REVIEW

Dynamic molecular linkers of the genome: the first decade of SMC proteins

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Structural maintenance of chromosomes (SMC) proteins are chromosomal ATPases, highly conserved from bacteria to humans, that play fundamental roles in many aspects of higher-order chromosome organization and dynamics. In eukaryotes, SMC1 and SMC3 act as the core of the cohesin complexes that mediate sister chromatid cohesion, whereas SMC2 and SMC4 function as the core of the condensin complexes that are essential for chromosome assembly and segregation. Another complex containing SMC5 and SMC6 is implicated in DNA repair and checkpoint responses. The SMC complexes form unique ring- or V-shaped structures with long coiled-coil arms, and function as ATP-modulated, dynamic molecular linkers of the genome. Recent studies shed new light on the mechanistic action of these SMC machines and also expanded the repertoire of their diverse cellular functions. Dissecting this class of chromosomal ATPases is likely to be central to our understanding of the structural basis of genome organization, stability, and evolution.

The chromosome is at the heart of all genetic processes. Its precise duplication and segregation are arguably the most important goal of the mitotic cell cycle, and programmed expression of its content, either genetic or epigenetic, is central to the development of an organism. While the astonishing advancement of genome biology in recent years has provided an advanced starting point for virtually all areas in biology, it does not solve an old problem in chromosome biology: How is the genomic DNA folded, organized, and segregated in the tiny space of a cell? The discovery of structural maintenance of chromosomes (SMC) proteins, almost a decade ago, provided a decisive clue to solve this longstanding question, and led to the identification of cohesin and condensins, two representative classes of SMC-containing complexes in eukaryotes. The proposed actions of cohesin and condensins offer a plausible, if not complete, explanation for the sudden appearance of thread-like "substances" (the chromosomes) and their longitudinal splitting during mitosis, first described by Walther Flemming (1882). Remarkably, SMC proteins are conserved among the three phyla of life, indicating that the basic strategy of chromosome organization may be evolutionarily conserved from bacteria to humans. An emerging theme is that SMC proteins are dynamic molecular linkers of the genome that actively fold, tether, and manipulate DNA strands. Their diverse functions range far beyond chromosome segregation, and involve nearly all aspects of chromosome behavior including chromosome-wide or long-range gene regulation and DNA repair. In this review article, we summarize our current understanding of SMC proteins with a major focus on studies published during the past three years. We start by describing the architecture and mechanistic actions of SMC protein complexes, and then discuss how the concerted actions of cohesin and condensin support the faithful segregation of chromosomes during mitosis and meiosis. Finally, emerging studies of a third SMC complex in eukaryotes and of bacterial SMC protein complexes are discussed.

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SMC protein complexes: a common theme with many variations

Basic architecture and enzymology of SMC proteins

SMC proteins are widely conserved in the three phyla of life (Cobbe and Heck 2004). They always form a dimer, which in turn associates with regulatory subunits to assemble a large protein complex. Most bacteria and archaea have a single SMC protein that forms a homodimer. In a subclass of Gram-negative bacteria such as *Escherichia coli*, a distantly related protein called MukB plays an equivalent role (Hiraga 2000). Individual eukaryotic organisms have at least six SMC family members that form three heterodimers in specific combinations: SMC1 and SMC3 constitute the core of the cohesin complexes (Haering and Nasmyth 2003), whereas SMC2 and SMC4 are central components of the condensin complexes (Hirano 2005). SMC5 and SMC6,

whose primary sequences are slightly divergent from those of SMC1–SMC4, are part of a complex implicated in DNA repair and checkpoint responses (Lehmann 2005).

Each SMC subunit is self-folded by antiparallel coiled-coil interactions, creating a rod-shaped molecule with an ATP-binding cassette (ABC)-like "head" domain at one end and a "hinge" domain at the other. Two SMC subunits then associate with each other through their hinge domains, producing a V-shaped dimer (Fig. 1A, panel a; Melby et al. 1998; Anderson et al. 2002). This basic folding scheme seems applicable to all SMC dimers (Haering et al. 2002; Hirano and Hirano 2002). It is important to note that the SMC dimer is a huge molecule: Each coiled-coil arm is ~50 nm long, a length equivalent to that of 150 bp of double-stranded DNA (dsDNA). How does this two-armed structure interact with DNA and manipulate its conformation? As has been predicted from crystal structures of other ABC ATPases (Hopfner et al. 2000; Smith et al. 2002), recent studies demonstrate that ATP binding to the SMC head domains drives the formation of a nucleotide-sandwiched dimer (Fig. 1A, panel b; Haering et al. 2004; Lammens et al. 2004). Biochemical work using the *Bacillus subtilis* SMC protein shows that ATP binding and hydrolysis modulate engagement and disengagement of the head domains, respectively, and thereby play a crucial role in the dynamic interaction between SMC proteins and DNA (Hirano et al. 2001; Hirano and Hirano 2004). Dimerization at the hinge domain is very tight and is ATP-independent, and mutational analysis shows that this domain acts as an essential determinant of SMC–DNA interactions (Hirano and Hirano 2002). Moreover, evidence is available that different SMC dimers interact with each other in both energy-dependent and -independent manners (Hirano et al. 2001; Sakai et al. 2003; Stray and Lindsley 2003; Hirano and Hirano 2004), implying that their action is highly dynamic and complex. Thus, much remains to be learned regarding even the basic enzymology of SMC proteins.

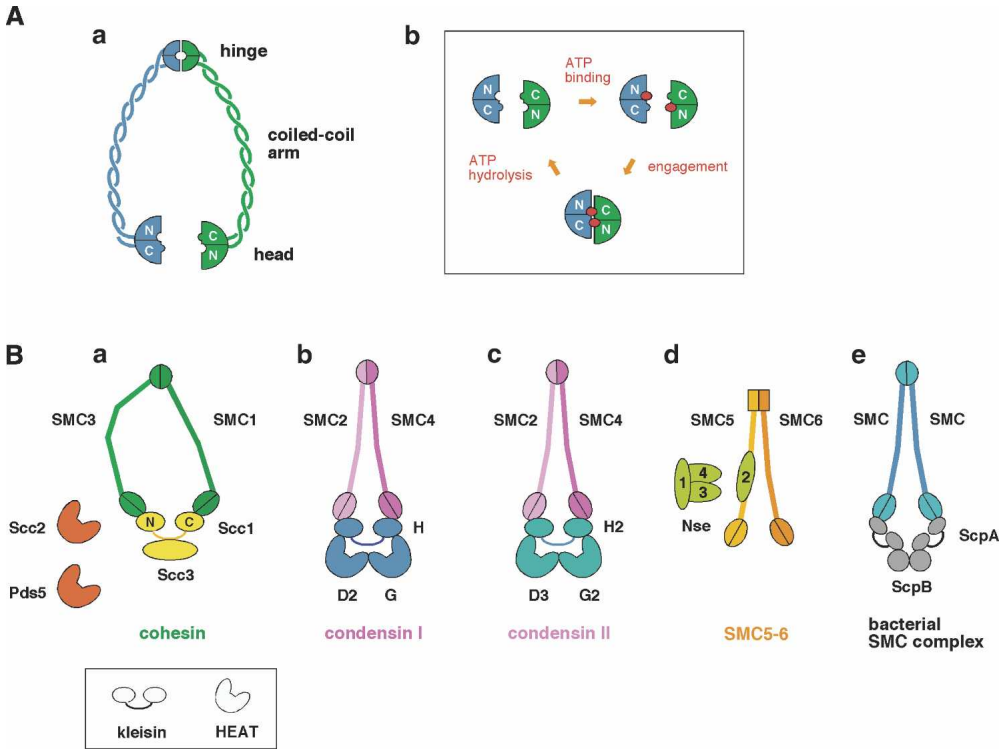

Figure 1. Architecture and subunit composition of SMC protein complexes. (*A*) Each SMC subunit self-folds by antiparallel coiled-coil interactions and forms a hinge domain at one end and an ATP-binding head domain, composed of its N- and C-terminal sequences, at the other end. (Panel *a*) A hinge–hinge interaction between two subunits mediates dimerization, thereby producing a V-shaped molecule. (Panel *b*) Two ATP molecules (red) are sandwiched between two SMC head domains and induce their engagement. Subsequent disengagement is triggered by ATP hydrolysis. The head–head engagement may occur either intramolecularly within a dimer or intermolecularly between different dimers. (*B*, panel *a*) An SMC1–SMC3 heterodimer functions as the core of the cohesin complex, which contains two other non-SMC subunits, Scc1/Mcd1/Rad21 and Scc3/SA. An SMC2–SMC4 heterodimer acts as the core of condensin I (panel *b*) and condensin II (panel *c*). The CAP-D2, CAP-G, CAP-D3, and CAP-G2 subunits contain HEAT repeats, whereas the CAP-H and CAP-H2 subunits belong to the kleisin family of proteins, like the Scc1 subunit of cohesin. (Panel *a*) Two cohesin regulators, Scc2 and Pds5, share HEAT repeats, although they are not tightly associated with cohesin. (Panel *d*) An SMC5–SMC6 heterodimer functions as part of a complex that contains Nse1, Nse2, Nse3, and Nse4. (Panel *e*) The *B. subtilis* SMC protein complex is composed of an SMC homodimer, a kleisin subunit (ScpA), and another small subunit called ScpB.

