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Comprehensive Analysis of the Role of Forkhead Box J3 (*FOXJ3*) in Human Cancers

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Abstract: Forkhead box J3 (*FOXJ3*) is a member of the forkhead box (*Fox*) family. Recently, increasing evidence has revealed the relationship between Fox family members and cancer. *FOXJ3* is involved in various types of cancer, including lung cancer, tongue squamous carcinoma, and prostate cancer; however, a comprehensive pan-cancer analysis of *FOXJ3* remains lacking. Here, we explored the function of *FOXJ3* across cancers using online websites and databases including TIMER2.0, SangerBox, UALCAN, GEPIA2.0, cBioPortal, CancerSEA, STRING, BioGRID and Metascape to analyze the role of *FOXJ3* in cancers. Abnormal expression of *FOXJ3* was found in various tumors. The genetic alteration percentage in tumors was determined, and elevated *FOXJ3* expression was found to be associated with worse overall survival in brain lower grade glioma(LGG), liver hepatocellular carcinoma (LIHC), sarcoma (SARC) and thyroid carcinoma. Elevated *FOXJ3* expression was related to worse prognosis with disease-free survival in adrenocortical carcinoma, LGG and LIHC. *FOXJ3* expression was related to immune infiltration in several cancers. Enrichment analysis showed that histone modification, the TGF- β signaling pathway, and chromatin organization were the top three enriched ontology clusters of the top 100 similar genes of *FOXJ3*. Our pan-cancer analysis provides comprehensive insights into *FOXJ3* from the perspective of bioinformatics in different cancers, where it serves as a potential biomarker for prognosis, especially in LGG and LIHC. *FOXJ3* is also correlated with immune infiltrates in certain human tumors.

Key words: *FOXJ3*; cancer; genetic alteration; prognosis

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0 Introduction

Cancer is a disease with a high incidence rate and mortality, representing one of the main causes of death globally. In terms of appropriate therapy, various novel approaches have been discovered that have obvious ad-

vantages compared to traditional therapies. Targeted therapy is the hot spot of current research because of its remarkable clinical success in many cancers, such as pulmonary adenocarcinoma^[1], hepatocellular carcinoma^[2], and anaplastic thyroid carcinoma^[3]. Bioinformatics analysis was used to explore new biomarkers that can be

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used as indicators for cancer diagnosis and prognosis.

The *Fox* genes encode a family of transcription factors with 100 amino acids, which are characterized by a DNA binding domain comprising approximately 100 amino acids. According to phylogenetic analysis, Fox proteins can be divided into 19 subfamilies^[4]. Fox proteins participate in development, differentiation, proliferation, apoptosis, and other multiple biological processes, while increasing research has revealed that they may also participate in the progression of cancer^[5]. *FOXJ3*, located on chromosome 1^[6]. In non-small-cell lung cancer (NSCLC), *FOXJ3* is the target of miR-106b-5p, which regulates NSCLC cell proliferation and invasion^[7]. miR-517a-3p promotes growth in lung cancer cells by regulating the expression of *FOXJ3* by binding to the *FOXJ3* promoter^[8]. miR-425-5p may contribute to prostate cancer progression by directly targeting *FOXJ3*^[9]. The expression level of *FOXJ3* has been found to be elevated in patients with tongue squamous carcinoma (TSCC), and *FOXJ3* could promote migration in SCC15 cells, suggesting that *FOXJ3* may be involved in the progression of TSCC^[10]. These studies suggest that *FOXJ3* may act as a regulator in cancer. In this study, we used several databases to investigate the role of *FOXJ3* and its genetic alteration characteristics, as well as its association with prognosis and immune infiltration of multiple cancers.

1 Methods

1.1 TIMER Analysis

TIMER2.0^[11] web server (<http://timer.cistrome.org/>) is a database which provides comprehensive analysis of immune infiltration levels for the Cancer Genome Atlas (TCGA). We used the "cancer exploration" module to investigate the expression of *FOXJ3* in various cancers. Cancer-associated fibroblast (CAFs), endothelial cell and eosinophil were chosen for detailed analysis of the association between *FOXJ3* expression and immune infiltrates. Estimations were conducted by the EPIC, MCPOUNTER, XCELL and TIDE algorithms.

1.2 SangerBox Analysis

FOXJ3 expression among various kinds of tumors based on TCGA combined with Genotype Tissue Expression (GTEx) cohort searched by SangerBox^[12] (<http://SangerBox.com/Tool>).

1.3 UALCAN Analysis

UALCAN (<http://ualcan.path.uab.edu.>)^[13] is a web resource that can analyze cancer. UALCAN provides the protein expression analysis of *FOXJ3* through the data from Clinical Proteomic Tumor Analysis Consortium (CPTAC) and the International Cancer Proteogenome Consortium datasets. The phosphorylation level of *FOXJ3* across tumors was also investigated by UALCAN.

1.4 Genetic Alteration Analysis

The characteristics of *FOXJ3* genetic alterations were searched through cBioPortal database^[14] (<https://www.cbioportal.org/>) which is an open-access resource provides multidimensional cancer genomics data sets. The alteration frequency was shown in the "Cancer Types Summary" module and the detailed mutation sites were shown in the "Mutations" module.

1.5 GEPIA2 Analysis

GEPIA2^[15] was used to obtain overall survival (OS) and disease-free survival (DFS) map data of *FOXJ3* across tumors, according to the expression threshold value of the cutoff-high (50%) and cutoff-low (50%). The correlation between *FOXJ3* expression and survival probability of patients was explored. Similar genes of *FOXJ3* was obtained by GEPIA 2.0.

1.6 Single-Cell Analysis

CancerSEA (<http://biocc.hrbmu.edu.cn/CancerSEA/home.jsp>)^[16] was performed to explore the functional states of cancer cells at a single cell resolution. Single cell analysis was performed to investigate the biological functions of *FOXJ3* by exploring CancerSEA.

