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Aurora Kinases: Their Role in Cancer and Cellular Processes

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Abstract: Aurora kinases, belonging to a highly conserved family of serine/threonine kinases with critical roles in the regulation of the cell cycle, comprise three members: Aurora kinase A, B, and C, which serve as key mitotic regulators essential for maintaining chromosome stability. Aurora kinases play crucial roles in multiple events in mitotic such as the coordination of chromosomal and cytoskeletal events, regulation of the spindle assembly checkpoint pathway and cytokinesis to ensure the smooth progression of the cell cycle. Besides their mitotic functions, Aurora kinases are also involved in the regulation of meiosis. Gene amplification/mutation and overexpression of Aurora kinases have been detected in various solid and haematological cancers. In human tumours, Aurora kinases exhibit oncogenic roles associated with their mitotic roles, which drive the cancer cell proliferation and survival. Deregulation of Aurora kinase activity causes failure in centrosome function, spindle assembly, chromosomal alignment, and cytokinesis, eventually resulting in the mitotic abnormalities and genetic instability. These findings emphasize the crucial functions of Aurora kinases in cancer, prompting their recognition as valuable targets for cancer therapy. This review provides an overview of the structures and functions of Aurora kinases and sheds light on their oncogenic roles in cancer.

Aurora Kinazların Kanser ve Hücresel Süreçlerdeki Rolü

Anahtar Kelimeler
Aurora kinazlar, Serin/Treonin kinazlar, Kanser, Hücre döngüsü düzenleyicileri, Onkogenler

Öz: Aurora kinazlar, Aurora A, B ve C şeklinde tanımlanan üç üyeye sahip, hücre döngüsünün düzenlenmesinde kritik rolleri olan yüksek oranda korunmuş serin/treonin kinaz ailesine ait proteinlerdir. Aurora kinazlar, kromozom stabilitesinin korunmasında önemli rolleri olan mitotik düzenleyiciler olarak hizmet etmektedir. Mitozdaki çeşitli olaylarda kritik roller üstlenen Aurora kinazlar, kromozomal ve sitoskeletal olayların koordinasyonu, iğ ipliği oluşumu kontrolü ve sitokinez gibi olaylarda görev alarak hücre döngüsünün sorunsuz ilerlemesini sağlamaktadır. Mitotik fonksiyonlarının yanı sıra, Aurora kinazlar mayoz bölünmenin düzenlenmesi süreçlerinde de yer almaktadırlar. Aurora kinazların gen amplifikasyonu/mutasyonu ve aşırı ifadesi çeşitli solid ve hematolojik kanserlerde tespit edilmiştir. Aurora kinazlar mitotik rolleri ile ilişkilendirilen onkojenik fonksiyonları ile kanser hücrelerinin çoğalması ve hayatta kalmalarını sağlamaktadırlar. Aurora kinaz aktivitesinin bozulması, sentrozom fonksiyonunda, iğ ipliklerinin oluşumunda, kromozomal hizalanmada ve sitokinezde sorunlara neden olarak mitotik anormallikler ve genetik istikrarsızlığa yol açmaktadır. Bu bulgular, Aurora kinazların kanserdeki önemli fonksiyonlarını vurgulayarak kanser terapötikleri için değerli hedefler olarak tanınmalarını sağlamaktadır. Bu derleme, Aurora kinazların yapı ve fonksiyonlarına genel bir bakış sunarak, bu kinazların kanserdeki onkojenik rollerini aydınlatmaktadır.

