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Current Opinion in Cell Biology

Control of chromosome interactions by condensin complexes

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Although condensin protein complexes have long been known for their central role during the formation of mitotic chromosomes, new evidence suggests they also act as global regulators of genome topology during all phases of the cell cycle. By controlling intra-chromosomal and inter-chromosomal DNA interactions, condensins function in various contexts of chromosome biology, from the regulation of transcription to the unpairing of homologous chromosomes. This review highlights recent advances in understanding how these global functions might be intimately linked to the molecular architecture of condensins and their extraordinary mode of binding to DNA.

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Current Opinion in Cell Biology 2015, **34**:94–100

This review comes from a themed issue on **Cell nucleus**

Edited by **Katherine L Wilson** and **Karsten Weis**

For a complete overview see the Issue and the Editorial

Available online 18th June 2015

http://dx.doi.org/10.1016/j.ceb.2015.05.008

Introduction: composition and architecture of condensin complexes

Eukaryotic condensins are built from five different subunits, which assemble to form complexes of more than half a megadalton in size (reviewed in [1,2]). The single condensin complex encoded by yeast genomes contains two subunits of the Structural Maintenance of Chromosomes (SMC) protein family, one subunit of the kleisin protein family, and two subunits that are predicted to be largely composed of α-helical HEAT (Huntingtin, Elongation factor 3, the A subunit of protein phosphatase 2A, TOR lipid kinase) repeat motifs. In most metazoan organisms, two different versions of condensin exist. Both versions share the same set of SMC subunits but differ in the composition of their kleisin and HEAT-repeat subunits (see Table 1).

The two SMC subunits are characterized by ~45-nm long anti-parallel coiled coils that connect adenosine triphosphate (ATP) Binding Cassette ATPase 'head' domains at one end of the coil to 'hinge' dimerization domains at the other end (Figure 1a). Association of Smc2 and Smc4 via their hinge domains results in the formation of stable heterodimers [3]. Additional interactions between the Smc2 and Smc4 head domains upon ATP binding, and their dissociation upon ATP hydrolysis, are thought to drive large-scale structural rearrangements, which might be fundamental for condensin complexes to engage DNA (see below). The simultaneous binding of both SMC head domains to different ends of the kleisin subunit results in the formation of a large annular structure that resembles the architecture of cohesin, another eukaryotic SMC–kleisin protein complex whose major function is to hold together sister chromatids (reviewed in [4]). In addition to bridging the SMC heads, the condensin kleisin subunit functions as a scaffold for the assembly of the two HEAT-repeat subunits [5,6••].

The kleisin subunit of prokaryotic condensin complexes binds to the ATPase head domains of an SMC homodimer to create a ring-shaped architecture similar to that of eukaryotic condensins (Figure 1b; reviewed in [7]). The central region of the prokaryotic kleisin subunit binds a pair of proteins that are composed of winged-helix domains and share no apparent homology with eukaryotic HEAT-repeat subunits [8,9••]. Remarkably, the two ends of the prokaryotic kleisin protein contact the SMC head domains in fundamentally different ways: the N terminus binds the coiled coil region adjacent to the SMC head domain, whereas the C terminus contacts the ATPase head domain surface opposite the coiled coil [9••]. The discovery that the eukaryotic cohesin kleisin subunit makes analogous (asymmetric) contacts with the ATPase heads of its associated SMC heterodimer [10–12] suggests that this asymmetry is a conserved feature of all SMC protein complexes, including eukaryotic condensins (Figure 1a).

Condensins control chromosome interactions

Recent genome-wide mapping and functional studies have revealed that condensin complexes are not only essential for the formation of properly folded mitotic chromosomes, but also affect the three-dimensional organization of specific chromosome regions in the interphase nucleus.

