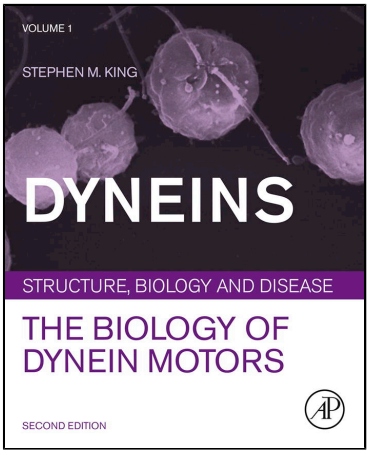

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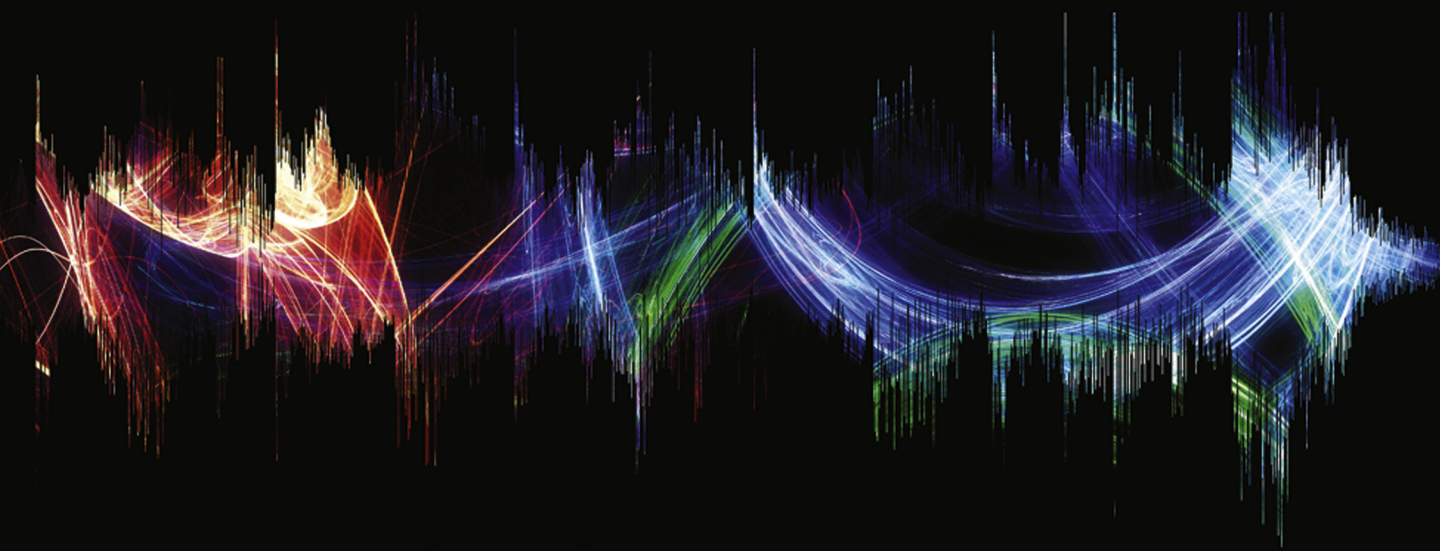

