

Original Review Article**DOI: 10.26479/2018.0405.07****ROLE OF AURORA KINASES IN CANCER: A COMPREHENSIVE REVIEW****Pujan N Pandya^{1*}, Archana U Mankad¹, Rakesh M Raval²**

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ABSTRACT: Aurora kinase is a vital Serine–threonine protein kinase family comprising of three protein members, playing an indispensable role in the cell cycle. Protein kinases work in concordance during the cell cycle. Their inter-relationship is necessary for the maintenance of a stable haemostatic mechanism of the cell cycle. Aberrant expression of different protein kinases and their altered signaling mechanism during the cell cycle, from its onset till the cytokinesis phase, is an important hallmark in cancer. These three Aurora kinases are overexpressed in cancer. Alterations in cell cycle and the overexpression of Aurora Kinases are related to the pathogenesis of cancer which occurs due to the altered functionality of these kinases and the resulting change in cellular signalling mechanisms. Combating the overexpression of the Aurora kinases with the help of certain competitive and selective inhibitors is required. This review throws light on the structural and functional insights into the Aurora kinase family, their role in cell cycle, their overexpression related to the different cancers and the information relating to certain Aurora kinase inhibitors.

KEYWORDS: Cell cycle, Aurora Kinase Family, Overexpression, Cancer, Aurora kinase inhibitors.

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1. INTRODUCTION**The Aurora Kinase Family**

Aurora Kinase Family is a serine-threonine protein kinase family, consisting of three kinases viz. Aurora A, Aurora B and Aurora C. They play a major role during different phases of cell cycle and in regulation of structure, functions, interactions and vital signalling mechanisms during its varied

phases [1, 2, 3]. The origin of the word “Aurora” dates back to the Latin origin. Literal meaning of the word “Aurora” means, “Dawn”. It symbolises a luminous emission during dawn which occurs in both the hemispheres due to the charged solar particles which are guided towards the magnetic lines of the globe. The Aurora gene was first spotted during the screening of mutations in *Drosophila Melanogaster* genes that regulated the cell cycle [4]. Since then, a colossal amount of structural and functional profiles for Aurora kinases in different species are being elucidated as they play vital roles during cell cycle mechanism [1, 3]. Aurora protein kinase family, possesses a C-terminal domain, which is conserved in all the three family members and an N-terminal domain having low sequence conservation [1, 2]. The catalytic domain shares more than 70% homology amongst the three Aurora kinases [5]. The Aurora kinase family also have a conserved KEN box, for the mechanism of the KEN-box-dependent degradation [6]. Aurora- A protein, from the Aurora family is found to be present among all the vertebrate organisms. Phylogenetic studies shows that the Aurora-B and Aurora-C in *Homo sapiens* must have arose from a gene duplication phenomena in mammals [5, 7]. According to the structural profiles of the three auroras, Aurora A is structurally more similar to Aurora B, then to Aurora C. Whereas, Aurora B and Aurora C, shares more similarity compared with others [3, 8]. The basic information regarding the three Aurora kinase available from NCBI gene and protein database are shown in the below table. (Reference link: <https://www.ncbi.nlm.nih.gov/gene/?term=Aurora+kinase>)

Table 1: Information regarding the three Aurora Kinases provided by NCBI gene database

Sr. No.	Aurora Kinase official name by HGNC	Official Symbol	Chromosomal location by HGNC	Other names used	Amino acid chain length
1.	aurora kinase A	AURKA	20q13.2	AIK; ARK1; AURA; BTAK; STK6; STK7; STK15; PPP1R47	403
2.	aurora kinase B	AURKB	17p13.1	AIK2; AIM1; ARK2; AurB; IPL1; STK5; AIM-1; ARK-2; STK-1; STK12; PPP1R48; aurkb-sv1; aurkb-sv2	344
3.	aurora kinase C	AURKC	19q13.43	AIE2; AIK3; ARK3; AurC; SPGF5; STK13; HEL-S-90; aurora-C	309

The following figure 1 shows the top most functional proteins associated with the three Aurora kinase Proteins in the protein-protein Association network, prepared using STRING database [9].

