© 2019. Published by The Company of Biologists Ltd | Journal of Cell Science (2019) 132, jcs220491. doi:10.1242/jcs.220491

REVIEW

SUBJECT COLLECTION: EXPLORING THE NUCLEUS

Condensins and cohesins – one of these things is not like the other!

Robert V. Skibbens

ABSTRACT

Condensins and cohesins are highly conserved complexes that tether together DNA loci within a single DNA molecule to produce DNA loops. Condensin and cohesin structures, however, are different, and the DNA loops produced by each underlie distinct cell processes. Condensin rods compact chromosomes during mitosis, with condensin I and II complexes producing spatially defined and nested looping in metazoan cells. Structurally adaptive cohesin rings produce loops, which organize the genome during interphase. Cohesin-mediated loops, termed topologically associating domains or TADs, antagonize the formation of epigenetically defined but untethered DNA volumes, termed compartments. While condensin complexes formed through *cis*-interactions must maintain chromatin compaction throughout mitosis, cohesins remain highly dynamic during interphase to allow for transcription-mediated responses to external cues and the execution of developmental programs. Here, I review differences in condensin and cohesin structures, and highlight recent advances regarding the intramolecular or *cis*-based tetherings through which condensins compact DNA during mitosis and cohesins organize the genome during interphase.

KEY WORDS: Condensin, Cohesin, SMC, Structural maintenance of chromosomes, TADs, Transcription, Chromosome compartmentalization

Introduction

The genome of a cell undergoes a myriad of complex structural contortions. For instance, the products of chromosome duplication, termed sister chromatids, become tethered together during S phase in a process that is coupled to DNA replication (reviewed in Skibbens, 2008; Villa-Hernández and Bermejo, 2018). Even as these sisters remain tethered together (termed cohesion), each chromatid tightly condenses during mitosis to produce highly compacted entities that are typically easily discernible under a light microscope. Upon exiting mitosis, chromosomes decondense; this allows the cell to establish distinct chromosomal domains or territories through which the genome is organized and gene transcription regulated during interphase. Finally, *de novo* DNA tethering of sister chromatids can arise at any time after S phase to promote repair of damaged DNA (reviewed in Dorsett and Merkenschlager, 2013; Jeppsson et al., 2014; Skibbens, 2016; Gelot et al., 2016). A family of highly conserved structural maintenance of chromosome (SMC) complexes is critical for all of these aspects of chromosome biology. Of primary interest here are the condensin and cohesin SMC complexes that modulate chromosome structure and, in combination, impact chromosome segregation during mitosis, as well as regulate gene transcription during interphase. SMC-related complexes that function specifically in either DNA damage or in dosage-compensation are reviewed elsewhere (see Losada and Hirano, 2005; Csankovszki et al., 2009; Gligoris and Löwe, 2016; Pezic et al., 2017).

Condensin and cohesin complexes both promote DNA looping by tethering together DNA loci within a single DNA molecule. These intramolecular, or *cis*-based, tetherings, however, play very different roles throughout the cell cycle. Condensins promote chromatin condensation (also termed compaction) in preparation for chromosome segregation during mitosis (see Hirano, 2016; Jeppsson et al., 2014); however, the mechanism through which condensins achieve the monumental task of compacting entire genomes remains mostly obscure. Chromosome compaction also requires cohesins, which bind to DNA before condensin, such that the mitotic *cis*-tethering activities of these two SMCs are likely interdependent and complex (Guacci et al., 1997; Skibbens et al., 1999; Hartman et al., 2000; Lavoie et al., 2002; D'Ambrosio et al., 2008; Guacci and Koshland, 2012; Tedeschi et al., 2013; Harris et al., 2014; Challa et al., 2016). Recent studies expand the roles of cohesin *cis*-based DNA tetherings to include interphase. Here, cohesins produce loops that establish genome-wide organization and impact transcription states within the nucleus. The role of cohesins is even more nuanced in that cohesins produce intermolecular or *trans*-based tetherings, which tether together sister chromatids during portions of both interphase and mitosis. Intriguingly, the roles of cohesins in *cis*- and *trans*-tetherings are genetically separable (Rowland et al., 2009; Sutani et al., 2009; Rolef Ben-Shahar et al., 2008; Guacci and Koshland, 2012; Rudra and Skibbens, 2013; Tong and Skibbens, 2014). Future studies are necessary to address the fundamental question as to how cohesins are directed toward either *cis*- or *trans*-based tetherings.

How do cohesins and condensins regulate such different aspects of chromosome biology? To address these issues, this Review starts at a 'micro' level by discussing cohesin and condensin structure, before turning to exciting new evidence that condensins uni-directionally translocate along DNA and extrude DNA loops, whereas cohesins entrap and bi-directionally diffuse along DNA. The Review then shifts to a more 'macro' level by highlighting the coordination of two distinct condensin complexes (termed condensin I and II), which compact the genome during mitosis. Finally, I turn to cohesin complexes that produce dynamic and responsive genomic architectures within the nucleus during interphase through which gene transcription is regulated. For a discussion of cohesin roles in mitotic chromosome segregation, the reader is directed to several in-depth reviews on the topic (e.g. Jeppsson et al., 2014; Marston, 2014; Skibbens, 2016; Morales and Losada, 2018).

Structural considerations of cohesins and condensins

All SMC complexes contain ∼100-nm-long SMC subunits that fold at a centrally positioned 'hinge' so that the globular N- and

Department of Biological Sciences, 111 Research Drive, Lehigh University, Bethlehem, PA 18015, USA.

*Author for correspondence (rvs3@Lehigh.edu)

R.V.S., 0000-0003-4216-8306

Journal of Cell Science (2019) 132, jcs220491. doi:10.1242/jcs.220491

C-termini can interact to form an ATPase 'head'. The folded over 50-nm-long SMC subunits heterodimerize (apart from archaea SMCs, which homodimerize) primarily through hinge–hinge interactions, but also interact through head–head binding. ATPase heads are then bound by a capping subunit, which further recruits other non-SMC subunits, all of which are unique to each type of SMC complex. At the most fundamental level, however, these complexes are defined by their associated SMC subunits: Smc1 and Smc3 for cohesins, and Smc2 and Smc4 for condensins (Fig. 1).

The 'Gumby' model of cohesins

Gumby is a highly malleable clay figure featured in numerous animation films and parodied by Eddie Murphy (Saturday Night Live). A wealth of evidence indicates that cohesins are equally malleable. For instance, the elongated (50 nm) coiled coil domains of Smc1 and Smc3 are floppy and often observed to fold back on themselves, so that the head and hinge of cohesin are in close proximity. Electron microscopy (EM) studies in addition result in images in which the coiled coil domains separate for some portion of their length to create a lumen within the cohesin complex (Melby et al., 1998; Anderson et al., 2002; Yoshimura et al., 2002; Sakai et al., 2003; Huis in 't Veld et al., 2014; Gligoris et al., 2014; Barysz et al., 2015; Diebold-Durand et al., 2017) (Fig. 2). The description of cohesin as a 'huge triangular ring' of 40 nm in diameter (Gruber et al., 2003), and subsequent studies showing that cohesin diffuses bi-directionally along DNA and dissociates from linearized DNA, led to a popular model that cohesins entrap DNA (or even two DNA molecules) within a central lumen (Haering et al., 2002; Gruber et al., 2003; Ivanov and Nasmyth, 2005; Stigler et al., 2016; Davidson et al., 2016), although several findings negate many aspects of this model (see below).

Given that DNA can adopt complex secondary structures and is often bound by protein (e.g. histones, transcription factors, chromatin remodeling complexes and silencers), it became important to more rigorously ascertain the size of the cohesin lumen and the limits, if any, to cohesin diffusion along DNA. A convergence of studies revealed that cohesin can migrate past small barriers of up to 11 nm in diameter (e.g. nucleosomes, and the catalytically inactive EcoRI and dCas9), but failed to diffuse past more moderately sized barriers of ∼20 nm (the size of digoxigenin-quantum dots or EcoR1 tagged with quantum dots) (Ivanov and Nasmyth, 2005; Stigler et al., 2016; Davidson et al., 2016). Crosslinking studies further revealed that the majority – but not all – of the coiled-coil domains of the cohesin SMC subunits are closely apposed and form a mostly flattened structure (Huis in 't Veld et al., 2014; Gligoris and Löwe, 2016) (Fig. 2). Thus, more contemporary models suggest that cohesins entrap DNA, but only a single DNA molecule, such that the tethering of two DNA loci requires cohesin oligomerization (reviewed in Skibbens, 2016; Rankin and Dawson, 2016; Matityahu and Onn, 2018). Cohesin oligomerization is strongly supported by findings that epitope-tagged Smc3 can co-immunoprecipitate Smc3 that bears a different epitope tag, and that Mcd1 similarly can co-immunoprecipitate other Mcd1 (Scc1 or RAD21 in metazoans) proteins (Haering et al., 2002; Sakai et al., 2003; Mc Intyre et al., 2007; Zhang et al., 2008; Huis in 't Veld et al., 2014). Genetic studies further support oligomerization, as expression of two different alleles of the same cohesin subunit (both of which are non-functional) in combination rescue cell viability (Eng et al., 2015). Another challenge to the model that one ring entraps two chromatid sisters is based on cohesin inactivation during mitosis. Instead of cohesin dissociation for either one or both sisters, cohesins remained bound to each sister, suggesting that

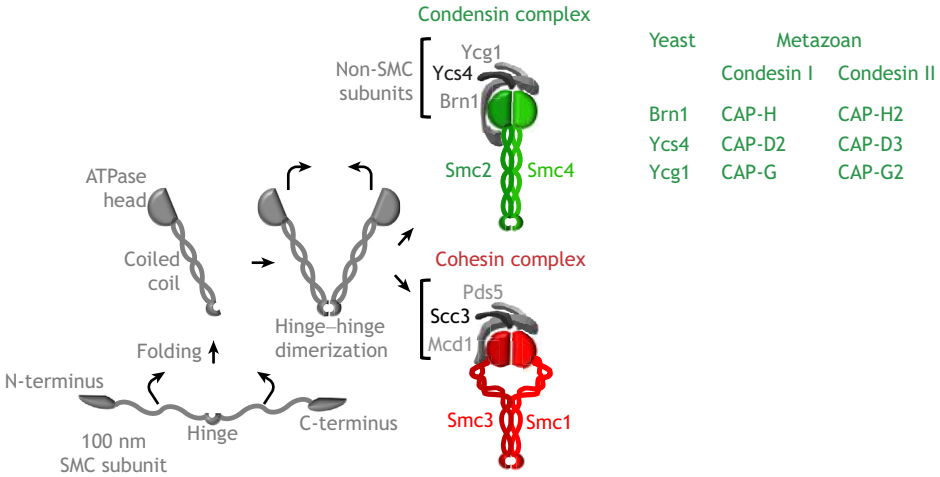

Fig. 1. SMC assemblies. The stereotypical folding and dimerization of SMC subunits is shown in gray; 100-nm-long SMC proteins fold at a central hinge and allow for N- and C-terminal binding to form ATPase heads. SMCs dimerize predominantly through hinge-hinge binding but also head–head binding. Condensins (shown in green) are formed from Smc2 and Smc4 heterodimers that recruit the non-SMC subunits Brn1, Ycs4 and Ycg1 to form flexible rods (see Fig. 2). Cohesins (shown in red) are formed from Smc1 (SMC1a or SMC1b in metazoans) and Smc3 heterodimers that recruit the non-SMC subunits Mcd1, Scc3 and Pds5 to form flattened rings (shown) but can adopt other conformations, such as rods, open V-shapes or C-clamps (not shown). Yeast contain single copies of Brn1, Ycs4 and Ycg1, but metazoan cells contain paralogs, which give rise to unique subtypes termed condensin I (CAP-H, CAP-D2 and CAP-G, encoded by *NCAPH, NCAPD2* and *NCAPG*, respectively) and condensin II (CAP-H2, CAP-D3, and CAP-G2, encoded by *NCAPH2, NCAPD3* and *NCAPG2*, respectively). Metazoan cells also contain subunit paralogs (RAD21 or RAD21L for Mcd1, SA1/STAG1, SA2/STAG2 or SA3/STAG3 for Scc3, and PDS5a or PDS5b/APRIN for Pds5), but the assembly of non-SMC subunits into cohesin complexes is less well defined. Note that metazoan cells also contain Sororin, which is absent in yeast (reviewed in Jeppsson et al., 2014; Marston, 2014).