Dyneins: Structure, Biology And Disease, Second Edition, 2018, 516-533

18

Role of cytoplasmic dynein and dynactin in mitotic checkpoint silencing

Cody W. Lewis, Gordon K. Chan
University of Alberta, Edmonton, AB, Canada

Cells need to maintain their genomic stability; therefore chromosomes must be faithfully segregated during mitosis. The failure to correctly segregate chromosomes induces aneuploidy, which causes genetic diseases including Klinefelter syndrome [1] and Down syndrome [2] and is associated with cancer [3]. To achieve faithful chromosome segregation, forces are required to congress the chromosomes to the metaphase plate and pull sister chromatids apart during anaphase. The forces are generated through the attachment of microtubules (MTs) to kinetochores. MT dynamics and molecular motors contribute to generating the force required for chromosome alignment and segregation. Cytoplasmic dynein/dynactin plays an important role in transporting cargos such as chromosomes and regulatory proteins during mitosis. The mitotic checkpoint is a fail-safe mechanism that prevents premature chromosome segregation. Even if a single chromosome is unaligned, the mitotic checkpoint prevents mitotic exit by generating an "anaphase wait" signal [4]. The mitotic checkpoint monitors kinetochore–MT attachment and tension to ensure that all chromosomes are properly attached and aligned before the onset of anaphase. Once metaphase alignment occurs, the mitotic checkpoint is silenced for anaphase to proceed. In this review, the role of cytoplasmic dynein/dynactin in mitotic checkpoint silencing will be discussed.

18.1 Kinetochore

The kinetochore is a complex protein structure that is assembled on the centromeric chromatin of the sister chromatids. The kinetochore serves as the site of MT attachment as well as mitotic checkpoint regulation. The kinetochore is composed of approximately 200 different constitutive (always present) and transient proteins [5,6]. It appears as a trilaminar stack of plates

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Dyneins: Structure, Biology And Disease, Second Edition, 2018, 516-533

when viewed by transmission electron microscopy with conventional glutaraldehyde fixation [7]. The composition of the inner and outer layers is well characterized, whereas the composition of the middle layer is not well defined. More gentle fixation technique, high-pressure freezing, revealed that the outer layer is composed of a network of fine fibers [8,9]. The inner layer is composed of constitutive proteins and complexes that link the kinetochore to centromeric DNA. The inner layer contains proteins such as the histone H3 variant centromere-associated protein (CENP)-A and DNA-binding proteins CENP-B and CENP-C [10]. On the centromeric DNA, the constitutive centromere-associated network serves as a platform for the assembly of the kinetochore during mitosis [11]. The outer kinetochore layer contains many transient proteins that accumulate on the kinetochore during late G2 phase and early mitosis. When MTs are not attached, the outermost kinetochore layer appears as a fibrous protein network, the fibrous corona [7]. This outer layer contains dynein/dynactin [12–15], CENP-E [16] (a kinesin-like motor protein), KMN protein complexes (Knl1, Mis12/Nsl1/Dsn1, Ndc80/Nuf2/Spc24/Spc25) [17], and the spindle- and kinetochore-associated (Ska) complex, [18–24] which directly interface with the MTs allowing the chromosomes to be moved and positioned at the metaphase plate. The outer kinetochore plate also contains crucial mitotic checkpoint protein complexes including the RZZ (Roughdeal, ZW10, and Zwilch) [25–30], Mad1/Mad2 [31–34] and the mitotic checkpoint complex (MCC) [35–37]. For detailed reviews of the structure and assembly of the kinetochore, please see recent publications [5,38]. Cytoplasmic dynein/dynactin, from *Caenorhabditis elegans* to human, is recruited to the kinetochores during mitosis. The kinetochore recruitment of dynein/dynactin has been shown to require the RZZ complex, as well as other proteins such as Spindly, NUDE, NUDEL, and Lis1 but the precise molecular mechanism is still unclear (reviewed in Ref. [39]).

18.2 Kinetochore–microtubule attachment and error correction

Bipolar attachment of kinetochores to spindle MTs is essential for aligning chromosomes at the metaphase plate. Kinetochores can attach to spindle MTs through lateral (binding the surface of the MT) or end-on attachment (kinetochore binding to the end of the MT); however, the desired outcome is to achieve bioriented end-on MT attachment [40]. During prometaphase, kinetochore–MT attachments are made in a stochastic manner and some of these are not conducive for faithful chromosome segregation. For example, if both sister kinetochores become anchored to MTs originating from the same spindle pole (syntelic attachments), then the forces necessary to segregate

