Original Article

Upregulation of CKS2 in immunosuppressive cells is associated with metastasis and poor prognosis in prostate cancer: a single-cell RNA-sequencing analysis

Xiaoxing Liang[1,2#], Renlun Huang[1,2#], Xinyue Ping[3], Wei Deng[1,2], Songtao Xiang[1,2], Zhichao Wang[1,2], Jiadong Cao[1,2]

[1]The Second Clinical College of Guangzhou University of Chinese Medicine, Guangzhou, China; [2]Department of Urology, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, China; [3]The First Clinical College of Guangzhou University of Chinese Medicine, Guangzhou, China

Contributions: (I) Conception and design: J Cao, Z Wang; (II) Administrative support: J Cao; (III) Provision of study materials or patients: X Liang, R Huang; (IV) Collection and assembly of data: X Liang, R Huang; (V) Data analysis and interpretation: X Ping, W Deng, S Xiang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Zhichao Wang, MD; Jiadong Cao, MD. The Second Clinical College of Guangzhou University of Chinese Medicine, Guangzhou, China; Department of Urology, Guangdong Provincial Hospital of Chinese Medicine, Dade Road 111, Guangzhou, 510000, China. Email: 13602495696@163.com; 121587061@qq.com.

Background: Metastasis worsens prostate cancer (PCa) prognosis, with the immunosuppressive microenvironment playing a key role in bone metastasis. This study aimed to investigate how an immunosuppressive environment promotes PCa metastasis and worsens prognosis of patients with PCa.

Methods: Candidate oncogenes were identified through analysis of the Gene Expression Omnibus (GEO) database. A prognostic model was developed for the purpose of identifying target genes. A single-cell RNA sequencing data from GEO database was used to analyze the localization of target genes in the tumor microenvironment. A pan-cancer analysis was conducted to study the cancer-causing potential of target genes across different types of tumors.

Results: Fifty-one genes were found to be differentially expressed in bone metastasis compared to non-metastatic PCa, with CKS2 identified as the most significant gene associated with poor prognosis. CKS2 was shown to be linked to an immunosuppressive microenvironment and osteoclastic bone metastases, as shown by its negative correlation with immune cell infiltration and osteoblast-related gene expression. Moreover, CKS2 was found in immunosuppressive cells and was linked to bone metastasis in PCa. It was also overexpressed in different types of tumors, making it as an oncogenic gene.

Conclusions: This research offers a new perspective on the potential utility of CKS2 as a therapeutic target for the prevention of metastatic PCa.

Keywords: CKS2; bone metastasis; prostate cancer (PCa); single-cell RNA-sequencing analysis (single-cell RNA-seq analysis)

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Introduction

Prostate cancer (PCa) is the most commonly diagnosed cancer in men worldwide, with a top 5 mortality rate among all cancers (1). Metastasis is the primary cause of mortality in PCa, with bone being the most common site for metastasis. Research indicates that 70% of metastatic PCa patients have bone metastasis (2). Furthermore, the 5-year survival rate is significantly lower in patients with bone metastasis compared to those without (3). Nevertheless, despite these observations, the efficacy of current treatments for patients with metastatic PCa is limited, underscoring the pressing need for the identification of novel targets for drug therapy in PCa.

The tumor microenvironment (TME) serves as a complex ecosystem that plays a crucial role in tumor progression. Various immune cells, including T-cells, B cells, natural killer cells (NK cells), macrophages, myeloid-derived suppressor cells (MDSCs), and regulatory T-cells (Tregs), are commonly found in the TME and are known to significantly impact cancer cell proliferation and metastasis. However, it is important to note that immune cells surrounding cancer cells can play a dual role. While an abundance of T-cells can be beneficial in eradicating cancer cells, certain immune cells have the ability to switch from suppressing tumors to promoting their growth. More specifically, T-cells may convert into Tregs, and macrophages may transition into tumor-associated macrophages (TAMs) within the TME, ultimately aiding in immune evasion and the advancement of tumors (4,5). Tumor-secreted factors could make these immune cells change their function (6). However, there was limited knowledge regarding the specific gene targeted for its potential immune suppressive function in immune cells.

In this study, we utilized single-cell RNA-sequencing analysis, immune cell infiltrated-associated analysis, as well as data from The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) databases to validate immune suppressive-associated genes in immune cells and examined the correlation between these genes and progression-free survival (PFS). We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2100/rc).

Highlight box

Key findings

- CKS2 in immunosuppressive cells was associated with metastasis and poor prognosis in prostate cancer (PCa).

What is known and what is new?

- The immunosuppressive microenvironment plays a key role in bone metastasis.
- CKS2 was found in immunosuppressive cells and was linked to bone metastasis in PCa.

What is the implication, and what should change now?

- CKS2 as a therapeutic target for the prevention of metastatic PCa.

Methods

Differentially expressed mRNA analysis

The microarray data utilized in this study were obtained from the GEO database (https://www.ncbi.nlm.nih.gov/geo/), with raw data being downloaded in MINiML format. Differential expression analysis of mRNA was conducted using the limma package in R software, with adjusted P values employed to mitigate false positive results within the GEO datasets. Criteria for defining differential mRNA expression included an adjusted P value of less than 0.05 and a log (fold change) greater than 1 or less than –1. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

GO and KEGG enrichment analysis

In order to validate the potential targets' underlying function, the data underwent analysis through functional enrichment methods. Gene Ontology (GO) serves as a commonly utilized tool for gene annotation, particularly in molecular function (MF), biological pathways (BPs), and cellular components (CCs). Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis is a valuable resource for investigating gene functions and related high-level genome functional information. To enhance comprehension of mRNA carcinogenesis, the ClusterProfiler package (version: 3.18.0) in R was utilized for analyzing GO function enrichment analysis.

The least absolute shrinkage and selection operator (LASSO) regression

RNA-sequencing expression profiles at level 3, along with associated clinical data for PCa, were obtained from the TCGA dataset. The counts data were converted to Trans Per Kilobase of exon model per Million mapped reads (TPM) and normalized using the log2 (TPM+1) transformation, with a focus on retaining samples with

corresponding clinical information. Subsequently, the dataset was narrowed down to include only PCa samples for further analysis. Survival differences between groups were assessed using the log-rank test, while the predictive accuracy of the targets gene and risk score was evaluated using time receiver operating characteristic (ROC) analysis version 0.4. The LASSO regression algorithm was employed for feature selection, utilizing 10-fold cross-validation and the R package for analysis. The data was initially analyzed using multi-factor Cox regression, followed by iterative refinement using the step function. The final model was selected based on optimization criteria. Kaplan-Meier (KM) curves were generated, and statistical significance was assessed using log-rank tests and univariate Cox proportional hazards regression to calculate hazard ratios (HRs) with 95% confidence intervals (CIs). The analysis methods and R packages utilized in this study were implemented using R (Foundation for Statistical Computing, 2020) version 4.0.3. A P value of less than 0.05 was deemed to be statistically significant.

