Oncology and Translational Medicine
DOI 10.1007/s10330-021-0515-5
December 2021, Vol. 7, No. 6, P294–P304

ORIGINAL ARTICLE

Effect of *UBR5* on the tumor microenvironment and its related mechanisms in cancer*

Guangyu Wang[1], Sutong Yin[2], Justice Afrifa[3], Guihong Rong[4], Shaofeng Jiang[5], Haonan Guo[4] (✉), Xianliang Hou[1] (✉)

[1] Central Laboratory, Guangxi Health Commission Key Laboratory of Glucose and Lipid Metabolism Disorders, The Second Affiliated Hospital of Guilin Medical University, Guilin 541199, China
[2] Reproductive Medical Center, No. 924 Hospital of Chinese People's Liberation Army, Guilin 541001, China
[3] Department of Medical Laboratory Science, School of Allied Health Sciences, University of Cape Coast, Cape Coast, Ghana
[4] Department of Clinical Laboratory, The Affiliated Hospital of Guilin Medical University, Guilin 541001, China
[5] Guangxi Key Laboratory of Tumor Immunology and Microenvironmental Regulation, Guilin Medical University, Guilin 541199, China

Abstract

Objective *UBR5*, recently identified as a potential target for cancer therapeutics, is overexpressed in multiple malignant tumors. In addition, it is closely associated with the growth, prognosis, metastasis, and treatment response of multiple types of cancer. Although emerging evidence supports the relationship between *UBR5* and cancer, there are limited cancer analyses available.

Methods In this study, online databases (TIMER2, GEPIA2, UALCAN, c-BioPortal, STRING) were employed to comprehensively explore expression levels and prognostic values of the *UBR5* gene in cancer, using bioinformatic methods.

Results We found that various characteristics of the *UBR5* gene such as gene expression, survival value, genetic mutation, protein phosphorylation, immune infiltration, and pathway activities in the normal tissue were remarkably different from those in the primary tumor. Furthermore, "protein processing in spliceosome" and "ubiquitin mediated proteolysis" have provided evidence for their potential involvement in the development of cancer.

Conclusion Our findings may provide insights for the selection of novel immunotherapeutic targets and prognostic biomarkers for cancer.

Received: 31 August 2021
Revised: 20 September 2021
Accepted: 25 October 2021

Key words: *UBR5*; cancer; tumor; prognosis; biomarker

Despite its declining incidence in many developed countries, cancer remains the most common cause of death across the globe. More than nineteen million people were diagnosed and over nine million people died as a result of cancer in 2020 alone. Cancer is characterized by a high degree of malignancy, rapid development and poor prognosis [1–3]. In the wake of the rapid strides being made by scientists and clinicians to explore novel prognostics, diagnostics and therapeutic options, cancer still remains one of the most elusive diseases in terms of treatment and management.

The human *UBR5* gene, which is widely expressed in various cell types, has 59 exons encoding approximately 10 kb of mRNA and > 300 kDa of protein [4]. It is highly conserved in metazoans, has unique structural features, and has been implicated in the regulation of the DNA damage response, metabolism, transcription, and apoptosis [5–7]. *UBR5* is a key regulator of cell signaling

✉ Correspondence to: Xianliang Hou. E-mail: houxl115@126.com; Haonan Guo. E-mail: guohaonan@glmc.edu.cn
*Supported by grants from the Guangxi Natural Science Foundation (No. 2019GXNSFBA245032), the Guangxi Science and Technology Plan Project (No. Gui Ke AD20238021), the open funds of the Guangxi Key Laboratory of Tumor Immunology and Microenvironmental Regulation (No. 203030302008, 203030302018 and 2020KF010), Guilin Science Research and Technology Development Project (No. 20190218-5-5), and the Basic Ability Enhancement Program for Young and Middle-aged Teachers of Guangxi (No. 2021KY0496).

