



ISSN: 0975-766X
CODEN: IJPTFI
Research Article

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**INHIBITORS OF AURORA KINASES IN CANCER THERAPY
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Received on 24-08-2011

Accepted on 06-09-2011

Abstract

Cell division in mammalian cells is driven by protein kinases, that regulate progression through the various phases of cell cycle. The Aurora kinases, a family of serine/threonine protein kinases, regulate many processes during cellular division. So far three Aurora kinases designated as Aurora A, Aurora B, Aurora C are identified in mammalian cells which are found to be involved in multiple mitotic events such as regulation of spindle assembly check point pathway, function of centrosomes, cytoskeleton and cytokinesis. Dysregulation of Aurora kinases can cause aneuploidy which is a land mark of many human cancers. Aurora kinases are essential to ensure error free cell division, but their aberrant expression leads to centrosome amplification and malignant transformation, by the phosphorylation of tumor suppressor genes such as p53. For this reason the Aurora kinases are potential targets in treatment of cancer. The Aurora kinase inhibitors efficiently target highly proliferating cells, induce cytokinesis failure and ultimately cell death. The present review discusses the structure, type, function, regulation and association of Aurora kinases with cancer and the recently developed inhibitors of Aurora kinases in the treatment of cancer.

Key words: Protein kinases, Aurora kinases, cancer, centrosome amplification.

Introduction

Aurora kinases are serine/threonine kinases that are essential for cell proliferation. The enzyme helps the dividing cell dispense its genetic materials to its daughter cells. More specifically, Aurora kinases play a crucial role in cellular division by controlling chromatid segregation. Defects in this segregation can cause genetic instability, a

condition which is highly associated with tumorigenesis (Bolanos-Garcia, 2005). Three Aurora kinases have been identified in mammalian cells to date:

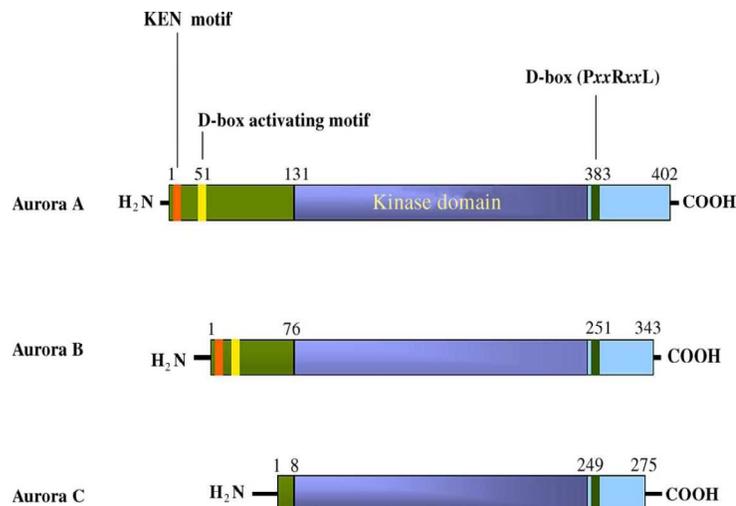
Aurora A (aka Aurora 2) functions during prophase of mitosis and is required for correct function of the centrosomes.

Aurora B (aka Aurora 1) functions in the attachment of the mitotic spindle to the centromere. **Aurora C** (*AURKC*) works in germ-line cells and little is known about its function. Besides being implicated as mitotic regulators, these kinases have generated significant interest in the cancer research field due to their elevated expression profiles in many human cancers (Giet & Prigent, 1999).

Structure of Aurora kinases

Domain organisation of Aurora kinases A–C is shown in figure 1.

Figure 1: Domain organisation of Aurora kinases A–C.



As shown in the figure 1, Aurora kinases present three domains: N-terminal domain of 39 to 129 residues in length, a protein kinase domain and a short C-terminal domain containing 15 to 20 residues. The N-terminal domain of three proteins share low sequence conservation, which determines selectivity during protein-protein interactions (Bolanos-Garcia, 2005).

