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REVIEW

Recent advances in understanding the role of Cdk1 in the Spindle Assembly Checkpoint [version 1; peer review: 2 approved]

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Abstract

The goal of mitosis is to form two daughter cells each containing one copy of each mother cell chromosome, replicated in the previous S phase. To achieve this, sister chromatids held together back-to-back at their primary constriction, the centromere, have to interact with microtubules of the mitotic spindle so that each chromatid takes connections with microtubules emanating from opposite spindle poles (we will refer to this condition as bipolar attachment). Only once all replicated chromosomes have reached bipolar attachments can sister chromatids lose cohesion with each other, at the onset of anaphase, and move toward opposite spindle poles, being segregated into what will soon become the daughter cell nucleus. Prevention of errors in chromosome segregation is granted by a safeguard mechanism called Spindle Assembly Checkpoint (SAC). Until all chromosomes are bipolarly oriented at the equator of the mitotic spindle, the SAC prevents loss of sister chromatid cohesion, thus anaphase onset, and maintains the mitotic state by inhibiting inactivation of the major M phase promoting kinase, the cyclin B-cdk1 complex (Cdk1). Here, we review recent mechanistic insights about the circuitry that links Cdk1 to the SAC to ensure correct achievement of the goal of mitosis.

Keywords

Cdk1, APC/C, MCC, Cdc20, CCAN, Mps1, Mad1, Mad2, Bub1, spindle assembly checkpoint, SAC.

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Introduction

Maintenance of genome stability through cell generations is a crucial feature that grants health to cells, organs and organisms. In humans, genome instability is causally linked to pathological outcomes such as cancer, degenerative disorders and physical and mental retardation[1–3]. Cells have developed several mechanisms to surveil that each step required for cell division is healthy and thoroughly completed before passing to the next one. This is achieved through mechanisms called cell cycle checkpoints[4–8]. If cells experience DNA damage or sense that DNA replication or assembly of the mitotic spindle is incomplete, checkpoint mechanisms halt cell cycle progression to repair damage or complete previous cell cycle stages before moving forward in their division process. If repair or completion is frustrated, then healthy checkpoints promote cell death[9–13]. This short review will be focused on recent advancements in the mechanistic understanding of the Spindle Assembly Checkpoint (SAC), the checkpoint that prevents formation of cells with an abnormal chromosome number by delaying mitosis exit until bipolar attachment of all replicated chromosomes[14].

Progression through mitosis: a cycle of Cdk1 activation/inactivation

Progression through mitosis is granted by a wave of cyclin B-cdk1 complex (Cdk1) activity[15,16]. Cdk1 is activated at the onset of mitosis by reversal of inhibitory phosphorylations of the cdk1 moiety at threonine 14 and tyrosine 15. These phosphorylations, operated by the Myt1 and Wee1 kinases, allow accumulation of enough inactive Cdk1, during S phase and G_2, to rapidly induce mitosis upon their reversal[17,18]. Dephosphorylation and activation of Cdk1 are granted by the dual-specificity phosphatase Cdc25[19]. Upon initial activation, Cdk1 phosphorylates and inhibits Myt1 and Wee1 while it phosphorylates and further activates Cdc25; this way, Cdk1 promotes positive feedback loops for its own activation[20–22]. For mitosis onset, Cdk1 activity also represses major phosphatase activities (like that of PP1 and PP2A) that otherwise would antagonize Cdk1 action. The catalytic activity of PP1 is directly inhibited by Cdk1-dependent phosphorylation, while the activity of PP2A in which B55 is the holoenzyme regulatory subunit, PP2A-B55, is kept inhibited in mitosis by the aid of Greatwall kinase (Gwl). Gwl is stimulated by Cdk1 and phosphorylates Ensa/Arpp19, two small molecules, transforming them into potent PP2A-B55 inhibitors[22].

Inactivation of Cdk1 at the end of mitosis instead depends on the ubiquitin-dependent degradation of cyclin B[14,23–25]. This is initiated by the ubiquitin ligase Anaphase Promoting Complex/Cyclosome (APC/C) in association with its coactivator Cdc20. APC/C^{Cdc20} also promotes the degradation of securin, an inhibitor of separase, the protease that cleaves the protein bridge that holds sister chromatid centromeres together[14,26–28]. This way, the onset of anaphase and Cdk1 inactivation are tightly coupled by this irreversible degradative mechanism. Initial evidence indicated that APC/C^{Cdc20} activity required Cdk1-dependent phosphorylation; recently, the APC/C members that are directly phosphorylated by Cdk1 were identified[29–33]. Thus, Cdk1 is also promoting a negative feedback for its own inactivation. Nevertheless, final APC/C^{Cdc20} activation is under the control of the SAC, which inhibits APC/C^{Cdc20} until bipolar attachment of all replicated chromosomes[14].

