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The expression and prognosis for Aurora kinases in human non-small cell lung cancer

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Abstract

Background Aurora kinases (AURKs), members of the serine/threonine kinases gene family, have been implicated in various human cancers, including lung cancer. However, the expression and clinical significance of AURKA, AURKB, and AURKC in non-small cell lung cancer (NSCLC) remain unclear.

Methods Comprehensive bioinformatics analyses were conducted using databases such as The Cancer Genome Atlas (TCGA), Gene Expression Profiling Interactive Analysis (GEPIA), and Kaplan-Meier Plotter. Immunohistochemistry (IHC) was performed on tissue microarrays (TMAs) from 29 lung adenocarcinoma (LUAD) patients. AURKA/B knockdown and overexpression cell models were successfully established in LUAD cells. The proliferative capacity of the stable cells was assessed using colony formation assays and CCK-8 assays.

Results AURKA and AURKB were upregulated in lung cancer tissues compared to normal, while AURKC was downregulated. High expression of AURKA and AURKB was associated with advanced tumor stage and poor survival outcomes in LUAD patients. AURKA and AURKB expression levels correlated with immune cell infiltration and immune checkpoint genes, suggesting potential roles in immunotherapy. In vitro experiments have demonstrated that AURKA and AURKB played crucial roles in promoting proliferation of LUAD cells.

Conclusion This study highlights the prognostic value of AURKA and AURKB in NSCLC, particularly LUAD, and identifies them as potential therapeutic targets or prognostic biomarkers.

Keywords AURKs, LUAD, Potential marker, Prognosis

1 Background

Lung cancer is the leading cause of cancer-related deaths worldwide, with a poor 5-year survival rate that ranges from 10 to 20% [1, 2]. Lung cancer is histopathologically divided into two main types: small cell lung cancer (SCLC) and NSCLC [3]. NSCLC accounts for approximately 85% of all lung cancers. It is divided into several subtypes, including LUAD and lung squamous cell carcinoma (LUSC) [4]. Despite many therapeutic options for lung cancer patients, such as radiotherapy, chemotherapy, and surgical resection, the results are often not satisfactory [5, 6]. Thus, it is important to identify prognostic markers for lung cancer patients.

The AURK protein family is a group of serine/threonine kinases that includes AURKA, AURKB, and AURKC in mammals. AURK proteins are mitotic kinases that promote cell proliferation through the G2/M stage of the cell cycle [7, 8]. AURKA and AURKB play important roles in the regulation of mitosis, whereas AURKC is specifically expressed in mammalian testis [9]. The deregulated expression of AURKs has been reported in many tumors such as ovarian cancer and prostate cancer [10, 11].

AURK proteins have been linked to lung cancer. Previous studies have shown that high expression of AURKA and AURKB is associated with poor prognosis in lung cancer. Both of these kinases promote lung cancer cell migration and invasion rates and have been found to repress response to chemotherapy and radiotherapy [12, 13]. Wang et al. reported that silencing AURKA expression inhibited tumorigenesis in vitro and in vivo. AURKA and its downstream transcription factor C-X-C motif chemokine ligand 5(CXCL5) activates cytotoxic autophagy in resistance to radiotherapy in NSCLC [14]. Wilkinson et al. reported that human lung cancer xenograft growth was inhibited by AZD1152, an inhibitor of AURKB, by suppressing phosphorylation of histone H3, accumulating 4 N DNA, and increasing the proportion of polyploid cells [15]. AURKC is also upregulated in many cancer cells and enhances cellular proliferation and migration. Khan et al. reported that inhibiting AURKC expression decreases the proliferation of HeLa cells, while increased expression of AURKC leads to increased tumor aggressiveness [16]. However, the expression of AURKs and the relationships with clinicopathological features and prognosis in lung cancer have yet to be fully explored.

In this study, we investigated the expression levels of AURKs in lung cancer by bioinformatics analysis and using patient samples. We also analyzed AURK expression and mutations to determine the expression profiles, potential biological functions, and correlations with immune cell infiltration in lung cancer patients.

2 Materials and methods

2.1 AURKs genes expression

The mRNA expression levels of AURKs across various cancer types were identified from the TIMER2.0 database (http://timer.cistrome.org/) and GEPIA (http://gepia.cancer-pku.cn/).TIMER2.0 includes a comprehensive dataset of 10,897 tumor samples across 32 cancer types [17]. The diffexp module within TIMER2.0 was utilized to illustrate the expression levels of AURKs in various cancers through box plots. GEPIA (Version 2.0, accessed April 22, 2023) is a public database that is used for differential expression analysis, profiling plotting, correlation analysis, patient survival analysis, similar gene detection on the strength of TCGA and Genotype-Tissue Expression (GTEx) data.

2.2 AURKs gene mutation, amplification, and methylation

The data regarding gene mutation, amplification, and methylation were downloaded from the cBioPortal database (https://www.cbioportal.org/). The methylation data were obtained from the HM450 platform. Both the association between AURKs expression and copy number alterations, as well as the relationship with methylation, were assessed using Pearson's correlation coefficients. Additionally, the "mafCompare" function in the "maftools" package was employed to compare mutation frequencies between high and low AURKs expression groups.

2.3 Relationship between AURKs expression and immunity

The R package "GSVA" was employed to investigate the relationship between AURKs and immune infiltrating cells using single-sample Gene Set Enrichment Analysis (ssGSEA). The R package "ESTIMATE" was utilized to examine the association between AURKs expression and stromal/immune cell infiltration across NSCLC [18]. Subsequently, heatmaps were generated to visualize Spearman's correlation coefficients between AURKs and NSCLC. Additionally, Spearman correlation analysis was conducted to assess the relationship between AURKs expression and immune checkpoint molecules.

The association between the AURKs expression levels, immune checkpoint genes were analyzed in the Lung cancer samples from the TCGA database using the Spearman's correlation analysis with the "ggplot2" (v3.3.3) R package. The correlation was considered significant with $p < 0.05$ as the threshold.

2.4 The linkedomics database

The LinkedOmics database (http://www.linkedomics.org/login.php) was utilized to explore 32 multi-dimensional datasets associated with TCGA cancers. The co-expression of AURKs was statistically evaluated using Pearson's correlation coefficient, and the results were visualized through heatmaps.

2.5 Patient samples

This study included tissue samples from 29 surgically resected LUAD patients at Fudan University Shanghai Cancer Center (FUSCC) between 2007 and 2012. Data on clinical variables were collected from patient medical records.

2.6 Survival analysis

The correlation between gene expression and survival rates was investigated using Kaplan-Meier analysis (Version 2023, accessed May 15, 2023, https://kmplot.com/analysis). This publicly accessible database encompasses datasets for lung cancer, ovarian cancer, gastric cancer, and breast cancer [18]. To assess the potential prognostic significance of AURKs mRNA, patients were stratified into two groups based on the median expression level of AURKs mRNA. The prognostic value of AURKs expression in NSCLC patients was evaluated through disease-free survival (DFS), distant metastasis-free survival (DMFS), first progression survival (FPS), overall survival (OS), and post-progression survival (PPS). Group differences were analyzed using the Log-rank test (95% confidence interval), with explicit stratification criteria (e.g., clinical stage: I, II, III, IV). Survival analysis was conducted by cancer type using the Kaplan-Meier method and Log-rank test ($p < 0.05$). Survival curves were generated using the R packages "survival" and "survminer". Additionally, Cox proportional hazards regression analysis was performed with the R packages "survival" and "forestplot" to explore the association between AURKs expression and survival outcomes in pan-cancer patients.

2.7 Analysis of DNA methylation status

DNA methylation status in the CpG sites of the *AURK* genes was analyzed in the LUAD/LUSC–TCGA datasets using the MethSurv database (https://biit.cs.ut.ee/methsurv/). The prognostic value of the CpG methylation status of *AURKs* was evaluated in the LUAD/LUSC samples.

