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Cohesin and a PLZF protein act together to direct a GABAergic neural fate and inhibit a tyraminergic neural fate

The development of diverse neuronal cell types is crucial for the function of the nervous system, and defects in neural development are associated with various neurological disorders in humans. In C. elegans, the tyraminergic RIM and octopaminergic RIC neurons in the head are involved in diverse sensorimotor behaviors, including reversals, head movements, and feeding, but the factors guiding the development of these neurons are largely unknown. We performed EMS mutagenesis screens for genes that when mutated cause changes in the number of RIM-like and RIC-like neurons using a tdc-1p::gfp reporter, which expresses GFP specifically in the RIM and RIC neurons. We screened approximately 75,000 haploid genomes and isolated 18 mutants that have extra or reduced numbers of GFP-positive cells. One isolate with extra RIM/RIC-like cells contains an opal mutation in coh-1. coh-1 encodes a homolog of RAD21, which is a subunit of the cohesin complex. Cohesin is a DNA-associated protein complex that mediates cohesion between replicated sister chromatids and functions in DNA repair and gene expression. coh-1 mutants have both extra RIM-like and extra RIC-like cells, and inhibition of other cohesin components also causes generation of extra RIM-like and RIC-like cells. The extra RIM-like or RIC-like cells in cohesin mutants are not “undead” sisters of RIM or RIC, suggesting that the cohesin complex inhibits fate changes to RIM-like or RIC-like cells rather than promoting the deaths of the sisters of RIM and RIC. Using diverse neuronal markers, we showed that the normal identities of the cells that acquired RIM-like status are the GABAergic RMED and RMEV neurons. In addition, three isolates from our mutagenesis screens with extra RIM/RIC-like cells contained nonsense mutations in eor-2. eor-2 encodes a co-factor of EOR-1, a homolog of the promyelocytic leukemia zinc finger (PLZF). eor-1/eor-2 and cohesin likely act together to prevent the cell-fate changes from RMED/V to RIM-like cells: (1) eor-1 mutants have RIM-like RMED/V cells; (2) the effects on the generation of extra RIM-like cells are not additive in cohesin; eor-1 double mutants; and (3) the expression of the majority of EOR-1 target genes is regulated by cohesin. In addition, in cohesin and eor-1 mutants the normally GABAergic RMED/V neurons fail to express the gene that encodes glutamic acid decarboxylase (GAD), the key enzyme in GABA biosynthesis, and have truncated neurites. Our data show that cohesin and the EOR-1 transcription factor are required together for the expression of the RMED/RMEV GABAergic neuronal identity and for inhibiting the expression of characteristics of tyraminergic neurons. We are currently finding the molecular mechanism by which cohesin and a PLZF transcription factor act together to direct cell fate determination. We hope this work will provide novel insights concerning the functions of the evolutionarily conserved cohesin complex and PLZF transcription factor in animal development.