Roles of Aurora Kinases in Mitosis and Tumorigenesis

Jingyan Fu, Minglei Bian, Qing Jiang, and Chuanmao Zhang

The Key Laboratory of Cell Proliferation and Differentiation of Ministry of Education and the State Key Laboratory of Bio-membrane and Membrane Biotechnology, College of Life Sciences, Peking University, Beijing, China

Abstract

Aurora kinases, which have been implicated in several vital events in mitosis, represent a protein kinase family highly conserved during evolution. The activity of Aurora kinases is delicately regulated, mainly by phosphorylation and degradation. Deregulation of Aurora kinase activity can result in mitotic abnormality and genetic instability, leading to defects in centrosome function, spindle assembly, chromosome alignment, and cytokinesis. Both the expression level and the kinase activity of Aurora kinases are found to be up-regulated in many human cancers, indicating that these kinases might serve as useful targets for the development of anticancer drugs. This review focuses on recent progress on the roles of Aurora kinases in mitosis and tumorigenesis. (Mol Cancer Res 2007;5(1):1–10)

Introduction

Aurora kinases represent a novel family of serine/threonine kinases crucial for cell cycle control. The first Aurora kinase was discovered in *Drosophila* (1). Because its mutations resulted in a failure of centrosome separation, leading to the formation of monopolar spindles, it was given the name "Aurora," reminiscent of the North Pole. Since then, homologues of Aurora have been identified in different species. *Saccharomyces cerevisiae* has a single Aurora kinase: Ipl1 (increases in ploidy 1; ref. 2). In *Caenorhabditis elegans* (3, 4), *Drosophila* (1, 5), and *Xenopus* (6, 7), there are two types of Aurora kinases: Aurora-A and Aurora-B. Mammals own at least three Aurora kinases: Aurora-A, Aurora-B, and Aurora-C (for nomenclature, see ref. 8).

Special interest in Aurora kinases has arisen since people discovered that defects in these kinases lead to severe mitotic abnormality. Silencing of Aurora-A leads to abnormal spindle morphology in *C. elegans, Drosophila*, and human cells (1, 9, 10), whereas disruption of Aurora-B causes chromosome misalignment and cytokinesis failure in both *Drosophila* and HeLa cells (11, 12), indicating their multiple roles in centrosome function, chromatid separation, and cytokinesis. Little is known about Aurora-C until recent reports show that Aurora-C is also a chromosomal passenger protein, and that it binds directly to INCENP and survivin *in vitro* (13-15). Given the facts that Aurora-C-INCENP can phosphorylate endogenous histone H3 in mammalian cells, and that Aurora-C could rescue the Aurora-B–silenced multinucleation phenotype in human cells, Aurora-B and Aurora-C may be functionally overlapping (13-15). Here, we will refer primarily to Aurora-A and Aurora-B because the expression of Aurora-C is largely limited to the testes, and because there is a paucity of Aurora-C–related data.

Aurora kinases are overexpressed in a variety of tumor cell lines (16-18), suggesting that these kinases might play a role in tumorigenesis. In particular, Aurora-A can transform certain cell lines when overexpressed (17, 19, 20). Inhibitors of Aurora kinases are used in cultured cells and xenograft models to treat cancer, and an encouraging effect has been shown (21, 22).

In this article, we mainly review the roles of Aurora kinases in the regulation of mitotic progression and tumorigenesis. We will also discuss these kinases as potential targets for cancer diagnosis and therapy.

Aurora Kinases and Their Subcellular Distribution

Aurora kinases comprise mainly two domains: a regulatory domain in the NH_2 terminus and a catalytic domain in the COOH terminus. The regulatory domain is diverse largely, whereas the catalytic domain with a short segment of diverse COOH terminus shares >70% homology among Aurora-A, Aurora-B, and Aurora-C (Fig. 1A). There is a D-Box in the COOH terminus and an A-Box in the NH_2 terminus of Aurora kinases, which are responsible for degradation (23-26). Sequence analysis and point mutations revealed that phosphorylation at the threonine site within the catalytic domain is required for the kinase activity (27, 28).

Crystal structures of the Aurora-A and Aurora-B catalytic domain have been resolved recently (28-30). Like other serine/threonine protein kinases, Aurora kinases contain two lobes in their catalytic domain joined up by a hinge. The N lobe is responsible for positioning the ATP phosphate group through an αC helix, whereas the activation loop within the C lobe is able to harbor substrates (28, 31). Only when the two lobes arrive at a certain conformation can the Aurora kinases fulfill

their kinase functions. Thus far, the NH_2-terminal domain has not yet been explored in the tertiary structure level.

Despite great similarities in sequences and structures, Aurora kinases are completely different in their subcellular distribution (Fig. 1B). Aurora-A localizes to the pericentriolar material from the end of S phase to the beginning of the next G_1 and spreads to the pole proximal ends of spindle microtubules during mitosis. In contrast, Aurora-B remains in the nucleus and moves to centromeres from prometaphase to metaphase. After anaphase begins, Aurora-B relocates gradually to the midzone and persists at the midbody until cytokinesis is completed. Moreover, Aurora-B undergoes different localizations along with at least three other partners: INCENP, survivin, and Borealin. They form a tight complex within the cell during mitosis and are named "chromosomal passengers" as they move precisely from site to site at specific times.

Aurora Kinases and Mitotic Control

Aurora-A and Aurora-B exhibit divergent functions in mitotic control, corresponding to different subcellular distribution of the two kinases. Aurora-A is mainly involved in

centrosome function, mitotic entry, and spindle assembly, whereas Aurora-B participates in chromatin modification, microtubule-kinetochore attachment, spindle checkpoint, and cytokinesis. Along with these two kinases, different partners and substrates take part in these processes.

Aurora-A Regulates Mitotic Spindle Assembly

The enrichment of Aurora-A either to the centrosome or microtubule compartment suggests that Aurora-A may play dual roles in mitotic spindle assembly (Fig. 2).

In G_2 phase, Aurora-A first localizes to pericentriolar material and is activated by the LIM protein Ajuba (32), which is required for centrosome maturation. Centrosome maturation takes place every cell cycle, referring to the recruitment of several pericentriolar material proteins that enhance microtubule nucleation ability in the late G_2 phase, such as γ-tubulin and some coiled-coil proteins (33). Depletion of Aurora-A decreases centrosomal γ-tubulin intensity as well as two other pericentriolar material components in *C. elegans* embryos (9). It has been corroborated in *Drosophila* and mammalian cells that Aurora-A is required to localize centrosomal protein
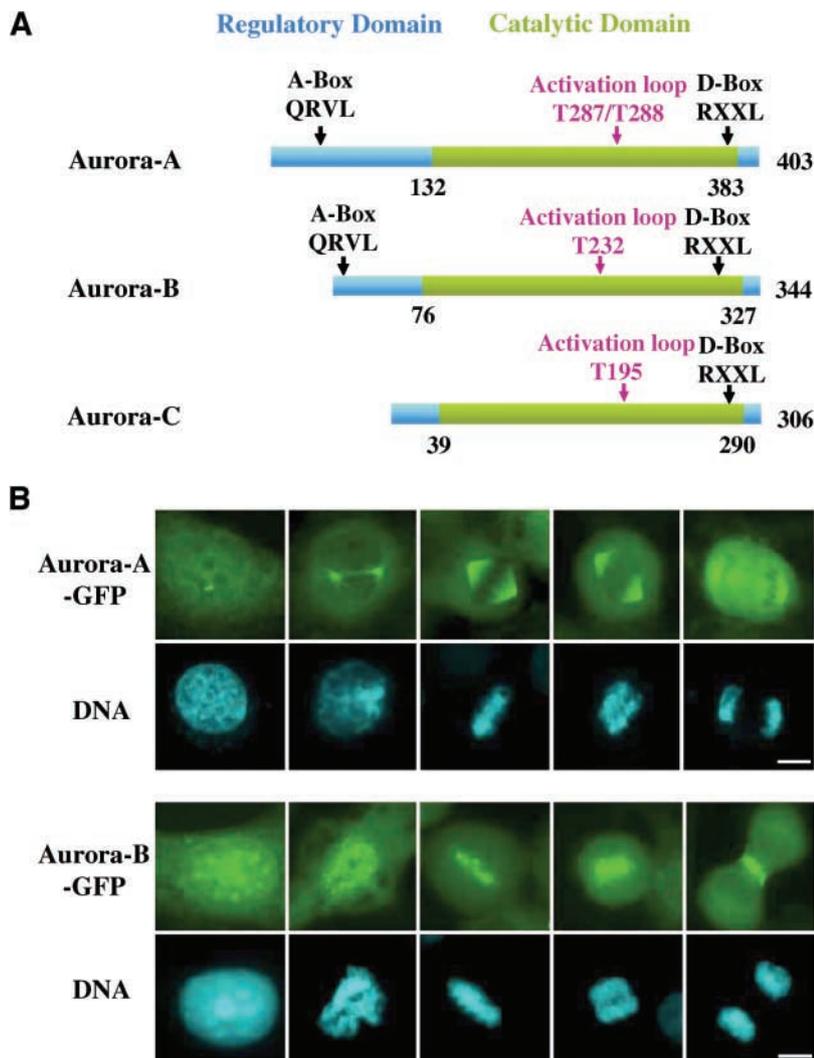