2.8 Immunohistochemistry

The paraffin blocks corresponding to the 29 LUAD patients were used to construct the tissue microarrays. Serial 4 μm tissue sections were generated and stained with anti-AURKA (Proteintech, 1:100) and anti-AURKB (Santa Cruz, 1:100). The expression of each marker was assessed using the H-score, which was calculated by multiplying the percentage of positive cells (0–100%) by the intensity of positive staining. The staining intensity was scored as follows: no = 0, weak = 1+, moderate = 2+, and strong = 3+. The median score of expression was used to stratify patients into low and high expression groups.

2.9 The cBioPortal database

The cBio Cancer Genomics Portal (Version 5.0,accessed May 18, 2023, http://cbioportal.org) is an open platform for exploring multi-faceted cancer genomics data that provides available data from more than 20 cancers [19]. The platform contains data resources, including gene mutations, putative copy number alterations (CNAs) from genomic identification, mRNA and protein expression Z scores.

2.10 Cell culture and construction of stable cell lines

LUAD cell lines A549 and PC9 were obtained from the American Type Culture Collection (ATCC) and cultured in Roswell Park Memorial Institute 1640 medium (RPMI-1640, Solarbio) or Dulbecco's Modified Eagle Medium (DMEM, Solarbio), supplemented with 10% fetal bovine serum (FBS). Cells were maintained in a humidified incubator at 37 ℃ with 5% CO2.

Stable silencing of AURKA/AURKB expression in cell lines was achieved by short hairpin RNAs (shRNAs), which were cloned and subsequently inserted into the pLKO.1 vector. The empty pLKO.1 vector served as a negative control. AURKA/AURKB-overexpressing cells were generated by cloning the AURKA/AURKB cDNA and inserting it into the pCDH-CMV-MCS-EF1-Puro vector, with the empty vector functioning as a negative control. Lentiviral particles were produced by co-transfecting the constructed plasmids using Hieff Trans™ Liposomal Transfection Reagent along with the psPAX packaging plasmid and the pMD.2G envelope plasmid. Cells stably expressing the transgenes were selected by puromycin. Both the knockdown and overexpression plasmids were procured from PPL (Public Protein/Plasmid Library, China).

2.11 Western blot analysis

Western blot analysis was performed to determine the expression levels of AURKA and AURKB proteins in cells. Briefly, cells were lysed using a solution containing 1% phenylmethanesulfonyl fluoride (PMSF) and phosphatase inhibitor complex III (1 mmol/L) (Sangon Biotech, Shanghai, China). The protein extracts were separated by 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and subsequently transferred onto polyvinylidene difluoride (PVDF) membranes (Merck, Darmstadt, Germany). The PVDF membranes were blocked with 10% non-fat milk for approximately 1 h at room temperature and then incubated overnight at 4 ℃ with anti-AURKA (Proteintech, 1:1000) and anti-AURKB (Santa Cruz, 1:500). Following three washes with Tris-buffered saline with Tween 20 (TBST), the membranes were incubated with horseradish peroxidase (HRP)-conjugated secondary antibodies for 1 h at room temperature.

Protein bands were visualized using enhanced chemiluminescence (ECL) reagents (Millipore, Boston, MA, USA).

2.12 Quantitative real-time PCR (qRT-PCR) analysis

Total RNA extraction was performed using TRIzol reagent (Invitrogen Corp., USA). Reverse transcription PCR was carried out with the PrimeScript RT reagent (TaKaRa, Japan). Subsequently, cDNA was synthesized from 1 μg of RNA using a ThermalCycler (Bio-Rad). Quantitative real-time PCR (qRT-PCR) was performed in a total reaction volume of 10 μL, containing primers and SYBR Green (TaKaRa, Japan). The human GAPDH gene served as the endogenous control.

The primer sequences utilized in this study were: AURKA, forward: GAGGTCCAA AACGTGTTCTCG and reverse: ACAGGATGAGGTACACTGGTTG; AURKB, forward: CAGTGGGACACCCGACATC and reverse: GTACACGTTTCCAAACTTGCC; GAPDH, forward: GGAGCGAGATCCCTCCAAAAT and reverse: GGCTGTTGTCAT ACTTCTCATGG.

2.13 Colony formation assay

Ten hundred cells were seeded into six-well plates at a single-cell density. Fresh medium was replenished every three days to ensure optimal cell growth conditions. After 10 days of incubation, colonies were stained with gentian violet (Solarbio), and colonies containing more than 50 cells were quantified in each well.

2.14 Statistical analysis

All data were analyzed using SPSS 22.0 software. Student's t-test and chi-square test analyses were performed to assess the differences between groups. $p < 0.05$ indicated statistical significance (*refers to $P < 0.05$; ** refers to $P < 0.01$; *** refers to $P < 0.001$).

All gene expression data in this study were normalized using log2 transformation. Comparisons between normal and cancerous tissues were conducted using a two-sample t-test, with $P < 0.05$ indicating statistical significance. Kaplan-Meier curves, log-rank tests, and Cox proportional hazards regression models were employed for all survival analyses in this study. Correlation analysis between two variables was performed using either Spearman's or Pearson's test, with $P < 0.05$ considered statistically significant. All statistical analyses were performed using R software.

3 Results

3.1 AURK mRNA expression in lung cancer

TIMER2.0, which consists of immune, exploration and estimation components, is an online database for the systematic analysis of various cancer types. Three AURKs have been reported in mammalian cells. We compared the mRNA expression of the three AURKs in various cancers using the TIMER2.0 database (Fig. 1A). The expressions of AURKA and AURKB mRNAs were upregulated in many types of cancers.

We then compared AURKs mRNA expressions between lung cancer and normal lung tissues using GEPIA. AURKA and AURKB mRNA levels were markedly upregulated in lung cancer tissues compared with normal lung samples, whereas AURKC mRNA showed no significant differences (Fig. 1B). We further analyzed the expression of AURK family genes in different pathological types of lung cancer, including LUAD and LUSC