1.7 STRING Analysis

STRING^[17] (<https://string-db.org/>) was used to perform protein-protein interaction (PPI) network analysis on *FOXJ3*. "FOXJ3" was queried in the "protein name", then in the organism module "Homo sapiens" was selected. The parameters as following: meaning of network edges selected "evidence", "experiments" and "database" was chosen in active interaction sources. "Low confidence (0.150)" was selected in the minimum required interaction score, and "no more than 50 interactors" in the 1st shell was chosen.

1.8 BioGRID Analysis

BioGRID^[18] (<https://thebiogrid.org/>) (version: 4.4) was used to generate a network of *FOXJ3*-protein interaction network. "FOXJ3" was queried and "Homo sapi-

ens" was selected. Switch View selected "Network" with the layout set to "concentric circles".

1.9 Metascape

Metascape^[19] (<https://metascape.org/>) was used to conduct enrichment analysis on the similar genes of *FOXJ3* obtained from GEPIA2.

2 Results

2.1 Expression of *FOXJ3* Across Normal and Cancer Tissues

TIMER2.0 was used to detect *FOXJ3* expression across various normal and cancer tissues based on TCGA (Fig. 1). The results revealed that *FOXJ3* was upregulated in cholangio carcinoma (CHOL), esophageal carci-

noma (ESCA), head and neck squamous cell carcinoma (HNSC), kidney renal clear cell carcinoma (KIRC), liver hepatocellular carcinoma(LIHC) and stomach adenocarcinoma (STAD) tissues; whereas it was decreased in breast invasive carcinoma (BRCA), colon adenocarcinoma (COAD), glioblastoma multiforme (GBM), kidney chromophobe (KICH), kidney renal papillary cell carcinoma (KIRP), thyroid carcinoma (THCA) and uterine corpus endometrial carcinoma(UCEC), compared with the corresponding normal tissues (Fig. 1(a)). Furthermore, the expression of *FOXJ3* among normal and cancer tissues were detected with TCGA and GTEx database by SangerBox.

We observed that *FOXJ3* expression was higher in adrenocortical carcinoma (ACC), BRCA, CHOL, COAD, ESCA, GBM, HNSC, KIRC, acute myeloid leu-

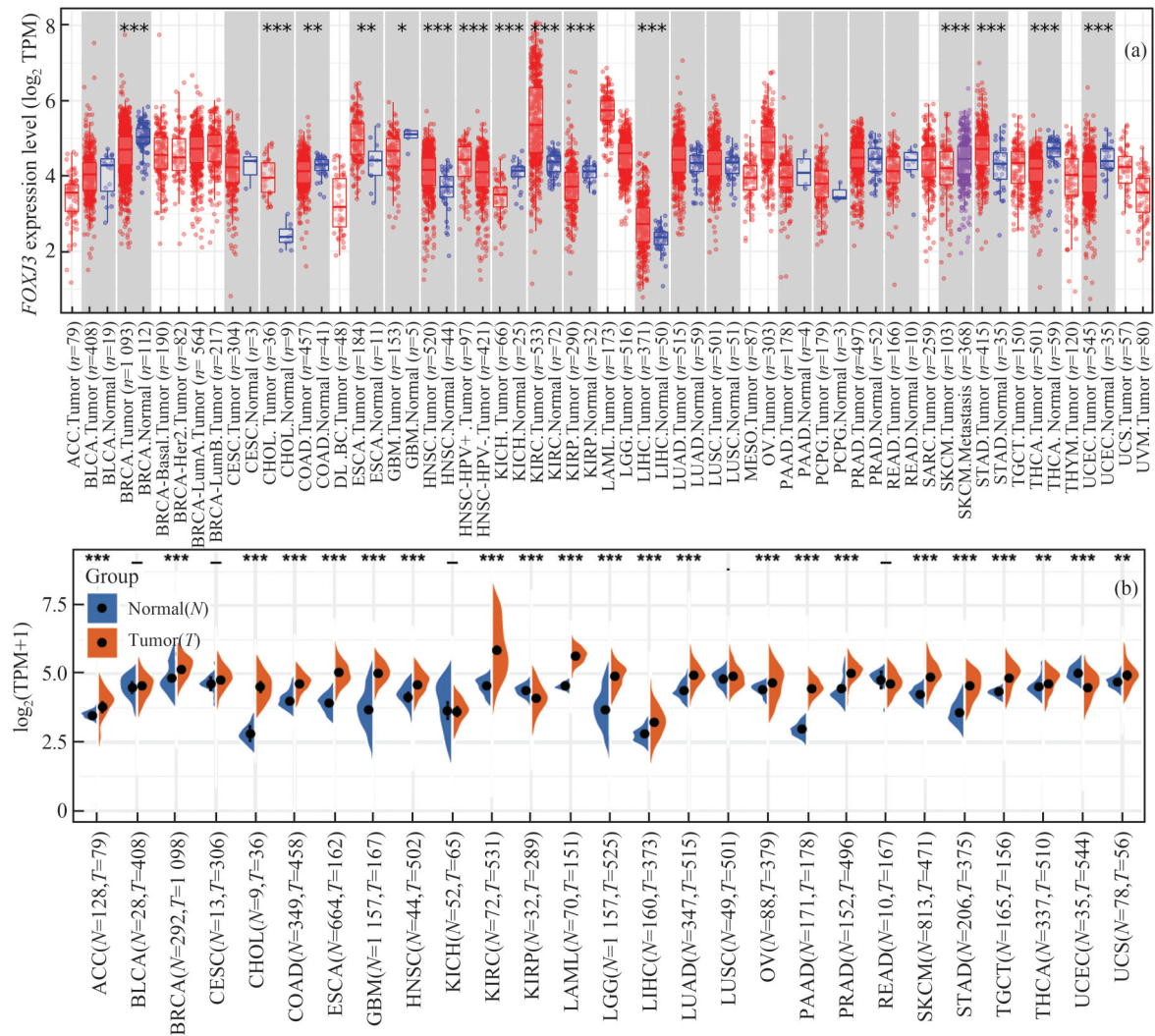


Fig. 1 The expression of *FOXJ3* across cancer and normal tissues

(a) The *FOXJ3* gene expression in pan cancer from TCGA data; (b) The expression of *FOXJ3* gene across cancer and normal tissues based on TCGA and GTEx data, * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

kemia (AML), brain lower grade glioma (LGG), LIHC, lung adenocarcinoma (LUAD), ovarian serous cystadenocarcinoma (OV), pancreatic adenocarcinoma (PAAD), prostate adenocarcinoma (PRAD), skin cutaneous melanoma (SKCM), STAD, testicular germ cell tumors (TGCT), THCA and uterine carcinosarcoma (UCS) than normal tissues, while lower in KIRP and UCEC

compared to normal tissues (Fig.1(b)).

