Cohesin loading and sliding

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Summary

Cohesin is best known as a crucial component of chromosomal stability. Composed of several essential subunits in budding yeast, cohesin forms a ring-like complex that is thought to embrace sister chromatids, thereby physically linking them until their timely segregation during cell division. The ability of cohesin to bind chromosomes depends on the Scc2–Scc4 complex, which is viewed as a loading factor for cohesin onto DNA. Notably, in addition to its canonical function in sister chromatid cohesion, cohesin has also been implicated in gene regulation and development in organisms ranging from yeast to human. Despite its importance, both as a mediator of sister chromatid cohesion and as a modulator of gene expression, the nature of the association of cohesin with chromosomes that enables it to fulfill both of these roles remains incompletely understood. The mechanism by which cohesin is loaded onto chromosomes, and how cohesin and the related condensin and Smc5–Smc6 complexes promote DNA interactions require further elucidation. In this Commentary, we critically review the evidence for cohesin loading and its subsequent apparent sliding along chromosomes, and discuss the implications gained from cohesin localisation studies for its important functions in chromosome biology.

Key words: Smc complexes, Chromosome dynamics, Cohesin

Introduction

Cohesin is a crucial component of chromosomal stability (Guacci et al., 1997; Losada et al., 1998; Michaelis et al., 1997). It consists of at least six subunits, the structural maintenance of chromosome (Smc) proteins Smc1 and Smc3, sister chromatid cohesion protein 1 (Scc1) (also known as Mcd1 or Rad21), Scc3 (also known as SA or stromalin), Pds5 and Wapl, which are all evolutionarily conserved. Additional factors, such as sororin, associate with cohesin at least in some organisms to facilitate its function. The cohesin subunits Smc1 and Smc3 are flexible coiled-coil proteins that are linked tail to tail at the hinge and head to head at their ABC-type ATPase heads to form a heterodimer. The Scc1 protein associates with the Smc1 and Smc3 heads to stabilise their interaction and to recruit the remaining Scc3, Pds5 and Wapl subunits (Fig. 1). Together, these proteins form a ring-like complex that physically connects sister chromatids by topological embrace from S phase until the metaphase to anaphase transition (Anderson et al., 2002; Haering et al., 2008; Haering et al., 2002). Cohesin must bind chromosomes before the onset of DNA replication to be able to establish functional linkages, and the loading of cohesin onto DNA depends on the Scc2–Scc4 cohesin loader complex (Uhlmann and Nasmyth, 1998; Ciosk et al., 2000). Cohesin is thought to mediate cohesion by encircling the sister strands until the cleavage of its Scc1 subunit by the protease separase opens the cohesin ring, thereby releasing the sister chromatids to segregate into separate daughter cells (Uhlmann et al., 2000). Thorough evidence has been provided to demonstrate the topological binding of cohesin to DNA. Importantly, cohesin rings maintain topological association between circular sister minichromosomes even after their denaturation, if covalent cross-links have been introduced to maintain the topology of its intersubunit interactions (Haering et al., 2008). By linking sister chromatids, the cohesin rings counteract the bipolar pulling force of mitotic spindle microtubules and thereby promote the proper biorientation of chromosomes on the metaphase spindle, preventing the precocious segregation of sister chromatids during cell division. The cohesin complex also plays a role in chromosome condensation, at least in budding yeast, and during the repair of double-stranded DNA breaks by homologous recombination between sister chromatids (Guacci et al., 1997; Sjögren and Nasmyth, 2001).

