Condensin: crafting the chromosome landscape

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The successful transmission of complete genomes from mother to daughter cells during cell divisions requires the structural re-organization of chromosomes into individualized and compact structures that can be segregated by mitotic spindle microtubules. The multi-subunit condensin protein complex plays a central part in this chromosome condensation process, but the mechanisms behind its actions are still poorly understood. An increasing body of evidence suggests that, in addition to their role in shaping mitotic chromosomes, condensin complexes have important functions in directing the three-dimensional arrangement of chromatin fibers within the interphase nucleus. To fulfill their different functions in genome organization, the activity of condensin complexes and their localization on chromosomes need to be strictly controlled. In this review article, we outline the regulation of condensin function by phosphorylation and other posttranslational modifications at different stages of the cell cycle. We furthermore discuss how these regulatory mechanisms are used to control condensin binding to specific chromosome domains and present a comprehensive overview of condensin's interaction partners in these processes.

Introduction: condensin complexes

Throughout the cell cycle, chromosomes undergo considerable structural rearrangements in order to allow, for example, the complete duplication of a cell's genetic material during DNA replication or the maintenance of genomic integrity during DNA repair processes. These conformational changes become particularly obvious at the onset of mitosis, when entangled interphase chromatin fibers partially resolve, shorten and finally convert into a set of compact rod-shaped chromosomes that can be segregated by mitotic spindle microtubules.

One of the key components involved in the formation and maintenance of mitotic chromosome architecture are multi-subunit protein complexes named condensins (Hirano et al. 1997). Condensins have been identified in all eukaryotic genomes sequenced to date (reviewed in Hirano 2012; Hudson et al. 2009) and function in different aspects of chromosome metabolism (reviewed in Wood et al. 2010). Notably, condensin-like complexes are also found in almost all prokaryotic species (reviewed in Graumann and Knust 2009), suggesting that their origin pre-dates the arrival of nucleosomes as the major chromosome organizing unit. Eukaryotic condensin complexes contain two subunits of the structural maintenance of chromosomes (SMC) protein family named SMC2 and SMC4. These proteins are characterized by a 50 nm long anti-parallel coiled coil that separates an ATP-binding cassette (ABC) ATPase 'head' domain at one end from a 'hinge' domain at the other end (Anderson et al. 2002). The two SMC subunits associate with each other via their hinge domains to form a V-shaped molecule with the ATPase domains located at the apices of the coiled coil arms (Fig. 1a). The head domains are thought to engage upon sandwiching two molecules of ATP between them and to disengage upon ATP hydrolysis (Lammens et al. 2004). While its purpose is still poorly understood, this ATPase cycle must be essential for condensin function, since mutations that interfere with either step render condensin non-functional *in vivo* (Hudson et al. 2008). A comparison of the crystal structures of ATP-bound and nucleotide-free ATPase SMC head domains surprisingly shows no large conformational differences (Lammens et al. 2004). It is nevertheless conceivable that ATP binding might cause large-scale structural rearrangements when the head domains are bound to the other subunits of the condensin complex. For instance, ATP binding induces a substantial rotation of the coiled coils attached to the head domains of the SMC-related RAD50 protein when the latter are bound to their partner protein MRE11 (Lammens et al. 2011; Möckel et al. 2012).

In *bona fide* SMC complexes, the SMC binding partner is a member of the evolutionary conserved 'kleisin' protein superfamily. The β- or γ-kleisin subunits of eukaryotic condensin complexes (see below) bind via an alpha-helical domain at their N termini to the SMC2 head domain and via a winged-helix domain at their C termini to the SMC4 head domain (Onn et al. 2007). Recent crystal structures of the N- or C-terminal domains of prokaryotic kleisins in complex with SMC heads suggest that the N-terminal alpha-helical domain forms a triple helix with the SMC coiled-coil in vicinity of the head, while the C-terminal winged-helix domain interacts with two beta-strands at the opposite face of the SMC head (Bürmann et al. 2013). The same asymmetry of binding might also apply to eukaryotic condensin complexes. Connection of the SMC ATPase domains through the kleisin subunit can therefore create a closed ring structure (kleisimo, Greek for 'closure') even when the head domains were not engaged by ATP binding (Fig. 1a). Condensin has been suggested to use this ring structure to bind to chromosomes by encircling DNA, consistent with recent experiments using condensin-bound yeast minichromosomes (Cuylen et al. 2011). In addition to bridging the SMC2 and SMC4 head domains, the kleisin subunit recruits to the complex two proteins that are predicted to contain a number of alpha-