Dyneins: Structure, Biology And Disease, Second Edition, 2018, 516-533

sister chromatids would not be present, which would induce aneuploidy if not corrected (reviewed in Refs. [41,42]). An error correction mechanism exists and is regulated by reversible phosphorylations [43]. Incorrectly attached MTs can be destabilized through increased phosphorylation of the KMN complex, the mitotic centromere–associated kinesin (MCAK) of the kinesin 13 family of MT depolymerases [44,45], and other proteins by kinases such as Aurora B [46,47], Plk1 [48], and Cdk1/cyclin A [49]. The chromosomal passenger complex (CPC), containing the catalytic module Aurora B kinase and the scaffolding protein INCENP, localizes to the inner centromere and acts as a kinetochore tension sensor. In response to incorrectly attached kinetochore and unequal kinetochore tension, the CPC promotes error correction by destabilizing kinetochore–MT attachment and activates the mitotic checkpoint (reviewed in Ref. [50]). Once the kinetochore–MT attachment is severed, the phosphorylation of the KMN complex is reversed by proteins phosphatases (PP1 and PP2A) [46,51], which allows the kinetochore to reattach to MTs and eventually achieve correct attachment. The mitotic checkpoint prevents premature anaphase to allow time for the error correction and all chromosomes to align at the metaphase plate.

18.3 The mitotic checkpoint

The mitotic checkpoint prevents the metaphase–anaphase transition by inhibiting the degradation of cyclin B and securin. Cyclin B is a Cdk1 regulatory subunit that is needed to drive mitosis [52], whereas securin is a repressor of separase, an enzyme that hydrolyzes RAD21, a subunit of the cohesin complex that holds sister chromatids together [53]. The mitotic checkpoint detects chromosome alignment by monitoring (1) kinetochore–MT attachment and (2) equal sister kinetochore tension. The kinetochore sends out an "anaphase-wait" signal when these two conditions are not satisfied. The unattached or unaligned kinetochore recruits sensor and effector proteins that inhibit the anaphase promoting complex/cyclosome (APC/C) [54,55]. The APC/C is an E3 ubiquitin ligase, which together with its coactivator Cdc20 [53] triggers the onset of anaphase through the degradation of cyclin B and securin. Mitotic checkpoint genes were originally identified in budding yeast genetic screens [31,56,57]. Bub1, Bub3, Mad1, Mad2, Mad3, and Mps1 were found to be conserved from yeast to human [58,59]. Many conserved kinetochore kinases, including Bub1, Plk1, Mps1, and Aurora B, were also identified to be important mitotic checkpoint signaling regulators [60]. During prometaphase, the RZZ complex localizes to kinetochores where it is required for the recruitment of Mad1 and Mad2 [61,62]. With the formation of a Mad1/Mad2 tetramer at the kinetochore of an unaligned chromosome, Mad2 undergoes a templated conversion from the open inactive form (O-Mad2) to the closed active form (C-Mad2) [63–66]. The closed Mad2 interacts with BubR1, and Bub3 to bind Cdc20, and form the

Dyneins: Structure, Biology And Disease, Second Edition, 2018, 516-533

MCC [36,67,68]. The MCC directly binds the APC/C and inhibits its activity, thereby preventing anaphase onset (reviewed in Ref. [60]). However, once the mitotic checkpoint is satisfied, the MCC is disassembled, allowing free Cdcd20 to activate the APC/C. The inactivated MCC and other mitotic checkpoint proteins are removed from the kinetochore during metaphase by dynein/dynactin [69,70].

18.4 Mitotic checkpoint silencing

The silencing of the mitotic checkpoint occurs in at least three ways: (1) molecular disassembly of the MCC; (2) displacement of the Mps1 kinase from kinetochore following kinetochore–MT attachment; and (3) dynein/dynactin-mediated shedding of mitotic checkpoint proteins from kinetochores (reviewed in detail in the subsequent sections).

