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REVIEW

Mitotic Failures in Cancer: Aurora B Kinase and its Potential Role in the Development of Aneuploidy

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Abstract One of the basic requirements during the process of cell division is to maintain genetic integrity and ensure normal ploidy. The family of Aurora kinases, composed of Aurora A, B and C, takes a major role in the control of centrosome cycle, mitotic entry, chromosome condensation and coordination of chromosomal movements. Deregulation of kinase expression was described in a series of different malignancies which was also associated with aneuploidy. Recently, Aurora kinases gained significant interest as potential therapeutic targets in oncology. While there is increasing evidence about the activities of Aurora A kinase during cancer progression, data are controversial regarding the role of Aurora B. In this review the biology of Aurora kinases and its potential relation to cancer progression is discussed with special focus on functional changes and determination of Aurora B kinase.

Keywords Cell division · Mitotic failure · Aurora kinase · Aneuploidy · Cancer progression

Introduction

Aggressive histological appearance in malignancy is marked by irregular enlarged nuclear morphology and the occurrence of atypical mitoses. These common features are tightly associated with failures of cell division and the formation of aneuploidy. The normal cell division requires a complex regulation including accurate timing and spatial organization. To ensure normal ploidy, the strict control of centrosome cycle and mitotic entry, chromosome condensation and coordination of chromatide separation are needed [1]. A well-known set of protein kinases is the family of Aurora kinases, which take a significant part in the regulation of the mentioned processes [2–4]. The Aurora kinase-family is consisted of Aurora-A, -B and -C, all evolutionary highly conserved Ser/Thr kinases [5]. The localization and function of the individual members is basically different which is due to the N-terminal region showing little sequence homology [6].

Genetic aberrations and changes in kinase function of Aurora A and Aurora B was studied in several malignancies in detail. While a special role in tumor progression and predictive value was suggested for Aurora A, much less information is available for Aurora B for which both hyper- and hypofunction was reported. In the present overview we focus primarily on Aurora kinase B and its possible connection with the formation of aneuploid cell populations and cancer progression following a brief review of the recent data on the Aurora kinase family.

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Aurora A

The A type Aurora kinase often referred as the ‘polar kinase’ is required for the correct centrosome cycle [7–9]. The multiple substrates identified clearly demonstrate the kinase’s central role during the cell division process (Tables 1). The kinase activity depends on the phosphorylation of its activation loop (the T288 residue). Dephosphorylation by protein phosphatase 1 or 2A results in kinase inactivation. Cofactors (such as the GTPase ran and TPX2) are needed to activate the kinase. TPX2 dissociates from importin α and β before mitotic spindle formation and binds Aurora A [10–12] which is followed by relocalization to the centrosome and proximal microtubules [6, 12, 13] and phosphorylation of CDC25B which contributes to G2/M transition [14]. Aurora A is concentrated at centrosomes and mitotic spindle in prophase and metaphase, localization turns later rapidly to a diffuse cytoplasmic pattern [15]. Aurora A expression happens in a

Table 1 List of Aurora A kinase substrates with specific function during cell cycle

