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Establishing Correct Kinetochore-microtubule Attachments in Mitosis and Meiosis

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Abstract

Faithful chromosome segregation in mitosis and meiosis requires that chromosomes properly attach to spindle microtubules. Initial kinetochore-microtubule attachments are often incorrect and rely on error correction mechanisms to release improper attachments, allowing the formation of new attachments. Aurora B kinase, and in mammalian germ cells Aurora C kinase, function as the enzymatic component of the Chromosomal Passenger Complex (CPC), which localizes to the inner centromere/kinetochore and phosphorylates kinetochore proteins for microtubule release during error correction. In this review, we discuss recent findings of the molecular pathways that regulate the chromosomal localization of Aurora B and C kinases in human cell lines, mice, fission yeast, and budding yeast. We also discuss differences in the importance of localization pathways between mitosis and meiosis.

Keywords

meiosis; mitosis; biorientation; Aurora B; Aurora C; Aurora kinases; chromosome segregation

Introduction

A requirement for faithful chromosome segregation is establishing proper attachments between chromosomes and spindle microtubules. During mitotic metaphase, biorientation occurs when the kinetochores on the two sister chromatids make end-on attachments to microtubules emanating from opposite spindle poles (Figure 1) (1). The poleward spindle forces that pull kinetochores in opposite directions are resisted by cohesins that encircle the two sister chromatids, holding them together. Biorientation is associated with tension within and between the kinetochores (2–5). Meiosis I has a unique chromosome configuration in which paired homologous chromosomes are physically linked together by crossovers. Biorientation in metaphase I occurs when the two sister chromatid kinetochores co-orient and the kinetochores of homologous chromosomes attach to microtubules from opposite spindle poles (Figure 2) (6). In meiosis I, the spindle forces are resisted by the crossover

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combined with the cohesins along the chromosome arms. In metaphase II, biorientation occurs similarly to mitosis in that sister chromatid kinetochores are attached to microtubules from opposite spindle poles (Figure 2).

Most initial attachments are incorrect and must be released to make proper attachments. Correction of errors in kinetochore-microtubule attachments occurs through the activity of the evolutionarily conserved Aurora B kinase and its paralog expressed in mammalian germ cells Aurora C (6–8). Aurora B/C releases improper kinetochore-microtubule attachments, mediated partly by the phospho-regulation of kinetochore proteins that bind microtubules (9–16). Aurora B/C activity leads to the release of attachments that are not under tension, allowing another round of microtubule binding to establish proper attachments. For example, a lack of tension occurs when both sister kinetochores attach to the same pole in mitosis or meiosis II, or when homologous chromosomes attach to the same pole in meiosis I (2, 3).

A third Aurora kinase, Aurora A kinase, localizes to spindle poles and functions in bipolar spindle assembly in mitosis and meiosis and centrosome maturation in mitosis (17–19). Although the major role of Aurora A is in spindle assembly, several studies now suggest that Aurora A phosphorylates kinetochore proteins to contribute to error correction of kinetochore-microtubule attachments in mitosis and meiosis I (20–26). Aurora A can perform these roles through its localization both at the spindle poles and, surprisingly, at kinetochores (20–23). These findings were the subject of a recent review (see (27)), so we only highlight new work on Aurora A kinase localization in meiosis.

The mechanism of how Aurora B selectively destabilizes microtubule-kinetochore interactions is currently under debate and the topic of several recent reviews (see (1, 7, 28)). In this review, we discuss multiple molecular pathways that localize Aurora B and Aurora C to the inner centromere and kinetochore in both mitosis and meiosis. We highlight several recent papers suggesting new recruitment mechanisms and how the importance of different recruitment pathways differ between mitosis and meiosis and among different model organisms.