2.2 Protein Expression of FOXJ3

Protein expression of FOXJ3 is shown in Fig. 2. Compared with normal tissues, the protein expression of FOXJ3 was increased in breast cancer, ovarian cancer, clear cell renal cell carcinoma, LUAD, and GBM, while it was decreased in UCEC.

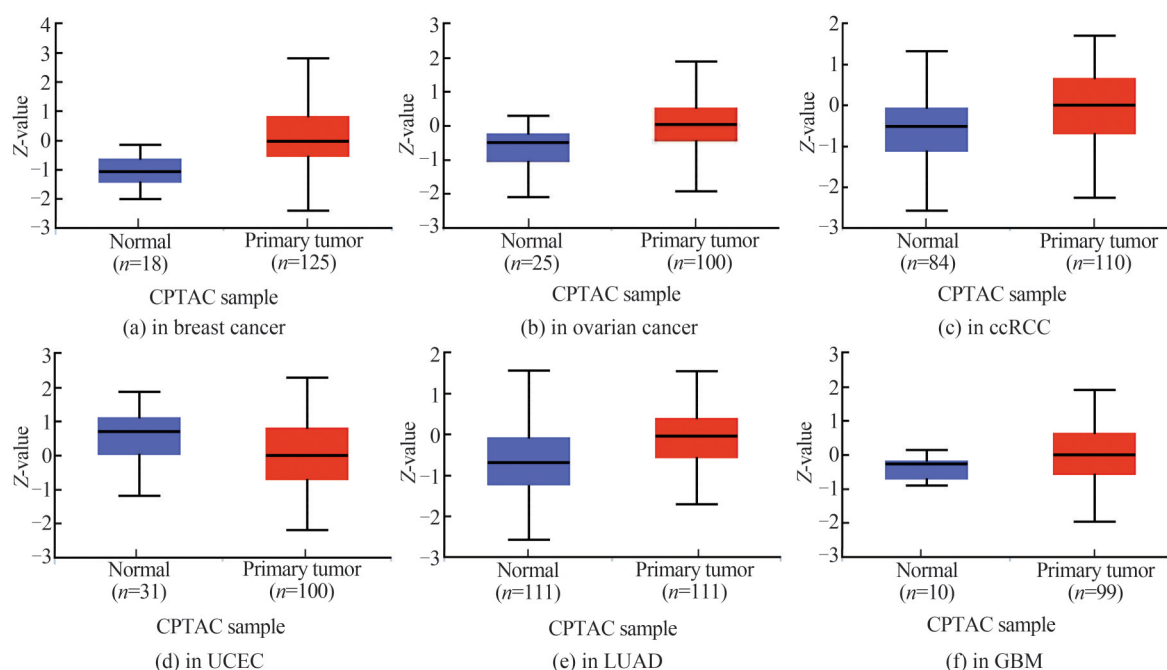


Fig. 2 Protein expression of FOXJ3 in cancers

2.3 Protein Phosphorylation Analysis of FOXJ3

We used UALCAN to explore the phosphorylation levels of FOXJ3 across cancers. The S223 locus of FOXJ3 showed a higher phosphorylation level in breast cancer ($p=1.66E-04$), whereas it was decreased in PAAD ($p=3.48E-13$) and GBM ($p=1.12E-02$). The T216 locus of FOXJ3 showed reduced phosphorylation in clear cell renal cell carcinoma (ccRCC) ($p=5.54E-12$), whereas it was increased in LUAD ($p=1.10E-32$) and hepatocellular carcinoma ($p=2.56E-12$) (Fig. 3). These results suggest that FOXJ3 protein phosphorylation at S223 and T216 play a vital role in the occurrence and development of cancer.

2.4 Alterations of FOXJ3 Across Cancers

We used the CBioPortal to analyze the genetic alteration characteristics of FOXJ3 and found that patients with UCEC had the highest frequency of FOXJ3 altera-

tions (46/529, 8.7%). The frequency of FOXJ3 alterations in OV (43/584, 7.36%), bladder urothelial carcinoma (BLCA) (23/411, 5.6%), pheochromocytoma and paraganglioma (PCPG) (5/178, 2.81%), esophageal adenocarcinoma (5/182, 2.75%), STAD (11/440, 2.5%), SKCM (11/444, 2.48%), sarcoma (SARC) (6/255, 2.35%), diffuse large B-cell lymphoma (1/48, 2.08%), colorectal adenocarcinoma (12/594, 2.02%), LUAD (11/566, 1.94%), BRCA (21/1084, 1.94%), LUSC (6/487, 1.23%), GBM (7/592, 1.18%), MESO (1/87, 1.15%), ACC (1/91, 1.1%), PAAD (2/184, 1.09%), cervical squamous cell carcinoma (3/297, 1.01%), HNSC (5/523, 0.96%), KIRP (2/283, 0.71%), TGCT (1/149, 0.67%), LAML (1/200, 0.5%), KIRC (2/511, 0.39%), LIHC (1/372, 0.27%) and LGG (1/514, 0.19%) are shown in Fig. 4(a).

FOXJ3 gene modifications, including types, sites, and case numbers, are displayed in Fig. 4(b). The main type FOXJ3 alteration was a missense mutation.

