Temporal and Spatial Regulation of Targeting Aurora B to the Inner Centromere

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Successful partitioning of chromosomes in mitosis relies on the bipolar attachment of sister chromatids at metaphase. For this biorientation, the chromosomal passenger complex (CPC), composed of catalytic kinase Aurora B and regulatory components (INCENP, Survivin, and Borealin), must be localized at the center of paired kinetochores, the site called the inner centromere. It is largely unknown what defines the inner centromere and how the CPC is targeted to this site. Recent studies point out that the shugoshin protein (SGO), originally identified as a cohesin protector, also acts as a conserved centromeric adapter of the CPC. Phosphorylation of the CPC by Cdk1 promotes direct binding with shugoshin, thus explaining how the CPC is targeted to the centromere in a timely manner at prometaphase during the cell cycle. Moreover, the phosphorylation of histone H3 threonine 3 (H3-pT3) mediated by Haspin cooperates with Bub1-mediated H2A-S121 phosphorylation in targeting the CPC to the inner centromere. H3-pT3 promotes nucleosome binding of Survivin, whereas H2A-pS121 facilitates the binding of shugoshin. Haspin colocalizes with cohesin by associating with Pds5, a cohesin-binding protein, and Bub1 localizes at kinetochores. Thus, the inner centromere is defined by the spatial intersection of two histone marks mediated by cohesin- and kinetochore-associated kinases.

For the proper partition of chromosomes to daughter cells, sister chromatids must be held together before mitotic chromosome segregation. This cohesion of sister chromatids is established during DNA replication dependent on the cohesin complex and is maintained until metaphase when sister kinetochores attach to microtubules (MTs) emanating from the opposite spindle poles (bipolar attachment) (Nasmyth et al. 2000). In animal mitotic cells, however, most cohesin dissociates from the chromosome arms during prophase (called “prophase pathway”), in a manner dependent on the phosphorylation of cohesin by mitotic kinases such as Polo-like kinase (Losada et al. 2002; Hauf et al. 2005). However, centromeric cohesin is retained until metaphase through the function of shugoshin (Sgo/MEI-S332) (Lee et al. 2005; Watanabe 2005). This shugoshin-dependent centromeric protection is essential for mitotic chromosome segregation in mammalian cells. In most organisms, shugoshin is required for meiotic chromosome segregation, where the stepwise dissociation of cohesin is more crucial (Miyazaki and Orr-Weaver 1994; Watanabe 2005). Shugoshin collaborates with protein phosphatase 2A (PP2A) to prevent phosphorylation of cohesin and, thereby, its dissociation (Kitajima et al. 2006; Riedel et al. 2006; Tang et al. 2006). Although shugoshin was first characterized as a protector of centromeric cohesin (Kitajima et al. 2004; Marston et al. 2004; Rabitsch et al. 2004), a study in budding yeast suggested that it was also involved in sensing the lack of tension on mitotic chromosomes (Indjeian et al. 2005).

Accurate segregation of chromosomes during cell division requires sister chromatids to be captured by MTs from the opposite spindle poles (bipolar attachment or

biorientation). This is accomplished by a trial-and-error process of kinetochore-microtubule (KT-MT) attachment that is essential and relies largely on the CPC, which includes catalytic kinase Aurora B and regulatory subunits Borealin, Survivin, and INCENP and locates at centromeres (Hauf et al. 2003; Cheeseman et al. 2006; DeLuca et al. 2006; Ciferri et al. 2008; Tanaka 2008). In the absence of tension across centromeres, Aurora B phosphorylates the MT-anchoring kinetochore proteins, thereby destabilizing the attachment, whereas the bipolar attachment of kinetochores produces a tension that brings about the spatial separation of kinetochores from Aurora B, thereby stabilizing the attachment (Fig. 1) (Pinsky and Biggins 2005; Tanaka 2008; Liu et al. 2009). Thus, Aurora B must be targeted and anchored precisely at the center of paired kinetochores, a site called the inner centromere (Ruchaud et al. 2007; Kelly and Funabiki 2009).