Table 1. Components of eukaryotic SMC complexes

	S. cerevisiae	*S. pombe*	*C. elegans*	DCC[d]	*D. melanogaster*	*A. thaliana*	*X. laevis*	*H. sapiens*
Cohesin								
SMC1	Smc1	Psm1	SMC-1		DmSMC1	AtSMC1	XSMC1	hSMC1α
SMC3	Smc3	Psm3	SMC-3		DmSMC3	AtSMC3	XSMC3	hSMC3
kleisin	Scc1/Mcd1	Rad21	SCC-1/COH-2[a]		DmRAD21	SYN2-4?[b]	XRAD21	hScc1/hRAD21
?	Scc3	Psc3	SCC-3		DmSA,CG13916	CAB45374	XSA1, XSA2	hSA1, hSA2
SMC1β (meiosis)	-	-	-		-	-	-	hSMC1β
kleisin (meiosis)	Rec8	Rec8	REC-8		C(2)M?[c]	SYN1/DIF1	AAH87346	hRec8
? (meiosis)	-	Rec11	-		-	-	?	hSA3/STAG3
Condensin								
SMC2 (I&II)	Smc2	Cut14	MIX-1	MIX-1	DmSMC2	AtCAP-E1, E2	XCAP-E	hCAP-E/hSMC2
SMC4 (I&II)	Smc4	Cut3	SMC-4	DPY-27	DmSMC4/gluon	AtCAP-C	XCAP-C	hCAP-C/hSMC4
HEAT (IA)	Ycs4	Cnd1	-	DPY-28	CG1911	CAB72176	XCAP-D2	hCAP-D2/CNAP1
HEAT (IB)	Ycs5/Ycg1	Cnd3	-	-	CG17054	BAB08309	XCAP-G	hCAP-G
kleisin (IC)	Brn1	Cnd2	-	DPY-26	Barren	AAC25941	XCAP-H	hCAP-H
HEAT (IIA)	-	-	HCP-6		CG31989	At4g15890	XCAP-D3	hCAP-D3
HEAT (IIB)	-	-	F55C5.4		-	At1g64960	XCAP-G2	hCAP-G2
kleisin (IIC)	-	-	C29E4.2		CG14685	At3g16730	XCAP-H2	hCAP-H2
SMC5-6 complex								
SMC5	Smc5	Spr18/Smc5	C27A2.1		CG32438	CAC01791	BAC56936	hSMC5
SMC6	Rhc18	Rad18/Smc6	C23H4.6, F54D5.14		CG5524	MIM	BAC56937	hSMC6
Ubiquitin ligase?	Nse1	Nse1	T23F6.3?		CG11329	At5g21140	MGC68739	hNse1
SUMO ligase	Mms21	Nse2	2G118		CG13732	At3g15150	MGC53049	hNse2
(MAGE)[e]	YDR288W	Nse3	-?		(CG10059)[e]	(At1g34770)[e]	(many)[e]	(>55 paralogs)[e]
?	Qri2	Nse4/Rad62	H21P03.2		CG13142	At1g51130, At3g20760	CA983359	hQri2, hNse4
?	YML023C[f]	-	?		?	?	?	?
?	Kre29[f]	-	?		?	?	?	?

[a] The genome of *C. elegans* encodes two additional SCC-1/REC-8-like proteins, COH-1 and COH-3. COH-1 may have a non-mitotic role in development while depletion of COH-3 shows no apparent phenotype (Mito et al. 2003).

[b] Among the four SCC1/REC8 paralogs present in the genome of *A. thaliana,* only SYN1 has been shown to have a role in cohesion during meiosis. The putative cohesion function of SYN2, SYN3 and SYN4 remains to be determined (Cai et al. 2003).

[c] There is no obvious Rec8 ortholog in *D. melanogaster*. Instead, C(2)M encodes a distant kleisin-α family member that associates with DmSMC3 and has a role in SC formation (Heidmann et al. 2004).

[d] The dosage compensation complex (DCC) is unique to *C. elegans* (Hagstrom and Meyer 2003).

[e] MAGE (melanoma antigen-encoding) is a family of proteins widely expressed in human cancer cells (Barker and Salehi 2002).

[f] No obvious orthologs of YML023C or Kre29 are found in species other than those closely related to *S. cerevisiae*.

Cohesins: ring-shaped linkers composed of SMC1 and SMC3

In the cohesin complex, the SMC1–SMC3 heterodimer associates with the non-SMC subunits Scc1 (also known as Mcd1/Rad21) and Scc3/SA (Table 1; Fig. 1B, panel a). Subunit–subunit interaction assays have shown that cohesin forms a tripartite ring in which the open-V structure of the SMC heterodimer is closed by the simultaneous binding of the N- and C-terminal regions of Scc1 to the head domains of SMC3 and SMC1, respectively (Haering et al. 2002). Such a structure is consistent with the electron micrographs of cohesin complexes purified from *Xenopus laevis* eggs or human cells (Anderson et al. 2002). Scc1 is now classified as a member of a superfamily of proteins termed "kleisins", which include the condensin subunits CAP-H and CAP-H2 (see below; Table 1; Schleiffer et al. 2003). The C terminus of Scc1 forms a winged helix, a folding motif found in many DNA-binding proteins, and binds to the "outer" surface of the Smc1 head domain (Haering et al. 2004). Functional data, however, suggest that the winged helix motif of Scc1 does not interact directly with DNA.

The ring-like structure of cohesin has led to the proposal that the complex may hold sister chromatids together by embracing two DNA duplexes within its coiled-coil arms (Haering et al. 2002). This ring model is appealing because it nicely explains how proteolytic cleavage of the Scc1 subunit of the complex might open the ring and thereby trigger sister chromatid separation at the anaphase onset (Fig. 2A; Uhlmann et al. 1999). Some predictions of this model have been successfully tested by genetic experiments in *Saccharomyces cerevisiae*; for example, opening the ring by cleavage of a site engineered in the coiled-coil arm of SMC3 promotes release of cohesin from chromosomes (Gruber et al. 2003), and an "open" complex that lacks a coiled-coil domain or one of the heads fails to bind to chromatin (Weitzer et al. 2003). Nevertheless, the model remains to be tested critically in vitro using purified or reconstituted components. Biochemical analysis of cohesin components is still at a primitive stage: The purified complex displays a modest affinity for DNA or chromatin, and no ATP-dependent in vitro activity has been reported to date (Losada and Hirano 2001a; Sakai et al. 2003; Kagansky et al. 2004). Future studies should test whether a single cohesin complex can indeed accommodate two DNA duplexes within its coiled-coil arms, and determine how

