Serican Journal of Medicine
2025, VOL. 2, NO. 3, 23694
https://doi.org/10.17161/sjm.v2i3.23694

Aurora kinase A in urological cancers

Jennifer Grasso[1], Cheng Zhang[1] and Ka-wing Fong[1,2*]

[1]Department of Toxicology and Cancer Biology, University of Kentucky, Lexington, KY, USA; [2]Markey Cancer Center, University of Kentucky, Lexington, KY, USA.
* Corresponding author: Ka-wing Fong, Ph.D., Department of Toxicology and Cancer Biology, University of Kentucky, 760 Press Ave, Lexington, KY 40536. Phone: 859-562-3455, Fax: 859-323-1059. E-mail: willfongkw@uky.edu

ABSTRACT

Aurora kinases are a family of serine/threonine kinases of whom function to preserve the integrity and fidelity of chromosomal segregation. In mammals, aurora kinase A (AURKA) is vital to the mitotic phase of the cell cycle as a consequence of its spatial and timely interactions with various types of cell cycle substrates. Since AURKA is present in all of the mammalian somatic cell cycles, it is also detectable in many different types and stages of cancers. Specific activation sites, feedback loops, and substrate interactions have been identified and linked to the progression of urological cancers. It is inarguable that the slightest hint of disorder among AURKA can disrupt the cell cycle's ability to regulate the growth and progression of cells in all conditions due to its direct interactions with tumor suppressing molecules. Discovering that AURKA interacts with PDGFR-β, FOXO3a, PLK1, TPX2, SPOP, YBX1 and CXCR7 in ways that were unknown during last five years has revealed new targeted treatment options that may surpass current methodology in efficiency and length of remission. The aim of this paper is to highlight AURKA's oncogenic role in urological cancers, in addition to emphasizing newfound pathways and mechanisms that introduce the prostate cancer research field to more options for therapeutic approaches.

ARTICLE HISTORY
Received: March 10, 2025
Revised: June 16, 2025
Accepted: June 23, 2025

KEYWORDS
urological cancer, phosphorylation, aurora kinase A

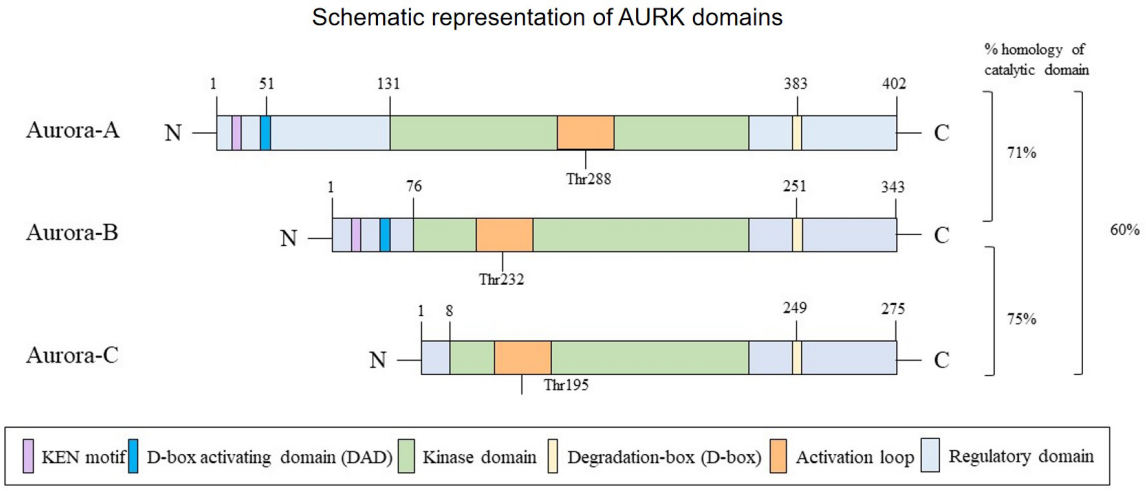
Introduction

The aurora kinases are serine/threonine kinase family associated with cell cycle regulation. In 1993, Clarence S. M. Chan and David Botstein discovered the ancestorial aurora kinase in Saccharomyces cerevisiae, baker's yeast, and named it IPL1 [1]. The following year, Chan and two other colleagues revealed IPL1 to be protein kinase responsible for the precision and accuracy in chromosomal segregation [2]. By 1995, Glover, et. al identified AURKA in fruit flies and identified it to be homologous to IPL1 via speciation [3]. Invertebrates possess AURKA and aurora kinase B (AURKB) as orthologs, and a duplication of AURKB led to the existence of three aurora kinase family members in mammalian vertebrates. Despite playing different roles within the cell cycle, aurora kinase orthologs A and B share such a high sequence similarity that a single G-N amino acid change has the ability to convert a functional aurora kinase A into a mutant that takes on aurora kinase B's function [4]. Furthermore, the percentage of conservation between AURKA and AURKB is 71%, which leads researchers to theorize that the division of the aurora kinase family is relatively recent compared to non-vertebrates [5].

Aurora Kinase Family Background

Aurora kinase homologs A, B and C all consist of a protein kinase, N-terminal, and C-terminal domain [6]. Regulatory sequences that guide the docking of other substrates and proteins are found within the N- and C-terminals **(Figure 1)**. Twelve kinase subdomains exist between the two lobes, and each serves an individual role in the control of substrate binding traffic. The destruction box (D-Box), responsible for the ubiquitination and degradation of the aurora kinase following cell division, is located on the C-terminal. Within the protein kinase domain, the activation loop resides. The activation loop allows for a post-translational intermolecular trans-phosphorylation to occur and allow the kinase to take on an active conformation [7]. This process, known as auto-phosphorylation, is a prerequisite for co-factor binding in each aurora kinase homolog. Auto-phosphorylation via Thr288 AURKA establishes a positive feedback loop fixes AURKA in its active conforma-

Figure 1: 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 recognizes anaphase-promoting complex. The D-box identify ubiquitin and the D-box activating domain (DAD). The activation loop is required for kinase activity. Phosphorylation of conserved threonine residues at Thr288 (AURKA), Thr232 (AURKB) and Thr195 (AURKC).



tion from the G2 phase to the end of the M phase. AURKA is responsible for the flawless maturation and separation of centrosomes at the beginning of the mitotic phase, in addition to the proper assembly of mitotic spindles. Without this positive feedback loop, AURKA would not be able to peak in its activity throughout the M phase. Abnormal AURKA expression directly promotes oncogenic phenotypes in the cell cycle's products, which has been linked to the origin of various urological cancers.

