Aurora kinases as an anti-cancer target

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Abstract

The Aurora family of serine/threonine kinases plays an important role in chromosome alignment, segregation and cytokinesis during mitosis. Recent studies have found aberrant expression of Aurora kinases in a variety of human solid tumors and hematological malignancies, suggesting they have a role in carcinogenesis. This review highlights the function of Aurora kinases in the regulation of mitosis and presents the rationale for these kinases as an anti-cancer target. We also review recently developed inhibitors of Aurora kinases.

Key words. Aurora kinase; cancer; leukemia; mitosis.

1. Introduction

The Aurora family of serine/threonine kinases plays an important role in chromosome alignment, segregation and cytokinesis during mitosis. The family has three members: Aurora A, B and C, which share 67-76% amino acid sequence identity in their catalytic domains, but show little N-terminus similarity [1,2]. Aurora A localizes on centrosomes and has a crucial role in each step of mitosis [2]. Aurora B is a chromosomal passenger protein that localizes at centromeres during the prometaphase and subsequently relocates to midzone microtubules and midbodies during anaphase and telophase [1,3]. Aurora B is involved in chromosome alignment, kinetochore-microtubule biorientation, activation of the spindle assembly checkpoint and cytokinesis [1,3]. Aurora C is specifically expressed in the testis and plays a role in spermatogenesis [4]. It was recently found that Aurora C also acts as a chromosomal passenger protein and might compensate for lost Aurora B function [5].

Aurora A and B are overexpressed in a variety of solid tumors, including those from colon [6,7], breast [7-10], prostate [11], pancreas [12], thyroid [13], and head and neck [14]. In addition, it has been found recently that Aurora A and B are aberrantly expressed in hematological malignancies including acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), and acute lymphoblastic leukemia (ALL) [15]. The significance of aberrant expression of Aurora kinases remains elusive, although high levels are associated with advanced clinical stage and poor prognosis in individuals with colorectal [7] and prostate [11] cancers and head and neck squamous-cell carcinoma [14]. Other studies have found aberrant expression of Aurora A kinase in early stage breast and ovarian cancers [16,17]. Examination of the relationship between Aurora C and cancer is limited; however several studies have found aberrant expression of Aurora C in colorectal, breast, and prostate cancers [5, 18].

These observations suggest that Aurora kinases might be a promising molecular target for cancer treatment. A number of small-molecule inhibitors targeting Aurora kinases have been developed, which include MK0457 (formerly VX-680) [19], AZD1152 [20-22], MLN8054 [23], and PHA-739358 [24]. These compounds showed anti-tumor activity in preclinical studies and clinical trials are ongoing in the United States and Europe.

2. Biological function of Aurora kinases.

Aurora A. Aurora A is expressed widely in proliferating normal tissues, with expression being highest at the G2/M phase of the cell cycle; levels are then rapidly decreased by degradation via the ubiquitin-proteasome pathway [25,26]. Aurora A localizes on duplicated centrosomes from the end of S phase to the beginning of the following G1 phase and plays a crucial role in each step of mitosis. For example, it regulates the maturation of centrosomes by interacting with transforming acid coiled-coil (TACC) proteins; activated TACC is recruited to the centrosome and forms a complex with microtubule-associated proteins such as Msps/XMAP215, centrosomin, and γ-tubulin, leading to growth of microtubules, which consequently promote maturation of the centrosome [Fig 1A, 27-31].

Aurora A also regulates mitotic entry by interacting with Ajuba, a LIM protein [32]: the phosphorylated form of Ajuba binds to Aurora A, leading to activation of Aurora A at late G2 phase. Interaction of Ajuba and Aurora A is essential for recruitment of the cyclin B1/CDK1 complex to the centrosome, where it becomes activated and commits cells to mitosis [Fig 1B, 32].

