Kinase Signaling in the Spindle Checkpoint*

PUBLISHED, JBC PAPERS IN PRESS, FEBRUARY 19, 2009, DOI 10.1074/jbc.R900005200

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The spindle checkpoint is a cell cycle surveillance system that ensures the fidelity of chromosome segregation. In mitosis, it elicits the “wait anaphase” signal to inhibit the anaphase-promoting complex or cyclosome until all chromosomes achieve bipolar microtubule attachment and align at the metaphase plate. Because a single kinetochore unattached to microtubules activates the checkpoint, the wait anaphase signal is thought to be generated by this kinetochore and is then amplified and distributed throughout the cell to inhibit the anaphase-promoting complex/cyclosome. Several spindle checkpoint kinases participate in the generation and amplification of this signal. Recent studies have begun to reveal the activation mechanisms of these checkpoint kinases. Increasing evidence also indicates that the checkpoint kinases not only help to generate the wait anaphase signal but also actively correct kinetochore-microtubule attachment defects.

The Spindle Checkpoint

Faithful segregation of duplicated chromosomes into each daughter cell is essential for genetic stability. Defects in chromosome segregation result in aneuploidy, which is a hallmark of cancer cells. The spindle checkpoint is a cell cycle surveillance system that monitors kinetochore-microtubule attachment and guards against chromosome missegregation (1, 2). When activated, the spindle checkpoint inhibits the multisubunit ubiquitin ligase, the APC/C, through interfering with the functions of its mitotic activator, Cdc20 (3, 4). Inhibition of APC/C blocks sister chromatid separation and mitotic exit until all pairs of opposing sister kinetochores attach to microtubules emanating from the two opposite spindle poles, referred to as amphitelic attachment. Once all sister chromatids achieve amphitelic attachment, the spindle checkpoint is turned off, and APC/C is activated. APC/C then promotes the degradation of securin and cyclin B (Fig. 1). Degradation of securin and cyclin B activates separase, which cleaves cohesin to trigger separation of sister chromatids. Cyclin B degradation also inactivates Cdk1 to allow mitotic exit. The separated sister chromatids are then distributed evenly into the two daughter cells through their attachment to the mitotic spindle.

The core components of the spindle checkpoint in human cells include Bub1 (budding uninhibited by^cencopy;enomyl 1), Bub3, BubR1, Mad1 (mitotic arrest deficiency 1), Mad2, Mps1 (monopolar spindle 1), and the CPC that consists of Aurora B, INCENP, survivin, and borealin (1, 2). They are recruited to kinetochores at prometaphase and promote the formation of the mitotic checkpoint complex, consisting of BubR1, Bub3, Mad2, and Cdc20, for APC/C inhibition (Fig. 1). A single unattached kinetochore is sufficient to activate the spindle checkpoint, suggesting that certain steps of checkpoint signaling must be catalytic. Indeed, several spindle checkpoint components are protein kinases, including Bub1, BubR1, Mps1, and Aurora B. The kinase activities of Bub1, Mps1, and Aurora B are required for the spindle checkpoint. Recent studies have shed light on the activation mechanisms of these kinases. It has also become increasingly clear that, in addition to monitoring kinetochore-microtubule attachment, the spindle checkpoint kinases actively promote proper attachment of microtubules to kinetochores. The dual functions of these checkpoint kinases ensure equal partition of sister chromatids during mitosis and maintain genetic stability.

Activation of the Spindle Checkpoint Kinases by Kinetochore Recruitment

The kinetochore localization of spindle checkpoint components is a prerequisite for checkpoint signaling (Fig. 1). The recruitment of spindle checkpoint proteins to kinetochores is hierarchical, i.e. the kinetochore recruitment of some depends on the prior recruitment of others. Aurora B, Mps1, and Bub1 lie at the top of this hierarchy, whereas BubR1, Mad1, and Mad2 lie downstream (5–8). The kinetochore localization of the spindle checkpoint kinases appears to be required for their activation and function. For instance, chromosome-bound Bub1 is hyperphosphorylated (9). In addition to the core spindle checkpoint kinases such as Mps1, Bub1, BubR1, and Aurora B, several other kinases, including Plk1 (polo-like kinase 1), Nek2A, Chk1, MAPK, and Cdk1, localize to kinetochores (10–15), suggesting that the kinetochore is a hub for kinase signaling. Recent studies have begun to delineate the molecular mechanisms by which these kinases are recruited to and activated at the kinetochores. A conserved network of kinetochore proteins referred to as the KMN network is necessary and sufficient for capturing microtubules in Caenorhabditis elegans (16). The KMN network consists of KNL-1, the Mis12 complex, and the Ndc80 complex. The calponin homology domains of an Ndc80 dimer (called Hecl in humans) directly bind to microtubules, and this interaction is regulated by phosphorylation of the N-terminal domain of Ndc80 by Aurora B (17). KNL-1 has additional microtubule-binding activities that strengthen microtubule binding of the KMN network (16).