Substrate name	Substrate function	Sites	Reference
AIP	Negative regulator of Aurora A	Ser70	[55]
ASAP	Spindle formation	Ser625	[56]
BRCA1	G2/M transition	Ser308	[57]
Cas-L/NEDD9	Cytoskeleton organization	not mapped	[58]
CDC25B	G2/M transition	Ser353	[14, 59]
CENP-A	Enrichment of Aurora-B at inner centromeres	Ser7	[60]
CENP-E	Chromosome movement, spindle elongation	Thr422	[61]
CPEB	RNA binding	Thr171, Ser177	[62, 63]
EB3	Microtubule dynamics, mitotic spindle regulation	Ser176	[64]
FAF1	Promotes cell death	Ser289, Ser291	[65]
GEF-H1	Guanine nucleotide exchange factor for Rho	Ser885	[66]
GSK3	Control of cellular response to damaged DNA	Ser9	[67]
Histone H1	Chromatin regulation	Not mapped	[68]
Histone H3	Chromatin regulation	Ser10	[40]
HURP	Stabilizes kinetochore microtubules	Ser627, Ser725, Ser757, Ser830	[69]
Kif2a	Microtubule-associated motor protein	not mapped	[70]
LATS2	Spindle formation	Ser83	[71]
MBD3	Nucleosome remodeling and histone deacetylase activities	Ser24	[72]
NDEL1	Thiol-activated oligopeptidase	Ser251	[73]
p41-Arc	Required for the formation of branched networks of actin filaments	Thr21	[74]
p53	Cell cycle regulation, tumor suppressor	Ser315	[75]
PARD-3	Adapter protein involved in asymmetrical cell division and cell polarization processes	Ser962	[76]
PLK1	Regulates centrosome maturation and spindle assembly	Thr210	[77, 78]
PP1	Control of chromatin structure and cell cycle progression	not mapped	[79]
PSRC1	Regulates mitotic spindle dynamics	Ser65	[80]
Ral-A	Multifunctional GTPase	Ser194	[81, 82]
RASSF1A	Tumor suppressor	Thr202 and/or Ser203	[83]
TACC3	Microtubule-dependent coupling of the nucleus and the centrosome	Ser558	[84]
TPX2	Spindle assembly factor	On Ser, not mapped	[12]
TRF1	Inhibitor of telomerase	Ser296	[85]
Vimentin	Class-III intermediate filament	Ser72	[86]
ZNF239 / MOK-2	Transcriptional regulation	Ser46	[87]

Data source: Kinasource Database, Uniprot

dynamic fashion starting from the late S phase of the cell cycle and ending with the termination of the M phase with a peak in prometaphase [5]. The major activity was suggested during late mitotic events since Aurora A overexpression triggers the termination of mitosis without cytokinesis, thus it can be considered as a predisposition to aneuploidy [16]. Kinase overexpression was found to be associated with polyploid cell clones owing multiple centrosomes in the absence of p53 activity [17]. Aurora A overexpression was associated with the amplification of the coding AURKA gene which is located at 20q13. Gene amplification was first reported in breast cancer [18] followed by a wide range of epithelial tumours including colon, bladder, ovarian and pancreatic carcinoma [8].

In contrast to overexpression, the absence of Aurora A function results in delayed mitotic entry [19]. Inhibition of the kinase leads to various mitotic defects including misalignment of chromosomes, improper centrosome maturation and separation, multipolar spindles and failure in cytokinesis [9].

Aurora C

Aurora C was shown to be closely related to Aurora B, sharing 83 % identity in amino acid sequence [3]. Information about the specific functions of Aurora C is limited. Recent works presented its role in spermatogenesis [20] and oogenesis [21], circadian rhythm and cellular morphology [22].

Table 2 Known substrates of Aurora B kinase and their function in cell division

Substrate	Function	Sites	Reference
Autophosphorylation		Thr232	[88]
CENP-A	Enrichment of Aurora-B at inner centromeres	Ser7	[89]
CENP-E	Chromosome movement, spindle elongation	Thr422	[61]
EB2	Microtubule dynamics, mitotic spindle regulation	not mapped	[64]
EB3	Microtubule dynamics, mitotic spindle regulation	Ser176	[64]
Hec1	Kinetochor protein	Ser5, Ser15, Thr49, Ser55, Ser69 and possibly Ser44	[90]
Histone H3	Chromosome condensation	Ser10, Ser28	[40, 91]
INCENP	Kinetochor protein	Ser894, Ser895	[92]
MCAK	Microtubule depolymerizing	Thr95, Ser110, Ser196	[93]
MgcRacGAP 1	Attachment of spindle microtubules to kinetochore	Ser387, Ser410	[94]
MKLP1	Plus-end-directed motor enzyme	Ser812, Ser814	[95]
NSUN2	RNA methyltransferase	Ser139	[96]
Shugoshin-2	Regulates sister chromatid cohesion	Thr537, Thr620	[97]
Survivin	Kinetochor protein	Thr117	[98]
Vimentin	Class-III intermediate filament	Ser6, Ser24, Ser38, Ser46, Ser64, Ser65, Ser72, Ser86	[99]

Data source: Kinasource Database, UniProt

In human tissues Aurora C is expressed at a low level in the prostate, the spleen and human fibroblasts [2], and higher levels in the normal placenta, oocytes, colon and mammary gland epithelium. The expression peaks in G2/M, with a localization at the centrosomes from anaphase to cytokinesis [23, 24].