Journal of Cell Science (2019) 132, jcs220491. doi:10.1242/jcs.220491

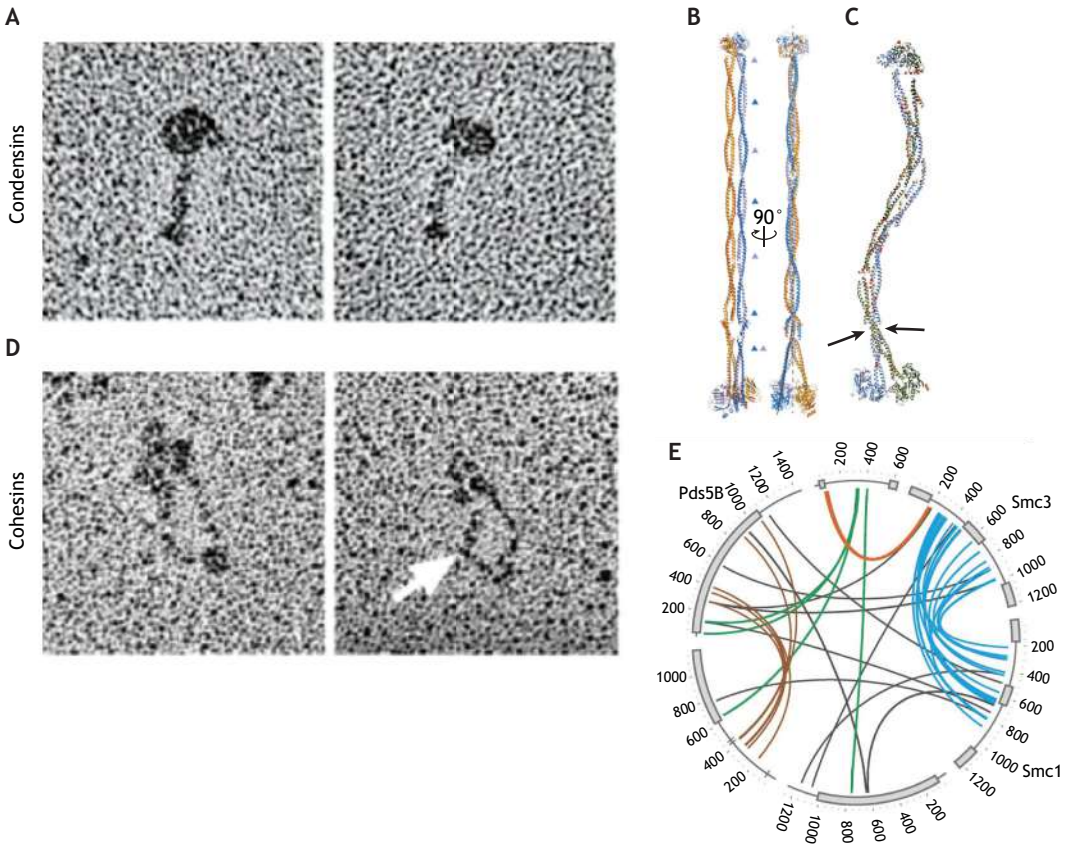

Fig. 2. Condensin rods versus cohesin rings. Numerous strategies have revealed that condensins predominantly form lumen-less rods, whereas cohesins form flattened rings. (A–C) Images obtained by EM of human condensins (A) are placed next to schematics that summarize crystallographic analyses of both archaea (B) and chicken (C) condensins. All strategies produce evidence that condensins predominantly exhibit lumen-less rod-like structures that are conserved across evolution. Arrows in C highlight updated SMC coiled coil alignments (Barysz et al., 2015). (D,E) Images obtained by EM of human cohesins (D) are placed next to a schematic (E) that summarizes the extensive intermolecular cross-links (blue lines) between SMC1 and SMC3 coiled-coil domains identified by chemical cross-linking studies of human cohesins. The combination of these studies suggests that cohesins can adopt a ring shape, but that extensive regions of the coiled coil domains typically are closely apposed. Arrow in right panel of D indicates flexible hinge in SMC coiled coil domain within the cohesin complex (Anderson et al., 2002). See Fig. 1 for a schematic that represents cohesin as a somewhat flattened structure. Note that it remains controversial as to the extent to which any of these structures, extricated from cells, represent fully assembled and functional complexes. Images in A and D are modified from Anderson et al. (2002), with permission from Rockefeller Press). The image in B is modified from Diebold-Durand et al. (2017) and the image in C is modified from Barysz et al. (2015) where they were published under a CC BY 4.0 license (http://creativecommons.org/licenses/by/4.0/). The image in E is modified from Huis in 't Veld et al. (2014) with permission from the AAAS.

cohesion occurs through the oligomerization of cohesins that each associate with one sister (Kulemzina et al., 2012; Eng et al., 2014, 2015; Tong and Skibbens, 2015).

If cohesins topologically entrap a DNA molecule and diffuse in a bi-directional manner and in the absence of ATP, what drives cohesin migration? Early studies suggested that cohesins are either redistributed (release and rebind) or pushed along DNA *in vivo* by migrating transcription complexes (Glynn et al., 2004; Lengronne et al., 2004). Intriguingly, *in vitro* analyses documents that even DNA translocases with small diameters (FtsK at 13 nm and T7 RNA polymerase at 6 to 8 nm) can push cohesin along DNA (Stigler et al., 2016; Davidson et al., 2016; Kim and Larson, 2007); findings that also suggest that the cohesin lumen is quite limited. It is further worth keeping in mind that the highly flexible coiled-coil SMC domains allow the Gumby-esque cohesin to convert between numerous conformations that include partially flattened rings with a lumen, lumen-less rods, open V-shaped structures and folded-over rings that form C-shaped clamps (Huang et al., 2005; Skibbens, 2016; Xu et al., 2018). While DNA entrapment is certainly one and an important feature of cohesin, lateral (non-topological) binding to DNA may be equally important. Future structural studies are required to differentiate between the manners through which cohesins bind either a single DNA locus, tether together (possibly as oligomers) two DNA loci, direct cohesin toward *cis*- versus *trans*-tethers and enable cohesin to migrate along DNA.

Condensin – the uptight and slim sibling of cohesin

Generating testable models of condensin activity must be similarly predicated on a clear and defined condensin structure, and this appears to be distinct from that of cohesins. For instance, early pioneering EM and atomic force microscopy (AFM) analyses of both archaeal SMC complexes and eukaryotic condensins yielded images of lumen-less rod-like structures that were quite distinct from those of cohesin open V or ring-like structures (Melby et al., 1998; Anderson et al., 2002; Yoshimura et al., 2002) (Fig. 2). Chemical cross-linking and mass spectroscopy studies of both yeast and chick condensins indeed confirm that massive intermolecular cross-links occur along the entire length of Smc2 and Smc4 coiled-coil domains – revealing a closed rod-like structure in the absence of a central lumen (Barysz et al., 2015; Soh et al., 2015) (Fig. 2). Crystallographic and EM studies of archaea SMC complexes produced similar results, in which SMC coiled-coil domains are closely apposed along their entire length (a single and minor interruption occurs that is compensated for by an additional flanking

crosslink) (Diebold-Durand et al., 2017; Soh et al., 2015) (Fig. 2). Intriguingly, crosslinks between SMC ATPase head domains were detected only in ATP hydrolysis mutants (Barysz et al., 2015; Diebold-Durand et al., 2017). Thus, SMC heads may adopt different conformations (or be separate and re-close) during cycles of ATP binding and hydrolysis.

The predominant findings that condensins exist as flexible but lumen-less rods are difficult to reconcile with current depictions of condensins as gaping circular rings (Ganji et al., 2018; Thattikota et al., 2018; Thadani et al., 2018; Kschonsak et al., 2017; Yuen and Gerton, 2018). Consider for a moment the extrication of condensins from both DNA and cells as analogous to whacking a candy-filled piñata to obtain a toy hidden inside. Prior to analyzing structure, yeast condensins for instance must endure mechanical and chemical assaults sufficient to disrupt (1) the heavily cross-linked polysaccharide/chitin cell walls, (2) the plasma membrane and nuclear double-membrane phospholipid bilayers, (3) protein complex interactions and (4) the phosphodiester backbones of DNA molecules (Melby et al., 1998; Anderson et al., 2002; Yoshimura et al., 2002; Barysz et al., 2015; Diebold-Durand et al., 2017). While such studies remain instrumental for informing views of SMC substructure, it may be naïve to imagine that the structures that remain after such a series of 'whacks' represent fully assembled and functional condensin (or cohesin) complexes. On the other hand, the ability of condensins to retain a rod-like structure is impressive and suggests that this lumen-less assembly is one aspect of a higher-order and functional complex. In contrast, liquid AFM analysis of condensin subcomplexes (containing only Smc2 and Smc4) found that the coiled-coil domains are highly flexible (persistence length of only 4 nm!) and can in addition separate to form a lumen or fold to promote hinge-to-head binding (Eeftens et al., 2016). A conservative interpretation of these highly fluctuating structures is that non-SMC subunits impact coiled-coil interactions to promote rod assembly and possibly oligomerization. Resolving the structure and dynamics through which a fully assembled and functional condensin complex translocates and extrudes DNA loops thus awaits future studies. One must similarly view with caution the popular notion that condensins entrap DNA. A finding typically cited to support entrapment is that condensins dissociate from linearized DNA molecules (Cuylen et al., 2011). This observation, however, is readily explained by reports that condensins are translocases that can step along DNA in the absence of entrapment (discussed below). Further challenging the notion of condensin entrapment are reports that archaea condensins dissociate from DNA, instead of accumulating, at barriers to migration and that any number of condensin subcomplexes (and even parts of an SMC protein) bind to DNA (Akhmedov et al., 1998; Akhmedov et al., 1999; Kimura and Hirano, 1997, 2000; Kimura et al., 1999; Weitzer et al., 2003; Arumugam et al., 2003; Strick et al., 2004; Bernard et al., 2006; Terakawa et al., 2017; Wang et al., 2017; Kschonsak et al., 2017; Ganji et al., 2018). These findings give rise to a range of possibilities through which condensin rods can associate with DNA.