Currently, three players have been identified that facilitate mitotic checkpoint silencing through the disassembly of the MCC: p31^{comet}/thyroid hormone receptor interactor 13 (TRIP13), CCT chaperonin, and CUEDC2. p31^{comet} is a Mad2-interacting protein, which binds preferentially to C-Mad2 and blocks conversion of O-Mad2 to C-Mad2 [71–74]. Mad2-p31^{comet} binding also promotes disassembly of Cdc20 from BubR1 and Bub3 of the MCC [75]. TRIP13, an AAA ATPase, binds p31^{comet} and participates in the disassembly of MCC [76,77]. TRIP13 forms a hexameric oligomer ring structure in vitro and catalyzes the conversion of C-Mad2 to O-Mad2 [78,79]. CCT chaperonin (TCP1–Ring complex) is an ATP-independent complex that mediates the disassembly of mitotic checkpoint subcomplexes that lack Mad2 [80]. CUEDC2, a CUE domain-containing protein, is required for the release of Mad2 from the APC/C during mitotic exit [81]. Following phosphorylation by Cdk1, CUEDC2 binds to Cdc20 but the detailed mechanism that leads to the disassembly of MCC is unclear.

Another pathway, conserved from yeast to humans, has been described to disassemble the MCC through APC/C-dependent autoubiquitylation of Cdc20 and subsequent degradation [82–85]. The E2 ubiquitin-conjugating enzyme, UbcH10 [86,87], and the APC/C subunit APC15 [83–85] are critical in this process. Recent structural analysis of recombinant APC/C and MCC revealed that a conformational change allows the autoubiquitylation of Cdc20 [88]. This conformational change might be facilitated by p31^{comet} in higher eukaryotes [86,89].

The MCC silencing mechanisms described above do not take into account the role of the mitotic checkpoint in monitoring kinetochore–MT attachments and tension. Mps1, a kinase that is required for the initiation of the mitotic checkpoint, binds to the kinetochore through interaction with the

Dyneins: Structure, Biology And Disease, Second Edition, 2018, 516-533

kinetochore MT–binding protein, Ndc80 [90]. On binding of MT to Ndc80, the Mps1-binding site becomes inaccessible and releases Mps1 from the kinetochore [91,92]. This results in weakened kinetochore Mps1 signaling and contributes to mitotic checkpoint silencing. In budding yeast, kinetochore–MT end-on attachment displaces Mps1 kinase from its substrate Spc105 (Knl1 orthologue) [93]. The budding yeast Dam1 complex, a 10-member protein ring complex, binds to kinetochore MTs and is the functional equivalent of the metazoan Ska complex [94–96]. The Dam1 complex is recruited to MT after attachment and might physically shield the Mps1 kinase from Spc105 and initiate checkpoint silencing [93]. Kinetochore–MT attachment–induced displacement of Mps1 is proposed to be a mechanical switch that turns off kinetochore mitotic checkpoint signaling in yeast. On the other hand, protein phosphatases counteract the mitotic kinases and are required for mitotic checkpoint silencing. PP1 is targeted to kinetochores through different proteins including Knl1 [97], CENP-E [98], Sds22 [99], and the Ska complex [100]. Knl1-mediated PP1 kinetochore localization is required to counterbalance Aurora B kinase phosphorylation and mitotic checkpoint silencing [101,102]. The Ska complex, a kinetochore and MT-binding protein complex, has been found to recruit PP1 to metaphase kinetochores and drives the metaphase–anaphase transition [100]. PP1 might target different phosphorylation sites depending on the specific targeting protein. The precise mechanism is not known but it is reasonable to hypothesize that kinetochore–MT attachment allows the recruitment of the Ska-PP1 complex and reverses mitotic checkpoint signaling.