Localization of Aurora kinases

The level of both kinases is substantially reduced in G1 cells.

Aurora A

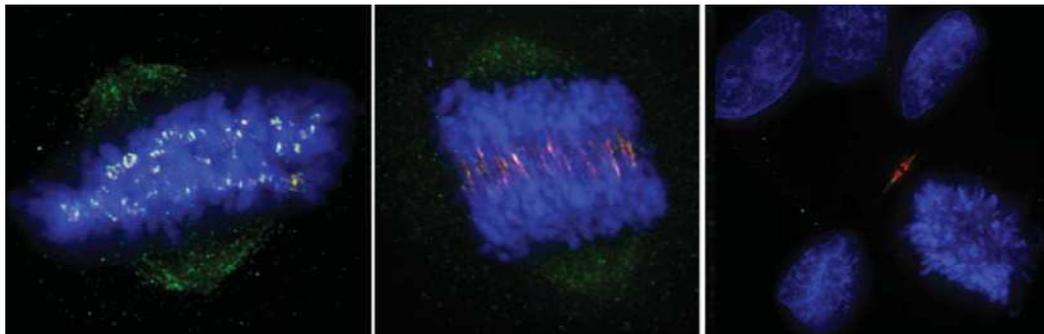
In prophase Aurora A is concentrated around the centrosomes, in metaphase on the microtubules near the spindle poles, in anaphase on the polar microtubules, but some might also be located in the spindle midzone.

Aurora B

Aurora B is nuclear, in prophase and metaphase Aurora B is localised to inner centromere. In anaphase they are concentrated in the spindle midzone microtubules and at the cell cortex at the site of cleavage-furrow ingression. In cytokinesis both kinases are concentrated in the midbody.

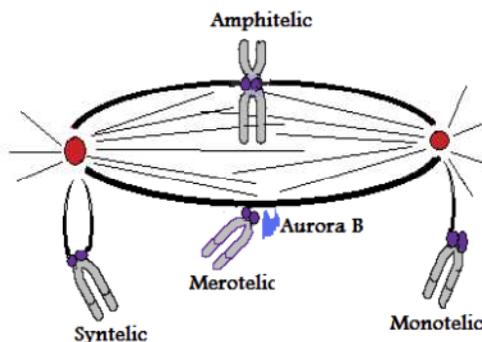
The relative localization of Aurora A and Aurora B in mitotic cells is shown in figure 2.

Figure 2: The relative localization of Aurora A and Aurora B in mitotic cells:



Aurora A (green boxes) Aurora B (red circles). The inset boxes show the results of fluorescence recovery after photobleaching (FRAP) studies, and indicate that Aurora A and B are dynamic at centrosomes and centromeres, respectively, but that Aurora B becomes immobile when targeted to the spindle midzone. Restoration microscopy of Aurora B (red staining), inner centromere protein (INCENP; green staining), and DNA (blue staining) in mitotic HeLa cells in (b) metaphase, (c) anaphase and (d) cytokinesis.

Figure 3: The role of Aurora B in chromosome biorientation.



Schematic diagram of centrosomes (red), spindle (microtubule-black lines), various chromosome orientations (gray) or attachments to spindle microtubules, and Aurora B (blue).

Aurora A kinase

Aurora A kinase also known as **serine/threonine-protein kinase 6** is an enzyme that in humans is encoded by the *AURKA* gene (Sen S *et al.*, 1997). Aurora A is a member of a family of mitotic serine/threonine kinases (Zhou H *et al.*, 1998). It is implicated with important processes during mitosis and meiosis whose proper function is integral for healthy cell proliferation. Aurora A is activated by one or more phosphorylations and its activity peaks during the G2 phase to M phase transition in the cell cycle (Hannak E *et al.*, 2001).