Mps1 and the SAC, in brief

The SAC inhibits APC/C^{Cdc20} activation by forming a diffusible Mitotic Checkpoint Complex (MCC), composed of the proteins Mad2, Bub3, BubR1, and Cdc20 itself, in which Cdc20 is restrained from activating APC/C[14,34–37]. MCC forms at unattached kinetochores, proteinaceous centromeric structures deputed to interact with spindle microtubules and permit chromosome segregation (Figure 1)[14]. MCC formation requires the action of crucial SAC kinases like Plk1, Aurora B, and Mps1[38–40]. These kinases also have important roles in correcting faulty chromosome–microtubule interactions to promote correct, end-on, bipolar chromosome–microtubule attachments[41]. Here, however, we will primarily review recent advancements in the regulation of Mps1 in SAC control and its dependence on Cdk1 activity. Mps1 binds unattached kinetochores where it phosphorylates SAC proteins and activates them and then gets released from kinetochores upon stable microtubule binding, perhaps by competition mechanisms[42–46]. The bridge deputed to connect centromeres to microtubules is called the KMN network and is composed by the Knl1 complex, the Mis12 complex, and the Ndc80 complex[46–50]. The KMN, in the outer kinetochore, interacts with the inner kinetochore Constitutive Centromere Associated Network (CCAN), a protein network that assembles onto Cenp-A nucleosomes, a histone H3 variant found at centromeric nucleosomes[51–53]. Mps1 localizes at unattached kinetochores primarily by interacting with the Ndc80 complex[54]. At kinetochores, Mps1 phosphorylates the “MELT” repeats of Knl1, promoting kinetochore recruitment of the BubR1-Bub3 and Bub1-Bub3 complexes (Figure 2), while Knl1 dephosphorylation by PP1 appears involved in SAC silencing[43,55–58]. Mps1 also phosphorylates Bub1, further promoting kinetochore recruitment of Mad1, another crucial SAC protein needed for the activation of Mad2[59–61]. Mad1 recruitment at kinetochores is also facilitated by the Rod-Zwilch-ZW10 (RZZ) complex[62]. In addition, phosphorylation of Mad1 by Mps1 helps the Mad1-dependent conversion of Mad2 into the functional conformation required to inhibit Cdc20 in the MCC[59,60]. Thus, Mps1 is a crucial effector of the SAC mechanism by promoting MCC formation (Figure 2).

Cdk1 and the SAC

The observation that APC/C activity was promoted by Cdk1-dependent phosphorylation, while APC/C activation was inhibited by the SAC until spindle assembly, reinforced the idea that checkpoint mechanisms would oppose the forward trend of the basic cell cycle engine[4]. However, in 2003, a few independent observations, from yeast and vertebrates, changed this view by showing that Cdk1 was instrumental to the SAC action[63–65]. Indeed, in yeast, SAC-defective cdk1 mutants were described and Bub1 was shown to be phosphorylated by Cdk1 for SAC proficiency[63,64]. In the Xenopus egg extract system and in human somatic cells, Cdk1 activity was revealed to be required to sustain SAC-dependent arrest and the ability

