Minireview

Condensin goes with the family but not with the flow

Marc R Gartenberg* and Matthias Merkenschlager†

Addresses: *Department of Pharmacology, Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, Piscataway, NJ 08854, USA. †Lymphocyte Development Group, MRC Clinical Sciences Centre, Imperial College, London W12 0NN, UK.

Correspondence: Marc R Gartenberg. Email: gartenbe@umdnj.edu.
Matthias Merkenschlager. Email: matthias.merkenschlager@csc.mrc.ac.uk.

Published: 6 October 2008

*Genome **Biology*** 2008, **9:**236 (doi:10.1186/gb-2008-9-10-236)

The electronic version of this article is the complete one and can be found online at http://genomebiology.com/2008/9/10/236

Abstract

Condensin and cohesin are loaded onto yeast chromosomes by a common mechanism at RNA polymerase III transcribed genes. Whereas cohesin translocates from these loading sites to mediate cohesion at secondary locations, condensin remains, bringing distant sites together into clusters.

Structural maintenance of chromosome proteins, or SMCs for short, are components of a variety of complexes that are central to the organization, utilization and segregation of chromosomes [1]. SMCs are unusually large proteins that fold on themselves to form long coiled coils with an ATPase head at one end. A dimerization motif at the other end allows the proteins to form SMC pairs, which in turn associate with additional structural and regulatory factors. The Smc1 and Smc3 dimer forms the core of the complex known as cohesin, which mediates sister-chromatid cohesion by directly binding sister chromatids together until the onset of anaphase. The Smc2 and Smc4 dimer forms the core of condensin, a protein complex that facilitates DNA chromosome condensation in preparation for mitotic segregation. An additional pair of proteins, Smc5 and Smc6, forms the core of a less well understood complex with important roles in several critical processes including DNA damage checkpoint response and repair. Figure 1a shows schematic representations of SMC complexes and their subunits.

Cohesin is the best studied of the SMC protein complexes. The head domains of the coiled-coil dimer are joined by a third conserved subunit known as a kleisin to form a large protein ring with the central void spanning 30-40 nm [2]. Cohesin binds DNA topologically by entrapping double-stranded DNA molecules within the ring [3]. An accumulating body of evidence supports the notion that cohesin mediates cohesion by embracing the DNA of both sister chromatids [4].

Much less is known about condensin [5]. The complex appears to be rod-like rather than ring-shaped in electron micrographs [6]. It also possesses a mitotically stimulated, ATP-dependent supercoiling activity not found in cohesin [7]. Despite these differences, the conserved structure of the kleisin and SMC subunits suggests that there might be similarities in the way condensin and cohesin associate with DNA. A step toward addressing this possibility was made when cohesin was mapped at high resolution across the budding and fission yeast genomes [8,9]. Massive amounts were found near the centromeres, where the complex counteracts the pulling forces of microtubules from opposite poles of the mitotic spindle. Cohesin was also found at discrete sites on chromosome arms in the intergenic regions between pairs of convergently transcribed genes. Now, a new study from the laboratory of Frank Uhlmann published in *Genes and Development* (D'Ambrosio *et al.* [10]) reports the genome-wide addresses of yeast condensin at high resolution. This work uncovers striking similarities - and significant differences - in the way these two SMC complexes assemble on chromosomes.

