Chromosome cohesion in mitosis and meiosis

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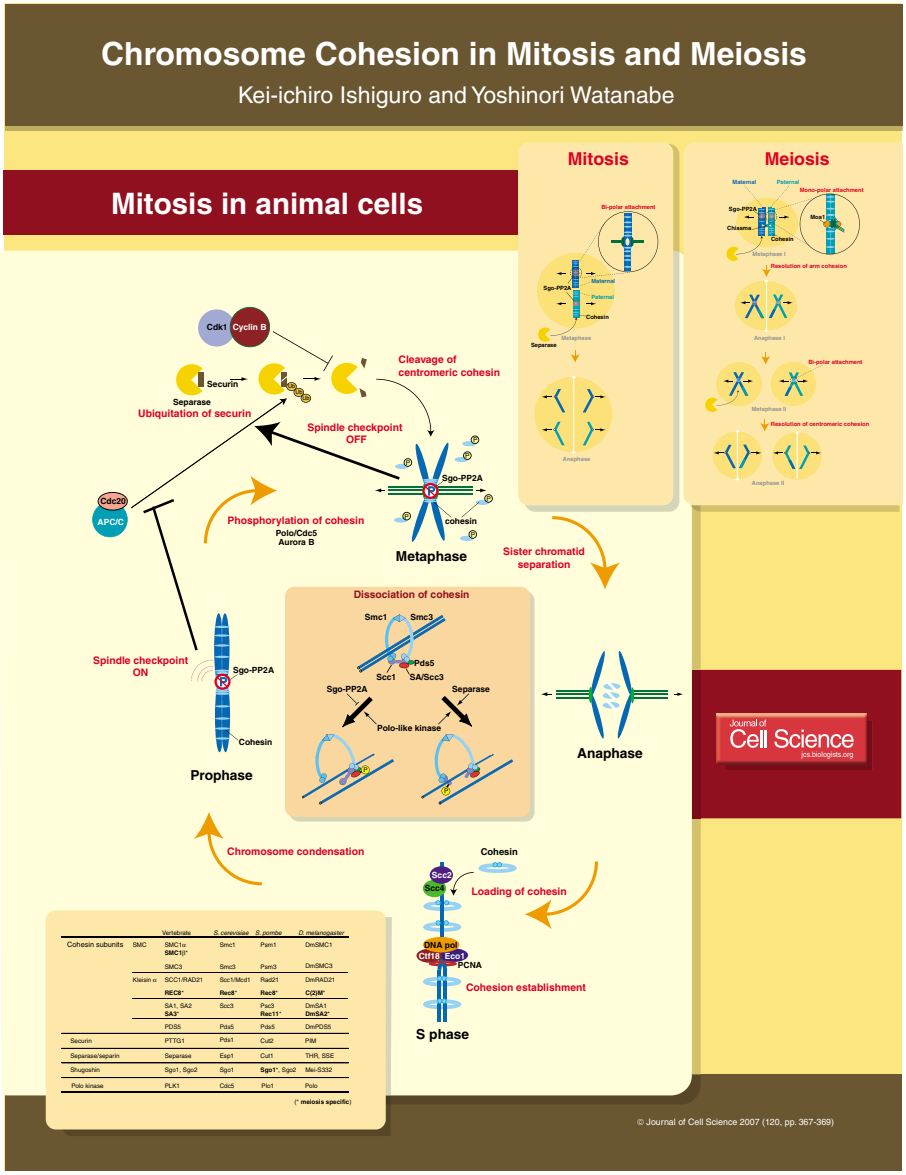
During mitosis and meiosis sister chromatids are held together by protein complexes. This cohesion is important not only for pairwise alignment of chromosomes on the mitotic spindle but also for the generation of tension across centromeres – it counteracts the pulling force of spindle microtubules, which ensures the bipolar attachment of chromosomes. Chromosome cohesion thus enables accurate chromosome segregation in both mitosis and meiosis.