Although the importance of cohesin in sister chromatid cohesion is well established, additional functions of cohesin, independent of its role in the cell cycle, have also been recognised. In Saccharomyces cerevisiae, mutations in the Smc1 and Smc3 cohesin subunits disrupt the function of the boundary elements that border the transcriptionally repressed ‘hidden MAT right’ (HMR) mating type locus and prevent the spread of silenced chromatin (Donze et al., 1999). This implicates the cohesin complex in boundary formation and functional delineation of the chromosome. In Schizosaccharomyces pombe, loss of Rad21, the fission yeast Scc1 orthologue, has been shown to result in the concomitant loss of G2-specific mRNA 3’-end formation and proximal polyA site selection at co-transcribed convergent gene units, indicating that cohesin regulates transcription termination at these sites (Gullerova and Proudfoot, 2008). In Drosophila melanogaster, Nipped-B, the orthologue of the budding yeast Scc2 cohesin loader, and the Scc3 cohesin subunit exert opposing effects on the long-range transcriptional activation of the Cut homeobox gene during development. Lowering cohesin dosage increases Cut expression, whereas decreasing Nipped-B levels diminish it (Rollins et al., 2004; Rollins et al., 1999). This suggests that the cohesin complex interferes with remote enhancer–promoter interaction, whereas the cohesin loader facilitates such long-range communication, perhaps by dynamically controlling cohesin binding to chromosomes. The observations that cohesin directly binds the Cut locus and its regulatory sequences in cultured cells, and that cell-line-specific differences in gene expression often reflect corresponding changes in cohesin binding patterns support the notion of cohesin-mediated gene regulation (Misulovin et al., 2008). Specific cohesin ablation in post-mitotic Drosophila neurons leads to defects in axon pruning...
and lethality. In this case, cohesin is thought to promote transcriptional activity of an ecdysone receptor gene (Pauli et al., 2008; Schuldiner et al., 2008). The requirement for cohesin in differentiated, post-mitotic cells provides clear evidence for a function of cohesin on chromosomes that is distinct from its role in cell division. A recent comprehensive analysis of the consequences of cohesin disruption on gene expression from polytene chromosomes in Drosophila salivary gland cells has revealed a role for cohesin in both the upregulation and downregulation of several genes in the vicinity of its binding sites (Pauli et al., 2010). How cohesin and changes to its expression levels result in distinct transcriptional outcomes at individual gene loci and in different cell types is incompletely understood (Schafä et al., 2009).

In zebrafish, cohesin has been shown to positively regulate the Runx transcription factors, which determine cell fate during early embryonic development. Downregulation of the Scc1 or Smc3 cohesin subunits leads to aberrant expression of Runx proteins in a dose-dependent manner, despite cell division being able to proceed (Horsfield et al., 2007). Finally, in mouse and human cells, cohesin-binding sites on chromosomes significantly overlap with those of the transcriptional insulator CCCTC-binding factor (CTCF) (Parelho et al., 2008; Wendt et al., 2008). This colocalisation is functionally relevant because depletion of cohesin subunits Scc1 or Smc3 recapitulates the loss of insulator function seen after CTCF depletion. Notably, the effect of cohesin on the well-characterised insulator at the H19-Igf2 locus is observed even in the G1 phase of the cell cycle, when sister chromatids are absent. Thus, cohesin facilitates the role of CTCF in insulating promoters from distant enhancers in a manner that is independent of its function in sister chromatid cohesion. Instead of promoting interactions between sister chromatids, the ability of cohesin to mediate long-range interactions along the chromosome could regulate gene expression (Hadjur et al., 2009; Nativio et al., 2009). A recent study implicates cohesin in the maintenance of the transcriptional profile of mouse embryonic stem cells and demonstrates cohesin-dependent long-range enhancer–promoter interactions at regions that are characterised by the presence of the mediator complex (Kagey et al., 2010).

The Scc2–Scc4 cohesin loader complex

The binding of cohesin to chromosomes is integral for its function. In S. cerevisiae, the loading of cohesin onto chromosomes requires a separate complex composed of the Scc2 and Scc4 proteins (Ciosk et al., 2000) (Fig. 1). When either Scc2 or Scc4 is impaired, cohesin complexes cannot stably associate with chromosomes and cohesin cannot be established. However, mutation of Scc2 or Scc4 does not affect cohesin complex assembly, suggesting that it functions specifically to facilitate the loading of cohesin onto chromosomes. Moreover, the Scc2–Scc4 loading complex becomes dispensable during S phase and in G2 (Ciosk et al., 2000; Lengronne et al., 2006), suggesting that it is required only for the initial loading of cohesin onto chromosomes, but is less important for the establishment of sister chromatid cohesion in S phase and is not required for maintaining cohesion.