1. INTRODUCTION

1.1 Aurora Kinases

Aurora kinases (AURKs) belong to the family of serine/threonine kinases that serve as mitotic regulators with crucial roles in various molecular events and structures involved in cell division such as centrosome duplication, chromosome condensation and separation, kinetochore-microtubule interactions, mitotic spindle formation, and completion of cytokinesis [1,2]. Aurora kinases are not only involved in the regulation of different steps during cell division but also contribute to the regulation of checkpoints that ensure proper cell cycle progression. Therefore, precisely coordinated temporal and spatial functions of Aurora kinases are crucial for maintaining chromosomal and genomic integrity during mitotic and meiotic processes (Figure 1) [3]. Because of their fundamental roles in cell cycle regulation, Aurora kinases were first identified in the late 1980s through genetic screening aimed at identifying the genes involved in controlling cell division. They were named after *Drosophila melanogaster* mutants displaying spindle defects resembling the phenomenon of the Northern Lights, also known as Aurora borealis [4]. Subsequently, additional homologs of Aurora kinases have been identified across in various species. In *Drosophila*, a second Aurora homolog was discovered, while *Caenorhabditis elegans* possesses two Aurora-related kinases, namely AIR-1/Aurora A and AIR-2/Aurora B [5,6]. In the budding yeast *Saccharomyces cerevisiae*, the single Aurora kinase gene, Ipl1 (Increased in Ploidy 1), has been detected, and phylogenetic trees show that Aurora members evolved from this single ancestor gene originating in *Urochordata* [7]. Similar to *Drosophila* and *C. elegans*, non-mammalian vertebrates such as the frog *Xenopus* possess two kinases, Aurora-A and -B [8]. Unlike other eukaryotes, only mammals have a third Aurora kinase called Aurora-C [9].

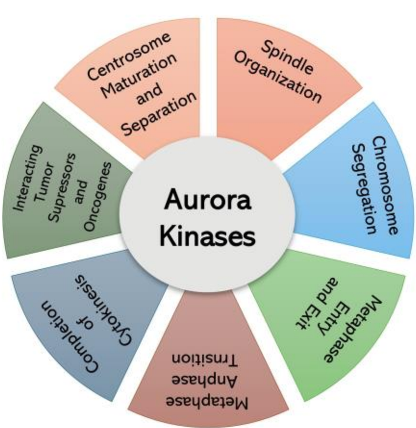

Figure 1. Functional diversity of Aurora kinases (AURKs) [2]

1.1.1. Structure and Functions of Aurora Kinases

Three Aurora kinases have been identified in humans: Aurora kinase A (AURKA), Aurora kinase B (AURKB) and Aurora kinase C (AURKC). Although AURKA and AURKB are ubiquitously expressed, the cellular distribution of AURKC is limited to meiotic cells including sperms and oocytes [10]. The size of Aurora kinases ranges from 309 to 403 amino acids, and they are composed of three domains: a highly conserved catalytic domain (250–300aa) involving the activation T-loop, a short C-terminal domain (15–20aa) regulating protein levels via proteasomal degradation and an N-terminal domain (39–139aa) with different lengths between kinases providing their different localization inside cells (Figure 2). Moreover, Aurora kinases have different percentages of homology in their catalytic domains as follows: 60% between AURKA and AURKC, 71% between AURKA and AURKB and 75% between AURKB and AURKC [7]. Although Aurora kinases are similar to each other in terms of the structure of the highly conserved catalytic domain, their N-terminal can vary in size and sequence, which allows for selective protein-protein interactions [11]. All members of the Aurora kinases display differences in their localization, substrates, regulatory partners, and function. Aurora A primarily regulates centrosome maturation and the assembly of bipolar spindles, whereas Aurora B and C play essential roles in condensation, kinetochore attachment, chromosome alignment during (pro-) metaphase, and cytokinesis [7].

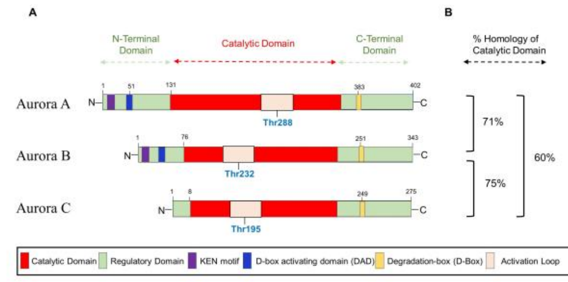

Figure 2. Structure and domains of Aurora kinases [7] Schematic representation of the Aurora A, B and C proteins with the indicated domains. The N-terminal and C-terminal domains contain regulatory motifs. The KEN regulatory motif is present in Aurora A and B and acts as an anaphase-promoting complex recognition signal. The D-box (Degradation Box) tag for ubiquitin identification and the D-box activating domain (DAD, or A-box), which is absent in Aurora B and C. Phosphorylation of conserved threonine residues at Thr288 (AURKA), Thr232 (AURKB) and Thr195 (AURKC), within the activation loop of the catalytic domain is required for kinase activity.

a. Percentages of homology of the catalytic domains are shown.

