36. A GENETIC PATHWAY FOR THE CONTROL OF THE SEXUALLY DIMORPHIC DEATHS OF THE CEM NEURONS

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During wild-type hermaphrodite development, 131 somatic cells undergo programmed cell death. While many genes involved in the execution of cell death have been identified, the mechanisms that control the commitment of specific cells to undergo programmed cell death are poorly understood. To date, mutations in four genes, *ces-1*, *-2*, and *-3* (cell death specification), and *egl-1*, have been found to affect specifically the deaths of particular cells. *ces-1* and *ces-2* encode transcription factors. Mutations in a transcriptional regulatory element of *egl-1*, which encodes a protein required for all somatic cell deaths, cause inappropriate expression of *egl-1* in the HSNs in hermaphrodites, resulting in their deaths.

To identify additional genes that act in the specification of cell death, we have performed a genetic screen for hermaphrodites in which the male-specific CEM neurons fail to undergo programmed cell death. The CEM neurons die during normal hermaphrodite development but survive and differentiate in males. The reporter *pkd-2::gfp* (kindly provided by Maureen Barr and Paul Sternberg) is expressed in the CEMs of males and in the CEMs of *ced-3(n717)* hermaphrodites, which are defective in essentially all programmed cell death. By using the *pkd-2::gfp* reporter as a marker for CEM survival, we were able to screen efficiently for survival of a single cell using a dissecting microscope equipped with fluorescence optics. A screen of 60,000 mutagenized haploid genomes yielded at least 154 independent mutations that cause survival of the CEMs, including 42 alleles of known cell-death genes and at least 64 mutations that cause sexual transformation. Among the isolates from our screen are nine mutations in four genes either new or not previously known to control CEM survival. These four genes act in three distinct stages of the CEM death decision. A new locus, defined by two isolates, acts in the determination of the sexual identity of the CEMs. This gene appears to be required to repress masculinization and acts upstream in the sex determination pathway to control both CEM death and HSN survival. Two genes seem to act to determine faithful expression of the CEM identity. Two isolates are alleles of the *Pax6* homolog *vab-3*, which is apparently required for efficient CEM cell death. Two isolates define a gene required for proper neuronal differentiation; these mutants are kinker Unc and have ventral cord defects, in addition to their defect in CEM death. Interestingly, mutants in this gene are very weakly Vab, and these mutations cause a strong Vab phenotype in combination with weak alleles of *vab-3*. On the basis of their broader defects in neuronal differentiation, we propose that these two genes are required for proper CEM differentiation rather than for specifically controlling CEM death. Finally, a new locus, defined by three isolates, causes strong CEM survival but not other obvious defects, and is not suppressed by mutations in sex determination. This gene may act downstream of sex determination and the determination of CEM identity to control CEM programmed cell death.