

MET-1 and MET-2, Two Putative Histone Methyltransferases, Are Redundantly Required for Proper Vulval Cell-Fate Determination in *C. elegans*

Erik Andersen and Bob Horvitz

HHMI, Dept. Biology, MIT, Cambridge, MA 02139 USA

The identification and characterization of genes that when mutated affect the vulval cell fate have helped lead to a fundamental understanding of the RTK/Ras, Wnt, and Notch signal transduction pathways. The synthetic Multivulva (synMuv) mutants may help to define a role in the specification of cell fate for chromatin remodeling and transcriptional modulation. The synMuv genes are grouped into at least three functionally redundant classes, A, B, or C, that negatively regulate the specification of the vulval cell fate. Animals mutant for one or more genes of the same class are non-Muv. Animals mutant for genes within any two classes are Muv. Several synMuv genes encode counterparts of proteins implicated in transcriptional repression and chromatin remodeling. Given the possible involvement of chromatin remodeling and the likely conservation of transcriptional repression mechanisms found in other organisms, we investigated whether histone methyltransferases (HMTs) play a role in vulval cell-fate specification.

Using database searches and protein alignments, we identified the 33 genes predicted to encode lysine-specific histone-tail HMTs that contain the evolutionarily-conserved enzymatic SET domain. We inactivated each of these 33 genes by RNAi and assayed for vulval defects. We also deleted a subset of the HMTs with cysteine-rich domains flanking the SET domain that are predicted to be enzymatic HMTs and assayed for vulval defects. Through these two approaches, we found that *met-1* or *met-2* loss of function conferred a synMuv phenotype in combination with class A or class C synMuv mutations, *mes-2* or *mes-4* loss of function suppressed the synMuv phenotype of *lin-15AB(n765ts)* mutants, and several other predicted HMTs are required for embryonic viability. MET-1 is a homolog of yeast Set2p and predicted to methylate histone H3 lysine 36 (H3K36). MET-2 is the homolog of human SETDB1 and predicted to methylate histone H3 lysine 9 (H3K9). Quantitative western blots of wild-type, *met-1*, and *met-2* extracts showed that *met-1* and *met-2* are required for both H3K9 and H3K36 trimethylation but not for H3K4 nor H3K27 trimethylation *in vivo*. Interestingly, *met-1; met-2* double mutants are Muv, but *met-1* and *met-2* do not act redundantly with mutations in class B synMuv genes. We will discuss the relevance of the redundancy of these putative HMTs with each other and the other synMuv genes in specifying the vulval cell fate in *C. elegans*. Little is known about the function of H3K36 HMTs outside of *S. cerevisiae* and even less is known about interactions with H3K9 HMTs. These studies may lead to further insight into the roles of H3K9 and H3K36 methylation in specifying a developmental cell fate in a multicellular organism.

Talk

Cell-fate specification: Post-embryonic

Gene expression

Keyword: Development: the vulva