Several proteins within this network have been implicated in recruiting spindle checkpoint proteins to kinetochores. The Ndc80 complex is required for the kinetochore recruitment of Mps1, Mad1, and Mad2 (18). Recently, Kiyomitsu et al. (19) showed that the human KNL-1 protein called blinkin was likely
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FIGURE 1. Activation mechanisms of the spindle checkpoint kinases at the kinetochores. The spindle checkpoint kinases are recruited to kinetochores in a hierarchical fashion. Kinetochore binding activates these kinases through multiple mechanisms, including phosphorylation of cofactors and activation loops and binding of cofactors. The active kinases then phosphorylate downstream checkpoint components and promote the formation of the mitotic checkpoint complex (MCC), which inhibits APC/C. APC/C inhibition stabilizes its substrates, securin and cyclin B, which block anaphase onset and mitotic exit. MT, microtubules.

the direct kinetochore receptor for Bub1 and BubR1. Therefore, blinkin and the KMN network appear to be the platform for the docking of Bub1, BubR1, and possibly other spindle checkpoint kinases at the kinetochores.

Microtubule binding reduces the concentrations of the spindle checkpoint kinases at the kinetochores. A similar set of kinetochore proteins, the KMN network, is responsible for both microtubule capture and recruitment of checkpoint proteins. Competitive binding of microtubules and spindle checkpoint proteins to the KMN network thus provides a straightforward on-and-off switch for the spindle checkpoint (15).

How does kinetochore recruitment activate the checkpoint kinases? Two recent studies suggest that kinetochore targeting elevates the local concentrations of these kinases and enhances their trans-autophosphorylation, leading to their activation. The first study by Kelly et al. (20) dealt with the activation mechanism of Aurora B. Aurora B had been shown to be activated by autophosphorylation at Thr\textsuperscript{232} in its activation loop and by phosphorylation of the C-terminal TSS motif in its binding partner INCENP (21–23). Kelly et al. showed that the microtubule destabilizing protein Op18 underwent Aurora B-dependent hyperphosphorylation after the addition of sperm nuclei or purified centrosomes in Xenopus egg extracts. When antibodies against the CPC were included in the extracts, Op18 was hyperphosphorylated without chromosomes or centrosomes. Antibody addition also increased the phosphorylation of the TSS motif of INCENP. These results suggested that induced dimerization of the CPC through antibody binding activated Aurora B. The results of Kelly et al. further suggested that the kinetochore and chromosome localization of CPC might enhance the autophosphorylation and activation of Aurora B because of its high local concentration and clustering at these structures.

In the second study, Kang et al. (24) showed that activation of Mps1 also involved trans-autophosphorylation of its activation loop. Mattison et al. (25) first reported that autophosphorylation of Thr\textsuperscript{676} in the activation loop of human Mps1 was required for its kinase activity in vitro and for the ability of Mps1 to induce centrosome duplication in human cells. Kang et al. (24) further showed that Mps1 Thr\textsuperscript{676} phosphorylation occurred in vivo and was elevated during mitosis. Ectopic expression of the Mps1 T676A mutant failed to sustain nocodazole-induced mitotic arrest of HeLa cells that were depleted of endogenous Mps1 by RNAi. Autophosphorylation of Mps1 at Thr\textsuperscript{676} could occur in trans, and chemical-induced dimerization of Mps1 increased its kinase activity in cells. These results suggested that the kinetochore localization and clustering of Mps1 might promote its trans-autophosphorylation, leading to its activation.

The proposed mechanism of chromosome- or kinetochore-induced clustering and activation of Aurora B and Mps1 is reminiscent of the ligand-induced dimerization of receptor tyrosine kinases (26). Future studies are needed to test whether this mechanism indeed accounts for the activation of spindle checkpoint kinases by unattached kinetochores in living cells. A recent study by Xu et al. (27) also uncovered a role of Mps1 autophosphorylation in its kinetochore targeting, suggesting the existence of a positive feedback loop for Mps1 kinetochore targeting and activation. Finally, the MAPK pathway mediates phosphorylation of a conserved residue in the Mps1 kinase domain. This phosphorylation event is required for the kinetochore localization of Mps1 (6, 27, 28).