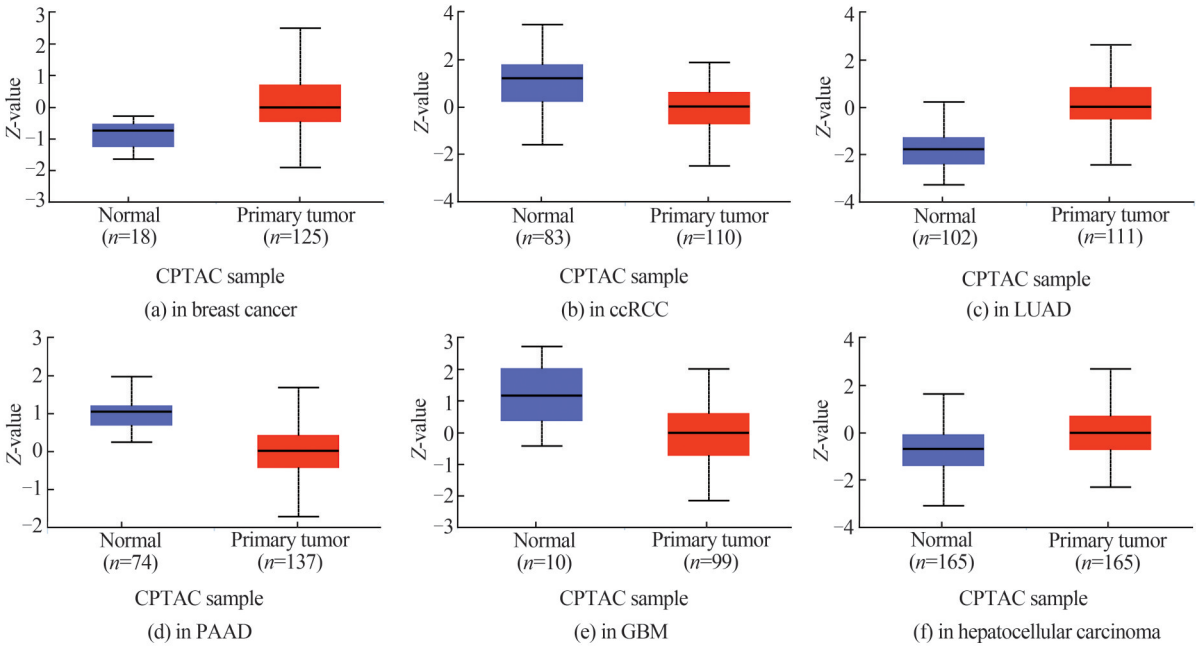


Fig. 3 Protein phosphorylation analysis of FOXJ3
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

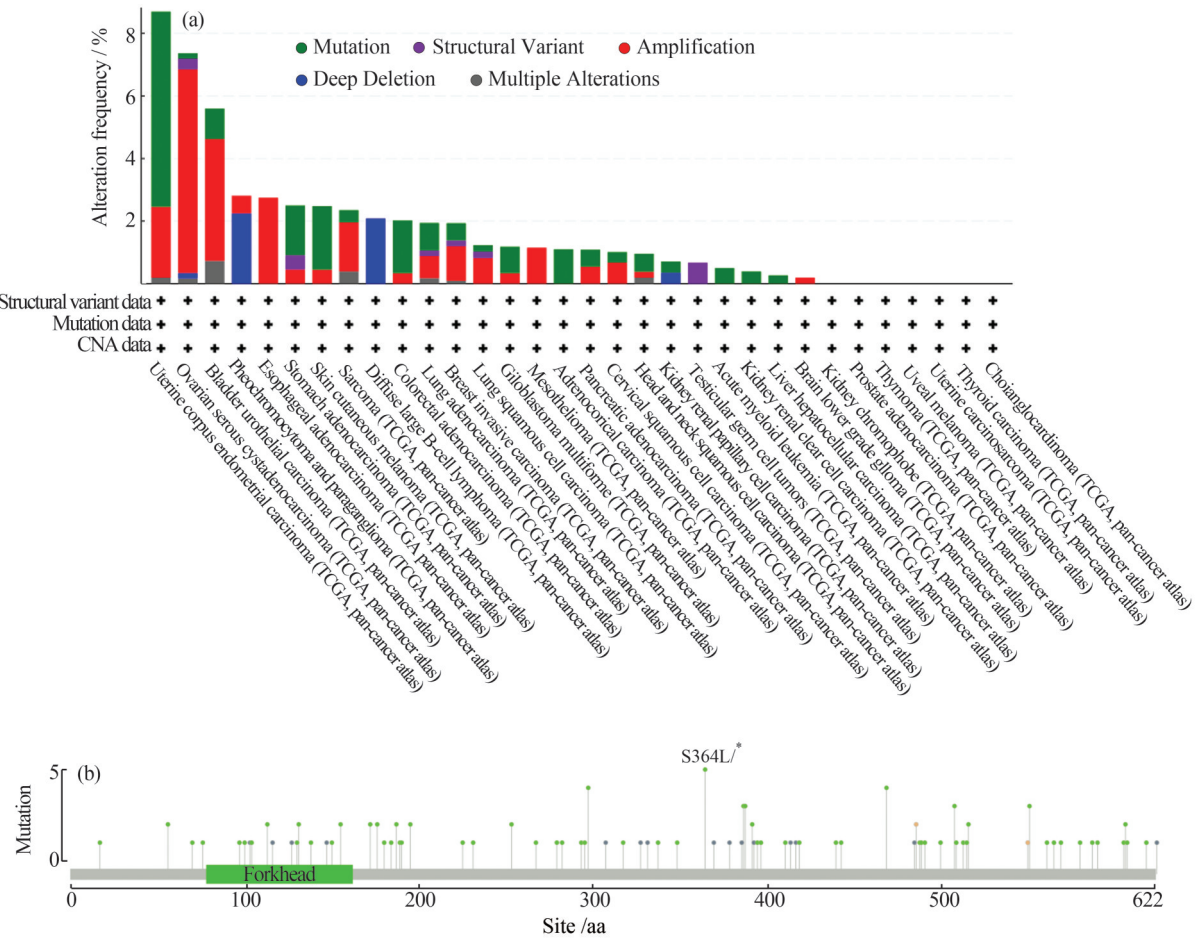


Fig. 4 FOXJ3 genetic alterations
(a) FOXJ3 alterations in TCGA pan-cancer datasets; (b) The mutation sites of FOXJ3