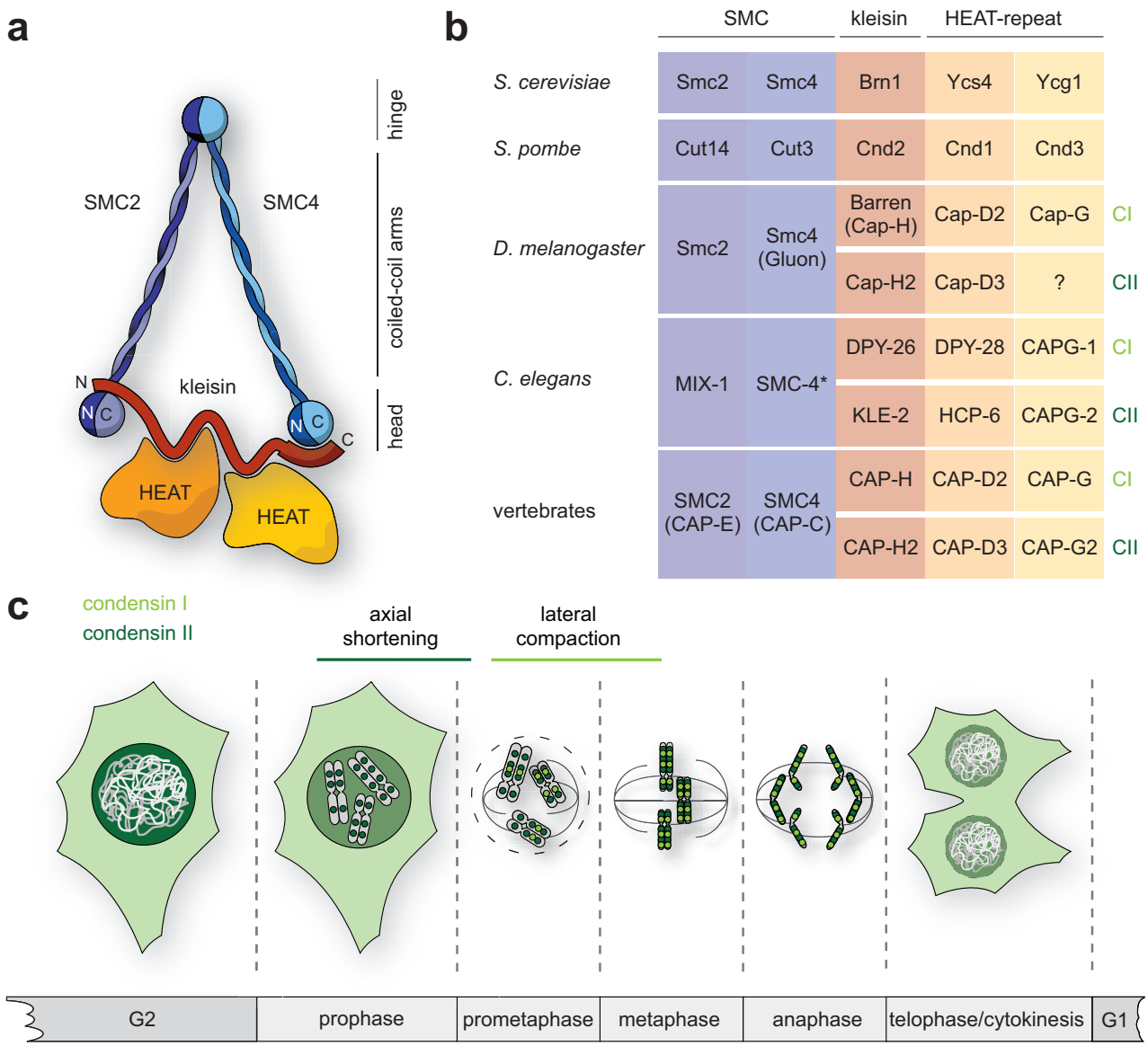

Fig. 1 Structure and localization of condensin complexes. **a** Condensin architecture. Condensin's SMC2 and SMC4 subunits dimerize via 'hinge' domains at one end of their ~50 nm long coiled-coil arms. The ATPase 'head' domains at the other end of the SMC2 and SMC4 coiled-coil arms bind to the N and C terminus of the kleisin subunit, respectively. The kleisin subunit recruits to the complex two additional subunits that contain HEAT repeat motives. **b** Nomenclature of condensin subunits. Metazoan genomes generally encode two condensin complexes named condensin I (CI) and II (CII), which share the same SMC2–SMC4 dimer but contain different sets of non-SMC subunits. In addition, a condensin-I like complex present in *C. elegans* contains DPY-27 in place of SMC-4 and has a role in gene dosage compensation (*). **c** Differential localization of condensin I and II complexes. Condensin II remains nuclear during interphase and contributes to the axial shortening of chromosome arms after binding to chromosomes at early prophase. Condensin I gains access to chromosomes after NEBD and contributes to the lateral compaction of chromosome arms.

helical HEAT (huntingtin–elongation factor 3–protein phosphatase 2A–TOR1) repeats (Neuwald and Hirano 2000). Metazoans express two different sets of the three 'non-SMC' subunits. Condensin I contains the γ-kleisin subunit CAP-H and the HEAT repeat subunits CAP-D2 and CAP-G. Condensin II contains the β-kleisin subunit CAP-H2 and the HEAT repeat subunits CAP-D3 and CAP-G2 (Fig. 1b) (Ono et al. 2003; Yeong et al. 2003).

Inactivation by mutation of any of the five condensin subunits in yeast or depletion of condensin I or II subunits in worms, flies or vertebrate cells cause severe chromosome segregation defects that are frequently characterized by a failure to resolve chromosome arms during anaphase (reviewed in Hirano 2012; Hudson et al. 2009). In temperature-sensitive yeast condensin mutants, the levels of mitotic chromosome compaction are reduced (Freeman et al. 2000; Lavoie et al. 2004; Saka et al. 1994). In vertebrate cells depleted of condensins, chromosome condensation is initially delayed, but eventually normal shaped metaphase chromosomes form (Gerlich et al. 2006; Hirota et al. 2004; Hudson et al. 2003). Nevertheless, these chromosomes are hypersensitive to mechanical forces under hypotonic buffer conditions (Ono et al. 2003), suggesting that their structural integrity is considerably compromised in the absence of condensin function.

Consistent with a role in shaping chromosomes during cell divisions, condensin complexes have been found to associate with mitotic chromosomes in all organisms studied so far. However, the two condensin complexes present in metazoan cells differ in their temporal and spatial binding to chromosomes (Gerlich et al. 2006; Hirota et al. 2004; Ono et al. 2003; Ono et

al. 2004). Condensin I is excluded from the nucleus during interphase, gains access to chromosomes after nuclear envelope breakdown (NEBD) during prometaphase, and remains bound to chromosomes until late anaphase (Fig. 1c). Condensin II, in contrast, localizes to the nucleus also during interphase and can be detected on chromosomes from early prophase until the end of mitosis (Yeong et al. 2003). The alternate immunostaining patterns of condensin I and II along the axes of chromosome arms and at centromeres suggests that the two complexes associate independently of each other with distinct chromosomal regions (Maeshima and Laemmli 2003; Ono et al. 2004). Moreover, the high or low turnover rates measured for condensin I or II, respectively, indicate that the two complexes bind to chromosomes with different dynamics (Gerlich et al. 2006). These differences in localization and kinetics suggest that condensin I and II perform non-redundant functions during the formation of mitotic chromosomes. Depletion experiments support the notion that condensin II is required for the early axial shortening of chromosome arms and that condensin I is involved in the lateral compaction that takes place after NEBD (Green et al. 2012; Shintomi and Hirano 2011). The mechanisms that determine the localization of condensin complexes to chromosomes are, however, still unclear and probably vary between organisms. For example, in the fission yeast *Schizosaccharomyces pombe*, access of condensin to chromosomes is controlled by its importin α-dependent translocation into the nucleus at the onset of mitosis (Nakazawa et al. 2008; Sutani et al. 1999). In contrast, the budding yeast condensin complex remains nuclear and bound to chromosomes throughout the cell cycle and its levels increase only moderately at centromeres, telomeres, and the ribosomal DNA (rDNA) cluster during mitosis (Bachellier-Bassi et al. 2008; D'Ambrosio et al. 2008; Freeman et al. 2000).

Although condensin has been extensively studied over the last decade, our current understanding of the molecular mechanisms behind its functions in organizing mitotic chromosomes is far from being complete. This review summarizes the current knowledge of the regulatory proteins that coordinate the activities of condensin complexes in eukaryotes through posttranslational modifications and the network of interaction partners that ensure condensin's correct association with chromosomes.

Modulators of condensin function

The localization of condensins to specific chromosome domains at defined cell cycle stages implies that an elaborated regulatory system must coordinate the function of these protein complexes. A growing body of evidence suggests that a major part of condensin regulation is achieved by phosphorylation of one or more of the five subunits of the complex. The identification of the specific residues that are modified, the kinases that phosphorylate them, and the phosphatases that revert these phosphorylations will therefore be crucial to understand how condensin is controlled. Detailed phosphorylation maps have been assembled for all condensin subunits based on data from high-throughput proteomic studies and site-directed mutation of candidate residues (Bazile et al. 2010; Hegemann et al. 2011; Nousiainen et al. 2006; St-Pierre et al. 2009). While these studies identified a large number of phospho-serine and -threonine residues in SMC4 and the three non-SMC subunits, no or only a single phosphorylated residue has been detected for SMC2 in human or yeast condensin complexes, respectively. Interestingly, most phosphorylation sites in the other subunits are clustered in relatively short and poorly conserved regions, which are predicted to be part of flexible peptide loops (Bazile et al. 2010). The preference for unstructured regions may be due to an increased accessibility of the target sites for the corresponding kinases.

