The *BarH* Class Homeodomain Gene *ceh-30*Controls Sexually Dimorphic CEM Neuron Survival Independently of CED-9 Bcl-2

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We identified the *BarH* class homeodomain transcription factor gene *ceh-30* as a cell-specific regulator of the sexually dimorphic survival of the male-specific CEM sensory neurons. *ceh-30* activity in the CEMs is directly controlled by the sex-determination protein TRA-1. The cell-protective role of *ceh-30* is likely evolutionarily conserved: expression of the mouse *ceh-30* homolog *Barhl1* can rescue the CEM survival defect of *ceh-30(*lf*)* males, and *Barhl1* knockout mice show a defect in the survival of differentiated sensory neurons highly reminiscent of the defect in CEM neuron survival of *ceh-30(*lf*)* males.

In the evolutionarily conserved core pathway for the execution of programmed cell death in *C. elegans*, the BH3-only Bcl-2 family killer protein EGL-1 negatively regulates the cell-protective Bcl-2-like protein CED-9. CED-9 acts through the adaptor CED-4 Apaf-1 to negatively regulate the caspase CED-3, which performs the cell-killing function. Nearly all regulators of programmed cell death known to function in *C. elegans* or in vertebrates act through the Bcl-2 superfamily. In particular, most regulators of specific cell deaths in *C. elegans* act through transcriptional control of the CED-9 regulator *egl-1*, and these regulators are ineffective in animals lacking *ced-9* function.

The deaths of the CEM neurons in hermaphrodites normally require the upstream killer gene *egl-1*. However, when we activated the cell-death program by loss of function of the EGL-1 target CED-9, the deaths of the CEM neurons were regulated by sexual dimorphism and by *ceh-30* almost as well as they were in wild-type animals, even in animals also lacking *egl-1* function. Thus, although *egl-1* function is normally needed for the hermaphrodite CEMs to die, sex determination, acting through *ceh-30*, regulates these deaths downstream of or in parallel to *egl-1* and *ced-9*. *ceh-30* might therefore determine whether the CEMs are sensitive to the activation of programmed cell death, whether caused by expression of *egl-1* or by loss of *ced-9*. This regulation by *ceh-30* does not require *bir-1* or *bir-2*, the only known *C. elegans* homologs of vertebrate proteins that regulate apoptosis independently of the Bcl-2 superfamily. *ceh-30* appears to regulate cell survival by a mechanism distinct from any known to exist in vertebrate apoptosis. As the cell-protective function of *ceh-30* appears to be evolutionarily conserved, we propose that the mouse *ceh-30* homolog *Barhl1* regulates apoptosis by a similarly novel mechanism.

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