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Research article

Pan-cancer analyses of Jab1/COPS5 reveal oncogenic role and clinical outcome in human cancer

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ABSTRACT

Jab1/COPS5 is associated with the progression of some cancers, however, its role in most cancers is still unclear.This study systematically explored the action and clinical application value of Jab1/COPS5 in different tumors based on large clinical data. We first identified by differential and survival analysis that Jab1/COPS5 was highly expressed as a high-risk gene in most cancers and was closely related to prognostic survival of patients based on the TCGA, GEO and CPTAC databases. Mutation analysis suggested that missense mutations were the main mutation type of Jab1. TMB and MSI were positively correlated with Jab1/COPS5 in most tumors, and patients with Jab1/COPS5 mutations had a poorer prognosis in prostate adenocarcinoma. By immune infiltration analysis, Jab1/COPS5 expression was positively correlated with the infiltration of CD8+ T cells in thymoma and uveal melanoma, and Jab1/COPS5 expression in testicular germ cell tumors was negatively correlated with the infiltration of cancer-associated fibroblasts. Correlation and enrichment analysis suggested that ARMC1, TCEB1 and UBE2V2 were positively correlated with Jab1/COPS5 expression and involved in multiple biological effects. In summary, this study systematically investigated the role of Jab1/COPS5 in different tumors, providing a theoretical basis for Jab1/COPS5 as a new biomarker in unresearched cancers and paving the way for targeted therapy and drug development.

1. Introduction

The total number of cancer cases in children worldwide is estimated to be 360,114 in 2015 according to the baseline model [1]. There were about 89,500 new cancer cases and 9,270 new cancer deaths among adolescents and young people in the United States by 2020 [2]. Cancer is a heavy burden for countries of all income levels and metastasis significantly reduces patient survival [3, 4, 5]. Hence, exploring new target sites plays a significant role in the early diagnosis and personalized treatment of cancer patients. Characterizing and identifying novel pan-cancer genes is essential for a better understanding of the extremely complex tumorigenesis process. In order to understand the role of Jab1/COPS5 in cancers, public cancer genomics databases, such as TCGA and GEO, provide a wealth of cancer-related functional genome data sets from various cancers [6, 7].

COP9 signalosome subunit 5 (COPS5) is known as C-Jun activation domain-binding protein-1 (Jab1) [8], which is also the 5th subunit of the constitutively photomorphogenic 9 signalosome complex (CSN) and is therefore also referred to CSN5. COPS5, located in chromosome 8Q13.2, encodes a soluble nuclear protein with a molecular weight of 38 kDa, which is a multifunctional protein involved in many biological effects, such as cell proliferation, signal transduction, apoptosis, cell cycle regulation and DNA damage repair [9, 10, 11]. Researches have reported that Jab1/COPS5 is associated with the pathogenesis of multiple cancers, such as prostate cancer, biliary tract cancer and breast cancer [12, 13, 14, 15].

However, it is unclear whether the prognostic value and expression of Jab1/COPS5 are the same in different tumors, whether the role of Jab1/COPS5 is consistent, and whether it can be used as a biomarker in all tumors for clinical applications. Our study systematically explored the role and clinical significance of Jab1/COPS5 in pan-cancer based on TCGA, GEO and CPTAC databases by multiple analysis, such as differential expression, survival and correlation analysis, immune infiltration, gene mutation and functional enrichment analysis, which may provide a

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theoretical basis for Jab1/COPS5 as a new diagnostic and therapeutic target in unstudied cancers.

2. Methods

2.1. Differential expression analysis

GEPIA2 allows for genetic differences, survival, correlation, clinical parameters analysis, etc [16]. At the genetic level, we investigated the differential expression of Jab1/COPS5 by R (v4.0.3) and GEPIA2 (http://gepia2.cancer-pku.cn/#degenes) in various tumor and normal samples. The ggpubr package was used to obtain box plot, which illustrate differential expression of Jab1/COPS5 between normal and tumor samples in TCGA database with the wilcoxon test. Since some tumors did not have normal samples for comparison in TCGA database, the differential expression results of Jab1/COPS5 in these tumors were obtained by GEPIA2 website under |Log2FC| Cutoff = 1, p-value Cutoff = 0.01, and log2 (TPM +1) for log-scale in matching TCGA normal and Genotype-Tissue Expression (GTEx) data.

UALCAN (http://ualcan.path.uab.edu/analysis-prot.html) can be used for gene, protein, methylation and phosphorylation differences, etc [17]. At the protein level, we obtained total protein differential data of Jab1/COPS5 between tumor and normal tissues in the CPTAC database. To explore the relationship between Jab1/COPS5 and pan-cancer clinical parameters, limma and ggpubr packages were used to obtain differential expression data for age, presented in box plot. We also obtained the differential expression of Jab1/COPS5 for clinical stage by GEPIA2 website in TCGA database.

2.2. Survival analysis

Cancer patients were divided into high and low groups based on the median value of expression of Jab1/COPS5. We submitted Jab1/COPS5 to the "Survival Map" in GEPIA2 website to acquire the heatmap of OS and DFS in TCGA database with the long-rank test and $P < 0.05$. We use "Survival Analysis" to obtain survival curves of OS and DFS in TCGA database. Survival and forestplot packages were used to acquire forest plots including DSS, OS, PFI and DFI with cox analysis, the survminer package for Kaplan–Meier survival curves including DSS, OS, PFI and DFI under the long-rank test and $P < 0.05$.