The first detectable level of AURKA expression is at the G2 checkpoint. Following auto-phosphorylation, AURKA is structurally able to allosterically bind other substrates that will alter its function. In the G2 phase, the cyclin A-CDK2 complex phosphorylates Bora via serine 112 [8]. Phosphorylated Bora seeks out AURKA to bind to its S112 site and activate the kinase. Previously, it was theorized that aurora kinase required phosphorylation of its activation loop at Thr288 in order to bind phosphorylated Bora. However, new evidence has revealed that phosphorylated Bora is able to allosterically bind aurora kinase A regardless of its activation state [9]. It is necessary to understand this mechanism for AURKA activation since it introduces AURKA to varying substrates during the G2-M phase.

Roles of AURKA in Urological Cancers

Since AURKA participates in every somatic cell's division cycle, its oncogenic association is observed among varying types of cancers. Included in this group of cancers are the urological cancers: prostate, renal, penile, testicular and bladder. Poor prognoses for patients are linked to an increased expression of AURKA in prostate and bladder cancers, as well as kidney diseases, specifically [10]. In addition to promoting cancerous phenotypes, AURKA is able to influence cancerous cells into adapting resistance to treatment in later stages. Its direct and indirect relationship with a multitude of feedback loops allow for it to be especially effective in complicating treatment options that would, otherwise, be sufficient in inhibiting tumor growth and cancer progression. Recent research has uncovered a multitude of high-profile substrates that interact with AURKA, commonly via phosphorylation, in the onset and progression of cancer. In this review, we provide a summary of substrates/interacting partners of AURKA to promote kidney, bladder and prostate cancers progression for the past five years **(Figure 2 & Table 1)**. In addition, we summarize the inhibitors of AURKA tested in treating urological cancers **(Table 2)**.

Kidney Cancer

PDGFR-β

In the context of kidney, abnormal expression of AURKA has been reported in renal cancers and polycystic kidney disease (PKD)-related renal cysts. A recent study reported high expression of AURKA in

Figure 2: Summary of AURKA substrates and its interacting partners in Urological Cancer progression.

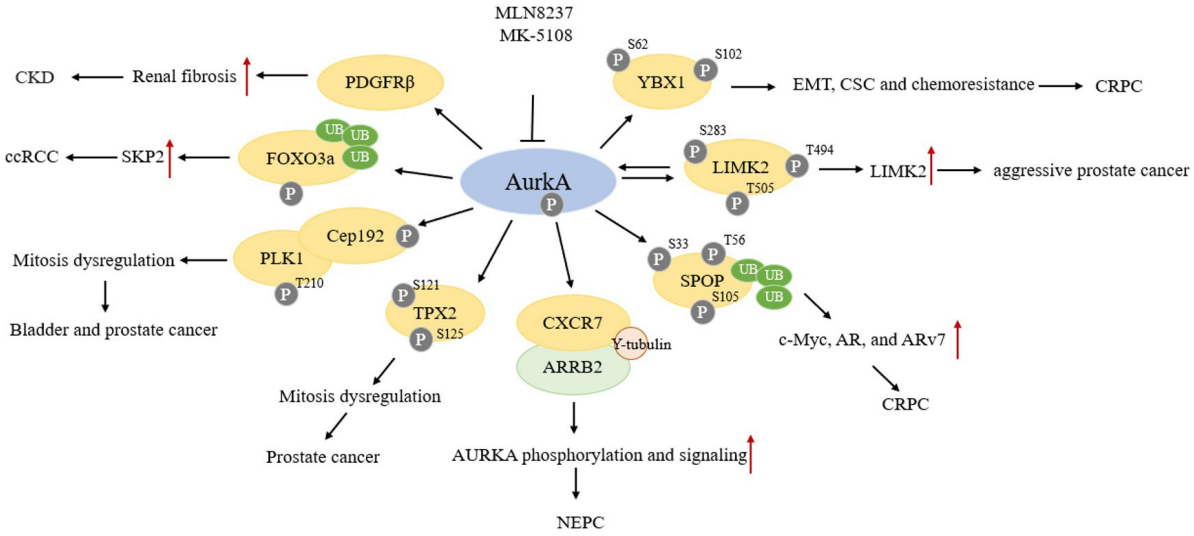


Table 1. Multifaceted role of AURKA in Urological disease.

Urological disease	Substrates/ Binding partners	Biological functions	References
CKD	PDGFRβ	Inhibition of AURKA by MK-5108 markedly attenuated renal fibrosis through decreasing the total and phosphorylation levels of PDGFRβ.	[11]
ccRCC	FOXO3a	AURKA causes an increase phosphorylation of FOXO3A, which its ubiquitylation and degradation by SKP2 mediating depends on the kinase activity of AURKA.	[14]
Bladder Cancer	PLK1	AURKA phosphorylates and activates Polo-like kinase 1 (Plk1) on threonine residue 210 (T210) to regulate mitosis and cell division.	[17]
Prostate Cancer	Cep192	AURKA promotes the activation of PLK1 at the centrosomes, which in turn phosphorylates CEP192, further enhancing its role in mitotic spindle formation.	[27]
	TPX2	AURKA interacts and phosphorylates TPX2 at S121 and S125. This phosphorylation event is crucial for normal spindle function and proper cell division.	[30]
	CXCR7	CXCR7-ARRB2 scaffold activates AURKA, leading to AURKA phosphorylation and subsequent promotion of NEPC growth.	[37]
	SPOP	AURKA phosphorylation of SPOP on its S33, S105, and T56 sites, leads to SPOP ubiquitylation and contributes to CRPC progression.	[39]
	LIMK2	AURKA phosphorylates LIMK2 at Serine 283, Threonine 494, and Threonine 505, which increases LIMK2's stability and promotes aggressive prostate cancer.	[42]
	YBX1	AURKA phosphorylates YBX1 at its S62 and S102 sites and stabilizes YBX1 and promotes its nuclear translocation, therefore increasing EMT, chemoresistance and tumorigenesis.	[45]

Table 2. AKIs in urological cancers studies.