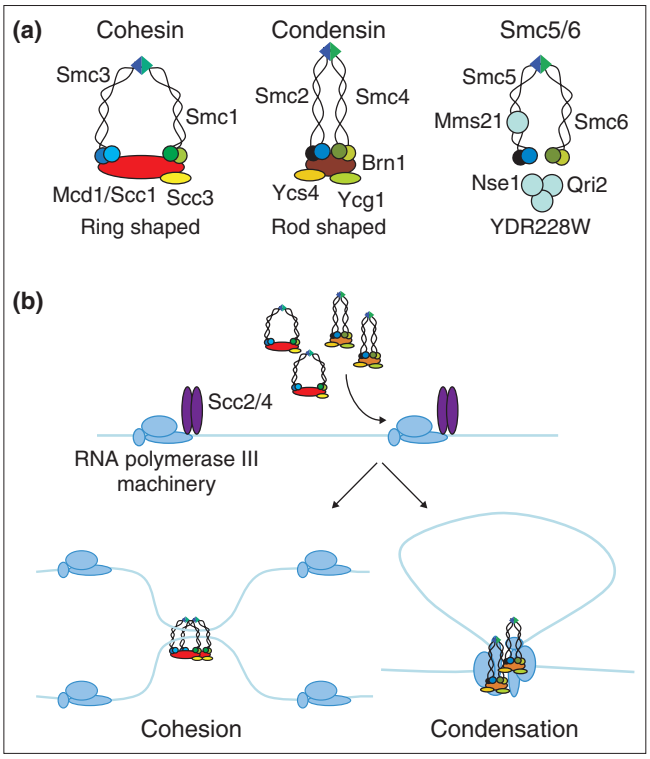

Figure 1
Structure, loading and repositioning of SMC complexes in budding yeast. **(a)** Schematic representation of cohesin, condensin and Smc5/6. Subunits are identified using the *Saccharomyces cerevisiae* nomenclature. The ring- and rod-like shapes of cohesin and condensin are based on electron micrographs. **(b)** Cohesin and condensin are both loaded by Scc2/4 (purple) at sites bound by the entire RNA polymerase III transcriptional apparatus (blue) or at sites bound by TFIIIC alone. Subsequently, cohesin moves to distant locations, embracing DNA and holding the newly replicated sister chromatids together from S phase until mitosis. Condensin stays in contact with the loading sites, bringing together distant TFIIIC sites.

Condensin and cohesin share a common assembly pathway

As with cohesin, D'Ambrosio *et al.* find condensin located at discrete sites, with the number of sites increasing proportionally with chromosome size. However, besides finding condensin with cohesin at centromeres and the rDNA array, where both complexes are known to act [11,12], there was little overlap between the remaining sites on chromosomal arms. Instead, condensin sites correlated most closely with the mapped positions of Scc2, an essential component of the cohesin-loading complex, which also contains Scc4. Previous work had shown that cohesin first associates with these sites and then rapidly redistributes to its final destinations [8]. To determine whether Scc2/4 participates in condensin loading, D'Ambrosio *et al.* turned to conditional mutants of either Scc2 or Scc4. They found that inactivating either protein not only reduced the amount of bound condensin but also eliminated cytological benchmarks of yeast chromosome condensation. Thus, the authors conclude that Scc2/4 is both a cohesin- and a condensin-loading complex. That the chromosomal association of Smc5/6 also requires Scc2/4 suggests that all the SMC complexes associate with DNA via the same pathway [13].

What does Scc2/4 do to achieve loading of SMC complexes? Previous work found that the ATPase activity of cohesin is essential for binding [14,15]. There was speculation that Scc2/4 in conjunction with the Smc1/3 ATPases opened up cohesin to place DNA within the protein ring. Whether condensin and Smc5/6 also bind DNA topologically awaits experimental validation. However, given that all three complexes are assembled on DNA by the same evolutionarily conserved complex, it seems like a reasonable hypothesis.

Condensin/cohesin loading sites defined by RNA polymerase III components

The new maps of condensin and Scc2/4 binding uncovered an additional relationship not appreciated in earlier studies of either complex [8,16]. D'Ambrosio *et al.* [10] discovered that the shared condensin- and Scc2/4-binding sites correspond closely to genes transcribed by RNA polymerase III. This set of genes included the majority of the yeast tRNA genes, of which there are 274 distributed across the genome. Both complexes were even found at some sites known as ETCs, where the general transcription factor TFIIIC binds in the absence of all other RNA polymerase III machinery [17]. While some condensin bound to sites with little or no TFIIIC (centromeres, for example), these results point strongly toward a condensin-loading pathway centered on TFIIIC.