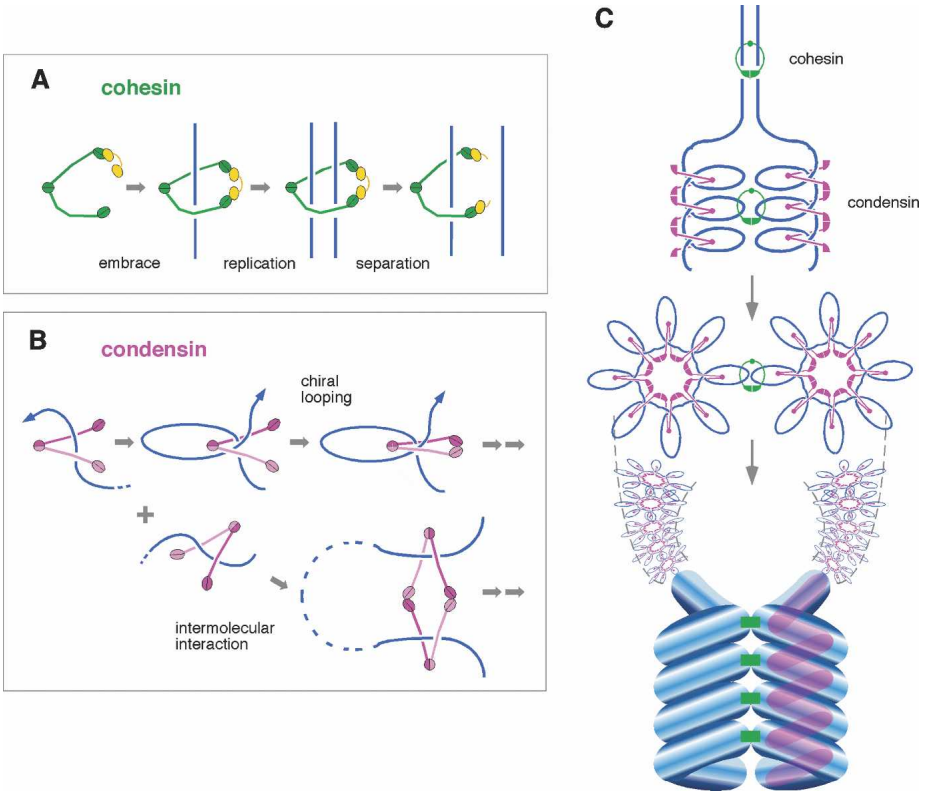

Figure 2. Hypothetical actions of cohesin and condensin. (*A*) According to the ring model, cohesin embraces DNA within its coiled-coil arms. The linkage between duplicated DNAs is established during DNA replication through an unknown mechanism. Cleavage of the Scc1 subunit (yellow) opens the ring and releases the chromatids for separation in anaphase. (*B*) Condensin may utilize the energy of ATP hydrolysis to create a chiral (positively supercoiled) loop. Alternatively, multiple condensins may associate with each other to make a DNA loop. Such association could be mediated by intermolecular head–head engagement (as shown here) or intermolecular coiled-coil interactions (not shown). For simplicity, no regulatory subunits are depicted in this cartoon. (*C*) Speculative model of how progressive release of cohesin and cooperative action of condensin lead to the assembly of a metaphase chromosome with two resolved sister chromatids. For simplicity, no distinction is made between condensins I and II.

the mechanical cycle of cohesin may be coupled to the catalytic cycle of the SMC subunits.

Condensins: V-shaped linkers composed of SMC2–SMC4

SMC2 and SMC4 constitute the core subunits of condensin. Vertebrate cells possess two different condensin complexes, condensins I and II, that are distinguished by their unique, yet related, sets of non-SMC regulatory subunits (Table 1; Fig. 1B, panels b,c; Ono et al. 2003; Yeong et al. 2003). Two of them, CAP-D2 and CAP-G in condensin I, and CAP-D3 and CAP-G2 in condensin II, contain HEAT repeats, a highly degenerate repeating motif implicated in protein–protein interactions (Neuwald and Hirano 2000). CAP-H and CAP-H2 belong to the kleisin family of proteins (Schleiffer et al. 2003). The regulatory subunits of condensins bind to the head domain(s) of the SMC heterodimer (Anderson et al. 2002; Yoshimura et al. 2002). Unlike the ring-like cohesin complex whose hinge is wide open, condensin I shows a V-shaped structure with the coiled-coil arms of the SMC heterodimer placed close together (Anderson et al. 2002). These remarkably different arm conformations of cohesin and condensin probably contribute to their specialized biochemical and physiological functions.

The phylogeny of condensin subunits sheds new light on the evolution of chromosome architecture. All of the non-SMC subunits of condensin I are highly conserved from yeast to humans, with the notable exceptions of the nematodes *Caenorhabditis elegans* and *Caenorhabditis briggsae* (Table 1; Ono et al. 2003). The non-SMC subunits of condensin II are found in plants and vertebrates but not in yeast. The apparent loss of condensin I in *C. elegans* and *C. briggsae* is puzzling but may be related to their unique, holocentric chromosome structure (Hagstrom et al. 2002; Stear and Roth 2002). Alternatively, an ancient condensin I complex in these organisms may have lost its mitotic functions during evolution and become specialized in dosage compensation, a process that equalizes expression of X-linked genes in the two sexes (Table 1; for review, see Hagstrom and Meyer 2003).

The holocomplex of condensin I, purified from either *Xenopus* eggs or HeLa cells, has the ability to introduce positive superhelical tension into dsDNA in an ATP-hydrolysis-dependent manner (e.g., Kimura and Hirano 1997). Most recently, a single-DNA-molecule nanomanipulation technique using magnetic tweezers has shown that condensin I is able to physically compact DNA in the presence of hydrolyzable ATP (Strick et al. 2004). The compaction reaction occurs in a highly dynamic and reversible fashion, possibly involving a looping mechanism. Both the supercoiling/knotting activity observed in biochemical assays and the compaction of single-DNA molecules are stimulated by cdk1-dependent phosphorylation of the non-SMC subunits (Kimura et al. 1998; Strick et al. 2004), suggesting that they may play a direct role in driving chromosome assembly during mitosis. Despite this progress, a number of questions remain to be answered regarding the action of condensins. In particular, it will be important to determine whether a single condensin complex may be sufficient to mediate some of these reactions (Bazett-Jones et al. 2002) or whether cooperative interactions of multiple condensin complexes may be crucial (Fig. 2B; Strick et al. 2004). It will also be important to compare and contrast the action of condensins and cohesin in the same set of functional assays (e.g., Losada and Hirano 2001a; Sakai et al. 2003).

The chromosome cycle supported by cohesin and condensins: an overview

A substantial body of evidence has accumulated over the past decade that the concerted action of cohesin and condensins contributes to the faithful segregation of chromosomes during the mitotic cell cycle (Fig. 3). In short, cohesin establishes sister chromatid cohesion between duplicating DNAs in S phase. A large structural reorganization of chromosomes starts in prophase, with initial release of cohesin and progressive loading of condensins, and culminates in the formation of metaphase chromosomes with well-resolved sister chromatids. This process, sister chromatid resolution, is a prerequisite of the final separation of sister chromatids that is triggered by proteolytic cleavage of cohesin at the onset of anaphase. The dynamic behavior of cohesin and condensins must be tightly regulated under the control of the cell cycle machinery and, not surprisingly, a large number of specialized factors participate in this regulation (Fig. 3). In the following four sections, we discuss the series of events that ensure the segregation of mitotic chromosomes in a temporal order. Whenever possible, we explore the mechanistic connection between the observable cytological events and the underlying molecular events.

Establishing, mobilizing, and stabilizing sister chromatid cohesion

Loading cohesin onto chromatin

A protein known as Scc2/Mis4 is required for loading of cohesin onto chromatin (Fig. 3A; Ciosk et al. 2000; Tomonaga et al. 2000). In *C. elegans*, TIM-1, a paralog of the *Drosophila melanogaster* clock gene *timeless*, performs a similar task (Chan et al. 2003). Scc2 and TIM-1 are HEAT-repeat proteins that physically interact with cohesin (Arumugam et al. 2003; Chan et al. 2003). It has been suggested that Scc2 may promote hydrolysis of ATP bound to cohesin's SMC heads and thereby stimulate the opening of the ring to allow loading onto chromatin (Fig. 4A; Arumugam et al. 2003). In *Xenopus* egg extracts, loading of Scc2 on chromatin, and therefore efficient loading of cohesin, depends on the assembly of prereplication complex (pre-RC) but not on the initiation of DNA replication (Gillespie and Hirano 2004; Takahashi et al. 2004). This requirement could be a mechanism unique to early embryonic cells. In *S. cerevisiae*, for in-

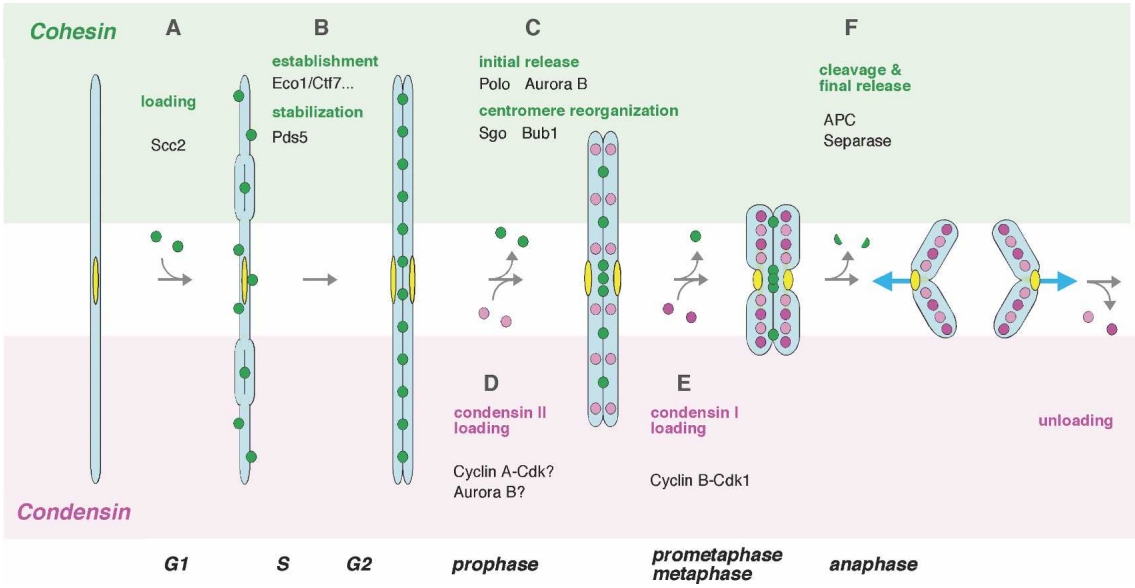

Figure 3. Overview of the mitotic chromosome cycle. The *top* and *bottom* parts of the cartoon indicate the major events regulating the dynamics of cohesin and condensin, respectively, along with their regulatory factors. (Green circle) Cohesin; (magenta circle) condensin I; (light-magenta circle) condensin II. See the text for details.

stance, cohesin is able to associate with chromatin in G1 cells depleted of the pre-RC component Cdc6 (Uhlmann and Nasmyth 1998). In HeLa cells, cohesin binds to chromatin at the end of mitosis, coincident with pre-RC assembly (Losada et al. 2000; Méndez and Stillman 2000; Sumara et al. 2000), but the interdependency of the two events remains to be investigated.