18.5 Dynein/dynactin and Spindly

Dynein/dynactin is recruited to kinetochores during mitosis in metazoans. Kinetochore recruitment is mediated by the RZZ complex [27,103] and Spindly [104,105]. Spindly is a mitotic cargo adaptor protein and together with dynein/dynactin forms an active tripartite complex [106]. Spindly binds to the kinetochore through interaction with the RZZ complex [104,107,108], which recruits the dynein/dynactin motor to kinetochores resulting in the assembly of the active complex [109]. Depletion of human Spindly by siRNA knockdown resulted in prolonged metaphase arrest [104,110,111] but did not cause the accumulation of mitotic checkpoint proteins after metaphase chromosome alignment [107,108] indicating the presence of an alternative mechanism(s) in removing mitotic checkpoint proteins from kinetochores after chromosome alignment. Gassmann et al. subsequently identified a conserved motif in Spindly that mediates kinetochore recruitment of dynein [112]. Through analysis of the Spindly motif mutant, it was found that Spindly is indeed required for dynein/dynactin-mediated shedding of kinetochore mitotic checkpoint proteins. Since Spindly depletion results in

Dyneins: Structure, Biology And Disease, Second Edition, 2018, 516-533

prolonged metaphase arrest, dynein/dynactin-mediated shedding of kinetochore mitotic checkpoint proteins must be a crucial checkpoint silencing mechanism.

18.6 Dynein/dynactin-mediated shedding of kinetochore mitotic checkpoint proteins

Since key mitotic checkpoint proteins require kinetochore localization for its checkpoint function, silencing of the checkpoint involves removing the kinetochore mitotic checkpoint proteins from the kinetochores at the end of mitosis. The dynein/dynactin motor transports the mitotic checkpoint proteins from the kinetochores to the spindle poles, a process that has been termed "shedding." Mad2 transport away from kinetochores toward the spindle pole was first observed by Howell et al. [113]. Howell et al. subsequently observed that ATP depletion resulted in the kinetochore depletion of many outer kinetochore proteins including dynein and Mad2 and their accumulation at the spindle poles in PtK1 cells [114]. Inhibition of dynein/dynactin activity through either microinjection of recombinant p50 dynamitin or antidynein antibody resulted in the failure of kinetochore depletion of Mad2 and mitotic arrest at metaphase. These results demonstrated the checkpoint silencing role of dynein/dynactin as the MT motor that mediates removal of mitotic checkpoint proteins from kinetochores at the end of metaphase. The dynein-dependent kinetochore Mad2 shedding is conserved in both *Drosophila* [115] and fission yeast [116].

Dynein light intermediate chain (LIC) was found to be an essential subunit that is required for kinetochore Mad2 shedding and mitotic checkpoint silencing [115,117]. While LIC1 siRNA-mediated depletion did not affect kinetochore recruitment of Mad2 and dynein [111,115,117] in HeLa cells, cells depleted of LIC1 are arrested in mitosis and failed to remove kinetochore Mad2 [117]. Cdk1 phosphorylation of LIC1 was shown to be required for kinetochore Mad2 shedding. More recently, a second isoform LIC2 was shown to play a nonredundant role with LIC1 in checkpoint silencing. Using quantitative imaging and siRNA-mediated depletion, Mahale et al. found that LIC2 is required for kinetochore shedding of Mad1, Mad2, ZW10, and BubR1 [118]. Comparatively, the depletion of LIC1 had little effect on the transport of BubR1. Codepletion of LIC1 and LIC2 provided an additive effect on mitotic arrest duration [111,119] and Mad2 kinetochore shedding [118]. LIC2 was found to copurify with Mad1, ZW10, and BubR1 in a TAP-tagged LIC2 expressing U-2 OS cell line. These results suggest that LIC1 and LIC2 might serve an overlapping role in mediating the dynein-dependent transport of kinetochore mitotic checkpoint proteins. LIC proteins have been shown to bind cargo adaptor proteins such as FIP3, RILP,

Dyneins: Structure, Biology And Disease, Second Edition, 2018, 516-533

BicD2, and Hook3 [120–124]. However, it is not clear whether LIC1 and LIC2 interact with the mitotic cargo adaptor Spindly and/or mitotic checkpoint proteins directly.

