Long non-coding RNA *TMPO-AS1* promotes aggressive triple-negative breast cancer by sponging hsa-let-7b-5p-mediated *AURKB* upregulation

Prerna Vats[1#], Bhavika Baweja[1#], Chainsee Saini[1], Ashok Kumar[2], and Rajeev Nema[1*]

ABSTRACT

Aurora kinase B (AURKB), a regulator of mitosis, is associated with aggressive breast cancer (BRCA) and poor patient outcomes, although its exact role remains unclear. This study performed an *in silico* analysis to investigate AURKB expression, regulation, and prognostic relevance in BRCA. Differential expression of *AURKB* was evaluated using the University of Alabama Cancer Database (UALCAN), the Encyclopedia of RNA Interactomes (ENCORI), OncoDB, The Cancer Genome Atlas (TCGA), Gene Expression Profiling Interactive Analysis 2 (GEPIA2), and TCGAnalyzeR v1.0. Survival analysis was conducted using the Kaplan–Meier plotter database, and subtype-specific associations were examined using the TCGA portal, the Tumor-Immune System Interactions and Drug Bank database, Breast Cancer Gene-Expression Miner v5.0 (bc-GenExMinerv5.0), UALCAN, and ENCORI. *AURKB*'s role in biological processes and metastasis was studied using the Cancer Single-cell State Atlas, TNMplot, and ExploRRNet. Transcription factors associated with *AURKB* were analyzed using Enrichr, ENCORI, Tumor Immune Estimation Resource, GEPIA2, OncoDB, UALCAN, and bc-GenExMinerv5.0. MicroRNAs were examined using miRNet, Transcriptome Alterations in Cancer Omnibus, CancerMIRNome, and ENCORI, while long non-coding RNAs were studied using ENCORI, OncoDB, UALCAN, and TCGAnalyzeR v1.0. Elevated *AURKB* levels were linked to decreased distant metastasis-free survival (Hazard ratio [HR] = 1.71), relapse-free survival (HR = 1.43), and overall survival (HR = 1.45). *AURKB* transcripts also showed elevated expression in BRCA with a $\log_2$ fold change of 3.03. A novel competing endogenous RNA (ceRNA) network was identified, where *AURKB* correlated positively with *E2F1* ($r = 0.806$) and *TMPO-AS1* ($r = 0.610$) but negatively with hsa-let-7b-5p ($r = -0.452$). *TMPO-AS1* also showed a negative correlation with hsa-let-7b-5p ($r = -0.204$). High *E2F1* expression was associated with worse OS (HR = 1.53), whereas higher hsa-let-7b-5p levels were linked to better prognosis (HR = 0.68). Binding affinity predictions supported interactions between hsa-let-7b-5p and *AURKB*, *E2F1*, *ESR1*, *PGR*, and *TMPO-AS1* (–16.40, –90, –50, –90, and –40 kcal/mol, respectively). Overall, *AURKB* dysregulation through this ceRNA network may promote BRCA progression, offering potential for new prognostic biomarkers and personalized therapies.

Keywords:
Breast cancer; Estrogen receptor- and progesterone receptor-negative; *AURKB*; The Cancer Genome Atlas; Metastasis; Prognosis

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1. Introduction

Breast cancer (BRCA) is one of the most prevalent cancers and a leading cause of cancer related deaths among females.[1] In 2022, approximately 2.3 million new cases were reported globally, and an estimated 6.8 million women were living with the disease by the end of that year.[2,3] BRCA is classified based on molecular subtypes into luminal A, luminal

B, human epidermal growth factor receptor 2 (HER2)-positive, and triple-negative breast cancer (TNBC) or basal subtype, which is the most aggressive.[4] In the United States of America, the 5-year survival rate for TNBC is as low as 8–16%.[5] The current diagnostic procedures include imaging and immunohistochemistry, which help in subtyping and classifying the disease to determine treatment approaches.[6] Recent developments in transcriptomic and genomic profiling have advanced the classification system based on subtyping, demonstrating prognostic and therapeutic features.[7,8] The introduction of minimally invasive procedures such as liquid biopsies could potentially increase the accuracy of detection of residual disease and prognostic and predictive biomarkers.[9] There is a growing drive to identify reliable biomarkers to aid early detection and to serve as prognostic indicators in TNBC.[10] Bioinformatic analysis of publicly available databases helps researchers understand the molecular mechanisms behind different types of cancer and discover new cancer prognostic and predictive biomarkers.[3,11-13]

Aurora kinases is family of serine-threonine kinases that regulate mitotic spindle formation.[14] They include Aurora kinase A (AURKA), Aurora kinase B (AURKB), and Aurora kinase C (AURKC).[14,15] Aurora kinase plays a crucial role in mitotic processes and cell-cycle regulation.[16,17] *AURKB*, along with others, regulates the cell cycle and plays a role in phosphorylating histone H3 for chromosome segregation during cell division. Induced *AURKB* expression is linked to tumorigenesis mediated by H-Ras.[18] AURKB has emerged as an important drug target due to its overexpression in various tumors.[19] Furthermore, the dysregulation of *AURKB* has been associated with uncontrolled proliferation, invasion, epithelial-mesenchymal transition, and metastasis.[20] Overexpression of AURKB indicates that aggressive cells are resistant to chemotherapy and radiotherapy, leading to poor prognosis in various cancers.[21] Recent studies further demonstrate that high phosphorylated AURKB levels correlate with taxane resistance and reduced apoptosis in TNBC patients, underscoring its predictive potential in treatment response.[22] Importantly, combinatorial strategies, such as co-targeting AURKB with protein kinase C inhibitors, have shown promise in restoring chemosensitivity and overcoming paclitaxel resistance in preclinical TNBC models, highlighting their translational relevance and therapeutic exploitability in BRCA.[23] Although several Aurora kinase inhibitors are being developed, limitations such as poor selectivity, dose-limiting toxicity, and suboptimal therapeutic outcomes restrict their application.[24] In this study, we investigated the dysregulation of *AURKB* in breast invasive carcinoma and identified the regulatory molecules involved. The current study also focuses on identifying transcription factors (TFs) associated with *AURKB* expression in BRCA. Furthermore, the competing endogenous RNA (ceRNA) network hypothesis, proposed by Salmena *et al.*,[25] explains the relationship between coding RNA (mRNA) and non-coding RNAs (microRNA [miRNA] and long non-coding RNA [lncRNA]) in cells and their regulation in gene expression.[25]

Our *in silico* study addresses this gap by integrating AURKB-focused therapeutic exploration with the regulatory axis of small non-coding RNAs and ceRNA interactions, thereby providing novel insights into post-transcriptional regulatory control of AURKB and its potential as a prognostic biomarker in BRCA. Furthermore, given that the tumor microenvironment also plays a critical role in cancer progression, *AURKB* gene expression associated with co-expressed genes is also analyzed in this study.

2. Materials and methods

2.1. *AURKB* expression analysis: Pan-cancer overview and breast cancer perspective

First, we analyzed the expression of *AURKB* across TCGA cancer types using various databases such as Tumor Immune Estimation Resource (TIMER) 2.0 (http://timer.cistrome.org),[26] the University of Alabama Cancer Database (UALCAN; https://ualcan.path.uab.edu),[27] Broad Genomic Data Analysis Center (GDAC) Firehose (https://gdac.broadinstitute.org/#),[28] and the Tumor-Immune System Interactions and Drug Bank database (TISIDB; http://cis.hku.hk/TISIDB/).[29] The differential expression of *AURKB* in BRCA was evaluated using the UALCAN, the Encyclopedia of RNA Interactomes (ENCORI; https://rnasysu.com/encori/),[30] OncoDB (https://oncodb.org/),[31] TCGA portal database, Gene Expression Profiling Interactive Analysis 2 (GEPIA2; https://gepia2.cancer-pku.cn/),[32] and TCGAnalyzeR v1.0 (http://tcganalyzer.mu.edu.tr/)[33] databases. Furthermore, the Kaplan–Meier (KM) plotter (https://kmplot.com/analysis/) database was used to study the effect of *AURKB* expression on the survival outcomes of BRCA patients,[34] determining distant metastasis-free survival (DMFS), relapse-free survival (RFS), and overall survival (OS) (Gene symbol, Affy ID: *AURKB*/*STK12*, 209464_at). TCGA portal, TISIBD, and Breast Cancer Gene-Expression Miner v5.0 (bc-GenExMiner v5.0) (https://bcgenex.ico.unicancer.fr/BC-GEM/GEM-Accueil.php?js=1) databases were used to evaluate *AURKB* expression in different subtypes of BRCA. *AURKB* expression in hormone receptor status (estrogen receptor [ER] and progesterone receptor [PR]) and TNBC pathological subtypes was investigated using bc-GenExMinerv5.0[35] and UALCAN. The ENCORI database was used to find the link between *AURKB* and *ESR1*/*PGR* genes.

2.2. Investigation of *AURKB's* role in biological processes and transcriptional control

We further investigated the role of *AURKB* in various biological processes using Cancer Single-cell State Atlas (CancerSEA) (https://ngdc.cncb.ac.cn/databasecommons/database/id/6092),[36] a database that examines cancer cell functional states at the single-cell level. The database depicts 14 functional states, including stemness, invasion, metastasis,

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proliferation, epithelial-mesenchymal transition (EMT), angiogenesis, apoptosis, cell cycle, differentiation, DNA damage, DNA repair, hypoxia, inflammation, and quiescence. We also examined TFs that regulate tissue-specific gene expression using the Enrichr database (https://maayanlab.cloud/Enrichr/).[37,38] Further analysis of *AURKB*'s involvement in metastasis was conducted using the TNMplot (https://tnmplot.com/analysis/) and Driver DBv4 (http://driverdb.tms.cmu.edu.tw) databases.[39] In addition, the Dependency Map (DepMap) portal database (https://depmap.org/portal/),[40] which integrates large-scale functional genomic screens to identify gene dependencies across cancer cell lines, was used to assess the *AURKB* gene effect across BRCA cell lines classified as primary and metastatic tumors. The correlation between TFs and the *AURKB* gene was analyzed using the ENCORI, TIMER, GEPIA2, OncoDB, UALCAN, and bc-GenExMiner v5.0 databases. The study also analyzed the expression level of *AURKB* and TFs associated with basal and TNBC and ER/PR status using the bc-GenExMiner v5.0 and ENCORI databases. The TF's effect on BRCA patient survival status was analyzed using KM plotter (Gene symbol: *E2F1*, Affy ID: "204947_at).

