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CHROMOSOME BIOLOGY

In and out through the same cohesin door

> “Wapl mediates both entry and exit of DNA and… Pds5 stabilizes the cohesin ring”

A new study published in *Cell* extends previous biochemical characterization of the fission-yeast cohesin complex to show that there are marked similarities in the mechanisms of DNA entry to and exit from the complex. Cohesin has crucial roles in chromosome organization and segregation by forming a ring around DNA, but the mechanism of DNA loading and unloading has been unclear until now.

The cohesin ring structure consists of an SMC (structural maintenance of chromosomes) protein heterodimer — formed by subunits Psm1 and Psm3 — together with non-SMC proteins. These include regulatory subunits (Rad21, Psc3, Pds5 and Wapl) and the cohesin loader complex Mis4–Ssl3. Psm1 and Psm3 interact through their hinge domains to form a V-shaped dimer and the two ends of the V, which contain the Psm1 and Psm3 head domains, interact with the regulatory subunits to close the ring. In this study, the authors added Pds5 and Wapl to their previously characterized cohesin tetramer (Psm1, Psm3, Rad21 and Psc3).

Pds5 markedly inhibited loading of the cohesin tetramer onto DNA in the presence of the cohesin loader and ATP. By contrast, Wapl compensated for the inhibitory effect of Pds5, indicating that Wapl facilitates cohesin loading onto DNA in an ATP-dependent manner.

However, in keeping with previous description of Wapl as a cohesin unloader, the addition of Wapl and Pds5 to previously assembled cohesin–DNA complexes led to almost complete loss of DNA in an ATP-dependent manner. The addition of increasing concentrations of Pds5 in the absence of Wapl prevented spontaneous unloading of DNA from cohesin. The authors therefore suggest that Wapl mediates both entry and exit of DNA and that Pds5 stabilizes the cohesin ring, thus inhibiting the dual function of Wapl.

Next the authors showed that Wapl facilitates both entry and exit of DNA by dissociating the amino-terminus of Rad21 from Psm3. During both loading and unloading, conserved lysine residues on the Psm3 head contacted DNA and triggered the necessary ATP hydrolysis. This contrasts with a previous proposal that DNA exits the cohesin ring through the SMC heads but enters the ring through a different reaction that involves opening of the SMC hinge.

The direction of the reaction could be reversed experimentally by changing the salt concentration. The authors therefore propose that small changes in the conformation of the cohesin complex alter the direction of DNA transport. In suppoort of this model, they showed that the cohesin loader complex binds to both the SMC hinge and close to the SMC heads on Psc3, which induces an ‘inside–out’ conformational change to the cohesin ring that exposes the inward-facing DNA-sensing lysines to enable DNA entry.

In summary, the results suggest a bidirectional model for DNA–cohesin interaction. First, DNA contacts the DNA-sensing lysines of Psm3, which weakens the Psm1–Psm3 head interaction. Next, Wapl facilitates opening of the Rad21–Psm3 interface. DNA going in either direction must pass these two separate ‘gates’ to load or unload from cohesin.

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ORIGINAL ARTICLE Murayama, Y. & Uhlmann, F. DNA entry into and exit out of the cohesin ring by an interlocking gate mechanism. *Cell* http://dx.doi.org/10.1016/j.cell.2015.11.030 (2015).