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The receptor tyrosine kinase/Ras pathway necessary for vulval induction in C. elegans is negatively regulated by two redundant pathways defined by the synthetic Multivulva (synMuv) class A and class B genes. Loss-of-function mutations in members of either class alone do not result in a Multivulva (Muv) phenotype, but animals homozygous for mutations in both a class A and a class B gene are Muv. The molecularly characterized synMuv class A genes encode novel proteins. Many of the class B synMuv genes, including lin-35 Rb, dpl-1 DP, efl-1 E2F, lin-53 RbAp48, hda-1 HDAC, and let-418 Mi-2, have homologs in other species that are involved in chromatin remodeling and transcriptional repression.

We have molecularly characterized a new class B gene, lin-61. LIN-61 is predicted to contain four MBT repeats, which are loosely defined sequences of approximately 100 amino acids found in a number of nuclear proteins, including the Drosophila Polycomb group protein Sex Comb on Midleg. We have identified the molecular lesions in ten lin-61 alleles. n3809, a nonsense mutation at amino acid 159, is predicted to delete two-thirds of the protein and is a presumptive null. Animals homozygous for lin-61 mutations, including lin-61(n3809), are viable. We have used antibodies to characterize the expression and localization of LIN-61 in N2 as well as in class A and class B synMuv mutants. We are trying to identify proteins that interact with LIN-61 by performing yeast two-hybrid screens and co-immunoprecipitation experiments. Pothof et al. have shown that RNAi of lin-61 results in an increased mutation rate. We are therefore testing various loss-of-function lin-61 alleles for this phenotype.

Some of the proteins that act in the synMuv B pathway physically interact in vitro, in yeast two-hybrid assays, or in vivo based upon co-immunoprecipitation experiment. These results along with homology to proteins in other species suggest that many synMuv proteins may function together in transcriptional regulatory complexes. We are using co-immunoprecipitation experiments to further explore in vivo physical interactions among the synMuv proteins. Such studies may allow us to assign functionality to some of the novel class B genes, to analyze the effects of various synMuv mutations on physical interactions, and to identify potential sub-complexes among the synMuv proteins.


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