Rings, bracelet or snaps: fashionable alternatives for Smc complexes

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The mechanism of higher order chromosome organization has eluded researchers for over 100 years. A breakthrough occurred with the discovery of multi-subunit protein complexes that contain a core of two molecules from the structural maintenance of chromosome (Smc) family. Smc complexes are important structural components of chromosome organization in diverse aspects of DNA metabolism, including sister chromatid cohesion, condensation, global gene repression, DNA repair and homologous recombination. In these different processes, Smc complexes may facilitate chromosome organization by tethering together two parts of the same or different chromatin strands. The mechanism of tethering by Smc complexes remains to be elucidated, but a number of intriguing topological alternatives are suggested by the unusual structural features of Smc complexes, including their large coiled-coil domains and ATPase activities. Distinguishing between these possibilities will require innovative new approaches.

Keywords: structural maintenance of chromosomes; sister chromatid cohesion; condensation

1. DISCUSSION

Mitotic chromosomes in eukaryotes have two features of higher chromatin organization that are obvious even in micrographs taken over 100 years ago. Firstly, replicated chromosomes (sister chromatids) are paired with each other by a process called sister chromatid cohesion. Secondly, condensation shortens the sister chromatids and resolves them into distinct adjacent domains. Condensation and sister chromatid cohesion are both essential for proper chromosome segregation (figure 1). Despite the early discovery of condensation and cohesion, very little is known about the molecular basis of these processes. Given this dearth of knowledge, the study of cohesion and condensation might identify novel activities for chromosome organization that were not uncovered by extensive studies of other forms of DNA metabolism like DNA replication and transcription.

Indeed, work from several laboratories has identified two novel protein complexes, cohesin and condensin, which help mediate sister chromatid cohesion and condensation, respectively (Guacci *et al.* 1997; Hirano *et al.* 1997; Michaelis *et al.* 1997). Remarkably, these two complexes share a related structure (figure 2). At the core of the complex is the structural maintenance of chromosome (Smc) proteins (reviewed in Koshland & Strunnikov 1996; Nasmyth *et al.* 2000; Hirano 2002). Each Smc molecule is a large, approximately 150 kDa, protein. The protein contains globular domains at its amino and carboxy termini. Extending from the globular domains are long helical domains, which are connected by a hinge domain. Folding at the hinge

allows the helical domains to form a long coiled coil (approximately 40 nm) and bring the two globular domains into proximity to form the head domain (Melby *et al.* 1998; Haering *et al.* 2002). Once assembled, the head domain can bind and hydrolyse ATP (Hirano *et al.* 2001).

Smc proteins assemble into elaborate complexes (figure 2). For the cohesin and condensin complexes, different pairs of non-identical Smc molecules dimerize to form heterodimers. Dimerization occurs when the hinge domains of each Smc molecule bind to each other (Haering *et al.* 2002). The head domains of each Smc molecule can also interact because a signature motif within the head domain of each Smc molecule binds to ATP associated with the head domain of the other Smc molecule (Hopfner *et al.* 2000; Arumugam *et al.* 2003; Weitzer *et al.* 2003). When two Smc molecules associate with each other simultaneously by hinge–hinge and head–head interactions, a ring is formed (Gruber *et al.* 2003). This ring can be observed by electron microscopy (Anderson *et al.* 2002). Cohesin and condensin complexes also have non-Smc subunits (Hirano 2002). While some non-Smc subunits appear to be unique to cohesin or condensin, and presumably are responsible in part for their distinct functions, one non-Smc subunit from cohesin and condensin shares sequence similarity. These related proteins are called kleisins (Schleiffer *et al.* 2003). A single kleisin protein can interact with the two head domains of the Smc heterodimer (Haering *et al.* 2002). These conserved and unusual structural features of cohesin and condensin suggest that Smc complexes share a potentially novel activity for DNA metabolism.

Additional studies demonstrate that Smc complexes function in processes other than sister chromatid

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One contribution of 17 to a Discussion Meeting Issue 'Chromosome segregation'.

Figure 1. Chromosome organization during mitosis. During the cell cycle, a chromosome is replicated during S phase. The duplicated copies of the chromosome are called sister chromatids (black and grey). Sister chromatids are held together from the time of replication in S phase until the onset of chromosome segregation during mitosis. This cohesion facilitates bipolar attachment of the sister kinetochores to the microtubules of the mitotic spindle, ensuring the orderly segregation of sister chromatids to opposite poles. At the onset of mitosis, sister chromatids become visibly condensed. Chromosome condensation separates sister chromatids into distinct domains, which facilitates subsequent sister chromatid segregation by the mitotic spindle. Condensation also shortens the length of the sister chromatids, which ensures that they are properly packaged into the dividing cell upon cytokinesis.

