ROADS TO RUIN: APOPTOTIC PATHWAYS IN THE NEMATODE CAENORHABDITIS ELEGANS

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Summary

Apoptosis is a cell suicide program used by animals to get rid of cells that are either superfluous or potentially dangerous. The same gene families – caspases, Apaf-1-like molecules, and Bcl-2 family members – control apoptosis in organisms as diverse as humans, Drosophila, and C. elegans, underscoring the conserved nature of the apoptotic program. There are at least three death-inducing pathways in C. elegans. During embryonic and larval development, cell death is specified through transcriptional regulation of the BH3 domain gene egl-1. Similarly, in response to DNA damage, germ cells in the adult hermaphrodite activate a p53-dependent pathway that leads to apoptosis through transcriptional upregulation of the BH3 domain proteins EGL-1 and CED-13. By contrast, death of these same oocytes during differentiation is regulated by an egl-1-independent pathway. Apoptotic cells are recognized and engulfed by their neighbours, in a process that requires the function of several, evolutionarily conserved engulfment proteins. These proteins act in two partially redundant signaling pathways, which coordinately regulate the activation of CED-10/Rac and the subsequent cytoskeletal rearrangements required for cell corpse engulfment. In this review, I will outline our understanding of these various apoptosis-inducing and apoptosis-induced pathways.

Introduction

Millions of our cells commit suicide every day. Why? And how? Is this process important? If yes, important for what? And what happens if it goes awry? These are the questions that drew me to study the cellular process known as programmed cell death, or apoptosis. In this review,
I wish to briefly review what we have learned about the molecular basis of apoptosis, using the simple nematode *C. elegans* as a model organism.

The process of controlled cell death was initially discovered by developmental biologists. Indeed, and rather surprisingly, development is characterized not only by rapid cell growth and cell division, but also by high rates of cell death (Glücksmann, 1951). In addition to its role in development, controlled cell death is also used extensively for homeostatic functions, or to eliminate aberrant, damaged, or harmful cells (reviewed in refs Baehrecke, 2002; Jacobson et al., 1997; Meier et al., 2000; Vaux and Korsmeyer, 1999). Although several forms of cell death have been described in multicellular organisms (see ref. Vaux and Korsmeyer, 1999), I will focus here exclusively on apoptosis. Apoptotic cells usually present characteristic morphological changes, including chromatin condensation and DNA laddering, loss of mitochondrial membrane potential and of plasma-membrane phospholipids asymmetry, and detachment from the cellular matrix (Kerr et al., 1972; Wyllie, 1980; Wyllie et al., 1980). Because dysregulation of apoptosis is associated with several human pathologies, such as cancer, autoimmune diseases and neurodegenerative disorders, a better understanding of apoptosis could have interesting prognostic and therapeutic implications.

*Developmental cell death in *C. elegans*

During *C. elegans* development, exactly one hundred and thirty-one somatic cells in the hermaphrodite die as a result of apoptosis (Sulston and Horvitz, 1977; Sulston et al., 1983). Most of these deaths occur around the middle of embryogenesis, between 250 and 500 minutes after fertilization. Death is a rapid and transient process: cells that die are swiftly engulfed by their neighbors and digested. Thus, by the time that embryos hatch (~800 minutes), hardly any cell corpses can be observed any more.

Genetic studies have identified many genes that function in one of multiple steps in C. elegans apoptosis (reviewed by Kinchen and
Hengartner, 2005). Epistasis analysis of these mutations allowed Horvitz and colleagues to place the genes into a largely linear pathway by which apoptosis cell death is thought to proceed (Figure 1; Metzstein et al., 1998). This pathway can be subdivided into three components – execution of apoptosis, engulfment of the apoptotic cell corpse, and degradation of the corpse within the engulfing cell. Upstream of this common core pathway are genes that influence the decision of individual cell types whether to live or die (Kinchen and Hengartner, 2005). I refer the interested reader to a recent review that covers these genes in more details (Lettre and Hengartner, 2006).

**Figure 1**
The genetic pathway for programmed cell death in C. elegans.
Genetic screens identified many genes that function in C. elegans apoptosis. These genes divided the apoptotic program into three distinct steps: killing of cells that need to die, recognition and phagocytic engulfment of apoptotic cells, and degradation of engulfed cells. Positive (→) and negative (⊥) genetic interactions are shown. Dashed lines represent indirect interactions. All the genes shown here act in most if not all cell deaths. Genetic screens also identified genes that control the decision of individual cells whether to live or die. These cell type-specific apoptotic regulators act upstream of the killing step (not shown).