Functions of Aurora A kinases:

Aurora A is involved in mitotic entry, separation of centriole pairs, accurate bipolar spindle assembly and alignment of metaphase chromosomes and completion of cytokinesis (Marumoto T *et al.*, 2003). The activity of Aurora A is closely related to centrosomes. Maturation of duplicated centrosomes by recruiting proteins including D-Tacc24, γ - tubulin25, SPD-2 (Kemp CA *et al.*, 2004) , and centromeric ChToh27 (Conte N *et al.*, 2003). Recently role of Aurora A in the promotion of nuclear envelop breakdown has been described. Aurora A orchestrates the formation of the mitotic spindle apparatus and helps to organize the motor proteins that 'pull the strings' during actual chromosome separation. Its activity therefore is essential for cell proliferation, which is a principal reason why the inhibition of Aurora kinases has become such an attractive strategy for developing the next generation of targeted cancer therapeutics.

Aurora B kinase

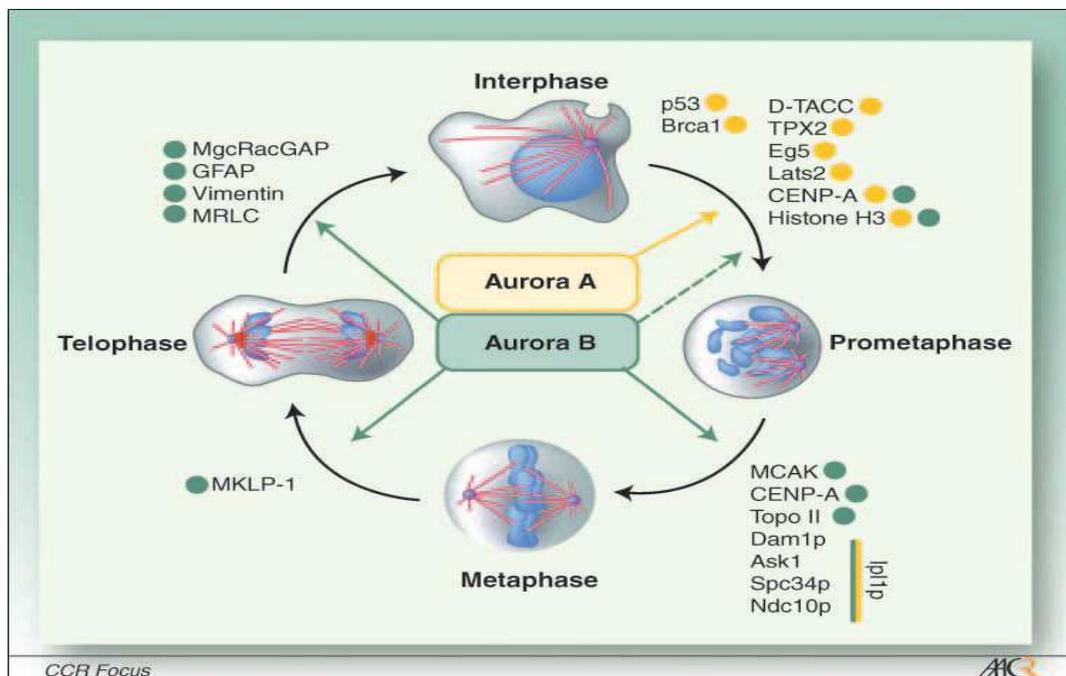
Aurora B kinase is a protein that functions in the attachment of the mitotic spindle to the centromere. **Aurora-B** kinases are chromosomal passenger proteins that are essential for a number of processes during mitosis. Aurora-B expression and activity in proliferating tissues are cell-cycle regulated, expression peaks at the G2-M transition, and kinase activity is maximal during mitosis (Bischoff *et al.*, 1998).