2.3. Regulation of *AURKB* by the competing endogenous RNA network

The ceRNA network is used to analyze gene expression levels in tumor conditions, involving the analysis of mRNA and its regulatory molecules, the non-coding RNAs. The non-coding regulatory network consists of both miRNAs and lncRNAs. The miRNA network associated with *AURKB* was analyzed using various databases, including miRNet (https://www.mirnet.ca/),[41] Transcriptome Alterations in Cancer Omnibus (TACCO; https://tacco.life.nctu.edu.tw),[42] CancerMIRome (http://bioinfo.jialab-ucr.org/CancerMIRNome/),[43] and ENCORI. Furthermore, the differential expression of miRNA across TCGA cancers was studied using the CancerMIRNome and TACCO databases, and specifically in BRCA patients was identified using the CancerMIRNome, UALCAN, ENCORI, and miRNACancerMap (http://cis.hku.hk/miRNACancerMAP) databases.[44] Survival analysis, prognosis, and pathways affected by miRNA in BRCA patients were studied using the CancerMIRNome, KM plotter, ENCORI, and ExploRRNet (https://mirna.cs.ut.ee)[45] databases, respectively. The next aim was to identify the lncRNA that sponges miRNAs regulating *AURKB*, thereby completing the ceRNA network. Enrichr, UALCAN, ENCORI, and bc-GenExMiner were employed to examine the correlations between *AURKB* and specific lncRNA expression across BRCA subtypes.

2.4. Analysis of cancer heterogeneity

Heterogeneity, defined here as the contribution of multiple genes to the tumor microenvironment, was also examined. The top 10 co-expressed genes of *AURKB* in BRCA were evaluated using the Enrichr database, and their correlation with the gene was identified using the TIMER database. A heterogeneous model was created using TCGAnalyzeR and the Gene Set Cancer Analysis databases (https://guolab.wchscu.cn/GSCA/#/),[46] emphasizing the importance of understanding heterogeneity in BRCA tumor progression.

2.5. Statistical analysis

Survival analyses were performed using the KM plotter database, where hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated, and log-rank tests were applied to assess statistical significance ($p<0.05$). Genes with HR > 1 were considered high-risk factors for poor prognosis. Differential expression analyses of *AURKB* between tumor and normal tissues were conducted using publicly available transcriptomic resources, including UALCAN, GEPIA2, OncoDB, and ENCORI. Depending on the database, built-in statistical methods such as Student's *t*-tests or Wilcoxon rank-sum tests were employed, with sample sizes ranging from $n = 59$ for normal samples and $n = 515$ for tumor samples. Correlation analyses between *AURKB* expression and other molecular features (TFs, lncRNAs, and miRNAs) were carried out using Pearson's and Spearman's correlation (r) tests, depending on data distribution. Cox proportional hazard regression was used to evaluate the independent prognostic significance of *AURKB* expression, adjusting for clinical variables. Pathway and functional enrichment analyses were performed using database-embedded tools, with enrichment significance defined as $p<0.05$.

3. Results

3.1. *AURKB* expression and its prognostic role: Pan-cancer and breast cancer analysis

First, we performed pan-cancer expression analysis of *AURKB* in tumor tissues and corresponding normal tissues using the TIMER2.0, UALCAN, and FIREHOSE Broad GDAC databases. *AURKB* expression levels were significantly higher in tumor tissues in most malignancies than in normal tissues (**Figure 1A-C**). As shown in Figure S1A and B, analysis using the TISIDB database showed the highest *AURKB* expression associated with BRCA molecular subtypes and immune subtypes. In addition, TCGA analysis using the UALCAN database revealed an average ninefold increase in *AURKB* gene expression in BRCA tumors compared to normal tissues (**Figure 2A**). As shown in **Figure 2B-E**, a consistent pattern of overexpression was observed using the ENCORI database ($p=1.1\times10^{-99}$), OncoDB database ($p=1.2\times10^{-134}$, $\log_2$ fold change = 3.02), TCGA portal ($p<0.05$), and GEPIA2 ($p<0.05$). In addition, the transcriptome data obtained from the TCGAnalyzeR database revealed a significant elevation in *AURKB* expression in BRCA, with a $\log_2$ fold change of 3.03 (**Figure 2F**).

As *AURKB* is highly upregulated in BRCA tumors, we explored its role in the survival outcome of patients using the KM plotter database. Comparison of the survival outcomes of patients with high and low *AURKB* expression levels showed a significant association between DMFS (HR = 1.71, 95% CI: 1.46–2.0, $p=1.3\times10^{-11}$), RFS (HR = 1.43, 95% CI: 1.29–1.59, $p=2.7\times10^{-12}$), and OS (HR = 1.45, 95% CI: 1.2–1.75, $p=0.00012$) (**Figure 2G-I**). There was approximately a threefold difference in the DMFS of patients with high and low expression levels of *AURKB*. BRCA patients with high expression of *AURKB* had a median survival of 45.6 months, and the patients with low expression had a median survival of 137 months (**Figure 2G**).

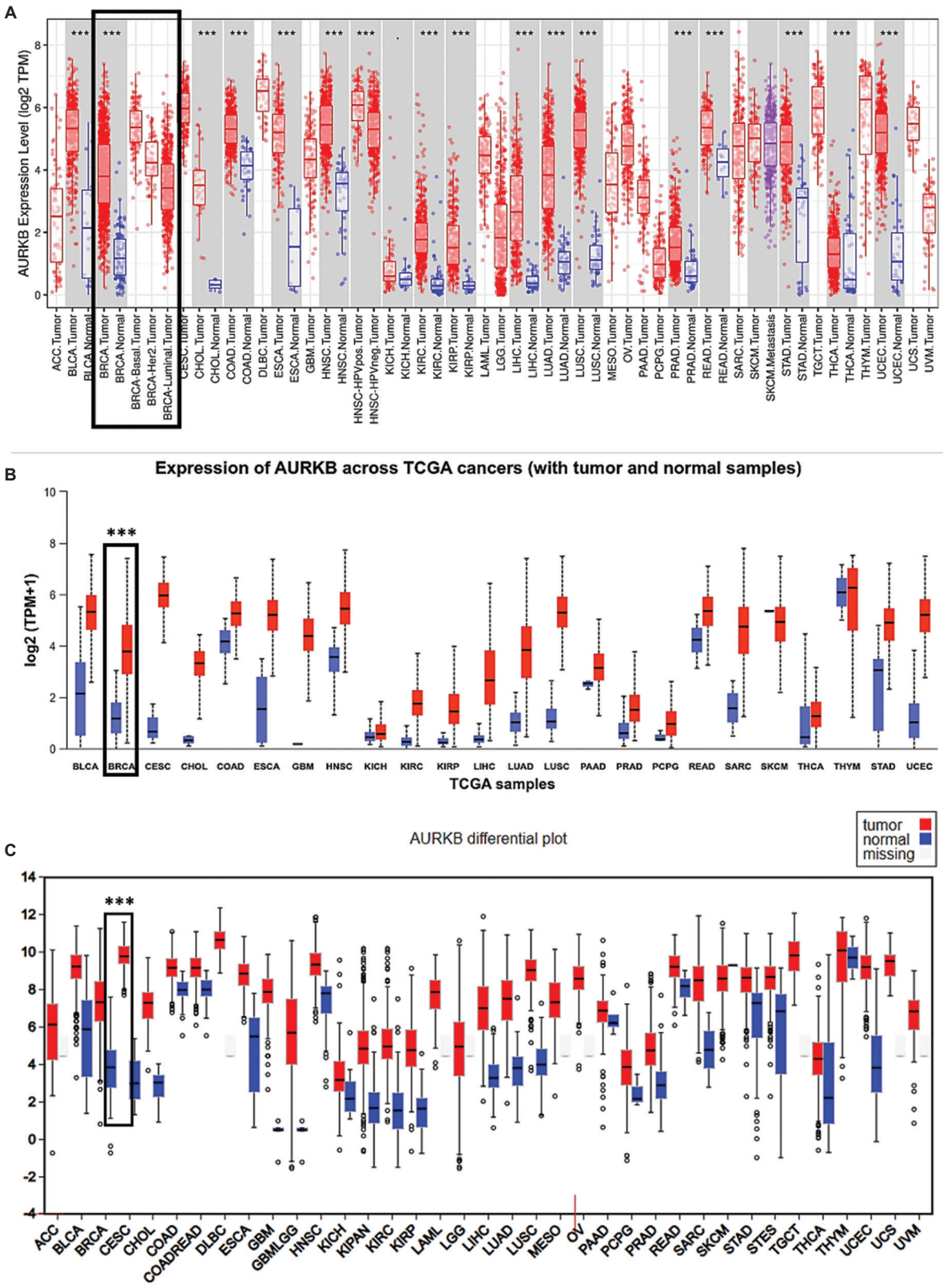
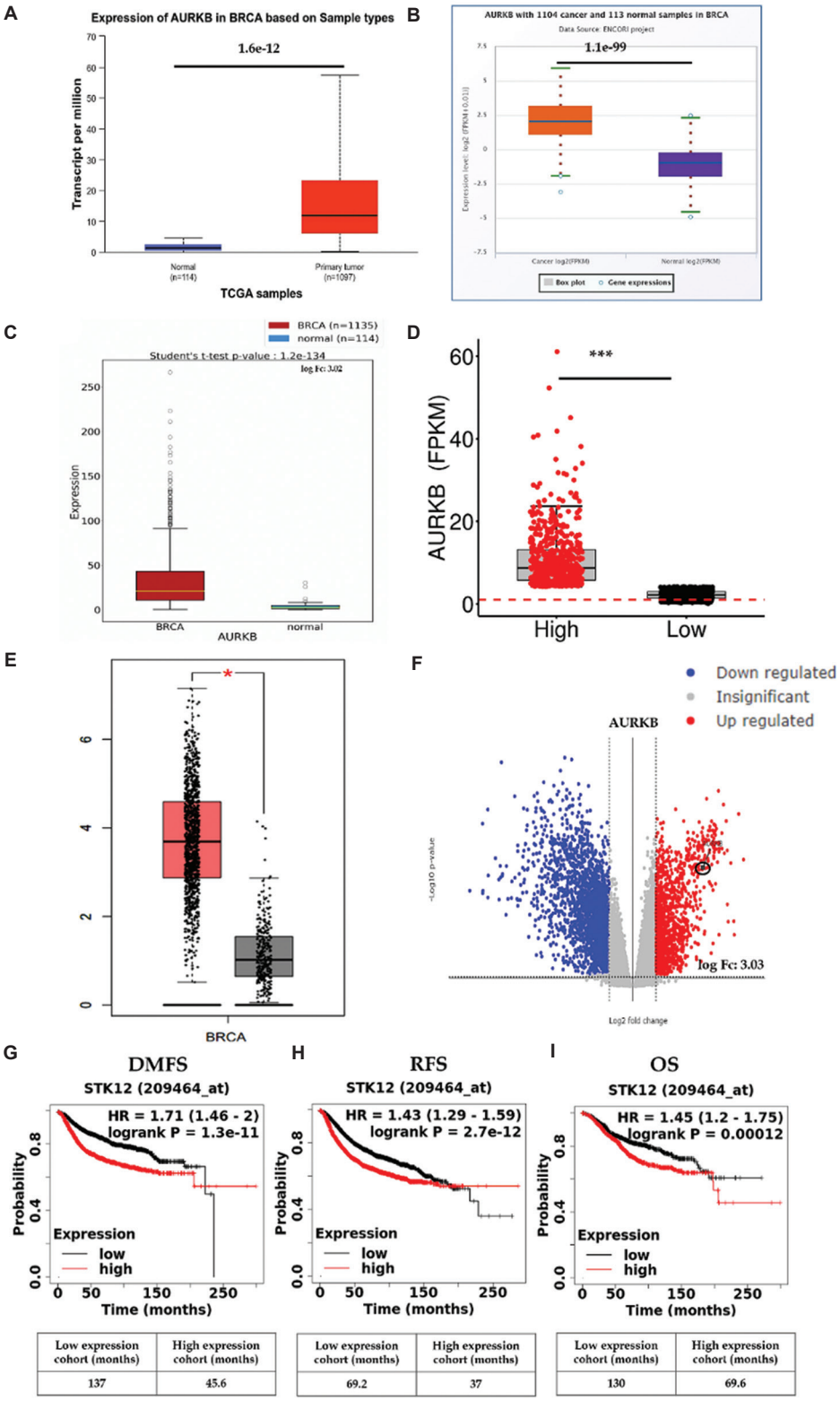