1.1.1.1. Aurora Kinase A (AURKA)

AURKA (also known as *AIK*, *ARKI*, *STK6*, *STK7* and *STK15*) maps to the 20q13.2 human chromosomal region and its cellular distribution is ubiquitous [12]. AURKA activity of AURKA is regulated through multiple mechanisms including phosphorylation/de-phosphorylation events and ubiquitin-mediated degradation [1]. The phosphorylation of AURKA by TPX2 (Targeting Protein for Xenopus kinesin-like protein 2) provides its activation and facilitates access to AURKA substrates. Moreover, the autophosphorylation of its activation segment at Thr288 (in humans) in the kinase domain is known to be critical for kinase activity [13]. Its inactivation can occur via the dephosphorylation of Thr288 by protein phosphatase 1 (PP1). During cell cycle

progression, AURKA proteins begin to localize around the replicated centrosomes during the S phase. Their activity and protein levels increased from the late G2 through to M phase. Finally, they undergo degradation by cadherin-1 (Cdh1)/anaphase-promoting complex/ cyclosome complex (APC) during mitosis and mitotic exit [14]. AURKA is involved in the regulation of several mitotic events occurring from late S-phase through the M phase such as centrosome maturation and separation, formation of bipolar spindle by interacting pericentriolar material (PCM), stimulation of mitotic entry, chromosome alignment during metaphase, mitotic exit and cytokinesis [15,16]. AURKA also plays a crucial role in spindle orientation by regulating the localization of nuclear mitotic apparatus protein (NuMA), thereby organizing mitotic spindle poles and coordinating spindle orientation [17,18]. Studies of AURKA mutations in *Drosophila melanogaster* have demonstrated defective chromosome and centrosome segregations, leading to the formation of polyploid cells [19]. Furthermore, defective AURKA activity results in impaired PCM function which is crucial for microtubule anchoring, and impaired mitotic spindle assembly, causing a transient spindle checkpoint-dependent mitotic arrest and subsequent apoptotic cell death [3,20]. Similarly, reduced AURKA activity results in proper NuMA distribution during metaphase, consequently impairing the orientation of bipolar spindles [12]. Apart from mitosis, AURKA plays a role in meiosis by stimulating oocyte maturation, polar-body extrusion, spindle positioning, and metaphase I exit [1]. Consequently, the diverse involvement of AURKA throughout cell division underscores its critical functions and potential implications during this dynamic period of cellular activity.