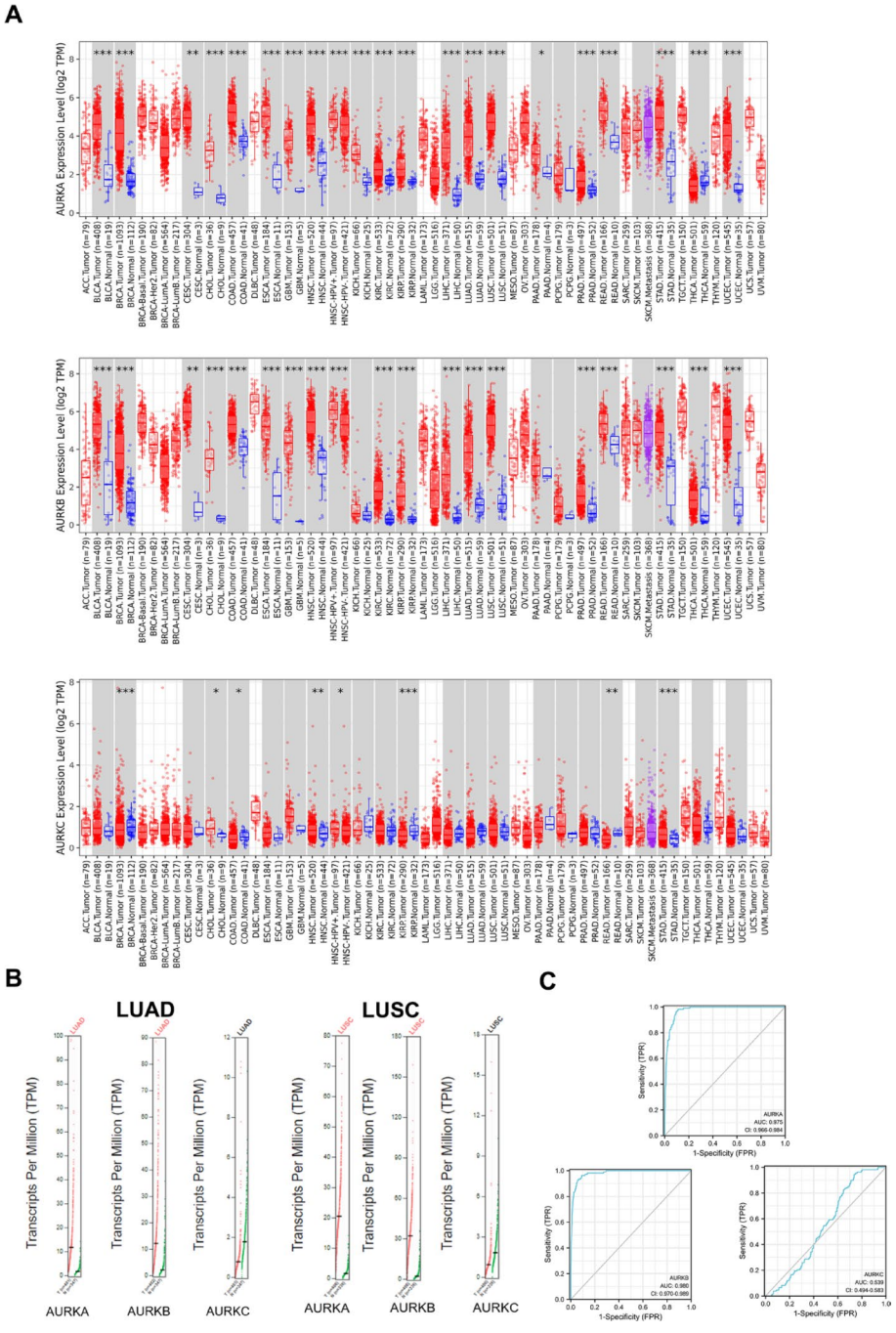

Fig. 1 The mRNA expression and ROC of AURKs in patients with lung cancer. **A** mRNA expression levels of AURKs in pan-cancer in TIMER. **B** mRNA expression levels of AURKs in LUAD (Left) and LUSC (Right) in GEPIA (Red: cancer; Green: normal). **C** ROC curve analysis of AURKs in patients with lung cancer (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$)

(Fig. 1B). Compared with the normal control, AURKA and AURKB mRNA levels were increased in both LUAD and LUSC, whereas AURKC mRNA was decreased in both LUAD and LUSC.

The receiver-operating characteristic (ROC) curve analysis revealed that the AUC for AURKA was 0.975 (95% CI 0.966–0.0.984) and the AUC for AURKB was 0.980 (95% CI 0.970–0.989), suggesting that AURKA and AURKB may be potential diagnostic biomarkers for lung cancer (Fig. 1C).

3.2 Relationship between AURKs mRNA expression and clinicopathological variables in patients with lung cancer

We next examine the relationship between AURKs mRNA expression and lung cancer tumor stage using GEPIA. The AURKA and AURKB groups significantly varied in LUAD ($P < 0.05$), whereas the AURKC group did not significantly differ in LUAD or LUSC (Fig. 2A, B).

To further explore the clinical value of AURKA and AURKB in LUAD, we evaluated the expression levels of these two proteins in tumor tissues from 29 LUAD patients. IHC analysis revealed that both AURKA and AURKB were expressed in the nucleus

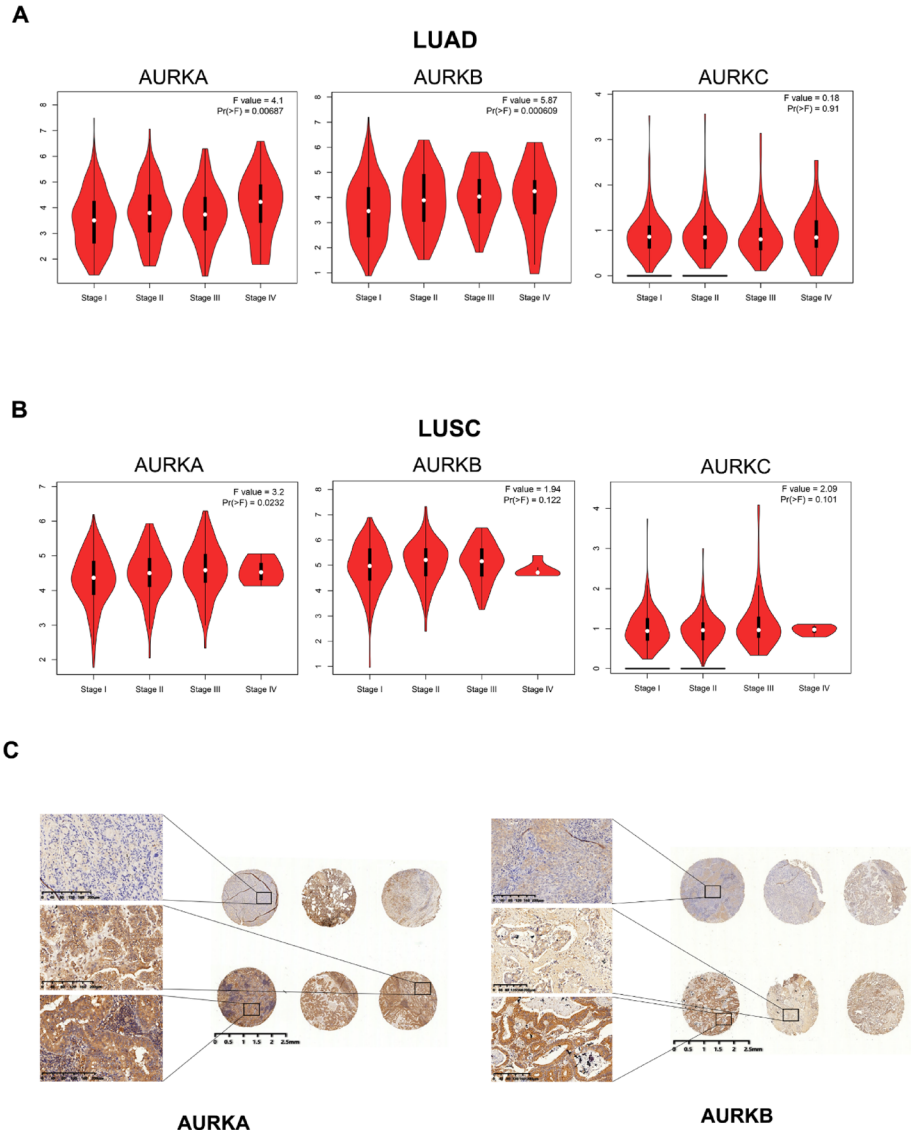

Fig. 2 Relationship between the mRNA expression of AURKs and clinicopathological variables in patients with lung cancer. **A** AURKs expression levels were compared among main pathological stages (stage I, stage II, stage III, stage IV) of LUAD. Genetic expression level was shown as log2 (TPM + 1). Analyses were conducted via the GEPIA database (http://gepia2.cancer-pku.cn). **B** AURKs expression levels were compared among main pathological stages (stage I, stage II, stage III, stage IV) of LUSC. Genetic expression level was shown as log2 (TPM + 1). Analyses were conducted via the GEPIA database (http://gepia2.cancer-pku.cn). **C** Representative images of LUAD immunostained with AURKA and AURKB in different gradations: 1+, 2+, 3+

and cytosol of cells. Compared with normal lung tissues, tumor tissues showed stronger staining intensities for AURKA and AURKB (Fig. 2C).

We then investigated the relationship between AURKA and AURKB expression and clinicopathological characteristics of the 29 LUAD cases (Tables 1 and 2). There was a significant correlation between AURKA and AURKB expression with the later stage of cancer, suggesting that their expression levels may be associated with LUAD progression. In future studies, we will further examine the correlations between AURKA/AURKB expression and clinical data of LUAD patients using a larger sample size.