Single cell RNA sequencing of PCa

The raw data for single-cell transcriptome profiling were acquired from the GEO database. The Seurat package was employed to create an object and eliminate cells of substandard quality. Subsequently, standard data preprocessing procedures were executed, including the calculation of gene number percentages, cell counts, and mitochondrial sequencing counts. Genes detected in fewer than three cells were excluded, and cells with fewer than 200 detected gene numbers were disregarded.

The Human Protein Atlas (HPA) database

Data of this manuscript about HPA database (https://www.proteinatlas.org/) were extracted from the HPA website.

Cox regression model and nomogram

RNA-sequencing expression profiles at level 3 and associated clinical data for PCa were obtained from the TCGA dataset. Univariate and multivariate Cox regression analyses were performed to identify the variables suitable for incorporation into the nomogram. The forest plot, created using the 'forestplot' R package, depicted the P value, HR, and 95% CI for each variable. A nomogram was constructed utilizing the outcomes of a multivariate Cox proportional hazards analysis to forecast the X-year overall recurrence. This nomogram offers a visual depiction of the variables that can be utilized to estimate the likelihood of recurrence for a specific patient, determined by the points assigned to each risk factor using the 'rms' R package.

Pan cancer analysis

For the CKS2 analysis, RNA-sequencing expression profiles (level 3) and relevant clinical data for the specified cohort were obtained from the TCGA dataset. The analysis was conducted using R version 4.0.3, with the implementation of appropriate methods and R packages. Unless otherwise specified, two-group data comparisons were performed using the Wilcoxon test, with statistical significance defined as $P<0.05$. For the purpose of PFS analysis, RNA-sequencing expression profiles (level 3) and corresponding clinical data for PCa were obtained from the TCGA dataset available at https://portal.gdc.cancer.gov. Univariate Cox regression analysis was conducted, and a forest plot was generated using the 'forestplot' R package to display the P value, HR, and 95% CI for each variable. All statistical analyses and data visualization were performed using R version 4.0.3. In cases where not specified, two-group comparisons were assessed using the Wilcoxon test. Statistical significance was defined as a P value less than 0.05.

Statistical analysis

Statistical analysis in this study used SPSS 24.0 software (Abbott Laboratories, USA). Data were presented as mean ± standard deviation (SD), with P values <0.05 considered significant.

Results

Different genes expression in PCa bone metastatic and PCa tissue

A total of 29 PCa bone metastasis samples and 22 PCa patient samples were obtained from the GEO dataset. Analysis revealed significant differential expression of 20 genes, with 11 genes (*CNN1*, *MYH11*, *ACTG2*, *PCP4*, *KRT15*, *ZFP36*, *MSMB*, *ANPEP*, *FOS*, *AZGP1*, and *NEFH*) showing downregulation and 9 genes (*SPP1*, *HBB*, *CKS2*, *COL1A1*, *COL1A2*, *HBA1*, *IBSP*, *MMP9*, and *HBD*) showing upregulation (*Figure 1A*,*1B*). As shown in *Figure 1C-1F*, the analysis of KEGG and GO function

enrichment revealed that genes involved in processes such as cell cycle regulation, the PI3K-Akt signaling pathway, organelle fission, nuclear division, extracellular structure organization, and extracellular matrix organization were significantly upregulated. Conversely, genes related to mineral absorption and response to metal ion were found to be downregulated.

CKS2, COL1A1, COL1A2 are associated with PCa PFS

Subsequently, the upregulated gene in PCa bone metastasis was selected for additional analysis. SPP1, HBB, CKS2, COL1A1, COL1A2, HBA1, IBSP, MMP9, and HBD were included in the signature model. Our findings indicated that COL1A1 and CKS2 are associated with an increased risk, while COL1A2 is associated with a protective effect on PCa PFS (*Figure 2A*). In KM survival analysis, those genes were divided into high risk and low risk group, and high risk group showed a low OS with a HR of 3.535 [95% CI: 2.208–5.658] which represented these model were risk factors model (*Figure 2B*). *Figure 2C* presented the expression profiles of upregulated genes in human samples, followed by an investigation into the impact of each gene on PFS. The ROC curve demonstrated a reliable prediction [area under the curve (AUC) >0.6] of the model in number 1, 3, 5 years of PFS with the AUC and 95% CI of 0.713 (0.63–0.795), 0.722 (0.667–0.777), 0.695 (0.62–0.771) respectively (*Figure 2D*). The subsequent analysis, as depicted in *Figure 2E*, revealed that elevated expression levels of CKS2, COL1A1, and COL1A2 were associated with a poorer PFS in PCa, with HRs and 95% CIs of 1.908 (1.225–2.9), 2.293 (1.48–3.555), and 1.653 (1.088–2.512), respectively. Notably, the AUC curves of these three genes were over 0.6 which revealed the predictable effect of these model. However, HBA1, HBB, MMP9, and SPP1 showed no difference in high expression and low expression group. Unfortunately, there were no enough data for the KM analysis in genes *HBD* and *IBSP*.

Multivariate analysis suggests that PFS of PCa could be predicted by risk gene CKS2

The anticipated effectiveness of the genes *CKS2*, *COL1A1*, and *COL1A2* was assessed. A total of 498 patients, along with their clinical information, were gathered from the TCGA dataset. Univariate Cox analysis revealed significant differences in CKS2, COL1A1, T stage, and N stage, which were deemed to be risk factors. Multivariate Cox analysis indicated that CKS2, COL1A1, and T stage were risk factors, whereas COL1A2 was identified as a protective factor (*Figure 3A*). Nomogram was applied to visualized the predicted model. As showed in *Figure 3B*, CKS2, COL1A1, COL1A2, and T stage combined to form a predicted model for 3 or 5 years PFS of PCa. More importantly, the C index was 0.707, which indicated the predicted model was reliable (*Figure 3C*).

CKS2 is associated with pro-tumor pathway

The immunosuppressive role of CKS2 facilitated immune evasion by tumor cells, allowing for continued proliferation. This study investigated the relationship between CKS2 and pro-tumor pathways, revealing a positive correlation between CKS2 expression and hypoxia signature, tumor proliferation signature, DNA repair function, G2M checkpoint, PI3k-Akt-Mtor pathway, v-myc avian myelocytomatosis viral oncogene homolog (MYC) targets, and DNA replication; conversely, a negative association was observed between CKS2 expression and the P53 pathway, transforming growth factor beta (TGFB), collagen formation, and degradation of extracellular matrixc (ECM) (*Figure 4A-4T*). This result indicated that CKS2 was a risk gene which not only suppressed the immune function but also associated with pro-tumor pathway.