In budding yeast, condensin localizes to tRNA genes and promotes the clustering of these genes near the nucleolus [13]. Recruitment of condensin to tRNA genes, and other genes transcribed by RNA polymerase (pol) III, might be

Table 1

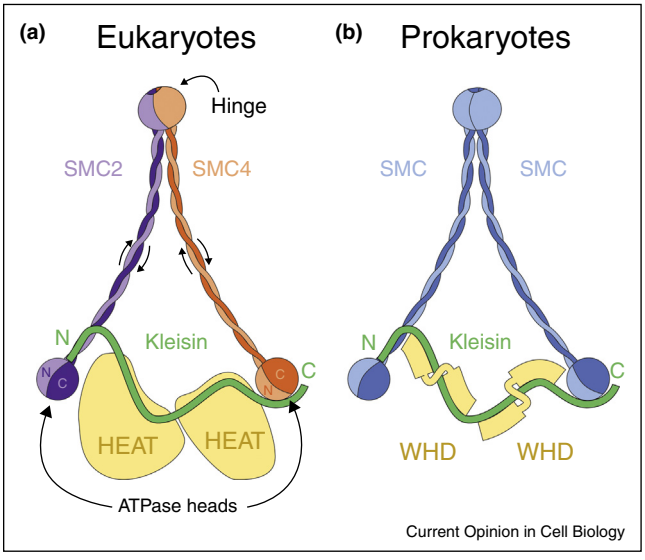
Designation of condensin subunits in different model organisms

Species	Type	SMC	SMC	Kleisin	HEAT	HEAT
S. cerevisiae		Smc2	Smc4	Brn1	Ycs4	Ycg1
S. pombe		Cut14	Cut3	Cnd2	Cnd1	Cnd3
C. elegans	I^{DC}	MIX-1	DPY-27	DPY-26	DPY-28	CAPG-1
	I	MIX-1	SMC-4	DPY-26	DPY-28	CAPG-1
	II	MIX-1	SMC-4	KLE-2	HCP-6	CAPG-2
D. melanogaster	I	Smc2	Smc4	Barren	Cap-D2	Cap-G
	II	Smc2	Smc4	Cap-H2	Cap-D3	–*
H. sapiens	I	SMC2	SMC4	CAP-H	CAP-D2	CAP-G
	II	SMC2	SMC4	CAP-H2	CAP-D3	CAP-G2

* There is no evidence for the existence of a second HEAT-repeat subunit in the *D. melanogaster* condensin II complex [57]. ^{DC} Dosage Compensation Complex.

mediated by direct interaction with the transcription factor complex TFIIIC [13,14]. TFIIIC-dependent recruitment to the large number of tRNA genes located near centromeres is suggested to play a role in accumulating ~240 condensin molecules into a cylindrical arrangement of ~350 nm diameter around the spindle axis as cells passage through mitosis [15•]. This condensin 'cylinder', surrounded by a 'barrel' of cohesin complexes, is proposed to create a 'chromatin spring' that balances spindle microtubule forces [16]. Another protein crucial for condensin complexes to accumulate near budding yeast centromeres, named shugoshin (Sgo1), is increasingly recognized as a hub that recruits different proteins to kinetochores [17•,18•].

Figure 1



The architecture of eukaryotic and prokaryotic condensin complexes. **(a)** In eukaryotic condensin, two different SMC subunits hetero-dimerize via their toroid-shaped 'hinge' domains situated at one end of their ~45-nm long intra-molecular anti-parallel coiled-coil region. The N-terminal and C-terminal halves of each SMC subunit are displayed in light and dark shading. The kleisin subunit connects the ATPase 'head' domains situated at the other ends of the SMC coiled coils to create a tripartite ring structure, and also recruits two additional subunits composed of α-helical HEAT-repeats. **(b)** In prokaryotic condensin, the kleisin subunit binds to the two ATPase head domains of an SMC homodimer and to two copies of a subunit composed of tandem winged-helix domains (WHD). The SMC-like MukBEF complexes found in many γ-proteobacteria (not shown) deviate in the arrangement of their kleisin subunits [8].

