Published in final edited form as:
Nat Rev Mol Cell Biol. 2012 December ; 13(12): 789–803. doi:10.1038/nrm3474.

The Chromosomal Passenger Complex (CPC): From Easy Rider to the Godfather of Mitosis

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Preface

Successful cell division requires the precise and timely coordination of chromosomal, cytoskeletal and membrane trafficking events. These processes are regulated by the competing actions of protein kinases and phosphatases. Aurora B is one of the most intensively studied kinases. In conjunction with the proteins INCENP, Borealin (also known as Dasra) and Survivin, it forms the Chromosomal Passenger Complex (CPC). This complex targets to different locations at differing times during mitosis,, where it regulates key mitotic events: correction of chromosome-microtubule attachment errors, activation of the spindle assembly checkpoint, and construction and regulation of the contractile apparatus that drives cytokinesis. Our growing understanding of the CPC has seen it develop from a mere passenger riding on chromosomes to one of the main controllers of mitosis.

Introduction

The chromosomal passenger hypothesis proposed that diverse mitotic events, including chromosome segregation and cytokinesis, could be coordinated by a set of proteins that localized to chromosomes during early mitosis, before transferring to the spindle midzone during late mitosis[1]. Interest in these proteins took off when it was realized that INCENP (Inner Centromere Protein), the first passenger protein identified[2], formed a complex with Aurora B kinase, a protein essential for accurate cell division[3, 4]. It is now known that the chromosomal passenger complex (**CPC**) is composed of four subunits: the enzymatic component Aurora B and the three regulatory and targeting components INCENP, Survivin and Borealin (also known as Dasra)[5–7] (Figure 1A).

Dynamic changes in CPC localisation throughout mitosis ensure the effective and spatially restricted phosphorylation of substrates involved in chromosome condensation, correction of erroneous kinetochore-microtubule attachments, activation of the spindle assembly checkpoint (SAC), and cytokinesis. When INCENP, Survivin or Borealin localisation and/or function are perturbed, the others do not localize properly, Aurora B activity is diminished and proper cell division is compromised[8–12]. A fifth putative passenger protein, the GEF (Guanine Exchange Factor) TD-60/Rcc2[13] does not stably associate with the CPC and its function in mitosis is not yet understood.

Here we discuss current knowledge concerning the structure, activation, localisation and targets of the CPC in mitosis, focusing on the regulation of the complex by other cellular

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activities and revealing how this regulation changes as mitosis progresses. Due to space constraints, we will not cover the functions of the CPC in meiosis. Our aim is to show how this critical signaling module is integrated structurally and mechanistically with the global cell cycle machinery, and with the intricate structures at kinetochores and the central spindle.

Composition and Structure of the CPC

Biochemical and structural studies reveal that the CPC is composed of a **localisation module** and a **kinase module** linked together by the central region of INCENP (Figure 1A)[5, 14, 15]. The localisation module is composed of the INCENP N-terminus, Survivin and Borealin associated with each other in a three-helix bundle[15, 16]. This bundle links the baculovirus IAP repeat (**BIR**) domain of Survivin[17, 18] and the C-terminus of Borealin, both of which are required for localisation to the centromere of chromosomes[16, 19–22]. This module is also required for localisation of the complex to the mitotic spindle and anaphase midbody, though the mechanism is poorly understood. The **kinase module** is composed of Aurora B bound to the highly conserved **IN-BOX** at the INCENP C-terminus[3].

AURORA B KINASE

Aurora B belongs to a highly conserved family of Serine-Threonine kinases first discovered in *Drosophila melanogaster*[23]. This family has three members: Aurora A, which functions at the mitotic spindle poles; Aurora B, which functions at the centromere, anaphase spindle and cell cortex; and Aurora C, which resembles Aurora B, but regulates meiosis and mitosis during early development[24]. Together with **Cyclin-dependent kinases** (Cdks) and **Polo-like kinases** (Plks) the Aurora kinases are master controllers that coordinate individual processes during cell division with the **checkpoints** that determine the overall progression of mitosis and meiosis[24, 25].

Aurora B activity is tightly regulated at multiple levels, including INCENP-binding, localisation, posttranslational modification and degradation. INCENP acts analogous to a cyclin in binding and activating Aurora B. It also contributes to the localisation and spatial regulation of the kinase. Aurora B activation is discussed in detail in the following section.

INCENP

INCENP, the platform on which the CPC assembles, was discovered in a monoclonal antibody screen for novel components of the mitotic chromosome scaffold[2]. The INCENP N-terminus is required for CPC localisation to centromeres[26]. INCENP residues 1–58 form a triple-helix bundle with Borealin and Survivin that is required for localisation to the centromere, anaphase spindle midzone and telophase midbody[12, 16, 26, 27]. INCENP also binds heterochromatin protein 1 (HP1)[26, 28, 29]. This is important for CPC localisation during interphase (see below).

INCENP is regulated by Aurora B and Cdk1, the cyclin-CDK complex that controls entry and exit from mitosis (Figure 1B). In budding yeast, phosphorylation of the INCENP homolog Sli15 by CDK and the Aurora B homolog Ipl-1 prevents the CPC from associating with the spindle midzone before anaphase[30, 31]. Yeast CDK also phosphorylates 6 sites on Sli15 that are required to activate the SAC, a signaling cascade that monitors chromosome attachment to the mitotic spindle and delays anaphase onset in response to unattached or tensionless kinetochores thus preventing chromosome segregation until proper kinetochore-microtubule attachments are formed[32]. Dephosphorylation of these sites at the onset of anaphase is necessary to prevent reactivation of the SAC when sister chromatids separate at anaphase onset and their kinetochores are no longer under tension[32, 33].

Phosphorylation of INCENP by CDK1 is required for PLK1 localisation to the inner centromere in mice[34], though this mechanism is not conserved in *D. melanogaster*[35]. However, INCENP and Aurora B are required for the activation of PLK1 at the inner centromere via phosphorylation of a residue on the T-loop of PLK1 in both *Drosophila* (Thr182) and humans (Thr210)[35].

Survivin

Survivin is composed of an N-terminal Zn^{2+}-coordinated BIR domain and a C-terminal helical extension. In vertebrates, mutations within the BIR domain prevent recruitment of the CPC to the centromere but do not perturb its localisation from anaphase onward[19, 36]. In *D. melanogaster*, a different mutation within the BIR domain prevents CPC localisation to the anaphase spindle midzone without affecting its centromeric localisation[37], indicating a potential contribution of the BIR domain to CPC localisation during anaphase.

Survivin was originally described as an inhibitor of apoptosis protein (IAP) that accumulated in G2 cells and was proposed to negatively regulate cell death in mitosis[38]. There is a vast literature on the involvement of Survivin in cell death regulation, however analysis of Survivin-null mutants in yeasts and vertebrates[19, 39, 40] has failed to identify significant abnormalities in cell death responses. Survivin has a nuclear export signal[41], and it has been suggested that Survivin in the cytoplasm may inhibit cell death while Survivin in the nucleus or associated with the CPC regulates mitosis[42].

Purified Survivin forms a “butterfly-shape” homodimer in solution[43–45]. Within the CPC however, the Survivin dimerization surface is contacted by Borealin[15, 16], blocking Survivin homodimer formation. A small molecule inhibitor, S12, disrupts CPC function during mitosis by binding a pocket near this dimerization interface and is being explored as an anti-cancer drug[46].

Survivin is phosphorylated in vitro by Aurora B[47, 48], CDK1[49, 50], PLK1[51, 52] and Casein Kinase II (CK2)[53] (Figure 1B). CDK phosphorylation of Thr34 was reported to be essential to prevent spontaneous apoptosis[54, 55], however DT40 cells expressing a survivin mutant in which this residue is substituted by an Alanine grow normally[19]. CK2 phosphorylation of Survivin appears to regulate interactions between Survivin and Borealin[53], and merits further study.