Recent genetic studies in *S. cerevisiae* suggest a functional contribution of the chromatin-remodeling complex RSC to sister chromatid cohesion: One study emphasizes a direct requirement for RSC in arm-specific loading of cohesin (Huang et al. 2004), whereas the other points out its role in establishment of cohesion but not cohesin loading per se (Baetz et al. 2004). Another study in HeLa cells reports that a subfraction of SNF2h/ISWI, the ATPase subunit of many remodeling complexes, copurifies with cohesin, and provides evidence in favor of its role in cohesin recruitment to a repetitive sequence (Hakimi et al. 2002). However, no such link between cohesion and ISWI was found in *Xenopus* egg extracts (MacCallum et al. 2002). Clearly, further analysis is required to clarify the functional link between the cohesion and chromatin remodeling machineries.

Building the linkage between sister chromatids

Eco1/Ctf7 is an essential gene in *S. cerevisiae* that is involved in the formation of cohesive structures during DNA replication, but not in their maintenance (Fig. 3B; Skibbens et al. 1999; Toth et al. 1999). Eco1/Ctf7 has an acetyl-transferase motif, and a purified recombinant protein acetylates cohesin subunits in vitro (Ivanov et al. 2002). The involvement of protein acetylation in the establishment of cohesion has also been suggested by a genetic study in *Drosophila*: An Eco1/Ctf7-like protein known as Deco and a protein belonging to a different class of acetyl-transferases named San are both required to prevent precocious sister chromatid separation (Williams et al. 2003). Nonetheless, a mutation in the key catalytic residue of Eco1/Ctf7 does not compromise high-fidelity chromosome transmission in yeast (Brands and Skibbens 2005), a result that casts doubt on the functional relevance of the acetyl-transferase activity in cohesion establishment. Eco1/Ctf7 interacts genetically with the sliding clamp PCNA as well as with the clamp loader replication factor C (RF-C) (Kenna and Skibbens 2003), further suggesting its role in linking cohesion to DNA replication. Other replication-related proteins implicated in cohesion include an "alternative" RF-C complex (containing Ctf8, Ctf18, and Dcc1), Ctf4 that associates with DNA polymerase α (Hanna et al. 2001; Mayer et al. 2001; Bermudez et al. 2003), and the Chl1 helicase (Skibbens 2004).

It remains unclear how the establishment of cohesion might be coupled to DNA replication at a mechanistic level. The growing number of replication-related cohesion factors is difficult to reconcile with a model in which the replication machinery simply passes through cohesin rings that have previously been loaded onto the parental chromatid (Fig. 4B, model 1; Haering et al. 2002). Another possibility is that cohesin undergoes a transient conformational change when it is met by a replication fork. After passage of the fork, the complex may return to the original conformation (Fig. 4B, model 2) or may be converted into a new structure that is proficient for cohesion (Fig. 4B, model 3). Alternatively, the replication machinery could push cohesin towards the termination sites (Fig. 4B, model 4), analogous to what has been proposed for the transcription machinery (Len-

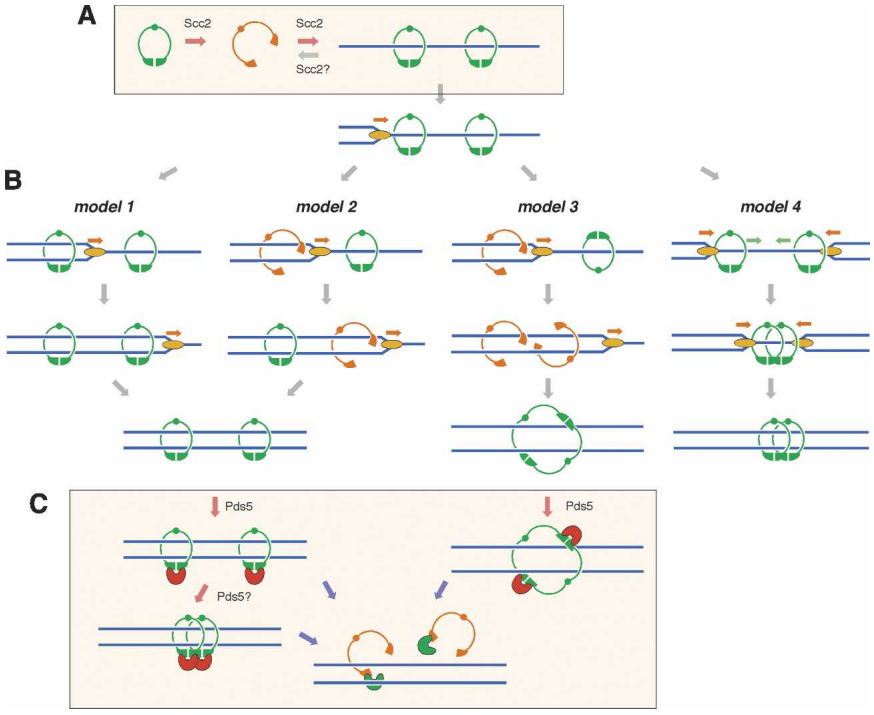

Figure 4. Regulation of cohesin dynamics during interphase. (*A*) Scc2 promotes loading of cohesin onto the parental chromatid before DNA replication. It may also be involved in transient unloading or mobilization of cohesin. Scc2 could mediate these functions by facilitating disengagement of the SMC head domains of cohesin. Two conformations of cohesin, with engaged and disengaged head domains, are represented in green and orange, respectively. (*B*) Speculative models for the establishment of cohesion during DNA replication. The replication machinery (yellow oval) could simply pass through the cohesin ring (model 1). Alternatively, passage of the replication fork could impose a conformational change in cohesin. The altered cohesin complex may return to the original conformation (model 2) or may generate a novel cohesive structure (model 3). Model 4 proposes that the replication forks push the cohesin complexes so that they accumulate at termination sites. Replication of the remaining short stretch of DNA could be facilitated by specialized factors such as the alternative RF-C. Subsequent action of the transcriptional machinery could then relocate cohesin from the termination sites to regions of convergent transcription (Glynn et al. 2004; Lengronne et al. 2004). (*C*) Pds5 (red oval) stabilizes cohesion, possibly by acting as a "closer" of the cohesin ring and/or by promoting intermolecular interactions between adjacent cohesin complexes. Pds5 could mediate these functions by suppressing disengagement of the SMC head domains of cohesin. In vertebrates, Pds5 may have an additional role in destabilizing cohesion and helping efficient release of cohesin in early mitosis. These apparently opposite actions of Pds5 could be regulated by cell cycle-specific modifications (represented by color change).

gronne et al. 2004; see below). Replication of the last short stretch of DNA where cohesin accumulates could be managed without additional factors but be completed most efficiently with help of replication-related cohesion factors such as the alternative RF-C complex. This would explain why many of these factors are nonessential for cell viability in yeast. Setting up a system in which replication-coupled cohesion can be reconstituted in vitro would surely help test these models.

Mobilizing and stabilizing cohesin

High-resolution mapping of cohesin-binding sites in yeast has revealed a preference of cohesin for sites of convergent transcription (Glynn et al. 2004; Lengronne et al. 2004). It is possible that some characteristic of these sites (e.g., specific histone modifications or higher-order chromatin structure) favors the binding of cohesin (Glynn et al. 2004). A more intriguing proposal is that the transcription machinery "pushes" the cohesin complexes until they reach the sites where RNA polymerases traveling in opposite directions meet (Lengronne et al. 2004). This model is supported by the observation that transcriptional activity changes the pattern of cohesin-binding sites. It remains to be determined, however, whether cohesin does actually slide along DNA or whether it dissociates from the initial loading sites and reassociates again farther down. In *scc2* mutants, cohesin is still able to associate with chromatin (perhaps in an abortive manner) but is unable to relocate (Lengronne et al. 2004). Scc2 might therefore function not only in the productive loading step but also in the dynamic mobilization or conformational change of cohesin during or after DNA replication.