Localization of Aurora B kinase in mitosis

Localization of Aurora B kinase to either the inner centromere or the kinetochore is crucial for its function in error correction. Aurora B kinase assembles into a complex called the Chromosomal Passenger Complex (CPC), which includes Survivin (also known as Bir1 in yeast), Borealin (also known as Dasra in Xenopus and Nbl1 in yeast), and Inner Centromeric Protein (INCENP, also known as Sli15 in yeast) (29–38). Survivin and Borealin bind to the N-terminus of INCENP and regulate the localization of the CPC to the centromere (34, 39–48). Aurora B binds to a region of INCENP near the C-terminus called the IN box and phosphorylates INCENP (32, 36, 49–53). Full activation of Aurora B requires binding to INCENP, phosphorylation of INCENP, and autophosphorylation, which may occur in trans (32, 46, 49, 51, 52, 54).

Work from human cell lines, Xenopus egg extracts, and fission and budding yeast have revealed the mechanisms of inner centromere localization of the CPC. Two highly conserved pathways function through two histone kinases, Haspin and Bub1. First, Haspin kinase

phosphorylates histone H3, which serves as a receptor for binding the Survivin subunit of the CPC (39, 43, 46, 47, 55). Second, Bub1 kinase phosphorylates histone H2A, which is bound by shugoshins (Sgo1 and Sgo2 in human cells) (47, 56–62). The Borealin subunit of the CPC then binds to human Sgo1 and Sgo2 (33, 37, 63). In fission yeast, Sgo2 but not Sgo1 is mainly responsible for the recruitment of the CPC (47, 63–65). Interestingly, fission yeast Sgo2 binds the Survivin subunit of the CPC (called Bir1) (63, 64). Budding yeast has only a single shugoshin, Sgo1, which binds phosphorylated histone H2A and also plays a role in maintaining Aurora B at the kinetochore (56, 66–69). However, whether Sgo1 directly binds Survivin (called Bir1) or Borealin (Nbl1) in budding yeast has not been established (70, 71). Therefore, although there are some organismal differences in subunit binding, the pathways of CPC inner centromere recruitment function similarly in different organisms.

Initially, Haspin and Bub1 pathways were proposed to cooperate to bring Aurora B to a chromatin region with overlapping histone H3T3ph and H2AT120ph marks (47). However, three recent studies from cell lines showed that tethering either Haspin or Bub1 individually to an ectopic chromatin location resulted in the recruitment of Aurora B to that location (72–74). Furthermore, these studies also show that each pathway individually recruits a distinct pool of Aurora B at the centromere (72–74). These results suggest that the two histone kinase pathways can function independently to bring Aurora B to the inner centromere.

Inhibition of either Haspin or Bub1 kinases causes decreased Aurora B inner centromere localization. In human cell lines and Xenopus egg extracts, the loss of Haspin kinase activity through depletion, drug inhibition, or mutation causes delayed chromosome alignment and some defective correction of erroneous attachments (43, 72, 75, 76). In contrast, drug inhibition of Bub1 kinase activity in cell lines does not result in alignment defects (61, 72). Mice with a deletion of the Bub1 kinase domain are viable, suggesting that the Bub1 kinase activity is not essential (77). However, mouse embryonic fibroblasts derived from a Bub1 kinase mutant mouse had delays in chromosome alignment and error correction. Aneuploidy rates in spleen, liver, and lung tissue were higher in the mutant mice than in wildtype. Additionally, inhibition of both the Haspin and the Bub1 kinase pathways in human cell lines causes more severe defects in chromosome alignment and segregation than mutating the individual pathways (72, 74). Therefore, although not essential, Bub1 kinase likely contributes to Aurora B localization for error correction in mammals.

In budding yeast, the Haspin kinase pathway is not as crucial for CPC recruitment as the Bub1 kinase pathway. Budding yeast cells with combined deletion of the two genes encoding Haspin kinase, *ALK1* and *ALK2*, do not have a growth defect but do show decreased Ipl1/Aurora B levels at the kinetochore (55, 78). In contrast, cells with a deletion of *SGO1* or *BUB1* grow slowly and have an increased risk of aneuploidy (56, 67, 71, 79, 80). Similarly, in fission yeast, inhibition of Haspin and Bub1 pathways gave more severe defects than the loss of the individual pathways (47). Overall, these results suggest that the Haspin and Bub1 pathways are additive for error correction in an unperturbed mitosis.