Orthologues of Scc2 are known in numerous organisms, including fission yeast (Mis4), Drosophila (Nipped-B) and human [Nipped-B like (NIPBL), also known as Delangin or Scc2] (Furuya et al., 1998; Gillespie and Hirano, 2004; Krantz et al., 2004; Rollins et al., 1999; Tonkin et al., 2004). More recently, orthologues of Scc4 have also been identified (Bernard et al., 2006; Seitan et al., 2006; Watrin et al., 2006). Like their budding yeast counterparts, these loading factors are essential for cohesin association with chromosomes during interphase and, consequently, their depletion prevents the establishment of sister chromatid cohesion during S phase. Also consistent with earlier findings in S. cerevisiae, neither cohesin levels nor its assembly are affected by loss of the cohesin loading complex. Mutations in the human Scc2–Scc4 complex that affect only one allele and do not lead to noticeable defects in sister chromatid cohesion can cause the severe developmental disorder Cornelia de Lange Syndrome (CdLS) (Krantz et al., 2004; Tonkin et al., 2004). This finding ascribes importance to the correct expression levels of the Scc2–Scc4 complex, which could perhaps be relevant to its role in transcriptional regulation. The genome-wide transcriptional profiling of cell lines derived from CdLS patients has revealed a signature of expression changes, both upregulation and downregulation, as well as reduced levels of cohesin association in the promoter regions of many of the affected genes (Liu et al., 2009).

The role of ATP hydrolysis

The Smc1 and Smc3 head domains of cohesin are formed by ABC-type ATPase domains, thereby raising the intriguing possibility that ATP binding and hydrolysis might be important for cohesin function. ATP binding and hydrolysis by cohesin has...
been demonstrated in vitro (Arumugam et al., 2006; Weitzer et al., 2003). The analysis of ATPase motif mutants in vivo has led to proposals for the contribution of ATP binding and hydrolysis to cohesin function (Arumugam et al., 2003; Weitzer et al., 2003). Mutations that are predicted to prevent ATP binding by Smc1 preclude the association of Scc1 with the Smc subunits. This indicates that correct assembly of the cohesin complex requires ATP. Cohesin complexes in which the Smc1 or Smc3 subunits carry mutations that are predicted to prevent hydrolysis of bound ATP fail to stably bind to chromosomes, although intact cohesin complexes are able to form. Thus, ATP hydrolysis appears to be essential for the loading of cohesin onto chromosomes (Fig. 1). Crystallographic and biochemical studies of a bacterial Smc head domain have identified an arginine finger within the ATPase that mediates its stimulation by DNA (Lammens et al., 2004). Mutation of the corresponding arginine fingers in both Smc1 and Smc3 subunits of the cohesin ATPase slows the loading of cohesin onto DNA, but does not interfere with the establishment or maintenance of sister chromatid cohesion once loading is complete (Lengronne et al., 2006). Further characterisation of cohesin ATPase activity in vitro has confirmed the predicted effects of ATPase motif mutations on its ability to hydrolyze ATP and suggests that the ATPase is regulated by Scc1 (Arumugam et al., 2006). Therefore, association of the Scc1 subunit not only links the Smc1 and Smc3 ATPase heads in the cohesin complex, but also might contribute to controlling the catalytic activity of the Smc1–Smc3 heterodimer.

**Head or hinge?**

Although the precise molecular consequences of ATP binding and hydrolysis by cohesin remain to be defined, the structural similarity of the Smc1 and Smc3 heads to the ATPase domains of ABC transporters has led to speculation that ATP hydrolysis might facilitate transport of DNA into the cohesin ring. As no long-lasting conformational changes of the cohesin complex during cell cycle progression have been detected using various combinations of Förster resonance energy transfer (FRET) probes attached to the cohesin complex (McIntyre et al., 2007), ATP binding and hydrolysis might therefore lead to a transient conformational change that permits DNA to enter the cohesin ring, similar to a gate opening. As part of such a reaction, at least one of the interfaces between the cohesin subunits must transiently open.

