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626. TWO NEW CELL-DEATH GENES AND ENGULFMENT CONTRIBUTE TO CELL KILLING

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The gene *ced-3*, which is the most downstream known component in the cell-death execution pathway, encodes a cysteine protease or caspase. How the CED-3 protease kills cells is unknown, and the identities and mechanisms of genes affecting the downstream processes of cell death has been a long-standing problem in the cell death field. Mutations in genes controlling cell-killing activities downstream of or parallel to *ced-3* might not have been previously identified because of their redundant nature. Animals with strong loss-of-function mutations in *ced-3* lack most if not all programmed cell deaths. However, there are weaker *ced-3* mutants that lack only a small percentage of programmed cell deaths. We reasoned that mutations in genes controlling subtle or redundant cell-killing activities might enhance a cell-killing defect conferred by a partial loss-of-function mutation in *ced-3*.

We performed a screen for enhancers of a partial *ced-3* loss-of-function allele and isolated 37 mutations. At least three are mutations in *ced-9*, two in *ced-4*, and six in *ced-3*. Nine mutations confer defects in cell-corpse engulfment, indicating a novel role for engulfment in promoting the killing process of programmed cell death. Because cell corpses are generated in engulfment-defective mutants, the proposed function of engulfment has long been solely the removal of unwanted apoptotic cell bodies. We found that engulfment mutations lead to the low-penetrance survival of cells that normally die in the presence of an intact core cell-killing pathway. Cell lineage analysis showed that cell death is typically initiated but occasionally incompletely executed in the absence of engulfment.

On the basis of complementation tests and map positions, we also defined at least two new cell-killing genes. Like engulfment mutants animals mutant for only these genes have subtle but detectable defects in programmed cell death. Genetic analyses place these genes downstream of or parallel to the anti-apoptotic gene *ced-9* and partially redundant with the cell-killing activity controlled by engulfment. We will discuss our characterization of these genes.