There are likely other pathways that recruit Aurora B to the kinetochore in human cells. The inhibition of Aurora B with a small molecule inhibitor causes a more severe defect in

chromosome alignment than the loss of both Haspin and Bub1 pathways (15, 16, 72, 81–84). Three recent studies showed that with loss of both pathways, Aurora B inner centromere localization is disrupted, but Aurora B kinetochore substrates are still phosphorylated (72–74). The phosphorylation of kinetochore substrates was not dependent on microtubules, eliminating the role of the microtubule-localized pool of Aurora B (72, 74, 85). A Haspin- and Bub1-independent pool of Aurora B was identified at the kinetochore and is proposed to phosphorylate substrates that regulate kinetochore-microtubule attachments (1, 7, 73, 86–90).

In budding yeast, there are two additional known pathways to recruit Ipl1/Aurora B to the centromere or kinetochore in addition to the Bub1 and Haspin kinase-dependent pathways. The third pathway also requires the Bir1 (Survivin) subunit of the CPC. Bir1 binds the inner centromere protein Ndc10, a component of the budding yeast centromeric DNA-binding Cbf3 complex (91, 92). Finally, in a recently discovered pathway, Ipl1/Aurora B localization is not dependent on the Bir1 component of the CPC. Instead, Sli15 (INCENP) directly binds the COMA kinetochore complex (containing Ctf19, Okp1, Mcm21, and Ame1, homologous to CENP-O,P,Q,U in mammals) (93, 94). Depletion of either Bir1 or Mcm21, a non-essential component of the COMA complex, reduces Ipl/Aurora B kinetochore localization (94). Double depletion of both *BIR1* and *MCM21* abolishes both biorientation and Ipl1/Aurora B localization. Overall, the results suggest that both Bir1-dependent and Bir1-independent pathways recruit Ipl1/Aurora B to the inner centromere and kinetochore.

An outstanding question in the field is how tension affects Aurora B substrate phosphorylation for correction of erroneous kinetochore-microtubule attachments. One of the prevailing models in the field, the spatial separation model, depends on the inner centromere localization of Aurora B, as this localization would allow Aurora B to discriminate between substrates that are spatially separated from the inner centromere (12, 95). In this model, a single pool of Aurora B at the inner centromere would phosphorylate substrates that are in close proximity to this pool but would be unable to phosphorylate substrates that are spatially separated when a kinetochore is under tension. However, studies in budding yeast, vertebrate cells, and human cells have shown that inner centromere localization of Aurora B is not essential for biorientation (45, 78, 96). In addition, the newly discovered kinetochore-localized pools of Aurora B are also important for phosphorylation of kinetochore proteins for error correction (72–74, 87, 88, 93, 94). Exciting future directions will be to test new models of how this pool could distinguish correct and incorrect attachments.

Establishing Biorientation in Meiosis

The unique chromosome configuration for biorientation in meiosis I requires several events leading up to metaphase I (Figure 2). Homologous chromosomes must pair and undergo crossovers, which physically tether the chromosomes together. The two sister kinetochores must co-orient to capture microtubules from the same pole. In mice, a protein called Meikin binds the kinetochore and recruits Polo kinase for co-orientation (97–99). In fission yeast, the meiosis-specific kinetochore protein Moa1 interacts with the meiosis-specific kleisin subunit of cohesin, Rec8, and recruits Polo-like kinase for co-orientation of sister

kinetochores (100). The Aurora B kinase homolog, Ark1, is also needed for co-orientation but functions independently of Moa1, Polo, and Rec8 (101). In budding yeast, a complex called monopolin interacts with Spo13 and clamps sister chromatid kinetochores. Monopolin is composed of the subunits Mam1, Lrs4, and Hrr25 and forms a V-shaped structure with two kinetochore-binding domains (102–105). Spo13 interacts with Polo kinase and recruits or stabilizes monopolin binding to the kinetochore (106–109). Although the functional orthologs Meikin, Moa1, and Spo13 do not share significant sequence homology, they all recruit Polo kinase for co-orientation of sister kinetochores in meiosis I (98).

