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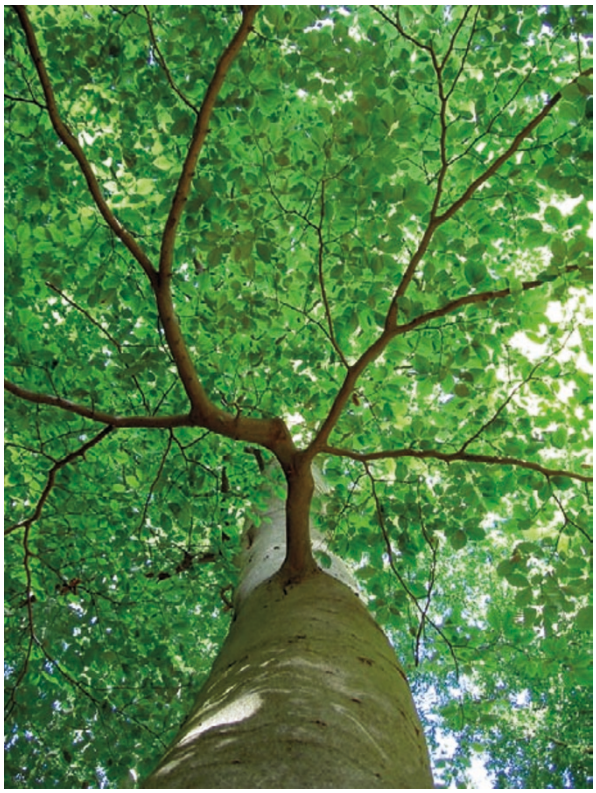
GENE EXPRESSION

Cohesin branches out

> “…cohesin might have additional functions that are independent of its role during cell division…”

The cohesin complex has a crucial role in holding together sister chromatids and ensuring accurate chromosome segregation during mitosis and meiosis. However, a flurry of studies now report evidence that cohesin might have additional functions that are independent of its role during cell division and instead involve gene regulation.

The cohesin complex, comprising SMC1, SMC3, SCC1/ RAD21 and SCC3/stromalin, is thought to mediate cohesion by forming a ring around sister chromatids. Schuldiner *et al.* discovered the cohesin subunits SMC1 and stromalin in a screen to identify mutations that affect a process called axon pruning (whereby inappropriate neuronal branches are ‘pruned’ away to refine the neural circuits) in postmitotic cells of the *Drosophila melanogaster* mushroom body, a brain structure involved in olfactory learning and memory. Overexpression of SMC1 rescues the pruning phenotype and restores levels of ecdysone receptor EcR-B1, which is a key regulator of axon pruning. The authors also identified SMC1 and stromalin in a parallel screen for mutations that affect dendrite targeting of olfactory projection neurons.



Using a cleverly designed *Rad21* mutant fly in which RAD21 can be cleaved by tobacco etch mosaic virus (TEV) protease in a tissue-specific manner, Pauli *et al.* also demonstrated a postmitotic role for cohesin in axon pruning. Cleavage causes severe chromosome missegregation in proliferating cells, presumably because the cohesin ring structure is disrupted. Surprisingly, RAD21 cleavage is lethal in postmitotic cells, and in addition to the axon pruning phenotype, the authors observed abnormal larval locomotion in cholinergic neurons.

So how does cohesin cause these diverse effects in neuronal morphogenesis? As previously suggested, and as indicated by the causal link between cohesin and EcR-B1 levels, cohesin seems to function in gene regulation. Parelho *et al.* and Wendt *et al.* analysed the genome-wide distribution of cohesins in mouse and human cells using chromatin immunoprecipitation and found that the distribution is not determined by transcription — in contrast to budding yeast, in which cohesins are presumed to be driven along chromosome arms by the transcriptional machinery. Instead, both groups found a strong preference for sequence motifs resembling that of CTCF, a zinc-finger protein that is associated with transcriptional insulators, boundary elements and imprinting control regions. Indeed, cohesin tends to accumulate at sites that bind CTCF, which is needed for cohesin accumulation. Both groups also showed in transient transfection assays that cohesin contributes to the insulator function of CTCF. Wendt *et al.* further showed that cohesin controls transcription of an imprinted gene locus.

How cohesin contributes to the transcriptional functions of CTCF remains an unanswered question for now. However, the new findings provide some much-needed insight into cohesin-associated developmental disorders such as Cornelia de Lange syndrome and Roberts syndrome.

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ORIGINAL RESEARCH PAPERS Schuldiner, O. *et al. piggyBac*-based mosaic screen identifies a postmitotic function for cohesin in regulating developmental axon pruning. *Dev. Cell* **14**, 227–238 (2008) | Pauli, A. *et al.* Cell-type-specific TEV protease cleavage reveals cohesin functions in *Drosophila* neurons. *Dev. Cell* **14**, 239–251 (2008) | Wendt, K. S. *et al.* Cohesin mediates transcriptional insulation by CCCTC-binding factor. *Nature* **451**, 796–801 (2008) | Parelho, V. *et al.* Cohesins functionally associate with CTCF on mammalian chromosome arms. *Cell* **132**, 422–433 (2008)

FURTHER READING Stedman, W. *et al.* Cohesins localize with CTCF at the KSHV latency control region and at cellular c-myc and H19/Igf2 insulators. *EMBO J.* 24 Jan 2008 (doi:10.1038/emboj.2008.1) | Misulovin, Z. *et al.* Association of cohesin and Nipped-B with transcriptionally active regions of the *Drosophila melanogaster* genome. *Chromosoma* **117**, 89–102 (2008)