related to the field of tumor biology. Recent studies have primarily demonstrated that *UBR5* plays an important role in the development of many tumors, and its expression may be closely associated with growth and proliferation of malignant tumors [8–9]. For example, in breast cancer, *UBR5* is coamplified with Myelocytomatosis (MYC) to limit MYC-dependent apoptosis by encoding a ubiquitin ligase [10]. Also in breast cancer, others have shown that triple-negative breast cancer (TNBC) metastasis and cisplatin resistance may be mediated by elevated *UBR5* expression [11–13]. Similarly, in colorectal cancer, Xie *et al*. concluded that an elevated *UBR5* levels play an oncogenic role and may be a potential prognostic marker [14]. The trends elucidated in the various studies point to the likelihood of *UBR5* as an oncogenic mediator in most cancers. However, contrary to other cancers, inactivating mutations have been observed in the *UBR5* gene, as is the case in approximately 18% of mantle cell lymphoma cases [15]. It is therefore clear that *UBR5* is a key cell signaling regulator that has been strongly associated with cancer; however, its function as a promoter or inhibitor of tumorigenesis still remains inconclusive.

In this study, we conducted an in-depth and comprehensive bioinformatic analysis of the expression of the *UBR5* gene and evaluated its potential as a therapeutic target and prognostic biomarker. Findings from this study will provide a better understanding of this gene, and help clinicians select appropriate therapeutic drugs and more accurately prognose long-term outcomes in cancer patients.

Materials and methods

TIMER2

TIMER2 (http://timer.cistrome.org/) is a reliable tool that provides the expression status of *UBR5* across The Cancer Genome Atlas (TCGA) datasets from different tumor tissues and adjacent normal tissues. It also provides a robust estimation of immune infiltration levels for TCGA or user-provided tumor profiles using six state-of-the-art algorithms. In this study, the expression status of *UBR5* across the TCGA dataset, and the correlation between the infiltration of immune cells and *UBR5* expression was evaluated [16–18].

GEPIA2

GEPIA2 (http://gepia2.cancer-pku.cn/#index) is a tool for analyzing the RNA sequencing expression data of 9,736 tumors and 8,587 normal samples from TCGA [19]. GEPIA2 was employed in this study to perform a differential *UBR5* expression analysis of tumor and adjacent normal tissue, expression of *UBR5* total protein, pathological stage analysis, and correlative prognostic analysis of the *UBR5* gene.

UALCAN

UALCAN (http://ualcan.path.uab.edu/index.html) is an interactive web resource that provides analysis based on TCGA and MET500 cohort data [20]. It allows analysis of relative expression of query genes across tumor and normal samples, as well as in various tumor sub-groups based on individual cancer stages, tumor grade or other clinicopathological features. Protein expression analysis was conducted using Clinical Proteomic Tumor Analysis Consortium (CPTAC) and the available datasets of six tumors were selected in our study.

cBioPortal

The cBioPortal (http://cbioportal.org) is a web resource for exploring, visualizing, and analyzing multidimensional cancer genomics data. This web resource provides the option of querying a single cancer study or querying across multiple cancer studies. It is also possible to view relevant genomic alterations in cancer samples and analyze multidimensional cancer genomics data [21]. The alteration frequency, type of alterations of *UBR5* and copy number alterations are shown in our study. In addition, we aimed to assess the genetic alterations of *UBR5* and its correlation with survival values in cancer patients, using data from TCGA.

STRING

STRING (https://string-db.org/) is a web resource that integrates all known and predicted associations between proteins [22]. We conducted a protein-protein interaction network analysis of differentially expressed levels of the *UBR5* gene, to explore the interactions among them with STRING.