For accurate chromosome segregation in meiosis II, the cohesin around the pericentromere must be protected from cleavage in meiosis I. If cohesins are cleaved in meiosis I, the two sister chromatids do not remain connected, and no tension bearing attachments can be established at metaphase II. Protecting cohesin from cleavage ensures that the sister chromatids remain together and resist spindle forces in metaphase II (Figure 2). Shugoshins, along with Meikin (mouse), Moa1 (fission yeast), or Spo13 (budding yeast), protect cohesins (98). Mice, humans, and fission yeast have two shugoshins, Sgo1 and Sgo2. In mice, Sgo2 is needed for meiotic cohesin protection, chromosome congression, and chromosome biorientation in meiosis I (110–112). In fission yeast, Sgo1 has a crucial role in cohesin protection (66). Sgo2 is dispensable for meiotic cohesin protection but interacts with the CPC for Aurora kinase localization in both mitosis and meiosis (64, 66, 101). Budding yeast has one shugoshin, Sgo1, that protects pericentromeric cohesin in meiosis and is important for biorientation in mitosis and meiosis by recruiting the CPC (67–69, 71, 113). Shugoshins mediate protection of cohesin by recruiting PP2A, a phosphatase that dephosphorylates Rec8 so that it cannot be cleaved by separase at anaphase I (58, 62). In budding yeast, Ipl1/Aurora B is needed to maintain PP2A levels at the kinetochore for cohesin protection (70).

Localization and Function of Aurora Kinases in Mammalian Meiosis

As in mitosis, Aurora B kinase is important for chromosome biorientation through the correction of kinetochore-microtubule attachments in both metaphase I and metaphase II. Mammals also express another Aurora kinase in the germline, Aurora C kinase (AURKC), which is important for biorientation (114–120). In the mouse germline, AURKC is the prevalent CPC kinase suggested to have replaced the major function of Aurora B kinase (AURKB) at the centromere regulating error correction of kinetochore-microtubule attachments (121–125). AURKC localizes to the spindle poles, centromeres and at the interchromatid axis of bivalents during metaphase I (126–129). Although AURKB localization to centromeres has been undetectable, AURKB localizes to the spindle in metaphase I and metaphase II and may have a role in chromosome alignment (121, 130).

Mice lacking AURKB or AURKC during meiosis have viable offspring, although they are subfertile, suggesting that the kinases mostly compensate for one another, but perhaps not as effectively as having both kinases (23, 119, 121, 131, 132). AURKB and AURKC share a consensus phosphorylation sequence and likely have overlapping substrates (133). When compared to wildtype and *Aurkc*$^{-/-}$ mice, AURKB conditional knockout (cKO) female mice are less fertile and have an increase in aneuploid eggs; these phenotypes are likely due

to too much AURKC activity (23). The increase in aneuploidy of *AurkB*$^{-/-}$ cKO mice is suppressed by adding a heterozygous deletion of AURKC. Therefore, AURKB negatively regulates and limits the activity of AURKC. In *Aurkc*$^{-/-}$ oocytes, AURKB is localized to the centromere, suggesting that AURKB corrects improper kinetochore-microtubule connections in the absence of AURKC (121).

Surprisingly, Aurora A kinase can compensate for the combined loss of both AURKB and AURKC to allow error correction of kinetochore-microtubule attachments. The *Aurkc*$^{-/-}$ *AurkB*$^{-/-}$ cKO double mutant female mice are fertile (23). Although Aurora A kinase (AURKA) normally functions in spindle assembly, AURKA localizes to the interchromatid axis in a CPC-dependent manner in the double mutant mice. The substrate INCENP is phosphorylated in the double mutant oocytes. In contrast, inhibition of AURKB and AURKC with the drug ZMM447439 shows no phosphorylation of INCENP, suggesting that the presence of AURKB/C prevents AURKA from binding to the CPC, likely by outcompeting AURKA. The AURKA compensation is meiosis-specific; deletion of AURKB in HeLa cells causes abnormal metaphase chromosome configurations and a lack of INCENP phosphorylation and AURKA at the interchromatid axis. An important future direction is to determine how AURKA compensation occurs in meiosis but not mitosis.