Condensins walk into the spotlight… and extrude!

Important insights into the mechanism of chromatin compaction have emerged from the discovery that condensins are DNA translocases. In bacteria such as *Bacillus subtilis*, the SMC complex that promotes chromosome compaction initially binds to DNA at the origin-proximal region termed ParS (partitioning DNA element), which recruits ParB (Minnen et al., 2011; Badrinarayanan et al., 2015). ChIP-seq analyses (a method through which protein–DNA sequence associations are identified) has demonstrated that newly bound SMC complexes translocate away from the ParS–ParB site, thereby zippering together the flanking chromatin until the distal end of the plasmid is reached (Wang et al., 2017). In eukaryotes, quantum-dot-labeled yeast condensins translocate along DNA molecules in which both ends of the DNA molecule were anchored to the substrate. Intriguingly, approximately half of the condensins moved in one direction or the other – but neither changed direction (Terakawa et al., 2017). Moreover, condensins could bind and transport a separate DNA molecule even as it migrated along a tethered DNA track – indicating the condensins have two DNA-binding sites (Terakawa et al., 2017). Biophysical studies focused on the impact of DNA as a floppy substrate, and explored the effect of replacing a tautly anchored DNA substrate for a floppy one. The resulting simulations succeeded in generating models in which condensin extrudes DNA loops (Fudenberg et al., 2016; Lawrimore et al., 2016, 2017). Consistent with this revelation, a tour de force of imaging provided new evidence that condensin migration is coupled to asymmetric loop extrusion (Ganji et al., 2018). Here, fluorescently labeled condensins were introduced into a flow chamber in which DNA molecules (visualized through Sytox Orange) were again anchored to the substrate. In this case, the DNA ends were anchored close together to provide condensin with a floppy or flexible DNA substrate. Upon addition of ATP, DNA loops formed that emanated from the site where condensin was bound (Ganji et al., 2018). Intriguingly, the distance between condensin and one of the DNA–surface anchor points remained fixed, whereas the distance between condensin and the opposing DNA–surface anchor point decreased. This suggests that one domain of condensin binds to and anchors itself to DNA, whereas a separate condensin domain actively drives migration along DNA and, concomitantly, loop extrusion (Lawrimore et al., 2017; Ganji et al., 2018). Whether unidirectional condensin translocation arises from discriminating between Watson/Crick strand polarities within the DNA duplex remains an intriguing possibility.

Integration of condensin structure and translocation properties into a coherent model becomes further complicated by step-size analyses. To address this point, experiments were performed where one end of a DNA molecule was tethered to a glass substrate, whereas the other end, which was attached to a streptavidin-coated magnetic bead, was kept under low-level tension (Keenholtz, et al., 2017). Upon addition of condensin and ATP, the DNA fiber quickly compacted, but analysis of bead migration (indicative of DNA compaction) revealed step sizes that were approximately four times the length of the 50 nm condensin complex (Keenholtz et al., 2017). Independent findings support an average step size for yeast condensins that peaks at about 200 nms (Eeftens et al., 2016). In fact, large steps are in agreement with classic biochemical studies of condensin purified from both *Xenopus* eggs and yeast (Kimura and Hirano, 1997; Kimura et al., 1999; Stray and Lindsley, 2003; Strick et al., 2004). Understanding how condensins (as rods) translocate over lengths greater than themselves remains a fundamental question of SMC biology (see Gruber, 2017; van Ruiten and Rowland, 2018 for more creative discussions of condensin ring migration). Large step sizes are easily accommodated by condensin binding to floppy DNA. In the absence of imposed architecture (nucleosomes, chromatin remodelers, SMC complexes, etc.), condensin could bind any proximal segment of a floppy, wriggling DNA and in a non-directed fashion (Fudenberg et al., 2016; Lawrimore et al., 2016, 2017). This model, however, does not easily lend itself to explain unidirectional motion or accommodate the tension that is likely generated on DNA during condensation.

Journal of Cell Science (2019) 132, jcs220491. doi:10.1242/jcs.220491

Imaging condensin translocation and loop extrusion, which occurs under conditions of flow that places DNA under tension, instead suggests that condensins indeed move in a directed fashion and under conditions in which the DNA substrate can become increasingly taut as condensation proceeds (Terakawa et al., 2017; Ganji et al., 2018). Thus, there may be an aspect of condensin, analogous to kinesin or dynein 'walking' along microtubules (albeit a much stiffer substrate than DNA), that allows condensins to use cycles of ATP binding and/or hydrolysis to produce head-over-head step sizes (in which coiled domains separate) of up to 100 nm. Indeed, AFM analyses captured condensins in which separate head domains could be considered as 'walking' on coiled-coil legs (Yoshimura et al., 2002; Eeftens et al., 2017). A variation on this latter possibility is that condensin may oligomerize to produce step sizes of up to 100 nm. In fact, eukaryotic and prokaryotic SMC rosettes, oligomers and extended fibers are clearly discernible from both EM and AFM images. Although oligomers typically predominate, monomers were instead chosen for detailed description – a limitation that continues to sway current thinking (Stray and Lindsley, 2003; Matoba et al., 2005; St-Pierre et al., 2009; Fuentes-Perez et al., 2012; Huis in 't Veld et al., 2014; Barysz et al., 2015). More recently, elution profiles obtained from size exclusion columns confirmed that condensins exist in both monomeric and oligomeric complexes (Keenholtz et al., 2017). Importantly, addition of the multimeric fraction to flow cells that contained DNA fibers produced robust compaction (Keenholtz et al., 2017), potentially linking oligomerization to compaction. Finally, bi-directional translocation of *B. subtilis* SMCs away from the ParS–ParB deposition site, which normally zippers plasmid DNA, provides additional evidence of oligomerization (Wang et al., 2017). Here, SMC migration was tested on a plasmid in which the DNA sequence flanking one side of ParS–ParB contained actively transcribed ribosomal RNA operons, while the other flanking sequence was largely devoid of active transcription. Migration was greatly decreased in the direction that contained the operon, but not in the direction that was free of active transcription (Wang et al., 2017). These findings argue that a separate SMC/condensin complex binds to and translocates along each side of the ParS–ParB deposition site, and that the flanking DNA sequences are tethered together through condensin oligomerizations – akin to that posited for cohesins (reviewed in Skibbens, 2008; Onn et al., 2008; Zhang et al., 2008). One may look forward to future studies that merge aspects of condensin ATPase cycles, unidirectional motility, and translocation/extrusion along a changing DNA landscape (Fudenberg et al., 2016; Lawrimore et al., 2016, 2017; Terakawa et al., 2017; Ganji et al., 2018).

Condensins and cohesins in the genomic context of *cis*-tethering

Condensins in chromosome compaction during mitosis

Historically, the defining features of mitotic cells included chromosome compaction followed by the segregation of chromosomes into newly forming daughter cells. The role of condensin in chromatin compaction and sister chromatid resolution are well established (reviewed in Kakui and Uhlmann, 2018; Kinoshita and Hirano, 2017; Kalitsis et al., 2017), but more recent studies distinguish between the activities of condensin I and II. To assess changes in chromosome architecture as cells progress from late interphase into mitosis, a recent study manipulated the cell cycle regulator cyclin-dependent kinase 1 (CDK1) in chicken lymphoblast DT40 cells to produce a highly synchronized G_2 cell cycle state (Gibcus et al., 2018). Upon release from the late interphase arrest, Hi-C (high-throughput sequencing) and computer-based modeling revealed that structures typical of the interphase genome rapidly disappeared (see 'cohesins in nuclear architecture during interphase' below). In its place, DNA formed a central helical scaffold, from which appeared regularly spaced large loops (Fig. 3). By late prophase, the helical scaffold became more compressed and the DNA loops increased in size (Gibcus et al., 2018). Condensin I is excluded from chromosomes until prometaphase after nuclear envelope breakdown (Walther et al., 2018), a finding that is in strong agreement with prior studies (Hirota et al., 2004; Ono et al., 2004, 2017; Gerlich et al., 2006). Thus, condensin II is the predominant driver of initial compaction described above that occurs during prophase. During prometaphase, smaller loops (40–60 kb in size) form that are nested within the helical array of larger loops (200–400 kb in size) (Gibcus et al., 2018) (Fig. 3). Super-resolution stimulated emission depletion (STED) imaging in prometaphase HeLa cells confirmed that condensin II is restricted to the center longitudinal axis of chromosome arms, whereas condensin I occupies a more distal and significantly broader volume of the chromosome (Walther et al., 2018). Individually depleting condensin II or condensin I resulted in targeted loss of the respective loops, consistent with a model that condensin II promotes the formation of initial scaffolding loops, whereas condensin I promotes the formation of subsequent nested loops (Gibcus et al., 2018). Even though cohesin and condensin are singly represented in yeast, spatial distribution is retained in that cohesins form a barrel that surrounds condensins aligned along the spindle axis (see Bloom, 2014).

Cohesins in nuclear architecture during interphase

Although cohesins are typically discussed with regard to their role in the *trans*-tethering required for sister chromatid segregation

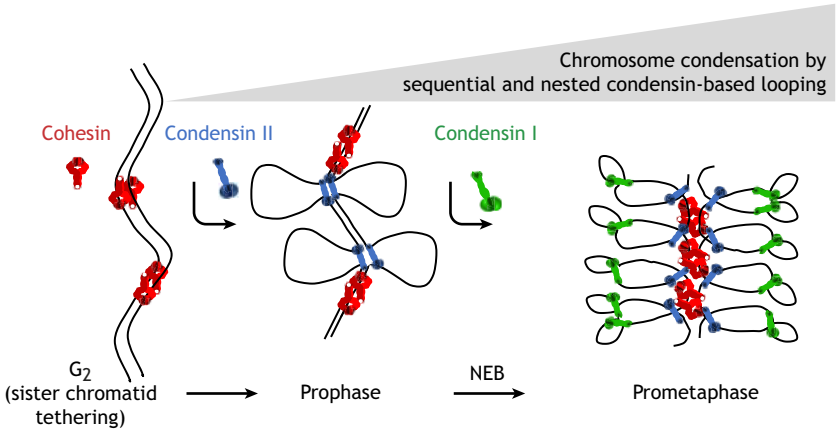

Fig. 3. Cell-cycle-regulated chromosome compaction by sequential recruitment of condensins II and I promotes the formation of nested loops. Replicated sister chromatids are tethered together by cohesins (red). During prophase, condensin II (blue) binds DNA and extrudes loops. After nuclear envelope breakdown (NEB), condensin I (green) binds the looped DNA and forms new loops that are nested within the condensin II-generated loops. As cells progress into late prometaphase, DNA loop extrusion and compression of the helical scaffold continues. Not shown is the role for cohesin in generating *cis*-based compaction, which also promotes chromosome condensation.