High expression of CKS2 correlates with the immune cell suppression and osteoblast gene low expression

A total of 498 samples of PCa patients sourced from TCGA dataset were included in an immuno-correlation analysis. Various immune cell types, including B cells, macrophages, myeloid dendritic cells, neutrophils, $CD4^+$ T cells, and $CD8^+$ T cells, were examined. The findings indicated a negative association between CKS2 expression and immune cells, particularly $CD4^+$ and $CD8^+$ T cells, and macrophage with the Spearman score and 95% CI of −0.10 (−0.19, −0.01), −0.13 (−0.22, −0.04), −0.23 (−0.32, −0.15) respectively. Whereas, COL1A1 and COL1A2 were positive related to all detected-immune cells (*Figure 5A*,*5B*). However, no significant correlation was observed between immune cell activity and other upregulated genes. PCa cells could infiltrate bone matrix and result to bone destruction and formatting pathological new bone (7). And the under mechanism of this is an imbalance of osteoblastic bone formation and osteoclastic bone resorption (8). Herein, we want to know whether CKS2, COL1A1 and COL1A2 were also associated with osteoblast and osteoclast genes.

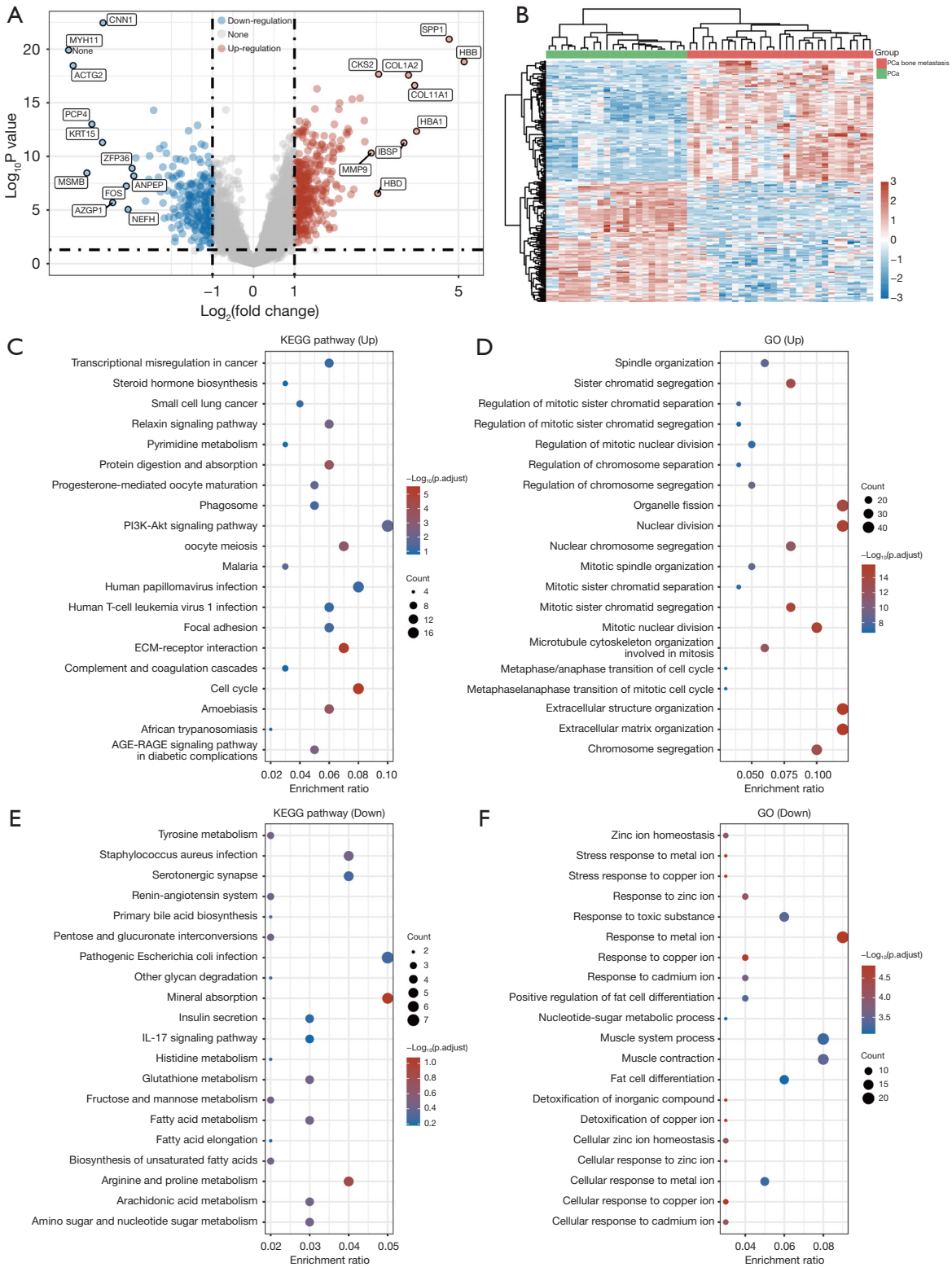

Figure 1 Different genes expression in PCa bone metastasis and PCa patients. (A,B) Volcano plot and Heatmap, different genes expression in 29 PCa bone metastasis and 22 PCa patients. (C-F) KEGG and GO function enrichment about the 20 target genes. PCa, prostate cancer; KEGG, Kyoto Encyclopedia of Genes and Genomes; ECM, extracellular matrixc; GO, Gene Ontology.