Haspin kinase phosphorylation of histone H3 is important for the localization of AURKC to the interchromatid axis in mouse oocytes (134, 135). Inhibition of Haspin kinase with the drug 5-Iodotubercidin (5-Itu) in late prometaphase I results in an increase in aneuploid eggs, an accelerated meiosis I, a weakened spindle assembly checkpoint response, and an approximately 60% decrease in AURKC and Survivin localization at the inter-chromatid axis (135, 136). There is also a decrease in inter-chromatid axis-localized phosphorylated INCENP, suggesting lower AURKC activity. Surprisingly, there was not a decrease of AURKC at the kinetochore, despite no detectable histone H3 phosphorylation. These results differ from those in mitosis in which inhibition of Haspin kinase causes a decrease in AURKB at the kinetochore (76). These results suggest that other recruitment pathways localize AURKC at the kinetochore. Furthermore, because the Haspin-inhibited oocytes have defects in chromosome alignment and segregation, the interchromatid axis-localized AURKC likely contributes to error correction and chromosome segregation.

Haspin kinase may work redundantly with other kinases for AURKC centromere recruitment. Bub1 kinase is a likely candidate due to its role in bringing Aurora B to the centromere in mitosis in human cells. However, loss of Bub1 kinase does not cause a major defect in chromosome segregation. Female mice lacking Bub1 kinase activity did not have a fertility defect, suggesting that correction of erroneous kinetochore-microtubule attachments still occurred (77). Oocytes lacking Bub1 kinase activity that were matured *in vitro* have a strong spindle checkpoint delay in metaphase I, likely because of chromosome congression defects. Eggs isolated in metaphase II do not show gross chromosomal aneuploidies suggesting that homologous chromosomes segregate normally. Therefore, oocytes lacking Bub1 kinase activity may have defects in chromosome alignment, but can segregate chromosomes properly after a spindle checkpoint delay (137). Another candidate is Mps1 kinase, which is involved in AURKC localization (138). If the Mps1 expressed in meiosis does not have the kinetochore binding domain, there are defects in chromosome alignment

at metaphase I, the spindle checkpoint response, and the normal timing of meiosis I. In addition, AURKC levels at chromosomes and centromeres were diminished without Mps1 kinetochore localization. However, because not all oocytes are aneuploid, there are likely multiple AURKC recruitment pathways that could function redundantly to bring AURKC to the centromere. Future work is needed to identify the additional centromere/kinetochore recruitment pathways and to determine how the pathways compensate for one another.

Localization and Function of Aurora Kinases in Budding and Fission Yeast

Budding yeast and fission yeast have only one Aurora kinase, Ipl1, and Ark1, respectively. Loss of Aurora B in budding or fission yeast meiosis causes massive chromosome mis-segregation due to a failure to correct initial improper attachments (70, 101, 109, 139). In budding yeast meiosis, cells lacking Bub1 have greatly reduced levels of Ipl1/Aurora B at the centromere (70, 140). We recently found that meiotic depletion of Bub1 results in massive chromosome mis-segregation, in which most chromosomes travel to the old spindle pole body (the budding yeast equivalent to the centrosome) due to a failure to correct initial attachments (140). Interestingly, the defect in meiosis II is more severe than that in meiosis I. For comparison, loss of Ipl1/Aurora B had a more severe defect than loss of Bub1 in meiosis I but a similar defect in meiosis II. The meiosis II results are surprising because the meiosis II division is assumed to be similar to mitosis. However, loss of Bub1 or Bub3 in mitosis does not cause massive chromosome mis-segregation, only an increased risk of single chromosome aneuploidy in each mitotic division (79, 80, 140). Our results suggest that the recruitment of Ipl1/Aurora B through the Bub1 pathway is crucial for correcting attachment errors in meiosis. An important future direction is to determine whether the other Ipl1/Aurora B recruitment pathways are also important for maintaining Ipl1/Aurora B levels at the centromere/kinetochore.