Journal of Cell Science (2019) 132, jcs220491. doi:10.1242/jcs.220491

during mitosis (reviewed in Rudra and Skibbens, 2013; Jeppsson et al., 2014; Marston, 2014; Morales and Losada, 2018), pioneering studies in yeast and *Drosophila* established two additional roles for cohesins. The first is that cohesins support *cis*-based DNA looping such that cohesin mutations produce dramatic chromosome condensation defects (Guacci et al., 1997). The second is that cohesins (and cohesin regulators) are required for transcription regulation and facilitate (via DNA looping) communication between distal DNA regulatory elements, such as enhancers and promotors (Rollins et al., 1999). Together, these studies form the foundation of current models in which cohesins generate higher-order chromatin structures that are critical for transcription regulation. Not surprisingly, cohesin pathways are critical for human development, and mutations can have devastating effects. Robert syndrome (RBS) and Cornelia de Lange syndrome (CdLS) are two cohesin-based developmental disorders that exhibit an overlapping suite of developmental defects that include cleft palate, microcephaly, profound limb reduction, syndactyly and, often, acute cognitive impairment (Krantz et al., 2004; Tonkin et al., 2004; Gillis et al., 2004; Schüle et al., 2005; Musio et al., 2006; Deardorff et al., 2007; Deardorff et al., 2012a,b; Vega et al., 2005). Given the range of tissues impacted by cohesin mutation, and the genome-wide effect that cohesins exert on gene transcription (see below), one should anticipate that the number of cohesin-related maladies or cohesinopathies (more recently termed transcriptomopathies and which include ribosomopathies) will increase significantly over time (Wendt et al., 2008; Xu et al., 2014; Yuan et al., 2015; Skibbens et al., 2013; Banerji et al., 2017a).

Topologically associating domains and compartments

Cohesins organize the interphase genome by balancing the dynamic formation of two opposing states, termed topologically associating domains (TADs) and compartments, which are the architectural yin and yang of transcription regulation. Here, I define a TAD as a DNA loop of up to a megabase of DNA and in which the loop base is associated with the insulator CCCTC-binding transcription repressor (CTCF) and cohesin (Fig. 4). It is tempting to speculate that the TAD base insulates looped and non-looped DNA from transcription and chromatin-remodeling factors that migrate along DNA. In terms of genome biology, the term compartment is narrowly defined: compartments are untethered, but self-interacting domains of transcriptionally active (open or A domains) or repressed (closed or B domains) chromatin states that may contain 5 to 50 megabases of DNA (Lieberman-Aiden et al., 2009; Schwarzer et al., 2017; Gassler et al., 2017; Rao et al., 2017; Haarhuis et al., 2017; Plys and Kingston, 2018). The coalescing of genomic DNA into compartments likely occurs through clustering of low-complexity and/or intrinsically disordered domains on DNA-binding proteins that self-assemble into liquid–liquid phases akin to oil droplets that aggregate on a water surface. This is a bit of an extreme analogy, however, in that self-forming DNA compartments are much more miscible and dynamic in their associations (Fig. 4). Clustering may also be driven by modifications that exhibit similar properties that occur on histones and transcription factors (Schwarzer et al., 2017; Rao et al., 2017; Haarhuis et al., 2017; Plys and Kingston, 2018). Compartments are dynamic and motile but can become anchored; therefore, repressed B compartments appear more peripheral in the nucleus and may interact with the nuclear lamina, whereas active A compartments are more centrally positioned (Hansen et al., 2018; Lieberman-Aiden et al., 2009).

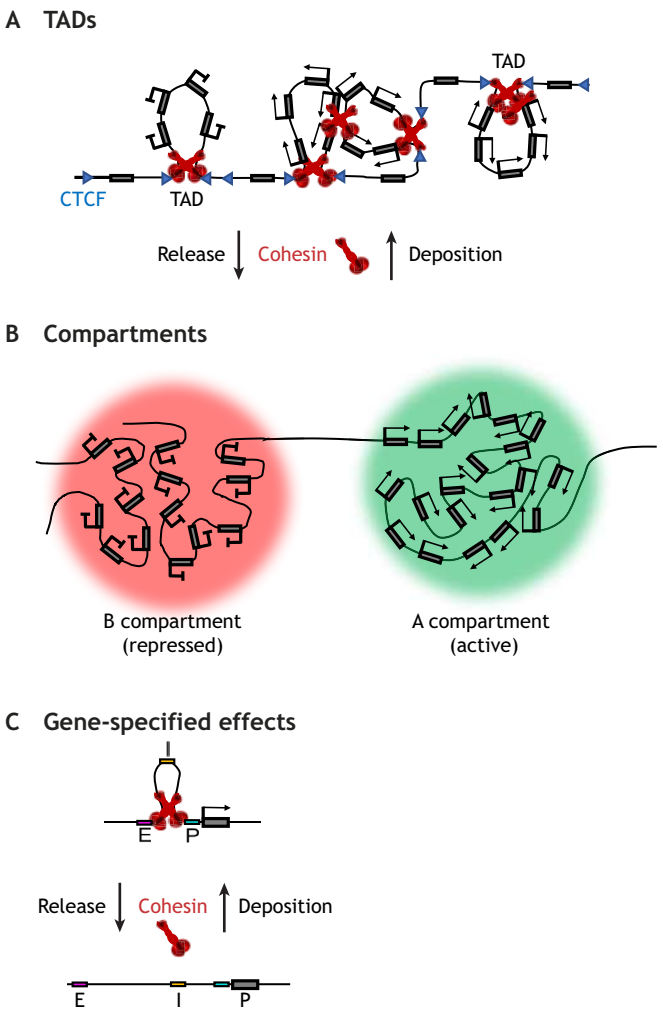

Fig. 4. Opposing roles for cohesin in transcription regulation. (A) TADs are large DNA loops that are defined by the persistence of cohesin (red) and CTCF (blue triangle) at the loop base. DNA loop extrusion mediated by cohesin occurs until cohesion encounters CTCF insulators along the genome. CTCF binds to DNA motifs asymmetrically, so that TAD loops are typically flanked by converging CTCF sites. Note that cohesins can connect TADs (both within and across chromosomes) to further define or insulate sequences from chromatin remodelers or transcription factors moving along DNA. (B) Compartments are untethered regions of DNA (i.e. reduced cohesin binding) that coalesce through low-complexity (intrinsically disordered) domain-containing protein clustering and aggregation of factors (such as histone and transcription complexes) that bear similar modifications. Compartments are divided into A (induced, green) and B (repressed, red) states. Cohesin promotes TAD formation, but the constrained loops it forms antagonize compartment formation – hence, the predominance of TADs and compartments depends largely on the deposition or release of cohesin. (C) Cohesins also regulate gene-specific effects on transcription. Shown here is a speculative model through which cohesin-dependent DNA looping (at a much smaller scale than TAD loops) brings into close apposition the enhancer (E) and promoter (P) for a specific gene to promote transcription (top). In this scenario, an insulator (I) is displaced from promoter in the extruded DNA loop. Cohesin release results in loss of the proximity between enhancer and promoter, and inhibition of transcription (bottom).

Cohesins promote TADs but antagonize compartments

Zebrafish is an exceptionally useful model system to link studies of cohesin-based transcription and development (Kawauchi et al., 2016; Muto and Schilling, 2017; Banerji et al., 2017a). A key stage in development is the transition from the maternal to zygotic control

of transcription (also termed zygotic genome activation; ZGA). Embryos with reduced levels of cohesin (RAD21) retain elevated levels of maternal mRNAs, suggesting that cohesin is critical for maternal mRNA turnover and subsequent expression of zygotic mRNAs (Rosa and Brivanlou, 2017; Meier et al., 2018). In embryos that contain wild-type levels of cohesin, ChIP-seq revealed an extensive increase in the number of cohesin-decorated DNA sites post-ZGA – especially at enhancers and/or promoters that carry histone modifications indicative of activated genes (Bogdanovic et al., 2012; Meier et al., 2018). If cohesins regulate transcription on a gene-by-gene basis, one would expect that those genes identified through altered mRNA levels would be the same genes that exhibit cohesin-binding to their enhancers and/or promoters. In fact, multiple studies document cohesin-dependent gene-specific transcription regulation (Rollins et al., 2004; Stedman et al., 2008; Rhodes et al., 2010; Gimigliano et al., 2012; Yan et al., 2013; Banerji et al., 2016, 2017b; Tsai et al., 2018). In post-ZGA zebrafish, however, only half of the genes that exhibit altered mRNA levels upon cohesin depletion corresponded to gene loci that were otherwise normally bound by cohesin (Meier et al., 2018). Thus, cohesins influence transcription through multiple mechanisms, which include gene-specific regulation, as well as more global effects – the latter of which are likely based on TAD and compartment formation (Fig. 4).

Early ChIP-seq analyses in yeast revealed that cohesin density and distribution along DNA correlate with DNA loop size (Guacci et al., 1997; Blat and Kleckner, 1999; Hartman et al., 2000; Glynn et al., 2004). Results obtained from a wide range of model systems define an active role for cohesin in TAD formation. Even as early as the one-cell stage of mouse zygotes, the interphase nuclear architecture contains TADs (Gassler et al., 2017). Cre-based knockout of the gene that encodes for the cohesin subunit RAD21 disrupted TADs in mouse embryos (Gassler et al., 2017). Depleting RAD21 from either HeLa cells or human colorectal carcinoma cells similarly abolished TADs during interphase (Wutz et al., 2017; Rao et al., 2017). Importantly, *RAD21* re-expression resulted in a rapid re-assembly of TADs, especially near super enhancers, which contain a high density of enhancers, transcription factors, activating histone modifications, cohesins and CTCF (Rao et al., 2017; Huang et al., 2018; Plys and Kingston, 2018).

What defines the loop length within a TAD? DNA loops could form through the oligomerization or capture of cohesins that decorate individual segments on a DNA molecule. An interesting notion is that this may promote gene-specific transcription. A more likely scenario, however, is that cohesins extrude DNA loops – a model predicated in part on observations of extrusion by condensin complexes and a role for ATP in cohesin-based looping (Lawrimore et al., 2017; Ganji et al., 2018; Vian et al., 2018). Loop lengths thus appear epigenetically defined by pauses that occur during loop extrusion (Fig. 4). Pauses arise through cohesin interactions with CTCF: cohesins bind and colocalize with CTCF at the base of TADs (Stedman et al., 2008; Wendt et al., 2008; Rubio et al., 2008; Parelho et al., 2008; Rao et al., 2014, 2017; Dixon et al., 2012; Wutz et al., 2017; Huang et al., 2018) and cohesin fails to migrate *in vitro* past DNA decorated with CTCF (Davidson et al., 2016). In support of the model that CTCF defines DNA loop length within TADs, CTCF degradation does not abolish TADs, but does alter TAD loop lengths (Wutz et al., 2017). Intriguingly, the dynamic nature of TADs during interphase starkly contrasts with the stable and CTCF-independent cohesion that occurs between sister chromatids during mitosis (reviewed in Rudra and Skibbens, 2013; Jeppsson et al., 2014; Marston, 2014; Morales and Losada, 2018). The mechanisms through which cohesin is directed toward these uniquely regulated *cis*- and *trans*-tetherings remains an intriguingly enigma.