Regulation of Spindle Checkpoint Kinases by Binding of Cofactors

In addition to the activation loop phosphorylation, several spindle checkpoint kinases can be activated through the binding of cofactors (Fig. 1). Rosasco-Nitcher et al. (29) recently showed that TD-60 (telophase disc-60kD) and microtubules cooperatively stimulated the Aurora B kinase activity in vitro and in Xenopus egg extracts. Preincubation of Aurora B with unphosphorylated substrates such as the histone H3 N-terminal tail prevented the autophosphorylation and activation of Aurora B. Prior phosphorylation of H3 Thr\textsuperscript{3} by the kinase haspin eliminated this inhibitory function of the H3 tail. Because haspin-dependent phosphorylation of H3 occurs at the centromeres (30), Rosasco-Nitcher et al. (29) proposed that priming phosphorylation of H3 Thr\textsuperscript{3} by haspin at the centromeres might establish a chromatin domain permissive for Aurora B activation. Therefore, Aurora B is regulated at several levels by binding of cofactors (including INCENP, TD-60, and microtubules), by autophosphorylation, and by priming phosphorylation on substrates.

Another example of kinase activation by cofactor binding is BubR1 activation by CENP-E, a kinetochore-bound motor protein (Fig. 1). BubR1 binds directly to Cdc20 and inhibits APC/C by acting as a pseudo-substrate (31–33). Inhibition of APC/C...
by BubR1 does not require the kinase activity of BubR1 (34). The BubR1 kinase activity is nevertheless required for the maintenance of the spindle checkpoint in mammalian cells in the presence of spindle poisons (33). Furthermore, Mao et al. (35) showed that a kinase-inactive mutant of BubR1 failed to restore the checkpoint in Xenopus extracts with BubR1 completely depleted. They proposed that BubR1 had two independent functions in the spindle checkpoint: 1) inhibition of APC/C in a kinase-independent manner and 2) phosphorylation of unidentified targets catalytically to activate the spindle checkpoint. They further showed that CENP-E was required for the spindle checkpoint and for the kinase activity of BubR1 in Xenopus egg extracts. CENP-E directly bound to the kinase domain of BubR1, and this binding greatly enhanced the kinase activity of BubR1 in vitro. Addition of microtubules silenced the activation of BubR1 by CENP-E in vitro (36), suggesting that kinetochore-microtubule attachment might inactivate BubR1 and the spindle checkpoint. Therefore, CENP-E was proposed to link kinetochore-microtubule attachment to spindle checkpoint inactivation. The mechanism by which CENP-E activates BubR1 remains to be established.

The mitotic kinase Plk1 regulates multiple processes in mitosis, including mitotic entry, spindle assembly, chromosome alignment, cytokinesis, and the spindle checkpoint (37). Plk1 is inactive during interphase partly because of autoinhibition, i.e., the C-terminal polo-box domain of Plk1 binds to and inhibits its N-terminal kinase domain (38). During mitosis, this inhibition is relieved by Thr\(^{210}\) phosphorylation in its activation loop. Plk1 is recruited to kinetochores through its interactions with Bub1 and INCENP (39, 40). It then generates tension-sensitive 3F3 epitopes on BubR1 and facilitates the kinetochore localization of BubR1, Mad2, and Cdc20 (41). Two recent studies provided additional insights into the activation mechanism of Plk1, which required the binding of a cofactor called Bora and Aurora A-dependent phosphorylation of Thr\(^{210}\) in the activation loop of Plk1 (42, 43). These two studies established Aurora A as an upstream activating kinase for Plk1 and, along with other results, suggested the following model for Plk1 activation at the G\(_2\)/M transition. In this model, Bora binds to Plk1 and causes a conformational change of Plk1 to expose Thr\(^{210}\), which is then recognized and phosphorylated by Aurora A to activate Plk1. In mitosis, Bora is phosphorylated by Plk1 and degraded, which allows the polo-box domain of Plk1 to interact with its mitotic substrates that have undergone priming phosphorylation. In this way, Plk1 is recruited to kinetochores and other cellular structures and efficiently phosphorylates multiple mitotic regulators.

**Promoting Proper Kinetochore-Microtubule Attachment by Spindle Checkpoint Kinases**

In addition to sensing the lack of proper kinetochore-microtubule attachment and blocking anaphase onset, several spindle checkpoint kinases, including Aurora B, Bub1, BubR1, Mps1, and Nek2A, directly promote correct kinetochore-microtubule attachment and actively participate in the correction of spindle defects (Fig. 2). The dual functions of these spindle checkpoint kinases in error detection and error correction are reminiscent of the DNA damage checkpoint kinases, which participate in both DNA damage sensing and repair (44).