Aurora B. Aurora B is also widely expressed in proliferating normal cells with maximum expression at the G2/M phase of the cell cycle [33]. Similar to Aurora A kinase, levels of Aurora B protein are regulated by proteasomal degradation [34]. Aurora B kinase belongs to the chromosome passenger protein family, which comprises inner centrosome protein (INCENP), survivin, and borealin [35]. These proteins form a chromosome passenger complex and localize on the kinetochores from the prophase to the metaphase and on the central spindle and the midbody in cytokinesis [1]. Aurora B is activated by autophosphorylation after association with the passenger complex [36-40]. Inhibition of Aurora B by RNA interference showed that it is required for cytokinesis [41], where its important function is regulation of the kinesin-like protein pavarotti, which is essential for establishment of the central spindle during anaphase [Fig 2A]. Disruption of Aurora B caused mis-localization of pavarotti, resulting in cytokinesis defect [42]. Cytoskeletal proteins in the cleavage furrow, such as myosin II regulatory light chain, vimentin, desmin and glial fibrillary acidic protein, are also substrates of Aurora B and participate in filament formation and cytokinesis [43-45]. Other functions of Aurora B relate to histone modification: it phophorylates histone H3 on Ser10 [41] and Ser28 [46], and centromere protein A on Ser7 [47]. Phosphorylation of histone H3 on Ser10 dissociates heterochromatin protein 1 (HP1) from heterochromatin at the onset of mitosis [48]; however, the biological effect of HP1 release remains unknown.

Aurora B is also implicated in microtubule-kinetochore attachment by interacting with the kinetochore-specific histone H3 variant CENP-A [Fig 2B, 49]. CENP-A is first phosphorylated on Ser7 by Aurora A during the prophase, recruiting Aurora B to the inner centromere [50]. Aurora B then maintains phosphorylation of CENP-A on Ser7

from late prophase through metaphase and regulates kinetochore functions [50]. Other Aurora B substrates include BubR1 and Mad2, mitotic checkpoint proteins. Inhibition of Aurora B by RNA interference compromised the mitotic checkpoint, resulting in increased numbers of aneuploid cells [51].

Aurora C. Aurora C is a much less extensively studied member of the Aurora kinase family. Aurora C is localized to Chr19q13 and was first isolated from a testis cDNA library [52]. Aurora C is specifically expressed in testis, as measured by northern blot analysis, and is believed to play an important role in spermatogenesis [4]. Recent studies found that Aurora C is also a chromosomal passenger protein and binds to INCENP, for which it has lower affinity than Aurora B [5]. In addition, forced expression of Aurora C rescued an Aurora-B-silenced phenotype of HeLa cells *in vitro*, suggesting that Aurora C might be able to compensate for lost Aurora B function [5].

3. Aurora kinases and cancer.

Aurora A. *Aurora A* is located on chromosome 20q13.2, a region commonly amplified in human malignancies, including those from colon, breast, pancreas, ovary, and prostate [6,7]. Although aberrant expression of Aurora A has been found in various tumor types, it does not always correlate with gene amplification. For example, amplification of Aurora A was found in only 3% of hepatocellular carcinomas (HCCs), although more than 60% of HCCs overexpressed Aurora A [53], suggesting that mechanisms other than gene amplification may contribute to the aberrant expression. Forced expression of *Aurora A* gene in murine NIH 3T3 cells induced abnormal centrosome number (amplification) and transformation *in vitro* [54]. In addition, forced

expression of Aurora A in near diploid human breast epithelial cells induced similar centrosome abnormality, as well as induction of aneuploidy [7]. Other groups also found that conditional expression of Aurora A in murine mammary epithelium induced accumulation of binucleated cells and transformation when p53 was deleted [55]. These findings suggest that Aurora A can act as an oncogene.

Interestingly, Aurora A interacts with and inactivates the tumor suppressor p53; Aurora A phosphorylates p53 on Ser315, facilitating MDM-2-mediated degradation of p53 in cancer cell lines [56]. Aurora A phosphorylates p53 on Ser215 and abrogates its DNA-binding ability, resulting in inhibited transcriptional activity [57].