Survivin ubiquitylation regulates the binding dynamics of the CPC at the centromere. Lys 63-linked ubiquitylation mediated by Ufd1 promotes the association of Survivin with centromeres, whereas de-ubiquitylation mediated by hFAM is required for its dissociation[56]. In addition, the budding yeast homologue of Survivin, Bir1 is regulated by SUMOylation[57]

BOREALIN

Borealin (also known as Dasra) was discovered in two independent studies of proteins that associate with mitotic chromosomes and chromosome scaffolds[11, 58].

The N-terminus of human Borealin participates in the three-helix bundle that makes up the CPC localisation module[16]. The yeast homologs of Borealin (Nbl1 in budding and fission yeast) are very small compared to their vertebrate counterparts but retain the region involved in three-helix bundle formation, suggesting this is an evolutionarily conserved function of Borealin[59, 60]. Sequence alignments performed after identification of the yeast proteins revealed that C. elegans CSC-1[61] is also a Borealin homolog. Thus, the four-member CPC is widely conserved across animalia and fungi[59]. In addition, many species contain paralogues of CPC components which may regulate the CPC in certain developmental contexts[11, 58, 62–65].

Essentially all Survivin in mitotic cells is associated with Borealin[11]. Borealin-Survivin forms a soluble 1:1 complex, however, in the presence of an INCENP N-terminal peptide, a 1:1:1 complex forms[16, 66]. The **central region** of Borealin (aa110–207) interacts with the ESCRT-III subunit Shrb/CHMP4C in *Drosophila* and humans[67, 68]. This conserved interaction is involved in regulating abscission, as discussed below.

Like other members of the CPC, Borealin is regulated by phosphorylation at multiple sites[69–73] (Figure 1B). Phosphorylation of Borealin by Cdk1 is required for interactions with Shugoshin 1 and 2 that are important for targeting the CPC to centromeres[73]. The Borealin **C-terminus** contains a **dimerization interface** that has been implicated in regulating its stability[72]. Phosphorylation of Thr230 on this interface by Mps1 kinase modulates Borealin dimerization and also Aurora B activity[66]. It was suggested that this modification is required for the CPC to function efficiently in error correction and chromosome alignment[70]. It is important to note, however, that Mps1 has a role in those processes which is independent of regulating Aurora B activity[74].

Borealin is SUMOylated in a RanBP2-dependent manner early in mitosis[75], and a reconstituted RanBP2/RanGAP1*SUMO1/Ubc9 complex has E3 ligase activity on the Borealin/Survivin/INCENP complex[76]. At anaphase onset the SUMO isopeptidase SENP3 catalyzes the removal of SUMO2/3 from Borealin. The function of this Borealin SUMOylation is unknown.

Mechanisms of Aurora B activation

Aurora B activation is a complex, multi-step process. Aurora B initially binds the IN-BOX of INCENP, which activates low levels of kinase activity. This enables Aurora B to phosphorylate a C-terminal TSS (threonine – serine –serine) motif on INCENP[10, 77] as well as Thr232 in the T-loop of its kinase domain, resulting in full activation of Aurora B (Figure 2A). Both of these phosphorylations likely occur in trans[78]. This explains why Aurora B activity is stimulated by increasing the local density of the CPC by adding chromatin to *Xenopus laevis* egg extracts[79] or targeting INCENP to an ectopic locus on chromosomes in vivo[80]. Microtubules can also activate Aurora B[79, 81–83] possibly through local enrichment of the CPC. This activation is stimulated by TD-60[82]. The density-dependent activation of Aurora B partially explains how kinase activation is coupled to CPC localisation at the inner-centromere and spindle midzone (Figure 2B).

Other kinases also regulate Aurora B activity. Full activation of human Aurora B requires phosphorylation of Ser311 by Chk1 kinase, best known for its role in the DNA damage checkpoint[84] (Figure 1B). Interestingly, Chk1 is localized to kinetochores during prometaphase[85] and Ser311-phosphorylated Aurora B is only detectable adjacent to the kinetochore. The kinetochore-proximal pool of Aurora B could function in Plk1 activation[35] and/or regulate microtubule binding at the kinetochore. Interactions between the CPC and Plk1 are complex, and full Aurora B activation is also promoted by Survivin phosphorylation by Plk1[52].

In C. elegans, Tousled-like kinase (TLK-1) is reportedly phosphorylated by Aurora B, which in turn triggers TLK-1 to further activate Aurora B kinase activity in an INCENP-dependent manner[86]. TLK-1 is also required for Aurora B localisation to the spindle midzone microtubules during late mitosis[87].

Ubiquitylation and SUMOylation of Aurora B also modulate its localisation and activity[88–90]. Mono-ubiquitylation of Aurora B by Cullin 3 (Cul3) E3 ubiquitin ligases regulates its removal from chromatin and promotes relocalisation of the CPC in anaphase[88]. SUMOylation of Aurora B within the kinase domain is required for correct mitotic

progression[89, 90]. Aurora B activity during mitotic exit is ultimately terminated when the kinase is degraded by the proteasome[91, 92].

Regulation of Aurora B activity

Phosphorylation of Aurora B substrates must be regulated for proper cell division. This requirement is best understood during early mitosis when Aurora B phosphorylates multiple substrates at the kinetochore to destabilize and correct erroneous kinetochore-microtubule attachments. Replacing the Aurora B phosphorylation sites on one such protein with phosphomimetic residues prevents the formation of stable kinetochore-microtubule attachments[93], indicating Aurora B phosphorylation must be coordinated with microtubule attachment status to balance error correction and chromosome segregation. Indeed, phosphorylation of kinetochore substrates is most prominent when kinetochores are not attached to microtubules and is reduced upon microtubule attachment[94–97]. How this regulation is achieved is the subject of intensive research.

A key aspect regulating this attachment-sensitive phosphorylation is recruitment of antagonistic phosphatases. During early mitosis, protein phosphatase I (PP1), the major counteracting phosphatase for Aurora B, is recruited to the outer kinetochore through Spc105/Blinkin/KNL1[95, 98], while its recruitment to bulk chromatin, mediated by the PP1 targeting subunit Repo-Man, is suppressed[99, 100]. Other proteins implicated in targeting PP1 to the kinetochore include Sds22[101], Kinesin-7 (CENP-E in human)[102], kinesin-8 (in fission yeast)[103], and Fin1 (in budding yeast)[104].

PP1 is not the only phosphatase that opposes Aurora B. The B56 subunit of PP2A, which stabilizes kinetochore-microtubule attachments by counteracting Aurora B phosphorylation, is enriched in the inner centromere in the absence of microtubule attachment, but dissociates from it upon bipolar attachment[105].

It has been proposed that tension-mediated stretching of centromeric chromatin shifts substrates away from Aurora B in the inner centromere towards phosphatases in the kinetochore[106–108]. Indeed, substrates at the inner centromere are less readily dephosphorylated upon microtubule attachment than those at the outer kinetochore[94, 109]. A problem for this model, however, is that even after the establishment of bipolar attachment, the distance between the inner kinetochore and the outer kinetochore rapidly fluctuates between full extension and relaxation[110].

Additional mechanisms control substrate recognition by Aurora B. During spindle assembly in *X. laevis* egg extract, the CPC must bind to both chromatin and microtubules[83]. The requirement for chromatin-binding, but not microtubule-binding, can be bypassed by artificially activating Aurora B. This indicates that CPC-microtubule binding promotes spindle assembly by a mechanism other than Aurora B activation, possibly by facilitating the recognition of critical substrates[83]. Substrate recognition can also be controlled by additional modifications of Aurora B substrates, including acetylation and phosphorylation of histone H3[82, 111] and methylation of Dam1[112]. Similar mechanisms may regulate phosphorylation of kinetochore substrates.

Phosphorylation of Aurora B substrates may also be regulated on a global scale during mitosis (Figure 3). Aurora B activity can be measured at a specific cellular location using Förster resonance energy transfer (FRET) sensors. A FRET sensor targeted to microtubules reveals that during anaphase, levels of Aurora B phosphorylation form a spatial gradient that is highest at the spindle midzone[80, 81, 109, 113] and decreases over a micron-scale distance surrounding this location[113]. Augmenting this gradient perturbs the function of the CPC during anaphase, suggesting it is functionally significant[113]. A phosphorylation gradient is

not obvious during early mitosis, however, treatment of cells with low dose Aurora B inhibitors reveals a gradient centered on chromosomes that decreases towards the spindle poles[113]. Similarly, a gradient along chromosomes can be seen temporarily after transient exposure to an Aurora B inhibitor [80]. While the function of these gradients is still unclear, these observations suggest that phosphorylation of Aurora B substrates is regulated on multiple scales.