2.3. Genetic alteration analysis

cBioPortal can be used for mutation analysis [18]. We submitted Jab1/COPS5 to the "Quick Search" at cBioPortal (https://www.cbioportal.org/) website to obtain the mutation type, frequency, copy number alteration (CNA) and structural variant in "Cancer Types Summary". The mutation site information and 3D structure of the Jab1/COPS5 protein were obtained through the "Mutations" model. We selected "Prostate Adenocarcinoma (TCGA, PanCancer Atlas)" and "Compassion/Survival" modes to obtain OS, DSS, DFS and PFS curves with altered and unaltered Jab1/COPS5 under the log-rank test. We then used the fmsb package for radar plots to probe the correlation of Jab1/COPS5 expression with TMB and MSI at the TCGA database, obtaining the differential promoter methylation level of Jab1/COPS5 between normal and tumor in the TCGA database at the UALCAN website.

2.4. Immune infiltration analysis

It has been reported that TIMER2 (http://timer.cistrome.org/) can be used for immune infiltration analysis [19]. We submitted Jab1/COPS5 to "Immune" and selected CD8+ T-cells or cancer-associated fibroblasts at TIMER2 website, using XCELL, TIDE, EPIC, TIMER, CIBERSORT-ABS, CIBERSORT, MCPCOUNTER and QUANTISEQ algorithms to probe the relationship between immune inflammatory cells and Jab1/COPS5 expression in the TCGA database, and presented it as a scatter plot and heatmap. Spearman's rank correlation analysis yielded P-values and partial correlation values.

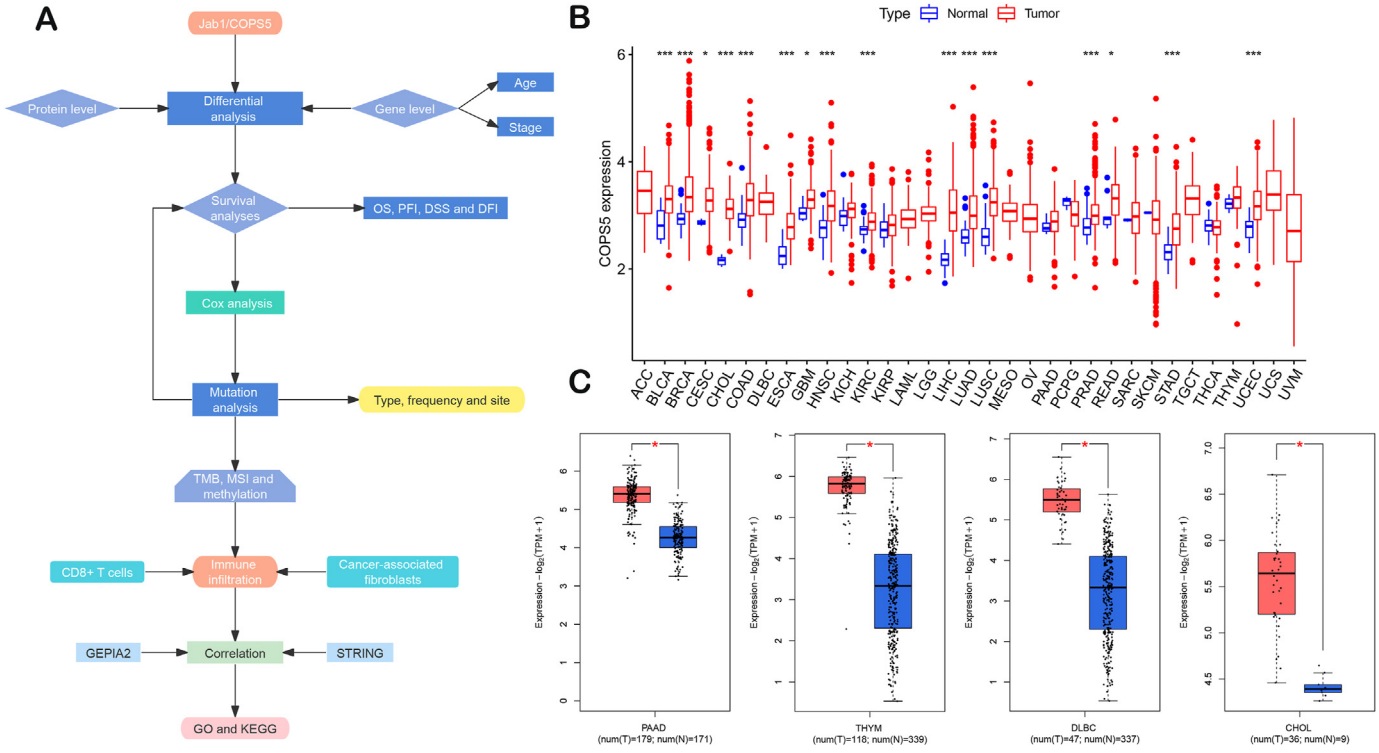

Figure 1. Differences of Jab1/COPS5 in various human tumors at gene levels. (A) Flow chart of this study.(B) Differential expression analysis by R software with wilcoxon test in TCGA database. (C) Differential expression analysis by GEPIA2 website under |Log2FC| Cutoff = 1, p-value Cutoff = 0.01, and log2 (TPM +1) for log-scale in matching TCGA normal and Genotype-Tissue Expression (GTEx) data.

2.5. Enrichment analysis of COPS5-related genes

We entered the "Similar Gene Detection" module to acquire the top 100 COPS5-related genes at the GEPIA2 website in the TCGA database, and explored the correlation between the screened genes and Jab1/COPS5 through the "correlation analysis" module with pearson correlation coefficients. The screened genes were then plotted in a heatmap using the "Gene_Corr" module at the TIMER2 website.