SHUGOSHIN REQUIRED FOR CPC TARGETING TO CENTROMERES

Fission yeast possess two shugoshin-like proteins, Sgo1 and Sgo2, both of which localize at the pericentromeric heterochromatin region, the site enriched with cohesin and crucial for centromeric cohesion. Sgo1 is meiosis I specific and has a crucial role in protecting centromeric cohesin during meiosis I, whereas Sgo2 is ubiquitously expressed and required for faithful chromosome segregation in mitosis and meiosis (Kitajima et al. 2004; Rabitsch et al. 2004). Sgo2 associates closely with Bir1/Survivin and is required for the full localization of the CPC at centromeres (Kawashima et al. 2007; Vanoosthuysen et al.

Figure 1. Establishment of bipolar attachment. Kinetochore-assembling core centromere (pink globule) protrudes from inner centromere, the site where Aurora B kinase accumulates and destabilizes kinetochore-microtubule attachment. Therefore, microtubule (MT) attachment to the kinetochore within the Aurora-B-active region (dark blue and light blue) is unstable (dashed pink line), whereas MT attachment far from Aurora B activity is stable (black line). Spindle assembly checkpoint is activated when unstable attachment is disconnected but is inactivated when all attachment is bipolar and thus stabilized (*bottom*).

2007). The overall phenotypes of *sgo2Δ*, not only during mitosis but also during meiosis, are explainable by the reduced activity of Aurora B. These results imply that in addition to its protective function, shugoshin has a crucial role in promoting the centromeric localization of the CPC, thereby ensuring bipolar attachment of kinetochores.

The requirement of shugoshin for CPC targeting to centromeres has also been shown in *Xenopus* (Rivera and Losada 2009). Although depletion of hSgo1, a canonical shugoshin in human mitotic cells, causes little defect in CPC localization, depletion of both shugoshin-like proteins hSgo1 and hSgo2 abolishes CPC localization to centromeres, validating that the second role of shugoshin is also conserved in mammals (Tsukahara et al. 2010). Centromeric localization of shugoshin is also influenced by the CPC, implying that centromere targeting of shugoshin and the CPC is interdependent (Resnick et al. 2006; Kawashima et al. 2007; Vanoosthuyse et al. 2007). Thus, whereas shugoshin was initially identified as a cohesin protector, the same or related protein acts as the centromeric CPC adapter in eukaryotes.

CDK1-DEPENDENT CPC PHOSPHORYLATION REQUIRED FOR CENTROMERE TARGETING

The cyclin-dependent kinase 1 (Cdk1)-cyclin B complex functions as a cell cycle engine to promote mitotic progression. The newly isolated fission yeast cyclin B mutant *cdc13-M7* shows a marked defect in chromosome biorientation but not in mitotic entry, suggesting that the Cdk1-cyclin B complex specifically targets the regulation of chromosome biorientation in addition to cell cycle pro-

Figure 2. Interaction between the CPC and shugoshin. Phosphorylation of fission yeast Survivin or human Borealin by Cdk1 promotes CPC binding to coiled-coil region of shugoshin. Intertwined configuration of Survivin, Borealin, and INCENP is based on the crystallographic study of the complex (Jeyaprasath et al. 2007). (Modified, with permission, from Tsukahara et al. 2010 [Nature Publishing Group].)

gression (Tsukahara et al. 2010). Accordingly, fission yeast Survivin/Bir1 is phosphorylated by Cdc2 in mitosis, and the nonphosphorylatable *bir1-8A* mutant impairs CPC localization and its function at centromeres. In contrast, the phosphomimetic *bir1-8D* mutant shows intact CPC targeting to centromeres and, crucially, suppresses the biorientation defect of the *cdc13-M7* mutant. Thus, phosphorylation of Bir1 is important for targeting the CPC to centromeres in prometaphase (Tsukahara et al. 2010).

The amino-terminal half of Bir1 (Bir1-N), which contains a CDK phosphorylation cluster, binds Sgo2, a centromeric CPC adapter, and phosphorylation of Bir1 is required for this interaction (Fig. 2). As in fission yeast, the inhibition of human cyclin B causes defects in chromosome biorientation (Chen et al. 2008). Consistently, the Cdk1-dependent phosphorylation of hBorealin (rather than Survivin in this case) promotes centromere targeting through association with both hSgo1 and hSgo2 (Tsukahara et al. 2010). Although the CPC subunit that interacts with shugoshin thus moves between yeast and metazoa, the overall regulation of CPC targeting to the centromere by Cdk1 is conserved, explaining how the cell cycle is linked to CPC targeting to centromeres and chromosome biorientation in eukaryotes (Fig. 2).