Compound	Disease	Mechanism	Clinical stage	References
MK-5108	CKD	MK-5108 inhibited the pro-fibrotic response in renal cells induced by PDGFRβ.	Pre-clinical	[12]
Alisertib (MLN8237)	ccRCC	MLN8237 reduces SKP2 expression by enhancing FOXO3.	Pre-clinical	[14]
	Urothelial Cancer	Longer progression-free survival was observed in carriers of the minor allele A of rs2273535 in AURKA	phase II (NCT02109328)	[47]
	NEPC	Patients with molecular features supporting Aurora-A and N-myc activation achieved significant clinical benefit from single-agent alisertib.	phase II (NCT01799278)	[48]

fibrotic kidneys of chronic kidney disease (CKD) patients and UUO mice, indicating its potential role in CKD and renal fibrosis. Additionally, it also showed that pharmacological inhibition (MK-5108) of AURKA significantly decreased the total and phosphorylation levels of platelet-derived growth factor receptor β (PDGFRβ) [11]. Previous studies have shown that upregulation of PDGFR-β promotes proliferation and differentiation in renal fibroblasts in CKD patients, which often introduces the pathway into end-stage renal disease (ESRD) [12]. Furthermore, sham-operated kidneys showed weak expressions of PDGFRβ and p-PDGFR-β at Tyr751 [11]. Summarily, inhibition of AURKA suppressed renal fibrosis possibly by regulating PDGFRβ signaling, suggesting that AURKA is a potential target for treatment of CKD. However, more investigating is required to solidify the mechanistic connection between AURKA and PDGFR-β.

FOXO3a

In addition to renal fibrosis, AURKA is recognized as an oncogenic driver in clear cell renal cell carcinoma (ccRCC). FOXO3a, which usually acts as a transcriptional repressor in the presence of the FOXO response element located on the SKP2 promoter region; however, phosphorylated FOXO3a, is unable to bind the SKP2 promoter, act as transcriptional activator [14]. AURKA is positively correlated with SKP2 by increasing phosphorylation of FOXO3a and contributes to the advancement of tumor formation and growth in ccRCC. Additionally, SKP2 mediated ubiquitylation and degradation of FOXO3a depend on kinase activity of AURKA. [13-14]. Since AURKA possesses the ability to inhibit FOXO3a via phosphorylation and prevent it from binding to and inhibiting SKP2 expression, it is evident that the increased expression of SKP2 is a direct result of increased AURKA activity [15].

Given that FOXO3a's repression of SKP2 is dependent on AURKA, it is logical to assume that Alisertib (MLN8237), a popular AURKA inhibitor choice for tumor suppression, would be successful in the case of ccRCC. While MLN8237 is successful in reducing tumorigenesis and cancer progression, the efficacy of this targeted therapy is limited by the oncogenic overexpression of other cancerous substrates, such as SKP2 in this case [13]. Thus, the inhibition of AURKA does not directly inhibit SKP2. This raises the question of whether dual inhibition of AURKA with its synergistic substrates can increase the efficacy of tumor suppression and promote a more positive prognosis.

Bladder Cancer

PLK1

When considering the bladder, AURKA regulation of Polo-like kinase 1 (Plk1) is regulated by Bora. Bladder cancer tissues exhibit elevated levels of Bora and Plk1 in comparison to healthy tissue and bladder cancer patients with elevated Plk1 expression experience poorer prognoses. Plk1, a novel regulator in the progression of the cell cycle through its checkpoints, on Thr210. AURKA regulates Plk1 dependent on Bora. Following the activation of AURKA by phosphorylated Bora, phosphorylated Plk1 simultaneously activates the cyclin B-CDK1 complex and prevents Wee1 from inactivating CDK1. This cascade commits AURKA to the mitotic transition in the cell cycle, where it can influence centrosome maturation and separation.

Since AURKA depends on Bora for activation and regulates Plk1 via phosphorylation, researchers theorized that decreasing BORA activity may reduce the migration and invasion incidence rates within the epithelial-mesenchymal transition (EMT) pathway [16]. Without Bora present to sufficiently activate

AURKA, entry to the mitotic cell cycle will not be granted and the cycle will remain in G2 arrest. However, the percentage of reliance the AURKA-Plk1 cascade places on Bora is complex and not well understood. Furthermore, targeting AURKA or Bora alone has not been as efficient in the inhibition of bladder cancer progression as targeting Plk1 might be.

Fortunately, Plk1-specific inhibitors are already under investigation since Plk1 is upregulated in many cancers, similar to AURKA. In bladder urothelial carcinoma, grade and stage is dependent on Plk1 expression. It was found that RO3280, a Plk1 inhibitor, stopped bladder cancer progression in a xenograft growth and rendered the cancer more sensitive to therapeutic intervention [17]. In addition, the milk thistle extract, silibinin, has an antitumor effect on Plk1's cell cycle kinetics. Silibinin is able to target the G2 and M phase of the cell cycle and downregulate Plk1 in bladder cancer, independent of Bora and AURKA targeting [18]. Another form of Plk1 inhibitor worth mentioning is use of selenium nanoparticles to deliver Plk1 siRNAs to bladder tumor sites [19]. While the variety of treatments for bladder cancer tumor proliferation target Plk1, more research is required to better understand the best target between the Bora, AURKA and Plk1 activation cascade in treating bladder cancers.

Prostate Cancer

In addition to bladder and kidney cancers, AURKA is prevalent in prostate cancer. Moreover, AURKA had been identified as an oncogene in prostate cancer since it contributes to therapeutic resistance and tumor progression [20]. Prostate cancer remains to be one of the most common causes of mortality in malignant male patients. When diagnosed late, prostate cancer is often fatal and lacks a specific line of treatment with trusted success. In other words, most late-stage prostate cancer patients are encouraged to enroll in clinical trials for the best chance of survival. Substrates of AURKA, specifically, have been identified as major contenders in the development of chemoresistance and progression into castration resistance prostate cancer (CRPC).

