Abstract/Session Information for Program Number 904A

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Abstract Content

Program Nr: **904A**

A Screen for Genes Synthetically Lethal with *lin-35*. **Mike Hurwitz**[1, 2], Bob Horvitz[1]. 1) HHMI, Dept. Biology, MIT, Cambridge, MA 02139, USA; 2) Dept. Adult Oncology, DFCI, Boston, MA 02114, USA.

The class B synMuv gene *lin-35* encodes a *C. elegans* protein similar to Rb, a tumor suppressor inactivated in a large number of human solid tumors. *lin-35* mutant animals provide a model for mammalian cells harboring mutant Rb genes. Since *lin-35* 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 targets could cause the specific deaths of Rb-deficient cells. We have screened the LGI RNAi library described by Fraser *et al.* (2000)[1] for genes that are essential specifically in *lin-35(n745)* animals. *lin-35(n745)* contains an early stop codon and is probably a null allele[2]. We have compared the phenotypes following RNAi of *lin-35(n745)* animals to the published RNAi phenotypes in the wild-type N2 strain[1]. Of the 2,445 dsRNAs we have screened, 2,128 did not cause phenotypes in either *lin-35(n745)* or N2 worms. 212 dsRNAs caused the same phenotypes in *lin-35(n745)* and N2 worms. 105 dsRNAs resulted in abnormal phenotypes in *lin-35(n745)*) worms but not in N2 worms. 73 of these dsRNAs caused severe phenotypes (embryonic lethality, sterility, larval arrest, larval lethality or severe growth delay), and 32 caused mild phenotypes (growth delay). 50 of the 105 dsRNAs correspond to genes with human counterparts, defined as having at least 25% identity over 75% of the length of the gene. These 105 genes may function in Rb-related or parallel pathways. We found no dsRNAs that were reported to have effects on the growth of N2 worms but did not have any effects on *lin-35(n745)* worms. Because *lin-35(n745)* animals are less healthy than N2 animals (decreased brood size and rare sterile animals)[3], it is possible that some of the synthetic phenotypes seen in *lin-35* mutants but not in N2 animals are caused by the non-specific additive effects of two harmful mutations. For example, RNAi of some genes may affect one cell type and the *lin-35* mutation another so that together these two distinct defects result in severely affected animals. Since the goal of this project is to identify pathways that are redundant within single cells, it is crucial to identify RNAs that cause cell-autonomous synthetic lethality. To find such genes, we are developing an assay to assess the effect of inactivation *lin-35* in a single tissue in combination with inactivation of any of the genes identified in our primary screen. [1]Fraser et al. Nature **408**: 325-30, 2000. [2]Lu, X., and H. R. Horvitz. Cell **95**: 981-91, 1998. [3]Fay et al. Genes & Develop **16**: 503-17, 2002.

Session Information

Session Title: CELL CYCLE REGULATION, CYTOKINESIS, MITOSIS

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Author: HURWITZ,MIKE;* HORVITZ,BOB.

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