Pds5 (also known as BimD or Spo76) is another protein that modulates the dynamic association of cohesin with chromatin (Fig. 3B). While this class of proteins is highly conserved from yeast to humans, the phenotypes observed in Pds5-deficient cells are somewhat variable among different organisms. For instance, Pds5 is essential for viability and is required to maintain cohesion in unperturbed mitosis in *S. cerevisiae* (Stead et al. 2003), whereas it is not essential in *Schizosaccharomyces pombe* and cohesion defects are observed only after prolonged G2/M arrest (Tanaka et al. 2001; Wang et al. 2002). The idea that Pds5 is important to reinforce cohesion is also supported by several studies in other organisms (Storlazzi et al. 2003; Wang et al. 2003). Vertebrate cells have two Pds5-like proteins, Pds5A and Pds5B, and mild cohesion defects are observed when the level of these proteins is decreased (Losada et al. 2005). Unexpectedly, metaphase chromosomes assembled in a Pds5-depleted *Xenopus* egg extract retain an elevated amount of cohesin, suggesting that vertebrate Pds5 could not only stabilize cohesion in interphase but also partici-

pate in its efficient dissolution in early mitosis (Fig. 4C). From a mechanistic point of view, it is interesting to note that, like Scc2, Pds5 contains multiple HEAT repeats (e.g., Neuwald and Hirano 2000). One possibility is that Scc2 and Pds5 use the same motif to modulate the SMC ATPase cycle of cohesin, but that they do so in opposite ways. For example, Scc2 could destabilize or mobilize cohesin's interaction with chromatin by acting as its "opener", whereas Pds5 may stabilize this interaction by acting as a "closer". The precise balance of the actions of Scc2 and Pds5 must be regulated tightly by cell cycle-specific modifications, such as sumoylation or phosphorylation, of each component (Stead et al. 2003; Gillespie and Hirano 2004; Losada et al. 2005). The existence of this intricate regulatory mechanism may partly be responsible for the rather complex and diverse phenotypes displayed by Pds5-deficient cells among different organisms.

Resolving and restructuring sister chromatids in early mitosis

Release of cohesin from chromosome arms

In vertebrates, most cohesin dissociates from chromatin at prophase, and only a small population, enriched in the pericentromeric region, remains on chromosomes by metaphase (Losada et al. 1998, 2000; Waizenegger et al. 2000). This step does not entail proteolysis of cohesin and is regulated by two mitotic kinases, polo and aurora B (Fig. 3C; Losada et al. 2002; Sumara et al. 2002; Giménez-Abián et al. 2004). Experiments in *Xenopus* egg extracts depleted of both polo and aurora B kinases showed that this initial release of cohesin is not required for condensin-mediated chromosome compaction. Instead, it is crucial for proper resolution of sister chromatids (Losada et al. 2002). Hauf et al. (2005) identified mitosis-specific phosphorylation sites in the cohesin subunits SA2 and Scc1 in HeLa cells, and generated stable cell lines expressing nonphosphorylatable versions of both proteins (SA2-12xA and SCC1-9xA). While expression of SCC1-9xA did not have a measurable effect, prophase release of cohesin complexes containing SA2-12xA was severely impaired. Interestingly, the separase-mediated pathway removed the high level of cohesin left all along the chromosomes, leading to apparently normal segregation in anaphase. Under this experimental condition, however, endogenous cohesin complexes containing wild-type SA2 (and SA1) are released with normal timing, making it difficult to address the functional importance of cohesin release in prophase.

Two-step loading of condensins

Release of cohesin from chromosome arms largely coincides with loading of condensins from prophase through prometaphase. Recent studies show that the spatial and temporal distributions of condensins I and II are differentially regulated during the cell cycle in HeLa cells (Hirota et al. 2004; Ono et al. 2004). Condensin II is predominantly nuclear during interphase, whereas condensin I is sequestered in the cytoplasm from interphase through prophase, and gains access to chromosomes only after the nuclear envelope breaks down in prometaphase. It was proposed that sequential activation of cyclin A–cdk1 and cyclin B–cdk1 could be responsible for the successive loading of condensin II and condensin I, respectively (Fig. 3D,E; Ono et al. 2004; Hirano 2005). How condensins are actually loaded on chromosomes is not fully understood. While the loading of cohesin requires the HEAT repeat protein Scc2, such a specialized loading factor has not yet been identified for condensins. It is tempting to speculate that the two intrinsic subunits containing HEAT repeats (e.g., CAP-D2 and CAP-G for condensin I) may perform a function analogous to Scc2. In fact, they are among the primary targets of cdk1-dependent phosphorylation, and their essential role in cell cycle-dependent loading of condensin I has been documented in both *Xenopus* egg extracts (Kimura and Hirano 2000) and tissue culture cells (Ball et al. 2002). Moreover, it is most likely that the cdk1-dependent phosphorylation directly stimulates the activity of condensins in vivo, as has been demonstrated in vitro (Kimura et al. 1998).

Condensins and chromosome architecture

A recent study combining light and electron microscopy in mammalian tissue culture cells suggests that the structural changes of chromosomes in early and mid-mitosis may be mechanistically distinct (Kireeva et al. 2004). A simple prediction from all emerging observations is that condensin II initiates the early stage of condensation by "hierarchical folding." Upon nuclear envelope breakdown (NEBD), condensin I could collaborate with condensin II to shape, resolve, and stabilize chromosomes by forming an "axial glue" structure within the chromatids. Nearly all subunits of condensin I have been found among the major components of a biochemically defined fraction known as the chromosome scaffold (Hudson et al. 2003; Maeshima and Laemmli 2003; Gassmann et al. 2005). At the level of light microscopy, condensins I and II apparently alternate along the axis of metaphase chromatids (Ono et al. 2003, 2004). The differential distribution of the two condensin complexes appears to be unique to individual chromosomes (T. Ono and T. Hirano, unpubl.), providing a possible molecular explanation for classical chromosome banding. It will be of great interest to determine how the differential distribution of condensins I and II may be specified in a chromosome-specific manner.

Consistent with the predictions described above, chromosome condensation within the prophase nucleus is delayed in cells depleted of condensin II-specific subunits, but not in those depleted of condensin I-specific subunits (Hirota et al. 2004; Ono et al. 2004). By metaphase, depletion of condensin I- or condensin II-specific subunits produces a distinct, highly characteristic defect in chromosome architecture, whereas depletion of the

SMC core subunits causes the severest defect (Ono et al. 2003). Distinct roles of condensins I and II in chromosome assembly have also been demonstrated convincingly in *Xenopus* egg cell-free extracts. It remains to be established, however, exactly how the two condensin complexes participate in the shaping and structural maintenance of metaphase chromatids (Gassmann et al. 2004; Hirano 2005). The extent of defects observed in condensin-deficient cells varies among different conditions and different organisms, thereby leaving room for divergent interpretations (Hagstrom et al. 2002; Coelho et al. 2003; Hudson et al. 2003; Chan et al. 2004; Dej et al. 2004; Hirota et al. 2004; Watrin and Legagneux 2005). Critical assignment of the role of individual subunits in vivo, along with a better understanding of their functions in vitro, will be essential in the future.

Sister chromatid resolution promoted by cohesin release and condensins' action

The two events discussed above, release of cohesin from chromosome arms and loading of condensins, are both required for proper assembly of metaphase chromosomes that are competent for segregation in anaphase. Figure 2C depicts a highly speculative view of how cohesin and condensins might behave and work during chromosome assembly. While cohesin release and condensin loading can be uncoupled experimentally in *Xenopus* egg extracts (Losada et al. 1998, 2002), it is reasonable to speculate that the two events are linked at a mechanistic level. In fact, a modest delay in cohesin release is observed in HeLa cells depleted of a condensin I subunit (Hirota et al. 2004). The third component important for sister chromatid resolution is topoisomerase II (topo II), an enzyme that catalyzes the transient passage of two DNA duplexes. It has been hypothesized that positive supercoiling or chiral looping of DNA supported by condensins may facilitate topo II-mediated decatenation of sister DNAs (Hirano 2000). Alternatively, condensin-mediated assembly of sister chromatid axes could provide a driving force that pushes the equilibrium of topo II action toward decatenation (e.g., Maeshima and Laemmli 2003; Kireeva et al. 2004). The two mechanisms are not mutually exclusive, because axial distribution of topo II in metaphase chromatids depends on functional condensins (Coelho et al. 2003). We also speculate that the collaborative action of condensins and topo II may be powerful enough to "drive" the resolution of sister chromatids in the absence of spindle forces (Paliulis and Nicklas 2004; Machin et al. 2005). Such a spindle-independent mechanism might also underlie SMC-mediated chromosome segregation in bacterial cells, as has been suggested before (Hirano 2002).