PLK1 and Cep192

Similar to the effect of Plk1 in bladder cancer, Plk1 is upregulated in prostate cancer and enhances the migration and invasion of malignant cells [21]. Thus, Plk1 has been identified as a promising therapeutic target. Utilizing LNCaP and PC3, human prostate cancer cell lines, the therapeutic agent L-shaped *ortho*-quinone analog TE6 was able to inhibit Plk1 in both the G2 and M phases with an acceptable safety profile [22]. Plk1, thus far, has only been introduced as a key regulator of cell cycle entry from the G2 phase. To further understand the importance of inhibiting it within the M phase, it is necessary to establish its function after the G2 phase. Following the G2-M transition, Plk1 promotes the degradation of Bora by the β-TrCP/SCF ubiquitin ligase, releasing an inactivated AURKA and Plk1 upon mitotic entry [23].

The Cep192-AURKA-Plk1 complex initiates a cascade that is the key to centrosome maturation and spindle formation in prophase. AURKA is bound by Cep192, a centrosome protein, via its Helix-1 site [24]. The Helix-1 site allows for Cep192 to noncompetitively bind AURKA, which allows AURKA to interact with other downstream substrates [25]. Cep192 is responsible for oligomerizing and localizing AURKA to the centrosome, where it is oxidized by Cys290. The formation of a disulfide Cys290-Cys290 linkage conformationally alters AURKA to induce trans-autophosphorylation activation [26]. Autophosphorylated AURKA phosphorylates Plk1 on its T-loop, activating Plk1. Once activated, Plk1 binds Cep192 [27].

Cep192-bound AURKA influences the path Plk1 takes when docking to Cep192 to promote the recruitment of γ-tubulin and formation of bipolar spindles. In the presence of Cep192-bound AURKA, Plk1 favored an interaction with the p-T44 motif. In the presence of Cep192 alone, Plk1 favors a C-terminal p-S995 motif instead [28]. However, Plk1 does prefer presence of Cep192-bound AURKA, which makes reversible oxidative modulation of Cys290 a plausible mechanism for inactivating Plk1 [29]. More research is needed to determine whether Plk1's bimodal activation will be affected by oxidation regulation.

TPX2

Targeting protein Xklp2 (TPX2) is an AURKA activator with phosphorylation sites at Ser121 and Ser125. As the nuclear envelope breaks down in prometaphase, spindle assembly molecule targeting protein Xklp2 (TPX2) is released to bind AURKA on its N-lobe in a fashion similar to Bora. Tpx2 places its N-terminal in alignment against AURKA's kinase domain to induce activation phosphorylation on AUR-

KA. Binding of Tpx2 and autophosphorylation are required for AURKA to localize to the spindle microtubules and participate in spindle assembly [30]. The expression of Tpx2-bound AURKA prevents spindle assembly defects that would result in apoptosis. Furthermore, Tpx2 stabilizes AURKA through its binding since it blocks inhibitors from docking its N-lobe [31].

Tpx2 is recognized as a therapeutic target for the inhibition of prostate cancer cell growth since decreased levels of Tpx2 leave AURKA unbound and likely inhibited, leading to defective spindle assemblies and apoptosis [32]. Other studies have noted that Tpx2 decreased prostate cancer cellular activity [33]. Once again, the oncogenic contributions of Tpx2 are not yet clear and require more investigation before it can be considered a strong medical target.

The Advanced Prostate Cancer Consensus Conference of 2024 identified major areas of clinical controversy associated with advanced prostate cancer patients. The major side effects caused by current hormonal therapy treatments were emphasized and categorized as a priority since the side effects of the most effective treatments are limited by the harm they introduce to the patient. In addition, metastatic patients are not guaranteed that their malignancy will not take on hormone- or castration-resistance during treatment, regardless of how rigorous [34].

CXCR7

Following androgen deprivation treatment (ADT), it is not uncommon for metastatic prostate cancer patients to relapse with CRPC within the first 5 years of remission. In addition, the loss of dependence on androgen receptor (AR) signaling leads to neuroendocrine features in CRPC tumors. The combination of neuroendocrine features and metastases in prostate cancer is known as neuroendocrine prostate cancer (NEPC) [35]. The upregulation of chemokine receptor CXCR7 has been identified in enzalutamide-resistant tumors, a common feature leading to NEPC [36]. Despite being classified as a G protein-coupled receptor, CXCR7 binds cytoplasmic β-arrestin (ARRB2) to form an active protein scaffold fit for kinases. The CXCR7-ARRB2 protein scaffold complex historically internalizes to clathrin-coated endosomes; however, recent investigation revealed that the complex is present in the centrosome of cycling cells. Unsurprisingly, AURKA is also upregulated in CRPC and NEPC, and AURKA activation is further enhanced by the presence of this complex. The structure of the CXCR7-ARRB2 scaffold allows for AURKA binding and substrate-activating for more efficient AURKA phosphorylation. The potential for CXCR7-ARRB2 to regulate AURKA through this discovered mechanism offers more variation in treatment development [37].

SPOP

In the cytoplasm, AURKA phosphorylates Speckle-type POZ protein (SPOP) within the MATH domain on its S33, S105, and T56 sites. SPOP, a tumor suppressor gene in prostate cancer, has been found to experience the highest frequency of mutations in prostate cancer [38]. Recently, the MATH domain was discovered to be post-translationally modified, rendering SPOP ineffective in tumor suppression. In healthy cells, wild-type SPOP ubiquitylates AURKA via proteasomal degradation, reducing oncogenic cellular growth and migration [39]. However, AURKA phosphorylation of SPOP increases CRPC progression by disrupting SPOP's ability to interact with its target proteins, such as c-Myc, AR, and ARv7, ultimately leading to the stabilization of these oncogenic proteins. Additionally, SPOP upregulation is one of the mechanisms by which enzalutamide exerts its efficacy, therefore, phospho-resistant SPOP decreases the tumor's sensitivity to enzalutamide [39]. Thus, researchers hypothesize that AURKA inhibitors may increase the amount of wild-type SPOP in prostate cancer patients, favoring AURKA inhibition as the most efficient treatment for CRPC patients currently known.

