64. *met-1* and *met-2*, Two Putative Histone Methyltransferases, May Act as Synthetic Multivulva Genes

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Repression of euchromatic gene transcription may occur through the specific covalent modification of histone tails leading to the recruitment of *trans*-acting repressive factors. In one model, through the actions of the Nucleosome Remodeling and Deacetylase (NuRD) complex, lysine 9 of histone H3 (H3K9) is deacetylated and methylated by a histone methyltransferase (HMTase), which ultimately leads to recruitment of heterochromatin protein 1 (HP1) and a transcriptionally silenced state.

Among the proteins encoded by the class B synthetic Multivulva (synMuv) genes are homologs of some NuRD complex members, including LIN-53 p48, HDA-1 HDAC, and LET-418 Mi-2. Within the Pn.p cells fated to adopt a non-vulval cell fate, a putative LIN-53/HDA-1/LET-418 transcriptional repression complex may be recruited to genes to be repressed through interaction with LIN-35 Rb and the sequence-specific heterodimeric transcription factor DPL-1 DP/EFL-1 E2F. Through the actions of the histone deacetylase HDA-1, histones may be deacetylated. After subsequent methylation of histones, the *C. elegans* HP1 homolog (and synMuv protein) HPL-2 may be recruited, leading to the repression of genes that would normally promote a vulval fate. Given this model, we decided to seek HMTase-encoding genes that interact genetically with the synMuv genes.

All known HMTases specific for modifying histone tail residues have an enzymatic SET domain. Through BLAST, Pfam, and SMART database searches we identified and classified the 31 genes predicted to encode SET-domain-containing proteins in *C. elegans*. The HMTases predicted to modify histone H3 lysines 4, 9, or 36 have conserved domains flanking the SET domain. There are nine genes in *C. elegans* predicted to encode such HMTases. Using existing mutant alleles or deletion alleles that we have generated, we tested all nine of these HMTases for a synMuv phenotype with mutations in synMuv class A or B genes. Additionally, we injected dsRNA to inactivate each of the 31 genes predicted to encode SET domain containing genes and tested for a synMuv phenotype with mutations in synMuv class A or B genes.

Mutations in two genes, *met-1* and *met-2,* cause a synMuv phenotype in combination with mutations in all synMuv class A genes but not with mutations in synMuv class B genes. Based upon sequence similarity, *met-1* is predicted to encode a histone H3 lysine 36 (H3K36) HMTase. In *S. cerevisiae*, methylation of H3K36 may play a role in transcriptional elongation or repression. We are currently testing whether perturbations in transcriptional elongation can cause a synMuv phenotype. *met-2* is predicted to encode a histone H3K9 HMTase. We are testing whether *met-2* plays a role in the recruitment of HPL-2. Interestingly, strains doubly mutant for *met-1* and *met-2* are synthetically Muv. We will discuss our model for the redundant actions of these putative histone methyltransferases and their interactions with the products of the synMuv genes.