Results

Aberrant expression of *UBR5* in patients with cancer

To understand the oncogenic role of human *UBR5*, we examined its expression status across the TCGA dataset from different cancer types using the TIMER2 approach. The expression level of *UBR5* in the tumor tissues of breast invasive carcinoma (BRCA), cholangiocarcinoma (CHOL), colon adenocarcinoma (COAD), esophageal carcinoma (ESCA), glioblastoma multiforme (GBM), head and neck squamous cell carcinoma (HNSC), liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), pheochromocytoma and paraganglioma (PCPG), prostate adenocarcinoma (PRAD), rectum adenocarcinoma (READ), and stomach adenocarcinoma (STAD) was higher than in normal tissues. On the contrary, the expression level of kidney chromophobe (KICH), kidney renal clear cell carcinoma (KIRC), thyroid carcinoma (THCA), and uterine corpus

endometrial carcinoma (UCEC) was lower than in normal tissues (Fig. 1a).

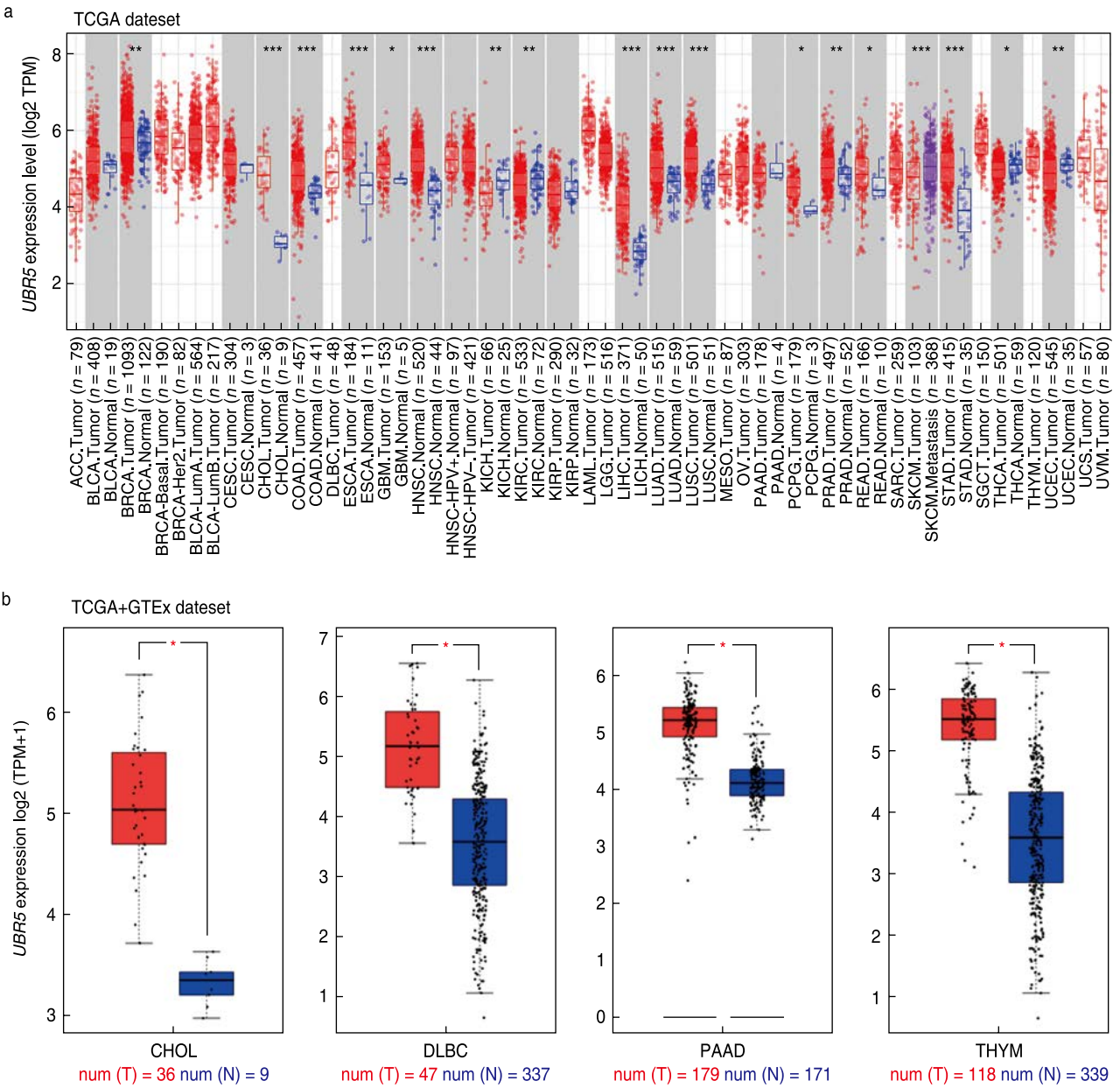
Based on clinical data extracted from the GTEx dataset, we compared the differential expression level of *UBR5* in tumor tissues with that in matched normal tissues of CHOL, lymphoid neoplasm diffuse large B-cell lymphoma (DLBC), pancreatic adenocarcinoma (PAAD), and thymoma (THYM). The results showed a significantly elevated *UBR5* expression among the tumor tissues ($P < 0.05$) compared to that in normal tissues (Fig. 1b).