**Four genes identify a conserved genetic pathway for the induction of cell death**

Genetic screens for mutants with abnormal cell death patterns identified four genes that regulate all somatic cell deaths in *C. elegans: ced-
3, ced-4, ced-9 and egl-1 (ced, cell death abnormal; egl, egg laying-defective). Loss-of-function (lf) mutations in ced-3, ced-4, and egl-1 result in survival of almost all (~131) doomed cells, indicating that these three genes have proapoptotic functions (Desai et al., 1988; Ellis and Horvitz, 1986). By contrast, ced-9 has antiapoptotic activity because a ced-9 gain-of-function (gf) mutation blocks apoptosis, whereas ced-9(lf) worms die during early development due to excessive cell death (Hengartner et al., 1992). Epistasis studies ordered these genes into a pathway, with egl-1 acting as a negative regulator of ced-9, and ced-9 in turn negatively regulating ced-4 and ced-3 (Figure 2; Metzstein et al., 1998).

**Figure 2**
Activation of the *C. elegans* cell death machinery: a model.
Apoptosis in *C. elegans* is controlled by worm homologues of key regulators of apoptosis in mammals. In living cells, CED-4 dimers are sequestered by CED-9 on the outer surface of mitochondria and maintained in an inactive conformation. Cells destined to die by apoptosis express the BH3 domain protein EGL-1. Binding of proapoptotic EGL-1 to CED-9 induces a conformational change in the latter, resulting in the release of the CED-4 dimer from the CED-9/CED-4 complex. Once freed from CED-9’s inhibitory interaction, two CED-4 dimers associate into a tetramer and recruit proCED-3 molecules to form the worm apoptosome. CED-3 becomes activated (through conformational change and/or proteolysis), and apoptosis is triggered.
The molecular identification of *ced-3*, *ced-4*, *ced-9* and *egl-1* in the 1990s provided important clues to understand how the apoptotic machinery is engaged, not only in worms, but also in all other species. Indeed, all four genes code for conserved apoptotic regulators (Figure 2). Thus, *ced-3* encodes a protease of the caspase (cysteine aspartyl protease) family, a group of enzymes pivotal for their role in the execution of apoptosis (Riedl and Shi, 2004; Xue et al., 1996; Yuan et al., 1993). Whereas several hundred caspase substrates have already been described in mammals, CED-3 substrates are still largely elusive (Earnshaw et al., 1999). CED-4 is an adaptor protein similar to mammalian apoptotic protease-activating factor 1 (Apaf-1; Yuan and Horvitz, 1992). Like their mammalian homologues, CED-3 and CED-4 oligomerize to form an apoptosome-like complex, and this interaction is required for CED-3 activation and apoptosis (Rodriguez and Lazebnik, 1999; Yang et al., 1998).

*ced-9* and *egl-1* encode members of the Bel-2 family: CED-9 is an anti-apoptotic protein with four Bcl-2 homology (BH) domains, whereas EGL-1 is a proapoptotic BH3-only domain protein (Conradt and Horvitz, 1998; Hengartner and Horvitz, 1994a; Hengartner and Horvitz, 1994b). In mammals, the Bcl-2 family includes pro- and antiapoptotic proteins, which all share at least one BH domain; these proteins play key roles in the control of apoptosis at the level of mitochondria (reviewed in Cory et al., 2003; Danial and Korsmeyer, 2004). The *C. elegans* genome encodes only three Bel-2 family members: CED-9, EGL-1 and the BH3-only domain protein CED-13. In contrast to EGL-1, CED-13 does not play a role in developmental apoptosis in worms; its only known function to date is a modest role in promoting germ cell death following DNA damage (Figure 3; Schumacher et al., 2005).

