A Screen for Genes Synthetically Lethal with lin-35 Rb

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The class B synMuv gene lin-35 encodes a C. elegans protein similar to Rb, a tumor suppressor inactivated in many human solid tumors. lin-35 mutants might provide a model for mammalian cells harboring mutant Rb genes. Because lin-35 null mutations are not lethal, we can screen for genes with functions required for viability in lin-35 mutants but not in wild-type animals to identify potential targets for cancer therapy. Pharmacologic inactivation of such target proteins could selectively kill Rb-deficient cells. We screened an LGI RNAi library1 for genes essential specifically in lin-35(n745) animals. n745 causes an early stop codon in lin-35 and is probably a null allele2. We have compared the phenotypes following RNAi of lin-35(n745) animals to the published RNAi phenotypes of the wild-type N2 strain. Of the 2445 dsRNAs we have screened, 2128 did not cause abnormalities in either lin-35(n745) or N2 worms. 212 dsRNAs caused similar abnormalities in lin-35(n745) and N2 worms. 105 dsRNAs resulted in abnormalities in lin-35(n745) but not in N2 worms. These 105 dsRNAs were tested in the RNAi-hypersensitive strain rrf-3(pk1426) to assess whether a more complete reduction of gene function by the dsRNAs generates more severe defects. Of the 105 dsRNAs,74 caused severe growth defects in rrf-3(pk1426) worms, suggesting that the effects seen in lin-35(n745) worms are related to the known increased sensitivity of lin-35 worms to RNAi3. To determine whether the effects of the 31 dsRNAs that caused apparent synthetic lethality in lin-35(n745) animals are strain- or allele-specific, we tested them on four other presumptive lin-35 null mutants (n2242, n2239, n2996, n373). In these strains, only three of the 31 dsRNAs caused lethality. Possibly, these other alleles are not nulls or the lin-35(n745) strain harbors background mutations that enhance the lethality of these dsRNAs. Currently, we are analyzing deletion alleles of lin-35 and the three genes that cause lethality in all of the lin-35 mutant strains to answer the above questions and to study the three likely positive genes identified in this screen. Also, we are screening the rest of the genome using the deletion allele of lin-35 that we have generated.

1. Fraser et al. (2000). Nature 408: 325.
2. Lu and Horvitz. (1998). Cell 95: 981.
3. Wang et al. (2005). Nature 436: 593.

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