The CPC in interphase and early mitosis

Few studies have explored the CPC during interphase because disrupting the complex produces obvious and dramatic defects during mitosis. However, recent work suggests that transient inhibition of Aurora B in interphase causes chromosome mis-segregation in the subsequent mitosis[114], suggesting that the CPC performs essential functions prior to mitotic entry.

CPC localisation during interphase

In vertebrate cultured cells, the CPC is first visualised on pericentromeric heterochromatin during late S phase[2, 114–117]. CPC targeting to heterochromatin involves HP1 binding to a PxVxL/I motif on INCENP[26, 28, 29] (Figure 4A). An HP1-binding site mutant of INCENP does not localize to heterochromatin during interphase but causes no mitotic defects in HeLa cells[29]. A fraction of HP1 is closely associated with centromeres in interphase due to interactions with Mis14, a component of the Mis12 kinetochore complex involved in microtubule binding by the KMN network[118]. Paradoxically, although the Mis14-HP1 interaction occurs solely during interphase, it is important for centromeric enrichment of the CPC in HeLa cells during mitosis[118]. Thus, the Mis14-HP1 interaction may facilitate CPC recruitment to the inner centromere prior to mitosis.

As cells enter mitosis, Aurora B phosphorylates histone H3 at Ser10 (H3S10ph)[119, 120]. This reportedly disrupts the HP1 binding to the adjacent trimethylated Lys9 (H3K9me3)[121, 122] and may function as a switch to shift from HP1-mediated recruitment of the CPC used during interphase to the mitotic modes of recruitment discussed below (Figure 4A). H3 Ser10 phsphorylation requires POGZ (pogo transposable element-derived protein with zinc finger domain), which is also required to remove HP1 and the CPC from chromosome arms[28], promoting their enrichment at the inner centromere.

CPC localisation in early mitosis

Centromeric enrichment of the CPC during mitosis is independent of DNA sequence[123], but instead requires the mitosis-specific phosphorylation of two histone tails: histone H3 Thr3 (H3T3ph) by Haspin kinase[124] and histone H2A Thr120 (H2AT120ph) by kinetochore-associated Bub1 kinase[22, 125] (Figure 4). H3T3ph is concentrated along the length of chromosomes between paired sister chromatids, but is most prominent at the inner centromere[22, 124, 126]. Haspin activity in this region depends on the cohesin regulator Pds5 and Swi6/HP1 in fission yeast[22]. H2AT120ph is enriched in the kinetochore-proximal region of the centromere, as Bub1 is a kinetochore-associated protein[22, 127], recruited by KNL-1. Maximal concentration of the CPC occurs at the inner centromere where these two histone modifications overlap[22] (Figure 4B).

The CPC binds to H3T3ph through the BIR domain of Survivin, which directly interacts with the free N-terminus and adjacent three amino acids of the H3 tail. This interaction is structurally analogous to the recognition of the N-terminus of the pro-apoptotic factor SMAC/Diablo by the anti-apoptotic factor XIAP[15, 128]. However, the binding affinity of Survivin to a hydrophobic SMAC peptide is 25-fold weaker than to a H3T3ph peptide[128], potentially explaining why Survivin knockouts in yeast and vertebrates lack an apoptotic

phenotype[19, 39, 40]. The phospho-specificity of Survivin can be regulated by pH[65], suggesting that Survivin-H3 interactions *in vivo* may be influenced by the local environment.

Phosphorylation of H2A Thr120 by Bub1 in humans (H2A Ser121 in fission yeast) recruits Shugoshin-like proteins (Sgo1 and Sgo2), which interact with either Borealin (in humans) or Survivin (in fission yeast) that has been phosphorylated by CDK1[73, 125]. It had previously been shown that the *D. melanogaster* homologue of Shugoshin, MeiS332 is interdependent with the CPC for localisation to centromeres[129]. The structural basis for Shugoshin interactions with H2AT120ph is unknown. Interestingly, it was recently discovered that the Survivin BIR domain can bind to the N-terminus of human Sgo1 in vitro[15]. This suggests a crosstalk between CPC recruitment pathways, the functional significance of this interaction remains to be tested. In *Drosophila*, NHK-1/VRK1 was also identified as a kinase for H2A T119 (corresponding to human H2A T120)[130]. However NHK-1-mediated phosphorylation of H2A is suppressed during mitosis by Polo kinase in *Drosophila* cells[131].

Aurora B kinase activity is involved in several feedback loops that facilitate the rapid and spatially restricted recruitment of the CPC to the centromere. First, Aurora B-dependent Haspin phosphorylation facilitates H3T3 phosphorylation[132], thereby creating the substrate for Survivin binding. Second, the CPC contributes to centromeric recruitment of Shugoshin proteins (and also Bub1 in *X. laevis*)[129, 133–136], which in turn are required for CPC localisation at centromeres[73, 125]. Third, Aurora B-dependent phosphorylation at H3S10 dissociates HP1 from H3K9me, facilitating the dissociation of the CPC from chromosome arms and its enrichment at centromeres[28]. Furthermore, since CPC localisation is dependent on cohesin and Pds5[22, 137, 138] likely through localisation of Haspin, Aurora B-mediated removal of cohesin from chromosome arms during prophase may restrict Haspin localisation and promote centromeric enrichment of the CPC.

Consistent with these observations, Aurora B inhibition can impair CPC localisation at centromeres[8, 10, 28, 97, 116, 132, 139], though this phenotype is not universal[89, 140, 141].

Although localisation to inner centromeres is one of the defining features of the CPC, paradoxically, lethality of chicken DT40 cells lacking the Survivin gene is rescued by a Survivin BIR mutant that is missing residues critical for binding the H3 N-terminal peptide and cannot accumulate at centromeres[19]. Thus, at least in DT40 cells, accumulation of the CPC at centromeres may not be essential for CPC function in mitosis.

Roles of the CPC in early mitosis

Aurora B catalyses one classic epigenetic mark of mitotic chromosomes, phosphorylation of histone H3 on serine 10 (H3S10ph)[119, 120]. INCENP depletion causes a substantial drop in H3S10ph levels in vitro and in vivo[8, 142]. The relationship between H3S10ph and mitotic chromosome compaction has been extensively explored, but while this modification may contribute to chromosome compaction during anaphase in budding yeast[143] its role in higher eukaryotes remains to be established.

Mitotic Chromosome Structure

One proposed function of the CPC in mitotic chromosome compaction is regulating the binding of condensin, a multimeric protein complex that is essential for the maintenance of mitotic chromosome architecture[137, 144–147]. In fission yeast, Aurora B-dependent phosphorylation of the kleisin Cnd2 promotes condensin recruitment to chromosomes[148, 149]. Phosphorylation of the human kleisin protein CAP-H by Aurora B promotes efficient association of condensin I, but not condensin II, to mitotic chromosomes

in human cells[145, 146, 149]. Phosphorylated kleisins can bind to the N-terminal tail of histone H2A, which may contribute to condensin recruitment[148, 149]. Indeed, chromosome condensation is impaired in yeast CPC mutants[137, 149–151]. This effect is much less pronounced in vertebrates.

Regulation of kinetochore-microtubule attachments

Accurate chromosome segregation requires kinetochores to establish correct, bioriented attachments to spindle microtubules. Classic experiments using microneedles to manipulate meiotic chromosomes in grasshopper spermatocytes first revealed that kinetochore-microtubule attachments are stabilized by tension[152]. The CPC, via Aurora B activity, plays a key role in regulating microtubule attachments in response to defective tension. Aurora B inhibition or Borealin depletion causes a dramatic increase in both **merotelic** and **syntelic** attachments[11, 153–156]. The CPC is required to destabilize and repair these erroneous attachments[5, 6, 25].