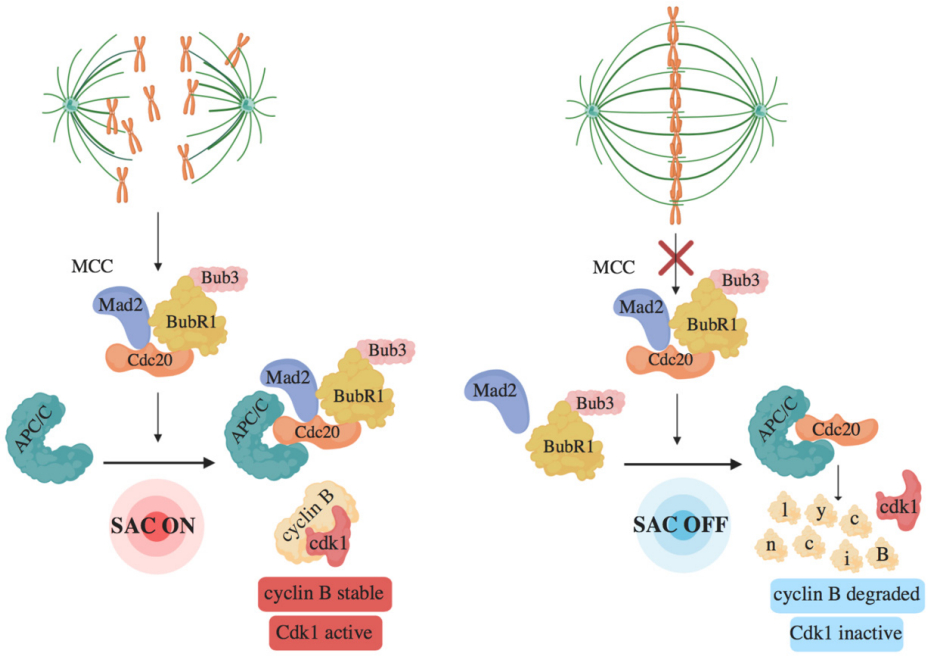

Figure 1. Unattached or incorrectly attached chromosomes promote formation of the Mitotic Checkpoint Complex (MCC). Until bipolar spindle assembly, the MCC, composed of Mad2, BubR1-Bub3, and Cdc20, forms, binds, and blocks APC/C action (SAC ON). Upon bipolar spindle assembly, MCC is dismantled and MCC-free Cdc20 activates APC/C (SAC OFF).

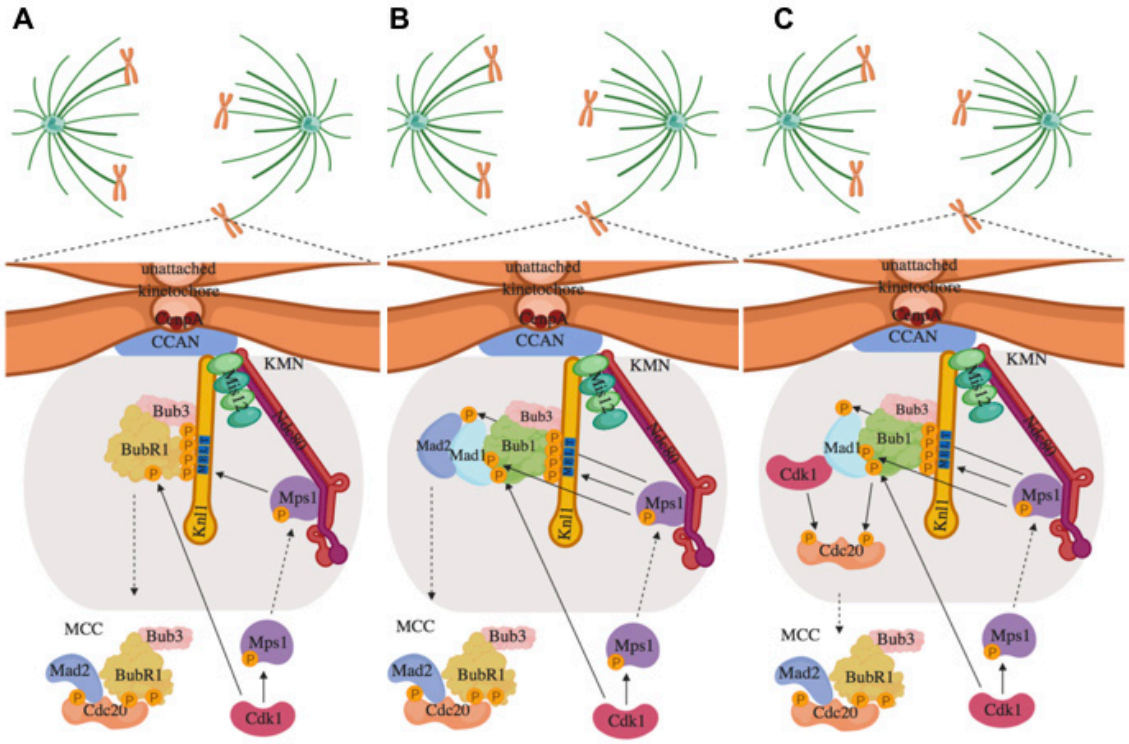

Figure 2. Paths to Mitotic Checkpoint Complex (MCC) formation. Cdk1 phosphorylation of Mps1 helps kinetochore recruitment of Mps1 to (**A**) recruit BubR1-Bub3 complex for its incorporation into MCC, (**B**) recruit Bub1-Bub3 for Mad1-Mad2 docking and Mad2 incorporation into MCC, and (**C**) recruit Bub1-Bub3 for Mad1-Cdk1 docking for Bub1- and Cdk1-dependent phosphorylation of Cdc20 and incorporation into MCC.