Establishment of sister chromatid cohesion in mitosis

Cohesion is mediated by the cohesin complex, which contains four core subunits: two subunits of the structural maintenance of chromosomes (SMC) protein family, Smc1 and Smc3; the kleisin family protein Scc1/Rad21; and an accessory subunit, Scc3/Psc3. In vertebrates, Scc3 has two isoforms: SA1 and SA2. Another protein, Pds5, is weakly associated with the cohesin complex and may regulate the dynamic interaction of cohesin with chromatin. The cohesin complex has been proposed to form a ring structure that encircles sister chromatids (Hirano, 2005; Nasmyth and Haering, 2005).

Cohesin binds to chromosomes before S phase and is converted into a physical linkage that binds sister chromatids. Eco1/Ctf7/Eso1, a factor involved in the formation of the cohesive structure, interacts with the clamp loader Ctf18/RF-C and the sliding clamp PCNA that enables DNA polymerases to slide along DNA, which suggests a link between DNA replication and cohesion (Skibbens, 2005). Scc2, together with its binding partner Scc4, is required to load cohesin onto chromosomes. In *Xenopus*, Scc2 associates with the DNA replication licensing complex (Hirano, 2005).



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Localization of cohesin in the genome

In yeast, cohesin along the chromosome arms is spaced at lower density at intergenic regions (Lengronne et al., 2004; Glynn et al., 2004). By contrast, large quantities of cohesin complexes are spread over a broad region around centromeres. Thus cohesion is tight around centromeres, counteracting the pulling force of kinetochore microtubules. The heterochromatin protein HP1/Swi6 at pericentromeric regions actively enriches cohesin, presumably through direct interaction with the cohesin subunit Scc3/SA, and strengthens centromeric cohesion in fission yeast and mammals (Pidoux and Allshire, 2004).

Cleavage of cohesin by separase at anaphase onset

Sister chromatid cohesin is maintained until metaphase. At the onset of anaphase, a specific endopeptidase called separase (Esp1 in *S. cerevisiae*/Cut1 in *S. pombe*) is activated to cleave the kleisin subunit Scc1/Rad21. This results in the opening of the cohesin ring, thereby triggering chromosome separation (Nasmyth and Haering, 2005; Uhlmann, 2003). Phosphorylation of Scc1 by Polo/CDC5 enhances its cleavability by separase.

Separase activity is sequestered by an inhibitory chaperone securin (PTTG1 in vertebrates, Pds1 in *S. cerevisiae*, Cut2 in *S. pombe*) until the metaphase-anaphase transition. In human and *Xenopus*, separase is also regulated in part by inhibitory binding of the CDK1–cyclin-B complex. The anaphase-promoting complex or cyclosome (APC/C) together with its activator Cdc20 promotes the ubiquitin-dependent destruction of securin, thereby allowing separase activation (Nasmyth and Haering, 2005; Uhlmann, 2003). The spindle assembly checkpoint ensures the destruction of securin takes place only after all sister chromatid pairs have aligned correctly on the mitotic spindle by inhibiting APC/C-Cdc20 activity until then (Musacchio and Hardwick, 2002).

Dissociation of cohesin by the prophase pathway in vertebrate mitosis

In vertebrate mitosis, most of the cohesin dissociates from the chromosome arms before metaphase, a process called the 'prophase pathway', which resolves sister chromatids and may be important for the ensuing segregation (Hirano, 2005). This dissociation requires the phosphorylation of cohesin subunit SA by Polo-like kinase (Plk), but does not require cleavage by separase (Hauf et al., 2005). In addition to Plk, Aurora B may contribute to this process. Most of the cohesin dissociated by prophase pathway is not cleaved even at anaphase, but instead relocates to chromatin in telophase to function in the next cell cycle. In spite of the prophase pathway, a small fraction of cohesin still persists around centromeres to preserve cohesion, which ensures the alignment of chromosomes on the spindle at metaphase.