**Molecular model of apoptosis activation in C. elegans**

The execution of apoptosis in *C. elegans* is regulated through a series of direct protein-protein interactions between the four main players described above (CED-3, CED-4, CED-9 and EGL-1; Figure 2). The
immediate cause of death in C. elegans is the proteolytic cleavage of CED-3 from its precursor form (proCED-3) into the processed, active enzyme. For this activation to occur, multiple proCED-3 molecules must associate with a CED-4 tetramer into a large oligomeric complex known as the C. elegans apoptosome. In the absence of apoptotic stimuli, however, CED-4 does not exist as a tetramer, but rather as an inactive dimer, sequestered on the outer surface of mitochondria through a direct protein-protein interaction with mitochondria-bound CED-9 (Figure 2; James et al., 1997; Spector et al., 1997; Wu et al., 1997a; Wu et al., 1997b). This sequestration (and possibly other limitations) prevents CED-4 from assembling with and activating CED-3. In the 131 cells destined to die, developmental cues lead to the expression of the proapoptotic EGL-1 protein. EGL-1 then binds via its BH3 domain to CED-9 and induces a conformational change that disrupts the CED-4/CED-9 interaction. Once released, CED-4 transloc-

Figure 3
The pathway for dsDNA break-induced germ cell apoptosis in C. elegans. Double-strand (ds) breaks in DNA, generated either through ionizing radiation or as the result of aberrant meiotic recombination, are sensed by several protein complexes that are highly conserved through evolution, and found from yeasts to humans. For example, HUS-1 and MRT-2 are part of the conserved 9-1-1 complex, a heterotrimer thought to be loaded onto sites of DNA damage. Cell cycle progression delay facilitates the repair process. The C. elegans p53 homolog, CEP-1, is responsible for the transcriptional activation of at least one BH3-only domain protein, EGL-1, that leads ultimately to the activation of the apoptotic machinery.
ates from mitochondria to the outer surface of the nuclear membrane, where it recruits CED-3 and activates apoptosis (Chen et al., 2000; Conradt and Horvitz, 1998; del Peso et al., 2000; del Peso et al., 1998; Seshagiri and Miller, 1997; Yang et al., 1998).

Conservation of the genetic pathway of apoptotic cell death between C. elegans and mammals

While the genetic pathways for apoptosis appear quite similar between C. elegans and higher metazoans (Figure 2), the biochemical mechanism by which the caspase is activated is, rather surprisingly, quite distinct. While CED-9 and Bcl-2 are both localized to the mitochondria (Chen et al., 2000; Hockenbery et al., 1990), the mammalian CED-4 homologue, APAF1, does not associate with Bcl-2 and is not localized to the mitochondrion; instead, APAF1 has been suggested to exist in a basal complex with Caspase-3 (Hausmann et al., 2000). In worms, transcriptional regulation of the BH3-only protein EGL-1 appears to be the major mechanism of control of developmental cell death, with EGL-1 displacing CED-4 from CED-9, and released CED-4 activating the CED-3 caspase and induction of cell death. By contrast, assembly of the mammalian apoptosome is regulated via controlled release of cytochrome c (cyt c) from the mitochondria – a step that is regulated either directly or indirectly by the Bcl-2 family (Hengartner, 2000; Zou et al., 1997). There is no known role for mitochondrial permeabilization and release of cytochrome c in the activation of CED-4 activity. Significantly, and consistently with this observation, CED-4 differs from APAF1 in that it does not have a cyt c interaction motif. Thus, it appears that while the proteins that mediate cell death have been conserved during evolution, they have also developed new abilities, and the control of cell death in mammals has become more complex.

Programmed cell death in the hermaphrodite germ line

The hermaphrodite gonad in C. elegans is a set of two bilaterally symmetrical tubes composed of a syncytium of germ cells surrounded
by the somatic sheath cells and joined together through a common uterus (Sulston, 1988). The gonad of the worm begins to develop in the early larval stages, when the progenitor cells Z(1-4) begin dividing. Z2 and Z3 will become the germ cells, while Z1 and Z4 generate the somatic gonad, which surrounds the germ cells and isolates them from the rest of the worm (Kimble and Hirsh, 1979).