The kinetochore captures dynamic microtubules through the ability of the KMN network to support load-bearing attachments to microtubule plus ends[157]. Aurora B regulates the stability of KMN-microtubule attachments. The unstructured, positively charged N-terminal tail of Ndc80, which interacts with the negatively charged C-terminal tails of tubulin[158–162], is phosphorylated on multiple sites by Aurora B. This weakens its microtubule-binding affinity in vitro[96, 158, 160, 163, 164]. Phosphomimetic Ndc80 mutants fail to support stable kinetochore-microtubule attachments[93], while nonphosphorylatable mutants hyperstabilise them, resulting in accumulation of syntelic and merotelic attachments in cells[96, 158]. Additional phosphorylation of components of the KNL-1 and Mis12 complexes, results in a synergistic decrease in microtubule binding affinity, allowing Aurora B to exquisitely control kinetochore-microtubule attachments [94, 165].

Aurora B regulates additional kinetochore proteins that cooperate with the KMN network to bind microtubules. In fungi, the ring-forming Dam1 complex forms a phospho-regulated load-bearing attachment to dynamic microtubules[166]. The Dam1 complex and its interactions with the Ndc80 complex are negatively regulated by Aurora B phosphorylation and constitute the major targets of the CPC for error correction in yeast[167, 168]. In higher eukaryotes, the Ska complex, which is proposed to be a functional analog of the Dam1 complex[169], is also negatively regulated by Aurora B phosphorylation[170].

Aurora B regulates the localisation and activity of the kinesin 13 MCAK, which functions as an important microtubule depolymerase. Interestingly, Aurora B phosphorylation recruits MCAK to the centromere by facilitating its interaction with centromeric Sgo2[171–174] while simultaneously suppressing both the MCAK microtubule-depolymerizing activity[171–175] and its accumulation at microtubule plus ends[176]. Why recruit MCAK to the centromere only to inhibit its activity? One possible explanation is that suppressing MCAK stabilises non-kinetochore microtubules near chromosomes to promote spindle assembly[58, 79, 176, 177]. An alternative hypothesis is that inner centromere Kin-I stimulator (ICIS), which can reverse Aurora B-mediated inhibition of the microtubule depolymerase Kif2a at centromeres [175], might do the same for MCAK at the centromere but not the kinetochore. This could allow MCAK to destabilize microtubules participating in merotelic attachments, while stabilizing k-MT attachments at the kinetochore. Aurora B-dependent recruitment of protein phosphatase 2A (PP2A) to Sgo2 may also facilitate dephosphorylation of MCAK and other kinetochore regulators to promote stable microtubule attachment [105, 174]. In addition to its regulation of MCAK, Aurora B also regulates microtubule stability by inhibiting the microtubule-stabilizing activity of the formin mDia3 at kinetochores[178].

Spindle Assembly Checkpoint Control

The SAC delays sister chromatid separation and cell cycle progression until all kinetochores attain bipolar microtubule attachments - for review, see[7].

The CPC was initially implicated in the SAC in budding yeast where it was found that the Aurora B yeast homologue Ipl1 is required for the checkpoint under conditions that permit microtubule attachment but prevent tension[179]. It was suggested that the CPC might create unattached kinetochores that are recognized by the SAC pathway[180]. Similarly, inhibition of Aurora B impaired the SAC in vertebrate tissue culture cells exposed to taxol, which causes a loss of kinetochore tension[19, 140, 141, 153, 181].

The CPC is required for all aspects of SAC activation and maintenance in fission yeast and in *X. laevis* egg extracts[133, 150, 182, 183]. Aurora B activity promotes kinetochore recruitment of key SAC components Mad1, Mad2, Bub1, BubR1, Mps1 and CENP-E (kinesin-7) in *X. laevis* and human cultured cells[133, 140, 184–186]. Tethering Mps1, an upstream activator of the SAC, to the kinetochore can bypass the checkpoint requirement for Aurora B in human cells, suggesting that a primary function of Aurora B for the SAC may be Mps1 recruitment[185, 187].

Recent studies in human cells further established the role of Aurora B in SAC activity independently of its capacity to destabilise kinetochore-microtubule attachments[186, 187]. Artificial targeting of Mad1 to the kinetochore revealed that Aurora B and Mps1 contribute to SAC maintenance in a step after recruitment of Mad1 and Mad2 to the kinetochore[187]. Reduced requirement of Aurora B in SAC activation in response to unattached kinetochores in budding yeast and human cells may be explained by the existence of an Aurora B-independent mechanism[188].

Much recent interest focuses on silencing of the SAC to allow chromosome segregation and mitotic exit, since the SAC is normally activated in every cell as it enters mitosis. Recruitment of PP1 to the kinetochore by KNL-1/Spc105/Blinkin is required for checkpoint silencing, but can be bypassed if Aurora B activity is compromised[103, 189, 190]. Thus, Aurora B promotes SAC activation whereas PP1 promotes SAC silencing in several ways. First, PP1 may antagonize the Mps1-dependent phosphorylation of KNL-1 by dissociating the checkpoint components Bub1 and Bub3[191–193]. Second, PP1 reverses the Aurora B-dependent phosphorylation of ZWINT-1 in humans and this promotes the dynein-mediated stripping of SAC components from the kinetochore[194]. Lastly, PP1 dephosphorylation of CENP-E also helps stabilize kinetochore microtubule attachments[102].

The CPC in late mitosis

The CPC's journey that started on the chromosomes finally comes to an end at the central spindle and the midbody, where it executes its functions in late mitosis including anaphase chromatid compaction, anaphase spindle stabilization (or destabilization in budding yeast) and cytokinesis. Removal of the CPC from chromosomes is also required to reform the nucleus and facilitates mitotic exit.

CPC relocalisation during anaphase

At the metaphase-anaphase transition a population of the CPC leaves the inner centromeres and transfers to **central spindle** microtubules (Figure 5A). Slightly later, the CPC also localises to the equatorial cortex, the region of the plasma membrane where the cytokinetic machinery is assembled[195]. Relocalisation of the CPC is coupled to cell cycle progression and is facilitated by three general events: cessation of chromosome targeting, active removal from chromosomes, and targeting to the central spindle. CPC relocalisation is mediated by a

decrease in Cdk1 activity and requires both phosphatase and Aurora B kinase activity[31, 141, 196].

Recruitment of the CPC to chromosomes is suppressed in late mitosis following the dephosphorylation of H3T3ph at anaphase onset[20, 197, 198]. Active removal of the CPC from chromosomes may also facilitate relocalisation to the spindle midzone. Aurora B is ubiquinated by two midzone-associated E3 ubiquitin ligase complexes, Cul3-KLHL9-KLHL13[88] and Cul3-KLHL21[199]. Ubiquinated Aurora B is subsequently removed from chromosomes by the AAA+ ATPase Cdc48/p97 and its adaptor proteins Ufd1-Npl4[200, 201]. This process contributes to the level and distribution of the CPC on chromosomes prior to anaphase and facilitates chromosome decondensation and nuclear reformation at the end of mitosis[200].

Transfer of the S. cerevisiae CPC to the spindle requires dephosphorylation of CDK sites on Sli15/INCENP by cdc14 phosphatase[31, 32]. Fission yeast cdc14/Clp1 binds Nbl1/Borealin[60]. Although dephosphorylation of a Cdk1 site in human INCENP is also required for translocation[196], the role of human Cdc14 phosphatase family members in mitotic exit is unclear.

CPC release from chromosomes and targeting to the central spindle requires the interaction of INCENP and Aurora B with MKLP2, a kinesin-6 that binds microtubules at the central spindle[196, 202–204] (Figure 5A). The CPC and MKLP2 only interact during anaphase when CDK1-mediated inhibitory phosphorylation is removed[196]. The CPC and MKLP2 are interdependent on each other for their localisation in most species, though not in Dictyostelium[205]. In budding yeast, which lacks Mklp2, Aurora B/Ipl1 is targeted to the spindle midzone at anaphase by the microtubule plus-end tracking protein Bim1 (the yeast homologue of EB1). This interaction is negatively regulated prior to anaphase by CDK phosphorylation of Aurora B[206]. In addition, Aurora B kinase activity[141], DNA topoisomerase II[207] and INCENP phosphorylation at Ser197 by an unidentified kinase[208] are also required for midbody localisation of the CPC.