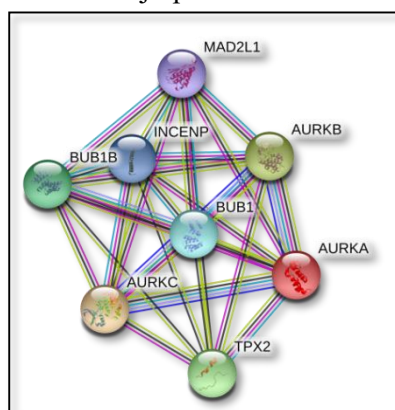


Figure 1: Protein-Protein Association Network of the three Aurora Kinases with the top most interacting proteins

Targeting the Aurora kinases and cell cycle for strategic cancer therapy

Different checkpoints and specific kinases relating to mitosis have been looked upon for targeting the unrestricted progression of the genomically unstable cells leading to cancer [10, 11]. Aurora A, Aurora B and Aurora C have been mapped on an intrinsically unstable and mutagenic region of chromosome, giving a good logical explanation for aberrant expression of Aurora kinases in human cancers [12].

Aurora A and its role in Cell Cycle

Activity of Aurora A is higher during the early phases of mitosis in cell cycle. It had been demonstrated that the levels of Aurora A was highest during the G2-M phase of cell cycle and was also associated with the kinase associated with cyclin-B [13]. Aurora A level is higher in the cells which have higher mitotic/meiotic Index. It is involved during the mitotic entry of the cells, progression of mitotic cycle, maturation of centromeres, separation of centriole pairs, the bipolar spindle assembly, aligning of the chromosomes during metaphase and for mechanism the cytokinesis [14, 15]. Aurora-A is essential for, maintenance of centrosome separation, the accumulation of centrosomal gamma tubulin and other pericentriolar material (PCM) components during G2 phase which indicates its presence in centrosomal region. It is mainly found in the PCM and at the two mitotic spindle poles [16]. Activation of Aurora A is done by phosphorylation mechanism and a protein associated with the microtubules, TPX-2 (Targeting Protein for Xklp2) which is an important substrate for Aurora A [17, 18]. Aurora A helps in contributing towards the spindle orientation by controlling NuMA (Nuclear Mitotic Apparatus), which helps in regulation of spindle assembly. It had been observed that the low activity of Aurora A results into a disorientation of bipolar spindle formation in the dividing cells. Moreover, for the correct distribution of the NuMA in the cells undergoing metaphase, the activity of Aurora A is required. It had been implicated that the phosphorylation of Aurora A to NuMA helps in regulation of its presence in metaphase [18, 19]. The following figure 2 shows the top ten functional proteins associated with Aurora A protein in the protein-protein interaction network prepared using STRING database [9].