LIMK2

LIM kinase2 (LIMK2), similar to AURKA, is overexpressed in prostate cancer and has been identified as a CRPC-specific target. Castration following ADT creates a hypoxic cellular environment, leading to the increased expression of LIMK2. LIMK2 overexpression is representative of aggressive cancerous phenotypes expressing EMT, chemoresistance and metabolic reprogramming [40]. In fact, phosphorylation resistant SPOP recognizes and degrades LIMK2 as a prostate cancer tumor suppressor in CRPC cells to reduce tumorigenesis [42]. In PC3 cells, which are metastatic, Aurora-A phosphorylates LIMK2 at Serine 283, Threonine 494, and Threonine 505, which increases LIMK2's stability and promotes aggressive prostate cancer. This phosphorylation is part of the oncogenic feedback loop where LIMK2 also stabilizes AURKA [43]. While LIMK2 and AURKA are not

currently known to directly bind or activate each other, dual inhibition of the two kinases may be more effective in CRPCs opposed to AURKA inhibition alone.

YBX1

While it has been scientifically known that the expression of Y-box binding protein-1 (YBX1) increases after androgen deprivation therapy (ADT), its connection to AURKA remained unknown [43]. In 2020, YBX1 was revealed to be a substrate of AURKA in prostate cancer. YBX1 is a cytoplasmic transcription factor that is translocated to the nucleus following events such as UV irradiation and chemotherapy [44]. In the nuclear presence of AURKA, AURKA phosphorylates YBX1 at its S62 and S102 sites, stabilizing YBX1 to the nucleus. In turn, YBX1 obstructs the ubiquitylation of AURKA and stabilizes AURKA, initiating a synergistic interaction that strongly promotes the progression into cancer stem cells (CSC) and EMT. To add, inhibiting the AURKA-YBX1 synergistic loop results in Enzalutamide sensitivity in C4-2 cells and Docetaxel in DU145 and C4-2 cells. In other words, the AURKA-YBX1 feedback loop induces resistance to chemotherapy medication [45].

Increased expression of phosphorylated YBX1 was discovered to decrease the ubiquitylation of androgen receptor (AR) proteins following translation, in addition to increasing the androgen receptor splice variant (ARv7) mRNA levels in castration-resistant prostate cancer cells. The mechanism that outlines phosphorylated YBX1's impact on AR and ARv7 mRNA and protein levels, respectively, is not yet understood. However, YBX1's phosphorylation via AURKA suggests that YBX1 is a novel substrate that may serve as a therapeutic target in late-stage prostate cancer patients exhibiting chemoresistance.

AURKA inhibitor in Urological Cancers

A series of molecules have been identified with anticancer activity in preclinical studies and clinical trials, including Y3295668, MK-8745, AKI603, MLN8237 ENMD-2076 and MK-5108 et.al [46], among them *MK-5108* and *Alisertib (MLN8237)* has been taken into consideration to overcome urological cancers as showing in **(Table 2)**.

MK-5108, an oral aurora a kinase inhibitor, shows robust selectivity for AURKA and antitumor effects on the growth of 14 tumor cell lines with IC50 values between 0.16 and 6.4 μM [47]. A recent study further confirming the pro-fibrotic role of AURKA while silencing AURKA showed anti-fibrotic effect. Furthermore, inhibition of AURKA by MK-5108 markedly attenuated renal fibrosis *in vitro*, indicating that AURKA inhibition may serve as a potential strategy for the prevention and treatment of CKD [12].

MLN8237 has been tested in clinical trials for multiple cancers for properties of MLN8237 in patients with advanced tumors and hematologic malignancies [46]. A recent study revealed that Aurora-A/FOXO3A/SKP2 axis promotes tumor progression in ccRCC, and the double inhibition of SKP2 (SZL P1-41) and Aur-A (MLN8237) shows significant synergistic effect *in vivo* and *in vitro* of ccRCC models, which indicates a potential new therapeutic strategy for ccRCC[13]. A phase 2 study of Alisertib in patients with relapsed or refractory transitional-cell carcinoma of the bladder and urothelial tract revealed that longer progression-free survival was observed in carriers of the minor allele A of rs2273535 in AURKA than in patients who were homozygous for the major allele T [47]. In prostate cancer, a phase II trial of the Alisertib for patients with castration-resistant and neuroendocrine prostate cancer has revealed that a subset of patients with Aurora-A and N-myc activation achieved significant clinical benefit from single-agent Alisertib at 50 mg twice daily for 7 days repeated every 21 days [48].

Future therapeutic direction

Throughout the past five years, AURKA has been categorized as an oncogene and novel therapeutic target in various cancers that plague the body. While this paper only focuses on the kidney, bladder and prostate, many other cancers are affected by AURKA expression and concentration levels. Research in breast, colorectal, pancreatic, and other cancers have tipped urological researchers to look into similar interactions in their own fields. Many of the substrates that were mentioned in this paper are not new to the urological field, but their positive correlation and regulatory roles with AURKA are more understood currently than they have been in the past. To add, the depth of AURKA's impact on CRPC and NEPC has not been as clear without the discovery of its interactions with YBX1, CXCR7, SPOP and LIMK2. Having uncovered the many different ways that AURKA is activated and enhanced has initiated the research deep dive into potential dual inhibitors and alternative medical approaches to AURKA. Further investigation and more information are required moving forward to determine the effectiveness of

newer approaches. Additional preclinical animal studies and clinical studies are required to illustrate the efficacy of AURKA inhibitor urological cancers, and combination effect of AURKA inhibitor with chemotherapy, radiotherapy and immunotherapy may provide a promising strategy for cancer treatment.

Funding support

This work was supported by NIH P20 GM121327

Author Contributions

J.G and C.Z wrote the entire manuscript. K.F. provide guideline, comment and edit the manuscript.