Figure 1. Human Aurora kinase structure and their subcellular distribution during mitosis. **A.** Aurora kinases contain mainly two domains: the NH_2-terminal regulatory domain (*blue*) and the COOH-terminal catalytic domain (*green*). The three homologues Aurora-A, Aurora-B, and Aurora-C share great homology in the catalytic domain yet differ in the NH_2-terminal domain and a small sequence in the COOH terminus (*blue*). Crucial structures (*arrows*). Phosphorylation at threonine within the activation loop is necessary for kinase activity (*red*). Besides, two boxes are identified as the recognition sites of APC/C^{Cdh1} and promoter of degradation (*black*): destruction box (D-Box) and D-Box-activating Box (DAD/A-Box), respectively. These features have been confirmed by experiments in both Aurora-A and Aurora-B; yet, the structure of Aurora-C is deduced by sequence alignment and seems to lack the A-Box. **B.** Aurora-A and Aurora-B are distinct in subcellular distribution during mitosis. By G_2 phase, Aurora-A localizes to pericentriolar material and persists throughout cell cycle. Additionally, it spreads to the minus ends of the mitotic spindle microtubules and midzone microtubules during mitosis. Diversely, Aurora-B and its "passenger" partners remain a part of centromeres from prometaphase to metaphase. After chromatids begin to separate, they relocate to midzone and persist at the midbody until cytokinesis is completed. These photographs were prepared by transfecting HeLa cells cultured on coverslips with Aurora-A-GFP and Aurora-B-GFP, respectively. After fixing with methanol and acetone (1:1), coverslips were stained with 4′,6-diamidino-2-phenylindole for DNA and mounted. Cells were viewed under an Olympus IX71 immunofluorescence microscope, and photographs were taken with SPOT cool CCD and SPOT image software. Bar, 5 μm.

Figure 2. Aurora-A functions in spindle assembly. Two pools of Aurora-A exist within the cell: the centrosome Aurora-A and the microtubule Aurora-A. Before nuclear envelope breakdown (*NEBD*), Aurora-A localizes to the centrosome, where it is activated by Ajuba. Active Aurora-A further recruits γ-tubulin, TACC/MAP215 complex, centrosomin, and other centrosomal proteins to promote centrosome maturation and microtubule nucleation ability. Distinctively, the microtubule Aurora-A is diffused into cytoplasm and remains inactive. Once the nuclear envelope breaks down, this pool of Aurora-A is activated by the Ran pathway. During this process, high concentration of RCC1 near chromosomes transforms Ran-GDP into a GTP-bound state, which later binds to importin-β and releases TPX2. TPX2 not only activates Aurora-A but also localizes it to the microtubules, where Aurora-A exerts its functions in spindle assembly. Inactive form (*yellow*) and active form (*green*) of Aurora-A.
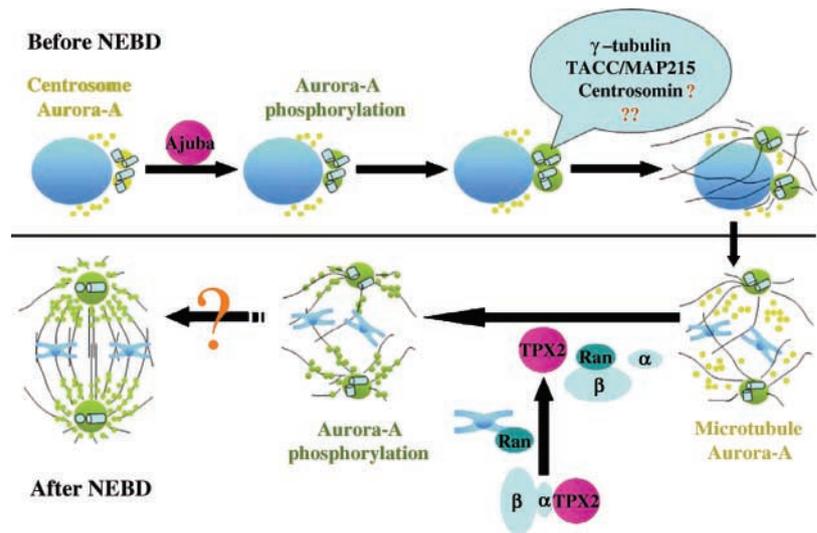
centrosomin, which could bind γ-tubulin and other centrosomal components (34, 35). Moreover, Aurora-A is necessary to recruit D-TACC/maskin to the centrosome and phosphorylates D-TACC/maskin at the centrosome in *Drosophila* and *Xenopus* (36-38). D-TACC/maskin forms a complex with Msps/XMAP215 and stabilizes microtubules around the centrosome by antagonizing the depolymerization activity of MCAK (37, 39). Therefore, it is convincing that Aurora-A facilitates centrosome maturation in microtubule nucleation ability by recruiting and/or phosphorylating centrosomal components, sequentially contributing to mitotic spindle assembly.

The second role of Aurora-A in spindle assembly is exerted when it localizes to the pole proximal ends of microtubules after nuclear envelope breakdown, prevailingly considered as a part of the Ran-spindle assembly pathway. Ran is a small GTPase and has been implicated in multiple mitotic events. During spindle assembly, high concentration of RCC1 near the chromosomal region transforms Ran-GDP into a GTP-bound state, which later releases the spindle assembly factors, such as TPX2 and NuMA, by inhibiting importin-α/β (40). The Ran-spindle assembly pathway was explored more extensively after the relation between TPX2 and Aurora-A was uncovered. The NH_2 terminus of TPX2 directly interacts with the COOH terminus of Aurora-A (41), triggering conformational changes in the activation segment of the kinase, thus not only stimulating the autophosphorylation but also burying the phosphothreonine site from protein phosphatase 1 dephosphorylation (28). TPX2 is also required for targeting Aurora-A to the spindle (41, 42). The interaction between Aurora-A and TPX2 undergoes the regulation of Ran-GTP gradient (42). Recently, profound evidence was shown that Aurora-A–coated magnetic beads could function as MTOCs in the presence of Ran-GTP in *Xenopus* egg extracts and induce bipolar spindle formation without centrosomes and chromatin, confirming the significance of Aurora-A in centrosome function and spindle assembly (43). It might be a hint that Ran directs spindle assembly by transforming its gradient of active form to the activity of protein kinases, such as Aurora-A, hence passing the commands on to the yet unknown downstream substrates.

Therefore, identifying the substrates of Aurora-A will be an exciting task in investigating the mechanism of spindle assembly.

Interestingly, three newly published articles identified HURP as a Ran-imporin-β–regulated protein involved in spindle assembly (44-46). HURP mainly concentrates at the chromosome proximal ends of mitotic spindle (45, 46), where it stabilizes kinetochore fibres and promises a normal interkinetochore tension and efficient kinetochore capture (45, 46). Such HURP distribution exhibits a Ran-GTP dose-dependent characteristic and is damaged by excessive importin-β or Ran-GDP (44, 45). It has been reported that Aurora-A phosphorylates and stabilizes HURP *in vitro* and *in vivo* during mitosis (47). Given the reverse gradient of their distribution on microtubules, it would be really important to investigate how Aurora-A and HURP correspond to the signal of the Ran pathway.