Even though condensin has been reported to be constitutively phosphorylated in human cells, phosphorylation patterns differ significantly between interphase and mitosis, consistent with the observed changes in electrophoretic mobility measured for condensin subunits isolated from either cell cycle stage (Hirano et al. 1997; Takemoto et al. 2006; Takemoto et al. 2004). Interestingly, many of the M phase specific phosphorylation sites do not strictly match the consensus sequences for well-known mitotic kinases, e.g. cyclin-dependent kinase (CDK) or polo-like kinase (PLK). One possibility is that individual residues might be modified by multiple kinases and/or phosphatases. Condensin's phosphorylation patterns might therefore be the result of the combined actions of different enzymes. Consistent with this model, at least six different enzymes have been found to modify condensin subunits: CDK, PLK, Aurora B kinase, casein kinase 2 (CK2), as well as the protein phosphatases 2A (PP2A) and Cdc14 (reviewed in Bazile et al. 2010; Hirano 2012). Although these kinases and phosphatases regulate condensin phosphorylation in most species studied, their effects on condensin function differ between organisms.

Cyclin-dependent kinase (CDK)

Cyclin B-Cdk1 was found to phosphorylate *in vitro* and *in vivo* the single condensin complex present in fission or budding yeasts (St-Pierre et al. 2009; Sutani et al. 1999; Ubersax et al. 2003) as well as the two condensin complexes present in metazoans (Kimura et al. 1998). In fission yeast, phosphorylation of the Cut3 (SMC4) subunit by Cdc2 (CDK) induces condensin accumulation in the nucleus upon entry into mitosis. In metazoans, condensin I becomes exposed to high levels of CDK activity after NEBD (Fig. 2a and b) and its CAP-D2 subunit seems to be the main target for phosphorylation. Although more indirect, there exists evidence that CDK also regulates the activity of condensin II; a recent study showed that CDK-mediated phosphorylation of the condensin II subunit CAP-D3 promotes early stages of chromosome condensation during prophase (Abe et al. 2011). Phosphorylation of CAP-D3 by CDK might then be the starting point for condensin hyper-phosphorylation by other kinases (see below). It has been suggested that this first wave of condensin phosphorylation during G2 and prophase might be mediated by cyclin A-Cdk1 (Fig. 2a) and initiates the axial shortening of chromosome arms by condensin II. Cyclin B-Cdk1 could then maintain (and further enhance) condensin II phosphorylation during later stages of mitosis when condensin I also gains access to chromosomes (Hirano 2005; Hudson et al. 2009; Ono et al. 2004). This sequential model of condensin activation via cyclin A and B remains to be confirmed experimentally.

Aurora B kinase

In addition to its roles in regulating mitotic spindle dynamics and kinetochore attachments, Aurora B kinase was found to control condensin function in a number of model organisms. However, the precise effects of Aurora activity seem to differ between species. In budding yeast, phosphorylation of the Ycg1 (CAP-G) condensin subunit during mitosis and maintenance of the compaction of the rDNA regions during anaphase both

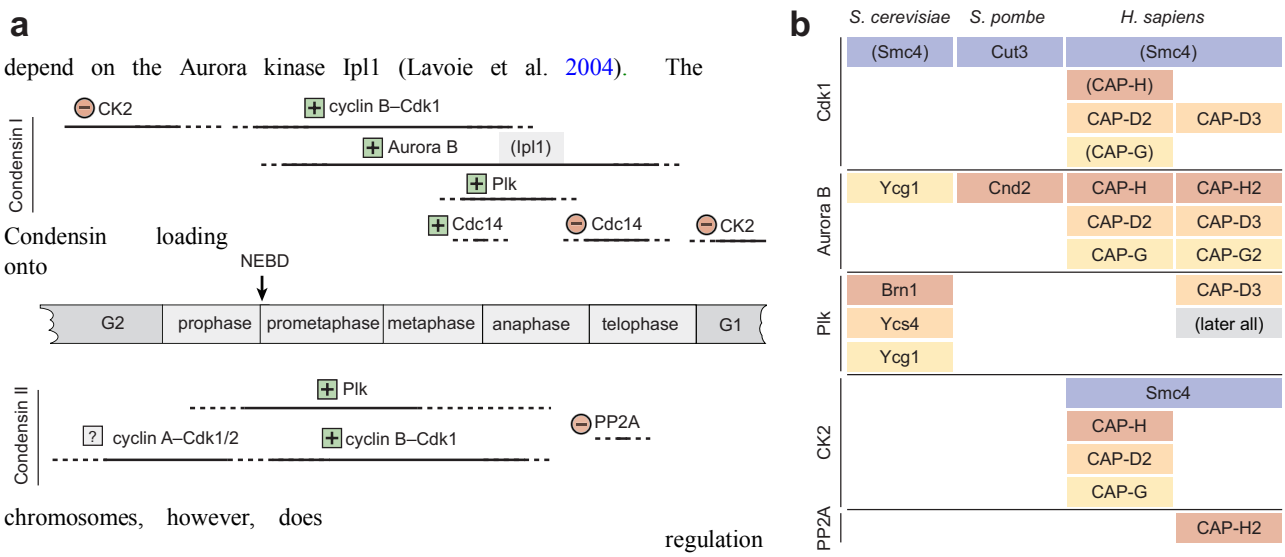

Fig. 2 Condensin regulation. **a** Kinases and phosphatases that regulate condensin localization and function during the cell cycle. Regulators that stimulate condensin binding to chromosomes or activity are indicated with a plus symbol, regulators that release condensin from chromosomes or inhibit its activity are indicated with a minus symbol, and regulators that have only been speculated to regulate condensin function are indicated with a question mark. Non-catalytic interactions are not depicted. The regulation by the Aurora kinase Ipl1 in *S. cerevisiae* is significant only during the metaphase-to-anaphase transition. See text for more details. **b** List of experimentally verified condensin subunits that are targeted by kinases and phosphatases.

not seem to be affected by Ipl1 mutation in this organism. In contrast, phosphorylation of the Cnd2 kleisin subunit of fission yeast condensin by the Aurora kinase Ark1 is, in addition to phosphorylation of the Cut3 (SMC4) subunit by CDK, necessary for the stable association of condensin with chromosomes until telophase (Nakazawa et al. 2008; Nakazawa et al. 2011; Tada et al. 2011). Aurora B kinase is also required for the accumulation of condensin I complexes on chromosomes from pro-metaphase until anaphase in *Drosophila melanogaster* (Giet and Glover 2001), *Caenorhabditis elegans* (Collette et al. 2011; Hagstrom and Holmes 2002; Kaitna et al. 2002), cultured human cells (Lipp et al. 2007), and frog egg extracts (Takemoto et al. 2007). Some earlier studies could, however, observe little or no effect of Aurora B depletion on the global levels of condensin associated with chromosomes in *C. elegans* (Maddox et al. 2006), HeLa cells (Ono et al. 2004), or *Xenopus laevis* egg extracts (Losada et al. 2002; MacCallum et al. 2002). One possible explanation for these discrepancies could be that different chromosomal regions might display variable levels of sensitivity to changes in Aurora B activity, depending on the model organism. For example, after Aurora B depletion in human cells, the amounts of condensin I (and to some extent condensin II) are most noticeably reduced at centromeric regions (Lipp et al. 2007). Differences probably also exist between mitosis and meiosis, since condensin I is largely absent from mitotic chromosomes but still present (albeit mislocalized) on meiotic chromosomes in *C. elegans* Aurora B mutants (Collette et al. 2011). The fact that in some species Aurora B kinase might be involved in chromosome condensation in a process that is independent of condensin (Mora-Bermúdez et al. 2007) furthermore complicates attempts to dissect direct effects of Aurora phosphorylation on condensin function. While recent work has revealed a role for the phosphorylation of condensin's kleisin subunit by Aurora B in recruitment of condensin to chromosomes in fission yeast and human cells (see below), additional work will be required to resolve the participation of the kinase in regulating condensin function in different organisms.