In the CPTAC dataset, we observed significantly higher expression of *UBR5* total protein in the primary tissues of breast cancer ($P < 0.001$), clear cell RCC ($P < 0.001$), colon cancer ($P < 0.001$), LUAD ($P < 0.001$), UCEC ($P < 0.001$) and ovarian cancer ($P < 0.05$), than in normal tissues (Fig. 1c).

To assess the association between *UBR5* expression and the pathological stages of cancer, the "Pathological Stage Plot" module of GEPIA2 was employed to analyze pathological data from COAD ($P < 0.001$), ESCA ($P < 0.05$) and KICH ($P < 0.001$) patients in the TCGA database (Fig. 1d).

Prognostic value of *UBR5* in patients with cancer

Patients were grouped into high-expression and low-expression groups. We examined the association between *UBR5* expression and the prognosis of patients with



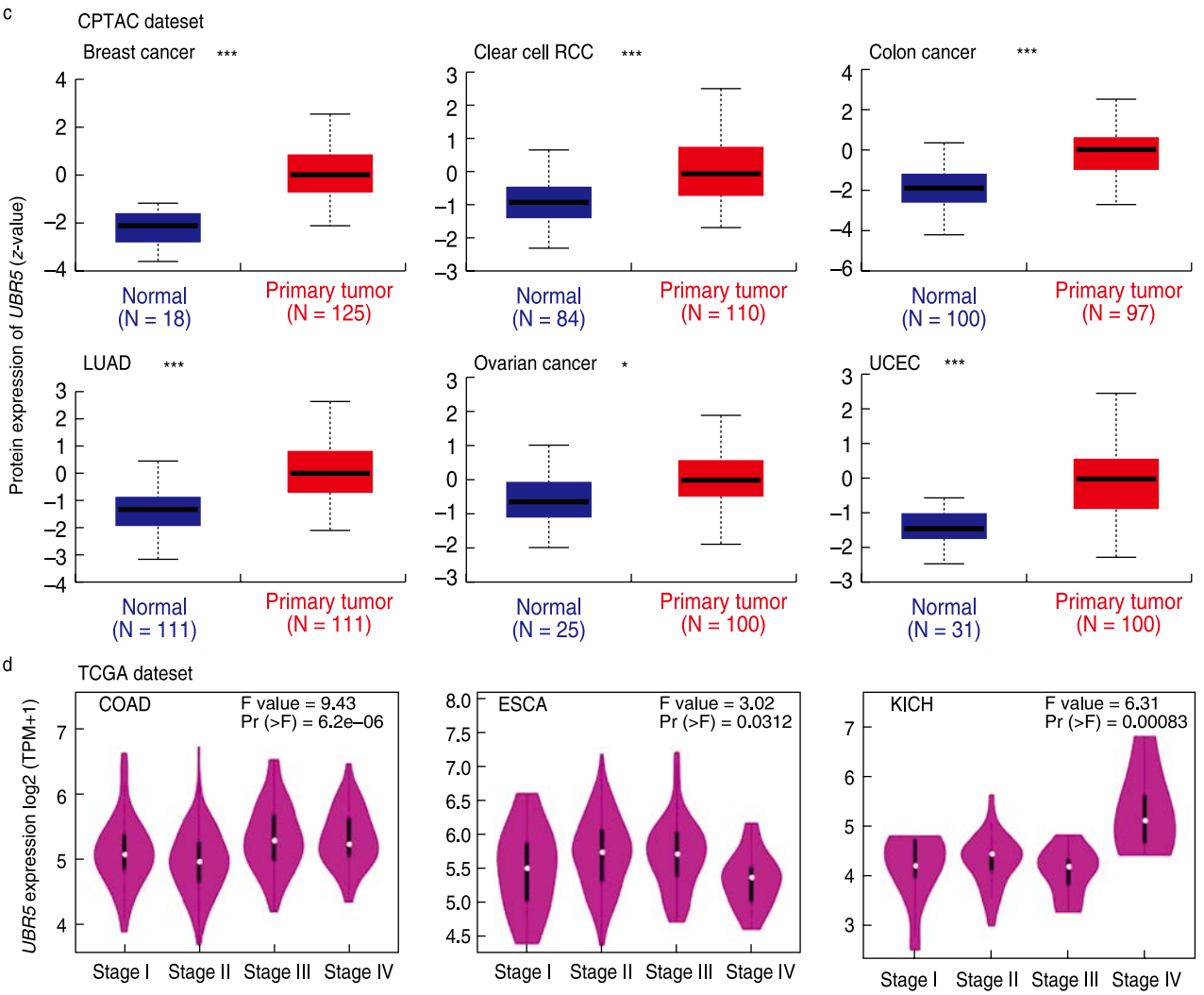


Fig. 1 Expression levels of the *UBR5* gene in different cancer samples. (a) *UBR5* expression status varies in different cancers through TIMER2, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$; (b) Differential expression of *UBR5* between the normal tissues and the tumor tissues through GEPIA2, $^{*}P < 0.05$; (c) Higher expression of *UBR5* total protein in the primary tissues through UALCAN, all $P < 0.05$; (d) Expression levels of *UBR5* in different pathological stages through GEPIA2, $P < 0.05$.