Like the reproductive tissues of higher organisms, including humans, cells in the germ line of *C. elegans* undergo extensive programmed cell death. Unlike the deaths that occur in the soma during development, death in the germ line does not follow a set pattern; there is no fixed lineage specifying which cells will live or die (Gumienny et al., 1999). The cell death machinery is largely conserved between developmental cell death and germ line cell death. The main difference, however, is that there appears to be no requirement for EGL-1 activity during physiological cell death in germ cell death; *egl-1(lf)* mutants show wild type levels of apoptotic death in the hermaphrodite germ line (Gumienny et al., 1999). In addition, a *ced-9(gf)* mutation that affects the CED-9/EGL-1 interaction also has little effect on germ cell death. This would suggest that there must be a novel mechanism for controlling the progression of programmed cell death in the hermaphrodite germ line independent of the BH3-only domain protein EGL-1. Indeed, we and others have been able to identify a number of genes that appear to control physiological germ cell death (Boag et al., 2005; Kritikou et al., 2006; Lettre et al., 2004; Navarro et al., 2001). Intriguingly, many of these genes encode predicted RNA binding proteins. This observation suggests that perhaps apoptosis in the *C. elegans* is regulated via control of mRNA translation and/or metabolism.

*Genotoxic stress induces germ cell apoptosis*

An effective response to DNA damage is essential for genomic stability and long-term survival of an organism. Defects in genes that mediate response to DNA damage, such as p53, have been implicated in numerous diseases and in predisposition to various cancers. My research group could recently show that *C. elegans* can be used with success
to study the molecular pathways that mediate DNA damage-induced apoptosis (Gartner et al., 2000).

Genotoxic insults activate two distinct responses in the hermaphroditic germ line. First, mitotic cells arrest in order to repair damage induced by irradiation. Second, meiotic nuclei that are too damaged to survive undergo programmed cell death and are efficiently removed by the engulfment apparatus (Gartner et al., 2000).

The molecular mechanisms that mediate the response to genotoxic insults are just beginning to be dissected in *C. elegans*. Both genetic and reverse genetic approaches have been successful in identifying genes important for these responses. For example, forward genetic screens led to the demonstration that *hus-1* and *mrt-2*, genes encoding subunits of a conserved PCNA-like heterotrimeric clamp, are required for apoptosis in response to double strand DNA (dsDNA) breaks (Ahmed and Hodgkin, 2000; Hofmann et al., 2002). Conversely, reverse genetic experiments showed that CEP-1 (*C. elegans* p53 homologue), the worm homologue of the mammalian p53 tumor suppressor gene, is required for DNA damage-induced apoptosis, but not cell cycle arrest (Derry et al., 2001; Schumacher et al., 2001).

How does CEP-1/p53 promote apoptosis? We found that transcription of *egl-1* is dependent on functional *cep-1*, suggesting that CEP-1 might act as a transcriptional activator of *egl-1* (Hofmann et al., 2002). Interestingly, p53 has been shown to directly regulate transcription of BH3-only domain containing proteins in mammals following genotoxic stress. Thus, the pathway that mediates DNA damage-induced apoptosis is surprisingly similar between nematodes and mammals (Figure 3).

*Engulfment and degradation of the apoptotic cell*

Engulfment is the process by which cells that have died, either by apoptotic or necrotic means, are cleared, usually by professional phagocytes or bystander cells (Kerr et al., 1972). *C. elegans*, which has no professional phagocytes, uses cells that are immediately adjacent to the
apoptotic cell to remove it, usually within a hour of the onset of apoptosis (Robertson and Thomson, 1982). Rapid elimination of apoptotic cells has been suggested to be important to prevent autoimmunity. Indeed, in mammals, secondary necrotic lysis of unengulfed apoptotic cells can result in local inflammation and exposure of auto-antigens to immune cells (Mevorach, 1999; Tan, 1994). The ability to remove apoptotic cells and prevent exposure of self-epitopes would thus appear to be essential to averting inappropriate immune responses and diseased states in the animal.

Genetic screens in *C. elegans* identified several genes which, when mutated, result in the accumulation of persistent apoptotic cell corpses (Figure 4). These mutations define two signaling pathways, which appear to act at least partially in parallel to each other, as double mutants defective in both pathways show a significantly stronger persistent cell corpse phenotype (Ellis et al., 1991; Hedgecock et al., 1983). By contrast, double mutants between genes within the same pathway are only as strong as the stronger single mutant (Ellis et al., 1991). Interestingly, mutations between the two pathways do not entirely block engulfment, suggesting that there may be a third salvage pathway that inefficiently removes dead cells throughout the life of the worm.