Aurora-A Regulates Centrosome Separation

Duplicated centriole pairs separate at the G_2-M transition, marching to the opposite poles of the cell for proper establishment of bipolar spindle. There is evidence that centrosome separation requires functional Aurora-A. RNA interference or microinjection of Aurora-A antibody in HeLa cells could prevent centrosome separation (10). In *C. elegans* embryos, Aurora-A knockdown by RNA interference could interrupt centrosome separation and spindle assembly (9). In *Xenopus*, a dominant-negative mutation of Aurora-A results in monopolar spindle (6, 48), a phenomenon similar to the inhibition of a kinesin-related protein XlEg5 (48). Because XlEg5 is phosphorylated by *Xenopus* Aurora-A both *in vivo* and *in vitro* (48), it might be possible that Aurora-A regulates centrosome separation by phosphorylating the kinesin-related proteins.

Aurora-A Regulates G_2-M Transition

Apart from the spindle assembly and centrosome separation, Aurora-A contributes to transition from G_2 to M phase.

Suppression of Aurora-A by RNA interference results in G_2-M arrest of HeLa cells and promotes apoptosis (49). Phosphorylation of CDC25B at the centrosome by Aurora-A was discovered in HeLa and U2OS cell lines, and this phosphorylation is an important step to relocalize cyclin B1 to the nucleus and activate cyclin-dependent kinase 1 for the cell to enter mitosis (50). It was also found that ectopic expression of Aurora-A could bypass the G_2-M checkpoint activated by DNA damage (50).

Aurora-B Regulates Chromatin Protein Modification

It has been found that Aurora-B phosphorylates histone H3 at Ser[10] and Ser[28] (51, 52) as well as its variant CENP-A at Ser[7] (53, 54) in mitosis. H3-S10 phosphorylation is now widely used in Aurora-B kinase assay; yet, the function remains largely unknown. In *Tetrahymena*, H3-S10 phosphorylation is required for chromosome condensation (55, 56); however, the connection between these two events is still elusive in mammalian cells. Moreover, a recent experiment showed that H3-S10 phosphorylation by Aurora-B allows the routine disassociation of HP1 from heterochromatin (57, 58), but the biological effect of HP1 release in mitosis is still unclear. Interestingly, Aurora-A also phosphorylates CENP-A (54). Phosphorylation of CENP-A by Aurora-A at Ser[7] in prophase is required for Aurora-B concentration to inner centromeres in prometaphase. Maintenance of later CENP-A phosphorylation state depends on Aurora-B activity and is required for proper microtubule-kinetochore attachment (54). It would be meaningful to explore how Aurora-A and Aurora-B cooperate in understanding the subtle regulation of mitosis.

Aurora-B Regulates Chromatid Separation

Accurate separation of chromatids requires attachment of each kinetochore to microtubules from the opposite poles. Two mechanisms in cells are raised to regulate this process: one is the correction of error attachment, and the other is the spindle checkpoint. Because Aurora-B inhibition causes a higher frequency of syntelic and/or merotelic attachments in cells during prometaphase and drives these cells to enter anaphase with no arrest and misaligned chromosomes (12, 22), it has long been proposed that Aurora-B plays a crucial role in both pathways.

Recently, two laboratories have discovered that Aurora-B phosphorylates centromeric MCAK to inhibit its microtubule depolymerization activity during the mitotic spindle assembly (59, 60). They found that, in mitosis, if microtubule-kinetochore attachment is in a bipolar fashion, Aurora-B may phosphorylate MCAK to keep the kinetochore microtubules in a more stable form. Otherwise, the phosphorylation of MCAK by Aurora-B is abolished, and the kinetochore microtubules are depolymerized to allow other microtubules to catch the unattached kinetochores (Fig. 3A). Phosphorylated and unphosphorylated MCAK proteins exhibit slight difference in localization, with the former closer to the inner centromere where Aurora-B is enriched and the latter closer to inner kinetochore bound of protein phosphatase 1 (59, 61, 62). It is conceivable that the dynamics of phosphorylation/dephosphorylation modification of MCAK protein might be the way that Aurora-B and protein phosphatase regulate the kinetochore-microtubule connection.

The other surveillance mechanism is the spindle checkpoint, which checks whether unattached kinetochores exist. The checkpoint proteins are located on unattached kinetochores and inhibit the APC/C activity to prevent cells from entering anaphase. Aurora-B is involved in the recruitment of checkpoint proteins to kinetochores (Fig. 3B). Cytostatic factor extracts depleted of Aurora-B show diminishment of Mps1, Bub1, CENP-E, Bub3, Mad1, and Mad2 to kinetochores (63). When cells treated with ZM447439, an inhibitor of Aurora-B, or depleted of Bub1 were done with checkpoint inducement,
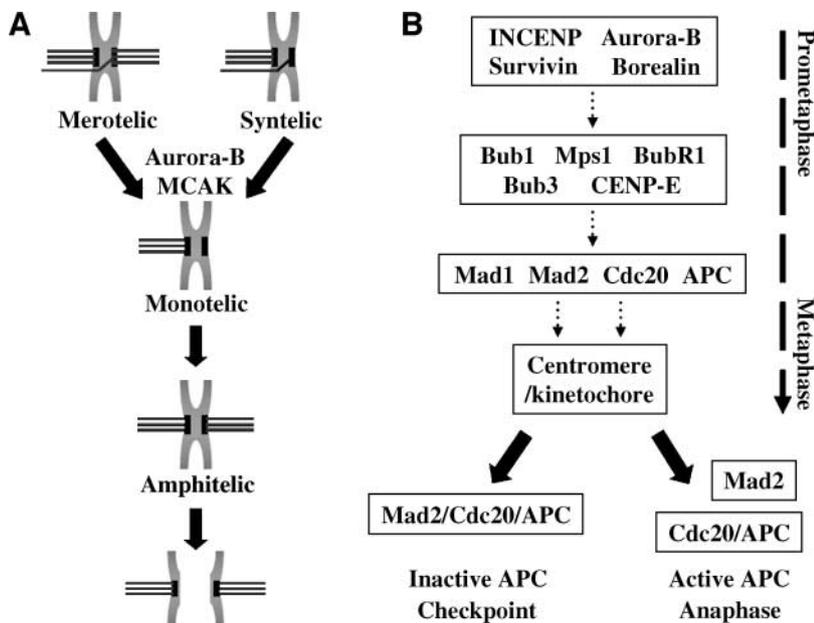

Figure 3. Aurora-B regulates chromatid separation. **A.** Aurora-B guarantees proper attachment between microtubules and kinetochores. After nuclear envelope breakdown, microtubules from opposite poles catch the sister kinetochores and form bipolar spindle, which later ensures accurate chromatid separation. During this process, error attachment, such as syntelic or merotelic, happens quite often. This error can be corrected through the monotelic form with the help of Aurora-B and MCAK before cells enter anaphase. **B.** Spindle checkpoint is activated when unattached kinetochores exist. It requires a large scale of checkpoint protein machinery, including Bub1-3, Mad1, Mad2, BubR1, Mps1, CENP-E, and Aurora-B, complexed with the other passenger members. These spindle checkpoint proteins are recruited to centromere/kinetochore as a certain cascade in the figure, with Aurora-B complex mostly upstream, and Mad1/Mad2 mostly downstream. Mad2 can directly interact with APC/C/Cdc20 and inhibit the activation of APC/C; thus, cell cycle is suspended in metaphase. In particular, Aurora-B complex is responsible for assembling all the other checkpoint proteins to centromere/kinetochore, therefore promising a functional checkpoint.

Bub1 and Aurora-B function in two different signaling pathways and converge on the mitotic checkpoint complex, which includes BubR1, Bub3, Mad2, and Cdc20 (64). However, whether Aurora-B is directly involved in checkpoint activation, or whether it just guarantees recruitment of checkpoint proteins, remains a mystery. Experiments using temperature-sensitive kinetochore mutants in budding yeast revealed that when kinetochores undergo tension defects, Aurora-B creates unattached kinetochores to activate the spindle checkpoint (65), but in higher eukaryotes, this has not yet been proven.