References

Chan, C. S., & Botstein, D. (1993). **Isolation and characterization of chromosome-gain and increase-in-ploidy mutants in yeast.** *Genetics*, *135*(3), 677-691. https://doi.org/10.1093/genetics/135.3.677

Francisco, L., Wang, W., & Chan, C. S. (1994). **Type 1 protein phosphatase acts in opposition to IpL1 protein kinase in regulating yeast chromosome segregation**. *Molecular and cellular biology*, *14*(7), 4731-4740. https://doi.org/10.1128/mcb.14.7.4731-4740.1994

Glover, D. M., Leibowitz, M. H., McLean, D. A., & Parry, H. (1995). **Mutations in aurora prevent centrosome separation leading to the formation of monopolar spindles**. *Cell*, *81*(1), 95-105. https://doi.org/10.1016/0092-8674(95)90374-7

Fu, J., Bian, M., Liu, J., Jiang, Q., & Zhang, C. (2009). **A single amino acid change converts Aurora-A into Aurora-B-like kinase in terms of partner specificity and cellular function**. *Proceedings of the National Academy of Sciences*, *106*(17), 6939-6944. https://doi.org/10.1073/pnas.0900833106

Cheetham, G. M., Knegtel, R. M., Coll, J. T., Renwick, S. B., Swenson, L., Weber, P., Lippke, J. A., & Austen, D. A. (2002). **Crystal structure of aurora-2, an oncogenic serine/threonine kinase**. *The Journal of biological chemistry*, *277*(45), 42419-42422. https://doi.org/10.1074/jbc.C200426200

Fatma, H., & Siddique, H. R. (2023). **Aurora kinase A and related downstream molecules: A potential network for cancer therapy**. *Advances in Protein Chemistry and Structural Biology*, *134*, 115-145. https://doi.org/10.1016/bs.apcsb.2022.10.005

Tavernier, N., Thomas, Y., Vigneron, S., Maisonneuve, P., Orlicky, S., Mader, P., Regmi, S. G., Van Hove, L., Levinson, N. M., Gasmi-Seabrook, G., Joly, N., Poteau, M., Velez-Aguilera, G., Gavet, O., Castro, A., Dasso, M., Lorca, T., Sicheri, F., & Pintard, L. (2021). **Bora phosphorylation substitutes in trans for T-loop phosphorylation in Aurora A to promote mitotic entry**. *Nature communications*, *12*(1), 1899. https://doi.org/10.1038/s41467-021-21922-w

Silva Cascales, H., Burdova, K., Middleton, A., Kuzin, V., Müllers, E., Stoy, H., Baranello, L., Macurek, L., & Lindqvist, A. (2021). **Cyclin A2 localises in the cytoplasm at the S/G2 transition to activate PLK1**. *Life Science Alliance*, *4*(3). https://doi.org/10.26508/lsa.202000980

Tavernier, N., Thomas, Y., Vigneron, S., Maisonneuve, P., Orlicky, S., Mader, P., Regmi, S. G., Van Hove, L., Levinson, N. M., Gasmi-Seabrook, G., Joly, N., Poteau, M., Velez-Aguilera, G., Gavet, O., Castro, A., Dasso, M., Lorca, T., Sicheri, F., & Pintard, L. (2021). **Bora phosphorylation substitutes in trans for T-loop phosphorylation in Aurora A to promote mitotic entry**. *Nature Communications*, *12*(1). https://doi.org/10.1038/s41467-021-21922-w

Miralaei, N., Majd, A., Ghaedi, K., Peymani, M., & Safaei, M. (2021). **Integrated pan-cancer of AURKA expression and drug sensitivity analysis reveals increased expression of AURKA is responsible for drug resistance**. *Cancer medicine*, *10*(18), 6428-6441. https://doi.org/10.1002/cam4.4161

Shin, H. J., Kim, H., Oh, S., Lee, J. G., Kee, M., Ko, H. J., Kweon, M. N., Won, K. J., & Baek, S. H. (2016). **AMPK-SKP2-CARM1 signalling cascade in transcriptional regulation of autophagy.** *Nature*, *534*(7608), 553-557. https://doi.org/10.1038/nature18014

Jiang, M., Bai, M., Xu, S., Wang, T., Lei, J., Xu, M., Huang, S., Jia, Z., & Zhang, A. (2021). **Blocking AURKA with MK-5108 attenuates renal fibrosis in chronic kidney disease**. *Biochimica et biophysica acta. Molecular basis of disease*, *1867*(11), 166227. https://doi.org/10.1016/j.bbadis.2021.166227

Li, P., Chen, T., Kuang, P., Liu, F., Li, Z., Liu, F., Wang, Y., Zhang, W., & Cai, X. (2022). **Aurora-A/FOXO3A/SKP2 axis promotes tumor progression in clear cell renal cell carcinoma and dual-targeting Aurora-A/SKP2 shows synthetic lethality.** *Cell Death & Disease*, *13*(7). https://doi.org/10.1038/s41419-022-04973-9

Kelly, K. R., Nawrocki, S. T., Espitia, C. M., Zhang, M., Yang, J. J., Padmanabhan, S., Ecsedy, J., Giles, F. J., & Carew, J. S. (2012). **Targeting Aurora A kinase activity with the investigational agent alisertib increases the efficacy of cytarabine through a FOXO-dependent mechanism**. *International journal of cancer*, *131*(11), 2693-2703. https://doi.org/10.1002/ijc.27579

Cheng, S., Peng, T., Zhu, X., Zhou, F., Wang, G., Ju, L., Xiao, Y., Liu, X., & Wang, X. (2020). **Bora regulates cell proliferation and migration in bladder cancer**. *Cancer Cell International*, *20*(1). https://doi.org/10.1186/s12935-020-01392-8

Liu, B., Meng, L. B., Su, J. Z., Fan, B., Zhao, S. B., Wang, H. Y., Li, T., Wang, T. Y., Zhang, A. L., & Ni, X. C. (2022). **PLK1 as one novel target for the poor prognosis of bladder cancer: An observational study.** *Medicine*, *101*(39), e30723. https://doi.org/10.1097/MD.0000000000030723

Barros, T. M. B., Lima, A. P. B., Almeida, T. C., & da Silva, G. N. (2020). **Inhibition of urinary bladder cancer cell proliferation by silibinin.** *Environmental and molecular mutagenesis*, *61*(4), 445–455. https://doi.org/10.1002/em.22363