The STRING database can be used to explore protein interactions [20]. Further, we submitted Jab1/COPS5 to the STRING (https://strin

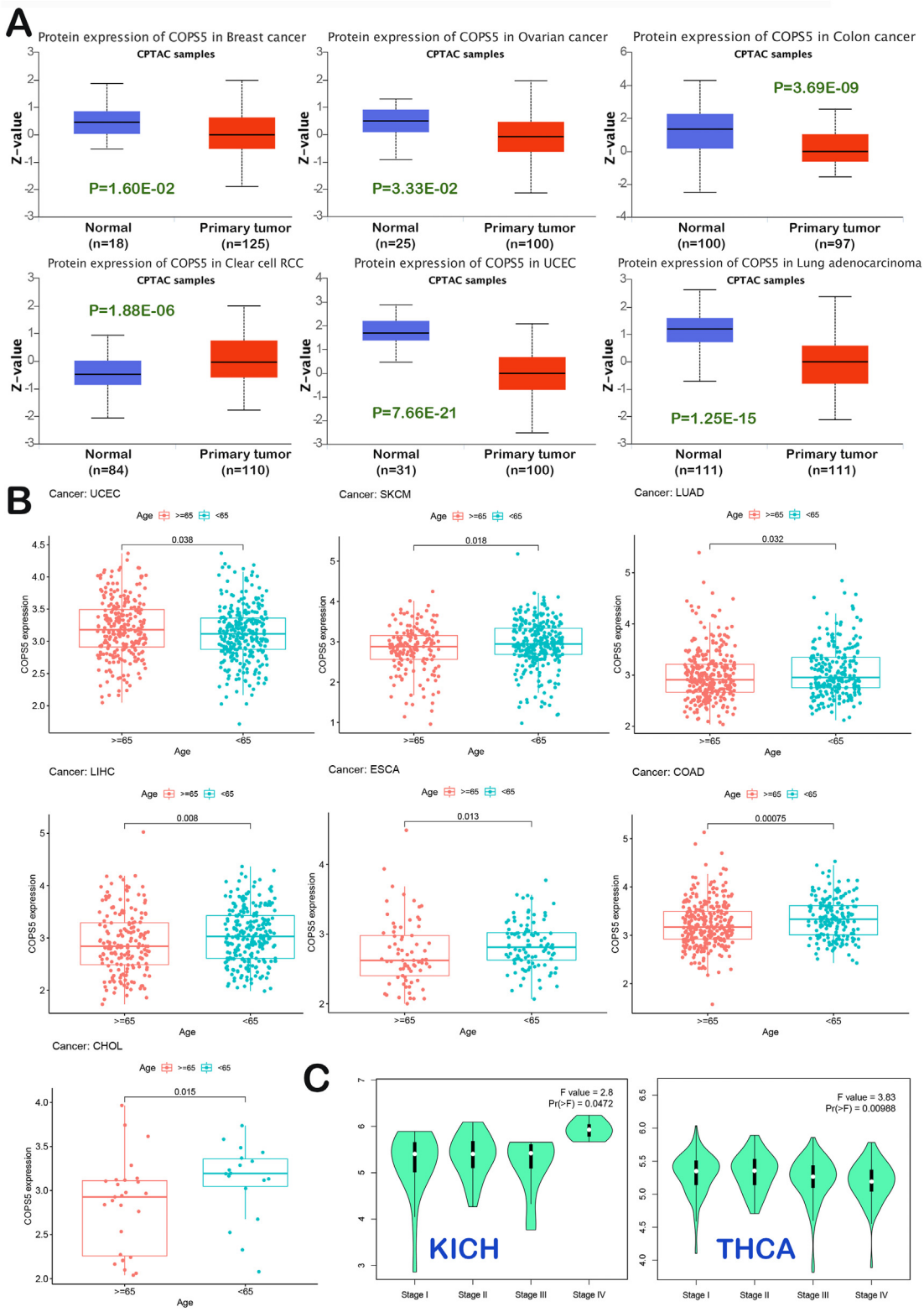

Figure 2. Differences of Jab1/COPS5 in various human tumors based on protein levels and clinical parameters. (A) At the protein level, differential expression analysis by UALCAN website in CPTAC database. (B) Relationship between Jab1/COPS5 expression and age by R software. (C) Relationship between Jab1/COPS5 expression and clinical stage by GEPIA2 website in TCGA database.

g-db.org/) website to obtain the PPI network with Homo sapiens, settings: Meaning of network edges (evidence), network type (full network), max number of interactors (within 50 interactors), active interaction sources (Experiments) and minimum required interaction score (low).We intersected the Jab1/COPS5-related genes screened in GEPIA2 and STRING to draw a venn diagram via the DRAW VENN DIAGRAM (http://bioinformatics.psb.ugent.be/webtools/Venn/) website. DAVID database can be used for functional enrichment analysis [21]. We combined the COPS5-related gene data screened in GEPIA2 and STRING to perform GO and KEGG enrichment analysis at the DAVID website (https://david.ncifcrf.gov/home.jsp) with "OFFICIAL_GENE_SYMBOL", "Homo sapiens" and "functional annotation chart", visualized by the ggplot2 R package with FDR <0.05.

3. Results

3.1. Jab1/COPS5 differs in various human tumors

The flow chart of this study was shown in Figure 1A. We analyzed TCGA data by R and found that Jab1/COPS5 was significantly differentially expressed in various tumors compared with normal samples, including BRCA, CHOL, BLCA, ESCA, KIRC, HNSC, LIHC, LUSC, PRAD, STAD, LUAD, COAD and UCEC (Figure 1B). Since some tumors in the TCGA database did not have normal samples as controls for differential analysis, the GEPIA2 website was used to obtain the differential expression results of Jab1/COPS5 in these tumors and normal samples, and the expression of Jab1/COPS5 was significantly different in PAAD,