Table 1 Correlations between AURKA expression and clinicopathological

Characters	Total	AURKA-low	AURKA-high	*p*
Gender				0.465
Male	25	11	14	
Female	3	2	1	
Age(years)				0.283
>60	16	6	10	
<60	12	7	5	
Vascular invasion				0.184
Positive	11	6	5	
Negative	7	6	1	
Unknown	10	5	5	
TNM				0.037
1	10	8	2	
2	6	5	1	
3	12	4	8	

Characteristics of patients with LUAD in FUSCC cohort.Low (H-score < 200; IHC negative) or high (≥ 200; IHC positive) for AURKA protein expression (*,$P < 0.05$)

3.3 Association of AURK mRNA expression with lung cancer patient prognosis

We next used Kaplan–Meier analysis to explore the correlation between AURKA and AURKB mRNA expression levels and the survival of lung cancer patients using the above publicly available database. Specifically, as shown in Fig. 3A, higher AURKA and AURKB mRNA expressions were significantly associated with the worse OS, FPS, and PPS of lung cancer patients (AURKA OS: HR = 1.63, $P = 4e\text{-}14$; PPS: HR = 1.51, $P = 0.0013$; FPS:

Table 2 Correlations between AURKB expression and clinicopathological

Characters	Total	AURKB-low	AURKB-high	*p*
Gender				0.313
Male	25	16	9	
Female	3	1	2	
Age(years)				0.188
>60	16	8	8	
<60	12	9	3	
Vascular invasion				0.065
Positive	11	6	5	
Negative	7	7	0	
Unknown	10	5	5	
TNM				0.037
1	10	8	2	
2	6	5	1	
3	12	4	8	

Characteristics of patients with LUAD in FUSCC cohort.Low (H-score < 200; IHC negative) or high (≥ 200; IHC positive) for AURKB protein expression (*,$P < 0.05$)

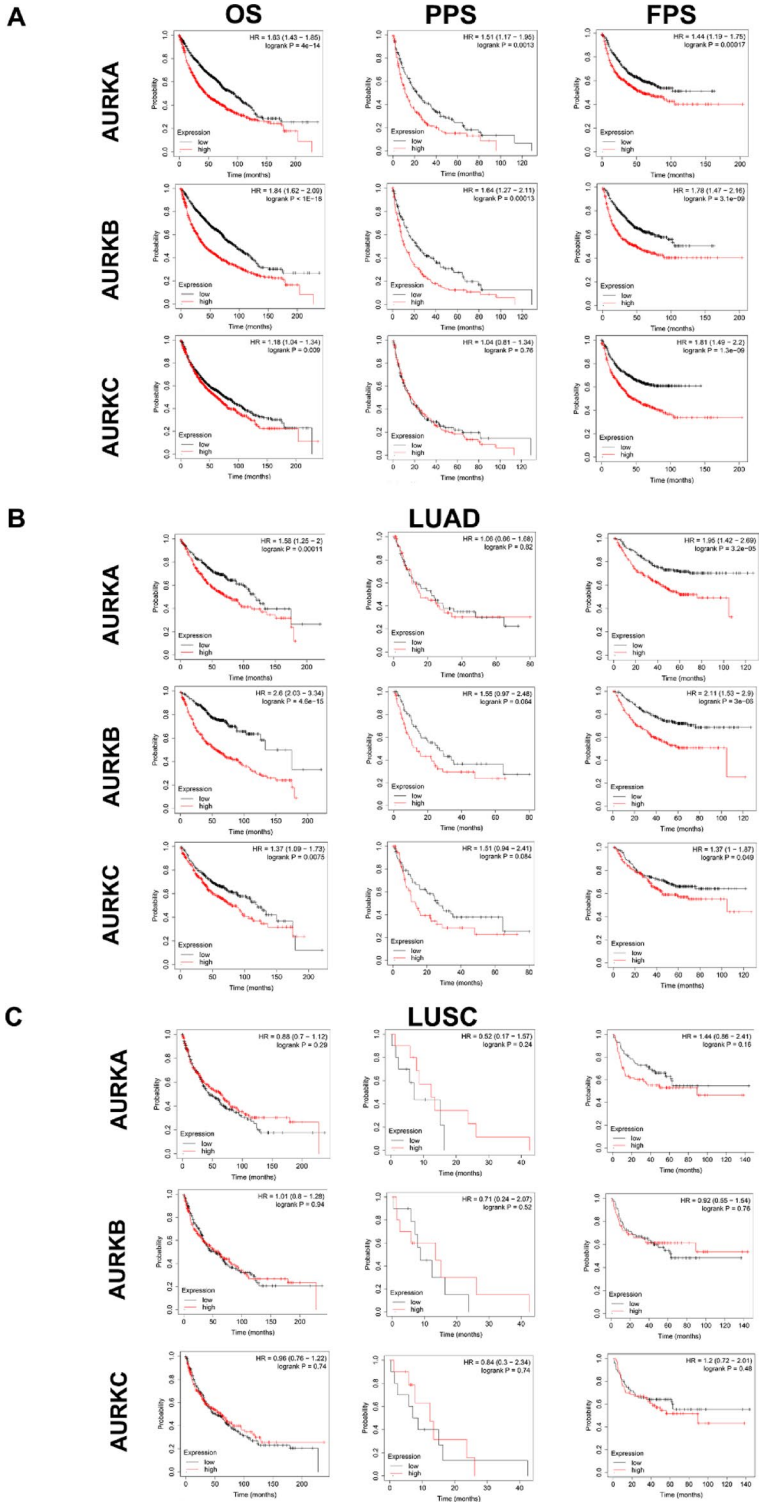

Fig. 3 Association of AURK mRNA expression with lung cancer patient prognosis. **A** The prognostic value of expression of AURKs in lung cancer by Kaplan-Meier Plotter(AURKA OS/PPS/FPS $n = 1925/344/982$; AURKB OS/PPS/FPS $n = 1925/982/344$;AURKC OS/PPS/FPS $n = 1925/344/982$). **B** The prognostic value of expression of AURKs in LUAD by Kaplan-Meier Plotter(AURKA OS/PPS/FPS $n = 719/125/461$; AURKB OS/PPS/FPS $n = 719/125/461$;AURKC OS/PPS/FPS $n = 719/125/461$) (https://kmplot.com/analysis). **C** The prognostic value of expression of AURKs in LUSC by Kaplan-Meier Plotter(AURKA OS/PPS/FPS $n = 524/20/141$; AURKB OS/PPS/FPS $n = 524/20/141$;AURKC OS/PPS/FPS $n = 524/20/141$).All the survival analyses were conducted via Kaplan–Meier Plotter database (https://kmplot.com/analysis)

HR = 1.44, *P* = 0.00017; AURKB OS: HR = 1.84, *P* < 1E-16; PPS: HR = 1.64, *P* = 0.00013; FPS: HR = 1.78, *P* = 3.1e-09). Patients with upregulated AURKC mRNA showed a lower OS and FPS (AURKC OS: HR = 1.18, *P* = 0.009; FPS: HR = 1.81, *P* = 1.3e-09).

We further analyzed the prognostic role of AURK mRNA expression in the survival of patients with different lung cancer subtypes. LUAD patients with higher expression levels of AURKs had lower OS and FPS (AURKA OS: HR = 1.58, *P* = 0.00011; FPS: HR = 1.95, *P* = 3.2e-05; AURKB OS: HR = 2.6, *P* = 4.6e-15; FPS: HR = 2.11, *P* = 3e-06;AURKC OS: HR = 1.37*P* = 0.0075; FPS: HR = 1.37, *P* = 0.049) (Fig. 3B, C). High expression of AURKs was not significantly associated with the prognosis of patients with LUSC.