1.1.1.2. Aurora Kinase B (AURKB)

AURKB (also known as *AIK2*, *AIM1*, *ARK2*, *AIRK2*, *IPL1*, *STK1*, *STK5*, and *STK12*) is located on the 17p13.1 human chromosomal region, and its expression, like AURKA, is ubiquitous [12]. The kinase activity and protein expression levels of Aurora kinase B change based on the stages of cell cycle progression, and its expression peaks at the transition from G2 to M phase and functions until the end of mitosis [11]. Mainly, AURKB plays crucial roles in chromosome condensation, alignment and biorientation, spindle-assembly checkpoint, kinetochore-microtubule interaction, direction of metaphase-to-anaphase transition process and completion of cytokinesis [21,22]. In early mitosis, AURKB localizes to in the inner centromere, where it phosphorylates histone H3 on Serine residues Ser10 and Ser28 and recruits other proteins of the large Chromosomal Passenger Complex (CPC) protein complex. AURKB acts as a kinase module of CPC with three non-enzymatic subunits: survivin, borealin and inner centromere protein (INCENP), to ensure accurate chromosome segregation [23]. During prophase, AURKB binds to and phosphorylates INCENP. This binding, in turn, triggers AURKB auto-phosphorylation of Thr232 within the activation loop of the catalytic domain, altering its conformation to induce kinase activity. Subsequently, the binding of survivin and borealin proteins completes the CPC. In prometaphase, AURKB, as part of the CPC, localizes to the kinetochores, and it is subjected to spindle assembly checkpoints (SAC), which play a role in the correction of impaired spindle kinetochore attachments. During the transition from metaphase to anaphase, AURKB relocates to the microtubules, ensuring proper alignment and segregation of sister chromatids. During late mitosis, AURKB phosphorylates several proteins, including vimentin and Rac-GTPase activating protein-1 (MgcRacGAP-1), which are involved in the formation of the cleavage furrow to complete cytokinesis [7,22,24]. Apart from its mitotic roles, AURKB extends its functionality to the DNA damage response (DDR), a critical process that determines cell fate by directing cells to either repair damage or undergo self-destruction [25]. AURKB suppresses the activity of the p53 protein by phosphorylating it at various subcellular regions, including S183, T211, and S215. This phosphorylation leads to rapid degradation of p53 through the polyubiquitination-proteasome pathway. This results in the downregulation of p53 target genes involved in regulating the cell cycle and apoptosis [11]. Furthermore, during meiosis, AURKB localizes to chromosomes at metaphase, where it regulates kinetochore-microtubule attachments and chromosome alignment, and to the spindle midzone during anaphase to facilitate cytokinesis [26]. Inhibition of AURKB leads to defective chromosome alignment and dysfunctional mitotic spindle checkpoint, resulting in impaired cytokinesis and endoreduplication followed by apoptosis induction [20]. In summary, the pivotal role of AURKB in orchestrating various aspects of cell division highlights its ability to maintain genomic stability and ensure the accurate chromosomal segregation during cell division processes.

1.1.1.3. Aurora Kinase C (AURKC)

A third and the most elusive member of the Aurora kinase family, *AURKC* (also known as *AIK3*, *AIE2*, *ARK3*, and *STK13*), maps to the 19q13.43 human chromosomal region, and its expression is predominantly in meiotically dividing gametes [10,12]. AURKC is predominantly expressed at its highest level in the mammalian testis, whereas low expression is detected in several somatic cells such as the placenta, lung, bladder, and skeletal muscle [27]. Aurora C protein and mRNA levels are low during the S phase and peak in the G2/M phase [28]. Similar to AURKB in mitosis, AURKC is the catalytic module of CPC and plays a role in the regulation of kinetochore-microtubule attachments, chromosome segregation, SAC, and cytokinesis in meiosis [29]. Therefore, as a member of the CPC, the subcellular localization of Aurora C was found to be similar to that of Aurora B [27]. AURKC also concentrates on the microtubule-organizing center to keep the integrity of bipolar spindles and coordinates the localization and function of both AURKA and AURKB in meiotic cells [29]. Regarding the regulation of AURKC, similar to AURKA and AURKB, autophosphorylation of a threonine within the activation loop activates the kinase activity of AURKC. However, AURKC lacks protein degradation markers, such as KEN and D-box activating domain motifs found in AURKA and AURKB, suggesting that they are differentially regulated.

Additionally, this situation also demonstrates that AURKC provides a longer-lasting form of AURKB during meiosis [10,30]. Several studies have shown that defective AURKC in male mice results in blunted sperm heads, abnormalities in acrosome detachment and chromatin condensation, highlighting the critical role of AURKC in male fertility [31]. Moreover, mutations in AURKC cause meiotic arrest in meiosis-I [32], resulting in larger sperms with multiple flagella and misshapen heads, a condition called macrozoospermia [10,33]. Similar to male mice, AURKC deletion causes subfertility and arrests embryonic development in female mice owing to abnormalities in meiosis [34].