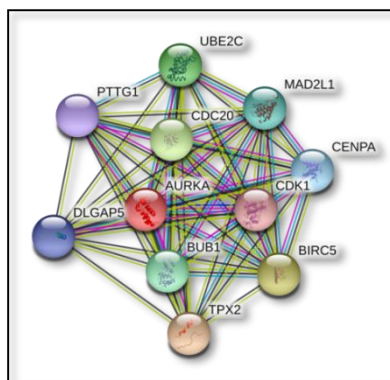


Figure 2: Protein-Protein Association network for Aurora A

Aurora A as a promising target

Aurora A, which is regarded as an oncogene, has been found to sufficiently transform the NIH/3T3 cells in inducing tumor formation in mice. Moreover it was found that along with mitotic defects, hyperplasia and genomic instability, there was overexpression of Aurora A induced tumor in the mice [20, 21]. Before and during the onset of mitosis cycle, Aurora A gets concentrated towards the centrosomes. Overexpression of Aurora A is related to the cellular transformation and amplification of centrosome and it is seen in certain tumor [22]. Reduced beta-catenin levels, during Wnt/ β -catenin pathway in multiple myeloma cells is related to changes seen at transcriptional level in Aurora A [23]. GSK-3 β (Glycogen Synthase Kinase- 3 Beta) is a vital protein kinase required for regulation of β -catenin phosphorylation which leads to its degradation [24]. Overexpression of Aurora A affects tumor cells by increasing its invasiveness and metastatic potential. Its overexpression has a correlation with higher expression of beta catenin in cytoplasm in the Oesophageal squamous cell carcinoma (ESCC). Phosphorylation mechanism of beta catenin by Aurora A is a novel mechanism for tumor malignancies [25]. Aurora A is one of the many regulators that promote the TERT (Telomerase Reverse Transcriptase) transcription via different mechanisms [26]. Overexpression of Aurora A affects the telomerase and hTERT (human Telomerase Reverse Transcriptase) activity through the upregulated c-Myc mechanism, by providing an additional mechanism for Aurora A in the malignancies. Knockdown of c-Myc through RNAi (RNA interference) lessened hTERT expression and activity of telomerase which is simulated by Aurora A [27]. The Aneuploidy phenomenon is associated with the overexpression of Aurora A. It results in provoking the mitotic checkpoint mechanism and clearance of cell population due to apoptosis [28]. Aurora A overexpression, provokes and promotes genomic instability in cells and gives a thrust for development of stem cell like activities in the cancerous cell, although its' oncogenic role is different in varied cancer types [28, 29, 30].

Aurora B and its role in cell cycle

Aurora B is a part of chromosomal passenger complex (CPC). The activity of Aurora B is high during the metaphase and functions through till the end of mitosis cycle . CPC consists of Aurora B,

INCENP (Inner centromere protein) and other two non-enzymatic subunits borealin and survivin. Establishment of a centromere is accomplished by the kinases, PLK1, Aurora B and mitotic checkpoint serine/threonine protein kinase BUB1 by recruitment of a CPC [31]. CPC regulates the errors occurring during the attachment of microtubule to the chromosomes, spindle assembly checkpoint activation and regulating the cohesion between the sister chromatids [32]. The activity of Aurora B is highly regulated at different levels and its activation is suggested as a complex multi-step process [33]. Aurora B forms a catalytic core in the CPC and for its activation, the mechanism of Aurora B phosphorylation at the Ser 331 Amino Acid location is required during mitosis. Ska (Spindle and Kinetochore association) complex is an important substrate for Aurora B and is important for its activity. The conserved activity of Aurora B helps in being the key regulators of Kinetochore and microtubule dynamics and attachment stability in the cells [34]. Aurora B has a role in correction of errors during the cell cycle. Moreover, phosphorylation of kinetochore substrates by Aurora B in the absence of tension would destabilize the incorrect attachments and allow re-orientation of the spindle poles [35]. The following figure 3 shows the top ten functional proteins associated with Aurora B in the protein-protein association network using STRING database [9].

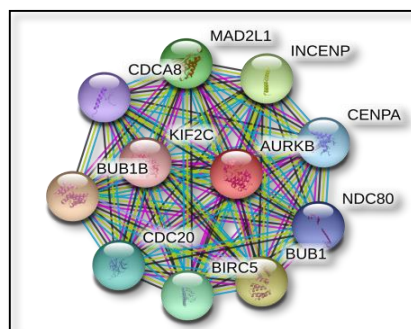


Figure 3: Protein-Protein Association Network for Aurora B.

