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# ***sem-4* Regulates Terminal Differentiation and Anteroposterior Patterning in the T Lineage**

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The *C. elegans* gene *sem-4* is a member of the *spalt* gene family. *spalt* genes encode Zn finger proteins expressed in neural tissue in worms, frogs, mice, fish, and human beings. In flies, *spalt* is involved in head and tail patterning; in worms, *sem-4* is expressed strongly in the head and tail. *sem-4* animals have many neuronal defects, including the production of ectopic touch-neuron-like cells in the tail. These ectopic cells arise inappropriately from the T lineage (where *sem-4* is expressed) and express several touch cell markers, including *mec-3*. Mitani *et al.* suggested that *sem-4* might negatively regulate *mec-3* in differentiating cells (Mitani S, Du H, Hall DH, Driscoll M, and Chalfie M, *Development* **119**, 773-783 (1993)). Basson and Horvitz proposed that mutations in *sem-4* transform the T.pp sublineage into a touch cell (PLM) sublineage (Basson M and Horvitz HR, *Genes & Dev.* **10**, 1953-1965 (1996)). We find that *sem-4* determines the cell fate of both terminally differentiating cells and precursors in the T lineage, through regulation of *mec-3* and interaction with the anteroposterior patterning genes *egl-5*, *mab-5*, and *lin-39*.

We have shown that *sem-4* directly represses *mec-3* expression and touch cell function when expressed ectopically in the six touch neurons. Zn fingers 2 and 3 are critical for this repression. Moreover, SEM-4 binds to at least two specific sites in the *mec-3* promoter and likely represses *mec-3* transcription directly through this interaction. Because ectopically expressed *sem-4* can prevent differentiation of the touch cells through direct repression of *mec-3*, we propose that *sem-4* normally represses *mec-3* expression and touch cell fate in the T lineage. These results delineate a direct role for *sem-4* in the process of terminal differentiation of T lineage neurons.

We have also examined regulation by *sem-4* of precursor cell fate in the T lineage. In *sem-4* animals, the fate of the T.pp precursor is variable, as is the number of cells ectopically expressing *mec-3*; T.pp gives rise to three distinct lineages which differ from the wild-type lineage and which produce different numbers of *mec-3* positive cells. One of these lineages resembles the wild-type T.pp lineage but produces one ectopic *mec-3* expressing cell. The second abnormal lineage resembles the PLM touch neuron lineage, as first suggested by Basson and Horvitz, and produces one ectopic *mec-3* expressing cell (Basson and Horvitz, 1996). The third abnormal lineage resembles the Q lineage (which generates the AVM and PVM touch neurons) and produces at least two ectopic *mec-3* expressing cells.

We find that mutations in the HOM-C genes affect the production of ectopic touch neurons in *sem-4* animals. Mutations in *egl-5*, *mab-5*, and *lin-39* decrease the production of ectopic touch neurons; mutation of *egl-5* produces the largest decrease. Mutation of each of the HOM-C genes affects the development of different touch cells: PVM migration is abnormal in *mab-5* mutants (Chalfie M, Thomson NJ, and Sulston J, *Science* **221**, 61-63, (1983)), AVM migration is abnormal in *lin-39* mutants (Clark SG, Chisholm AD, and Horvitz HR, *Cell* **74**, 43-55 (1993), Wang BB, Miller-Immergluck MM, Austin J, Robinson NT, Chisholm A, and Kenyon C, *Cell* **74**, 29-42 (1993)), and we find that *mec-3* expression in PLM neurons is significantly reduced in an *egl-5* mutant. These data suggest that the ectopic touch neurons in *sem-4* animals have characteristics of AVM, PVM, and PLM touch neurons. Therefore, the lineage transformations in *sem-4* animals may be homeotic transformations in which the T.pp lineage is transformed either to a different tail lineage (PLM) or to more anterior (AVM and PVM) touch neuron lineages. We propose that *sem-4* negatively regulates the HOM-C genes in the T lineage. This idea is consistent with evidence that mutations in *spalt* cause ectopic expression of *sex combs reduced*, the *Drosophila* homologue of *lin-39* (Casanova J, *Roux's Arch Dev Biol*, **198**, 137-140 (1989)). In other lineages, *sem-4* may positively regulate the HOM-C genes: Grant *et al.* found that *sem-4* interacts with *lin-39* and possibly with *mab-5* during vulval development (Grant K, Hanna-Rose W, and Han M, *Dev. Biol.* **224**, 496-506 (2000)); we have observed that *sem-4* animals exhibit an AVM migration defect very similar to that present in *lin-39* animals.