Aurora-B Regulates Cytokinesis

Aurora-B plays an essential role in cytokinesis. Depletion of Aurora-B produces polyploidy due to a failure in cytokinesis in *C. elegans* embryos and *Drosophila* S2 cells (4, 66). Although the mechanism has not yet been elucidated, several substrates of Aurora-B were identified, including the type III intermediate filament desmin and vimentin (67, 68), midbody component ZEN-4/MKLP1 (69, 70), and other proteins like TACC1 (71) and MgcRacGAP (72). Aurora-B and Rho, a prominent regulator of cytokinesis, share certain substrates but exert phosphorylation independently, suggesting that Aurora-B and Rho might coordinate in cytokinesis control (73). Moreover, Aurora-B activates Rho by converting MgcRacGAP to a RhoGAP during cytokinesis (72), indicating that Aurora-B is multifunctional in cytokinesis regulation.

Functional Regulation of Aurora Kinases

The activity of Aurora kinases undergoes strict regulation during mitosis. Aurora-A reaches the maximum activity at the G_2-M transition, whereas the activity of Aurora-B persists from metaphase to the end of mitosis (74). This mechanism of regulation turns out to be a complicated process of phosphorylation and degradation.

Aurora Protein Phosphorylation

Different from most kinases within the cell, Aurora kinases are activated through autophosphorylation at the activation loop (29).

Aurora-A is activated mainly by Ajuba (32) and TPX2 (42) as well as protein phosphatase inhibitor-2 (75), the focal scaffolding protein HEF1 (76), and a newly identified Bora protein (77). Phosphorylated Aurora-A is dephosphorylated by protein phosphatase 1 (78). Up to now, TPX2 obtains the best understanding as an Aurora-A activator. In the absence of TPX2, the Aurora-A activation site is exposed to protein phosphatase 1 and is dephosphorylated in a crucial threonine; after binding to TPX2, the activation segment of Aurora-A rotates so that the phosphothreonine is buried inside and protected from protein phosphatase 1 (28).

A recent report raised a new question in screening for TPX2 homologue in *C. elegans*. The report discovered that a protein named TPXL-1 has homology with the NH_2-terminal domain of TPX2 (79). Surprisingly, although TPXL-1 could bind to and activate Aurora-A, it has neither a NLS signal nor the ability of chromatin-dependent microtubule nucleation (79), which have been shown to be the basic characteristic of TPX2. Thus, it has been thought that TPXL-1 is not a true functional orthologue of TPX2 in *C. elegans* (80), and who will be the real activator of Aurora-A?

Less is investigated of Aurora-B regulators. Prevailing view believes that Aurora-B is regulated by other members of the passenger protein complex, especially activated by INCENP (81, 82). Crystal structure analysis showed that INCENP forms a crown around the N lobe of Aurora-B (30). Different from Aurora-A/TPX2 complex, INCENP induces the active conformation of the T loop allosterically. INCENP activates Aurora-B in a two-step process: it partially activates the kinase at the first step, with the N lobe and C lobe of Aurora-B in an open position; then, full activation of the kinase carries on after INCENP phosphorylation in a conserved TSS motif near the COOH terminus, and the two lobes of Aurora-B close (30). Up to the present, whether survivin bound to Aurora-B stimulates Aurora-B kinase activity remains contradictory (81, 82). Recombinant survivin can enhance an Aurora-B IP kinase assay in *Xenopus* mitotic extracts for >10-fold, and overexpression of survivin in HEK293 cells also elevates the Aurora-B kinase activity (81, 83). Nevertheless, another *in vitro* kinase assay using recombinant proteins showed that survivin does not detectably influence the activity of Aurora-B kinase (82).

Aurora Protein Degradation

Aurora kinases are barely detected after cells exit mitosis and enter G_1 phase. Destruction of both Aurora-A and Aurora-B is mediated by APC/C^{Cdh1} (23, 25, 84). Several domains within their sequences have been identified for degradation, including KEN-box, D-box, and A-Box (23, 24, 26). Nevertheless, they are not all necessary for the degradation of both Aurora-A and Aurora-B. Aurora-A destruction requires D-box and A-box but not KEN-box (26), whereas Aurora-B degradation needs intact KEN-box and A-box (23). This difference might partially explain the distinct temporal regulation of their kinase activity.

Discrimination between Aurora-A and Aurora-B

It is worth pointing out that Aurora-A and Aurora-B share little regulators or substrates despite their high similarity in sequence. How are they discriminated, for example, by TPX2? Using structure-based mutation, Byliss and Eyer found that a single amino acid mutation in Aurora-A to the homologue site of Aurora-B abolishes TPX2 recognition and vice versa (31, 85). It provides us a view that Aurora kinases experience delicate regulation in regulating mitosis events.

Aurora Kinases and Tumorigenesis

Aurora kinases are overexpressed in a wide range of human cancers. Human Aurora-A was first isolated as the product of gene *BTAK* (breast tumor amplified kinase, also named *STK15*) on chromosome 20q13, a region that is commonly amplified in primary breast tumors, colorectal cancers, and other cancer cell lines, including breast, ovarian, colon, prostate, neuroblastoma, and cervical cell lines (17, 19, 86). More strikingly, overexpression of Aurora-A transforms NIH 3T3 cells and Rat1 fibroblasts *in vitro*; when these cells were injected into nude mice, they grew into tumors (17, 19, 20). However, whether

Aurora-A is a potential oncogene remains controversial because no more cell lines were found to be transformed by overexpression of Aurora-A, and overexpression of Aurora-A in mouse model did not result in malignant tumor after a long latency (87). These data suggest that Aurora-A might be a promoting factor for tumorigenesis, and other factors are also needed in cell transformation process. For Aurora-B, the case is even more complicated. Aurora-B is also expressed at high level in primary human colorectal cancers and other tumor cell lines (18). Overexpression of Aurora-B results in multinucleation and polyploidy in human cells (16, 88). However, down-regulation or overexpression of an inactive form of Aurora-B yields the same polyploidization phenomenon. How Aurora kinases are involved in tumorigenesis would be discussed further below (Fig. 4).

Aurora Kinases in Centrosome Amplification and Aneuploidy

Overexpression of Aurora-A causes centrosome amplification both in cell cultures and in rat mammary model (89-91). This kind of centrosome amplification seems not due to centrosome duplication but as a result of cytokinesis failure and consequent multinucleation (89). Up until now, no evidence has shown that Aurora-A functions in cytokinesis directly, and it would be more likely that Aurora-A causes cytokinesis failure in an indirect way, possibly by affecting Aurora-B or other proteins that directly regulate cytokinesis. Aurora-A–induced
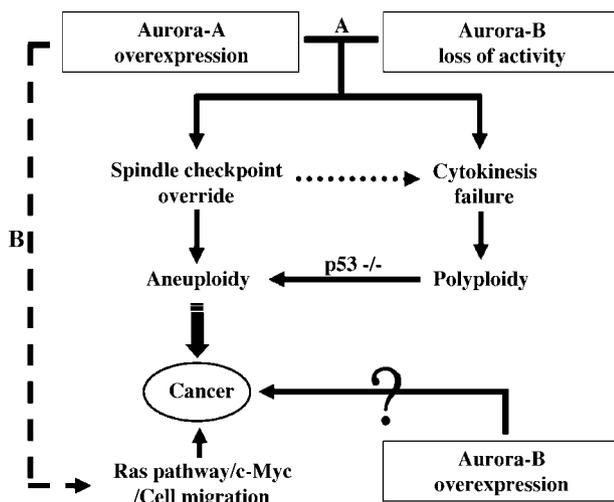

Figure 4. Aurora kinases and tumorigenesis. Up-regulation of Aurora kinases is related to a wide range of human cancers possibly due to their roles in mitosis control (**A**) and/or other pathways (**B**). Aurora-A overexpression or Aurora-B function disruption may override spindle checkpoint; thus, the cell divides with unequal genetic material and turns out to be aneuploidy. Besides, Aurora-A overexpression or Aurora-B function disruption may also lead to cytokinesis failure directly or indirectly, resulting in polyploidy. Under a second circumstance, if the cell loses its p53 and is unable to prevent itself from carrying on the next round of DNA replication, it may go to mitosis and also end up with aneuploidy, which is prevailingly considered associating with cancer. Apart from the mitosis aberrance, Aurora-A also participates in the Ras/Raf/MEK/ERK/MAP kinase pathway, induces telomerase activity, and enhances collagen I– induced cell migration, which may also contribute to tumorigenesis. Aurora-B overexpression is found in some cancer cells too, but the mechanism is still poorly understood.

polyploid cells would be arrested by a "G_1 phase post-mitotic checkpoint" dependent on the p53-Rb pathway, and most of the cells would die through apoptosis. However, when these cells unfortunately lose p53 functions as in $p53^{-/-}$ cells, they could not detect the hyperploidy and go on DNA replication and cell division, which might cause aneuploidy and abnormal centrosome number (89, 92).