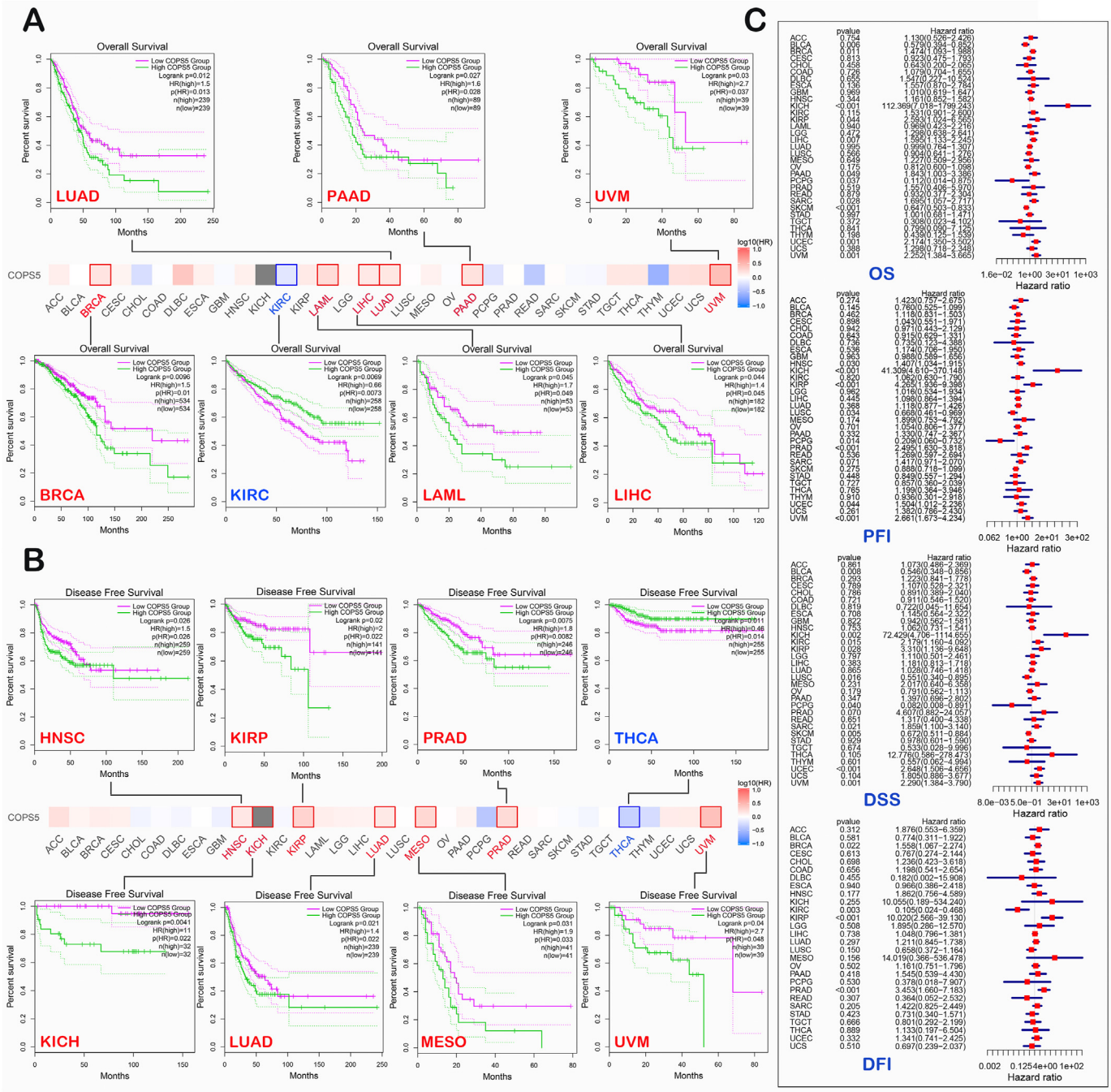

Figure 3. Association between Jab1/COPS5 and survival of patients with various tumors. OS (A) and DFS (B) analysis by GEPIA2 website with the long-rank test and $P < 0.05$. (C) Forest plots including DSS, OS, PFI and DFI by R software with cox analysis.

THYM, DLBC and CHOL under |Log2FC| Cutoff = 1, p-value Cutoff = 0.01, and log2 (TPM +1) for log-scale in matching TCGA normal and GTEx data (Figure 1C). Moreover, we obtained the total protein differential data of Jab1/COPS5 by UALCAN website between tumor and normal tissues in CPTAC database. The protein content of Jab1/COPS5 in breast cancer, colon cancer, UCEC, ovarian cancer and lung adenocarcinoma was lower than that in normal samples, while that in clear cell RCC was opposite (Figure 2A). Besides, Jab1/COPS5 expression was significantly higher in LIHC and COAD ($P < 0.01$) at age<65 in TCGA database by limma and ggpubr R package (Figure 2B). And we also discovered by GEPIA2 website that the clinical stage of KICH and THCA was associated with Jab1/COPS5 in TCGA database (Figure 2C).

3.2. Jab1/COPS5 is associated with survival of patients with various cancers

This study investigated the relationship between Jab1/COPS5 and prognosis of cancer patients. Results showed that KIRC patients with low level of Jab1/COPS5 expression were correlated with poor OS, while high level of Jab1/COPS5 expression was correlated with poor OS in patients of LUAD, BRCA, PAAD, UVM, LAML and LIHC (Figure 3A). Moreover, low expression of Jab1/COPS5 was correlated with poor DFS in THCA patients, while high expression of Jab1/COPS5 was correlated with poor DFS in patients of HNSC, KIRP, PRAD, KICH, LUAD, MESO and UVM (Figure 3B).

Subsequently, cox analysis showed that Jab1/COPS5 was a high risk gene for KICH and a low risk gene for SKCM in OS, and Jab1/COPS5 was also a high risk gene for KICH, KIRP, PRAD and UVM in PFI, a high risk gene for UCEC in DSS, and a high-risk gene for KIRP and PRAD in DFI in TCGA database with survival and forestplot R package (Figure 3C). We performed Kaplan-Meier survival analysis to further validate the association between Jab1/COPS5 and DSS, OS, PFI and DFI in pan-cancer patients under the long-rank test with survival and survminer R packages in TCGA database. Higher Jab1/COPS5 expression correlated with poorer DSS, OS, PFI and DFI in most cancers. While opposite effects were observed in DSS and OS of SKCM, OS of THYM, PFI of LUSC and DFI of KIRC, patients with lower Jab1/COPS5 expression correlated with poorer survival (Fig.4A-D).