2.5 Relationship Between Expression of *FOXJ3* and Prognosis

GEPIA2 was used to analyze the relationship between *FOXJ3* expression and prognosis. The OS significance map obtained by GEPIA2 showed that higher *FOXJ3* expression was correlated with worse OS of

LGG, LIHC, SARC, and THCA (Fig. 5(a)); while there was a correlation between highly expressed *FOXJ3* and poorer DFS of ACC, LGG and LIHC (Fig. 5(b)). Notably, *FOXJ3* was a risk factor for both OS and DFS of LIHC and LGG, which was significantly correlated with poor prognosis.

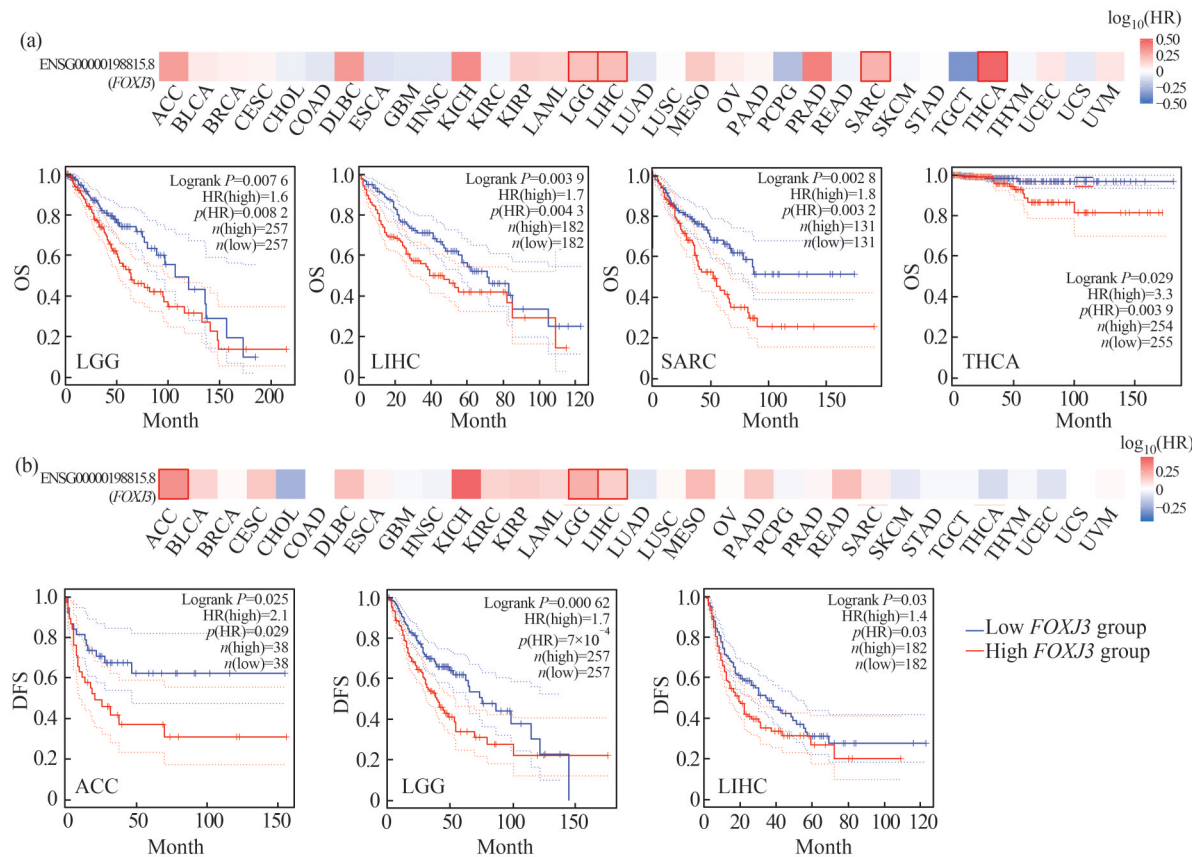


Fig. 5 Correlation between *FOXJ3* expression and prognosis of tumors

(a) Correlation of *FOXJ3* expression and OS in tumors; (b) Correlation of *FOXJ3* expression and DFS in tumors

2.6 Correlation Between *FOXJ3* Expression and Immune Infiltration Across Cancers

In our study, TIMER 2.0 was used to explore the association between immune infiltration and *FOXJ3* expression across cancers. According to EPIC, MCPOUNTER, XCELL and TIDE algorithms, *FOXJ3* expression and the estimated infiltration level of cancer associated fibroblast (CAF) was positive in HNSC, HNSC-HPV- and PAAD(Fig. 6(a)). *FOXJ3* expression and endothelial cell infiltration was positive in COAD, KIRC and THCA through analysis by EPIC, MCPOUNTER and XCELL algorithms (Fig. 6(b)). *FOXJ3* expression and eosinophil was analyzed by CIBERSORT, CIBERSORT-ABS and XCELL algorithms and showed a positive correlation in STAD

(Fig. 6(c)).

2.7 Biological Functions of *FOXJ3*

Single-cell analysis was performed to investigate the biological functions of *FOXJ3* using CancerSEA. The biological functions associated with *FOXJ3* in cancers was revealed by single-cell analysis. The results indicated that *FOXJ3* positively regulated the differentiation, angiogenesis, and inflammation of retinoblastoma cells, whereas it negatively regulated the DNA repair, cell cycle, and DNA damage of retinoblastoma cells (Fig. 7).