Aurora C shares interacting proteins (INCENP, survivin, borealin) and substrates (histone H3, CENP-A, INCENP and Borealin) with Aurora B [25] and has competitive functions in mitosis [22].

The kinase encoding AURKC gene (located in 19q13.43) was frequently reported to be deleted or rearranged in tumour tissues [23]. In addition, four missense mutations were also described in lung adenocarcinomas [26, 27]. In conflict with these data high expression levels were detected in lung and hepatocellular carcinoma and in thyroid cancer cell lines [23, 28, 29].

Aurora B

Aurora B kinase is known as one of the "chromosome passenger" proteins [5, 6, 30] as the kinase is primarily located along the chromosomes in the prophase followed by the concentration to the inner centromere regions during metaphase and transfer to the central spindle in anaphase finally accumulating in the midbody in telophase [31]. Key substrates are effector molecules of chromatin condensation, cytokinesis and microtubule-kinetochor attachment (Tables 2).

According to our recent knowledge there are at least two chromosomal passenger complexes [32]; a subcomplex of Aurora B and INCENP, and a holocomplex of Aurora B, survivin, INCENP and borealin. This holocomplex contains Aurora B as an enzymatic subunit, while the other three proteins control the targeting of the complex and the activity of Aurora B.

Starting in early G2 Aurora B is responsible for chromosome condensation by the phosphorylation of histone H3 on Ser10 [33]. During prometaphase it colocalizes with CPC complex proteins such as survivin, INCENP and Borealin [34]. As a member of CPC complex Aurora B regulates the spindle assembly checkpoint that delays mitotic progression until all chromosomes are attached properly in a bipolar fashion. The kinase has also a role in repair chromosome attachment errors by blocking APC/C, essential for mitotic progression in the absence of tension during merotelic or syntelic attachment [5].

The lack of Aurora B kinase activity was reported to be related with aneuploidy, genetic instability and tumourigenesis [35]. Inhibition of the kinase function was reported to initiate massive polyploidization in cell cultures and cell death in both p53 dependent and independent manner [31].

The AURKB gene encoding Aurora B kinase is located at the 17p13.1 locus. The gene was not reported to be commonly amplified and specific mutations were also not described [27]. However, overexpression at the mRNA and protein levels was reported in different types of cancer [8] including breast, colorectal, kidney, lung and prostate carcinoma. The frequent formation of aneuploidy and multinucleated cells could be observed in particular in cases with p53 insufficiency [36]. The latter observation further strengthens the hypothesis that Aurora B function inducing chromosome lagging and chromosome segregation errors [37] together with p53

insufficiency contributes to genetic instability and cancer progression.

Aurora B is the Initiator of Mitotic Chromosome Condensation

Histone phosphorylation required for proper chromosome segregation in both mitosis and meiosis is evolutionally highly conserved [33]. Aurora A and B were shown to physically interact with histone H3 indicating their responsibility in phosphorylation at Ser10 and 28 initiating the mitotic condensation during G2/M transition [38–41]. Experimental inhibition of Aurora B kinase function resulted in a dramatic reduction of Ser10 phosphorylation [42, 43]. On the opposite, the kinase overexpression caused increased phosphorylation at Ser10 associated with incomplete chromosome condensation and misalignment in the form of abnormal mitoses in HeLa cells [3]. Upon phosphorylation of histone H3 at Ser10 in G2 the dissociation of heterochromatin protein 1α (HP1α) and HP1γ is initialized which allows the structural reorganization of the chromatin prior mitosis [31].

In the line of the events phosphorylation of Ser28 and Ser10 gradually decreases and Aurora B dissociates from chromosomes [41] during the later phases of mitosis.