3.3. Correlation between Jab1/COPS5 mutation and tumor progression

We used the cBioPortal website to obtain the mutation type, frequency, CAN and structural variant of Jab1/COPS5 in tumors. As shown in Figure 5A, alteration frequency of uterine carcinosarcoma was the

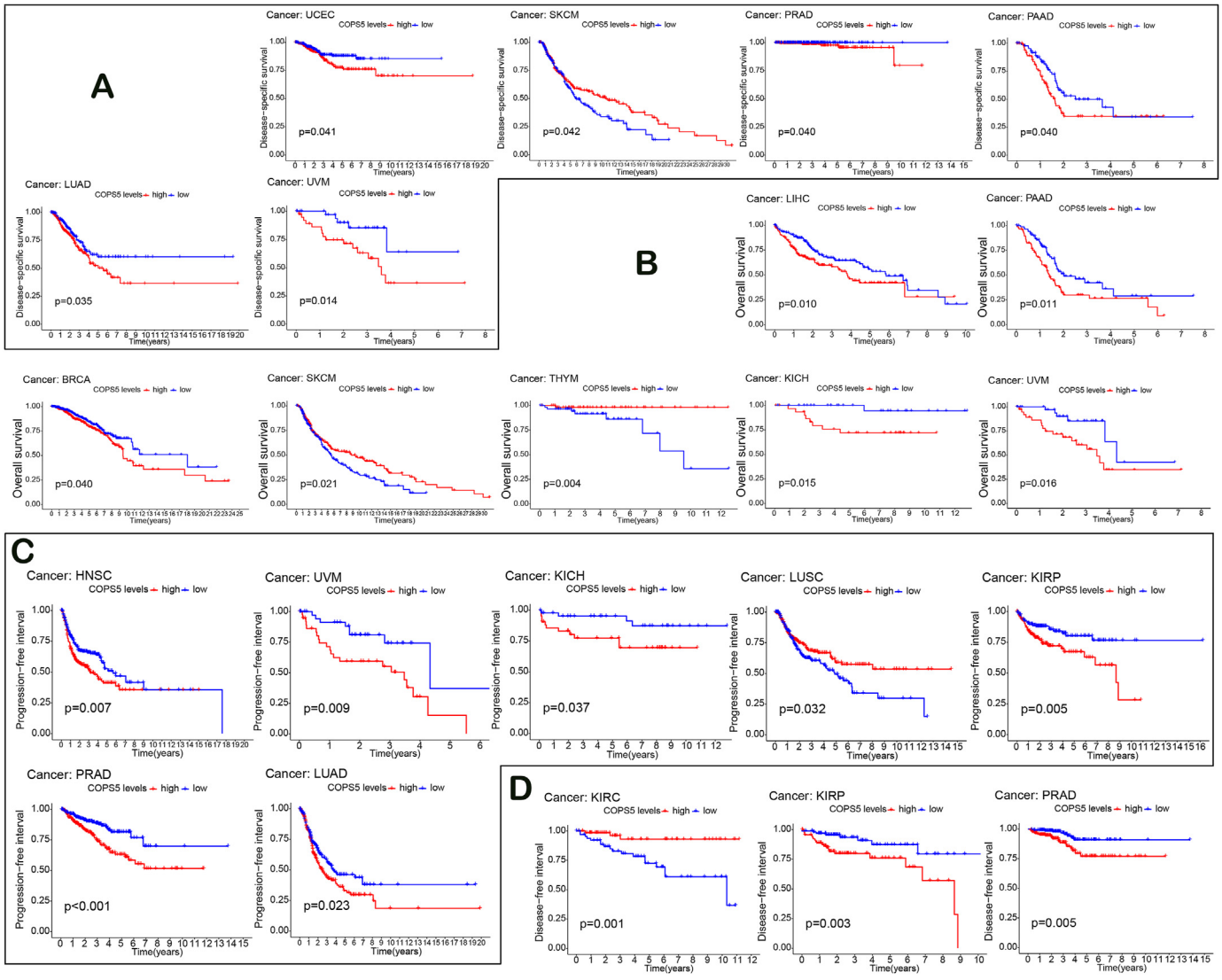

Figure 4. Kaplan–Meier survival analysis of Jab1/COPS5 under the long-rank test and $P < 0.05$ in TCGA database. DSS analysis (A), OS analysis (B), PFI analysis (C), and DFI analysis (D) of Jab1/COPS5 gene in various cancers. Red and blue indicates high and low Jab1/COPS5 expression group, respectively.