Figure 1. Expression pattern of *AURKB* in pan-cancer analysis. (A) The expression profile of AURKB was determined using the TIMER 2.0 database for tumor versus normal samples; the red bar-dot plot indicates tumor, and the blue bar-dot plot corresponds to normal tissue. Error bars represent the standard deviation, and ***p<0.001. (B) Expression of *AURKB* in pan-cancer analysis using the UALCAN database; tumors compared with matched normal samples. Red bars represent the tumor, and blue bars represent the normal tissue. (C) Expression of *AURKB* in different TCGA cancers using the Broad GDAC Firehose database.

Abbreviations: BRCA: Breast cancer; GDAC: Genome Data Analysis Center; TCGA: The Cancer Genome Atlas; TIMER: Tumor Immune Estimation Resource; TPM: Transcripts per million; UALCAN: University of Alabama Cancer Database.



Low expression cohort (months)	High expression cohort (months)
137	45.6

Low expression cohort (months)	High expression cohort (months)
69.2	37

Low expression cohort (months)	High expression cohort (months)
130	69.6

Figure 2. Expression profiling of *AURKB* in breast cancer. (A-F) mRNA expression was analyzed in normal breast tissue and primary tumors from the publicly available databases: (A) UALCAN (Normal n = 114, Tumor n = 1,097); (B) ENCORI (Normal n = 113, Tumor n = 1,104); (C) OncoDB (Normal n = 114, Tumor n = 1,135); (D) TCGA; (E) GEPIA2 (Normal n = 291, Tumor n = 1,085); and (F) TCGAnalyzeRv1.0. (G-I) Prognostic role of mRNA expression of *AURKB* in breast cancer patients. Kaplan–Meier survival curves were plotted for (G) DMFS (n = 2,765), (H) RFS (n = 4,929), and (I) OS (n = 1,879).

Note: * and *** represents p<0.05.

Abbreviations: BRCA: Breast cancer; DMFS: Distant-metastasis-free survival; ENCORI: Encyclopedia of RNA Interactomes; Fc: Fold change; FPKM: fragments per kilobase of transcript per million; GEPIA: Gene Expression Profiling Interactive Analysis; OS: Overall survival; RFS: Relapse-free survival; TCGA: The Cancer Genome Atlas; UALCAN: University of Alabama Cancer Database.

Based on these findings, *AURKB* appeared to be a predictive biomarker for poor prognosis in BRCA.

3.2. Correlation between *AURKB* expression and breast cancer subtypes

Next, we examined the expression of *AURKB* in BRCA molecular subtypes, including luminal A, luminal B, basal-like, and HER2-positive, using TCGA and TISIDB databases and found that overexpression of *AURKB* was significantly associated with the basal-like subtype (**Figure 3A** and **B**). To further validate our results, we used a dedicated BRCA transcriptomic database, bc-GenExMiner v5.0. *AURKB* expression was consistently significantly (p<0.0001) upregulated in basal-like subtypes compared to others (**Figure 3C** and **D**). The results mentioned above confirmed the association between *AURKB* overexpression and the basal-like subtype. In addition, we found that *AURKB* gene expression was strongly associated with ER$^-$, PR$^-$, and ER$^-$/PR$^-$ subtypes compared with ER$^+$/PR$^+$ subtypes (**Figure 3E-G**). A strong negative correlation between *AURKB* and ER 1 (*ESR1*; r = −0.495, p=1.96×10^{-69}) and *AURKB*