BUB1-DEPENDENT H2A PHOSPHORYLATION REQUIRED FOR SHUGOSHIN LOCALIZATION

Shugoshin localization at centromeres depends on the conserved SAC protein kinase Bub1, which is also required for proper chromosome segregation (Kitajima et al. 2004, 2005; Boyarchuk et al. 2007). Although several Bub1 substrate candidates have been suggested, the canonical substrate remained unknown more than 15 years after its discovery, even in genetically tractable organisms such as yeast. Recently, a biochemical approach in fission yeast identified serine 121 of histone 2A (H2A) as a Bub1 substrate (Kawashima et al. 2010). Crucially, the *h2a-S121A*

Figure 3. Shugoshin action. Shugoshin, which can associate with PP2A, CPC, and MCAK, is targeted to the nucleosome at inner centromeres through the SGO motif, which binds the nucleosome only when H2A is phosphorylated by Bub1. Localization of fission yeast Sgo1 and human hSgo1 at inner centromere is also mediated by interaction with the heterochromatin protein Swi6/HP1 through the PxVxL motif (Yamagishi et al. 2008). (KT-MT) Kinetochore-microtubule.

mutant, in which all cellular H2A-S121 is replaced by alanine, phenocopies the *bub1* kinase-dead (*bub1-KD*) mutant in losing the centromeric localization of shugoshin proteins, indicating that H2A-S121 is the canonical cellular substrate of Bub1. Artificial tethering of shugoshin to centromeres largely restores the *h2a-S121A*– or *bub1-KD*–related defects in chromosome segregation. The Bub1-H2A-shugoshin pathway is also conserved in human cells (Kawashima et al. 2010).

Shugoshin family proteins, although conserved among all eukaryotes, share limited amino acid sequence similarities in the coiled-coil region near the amino terminus and the basic region near the carboxyl terminus (Fig. 3) (Kitajima et al. 2004). This basic sequence, denoted as the SGO (shugoshin) motif, mediates the association with nucleosomes containing H2A-pS121 (Fig. 3, also see Fig. 4A) (Kawashima et al. 2010). In contrast, the coiled-coil region is responsible for the interaction with PP2A and the CPC and thereby for their recruitment to centromeres (Kawashima et al. 2007; Tsukahara et al. 2010). Recent studies in human cells have revealed that the middle non-conserved region of hSgo2 but not hSgo1 additionally binds MCAK, an MT depolymerase that has a key role in correcting attachment, to recruit it to centromeres (Tanno et al. 2010). Thus, shugoshin acts as a molecular hub, linking several centromeric proteins to the nucleosome at the inner centromere (Fig. 3).

HASPIN-DEPENDENT H3 PHOSPHORYLATION REQUIRED FOR CPC TARGETING TO CENTROMERES

In human cells, Haspin, a histone kinase that phosphorylates threonine 3 of H3, has been suggested to function in the centromeric protection of cohesin in parallel with shugoshin (Dai et al. 2006). It turns out that fission yeast Haspin-related kinase Hrk1 is dispensable for centromeric cohesin or Sgo1-related function but required for CPC targeting to centromeres, a function related to Sgo2 (Yamagishi et al. 2010). In fission yeast, Hrk1 phosphorylates H3-T3 only in M phase, and this phosphorylation is re-

Figure 4. (A) CPC targeting to centromeres and (B) genetic interaction of two histone phosphorylation pathways. (A) Whereas H3-pT3 associates with CPC, H2A-pS121 facilitates interaction of the nucleosome with shugoshin. Cdk1-dependent phosphorylation of CPC promotes binding to shugoshin, and neither protein can fully localize to chromatin without this phosphorylation (Tsukahara et al. 2010), suggesting that physical interaction between CPC and shugoshin creates synergistic association of these proteins with nucleosomes. Thus, phosphorylation of CPC contributes to chronological regulation of centromere targeting of CPC during the cell cycle, whereas two histone marks contribute to special regulation of the CPC. (B) Mutations in the two histone phosphorylation pathways cause no cumulative defects if combined within the intrapathway, whereas interpathway double mutations cause synthetic defects.