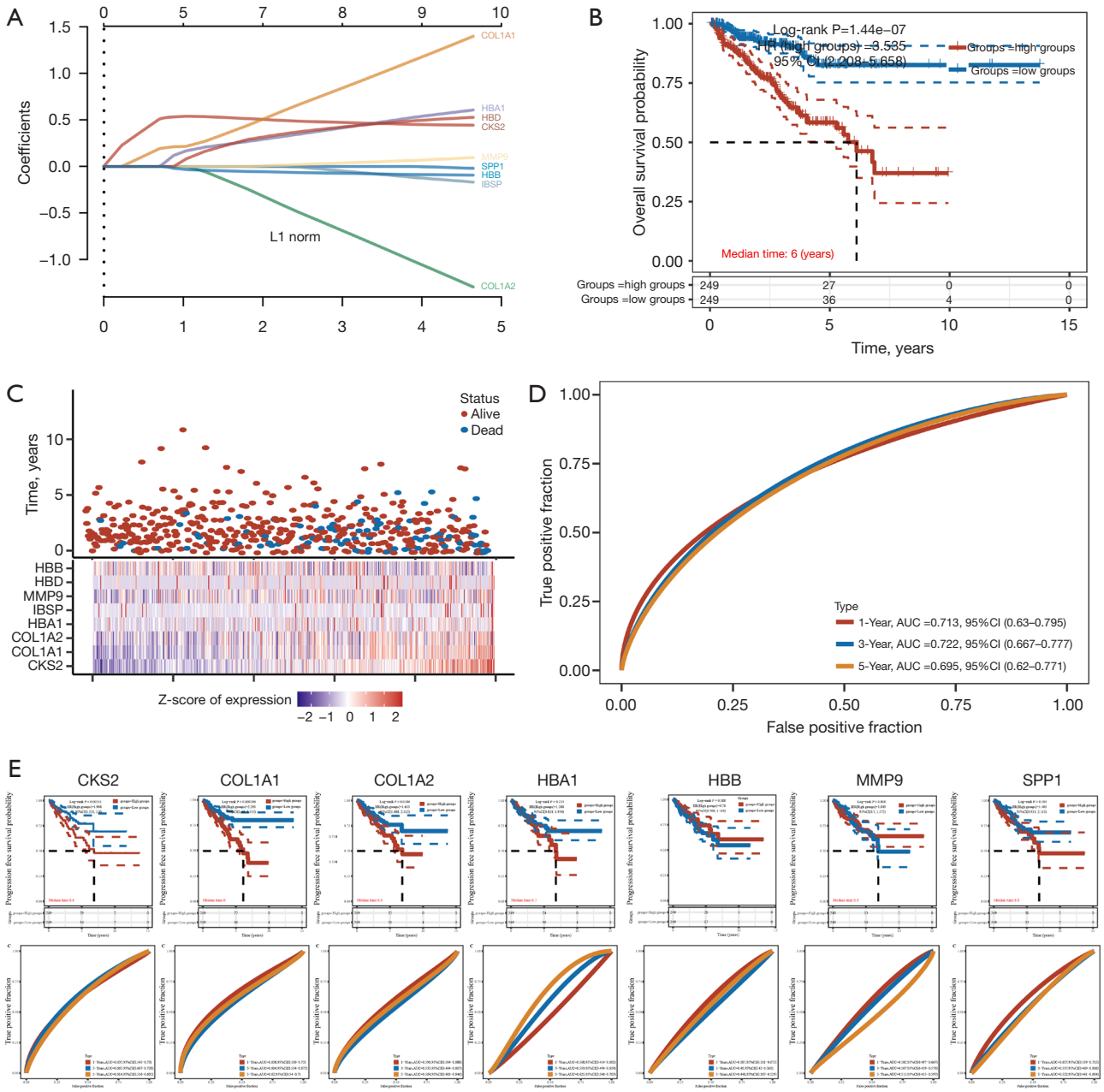

Figure 2 The target genes related to poor PFS in PCa. (A) LASSO regression about the 9 target genes. (B,C) Survival analysis about the 8 target genes. (D) ROC curve demonstrated a reliable prediction of the model. (E) The relation between PFS in prostate cancer and the expression levels of CKS2, COL1A1, COL1A2, HBA1, HBB, MMP9, and SPP. HR, hazard ratio; CI, confidence interval; AUC, area under the curve; PFS, progression-free survival; PCa, prostate cancer; LASSO, least absolute shrinkage and selection operator; ROC, receiver operating characteristic.

It was found that high expression of CKS2 may cause a low expression of osteoblast associated gene such as RUNX2, while high expression of COL1A1 and COL1A2 positively correlated with osteoclast associated genes (*Figure 5C*). Altogether, this result indicated that CKS2 may play an important suppressive role in immune cells. Moreover, CKS2, COL1A2, and COL1A2 may affect the bone metastasis micro-environment by relating to osteoblastic