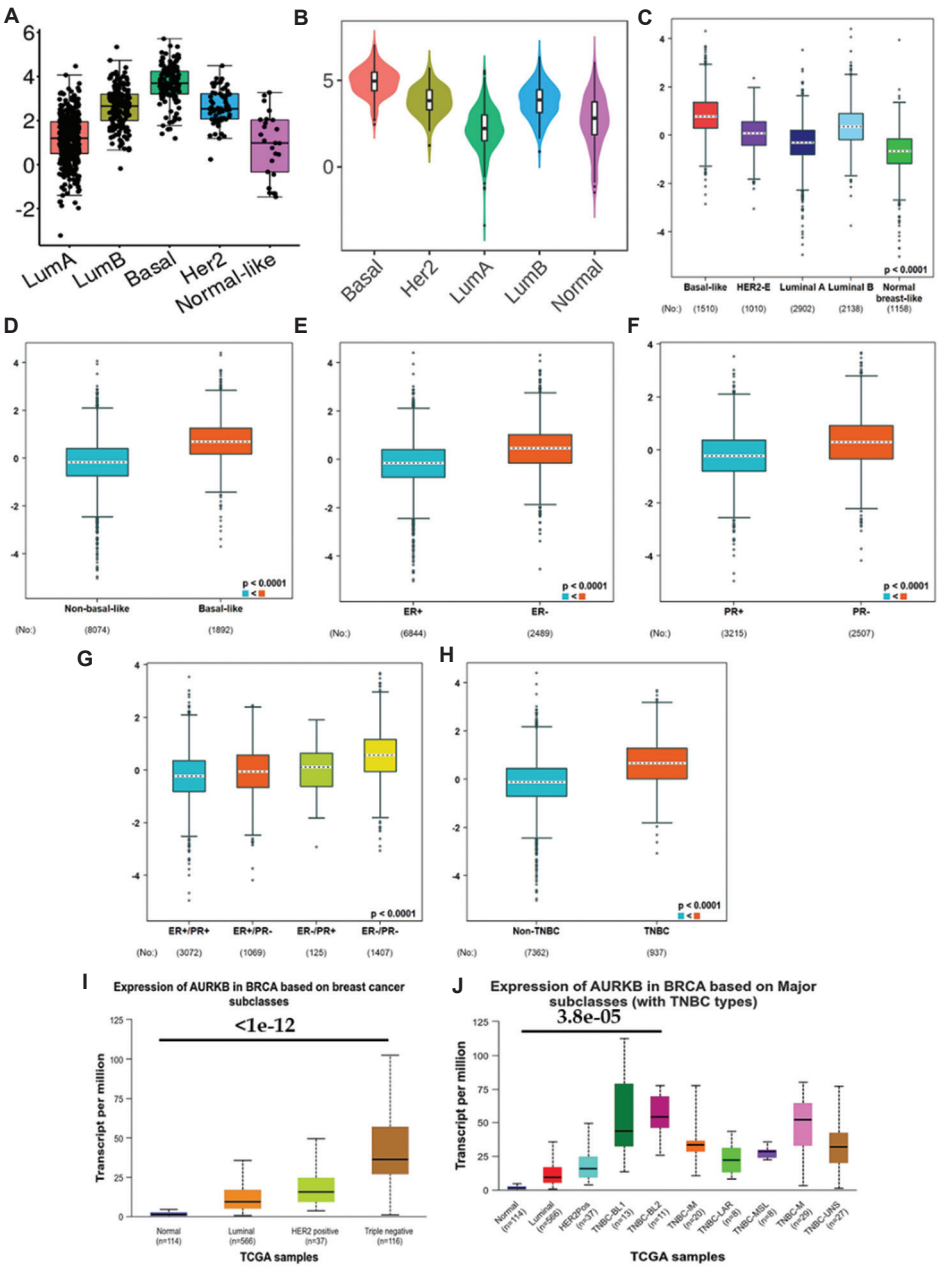


Figure 3. *AURKB* expression in breast cancer subtypes. (A-J) *AURKB* expression in overall breast cancer subtypes, such as luminal A (LumA), luminal B (LumB), basal, and HER2, analyzed using (A) TCGA, (B) TISIDB, and (C) bc-GenExMinerv5.0. (D-H) Expression analysis associated with hormone receptors analyzed using bc-GenExMinerv5.0: (D) Non-basal-like versus basal-like; (E) ER$^-$/ER$^+$; (F) PR$^-$/PR$^+$; (G) ER$^+$/PR$^+$; ER$^+$/PR$^-$; ER$^-$/PR$^+$; ER$^-$/PR$^-$; (H) Non-TNBC versus TNBC. (I and J) Further validation using the UALCAN database.
Abbreviations: BRCA: Breast cancer; ER: Estrogen receptor; HER2: Human epidermal growth factor receptor 2; PR: Progesterone receptor; TCGA: The Cancer Genome Atlas; TISIDB: Tumor-Immune System Interactions and Drug Bank; TNBC: Triple-negative breast cancer; UALCAN: University of Alabama Cancer Database.

and PR (*PGR*; r = −0.481, p=4.22×10^{-65}) using the ENCORI database (Figure S1C and D) suggested the association of *AURKB* with BRCA aggressiveness. We also compared *AURKB* expression between non-TNBC and TNBC subtypes using bc-GenExMiner. As shown in **Figure 3H**, we found significantly higher levels of *AURKB* in TNBC subtypes (p<0.0001), which were associated with aggressive forms of BRCA (p=<1×10^{-12}; **Figure 3I**). In addition, *AURKB* expression was found to be significantly associated with TNBC-basal-like 2, with a p-value of 3.8×10^{-05}, as depicted in **Figure 3J**, indicating a strong correlation with *AURKB* dysregulation, leading to aggressive forms of BRCA.

3.3. *AURKB* functional analysis

It is well established that biological processes are highly altered in tumor progression. The CancerSEA database was used to determine *AURKB*'s role in different functional states. As shown in **Figure 4A**, the results suggested that the overexpression of *AURKB* in BRCA was significantly correlated with cell cycle (r = 0.71), proliferation (r = 0.62), DNA damage (r = 0.51), invasion (r = 0.24), and EMT (r = 0.20), which are some of the hallmarks of cancer aggressiveness. The association of *AURKB* expression level with proliferation, EMT, and poor DMFS indicated its role in metastasis. Thus, to confirm our hypothesis, we analyzed the *AURKB* gene expression in tumors from BRCA patients associated with metastasis using the TNMplot database. As shown in **Figure 4B** and **C**, gene chip and RNA sequencing results showed significantly higher *AURKB* expression in metastatic tissue compared to normal tissues (p=5.37×10^{-70} and p=1.93×10^{-54}, respectively). Further validation using DriverDBv4 showed significant upregulation of *AURKB* in metastatic and BRCA cells, as shown in **Figure 4D**. Furthermore, an analysis of an RNAi dataset from the DepMap portal revealed a stronger gene dependency on *AURKB* in metastatic BRCA cell lines than in primary ones. Notably, the primary cell line MCF10A (control) exhibited a moderate gene effect score (−0.39), suggesting minimal reliance on *AURKB* for survival under normal conditions. In contrast, metastatic cell lines, including MCF7 and MDA-MB-231, showed more negative gene effect scores of −0.59 and −0.67, respectively, as shown in **Figure 4E**. These findings highlight a higher dependency on *AURKB* in metastatic and aggressive BRCA, particularly in MDA-MB-231, a TNBC cell line known for its invasiveness and metastatic potential. Overall, this supports the potential of *AURKB* as a therapeutic target in aggressive BRCA subtypes. In addition, based on the TISIDB database, we also analyzed the Gene Ontology of *AURKB* using biological process, molecular function, and cellular component (Table S1).

3.4. Analysis of regulatory factors of *AURKB*

TFs play a crucial role in regulating gene expression in both normal and tumor cells. The Enrichr database was used to identify TFs associated with *AURKB* expression (Table S2). MSigDB Hallmark data showed a significant correlation with E2F targets (p=1.88×10^{-10}), with the ENCORI and TIMER databases showing positive correlations between E2Fs (*E2F1*, *E2F2*, *E2F3*, *E2F4*, *E2F5*, *E2F6*, *E2F7*, and *E2F8*) and *AURKB* expression in BRCA, as shown in **Figure 5A-P**. However, the maximum correlation value was found between *E2F1* and *AURKB*, as shown in **Figure 5A** and **I**, using the ENCORI and TIMER databases (r = 0.806 and r = 0.777, respectively). To strengthen our data, we found a highly significant correlation between *E2F1* and *AURKB* in BRCA using various databases, including GEPIA2, OncoDB, UALCAN, and bc-GenExMiner, indicating a strong correlation between the two (r = 0.78, r = 0.7999, r = 0.63, and r = 0.40, respectively), as shown in **Figure 5Q-T**. Furthermore, *E2F1* expression in BRCA subtypes was significantly associated with basal-like and TNBC, and its upregulation in ER$^-$/PR$^-$ subtypes indicated its association with tumor aggressiveness, as shown in **Figure 5U** and **V**. The correlation analysis of *ESR1* and *PGR* genes using the ENCORI database showed a strong negative correlation with *AURKB*, with r values of −0.322 and −0.429, respectively, as shown in Figure S1E and F. The impact of *E2F1* overexpression on the survival outcomes of BRCA patients was also analyzed, observing that *E2F1* dysregulation in BRCA plays a major role in poor survival. The results showed a significant association with DMFS (HR = 1.47, 95% CI = 1.25–1.71, p=1.3×10^{-6}), RFS (HR = 1.45, 95% CI = 1.31–1.6, p=6.7×10^{-13}), and OS (HR = 1.53, 95% CI = 1.26–1.85, p=1.1×10^{-5}) in BRCA patients (Figure S1 G-I). *E2F1* plays a significant role in regulating *AURKB* expression levels in both normal and tumor cells.

3.5. Competing endogenous RNA network-associated regulation of *AURKB*

The regulatory mechanism behind the overexpression of *AURKB* in BRCA remains unknown. Recent research suggests that non-coding RNAs, part of the ceRNA network, play a significant role in the dysregulation of mRNA during tumor progression.[47,48] A ceRNA network was established using miRNet to identify the miRNAs linked to *AURKB* (Figure S2A). The network revealed various miRNAs (hsa-let-7b-5p, hsa-let-7e-5p, hsa-mir-16-5p, hsa-mir-24-3p, hsa-mir-125b-5p, hsa-mir-155-5p, hsa-mir-130a-3p, hsa-mir-34a-5p, hsa-mir-378a-3p, hsa-mir-1-3p, hsa-mir-106b-5p, hsa-mir-214-3p, hsa-mir-27a), with hsa-let-7b-5p being the most closely related to *AURKB*. To strengthen the data, expression levels of other AURKB-associated miRNAs were analyzed using the UALCAN database as listed in **Table S3.** It was observed that among the 14 miRNAs examined, only 6 exhibited significant downregulation in BRCA samples. Additionally, correlation analysis performed using the ENCORI database revealed that only hsa-let-7b-5p showed a strong negative correlation with AURKB, which suggests a potential direct relationship between hsa-let-7b-5p and AURKB in BRCA (**Table S4**). In addition, the study found a strong negative correlation between hsa-let-7b-5p and *AURKB* in BRCA patients using TACCO (r = −0.308), and further validation using the CancerMIRNome and ENCORI databases confirmed the strong negative correlation between both (r = −0.452, p=2.02×10^{-60}, and r = −0.338, p=2.35×10^{-30}, respectively) as shown in **Figure 6A-C**. Further research is needed to understand the relationship between these genes. Moreover, the individual expression of hsa-let-7b-5p was significantly downregulated in BRCA patients across various databases (CancerMIRNome, UALCAN,