Chromosome alignment is coordinately regulated by several classes of microtubule-based motors and by microtubule-binding proteins that control microtubule dynamics (45). Upon entry into mitosis, microtubules that originate from centrosomes search and capture the kinetochores of sister chromatids. The kinetochores initially attach to the side of a microtubule and move toward the pole from which the microtubule originates through molecular motors. During transport to the pole, this lateral attachment is converted to end-on attachment. Chromosome congression to the metaphase plate is then achieved through amphitelic kinetochore-microtubule attachment. Recent studies indicate that the spindle checkpoint kinases are required for chromosome alignment and promote stable amphitelic kinetochore-microtubule attachment.

**Stabilizing Microtubule Attachment by BubR1**—Lampson and Kapoor (46) first discovered a role of BubR1 in stabilizing kinetochore-microtubule attachment and in chromosome alignment (Fig. 2). They treated human cells with the proteasome inhibitor MG132 for 2 h to block cells at metaphase and then examined the presence of chromosome misalignment in these cells. About 30% of the BubR1-depleted cells contained misaligned kinetochores, whereas few of the Mad2-depleted cells did, suggesting that BubR1 had a checkpoint-independent role in chromosome alignment. The misaligned kinetochores in Figure 2. Dual functions of the spindle checkpoint kinases in sensing and correcting improper kinetochore-microtubule attachments. The spindle checkpoint kinases, including Aurora B, Bub1, BubR1, and Mps1, sense the existence of erroneous kinetochore-microtubule attachments and block the onset of anaphase. These kinases also actively promote proper kinetochore-microtubule attachment. The KMN network of kinetochore proteins serves as a receptor for both microtubules (MT) and checkpoint kinases. Competition between microtubules and checkpoint proteins for binding to the KMN network provides a simple on-and-off switch for checkpoint signaling. MCC, mitotic checkpoint complex.
BubR1-depleted cells were detached from microtubules and had elevated CENP-A phosphorylation, which was indicative of increased Aurora B activity. Several studies have established that Aurora B corrects improper kinetochore-microtubule attachment by selectively disassembling the kinetochore-microtubule fibers. Consistently, inhibition of Aurora B partially rescued the alignment defect of BubR1-depleted cells. Therefore, BubR1 stabilizes kinetochore-microtubule attachment in part by restraining the activities of Aurora B at kinetochores.

BubR1 also directly contributes to stable kinetochore-microtubule attachment. Zhang et al. (47) showed that the kinase activity of BubR1 was required for chromosome alignment in *Xenopus* egg extracts. The APC tumor suppressor protein and EB1, a microtubule plus-end-binding protein and a binding partner of APC, appeared to be the targets of BubR1 in this process. APC colocalized with BubR1 at the kinetochores. APC depletion caused similar chromosome alignment defects compared with BubR1 depletion. BubR1 phosphorylated APC *in vitro*, and this phosphorylation was required for the recruitment of APC to kinetochores. BubR1 and APC formed a ternary complex with microtubules *in vitro*. These results suggest that BubR1 recruits the APC-EB1 complex to kinetochores, thereby facilitating stable kinetochore-microtubule attachment. The current evidence therefore suggests that BubR1 stabilizes kinetochore-microtubule attachment in two ways: counteracting Aurora B activity and recruiting APC-EB1. It remains to be determined whether these two mechanisms are coordinated.

How is the function of BubR1 in chromosome alignment regulated? Qi et al. (39) first reported an interaction between BubR1 and Plk1 in mitosis. Several subsequent studies then showed that BubR1 was a substrate of Plk1 *in vivo* and *in vitro* (41, 48, 49). Two of these studies further showed that phosphorylation of BubR1 by Plk1 regulated the function of BubR1 in chromosome alignment (48, 49). In particular, Matsumura et al. (48) showed that Plk1 phosphorylated two sites in the kinase domain of BubR1. A BubR1 mutant mimicking phosphorylation at these sites rescued the chromosome alignment defects of cells depleted of both Plk1 and BubR1. The kinase-dead version of the same phospho-mimicking BubR1 mutant did not rescue the defects of BubR1 and Plk1 co-depletion. These results suggest that Plk1 phosphorylates BubR1 and stimulates its kinase activity, which then phosphorylates downstream targets such as APC to promote chromosome alignment. Very recently, BubR1 was shown to be phosphorylated by Mps1, and some of these phosphorylation events were also essential for the establishment of proper kinetochore-microtubule attachment (50).