3.4 AURK gene expression and mutation analysis in patients with lung cancer

The LinkedOmics database was used to explore the genes that were significantly correlated with the AURKs. The top 50 correlated genes, including both positively and negatively correlated genes, are shown in the heatmap plot in Fig. 4A. The genes most positively correlated with AURKA included BUB1 (r, 0.83), TPX2 (r, 0.82), and NCAPG (r, 0.82), while the genes most negatively correlated with AURKA included C1QTNF7 (r, −0.59) and CFAP221 (r, −0.59). The genes most positively correlated with AURKB

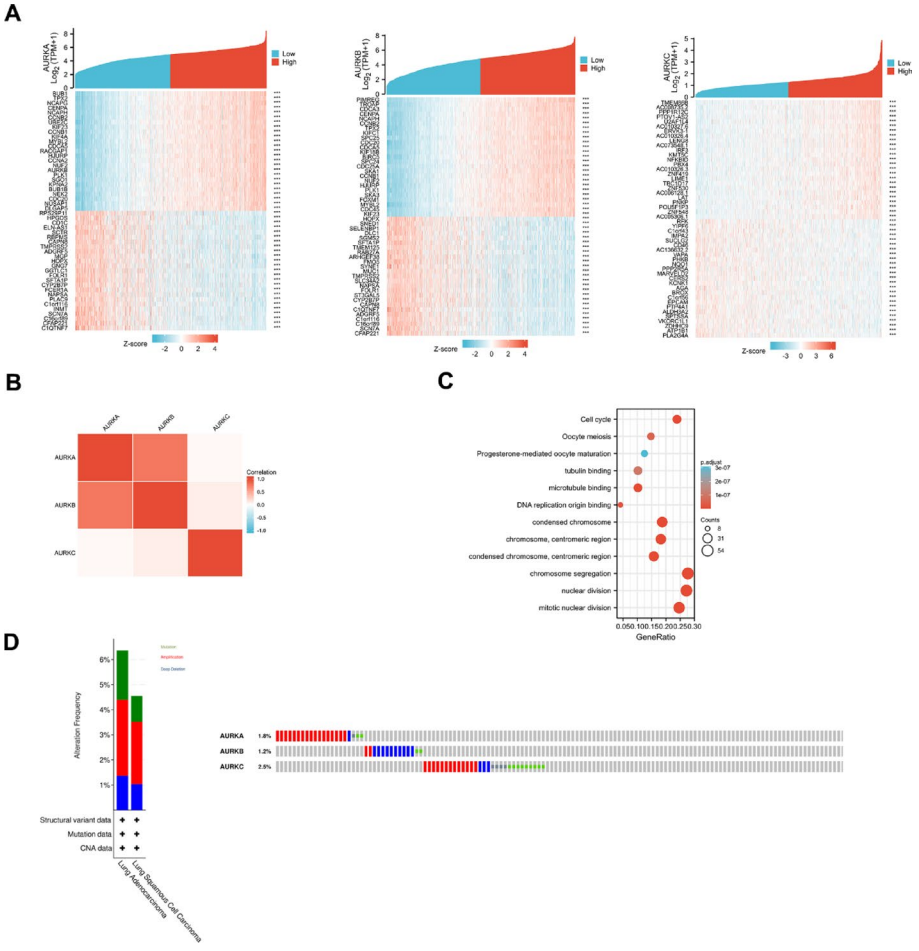

Fig. 4 AURKs gene expression and mutation analysis in patients with lung cancer. **A** Heatmap plot of top 50 genes included positively and negatively correlation to AURKs mRNA in the NSCLC patients with high- and low-AURKs expression (*n* = 872) from the TCGA-NSCLC project. **B** Correlation between every two AURKs. **C** GO analysis of AURKs in lung cancer. **D** Mutation and correlation analysis of AURKs in patients with lung cancer by cBioPortal database

included PIMREG (r, 0.89) and TROAP (r, 0.88), while the genes most negatively correlated with AURKB included CFAP221 (r, – 0.68) and SCN7 A (r, – 0.64). The genes most positively correlated with AURKC included TMEM86B (r, 0.47) and PPP1R12 C (r, 0.46), while the genes most negatively correlated with AURKC included PLA2G4 A (r, – 0.30) and ATP1B1 (r, – 0.30). We also assessed the correlations of AURK genes with each other (Fig. 4B). Pearson correlation analysis indicated that only AURKA and AURKB genes showed a positive correlation (r, 0.64).

Gene Ontology (GO) analysis is used to predict the potential functions of target genes by three terms: biological processes, cellular components, and molecular functions. We used GO analysis to predict the neighbor genes frequently associated with AURK alterations and functions. GO analysis showed an enrichment of GO terms indicative of functional maturation, such as cell cycle and oocyte meiosis, indicating that AURKs were closed related to the regulation of cell division (Fig. 4C).

The cBioPortal database was used to explore the mutational landscape of AURK family members. We analyzed the AURK networks, correlations, and alterations in lung cancer with the cBioPortal online tool(TCGA, Nat Genet 2016). Alteration of AURKs was observed in 63 of 1,144 NSCLC patients (5.5%). The findings revealed that the AURKs had a high frequency of genetic alterations in NSCLC (about 6% in LUAD and less 5% in LUSC), including mutations and amplification. AURKC mutation was the most common alteration (2.5%) and the most common form of alterations was gene amplification. The genetic changes in AURKA and AURKB were 1.8% and 1.2% respectively. Meanwhile, for AURKA, amplifications accounted for the highest proportion, while for AURKB, deep deletion accounted for the highest proportion. (Fig. 4D).

3.5 Correlation analysis between AURKs and immune cell infiltration in NSCLC

Overexpressed AURKA and AURKB promote tumor growth through various pathways. Whether AURKs are involved in the regulation of the tumor immune microenvironment in NSCLC remains unknown. We analyzed the correlations between AURKs and the main types of tumor-infiltrating immune cells in LUAD using TCGA database. As shown in Fig. 5A, AURKA expression was positively correlated with Th2 cells (r, 0.58, $P < 0.01$), Tgd (r, 0.22, $P < 0.01$), and NK CD56 dim cells (r, 0.13, $P < 0.01$). AURKB expression was similarly correlated with these three immune cell types. The expression levels of AURKA and AURKB were negatively correlated with other immune cell types. AURKC expression was positively associated with the main infiltrating immune cells (T cells, Th1 cells, Treg, and NK cells). These data indicate that AURKs may play different roles in immune infiltration in LUAD.

We further investigated the association between AURKs expression and the cells in the tumor microenvironment of lung cancer using TIMER2.0. Myeloid-derived suppressor cells are a population of immature myeloid cells with a strong immunosuppressive ability in the tumor microenvironment. Both AURKA and AURKB showed a positive association with myeloid-derived suppressor cells and negative association with cancer-associated fibroblasts and endothelial cells in LUAD and LUSC (Fig. 5B). AURKC showed a positive association with cancer-associated fibroblasts and endothelial cells in LUAD and LUSC.