Formation and stabilization of the spindle midzone

The central spindle is an organized structure formed from the bundled plus-ends of antiparallel microtubules. INCENP was the first protein shown to localise specifically to the central spindle during anaphase[2], and this structure is an important site of CPC action.

Central spindle formation requires the action of the microtubule bundling protein PRC1[209], the kinesin KIF4[210] and centralspindlin; a heterotetrameric complex formed by MKLP1 (a kinesin-6 protein) and MgcRacGAP (a Rho GAP)[211–213]. The CPC is required for centralspindlin localisation to the spindle midzone[4] (Figure 5A). Phosphorylation of MKLP1 by Aurora B promotes centralspindlin clustering and increases its microtubule-bundling activity, thereby stabilizing the central spindle[214]. The CPC also binds to PRC1 and KIF4 later during cytokinesis[215] though the function of these interactions is unclear.

Roles of the CPC in Cytokinesis

Cytokinesis requires the assembly and constriction of an equatorial contractile ring composed of actin, myosin and other cytoskeletal filaments. The site of contractile ring assembly and the timing of its constriction are coordinated closely with chromosome segregation to allow accurate partitioning of the genome and formation of the two daughter cells. The CPC plays an important role in coordinating and regulating these processes through its roles in central spindle formation, regulation of furrow ingression and abscission[5, 7, 24] (Figure 5B).

Regulation of contractile ring formation & function

Determining the site of cleavage furrow formation is a classic problem that inspired the elegant experiments of Raymond Rappaport[216]. The RhoA GEF Ect2 is important for this determination, as are the central spindle and astral microtubules [217]. What is less appreciated is that the CPC may have an as-yet unknown function early in contractile ring function. INCENP accumulates at the equatorial cortex in close proximity to the plasma membrane during early-mid anaphase, well before the initiation of furrowing[195] (Figure 5A). It is difficult to see this cortical population of INCENP in cells that remain flat during mitosis, however, where it was analysed, INCENP was shown to precede myosin II concentration at the equatorial cortex[218]. While the function of INCENP at this early stage is not known, it will be interesting to see if the CPC contributes to the early assembly of the contractile ring.

The CPC contributes to contractile ring maturation and constriction through indirect regulation of RhoA, a small GTPase that promotes actin polymerization and myosin II activation (Figure 5). The CPC recruits centralspindlin to the spindle midzone which in turn promotes localisation of the RhoGEF ECT2 to microtubules[219–222]. Additionally, Aurora B phosphorylation of the centralspindlin component MgcRacGAP induces its RhoGAP activity[223, 224]. RhoA is required for the assembly of the contractile ring[225], but a parallel suppression of Rac activity by MgcRacGAP is also thought to contribute[226]. A recent analysis in *C. elegans* indicates that the CPC and MgcRacGAP may function at the relatively late stage of compact contractile ring assembly by regulating actin filament assembly[227].

Aurora B also participates in RhoA regulation through inhibitory phosphorylation of the microtubule-binding GEF-H1[228] (Figure 5A). Phosphorylation of GEF-H1 prevents RhoA loading and activation at the equator but is reversed at the onset of cytokinesis to facilitate contractile ring formation [228]. In this way, Aurora B may prevent premature assembly of the contractile ring.

In addition to its action in regulating RhoA, the CPC has a broader role in regulating cytoskeletal dynamics during cytokinesis. It has been widely assumed that interactions between myosin II and actin filaments shorten the contractile ring during constriction, driving the furrowing of the associated membrane. In Dictyostelium, the INCENP N-terminus interacts with the actin cytoskeleton[205]. Aurora B activity also modulates Myosin binding to the cytoskeleton[215]. This may be via phosphorylation of Myosin Regulatory Light Chain II[229] though this was not confirmed in human cells[215].

The detailed mechanism of contractile ring constriction is not known[217], and other filaments may be involved. One candidate for such filaments are the septins[230], GTP-binding proteins that form ordered rings in the bud-neck of S. cerevisiae[231]. Septins are required for cytokinesis in budding yeast[232], *Drosophila*[233] and humans[234].

In budding yeast, a CPC sub-complex composed of Sli15/INCENP and Bir1p/Survivin regulates septin dynamics in anaphase and cytokinesis[235, 236] (Figure 5B). The interaction between the CPC and septins is also critical for cytokinesis in C. elegans[227]. It will be extremely interesting to see if the CPC regulates cytokinesis through septins in other animals, where Aurora B is known to phosphorylate Septin 1 *in vivo*[237]. Interestingly, S. pombe Ark1/Aurora B functions during cytokinesis but is not essential[60, 150]. This may be because septin filaments are not required for cytokinesis in *S. pombe*[238] as they are in *S. cerevisiae*[232]

A recent quantitative proteomics approach revealed that Aurora B undergoes a dramatic switch in binding partners during mitotic exit[215]. Aurora B activity is required for optimal interactions of a number of microtubule-associated proteins with the cytoskeleton. These

include Keratin-8 and Keratin-18 and the Formin FHOD-1[239], which interacts with the Rac1-GTPase and mediates actin polymerization.

The CPC contributes to furrow ingression by regulating intermediate filament (IF) assembly (Figure 5B). As is the case for the nuclear lamins[240], cytoplasmic IF phosphorylation can lead to reversible filament disassembly. Mutation of an Aurora B phosphorylation site on vimentin leads to the formation of IF bridges in cytokinesis and subsequent multinucleation[241]. Aurora B and Rho (ROCK) kinases also phosphorylate the IF proteins GFAP (Glial Fibrillar Acidic Protein) and Desmin. Mutation of these phosphorylation sites results in defects in filament disassembly in cytokinesis, suggesting that the CPC promotes IF disassembly to facilitate constriction of the contractile ring and allow abscission to occur[242].

Regulation of abscission

Abscission is the fusion of membranes that completes the separation of daughter cells during cytokinesis. Aurora B has been implicated in a checkpoint during cytokinesis that delays **abscission** in response to lagging chromatin in the intercellular bridge, the site of cleavage furrow ingression that connects daughter cells. Known as the abscission checkpoint (or "No-Cut" pathway in yeast where it was discovered)[243], this poorly understood but seemingly conserved checkpoint may prevent chromosome breakage and protect cells from tetraploidization[244].

The abscission checkpoint can also be activated by defects in nuclear pore reassembly during mitotic exit. Depletion of the nucleoporins Nup153 or Nup50 results in a delay in cytokinesis and the formation of cytoplasmic foci of active Aurora B that are not associated with the rest of the CPC subunits[245]. Inhibition of Aurora B permits the completion of cytokinesis, suggesting that in this checkpoint, Aurora B may act independent of the CPCto delay cytokinesis.

The mechanisms by which Aurora B regulates abscission in higher eukaryotes are beginning to emerge. During abscission in *Drosophila* and humans, Borealin binds to Shrb/CHMP4C (Charged multivesicular body protein)[67, 68] (Figure 5B), a component of the Endosomal Sorting Complex Required for Transport III (ESCRT-III). ESCRTs are conserved complexes involved in membrane budding processes. ESCRT-III in particular mediates membrane fission at the end of cytokinesis[246–248]. Borealin binding may facilitate phosphorylation of Shrb/CHMP4C by Aurora B and has been proposed to inhibit its ability to participate in abscission, thereby delaying premature cytokinesis.

Acknowledgments

HF is supported by a National Institutes of Health grant (R01GM075249). Work in the WCE lab is funded by The Wellcome Trust, of which WCE is a Principal Research Fellow [grant number 073915]. The Wellcome Trust Centre for Cell Biology is supported by core grant numbers 077707 and 092076.