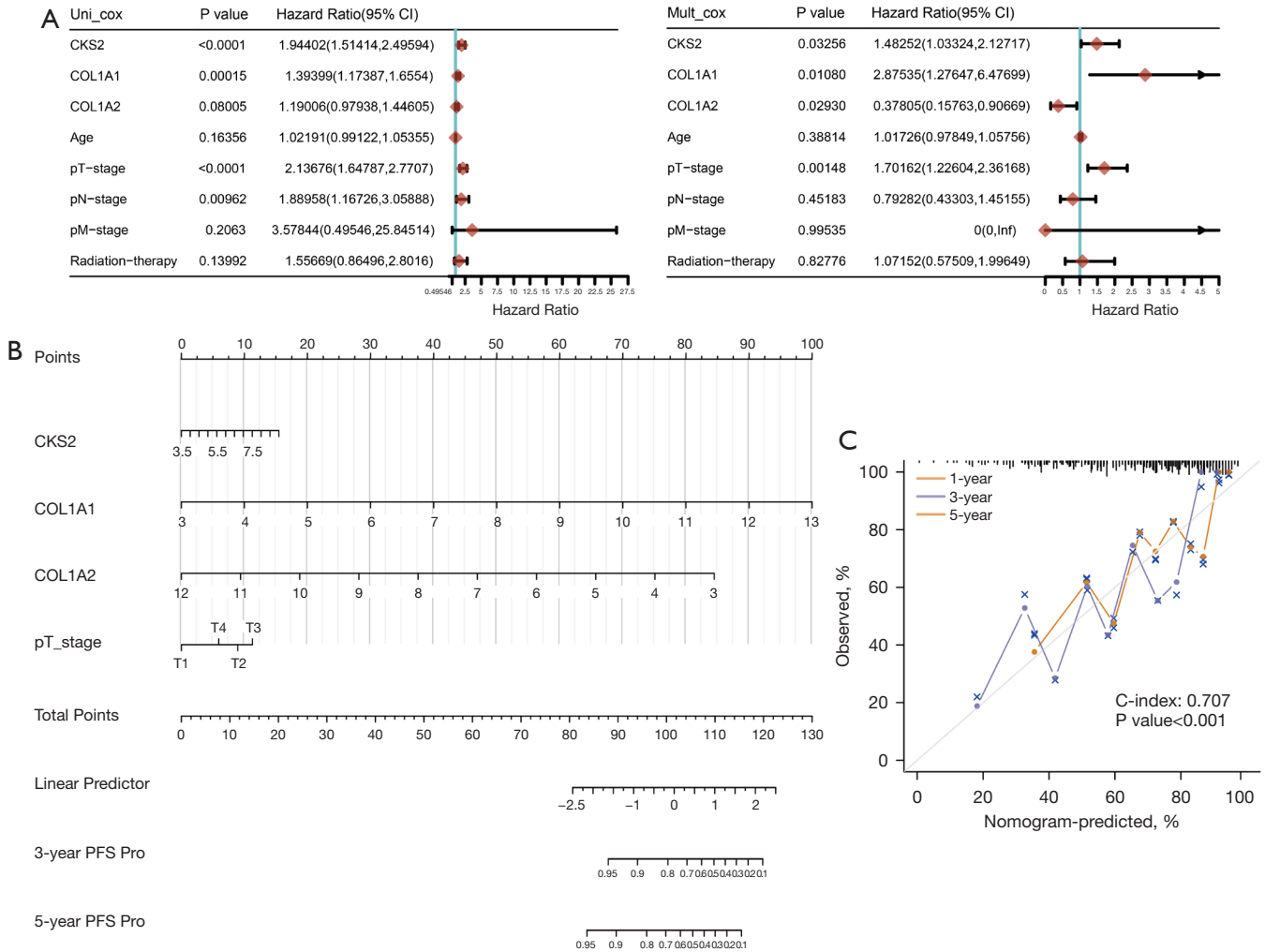

Figure 3 The predicted efficacy of gene CKS2 as well as COL1A1, COL1A2 were detected. (A) Univariate Cox analysis and multivariate Cox analysis showed that CKS2, COL1A1 as the risk factor. (B,C) Nomogram suggests that PFS of PCa could be predicted by risk gene CKS2. CI, confidence interval; inf, interferon; PFS, progression-free survival; PCa, prostate cancer.

and osteoclastic genes.

Single-cell RNA sequencing reveals that CKS2 is mainly expressed by immune cells

Single-cell RNA sequencing was utilized to determine the predominant expression of CKS2 in the TME. The 10x Genomics single-cell RNA sequencing data were obtained from the GEO database, followed by secondary manual annotation of cells, the annotation chart was shown in *Figure 6A*, in this dataset, PCa tumor immune microenvironment was divided into 6 types of cells: PCa cells, mononuclear cells, interstitial cells, neural progenitor cells, Tregs, haematopoietic stem and progenitor cells. As shown in *Figure 6B*, purple stain represented the location of CKS2 expression in those cells. Further single-cell detection found that CKS2 was mainly expressed by mononuclear cells, neural progenitor cells and Tregs (*Figure 6C*). To confirm this conclusion, HPA dataset was used to analysis the CKS2 expression in immune cells. The result demonstrated that CKS2 could be expressed by many kinks of immune cells, and it was predominantly expressed by T-cells and dendritic cells (*Figure 6D*,*6E*).

Pan-cancer analysis supports that CKS2 functions as a risk gene and is expressed in various cancer tissues

CKS2 was subsequently identified in 32 different types of

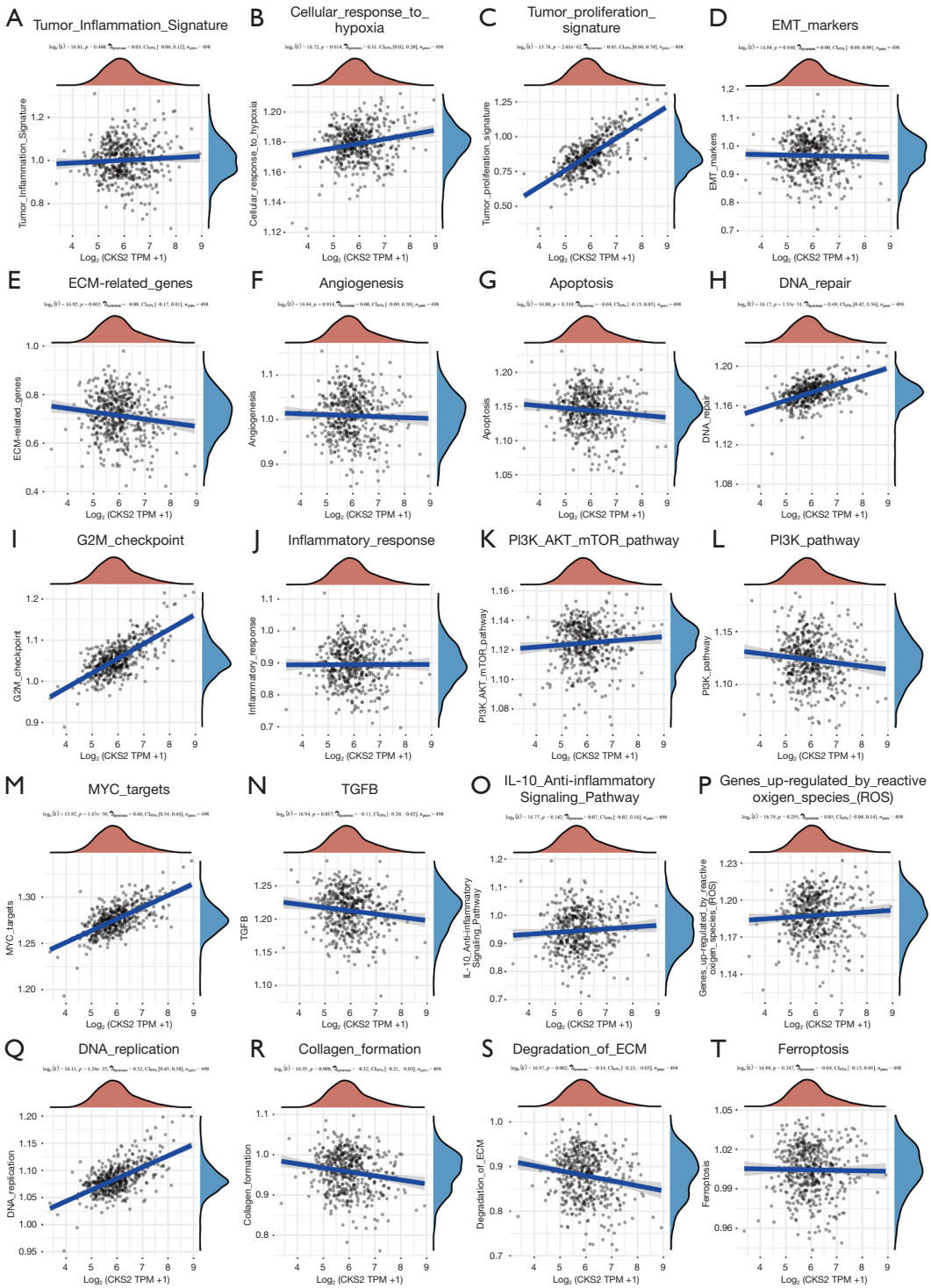

Figure 4 The relationship between the CKS2 expression and the activation of several pathway. (A-T) The correlation of the CKS2 expression and the activation of several pathway. CI, confidence interval; TPM, Trans Per Kilobase of exon model per Million mapped reads; MYC, v-myc avian myelocytomatosis viral oncogene homolog; TGFB, transforming growth factor beta; ECM, extracellular matrixc.