cancer using TCGA and GEO datasets. *UBR5* expression was linked to cancer prognosis: the Fig. 2 plot showing overall survival (OS) for BRCA ($P = 0.041$) within the TCGA project indicates that higher *UBR5* expression is linked to a poor prognosis. Disease-free survival (DFS) for PRAD ($P = 0.013$) and READ ($P = 0.037$) values also supported this conclusion.

Genomic alterations of *UBR5* in cancer

The cBioPortal was used to determine the genetic alteration status of *UBR5* in cancer, based on TCGA datasets. As shown in Fig. 3a, the highest alteration frequency was found in the bladder urothelial carcinoma tumor with "Amplification" as the primary type, whereas PCPG exhibited the lowest alteration among all of the cancer samples queried. It is noted that all uveal melanoma cases with genetic alterations showed copy number amplifications of *UBR5*. As shown in Fig. 3b, 519 mutations were identified in patients. Out of the alterations, 377 missense mutations, 126 truncating mutations, 4 in-frame mutations and 12 fusion mutations were detected. Missense mutations of *UBR5* were identified as the main type of genetic alteration, and E2121Kfs*28/E2121Rfs*13/K2120Rfs*13 alteration was predicted to induce a frame shift mutation of the *UBR5* gene. The 3D structure of the *UBR5* protein can be observed in Fig. 3c. In addition, genetic alterations have been found in patients with different types of cancer, which is related to survival prognoses. As shown in Fig. 3d, STAD cases with altered *UBR5* showed better