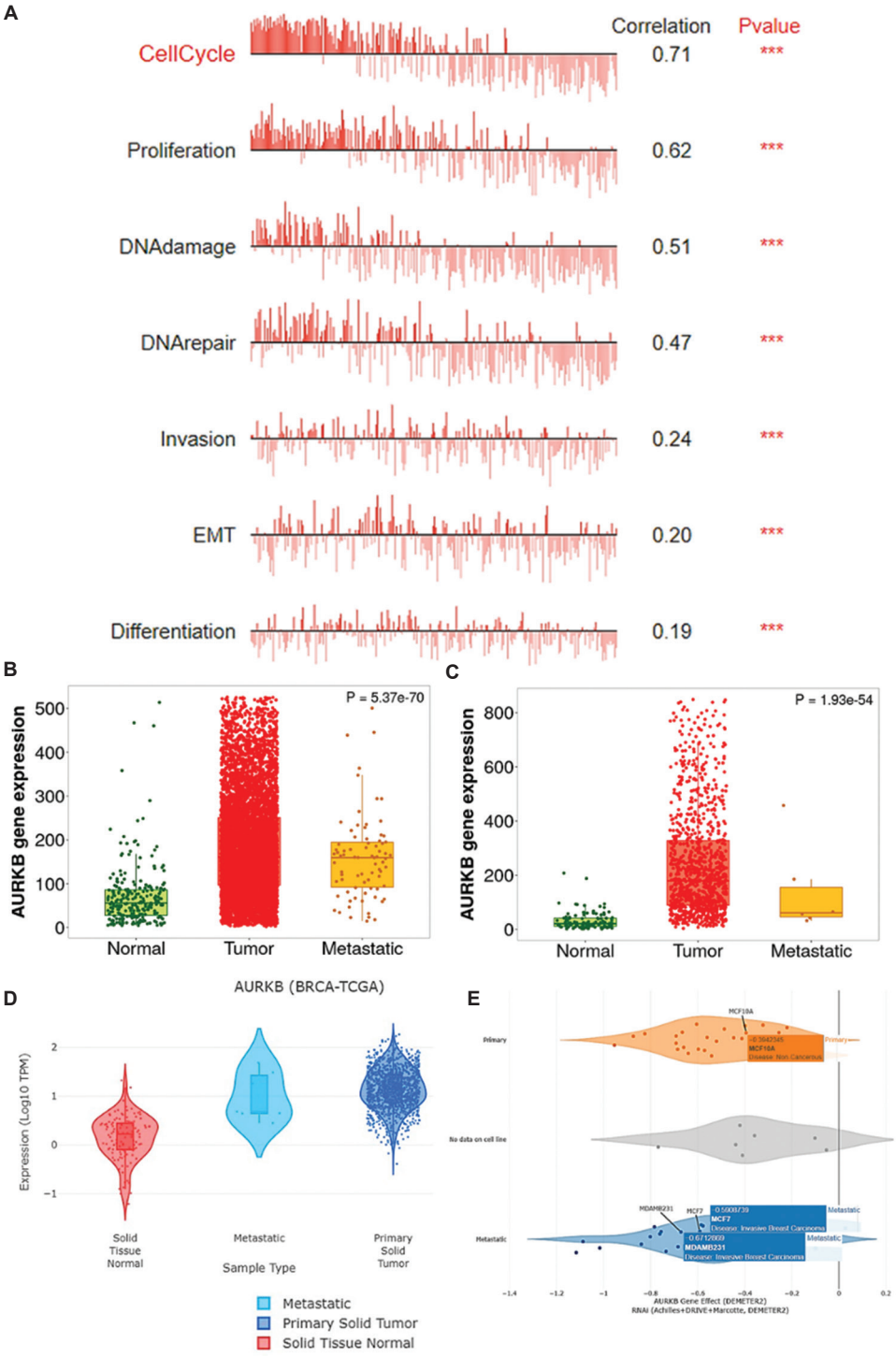


Figure 4. *AURKB* expression and biological functional states correlation in BRCA. (A) Cancer Single-cell State Atlas analysis. Boxplot of *AURKB* expression between normal, tumor, and metastasis in breast cancer patients using the (B) gene chip and (C) RNA sequencing TNMplot database. (D) Violin plot of *AURKB* expression in solid tissue normal, metastatic, and primary solid tumor from BRCA patients using the DriverDBv4 database. (E) Violin plot showing *AURKB* gene dependency scores across primary and metastatic BRCA cell lines from the Dependency Map RNAi dataset.
Note: ***$p<0.05$.
Abbreviations: BRCA: Breast cancer; EMT: Epithelial-mesenchymal transition; TCGA: The Cancer Genome Atlas; TPM: Transcripts per million.

ENCORI, and miRNACancerMap), as shown in **Figure 6D-G**. In addition, the binding affinity between hsa-let-7b-5p and *AURKB* was also observed by using the RNA22v2 database, and a strong binding was seen with an energy value of –16.40 kcal/mol, as shown in **Table 1**, which corroborated the correlation between hsa-let-7b-5p and *AURKB*. Furthermore,

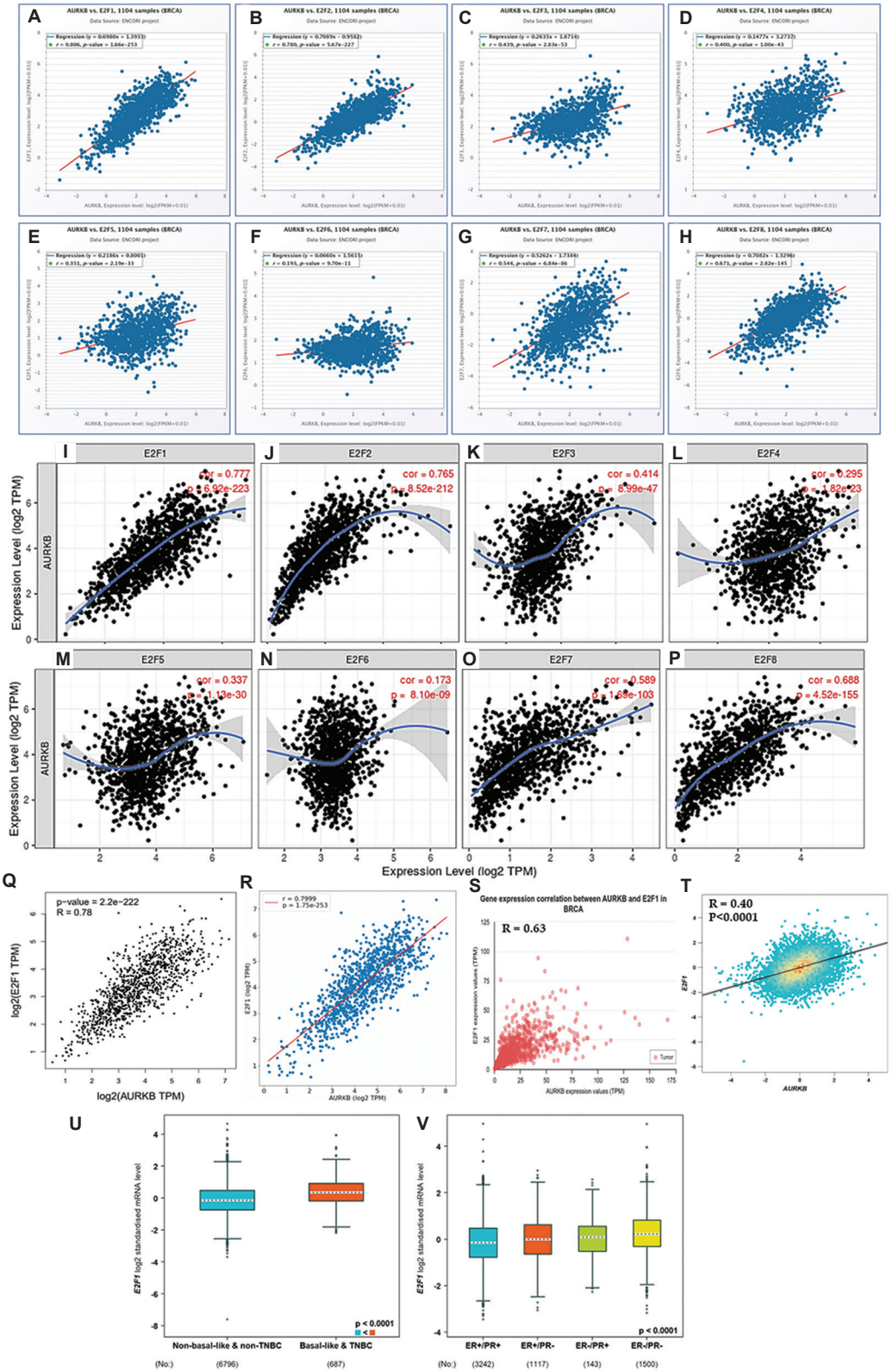


Figure 5. Expression correlation analysis between *AURKB* and the *E2F* family. Correlation between *AURKB* versus *E2F1*, *AURKB* versus *E2F2*, *AURKB* versus *E2F3*, *AURKB* versus *E2F4*, *AURKB* versus *E2F5*, *AURKB* versus *E2F6*, *AURKB* versus *E2F7*, and *AURKB* versus *E2F8* by using the (A-H) ENCORI database and (I-P) TIMER database. Close association between *E2F1* and *AURKB* using (Q) GEPIA2, (R) OncoDB, (S) UALCAN, and (T) bc-GenExMinerv5.0. Further analysis of *E2F1* expression associated with (U) basal and TNBC status and (V) ER/PR status using bc-GenExMinerv5.0.

Abbreviations: BRCA: Breast cancer; ER: Estrogen receptor; ENCORI: Encyclopedia of RNA Interactomes; GEPIA: Gene Expression Profiling Interactive Analysis; PR: Progesterone receptor; TCGA: The Cancer Genome Atlas; TIMER: Tumor Immune Estimation Resource; TNBC: Triple-negative breast cancer; TPM: Transcripts per million; UALCAN: University of Alabama Cancer Database.