Building sister centromeres/kinetochores in early mitosis

The fundamental contribution of cohesin and condensins to chromosome segregation is not restricted to chromosome arms. Emerging lines of evidence strongly suggest that they play important roles in assembling centromeric heterochromatin that helps create tight cohesion during mitosis, and in orienting sister kinetochores to allow proper attachment to the spindle (Fig. 3C–E).

Heterochromatin environment

Classical cytological observations suggest that sister chromatids are more tightly associated at heterochromatic regions (e.g., González et al. 1991), leading to the speculation that the particular structure or composition of heterochromatin could enhance recruitment of cohesin (Losada and Hirano 2001b). In fact, it was shown that the heterochromatin protein (HP)-1 homolog Swi6 binds to methylated Lys 9 of histone H3 and promotes cohesin loading at the centromeric repeats in *S. pombe* (Bernard et al. 2001; Nonaka et al. 2002). More recent studies have revealed that the RNA interference machinery regulates the establishment of heterochromatin, which in turn recruits cohesin to this region, in both *S. pombe* (Hall et al. 2003; Schramke and Allshire 2003) and vertebrate cells (Fukagawa et al. 2004). Intriguingly, even in *S. cerevisiae* that apparently lacks centromere-proximal heterochromatin, a functional centromere induces increased association of cohesin in a surrounding region spanning 20–50 kb (Weber et al. 2004). This observation implicates the existence of additional mechanisms to ensure stronger cohesion at centromeres.

Role of Sgo/Mei-S332 in centromeric cohesion: protection or active reconstruction?

The distinct regulation of arm and centromeric cohesion is even more crucial in meiosis than in mitosis. In meiosis, arm cohesion is dissolved in anaphase I, while centromeric cohesion persists until metaphase II (for review, see Nasmyth 2001). Unlike mitosis, both steps of cohesion dissolution in meiosis involve separase-mediated cleavage of cohesin, but the question is the same in both cases: What protects centromeric cohesin when arm cohesion is dissolved? A pioneering study in *Drosophila* identified a centromeric protein, known as Mei-S332, that may perform this job (Kerrebrock et al. 1995). More recently, independent genetic screens in *S. pombe* and *S. cerevisiae* have "rediscovered" proteins related to Mei-S332, leading to the definition of the shugoshin (or Sgo) family of proteins (Katis et al. 2004; Kitajima et al. 2004; Marston et al. 2004; Rabitsch et al. 2004). Although the contribution of Sgo/Mei-S332 proteins to mitotic chromosome segregation is modest in *Drosophila* or yeast, depletion of Sgo1, one of the two human members of this family, from HeLa cells causes premature separation of sister chromatids during mitosis (Salic et al. 2004; Tang et al. 2004; Kitajima et al. 2005). This phenotype is partially suppressed when cohesion is reinforced by expressing a nonphosphorylatable form of the cohesin subunit SA2 (McGuiness et al. 2005), consistent with a model in which Sgo1 protects centromeric cohesin from release in prophase (Fig. 5A). The spindle checkpoint protein Bub1 regulates Sgo1 localization at centromeres, and in its absence, Sgo1 and Scc1 are no longer enriched at this region

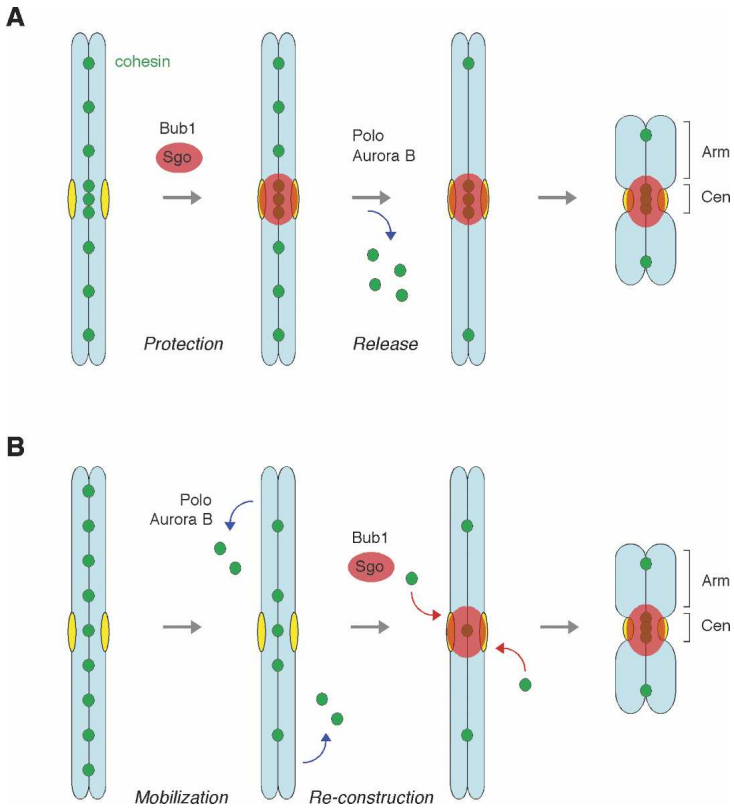

Figure 5. Two models for the action of Sgo in early mitosis. (*A*) Sgo is targeted to the centromeric region in a Bub1-dependent manner, and protects cohesin from the prophase dissociation pathway mediated by polo and aurora B. (*B*) A fraction of the cohesin complexes dissociated from the arms by the action of polo and aurora B is redistributed and concentrated at the centromeric region by the action of Sgo, which itself is under the regulation of Bub1. (Pink oval) Sgo; (green circle) cohesin; (yellow oval) kinetochore.

and instead localize along chromosome arms (Kitajima et al. 2005). The resulting chromosomes exhibit less-resolved sister chromatid arms and no clear primary constriction, a morphology also observed in cells lacking polo or aurora B function (Giménez-Abián et al. 2004; Ono et al. 2004; Hauf et al. 2005). Abrogation of the primary constriction could result from the lack of cohesin accumulation at centromeres (Giménez-Abián et al. 2004). Thus, Bub1, polo, and aurora B could be part of a network that regulates localization and/or function of Sgo1, which in turn directs redistribution of cohesin, or even its de novo loading, at centromeres in prophase. In this scenario, Sgo1 may not be just a protector and instead play a more active role in establishing centromeric cohesion during mitosis (Fig. 5B).

Centromeric cohesion opposes the pulling forces of the spindle microtubules and generates tension between sister kinetochores. This tension in turn stabilizes microtubule–kinetochore attachments by a mechanism that involves aurora B (for review, see Hauf and Watanabe 2004). Accordingly, depletion of cohesin causes not only premature separation but also defects in chromosome alignment that are accompanied by mislocalization of the chromosomal passenger complex containing aurora B (Sonoda et al. 2001; Vass et al. 2003). Evidence is also available that Sgo may interact directly with microtubules (Salic et al. 2004) and may act as a sensor that monitors tension imposed on sister centromeres (Indjeian et al. 2005). There is no doubt that future analysis will help uncover the mechanistic cross-talk between centromere cohesion and spindle checkpoint signaling.

Role of condensins in kinetochore orientation

Condensin function is also important for establishing the back-to-back orientation of sister kinetochores. Severe defects in kinetochore–microtubule interactions, indicative of merotelic attachments, are observed after condensin depletion in *Xenopus* egg extracts (Wignall et al. 2003), in HeLa cells (Ono et al. 2004), and most drastically, in *C. elegans* (Hagstrom et al. 2002; Stear and Roth 2002). In the holocentric chromosomes of *C. elegans*, numerous kinetochores assemble along the entire length of each chromatid, forming two "lines" on the outer surfaces of a metaphase chromosome. This process, referred to as sister centromere resolution, requires condensin II, whose localization at centromeres depends on the kinetochore protein HCP-4/CENP-C (Moore et al. 2005) and aurora B (Hagstrom et al. 2002). In human cells, a subpopulation of condensin II is enriched at or near the inner kinetochore plate (Ono et al. 2004). This enrichment, but not the distribution of condensin II along the arms, is under the control of aurora B. Thus, aurora B is likely to contribute to chromosome bi-orientation at multiple levels, which include specific targeting of condensins at the centromere/kinetochore region.

Separating sister chromatids in anaphase

The final dissolution of cohesion takes place at anaphase, once all chromosomes are properly bi-oriented on the metaphase plate so that the spindle checkpoint is satisfied. Upon activation of the anaphase-promoting

complex or cyclosome (APC/C), the cysteine protease separase is freed from securin and cleaves Scc1, thereby triggering sister chromatid separation (Fig. 3F; Uhlmann et al. 1999). Phosphorylation of Scc1 by polo facilitates its cleavage by separase in vitro, but this modification may not be essential in vivo (Alexandru et al. 2001; Hornig and Uhlmann 2004; Hauf et al. 2005). As a putative protector of centromeric cohesion, Sgo1's function may also be inactivated or down-regulated at the anaphase onset. In fact, Sgo1 is a substrate of the APC/C in vertebrates (Salic et al. 2004), but the precise timing or functional importance of its degradation remains to be determined. In *Drosophila*, delocalization of Sgo/MeiS332 from centromeres in anaphase requires two different pathways: One involves separase function (Lee et al. 2004) and the other involves phosphorylation by polo (Clarke et al. 2005). However, *polo* mutants are able to separate their chromosomes despite persistence of MeiS332 at centromeres, suggesting that the postulated inactivation of this protein may require neither its removal from centromeres nor its degradation.