Polo-like kinase (PLK)

of condensin by PLK is best characterized in the budding yeast *S. cerevisiae*. During early anaphase, Cdc5 (PLK) phosphorylates a considerable number of residues in the three non-SMC condensin subunits (St-Pierre et al. 2009). The activity of PLK is necessary for the proper condensation of the rDNA repeats *in vivo* and enhances the stimulatory effect of condensin on DNA supercoiling by topoisomerase I *in vitro* (see below). The latter also requires the prior phosphorylation of condensin by CDK, which suggests that CDK and PLK might act in concert to initiate and maintain the activation of condensin. A similar cooperative role of both kinases has also been proposed for the regulation of mammalian condensin II (Abe et al. 2011). For instance, in human cell lines, recruitment of PLK1 to condensin requires prior phosphorylation of the CAP-D3 subunit (on threonine 1415) by CDK. Once recruited, PLK1 can phosphorylate other condensin subunits.

Casein kinase 2 (CK2)

CK2 was reported to phosphorylate condensin I in HeLa cells. Unlike the condensin modification by the kinases discussed above, CK2 phosphorylation peaks during interphase and is greatly reduced during mitosis (Takemoto et al. 2006). Since CK2-mediated phosphorylation of condensin reduces the formation of topo I-dependent positive supercoils *in vitro* (see below), the kinase might act as a suppressor of condensin activity in interphase cells. This hypothesis presumes that upon entry into mitosis, CK2-inhibitory phosphorylations need to be reverted by phosphatases whose identities remain yet to be determined.

Phosphatases

Two phosphatases are known to regulate condensin binding to chromosomes during mitosis, either directly or indirectly. In budding yeast, the first wave of release of the Cdc14 phosphatase from the nucleolus by the Cdc-fourteen early anaphase release (FEAR) network is required to promote condensin enrichment at the rDNA repeats and consequently segregation of this region (D'Amours et al. 2004). A second wave of Cdc14 release, regulated during telophase by the mitotic exit network (MEN), might then serve as a mechanism

to again release condensin from chromosomes (Varela et al. 2009). The concerted decrease in CDK activity and the increase in Cdc14 activity could therefore inactivate condensin at the end of mitosis and, as a result, trigger chromosome decondensation.

In mammalian cells, protein phosphatase 2A (PP2A) dephosphorylates the CAP-H2 subunit of condensin II during anaphase (Takemoto et al. 2009; Yeong et al. 2003). CAP-H2 dephosphorylation might be a signal for the unloading condensin II from chromosomes at the exit of mitosis, although little direct evidence exists to support this hypothesis. Interestingly, PP2A is at the same time able to facilitate recruitment of condensin II to chromosomes during early stages of mitosis, presumably through direct protein-protein interactions that are independent of the phosphatase's catalytic activity (Takemoto et al. 2009). Thus, PP2A could play dual roles in regulating the association of condensin with chromosomes. Finally, PP2A was suggested to control condensin function at certain housekeeping genes (i.e. *hsp70*) that need to be accessible for transcription very soon after mitotic exit. The heat shock transcription factor 2 (HFS2) and the TATA-box binding protein (TBP) recruit both condensin and PP2A to the promoter regions of these genes (Xing et al. 2008; Xing et al. 2005). Local dephosphorylation of condensin at these promoters by PP2A might then prevent their compaction during mitosis and thereby keep them accessible for the transcription machinery.

In summary, a complex regulatory network involving several kinases and phosphatases controls the activity of condensin complexes (Fig. 2a). While our understanding of this network is probably still incomplete, some general principles emerge for the regulation of condensin complexes. In vertebrates, condensin I is maintained during interphase in an inactive state via CK2-dependent phosphorylation, low CDK activity and/or its exclusion from the cell nucleus. Activation of condensin I correlates with dephosphorylation of CK2 sites, cyclin B-dependent phosphorylation of CDK sites, and its access to chromosomes upon NEBD during pro-metaphase. Phosphorylation by CDK is necessary, but not sufficient, to promote proper condensin function, which requires in addition subsequent phosphorylation by PLK and Aurora B kinase. These two kinases maintain phosphorylation of condensin I during the later stages of mitosis, when CDK activity starts to decline. Condensin II is probably activated earlier than condensin I by cyclin A-dependent CDK phosphorylation, which is then maintained by cyclin B-dependent CDK activity and additional phosphorylation by PLK. De-activation of both condensins at the end of anaphase is then achieved by dephosphorylation through phosphatases (PP2A for condensin II and most likely Cdc14 for condensin I). In case of the single condensin complex present in yeasts, the activation mechanism is presumably similar to the activation of vertebrate condensin I complexes, with the exception that no negative regulation during interphase has yet been described.

Beyond phosphorylation

Phosphorylation is presumably not the only posttranslational modification that controls condensin function. Large-scale proteomic studies identified, for example, several acetylation sites in the SMC2, SMC4 and CAP-H subunits of human condensin complexes (reviewed in Bazile et al. 2010). The functional significance of these modifications is, however, still unknown. Considering that acetylation plays a key role in regulating the association of the condensin-related cohesin complex with chromosomes (reviewed in Nasmyth 2011), it is tempting to speculate that acetylation could have a similar function in controlling condensin binding and release from chromosomes. Another type of posttranslational modification has been detected on the budding yeast condensin subunits Smc4, Brn1 (γ-kleisin), and Ycs4 (CAP-D2). These three subunits are sumoylated during metaphase and anaphase (D'Amours et al. 2004; Denison et al. 2005; Hannich et al. 2005; Varela et al. 2009). While the precise biological role of these modifications is still unknown, sumoylation possibly controls condensin localization to specific chromosome regions such as centromeres or the rDNA locus (Bachellier-Bassi et al. 2008; D'Amours et al. 2004).