Conclusions

Recent studies have identified new molecular mechanisms involved in centromere/kinetochore localization of the CPC. Exciting future directions will be to further understand how these pathways are interconnected for full localization and activity of Aurora B/C kinase. Future studies should also aim to identify the molecular mechanisms of these novel recruitment pathways. In addition, recent studies have revealed key differences between Aurora kinase localization and function between mitosis and meiosis. Further study of these differences are warranted and will be crucial to our understanding of chromosome segregation in mitosis and meiosis.

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Summary:

- We discuss the mechanisms of localization of Aurora B and Aurora C kinases, which have conserved roles in correcting improper kinetochore-microtubule attachments in mitosis and meiosis.
- Recent studies have shown that in addition to the Haspin kinase and Bub1 kinase pathways for recruiting Aurora B/C to the centromere, other pathways also independently contribute to Aurora B/C kinase centromere and kinetochore localization.
- We highlight several recent studies showing that the importance of specific Aurora B/C recruitment pathways differ between mitosis and meiosis and among model organisms

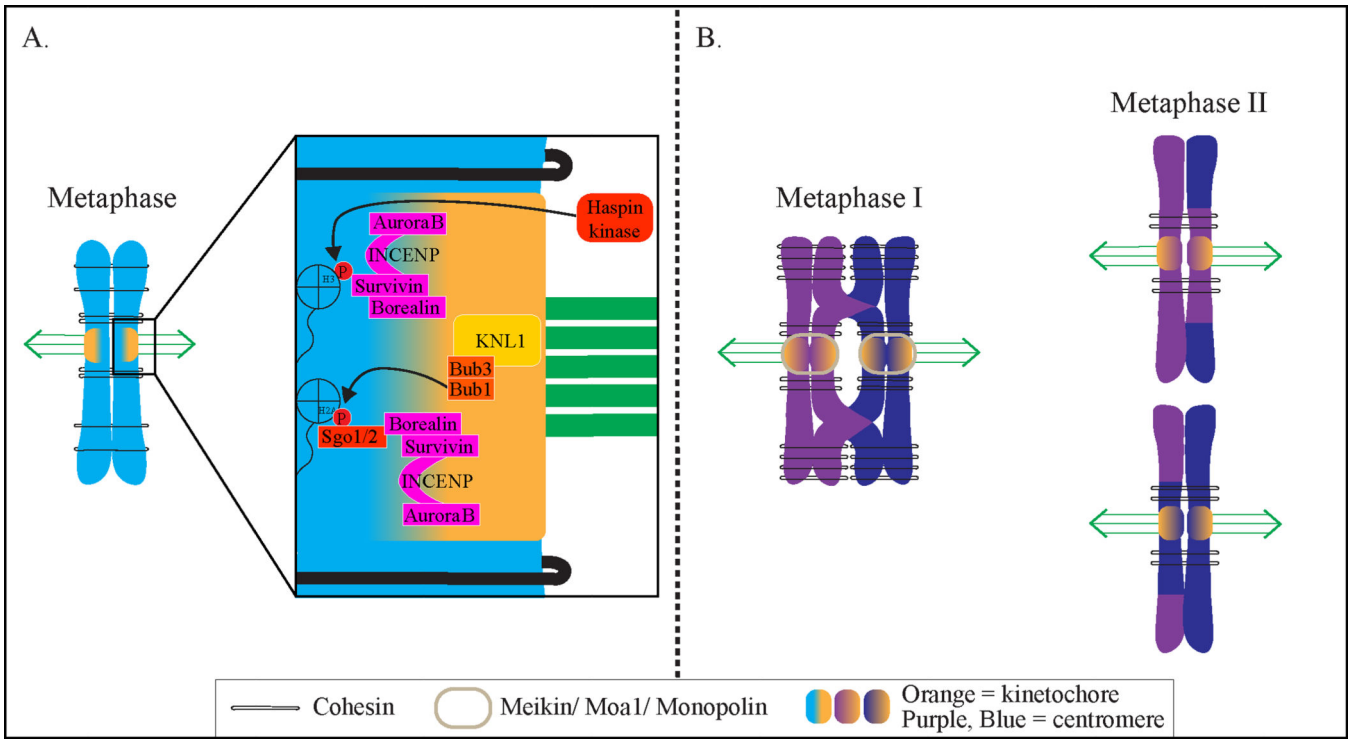

Figure 1:

Biorientation in mitosis and meiosis. A) Chromosomes are bioriented in mitosis when sister kinetochores are properly attached to microtubules from opposite poles. Inset shows two Aurora B recruitment pathways. B) In meiosis I (left), chromosomes biorient when sister kinetochores are attached to microtubules from the same pole and homologous chromosome kinetochores attach to opposite spindle poles. In meiosis II, biorientation occurs when sister chromatid kinetochores attach to microtubules from opposite spindle poles.

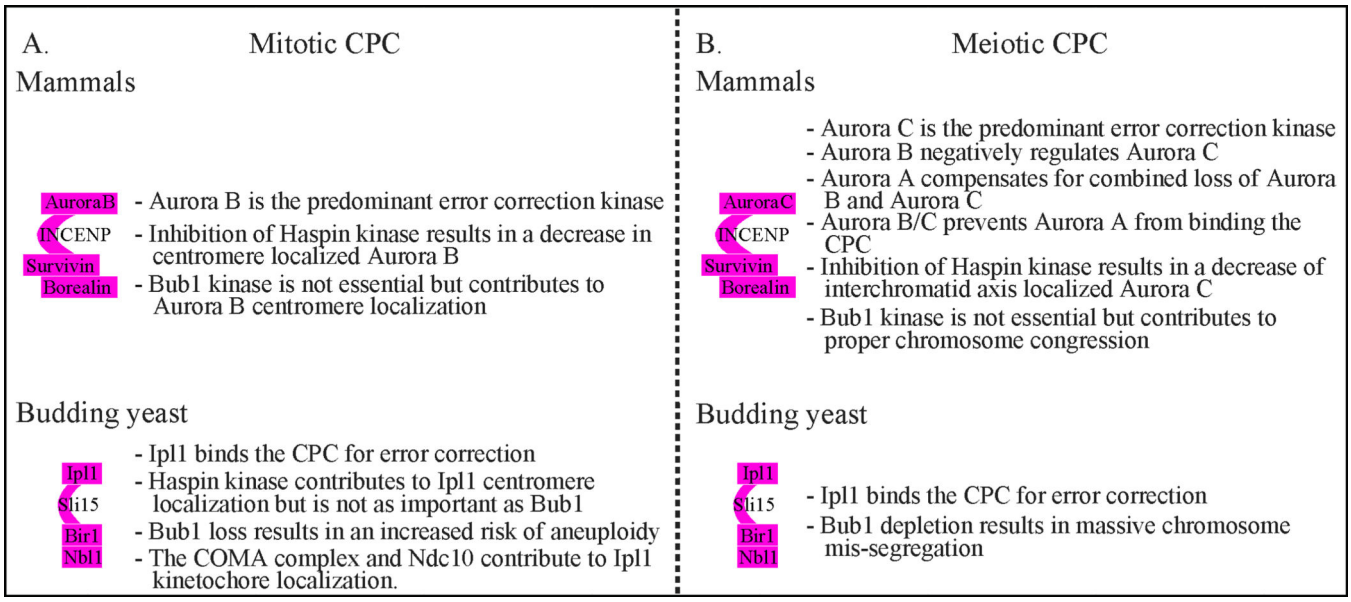

Figure 2:

Comparison of mitotic and meiotic CPC localization and function in mammals and budding yeast for error correction of kinetochore-microtubule attachments.