Figure 2. Smc complex assembly. A cartoon of an Smc protein is shown on the left. Folding of the Smc molecule at the hinge generates the head domain and brings the Walker A site (important for ATP binding) and Walker B motif (important for ATPase activity) in close proximity to form a functional ATPase. Smc molecules can dimerize through their hinge motifs. The signature motif of each head domain can bind to the ATP associated with the other head domain of the dimer, generating a closed ring. The ring is stabilized by the binding of a kleisin molecule and other non-Smc proteins (not shown). In principle, oligomers of the Smc complex could occur through interactions of the hinge domains or coiled-coil domains. Alternatively, oligomers may form by the signature motif binding to a head domain of another dimer.

cohesion and condensation (table 1). Cohesin and condensin have been implicated in DNA repair as well as mitotic and meiotic recombination (Aono *et al.* 2002; Bhalla *et al.* 2002; Yu & Koshland 2003). Furthermore, global transcription of the X chromosomes in *Caenorhabditis elegans* is controlled by the dosage compensation complex, a Smc complex closely related to condensin (Chuang *et al.* 1994; Lieb *et al.*

1998). Another Smc-like complex, MRX (*Mre11*, *Rad50*, *Xrs2*) is critical for DNA repair and possibly DNA replication (Alani *et al.* 1989; Johzuka & Ogawa 1995; Anderson *et al.* 2001). Finally, Smc complexes have been discovered in almost all eukaryotes and prokaryotes (Niki *et al.* 1991; Cobbe & Heck 2000; Soppa 2001). Taken together, these observations suggest that Smc complexes act in diverse forms of

Table 1. Smc complexes act in diverse forms of DNA metabolism.

Smc complex	function	references
cohesin	sister chromatid cohesion DNA repair	Jessberger <i>et al.</i> (1996), Guacci <i>et al.</i> (1997), Michaelis <i>et al.</i> (1997), Sjogren & Nasmyth (2001)
condensin	condensation, recombination, DNA repair	Hirano <i>et al.</i> (1997), Aho <i>et al.</i> (2002), Bhalla <i>et al.</i> (2002), Yu & Koshland (2003)
dosage compensation MRX	gene expression DNA repair, replication	Chuang <i>et al.</i> (1994), Lieb <i>et al.</i> (1996)
MukB/BsSMC	bacterial segregation	Alani <i>et al.</i> (1989), Johzuka & Ogawa (1995), Anderson <i>et al.</i> (2001), Costanzo <i>et al.</i> (2001)
		Niki <i>et al.</i> (1991), Britton <i>et al.</i> (1998), Melby <i>et al.</i> (1998), Case <i>et al.</i> (2004)

DNA metabolism in almost all living organisms. Thus the elucidation of the biochemical function of Smc complexes is even more imperative.

What could be the essential function of Smc complexes, and how would this function be useful for such diverse DNA-related processes? These DNA processes potentially share one common step, holding two DNA strands in close proximity. Certainly holding DNA strands in proximity is an intricate part of meiotic recombination, recombination-based DNA repair and sister chromatid cohesion. In addition, condensation probably requires holding together two distinct regions of the same strand to make loops or helices (Milutinovich & Koshland 2003). Similarly, loops have been postulated as an important feature for regulating gene expression (Chambeyron & Bickmore 2004). Such loops could be essential for dosage compensation. Thus, it seems likely that Smc complexes may serve as tethers to hold together different DNA strands or different parts of the same strand.

The most elaborated model for how Smc complexes tether DNA has come from studies of cohesins. This 'embrace' model builds on the ring form of Smc complexes that has been observed in solution (Haering *et al.* 2002). According to the model, hydrolysis of ATP destroys the interaction of the head domains, opening the ring and allowing the DNA strands to slide inside. Upon binding a new ATP molecule, the head domains re-close the ring, which now embraces the DNA (figure 3). This embrace is stabilized by a kleisin protein that binds to both heads. Consistent with an embrace of DNA, ATPase activity is required for cohesin to bind chromatin, and cleavage of either kleisin or Smc subunits destroys DNA binding (Arumugam *et al.* 2003; Gruber *et al.* 2003; Weitzer *et al.* 2003). The embrace involves minimal contact between the DNA and the Smc complex. In an apparent contradiction, cohesins are found enriched at specific regions of the chromosomes (Blat & Kleckner 1999; Laloraya *et al.* 2000; Glynn *et al.* 2004; Weber *et al.* 2004). However, a recent report has suggested that cohesins may slide to these regions, pushed by transcription (Lengronne *et al.* 2004). A ring is a structure that in principle could easily be pushed along chromosomes.

While current observations on cohesins are consistent with an embrace model, observations of other Smc and DNA-binding complexes suggest alternative models. *In vitro* DNA binding assays for condensin

Figure 3. Three models for how Smc complexes may tether two DNA molecules/chromatin. Each model shows two strands of DNA/chromatin. These strands may come from two distinct DNA molecules (as expected for recombination or sister chromatid cohesion), or from a single DNA/chromatin molecule that is folded back on itself (as expected for regulation of gene expression or condensation). In the first model, the Smc complex embraces the two DNA strands. The snap model proposes that each Smc complex can bind a single strand and that tethering results from the oligomerization of the Smc complexes. The bracelet model suggests that Smc complexes can oligomerize to form filaments. Such filaments could be used in a number of ways to mediate tethering. One possible mechanism is shown here.

and the bacterial condensin-like mukB complex indicate tight DNA binding (Case *et al.* 2004; Strick *et al.* 2004). Electron micrographs of condensin bound to DNA show DNA in proximity to the head domains rather than the coiled coil domains (Bazett-Jones *et al.* 2002). Finally, like cohesin, the ntrC1 protein is a ring that must also hydrolyse ATP to bind DNA (Yan & Kustu 1999). However, ATP hydrolysis in ntrC1 is thought to promote a conformation change that alters the position of defined loops of amino acids, which project into the ring (Lee *et al.* 2003). This suggests that ATP can promote conformation changes to mediate DNA binding by means other than the opening and closing of rings.