Aurora B as a Promising Therapeutic Target

Due to the ubiquitous regulatory function in cell division Aurora kinases have been recognized as potential therapeutic targets. A number of small molecules inhibiting Aurora B are currently under intense clinico-pharmacological studies (Table 3). Being specifically active in dividing cells Aurora kinase inhibition offers a treatment alternative with reduced side effects [44]. The effect of small molecule inhibitors is reflected in H3 histone phosphorylation inhibition and accumulation of hyperdiploid cells terminating in apoptosis [45]. Pan-Aurora kinase inhibition resulted in cellular changes similar to loss of Aurora B activity [46].

Table 3 Aurora kinase inhibitors currently under clinico-pharmacological investigation

Inhibitor	Clinical status
AT9283	Phase I
AS703569	Phase I
GSK1070916A	Phase I
CYC116	Phase I
VX-680	Phase I
PF-03814735	Phase I
MK0457	Phase I
MLN8237	Phase I /Phase II
SNS-314	Phase I
AMG 900	Phase I
AT 9283	Phase I
MLN8054	Phase I
Alisertib	Phase II

Data source: ClinicalTrials.gov

Changes of Aurora B Expression in Cancer

Aurora B kinase was reported to be overexpressed in different types of cancer (Table 4). The data, however, are controversial as the determination of the kinase expression was done by different methods. Qi et al [47] studied the expression of Aurora B and its correlation with cell proliferation in 40 oral squamous cell carcinoma cases. They showed the elevation of Aurora B and Ki67 expressing cell fractions in carcinomas compared to normal epithelial tissue (Aurora B 16.5±8.5 % compared to 4.4±1.9 %, and Ki67 49.7±18.1 % compared to 13.7±2.9 %), with a linear correlation between the two datasets (R=0,69). They also found a prominent kinase expression in cases with lymph node metastasis.

Kurai et al [48] compared the Aurora B expression of normal, hyperplastic and malignant human endometrium. They also found a strong association between the kinase expression and cell proliferation, determined by Ki67 immunohistochemistry. They showed that Aurora B kinase expression was significant in proliferative phase and markedly reduced in the secretory phase of the endometrial cycle and it was generally low in cancer samples. They stated that elevated Aurora B positivity was an indicator for poor prognosis compared with Aurora B negative cancers.

Sorrentino et al [49] investigated the expression of Aurora B in thyroid carcinoma in the context of cell proliferation. According to their results, Aurora B was not detectable in

Table 4 Aurora kinase B overexpression reported in human neoplastic changes

Tumour type	References
Hepatocellular cancer	[51]
Laryngeal squamous cell carcinoma	[50]
Oral squamous cell carcinoma	[47]
Prostate cancer	[100, 101]
Testicular cancer	[102, 103]
Colorectal carcinoma	[104]
Breast cancer	[105]
Astrocytoma	[106]
Clear cell renal cell carcinoma	[107]
AML	[108]
Non-Hodgkin's lymphoma	[109]
Non-small cell lung carcinoma	[110]
Thyroid carcinoma	[49]
Endometrial carcinoma	[48]

normal thyroid tissue and thyroid carcinoma cells showed increased Aurora B expression. Immunopositive cells were counted at a frequency of 0.5±0.2 and 29.6±3.4 % in case of Aurora B and 0.9±0.3 and 43.2±6.6 in case of Ki67, respectively.

In a contrast with this, García-Fernandez et al [50] found the mean Aurora B expression in laryngeal squamous cell carcinomas as high as 80.29±31.72 %, while the mean Ki67 was only at 40.49±25.65 %. They concluded that high Aurora B expression correlates with a higher rate of recurrence.

Lin et al [51] reported Aurora B mRNA overexpression in 61 % of the investigated hepatocellular carcinoma cases by RT-PCR, which correlated with protein levels as well. They found the Aurora B increase closely associated with aggressive tumour phenotype and clinical behaviour (advanced tumor stage and grade, poor overall survival rates).