The first engulfment signaling pathway is comprised of CED-1, CED-6, and CED-7. These three proteins are thought to act early in the activation of a signal transduction cascade (Figure 4). CED-1 is an integral membrane protein, which potentially functions as a receptor that recognizes dying cells. Interestingly, CED-1 is homologous to the SREC (Zhou et al., 2001b) and the CD91/LRP scavenger receptors, which has been previously implicated in the engulfment of apoptotic cells in cell culture systems (Ogden et al., 2001); antibody-mediated cross linking of the CD91/LRP receptor will stimulate uptake of bound erythrocytes (Ogden et al., 2001). Similarly, the only known receptor for engulfment in *Drosophila, croquemort/CD36*, is a scavenger receptor-family molecule (Franc et al., 1996), suggesting a conserved mechanism for the recognition of apoptotic cells by scavenger receptor family members. The ligand that CED-1 recognizes is still unknown; SREC has been implicated in binding acetylated low density lipoproteins (Ac-LDLs)
(Adachi et al., 1997), suggesting the CED-1 ligand may be a modified lipid.

Domain analysis of CED-6 has identified a PTB (phosphotyrosine binding) domain and a PxxP motif (involved in interactions with SH3 domains), supporting a function as an adapter protein; the interacting partner that utilizes the PxxP motif has yet to be identified. Both CED-1 and CD91/LRP have NPXY motifs that interact with CED-6 and its mouse orthologue GULP, respectively, suggesting that CED-1 uses the CED-6 adaptor protein to transmit a recognition signal into membrane movement. Consistent with this hypothesis, overexpression of CED-6 can partially rescue the engulfment defect of ced-1 mutants (Liu and Hengartner, 1998). The small adaptor protein CED-6 is thought to homodimerize after activation via a leucine zipper motif to induce engulfment by an as yet uncharacterized mechanism involving the CED-10 Rac GTPase (Su et al., 2000).

CED-7, like CED-1, is a plasma membrane protein. CED-7 is unique among the known engulfment genes in that it is required on both the engulfing as well as the dying cell for function in engulfment (Wu and Horvitz, 1998a). The mammalian CED-7 homologue, ABCA1, was cloned by homology to ABC transporters, and later discovered to be involved in the rearrangement of plasma membrane phospholipids (Hamon et al., 2000). One of the characteristics of mammalian apoptosis is the relocation of phosphatidylserine (PS), a membrane phospholipid normally found only in the inner membrane leaflet, to the outer leaflet of the cell membrane (Fadok and Henson, 1998). ABCA1 has been proposed to promote this PS translocation in both the engulfing and the dying cell, mediating an as yet uncharacterized recognition event. Whether CED-7 performs a similar function remains to be determined.

The second pathway in the worm that functions in engulfment is comprised of three genes: ced-2/crII, ced-5/dock180, and ced-12/elmo. These three genes encode a bipartite RacGEF, which we and others have shown acts on C. elegans CED-10/Rac1 (Kinchen and Hengartner, 2005). The most upstream member of this pathway is CED-2/CrII.
CrkII was first discovered in mammalian cells as a viral oncogene, v-Crk, that induces cell migration and increases metastatic potential. CrkII is essentially an adapter molecule comprised of one SH2 domain and two SH3 domains. The N-terminal CED-2/CrkII SH3 domain has been shown to bind to CED-5/Dock180 (Matsuda et al., 1996), through which a signal is transduced to Rac, leading to reorganization of the actin cytoskeleton (Kiyokawa et al., 1998). The order of this pathway has been confirmed in C. elegans, with ced-2/CrkII and ced-5/Dock180 functioning upstream of ced-10/Rac1 (Reddien and Horvitz, 2000; Wu and Horvitz, 1998b). Functional conservation of this signaling complex in engulfment in mammalian cells has also been shown (Albert et al., 2000; Gumienny et al., 2001).

CED-5/DOCK180 interacts with Rac1 via a basic region at the C-terminus (Kobayashi et al., 2001), and with CED-12/ELMO via a SH3 domain at the N-terminus (Gumienny et al., 2001; Wu et al., 2001; Zhou et al., 2001a). Recently, a particular domain at the C-terminus of Dock180 has been identified, named the DOCKER domain, which specifically binds to nucleotide free Rac1 and specifically loads GTP in order to activate Rac1 (Brugnera et al., 2002). Indeed, CED-12/ELMO appears to function in the stabilization of the Dock180::nt-free Rac transition state, functioning as a bipartite RacGEF with CED-5/Dock180.

