A Genetic Pathway for M4 Sister Cell Death

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In *C. elegans*, 131 somatic cells undergo programmed cell death during wild-type hermaphrodite development. While many genes involved in programmed cell death have been identified, it remains unclear how a particular cell is specified to survive or to die by programmed cell death. To identify genes involved in the specification of programmed cell death, we screened for mutants defective in the deaths of the sisters of the pharyngeal M4 motor neurons. The M4 neuron is generated during embryonic development and survives to regulate muscle contraction in the pharynx, while the M4 sister undergoes programmed cell death.

A genetic screen and a candidate-based approach identified five genes, *ceh-32*, *ceh-34*, *eya-1*, *pig-1* and *sptf-3*, required for M4 sister cell death. *ceh-32* and *ceh-34* encode Six class homeobox proteins. In *Drosophila*, the Six family homeobox gene *sine oculis* is a component of a conserved transcriptional network that specifies eye development. This transcriptional network includes *eyeless*, *eyes absent* and *dachshund*. We found that *C. elegans eya-1 eyes absent* is defective in M4 sister cell death but that *vab-3 eyeless* and *dac-1 dachshund* are not, suggesting that at least some of the components of this transcriptional network are required for M4 sister cell death in *C. elegans*. From the genetic screen we also isolated an *egl-1* mutant with two mutations in the 5' promoter of *egl-1*. One of these mutations, *n4820*, causes the M4 sister cell death defect, and this mutation affects a *sine oculis* consensus binding sequence. Gel-shift experiments showed that CEH-34 binds to this *sine oculis* consensus binding site in the *egl-1* promoter and that the *n4820* mutation disrupts this binding. Furthermore, *ceh-34(n4796)*, *eya-1(ok654)* and *egl-1(n4820)* mutants all are defective in M4 sister and I1 sister cell deaths but not in VC, RIM or RIC sister cell deaths. These results suggest that CEH-34 directly activates *egl-1* expression to control M4 sister and I1 sister cell deaths.

pig-1 encodes a serine/threonine kinase and affects asymmetric neuroblast divisions (Cordes *et al.,Develop.* 133, 2747, 2006), and *sptf-3* encodes a Sp1 family transcription factor. *pig-1(gm344)* additively enhances the M4 sister cell death defect of *ceh-34(n4796)*, *eya-1(ok654)* and *egl-1(n4820)*, and *pig-1* does not have a significant I1 sister cell-death defect, suggesting that *pig-1* functions independently of *ceh-34*, *eya-1* and *egl-1*.

We are analyzing how these genes interact to control M4 sister cell death.

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