If cohesins are indeed required for TAD formation, then inactivating cohesin regulators should similarly impact TAD formation. NIPBL in metazoan cells (and its homologs Scc2 in yeast and Nipped B in flies) is critical for cohesin deposition onto DNA (Rollins et al., 1999, 2004; Ciosk et al., 2000; Tonkin et al., 2004; Krantz et al., 2004). Indeed, depleting NIPBL resulted in reduced cohesin binding to DNA and genome-wide loss of TADs (Schwarzer et al., 2017). Accordingly, increasing cohesin residency should have the opposite effect. WAPL in metazoan cells (and the yeast homolog Rad61) promotes cohesin dissociation from DNA, such that WAPL depletion or mutation results in increased levels of cohesin binding to DNA (Kueng et al., 2006; Gandhi et al., 2006). CRISPR-based knockout of *WAPL* in haploid human leukemic cell lines and in mouse zygotes resulted in increased residency of cohesins on DNA and more robust detection of TADs that included longer DNA loops and increased interactions between adjoining TADs (Haarhuis et al., 2017; Gassler et al., 2017). Interestingly, cells depleted of WAPL proliferated normally (Haarhuis et al., 2017). One interpretation of this observation is that developmental programs (posited to account for RBS and CdLS) may be more sensitive to changes in transcription than single cells.

While cohesins are critical for TAD formation, these constrained looped structures antagonize compartment formation. For instance, depletion of RAD21 in mouse zygotes and human colorectal cells leads to increased compartment volumes that comprise a larger portion of the nucleus (Gassler et al., 2017; Rao et al., 2017). (Fig. 4). Reducing the levels of chromatin-bound cohesin through depletion of *MAU2* (a binding partner of NIPBL that promotes cohesin deposition onto DNA) similarly results in increased compartment volumes (Ciosk et al., 2000; Seitan et al., 2006; Haarhuis et al., 2017). The opposite is observed upon increasing cohesin residency through the depletion of WAPL – signal intensities, indicative of genomic compartmentalization, are reduced (Haarhuis et al., 2017; Wutz et al., 2017; Gassler et al., 2017). Taken together, these findings suggest that genomic compartments increase in response to cohesin loss (Fig. 4).

Cohesin and chromatin compaction during interphase

Altering the levels of cohesins can also produce a compaction of chromatin structure that is easily resolved by light microscopy (Tedeschi et al., 2013; Ouyang et al., 2016; Wutz et al., 2017). For instance, WAPL depletion (i.e. increasing cohesin residency) via RNAi in HeLa cells gives rise, during interphase, to pre-condensed worm-like chromatin structures termed vermicelli. Premature condensation further increases upon the co-depletion of the cohesin-binding and regulatory factor PDS5 (humans contain two paralogs; PDS5A and PDS5B) (Tedeschi et al., 2013; Ouyang et al., 2016; Wutz et al., 2017). Although Pds5 was first identified as supporting cohesin roles in both *trans*- and *cis*-tethering, Pds5 also binds to the cohesin release factor WAPL (termed Rad61 in yeast) and this association is highly conserved (Hartman et al., 2000; Panizza et al., 2000; Losada et al., 2005; Sutani et al., 2009; Shintomi and Hirano, 2009; Ouyang et al., 2016; Goto et al., 2017). In combination, these results suggest that Pds5 stabilizes cohesin tethers but can promote cohesin release in coordination with WAPL. Does this premature condensation during interphase involve condensins? Importantly, depletion of the condensin component Smc2 does not block vermicelli formation in cells co-depleted of WAPL and PDS5 (Wutz et al., 2017), indicating that chromatin compaction during interphase is mediated by cohesins.

Conclusions and perspectives

Organizing the genome throughout the cell cycle involves a hand-off of SMC complexes. In preparation for chromosome segregation during mitosis, cells employ a combination of condensin II and condensin I to generate a series of loops and nested loops to fully compact each chromosome. Chromosome compaction occurs even as cohesins, which are deposited much earlier during the cell cycle, tether together the sister chromatids. Several lines of evidence suggest that cohesins contribute to chromosome compaction during mitosis. Understanding the structural mechanisms through which cohesins and condensins promote chromosome compaction remains an outstanding, yet fundamental issue, in cell biology. As cells exit mitosis and return to an interphase state, condensins dissociate from the DNA and a new round of cohesins bind to DNA to organize the genome within the nucleus. Here, cohesins regulate a two-tiered system of organization. On the one hand, cohesins generate DNA loops whose sizes appear to be defined in part by CTCF. In regions devoid of cohesin and CTCF, DNA coalesces into epigenetically defined but untethered compartments of active or repressed chromatin.

Not only are the functions of cohesin and condensin mostly separated across the cell cycle, the structure and DNA-binding strategies of these two SMC complexes also appear to be different. Even the earliest structural studies of cohesins and condensins revealed strikingly different assemblies (or subassemblies) of cohesin rings and condesin rods – results largely confirmed over the past 20 years. Also different are their motile behaviors. Cohesins appear to diffuse bi-directionally along DNA, consistent with a ring entrapment. In contrast, condensins translocate unidirectionally and contain at least two distinct DNA-binding domains: one that anchors to DNA, while the other is dynamic and provides the driving force of DNA extrusion. Further differentiating the SMC complexes is that cohesin rings typically require a loading complex and ATP to entrap DNA, whereas condensins appear fully competent to bind DNA without either a loader or ATP. Further questions to be addressed are the extent to which tethering of DNA loci involves SMC oligomerization; however, several lines of evidence make this a plausible scenario for both cohesins and condensins. In summary, the field remains wide open with regard to the possible mechanisms through which SMC complexes produce DNA tetherings, in either *cis* or *trans*, and throughout the cell cycle.

Acknowledgements

R.V.S. thanks Drs Vincent Guacci and M. Kathryn Iovine, along with Skibbens laboratory members for comments and discussions during the writing of this Review. The author apologizes to colleagues whose work was either omitted or not treated in a more fully considered fashion due to space limitations and the rapid progress exemplified across the SMC field. R.V.S. gratefully acknowledges access to the previously published images in Fig. 2. Any opinions, findings, and conclusions or recommendations expressed in this study are those of the author and does not necessarily reflect the views of the National Institutes of Health.

Competing interests

The author declares no competing or financial interests.

Funding

The work of my laboratory is funded by the National Institutes of Health (R15GM110631 to R.V.S.). Deposited in PMC for release after 12 months.

References

Akhmedov, A. T., Frei, C., Tsai-Pflugfelder, M., Kemper, B., Gasser, S. M. and Jessberger, R. (1998). Structural maintenance of chromosomes protein C-terminal domains bind preferentially to DNA with secondary structure. *J. Biol. Chem.* **273**, 24088-24094.

Akhmedov, A. T., Gross, B. and Jessberger, R. (1999). Mammalian SMC3 C-terminal and coiled-coil protein domains specifically bind palindromic DNA, do not block DNA ends, and prevent DNA bending. *J. Biol. Chem.* **274**, 38216-38224.

Anderson, D. E., Losada, A., Erickson, H. P. and Hirano, T. (2002). Condensin and cohesin display different arm conformations with characteristic hinge angles. *J. Cell Biol.* **156**, 419-424.

Arumugam, P., Gruber, S., Tanaka, K., Haering, C. H., Mechtler, K. and Nasmyth, K. (2003). ATP hydrolysis is required for cohesin's association with chromosomes. *Curr. Biol.* **13**, 1941-1153.

Badrinarayanan, A., Le, T. B. K. and Laub, M. T. (2015). Bacterial chromosome organization and segregation. *Annu. Rev. Cell Dev. Biol.* **31**, 171-199.

Banerji, R., Eble, D. M., Iovine, M. K. and Skibbens, R. V. (2016). Esco2 regulates cx43 expression during skeletal regeneration in the zebrafish fin. *Dev. Dyn.* **245**, 7-21.

Banerji, R., Skibbens, R. V. and Iovine, M. K. (2017a). How many roads lead to cohesinopathies? *Dev. Dyn.* **246**, 881-888.

Banerji, R., Skibbens, R. V. and Iovine, M. K. (2017b). Cohesin mediates Esco2-dependent transcriptional regulation in a zebrafish regenerating fin model of Roberts Syndrome. *Biol. Open* **6**, 1802-1813.

Barysz, H., Kim, J. H., Chen, Z. A., Hudson, D. F., Rappsilber, J., Gerloff, D. L. and Earnshaw, W. C. (2015). Three-dimensional topology of the SMC2/SMC4 subcomplex from chicken condensin I revealed by cross-linking and molecular modelling. *Open Biol.* **5**, 150005.

Bernard, P., Drogat, J., Maure, J.-F., Dheur, S., Vaur, S., Genier, S. and Javerzat, J.-P. (2006). A screen for cohesion mutants uncovers Ssl3, the fission yeast counterpart of the cohesin loading factor Scc4. *Curr. Biol.* **16**, 875-881.

Blat, Y. and Kleckner, N. (1999). Cohesins bind to preferential sites along yeast chromosome III, with differential regulation along arms versus the centric region. *Cell* **98**, 249-259.

Bloom, K. S. (2014). Centromeric heterochromatin: the primordial segregation machine. *Annu. Rev. Genet.* **48**, 457-484.

Bogdanovic, O., Fernandez-Miñán, A., Tena, J. J., de la Calle-Mustienes, E., Hidalgo, C., van Kruysbergen, I., van Heeringen, S. J., Veenstra, G. J. C. and Gómez-Skarmeta, J. L. (2012). Dynamics of enhancer chromatin signatures mark the transition from pluripotency to cell specification during embryogenesis. *Genome Res.* **22**, 2043-2053.

Challa, K., Lee, M.-S., Shinohara, M., Kim, K. P. and Shinohara, A. (2016). Rad61/Wpl1 (Wapl), a cohesin regulator, controls chromosome compaction during meiosis. *Nucleic Acids Res.* **44**, 3190-3203.

Ciosk, R., Shirayama, M., Shevchenko, A., Tanaka, T., Toth, A., Shevchenko, A. and Nasmyth, K. (2000). Cohesin's binding to chromosomes depends on a separate complex consisting of Scc2 and Scc4 proteins. *Mol. Cell* **5**, 243-254.

Csankovszki, G., Collette, K., Spahl, K., Carey, J., Snyder, M., Petty, E., Patel, U., Tabuchi, T., Liu, H., McLeod, I. et al. (2009). Three distinct condensin complexes control C. elegans chromosome dynamics. *Curr. Biol.* **19**, 9-19.

Cuylen, S., Metz, J. and Haering, C. H. (2011). Condensin structures chromosomal DNA through topological links. *Nat. Struct. Mol. Biol.* **18**, 894-901.

D'Ambrosio, C., Schmidt, C. K., Katou, Y., Kelly, G., Itoh, T., Shirahige, K. and Uhlmann, F. (2008). Identification of cis-acting sites for condensin loading onto budding yeast chromosomes. *Genes Dev.* **22**, 2215-2227.

