CHROMOSOME SEGREGATION

An exit for sister chromatids

> “the Smc3–kleisin interface might be a potential exit gate”

The cohesin complex comprises a heterodimer of Smc1 and Smc3 bridged by the Scc1 kleisin subunit. These three subunits are thought to form a tripartite complex that holds newly replicated sister chromatids together to ensure proper chromosome segregation. It has been suggested that the Smc1–Smc3 interaction interface is the DNA entry gate. Dissociation of cohesin from chromatin is mediated by two processes: separase-dependent cleavage of Scc1, which initiates anaphase, and a proteolysis-independent process involving the regulated disengagement of Smc3 from the Scc1 kleisin, which has been proposed to create a gate through which DNA can exit the cohesin ring. However, insights into the open cohesin form that enables DNA exit was lacking. Two papers in *Science* now provide structural and functional information about this interface.

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Gligoris *et al.* determined the crystal structure of the amino-terminal domain (NTD) of yeast Scc1 bound to Smc3 at 3.3 Å. They report that the interface consists of two Scc1 helices that form a four-helix bundle when combined with the coiled coil emerging from the Smc3 ATPase domain. Mutations in key residues located at the Smc3–Scc1 interface disrupted the interaction between the two proteins. Next, the authors showed that cohesin forms single rings that trap one or both sister chromosomes *in vivo*.

In a second study, Huis in ’t Veld *et al.* used electron microscopy and crosslinking mass spectrometry to analyse human cohesin. They also found that the Scc1 NTD binds the coiled coil of Smc3 and that complexes containing Scc1 mutated in the Smc3-binding site adopted an open conformation. This resembled the structure of cohesin that had been proteolytically cleaved in its Scc1 subunit, mimicking the effect of separase in mitosis.

Both groups went on to show that disrupting the interaction between Scc1 and Smc3 abrogated the ability of cohesin to associate with centromeric DNA *in vivo* and to mediate cohesion. These findings suggest that the exit gate is formed by interactions between the Scc1 NTD and the Smc3 coiled coil. Finally, Huis in ‘t Veld *et al.* showed that inactivation of the release factor Wapl (a cohesin-associated protein) stably ‘locked’ wild-type cohesin on DNA, suggesting that the opening of this exit gate is regulated by Wapl.

In summary, the findings of these two complementary studies suggest that the Smc3–kleisin interface might be a potential exit gate. Further experiments are now required to elucidate the molecular mechanisms involved in opening of the cohesin ring.

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ORIGINAL RESEARCH PAPERS Gligoris, T. G. *et al.* Closing the cohesin ring: structure and function of its Smc3–kleisin interface. *Science* **346**, 963–967 (2014) | Huis in ’t Veld, P. J. *et al.* Characterization of a DNA exit gate in the human cohesin ring. *Science* **346**, 968–972 (2014)