According to an oversimplified view emphasized in early studies, arm cohesion is completely dissolved by metaphase while centromeric cohesion is released at the onset of anaphase (e.g., Waizenegger et al. 2000). This is clearly not the case in unperturbed mitosis: Arm cohesion is gradually lost in anaphase after sister centromeres separate and sister chromatids move toward opposite poles of the cell (Giménez-Abián et al. 2004; Paliulis and Nicklas 2004). A series of recent studies further suggests that certain chromosomal domains separate at later stages in anaphase, possibly through unique mechanisms. For example, the segregation of rDNA in *S. cerevisiae* occurs in mid-anaphase and requires Cdc14, a protein phosphatase that is activated by the FEAR (fourteen early anaphase release) network (D'Amours et al. 2004; Sullivan et al. 2004; Wang et al. 2004). Condensin is recruited to the rDNA locus in anaphase in a Cdc14-dependent manner and mediates the condensation and resolution of rDNA at this stage (Lavoie et al. 2004). The segregation defect observed in *cdc14* mutants is not relieved by inactivation of cohesin, suggesting that a distinct form of linkage exists at this locus. In mammalian cells, the separation of sister telomeres may use another mechanism involving tankyrase 1, a telomeric protein that has a poly(ADP-ribose) polymerase motif (Dynek and Smith 2004). In this case, it remains to be established whether the persistent linkage of telomeres observed in tankyrase 1-deficient cells is independent of cohesin.

Cohesin and condensins in meiotic chromosome segregation

In meiosis, two consecutive chromosome-segregation events follow a single round of DNA replication. Homologous chromosomes separate in meiosis I, while sister chromatids separate in meiosis II. This fact poses specific requirements for the regulation of cohesion and has most likely guided the emergence of meiosis-specific isoforms of the cohesin subunits Scc1 (known as Rec8), Scc3/SA, and even SMC1 (see Table 1). In *S. pombe* meiosis, Rec8 forms two different complexes: One containing Scc3 (referred to as Psc3 in this organism) localizes to the vicinity of centromeres, whereas the other containing the meiosis-specific version of Scc3 (known as Rec11) is found along the arms (Kitajima et al. 2003). Thus, meiotic isoforms may contribute to the differential susceptibility of the cohesin complex to cleavage by separase in meiosis I. Additional meiosis-specific functions have been hypothesized for meiotic cohesins; e.g., they could favor interhomolog invasion over invasion of the sister chromatid, thereby facilitating chiasmata formation (Martston and Amon 2004). Mammals have a meiosis-specific isoform of SMC1, known as SMC1β (Table 1). In mice, a cohesin complex(es) containing the canonical SMC1 (SMC1α) is most likely responsible for establishing cohesion in premeiotic S phase, whereas Smc1β is detected on chromosomes only after zygotene. Smc1β-deficient mice are sterile in both sexes, displaying defects in synapsis, recombination, and maintenance of cohesion both in chromosome arms and at centromeres (Revenkova et al. 2004). Rec8 was also detected at the axial elements of the synaptonemal complex (SC) in rat spermatocytes before SMC1β and SMC3, implying that the core and the regulatory subunits of the complex may be targeted to chromosomes separately (Eijpe et al. 2003). Support for this idea also comes from the observation that loss of TIM-1 function in *C. elegans* prevents localization of Rec8, but not of SMC1 and SMC3, to meiotic prophase chromosomes (Chan et al. 2003). Future analysis should determine the precise dynamics of the different cohesin complexes coexisting in meiotic cells, and their specific contributions to meiotic chromosome functions (e.g., Parra et al. 2004).

Condensin subunits also play crucial roles in the structural and functional organization of meiotic chromosomes. In *S. cerevisiae*, condensin subunits localize to the axial core of pachytene chromosomes and contribute to their axial compaction and individualization (Yu and Koshland 2003). The SC is not properly assembled in condensin mutants, leading to defects in homolog pairing and processing of double-strand breaks (DSBs). Evidence is also available that condensin participates in the resolution of recombination-dependent linkages between homologs in meiosis I and perhaps in the segregation of sister chromatids in meiosis II as well (Yu and Koshland 2003). A requirement for condensin function in both meiosis I and meiosis II is consistent with results from *Arabidopsis* (Siddiqui et al. 2003) and *C. elegans* (Chan et al. 2004). Unlike in *S. cerevisiae*, the condensin subunits associate with chromosomes only after exit from pachytene in *C. elegans*. This difference may be related to the fact that *S. cerevisiae* and *C. elegans* contain only condensin I or condensin II, respectively. However, the non-SMC components of the dosage compensation complex in *C. elegans* are also required for meiotic (but not mitotic) chromosome segregation (Lieb et al. 1996), providing an additional level of complexity to

this problem. Clearly, a number of questions remain to be addressed about the role of condensins in meiosis. For example, are there meiosis-specific condensin subunits? In vertebrates and plants, do condensins I and II differentially localize to meiotic chromosomes and perform nonoverlapping functions in their recombination and segregation?

Expanding roles of cohesin and condensins outside chromosome segregation

Cohesin and DNA repair

In late S and G2 phases, when two sister chromatids are available, cells prefer to repair DSBs by homologous recombination (HR). Results from studies of yeast (Birkenbihl and Subramani 1992; Sjögren and Nasmyth 2001) and vertebrate cells (Sonoda et al. 2001) suggested that DSB repair is impaired in the absence of cohesin. It was also shown that cohesin accumulates at sites of laser-induced DNA damage in an Mre11/Rad50-dependent manner in mammalian cells (J.S. Kim et al. 2002). Two recent studies in *S. cerevisiae* refined this idea by revealing that cohesin subunits are recruited to a region of ~100 kb surrounding a single DSB (Ström et al. 2004; Ünal et al. 2004). This DSB-induced recruitment of cohesin is Scc2-dependent and requires phosphorylation of H2AX by the DNA damage checkpoint kinases Mec1/ATM and Tel1/ATR (Ünal et al. 2004). Most importantly, cohesin loaded in response to DSBs establishes a de novo linkage between the damage chromatid and its undamaged sister, thereby facilitating DSB repair (Ström et al. 2004). This "excess" amount of cohesin may need to be removed to complete the repair process, possibly through a separase-dependent mechanism (Nagao et al. 2004). In mammalian cells, SMC1 is phosphorylated by ATM in response to ionizing irradiation (IR) (S.-T. Kim et al. 2002; Yazdi et al. 2002). Murine cells expressing a nonphosphorylatable form of SMC1 show decreased survival only after DNA damage, suggesting that this modification of cohesin is required for its role in DNA repair but not for its essential role in cohesion (Kitagawa et al. 2004). It is nonetheless possible that cohesion may be routinely reinforced during or after S phase through this DSB-induced loading mechanism, as DSBs can arise naturally during DNA replication. Furthermore, if the repeated sequences of heterochromatin were more prone to stalled forks and DSBs than the single-copy sequences of euchromatin, then DSB-induced loading of cohesin could provide a means to generate a higher density of cohesin in heterochromatin. In any case, these new studies provide a fresh view on the loading and action of cohesin, which appear to be much more dynamic than was anticipated.

Cohesin regulators and development

Reduced dosage of the Scc2 ortholog Nipped-B negatively affects the activation of the homeotic *cut* gene by a distant enhancer in *Drosophila* (Rollins et al. 1999). The observation that Nipped-B and cohesin have opposite effects on this long-range regulation supports the model that Scc2/Nipped-B acts both as a loader and as an unloader of cohesin, and thereby facilitates enhancer-promoter communication (Rollins et al. 2004). Certain developmental genes could be particularly sensitive to the presence of cohesin nearby their promoters and thus to reduced levels of Scc2. This might explain why mutation of one copy of the human *Nipped-B like* (*NIPBL*) gene cause Cornelia de Lange syndrome, a developmental disorder characterized by growth and cognitive retardation (Krantz et al. 2004; Tonkin et al. 2004). It remains to be determined, however, whether these developmental defects indeed derive from misregulation of cohesin or whether Scc2 may have a cohesin-independent function that affects the dynamics of other transcriptional regulators. Interestingly, a very recent study shows that mutations in *ESCO2,* the gene encoding one of the human holomogs of Eco1/Ctf7, cause Roberts syndrome, a recessive disorder also characterized by growth retardation and craniofacial anomalies. In this case, centromeric cohesion defects have been observed in the chromosomes of affected individuals (Vega et al. 2005).