quired for full localization of the CPC to centromeres. H3-T3 interacts directly with the conserved BIR domain of Survivin, and mutational analysis of the BIR domain indicates that this interaction is important for CPC targeting to centromeres (Fig. 4A). This mechanism is conserved in vertebrates (Kelly et al. 2010; Wang et al. 2010; Yamagishi et al. 2010). Genetic analyses in fission yeast reveal that this Hrk1-H3(pT3) pathway by which the CPC is localized to centromeres acts in a redundant capacity with the Bub1-H2A(pS121)-Sgo2 pathway; intrapathway double mutations cause no cumulative defects, whereas interpathway double mutations cause remarkable defects in chromosome biorientation (Fig. 4B). Importantly, the biorientation defects of double mutants such as *h3-T3A* and *h2a-S121A* are largely suppressed by ectopically localizing the CPC to centromeres. Thus, the primary readout of histone phosphorylation of H3-T3 and H2A-S121 is the localization of the CPC to the inner centromere, a process essential for setting up chromosome biorientation (Yamagishi et al. 2010).

Although Bub1 and Hrk1 kinases cooperate in targeting the CPC to centromeres, the activities of these kinases are distributed differently along the chromosome in fission yeast; Bub1 locates at kinetochores (Kawashima et al. 2010), whereas Hrk1 interacts with the cohesin-associating protein Pds5 and locates at cohesin sites along the

Figure 5. Intersection of two histone marks defines inner centromere. (A) Chromatin immunoprecipitation (ChIP) analysis of Survivin/Bir1, Hs-pT3, and H2A-pS121 throughout the kinetochore. (*cen*) Heterochromatic centromere, (*mat*) mating-type locus, (*tel*) telomere, and (*e1–4*) euchromatic arm region in mitotic fission yeast cells. (B) Prometaphase chromosome from HeLa cells stained with antibodies against H3-pT3, H2A-pT120, and Aurora B. DNA was costained with Hoechst 33342. (C) Depiction of a chromosome and definition of inner centromere. (Modified, with permission, from Yamagishi et al. 2010 [© AAAS]).

chromosome. Accordingly, H2A-pT121 is enriched at the core centromere and the adjacent pericentromeric region (the inner centromere in metazoans), whereas H3-pT3 distributes to heterochromatic regions where cohesin is enriched. The CPC localizes largely at the pericentromeric region, the intersection of H3-pT3 and H2A-pS121 distributions (Fig. 5A) (Yamagishi et al. 2010). In human prometaphase, chromosome H3-pT3 signals localize to the intersister region, whereas H2A-pT120 (equivalent to yeast H2A-pS121) signals locate along the interkinetochore axis, with signals culminating near kinetochores. Importantly, Aurora B signals are enriched in the merged region of these signals (Fig. 5B). Thus, the inner centromere in eukaryotes is principally defined by the intersection of two histone marks, H2A-pS121 and H3-pT3, that are mediated by kinetochore-associated kinase Bub1 and cohesin-associated kinase Haspin/Hrk1 (Fig. 5C) (Yamagishi et al. 2010).

CONCLUSIONS

The CPC has several noncentromeric roles during prophase such as phosphorylation of H3-S10 and localization of condensin onto global chromatin. In animal cells, CPC localization is dynamically narrowed down to the inner centromere during prometaphase (Ruchaud et al. 2007). For this redistribution, Bub1 kinase locating at kinetochores has a central role by localizing H2A-pS121 and shugoshin near the centromere (Kiyomitsu et al. 2007;

Kawashima et al. 2010). In addition to CPC targeting, shugoshin has a crucial role in protecting cohesin from the prophase dissociation pathway (Salic et al. 2004; Kitajima et al. 2005; McGuinness et al. 2005), which may lead to the enrichment of cohesin and thereby the enrichment of Haspin and H3-pT3 at centromeres. This will further promote the centromeric localization of the shugoshin-CPC, thus constructing a positive-feedback loop between cohesin and shugoshin at centromeres. In fact, localization interdependencies are observed not only between shugoshin and the CPC but also between shugoshin and cohesin in several organisms (Hamant et al. 2005; Kiburz et al. 2005; Dai et al. 2006; Resnick et al. 2006; Kawashima et al. 2007; Rivera and Losada 2009; Shintomi and Hirano 2009). Thus, the newly uncovered molecular network centered on cohesin-shugoshin-CPC has a fundamental role in coupling sister chromatid cohesion to chromosome biorientation in eukaryotes (Yamagishi et al. 2010).

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