Protection of centromeric cohesion in mitosis

The protection of centromeric cohesin from the prophase pathway is accomplished by the centromeric protein Shugoshin (Sgo)/Mei-S332 (Watanabe, 2005). Sgo acts in concert with protein phosphatase 2A (PP2A) containing a B56 regulatory subunit, which is likely to counteract Plk-dependent phosphorylation of cohesin and thereby prevents dissociation of cohesin from the centromeres (Kitajima et al., 2006; Riedel et al., 2006; Tang et al., 2006). Sgo may have another unidentified activity that protects cohesin at the centromere independently of PP2A (Kitajima et al., 2006). In addition, *S. cerevisiae* Sgo1 (Indjeian et al., 2005) and *S. pombe* Sgo2 (Kawashima et al., unpublished) play a role ensuring the bi-polar attachment of kinetochores by activating the spindle checkpoint, which senses loss of tension.

Stepwise cleavage of meiotic cohesin along the arm regions and at centromeres

The cohesin complex in meiosis differs from that in mitosis. Scc1/Rad21 is largely replaced by a meiotic counterpart, Rec8 (Nasmyth and Haering, 2005; Watanabe, 2004). In fission yeast, Rec8 associates with two Scc3-like partners, Rec11 and Psc3, the former in the arm regions and the latter at centromeres. In addition to Rec8, other meiosis-specific cohesin subunits, SA3 and SMC1β, are expressed and act in mammalian germ cells (Watanabe, 2004).

During meiotic chromosome segregation, the separase-mediated cleavage of Rec8 occurs only on the arm regions at anaphase I; centromeric Rec8 is protected from cleavage by Sgo (Lee et al., 2005; Nasmyth and Haering, 2005; Watanabe, 2005). Therefore, sister chromatid cohesion is preserved at centromeres throughout anaphase I until metaphase II, a period when bipolar attachment is established owing to the residual centromeric cohesion. At the onset of anaphase II, centromeric Rec8 is cleaved by separase, which results in sister chromatids segregating into each gamete. Thus, Rec8 along the arm regions and at centromeres is cleaved in a stepwise manner in the successive nuclear divisions of meiosis. As in mitotic animal cells, Sgo acts with PP2A in meiosis I to protect centromeric cohesin from separase cleavage. The dephosphorylation of Rec8 may be the crucial activity of Sgo-PP2A in meiosis (Brar et al., 2006; Kitajima et al., 2006; Riedel et al., 2006).

Cohesion-mediated mono-orientation of kinetochores

In fission yeast, centromeric Rec8 plays a specific role establishing the monopolar attachment of sister kinetochores at meiosis I, since mutations in Rec8 result in equational rather than reductional division at meiosis I. Whereas mitotic cohesin localizes preferentially to the pericentromeric region, meiotic cohesin also localizes to the core centromere. Therefore, the establishment of cohesion at the central core of centromeres conjoins the two kinetochore domains at meiosis I, whereas the core regions open to face opposite sides in mitosis (Watanabe, 2004). Mutations in Rec8 homologs in maize and *Arabidopsis* cause similar 'equational' division at meiosis I, suggesting the mechanism is conserved in plants (Chelysheva et al., 2005; Yu and Dawe, 2000). The fission yeast meiosis-specific protein Moa1, which interacts with Rec8 and localizes to the core centromere, is required for establishing the mono-orientation of kinetochores at meiosis I. Moa1 may assist Rec8 cohesin in establishing or maintaining cohesion at the core centromere (Yokobayashi and Watanabe, 2005). In budding yeast, a different set of proteins, called monopolins, is required for mono-orientation (Petronczki et al., 2006). The involvement of cohesin/cohesion in the regulation of the mono-orientation of kinetochores in this organism is not clear.

References

Brar, G. A., Kiburz, B. M., Zhang, Y., Kim, J. E., White, F. and Amon, A. (2006). Rec8 phosphorylation and recombination promote the step-wise loss of cohesins in meiosis. *Nature* **441**, 532-536.

Chelysheva, L., Daiallo, S., Vezon, D., Gendrot, G., Vrielynck, N., Belcram, K., Rocques, N., Marquez-Lema, A., Bhatt, A. M., Horlow, C. et al. (2005). AtREC8 and AtSCC3 are essential to the monopolar orientation of the kinetochores during meiosis. *J. Cell Sci.* **118**, 4621-4632.