Condensin's interaction with DNA and chromatin

A common feature of the posttranslational modifications described above is that they affect condensin's association with chromosomes. In order to understand the precise nature behind these regulatory activities and how condensin functions in structuring mitotic chromosomes, it will be essential to gain detailed insights into the interaction between condensin and its chromosome substrates. Although none of the condensin subunits appear to possess a canonical DNA binding motive, condensin holocomplexes isolated from *Xenopus* egg extracts can associate with various DNA substrates *in vitro* (Hirano and Hirano 1998; Hirano et al. 1997). Similarly, SMC2–SMC4 heterodimers from budding and fission yeast change the electrophoretic mobility of double- or single-stranded DNAs, respectively, in gelshift assays (Sakai et al. 2003; Stray and Lindsley 2003). Moreover, condensin complexes or subcomplexes can reconfigure DNA substrates in the test tube, at least when they are present in high molar excess. For example, Cut14–Cut3 (SMC2–SMC4) dimers purified from fission yeast cells support the annealing of single-stranded DNAs into double-stranded helices (Akai et al. 2011; Sakai et al. 2003; Sutani and Yanagida 1997). Moreover, *Xenopus* condensin holocomplexes (Kimura and Hirano 1997) or *C. elegans* SMC-4–MIX-1 dimers (Hagstrom and Holmes 2002) enhance the formation of positive DNA supercoils in an ATP-dependent manner when incubated with closed circular plasmids in the presence of type I topoisomerases *in vitro*. As already mentioned above, the stimulation of topo I-dependent supercoiling is strongly enhanced after condensin phosphorylation by CDK (Kimura et al. 1998; Kimura et al. 2001) or PLK (St-Pierre et al. 2009) and reduced after phosphorylation by CK2 (Takemoto et al. 2006). These findings suggest that phosphorylation might somehow modify the interaction between condensin and DNA substrates. Finally, when incubated with nicked circular plasmids in the presence of topo II, condensin holocomplexes (Kimura et al. 1999; Losada and Hirano 2001) or SMC2–SMC4 dimers (Stray et al. 2005) promote the formation of DNA knots into nicked circular

plasmids. The ability of condensin to change the conformation of DNA helices *in vitro* suggests that the complex might recognize and/or modulate a certain topology in DNA strands, for example DNAs that cross over. It has been proposed that over-winding of the DNA helix could be responsible for the compaction of chromosomes during mitosis (Kimura and Hirano 1997), which could act in concert with the decatenation activity of topo II (Baxter and Aragón 2012). This notion is consistent with the simultaneous requirement of both condensin and topo II for chromosome condensation *in vivo* (Cuvier and Hirano 2003) and *in vitro* (Adachi et al. 1991; Hirano and Mitchison 1993).

Several studies found that depletion of condensin from chromosomes reduces the resistance of mitotic chromosomes to mechanical stress caused, for example, by spreading them onto glass slides (Hirota et al. 2004; Oliveira et al. 2005) or by the pulling forces of the mitotic spindle exerted on their centromeric regions (Gerlich et al. 2006; Ribeiro et al. 2009). It has therefore been proposed that condensin is required to maintain the stiffness of mitotic chromosomes, potentially as part of a centromeric spring-like arrangement (Stephens et al. 2011) and/or along the chromosome arms (Renshaw et al. 2010). One possibility how condensin complexes could confer mechanic rigidity to mitotic chromosomes is by acting as linker molecules that tether loops of chromatid fibers. Different models exist about the potential organization of such loops. One model proposes that condensin complexes assemble into a proteinaceous scaffold along the central chromosome axes, which is consistent with the staining of condensins along the center line of human mitotic chromosomes (Hirota et al. 2004; Maeshima and Laemmli 2003; Ono et al. 2004; Saitoh et al. 1994). Alternatively, condensin could form a network of individual random linkages within condensed chromatids, a model that is compatible with mechanical measurements of isolated newt chromosomes (Poirier and Marko 2002). Tethering might be achieved by topologically encircling two distant regions of the same chromatid within the condensin ring structure (Cuylen et al. 2011), which would be similar to the linkage of two sister chromatids by their entrapment within cohesin rings (Haering et al. 2008). In this scenario, the catalytic activity of the SMC2–SMC4 subunits might regulate the size and frequency of the chromatin loops by modulating the opening and closing frequencies of the condensin rings. All the current models discussed above are still highly speculative.

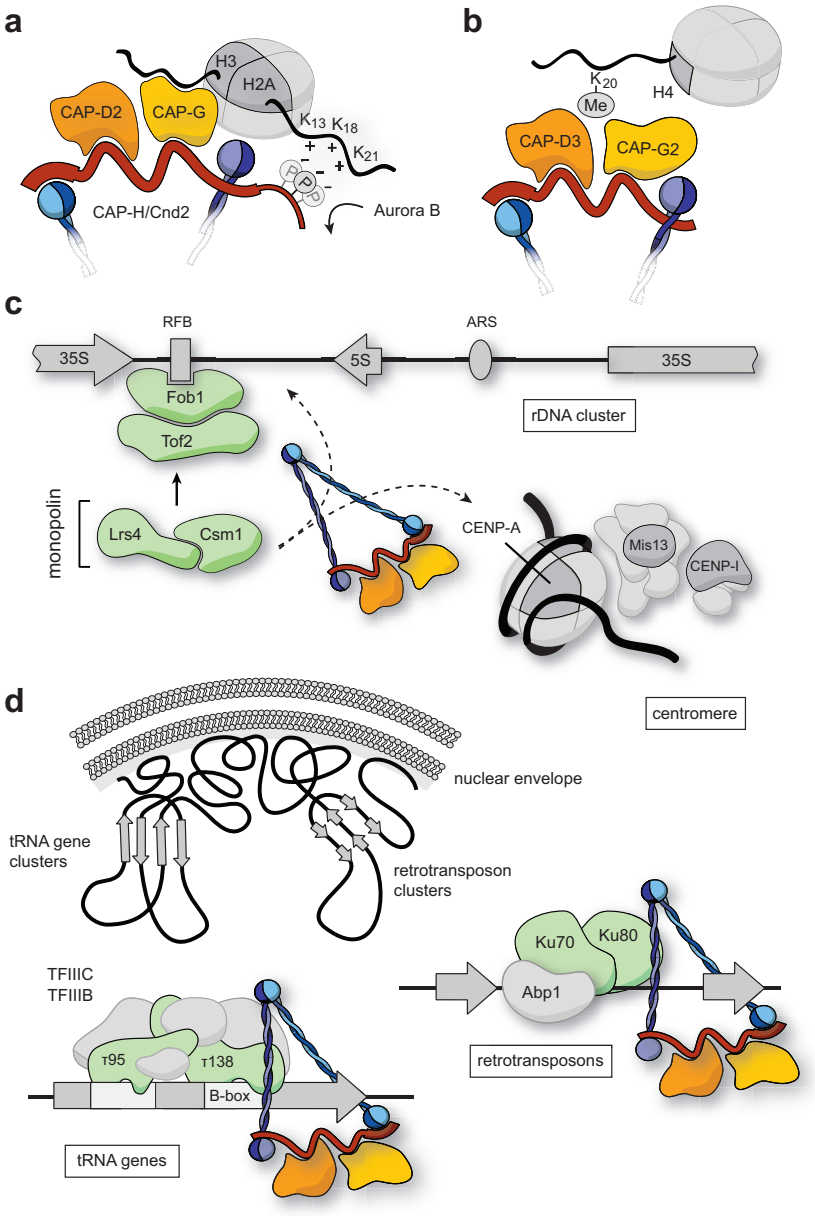

Fig. 3 Different mechanisms of condensin binding to chromosomes. **a** After phosphorylation by Aurora B, an N-terminal extension in the kleisin subunit of fission yeast condensin and human condensin I binds to the positively charged tails of histones H2A and H2A.Z. **b** The HEAT repeat subunits of human condensin II bind to the mono-methylated tail of histone H4. **c** In budding yeast, condensin is recruited to rDNA clusters by the monopolin protein complex, which is recruited via Fob1–Tof2 to the replication fork barrier (RFB). Monopolin, in cooperation with the CENP-A histone protein and the kinetochore subunits CENP-I and Mis13, also plays a role in the recruitment of condensin to centromeres. **d** In fission yeast, interspersed genetic elements including tRNA genes, 5S rRNA genes, or retrotransposons cluster in different domains of the nuclear periphery. Condensin has a role in this clustering process by interacting with, for example, the transcription factors general TFIIIB/C or the Ku70–Ku80 complex.