A simple model of a transport gate could consist of the two Smc head domains, which preclude entry of DNA while ATP is bound, but which transiently dissociate upon hydrolysis of ATP, thus allowing the passage of DNA (Fig. 2A). Separation of the Smc heads and dissociation of the interaction between Scc1 and either Smc1 or Smc3 would open the cohesin ring, thereby allowing DNA entry and its entrapment by cohesin. If the Smc heads indeed form such an entry gate, DNA transport through this gate requires prior or subsequent dissociation either of Smc1 from the Scc1 C terminus or of Smc3 from the Scc1 N terminus, or both. This model has been put to test by permanently connecting Scc1 to either the Smc1 or Smc3 subunit as a covalent fusion (Gruber et al., 2006). Locking either interaction did not abolish cohesin loading. However, an Smc3–Scc1–Smc1 fusion protein, which would lock both interactions, could not be created. From these results, it can be concluded that, if DNA indeed enters the cohesin ring through a gate between the ATPase heads, it is able to choose a route through the transient dissociation of either the Smc3–Scc1 or the Scc1–Smc1 interface.

A recent crystallographic study of the *Escherichia coli* Smc complex provides evidence of two mutually exclusive conformational states of a putative Smc head entry gate (Woo et al., 2009). The interface between the *E. coli* Scc1 orthologue (a homodimer of MukF subunits) and the Smc orthologue (MukB) is structurally similar to the budding yeast Scc1–Smc1 interaction. A winged helix domain of MukF is grafted onto the MukB ATPase domain. However, once the MukB heads dimerise in the presence of ATP, one of the two MukF–MukB interactions is disrupted due to a steric clash between the two MukF domains. Because of its symmetric nature, either one of the two MukF–MukB interfaces will be disrupted and replaced by interaction between MukB and a flexible MukF linker. Could this situation also apply to cohesin? Notably, the FRET signal observed between the Scc1 N terminus and Smc3 is weaker than that between the Scc1 C terminus and Smc1 (McIntyre et al., 2007). A possible reason for this is that indeed the Scc1 N terminus is displaced from the Smc3 head, with a yet-to-be-identified Scc1 linker peptide providing the interaction (Fig. 2A). If this conformation alternated with one in which the linker peptide dissociates and winged helix domains at both Scc1 termini bind to the disengaging Smc heads, following ATP hydrolysis, a transient path for DNA to enter the Smc ring could open. Although the interaction between the Scc1 N terminus and Smc3 might preferentially undergo such regulation, a similar conformational change is conceivable between the Scc1 C terminus and Smc1, which could rationalise the results obtained with covalent fusions between Scc1 and both Smc1 and Smc3.

An alternative mechanism for ring opening envisages that the ATP binding and hydrolysis cycle of the Smc heads causes a conformational change that is transmitted to the Smc hinge interface at the opposite side of the cohesin ring (Fig. 2B). DNA could then...
enter through transient dissociation of the Smc hinge. Support for this idea comes from experiments in which an additional dimerisation interface was engineered at the hinge that, once engaged, prevented cohesin loading onto DNA (Gruber et al., 2006). As a caveat, we do not know whether the engaged ectopic dimerisation domain might have had an adverse effect that obstructed DNA binding by different means than preventing hinge dissociation. In this model, conformational changes at the ATPase heads need to be transmitted to the hinge, which is located up to 35 nm away and appears to be connected to the heads merely by a flexible coiled coil. A possible means of achieving this involves a bending back of the hinge towards the heads, as has been observed in atomic force microscopy images of the fission yeast Smc1–Smc3 dimer (Sakai et al., 2003). In this way, the ATPase heads might come into direct contact with the hinge domain; some biochemical evidence has been observed for this (McIntyre et al., 2007). Clearly, the mechanism by which cohesin, and other Smc complexes, are loaded onto DNA is a topic of outstanding interest. The topological embrace might be complemented, at specific locations, by non-topological interactions (Chang et al., 2005). Their relative contributions to sister chromatid cohesion and gene regulation will be important to dissect.