2.8 Related Gene of *FOXJ3*

The *FOXJ3* protein interactions according to BioGRID4.4 are shown in Fig. 8(a). The STRING tool was used to obtain the *FOXJ3* correlation protein that were

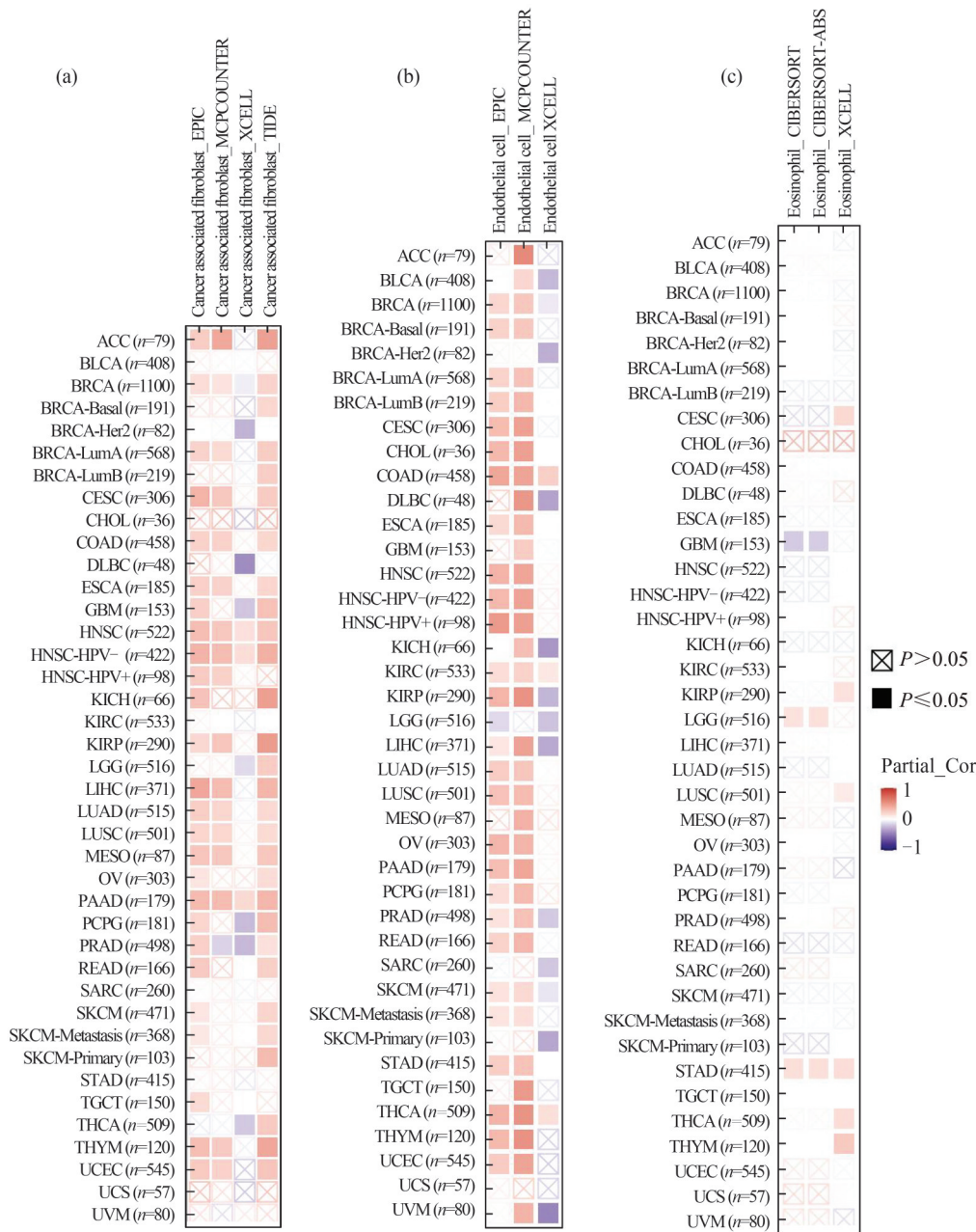


Fig. 6 Relationship between *FOXJ3* expression and infiltration of CAFs, endothelial cells and eosinophil

(a) The correlative between the level of *FOXJ3* and cancer associated fibroblast was analyzed EPIC, MCPOUNTER, XCELL and TIDE algorithms; (b) The correlative between the level of *FOXJ3* and endothelial cells was analyzed EPIC, MCPOUNTER and XCELL algorithms; (c)The correlative between the level of *FOXJ3* and eosinophil was analyzed by CIBERSORT, CIBERSORT-ABS and XCELL algorithms

selected by "experiments" and "database" active interaction sources, minimum required interaction score "Low confluence (0.150)", max number of interactors to show "no more than 50 interactors" (Fig. 8(b)). To explore the functional mechanism of *FOXJ3* in carcinogenesis, we obtained the 100 most similar genes of *FOXJ3* using GEPIA2. The Metascape database was used to analyze the potential functional mechanism of *FOXJ3* and simi-

lar genes to *FOXJ3* in cancers. The heatmap of gene ontology (GO) enriched terms is shown in Fig. 8(c). The top ten GO-enriched terms include histone modification, TGF- β signaling pathway, chromatin organization, DNA-templated transcription, estrogen-dependent gene express, hepatitis B infection, nuclear-transcribed mRNA catabolic process, DNA IR (ionizing radiation)-double strand breaks and cellular response via ATM