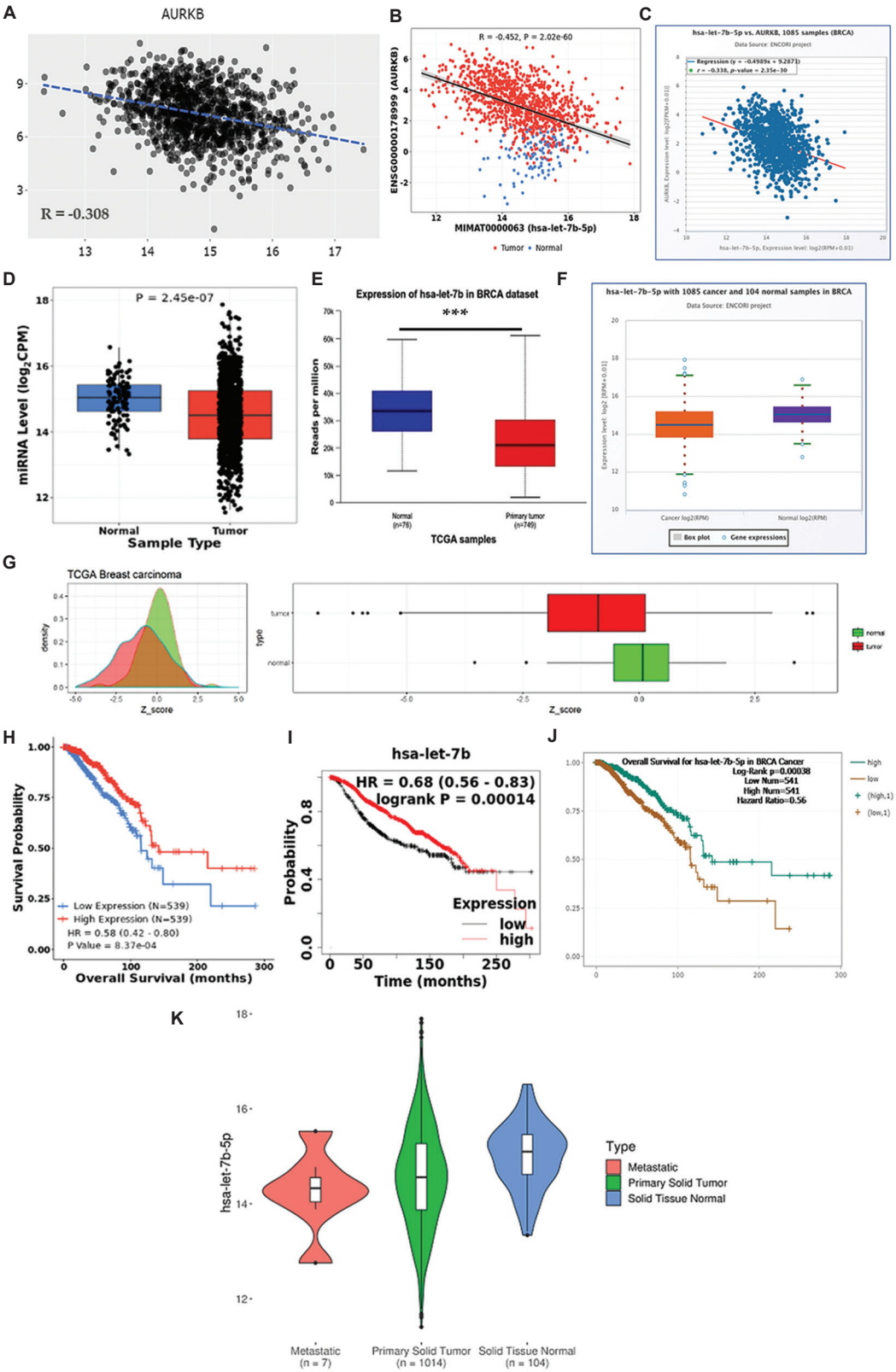


Figure 6. MicroRNA-based analysis. Correlation between hsa-let-7b-5p and *AURKB* using (A) TACCO, (B) CancerMIRNome, and (C) ENCORI. Boxplot showing differential expression analysis of hsa-let-7b-5p in tumor compared to normal tissues using (D) CancerMIRNome, (E) UALCAN, (F) ENCORI, and (G) miRNACancerMap. Survival analysis of hsa-let-7b-5p overexpression on BRCA patients using (H) CancerMIRNome, (I) KM plotter, and (J) ENCORI. Involvement of hsa-let-7b-5p in metastasis was evaluated using the ExploRRnet database.

Note: ***$p<0.05$.

Abbreviations: BRCA: Breast cancer; ENCORI: Encyclopedia of RNA Interactomes; HR: Hazard ratio; KM: Kaplan–Meier; miRNA: MicroRNA; TACCO: Transcriptome Alterations in Cancer Omnibus; TCGA: The Cancer Genome Atlas; UALCAN: University of Alabama Cancer Database.

Table 1. Binding affinities between microRNA-hsa-let-7b-5p and genes

MicroRNA	Transcript	Leftmost position of predicted target site	Binding affinity (kcal/mol)	Heteroduplex	*p*-value
hsa-let-7b-5p MIMAT0000063	*AURKB* NM_001313950.2	1,034	−16.40	AACTCTCGGAGGGTGCTGCCTCC |||: |: |: |:||:|||| TTGG-TGTGTTGGATGATGGAGT	1.5×10^{-2}
	E2F1 NM_005225.3	1,116	−13.90	CACCAC-CA-CC-ATCATCTCC ||||| || || |: |:||| TTGGTGTGTTGGATGATGGAGT	9.6×10^{-3}
	ESR1 NM_000125.4	2,897	−19.50	GACCACA-AATCAACTAGCTCC :|||||| ||:| |||| ||| TTGGTGTGTTGGATGATGGAGT	2.0×10^{-2}
		2,924	−12.50	AGCCATTTCTAAAATGGCAGCTTCA |:|||: :|| :| :|:||| TTGGTG--TGTT-GGATGATGGAGT	2.0×10^{-2}
	PGR NM_000926.4	5,391	−12.90	TGCCAC-TAA--AAATACCTTT :|||| :|| |||||: TTGGTGTGTTGGATGATGGAGT	6.5×10^{-2}
		8,163	−12.50	AATCTCACCTCCTTCAACTTTC ||:| ||| ||| | ||:|: TTGGTGTGTTGGATGATGGAGT	6.1×10^{-2}
		8,214	−12.10	TGCCCTACATCTTCCTTCTTCT :|| :||| |:| || |:|| TTGGTGTGTTGGATGATGGAGT	8.0×10^{-2}
	TMPO-AS1 NR_027157.1	777	−12.10	CGCCG--TTTCCT-CTCCCTCC :||: ||| || |||| TTGGTGTGTTGGATGATGGAGT	7.8×10^{-3}
		3,054	−12.40	GTTCACATCTCCTCAAATTTCA :||||: ||| |::||| TTGGTGTGTTGGATGATGGAGT	3.5×10^{-2}

the differential expression analysis of hsa-let-7b-5p across various TCGA cancers revealed a significant downregulation, as visualized using the CancerMIRNome database (Figure S2B). In addition, TACCO, a transcriptomic-based database, also demonstrated a significant downregulation of hsa-let-7b-5p levels, with a fold change of −1.26 specifically observed in BRCA patients, as listed in Table S5.

This downregulation was associated with poor survival in BRCA patients. This underscores the importance of understanding the role of individual expression in cancer treatment. In addition, the effect of hsa-let-7b-5p expression level in tumors on the survival outcomes of BRCA patients was analyzed using the CancerMIRNome, KM Plotter, and ENCORI databases. As shown in **Figure 6H-J**, BRCA patients with low expression levels of hsa-let-7b-5p had significantly associated with poor OS (CancerMIRNome: HR = 0.58, p=8.37×10^{-4}; KM plotter: HR = 0.68, p=0.00014; ENCORI: HR = 0.56, p=0.00038). Interestingly, we also found that hsa-let-7b-5p is associated with worse prognosis, tumorigenesis, recurrence, metastasis, malignant transformation, immune resistance, drug resistance, and cell migration in BRCA (Figure S2C and D). Given the established connection between downregulated hsa-let-7b and poor prognosis of BRCA patients, we explored its involvement in metastasis. The ExploRRnet database showed a downregulation in hsa-let-7b expression in patients with metastases compared to patients with only tumors and normal individuals (**Figure 6K**). Further correlation analysis using the ENCORI database with transcriptional factor *E2F1* showed significant negative correlation with let-7b-5p (r = −0.310) and positive association with *ESR1* (r = 0.267) and *PGR* (r = 0.274) genes, as shown in Figure S2 E-G, suggesting that hsa-let-7b-5p levels decrease with increasing *E2F1* but increase with elevated *ESR1* and *PGR* levels. Hence, downregulation of hsa-let-7b-5p could be a better prognosis biomarker for TNBC. Furthermore, a strong and steady interaction of hsa-let-7b-5p with *E2F1*, *ESR1*, and *PGR,* with binding affinities of −13.90 kcal/mol, −19.50 kcal/mol, and −12.90 kcal/mol, respectively, confirms a significant association between the molecules as shown in **Table 1**.

The study next aimed to identify the regulatory molecule of hsa-let-7b, an lncRNA that affects miRNA stability and downregulates its expression in cancer cells. The Enrichr database was used to identify lncRNAs associated with *AURKB*. A list of the top 20 lncRNAs was exported from lncHUB (Table S6) and analyzed using the UALCAN database (Table S7). It was found that seven out of 20 lncRNAs, *DEPDC1-AS1*, *CSRP3-AS1*, *RRM1-AS1*, *RRM1-AS1*, *DDX11-AS1*, *LINC01775*, *HMMR-AS1*, and *TMPO-AS1*, were upregulated in breast invasive carcinoma cases. Furthermore, the correlation values between these lncRNAs and *AURKB* were explored using

the ENCORI database, and they revealed a significant positive correlation between *TMPO-AS1* and *AURKB*, with an *r* value of 0.610 and a *p*-value of 1.58×10^{-113} (Table S8 and **Figure 7A**). As shown in **Figure 7B** and **C**, the same results were obtained using the OncoDB and GEPIA2 databases, whose correlation values were 0.5184 and 0.43, respectively. Furthermore, ENCORI revealed a high positive connection between lncRNA *TMPO-AS1* and transcriptional factor *E2F1* ($r = 0.624$, $p=3.81\times10^{-120}$), as shown in **Figure 7D**. To complete the ceRNA network, we studied the correlation between *TMPO-AS1* and hsa-let-7b-5p and found, as predicted, a significant negative correlation between both non-coding RNAs ($r = -0.204$ and $p=1.12\times10^{-11}$), as shown in **Figure 7E**. The negative interaction between *TMPO-AS1* and hsa-let-7b demonstrates that the lncRNA might serve as a sponge for miRNA, suppressing its function and expression in TNBC patients. In addition, the binding energy values of −12.10 kcal/mol and −12.40 kcal/mol indicate a stable interaction, supporting the idea that *TMPO-AS1* can effectively sponge hsa-let-7b, preventing it from regulating *AURKB* (**Table 1**). Furthermore, a network created using miRNet (Figure S3A) showed a direct association between *TMPO-AS1*, hsa-let-7b-5p, and *AURKB*. The study further analyzed the differential expression of *TMPO-AS1* in BRCA using various databases (ENCORI, OncoDB, UALCAN, and TCGAnalyzeR), revealing a significant upregulation in tumor tissues compared to normal (**Figure 7F-I**). Furthermore, we analyzed the expression of *TMPO-AS1* in different subtypes of BRCA and found that *TMPO-AS1* is significantly overexpressed in TNBC and basal-like subtypes (**Figure 7J-L**). The ENCORI database found a negative correlation between *TMPO-AS1* and *ESR1* ($r =- 0.167$) and *PGR* ($r = -0.232$), confirming its association with aggressiveness (Figure S3B and C). *TMPO-AS1* expression correlates with *E2F1* expression, whereas a decrease in *TMPO-AS1* expression was observed with increased *ESR1* and *PGR* expressions. This supports the hypothesis that the *AURKB*/*E2F1*/hsa-let-7b/*TMPO-AS1* axis is associated with the aggressive form of BRCA.