Shahidi, M., Abazari, O., Dayati, P., Reza, J. Z., Modarressi, M. H., Tofighi, D., Haghiralsadat, B. F., & Oroojalian, F. (2023). **Using chitosan-stabilized, hyaluronic acid-modified selenium nanoparticles to deliver CD44-targeted *PLK1* siRNAs for treating bladder cancer**. *Nanomedicine (London, England)*, *18*(3), 259-277. https://doi.org/10.2217/nnm-2022-0198

Chen, X., Ma, J., Wang, X., Zi, T., Qian, D., Li, C., & Xu, C. (2022). ***CCNB1* and *AURKA* are critical genes for prostate cancer progression and castration-resistant prostate cancer resistant to vinblastine.** *Frontiers in endocrinology*, *13*, 1106175. https://doi.org/10.3389/fendo.2022.1106175

Liu, B., Meng, L. B., Su, J. Z., Fan, B., Zhao, S. B., Wang, H. Y., Li, T., Wang, T. Y., Zhang, A. L., & Ni, X. C. (2022). **PLK1 as one novel target for the poor prognosis of bladder cancer: An observational study.** *Medicine*, *101*(39), e30723. https://doi.org/10.1097/MD.0000000000030723

Zhang, S., Yu, J., Tan, X., Cheng, S., Liu, H., Li, Z., Wei, S., Pan, W., & Luo, H. (2024). **A novel L-shaped ortho-quinone analog as PLK1 inhibitor blocks prostate cancer cells in G_2 phase**. *Biochemical pharmacology*, *219*, 115960. https://doi.org/10.1016/j.bcp.2023.115960

Seki, A., Coppinger, J. A., Jang, C. Y., Yates, J. R., & Fang, G. (2008). **Bora and the kinase Aurora a cooperatively activate the kinase Plk1 and control mitotic entry**. *Science (New York, N.Y.)*, *320*(5883), 1655-1658. https://doi.org/10.1126/science.1157425

Park, J.-G., Jeon, H., Shin, S., Song, C., Lee, H., Kim, N.-K., Kim, E. E., Hwang, K. Y., Lee, B.-J., & Lee, I.-G. (2023). **Structural basis for CEP192-mediated regulation of Centrosomal AURKA.** *Science Advances*, *9*(16). https://doi.org/10.1126/sciadv.adf8582

Raab, M., Matthess, Y., Raab, C. A., Gutfreund, N., Dötsch, V., Becker, S., Sanhaji, M., & Strebhardt, K. (2022). **A dimerization-dependent mechanism regulates enzymatic activation and nuclear entry of PLK1.** *Oncogene*, *41*(3), 372-386. https://doi.org/10.1038/s41388-021-02094-9

Tavernier, N., Sicheri, F., & Pintard, L. (2021). **Aurora a kinase activation: Different means to different ends**. *Journal of Cell Biology*, *220*(9). https://doi.org/10.1083/jcb.202106128

Joukov, V., Walter, J. C., & De Nicolo, A. (2014). **The Cep192-organized aurora A-Plk1 cascade is essential for centrosome cycle and bipolar spindle assembly**. *Molecular cell*, *55*(4), 578-591. https://doi.org/10.1016/j.molcel.2014.06.016

Meng, L., Park, J. E., Kim, T. S., Lee, E. H., Park, S. Y., Zhou, M., Bang, J. K., & Lee, K. S. (2015). **Bimodal Interaction of Mammalian Polo-Like Kinase 1 and a Centrosomal Scaffold, Cep192, in the Regulation of Bipolar Spindle Formation**. *Molecular and cellular biology*, *35*(15), 2626-2640. https://doi.org/10.1128/MCB.00068-15

Byrne, D. P., Shrestha, S., Galler, M., Cao, M., Daly, L. A., Campbell, A. E., Eyers, C. E., Veal, E. A., Kannan, N., & Eyers, P. A. (2020). **Aurora A regulation by reversible cysteine oxidation reveals evolutionarily conserved redox control of Ser/Thr protein kinase activity**. *Science signaling*, *13*(639), eaax2713. https://doi.org/10.1126/scisignal.aax2713

Bayliss, R., Sardon, T., Vernos, I., & Conti, E. (2003). **Structural basis of Aurora-A activation by TPX2 at the mitotic spindle**. *Molecular cell*, *12*(4), 851-862. https://doi.org/10.1016/s1097-2765(03)00392-7

Li, H., Wang, Y., Lin, K., Venkadakrishnan, V. B., Bakht, M., Shi, W., Meng, C., Zhang, J., Tremble, K., Liang, X., Song, J. H., Feng, X., Van, V., Deng,

P., Burks, J. K., Aparicio, A., Keyomarsi, K., Chen, J., Lu, Y., Beltran, H., … Zhao, D. (2022). **CHD1 Promotes Sensitivity to Aurora Kinase Inhibitors by Suppressing Interaction of AURKA with Its Coactivator TPX2.** *Cancer research*, *82*(17), 3088-3101. https://doi.org/10.1158/0008-5472.CAN-22-0631

Pan, H. W., Su, H. H., Hsu, C. W., Huang, G. J., & Wu, T. T. (2017). **Targeted TPX2 increases chromosome missegregation and suppresses tumor cell growth in human prostate cancer.** *OncoTargets and therapy*, *10*, 3531-3543. https://doi.org/10.2147/OTT.S136491

Shao, T., Jiang, X., Bao, G., Li, C., & Guo, C. (2022). **Comprehensive Analysis of the Oncogenic Role of Targeting Protein for Xklp2 (TPX2) in Human Malignancies**. *Disease markers*, *2022*, 7571066. https://doi.org/10.1155/2022/7571066

Gillessen, S., Turco, F., Davis, I. D., Efstathiou, J. A., Fizazi, K., James, N. D., Shore, N., Small, E., Smith, M., Sweeney, C. J., Tombal, B., Zilli, T., Agarwal, N., Antonarakis, E. S., Aparicio, A., Armstrong, A. J., Bastos, D. A., Attard, G., Axcrona, K., Ayadi, M., Omlin, A. (2025). **Management of Patients with Advanced Prostate Cancer. Report from the 2024 Advanced Prostate Cancer Consensus Conference (APCCC).** *European urology*, *87*(2), 157-216. https://doi.org/10.1016/j.eururo.2024.09.017