1.1.2. Aurora Kinases and Cancer

The connection between Aurora kinases and cancer development relies on their crucial functions in different stages of the cell cycle. As mentioned above, these mitotic kinases are essential for maintaining genomic integrity and proper cell division, playing critical roles in mitotic entry, centrosome and kinetochore function, spindle assembly, microtubule dynamics, spindle assembly checkpoint, chromosome segregation, and cytokinesis. Consequently, any dysregulation of Aurora kinase activity can cause mitotic abnormalities and genetic instability. Given that genetic instability, and subsequently to uncontrolled cell proliferation, constitutes a hallmark of tumorigenesis, the aberrant expression of Aurora kinases may emerge as a potential catalyst for cancer development [35]. Overexpression and/or gene amplifications of AURKs has been demonstrated in various human cancers (Figure 3). Moreover, AURKA, B, and C exhibited intrinsic instability, with frequent defects, amplifications, and mutational regions identified at 20q13.2, 17p13.1, and 10q13, respectively. These observations highlight the abnormal expression of Aurora kinases in human cancers, offering a clear explanation for their dysregulation in such contexts [14]. Overexpression of AURKA and AURKB is frequently observed in aneuploid tumours, which constitute approximately 90% of human malignancies [7,36] and gene amplification of AURKs has been linked to chemotherapy resistance and higher grades of malignancy [37]. Despite the overexpression and/or gene amplifications, there is no reported evidence of a natural deficiency of AURKs in human tumours thus far [14]. Moreover, Aurora kinase gene polymorphisms have been found to be related to an increased risk or early onset of cancer [38]. These findings underscore the intricate role of Aurora kinases in cancer pathogenesis and highlight their potential implications for therapeutic strategies.

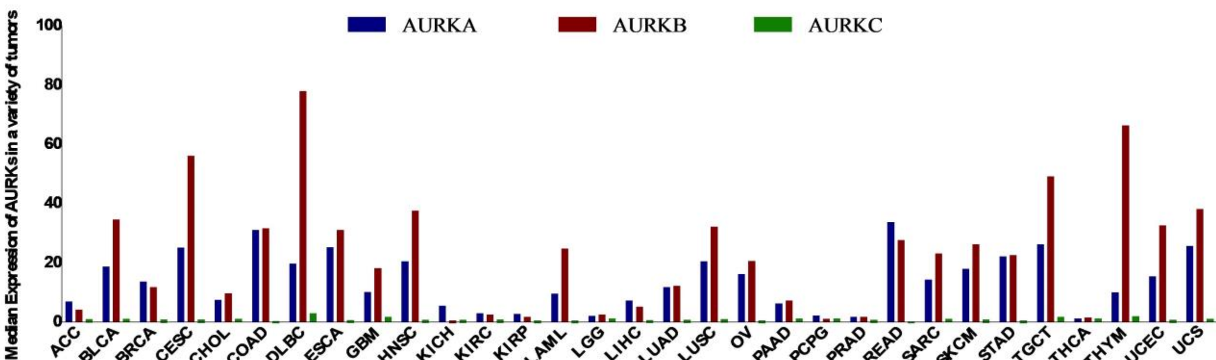

Figure 3. The median expression of AURKs in a variety of tumours. The data is obtained from Gene Expression Profiling Interactive Analysis (GEPIA) [39]. ACC—Adrenocortical carcinoma, BLCA—Bladder Urothelial Carcinoma, BRCA—Breast invasive carcinoma, CESC—Cervical squamous cell carcinoma and endocervical adenocarcinoma, CHOL—Cholangio carcinoma, COAD—Colon adenocarcinoma, DLBC—Lymphoid Neoplasm Diffuse Large B-cell Lymphoma, ESCA—Esophageal carcinoma, GBM—Glioblastoma multiforme, HNSC—Head and Neck squamous cell carcinoma, KICH—Kidney Chromophobe, KIRC—Kidney renal clear cell carcinoma, KIRP—Kidney renal papillary cell carcinoma, LGG—Brain Lower Grade Glioma, LIHC—Liver hepatocellular carcinoma, LUAD—Lung adenocarcinoma, LUSC—Lung squamous cell carcinoma, OV—Ovarian serous cystadenocarcinoma, PAAD—Pancreatic adenocarcinoma, PCPG—Pheochromocytoma and Paraganglioma, PRAD—Prostate adenocarcinoma, READ—Rectum adenocarcinoma, SARC—Sarcoma, SKCM —Skin Cutaneous Melanoma, STAD—Stomach adenocarcinoma, TGCT—Testicular Germ Cell Tumours, THCA—Thyroid carcinoma, THYM—Thymoma, UCEC—Uterine Corpus Endometrial Carcinoma, UCS—Uterine Carcinosarcoma