Overexpression of Aurora-B also leads to centrosome amplification and increased ploidy, and the absence of p53 exacerbates this phenotype (88, 89). Nevertheless, Aurora-B– induced centrosome amplification is possibly due to other pathways. It has been reported that Aurora-B overexpression induces chromosomes lagging in metaphase, chromosome segregation error, and errors in cytokinesis, and thus may play a role in carcinogenesis (93).

Aurora Kinases with Spindle Checkpoint Defect and Chromosome Instability

Cells overexpressing Aurora-A override the mitotic spindle checkpoint and enter anaphase despite abnormal spindle formation (91). Interestingly, the checkpoint protein Mad2 remains at the kinetochores from prometaphase to anaphase, suggesting a persistently activated spindle checkpoint (91). Therefore, it might be possible that Aurora-A disrupts the interaction between Mad2 and cdc20 or prematurely activates APC/C proteolytic functions. It has been found that, when Aurora-A overexpression overrides the spindle checkpoint triggered by nocodazole, a microtubule destabilizer, BubR1 is significantly reduced, and a subunit of APC/C cdc27 could not be phosphorylated (94).

Depletion of Aurora-B or overexpression of an inactive form in cells would also compromise the spindle checkpoint because the activity of Aurora-B is required for checkpoint protein recruitment. Because cytokinesis would also fail without Aurora-B activity, it makes a good explanation why down-regulation of Aurora-B generates increased ploidy.

Aurora Kinases in Tumor Suppressor Gene Dysfunction and Cell Viability

Aurora-A interacts with several tumor suppressor gene products, including p53 (92, 95, 96), BRCA1 (97), NM23-H1 (98), and Chfr (99), and it might be a powerful way to promote cell viability and tumorigenesis. Thus far, the interaction between Aurora-A and p53 has been well investigated. On one hand, p53 suppresses Aurora-A–induced centrosome amplification and cellular transformation (100), whereas on the other hand, Aurora-A phosphorylates p53 and thus inhibits p53 activity and promotes degradation of this protein. Two Aurora-A phosphorylation sites have been identified in p53. By phosphorylating Ser^{215}, Aurora-A abrogates the DNA-binding and transactivation activity of p53 and subsequently inhibits downstream target genes of p53, such as *p21* and *PTEN* (96). Phosphorylation of Ser^{315} will enhance the affinity of p53 with Mdm2, which promotes ubiquitination and degradation of the p53 protein (95). Besides, Aurora-A directly binds to BRCA1 and phosphorylates it at Ser^{308}, and abortion of this phosphorylation process can decrease the number of cells in M phase in mouse embryo fibroblasts (97). In addition, Aurora-A

is regulated by Chfr, a mitotic checkpoint protein and tumor suppressor. Chfr interacts with and ubiquitinates Aurora-A both *in vitro* and *in vivo* (99). Taken together, Aurora-A and tumor suppressor gene products are antagonistic in cell viability control. The balance of quantity and activity between Aurora-A and tumor suppressor gene products might be important to maintain the normal growth rate of cells.

Aurora Kinases in Other Signaling Pathways and Tumorigenesis

Recent studies found that Aurora-A is a downstream target of mitogen-activated protein kinase 1/ER2 in pancreatic cancer (101). In human carcinogenesis, the Ras/Raf/MEK/ERK/MAP kinase pathway would be enhanced, and the cell response to growth signals is known to increase (102). Therefore, Aurora-A overexpression might drive cells into a faster growing state.

In addition, Aurora-A induces telomerase activity and human telomerase reverse transcriptase by up-regulation of c-Myc (103). Because increase of telomerase activity is frequently seen in many cancer cells and would elongate cell survival time, Aurora-A might promise cell a longer life.

Furthermore, both Aurora-A and Aurora-B promote inappropriate cellular mobility (23, 104), which underlies invasion and metastasis of tumor cells (105). Aurora-A enhances collagen I–induced cell migration and anchorage-independent growth in Aurora-A–stable cell line by activating RalA (104). In the case of Aurora-B, overexpression or nondegradation mutants could promote anchorage-independent growth in soft agar (23). However, the molecular mechanism has not yet been elucidated.

Aurora Kinases, Tumor Diagnosis, and Therapy

Cancers vary greatly in their cause, symptoms, response to treatment, and possibility of cure, which cause difficulty in their diagnosis and therapy. Considering that Aurora kinases play a critical role in tumorigenesis, it might be of great importance to evaluate Aurora kinases in cancer detection and therapy.

Aurora Kinases in Tumor Detection and Prognosis

Elevated expression of Aurora-A has been detected in >50% of colorectal, ovarian, and gastric tumors and in 94% of invasive duct adenocarcinomas of the breast (21). Could Aurora-A serve as a clinical tumor prognosis marker? Microarray-based screening for molecular markers in medulloblastome revealed positive staining for Aurora-A and identified it as an independent prognostic factor for overall survival (106). However, experiments comparing the level of Aurora-A expression in human breast tumor specimens with clinical variables revealed no association between Aurora-A staining and tumor size, lymph node status, or hormone receptor status (107).

Despite the above debate, studies of the polymorphism of Aurora-A have proven that Aurora-A is a candidate low-penetrance tumor-susceptibility gene in mouse and human (108), raising the possibility that it might be useful as a caution of predisposition to cancer. Two functional coding single nucleotide polymorphisms as 91T>A and 169G>A are associated with occurrence of esophageal squamous cell carcinoma and increase the risk of esophageal cancer and gastric cancer (109-111). More clinical evidence is needed to answer if the genotype of Aurora-A would be involved in determining "cancer susceptibility."

Aurora Kinase Inhibitors in Cancer Therapy

Cancers are characterized by the unrestrained growth of cells. Therefore, modulation of abnormal cell cycle regulation would be a valuable therapeutic strategy to many tumor types. RNA interference targeting Aurora-A suppresses tumor growth and enhances the sensitivity to chemotherapy and UV irradiation–induced apoptosis in human cells (112, 113), showing its potential as a target for cancer therapy.

Thus far, several inhibitors of Aurora kinases have been reported (for review, see refs. 114, 115). One of them, VX-680, was designed against the ATP-binding site of Aurora kinases and was proven a high potent, selective, and reversible inhibitor. It greatly inhibits tumor growth in three xenograft models *in vivo*, including leukemia and colon and pancreatic tumors (21). This molecule ensures the possibility to use Aurora kinases as a target for cancer therapy. Other inhibitors of Aurora kinases have been analyzed, such as ZM447439 (22) and Hesperadin (12). Although it is not clear whether Hesperadin would cause tumor cell death, ZM447439 has shown its ability. In colony formation assay, ZM447439 is more toxic to proliferating cells than nondividing cells (22), indicating that it might also be a selective drug to kill tumor cells. These inhibitors provide us a powerful tool to explore the relationship among molecular mechanisms, clinical symptom, and disease therapy.

Perspectives

The Aurora kinase family provides a new concept to understand the mitosis process, tumorigenesis, and the possible relationship between them. It is known that cyclin-dependent kinases provide a regulatory system of the cell cycle. They require cyclins as binding subunits to achieve their kinase activity and affect downstream substrates. Likewise, Aurora kinases also bind to their partners, such as TPX2 and INCENP, to maintain kinase activity. Interestingly, Aurora-A and Aurora-B show much difference in subcellular distribution and carry out divergent functions that are tightly related to their distribution, even if they share >70% homology in their catalytic domain. It might be intriguing to establish and compare the regulation networks of different Aurora kinases. At the mean time, it might be meaningful to investigate the relationship between the cyclin-dependent kinase regulatory system and the Aurora-like regulatory systems.

It is striking to note that deregulation of a single mitotic regulator might lead to huge risk of tumorigenesis. Of particular interest, Aurora kinases are shown to be candidate targets to inhibit tumor cell growth. We believe that uncovering the molecular function of Aurora kinases will bring great rewards in understanding cell cycle control and provide new strategies for drug design in cancer therapy.