**Localisation of cohesin and its loader**

As an important approach to gain insight into the nature of cohesin association with chromosomes, several studies have addressed the chromosomal localisation pattern of cohesin and its loading complexes in various model organisms. Initial chromatin immunoprecipitation (ChIP) analyses of cohesin distribution along a budding yeast chromosome revealed its prominent enrichment at the centromere and its binding at distinct sites, approximately every 10–15 kb along chromosome arms (Blat and Kleckner, 1999; Megee et al., 1999; Tanaka et al., 1999). The binding pattern of cohesin correlates with AT-rich regions, although no specific consensus sequence has been identified. Subsequent high-resolution ChIP microarray studies revealed that budding yeast cohesin is predominantly enriched in intergenic regions between convergent RNA-polymerase-II-transcribed genes (Glynn et al., 2004; Lengronne et al., 2004). These include tRNA and other RNA-polymerase-III-transcribed genes, as well as strongly expressed tRNA-polymerase-I-transcribed genes (Lengronne et al., 2009), whereas binding along the chromosome arms correlates with AT-rich regions, although no specific consensus sequence has been identified. Sliding along DNA might therefore be, to varying degrees, a feature common to all three Smc ring complexes.

**Box 1. Smc complexes slip sliding away**

Like cohesin, condensin and the Smc5–Smc6 complex are evolutionarily conserved chromosomal protein complexes that consist of Smc heterodimers and additional non-Smc subunits. Condensin is essential for mitotic chromosome condensation, whereas the Smc5–Smc6 complex plays an as yet poorly understood essential role that is related to DNA repair. Although condensin seems rod shaped in electron micrographs, as opposed to the ring-like appearance of cohesin (Anderson et al., 2002), the molecular arrangement of its subunits suggests that condensin also forms a ring that might be capable of associating with chromosomes by topological embrace. Like cohesin, the association of budding yeast condensin with chromosomes is, at least in part, facilitated by the Scc2–Scc4 complex. Whereas most condensin remains in close association with Scc2–Scc4 binding sites, some evidence has been obtained that it relocates downstream along genes transcribed by RNA polymerases I and II (D’Ambrosio et al., 2008; Johzuka and Horiiuchi, 2007). Condensin might less readily slide along chromosomes compared with cohesin or, alternatively, its more rapid dissociation and turnover rate on chromosomes might limit such translocation. So far, evidence for the involvement of Scc2–Scc4 in condensin loading has not been obtained in organisms other than budding yeast, suggesting the possibility that condensin can also associate with chromosomes in an Scc2–Scc4-independent fashion. The Smc5–Smc6 complex has important roles in DNA repair, probably in part through its association with specific additional subunits that participate in DNA repair. Its binding to chromosomes along chromosome arms, but not at sites of DNA damage, depends on Scc2–Scc4 (Betts Lindroos et al., 2006). The association pattern of the Smc5–Smc6 complex with chromosomes displays similarities with cohesin in its preference for convergent intergenes, but also follows additional determinants of binding that remain poorly understood. Sliding along DNA might therefore be, to varying degrees, a feature common to all three Smc ring complexes.
characterise the regions that are recognised by the Scc2–Scc4 complex, such as centromeres, transcribed genes and also DNA break sites, at which Scc2–Scc4 is required for the loading of additional cohesin (Ström et al., 2004).

In Drosophila, ChIP experiments revealed a localisation pattern with striking similarities to, but also notable differences from, what has been observed in budding yeast. The binding sites for the cohesin loader subunit Nipped-B are preferentially found in transcribed regions and their distribution overlaps with that of RNA polymerase II (Misulovin et al., 2008), consistent with the notion that transcriptional activity correlates with cohesin loading sites. Variations in the binding patterns between three different Drosophila cell lines revealed some cell-type specificity in cohesin distribution, consistent with the influence of specific gene expression patterns. In contrast to budding yeast, the distribution of cohesin is almost indistinguishable from that of Nipped-B. One reason for this difference could be a more stable interaction between Nipped-B and cohesin in Drosophila, compared with the relatively weak physical interactions between Scc2–Scc4 and cohesin in budding yeast. The dynamics of Nipped-B binding to Drosophila chromosomes appears to be largely determined by that of the cohesin complex (Gause et al., 2010). This implies that the distribution of Nipped-B might also be under the influence of cohesin. For instance, after loading at promoter regions of strongly expressed genes, Nipped-B might translocate downstream along the transcribed gene together with cohesin.