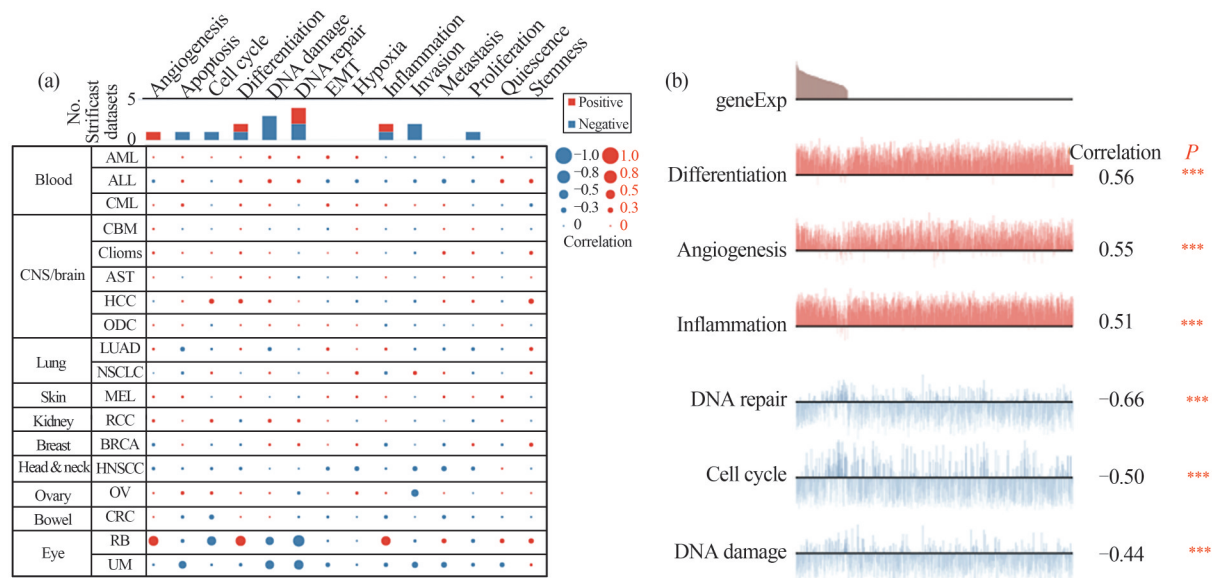


Fig. 7 Biological processes regulated by *FOXJ3*, as analyzed by CancerSEA

(a) The biological function associated with *FOXJ3* in cancer cells by single cell analysis; (b) Association of *FOXJ3* with differentiation, angiogenesis, inflammation, DNA repair, cell cycle, and DNA damage of retinoblastoma cells; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

(ataxia telangiectasia mutated), chromatin modifying enzymes, and pathways affected in adenoid cystic carcinoma.

3 Discussion

Forkhead transcription factors, which have conserved "forkhead" DNA-binding domain, play important roles in the processes of cellular fate determination, proliferation, apoptosis, and differentiation^[20]. Members of the forkhead transcription factors could regulate the expression of countless genes by a DNA-binding mechanism or protein–protein interactions. *FOXJ3* may play a vital role during the progress of myofiber identity and muscle regeneration in mice by activating Mef2c^[21]. FOXA has been shown to activate ABCC2 and ABCC3 transcription in Sf9 cells^[22], while FOX-2 has been shown to interact with ataxin-1^[23]. In cancer, some members of the *FOX* family may serve as diagnostic and prognostic biomarkers. High expression of FOXD1 is associated with poor OS and DSF in patients with colorectal cancer^[24]. The expression of FOXC1 is highly expressed in triple-negative breast cancer, where it may serve as a therapeutic target or biomarker^[25]. FOXE1 expression has also been shown to be higher in papillary thyroid cancer tissues than in adjacent non-tumor tissues, and its expression is correlated with clinical prognosis. *FOXE1* is a potential therapeutic target and may

be a prognosis biomarker for papillary thyroid cancer^[26]. FOXM1 has been demonstrated to be upregulated in endometrial cancer, where its high expression is associated with poor prognosis. Silencing the expression of *FOXM1* could suppress the growth of AN3CA and ISHIKAWA cells, and *FOXM1* may be a prognostic biomarker for endometrial cancer^[27]. In recent years, the importance of the *FOX* family in human cancers has drawn increasing attention.

We analyzed the molecular features of *FOXJ3*, including gene expression, protein expression, survival prognosis, genetic alteration, and immune infiltration. We explored the expression of *FOXJ3* across cancer types by TIMER2.0. The results revealed that *FOXJ3* was upregulated in CHOL, ESCA, HNSC, KIRC, LIHC and STAD; whereas it was decreased in BRCA, COAD, GBM, KICH, KIRP, THCA and UCEC. The results showed differences in *FOXJ3* expression between tumor and normal tissues based on TCGA. The Clinical Proteomic Tumor Analysis Consortium data from UALCAN provide several types of tumor expression of *FOXJ3*. *FOXJ3* protein expression is upregulated in breast cancer, ovarian cancer, clear cell renal cell carcinoma, LUAD, and GBM but is decreased in UCEC. These findings urged us to further investigate the expression of *FOXJ3* across cancers.

The relationship between prognosis and *FOXJ3* expression was investigated by GEPIA2, with the results