The overexpression of Aurora B in cancer

Aurora B is considered as a strong biomarker for mitotic errors causing aneuploidy, chromosomal instability and tumors. Aurora B overexpression is related to the increased proliferation in cancer cells. Its overexpression has been found to be related with the tumors and its frequent increased activity is also linked to breast cancer carcinoma [36]. It is found to be overexpressed in different cancer tumors like glioma, thyroid carcinoma and colon cancer [36, 37]. Overexpression of Aurora B is considered as a potent independent biomarker for prediction of tumor obtrusiveness and for the poor prognostic behaviour of Hepatocellular carcinoma [38]. During inhibition of Aurora B an interference with normal chromosome alignment is observed along with the overriding of Mitotic spindle checkpoint and cytokinesis failure, endoreduplication and hence cell death [39]. Aurora B is an attractive target for cancer therapeutics as the Inhibition of its activity, gives rise to an antiproliferative phenotype [38]. Increased levels of Aurora B have been a cause for defective

chromosomal segregation. Whereas, its absence is a cause for aneuploidy, as there occurs an inability of Aurora B for resolving incorrect KT-MT (Kinetochore- Microtubule) attachment errors [41, 42]. TRF1 (Telomeric Repeat Factor-1) acts as a regulator of Aurora B. Relation between Aurora B and TRF1 is also known as there is a requirement of TRF1 for the functions of Aurora B underlying the centromeres. Its regulation involves the other interacting proteins as well, as the TRF1 does not directly bind to Aurora B. Dysfunction of TRF1 is related to the hampered functioning of Aurora B which leads to aneuploidy and cancers [43].

Aurora C and its role in mitosis

Though less information is available for Aurora C, it is found that Aurora C plays a vital role during the events in cell mitosis and functions in spermatogenesis [44]. The mRNA protein expression of Aurora C and Aurora B are high during the G2/M phase [45, 46]. It has been found that, Aurora C performs a cooperative, non-overlapping function with Aurora B during mitosis cell cycle. when there is a the lack of Aurora B in the in the somatic cells , Aurora C helps in compensating its loss by its supportive expression during the cell cycle through its interaction with INCENP [47, 48]. Moreover it has also been found that the localization of Aurora C was similar to that of Aurora B at the CPC. As the localization of different kinases relates to its functions during that particular phase, it can be said that Aurora C also plays an important role in mitosis other than meiosis [49]. Also, during female mouse meiosis, Aurora C have been found to be present during the pro-metapase I and metaphase I stages during cell division, at the centromere and the chromosome arms. Moreover, during metaphase II it was found to be concentrated at the centromeres where phosphorylation of Aurora C occurs at Thr 171. While during the anaphase to telophase transition Aurora C dephosphorylates and localizes itself to the midzone and midbody [52]. The following figure 4 shows the top ten functional proteins associated with Aurora B in the protein-protein association network prepared using STRING database [9].

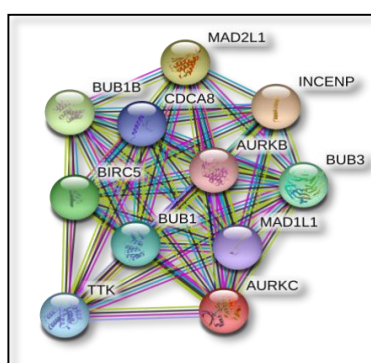


Figure 4:Protein-Protein association Network for Aurora C Protein.

The overexpression of Aurora C in cancer

Overexpression of Aurora C has an oncogenic activity resulting in aberrant cell division which results in amplification of centrosomes and multi-nucleation phenomena [53]. Overexpression of

Aurora C is indicated in varied somatic cancer. Its overexpression relates to the tumorigenicity of cancerous cells, with its positive correlation with colorectal cancer, thyroid cancer cell line and different malignancies [50, 53]. Gene amplification at the DNA level was observed due to Aurora C overexpression in breast cancer cell lines. Over expression of Aurora C was observed in the invasive cancer cell lines compared to that in non-invasive breast and prostate cancer cell line [54]. It was observed that in human cervical and colorectal cancers, the Expression levels of Aurora C was higher especially in the tumor specific regions than compared to normal tissue regions. It has been also seen that Aurora C overexpression has a positive correlation with lymph node metastasis and in colorectal cancers [53]. Along with Aurora C, the over expression of the survivin genes may also play a vital role in colorectal cancer development [55].