3.6. *AURKB* in tumor aggressiveness associated with proliferation and heterogeneity

Breast cancer is a heterogeneous disease characterized by the dysregulation of several genes, contributing to its aggressiveness. This study analyzed co-expressed genes associated with AURKB using the Enrichr database and found that the top 10 genes, including *BIRC5*, *CDC20*, *CDC45*, *CDCA5*, *CDCA8*, *KIF2C*, *KIFC1*, *PLK1*, *RRM2*, and *TROAP*, were associated with BRCA proliferation and aggressiveness. The gold standard proliferation marker *MKI67*, *ESR1*/*PGR*, and transcriptional factor *E2F1* were also included in the gene list. The correlation between *AURKB* and the top 10 co-expressed genes, along with *MKI67*, *E2F1*, *ESR1*, and *PGR*, was analyzed using the TIMER database. Results showed a strong, positive, and significant ($p<0.05$) correlation between *AURKB* and co-expressed genes, such as *BIRC5* ($r = 0.848$), *CDC20* ($r = 0.864$), *CDC45* ($r = 0.815$), *CDCA5* ($r = 0.842$), *CDCA8* ($r = 0.825$), *KIF2C* ($r = 0.86$), *KIFC1* ($r = 0.859$), *PLK1* ($r = 0.864$), *RRM2* ($r = 0.683$), and *TROAP* ($r = 0.872$), along with *MKI67* ($r = 0.705$) and *E2F1* ($r = 0.777$), as shown in **Figure 8A-L**. The negative association between *AURKB*, *ESR1*, and *PGR* suggests a strong association between *AURKB* overexpression and aggressiveness in BRCA cases **(Figure 8M** and **N)**. Transcriptomic analysis for *AURKB*, co-expressed genes, and *MKI67* using TCGAnalyzeR showed a log2 fold change of each gene (fold change = 2.7 to 3.7) based on expression in normal versus tumor (Table S9). *E2F1* was found downstream of all the genes and could be a potential regulator of *AURKB* and its co-expressed genes, with a log2 fold change of 2.09 (**Figure 8O**). The enrichment analysis of genes across pathological stages using the Gene Set Cancer Analysis database showed a similar expression pattern across all genes, with overexpression in Stage IV BRCA patients (**Figure 8P**).

4. Discussion

Breast cancer remains a formidable global health challenge, particularly its aggressive subtypes like TNBC, which are characterized by high rates of recurrence, metastasis, and limited targeted therapeutic options.[6] While some advancements in current treatment have been made, current strategies, such as surgery, chemotherapy, and radiation, remain limited due to drug resistance, significant side effects, and the absence of defined molecular targets.[49] Consequently, the OS rates for metastatic TNBC have remained stagnant over the past few decades, emphasizing the urgent need for innovative therapeutic approaches.

Our study fills this essential gap by offering a detailed analysis of *AURKB* dysregulation and its regulatory network in BRCA. Aberrant gene expression plays a crucial role in TNBC progression, with *AURKB* emerging as a key player.[22] AURKB is a serine/threonine kinase essential for mitotic processes, including chromosome condensation, bipolar spindle formation, and cytokinesis.[50] Dysregulation of *AURKB* disrupts mitosis, leading to polyploidy and increased tumorigenesis, and has been associated with therapy resistance, along with affecting survival outcomes in various cancers, including BRCA.[14,18,20,21,22] Understanding the molecular mechanism underlying *AURKB* dysregulation is essential for advancing knowledge and identifying novel prognostic biomarkers. Phosphorylation is necessary for AURKB's activity, which relies on histone H3 phosphorylation to promote mitotic chromosome condensation.[51] *AURKB* can also regulate mitotic centromere-associated kinesin, which can bind centromeres and microtubules.[22]

Our findings consistently showed that *AURKB* is significantly upregulated across various types of cancer, with robust overexpression in BRCA, particularly within its more aggressive basal-like and TNBC subtypes (bc-GenExMiner v5.2). This widespread overexpression, along with its strong link to poor patient outcomes, including notably reduced DMFS, RFS, and OS, solidifies *AURKB* as a valuable prognostic biomarker. The clinical importance of this is heightened because TNBC, which lacks traditional hormone receptors (ER/PR) and HER2, requires new molecular targets for effective treatment.[6] The threefold difference in DMFS between high and low *AURKB*-expressing BRCA patients further underscores its ability to predict aggressive disease progression. This supports existing research that highlights *AURKB*'s role in driving uncontrolled

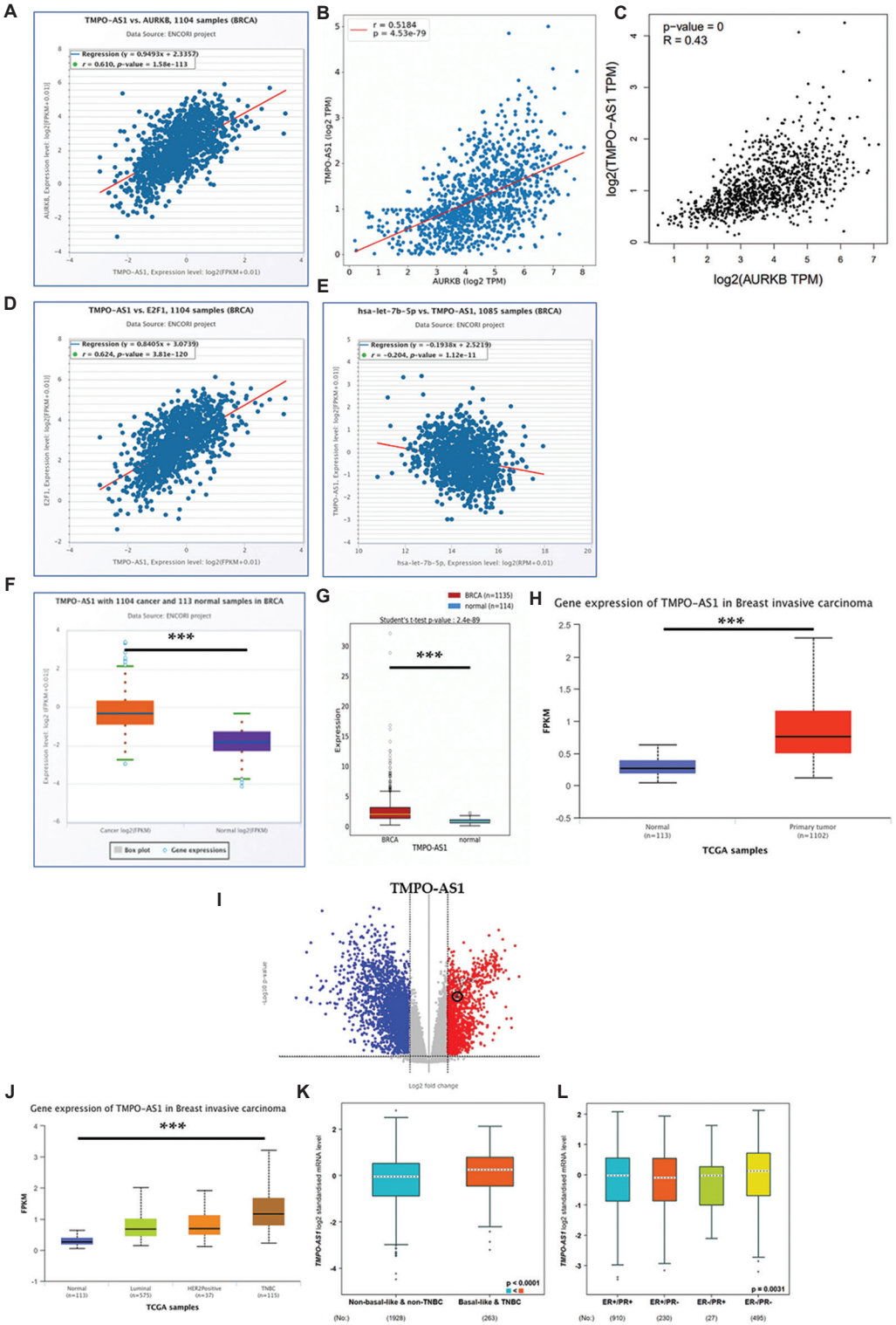


Figure 7. Long non-coding RNA-based analysis. (A-C) Correlation between *TMPO-AS1* and *AURKB* using (A) ENCORI, (B) OncoDB, and (C) GEPIA2. (D) Correlation of *TMPO-AS1* versus *E2F1* and (E) correlation of hsa-let-7b-5p versus *TMPO-AS1* using the ENCORI database. Boxplot of *TMPO-AS1* expression in cancer compared to normal samples using (F) the ENCORI database, (G) OncoDB, and (H) UALCAN. (I) A volcano plot showing upregulation of *AURKB* expression in BRCA using TCGAnalyzeRv1.0. (J-L) Boxplot of *TMPO-AS1*, expression according to normal versus tumors from patients with different histological subtypes, such as (J) normal versus luminal versus HER2 versus TNBC using UALCAN, (K) basal and TNBC status, and (L) ER/PR status using bc-GenExMinerv5.0.