The analysis of the fission yeast cohesin loader (Mis4–Ssl3) and cohesin revealed a localisation pattern that shows aspects reminiscent of both budding yeast and Drosophila (Schmidt et al., 2009). Again, the fission yeast cohesin loader was found at places of strong transcriptional activity. But whereas most cohesin accumulates between convergent gene pairs that are distant from these loading sites, as observed in budding yeast, there is also evidence of coinciding binding sites for Mis4–Ssl3 and cohesin, as is the case in Drosophila. Therefore, it is possible that the interaction of cohesin with its loader is stronger in Drosophila and fission yeast, such that loading intermediates remain detectable for a longer period or indeed some of the loader remains associated with cohesin during its translocation. Alternatively, different sub-pools of cohesin might exist in Drosophila and fission yeast. A subset of cohesin might be bound to chromosomes in a very dynamic fashion in these organisms, thereby remaining preferentially detectable at its loading sites. Only a more stable subset would translocate away from the loading sites, corresponding to the majority of cohesin in budding yeast, but potentially to only a small fraction of cohesin in Drosophila. The behaviour of the ‘dynamic’ subset of cohesin could be similar to that of the condensin complex, which, in budding yeast, makes use of the same Scc2–Scc4 loader complex and shows close overlap with its loading sites (Box 1) (D’Ambrosio et al., 2008).

In mammalian cells, the cohesin loader subunit Scc2 is found to colocalise with the transcriptional mediator complex at promoter regions of expressed genes (Kagey et al., 2010). Cohesin is also detected at these sites, but in addition a major fraction of mouse and human cohesin colocalises with the CTCF insulator, with a preference for regions in the vicinity of transcribed genes (Wendt et al., 2008). Whether and how human cohesin translocates from its loading sites to CTCF-binding sites is not known, as either no or only a very minor Scc2 peak is detectable at the CTCF sites. It is also not known how much cohesin might be distributed between these distinct enrichment sites in a more broadly spread out manner.

Depletion of cohesin subunits mimics loss of CTCF or mediator with regard to their roles in modulating promoter–enhancer interactions and gene expression, respectively. Cohesin has been shown to establish interactions between neighbouring binding sites; this could be the molecular basis for its role in regulating gene expression both at sites bound by CTCF and at promoter regions associated with mediator (Hadjur et al., 2009; Nativio et al., 2009; Kagey et al., 2010; Schmidt et al., 2010).

**Cohesin translocation along chromosomes**

How does budding yeast cohesin move from the sites where it is loaded onto chromosomes by Scc2–Scc4 to its more permanent residence at sites between convergent gene pairs? The act of RNA polymerase II transcription might be intrinsically linked to this translocation, as suggested by the observation of the downstream movement of cohesin in response to transcriptional induction at a number of investigated loci (Glynn et al., 2004; Lengronne et al., 2004). Coupled with compelling evidence for a topological interaction between cohesin and chromosomes (Haering et al., 2004), these findings raise the possibility that cohesin relocates from its initial binding sites on chromosomes by sliding along chromatin, while remaining topologically bound. The motor for this movement might simply be the ‘pushing’ of the transcription machinery towards the end of transcription units. Alternatively, cohesin might dissociate from sites of initial Scc2–Scc4 binding and then be newly reloaded further downstream. In this reloading model, translocation would require the dissociation of the cohesin complex and its subsequent re-association at a downstream binding site (Fig. 3).

As these models make specific predictions about the molecular nature of cohesin translocation along chromosomes, it will be possible to differentiate between them using experimental tests. If
cohesin translocation is due to sliding of the cohesin ring in response to the advancing transcription machinery, alterations in the transcriptional termination pattern should change sites of cohesin deposition. With sufficient temporal resolution, it should also be possible to detect translocation intermediates on transcription units as cohesin moves along. Alternatively, if reloading is required for cohesin translocation, the continued activity of the Scc2–Scc4 complex should be required during translocation, and ATP hydrolysis by cohesin should also contribute to the change in localisation.