In fission yeast, condensin is also recruited to tRNA genes and causes these genes to cluster near centromeres [19]. In addition, fission yeast condensin is recruited to long terminal repeat (LTR) retrotransposons by the Ku70–Ku80 heterodimer, a component of the non-homologous end-joining (NHEJ) DNA damage repair pathway. Together, these protein complexes function in the clustering of LTR retrotransposons at centromeres [20]. The precise role of condensin complexes at LTR retrotransposons is not yet understood. One intriguing possibility is that they suppress transposition, since mutations in *Drosophila* condensin II result in the mobilization and loss of retrotransposon sequences [21]. Interestingly, the *Drosophila* condensin II complex counteracts the pairing of homologous retrotransposon loci on different chromosomes. This suggests that condensin complexes can, depending on the chromosomal context, either promote or counteract the association of certain genomic loci.

The role of the *Drosophila* condensin II complex in preventing inter-chromosomal contacts is not limited to retrotransposons. For example, when condensin II subunits are mutated, polytene chromosomes that should separate during nurse cell development instead remain together, as do centromeric heterochromatin regions of homologous chromosomes [22,23]. Condensin II mutations also enhance a process termed transvection, in which gene expression from one allele is boosted by association with the other allele on the homologous chromosome [24]. These interphase activities of condensin II are thought to be inhibited by ubiquitin-dependent degradation of the kleisin subunit by the SCF (Skp, Cullin, F-box containing) complex [25] and are also controlled by association with a chromodomain-containing protein

named Mrg15 [26]. The role of condensin II complexes in preventing inter-chromosome association appears to be conserved in mammals, since neuronal stem cells and postmitotic neurons of condensin II knockout mice have fewer (and larger) 'chromocenters', which form by associations between centromeric H3K9me3-marked heterochromatin regions [27•].

Loading condensin complexes onto chromosomes

To obtain insights into the molecular mechanisms behind the positive and negative control of chromosome interactions by condensins, it will be necessary to understand how condensin complexes associate with their chromosome substrates. Studies in budding yeast suggest that loading onto chromosomes of condensin, in analogy to cohesin, is promoted by the conserved DNA-binding protein Scc2 and its partner Scc4 [14]. Similarly in cultured human cells, knockdown of SCC2 (NIPBL) reduces condensin II binding to chromosomes [28•]. A loss-of-function mutation of SCC-2 in *Caenorhabditis elegans*, by contrast, seems to have little effect on chromosomal condensin levels [29]. Whether Scc2–Scc4 directly regulates condensin loading onto chromosomes, or functions indirectly, either via loading cohesin onto chromosomes, which in turn recruits condensin-loading factors like Sgo1 [17•], or via maintaining nucleosome-free promoter regions [30], remains to be determined.

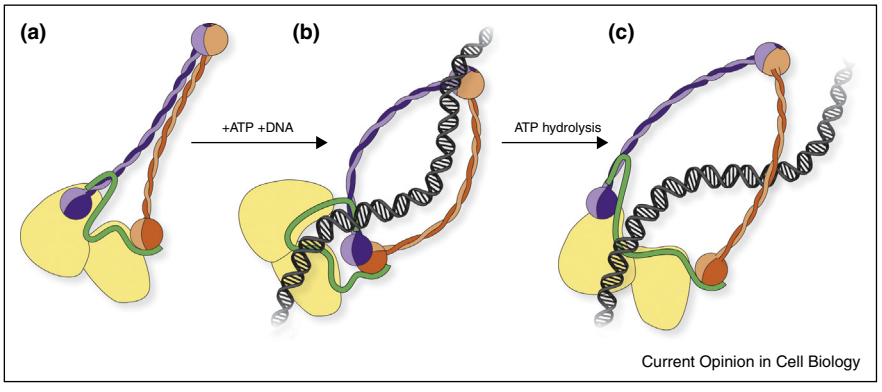
New studies find close links between transcriptional activity and the localization of condensin complexes on chromosomes. Condensin enrichment at gene promoters correlates with higher levels of transcription of downstream genes in both *C. elegans* [31] and cultured chicken cells [32•]. In cultured human cell lines, the amount of condensin II that localizes to mRNA-encoding genes corresponds to the level of RNA polymerase II at these genes, and inducing transcription of a selected target gene is sufficient to target condensin II [28•]. Furthermore, condensin levels at tRNA genes are higher in fission yeast mutants with higher levels of RNA pol III transcripts [33]. Apparently, condensin complexes prefer to localize at sites of active transcription, possibly reflecting their more accessible chromatin architecture.