Davidson, I. F., Goetz, D., Zaczek, M. P., Molodtsov, M. I., Huis In 't Veld, P. J., Weissmann, F., Litos, G., Cisneros, D. A., Ocampo-Hafalla, M., Ladurner, R. et al. (2016). Rapid movement and transcriptional re-localization of human cohesin on DNA. *EMBO J.* **35**, 2671-2685.

Deardorff, M. A., Kaur, M., Yaeger, D., Rampuria, A., Korolev, S., Pie, J., Gil-Rodríguez, C., Arnedo, M., Loeys, B., Kline, A. D. et al. (2007). Mutations in cohesin complex members SMC3 and SMC1A cause a mild variant of Cornelia de Lange syndrome with predominant mental retardation. *Am. J. Hum. Genet.* **80**, 485-494.

Deardorff, M. A., Bando, M., Nakato, R., Watrin, E., Itoh, T., Minamino, M., Saitoh, K., Komata, M., Katou, Y., Clark, D. et al. (2012a). HDAC8 mutations in Cornelia de Lange syndrome affect the cohesin acetylation cycle. *Nature* **489**: 313-317.

Deardorff, M. A., Wilde, J. J., Albrecht, M., Dickinson, E., Tennstedt, S., Braunholz, D., Mönnich, M., Yan, Y., Xu, W., Gil-Rodríguez, M. C. et al. (2012b). RAD21 mutations cause a human cohesinopathy. *Am. J. Hum. Genet.* **90**: 1014-1027.

Diebold-Durand, M.-L., Lee, H., Ruiz Avila, L. B., Noh, H., Shin, H.-C., Im, H., Bock, F. P., Bürmann, F., Durand, A., Basfeld, A. et al. (2017). Structure of full-length SMC and rearrangements required for chromosome organization. *Mol. Cell* **67**, 334-347.

Dixon, J. R., Selvaraj, S., Yue, F., Kim, A., Li, Y., Shen, Y., Hu, M., Liu, J. S. and Ren, B. (2012). Topological domains in mammalian genomes identified by analysis of chromatin interactions. *Nature* **485**, 376-380.

Dorsett, D. and Merkenschlager, M. (2013). Cohesin at active genes: a unifying theme for cohesin and gene expression from model organisms to humans. *Curr. Opin. Cell Biol.* **25**, 327-333.

Eeftens, J. M., Katan, A. J., Kschonsak, M., Hassler, M., de Wilde, L., Dief, E. M., Haering, C. H. and Dekker, C. (2016). Condensin Smc2-Smc4 dimers are flexible and dynamic. *Cell Rep.* **14**, 1813-1818.

Eeftens, J. M., Bisht, S., Kerssemakers, J., Kschonsak, M., Haering, C. H. and Dekker, C. (2017). Real-time detection of condensin-driven DNA compaction reveals a multistep binding mechanism. *EMBO J.* **36**, 3448-3457.

Eng, T., Guacci, V. and Koshland, D. (2014). ROCC, a conserved region in cohesin's Mcd1 subunit, is essential for the proper regulation of the maintenance of cohesion and establishment of condensation. *Mol. Biol. Cell* **25**, 2351-2364.
Eng, T., Guacci, V. and Koshland, D. (2015). Interallelic complementation provides functional evidence for cohesin-cohesin interactions on DNA. *Mol. Biol. Cell* **26**, 4224-4235.
Fudenberg, G., Abdennur, N., Imakaev, M., Goloborodko, A. and Mirny, L. A. (2016). Emerging evidence of chromosome folding by loop extrusion. *Cold Spring Harb. Symp. Quant. Biol.* **82**, 45-55.
Fuentes-Perez, M. E., Gwynn, E. J., Dillingham, M. S. and Moreno-Herrero, F. (2012). Using DNA as a fiducial marker to study SMC complex interactions with the atomic force microscope. *Biophys. J.* **102**, 839-848.
Gandhi, R., Gillespie, P. J. and Hirano, T. (2006). Human Wapl is a cohesin-binding protein that promotes sister-chromatid resolution in mitotic prophase. *Curr. Biol.* **16**, 2406-2417.
Ganji, M., Shaltiel, I. A., Bisht, S., Kim, E., Kalichava, A., Haering, C. H. and Dekker, C. (2018). Real-time imaging of DNA loop extrusion by condensin. *Science* **360**, 102-105.
Gassler, J., Brandão, H. B., Imakaev, M., Flyamer, I. M., Ladstätter, S., Bickmore, W. A., Peters, J. M., Mirny, L. A. and Tachibana, K. (2017). A mechanism of cohesin-dependent loop extrusion organizes zygotic genome architecture. *EMBO J.* **36**, 3600-3618.
Gelot, C., Guirouilh-Barbat, J. and Lopez, B. S. (2016). The cohesin complex prevents the end-joining of distant DNA double-strand ends in S phase: Consequences on genome stability maintenance. *Nucleus* **7**, 339-345.
Gerlich, D., Koch, B., Dupeux, F., Peters, J.-M. and Ellenberg, J. (2006). Live-cell imaging reveals a stable cohesin-chromatin interaction after but not before DNA replication. *Curr. Biol.* **16**, 1571-1578.
Gibcus, J. H., Samejima, K., Goloborodko, A., Samejima, I., Naumova, N., Nuebler, J., Kanemaki, M. T., Xie, L., Paulson, J. R., Earnshaw, W. C. et al. (2018). A pathway for mitotic chromosome formation. *Science* **359**, eaao6135.
Gimigliano, A., Mannini, L., Bianchi, L., Puglia, M., Deardorff, M. A., Menga, S., Krantz, I. D., Musio, A. and Bini, L. (2012). Proteomic profile identifies dysregulated pathways in Cornelia de Lange syndrome cells with distinct mutations in SMC1A and SMC3 genes. *J. Proteome Res.* **11**, 6111-6123.
Gillis, L. A., McCallum, J., Kaur, M., DeScipio, C., Yaeger, D., Mariani, A., Kline, A. D., Li, H. H., Devoto, M., Jackson, L. G., and Krantz, I. D. (2004). NIPBL mutational analysis in 120 individuals with Cornelia de Lange syndrome and evaluation of genotype-phenotype correlations. *Am. J. Hum. Genet.* **75**, 610-623.
Gligoris, T. and Löwe, J. (2016). Structural insights into ring formation of cohesin and related Smc complexes. *Trends Cell Biol.* **26**, 680-693.
Gligoris, T. G., Scheinost, J. C., Bürmann, F., Petela, N., Chan, K. L., Uluocak, P., Beckouët, F., Gruber, S., Nasmyth, K., and Löwe, J. (2014). Closing the cohesin ring: structure and function of its Smc3-kleisin interface. *Science* **346**, 963-967.
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.
Goto, Y., Yamagishi, Y., Shintomi-Kawamura, M., Abe, M., Tanno, Y. and Watanabe, Y. (2017). Pds5 regulates sister-chromatid cohesion and chromosome bi-orientation through a conserved protein interaction module. *Curr. Biol.* **27**, 1005-1012.
Gruber, S. (2017). Shaping chromosomes by DNA capture and release: gating the SMC rings. *Curr. Opin. Cell Biol.* **46**, 87-93.
Gruber, S., Haering, C. H. and Nasmyth, K. (2003). Chromosomal cohesin forms a ring. *Cell* **112**, 765-777.
Guacci, V. and Koshland, D. (2012). Cohesin-independent segregation of sister chromatids in budding yeast. *Mol. Biol. Cell.* **23**, 729-739.
Guacci, V., Koshland, D. and Strunnikov, A. (1997). A direct link between sister chromatid cohesion and chromosome condensation revealed through the analysis of MCD1 in S. cerevisiae. *Cell* **91**, 47-57.
Haarhuis, J. H. I., van der Weide, R. H., Blomen, V. A., Yáñez-Cuna, J. O., Amendola, M., van Ruiten, M. S., Krijger, P. H. L., Teunissen, H., Medema, R. H., van Steensel, B. et al. (2017). The cohesin release factor WAPL restricts chromatin loop extension. *Cell* **169**, 693-707.e14.
Haering, C. H., Löwe, J., Hochwagen, A. and Nasmyth, K. (2002). Molecular architecture of SMC proteins and the yeast cohesin complex. *Mol. Cell* **9**, 773-788.
Hansen, A. S., Cattoglio, C., Darzacq, X. and Tjian, R. (2018). Recent evidence that TADs and chromatin loops are dynamic structures. *Nucleus* **9**, 20-32.
Harris, B., Bose, T., Lee, K. K., Wang, F., Lu, S., Ross, R. T., Zhang, Y., French, S. L., Beyer, A. L., Slaughter, B. D. et al. (2014). Cohesion promotes nucleolar structure and function. *Mol. Biol. Cell* **25**, 337-346.
Hartman, T., Stead, K., Koshland, D. and Guacci, V. (2000). Pds5p is an essential chromosomal protein required for both sister chromatid cohesion and condensation in Saccharomyces cerevisiae. *J. Cell Biol.* **151**, 613-626.
Hirano, T. (2016). Condensin-based chromosome organization from bacteria to vertebrates. *Cell* **164**, 847-857.
Hirota, T., Gerlich, D., Koch, B., Ellenberg, J. and Peters, J. M. (2004). Distinct functions of condensin I and II in mitotic chromosome assembly. *J. Cell Sci.* **117**, 6435-6445.
Huang, C. E., Milutinovich, M. and Koshland, D. (2005). Rings, bracelet or snaps: fashionable alternatives for Smc complexes. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **360**, 537-542.
Huang, J., Li, K., Cai, W., Liu, X., Zhang, Y., Orkin, S. H., Xu, J. and Yuan, G.-C. (2018). Dissecting super-enhancer hierarchy based on chromatin interactions. *Nat. Commun.* **9**, 943.
Huis in 't Veld, P. J., Herzog, F., Ladurner, R., Davidson, I. F., Piric, S., Kreidl, E., Bhaskara, V., Aebersold, R. and Peters, J.-M. (2014). Characterization of a DNA exit gate in the human cohesin ring. *Science* **346**, 968-972.
Ivanov, D. and Nasmyth, K. (2005). A topological interaction between cohesin rings and a circular minichromosome. *Cell* **122**, 849-860.
Jeppsson, K., Kanno, T., Shirahige, K. and Sjögren, C. (2014). The maintenance of chromosome structure: positioning and functioning of SMC complexes. *Nat. Rev. Mol. Cell Biol.* **15**, 601-614.
Kakui, Y. and Uhlmann, F. (2018). SMC complexes orchestrate the mitotic chromatin interaction landscape. *Curr. Genet.* **64**, 335-339.
Kalitsis, P., Zhang, T., Marshall, K. M., Nielsen, C. F. and Hudson, D. F. (2017). Condensin, master organizer of the genome. *Chromosome Res.* **25**, 61-76.
Kawauchi, S., Santos, R., Muto, A., Lopez-Burks, M. E., Schilling, T. F., Lander, A. D. and Calof, A. L. (2016). Using mouse and zebrafish models to understand the etiology of developmental defects in Cornelia de Lange Syndrome. *Am. J. Med. Genet. C Semin. Med. Genet.* **172**, 138-145.
Keenholtz, R. A., Dhanaraman, T., Palou, R., Yu, J., D'Amours, D. and Marko, J. F. (2017). Oligomerization and ATP stimulate condensin-mediated DNA compaction. *Sci. Rep.* **7**, 14279.
Kim, J. H. and Larson, R. G. (2007). Single-molecule analysis of 1D diffusion and transcription elongation of T7 RNA polymerase along individual stretched DNA molecules. *Nucleic Acids Res.* **35**, 3848-3858.
Kimura, K. and Hirano, T. (1997). ATP-dependent positive supercoiling of DNA by 13S condensin: a biochemical implication for chromosome condensation. *Cell* **90**, 625-634.
Kimura, K. and Hirano, T. (2000). Dual roles of the 11S regulatory subcomplex in condensin functions. *Proc. Natl. Acad. Sci. USA.* **97**, 11972-11977.
Kimura, K., Rybenkov, V. V., Crisona, N. J., Hirano, T. and Cozzarelli, N. R. (1999). 13S condensin actively reconfigures DNA by introducing global positive writhe: implications for chromosome condensation. *Cell* **98**, 239-248.
Kinoshita, K. and Hirano, T. (2017). Dynamic organization of mitotic chromosomes. *Curr. Opin. Cell Biol.* **46**, 46-53.
Krantz, I. D., McCallum, J., DeScipio, C., Kaur, M., Gillis, L. A., Yaeger, D., Jukofsky, L., Wasserman, N., Bottani, A., Morris, C. A. et al. (2004). Cornelia de Lange syndrome is caused by mutations in NIPBL, the human homolog of Drosophila melanogaster Nipped-B. *Nat. Genet.* **36**, 631-635.
Kschonsak, M., Merkel, F., Bisht, S., Metz, J., Rybin, V., Hassler, M. and Haering, C. H. (2017). Structural basis for a safety-belt mechanism that anchors condensin to chromosomes. *Cell* **171**, 588-600.e24.
Kueng, S., Hegemann, B., Peters, B. H., Lipp, J. J., Schleiffer, A., Mechtler, K. and Peters, J.-M. (2006). Wapl controls the dynamic association of cohesin with chromatin. *Cell* **127**, 955-967.
Kulemzina, I., Schumacher, M. R., Verma, V., Reiter, J., Metzler, J., Failla, A. V., Lanz, C., Sreedharan, V. T., Rätsch, G. and Ivanov, D. (2012). Cohesin rings devoid of Scc3 and Pds5 maintain their stable association with the DNA. *PLoS Genet.* **8**, e1002856.
Lavoie, B. D., Hogan, E. and Koshland, D. (2002). In vivo dissection of the chromosome condensation machinery: reversibility of condensation distinguishes contributions of condensin and cohesin. *J. Cell Biol.* **156**, 805-815.
Lawrimore, J., Aicher, J. K., Hahn, P., Fulp, A., Kompa, B., Vicci, L., Falvo, M., Taylor, R. M., II and Bloom, K. (2016). ChromoShake: a chromosome dynamics simulator reveals that chromatin loops stiffen centromeric chromatin. *Mol. Biol. Cell* **27**, 153-166.
Lawrimore, J., Friedman, B., Doshi, A. and Bloom, K. (2017). RotoStep: a chromosome dynamics simulator reveals mechanisms of loop extrusion. *Cold Spring Harb. Symp. Quant. Biol.* **82**, 101-109.
Lengronne, A., Katou, Y., Mori, S., Yokobayashi, S., Kelly, G. P., 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.
Lieberman-Aiden, E., van Berkum, N. L., Williams, L., Imakaev, M., Ragoczy, T., Telling, A., Amit, I., Lajoie, B. R., Sabo, P. J., Dorschner, M. O. et al. (2009). Comprehensive mapping of long-range interactions reveals folding principles of the human genome. *Science* **326**, 289-293.
Losada, A. and Hirano, T. (2005). Dynamic molecular linkers of the genome: the first decade of SMC proteins. *Genes Dev.* **19**, 1269-1287.
Losada, A., Yokochi, T. and Hirano, T. (2005). Functional contribution of Pds5 to cohesin-mediated cohesion in human cells and Xenopus egg extracts. *J. Cell Sci.* **118**, 2133-2141.
Marston, A. L. (2014). Chromosome segregation in budding yeast: sister chromatid cohesion and related mechanisms. *Genetics* **196**, 31-63.
Matityahu, A. and Onn, I. (2018). A new twist in the coil: functions of the coiled-coil domain of structural maintenance of chromosome (SMC) proteins. *Curr. Genet.* **64**, 109-116.

