Life and Death Decisions: *ced-9* and Programmed Cell Death in *Caenorhabditis elegans*

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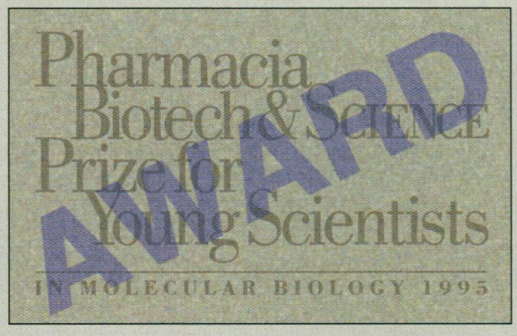
Programmed cell death (PCD), or apoptosis, is a conserved terminal differentiation program that multicellular organisms have evolved to get rid of cells that are not needed, that are in the way, or that are potentially dangerous. PCD can be equated with cell suicide in the sense that the dying cell plays an active role in promoting its own demise and removal from the organism (*1*).

Superficially, PCD is the opposite of cell division: Cell division creates a new cell, whereas PCD eliminates an already existing cell. However, these two processes also have much in common. (i) Both are very complex. In cell division the organism builds a whole new cell, whereas in PCD it has to precisely and cleanly get rid of a cell without damaging any of the surrounding cells. (ii) Both are tightly regulated. It is important that new cells are generated only when needed. Similarly, it is crucial that cells are eliminated only when necessary but that, if a cell has to be removed, the death process is swift and efficient.

The importance for the organism of maintaining tight control over which cells will live and which will die is underscored by the observation that breakdown in the regulation of PCD is associated with several types of cancer, with autoimmunity, and possibly with neurodegenerative diseases. Thus, understanding how PCD is controlled might lead to the introduction of new therapies for these diseases.

As the molecular mechanisms underlying PCD in mammals are sure to be very complex, it would be useful to study this process in a simpler organism, if possible by genetic means. The small nematode *Caenorhabditis elegans* is a particularly good choice for such an enterprise, as its pattern of cell death has been completely described. Of the 1090 somatic cells generated during C. *elegans* hermaphrodite development, exactly 131 undergo PCD (*2–4*). These deaths are highly reproducible from animal to animal. The same cells always die, and each cell dies at its own characteristic point in development.

Genetic studies have led to the isolation of many mutations that affect PCD in C. *elegans*. These mutations have identified over 14 genes, which have been placed into a genetic pathway (*1*, *5*, *6*). The activities of two genes, *ced-3* and *ced-4* (cell death abnormal), are essential for PCD in C. *elegans*. Mutations that inactivate either gene result in the survival of all 131 cells that normally die (*7*). Genetic studies have suggested that both *ced-3* and *ced-4* act as part of an endogenous suicide program that is activated within a cell that wishes to die (*8*).



How is this suicide program controlled such that only cells scheduled to die are eliminated and needed cells are left unscathed? My thesis work centered on the characterization of a C. *elegans* gene that provides at least part of the answer. This gene, *ced-9*, acts as a negative regulator of PCD and is required to protect cells that should be preserved from death (*9*). Genetic studies indicated that *ced-9* activity is both necessary and sufficient to block cell death. For example, either a gain-of-function mutation in the *ced-9* gene or an overexpression of wild-type *ced-9* results in the survival of cells that normally die. Conversely, mutations that inactivate *ced-9* cause many cells that normally live to undergo PCD. The *ced-9* gene appears to function by negatively regulating the activities of the *ced-3* and *ced-4* genes, keeping the cell death program off in cells that are scheduled to live. These results indicate that many, if not all, cells in C. *elegans* carry the information and machinery necessary to undergo PCD but that the program is usually suppressed through the activity of the *ced-9* gene.

How does *ced-9* act to prevent cell death? Cloning of *ced-9* revealed that the CED-9 protein shows significant similarity to the product of the mammalian oncogene *bcl-2* (*10*). Interestingly, the proposed function of *bcl-2* in mammals is identical to that proposed for *ced-9* in C. *elegans*: the prevention of cells from undergoing PCD. For example, overexpression of *bcl-2* prevents or delays the programmed death of immune cells subjected to a variety of stimuli, such as removal of growth factors, treatment with glucocorticoids, or irradiation with low doses of gamma rays (*11*). These similarities in both sequence and function strongly suggest that *bcl-2* is a vertebrate homolog of *ced-9*. Further support for this hypothesis has come from the observation that *bcl-2* can prevent PCD in C. *elegans* and can even substitute for *ced-9*, suggesting that the function of these two genes has also remained conserved at the molecular level (*10*, *12*).

What do these findings tell us about the nature and mechanisms of PCD? First, the involvement of *ced-9*/*bcl-2* family members in the control of PCD in both C. *elegans* and mammals suggests that the biological phenomenon of PCD probably predates the separation of nematodes and vertebrates and thus is of very ancient origin. Second, it seems reasonable to propose that not only *ced-9* but also the entire pathway in which *ced-9* acts has been conserved through evolution. [Strong evidence in support of this hypothesis has emerged from the study of the C. *elegans* cell death gene *ced-3* (*13*).] If so, there may well be a single molecular mechanism for PCD common to all metazoans.

That the death program is probably the same in worms and humans once again demonstrates that, at the cellular and molecular level, living organisms are more similar to each other than their dramatic morphological differences would suggest and shows the power of using "simple" models for the study of complex biological problems.

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