Whether condensin complexes in return influence transcriptional activity is, however, less clear. Depletion of condensin in human embryonic stem cells affects gene expression profiles, but considerably less so than depletion of, for example, cohesin [28•]. Cohesin is proposed to regulate gene expression by stabilizing enhancer-promoter loops (reviewed in [34]), and the enrichment of condensin II at enhancers in embryonic stem cells suggests a similar role. However, very few enhancers bind condensin in cultured *Drosophila* cells [35]. Definitive evidence for a gene regulatory function of a condensin complex comes from *C. elegans*, where a specialized dosage compensation complex (DCC; see Table 1) down-regulates transcription from the two X chromosomes in hermaphrodite animals (reviewed in [36]). Whether condensin complexes have a single unified role in gene regulation across species remains an open question.

The mechanism of condensin loading

The molecular basis of condensin association with chromosomes is a central unresolved issue. Condensin complexes form tripartite ring structures (Figure 1a) that might entrap chromatin fibers in a manner equivalent to cohesin complexes (reviewed in [37]). Consistent with this idea, 'forced' opening of the condensin ring structure, achieved by site-specific proteolytic cleavage, releases budding yeast condensin from chromosomes [38] and prevents clearance of chromosome arms from

Figure 2

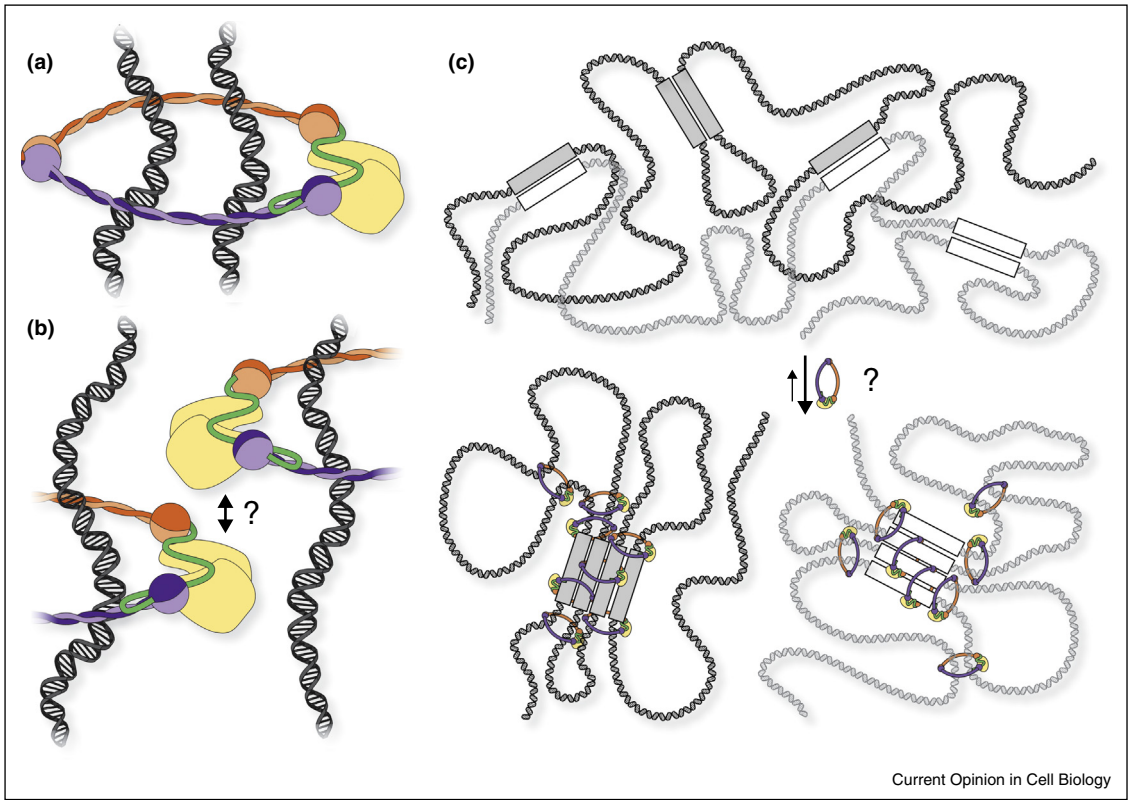


A hypothetical mechanism for the entrapment of DNA helices within condensin rings. **(a)** Recent structural studies suggest that isolated condensin complexes assume a rod-shaped conformation [41••]. **(b)** ATP-dependent dimerization of the SMC heads might trigger separation of the coiled coils into a ring-shaped conformation. This might expose new contacts between the hinge domain and the DNA helix captured by the HEAT-repeat subunits [6••]. **(c)** DNA binding might stimulate ATP hydrolysis and transfer the captured DNA into the ring, presumably via transient dissociation of one of the three ring subunit interfaces.

the cell midzone during anaphase segregation [39]. Final proof for the condensin ring hypothesis is, however, still missing. If DNA were indeed entrapped within the condensin ring, one would, for example, expect that chemical cross-linking of the three interfaces between the ring subunits would create covalent catenanes with circular chromosomes, similar to those created by covalent circularization of cohesin rings [10,40]. Such experiments will be essential to resolve the mechanisms behind condensin function.