1.1.2.1. Aurora Kinase A in Cancer

Aurora kinase A is a bona-fide oncogene, and its expression in tumours is frequently related to gene amplification, genetic instability, malignant transformation, poor histological differentiation, and prognosis [38]. Amplification of AURKA has been observed in various solid and haematological cancers (Table 1). Furthermore, AURKA tissue expression has been demonstrated to be a predictive and prognostic factor in several cancers, including colorectal, breast and gastric tumours [7]. High AURKA expression stimulates carcinogenesis by promoting epithelial-mesenchymal transition (EMT), metastasis, cancer cell proliferation, self-renewal of cancer stem cells, and resistance to apoptosis [40]. Mutation or upregulation of AURKA also leads to therapeutic resistance such as cisplatin resistance, by enhancing the DNA repair pathway [37]. In addition to the well-known phenomenon of overexpression of Aurora kinase A, it can interact with a variety of other proteins, including tumour suppressors and oncogenes, thus contributing to carcinogenesis. AURKA interacts with tumour suppressor genes that control centrosome duplication, cell cycle checkpoints and chromosomal stability, thereby contributing to centrosome amplification and cytokinesis failure. For instance,

AURKA interacts with the p53 tumour suppressor at multiple levels through phosphorylation of Ser315 residues, which enhances Mdm2-mediated p53 degradation [28], and on Ser215, which inactivates its transcriptional activity [41], subsequently inhibiting downstream targets such as PTEN and p21 [42]. Another tumour suppressor protein associated with AURKA, BRCA1, is involved in coordinating DNA replication with the centrosome duplication cycle. Phosphorylation of BRCA1 by AURKA at Ser308 disrupts the G2/M checkpoint, leading to centrosome amplification and chromosomal instability [43]. Regarding the relationship between oncogenes and AURKA, it has been found that AURKA facilitates the oncogenic effects of well-known oncogenes such as Myc and FOXM1 in cancers, and that the overexpression or activation of these oncogenes and AURKA are frequently found together in human cancers [14,44]. Furthermore, AURKA engages with a multitude of substrates crucial in various cancer-promoting signalling pathways, notably polo-like kinase 1 (PLK1), β-catenin, and Akt. PLK1 acts as a pivotal cell cycle regulator, with its phosphorylation at the Thr210 region by AURKA being linked to essential processes like chromosome segregation, spindle assembly, and centrosome maturation [45]. AURKA's role is required for the activation of PLK1 to stimulate mitotic entry [46]. Overexpression of AURKA promotes PLK1 activity, accelerating centrosome amplification, chromosomal instability, faulty chromosomal segregation, and ultimately tumorigenesis [43]. Moreover, AURKA contributes to the downregulation of β-catenin and E-cadherin expression that is pivotal in regulating cell-cell adhesion, thereby promoting EMT [14]. In human osteosarcoma cells, AURKA stimulates the phosphorylation of Akt and mTOR oncoproteins to increase the tumorigenicity [47]. Consequently, aberrant AURKA expression drives tumorigenesis by enhancing proliferation, evading apoptosis, inducing EMT, and promoting genomic instability. Given its critical role in cancer development, AURKA emerges as a potential target for cancer therapy. In this regard, several small molecules designed to inhibit AURKA have been developed. These inhibitors have undergone preclinical testing, and some have advanced to clinical trials, either as monotherapies or in combination with traditional treatments [40].