Vlachostergios, P. J., Puca, L., & Beltran, H. (2017). **Emerging Variants of Castration-Resistant Prostate Cancer**. *Current oncology reports*, *19*(5), 32. https://doi.org/10.1007/s11912-017-0593-6

Li, S., Fong, K. W., Gritsina, G., Zhang, A., Zhao, J. C., Kim, J., Sharp, A., Yuan, W., Aversa, C., Yang, X. J., Nelson, P. S., Feng, F. Y., Chinnaiyan, A. M., de Bono, J. S., Morrissey, C., Rettig, M. B., & Yu, J. (2019). **Activation of MAPK Signaling by CXCR7 Leads to Enzalutamide Resistance in Prostate Cancer**. *Cancer research*, *79*(10), 2580-2592. https://doi.org/10.1158/0008-5472.CAN-18-2812

Gritsina, G., Fong, K. W., Lu, X., Lin, Z., Xie, W., Agarwal, S., Lin, D., Schiltz, G. E., Beltran, H., Corey, E., Morrissey, C., Wang, Y., Zhao, J. C., Hussain, M., & Yu, J. (2023). **Chemokine receptor CXCR7 activates Aurora Kinase A and promotes neuroendocrine prostate cancer growth**. *The Journal of clinical investigation*, *133*(15), e166248. https://doi.org/10.1172/JCI166248

Barbieri, C. E., Baca, S. C., Lawrence, M. S., Demichelis, F., Blattner, M., Theurillat, J. P., White, T. A., Stojanov, P., Van Allen, E., Stransky, N., Nickerson, E., Chae, S. S., Boysen, G., Auclair, D., Onofrio, R. C., Park, K., Kitabayashi, N., MacDonald, T. Y., Sheikh, K., Vuong, T., Garraway, L. A. (2012). **Exome sequencing identifies recurrent SPOP, FOXA1 and MED12 mutations in prostate cancer.** *Nature genetics*, *44*(6), 685-689. https://doi.org/10.1038/ng.2279

Nikhil, K., Kamra, M., Raza, A., Haymour, H. S., & Shah, K. (2020). **Molecular interplay between AURKA and SPOP dictates CRPC pathogenesis via androgen receptor.** *Cancers*, *12*(11), 3247. https://doi.org/10.3390/cancers12113247

Nikhil, K., Chang, L., Viccaro, K., Jacobsen, M., McGuire, C., Satapathy, S. R., Tandiary, M., Broman, M. M., Cresswell, G., He, Y. J., Sandusky, G. E., Ratliff, T. L., Chowdhury, D., & Shah, K. (2019). **Identification of LIMK2 as a therapeutic target in castration resistant prostate cancer.** *Cancer letters*, *448*, 182-196. https://doi.org/10.1016/j.canlet.2019.01.035

Nikhil, K., Haymour, H. S., Kamra, M., & Shah, K. (2021). **Phosphorylation-dependent regulation of SPOP by LIMK2 promotes castration-resistant prostate cancer**. *British journal of cancer*, *124*(5), 995-1008. https://doi.org/10.1038/s41416-020-01197-6

Johnson, E. O., Chang, K. H., Ghosh, S., Venkatesh, C., Giger, K., Low, P. S., & Shah, K. (2012). **LIMK2 is a crucial regulator and effector of Aurora-A-kinase-mediated malignancy.** *Journal of cell science*, *125*(Pt 5), 1204-1216. https://doi.org/10.1242/jcs.092304

Giménez-Bonafé, P., Fedoruk, M. N., Whitmore, T. G., Akbari, M., Ralph, J. L., Ettinger, S., Gleave, M. E., & Nelson, C. C. (2004). **YB-1 is upregulated during prostate cancer tumor progression and increases P-glycoprotein activity**. *The Prostate*, *59*(3), 337-349. https://doi.org/10.1002/pros.20023

Stein, U., Jürchott, K., Walther, W., Bergmann, S., Schlag, P. M., & Royer, H. D. (2001). **Hyperthermia-induced nuclear translocation of transcription factor YB-1 leads to enhanced expression of multidrug resistance-related ABC transporters.** *The Journal of biological chemistry*, *276*(30), 28562-28569. https://doi.org/10.1074/jbc.M100311200

Nikhil, K., Raza, A., Haymour, H. S., Flueckiger, B. V., Chu, J., & Shah, K. (2020). **Aurora Kinase A-YBX1 Synergy Fuels Aggressive Oncogenic Phenotypes and Chemoresistance in Castration-Resistant Prostate Cancer.** *Cancers*, *12*(3), 660. https://doi.org/10.3390/cancers12030660

Du, R., Huang, C., Liu, K. et al. **Targeting AURKA in Cancer: molecular mechanisms and opportunities for Cancer therapy**. *Mol Cancer 20, 15* (2021). https://doi.org/10.1186/s12943-020-01305-3

Necchi, A., Pintarelli, G., Raggi, D., Giannatempo, P., & Colombo, F. (2017). **Association of an aurora kinase a (AURKA) gene polymorphism with progression-free survival in patients with advanced urothelial carcinoma treated with the selective aurora kinase a inhibitor alisertib**. *Investigational new drugs*, 35(4), 524-528. https://doi.org/10.1007/s10637-017-0440-5

Beltran, H., Oromendia, C., Danila, D. C., Montgomery, B., Hoimes, C., Szmulewitz, R. Z., Vaishampayan, U., Armstrong, A. J., Stein, M., Pinski, J., Mosquera, J. M., Sailer, V., Bareja, R., Romanel, A., Gumpeni, N., Sboner, A., Dardenne, E., Puca, L., Prandi, D., Rubin, M. A., Tagawa, S. T. (2019). **A Phase II Trial of the Aurora Kinase A Inhibitor Alisertib for Patients with Castration-resistant and Neuroendocrine Prostate Cancer: Efficacy and Biomarkers.** *Clinical cancer research*: an official journal of the American Association for Cancer Research, 25(1), 43-51. https://doi.org/10.1158/1078-0432.CCR-18-1912