A receptor has yet to be discovered that signals to the CED-2/5/12 signaling complex. In mammalian cells, integrin receptors (\(\alpha_v\beta_3\) and \(\alpha_v\beta_5\)) act upstream of these proteins, with p130Cas bridging the activated integrin receptor and the CrkII adaptor protein (Albert et al., 2000); this does not seem to be the case in C. elegans, however, as integrin mutants show little defect in engulfment of apoptotic corpses (Gumienny et al., 2001). Integrin receptor function in engulfment in mammalian tissue culture systems may be a case where increased adhesion to cells also increases the number of cells that are engulfed; further study to ascertain this difference is needed.

We could recently show that the two signaling pathways that I described above converge at the level of CED-10/Rac1 (Kinchen et al., 2005).
Our current data suggest that the two pathways cooperate to recruit CED-10 to the right region on the plasma membrane, and then stimulate GTP loading, leading to a selective rearrangement of the actin cytoskeleton in the direction of the apoptotic cell that needs to be engulfed (Gumienny et al., 2001; Wu et al., 2001; Zhou et al., 2001a). The small GTPase Rac has been implicated in rearrangement of the actin cytoskeleton and remodeling of the plasma membrane in response to extracellular stimuli, known as ‘membrane ruffling’. Rac, like other GTPases, cycles between a GDP-bound, inactive conformation and a GTP-bound, active conformation based on molecules that promote GTP exchange (GAPs or GTPase activating proteins), proteins that promote GTP/GDP hydrolysis (GEFs or guanine nucleotide exchange factors), and proteins that keep GDP from dissociating (GDIs or guanine nucleotide dissociation inhibitors). Our data strongly suggest that Dock180 (the CED-5 homologue) is the RacGEF for this process (Brugnera et al., 2002). By contrast, the nature of the GAP (and possibly the GDI)

Figure 4
Two pathways converge to mediate the removal of apoptotic cells in C. elegans. At least two partially redundant signaling pathways mediate engulfment of apoptotic cells in C. elegans. The two pathways cooperate to activate CED-10/Rac, which then promotes actin cytoskeleton rearrangements and «migration» of the engulfing cell around the apoptotic cell corpse. Both signaling pathways are conserved: mammalian homologs of these genes have also been implicated in the removal of apoptotic cells. Many steps in the signaling cascade shown are still unclear (question marks).
involved in phagocytosis is still unknown. Similarly, the Rac effectors that function in engulfment in *C. elegans* remain to be identified.

**Suicide vs. Murder – suggestions of phagocyte-mediated cell killing**

A picture of engulfment as more than just a janitor has recently begun to emerge. This work comes from many sources and suggests that, in worms, apoptosis is not always determined by the core apoptotic machinery (CED-3, -4, -9, and EGL-1), but rather can be mediated by neighboring cells.

Observations from my laboratory and others have shown that the programmed cell death pathway is not as linear as our models would have us believe (Figure 2). Indeed, in weak *ced-3* mutants, cells that are not visibly apoptotic can be ‘murdered’ dependent on the engulfment machinery (Hoeppner et al., 2001; Reddien et al., 2001). This close interplay between genes involved in apoptosis and genes involved in engulfment suggests that the linear pathway we conveniently use to think about programmed cell death is not entirely correct, and that there is some overlap between what has previously been thought of as two distinct processes. This could be due to early processing of the ‘eat-me’ signal by the activated CED-3 caspase, such that a late activation of an caspase inhibitor may be able to stop apoptosis of the cell, but not the exposure of the ‘eat-me’ signal (Hoeppner et al., 2001). The engulfment machinery would then remove these cells, without the semi-apoptotic cell undergoing the phenotypic stages of apoptosis. Alternately, the ‘eat-me’ signal may be generated in a caspase-independent manner. Under this scenario, the cell could be efficiently removed even when activation of CED-3 was suboptimal. Further characterization of engulfment mediated cell death should provide an answer.

**Conclusion**

Genetic studies of apoptosis in *C. elegans* have led, over the last 20 years, to the development of many important concepts about how
apoptosis works. However, it is clear that what we know pales in comparison with what we still ignore. The fact that a large fraction of the genes that control cell death in C. elegans are conserved and also regulate apoptosis in mammals suggests that much useful knowledge about ourselves can still be extracted from a dedicated study of this humble crawler. I hope that this concise overview will have given the reader a bird's view of the terrain surveyed so far, and a thirst for more adventuring. Let us learn from the worm!

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