1.1.2.2. Aurora Kinase B in Cancer

Aurora B is frequently expressed at high levels in several human cancers, and its expression level has been related to aneuploidy and genetic instability [38]. AURKB overexpression has been detected in a wide range of human cancers (Table 1). Overexpression of AURKB promotes the impaired chromosome segregation, cytokinesis failure and chromosome lagging in metaphase in cancer cells [48]. In addition, AURKB plays a significant role in tumorigenesis by interacting with specific proteins, including the MYC oncogenic protein, Breakpoint Cluster Region-Abelson Leukemia (Bcr-Abl) oncoprotein, p53, and Cyclin-dependent kinase 1 (Cdk1) [11]. In human retinoblastoma, the direct regulation of AURKB by MYCN, a member of the MYC proto-oncogene family, has been elucidated, highlighting the enrichment of a MYCN binding motif on the AURKB promoter [22]. Additionally, the upregulation of both AURKA and AURKB by c-MYC has been demonstrated in B-cell lymphoma [49]. Furthermore, Jiang et al. (2020) showed that AURKB stabilizes the MYC oncoprotein by phosphorylating it at the Ser67 position in T-cell acute lymphoblastic leukemia [50]. The Bcr-Abl oncoprotein, a product of the Philadelphia chromosome in human leukemias, is associated with constitutively activated tyrosine kinase, which plays a role in regulating various biological processes such as survival, invasion, growth, and angiogenesis in carcinogenesis [51,52]. Yang et al. (2014) showed that the Bcr-Abl oncoprotein stimulates the expression of both AURKA and AURKB via the AKT signalling pathway to promote clonogenic growth [53]. Furthermore, another study revealed that the progression of Chronic Myeloid Leukemia, a neoplastic disease arising from hematopoietic stem cells driven by the BCR-ABL oncogene, is associated with the aberrant expression of the AURKB gene [54]. Importantly, AURKB induces proteasome-mediated degradation of p53 by phosphorylating it at the Ser183, Thr211, and Ser215 regions to suppress its activity [11]. In addition, AURKB suppresses the expression of downstream target genes regulated by p53, thereby contributing to cell cycle inhibition. For instance, the overexpression of AURKB reduces the level of the p53 target p21Cip1 (cyclin-dependent kinase-interacting protein-1), known as a cell cycle inhibitor, and its inverse correlation has been demonstrated in human leukemias. This illustrates the contribution of AURKB to tumorigenesis by suppressing the activity of the cell cycle inhibitor p21Cip1 and promoting chromosomal instability [55]. Additionally, the decreased expression of the cell cycle inhibitor p21Cip1 by AURKB causes abnormal activation of Cdk1, allowing cell cycle progression and thus promoting cell survival. Moreover, Cdk1 induces the activation of the acetyltransferase TIP60, resulting in the acetylation and activation of AURKB, which in turn leads to aneuploidy and uncontrolled cell cycle progression [14]. In addition to its pivotal roles in tumorigenesis, the overexpression of AURKB also serves as a significant indicator of disease progression and overall survival in various cancers. Studies have demonstrated its association with reduced overall survival in metastatic colorectal cancer [56] and breast cancer [57]. Similarly, patients with adenocarcinoma subtype of non-small cell lung carcinoma exhibit notably shorter survival times when AURKB is overexpressed in their tumour cells [58]. Moreover, AURKB expression correlates with poor prognosis and is often observed in higher grades of malignancy across various neoplastic lesions, suggesting its potential utility as a prognostic marker and predictor for aggressive tumours [59]. Furthermore, AURKB expression has been investigated as a prognostic marker in gastric cancer [60], oral cancer [61] and glioblastoma [62]. Variants of AURKB in hepatocellular carcinoma have been linked to advanced stages, poor prognosis, and tumour recurrence [63]. Notably, in colorectal cancer, prostate cancer, ovarian, and thyroid carcinomas, the degree of AURKB overexpression is directly proportional to disease grade or dedifferentiation status, indicating its

role in disease progression [64–68]. High expression of AURKB was detected in papillary and anaplastic thyroid carcinomas, the, with further overexpression observed in advanced stages, suggesting a growth advantage for neoplastic cells [59,68,69]. This evidence points to the targeting of AURKB for cancer therapy and the development of small AURKB inhibitors. These inhibitors have been extensively studied in preclinical and clinical studies across various tumour types [70].