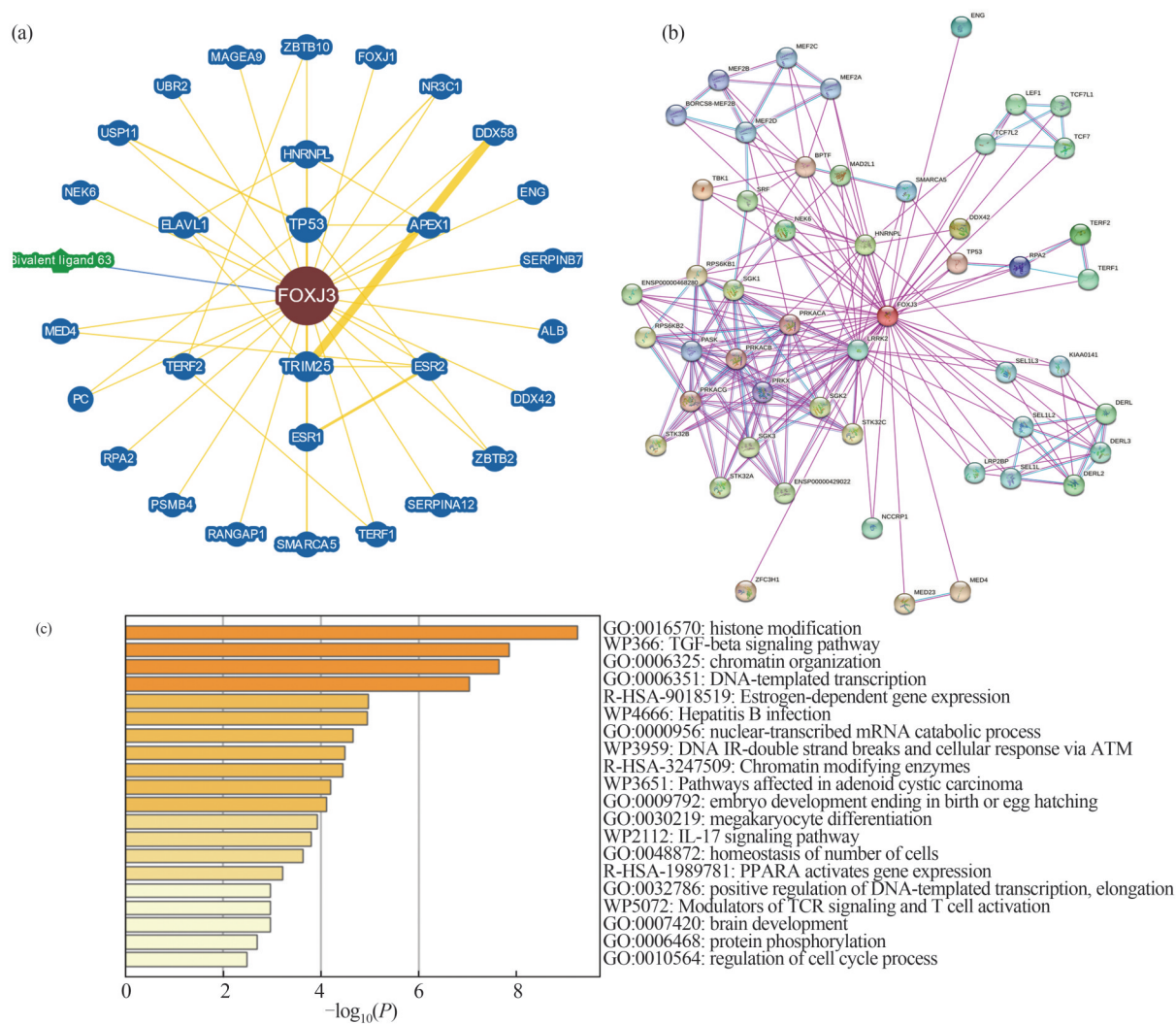


Fig. 8 Related gene of *FOXJ3*

(a) Protein interactions of *FOXJ3* obtained by BioGRID; (b) The *FOXJ3* correlation protein obtained by the STRING tool; (c) Heat map of gene ontology (GO) enriched terms of *FOXJ3* and its 100 most similar genes

revealing that *FOXJ3* expression was significantly correlated with OS and DFS in LGG and LIHC. TIMER2.0 TCGA data analysis showed that *FOXJ3* expression was upregulated in LIHC, whereas TCGA and GTEx data analyzed by SangerBox showed that *FOXJ3* expression was upregulated in both LGG and LIHC. Taken together, these findings suggest that *FOXJ3* may serve as a prognostic biomarker for LGG and LIHC. Immunotherapy, as one of the most appealing approaches for treating tumors, has shown great progress recently. The study found that the *FOXJ3* level was related to cancer immunity. We found a significant correlation between *FOXJ3* expression and CAFs in HNSC, HNSC-HPV, and PAAD. In COAD, KIRC, and THCA, *FOXJ3* expression was related to endothelial cell infiltration, while

FOXJ3 levels were positive with the eosinophil in STAD.

We also found that histone modification, the TGF- β signaling pathway, and chromatin organization were the top three GO enriched terms in which *FOXJ3* and its similar genes may be involved. Histone modifications are included in epigenetic modification, which plays an important role in cancer. Histone modifications are involved in a series of cellular processes and other important biological processes, while altered epigenetic modification is found in cancer. The promoter methylation of *BRCA-1* in malignant breast tumors has also been shown to be higher than that in benign breast tumors, and both the methylation of H4K20 and acetylation of H3K18 are lower in malignant breast tumors than in benign breast

tumors^[28]. In lung cancer cells, the acetylation of both histones H3 and H4 could regulate the expression of *MYO18B*, and histone deacetylation surrounding the promoter region is related to *MYO18B* silencing^[29]. The detection of epigenetic modifications may be helpful for cancer therapy.

The TGF- β signaling pathway is related to various biological processes, and its dysfunction is a hallmark of many human diseases, including cancer. Retinoid X receptor α has been shown to promote the growth of pancreatic cancer cells and suppress their apoptosis by activating the TGF- β /Smad signaling pathway^[30]. Moreover, G-protein coupled receptor 34 promotes glioma carcinogenesis by regulating TGF- β /Smad signaling^[31]. Chromatin organization is associated with carcinogenesis by affecting gene expression and regional mutation frequencies. The loss of *BRG1* has been found to increase the potential of tumorigenicity in NSCLC cells, while the loss of *BRG1* is related to variations in chromatin structure^[32]. HP1 α , a member of the heterochromatin protein 1 (HP1) family, participates in the proliferation of HepG2 cells, while in HP1 α -depleted cells, the level of DNA methylation exhibits a global decrease, and perturbed chromatin organization^[33]. All of the top three GO-enriched terms of *FOXJ3* and its similar genes were related to cancer progression, further highlighting its importance in cancer.

4 Conclusion

Through pan-cancer analysis of *FOXJ3*, we observed a statistical association between *FOXJ3* expression and prognosis, protein phosphorylation, and immune cell infiltration in cancers. These findings will help to further our understanding of *FOXJ3* in tumors from various perspectives.

Conflicts of Interest

The authors indicated no potential conflicts of interest.

Author contributions

All authors contributed to data acquisition, data interpretation, and reviewed and approved the final version of this manuscript.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

able request.

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