Programmed cell death protein 1(PDCD1) and Cytotoxic T lymphocyte-associated antigen 4 (CTLA4) are important immune checkpoint proteins that are associated with

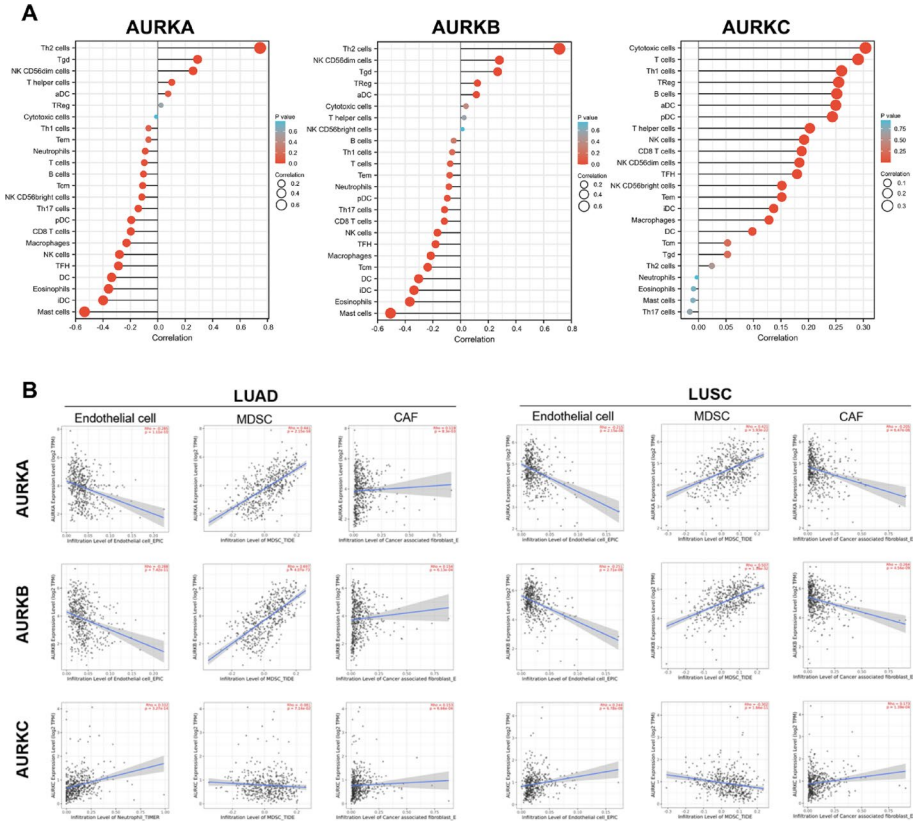

Fig. 5 Correlation analysis between AURKs and immune cell infiltration in NSCLC. **A** Correlation between AURKs and the main immune cells in LUAD. **B** Correlation between AURKs and the cells in the tumor microenvironment of LUAD and LUSC.Spearman's rank correlation was used for AURK-immune checkpoint associations, with coefficients and two-tailed p-values reported

tumor immune escape [20]. AURK expression levels showed positive correlation with the expression levels of PDCD1 and only AURKC showed a positive correlation with CTLA4 in the LUAD samples of TCGA dataset (Fig. 6A, B).

3.6 Methylation status of the AURK genes is associated with the prognosis of NSCLC

DNA methylation is a common epigenetic mechanism that plays a vital role in tumorigenesis [21]. Changes in the methylation status of several genes have been associated with the growth and progression of multiple cancers [22]. DNA methylation levels in the AURK genes and the prognostic value of the CpG islands in the AURKs genes were investigated using MethSurv. The analysis revealed that 10 and 12 methylated CpG islands in AURKB and AURKC showed elevated levels of DNA methylation in LUAD, respectively (Fig. 7A). The results also revealed 2, 10 and 11 methylated CpG islands with elevated levels of DNA methylation in AURK genes in LUSC (Fig. 7B).

The methylation levels of two CpG islands in AURKB—cg18576335 and cg21724796—were associated with prognosis in NSCLC ($P < 0.05$) (Table 3). The methylation levels of seven CpG islands in AURKC—cg06643849, cg25432232, cg06643849, cg15128510, cg19603903, cg23371413, and cg25802888—were associated with prognosis in NSCLC ($p < 0.05$).

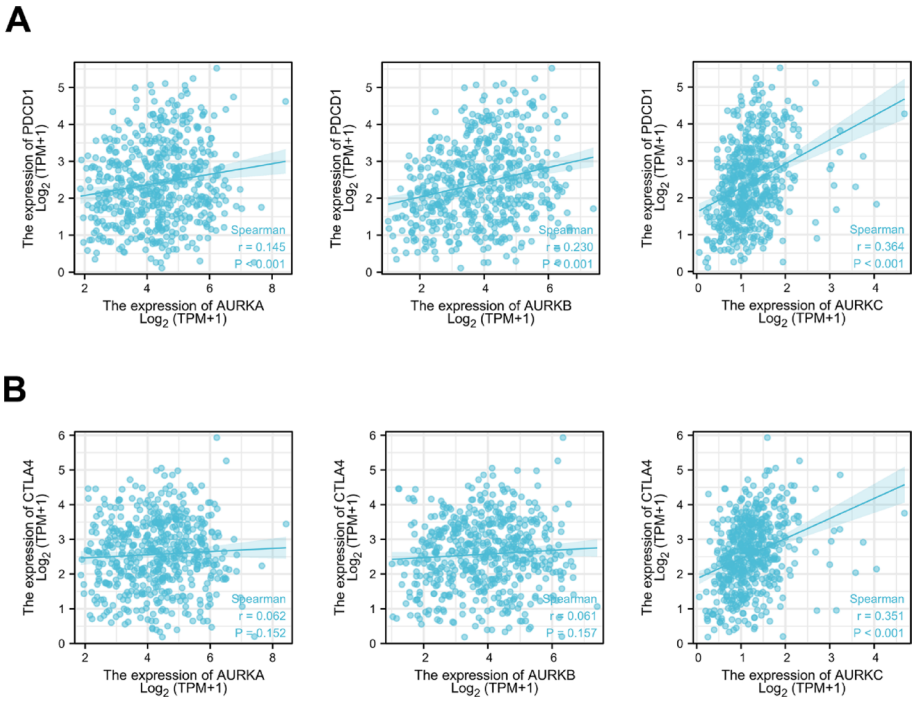

Fig. 6 The correlation analysis between the expression levels of CTLA4, PDCD1, and AURKs in LUAD. **A** The correlation analysis results between the expression levels of AURKs and the expression levels of PDCD1 in the TCGA-LUAD dataset. **B** The correlation analysis results between the expression levels of AURKs and the expression levels of CTLA4 in the TCGA-LUAD dataset

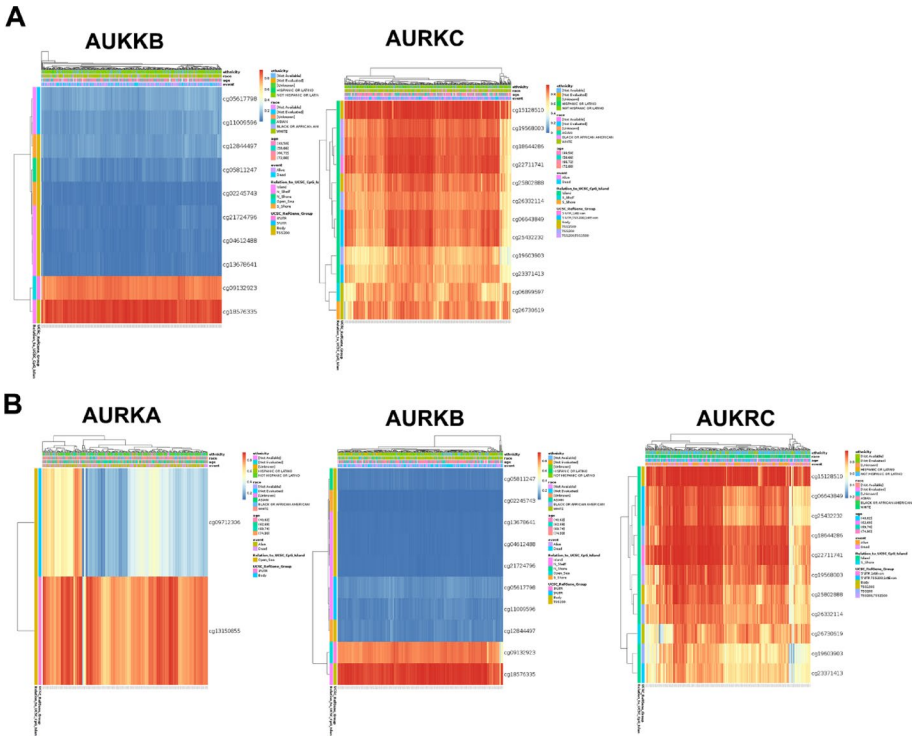

Fig. 7 DNA methylation levels in the *AURKs* gene are associated with the prognosis of patients with NSCLC. **A** DNA methylation levels in the *AURKB/C* gene are associated with the prognosis of LUAD patients. **B** DNA methylation levels in the *AURKA/B/C* gene are associated with the prognosis of LUSC patients