Functions of Aurora B kinases:

Aurora B kinases are essential for chromosome condensation, kinetochore function, cytokinesis and the proper function of the spindle-assembly checkpoint when spindle tension is perturbed. Their regulation involves association with the chromosomal passenger proteins INCENP and survivin, which are important both for targeting and activation of the kinase. Amphitelic attachment of sister chromatid kinetochores, where both the kinetochores are attached to opposite poles is the correct attachment (biorientation). Defects in chromosome biorientation leads to monotelic (one kinetochore attached to spindle pole), merotelic (one kinetochore attached to both spindle poles), and Syntelic attachments (both kinetochores attached to same spindle pole). Aurora B is involved in correcting merotelic and syntelic attachments. Aberrant expression of Aurora B compromises chromosomal biorientation (amphitelic) leading to genetic instability (aneuploidy)

Cell cycle execution points and targets of aurora A and B kinases are shown in figure 4.

Figure 4: Cell cycle execution points and targets of aurora A and B kinases.



Substrates phosphorylated in each phase of the cell cycle by each kinase are detailed, with orange circles denoting targets of aurora A and green circles denoting targets of aurora B. Orange/green line, known substrates of the single yeast aurora kinase IpI1p. Adapted with permission from Macmillan Publishers Ltd: (Andrews PD., 2005).

Aurora C kinase:

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 (M. Bernard *et al.*, 1998). Aurora C is specifically expressed in testis, as measured by northern blot analysis, and is believed to play an important role in spermatogenesis (C.J. Tang *et al.*, 2006). 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. 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 (K. Sasai *et al.*, 2004).

Regulation of Aurora Kinases

Phosphorylation, dephosphorylation are the two predominant mechanisms regulating Aurora A activity most of which have been deduced from invertebrates. Generally, phosphorylation of Aurora kinase stimulates kinase activity. Three phosphorylation sites Ser-53, Thr-295, and Ser-349 were identified. Mutations in Thr-295 and Ser-349 reduced or abolished the activity of Aurora A (Littlepage LE *et al.*, 2002). To date the best known regulators of Aurora B include Survivin and INCENP. Survivin binds to the catalytic domain of Aurora B and enhances the kinase activity and targeting to its substrates. Lower levels of phosphorylated Histone H3 correlates with the absence of Survivin, confirming that Aurora B activity is enhanced by survivin (Chen J *et al.*, 2003). Survivin is also involved in the localization of Aurora B to different locations during mitosis. Levels of Aurora C peak in the later stages of mitosis after Aurora B. Aurora C is regulated by INCENP like Aurora B, through the C-terminal region. Aurora C may rescue the genetic stability of the cells complementing Aurora B functions in its absence (Sasai K *et al.*, 2004). However regulation of Aurora C is not completely known and further work is needed. Aurora C is predicted to turn over by APC-ubiquitin-proteasome pathway through the recognition of D-box.

Aurora Kinases in Cancer

Deregulation in Aurora kinases has been linked to tumorigenesis. Out of the three family members, AURKA is consistently associated with cancers. AURKB has also recently been reported to contribute to tumorigenesis, but the role of AURKC is not yet properly associated.

AURKA's Role in tumor development

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 (Y. Miyoshi *et al.*, 2001). Aurora A phosphorylates p53 on Ser215 and abrogates its DNA-binding ability, resulting in inhibited transcriptional activity (Q. Liu *et al.*, 2004). Aurora A also interacts with the breast cancer susceptibility gene BRCA1. Aurora A colocalizes with BRCA 1 in centrosomes and phosphorylates BRCA 1 on Ser308, leading to impairment of its function as a G2/M checkpoint keeper (M. Ouchi *et al.*, 2004). 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 (S. Anand *et al.*, 2003).

AURKB's Role in tumor development

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 (W.F. Zeng *et al.*, 2007), malignant mesothelioma (F. Lopez-Rios *et al.*, 2006), and hematological malignancies (T. Ikezoe *et al.*, 2007). High levels of Aurora B are associated with adverse clinical outcomes in patients with endometrial carcinoma (M. Kurai *et al.*, 2005). Forced expression of Aurora B in Chinese hamster embryo cells⁷ resulted in chromosome instability and increased tumor invasiveness in association with constitutive expression of phosphorylated (p)-histone H3 on Ser10 (T. Ota *et al.*, 2002), suggesting that Aurora B can act as an oncogene.

