Translational Regulators GCN-1 and ABCF-3 Maternally Contribute to General Programmed Cell Death

Takashi Hirose and Bob Horvitz
HHMI, Dept. Biology, MIT, Cambridge, MA 02139 USA

In *C. elegans*, 131 somatic cells undergo apoptosis during wild-type hermaphrodite development. Extensive genetic screens have identified the BH3-only gene *egl-1*, the *BCL-2* homolog *ced-9*, the *APAF-1* homolog *ced-4* and the caspase gene *ced-3*, which together define an evolutionarily conserved cell-death execution pathway that drives most somatic cell deaths. Most screens for cell-death mutants have been performed by examining the F2 generation, so it is possible that maternal-effect genes involved in the cell-death execution pathway remain to be identified.

From a genetic screen for mutations that cause a defect in the death of the sister of the pharyngeal M4 motor neuron, we identified *ceh-32*, *ceh-34*, *eya-1*, *sptf-3* and *pig-1*, all of which promote cell-type specific apoptosis. We also identified *gcn-1* and *abcf-3* and showed that these genes promote apoptosis of most somatic cells. Maternal *gcn-1* and *abcf-3* are sufficient and partially required for the M4 sister to undergo apoptosis. These results suggest that maternally-contributed *gcn-1* and *abcf-3* function plays an important role in promoting apoptosis of possibly all somatic cells. GCN-1 and ABCF-3 proteins are highly conserved. The *S. cerevisiae* homologs of GCN-1 and ABCF-3 physically interact and are required for the phosphorylation of a conserved serine residue of eukaryotic initiation factor 2α (eIF2α), the phosphorylation of which causes a general inhibition of protein translation and the specific activation of translation of select mRNAs. We find that the *C. elegans* GCN-1 and ABCF-3 proteins interact *in vivo* and are required for the phosphorylation of eIF2α, suggesting a conserved function in translational regulation. To determine where GCN-1 and ABCF-3 function in the cell-death pathway, we performed genetic analyses of the interactions of *gcn-1* and *abcf-3* with known cell-death genes in the regulation of M4 sister cell death. GCN-1 and ABCF-3 act independently of *ced-9* and function in parallel to *ceh-34*, *sptf-3* and *pig-1*. We propose that GCN-1 and ABCF-3 act together to promote apoptosis generally through translational regulation in a pathway distinct from the known cell-death pathway.

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Research area: Cell death and neurodegeneration
No. characters (counting spaces): 2176