Aurora A also interacts with the breast cancer susceptibility gene BRCA 1. Aurora A colocalizes with BRCA 1 in centrosomes and phophorylates BRCA 1 on Ser308, leading to impairment of its function as a G2/M checkpoint keeper [58]. Thus, it may also be involved in the carcinogenesis of breast cancer.

Overexpression of Aurora A causes resistance to Taxol-mediated apoptosis in cancer cells. Taxol, a tubulin depolymerizing agent, activates the spindle checkpoint in HeLa cells, but this is overridden by Aurora A, resulting in escape from apoptosis [59].

Aurora B. The contribution of Aurora B to carcinogenesis has been less studied than that of Aurora A. Aurora B is located on chromosome 17p13.1, a region not typically amplified in human malignancies; however, overexpression of Aurora kinase B has been shown in a variety of human cancers, including glioblastoma multiforme [60], malignant mesothelioma [61], and hematological malignancies [15]. High levels of Aurora B are associated with adverse clinical outcomes in patients with endometrial carcinoma [62]. Forced expression of Aurora B in Chinese hamster embryo cells

resulted in chromosome instability and increased tumor invasiveness in association with constitutive expression of phosphorylated (p)-histone H3 on Ser10 [63], suggesting that Aurora B can act as an oncogene.

Aurora C. The involvement of Aurora C in carcinogenesis has been the least explored of all the Aurora kinase family. The few available studies found that Aurora C was overexpressed in colorectal, breast, and prostate cancers [5, 18]. The level of expression of Aurora C correlated with the degree of dysplastic change in colorectal cancer cells [18]. Forced expression of Aurora C in HeLA cells produced polyploidy, which was augmented by inactivation of p53 [64]. These observations suggest that Aurora C might be a promising molecular target for cancer treatment.

4. Development of Aurora kinase inhibitors. Evidence linking Aurora kinases to malignancies has raised the possibility of targeting these kinases for cancer therapy. A number of small-molecule inhibitors with activity against Aurora A and/or B have been developed. The first generation of this class of compound included Hesperadin, ZM447439, and MK0457 (formally VX-680). The next generation of Aurora kinase inhibitor has been developed and includes AZD1152, a potent and selective inhibitor of Aurora B kinase; MLN8054, an orally available selective inhibitor of Aurora A kinase; and the pan-Aurora kinase inhibitor PHA-739358. Some of these agents are undergoing evaluation in clinical trials.

Hesperadin. Hesperdin (Boehringer Ingelheim) is a novel indolinone with specific activity against Aurora B kinase, as it was shown to inhibit p-histone H3 with an IC_{50} of 250 nM. It was the first proven inhibitor of Aurora kinase B, but has not been verified in

clinical trials. Hesperadin induced polyploidy in HeLa cells [Table 1, 65].

ZM447439. ZM447439 (AstraZeneca) is an ATP-competitive selective inhibitor of Aurora kinase A and B (IC_{50} 110 nM and 130 nM for Aurora A and B, respectively), which compromises chromosomal alignment and cell division as well as mitotic checkpoint in HeLa, A549, MCF-7 and DLD1 cells [Table 1, 51]. The phenotypes induced by ZD447439 were due to Aurora B inhibition, as determined by RNA interference experiments [51]. In addition, a recent study found that ZM447439 was active against hematological malignancies including AML and Philadelphia chromosome-positive ALL [15]. This study also found that cells expressing wild-type p53 were more sensitive to ZM447439-mediated growth inhibition than cells possessing the mutated p53 gene. These observations suggest that the p53-dependent post-mitotic checkpoint played an important role in Aurora kinase inhibitor-mediated apoptosis. ZM447439 has not been developed in clinical trials.