Matoba, K., Yamazoe, M., Mayanagi, K., Morikawa, K. and Hiraga, S. (2005). Comparison of MukB homodimer versus MukBEF complex molecular architectures by electron microscopy reveals a higher-order multimerization. *Biochem. Biophys. Res. Commun.* **333**, 694-702.

Mc Intyre, J., Muller, E. G. D., Weitzer, S., Snydsman, B. E., Davis, T. N. and Uhlmann, F. (2007). In vivo analysis of cohesin architecture using FRET in the budding yeast Saccharomyces cerevisiae. *EMBO J.* **26**, 3783-3793.

Meier, M., Grant, J., Dowdle, A., Thomas, A., Gerton, J., Collas, P., O'Sullivan, J. M. and Horsfield, J. A. (2018). Cohesin facilitates zygotic genome activation in zebrafish. *Development* **145**, dev156521.

Melby, T. E., Ciampaglio, C. N., Briscoe, G. and Erickson, H. P. (1998). The symmetrical structure of structural maintenance of chromosomes (SMC) and MukB proteins: long, antiparallel coiled coils, folded at a flexible hinge. *J. Cell Biol.* **142**, 1595-1604.

Minnen, A., Attaiech, L., Thon, M., Gruber, S. and Veening, J.-W. (2011). SMC is recruited to oriC by ParB and promotes chromosome segregation in Streptococcus pneumoniae. *Mol. Microbiol.* **81**, 676-688.

Morales, C. and Losada, A. (2018). Establishing and dissolving cohesion during the vertebrate cell cycle. *Curr. Opin. Cell Biol.* **52**, 51-57.

Musio, A., Selicorni, A., Focarelli, M. L., Gervasini, C., Milani, D., Russo, S., Vezzoni, P. and Larizza, L. (2006). X-linked Cornelia de Lange syndrome owing to SMC1L1 mutations. *Nat. Genet.* **38**, 528-530.

Muto, A. and Schilling, T. F. (2017). Zebrafish as a Model to Study Cohesin and Cohesinopathies. *Methods Mol. Biol.* **1515**, 177-196.

Onn, I., Heidinger-Pauli, J. M., Guacci, V., Ünal, E. and Koshland, D. E. (2008). Sister chromatid cohesion: a simple concept with a complex reality. *Annu. Rev. Cell Dev. Biol.* **24**, 105-129.

Ono, T., Fang, Y., Spector, D. L. and Hirano, T. (2004). Spatial and temporal regulation of Condensins I and II in mitotic chromosome assembly in human cells. *Mol. Biol. Cell* **15**, 3296-3308.

Ono, T., Sakamoto, C., Nakao, M., Saitoh, N. and Hirano, T. (2017). Condensin II plays an essential role in reversible assembly of mitotic chromosomes in situ. *Mol. Biol. Cell* **28**, 2875-2886.

Ouyang, Z., Zheng, G., Tomchick, D. R., Luo, X. and Yu, H. (2016). Structural basis and IP6 Requirement for Pds5-dependent cohesin dynamics. *Mol. Cell* **62**, 248-259.

Panizza, S., Tanaka, T., Hochwagen, A., Eisenhaber, F. and Nasmyth, K. (2000). Pds5 cooperates with cohesin in maintaining sister chromatid cohesion. *Curr. Biol.* **10**, 1557-1564.

Parelho, V., Hadjur, S., Spivakov, M., Leleu, M., Sauer, S., Gregson, H. C., Jarmuz, A., Canzonetta, C., Webster, Z., Nesterova, T. et al. (2008). Cohesins functionally associate with CTCF on mammalian chromosome arms. *Cell* **132**, 422-433.

Pezic, D., Weeks, S. L. and Hadjur, S. (2017). More to cohesin than meets the eye: complex diversity for fine-tuning of function. *Curr. Opin. Genet. Dev.* **43**, 93-100.

Plys, A. J. and Kingston, R. E. (2018). Dynamic condensates activate transcription. *Science* **361**, 329-330.

Rankin, S. and Dawson, D. S. (2016). Recent advances in cohesin biology. *F1000Res* **5**, Rev-1909.

Rao, S. S. P., Huntley, M. H., Durand, N. C., Stamenova, E. K., Bochkov, I. D., Robinson, J. T., Sanborn, A. L., Machol, I., Omer, A. D., Lander, E. S. et al. (2014). A 3D map of the human genome at kilobase resolution reveals principles of chromatin looping. *Cell* **159**, 1665-1680.

Rao, S. S. P., Huang, S.-C., Glenn St Hilaire, B., Engreitz, J. M., Perez, E. M., Kieffer-Kwon, K.-R., Sanborn, A. L., Johnstone, S. E., Bascom, G. D., Bochkov, I. D. et al. (2017). Cohesin loss eliminates all loop domains. *Cell* **171**, 305-320.e24.

Rhodes, J. M., Bentley, F. K., Print, C. G., Dorsett, D., Misulovin, Z., Dickinson, E. J., Crosier, K. E., Crosier, P. S. and Horsfield, J. A. (2010). Positive regulation of c-Myc by cohesin is direct, and evolutionarily conserved. *Dev. Biol.* **344**: 637-649.

Rolef Ben-Shahar, T., Heeger, S., Lehane, C., East, P., Flynn, H., Skehel, M. and and Uhlmann, F. (2008). Eco1-dependent cohesin acetylation during establishment of sister chromatid cohesion. *Science* **321**, 563-556.

Rollins, R. A., Morcillo, P. and Dorsett, D. (1999). Nipped-B, a Drosophila homologue of chromosomal adherins, participates in activation by remote enhancers in the cut and Ultrabithorax genes. *Genetics* **152**, 577-593.

Rollins, R. A., Korom, M., Aulner, N., Martens, A. and Dorsett, D. (2004). Drosophila nipped-B protein supports sister chromatid cohesion and opposes the stromalin/Scc3 cohesion factor to facilitate long-range activation of the cut gene. *Mol. Cell. Biol.* **24**, 3100-3111.

Rosa, A. and Brivanlou, A. H. (2017). Role of microRNAs in zygotic genome activation: modulation of mRNA during embryogenesis. *Methods Mol. Biol.* **1605**, 31-43.

Rowland, B. D., Roig, M. B., Nishino, T., Kurze, A., Uluocak, P., Mishra, A., Beckouët, F., Underwood, P., Metson, J., Imre, R. et al. (2009). Building sister chromatid cohesion: smc3 acetylation counteracts an antiestablishment activity. *Mol. Cell* **33**, 763-774.