1.1.2.3. Aurora Kinase C in Cancer

AURKC is highly expressed in several cancers (Table 1). Even though AURKC overexpression has been observed across various cancer types, its precise oncogenic function remains unclear due to insufficient understanding of its role within the cellular context [71]. However, it is hypothesized that AURKC may contribute to centrosome amplification and multinucleation in cancer cells, potentially providing a survival advantage [72]. Moreover, Bejar et al. (2021) demonstrated that meiotic gene activation can drive tumour progression, further highlighting the potential significance of AURKC as a target for novel anti-cancer therapy [29]. Additionally, AURKC may exert an oncogenic role by phosphorylating several proteins involved in carcinogenesis, such as transforming acidic coiled-coil 1 protein (TACC1) [73] and telomeric-repeat binding factor 2 protein (TRF2) [74]. Notably, the overexpression of TACC1 has been shown to stimulate cell transformation and serve as a prognostic marker in breast cancer [75,76]. Similarly, TRF2 plays a critical role in telomere length regulation, and its phosphorylation by AURKC has been implicated in promoting tumorigenesis by reducing telomere length [10,74,77]. In conclusion, investigating the normal function of AURKC in meiotic cells through ongoing studies is essential for a comprehensive understanding of its role in cancer progression. While AURKA and AURKB have been extensively studied in this context, the association of AURKC in carcinogenesis remains relatively unexplored, with only a few AURKC inhibitors developed thus far [78]. Therefore, further investigation into AURKC's role in cancer and the development of targeted inhibitors may reveal new therapeutic options for cancer treatment and prevention.

Table 1. Summary of Aurora kinases and their overexpression/amplification in a wide range of tumour types [14].

Kinases	Localization	Function	Tumour Types	References
AURKA	Centrosome Spindle microtubule Midbody	Mitotic entry, Centrosome maturation/separation, Bipolar spindle microtubule formation, Chromosome alignment, Cytokinesis, Mitosis exit	Breast cancer	[79,80]
			Cervical cancer	[81,82]
			Colorectal cancer	[83,84]
			Esophageal squamous cell carcinoma	[85,86]
			Gastric/Gastrointestinal cancer	[87,88]
			Glioma	[89,90]
			Leukemia	[91,92]
			Lung cancer	[93,94]
			Oral cancer	[95,96]
			Ovarian cancer	[97,98]
			Prostate cancer	[99,100]
AURKB	Chromosome Kinetochore Midbody	Chromosome condensation, Chromosome Alignment, Chromosome Biorientation, Regulating SAC Kinetochore-microtubule-interaction, Cytokinesis	Breast cancer	[80,101]
			Cervical cancer	[102]
			Colorectal cancer	[103,104]
			Gastric/Gastrointestinal cancer	[87]
			Glioma	[89,105]
			Leukemia	[106]
			Lung cancer	[107,108]
			Oral cancer	[61,109]
			Ovarian cancer	[98,110]
			Prostate cancer	[100,111]
			Tyroid Cancer	[68]
AURKC	Chromosome Midbody	Kinetochore-Microtubule Attachment, Regulating SAC, Meiotic chromosome segregation Cytokinesis	Breast cancer	[112]
			Cervical cancer	[113,114]
			Colorectal cancer	[114,115]
			Glioma	[105]
			Prostate cancer	[100,112]

2.CONCLUSION

The Aurora kinase family offers a novel perspective for understanding the processes of mitosis, carcinogenesis, and their potential relationship. Aurora kinases serve as mitotic regulators and play an indispensable role in cell cycle progression. They interact with various partners to sustain their kinase activity and influence numerous downstream targets, including critical tumour suppressor proteins and oncoproteins. Therefore, exploring the link between interacting substrates and their effects on Aurora kinase regulation is significant, highlighting the importance of establishing regulatory networks for each Aurora kinase. Notably, the deregulation of a single mitotic regulator can significantly increase the risk of tumorigenesis. Amplification and overexpression of Aurora kinases have been found in numerous human tumours, and their aberrant expression triggers oncogenic

transformation, leading to the deregulation of multiple tumour suppressor and oncoprotein-regulated pathways. This ultimately results in genomic instability and tumorigenesis. The extensive network of Aurora kinases, encompassing different protein-protein interactions across a wide range of signalling pathways, supports the choice of Aurora kinases as potent targets for further exploration in drug discovery. The development of Aurora kinase inhibitors with fewer side effects and enhanced pharmacokinetic efficiency is required to counteract the overexpression of Aurora kinases and the deregulation of associated kinases involved in carcinogenesis. Therefore, Aurora kinases have emerged as promising targets to inhibit tumour cell growth and revealing the molecular functions of Aurora kinases will yield valuable insights for comprehending cell cycle control and provide novel strategies for drug design in cancer therapy.

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