Studying transport of kinetochore proteins was made easier with the discovery by Arasaki et al. that the small molecule nordihydroguaiaretic acid (NDGA) affects dynein/dynactin cellular functions [125]. Of particular interest is that NDGA treatment resulted in shedding of kinetochore proteins such as ZW10 and EB1 accompanied by their accumulation at the spindle poles in HeLa cells. Most interestingly, the authors showed that NDGA treatment enhanced ZW10 interaction with dynein intermediate chain and the dynactin $p150^{Glued}$. Further investigation showed that transport of kinetochore proteins such as the RZZ complex is dependent on kinetochore–MT attachments (either bipolar or monopolar) but is independent of kinetochore tension and Aurora B kinase activity [69]. Not surprisingly, proteins that are dynamic components of the kinetochores such as Mad2, Mps1, Plk1 [126,127], Spindly, and the RZZ complex [25,128] respond to NDGA treatment by kinetochore shedding and spindle pole accumulation. Proteins that are known to be stable components of the kinetochore such as Zwint-1, MCAK, and Aurora B [126,127,129] do not respond to NDGA treatment. While NDGA treatment produced clear results for some kinetochore proteins, some are difficult to interpret and/or variable. NDGA from different sources and different batches has different potency and activity, and the assay requires careful quality control (Vos and Chan, unpublished data). Silva et al. performed the sodium azide/2-deoxyglucose ATP depletion assay and found that BubR1 and Bub1 substantially relocalized from kinetochores to spindle poles at metaphase, while NDGA treatment did not result in accumulation of BubR1 at spindle poles [130]. The length of ATP depletion seems to affect the behavior of BubR1 in this assay; nonetheless, BubR1 and Bub1 are dynein cargos. BubR1 kinetochore removal during metaphase is independent of dynein, and other mechanism of removal exists [117]. ATP depletion and NDGA probably affect different targets. Surprisingly, Hec1 and Mis12, components of the KMN complex, were observed to localize to spindle poles at metaphase. It is not clear whether there were significant accompanying kinetochores shedding with the spindle pole accumulation of Hec1 and Mis12; nonetheless, Hec1 and Mis12 are dynein cargos. It is not intuitive why the KMN complex would be disassembled from kinetochores at metaphase as they are required for stable end-on kinetochore–MT attachment; however, it has been observed that the KMN complex starts to disassemble before anaphase onset [131]. Another interesting observation is that Cdc20, a component of the MCC, is not transported to spindle poles in either NDGA treatment or ATP depletion assays [69,130]. Since Mad2, BubR1, and Bub3 are all transported to the spindle poles at metaphase, this implies that the MCC must be at least partially disassembled at metaphase. The precise mechanisms of action for

Dyneins: Structure, Biology And Disease, Second Edition, 2018, 516-533

NDGA and ATP depletion remain elusive but disassembly of MCC has been shown to require ATP [75]. Nonetheless, both NDGA and ATP depletion are valuable research tools.

Other dynein cargos of interest include APC3 (Cdc27), a component of APC/C, and cyclin B. Cyclin B localizes to chromosomes, kinetochores, the mitotic spindle, and spindle poles during mitosis [132]. Degradation of cyclin B is a signature event for metaphase–anaphase transition and was observed to be spatially regulated starting from the metaphase mitotic spindle [133]. In *Drosophila* syncytial embryos, cyclin B degradation starts from the spindle poles toward the spindle equator in a wave at late metaphase [134]. Cyclin B also binds the APC/C through Cdk cofactor Cks and the APC3 subunit [135]. APC/C subunits, including APC3, have been reported to localize at centrosomes, MTs, chromosomes, and kinetochores. APC/C at spindle poles has been reported to be hypophosphorylated and might represent an inactive pool [136]. APC/C subunits have also been reported to localize to centromeres, mitotic spindle, and spindle poles [137,138]. A phosphospecific APC1 antibody was shown to label both kinetochores and spindle poles indicating that APC/C might be spatially regulated. It is unclear whether dynein-mediated transport of cyclin B and APC3 to spindle poles is required for spatial and temporal regulation of cyclin B degradation.