References

1. Glover DM, Leibowitz MH, McLean DA, Parry H. Mutations in aurora prevent centrosome separation leading to the formation of monopolar spindles. Cell 1995;81:95–105.

2. Chan CS, Botstein D. Isolation and characterization of chromosome-gain and increase-in-ploidy mutants in yeast. Genetics 1993;135:677–91.

3. Schumacher JM, Ashcroft N, Donovan PJ, Golden A. A highly conserved centrosomal kinase, AIR-1, is required for accurate cell cycle progression and segregation of developmental factors in Caenorhabditis elegans embryos. Development 1998;125:4391–402.

4. Schumacher JM, Golden A, Donovan PJ. AIR-2:An Aurora/Ipl1-related protein kinase associated with chromosomes and midbody microtubules is required for polar body extrusion and cytokinesis in Caenorhabditis elegans embryos. J Cell Biol 1998;143:1635–46.

5. Mesilaty-Gross S, Reich A, Motro B, Wides R. The Drosophila STAM gene homolog is in a tight gene cluster, and its expression correlates to that of the adjacent gene ial. Gene 1999;231:173–86.

6. Roghi C, Giet R, Uzbekov R, et al. The Xenopus protein kinase pEg2 associates with the centrosome in a cell cycle-dependent manner, binds to the spindle microtubules and is involved in bipolar mitotic spindle assembly. J Cell Sci 1998;111:557–72.

7. Adams RR, Wheatley SP, Gouldsworthy AM, et al. INCENP binds the Aurora-related kinase AIRK2 and is required to target it to chromosomes, the central spindle and cleavage furrow. Curr Biol 2000;10:1075–8.

8. Nigg EA. Mitotic kinases as regulators of cell division and its checkpoints. Nat Rev Mol Cell Biol 2001;2:21–32.

9. Hannak E, Kirkham M, Hyman AA, Oegema K. Aurora-A kinase is required for centrosome maturation in Caenorhabditis elegans. J Cell Biol 2001;155:1109–16.

10. Marumoto T, Honda S, Hara T, et al. Aurora-A kinase maintains the fidelity of early and late mitotic events in HeLa cells. J Biol Chem 2003;278:51786–95.

11. Adams RR, Maiato H, Earnshaw WC, Carmena M. Essential roles of Drosophila inner centromere protein (INCENP) and aurora B in histone H3 phosphorylation, metaphase chromosome alignment, kinetochore disjunction, and chromosome segregation. J Cell Biol 2001;153:865–80.

12. Hauf S, Cole RW, LaTerra S, et al. The small molecule Hesperadin reveals a role for Aurora B in correcting kinetochore-microtubule attachment and in maintaining the spindle assembly checkpoint. J Cell Biol 2003;161:281–94.

13. Sasai K, Katayama H, Stenoien DL, et al. Aurora-C kinase is a novel chromosomal passenger protein that can complement Aurora-B kinase function in mitotic cells. Cell Motil Cytoskeleton 2004;59:249–63.

14. Li X, Sakashita G, Matsuzaki H, et al. Direct association with inner centromere protein (INCENP) activates the novel chromosomal passenger protein, Aurora-C. J Biol Chem 2004;279:47201–11.

15. Yan X, Cao L, Li Q, et al. Aurora C is directly associated with Survivin and required for cytokinesis. Genes Cells 2005;10:617–26.

16. Tatsuka M, Katayama H, Ota T, et al. Multinuclearity and increased ploidy caused by overexpression of the aurora- and Ipl1-like midbody-associated protein mitotic kinase in human cancer cells. Cancer Res 1998;58:4811–6.

17. Zhou H, Kuang J, Zhong L, et al. Tumour amplified kinase STK15/BTAK induces centrosome amplification, aneuploidy and transformation. Nat Genet 1998;20:189–93.

18. Katayama H, Ota T, Jisaki F, et al. Mitotic kinase expression and colorectal cancer progression. J Natl Cancer Inst 1999;91:1160–2.

19. Bischoff JR, Anderson L, Zhu Y, et al. A homologue of Drosophila aurora kinase is oncogenic and amplified in human colorectal cancers. EMBO J 1998;17:3052–65.

20. Littlepage LE, Wu H, Andresson T, Deanehan JK, Amundadottir LT, Ruderman JV. Identification of phosphorylated residues that affect the activity of the mitotic kinase Aurora-A. Proc Natl Acad Sci U S A 2002;99:15440–5.

21. Harrington EA, Bebbington D, Moore J, et al. VX-680, a potent and selective small-molecule inhibitor of the Aurora kinases, suppresses tumor growth in vivo. Nat Med 2004;10:262–7.

22. Ditchfield C, Johnson VL, Tighe A, et al. Aurora B couples chromosome alignment with anaphase by targeting BubR1, Mad2, and Cenp-E to kinetochores. J Cell Biol 2003;161:267–80.

23. Nguyen HG, Chinnappan D, Urano T, Ravid K. Mechanism of Aurora-B degradation and its dependency on intact KEN and A-boxes: identification of an aneuploidy-promoting property. Mol Cell Biol 2005;25:4977–92.

24. Castro A, Vigneron S, Bernis C, Labbe JC, Prigent C, Lorca T. The D-Box-activating domain (DAD) is a new proteolysis signal that stimulates the silent D-Box sequence of Aurora-A. EMBO Rep 2002;3:1209–14.

25. Castro A, Arlot-Bonnemains Y, Vigneron S, Labbe JC, Prigent C, Lorca T. APC/Fizzy-Related targets Aurora-A kinase for proteolysis. EMBO Rep 2002;3:457–62.

26. Crane R, Kloepfer A, Ruderman JV. Requirements for the destruction of human Aurora-A. J Cell Sci 2004;117:5975–83.

27. Eyers PA, Maller JL. Regulation of Xenopus Aurora A activation by TPX2. J Biol Chem 2004;279:9008–15.

28. Bayliss R, Sardon T, Vernos I, Conti E. Structural basis of Aurora-A activation by TPX2 at the mitotic spindle. Mol Cell 2003;12:851–62.

29. Cheetham GM, Knegtel RM, Coll JT, et al. Crystal structure of aurora-2, an oncogenic serine/threonine kinase. J Biol Chem 2002;277:42419–22.

30. Sessa F, Mapelli M, Ciferri C, et al. Mechanism of Aurora B activation by INCENP and inhibition by hesperadin. Mol Cell 2005;18:379–91.

31. Bayliss R, Sardon T, Ebert J, Lindner D, Vernos I, Conti E. Determinants for Aurora-A activation and Aurora-B discrimination by TPX2. Cell Cycle 2004;3:404–7.

32. Hirota T, Kunitoku N, Sasayama T, et al. Aurora-A and an interacting activator, the LIM protein Ajuba, are required for mitotic commitment in human cells. Cell 2003;114:585–98.

33. Meraldi P, Nigg EA. The centrosome cycle. FEBS Lett 2002;521:9–13.

34. Berdnik D, Knoblich JA. Drosophila Aurora-A is required for centrosome maturation and actin-dependent asymmetric protein localization during mitosis. Curr Biol 2002;12:640–7.

35. Terada Y, Uetake Y, Kuriyama R. Interaction of Aurora-A and centrosomin at the microtubule-nucleating site in Drosophila and mammalian cells. J Cell Biol 2003;162:757–63.

36. Giet R, McLean D, Descamps S, et al. Drosophila Aurora A kinase is required to localize D-TACC to centrosomes and to regulate astral microtubules. J Cell Biol 2002;156:437–51.

37. Kinoshita K, Noetzel TL, Pelletier L, et al. Aurora A phosphorylation of TACC3/maskin is required for centrosome-dependent microtubule assembly in mitosis. J Cell Biol 2005;170:1047–55.

38. Barros TP, Kinoshita K, Hyman AA, Raff JW. Aurora A activates D-TACC-Msps complexes exclusively at centrosomes to stabilize centrosomal microtubules. J Cell Biol 2005;170:1039–46.

39. Lee MJ, Gergely F, Jeffers K, Peak-Chew SY, Raff JW. Msps/XMAP215 interacts with the centrosomal protein D-TACC to regulate microtubule behaviour. Nat Cell Biol 2001;3:643–9.

40. Clarke PR, Zhang C. Ran GTPase: a master regulator of nuclear structure and function during the eukaryotic cell division cycle? Trends Cell Biol 2001;11:366–71.