AURKC's Role in tumor development

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. The level of expression of Aurora C correlated with the degree of dysplastic change in colorectal cancer cells. Forced expression of Aurora C in HeLA cells produced polyploidy, which was augmented by inactivation of p53 (S. Dutertre *et al.*, 2005). These observations suggest that Aurora C might be a promising molecular target for cancer treatment.

Inhibitors of Aurora kinases:

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, MLN8054, PHA-739358. Some of these agents are undergoing evaluation in clinical trials.

Aurora kinase inhibitors are listed in Table 1.

Table 1: Aurora kinase inhibitors in clinical trials.

Inhibitor	AURKA inhibition	AURKB inhibition	AURKC inhibition	Manufacturer	Clinical status
AZD1152	+	+	-	Astra Zeneca	Phase I
VX-680	+	+	+	Vertex/Merck	Discontinued
MLN8054	+	+	-	Millennium	Discontinued
MLN8237	+	+	-	Millennium	Phase II
PHA-680632	+	+	-	Nerviano	Preclinical
PHA-739358	+	+	+	Nerviano	Phase II
Hesperidin	-	+	-	Boehringer-Ingelheim	Preclinical

Inhibitor	AURKA inhibition	AURKB inhibition	AURKC inhibition	Manufacturer	Clinical status
ZM447439	+	+	-	Astra Zeneca	Phase I
JNJ-770621	+	+	-	Johnson & Johnson	Preclinical
SU6668	+	+	-	Pfizer	Discontinued
CCT129202	+	+	+	Chroma Therapeutics Ltd.	Preclinical
AT9283	+	+	-	Astrex Therapeutics	Phase I
MP529	+	+	-	SuperGen	Preclinical
SNS314	+	+	+	Sunesis Pharmaceuticals	Phase I
R763	-	+	-	Rigel Pharmaceuticals	Phase I
ENMD2076	+	+	-	EntreMed	Phase I
XL228	+	+	+	Exelixis	Phase I
TTP607	+	+	+	TransTech Pharma	Phase I
PF-03814735	+	+	-	Pfizer	Phase I
CYC116	+	+	+	Cyclacel	Phase I

Hesperidin

Hesperidin (Boehringer-Ingelheim) is specific for AURKB as indicated by the reduction of histone H3 phosphorylation and exhibiting the similar phenotype to AURKB knockdown. It has cross reactivity for six other kinases (AMPK, LCK, MKK1, MAPKAP-K1, CHK1, and PHK (Haufs *et al.*, 2003) and proved useful to understand the biology of AURKB function. Hesperidin impairs the localization of checkpoint proteins such as BUB1 and BUBR1 to kinetochore, and induces cytokinesis and polyploidy. Hesperidin was instrumental in understanding the role of AURKB in syntelic orientation of chromosomes and spindle assemble checkpoint.

ZM447439

ZM447439 (AstraZeneca) inhibits AURK-A and -B resulting in the reduction of phosphorylation of histone H3. ZM447439 treatment causes defects in chromosome alignment, segregation, and cytokinesis; most likely by interfering with the spindle integrity checkpoint (Gadea BB and Ruderman JV, 2005). The effects mediated by ZM447439 (reduction in H3 phosphorylation, inhibition of kinetochore localization of BUBR1, MAD2, and Cenp-E) are characteristic to AURKB inhibition rather than AURKA (Ditchfield C *et al.*, 2003). ZM447439 induces apoptosis in a concentration- and time-dependent manner, following polyploidization.