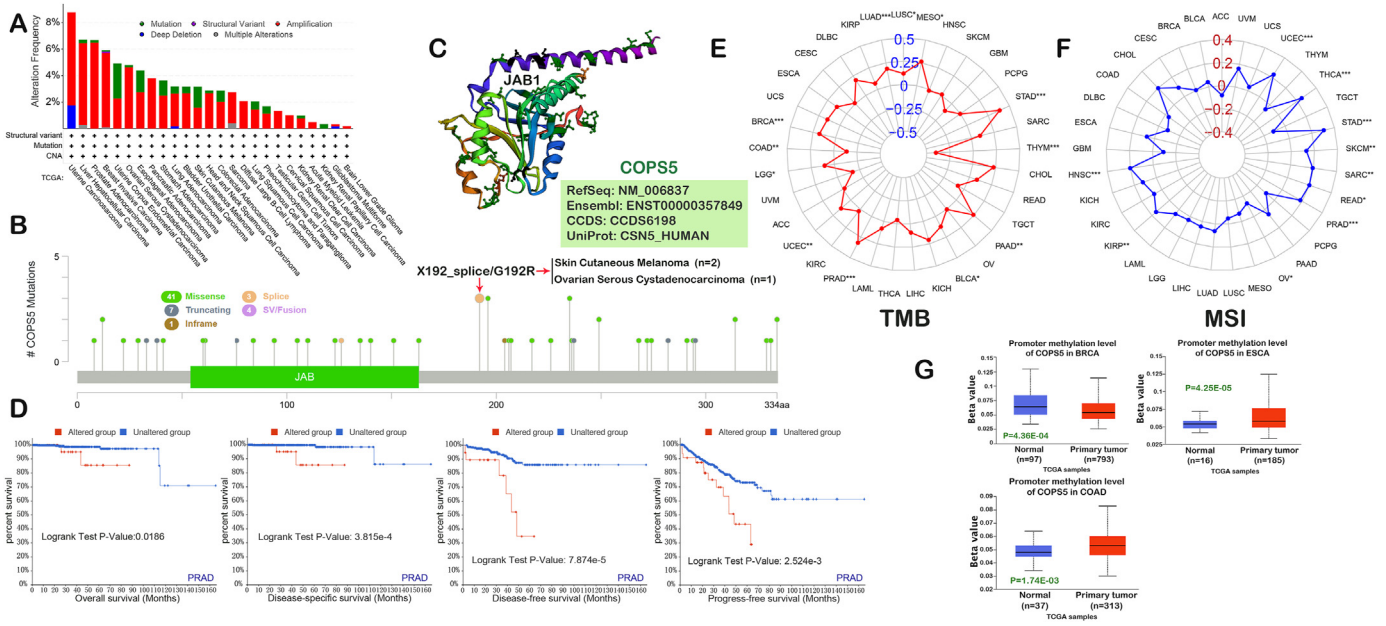

Figure 5. Jab1/COPS5 mutations related to tumor progression. (A) Mutation frequency and type at cBioPortal website. (B) Mutation sites at cBioPortal website. (C) The 3D structure at cBioPortal website. (D) Survival analysis of Jab1/COPS5 mutations in PRAD at cBioPortal website. (E) Correlation of Jab1/COPS5 with TMB by R software in pan-cancer. (F) Correlation of Jab1/COPS5 with MSI by R software in pan-cancer. (G) Promoter methylation level of Jab1/COPS5 in BRCA, ESCA and COAD at the UALCAN website.

highest among all TCGA tumors (8.77%), with amplification being the dominant frequency (7.02%). According to the mutation sites and types, results showed that the missense mutation of Jab1/COPS5 was the main mutation type. The X192_splice/G192R alteration is located at 192 site of the Jab1/COPS5 protein, which has been found in ovarian serous cystadenocarcinoma (n = 1) and skin cutaneous melanoma (n = 2) (Figure 5B). We can observe the 3D structure of Jab1/COPS5 protein in Figure 5C. Subsequently, we probed the relationship between Jab1/COPS5 mutations and survival prognosis. As shown in Figure 5D, PRAD patients with altered Jab1/COPS5 showed poor prognosis in OS, DSS, DFS and PFS. Besides, the relationship between Jab1/COPS5 expression and TMB and MSI in the TCGA database was explored, and results suggested that Jab1/COPS5 was positively correlated with TMB of BLCA, LUAD, MESO, LUSC, LGG, UCEC, PAAD, BRCA, PRAD and STAD and negatively correlated with TMB of THYM and COAD (Figure 5E). Moreover, Jab1/COPS5 was positively correlated with MSI in HNSC, KIRP, PRAD, READ, SARC, SKCM, STAD, THCA and UCEC and negatively correlated with MSI in OV (Figure 5F). In addition, we also explored the differences in the promoter methylation level of Jab1/COPS5 between normal tissue and tumor in TCGA cases. As shown in Figure 5G, the