of MCC members to block the APC/C[65,66]. Cdk1-dependent phosphorylation of Cdc20 appeared to have a role in reducing Cdc20 affinity for APC/C while increasing that for other MCC proteins[65–68]. Thus, Cdk1, the cell cycle engine, though paving the way for its own inactivation by phosphorylating APC/C, was instrumental for the checkpoint SAC that would block APC/C activation until correct spindle assembly[66]. These observations also helped to explain why the SAC does not get reactivated at the onset of anaphase, when loss of chromatid cohesion causes loss of kinetochore tension, a condition that would have activated the SAC at earlier stages[69,70]. This was shown to be due to the concomitant reduction of Cdk1 because of the mentioned coupling of anaphase onset with degradation of cyclin B[69,70]. A few years later, the notion that Cdk1 was required for the SAC function was reinforced by the findings that, in the Xenopus egg extract system, Mps1 was phosphorylated by Cdk1 and that this phosphorylation substantially helped Mps1 activity in its fundamental role for the SAC[71].

Very recently, through careful biochemical dissection, important observations have described in closer detail how Cdk1 is an integral part of the SAC mechanisms[72,73]. Indeed, it has been shown that kinetochore localization of Mps1, in human cells, greatly depends on direct phosphorylation by Cdk1; thus, Cdk1 controls activity and localization of Mps1[72]. Mps1, in turn, helps kinetochore localization of Cdk1[73–76]. As mentioned earlier, by phosphorylating Knl1, Mps1 creates a docking site for kinetochore localization of Bub1, and cooperative Cdk1- and Mps1-dependent phosphorylations of Bub1 are required to recruit Mad1 at kinetochores[42,43,50,59,77]. Kinetochore localization of Mad1 is crucial for its ability to convert Mad2 in the effective form that incorporates into the MCC[61]. However, it has also recently been shown that Mad1 stably interacts with Cdk1 and that Mps1, through kinetochore recruitment of Mad1, in turn, promotes kinetochore localization of Cdk1 (Figure 2)[72,73]. At kinetochores, Cdk1 may further phosphorylate other substrates to sustain the SAC like Cdc20 or BubR1 and possibly also help error correction and SAC resolution by favoring BubR1 interaction with the protein phosphatase PP2A-B56[65,78–80]. Recent evidence also indicated how the indirect downregulation of the protein phosphatase PP2A-B55 activity by Cdk1 is instrumental for the SAC-promoting action of Cdk1 itself[72,81]. In addition, it should be noted that kinetochore localization of Mps1 is favored by the activity of Aurora B, perhaps by phosphorylating members of the Ndc80 complex[42]. However, centromere localization of Aurora B depends on other components of the Chromosomal Passenger Complex (CPC), composed of survivin, borealin, INCENP, and Aurora B itself, and Cdk1 activity is required, directly and indirectly, for CPC centromeric localization[82–84]. Thus, even by mastering CPC localization, Cdk1 affects Mps1 and is fundamental for SAC action.

Concluding remarks and further questions

The recent advancements, reviewed here, in the mechanisms of mitotic exit and in particular in how Cdk1 mechanistically serves the SAC, suggest that Cdk1 is an integral part of the SAC system. Thus, perhaps the cell cycle engine, Cdk1, and the checkpoint, SAC, are not to be viewed any longer as separate mechanisms but rather as integrated systems that ensure correct execution of complex biological tasks. Important hints have also been recently provided on how the SAC can be silenced, such as on priming mechanisms for protein phosphatases that would reverse SAC-activating phosphorylations upon bipolar chromosome attachments, in addition to the notion that the MCC itself undergoes proteasome-dependent turnover for rapid SAC silencing[79,84–88]. Nevertheless, major phosphatases like PP1 and PP2A are directly or indirectly inhibited by Cdk1 activity[22]. Thus, it is still unclear whether chromosome attachment and kinetochore tension are sufficient to dislodge kinases and let phosphatases take the upper hand for SAC silencing or whether these conditions also affect the activity of crucial SAC kinases[40]. Based on our previous observations, we hypothesize in this regard that Cdk1 activity could be locally downregulated by non-proteolytic means upon bipolar chromosome attachment and that this would lead to SAC silencing[89–92]. If this were true, a proteolysis-independent negative control of Cdk1 would be required for SAC silencing, ahead of and for final, proteolysis-dependent, Cdk1 inactivation and mitotic exit.

Abbreviations

APC/C, Anaphase Promoting Complex/Cyclosome; Cdk1, cyclin B-cdk1 complex; CPC, Chromosomal Passenger Complex; Gwl, Greatwall kinase; CCAN, Constitutive Centromere Associated Network; KNM, Knl1 complex, Ndc80 complex, Mis12 complex; MCC, Mitotic Checkpoint Complex; SAC, Spindle Assembly Checkpoint

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