AZD1152

AZD1152 (AstraZeneca) is a novel acetanilide-substituted pyrazole-aminoquinazoline drug that is converted rapidly to the active drug AZD1152 hydroxy-QPA (AZD1152-HQPA) in human plasma (Wilkinson RW *et al.*, 2007). AZD1152-HQPA is a specific inhibitor of the enzymatic activity of Aurora kinases, with selectivity for AURKB. AZD1152 blocks phosphorylation of histone H3 and increases the population of cells with 4N/8N DNA content. Preclinical efficacy of AZD1152 in human leukemia cells was also recently shown. AZD1152 synergistically increased the antiproliferative effect of vincristine and daunorubicin (Yang J *et al.*, 2007). Recently, in a phase I clinical trial in solid tumor patients, AZD1152 was reported to be tolerated up to 300 mg when administered intravenously with significant disease stabilization reported in five of eight patients (Schellens JH *et al.*, 2006). AZD1152 was given as a weekly 2-hour infusion to patients with advanced pretreated solid tumors.

PHA-739358

PHA-739358 (Nerviano) is more potent than its predecessor PHA-680632 and inhibits all three Aurora kinases, A, B, and C. It has a high cross-reactivity for other kinases mutated or overexpressed in cancers like Ret, Trk-A, and ABL. It inhibits phosphorylation of AURKA on T288 and reduces histone H3 phosphorylation indicating AURKB inhibition (Carpinelli P *et al.*, 2007). PHA-739358 is currently being evaluated in a phase II clinical trial in CML. PHA-739358 has significant antitumor activity in transgenic tumor models with a favorable preclinical safety profile; principal target organs of PHA-739358 are the hemolymphopoietic system, gastrointestinal tract, male reproductive organs, and kidneys. Renal effects, however, are only seen at high drug exposure.

Conclusion

The principal goal in the development of Aurora kinase inhibitors is to assess whether the administration of these small molecules to patients will yield a clinical benefit. Both pharmaceutical companies as well as clinicians presently consider Aurora kinases “*hot property.*” Pharmaceutical companies are investing in the development of different inhibitors to target Aurora kinases. For a clinician, the fact that small molecule Aurora kinase inhibitors could be effective at killing cancer cells has shed more light on these kinases; however, it seems appropriate to voice a cautionary note about the overall efficacy of such inhibitors in cancer treatment. Nevertheless, the frequent overexpression of Aurora kinases in solid tumors and their contribution to biological processes and signaling pathways, critical for cancer cells, highlight them as *the rising stars in targeted therapy* and *the future of personalized therapy in cancer.*

References:

Journals:

1. Bischoff, J. R. et al. A homologue of Drosophila aurora kinase is oncogenic and amplified in human colorectal cancers. EMBO J. 17, 3052–3065 (1998).
2. Bolanos-garcia V M. Aurora kinases. The International Journal of Biochemistry & Cell Biology 37 (2005) 1572–1577.
3. Carpinelli P, Ceruti R, Giorgini ML, et al. PHA-739358, a potent inhibitor of Aurora kinases with a selective target inhibition profile relevant to cancer. Mol Cancer Ther 2007; 6:3158–68. Abstract/FREE Full Text
4. Chen J, Jin S, Tahir SK, Zhang H, Liu X, Sarthy AV, McGonigal TP, Liu Z, Rosenberg SH, Ng SC. Survivin enhances Aurora-B kinase activity and localizes Aurora B in human cells. J. Biochem. 2003; 278:486-90.
5. Crane, R. et al. (2003). "Aurora A, Meiosis and Mitosis". Biology of the Cell 96 (3): 215-229.doi:10.1016/j.biolcel.2003.09.008.PMID 15182704.http://cellbio.med.harvard.edu/faculty/ruderman/publications/Crane_Aur_A_Biol_Cell_2004.pdf
6. 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. Abstract/FREE Full Text