Condensins, checkpoint responses, and gene repression

A potential involvement of condensin in the DNA damage checkpoint was suggested by a genetic study of *S. pombe* that describes a condensin mutant being unable to activate the checkpoint kinase Cds1/Chk2 in the presence of hydroxyurea (Aono et al. 2002). However, the molecular mechanism underlying this observation remains to be determined. The role of condensin subunits in transcriptional repression has been described in *S. cerevisiae* (Bhalla et al. 2002; Machin et al. 2004) and *Drosophila* (Lupo et al. 2001; Dej et al. 2004; Jager et al. 2005). In *Arabidopsis*, reduced expression of SMC2 causes a defect in seed or meristem development (Liu et al. 2002; Siddiqui et al. 2003). Although global defects in chromatin structure, especially at heterochromatin or repetitive regions of the genome, may be sufficient to account for these diverse phenotypes, more specific involvement of condensin subunits in transcriptional regulation cannot be excluded. For example, a recent paper reported that a subfraction of condensin may interact with epigenetic machineries such as a DNA methyltransferase in mammalian cells (Geiman et al. 2004). In *C. elegans*, a specialized condensin-like complex is known to function as a major regulator of dosage compensation (for review, see Hagstrom and Meyer 2003). It is of considerable interest to determine the mechanism by which this dosage compensation complex (DCC) reconfigures the X chromosome to confer the twofold (and only twofold) chromosome-wide repression of gene expression. Further analysis of this system should help reveal the potential involvement of the canonical condensins in mitotic gene repression, and determine how some genes might partially escape such repression (Xing et al. 2005).

The third man: linkers for DNA repair composed of SMC5 and SMC6

Eukaryotes have a third SMC complex that is composed of the SMC5–SMC6 heterodimer and four non-SMC subunits, Nse1–Nse4 (Table 1; McDonald et al. 2003; Harvery et al. 2004; Morikawa et al. 2004; Sergeant et al. 2005). The cellular function of this complex is not fully understood, but it is related to the DNA damage response. In fact, the gene encoding SMC6/Rad18 was originally identified in a genetic screen for radiosensitive mutants in *S. pombe* (Lehmann et al. 1995). Genetic studies have shown that hypomorphic mutations of other subunits of the complex also cause hypersensitivity to DNA damage (e.g., McDonald et al. 2003), and further suggest a role of the complex in HR-mediated repair as well as in meiosis (Morikawa et al. 2004; Pebernard et al. 2004). Establishment of the G2 checkpoint after IR seems normal in *smc6/rad18* mutant cells, but they exit the arrest without having repaired the DNA damage (Harvery et al. 2004). Thus, accumulation of unrepaired DNA damage after multiple rounds of division may account for the cell lethality observed in this mutant (Lehmann 2005). Most recently, a specific role of SMC5 and SMC6 in the segregation of repetitive chromosome regions was reported (Torres-Rosell et al. 2005).

Despite a wealth of genetic analyses in yeast, the biochemical characterization of the SMC5–SMC6 complex is just starting to emerge (Sergeant et al. 2005). In *S. pombe*, SMC5 and SMC6 dimerize through their hinge domains, like other SMC proteins. Nse2 binds to the coiled-coil domain of SMC5, which in turn recruits a subcomplex composed of Nse1, Nse3, and Nse4/Rad62, most likely through an Nse2–Nse3 interaction (Fig. 1B, panel d). It is important to note that the proposed architecture of the SMC5–SMC6 complex differs significantly from those of cohesin and condensins (Fig. 1B, panels a–c). In *S. cerevisiae*, two additional subunits (YML023C and Kre29) were identified in the same complex (Zhao and Blobel 2005) or in a second complex containing SMC5 and SMC6 (Table 1; Hazbun et al. 2003).

The primary structure of the non-SMC subunits of the SMC5–SMC6 complex provides important clues to their possible functions. Nse1 contains a RING-finger motif that is conserved in E3 ubiquitin ligases (Fujioka et al. 2002; McDonald et al. 2003). Nse2 has another RING-finger motif, characteristic of SUMO ligases, and is able to sumoylate in vitro some subunits of the complex, including SMC6 (Andrews et al. 2005). A mutation in the RING-finger motif abolishes the in vitro sumoylation activity and decreases the level of SMC6 sumoylation in vivo. These mutant cells are sensitive to DNA damaging agents but are viable, suggesting that the sumoylation activity of the SMC5–SMC6 complex is important for its function in DNA repair, but not critical for its essential function. Moreover, a mutation in the SUMO ligase domain of *S. cerevisiae* Nse2/Mms21 leads to formation of irregular nucleoli and defects in telomere functions (Zhao and Blobel 2005). These phenotypes could result from defective sumoylation of proteins, other than the SMC5–SMC6 complex, involved in maintaining nucleolar and telomere structure. Alternatively, the SMC5–SMC6 complex may have a role in preventing promiscuous recombination between repeated sequences so that regions containing DNA repeats such as rDNA or telomeres would be particularly sensitive to loss of its function. At least two other SMC-related complexes, cohesin and the Rad50-containing complex MRX, have a role in recombinational repair. Why does the cell need so many "similar" complexes for the same job? Defining and contrasting the mechanisms by which these SMC complexes contribute to DNA repair will be an important goal of future research.

Bacterial SMC linkers

Recent technical improvements in cell imaging combined with powerful bacterial genetics have uncovered a number of similarities in the chromosome segregation machineries of bacteria and eukaryotes (for review, see Sherratt 2003). The appreciation of SMC proteins as major chromosome organizers from bacteria to humans is one of the best examples. Disruption of the *smc* gene in *Bacillus subtilis* causes decondensation and mis-segregation of chromosomes (e.g., Britton et al. 1998), indicating that the bacterial SMC protein shares related, if not identical, functions with the eukaryotic SMC complexes in vivo. More recent studies show that the bacterial SMC dimer forms a complex with two regulatory subunits called ScpA and ScpB (Fig. 1B, panel e; Mascarenhas et al. 2002; Soppa et al. 2002; Volkov et al. 2003; Hirano and Hirano 2004). ScpA belongs to the kleisin superfamily, further extending the similarity between bacterial and eukaryotic SMC complexes (Schleiffer et al. 2003). It is most likely that the SMC–ScpA–ScpB complex contributes to chromosome segregation by "pulling" duplicated DNA strands to opposite poles of the cell using a mechanism that may involve DNA supercoiling (Lindow et al. 2002a). These results imply that the bacterial SMC complex may be much closer to condensins than cohesin. Nevertheless, evidence is also available that *B. subtilis* SMC (or its distant relative MukB in *E. coli*) may have cohesin-like functions such as keeping together the newly replicated sister DNAs (Sunako et al. 2001; Lindow et al. 2002b) or promoting DNA repair (Dervyn et al. 2004). From an evolutionary point of view, bacterial SMC proteins belong to the main branch of the SMC family that includes SMC1, SMC2, SMC3, and SMC4 but not SMC5 or SMC6 (Cobbe and Heck 2004). Thus, the bacterial SMC could be the common ancestor of condensins and cohesin. Further analysis of these primitive forms of SMC protein complex will continue to make great contributions to our understanding of the basic mechanisms of SMC action as well as the evolution of the SMC-mediated segregation machinery.

Future directions

A decade has passed since the first set of research papers reported the identification of SMC proteins and their

crucial involvement in higher-order chromosome organization and segregation. Subsequent work has extended our knowledge about their fundamental roles in many aspects of chromosome functions and revealed the essential features of their unique architecture. What might be the major challenges in the coming years? First, we are only beginning to get a glimpse of the mechanism of action of SMC protein complexes. We wish to know, for example, whether a single cohesin complex is indeed able to hold two sister chromatids within its coiled-coil space, and how the postulated enzymatic and structural functions of condensins might be coordinated and coupled to their ATPase cycle. Second, a genome-wide mapping of preferred binding sites of these complexes, as has been initiated in yeast, must be applied to more complex genomes including that of humans. Advanced imaging approaches should complement such efforts to decipher the dynamics of cohesin and condensins during the cell cycle or other events such as DNA repair. Third, it has become increasingly clear that analyses of SMC proteins in a variety of systems create a fertile playground for exploring the common themes and variations in chromosome architecture and dynamics. It will continue to be important to compare and contrast monocentric and holocentric chromosomes, mitosis and meiosis, and the eukaryotic and bacterial systems. Other critical questions to be addressed include the potential crosstalk of SMC proteins with the epigenetic machinery, and the essential function of the SMC5–SMC6 complex in maintaining genome stability. There is no doubt that answering these questions will not only advance our understanding of chromosome biology but will also have a great impact on other areas such as cancer biology, genome biology, and evolutionary biology.

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