MK0457. MK0457 (VX-680; Merk/Vertex) is an ATP-competitive pan-Aurora kinase inhibitor (IC_{50} 0.6, 18, and 4.6 nM for Aurora A, B, and C, respectively) [Table 1, 19]. *In vitro* study showed that MK0457 induced endoreduplication in cancer cells, a characteristic feature of phenotype mediated by inhibition of Aurora B kinase by RNA interference. Preclinical study showed that MK0457 inhibited proliferation of human myelogenous leukemia HL60 and colon cancer HCT116 cells in a murine xenograft model [19]. MK0457 effectively inhibited colony formation of freshly isolated AML cells with internal tandem duplication mutations in the fms-like tyrosine kinase (FLT3) gene [19]. MK0457 possesses many off-targets including FLT3 kinase. Interestingly, MK0457 was able to inhibit imatinib- or dasatinib-resistant ABL kinase mediated by T315I mutation [66]. A recent clinical study showed that MK0457 was active in

individuals with imatinib-resistant CML or ALL patients possessing T315I-BCR/ABL mutation [66]. A phase 1 clinical trial of MK0457 in 22 heavily pre-treated patients found a recommended dose of 10 mg/m/h, continuous 24 h infusion for 5 days every 28 days. Neutropenia was the dose-limiting toxicity. One patient with pancreatic cancer and another with non-small-cell lung cancer achieved stable disease as their best response, which lasted over 6 months [67].

AZD1152. AZD1152 (AstraZeneca) is a novel acetanilide-substituted pyrazole-aminoquinazoline prodrug that is converted rapidly to the active drug AZD1152 hydroxy-QPA (AZD1152-HQPA) in human plasma [20]. AZD1152-HQPA is a specific and selective inhibitor of the enzymatic activity of Aurora B kinase (IC_{50} 0.37 nM versus 1368 nM for Aurora B and A kinases, respectively); the inhibitor had even lower activity against a panel of more than 50 other serine-threonine and tyrosine kinases including FLT3, JAK2, and ABL [Table 1, 20,22]. Preclinical studies showed that AZD1152 was active against a variety of solid tumors including colon, breast, and lung cancers, as well as myelogenous leukemia in a tumor xenograft model [21,22]. These studies demonstrated phosphorylated-histone H3 as a biomarker of Aurora inhibition. Of note, AZD1152 potentiated the anti-tumor effects of the tubulin depolymerizing agent vincristine and the topoisomerase II inhibitor daunorubicin in AML cells *in vitro* and *in vivo* [22]. In addition, AZD1152 was able to inhibit the proliferation of imatinib-resistant ALL cells with Philadelphia chromosome, although it was not active against BCR/ABL [22].

A recent Phase 1 trial of AZD1152 in 19 patients showed that the maximum tolerated dose was 200 mg, given as a 2-h weekly infusion. As with MK0457, neutropenia was the dose-limiting toxicity. Stable disease for longer than 25 weeks was

the best response achieved in three patients (one with melanoma, one with nasopharyngeal carcinoma and one with adenoid cystic carcinoma) [68].

MLN8054. MLN8054 is an orally available, potent and selective inhibitor of Aurora A kinase (IC_{50} 4 nM versus 172 nM for Aurora A and B kinase, respectively) [Table 1, 23]. Exposure of cells to low concentrations of MLN8054 induced abnormal mitotic spindle formation and chromosomal alignment defects, characteristics of Aurora A inhibition; however, downregulation of p-histone H3 was shown on exposure to higher concentrations, consistent with Aurora B inhibition. MLN8054 is currently being evaluated in a phase 1 trial for patients with advanced solid tumors.