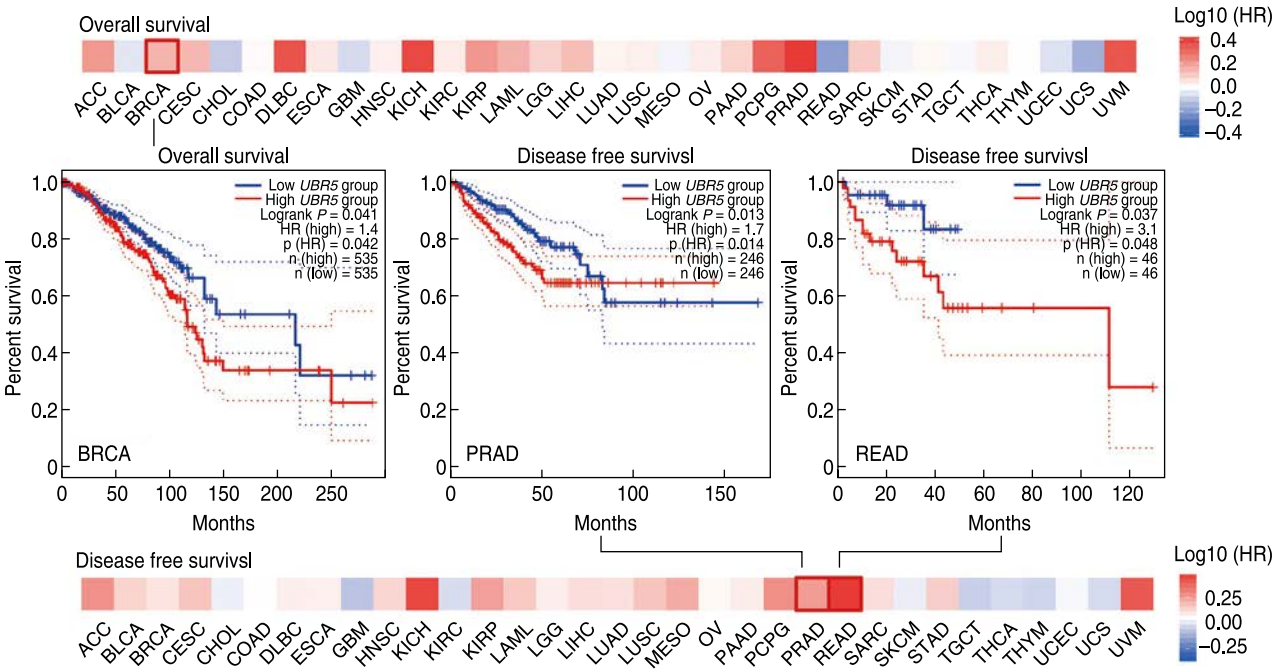
