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Dongyeop Lee, Takashi Hirose, and Bob Horvitz

Cohesin and a PLZF Protein Direct GABAergic Neuronal Development

Cohesin is a DNA-associated protein complex that regulates diverse cellular processes by altering DNA orientation. The roles of cohesin proteins in sister-chromatid cohesion and meiosis are relatively well-known. However, little is known about the role of cohesin in nervous system development. We have discovered that cohesin and EOR-1, a homolog of the promyelocytic leukemia zinc finger (PLZF) transcription factor, act together to guide specific GABAergic neuron development by preventing those neurons from expressing aspects of other neuronal fates. We performed EMS mutagenesis screens using a tdc-1p::GFP reporter, which expresses GFP specifically in the tyraminergic RIM and octopaminergic RIC neurons, and identified mutations in coh-1 and eor-2 that cause generation of extra RIM/RIC-like cells. coh-1 encodes a homolog of RAD21, a subunit of the cohesin complex. coh-1 mutants have extra RIM-like cells, and inhibition of other cohesin components also caused generation of extra RIM-like cells. The extra RIM-like cells in cohesin mutants are not “undead” sisters of RIM, suggesting that the cohesin complex inhibits fate changes to RIM-like cells rather than promoting the deaths of the sisters of RIM. Using diverse neuronal markers, we showed that the normal identities of the cells that acquire tyraminergic RIM-like traits in cohesin mutants are the GABAergic RMED and RMEV neurons. Our screen also identified eor-2, which encodes a co-factor of EOR-1 (PLZF). Similar to cohesin mutants, eor-1 mutants generate GABAergic RMED/V that express tyraminergic RIM markers. In addition, in cohesin and eor-1 mutants the normally GABAergic RMED/V neurons fail to express unc-25, which encodes a key enzyme in GABA biosynthesis, and have truncated neurites, suggesting that the tyraminergic-like RMED/V lost their GABAergic functions. Interestingly, we found that TRA-4, another homolog of PLZF mediates the generation of the tyraminergic-like RMED/V when cohesin or eor-1 is genetically inhibited, indicating that the two PLZF proteins play different roles in the development of the same neurons. We now hope to identify the molecular mechanism by which cohesin and PLZF transcription factors direct neuronal cell-fate determination. No previous interaction has been reported between cohesin and PLZF, and we hope that our experiments will provide novel insights into the functions of the evolutionarily conserved cohesin complex and PLZF transcription factors in animal development.