1999 International Worm Meeting abstract 795

The inhibitor-of-apoptosis (IAP)-like protein BIR-1 is required for cytokinesis

EK Speliotes[1], A Uren[2], D Vaux[2], HR Horvitz[1]

[1] HHMI, Dept. Biology, MIT, Cambridge, MA 02139.
[2] WEHI, Melbourne, Australia.

Determining whether common mechanisms mediate aspects of mitosis and apoptosis is fundamental to understanding both normal biology and disease. We are studying *bir-1* and *bir-2*, two genes that encode proteins with sequence similarity to the evolutionarily conserved IAP family of proteins, some of which protect against programmed cell death (PCD) when overexpressed. The normal functions of IAPs and how these functions relate to the ability of this family of proteins to protect against PCD, if at all, remain to be determined.

bir-1(RNA*i*) embryos have defects in a late stage of cytokinesis and arrest with multinucleate cells. In *bir-1*(RNA*i*) embryos, meiotic divisions are completed, but polar bodies are not extruded; multiple nuclei within a common cytoplasm may stay separate from one another and divide asynchronously or may fuse to form large polyploid nuclei. During mitosis, condensed chromosomes from polyploid nuclei are separated by multipolar spindles. Other events including pronuclear migration, pseudocleavage, and the timing and position of the first mitotic division appear to be unaffected. *bir-1*(RNA*i*) embryos generated by *ced-3* and *ced-4* mutant mothers also arrest, suggesting that this phenotype is not caused by ectopic activation of a cell death program. Animals homozygous for the *bir-1* deletion *n3329* produce multinucleate embryos consistent with the RNA*i* results. *bir-1*(*n3329*) homozygotes are also variably thin, Unc, Mig(DTC), Pvl, Ste and can burst at the vulva, as can animals that escape the embryonic lethality following RNA*i*, suggesting that *bir-1* may be needed for normal development of many tissues. Animals homozygous for a deletion of *bir-2* (provided by R. Barstead) and *bir-2*(RNA*i*) animals do not show any gross defects.

bir-1 is most similar to human survivin, a G2/M-upregulated, spindle-associated protein that protects against PCD and is expressed in high-grade tumors. We are currently testing whether survivin can substitute for *bir-1* in worms, characterizing single and double *bir* mutants, determining the expression patterns of BIRS, and analyzing BIR two-hybrid interacting proteins. We hope our studies of *birs* will help us to better understand cytokinesis and the mechanism(s) of action of the IAPs.