Histological Determination of Aurora B Kinase Expression

In most of the studies Aurora B expression was investigated as a single functional marker in pathological conditions. However, effective testing should consider that in physiological conditions the kinase expression is strongly cell cycle dependent [47]. Activity is scheduled to G2 and M phases, therefore increased G2 and/or mitotic phase fractions due to increased cell growth will result in elevated Aurora B levels. Highly aggressive and intensely proliferating cell populations are expected to show proportionally high levels of Aurora B expression. Further, extended G2 phase or G2 arrest is another potential mechanism resulting normally scheduled Aurora B overexpression. G2 phase arrest was reported in malignancies due to secondary genetic defects or biochemical manipulation of the cell cycle control [52–54].

Ideally, the determination of Aurora B expression should be relativated to the cycling fraction that can be estimated e.g. by the Ki67 (Mib-1) positive fraction widely determined by IHC. By the application of this method in our recent study the frequent occurrence and an independent effect of Aurora B protein overexpression further to increased cell proliferation could not be verified in breast carcinoma. Moreover, hyperplastic germinal centers in reactive lymph nodes presented with a significantly higher Aurora B expression than aggressive B-cell lymphomas in another study. For the analysis of Aurora B activity the downstream target phosphorylated histone H3 as the major substrate of Aurora B activity could also be considered (Fig. 1).

Concluding Remarks

Abnormal function of the Aurora kinase family including the B-type kinase may result in complex changes in the regulation of mitotic processes. Due to the general interest, genetic abnormities and related changes in kinase expression may predict the success of evolving anti-Aurora therapies. The kinase protein quantity can be determined histologically by IHC or PCR but expression (increase or decrease) seems to be dependent from the cell proliferation rate reflected by well-established cell proliferation markers.

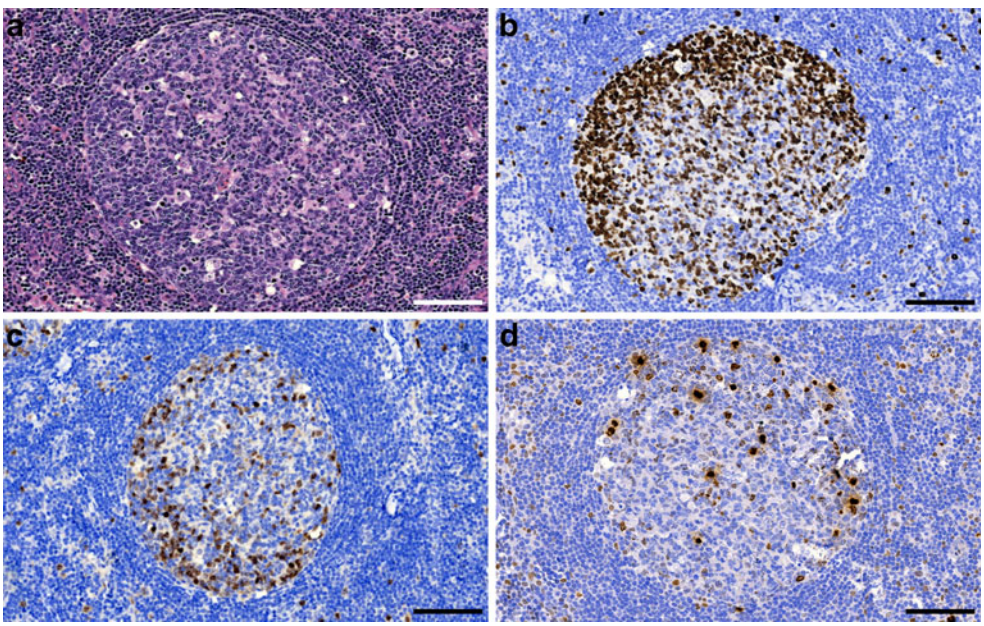

Fig. 1 Photomicrograph shows HE staining (**a**), Ki-67 (**b**), Aurora B (**c**) and phospho-histone H3 (**d**) immunostaining of a germinal center in a reactive lymph node. To obtain information about possible deregulation of Aurora B cell proliferation activity and phosphorylated histone H3 expression should be considered. (Scalebar: 100 μm)

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