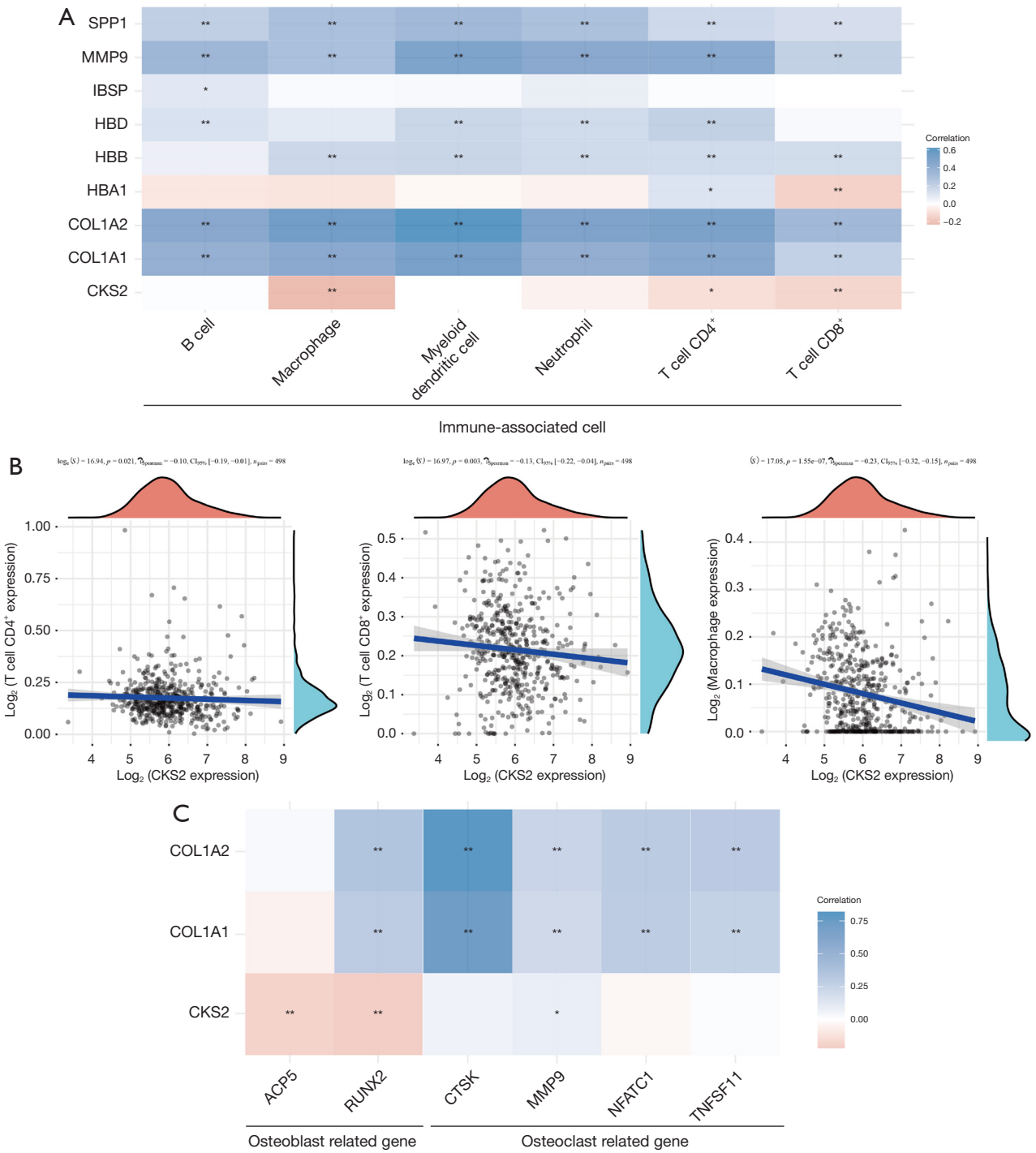

Figure 5 Immuno-correlation analysis about the relationship between upregulated-gene and TME. (A,B) The expression of CKS2 positively related to immunosuppression microenvironment. (C) The relationship between the expression of CKS2 and the expression of osteoblast and osteoclast genes in bone metastasis environment. *, P<0.05; **, P<0.01. CI, confidence interval; TME, tumor microenvironment.