Table 3 Effects of methylation levels in the CpG sites of the *AURKs* gene on the prognosis of NSCLC patients

	CpG island	Cancer	HR	*p*-value
AURKA	3'UTR-cg13150855	LUAD	1.175	0.319302236
	Body-cg09712306	LUSC	0.825	0.239658536
	3'UTR-cg13150855	LUSC	0.812	0.261490708
AURKB	TSS200-cg02245743	LUAD	1.13	0.503412633
	TSS200-cg04612488	LUAD	0.865	0.432056066
	5'UTR-cg05617798	LUAD	1.184	0.293314933
	5'UTR-cg05811247	LUAD	0.88	0.486759745
	3'UTR-cg09132923	LUAD	1.121	0.484185767
	3'UTR-cg11009596	LUAD	0.836	0.316434635
	TSS200-cg12844497	LUAD	1.187	0.38891914
	TSS200-cg13678641	LUAD	1.164	0.417692787
	Body-cg18576335	LUAD	**0.725**	**0.045188025**
	TSS200-cg21724796	LUAD	1.176	0.313514314
	TSS200-cg02245743	LUSC	1.189	0.296013782
	TSS200-cg04612488	LUSC	0.806	0.223858674
	5'UTR-cg05617798	LUSC	1.427	0.080526468
	Body-cg05811247	LUSC	0.821	0.223461342
	3'UTR-cg09132923	LUSC	0.815	0.272863106
	5'UTR-cg11009596	LUSC	1.253	0.186453199
	TSS200-TSS200-cg12844497	LUSC	0.789	0.209849425
	TSS200-cg13678641	LUSC	0.759	0.117157902
	Body-cg18576335	LUSC	1.369	0.078920506
	TSS200-cg21724796	LUSC	**0.647**	**0.028907373**
AURKC	**5'UTR; TSS200;1 stExon-cg06643849**	LUAD	**1.557**	**0.029305014**
	Body-cg06899597	LUAD	0.837	0.268250858
	TSS1500-cg15128510	LUAD	1.168	0.408040673
	TSS200-cg18644286	LUAD	1.344	0.086938904
	TSS200;TSS1500-cg19568003	LUAD	1.342	0.125187323
	TSS200-cg19603903	LUAD	0.85	0.311129559
	5'UTR;1 stExon-cg22711741	LUAD	1.331	0.100375647
	5'UTR; TSS200;1 stExon-cg23371413	LUAD	1.283	0.121106665
	5'UTR; TSS200;1 stExon-cg25432232	LUAD	**1.412**	**0.041232459**
	TSS1500-cg25802888	LUAD	1.265	0.212258837
	TSS200-cg26332114	LUAD	1.259	0.225030752
	Body-cg26730619	LUAD	0.801	0.202733636
	5'UTR; TSS200;1 stExon-cg06643849	**LUSC**	**0.665**	**0.01950632**
	TSS1500-cg15128510	LUSC	**0.525**	**0.002156909**
	TSS200-cg18644286	LUSC	0.701	0.070523771
	TSS200;TSS1500-cg19568003	LUSC	0.714	0.052238897
	TSS200-cg19603903	LUSC	**0.688**	**0.02111639**
	5'UTR;1 stExon-cg22711741	LUSC	0.749	0.141670136
	5'UTR; TSS200;1 stExon-cg23371413	LUSC	**0.691**	**0.021744732**
	5'UTR; TSS200;1 stExon-cg25432232	LUSC	0.785	0.135911375
	TSS1500-cg25802888	LUSC	**0.67**	**0.013777611**
	TSS200-cg26332114	LUSC	0.742	0.129121228
	Body-cg26730619	LUSC	0.807	0.271401096

3.7 AURKA and AURKB exhibit a proliferation-promoting effect in LUAD

Our results demonstrated that AURKA and AURKB were associated with a poor prognosis and immune infiltration in LUAD. Consequently, we investigated the functional role of AURKA and AURKB in LUAD cells (PC9 and A549). We changed target genes expression using shRNA and cDNA in LUAD cell lines, confirming the downregulation

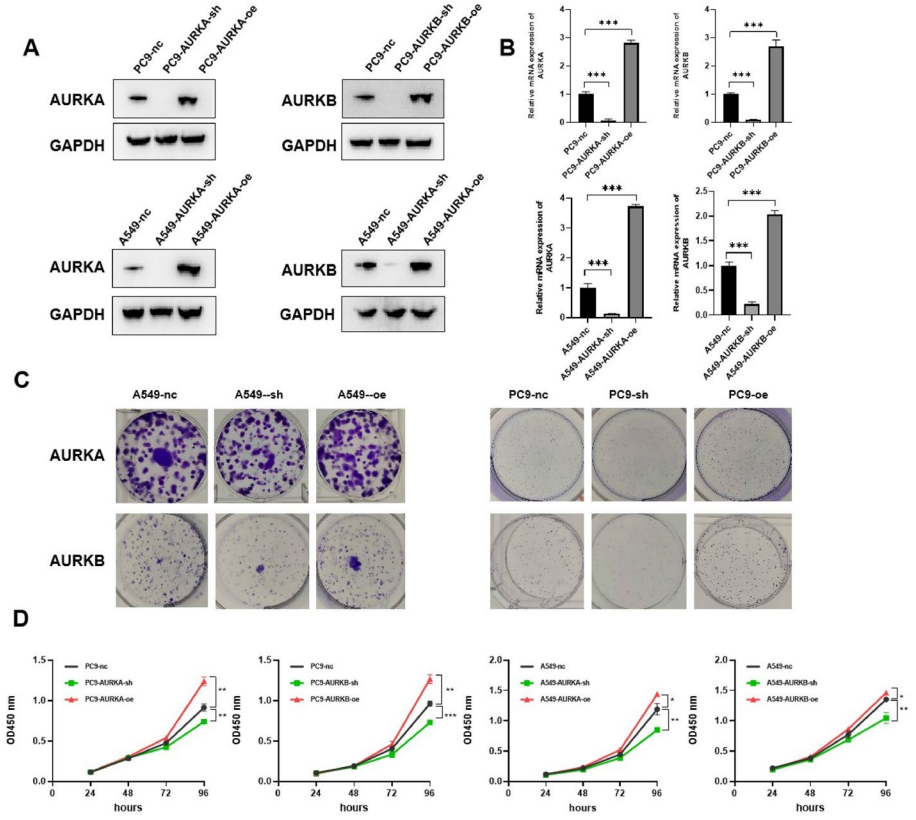

Fig. 8 AURKA and AURKB exhibit a proliferation-promoting effect in LUAD. **A**, **B** Examination of AURKA and AURKB expression in AURKA/AURKB-knockdown and overexpression cells by **A** Western blot. **B** qRT-PCR. **C** cell colony formation assay and **D** CCK-8 assay of proliferation of AURKA/AURKB-knockdown and overexpression cells (*$P <$ 0.05, **$P < 0.01$, ***$P < 0.001$)

and upregulation via western blot and quantitative real-time PCR (qRT-PCR) (Fig. 8A, B). Cell proliferation and colony formation assays revealed that both proliferation and colony formation capacities were significantly reduced in the AURKA and AURKB knockdown group compared to the control group. Meanwhile, the overexpression of the two target genes has been demonstrated to significantly enhance cell proliferation and colony formation capability (Fig. 8C, D).

4 Discussion

Studies have showed that dysregulation of AURKs is involved in the tumorigenesis and prognosis of multiple cancers. However, detailed analysis of AURKs in different subtypes of lung cancer has not been performed. To our knowledge, this study is the first to discuss the prognostic value of AURK mRNA expression in LUAD and LUSC. We believe that this work will bring new directions for improving treatment efficacy and enhancing the precision treatment for lung cancer patients.