A recent crystal structure of the Smc2–Smc4 hinge and adjacent coiled coils, as well as cross-linking experiments, demonstrate that the Smc2 and Smc4 coiled coils can associate over a considerable portion of their lengths (Figure 2a) [41••]. This notion is consistent with the rod-like appearance of Smc2–Smc4 heterodimers seen by electron microscopy [3]. Is this rod-like conformation compatible with DNA entrapment between the coiled coils, as predicted by the ring hypothesis? Experiments with *Bacillus subtilis* SMC homodimers suggest that the coiled coils come apart upon ATP binding by the head domains [41••]. Thus, ATP binding might drive disengagement of the coils from a rod-like (Figure 2a) into a ring-like conformation (Figure 2b). ATP hydrolysis might then promote the temporary disengagement of one of the interfaces between ring subunits, allowing DNA passage into the ring to complete the loading cycle (Figure 2c). One candidate 'gate' in the complex is the SMC hinge interface, which, in the cohesin complex, has been proposed to disengage for DNA entry in response to ATP-dependent conformational changes [42,43]. If the SMCs could not return to the rod-shaped conformation as long as DNA were present between the coiled coils, this would provide an elegant mechanism to prevent ring re-opening after DNA entrapment. In this scenario, the DNA helix might initially be positioned for ring entry by additional interactions with the SMC hinge domain [44] and/or the kleisin–HEAT repeat subunits [6••] (Figure 2b). Even though first experiments failed to detect any effect of ATP on the Smc2–Smc4 coiled coil crosslinking efficiency of yeast condensin complexes

Figure 3



Hypothetical regulation of chromosome interactions via intra-chromosomal linkages. **(a)** Condensin rings might connect distant segments of one chromosome, or different chromosomes, by encircling them within the same ring structure. **(b)** Alternatively, each condensin ring might entrap a single chromatin fiber, and then associate at the protein–protein level to form clusters. **(c)** The formation of intra-chromosomal linkages between condensin-bound regions (e.g., tRNA genes, shown as boxes) might help to prevent the association of regions from different chromosomes (shown as light and dark DNA helices). How condensin complexes favor intra-chromosomal and disfavor inter-chromosomal linkages are important open questions.