PHA-739358. PHA-739358 (Nerviano Medical Sciences) is an ATP-competitive pan-Aurora kinase inhibitor (IC_{50}s of 13, 79, and 61 nM for Aurora A, B, and C, respectively) [Table 1, 24]. As with MLN8054, phenotypic changes in cells shift from Aurora A to Aurora B inhibition on exposure to higher concentrations of the agent. PHA-739358 showed significant cross-reactivity with ABL in a biochemical assay, with an IC_{50} of 25 nM [24]. Notably, PHA-739358 was active against T315I BCR/ABL mutation [69]. PHA-739358 is currently being evaluated in clinical trials in solid and hematological malignancies, including imatinib-resistant CML.

Thus, the inhibitors of Aurora kinase activity are well tolerated and produce some clinical benefits. Preclinical studies have found that inhibition of Aurora kinase A and B sensitizes malignant cells to apoptosis mediated by tubulin depolymerizing agents [22,59]. Clinical trials are warranted to evaluate the efficacy of combining Aurora kinase inhibitor and this class of chemotherapeutic agents.

5. Conclusions. Recent elucidation of the biological function of Aurora kinases in

normal and cancer cells has led to the development of small-molecule inhibitors. Preclinical as well as preliminary results of clinical trials suggest that this class of agent is promising for cancer treatment, although the molecular mechanisms by which inhibitors of Aurora kinases induce the growth arrest and apoptosis of cancer cells remain to be fully elucidated. Also, several issues concerning this class of agent have not been addressed: for example, it is not known which Aurora kinase is the best target for cancer treatment. Further studies are clearly required to incorporate this class of agent in the future treatment strategy for cancer.

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Figure Legends.

Figure 1. Function of Aurora A kinase. (A), Aurora A phosphorylates transforming acid coiled-coil (TACC) proteins. The activated TACC and Aurora A are recruited to the centrosome and form a complex with microtubule-associated proteins such as Msps/XMAP215, centrosomin, and γ-tubulin, leading to growth of microtubules, which consequently promotes maturation of the centrosome. **(B),** Aurora A phosphorylates Ajuba. The phosphorylated form of Ajuba binds to Aurora A, leading to activation of Aurora A at late G2 phase. Aurora A and Ajuba consequently activate cyclin B1/CDK1 complex, resulting in commitment of cells to mitosis.

Figure 2. Function of Aurora B kinase. (A), Aurora B is activated by autophosphorylation after association with the passenger complex, which consists of inner centrosome protein (INCENP), survivin, and borealin. Activated Aurora B recruits pavarotti to the central spindle region during anaphase. Pavarotti is essential for establishment of the central spindle. **(B),** CENP-A is first phosphorylated on Ser7 by Aurora A during prophase, which recruits Aurora B to the inner centromere. Aurora B then maintains phosphorylation of CENP-A on Ser7 from late prophase through metaphase and regulates kinetochore functions.

Table(s)

Table 1. Aurora kinase inhibitors.

Aurora kinase inhibitor	Chemical class	Aurora A IC50	Aurora B IC50	Other targets	References
Hesperadin (Boehringer Ingelheim)	Indolinone	Not available	250 nM	Not available	65
ZM447439 (AstraZeneca)	Quinazoline derivative	110 nM	130 nM	LCK 0.88 μM SRC 1.03 μM	51,67
MK0457 (Merck)	4,6 Diaminopyrimidine	0.6 nM	18 nM	FLT3 30 nM	19
AZD1152 (AstraZeneca)	Quinazoline derivative	1368 nM	0.37 nM	Not available	20-22,68
MLN8054 (Millennium)	Benzazepine derivative	4 nM	172 nM	CHK2 28 μM PLK 53 μM	23
PHA-739358 (Nerviano Medical Sciences)	3-aminopyrazole derivative	13 nM	79 nM	ABL 25 nM	24

Figure(s)

