addition to *ced-3*, the *C. elegans* genome contains three other caspase homologs: *csp-1*, *csp-2* and *csp-3*. To test the possible roles of the *csp* genes in programmed cell death, we isolated deletion alleles of *csp-1*, *csp-2* and *csp-3*. The deleted regions of *csp-1* and *csp-2* encompass their respective caspase active sites. CSP-3 does not contain an active site, indicating that it is likely not a protease; we isolated a deletion that removes most of the *csp-3* coding region. We tested *csp* mutants for the survival of cells that normally die and observed that mutations in single or multiple *csp* genes do not obviously affect programmed cell death. However, *csp-1* mutations enhance the death defects of partial loss-of-function *ced-3* and *ced-4* alleles, indicating that *csp-1* promotes programmed cell death. *csp-2* and *csp-3* mutations do not appear to modify the *ced-3* phenotype. Interestingly, we observed *csp-1* death-enhancing activity in only a subset of hermaphroditic cells fated to die, including some cells of the anterior pharynx. By contrast, the deaths of the RIM and RIC sister-cells as well as deaths that occur in the ventral cord and the postdeirid are not dependent on *csp-1*. Thus, *csp-1* might contribute to the deaths of a specific subset of cells that die during development. Expression of a *csp-1* cDNA from the neuron-specific *mec-7* promoter causes the ectopic deaths of touch neurons. These *csp-1*-mediated deaths occur in the absence of *ced-3* or *ced-4* function, indicating that the canonical pathway for programmed cell death might not be required for *csp-1* killing activity. To identify genes that regulate, activate or mediate *csp-1* killing function, we are screening for mutations that suppress or enhance the ectopic deaths caused by the *mec-7::csp-1* transgene.

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