Note: ***$p<0.05$.

Abbreviations: BRCA: Breast cancer; ENCORI: Encyclopedia of RNA Interactomes; ER: Estrogen receptor; GEPIA: Gene Expression Profiling Interactive Analysis; FPKM: fragments per kilobase of transcript per million; HER2: Human epidermal growth factor receptor 2; PR: Progesterone receptor; TCGA: The Cancer Genome Atlas; TNBC: Triple-negative breast cancer; UALCAN: University of Alabama Cancer Database.

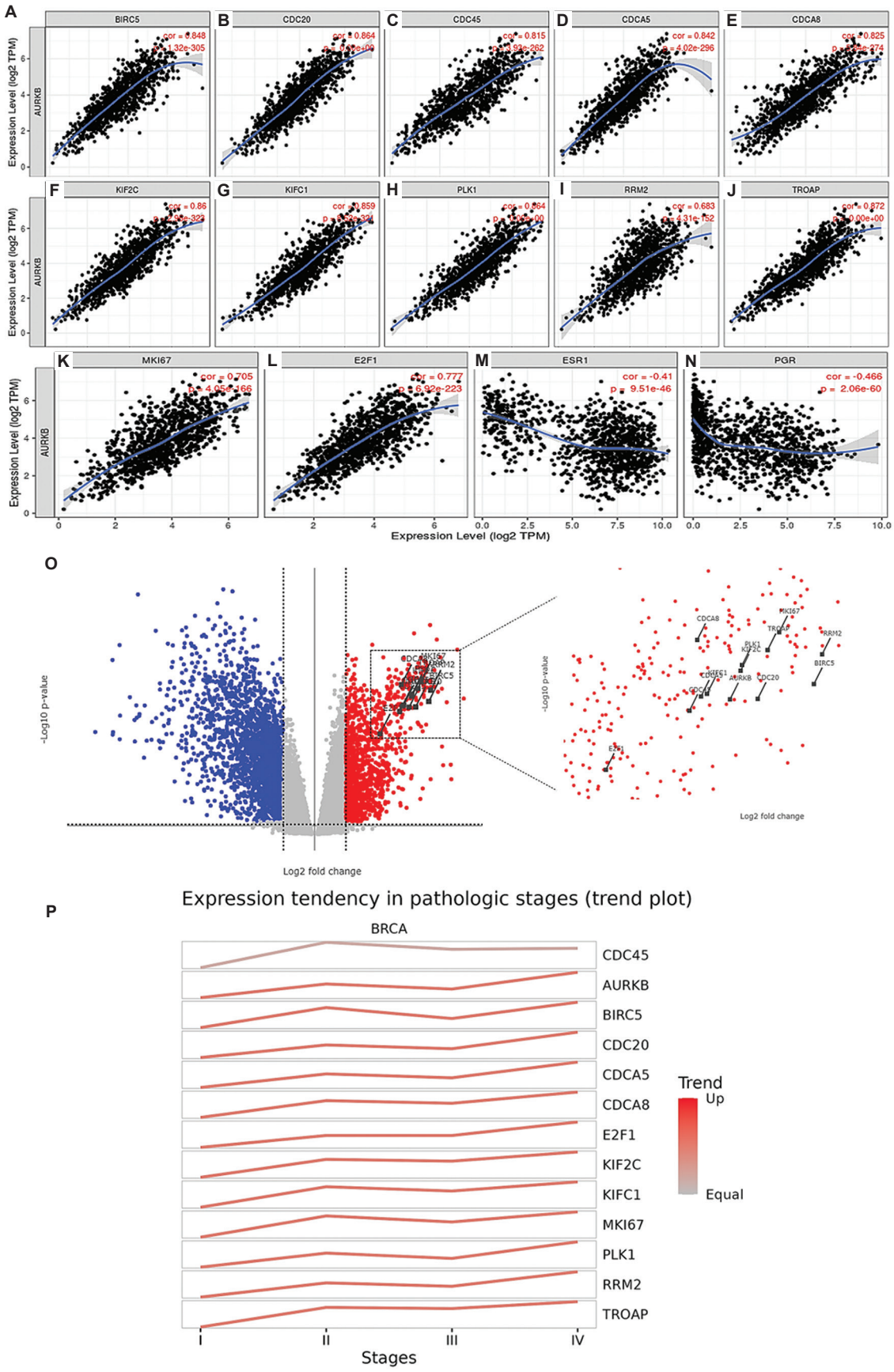


Figure 8. Heterogeneity and proliferation analysis associated with co-expressed genes, *MKI67* and *E2F1*. (A-N) TIMER, (O) TCGAnalyzeRv1.0, and (P) Gene Set Cancer Analysis.

Abbreviations: BRCA: Breast cancer; TIMER: Tumor Immune Estimation Resource; TCGA: The Cancer Genome Atlas; TPM: Transcripts per million.

growth, invasion, and spread in various cancers.

A key strength of our study lies in elucidating a novel ceRNA network that provides mechanistic insights into *AURKB* dysregulation. We identified a robust positive correlation between *AURKB* and the TF *E2F1*, a known regulator of cell cycle progression and proliferation. Furthermore, we uncovered a complex interplay involving the lncRNA *TMPO-AS1* and the tumor-suppressive miRNA hsa-let-7b-5p. The negative correlation between hsa-let-7b-5p and *AURKB*, coupled with the negative correlation between *TMPO-AS1* and hsa-let-7b-5p, strongly supports the idea of a molecular sponge mechanism. In this model, the elevated expression of *TMPO-AS1* acts as a "sponge," sequestering hsa-let-7b-5p and thereby preventing it from binding to and inhibiting its target mRNA, *AURKB*. This effectively derepresses *AURKB* expression, contributing to its observed upregulation in BRCA. The predicted strong binding affinities between hsa-let-7b-5p and its targets, including *AURKB* and *E2F1*, provide further biochemical support for this proposed ceRNA network. This intricate regulatory loop, involving transcriptional activation by *E2F1* and post-transcriptional control through the lncRNA-miRNA interaction, offers a multi-layered explanation for AURKB overexpression in aggressive BRCA.

The functional analysis reinforces *AURKB*'s multifaceted role in cancer aggressiveness. Its strong correlation with cellular processes such as cell cycle progression, proliferation, DNA damage, EMT, and invasion directly implicates *AURKB* in the hallmarks of cancer. The increased dependence on *AURKB* observed in metastatic BRCA cell lines, especially the highly invasive TNBC cell line MDA-MB-231, further underscores its critical role in metastatic spread. This finding is particularly significant given the clinical challenges posed by metastatic TNBC, where treatment options are limited and prognosis remains poor. Mechanistically, *AURKB* upregulation in TNBC has been linked to increased chromosomal instability, deregulation of phosphoinositide 3-kinase/protein kinase B and *MYC* signaling, and suppression of apoptosis, all of which collectively promote uncontrolled proliferation, EMT, and metastatic potential.[52] The identification of this *E2F1*/*TMPO-AS1*/hsa-let-7b-5p ceRNA network not only enhances our fundamental understanding of *AURKB* regulation in BRCA but also offers tangible opportunities for clinical translation. The components of this network could serve as new diagnostic and prognostic biomarkers for identifying patients at high risk of aggressive disease progression or recurrence. In addition, targeting specific nodes within this network, such as inhibiting *AURKB* activity, disrupting the *TMPO-AS1*/hsa-let-7b-5p interaction, or modulating *E2F1* activity, could lead to innovative personalized therapeutic strategies for BRCA. While our study primarily relies on comprehensive *in silico* analyses of publicly available (Table S10), the consistent and statistically significant findings across multiple datasets provide a strong foundation for future experimental validation in preclinical models and ultimately in clinical trials. Addressing the challenges of TNBC requires a multi-pronged approach, and the insights gained from this study offer a promising path for developing targeted interventions to improve survival and quality of life for patients battling this aggressive disease.

While our research provides new insights into the role of *AURKB* and its regulatory network in BRCA, certain limitations must be acknowledged. The findings are derived from *in silico* analyses of publicly available datasets, which may be subject to heterogeneity and database-specific biases. Future prospective studies with larger clinical cohorts, along with experimental validation in cellular and *in vivo* models, will be essential to confirm these observations and enhance their translational significance.

5. Conclusions

This study identifies *AURKB* as a key driver of malignancy and a strong prognosticator of patient outcomes in aggressive BRCA. *AURKB* upregulation was observed in clinically challenging subtypes, including basal-like and TNBC. Higher *AURKB* levels were closely linked to reduced DMFS, RFS, and OS, making it an important biomarker for risk stratification in patients with estrogen and PR-negative tumors. The research also uncovers a key mechanistic basis for this overexpression, involving a novel ceRNA network. The lncRNA *TMPO-AS1*, controlled by *E2F1*, acts as a sponge for miRNAs that would otherwise inhibit *AURKB* expression. This finding offers a detailed molecular understanding of the post-transcriptional dysregulation that drives AURKB's oncogenic activity in aggressive BRCA. The effects of this dysregulation are significant, as AURKB is deeply involved in essential cancer processes. Its activity is strongly linked to features such as rapid cell cycle G2/M progression, increased cellular growth, genomic instability, and the development of migratory and invasive abilities through EMT. This research presents a compelling dual role for AURKB as both a precise prognostic biomarker and a potential therapeutic target. By clarifying its upstream regulatory network and downstream effects, these findings provide a vital foundation for advancing next-generation precision medicine strategies.

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Conflicts of interest statement
The authors declare that they have no conflicts of interest.
Author's contributions
Conceptualization: RN and AK; *Formal analysis*: AK; *Methodology*: PV, BB, and CS; *Writing – original draft:* RN, PV, BB, and CS; *Writing – review & editing:* AK. All authors read and approved the final manuscript.
Ethics approval and consent to participate
Not applicable.
Consent for publication
Not applicable.
Availability of data
The data for this *in silico* study were sourced from publicly accessible databases. The respective references for these datasets are provided in the methodology section for transparency and reproducibility.

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