Glynn, E. F., Megee, P. C., Yu, H. G., Mistrot, C., Unal, E., Koshland, D. E., DeRisi, J. L. and Gerton, J. L. (2004). Genome-wide mapping of the cohesin complex in the yeast *Saccharomyces cerevisiae*. *PLoS Biol.* **2**, e259.

Hauf, S., Roitinger, E., Koch, B., Dittrich, C. M., Mechtler, K. and Peters, J.-M. (2005). Dissociation of cohesin from chromosome arms and loss of arm cohesion during early mitosis depends on phosphorylation of SA2. *PLOS Biol.* **3**, e69.

Hirano, T. (2005). Dynamic molecular linkers of the genome: the first decade of SMC proteins. *Genes Dev.* **19**, 1269-1287.

Indjeian, V. B., Stern, B. M. and Murray, A. W. (2005). The centromeric protein Sgo1 is required to sense lack of tension on mitotic chromosomes. *Science* **307**, 130-133.

Kitajima, T. S., Sakuno, T., Ishiguro, K., Iemura, S., Natsume, T., Kawashima, S. A. and Watanabe, Y. (2006). Shugoshin collaborates with protein phosphatase 2A to protect cohesin. *Nature* **441**, 46-52.

Lee, J. Y., Hayashi-Hagihara, A. and Orr-Weaver, T. L. (2005). Roles and regulation of the Drosophila centromere cohesion protein MEI-S332 family. *Philosophical*

Transactions of the Royal Society of London–Series B: Biological Sciences **360**, 543-552.
Lengronne, A., Katou, Y., Mori, S., Yokobayashi, S., Kelly, G., Itoh, T., Watanabe, Y., Shirahige, K. and Uhlmann, F. (2004). Cohesin relocation from sites of chromosomal loading to places of convergent transcription. *Nature* **430**, 573-578.
Musacchio, A. and Hardwick, K. G. (2002). The spindle checkpoint: structural insights into dynamic signalling. *Nat.* Rev *Mol. Cell. Biol.* **3**, 731-741.
Nasmyth, K. and Haering, C. H. (2005). The structure and function of SMC and kleisin complexes. *Annu. Rev. Biochem.* **74**, 595-648.
Petronczki, M., Matos, J., Mori, S., Gregan, J., Bogdanova, A., Schwickart, M., Mechtler, K., Shirahige, K., Zachariae, W. and Nasmyth, K. (2006). Monopolar attachment of sister kinetochores at meiosis I requires casein kinase 1. *Cell* **126**,1049-1064.
Pidoux, A. and Allshire, R. (2004). Kinetochore and heterochromatin domains of the fission yeast centromere. *Chromosome Res.* **12**, 521-534.
Riedel, C. G., Katis, V. L., Katou, Y., Mori, S., Itoh, T., Helmhart, W., Galova, M., Petronczki, M., Gregan, J., Cetin, B. et al. (2006). Protein phosphatase 2A protects centromeric sister chromatid cohesion during meiosis I. *Nature* **441**, 53-61.
Skibbens, R. V. (2005). Unzipped and loaded: the role of DNA helicases and RFC clamp-loading complexes in sister chromatid cohesion. *J. Cell Biol.* **169**, 841-846.
Tang, Z., Shu, H., Qi, W., Mahmood, N. A., Mumby, M. C. and Yu, H. (2006). PP2A is required for centromeric localization of Sgo1 and proper chromosome segregation. *Dev. Cell* **10**, 575-585.
Uhlmann, F. (2003). Chromosome cohesion and separation: from men and molecules. *Curr. Biol.* **13**, R104-114.
Watanabe, Y. (2004). Modifying sister chromatid cohesion for meiosis. *J. Cell Sci.* **117**, 4017-4023.
Watanabe, Y. (2005). Shugoshin: guardian spirit at the centromere. *Curr. Opin. Cell Biol.* **17**, 590-595.
Yokobayashi, S. and Watanabe, Y. (2005). The kinetochore protein Moa1 enables cohesion-mediated monopolar attachment at meiosis I. *Cell* **123**, 803-817.
Yu, H.-G. and Dawe, R. K. (2000). Functional redundancy in the maize meiotic kinetochore. *J. Cell Biol.* **151**, 131-141.

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