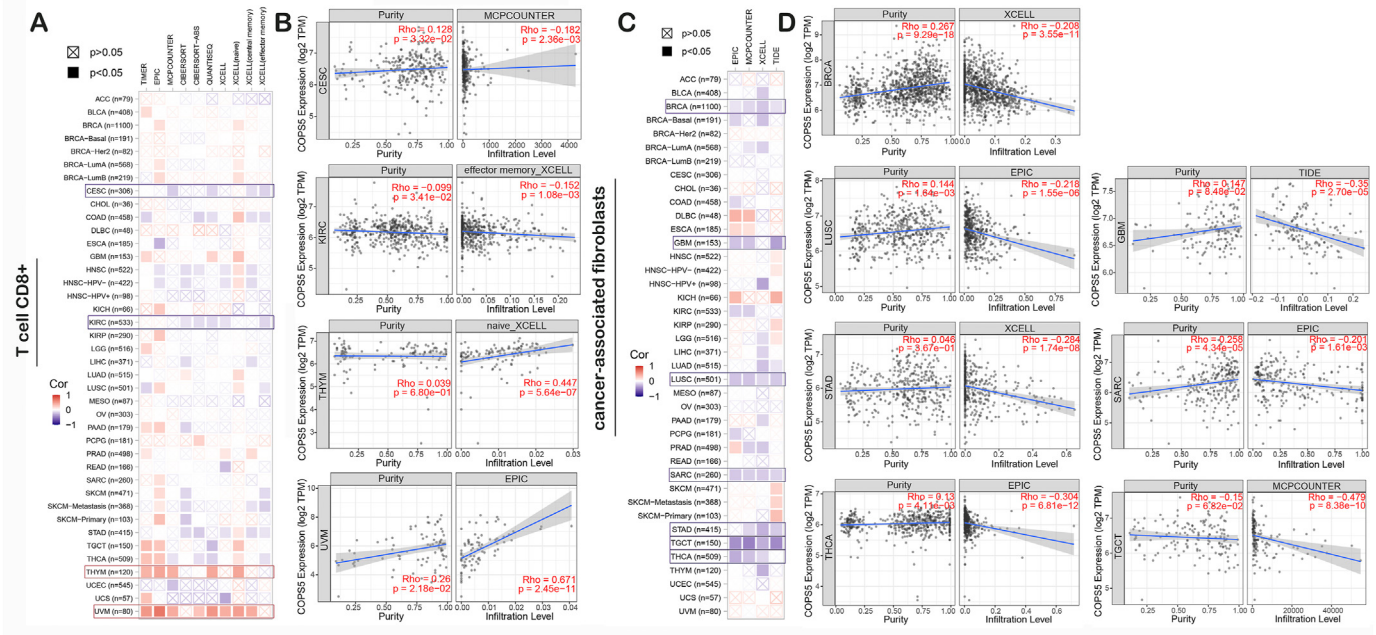

Figure 6. Correlations between Jab1/COPS5 and immune infiltration. (A) Heatmap of Jab1/COPS5 and CD8+ T-cells in pan-cancer. (B) A scatter plot of Jab1/COPS5 and CD8+ T-cells in pan-cancer. (C) Heatmap of Jab1/COPS5 and cancer-associated fibroblasts in pan-cancer. (D) A scatter plot of Jab1/COPS5 and cancer-associated fibroblasts in pan-cancer.

methylation level of Jab1/COPS5 promoter in normal tissue is higher than that in BRCA, while lower than that in ESCA and COAD.

3.4. Correlation between Jab1/COPS5 expression and immune infiltration

We explored the relationship between immune infiltrating cells and Jab1/COPS5 expression of tumor in the TCGA database through XCELL, TIDE, EPIC, TIMER, CIBERSORT-ABS, CIBERSORT, MCPCOUNTER and QUANTISEQ algorithms at TIMER2 website. We discovered that Jab1/COPS5 was negatively correlated with infiltrating CD8+ T-cells in KIRC and CESC based on partial algorithm, while Jab1/COPS5 was positive correlated with infiltrating CD8+ T-cells in THYM and UVM on the basis of most algorithms (Fig. 6A,B). Moreover, we found that infiltrating cancer-associated fibroblasts was negatively correlated with Jab1/COPS5 in BRCA, TGCT, GBM, THCA, LUSC, STAD and SARC according to all or most algorithms(Fig. 6C,D).

3.5. Jab1/COPS5 and related genes involved in biological processes

To further explore the molecular mechanism of Jab1/COPS5 in tumor progression, our study screened the top 100 genes associated with Jab1/COPS5 in all TCGA tumors by GEPIA2 website and found that Jab1/COPS5 was positively correlated with ARMC1, TCEB1, UBE2V2, DCAF13, UBR5 and ENY2 by pearson and spearman's rank correlation test (Fig. 7A,B). To investigate the interaction of Jab1/COPS5 protein, we obtained the PPI network through the STRING website and then intersected the Jab1/COPS5-related genes screened in GEPIA2 and STRING to obtain RNF139, EIF3H and DENR (Fig. 7C,D). The Jab1/COPS5-related genes screened in GEPIA2 and STRING were subjected to GO and KEGG enrichment analysis, and KEGG results showed that Jab1/COPS5-related genes were enriched in ubiquitin mediated proteolysis and cell cycle (Figure 7E). GO enrichment results indicated that Jab1/COPS5-related genes are mainly located in nucleoplasm, COP9 signalosome and cullin-RING ubiquitin ligase complex, which had the function of protein and ubiquitin protein ligase binding, and ubiquitin protein ligase activity and were involved in biological processes such as DNA damage recognition, nucleotide-excision repair and cullin deneddylation (Figure 7F).

4. Discussion

Previous studies have suggested that Jab1/COPS5 protein plays an essential role in a number of fundamental biological processes in human cancers. The expression of Jab1/COPS5 is significantly elevated in various cancers, such as epithelial ovarian tumors [22, 23], hepatocellular carcinoma [24, 25], non-small cell lung cancer [26], pancreatic adenocarcinoma [27], esophageal squamous cell carcinoma and breast cancer [28, 29]. More and more studies pay attention to the analysis of the function of Jab1/COPS5 in cancer. For example, inhibition of Jab1/COPS5 promotes the increase of p27 level and thus suppresses the proliferation of cancer cells, such as serous ovarian cancer and nasopharyngeal carcinoma cells [30, 31]. Jab1/COPS5 and LASP1 synergistically activate the PI3K/Akt pathway and contribute to 14-3-3σ ubiquitination and degradation, thereby promoting the development of colorectal cancer [32]. Jab1/-COPS5 and Rad51 were associated with drug resistance in breast cancer, and knockdown of Jab1/COPS5 and impeded the progression of breast cancer [33]. Jab1/COPS5 activates the PI3K/Akt signaling pathway in osteosarcoma cells by decreasing the level of EGFR ubiquitination [34]. Silencing Jab1/COPS5 can inhibit metastasis of hepatocellular carcinoma in nude mice by inhibiting HK2 protein expression and glycolysis [35]. Moreover, Jab1/COPS5 regulates cellular metabolism and repairs DNA damage to protect the genomic stability of embryonic stem cells [36]. Jab1/COPS5 mediates p53 degradation, while Asrij/OCIAD1 inhibits this process and suppresses the proliferative capacity of murine hematopoietic stem cells [37]. The deficience of Jab1/COPS5 in mouse oligodendrocytes develops DNA damage and repair in myelinating glial cells and causes oxidative stress, chronic inflammation and senescence [38].