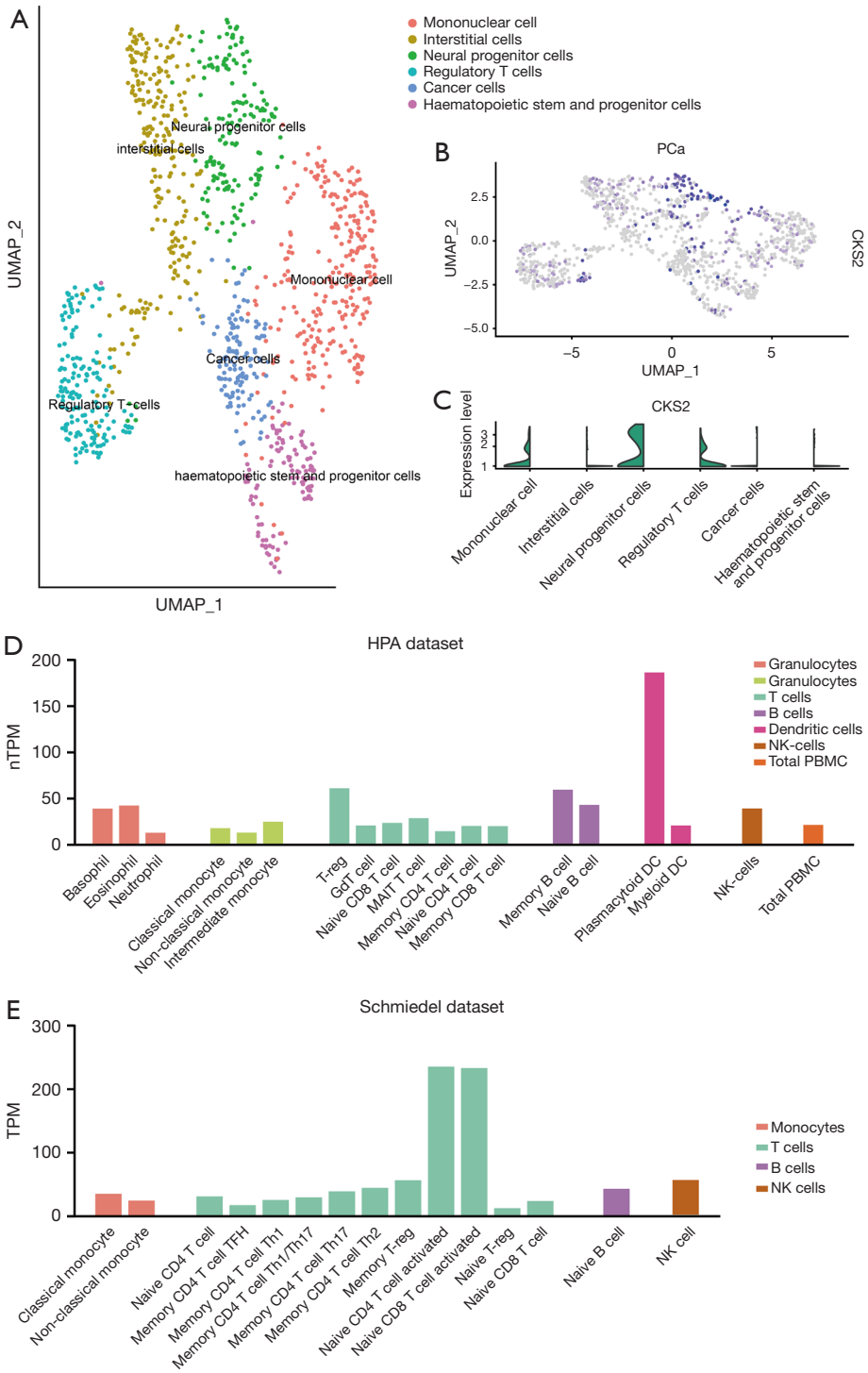

Figure 6 Single-cell RNA sequencing of the tumor immune micro-environment. (A) UMAP analysis about the data obtained from single-cell RNA sequencing in PCa tumor immune micro-environment. (B,C) The CKS2 expression in different cell type. (D) The CKS2 expression in immune cells obtained from HPA dataset. (E) CKS2 expression in immune cells obtained from Schmiedel dataset. UMAP, uniform manifold approximation and projection; PCa, prostate cancer; nTPM, Transcripts Per Kilobase of exon model per Million mapped reads; NK, natural killer; PBMC, peripheral blood mononuclear cell; Treg, regulatory T-cell; DC, dendritic cells; HPA, Human Protein Atlas; TPM, Trans Per Kilobase of exon model per Million mapped reads.

cancer tissues from the TCGA dataset. It is noteworthy that the majority of the detected cancer tissues exhibited higher expression levels of CKS2 compared to normal tissues, with the exception of pheochromocytoma and paraganglioma. Additionally, a few cancer tissues lacked corresponding normal tissue samples, thereby limiting the analysis of their results (*Figure 7A*). The expression levels of CKS2 in various cancer tissues were depicted in *Figure 7B*. The 10 types of cancer that exhibited the highest levels of CKS2 expression were adrenocortical carcinoma, stomach adenocarcinoma, pancreatic adenocarcinoma, brain lower grade glioma, breast invasive carcinoma, lymphoid neoplasm diffuse large B-cell lymphoma, prostate adenocarcinoma, lung adenocarcinoma, bladder urothelial carcinoma, and sarcoma. The pan-cancer PFS analysis demonstrated that elevated levels of CKS2 were associated with a decreased PFS in various cancer types, including adrenocortical carcinoma, kidney renal clear cell carcinoma, kidney renal papillary cell carcinoma, brain lower grade glioma, liver hepatocellular carcinoma, mesothelioma, pancreatic adenocarcinoma, and prostate adenocarcinoma. Moreover, the expression of CKS2 was found to be positively correlated with tumor mutational burden (TMB) in multiple types of cancer tissues (*Figure 7C*).

Discussion

PCa manifests the asymptomatic solid malignancy at the early stage. Once metastasis occurs, PCa becomes incurable. Immune suppressive micro-environment plays an important role in immune escape. Many studies have elucidated the underlying mechanism of immune escape. For cancer cells, it was reported that *OGN*, *JAM2*, *RERG*, *OLFML2B*, and *ADAMTS1* genes in stomach adenocarcinoma were correlated with immune cells and poor overall survival (9). Additionally, the study confirmed a correlation between the expression level of ATG5 and tumor immune infiltration and TME, particularly in breast invasive carcinoma, kidney renal clear cell carcinoma, and liver hepatocellular carcinoma (10). A separate study discovered that the upregulation of SPP1 in cancer cells was associated with decreased infiltration of $CD8^+$ T cells and M2-type macrophages (11). For immune cells, cancer-associated fibroblasts (CAFs) and TAMs contributed to the immune suppressive function by secreting cytokines, chemokines (12,13). CXCL1 could induce the native T cells to Treg which is a heterogeneous subset of immunosuppressive T cells and favor tumor progression (4,14).

The aforementioned genes have been identified as being present in cancer cells, with the immune cells' mechanism operating at a cellular interactive level. The specific targets within the immune cells' genes require further investigation. Our research revealed a significant upregulation of CKS2, COL1A1, and COL1A2 in bone metastasis of PCa. However, only CKS2 was found to be associated with poor immune function. Subsequently, single-cell RNA sequencing was utilized to determine that CKS2 was located in immune cells rather than cancer cells. The study revealed a positive correlation between elevated CKS2 expression and immunosuppressive activity. It is hypothesized that various factors such as cytokines, chemokines, or small molecules from cancer cells may influence immune cell function by increasing CKS2 levels.

The protein coding gene CKS2 has been implicated in small cell lung cancer and is linked to cyclin-dependent protein serine/threonine kinase regulator activity, as evidenced by GO annotations. A study has examined the involvement of CKS2 in different cancer types, revealing its association with poor prognosis and reduced immune cell infiltration in lung adenocarcinoma (15). CKS2 also promotes epithelial ovarian and breast cancer progression and metastasis (16,17). In our research, it was observed that CKS2 was not only linked to a decreased PFS in PCa, but also that immune cells prominently express CKS2. Additionally, while COL1A1 and COL1A2 were found to have a significant impact on PFS, the positive correlation between these genes and immune cells suggests that they may play a role in promoting immune function rather than suppressing it.