The mitotic kinase Nek2A also plays a role in kinetochore-microtubule attachment (51). It directly phosphorylates Hec1 (a subunit of the Ndc80 complex), enhances the microtubule-binding affinity of Ndc80, and stabilizes the correct kinetochore-microtubule attachment in human cells.

**Conversion from Side-on Attachment to End-on Attachment by Bub1**—Establishing stable amphitelic kinetochore-microtubule attachment is critical for chromosome alignment at metaphase. Taylor and co-workers (52) first showed that depletion of Bub1 by RNAi in human cells greatly increased the percentage of cells with misaligned chromosomes at metaphase, implicating a role of Bub1 in chromosome congression. Meraldi and Sorger (53) also reported that Bub1 functions in chromosome congression. In their study, HeLa cells were treated with the proteasome inhibitor MG132 to block them at metaphase. About 60% of Bub1 RNAi cells at metaphase showed chromosome congression errors. The kinetochores of unaligned chromosomes exhibited side-on microtubule attachment. The interkinetochore distance of unaligned chromosomes was 1 μm compared with 2 μm in aligned ones, indicating reduced tension between the unaligned sister kinetochores. These results support a role of Bub1 in promoting the correct kinetochore-microtubule attachment.

Logarinho et al. (54) confirmed and extended these results. They showed that 10–30% of cells depleted of Bub1, Bub3, and BubR1 at metaphase had more than four misaligned chromosomes. The misaligned chromosomes in Bub3-depleted cells exhibited side-on microtubule attachment, as observed in Bub1-depleted cells. Inhibition of Aurora B further increased the chromosome alignment defects in Bub1- or Bub3-depleted cells, suggesting that the microtubule attachment defects caused by Bub1 or Bub3 depletion were corrected by Aurora B.

The prevalence of side-on microtubule attachment in Bub1- or Bub3-depleted cells suggests that the Bub1-Bub3 complex promotes the conversion of side-on attachment to end-on attachment. The mechanism by which Bub1-Bub3 accomplishes this task is unknown. Bub1-Bub3 regulates multiple mitotic processes such as protecting centromeric cohesion through shugoshin (Sgo1) and recruiting CENP-E and BubR1 to kinetochores (52, 55). It will be important to determine whether Bub1-Bub3 directly contributes to chromosome alignment or indirectly through Sgo1, CENP-E, or BubR1.

**Severing Faulty Microtubule Attachment**—Aurora B has long been known to sever erroneous kinetochore-microtubule attachment (56). Two recent studies have established a role of Mps1 in this process through activating Aurora B. Tanaka and co-workers (57) showed that, similar to Aurora B, Mps1 promoted chromosome bi-orientation in budding yeast. This study failed, however, to reveal a cross-talk between Mps1 and Aurora B.

In the second study, Kops and co-workers (58) showed that the role of Mps1 in chromosome alignment was conserved in human cells. Many misaligned chromosomes in Mps1-depleted cells were adjacent to the centrosomes and exhibited no localization of CLIP-170 at their kinetochores, indicative of syntelic kinetochore-microtubule attachment. Unlike in budding yeast, Mps1 acted upstream of Aurora B in correcting faulty kinetochore-microtubule attachment. In Mps1-depleted cells, the Aurora B activity at the kinetochores was weaker as judged by CENP-A phosphorylation. Mps1 phosphorylated borealin, a CPC subunit, and activated the kinase activity of Aurora B *in vitro*. A phospho-mimicking mutant of borealin rescued the chromosome alignment defects caused by Mps1 depletion but not those caused by BubR1 or Plk1 depletion, indicating that borealin was the major target of Mps1 in chromosome alignment. Therefore, Mps1 corrects syntelic kinetochore-microtubule attachment through phosphorylating borealin and activating Aurora B at the kinetochores.
Concluding Remarks

The spindle checkpoint ensures the accuracy of chromosome segregation and genetic stability. Malfunction of the spindle checkpoint leads to aneuploidy, which contributes to cancer and birth defects (59). Recent studies have revealed three general features of the spindle checkpoint. First, similar to the DNA damage checkpoint, the spindle checkpoint not only halts the cell cycle by sensing defects in kinetochore-microtubule attachment but also actively promotes the correction of these defects. Second, the spindle checkpoint kinases can be activated by multiple mechanisms at the kinetochores and play vital roles in both processes. Finally, microtubules and the spindle checkpoint proteins share the same receptors at the kinetochores. Competition between microtubule and spindle checkpoint proteins for binding to these receptors provides a simple on-and-off switch for checkpoint signaling.

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