D'Ambrosio *et al.* [10] embarked on a series of experiments to determine whether TFIIIC causes, or just coincides with, condensin binding. First, they showed that introduction of a high-affinity TFIIIC recognition element, the B box, was sufficient to recruit both TFIIIC and condensin. Next they showed that deletion of an existing tRNA gene reduced the surrounding Scc2/4 and condensin. Finally, they demonstrated that inactivation of one of the TFIIIC subunits reduced the amount of Scc2/4 and condensin bound to chromosomes. Taken together, these data strongly support a model in which TFIIIC recruits Scc2/4, which in turn loads condensin onto chromosomes.

SMC family choices: to take root or leave the nest

Unlike cohesin, condensin remains at the Scc2/4 sites throughout the cell cycle, suggesting that the two SMC complexes differ in their mobility after loading. Topological linkage, it was reasoned, endows cohesin with the ability to sample many sites without ever leaving DNA. Thus, sites of loading need not coincide with sites of action. This is probably the case for the silenced *HMR* mating-type locus, where the requirement for a neighboring tRNA gene in cohesion can now be explained in terms of Scc2/4-mediated

loading of cohesin at the gene followed by translocation of the complex to *HMR* [18]. Similarly, when cohesin accumulation was monitored at representative convergent gene pairs, the complex was found first at Scc2/4 sites, sometimes situated more than 10 kb away [8]. It appears, therefore, that cohesin translocation allows the loading and accumulation sites to be separated by substantial distances (Figure 1b).

Why does condensin not translocate after Scc2/4 loading? A simple explanation might be that the complex does not assemble with DNA trapped inside a topological embrace. Alternatively, the complex binds topologically but remains fixed to serve a dedicated function at loading sites. A more fanciful explanation for the apparent persistence of condensin at loading sites is that the complex is actually quite mobile, but translocates while maintaining contact with the original loading site. If the migrating complex were only to stop when encountering another loading site (or fall off in between) then it would appear as if condensin complexes were only at loading sites. In this way, condensin could bring together distant sites into clusters. Indeed, TFIIIC-bound elements in fission yeast form clusters at the nucleolus and nuclear periphery [19].

Budding yeast tRNA genes cluster at the nucleolus, too [20]. In the same issue of *Genes and Development*, a team led by David Engelke reported that clustering of the budding yeast tRNA genes, and the attendant silencing of adjacent RNA polymerase II reporter constructs, requires functional condensin genes (Haeusler *et al.* [21]). These findings suggest that condensin, either through the ability to oligomerize or the ability of single complexes to bind multiple sites, brings together the dispersed tRNA genes (Figure 1b). Accordingly, condensin might be retained at TFIIIC sites to serve as a structural element in the three-dimensional folding of chromosomes. This level of organization persists throughout the cell cycle, and conceivably may precede additional levels of packaging at mitosis.

The results of D'Ambrosio *et al.* [10] raise intriguing questions as to how and why condensin stays in touch with its loading sites, while cohesin moves away. The explanation is likely to relate to the specialized functions of the different SMC complexes, and the need to distinguish between intra-chromatid and inter-chromatid contacts when implementing cohesion and condensation for the accurate segregation of chromosomes at mitosis.

Acknowledgements

This work was supported by funding to MRG from the NIH (GM51402) and the March of Dimes (1-FY08-481) and to MM from the Medical Research Council, UK.