[41••], this model is not yet ruled out. More sensitive assays may be needed to detect structural re-arrangements in eukaryotic condensin holocomplexes.

Models for condensin-mediated regulation of chromosome interactions

Can the entrapment of chromatin fibers explain both the positive and negative effects of condensins on chromosome interactions? If condensins encircled two (or more) DNA helices simultaneously (Figure 3a), they could act as a topological linkers. Alternatively two (or more) condensin complexes, each entrapping a single DNA helix, might interact as described for the condensin-like *Escherichia coli* MukBEF complex [8,45] (Figure 3b). Independent of which of these two models is correct, condensin-mediated chromosome linkages could explain the clustering of regions (e.g., tRNA genes) that are otherwise dispersed throughout the genome. If condensin complexes preferentially linked regions that are located on the same chromosome to selectively form intra-chromosomal clusters, those regions might be protected from inter-chromosomal associations (Figure 3c). Such a protective role could explain why condensin II complexes are required to retain the spatial separation of homologous chromosomes and centromeric heterochromatin regions in *Drosophila*. The same mechanism might be the basis for condensin II function in the resolution of sister chromatids during S phase in human cells [46] and for condensin function during the decatenation of intertwined ring chromosomes during mitosis in budding yeast [47]. By generating intra-chromosomal linkages, condensin might shift the equilibrium between catenation and decatenation reactions, catalyzed by topoisomerase II, towards decatenation. Alternatively, condensin might actively promote decatenation by introducing positive DNA supercoils, known to promote decatenation of ring chromosomes by topoisomerase II [48]. Condensin-mediated overwinding of the DNA double helix is also suggested as a mechanism to drive chromosome condensation [49,50].

Similarly, the prokaryotic condensin complex is required for efficient resolution of replicated chromosomes in fast growing *B. subtilis* cells, particularly at origins of replication, to which condensin is recruited by the DNA-binding protein ParB [51–54]. The discovery that the SMC protein in *E. coli*, MukB, directly interacts with and activates the type-II topoisomerase IV could explain how condensin-bound regions are decatenated [55,56]. However, MukB does not stimulate decatenation of multiple linked DNA molecules by topoisomerase IV *in vitro*, and mutation of one of the subunits of topoisomerase IV does not prevent origin resolution in *B. subtilis* [52]. Since the decatenation activity of eukaryotic topoisomerase II is likewise unaffected by condensin complexes isolated from budding yeast [47], any effects of condensin complexes on chromosome decatenation *in vivo* might be indirect.

Conclusions and outlook

The expanding roles for condensin — from organizer of mitotic chromosomes to global regulator of genome architecture throughout the cell cycle — have raised significant interest in understanding its working principles. Does condensin function primarily as an enzyme that alters DNA supercoiling, as a structural chromatin linker, or as a combination of both? One possible option is that condensin complexes change DNA topology by inducing the formation of intra-chromosomal DNA crossings. Ring formation around this type of crossing site would ensure that a single condensin complex entraps two DNA helices of the same chromosome. Understanding these topological connections will require identifying the entry and exit gates for DNA within the condensin ring, resolving the still-enigmatic role of the SMC ATPase activity, and determining how chromosome association dynamics are regulated chromosome-wide and at specific loci. The mechanisms by which SMC–kleisin protein complexes manipulate and encircle DNA will be essential to understand genome organization in all living species.

Acknowledgements

We thank all members of the Haering group for comments and suggestions. Work in the authors' laboratory is funded by EMBL and grants HA5853/1-2 and HA5853/2-1 from the German Research Foundation.

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