These observations raise the possibility that one should consider alternative mechanisms for the function of Smc complexes other than those suggested by the embrace model. One potentially useful paradigm for thinking about rings comes from studies of the recA family of proteins. Most of these proteins oligomerize to form filaments that bind to DNA (McGrew & Knight 2003). One family member, the Dmc1 protein from humans, has been crystallized, and it forms a beautiful ring as a monomer. However, recent experiments suggest that the Dmc1 protein can bind to ssDNA as a filament (Kinebuchi *et al.* 2004). These observations suggest that the soluble Dmc1 ring is either a storage form or a precursor to an oligomeric form, which is active for recombination. In this light, the soluble ring of Smc proteins may simply be a precursor to an oligomeric form that is induced upon chromatin binding. We can imagine several ways in which an oligomer might tether two DNA molecules, including as a bracelet or a snap (figure 3). The mechanism of oligomerization in these two models differs. In the case of the bracelet, the mechanism of oligomerization occurs by interaction between head domains of two different Smc heterodimers. Indeed, the biochemical analyses of cohesin binding to chromatin have defined a connectivity of subunits, which, though interpreted to support a ring structure (Haering *et al.* 2002), are equally consistent with the bracelet topology. Alternatively, oligomerization could occur by interaction of the coiled-coil or hinge domains between two Smc complexes. These types of oligomerization have precedent in the assembly of myosin filaments and the formation of the synaptonemal complex.

Several observations are consistent with the oligomerization of Smc complexes. Dimers of Smc complexes have been observed by atomic force microscopy. However, the efficiency of such oligomerization is low (Yoshimura *et al.* 2002). This poor efficiency could reflect that this aggregation is an artefact of *in vitro* conditions, or that efficient oligomerization requires missing factors such as chromatin. Indeed, Smc complexes can bind to DNA *in vitro* in a highly cooperative fashion (Sakai *et al.* 2003; Stray & Lindsley 2003). In addition, mapping of cohesin binding sites by chromatin immunoprecipitation has defined cohesin associated regions (CARs) that occur at approximately 10 kb intervals (Blat & Kleckner 1999; Laloraya *et al.* 2000). These CARs often span 800–1500 base pairs (Laloraya *et al.* 2000). This broad size is consistent with cohesin binding to CARs as an oligomer, potentially as

a filament or as stacks of snaps. Clearly, there are other explanations for the broad size of CARs. Since the requirement for oligomerization differentiates the snap and bracelet models from the embrace, it is critical to establish the stoichiometry of Smc complexes needed for DNA binding under physiological conditions.

In addition to oligomerization, Smc molecules may undergo changes in conformation to perform their function. The head domains of Smc complexes and their mode of shared ATP binding have significant structural similarity to ABC transporters (Hopfner *et al.* 2000). A study of ATP function in one ABC transporter suggests that ATP binding and hydrolysis may twist the two heads relative to each other (Locher *et al.* 2002). This twisting propagates a conformation change in associated subunits that traverse the membrane, causing them to release their bound ligand into the cell. Thus it is possible that ATP hydrolysis may also be used to regulate large structural changes in Smc proteins. Interestingly, the analysis of purified condensin complex by atomic force microscopy reveals two predominant forms (Yoshimura *et al.* 2002). One has the expected structure, with the coiled-coil region fully extended from the head domains. In the other, the coiled coils are bent in half, such that the hinge domain is brought in close proximity to the heads. If conformational changes are an important part of Smc complex function, then the function of the different domains of Smc molecules might be more complex than is currently envisioned.

Since existing data are consistent with three very different models for Smc structure and function, there is clearly much to learn before we can understand their mechanism of action. The value of the models is that they do focus on key questions. Are the chromatin binding and tethering of two segments of DNA separable activities? Is oligomerization of Smc complexes essential for their function, and if so, is this oligomerization mediated through known interaction interfaces (the bracelet model) or the unknown interfaces of the hinge, coiled-coil or a yet-to-be studied region of Smc molecules (snap)? Is the function of ATP to promote ring opening or a conformational change necessary for oligomerization?

One way to address these important questions about Smc complexes would be to analyse intermediates in their assembly or their interaction with chromatin. To trap these types of intermediates, we have isolated dominant negative mutations in Smc molecules of cohesin and condensin of budding yeast. Dominant mutants are likely to initiate but fail to complete Smc complex assembly or function. We hope that this type of analysis will provide important new insights into Smc complexes and their critical function in so many different aspects of DNA metabolism.

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