Different types of Cancers related to the overexpression of Aurora kinases

Since, the over expression of Aurora kinases is correlated to cancer pathogenesis, below table summarizes the different types of cancer wherein, Aurora kinase overexpression have been observed (+ sign signifies the overexpression of the related protein with the related cancer type).

Table: 2 summary of different types of Cancer and the related overexpression of specific Aurora kinase proteins

Cancer type	Aurora A overexpression	Aurora B overexpression	Aurora C overexpression	References
Oral Squamous cell Carcinoma (OSCC)	+	+		56, 57
Squamous Cell Carcinoma of Head and Neck (SCCHN)	+	+		58,59
Gatrouintestinal Cancer	+			60
Esophageal squamous cell carcinoma (ESCC)	+			25, 61
Colorectal cancer	+	+	+	24, 62, 53
Breast Cancer	+		+	27,36, 54,63
Cervical cancer	+		+	53,64,65
Prostate Cancer	+	+	+	66
Ovarian Cancer	+	+		27, 68,69
Thyroid Cancer	+	+		70,71
Multiple Myeloma	+	+		72,73,74
Hepatocellular Carcinoma	+	+		40,75
Leukemia	+	+		76,77

Renal cancer	+	+		78,79
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Aurora kinase inhibitors

Looking at the role of Aurora kinases at different stages in cell cycle and in the pathogenesis of cancer, various Aurora kinase inhibitors have come into existence for strategic cancer therapy [80]. Single selective Aurora kinase inhibitors and pan aurora kinase inhibitors have come into existence that has a valuable impact on the kinases and also in biological research. But, certain side effects exists for these inhibitors too [80, 81]. Multiple kinase compounds had been also designed which, in combination with certain therapies targets the proteins and the pathway responsible for the pathogenesis responsible for cancer related malignancies. Table 3 summarizes the information related to some Aurora kinase inhibitors available from the Therapeutic Target Database (TTD) [82] (Reference link : <https://db.idrblab.org/ttd/>).

Table 3: Information regarding the different Aurora Kinase Inhibitors available from TTD Therapeutic Target Database (TTD). Reference link : <http://bidd.nus.edu.sg/group/cjttd/>

Sr.No	Drug Name	Aurora Kinase Target/s	Clinical trial Stage
1	MLN 8237 (Alisertib)	Aurora A, Aurora B	Phase 3
2	Barasertib(AZD-1152-HQPA)	Aurora B	Investigative
3	CYC116	Aurora A, Aurora B	Phase 1
4	PHA 739358 (Danusertib)	Aurora A, Aurora B	Phase 2
5	AT9283	Aurora A, Aurora B	Phase 3
6	PF 03814735	Aurora A, Aurora B	Discontinued in Phase 1
7	AMG 900	Aurora A, Aurora B	Phase 1
8	VX-680 (tozasertib)	Aurora A, Aurora B	Phase 2
9	MLN8054	Aurora A,	Phase 1
10	VX-689(MK-5108)	Not available in database	Phase 1
11	SNS 314 (SN 314)	Aurora A, Aurora B	Phase 1
12	TAK 901	Aurora B	Phase 1
13	GSK1070916	Aurora B	Phase 1
14	PF 03814735	Aurora A, Aurora B	Discontinued in Phase 1
15	ENMD-2076	Aurora A	Phase 2
16	ZM 447439	Aurora A	Investigative
17	BI 811283	Aurora B	Phase 1
18	PHA 680632	Aurora A, Aurora B	Investigative

4. CONCLUSION

A comprehensive study on the Aurora Kinase protein family reveals its vital functionality in different stages of the cell cycle. Aberrant overexpression of these Aurora kinases is related to the pathogenesis of cancer and related anomalies. There are various inhibitors which help in controlling the overexpression of the Aurora kinases in the mitotic cells. Protein-Protein interaction as evident from the string interaction justify for selecting aurora kinases as potent target for further drug discovery. A well designed inhibitor with lower side effects and higher pharmacokinetic efficacy is required to ward off the proliferation induced due to the overexpression of Aurora kinases and related kinases during carcinogenesis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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