Recently, the dynein/dynactin-mediated streaming behavior of mitotic checkpoint proteins to the spindle poles has been incorporated into a spatiotemporal mitotic checkpoint silencing mathematical model [139]. The model postulates that the spindle poles act as a signal integrator for checkpoint silencing, receiving transport of mitotic checkpoint proteins from the attached kinetochores. Presence of unattached kinetochore somehow inhibits poleward flux of mitotic checkpoint proteins. Only when the last kinetochore achieves MT attachment, mitotic checkpoint proteins accumulate at the spindle poles and trigger mitotic checkpoint silencing. However, NDGA treatment of cells results in accumulation of mitotic checkpoint protein at the spindle poles but does not cause premature silencing [69,125]. The relationship between mitotic checkpoint protein accumulation at spindle poles and the silencing trigger might be more complicated. While many aspects of the model require experimental validation, the model does offer a possible solution as a robust mechanism for mitotic checkpoint silencing [139,140]. Based on the current literature, a mitotic checkpoint silencing model is depicted in Fig. 18.1.

18.7 Outstanding questions

APC/C^{Cdc20} activation [141], Cdk1/cyclin B inactivation [142–145], and CPC removal from chromosomes [146,147] are all crucial steps for mitotic checkpoint silencing and onset of anaphase. There are still significant outstanding