In eukaryotes, most DNA within the cell

nucleus is wrapped around octamers of the four core histone proteins H2A, H2B, H3, and H4 to form nucleosomes, the basic unit of chromatin. A recent study reported the co-purification of core histones with condensin I complexes from the nuclear fraction of human cells (Tada et al. 2011) (Table 1). *In vitro* reconstitution experiments with individual histone proteins suggest that the interaction with nucleosomes is mediated via the binding of the γ-kleisin subunit to the positively charged N-terminal tails of histone H2A or its H2A.Z isoform. This notion is supported by the finding that mutation of arginine residues in the N-terminal tail of histone H2A and/or depletion of H2A.Z in fission yeast reduce the levels of chromosome-bound condensin and cause chromosome segregation defects (Kim et al. 2009; Tada et al. 2011). It is conceivable that this interaction could be regulated by histone modifications, since yeast mutants that express a version of H2A.Z whose N-terminal tail cannot be acetylated show similar missegregation defects (Kim et al. 2009). Moreover, phosphorylation of the N terminus of the kleisin subunit by Aurora B kinase enhances binding to histone H2A, which is consistent with the requirement of Aurora B function for condensin association with chromosomes *in vivo* (Nakazawa et al. 2011; see above). Condensin loading onto chromosomes may therefore rely on an electrostatic interaction between the phosphorylated (negatively charged) γ-kleisin N terminus and the (positively charged) histone H2A tail 'receptor' (Fig. 3a) (Tada et al. 2011). How the N-terminal extension in the γ-kleisin subunit binds the histone tails is still unknown. This interaction might, however, not serve to dock condensin to chromosomes in all organisms, since the N-terminal extension seems to be absent from the γ-kleisins of some fungi (including *S. cerevisiae, Pichia pastoris*, and *Encephalitozoon cuniculi*). Moreover, vertebrate β-kleisins also apparently lack such an N-terminal extension, suggesting that distinct loading mechanisms could exist for condensin II complexes.

The binding of condensin to nucleosomes is not limited to histone H2A and H2A.Z. One study suggests that a C-terminal region of the condensin I HEAT repeat subunit CAP-D2 is able to interact with the core histone H3 and the linker histone H1 (Ball et al. 2002). Another study suggests that the condensin II HEAT repeat subunits CAP-D3 and CAP-G2 bind to histone H4 tails when the latter are mono-methylated at lysine residue 20 (Liu et al. 2010) (Fig. 3b). Since methylation of this residue temporally coincides with condensin II binding to chromosomes, enzymes that control this histone modification, including the demethylase PHF8, might indirectly regulate condensin loading onto chromosomes. In summary, the binding to nucleosomes appears to be an important step in the recruitment of condensin complexes to chromosomes, but the detailed mechanisms behind the recognition of certain histones and/or histone modifications by condensin complexes are not yet fully understood.

Condensin localization to specific chromosome loci

The description of genome-wide condensin binding maps has so far been mainly limited to yeast cells. Chromatin immunoprecipitation followed by microarray (ChIP-chip) or massive parallel sequencing analysis (ChIP-seq) studies showed an enrichment of condensin at centromeric and pericentromeric domains, telomeres, and repetitive regions of the genome such as the ribosomal DNA (rDNA) clusters (D'Ambrosio et al. 2008; Wang et al. 2005). The preferential binding to these loci suggests that condensin complexes might load onto chromosomes directly at these regions by either recognizing particular chromatin features or by the specific localization of condensin loading factors to these regions. Alternatively, condensin complexes might first bind at other chromosomal locations and then translocate along chromosomes to reach their target sites. In the following sections, we discuss the recruitment and function of condensin complexes at individual chromosome sites.

Centromeres

Centromeric chromosome domains function as building platforms for the assembly of kinetochore protein complexes, which in turn mediate the connection to spindle microtubules during mitotic and meiotic cell divisions. Basis for this function is the assembly of a specialized chromatin structure, which consists of nucleosomes that contain the histone variant CENP-A (CenH3) in place of the canonical histone H3 and a number of proteins that are part of a constitutively centromere associated network (CCAN) (reviewed in Santaguida and Musacchio 2009). The binding of condensin complexes to centromeres has been described on the basis of ChIP data in budding and fission yeast (D'Ambrosio et al. 2008; Nakazawa et al. 2008; Tada et al. 2011; Tanaka et al. 2012; Wang et al. 2005) and their co-localization with kinetochore proteins by immunofluorescence microscopy in budding yeast (Brito et al. 2010), fission yeast (Nakazawa et al. 2008), human cells (Ono et al. 2004), *D. melanogaster* (Steffensen et al. 2001), *C. elegans* (Hagstrom and Holmes 2002), and *X. laevis* chromosomes (Shintomi and Hirano 2011). Interestingly, condensin II is required for the stable assembly of CENP-A at centromeres in *Xenopus* egg extract, potentially by reinforcing the entire centromeric structure (Bernad et al. 2011).

Several factors are involved in the recruitment of condensin complexes to centromeres. In *S. cerevisiae*, the Mam1–Csm1–Lrs4 monopolin complex (Rabitsch et al. 2003) in concert with casein kinase 1 (CK1) (Petronczki et al. 2006) and Aurora B kinase (Monje-Casas et al. 2007) ensures co-orientation of sister kinetochores toward the same spindle pole during the first meiotic division, presumably by physically clamping together kinetochores (Corbett et al. 2010). The Pcs1–Mde4 monopolin complex in *S. pombe* presumably uses a similar mechanism to prevent the attachment of one kinetochore to spindle microtubules emanating from opposite cell poles (merotelic attachment) during mitosis (Gregan et al. 2007). Interestingly, kinetochore co-orientation during budding yeast meiosis I requires also condensin (Brito et al. 2010), suggesting that monopolin and condensin complexes cooperate in controlling the correct attachment of kinetochores to spindle microtubules. This hypothesis is supported by the observation that condensin and monopolin interact in two-hybrid and co-immunoprecipitation experiments in budding (Johzuka et al. 2006; Wysocka et al. 2004) and fission yeast (Tada et al. 2011). Fission yeast cells that lack the monopolin subunit Pcs1 localize less condensin to centromeres and display an increased frequency of lagging chromosomes. Notably, the later defect is partially rescued by artificial recruitment of condensin to centromeres by fusion of the kleisin subunit Cnd2 to part of the kinetochore protein Cnp3 (CENP-C). This suggests that the role of monopolin is to recruit condensin to kinetochores, where it might either act directly on kinetochore subunits or convert the underlying chromatin structure in a way that enables the co-orientation of microtubule binding sites in a kinetochore assembly (Fig. 3c). Consistent with the latter hypothesis, the

elasticity of centromeric chromatin in bi-oriented chromosomes is dramatically increased in vertebrate cells depleted of SMC2 or CAP-D2 (Gerlich et al. 2006; Ribeiro et al. 2009) or in *D. melanogaster* cells depleted of the γ-kleisin subunit Barren (Oliveira et al. 2005). While the structural integrity of budding yeast centromeres is similarly affected in budding yeast condensin mutants, condensin is recruited to centromeres independently of the monopolin subunits Csm1 or Lrs4 in this organism (Brito et al. 2010). It is hence conceivable that other proteins contribute to targeting condensin to centromeric chromosome regions. The findings that mutation of the centromere-specific histone Cnp1 (CENP-A), the inner centromere proteins Mis6 (CENP-I), or the kinetochore subunit Mis13 in fission yeast as well as depletion of CENP-I by RNAi in human cells reduces the localization of Cut14 (SMC2) or CAP-H2 to centromeres are consistent with this notion (Nakazawa et al. 2008). Since no homologs of monopolin proteins could so far be identified in metazoans, the enrichment of condensin at centromeres might be regulated by multiple kinetochore components whose roles in this process might vary between species.