GLOSSARY

GEF	guanine exchange factor - enzyme that activates small GTPases by stimulating the release of GDP and allowing the formation of the active GTP-bound form
Spindle midzone	the region of the anaphase spindle, composed of overlapping anti-parallel microtubules from opposite spindle poles, also known as the central spindle

kinetochore	complex protein super-assembly located at centromeres that mediates microtubule attachment and regulates chromosome segregation
BIR (Baculovirus IAP repeat) domain	a Zn^{2+}-coordinated globular domain involved in protein–protein interactions present in all IAP proteins
centromere	specialised chromatin at the primary constriction of mitotic chromosomes that is the site of kinetochore assembly and the focal point for sister chromatid cohesion
midbody	dense structure derived from the remnants of the central spindle during late telophase. It is present in the intercellular bridge that connects daughter cells during cytokinesis
CDKs	cyclin dependent kinases - family of highly conserved Serine-Threonine kinases involved in the regulation of cell cycle progression characterized by their association and regulation by cyclins
Plks	polo-like kinases –first identified in D. melanogaster, they are involved in many aspects of cell cycle regulation including chromosome-microtubule interactions, centrosome duplication
checkpoints	biochemical signaling networks that monitor whether key processes have taken place before allowing progression to the next cell cycle stage
Inner centromere	the region of the centromere located between paired sister chromatids
SUMOylation	posttranslational modification by reversible conjugation of Small Ubiquitin-like Modifier (SUMO) proteins; involved in regulation of the cell cycle, DNA repair, gene expression nuclear transport and protein stability
E3 ligases	enzymes that promote the attachment of ubiquitin or SUMO to a protein, leading to a variety of outcomes, including changes in binding partners, sorting into different subcellular compartments or degradation
Förster resonance energy transfer (FRET)	a method for detecting associations between proteins by measuring the transfer of energy over distances of a few nanometers between fluorescent probes attached to the proteins
KMN network	an important microtubule-binding module of the outer kinetochore formed of the NDC80, MIS12, and KNL1 complexes
condensins	large heteropentameric complexes essential for chromosome architecture that are composed of two structural maintenance of chromosomes (SMC) subunits and three auxiliary non-SMC subunits
kleisin	subunit that bridges the ATPase heads of SMC proteins in SMC complexes, converting them into closed rings
merotelic attachment	a single kinetochore attaches to microtubules from both spindle poles

syntelic attachment	both sister kinetochores attach to microtubules from the same pole
kinesins	superfamily of microtubule associated motor proteins whose functions include the transport of cargo along microtubules and regulation of microtubule dynamics
formins	proteins defined by the presence of a catalytic FH2 [formin homology 2] domain that interact with actin and regulate its polymerization
AAA+ ATPase	ATPases with associated diverse cellular activities- hexameric ATPase that couple ATP hydrolysis to translocation or remodeling of macromolecules in a wide range of cellular processes
DNA topoisomerase II	abundant nuclear enzyme that relieves tolopogical stress in DNA by passing one duplex through another using an ATP-regulated protein gate
GAP	GTPase Activating Protein that activates small GTPases by stimulating them to hydrolize GTP into GDP

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Perspectives

The switching of the CPC from interactions with chromatin and the kinetochore in early mitosis to a role in regulating cytoskeletal events during mitotic exit provides strong confirmation of the original CPC hypothesis[1]. This complex temporally and spatially regulated signaling module can send and receive signals from both chromatin and cytoskeletal components. It can fine-tune highly local protein-protein interactions while simultaneously regulating the global effects of the SAC. Some of the many key questions that remain to be solved include the mechanistic basis for Aurora B kinase activation beyond density-dependent autophosphorylation, the control of substrate recognition, and how the spatial distribution of kinase and phosphatase activities is balanced. Beyond this, the functions of the CPC during interphase remain largely uncharted territory, though initial results are beginning to come in[249]. The journey of discovery is clearly far from over for the CPC.

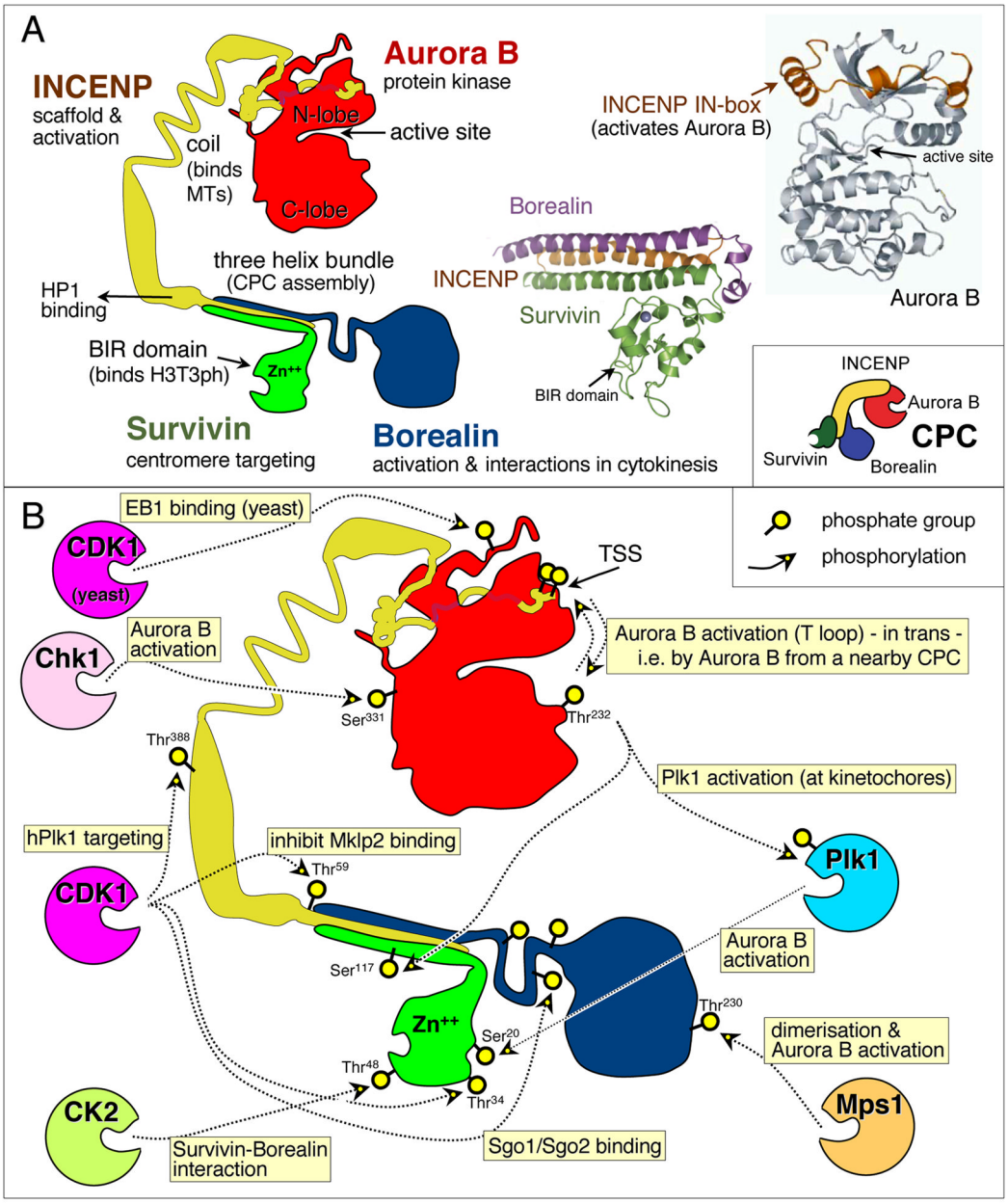

FIGURE 1. Structure and regulation of the chromosomal passenger complex (CPC)

(A, Left) Diagram of the CPC, which is formed by Aurora B, INCENP, Survivin and Borealin. The diagram shows domains and functions for each CPC component. **(Right, upper)**: the crystal structure of full length Aurora B complexed with the INCENP C-terminus (AA790-894) (adapted with permission from ref [78]). **(Right, bottom)**: the crystal structure of the three-helix bundle of INCENP(AA1-58), Borealin (AA10-109) and full length Survivin (adapted with permission from ref [16]).