Dyneins: Structure, Biology And Disease, Second Edition, 2018, 516-533

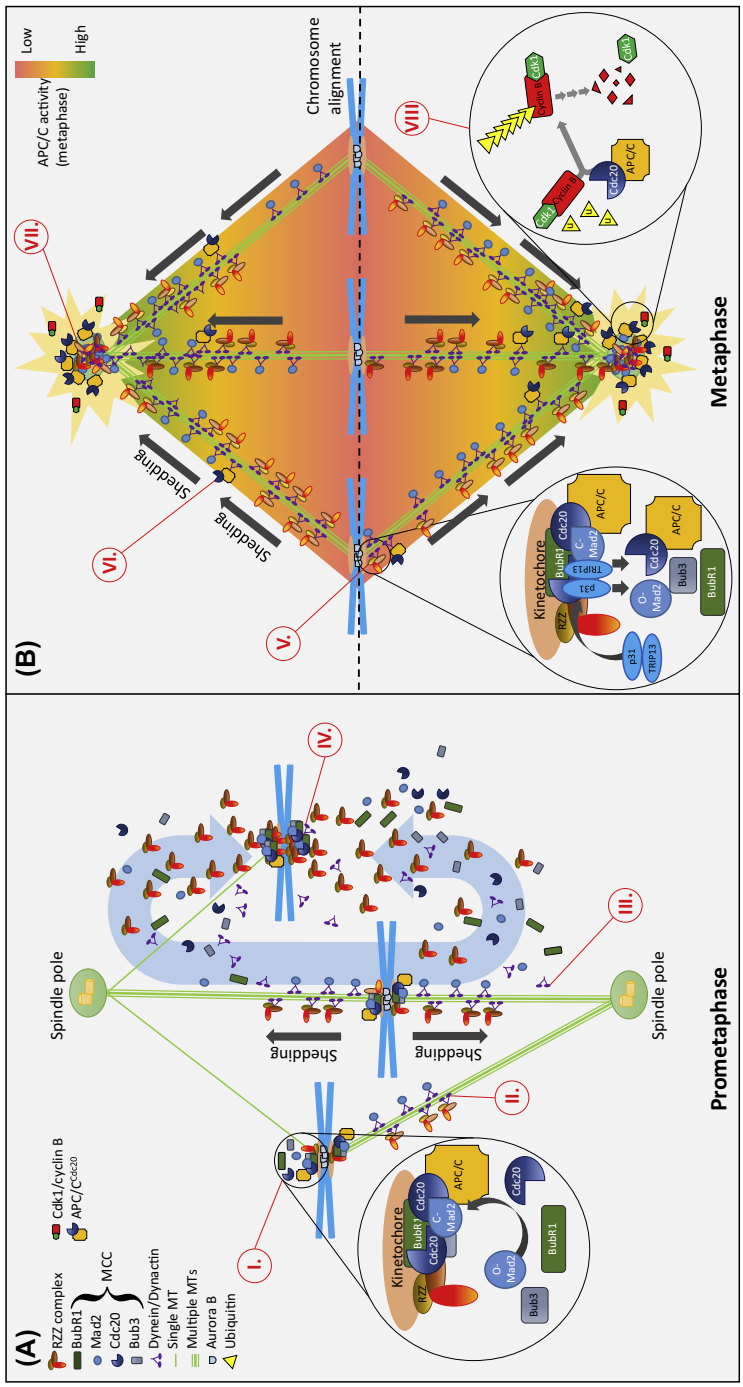

Figure 18.1 Mitotic checkpoint silencing in mammalian cells is facilitated by dynein/dynactin-mediated transport of kinetochore mitotic checkpoint proteins along spindle microtubules (MTs) to the poles. (A) During prometaphase, MTs emanating from spindle poles attach to kinetochores. I. Unattached kinetochores or kinetochores lacking a "full" complement of MT attachments recruit dynein/dynactin and mitotic checkpoint proteins such as RZZ (Roughdeal, ZW10, and Zwilch) and Mad2. Here the kinetochore serves as a platform for the assembly of the mitotic checkpoint complex (MCC), which is composed of BubR1, Bub3, Mad2, and Cdc20; inactive O-Mad2 is converted to active C-Mad2 (see *inset circle*). II. Kinetochores that have achieved bipolar attachment engage dynein/dynactin-mediated transport of mitotic checkpoint proteins from the kinetochore toward the spindle poles (shedding). III. During transport, dynein/dynactin and the mitotic checkpoint proteins, which are not stably interacting with MTs, fall off the mitotic spindle. IV. Dynein/dynactin and the mitotic checkpoint proteins are recruited back to unattached kinetochores to maintain the active state of the mitotic checkpoint. (B) During metaphase, kinetochores achieve bipolar spindle attachment. V. Bipolar attachment of kinetochores stimulates the disassembly of MCC, which is partly facilitated by the binding of $p31^{Comet}$/TRIP13 to Mad2 (see *inset circle*). VI. The disassembled MCC components as well as other mitotic checkpoint proteins undergo dynein/dynactin-mediated shedding to spindle poles. VII. Mitotic checkpoint proteins (e.g., Mad2 and the RZZ) and components of the APC/C (e.g., Cdc27) accumulate at the spindle poles. VIII. Once all kinetochore–MT attachments are made, mitotic checkpoint silencing occurs, which leads to the activation of the APC/C^{Cdc20}. The APC/C^{Cdc20} is first activated at the spindle poles where it ubiquitylates cyclin B, but its activity spreads outward to the kinetochores to allow ubiquitylation of securin. Color gradient shows the progression of APC/C^{Cdc20} activity.

questions on the mechanism of mitotic checkpoint silencing specifically related to dynein/dynactin-mediated shedding of kinetochore mitotic checkpoint proteins. It is not known how kinetochore–MT attachment activates the dynein/dynactin-mediated transport. In HeLa cells where each kinetochore attaches to an average of 17 MTs [148,149], the mechanism that coordinates and initiates dynein/dynactin transport is not clear. Phosphorylation of dynein intermediate chain is required for its localization at kinetochores during mitosis and regulates dynein/dynactin-mediated transport [150,151]. Dephosphorylation of dynein intermediate chain by PP1γ stimulates dynactin binding and poleward transport; whether other posttranslational modifications of dynein/dynactin specify distinct regulatory roles in checkpoint silencing has yet to be examined in detail. Some kinetochore proteins are transported toward the spindle poles and others are not. The mechanism that determines cargo selectivity is not known. After final kinetochore attachment and alignment, the initial trigger that activates checkpoint silencing is not known. Mitotic checkpoint proteins accumulate at the spindle poles and are then released into the cytoplasm. The mechanism that governs checkpoint protein binding and release at spindle poles is not known.

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