DNA sequences targeted by RNA polymerase I or III

Probably the best characterized condensin binding region is the rDNA cluster on the right arm of budding yeast chromosome XII (Freeman et al. 2000; Wang et al. 2006). This cluster contains approximately 200 tandem copies of a 9.1 kb DNA sequence that encodes the 35S and 5S ribosomal RNA genes, which are transcribed by RNA polymerases (pol) I or III, respectively (Fig. 3c). Condensin enrichment at the rDNA depends on Fob1, a protein that binds to a replication fork barrier (RFB) sequence element within the rDNA repeat and controls unidirectional replication of the repeats (Johzuka et al. 2006), the monopolin proteins Lrs4 and Csm1 (Johzuka and Horiuchi 2009), as well as release and activation of the Cdc14 phosphatase from the nucleolus during early anaphase (D'Amours et al. 2004; Wang et al. 2004). The role of the latter for condensin recruitment is presumably the inhibition of RNA pol I transcription by dephosphorylating polymerase subunits (Clemente-Blanco et al. 2009). Condensin accumulation at rDNA clusters can also be observed during mitosis in the fission yeast *S. pombe*. Surprisingly, condensin levels are diminished by mutations in the Acr1 subunit of the RNA pol I upstream activating factor complex or in RNA pol I itself (Nakazawa et al. 2008). This suggests that, in contrast to what is the case in budding yeast, active transcription by RNA pol I is a prerequisite for condensin localization to the rDNA region. One possibility is that condensin complexes are first recruited to transcription initiation sites of genes actively transcribed by RNA pol I (or RNA pol III, see below) but remain inactive. Shutdown of transcription might then be a prerequisite for condensin's activation during anaphase. If condensin indeed functioned by linking distant regions of a chromosomes through their entrapment with its ring structure (Cuylen and Haering 2011), it might be conceivable that in the first step condensin encircles only a single DNA fiber. Entrapment of a second DNA might then only be possible once polymerases and nascent RNAs have been removed. Similarly, RNA-DNA hybrids would probably need to be removed if condensin functioned by changing the topological state of the DNA strands.

Genome-wide mapping of condensin binding sites in budding yeast also revealed a correlation with genes transcribed by RNA pol III, which include the genes encoding tRNAs and the 5S rDNA. Co-immunoprecipitation and co-localization of condensin and the RNA pol III general transcription factors TFIIIB/C suggest that condensin may be recruited via a direct interaction with the subunits of the core RNA pol III machinery (Fig. 3d and Table 1) (D'Ambrosio et al. 2008; Haeusler et al. 2008). Further evidence for this possibility comes from the findings that a gain-of-function allele of the B-box binding subunit of TFIIIC suppresses a mutation in the fission yeast condensin complex (Iwasaki et al. 2010; Tada et al. 2011) and that insertion of a B-box element of the RNA pol III promoter into a region of a budding yeast chromosome that is normally devoid of condensin is sufficient to ectopically recruit condensin complexes (D'Ambrosio et al. 2008). In fission yeast, TFIIIB/C apparently recruits condensin even to regions that are not actively transcribed by RNA pol III, so-called chromosome organizing clamps (Noma et al. 2006).

Interestingly, condensin localization to tRNA genes in budding yeast is reduced in mutants of the SCC2 subunit of the SCC2–SCC4 complex (D'Ambrosio et al. 2008), which is required for loading of the condensin-related cohesin complex onto chromosomes (Ciosk et al. 2000). SCC2–SCC4 might therefore act as a general loading factor for SMC protein complexes. However, the overall levels of condensin subunits that can be recovered in chromosome-bound fractions are not obviously affected by either SCC2 mutation in budding yeast (Ciosk et al. 2000) or SCC4 depletion in human cells (Watrin et al. 2006). This suggests that alternative pathways for condensin recruitment must exist.

While tDNAs are rarely present in direct repeats in the genomes of budding or fission yeast, they nevertheless cluster within the three-dimensional space of the nucleus, either close to the nucleolus or in the vicinity of centromeres, respectively. Localization to centromeres can also be observed for some of the RNA pol III-transcribed 5S rRNA genes that are dispersed throughout the fission yeast genome. Interestingly, the formation of these clusters in both yeast species depends on condensin (Haeusler et al. 2008; Iwasaki et al. 2010) (Fig. 3d). Condensin therefore contributes to the organization of chromosome arrangements not only during mitosis but also during interphase. Clustering during interphase might serve different purposes. For example, assembly of repetitive DNA sequences such as rDNA sequences into a restricted space might prevent genomic destabilization by homologous recombination (Bhalla et al. 2002; Tsang et al. 2007). This could be particularly important for less stable genomic elements, such as retrotransposons, which, in fission yeast, have recently been reported to also cluster in the vicinity of centromeres in a manner that relies on condensin (Tanaka et al. 2012). Alternatively, condensin-dependent gathering of tRNA genes and retrotransposons close to centromeres, and consequently to the nuclear periphery, might be required for down-regulating their transcription (Iwasaki et al. 2010).

Sites of DNA damage

Condensin's role in guarding genomic integrity is not limited to tRNA or rRNA genes, or retrotransposons. Several lines of evidence indicate that condensin plays a role in the detection and/or repair of DNA damage genome-wide (reviewed in Wu and Yu 2012). For example, mutations in the putative Cut14 (SMC2) binding site in the fission yeast γ-kleisin subunit Cnd2 or in the Cut14 hinge domain render cells hypersensitive to hydroxyurea (HU)-induced replication fork stalling and UV-

induced thymidine dimer formation (Akai et al. 2011; Aono et al. 2002). These defects are suppressed by overexpression of Cti1, a protein that accumulates on chromosomes following DNA damage and binds to the hinge domain of Cut14. Condensin and Cti1 might hence be part of the same DNA damage repair pathway (Chen et al. 2004). The precise function of condensin in this pathway is still unresolved. Notably, patches of the single-stranded DNA binding protein Ssb1 accumulate in the Cut14 mutant in the presence of HU or in the Cnd2 mutant upon shift to the restrictive temperature. The findings that, *in vitro*, the Cut14–Cut3 (SMC2–SMC4) dimer promotes release of single-stranded binding proteins from DNA and re-annealing of DNA duplexes (Akai et al. 2011; Sutani and Yanagida 1997) support the proposal that condensin's primary function might be in the clearance of chromosomal proteins from DNA and/or the removal of RNA–DNA hybrids, either for condensin's function in DNA damage repair during interphase or in chromosome organization during mitosis (Yanagida 2009). This "clearance model", albeit fascinating, will require additional experimental confirmation *in vivo*.