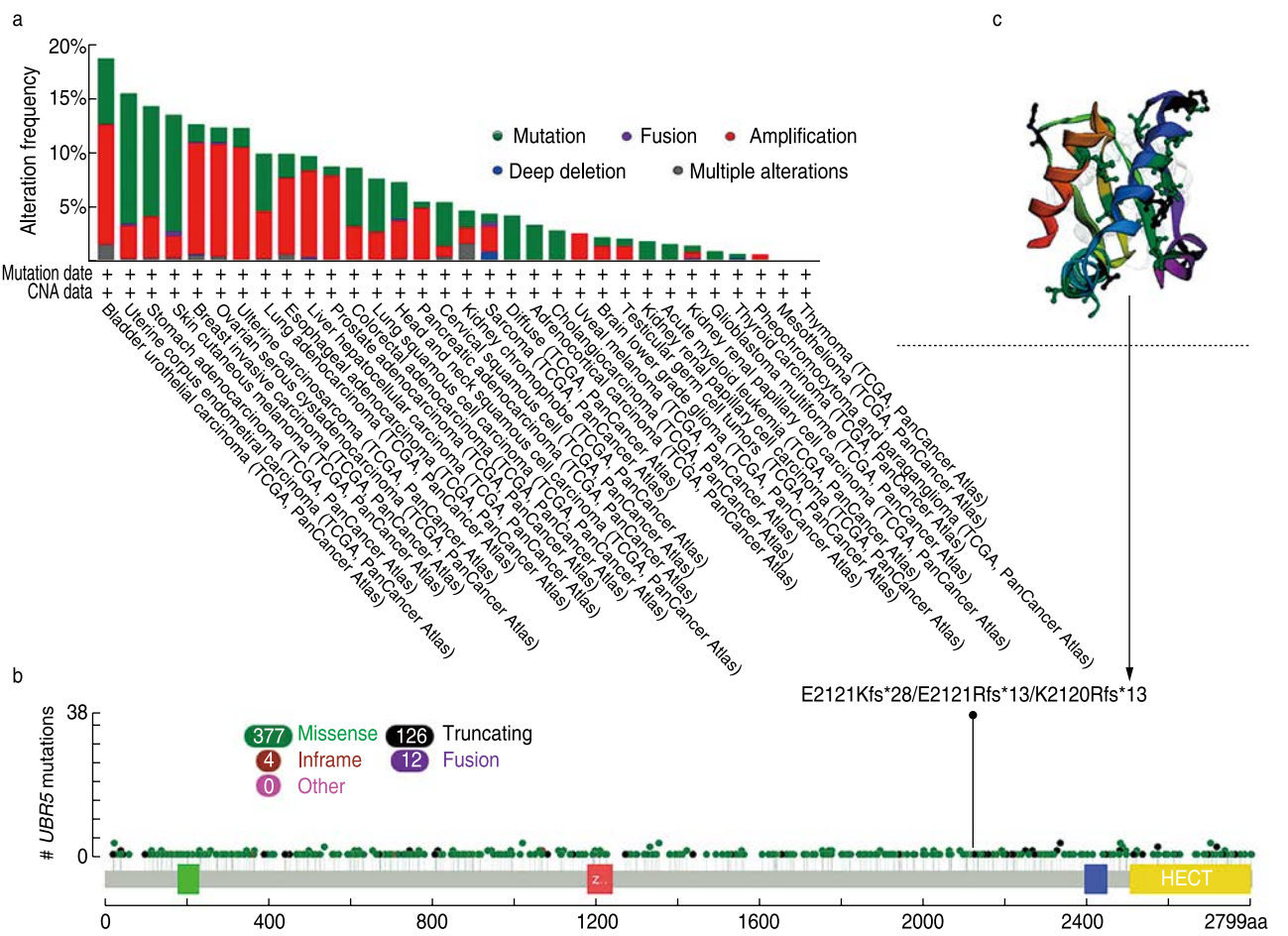


