Translational Regulators GCN-1 and ABCF-3 Act Together to Promote Developmental and DNA Damage-Induced Germ-Cell Deaths

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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 developmental somatic cell deaths and DNA damage-induced germ-cell deaths. While the transcriptional induction of apoptotic genes is crucial to initiating an apoptotic program, less is known about translational controls in cell death.

From a genetic screen for mutations that cause a defect in the death of the sister of the pharyngeal M4 motor neuron, we identified the translational regulators GCN-1 and ABCF-3, which promote M4 sister cell death during embryonic development. GCN-1 and ABCF-3 are not obviously involved in the physiological germ-cell deaths that occur during oocyte maturation. By striking contrast, these proteins play an essential role in the deaths of germ cells in response to ionizing irradiation. 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), resulting in the specific activation of translation of select mRNAs. We found 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 control.

To identify the translational targets of GCN-1 and ABCF-3, we performed mRNA-seq and ribosome profiling (Ribo-seq) analyses, which together generated a quantitative and comprehensive list of genes regulated by GCN-1 and ABCF-3 at the translational level. These analyses showed that *gcn-1* and *abcf-3* do not have major effects on the translation of the known cell-death genes but do control translation of several candidates that might be involved in the M4 sister cell death and in germ-cell deaths induced by ionizing radiation. We are testing if these candidates are involved in these cell deaths. We propose that GCN-1 and ABCF-3 act together to promote developmental and DNA damage-induced germ-cell deaths through translational control in a pathway distinct from the known cell-death pathway.

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