There is a paucity of information regarding the mechanisms that contribute to the predilection of PCa for bone metastasis. Our hypothesis suggests that immune cells may migrate to the bone before cancer cells, where they create a pre-metastatic niche in response to signals from primary cancer cells, known as the pre-metastatic bone niche (PMBN) (6). In this particular TME, immune cells, including macrophages, T cells, and monocytes, undergo phenotypic changes to become protumor cells such as TAMs, Tregs, and MDSCs, with the purpose of promoting the adhesion of primary cancer cells to bone. It is worth noting that PCa is classified as osteolytic, osteosclerotic, or mixed lesions (18). Therefore, it is imperative to investigate the interplay between immune cells and bone cells, specifically osteoblasts and osteoclasts, within the TME of PCa bone metastases.

Our research findings, derived from an analysis of

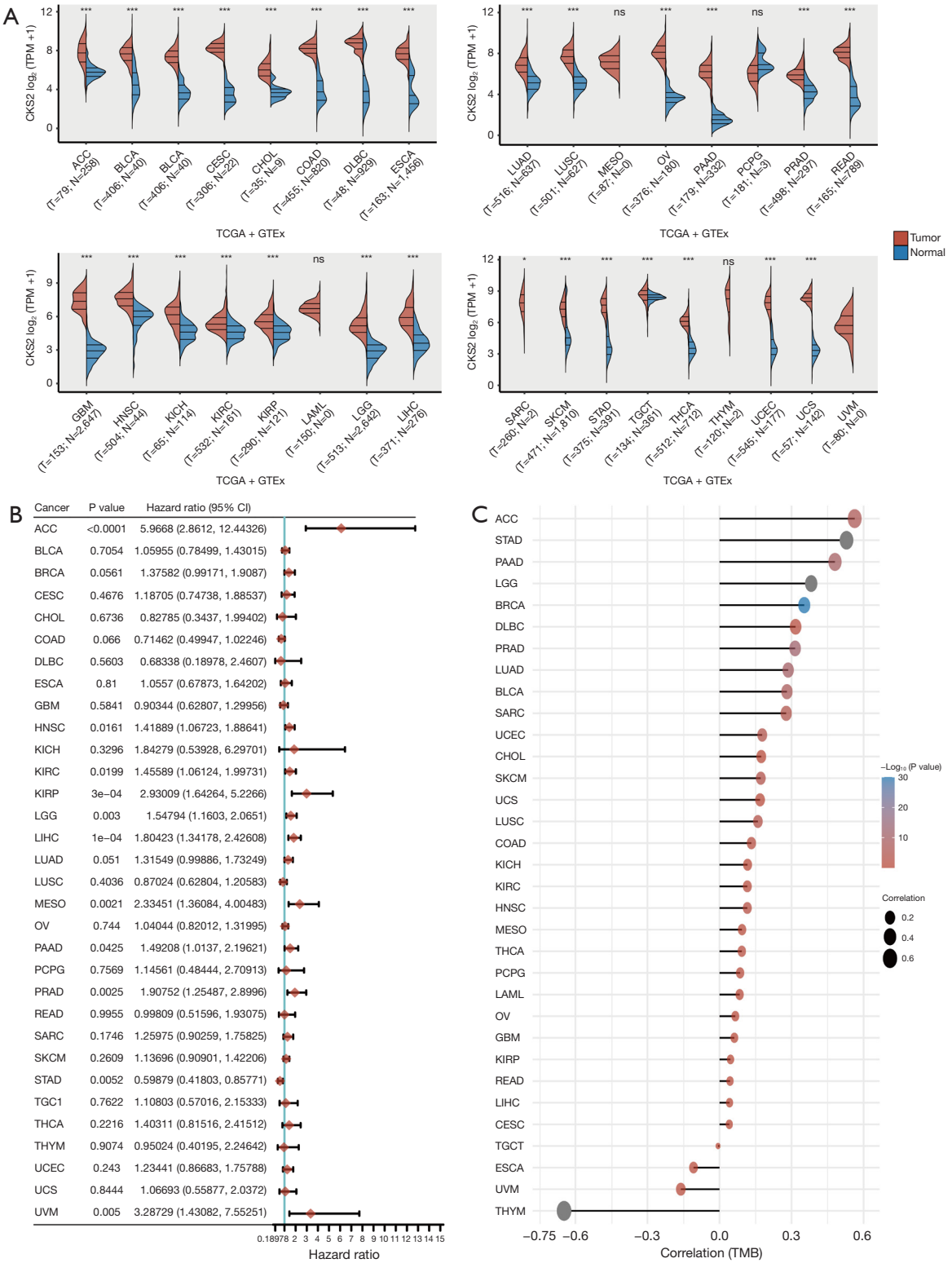

Figure 7 Pan-cancer analysis about the CKS2 expression and the clinical characteristics of many kinds of cancer tissue. (A,B) Pan-cancer analysis about the different expression of CKS2 between tumor tissue and normal tissue. (B) Pan-cancer PFS between the CKS2 expression and many kinds of cancer. (C) The correlation between CKS2 expression with TMB in multiple types of cancer tissues. *, P<0.05; ***,

P<0.001; ns, not significant or uncountable. TPM, Trans Per Kilobase of exon model per Million mapped reads; ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; DLBC, lymphoid neoplasm diffuse large B-cell lymphoma; ESCA, esophageal carcinoma; TCGA, The Cancer Genome Atlas; GTEx, Genotype-Tissue Expression; GBM, glioblastoma multiforme; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LGG, brain lower grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; TGCT, testicular germ cell tumors; THCA, thyroid carcinoma; THYM, thymoma; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma; UVM, uveal melanoma; CI, confidence interval; TMB, tumor mutational burden; PFS, progression-free survival.

data sourced from the public GEO database, demonstrate a significant relationship between heightened CKS2 expression in PCa patients with bone metastases and the establishment of an immunosuppressive microenvironment within the bone. Furthermore, a negative association was identified between CKS2 expression and the expression levels of osteogenic genes. There is increasing evidence suggesting that the formation of immunosuppressive microenvironment is the key point for the formation of PCa PMBN (6), and the immunosuppressive microenvironment mainly promotes osteoclastic bone metastasis of PCa (19,20). Therefore, our study provides a direct target for the targeted regulation of immunosuppressive cells.

Conclusions

CKS2 shows potential as a target for enhancing the immunosuppressive microenvironment through the regulation of immunosuppressive cells, thereby impeding the bone metastasis of PCa.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2100/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2100/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2100/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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