41. Kufer TA, Sillje HH, Korner R, Gruss OJ, Meraldi P, Nigg EA. Human TPX2 is required for targeting Aurora-A kinase to the spindle. J Cell Biol 2002;158:617–23.

42. Tsai MY, Wiese C, Cao K, et al. A Ran signalling pathway mediated by the mitotic kinase Aurora A in spindle assembly. Nat Cell Biol 2003;5:242–8.

43. Tsai MY, Zheng Y. Aurora A kinase-coated beads function as microtubule-organizing centers and enhance RanGTP-induced spindle assembly. Curr Biol 2005;15:2156–63.

44. Koffa MD, Casanova CM, Santarella R, Kocher T, Wilm M, Mattaj IW. HURP is part of a Ran-dependent complex involved in spindle formation. Curr Biol 2006;16:743–54.

45. Sillje HH, Nagel S, Korner R, Nigg EA. HURP is a Ran-importin beta-regulated protein that stabilizes kinetochore microtubules in the vicinity of chromosomes. Curr Biol 2006;16:731–42.

46. Wong J, Fang G. HURP controls spindle dynamics to promote proper interkinetochore tension and efficient kinetochore capture. J Cell Biol 2006;173:879–91.

47. Yu CT, Hsu JM, Lee YC, Tsou AP, Chou CK, Huang CY. Phosphorylation and stabilization of HURP by Aurora-A: implication of HURP as a transforming target of Aurora-A. Mol Cell Biol 2005;25:5789–800.

48. Giet R, Uzbekov R, Cubizolles F, Le Guellec K, Prigent C. The Xenopus laevis aurora-related protein kinase pEg2 associates with and phosphorylates the kinesin-related protein XlEg5. J Biol Chem 1999;274:15005–13.

49. Du J, Hannon GJ. Suppression of p160ROCK bypasses cell cycle arrest after Aurora-A/STK15 depletion. Proc Natl Acad Sci U S A 2004;101:8975–80.

50. Cazales M, Schmitt E, Montembault E, Dozier C, Prigent C, Ducommun B. CDC25B phosphorylation by Aurora-A occurs at the G_2/M transition and is inhibited by DNA damage. Cell Cycle 2005;4:1233–8.

51. Hsu JY, Sun ZW, Li X, et al. Mitotic phosphorylation of histone H3 is governed by Ipl1/aurora kinase and Glc7/PP1 phosphatase in budding yeast and nematodes. Cell 2000;102:279–91.

52. Goto H, Yasui Y, Nigg EA, Inagaki M. Aurora-B phosphorylates Histone H3 at serine28 with regard to the mitotic chromosome condensation. Genes Cells 2002;7:11–7.

53. Zeitlin SG, Shelby RD, Sullivan KF. CENP-A is phosphorylated by Aurora B kinase and plays an unexpected role in completion of cytokinesis. J Cell Biol 2001;155:1147–57.

54. Kunitoku N, Sasayama T, Marumoto T, et al. CENP-A phosphorylation by Aurora-A in prophase is required for enrichment of Aurora-B at inner centromeres and for kinetochore function. Dev Cell 2003;5:853–64.

55. Wei Y, Mizzen CA, Cook RG, Gorovsky MA, Allis CD. Phosphorylation of histone H3 at serine 10 is correlated with chromosome condensation during mitosis and meiosis in Tetrahymena. Proc Natl Acad Sci U S A 1998;95:7480–4.

56. Wei Y, Yu L, Bowen J, Gorovsky MA, Allis CD. Phosphorylation of histone H3 is required for proper chromosome condensation and segregation. Cell 1999; 97:99–109.

57. Hirota T, Lipp JJ, Toh BH, Peters JM. Histone H3 serine 10 phosphorylation by Aurora B causes HP1 dissociation from heterochromatin. Nature 2005;438: 1176–80.

58. Fischle W, Tseng BS, Dormann HL, et al. Regulation of HP1-chromatin binding by histone H3 methylation and phosphorylation. Nature 2005;438: 1116–22.

59. Andrews PD, Ovechkina Y, Morrice N, et al. Aurora B regulates MCAK at the mitotic centromere. Dev Cell 2004;6:253–68.

60. Lan W, Zhang X, Kline-Smith SL, et al. Aurora B phosphorylates centromeric MCAK and regulates its localization and microtubule depolymerization activity. Curr Biol 2004;14:273–86.

61. Ohi R, Sapra T, Howard J, Mitchison TJ. Differentiation of cytoplasmic and meiotic spindle assembly MCAK functions by Aurora B-dependent phosphorylation. Mol Biol Cell 2004;15:2895–906.

62. Gorbsky GJ. Mitosis: MCAK under the aura of Aurora B. Curr Biol 2004;14: R346–8.

63. Vigneron S, Prieto S, Bernis C, Labbe JC, Castro A, Lorca T. Kinetochore localization of spindle checkpoint proteins: who controls whom? Mol Biol Cell 2004;15:4584–96.

64. Morrow CJ, Tighe A, Johnson VL, Scott MI, Ditchfield C, Taylor SS. Bub1 and aurora B cooperate to maintain BubR1-mediated inhibition of APC/CCdc20. J Cell Sci 2005;118:3639–52.

65. Pinsky BA, Kung C, Shokat KM, Biggins S. The Ipl1-Aurora protein kinase activates the spindle checkpoint by creating unattached kinetochores. Nat Cell Biol 2006;8:78–83.

66. Giet R, Glover DM. *Drosophila* aurora B kinase is required for histone H3 phosphorylation and condensin recruitment during chromosome condensation and to organize the central spindle during cytokinesis. J Cell Biol 2001;152:669–82.

67. Kawajiri A, Yasui Y, Goto H, et al. Functional significance of the specific sites phosphorylated in desmin at cleavage furrow: Aurora-B may phosphorylate and regulate type III intermediate filaments during cytokinesis coordinatedly with Rho-kinase. Mol Biol Cell 2003;14:1489–500.

68. Goto H, Yasui Y, Kawajiri A, et al. Aurora-B regulates the cleavage furrow-specific vimentin phosphorylation in the cytokinetic process. J Biol Chem 2003; 278:8526–30.

69. Severson AF, Hamill DR, Carter JC, Schumacher J, Bowerman B. The aurora-related kinase AIR-2 recruits ZEN-4/CeMKLP1 to the mitotic spindle at metaphase and is required for cytokinesis. Curr Biol 2000;10:1162–71.

70. Guse A, Mishima M, Glotzer M. Phosphorylation of ZEN-4/MKLP1 by aurora B regulates completion of cytokinesis. Curr Biol 2005;15:778–86.

71. Delaval B, Ferrand A, Conte N, et al. Aurora B -TACC1 protein complex in cytokinesis. Oncogene 2004;23:4516–22.

72. Minoshima Y, Kawashima T, Hirose K, et al. Phosphorylation by aurora B converts MgcRacGAP to a RhoGAP during cytokinesis. Dev Cell 2003;4: 549–60.

73. Yokoyama T, Goto H, Izawa I, Mizutani H, Inagaki M. Aurora-B and Rho-kinase/ROCK, the two cleavage furrow kinases, independently regulate the progression of cytokinesis: possible existence of a novel cleavage furrow kinase phosphorylates ezrin/radixin/moesin (ERM). Genes Cells 2005;10:127–37.

74. Katayama H, Brinkley WR, Sen S. The Aurora kinases: role in cell transformation and tumorigenesis. Cancer Metastasis Rev 2003;22:451–64.

75. Satinover DL, Leach CA, Stukenberg PT, Brautigan DL. Activation of Aurora-A kinase by protein phosphatase inhibitor-2, a bifunctional signaling protein. Proc Natl Acad Sci U S A 2004;101:8625–30.

76. Pugacheva EN, Golemis EA. The focal adhesion scaffolding protein HEF1 regulates activation of the Aurora-A and Nek2 kinases at the centrosome. Nat Cell Biol 2005;7:937–46.

77. Hutterer A, Berdnik D, Wirtz-Peitz F, Zigman M, Schleiffer A, Knoblich JA. Mitotic activation of the kinase Aurora-A requires its binding partner Bora. Dev Cell 2006;11:147–57.

78. Katayama H, Zhou H, Li Q, Tatsuka M, Sen S. Interaction and feedback regulation between STK15/BTAK/Aurora-A kinase and protein phosphatase 1 through mitotic cell division cycle. J Biol Chem 2001;276:46219–24.