References

1. Nasmyth K, Haering CH: **The structure and function of SMC and kleisin complexes.** *Annu Rev Biochem* 2005, **74:**595-648.
2. Gruber S, Haering CH, Nasmyth K: **Chromosomal cohesin forms a ring.** *Cell* 2003, **112:**765-777.
3. Ivanov D, Nasmyth K: **A topological interaction between cohesin rings and a circular minichromosome.** *Cell* 2005, **122:**849-860.
4. Haering CH, Farcas AM, Arumugam P, Metson J, Nasmyth K: **The cohesin ring concatenates sister DNA molecules.** *Nature* 2008, **454:**297-301.
5. Hirano T: **At the heart of the chromosome: SMC proteins in action.** *Nat Rev Mol Cell Biol* 2006, **7:**311-322.
6. Anderson DE, Losada A, Erickson HP, Hirano T: **Condensin and cohesin display different arm conformations with characteristic hinge angles.** *J Cell Biol* 2002, **156:**419-424.
7. Kimura K, Hirano T: **ATP-dependent positive supercoiling of DNA by 13S condensin: a biochemical implication for chromosome condensation.** *Cell* 1997, **90:**625-634.
8. Lengronne A, Katou Y, Mori S, Yokobayashi S, Kelly GP, Itoh T, Watanabe Y, Shirahige K, Uhlmann F: **Cohesin relocation from sites of chromosomal loading to places of convergent transcription.** *Nature* 2004, **430:**573-578.
9. Glynn EF, Megee PC, Yu HG, Mistrot C, Unal E, Koshland DE, DeRisi JL, Gerton JL: **Genome-wide mapping of the cohesin complex in the yeast *Saccharomyces cerevisiae*.** *PLoS Biol* 2004, **2:**E259.
10. D'Ambrosio C, Schmidt CK, Katou Y, Kelly G, Itoh T, Shirahige K, Uhlmann F: **Identification of cis-acting sites for condensin loading onto budding yeast chromosomes.** *Genes Dev* 2008, **22:**2215-2227.
11. Yong-Gonzalez V, Wang BD, Butylin P, Ouspenski I, Strunnikov A: **Condensin function at centromere chromatin facilitates proper kinetochore tension and ensures correct mitotic segregation of sister chromatids.** *Genes Cells* 2007, **12:**1075-1090.
12. Lavoie BD: **pRb and condensin—local control of global chromosome structure.** *Genes Dev* 2008, **22:**964-969.
13. Lindroos HB, Ström L, Itoh T, Katou Y, Shirahige K, Sjögren C: **Chromosomal association of the Smc5/6 complex reveals that it functions in differently regulated pathways.** *Mol Cell* 2006, **22:**755-767.
14. Arumugam P, Gruber S, Tanaka K, Haering CH, Mechtler K, Nasmyth K: **ATP hydrolysis is required for cohesin's association with chromosomes.** *Curr Biol* 2003, **13:**1941-1953.
15. Weitzer S, Lehane C, Uhlmann F: **A model for ATP hydrolysis-dependent binding of cohesin to DNA.** *Curr Biol* 2003, **13:**1930-1940.
16. Wang BD, Eyre D, Basrai M, Lichten M, Strunnikov A: **Condensin binding at distinct and specific chromosomal sites in the *Saccharomyces cerevisiae* genome.** *Mol Cell Biol* 2005, **25:**7216-7225.
17. Moqtaderi Z, Struhl K: **Genome-wide occupancy profile of the RNA polymerase III machinery in Saccharomyces cerevisiae reveals loci with incomplete transcription complexes.** *Mol Cell Biol* 2004, **24:**4118-4127.
18. Dubey RN, Gartenberg MR: **A tDNA establishes cohesion of a neighboring silent chromatin domain.** *Genes Dev* 2007, **21:**2150-2160.
19. Noma K, Cam HP, Maraia RJ, Grewal SI: **A role for TFIIIC transcription factor complex in genome organization.** *Cell* 2006, **125:**859-872.
20. Haeusler RA, Engelke DR: **Spatial organization of transcription by RNA polymerase III.** *Nucleic Acids Res* 2006, **34:**4826-4836.
21. Haeusler RA, Pratt-Hyatt M, Good PD, Gipson TA, Engelke DR: **Clustering of yeast tRNA genes is mediated by specific association of condensin with tRNA gene transcription complexes.** *Genes Dev* 2008, **22:**2204-2214.