Another indication that condensin plays a role in DNA damage repair comes from the discovery that a small fraction of the DNA break sensor protein poly(ADP-ribose) polymerase 1 (PARP-1) co-immunoprecipitates with condensin I from human cells in S or G2 phase, and this fraction increases notably in the presence of HU and other DNA damaging agents (Heale et al. 2006). Consistent with a role for condensin I in base excision repair, the repair of single-stranded DNA breaks in cells depleted for SMC2 or CAP-D2 is considerably delayed. Condensin I and PARP-1 are both recruited to sites of laser-induced DNA breaks, but at least the initial accumulation of the former at these sites does not depend on the presence of the latter (Kong et al. 2011). Condensin I might therefore directly recognize DNA lesions and/or play part in the DNA damage response pathways that could result in the ADP-ribosylation of certain target proteins.

Condensin II was found to co-immunoprecipitate with MCPH1, a protein that is frequently mutated in patients with the neurodevelopmental disorder microcephaly and has a putative role in DNA damage response (Wood et al. 2008). Depletion of the condensin II subunit CAP-D3 in human cells causes a decrease in the efficiency to repair DNA double-strand breaks by homologous recombination (HR). The same decrease in repair efficiency can be observed in mouse embryonic fibroblast (MEF) cells derived from MCPH1$^{-/-}$ knock-out mice. These findings suggest that condensin II and MCPH1 cooperate in HR-mediated DNA damage repair. Interestingly, a fraction of MCPH1$^{-/-}$ MEFs displays condensed chromosomes even during interphase, which is similar to the premature condensation observed in some cells derived from microcephaly patients (Trimborn et al. 2006). Depletion of condensin II in these cells reduces the portion of cells with condensed interphase chromosomes, which implies that the aberrant condensation might be due to a failure to inhibit condensin II activity during interphase in the absence of MCPH1. MCPH1 might achieve this inhibitory effect by competing with condensin II for binding to chromosomes (Yamashita et al. 2011) and could thereby reverse the early phase of chromosome condensation in response to DNA damage. This model is, however, still highly speculative.

Additional proteins targeting condensin to chromosomes

In addition to the condensin interaction partners discussed above, several other proteins have been implicated in regulating the association of condensin complexes with chromosomes. However, the functional significance of the roles of these proteins in condensin loading is in all cases still poorly understood. For example, the homolog of the human tumor suppressor protein retinoblastoma (pRB) in *Drosophila* (named RBF1) and Cap-D3 were reported to co-immunoprecipitate and co-localize on polytene chromosomes, and the interaction between the proteins was found to be conserved in human cells (Longworth et al. 2008). Cap-D3 association with chromosomes is notably reduced in *rbf1* mutant flies or cells depleted of RBF1. Furthermore, expression of wild-type pRB in a human cell line in which both endogenous pRB alleles are mutated leads to an increase in the levels of CAP-D3 on chromosomes. These experiments suggest that pRB functions in the loading of condensin II onto chromosomes in some direct or indirect way. Loading of condensin II by pRB might be particularly important for the integrity of centromeric chromatin regions, which could explain the kinetochore orientation and consequently chromosome segregation defects in cells depleted for pRB (Manning et al. 2010).

Another protein that was suggested to play a role in loading condensin complexes onto chromosomes is the A Kinase–Anchoring Protein 95 (AKAP95), a protein that accumulates on mitotic chromosomes upon NEBD (Steen et al. 2000), and might bind to the CAP-H subunit of condensin I via a C-terminal zinc-finger domain (Eide et al. 2002). It has, however, remained uncertain whether AKAP95 indeed plays a direct role in targeting condensin to chromosomes.

Once bound to chromosomes, condensin might act as a docking platform for other chromosomal proteins. Depletion of the SMC2 subunit in chicken DT40 cells causes the loss of topo II and the chromosomal passenger complex protein INCENP from centromeric regions (Hudson et al. 2003) and loss of the chromokinesin KIF4 from the axes of mitotic chromosomes (Hudson et al. 2009). Chromosome binding of chromokinesin and condensin are apparently inter-dependent, since depletion of KIF4A from human fibroblasts by RNAi or repression of KIF4 expression in DT40 cells also affect the association of condensin I (and at least to some extent also condensin II) with mitotic chromosomes (Mazumdar et al. 2004; Samejima et al. 2012), which is consistent with the co-purification of condensin and KIF4A from human cells (Geiman et al. 2004; Mazumdar et al. 2004). The activities of both condensin and chromokinesin have been recently suggested to be equally important for mitotic chromosome condensation (Samejima et al. 2012).

Conclusions: The complexity of controlling condensin complexes

In this article, we have reviewed the regulatory framework of posttranslational modifications and protein-protein interactions that control the action of condensin complexes. While recent years have seen remarkable advances towards a comprehensive understanding of condensin function, a number of important questions remain to be answered. In order to understand how the phosphorylation of a few serine residues within one condensin subunit can so dramatically alter the activity of the half-mega-Dalton holocomplex, further insights into the three-dimensional arrangements of the different subunits in the complex are needed. This goal will presumably require the combination of

biochemistry with structural biology approaches at different scales of resolution, ranging from X-ray crystallography of subcomplexes to reconstitutions of condensin holocomplexes based on electron microscopy techniques. Similar approaches will be indispensable to further understand how condensin binds to its chromosomal substrate.

Another challenge for the future will be to find out how condensin is able to change the three-dimensional organization of chromosomes. Does condensin merely stabilize folded chromatin fibers by acting as a molecular linker (Cuylen and Haering 2011), does it actively twist and knot DNA helices (Baxter and Aragón 2012), or does it employ a combination of these two modes of action? Does the ATPase activity of the SMC2–SMC4 dimer act as molecular switch that changes the conformation of the complex, potentially by opening or closing the ring architecture, or is it the motor behind a molecular machine that uses the energy of ATP hydrolysis to power DNA over-winding? Answering these questions will probably need to await a assays that allow the reconstitution of condensin binding to well-defined chromatin substrates in the test tube.

An increasing amount of evidence indicates that condensin complexes modulate chromosomal architecture not only during cell divisions but also during interphase, with roles ranging from the maintenance of genomic integrity, compartmentalization of chromosomal domains, to the regulation of gene expression. A role for condensin in the control of transcription might be particularly important in some organisms such as *C. elegans*, where a specialized version of condensin complexes exists for this purpose (reviewed in Wood et al. 2010). Understanding how condensins can fulfill all these functions at specific chromosome locations and how their localization to these regions is controlled will undoubtedly benefit from further advances in cell biological approaches. This includes the further development of super-resolution imaging techniques, which might allow the precise localization of condensin complexes in relation to other chromosomal components, and novel biophysical approaches that quantitatively measure chromosome structure inside living cells. While many questions regarding the function of condensin complexes are still unanswered, there is no question that exciting times are ahead in the exploration of the molecular mechanisms that shape chromosomes.

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