(B) Phospho-regulation of the CPC showing phosphorylations (yellow spheres) that regulate CPC localisation and function throughout mitosis (pale yellow boxes). Multiple kinases (coloured spheres) phosphorylate the CPC (plain arrows) to regulate CPC function. Additionally, Aurora B activates its own kinase activity by phosphorylating its T-loop (T232) and the INCENP TSS-motif (dotted arrows). Note that some of the depicted

phosphorylations are present throughout mitosis (AurB T232) while others are present at specific stages of mitosis (INC T388, T58).

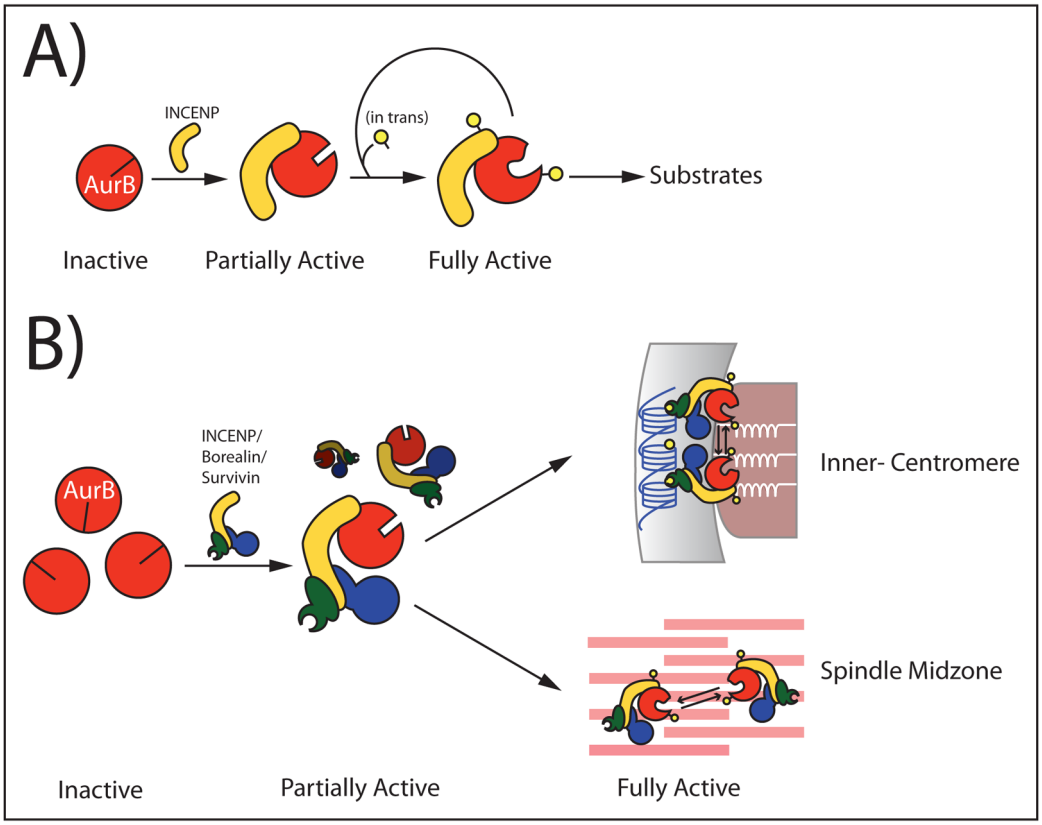

FIGURE 2. Coupling of Aurora B kinase Activation to CPC formation and localisation

(A) Activation of Aurora B (red circle) requires binding to INCENP (yellow) and phosphorylation in a feedback loop. Both of these phosphorylations are catalysed in trans. **(B)** Aurora B activation is coupled to CPC localisation in vivo. The localisation module of INCENP, Survivin and Borealin targets the CPC to histones at the inner-centromere and microtubules at the spindle midzone during early and late mitosis, respectively. Enrichment of the CPC at these locations facilitates auto-phosphorylation in trans, leading to full Aurora B activation.

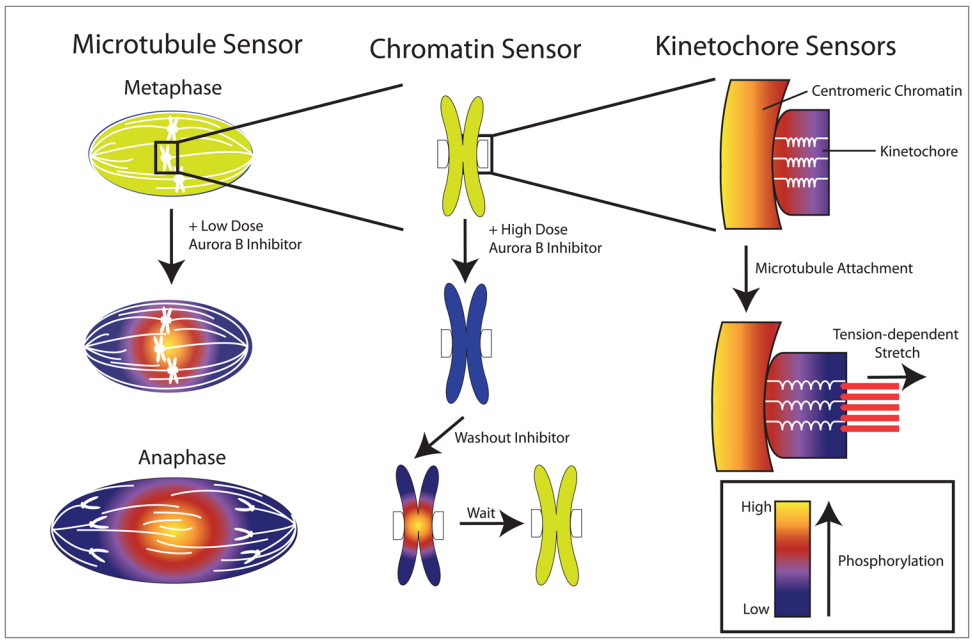

FIGURE 3. The CPC produces spatial gradients of Aurora B activity throughout mitosis

(left) At metaphase, Aurora B phosphorylation (detected with a FRET sensor probe on microtubules) is high throughout the spindle and does not form a gradient. Addition of low dose Aurora B inhibitors reveals a phosphorylation gradient where activity is highest around chromatin and decreases towards the spindle poles. During anaphase, an Aurora B phosphorylation gradient is centred at the spindle midzone.

(middle) At metaphase, Aurora B activity is high along the chromosome (FRET sensor probe on chromatin). A transient pulse of high dose Aurora B inhibitors followed by washout leads to the production of a phosphorylation gradient emanating from the centromere and decreasing along the arms. This gradient rapidly disappears as Aurora B activity recovers.

(right) Unattached kinetochores exhibit a gradient of Aurora B activity emanating from centromeric chromatin towards the kinetochore (FRET sensor probes at various kinetochore locations). Microtubules (red) attach to the kinetochore, generating tension that physically stretches the kinetochore (visualized by stretching of the white kinetochore springs). This change pulls substrates at the kinetochore away from centromeric chromatin, resulting in a decrease in Aurora B activity along the kinetochore. Sensors on centromeric chromatin do not change their relative position upon microtubule binding and remain highly phosphorylated.

