

Assisted Suicide: a Caspase- and Engulfment-Dependent Cell Death

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Programmed cell death is an evolutionarily conserved process that plays critical roles in animal development. During programmed cell death, proteases known as “caspases” are activated in the dying cell, which is engulfed by a neighboring cell and degraded. Almost all *C. elegans* cell deaths are believed to be “suicides” — *e.g.*, they are caspase-dependent and do not require engulfment. However, the death of the cell B.al/rapaav has been considered a potential example of “murder,” based on reports that this death depends on engulfment genes and the presence of the engulfing cell P12.pa. B.alapaav and B.arapaav are generated in the male tail during the late L3 stage. During the early L4 stage one of these cells dies, and the other survives and adopts an epithelial fate. The decision of which cell dies and which survives is stochastic. The cell that dies is engulfed by the neighboring cell P12.pa.

That the B.al/rapaav cell death is engulfment-dependent contrasts with most *C. elegans* cell deaths. We and others have found that mutations in the engulfment pathway cause both B.alapaav and B.arapaav to survive. However, we have found that if the engulfing cell P12.pa is ablated, the B.al/rapaav death fails to occur in approximately 60% of animals. We discovered that in the other 40%, the dying B.al/rapaav can be engulfed by other neighboring cells in the absence of P12.pa.

The B.al/rapaav cell death is known to be caspase-dependent, leading to the suggestion that cell-interactions might activate the cell-death pathway in the dying cell and hence that this death might be an “induced suicide.” We observed that when the B.al/rapaav cell death is blocked by engulfment defects or P12.pa ablation, the undead cell still initiates the cell-death pathway. Similar to cells that are about to die, the undead cells in engulfment mutants look round and cytoplasmically refractile as seen using Nomarski microscopy and expose phosphatidylserine on their surfaces. By contrast, the undead cell in mutants of the suicide pathway genes *egl-1*, *ced-9*, *ced-4*, or *ced-3* appear healthy, suggesting that in engulfment mutants the cell-death pathway fails at a point after caspase activation. *egl-1* and *ced-3* are expressed in the dying or undead cell in wild-type and engulfment-defective worms, and these genes are required for the B.al/rapaav cell death, suggesting that the core cell-death pathway is necessary but is not sufficient for this cell death. We conclude that this death is an “assisted suicide.” Studies of this assisted suicide should facilitate understanding of the cell-autonomous and cell non-autonomous mechanisms that sensitize cells to the death process not only in *C. elegans* but also in other organisms, including humans.