Evidence for cohesin translocation has also been seen in fission yeast and is based on the distinct localisation of the loader and the majority of cohesin, as well as the relocation response of cohesin to changes in the transcriptional landscape (Gullerova and Proudfoot, 2008; Schmidt et al., 2009). If cohesin loading onto DNA follows a universally conserved mechanism, the question arises as to why accumulation of cohesin at convergent intergenes has not been seen in the studies conducted in Drosophila or human cells. It is formally possible that cohesin translocation occurs in all species, but that it is more difficult to detect in organisms with longer genes. This could be due to the limited stability of most cohesin molecules on chromosomes; for example, human cohesin dissociates from chromatin with a half-life of approximately 20 minutes (Gerlich et al., 2006b). As RNA polymerase II progresses at a speed of approximately 2 kb/minute, translocation along a human gene of 200 kb would require a time of 100 minutes. As a result, most cohesin might not be bound to chromosomes sufficiently long to reach the end of a gene. Thus, the detected sites of cohesin binding to active genes, in particular in Drosophila, might actually represent sliding intermediates. By contrast, genes in budding or fission yeast rarely exceed 10 kb in length, requiring a translocation time of only a few minutes.

It should also be noted that a statistical over-representation of introns are found to be human cohesin association sites. Whether this is owing to pausing of the transcription machinery during co-transcriptional splicing, with a consequent increase in cohesin deposition at these sites, is not currently known. It is also noteworthy that the human cohesin loader does not colocalise with the majority of the cohesin peaks at CTCF-binding sites (Kagey et al., 2010). The relationship between the cohesin population that is found with Scc2–Scc4 at mediator-binding sites and that found at CTCF-binding sites merits further investigation.

Conclusions and perspectives

A picture has begun to emerge by which cohesin associates with chromosomes in a dynamic manner. Much of the cohesin in most organisms might undergo repeated cycles of binding and dissociation, in its course promoting transient interactions either between neighbouring binding sites on the same chromosome to influence gene regulation or between sister chromatids to facilitate sister chromatid cohesion. This pool of cohesin might never move far away from its loading site. This mode of behaviour might be similar to that of condensin and the Smc5–Smc6 complex. The types of DNA interactions that are mediated by the distinct Smc complexes are likely to overlap, but specific interactions of individual complexes might be achieved by protein interactions that are unique to the respective complexes. These similarities predict that there is cross-talk between the activities of the different Smc complexes, which could explain how cohesin can also contribute to chromosome condensation in budding yeast (Gucci et al., 1997) and probably also in other organisms. More overlap between these complexes in processes including transcriptional regulation, interphase chromosome organisation, repair of DNA damage, restart of broken down replication forks and others is likely to emerge.

What makes cohesin unique in its essential and defining role in sister chromatid cohesion? Among the budding yeast Smc complexes, cohesin displays the most pronounced translocation along chromosomes after being loaded. Translocation is also apparent in the case of the Smc5–Smc6 complex, but is much less pronounced, if hardly detectable, for condensin (Box 1). This might be a consequence of the greater stability of cohesin on DNA once it has been loaded compared with that of other Smc complexes (Gerlich et al., 2006a; Gerlich et al., 2006b). During DNA replication, a subset of cohesin molecules takes on a specific role to establish close to permanent links between the newly synthesized sister chromatids. This establishment of sister chromatid cohesion involves acetylation of two lysine sidechains that emerge from the Smc3 ATPase head domain, which are unique to Smc3 and not found on condensin or the Smc5–Smc6 complex, during DNA replication (for a review, see Uhlmann, 2009).

It, as has been postulated, the Scc2–Scc4 complex facilitates cohesin ring opening in an ATP-hydrolysis-dependent manner, then physically relocating cohesin away from the loading sites might be part of the mechanism that stabilises cohesin on chromosomes, as it will avoid contact with Scc2–Scc4 and consequent ring opening and dissociation. Owing to its ability to move along DNA while remaining topologically bound to chromosomes, cohesin might be able to achieve stability during dynamic cellular processes. That is, cohesin stably holds onto sister chromatids, while at the same time allowing transcription and possibly other forms of DNA metabolism to continue unhindered underneath and, if necessary, moving out of the way by lateral translocation. Thus, the apparent sliding of cohesin along the chromosome might not be an oddity, but rather a crucial aspect of its mechanism of action. A more dynamic mode of association at the Scc2–Scc4-binding sites in turn might be conducive to engaging in the long-range chromatin interactions that specify transcriptional regulation.

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