Although these studies reveal that Jab1/COPS5 is associated with progression of some tumors, whether Jab1/COPS5 functions and plays the same function in all tumors is unclear due to the high heterogeneity of

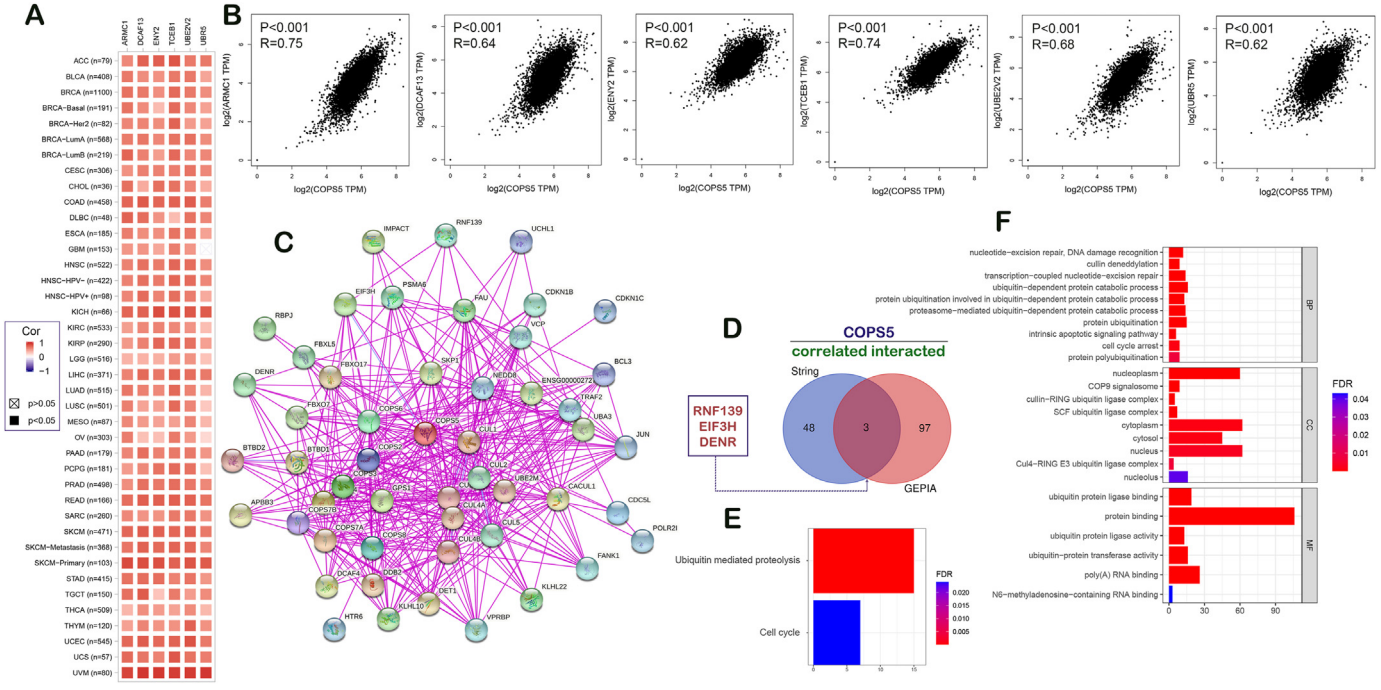

Figure 7. Jab1/COPS5 and related genes in tumors. (A) Heatmap of Jab1/COPS5-related genes in pan-cancer at TIMER2 website. (B) A scatter plot of Jab1/COPS5-related genes in pan-cancer at GEPIA2 website. (C) PPI network of Jab1/COPS5 at STRING database. (D) Intersecting the Jab1/COPS5-related genes screened in GEPIA2 and STRING to obtain RNF139, EIF3H and DENR. (E) Combining Jab1/COPS5-related genes screened in GEPIA2 and STRING for KEGG enrichment analysis. (F) Combining Jab1/COPS5-related genes screened in GEPIA2 and STRING for GO enrichment analysis.

tumors. Therefore, our study performed a pan-cancer analysis of Jab1/COPS5. We systematically explored the relationship and clinical significance between Jab1/COPS5 and pan-cancer. This study first performed differential and survival analysis based on TCGA, GEO and CPTAC databases and suggested that high level of Jab1/COPS5 expression occurred in most cancers compared to normal tissues and was correlated with poor prognosis. We also found that missense mutations of Jab1/COPS5 was the predominant mutation type. TMB and MSI were positively correlated with Jab1/COPS5 expression in most cancers. In PRAD, a TCGA cancer example, patients with Jab1/COPS5 alteration had poor prognosis. Subsequently, we investigated the association between Jab1/COPS5 and CD8+ T-cells and cancer-associated fibroblasts in each cancer and obtained Jab1/COPS5 expression-related genes for enrichment analysis to explore their molecular functions.

Our study provides a theoretical basis for Jab1/COPS5 as a new biomarker in unstudied cancers and paves the way for targeted drug development. Although we performed data integration and biometric analysis across multiple databases, there are still some limitations. First, this study initially revealed that Jab1/COPS5 play a critical role in the occurrence and development of multiple tumors based on clinical data, but it is necessary to verify our results and elucidate the specific molecular mechanisms of Jab1/COPS5 in multiple tumors in vivo and in vitro. Second, the type of data we analyzed was mainly bulk RNA-seq and did not describe the role of Jab1/COPS5 at the single cell level or in spatial locations. Tumor tissue has different cell populations distributed in different spatial locations, and how the expression of Jab1/COPS5 in these cell populations changes with the progression of the disease is a question that needs further investigation.

5. Conclusion

We systematically explored the clinical significance and prognostic value of Jab1/COPS5 in pan-cancer by differential expression, survival prognosis, gene mutation, TMB, MSI, DNA methylation, immune infiltration, correlation and functional enrichment analysis. The research provided a theoretical basis for Jab1/COPS5 as a new biomarker in cancers and paved the way for targeted therapy and drug development.

Declarations

Author contribution statement

Liping Wang, Xiaojiao Zeng: Analyzed and interpreted the data; Wrote the paper.

Gui Yang: Analyzed and interpreted the data.

Guohong Liu, Yunbao Pan: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

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Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of interest's statement

The authors declare no competing interests.

Additional information

No additional information is available for this paper.

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