79. Ozlu N, Srayko M, Kinoshita K, et al. An essential function of the C. elegans ortholog of TPX2 is to localize activated aurora A kinase to mitotic spindles. Dev Cell 2005;9:237–48.

80. Karsenti E. TPX or not TPX? Mol Cell 2005;19:431–2.

81. Bolton MA, Lan W, Powers SE, McCleland ML, Kuang J, Stukenberg PT. Aurora B kinase exists in a complex with survivin and INCENP and its kinase activity is stimulated by survivin binding and phosphorylation. Mol Biol Cell 2002;13:3064–77.

82. Honda R, Korner R, Nigg EA. Exploring the functional interactions between Aurora B, INCENP, and survivin in mitosis. Mol Biol Cell 2003;14:3325–41.

83. Chen J, Jin S, Tahir SK, et al. Survivin enhances Aurora-B kinase activity and localizes Aurora-B in human cells. J Biol Chem 2003;278:486–90.

84. Taguchi S, Honda K, Sugiura K, Yamaguchi A, Furukawa K, Urano T. Degradation of human Aurora-A protein kinase is mediated by hCdh1. FEBS Lett 2002;519:59–65.

85. Eyers PA, Churchill ME, Maller JL. The Aurora A and Aurora B protein kinases: a single amino acid difference controls intrinsic activity and activation by TPX2. Cell Cycle 2005;4:784–9.

86. Sen S, Zhou H, White RA. A putative serine/threonine kinase encoding gene BTAK on chromosome 20q13 is amplified and overexpressed in human breast cancer cell lines. Oncogene 1997;14:2195–200.

87. Zhang D, Hirota T, Marumoto T, et al. Cre-loxP-controlled periodic Aurora-A overexpression induces mitotic abnormalities and hyperplasia in mammary glands of mouse models. Oncogene 2004;23:8720–30.

88. Araki K, Nozaki K, Ueba T, Tatsuka M, Hashimoto N. High expression of Aurora-B/Aurora and Ipll-like midbody-associated protein (AIM-1) in astrocytomas. J Neurooncol 2004;67:53–64.

89. Meraldi P, Honda R, Nigg EA. Aurora-A overexpression reveals tetraploidization as a major route to centrosome amplification in p53$^{-/-}$ cells. EMBO J 2002;21:483–92.

90. Goepfert TM, Adigun YE, Zhong L, Gay J, Medina D, Brinkley WR. Centrosome amplification and overexpression of aurora A are early events in rat mammary carcinogenesis. Cancer Res 2002;62:4115–22.

91. Anand S, Penrhyn-Lowe S, Venkitaraman AR. AURORA-A amplification overrides the mitotic spindle assembly checkpoint, inducing resistance to Taxol. Cancer Cell 2003;3:51–62.

92. Fujiwara T, Bandi M, Nitta M, Ivanova EV, Bronson RT, Pellman D. Cytokinesis failure generating tetraploids promotes tumorigenesis in p53-null cells. Nature 2005;437:1043–7.

93. Ota T, Suto S, Katayama H, et al. Increased mitotic phosphorylation of histone H3 attributable to AIM-1/Aurora-B overexpression contributes to chromosome number instability. Cancer Res 2002;62:5168–77.

94. Jiang Y, Zhang Y, Lees E, Seghezzi W. AuroraA overexpression overrides the mitotic spindle checkpoint triggered by nocodazole, a microtubule destabilizer. Oncogene 2003;22:8293–301.

95. Katayama H, Sasai K, Kawai H, et al. Phosphorylation by aurora kinase A induces Mdm2-mediated destabilization and inhibition of p53. Nat Genet 2004; 36:55–62.

96. Liu Q, Kaneko S, Yang L, et al. Aurora-A abrogation of p53 DNA binding and transactivation activity by phosphorylation of serine 215. J Biol Chem 2004; 279:52175–82.

97. Ouchi M, Fujiuchi N, Sasai K, et al. BRCA1 phosphorylation by Aurora-A in the regulation of G_2 to M transition. J Biol Chem 2004;279:19643–8.

98. Du J, Hannon GJ. The centrosomal kinase Aurora-A/STK15 interacts with a putative tumor suppressor NM23–1. Nucleic Acids Res 2002;30:5465–75.

99. Yu X, Minter-Dykhouse K, Malureanu L, et al. Chfr is required for tumor suppression and Aurora A regulation. Nat Genet 2005;37:401–6.

100. Chen SS, Chang PC, Cheng YW, Tang FM, Lin YS. Suppression of the STK15 oncogenic activity requires a transactivation-independent p53 function. EMBO J 2002;21:4491–9.

101. Furukawa T, Kanai N, Shiwaku HO, Soga N, Uehara A, Horii A. AURKA is one of the downstream targets of MAPK1/ERK2 in pancreatic cancer. Oncogene 2006;25:4831–9.

102. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. Nature 2002;417:949–54.

103. Yang H, Ou CC, Feldman RI, Nicosia SV, Kruk PA, Cheng JQ. Aurora-A kinase regulates telomerase activity through c-Myc in human ovarian and breast epithelial cells. Cancer Res 2004;64:463–7.

104. Wu JC, Chen TY, Yu CT, et al. Identification of V23RalA-Ser194 as a critical mediator for Aurora-A-induced cellular motility and transformation by small pool expression screening. J Biol Chem 2005;280:9013–22.

105. Norton L, Massague J. Is cancer a disease of self-seeding? Nat Med 2006; 12:875–8.

106. Neben K, Korshunov A, Benner A, et al. Microarray-based screening for molecular markers in medulloblastoma revealed STK15 as independent predictor for survival. Cancer Res 2004;64:3103–11.

107. Royce ME, Xia W, Sahin AA, et al. STK15/Aurora-A expression in primary breast tumors is correlated with nuclear grade but not with prognosis. Cancer 2004;100:12–9.

108. Ewart-Toland A, Briassouli P, de Koning JP, et al. Identification of Stk6/STK15 as a candidate low-penetrance tumor-susceptibility gene in mouse and human. Nat Genet 2003;34:403–12.

109. Ju H, Cho H, Kim YS, et al. Functional polymorphism 57Val>Ile of aurora kinase A associated with increased risk of gastric cancer progression. Cancer Lett 2006;242:273–9.

110. Kimura MT, Mori T, Conroy J, et al. Two functional coding single nucleotide polymorphisms in STK15 (Aurora-A) coordinately increase esophageal cancer risk. Cancer Res 2005;65:3548–54.

111. Miao X, Sun T, Wang Y, Zhang X, Tan W, Lin D. Functional STK15 Phe31Ile polymorphism is associated with the occurrence and advanced disease status of esophageal squamous cell carcinoma. Cancer Res 2004;64:2680–3.

112. Hata T, Furukawa T, Sunamura M, et al. RNA interference targeting aurora kinase a suppresses tumor growth and enhances the taxane chemosensitivity in human pancreatic cancer cells. Cancer Res 2005;65:2899–905.

113. Wang XX, Liu R, Jin SQ, Fan FY, Zhan QM. Overexpression of Aurora-A kinase promotes tumor cell proliferation and inhibits apoptosis in esophageal squamous cell carcinoma cell line. Cell Res 2006;16:356–66.

114. Andrews PD. Aurora kinases: shining lights on the therapeutic horizon? Oncogene 2005;24:5005–15.

115. Keen N, Taylor S. Aurora-kinase inhibitors as anticancer agents. Nat Rev Cancer 2004;4:927–36.

Roles of Aurora Kinases in Mitosis and Tumorigenesis

Jingyan Fu, Minglei Bian, Qing Jiang, et al.

Mol Cancer Res 2007;5:1-10.

Updated version	Access the most recent version of this article at: http://mcr.aacrjournals.org/content/5/1/1

Cited articles	This article cites 114 articles, 53 of which you can access for free at: http://mcr.aacrjournals.org/content/5/1/1.full#ref-list-1
Citing articles	This article has been cited by 54 HighWire-hosted articles. Access the articles at: http://mcr.aacrjournals.org/content/5/1/1.full#related-urls

E-mail alerts	Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions	To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
Permissions	To request permission to re-use all or part of this article, use this link http://mcr.aacrjournals.org/content/5/1/1. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.