Rubio, E. D., Reiss, D. J., Welcsh, P. L., Disteche, C. M., Filippova, G. N., Baliga, N. S., Aebersold, R., Ranish, J. A. and Krumm, A. (2008). CTCF physically links cohesin to chromatin. *Proc. Natl. Acad. Sci. USA.* **105**, 8309-8314.

Rudra, S. and Skibbens, R. V. (2013). Cohesin codes - interpreting chromatin architecture and the many facets of cohesin function. *J. Cell Sci.* **126**, 31-41.

Sakai, A., Hizume, K., Sutani, T., Takeyasu, K. and Yanagida, M. (2003). Condensin but not cohesin SMC heterodimer induces DNA reannealing through protein-protein assembly. *EMBO J.* **22**, 2764-2775.

Schüle, B., Oviedo, A., Johnston, K., Pai, S. and Francke, U. (2005). Inactivating mutations in ESCO2 cause SC phocomelia and Roberts Syndrome: No phenotype-genotype correlation. *Am. J. Hum. Genet.* **77**, 1117-1128.

Schwarzer, W., Abdennur, N., Goloborodko, A., Pekowska, A., Fudenberg, G., Loe-Mie, Y., Fonseca, N. A., Huber, W., Haering, C. H., Mirny, L. et al. (2017). Two independent modes of chromatin organization revealed by cohesin removal. *Nature* **551**, 51-56.

Seitan, V. C., Banks, P., Laval, S., Majid, N. A., Dorsett, D., Rana, A., Smith, J., Bateman, A., Krpic, S., Hostert, A. et al. (2006). Metazoan Scc4 homologs link sister chromatid cohesion to cell and axon migration guidance. *PLoS Biol.* **4**, e242.

Shintomi, K. and Hirano, T. (2009). Releasing cohesin from chromosome arms in early mitosis: opposing actions of Wapl-Pds5 and Sgo1. *Genes Dev.* **23**, 2224-2236.

Skibbens, R. V. (2008). Mechanisms of sister chromatid pairing. *Int. Rev. Cell Mol. Biol.* **269**, 283-339.

Skibbens, R. V. (2016). Of rings and rods: regulating cohesin entrapment of DNA to generate intra- and intermolecular tethers. *PLoS Genet.* **12**, e1006337.

Skibbens, R. V., Corson, L. B., Koshland, D. and Hieter, P. (1999). Ctf7p is essential for sister chromatid cohesion and links mitotic chromosome structure to the DNA replication machinery. *Genes Dev.* **13**, 307-319.

Skibbens, R. V., Colquhoun, J. M., Green, M. J., Molnar, C. A., Sin, D. N., Sullivan, B. J. and Tanzosh, E. E. (2013). Cohesinopathies of a feather flock together. *PLoS Genet.* **9**, e1004036.

Soh, Y.-M., Bürmann, F., Shin, H.-C., Oda, T., Jin, K. S., Toseland, C. P., Kim, C., Lee, H., Kim, S. J., Kong, M.-S. et al. (2015). Molecular basis for SMC rod formation and its dissolution upon DNA binding. *Mol. Cell* **57**, 290-303.

Stedman, W., Kang, H., Lin, S., Kissil, J. L., Bartolomei, M. S. and Lieberman, P. M. (2008). Cohesins localize with CTCF at the KSHV latency control region and at cellular c-myc and H19/Igf2 insulators. *EMBO J.* **27**, 654-666.

Stigler, J., Çamdere, G. Ö., Koshland, D. E. and Greene, E. C. (2016). Single-molecule imaging reveals a collapsed conformational state for DNA-bound cohesin. *Cell Rep.* **15**, 988-998.

St-Pierre, J., Douziech, M., Bazile, F., Pascariu, M., Bonneil, E., Sauvé, V., Ratsima, H. and D'Amours, D. (2009). Polo kinase regulates mitotic chromosome condensation by hyperactivation of condensin DNA supercoiling activity. *Mol. Cell* **34**, 416-426.

Stray, J. E. and Lindsley, J. E. (2003). Biochemical analysis of the yeast condensin Smc2/4 complex: an ATPase that promotes knotting of circular DNA. *J. Biol. Chem.* **278**, 26238-26248.

Strick, T. R., Kawaguchi, T. and Hirano, T. (2004). Real-time detection of single-molecule DNA compaction by condensin I. *Curr. Biol.* **14**, 874-880.

Sutani, T., Kawaguchi, T., Kanno, R., Itoh, T. and Shirahige, K. (2009). Budding yeast Wpl1(Rad61)-Pds5 complex counteracts sister chromatid cohesion-establishing reaction. *Curr. Biol.* **19**, 492-497.

Tedeschi, A., Wutz, G., Huet, S., Jaritz, M., Wuensche, A., Schirghuber, E., Davidson, I. F., Tang, W., Cisneros, D. A., Bhaskara, V. et al. (2013). Wapl is an essential regulator of chromatin structure and chromosome segregation. *Nature* **501**, 564-568.

Terakawa, T., Bisht, S., Eeftens, J. M., Dekker, C., Haering, C. H. and Greene, E. C. (2017). The condensin complex is a mechanochemical motor that translocates along DNA. *Science* **358**, 672-676.

Thadani, R., Kamenz, J., Heeger, S., Muñoz, S. and Uhlmann, F. (2018). Cell-cycle regulation of dynamic chromosome association of the condensin complex. *Cell Rep.* **23**, 2308-2317.

Thattikota, Y., Tollis, S., Palou, R., Vinet, J., Tyers, M. and D'Amours, D. (2018). Cdc48/VCP promotes chromosome morphogenesis by releasing condensin from self-entrapment in chromatin. *Mol. Cell* **69**, 664-676.e5.

Tong, K. and Skibbens, R. V. (2014). Cohesin without cohesion: a novel role for Pds5 in Saccharomyces cerevisiae. *PLoS ONE* **9**, e100470.

Tong, K. and Skibbens, R. V. (2015). Pds5 regulators segregate cohesion and condensation pathways in Saccharomyces cerevisiae. *Proc. Natl. Acad. Sci. USA.* **112**, 7021-7026.

Tonkin, E. T., Wang, T.-J., Lisgo, S., Bamshad, M. J. and Strachan, T. (2004). NIPBL, encoding a homolog of fungal Scc2-type sister chromatid cohesion proteins and fly Nipped-B, is mutated in Cornelia de Lange syndrome. *Nat. Genet.* **36**, 636-641.

Tsai, P.-F., Dell'Orso, S., Rodriguez, J., Vivanco, K. O., Ko, K.-D., Jiang, K., Juan, A. H., Sarshad, A. A., Vian, L., Tran, M. et al. (2018). A muscle-specific enhancer RNA mediates cohesin recruitment and regulates transcription in trans. *Mol. Cell* **71**, 129-141.e8.

van Ruiten, M. S. and Rowland, B. D. (2018). SMC complexes: universal DNA looping machines with distinct regulators. *Trends Genet.* **34**, 477-487.

Vega, H., Waisfisz, Q., Gordillo, M., Sakai, N., Yanagihara, I., Yamada, M., van Gosliga, D., Kayserili, H., Xu, C., Ozono, K., et al. (2005). Roberts syndrome is caused by mutations in ESCO2, a human homolog of yeast ECO1 that is essential for the establishment of sister chromatid cohesion. *Nat. Genet.* **37**: 468-470.

Vian, L., Pękowska, A., Rao, S. S. P., Kieffer-Kwon, K.-R., Jung, S., Baranello, L., Huang, S.-C., El Khattabi, L., Dose, M., Pruett, N., et al. (2018). The energetics and physiological impact of cohesin extrusion. *Cell* **173**, 1165-1178.e20.

Villa-Hernández, S. and Bermejo, R. (2018). Replisome-cohesin interfacing: a molecular perspective. *BioEssays* **40**, e1800109.

Walther, N., Hossain, M. J., Politi, A. Z., Koch, B., Kueblbeck, M., Ødegård-Fougner, Ø., Lampe, M. and Ellenberg, J. (2018). A quantitative map of human Condensins provides new insights into mitotic chromosome architecture. *J. Cell Biol.* **217**, 2309-2328.

Wang, X., Brandão, H. B., Le, T. B. K., Laub, M. T. and Rudner, D. Z. (2017). Bacillus subtilis SMC complexes juxtapose chromosome arms as they travel from origin to terminus. *Science* **355**, 524-527.

Weitzer, S., Lehane, C. and Uhlmann, F. (2003). A model for ATP hydrolysis-dependent binding of cohesin to DNA. *Curr. Biol.* **13**, 1930-1940.

Wendt, K. S., Yoshida, K., Itoh, T., Bando, M., Koch, B., Schirghuber, E., Tsutsumi, S., Nagae, G., Ishihara, K., Mishiro, T. et al. (2008). Cohesin mediates transcriptional insulation by CCCTC-binding factor. *Nature* **451**, 796-801.

Wutz, G., Várnai, C., Nagasaka, K., Cisneros, D. A., Stocsits, R. R., Tang, W., Schoenfelder, S., Jessberger, G., Muhar, M., Hossain, M. J. et al. (2017). Topologically associating domains and chromatin loops depend on cohesin and are regulated by CTCF, WAPL, and PDS5 proteins. *EMBO J.* **36**, 3573-3599.

Xu, B., Lu, S. and Gerton, J. L. (2014). Roberts syndrome: a deficit in acetylated cohesin leads to nucleolar dysfunction. *Rare Dis.* **2**, e27743.

Xu, X., Kanai, R., Nakazawa, N., Wang, L., Toyoshima, C. and Yanagida, M. (2018). Suppressor mutation analysis combined with 3D modeling explains cohesin's capacity to hold and release DNA. *Proc. Natl. Acad. Sci. USA* **115**, E4833-E4842.

Yan, J., Enge, M., Whitington, T., Dave, K., Liu, J., Sur, I., Schmierer, B., Jolma, A., Kivioja, T., Taipale, M. et al. (2013). Transcription factor binding in human cells occurs in dense clusters formed around cohesin anchor sites. *Cell* **154**, 801-813.

Yoshimura, S. H., Hizume, K., Murakami, A., Sutani, T., Takeyasu, K. and Yanagida, M. (2002). Condensin architecture and interaction with DNA: regulatory non-SMC subunits bind to the head of SMC heterodimer. *Curr. Biol.* **12**, 508-513.

Yuan, B., Pehlivan, D., Karaca, E., Patel, N., Charng, W.-L., Gambin, T., Gonzaga-Jauregui, C., Sutton, V. R., Yesil, G., Bozdogan, S. T., et al. (2015). Global transcriptional disturbances underlie Cornelia de Lange syndrome and related phenotypes. *J. Clin. Invest.* **125**, 636-651.

Yuen, K. C. and Gerton, J. L. (2018). Taking cohesin and condensin in context. *PLoS Genet.* **14**, e1007118.

Zhang, N., Kuznetsov, S. G., Sharan, S. K., Li, K., Rao, P. H. and Pati, D. (2008). A handcuff model for the cohesin complex. *J. Cell Biol.* **183**, 1019-1031.