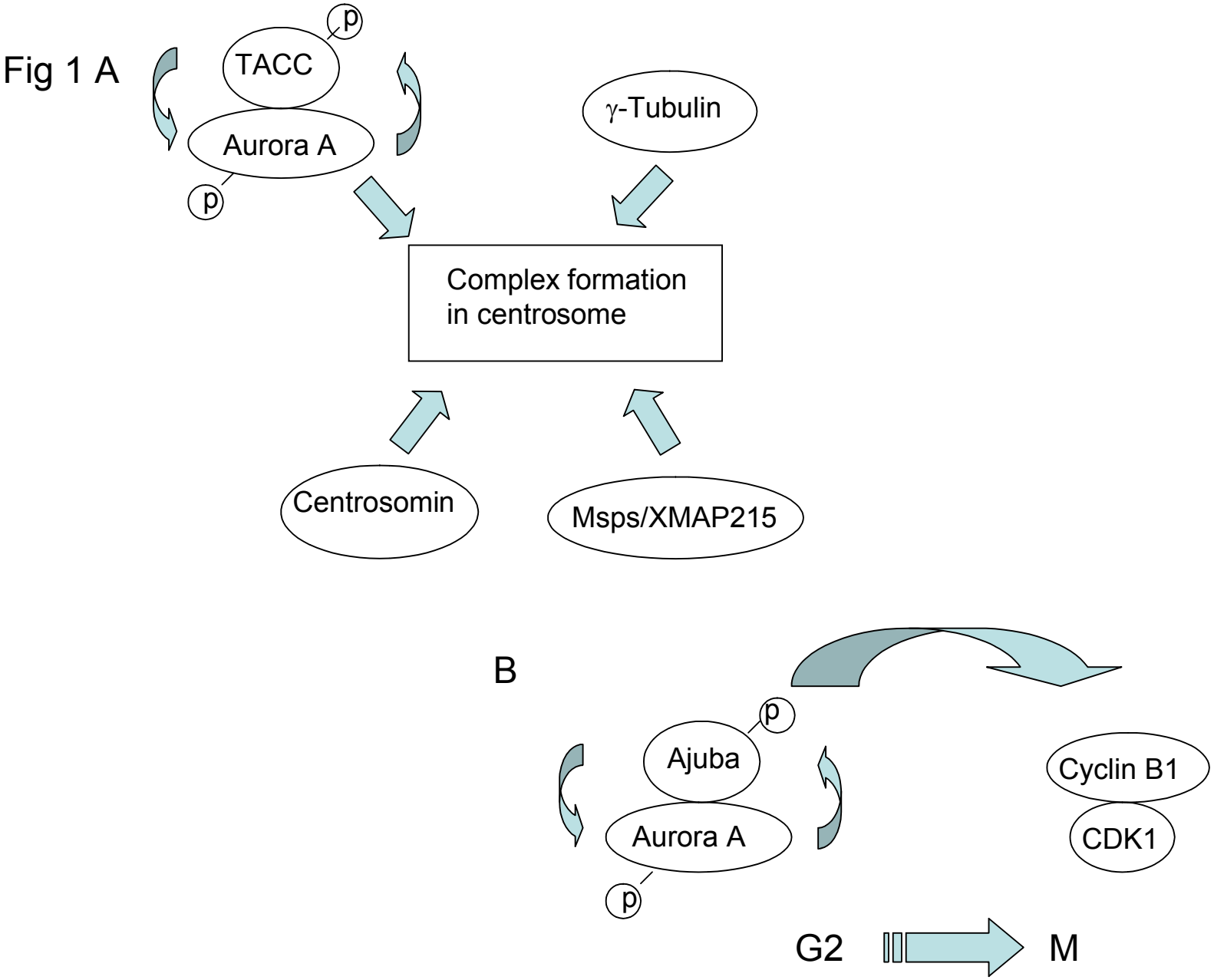
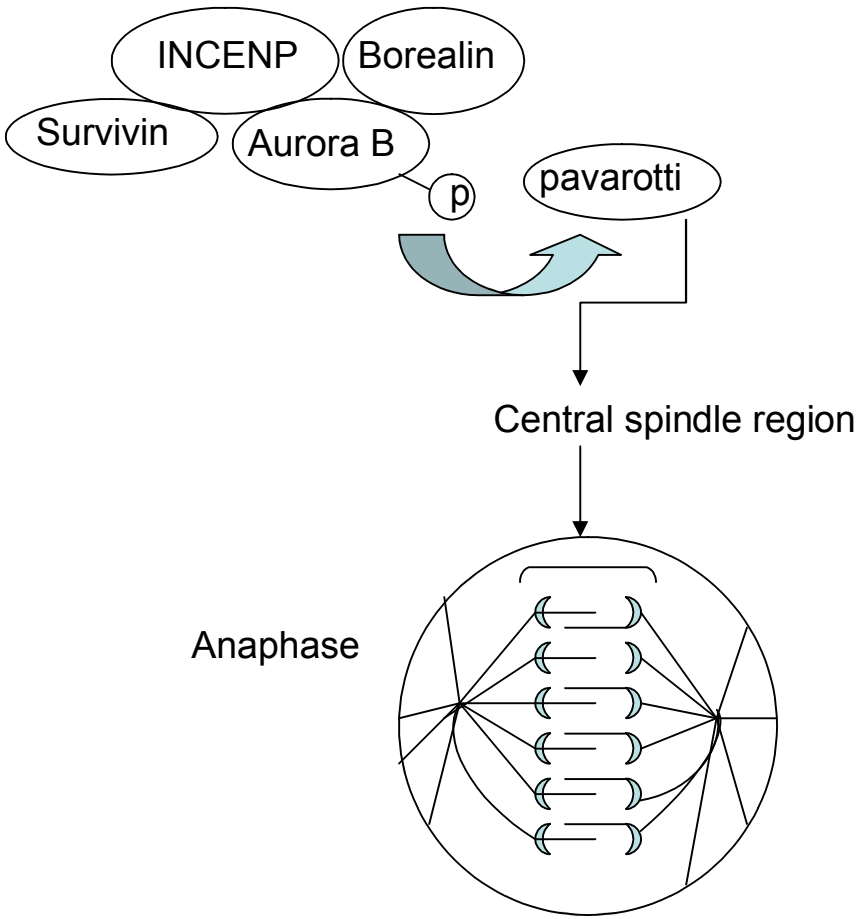
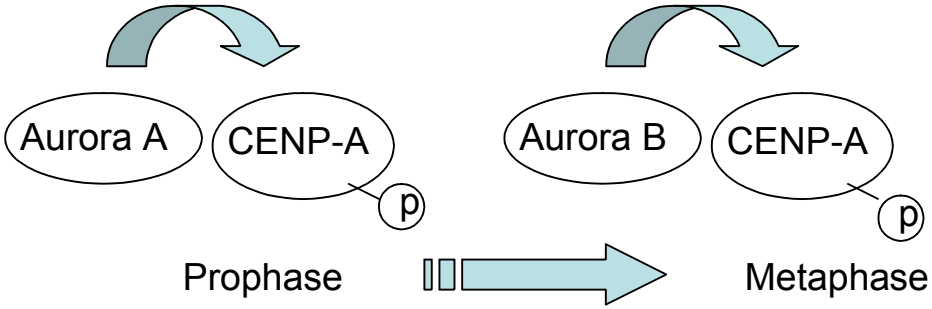


Fig 1 A
p
TACC
Aurora A
p
γ-Tubulin
Complex formation
in centrosome
Centrosomin
Msps/XMAP215
B
p
Ajuba
Aurora A
p
Cyclin B1
CDK1
G2
M

Fig 2A


INCENP
Borealin
Survivin
Aurora B
p
pavarotti
Central spindle region
Anaphase

B


Aurora A
CENP-A
p
Aurora B
CENP-A
p
Prophase
Metaphase

*** Reviewer suggestions**

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