7. Gadea BB, Ruderman JV. Aurora kinase inhibitor ZM447439 blocks chromosome-induced spindle assembly, the completion of chromosome condensation, and the establishment of the spindle integrity checkpoint in *Xenopus* egg extracts. *Mol Biol Cell* 2005; 16: 1305–18. Abstract/FREE Full Text
8. Giet R, Prigent C. Aurora/Ipl1p-related kinases, a new oncogenic family of mitotic serine-threonine kinases. *Journal of Cell Science* 112 (1999) 3591–3601
9. Hannak E, Kirkham M, Hyman AA, Oegema K (December 2001). "Aurora-A kinase is required for centrosome maturation in *Caenorhabditis elegans*". *J. Cell Biol.* 155 (7): 1109–16. doi :10.1083/jcb.200108051. PMC 2199344. PMID 11748251.
10. 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. Abstract/FREE Full Text
11. Marumoto T, Honda S, Hara T, Nitta M, Hirota T, Kohmura E, Saya H. Aurora-A Kinase Maintains the Fidelity of Early and Late Mitotic events in HeLa Cells. *J. Biol. Chem.* 2003; 278:51786-95.
12. M. Ouchi, N. Fujiuchi, K. Sasai, H. Katayama, Y.A. Minamishima, P.P. Ongusaha, C. Deng, S. Sen, S.W. Lee, T. Ouchi, BRCA1 phosphorylation by Aurora-A in the regulation of G2 to M transition. *J Biol Chem.* 279(2004)19643-8.
13. Q. Liu, S. Kaneko, L. Yang, R.I. Feldman, S.V. Nicosia, J. Chen, J.Q. Chen, Aurora-A abrogation of p53 DNA binding and transactivation activity by phosphorylation of serine 215, *J Biol Chem.* 279(2004)52175-82.
14. Schellens JH, Boss D, Witteveen PO, et al. Phase I and pharmacological study of the novel aurora kinase inhibitor AZD1152 [abstract]. *J Clin Oncol* 2006; 24:3008.
15. W.F. Zeng, K. Navaratne, R.A. Prayson, R.J. Weil, Aurora B expression correlates with aggressive behaviour in glioblastoma multiforme, *J Clin Pathol.* 60(2007)218-21.

16. Wilkinson RW, Odedra R, Heaton SP, et al. AZD1152, a selective inhibitor of Aurora B kinase, inhibits human tumor xenograft growth by inducing apoptosis. *Clin Cancer Res* 2007; 13:3682–8. Abstract/FREE Full Text
17. Yang J, Ikezoe T, Nishioka C, et al. AZD1152, a novel and selective aurora B kinase inhibitor, induces growth arrest, apoptosis, and sensitization for tubulin depolymerizing agent or topoisomerase II inhibitor in human acute leukemia cells in vitro and in vivo. *Blood* 2007; 110:2034–40. Abstract/FREE Full Text
18. Y. Miyoshi, K. Iwao, C. Egawa, S. Noguchi. Association of centrosomal kinase STK15/BTAK mRNA expression with chromosomal instability in human breast cancers. *Int J Cancer*. 92(2001)370-3.

Books:

1. Andrews PD. Aurora kinases: shining lights on the therapeutic horizon? *Oncogene* 2005; 24:5005¹⁵.
2. Bandobashi, K. Togitani, H.P. Koeffler, H. Taguchi. A novel treatment strategy targeting Aurora kinases in acute myelogenous leukemia, *Mol Cancer Ther*. 6(2007)1851-7.
3. C.J. Tang, C.Y. Lin, T.K. Tang, Dynamic localization and functional implications of Aurora-C kinase during male mouse meiosis, *Dev Biol*. 290(2006)398-410.
4. Conte N, Delaval B, Ginestier C, Ferrand A, Isnardon D, Larroque C, Prigent C, Seraphin B, Jacquemier J, Birnbaum D. TACC1–chTOG–Aurora A protein complex in breast cancer. *Oncogene* 2003; 22:8102-16.
5. F. Lopez-Rios, S. Chuai, R. Flores, S. Shimizu, T. Ohno, K. Wakahara, P.B. Illei, S. Hussain, L. Krug, M.F. Zakowski, et al, . Global gene expression profiling of pleural mesotheliomas: overexpression of aurora kinases and P16/CDKN2A deletion as prognostic factors and critical evaluation of microarray-based prognostic prediction, *Cancer Res*. 66(2006)2970-9.
6. Kemp CA, Kopish KR, Zipperlen P, Ahringer J, O'Connell KF. Centrosome maturation and duplication in *C. elegans* require the coiled-coil protein SPD-2. *Dev. Cell* 2004; 6:511–23.
7. K. Sasai, H. Katayama, D.L. Stenoien, S. Fujii, R. Honda, M. Kimura, Y. Okano, M. Tatsuka, F. Suzuki, E.A. Nigg, et al, Aurora-C kinase is a novel chromosomal passenger protein that can complement Aurora-B kinase function in mitotic cells. *Cell Motil Cytoskeleton*. 59(2004)249-63.

