

28. A NEW CLASS OF SYNMUV MUTATIONS IS PREDICTED TO DISRUPT A HISTONE ACETYLTRANSFERASE COMPLEX

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Elegant studies, primarily of budding yeast and mammalian cells in culture, have shown that covalent modifications of histones can regulate chromatin structure and accessibility. In multicellular organisms, mutations that affect proteins involved in chromatin modification often result in specific developmental defects. In *C. elegans*, mutations in the class B synthetic multivulva (synMuv) genes are proposed to disrupt histone deacetylation. Loss of zygotic function of these genes, together with loss of class A synMuv gene function, results in the specific transformation of P3.p, P4.p and P8.p from non-vulval to vulval cell fates. To further understand how these cell fates are specified, we screened for additional synMuv mutations. We uncovered a genetically distinct class of mutations that are predicted to disrupt a protein complex that, somewhat surprisingly, is implicated in histone acetylation.

We screened for mutations that cause a Muv phenotype in a class A synMuv background. As predicted, we recovered many mutations in known class B synMuv genes. In addition, we isolated mutations such as *n3712*, which differs from class B synMuv mutations in two important respects. First, unlike most class B synMuv mutations, *n3712* alone causes weakly penetrant ectopic vulval cell-fate transformations. Second, the penetrance of these cell fate transformations is enhanced in *n3712*; *synMuvB* double mutants, whereas synthetic interactions are generally not observed in *synMuvB*; *synMuvB* double mutants. Therefore, *n3712* and similar mutations define a new class of genes that synthetically interact with both class A and class B synMuv genes.

We cloned the gene defined by *n3712* and found that it encodes a protein similar to mammalian TRRAP (transcription/transformation domain-associated protein). *n3712* and five other allelic mutations introduce nonsense codons and are predicted to result in a loss of gene function. TRRAP and its yeast homolog Tra1p are proposed to bridge interactions between transcription factors and histone acetyltransferases. Using mutations and RNA-mediated interference we identified a histone acetyltransferase and other genes that show genetic interactions similar to those of *n3712* and are predicted to encode proteins that form a complex with the worm TRRAP homolog. We will discuss our characterization of these mutants and models of how complexes that mediate histone deacetylation and histone acetylation may cooperate to negatively regulate Ras signaling during vulval induction.