AURKA is the most well-studied AURK in cancers. Overexpression of AURKA has been found in human malignancies, where it acts as an oncogene. AURKA subcellular localization appears as a diffuse distribution in both the nucleus and cytoplasm. AURKA plays various roles in supporting cancer progression by (a) promoting cell cycle progression, (b) upregulating anti-apoptotic signaling, (c) inducing genomic instability, and (d) facilitating the Epithelial-Mesenchymal Transition (EMT) [23–25]. Recently, a key role

for AURKA in drug resistance in lung cancer has been discovered. Shah et al. reported that AURKA activation via targeting protein for xenopus kinesin-like protein 2 was a feature of most acquired resistant epidermal growth factor receptor (EGFR)-mutant lung cancers. However, AURKA inhibitors inhibited this adaptive survival process and increased the response time and intensity of EGFR inhibitor responses in clinical models. Overexpressed EGFR in stage I LUAD formed a complex with AURKA, which resulted in decreased phosphorylation of EGFR at Thr654 and Ser1046. These results showed a positive correlation between AURKA expression and EGFR phosphorylation [26]. In our study, results derived from multiple databases suggested that AURKA expression was higher in lung cancer than in normal tissues. Our data also established correlations between AURKA expression and lung cancer patient survival, such as OS, FPS, and PPS.

AURKB protein is part of the chromosomal passenger complex, with a broad cellular localization during cell development [27]. Overexpression of AURKB is common in various types of human malignant cancers, including lung cancer. Smith et al. found that overexpression of AURKB correlated with genetic instability in NSCLC, which was generally driven from one allele [28]. Tanaka et al. identified AURK inhibitors, as potent enhancers of osimertinib, promoted apoptosis in EGFR-mutant by high throughput screening in NSCLC-related cell lines. Concurrent inhibition of EGFR and AURKB maximized BIM- and PUMA-mediated apoptosis to induce cancer cell death. Mechanistically, inhibiting AURKB stabilized BIM by reducing phosphorylation of Ser87, and transactivated PUMA through FOXO1/3 [12]. In this study, we found that the mRNA expression of AURKB was higher in lung cancer tissues including LUAD and LUSC than in normal tissues, and this expression was remarkably correlated with tumor stage in LUAD patients. Higher AURKB expression levels were significantly correlated with lower OS, FPS, and PPS in LUAD patients, which is consistent with the oncogenic role of AURKB. Furthermore, logistic regression analysis showed that the AURKA/B expression levels positively correlated with gender, age and smoking status in patients with LUAD (Supplementary Tables 1, 2).

Currently, little is known about the function of AURKC in tumor progression. Zekri et al. reported that AURKC may accelerate tumor development depending on its similarity or synergistic biological functions with AURKB and the gene amplification and overexpression in cancers [29]. In this study, we found that AURKC expression was lower in lung cancer tissues than in normal lung tissue, and its expression was not correlated with tumor stage in LUAD and LUSC.

As we all know, gene amplification is a common cause of protein or mRNA overexpression, while overexpression can also occur through a variety of other regulatory mechanisms, including transcriptional activation, epigenetic dysregulation, post-transcriptional stabilization [30, 31]. In this study, we found that the genetic alternations of AURKs included amplification, missense mutation, and deep deletion, which may be important for lung cancer progression. The amplification accounted for the majority of gene alternations of AURKA, suggesting that amplification may be involved in tumorigenic progression [25]. Interestingly, AURKB most frequently exhibited deep deletion rather than amplification, which suggesting that the mechanism driving AURKB overexpression is distinct from AURKA. Smith SL et al. have found that elevated level of AURKB expression is generally driven from one allele, and correlates with the level of

genetic instability in NSCLC [28]. This could explain the high frequency of amplification of AURKA and the relatively low frequency of amplification of AURKB.

Whether AURKs play any role in cancer progression by modulating the TIME remains unclear. Schneider et al. found that epitopes derived from AURKA and AURKB triggered cellular immune responses in patients with acute myeloid leukemia, making these epitopes potential targets for specific immunotherapy strategies [32]. We evaluated the relationship between AURK expression levels and immune-related cells and immune checkpoint genes. Our results demonstrated positive correlations between the expression levels of AURKA/B and Th2, Tgd, and NK CD56 dim cells. Additionally, a positive correlation was observed between the expression levels of AURKs and PDCD1 in LUAD samples. These findings suggest that AURK inhibitors might serve as a potential immunotherapeutic strategy; however, further research is required to elucidate their functional role in regulating the response to immunotherapy.

While our study provides valuable insights into the role of AURKs in NSCLC, it has several limitations: (1) Public databases may introduce selection bias due to heterogeneous sample collection protocols, batch effects, or incomplete clinical annotations. To mitigate this, we cross-validated results across multiple platforms and applied stringent statistical filters; (2)Platform-specific technical biases were minimized by focusing on consensus differentially expressed genes across datasets; (3)Small LUAD Sample Size:Our cohort of 29 LUAD tissues, though limited, was rigorously matched with adjacent normal tissues to reduce confounding factors. We acknowledge that a larger sample size would enhance statistical power, particularly for subgroup analyses. To address this, we are collaborating with multicenter clinical repositories to expand validation in an independent cohort; (4) Single-core sampling in TMAs may not fully capture spatial heterogeneity, particularly in tumors with high intratumoral variability (e.g., necrotic zones, invasive fronts, or mixed molecular subtypes). While we selected the most representative tumor cores through expert pathological review (based on H&E-stained cellular density and morphological consistency), interpretation of protein expression results from single cores requires caution. Biological heterogeneity might not be fully represented in TMAs. To mitigate this, we will employ multi-marker integration such as PD-L1, Ki-67, and tumor-infiltrating lymphocyte markers) to comprehensively assess tumor phenotypes and utilized statistical methods to identify potential subgroups in future research. We also recommend future studies adopt multi-core sampling (3–4 representative cores per case) to enhance TMA representativeness and validate spatial distribution patterns of key markers via whole-slide IHC.

5 Conclusion

We comprehensively explored the expression and prognostic value of AURKs in NSCLC. Our results suggested that AURKA and AURKB are potential therapeutic targets for NSCLC, especially in LUAD.

Abbreviations

AUC	Area under the curve
AURK	Aurora kinase
CAF	Cancer associated fibroblast
CI	Confidence interval
EMT	Epithelial-mesenchymal transition
GEPIA	Gene expression profiling interactive analysis
GO	Gene ontology

LUAD	Lung adenocarcinoma
LUSC	Lung squamous cell carcinoma
MDSC	Myeloid-derived suppressor cell
NSCLC	Non-small cell lung cancer
OC	Ovarian cancer
OS	Overall survival
PCa	Prostate cancer
FPS	Progression-free survival
PPS	Post-progression survival
ROC	Receiver operating characteristic
SCLC	Small cell lung cancer
TIME	Tumor immune microenvironment

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s12672-025-02878-5.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Author contributions

Contributions: (I) Conception and design: Zhaodong Ji, Juan Liu and Yue Wang; (II) Administrative support: Juan Liu; (III) Provision of study materials or patients: Zhaodong Ji; (IV) Collection and assembly of data: Zhaodong Ji, Yue Wang and Jiaxue Xu; (V) Data analysis and interpretation: Zhaodong Ji and Yue Wang; (VI) Manuscript writing: Zhaodong Ji and Jiaxue Xu; (VII) Final approval of manuscript: All authors.

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Data availability

Data is provided within supplementary information files. Further inquiries can be directed to the corresponding authors.

Declarations

Competing interests

The authors declare no competing interests.

Ethical approval

This study was approved by the Institutional Review Board of Fudan University Shanghai Cancer Center (IRB2008223-9). The use of human tissues conformed the guidelines of the Declaration of Helsinki.

Consent to participate

Informed consent was obtained from all participants included in the study in agreement with institutional guidelines.

Consent for publication

Not applicable.

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