8. 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.
9. M. Bernard, P. Sanseau, C. Henry, A. Couturier, C. Prigent, Cloning of STK13, a third human protein kinase related to *Drosophila aurora* and budding yeast Ipl1 that maps on chromosome 19q13.3-ter. *Genomics.* 53(1998)406-9.
10. M. Kurai, T. Shiozawa, H.C. Shih, T. Miyamoto, Y.Z. Feng, H. Kashima, A. Suzuki, I. Konishi, Expression of Aurora kinases A and B in normal, hyperplastic, and malignant human endometrium: Aurora B as a predictor for poor prognosis in endometrial carcinoma, *Hum Pathol.* 36(2005)1281-8.
11. Portier N, Audhya A, Maddox PS, Green RA, Dammermann A, Desai A, Oegema K. A microtubule-independent role for centrosomes and Aurora A in nuclear envelope breakdown. *Dev. Cell* 2007; 12:515-29.
12. S. Anand, S. Penrhyn-Lowe, A.R. Venkitaraman, AURORA-A amplification overrides the mitotic spindle assembly checkpoint, inducing resistance to Taxol. *Cancer Cell.* 3(2003)51-62.
13. Sasai K, Katayama H, Stenoien DL, Fujii S, Honda R, Kimura M, Okano Y, Tatsuka M, Suzuki F, Nigg EA, Earnshaw WC, Brinkley WR, Sen S. Aurora-C is a novel chromosomal passenger protein that can complement Aurora-B kinase function in mitotic cells. *Cell Motil. Cytoskeleton* 2004; 59:249-63.
14. S. Dutertre, E. Hamard-Péron, J.Y. Cremet, Y. Thomas, C. Prigent, The absence of p53 aggravates polyploidy and centrosome number abnormality induced by Aurora-C overexpression. *Cell Cycle.* 4(2005)1783-7. .
15. 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.
16. T. Ikezoe, Y. Jing, C. Nishioka, T. Tasaka, A. Taniguchi, Y. Kuwayama, N. Komatsu, K. Sen S, Zhou H, White RA (May 1997). "A putative serine/threonine kinase encoding gene BTAK on chromosome 20q13 is amplified and overexpressed in human breast cancer cell lines". *Oncogene* 14 (18): 2195–200. doi:10.1038/sj.onc.1201065. PMID 9174055.

17. T. Ota, S. Suto, H. Katayama, Z.B. Han, F. Suzuki, M. Maeda, M. Tanino, Y. Terada, M. Tatsuka, Increased mitotic phosphorylation of histone H3 attributable to AIM-1/Aurora-B overexpression contributes to chromosome number instability, *Cancer Res.* 62(2002)5168-77.
18. Zhou H, Kuang J, Zhong L, Kuo WL, Gray JW, Sahin A, Brinkley BR, Sen S (October 1998). "Tumour amplified kinase STK15/BTAK induces centrosome amplification, aneuploidy and transformation". *Nat. Genet.* 20 (2): 189–93. doi:10.1038/2496. PMID 9771714.

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