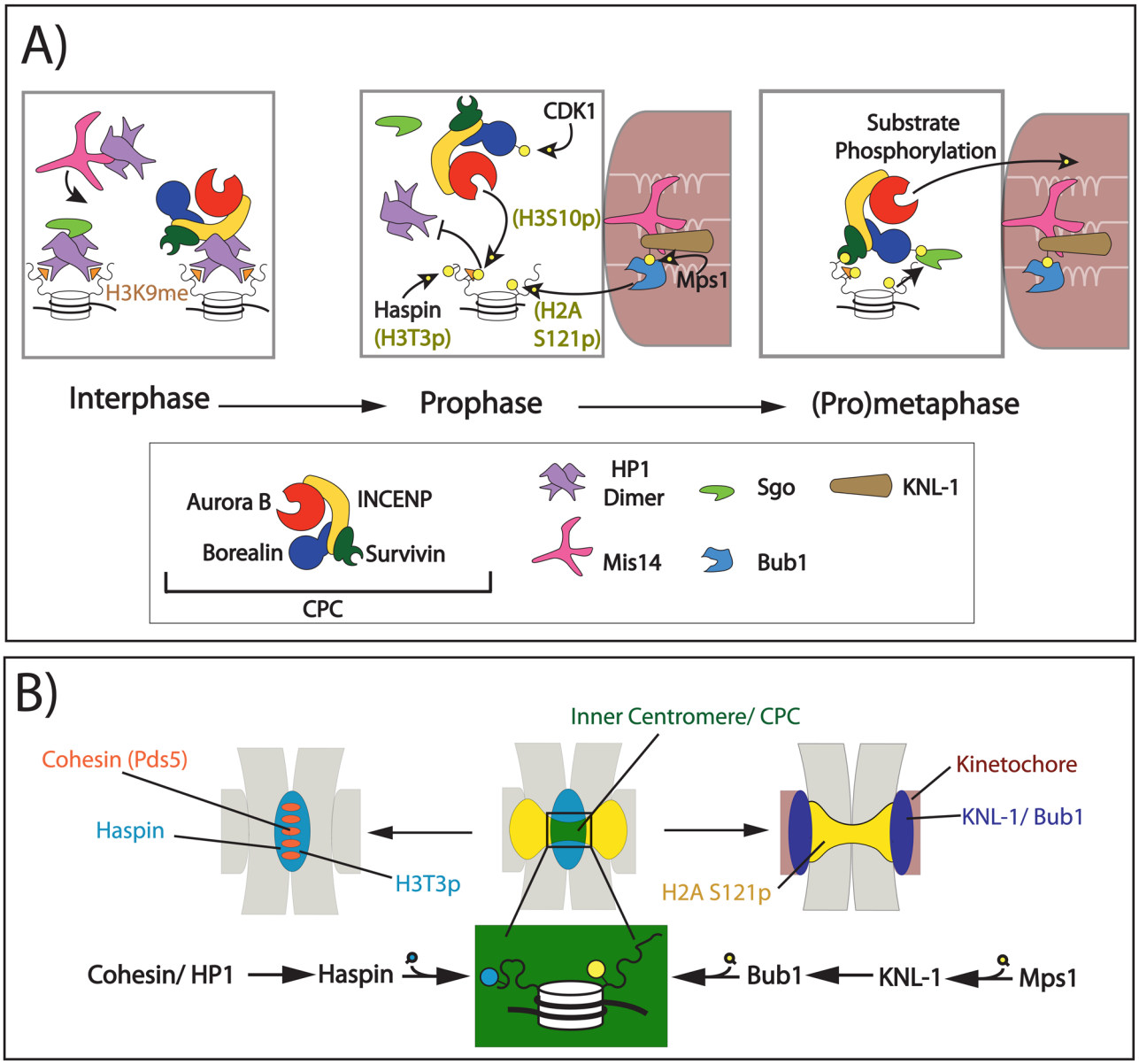

FIGURE 4. Recruitment of the CPC to centromeres during early mitosis

(A) During interphase, the CPC is targeted to heterochromatin through the interaction of INCENP (yellow) with dimeric HP1 (purple). HP1 requires Mis14 (pink) for proper localisation. HP1 also recruits Shugoshin proteins (green) through a similar mechanism. At the beginning of prophase, active Aurora B phosphorylates histone 3 Ser10, displacing HP1 from the adjacent H3K9me mark. A series of kinases then phosphorylate the CPC and centromeric histone tails to recruit the CPC to the inner centromere by (pro)metaphase. The BIR-domain of Survivin (green) binds H3T3ph while Borealin that has been phosphorylated by CDK1 binds shugoshin proteins, which interact with H2A S121ph.

(B) Overlap between H3T3ph (blue) and H2A S121ph (yellow) defines the inner centromere (green) and recruits the CPC. H3T3ph is deposited by Haspin kinase recruited to centromeric chromatin by cohesin/HP1 (Left). H2A S121ph is deposited by Bub1 kinase, which is recruited to the kinetochore (red) by KNL-1 (purple) phosphorylated by MPS1 kinase (Right).

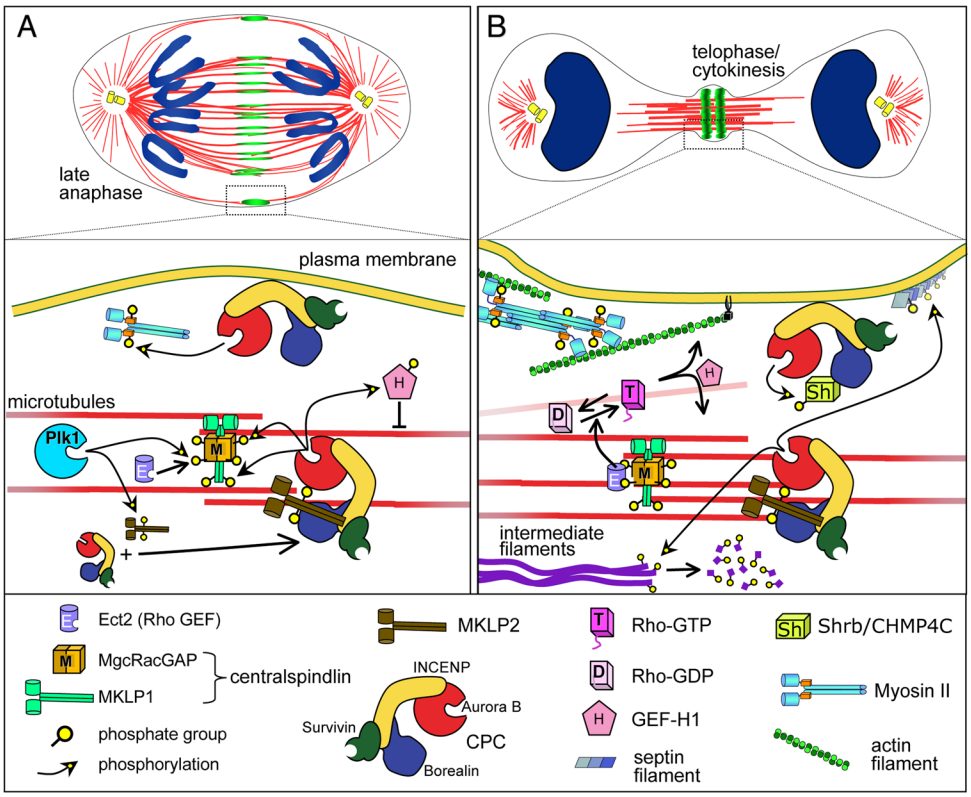

FIGURE 5.

CPC re-localisation and function in mitotic exit

(A) At anaphase onset, the CPC relocalises from chromosomes to the spindle midzone where Aurora B activity promotes centralspindlin recruitment. This stabilizes the spindle midzone and recruits factors important for late telophase/cytokinesis such as the RhoGEF Ect2 (purple). Aurora B also phosphorylates the RhoGEF H1 (pink) to prevent its targeting to microtubules prior to telophase. Additionally, a small population of the CPC accumulates at the cell cortex where cleavage furrow ingression will occur.

(B) During telophase and cytokinesis, Ect2 stimulates the conversion of inactive Rho-GDP to active Rho-GTP. Dephosphorylated Rho GEF now also activates Rho near microtubules. This promotes actin polymerization and contractile ring formation. Aurora B-mediated phosphorylation of Septin filaments (running out of the plane of the page in this diagram) may also be important in contractile ring formation. The CPC promotes disassembly of intermediate filaments (dark purple) that could otherwise obstruct cleavage furrow constriction. In the presence of lagging chromosomes, it also activates the abscission checkpoint to prevent the completion of cytokinesis. Checkpoint activation involves recruitment of the membrane fusion protein Shrb/CHMP4C (yellow square) to Borealin and inactivation of its membrane fusion activity by Aurora B-mediated phosphorylation.