Fig. 2 Relationship between *UBR5* gene expression level and survival in cancer patients using GEPIA2. Clinical survival curves of BRCA (OS), PRAD (DFS), and READ (DFS) are presented, P < 0.05.



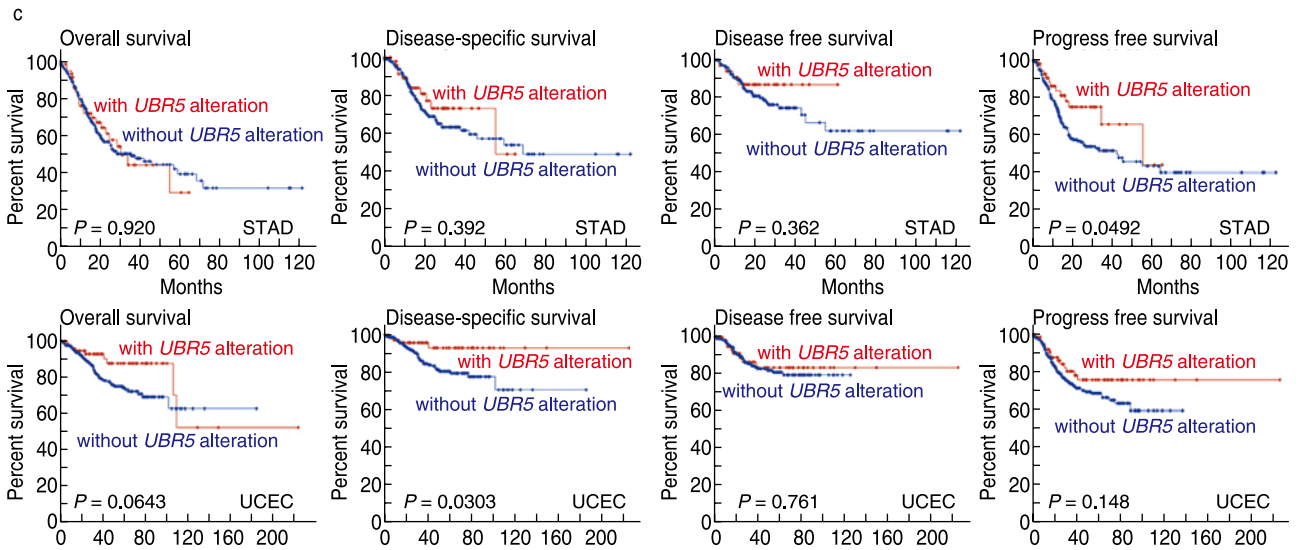


Fig. 3 Genetic features of mutations of *UBR5* in different tumors (cBioPortal). (a) Alteration frequency in different tumor samples; (b) Sites and case number of *UBR5* genetic alterations; (c) 3D structure of the *UBR5* protein; (d) Clinical survival curve of STAD and UCEC.

prognosis in progression-free (P = 0.0492), but not overall (P = 0.920), disease-specific (P = 0.392) and disease-free (P = 0.362) survival, compared with cases without *UBR5* alteration. UCEC cases with altered *UBR5* showed better prognosis in disease-specific (P = 0.0492), but not overall (P = 0.0643), disease-free (P = 0.761) and progression-free survival (P = 0.148), compared with cases without *UBR5* alteration.

Protein phosphorylation of *UBR5* in patients with cancer

We also investigated *UBR5* phosphorylation levels using the CPTAC dataset. Clear cell clear cell renal cell carcinoma (RCC), ovarian cancer, LUAD, UCEC and breast cancer were analyzed. The analysis of *UBR5* phosphoprotein expression level is presented in Fig. 4a. The clinical data showed a higher phosphorylation level of the S327 locus in all primary tumor tissues compared with that seen in normal tissues (Fig. 4b–f, all P < 0.05), followed by a lower phosphorylation level of the S636 locus for colon cancer (Fig. 4f, P = 1.2e-06), LUAD (Fig. 4d, P = 1.8e-05), colon cancer (Fig. 4f, P = 1.3e-14) and the S1549 locus for ovarian cancer (Fig. 4c, P = 5.2e-03),

Immune cell infiltration of *UBR5* in patients with cancer

Next, we used the TIMER2, TIDE, XCELL, MCPCOUNTER and EPIC algorithms to assess the correlations of *UBR5* expression with immune infiltration levels. Heat map of different expressed *UBR5* gene are further presented in Fig. 5a. We found a significant negative correlation between *UBR5* expression and the estimated infiltration value of cancer-associated fibroblasts for Testicular Germ Cell Tumor (TGCT). (Fig. 5b, *cor* = –0.242, P = 3,11e-03)

Enrichment analysis of *UBR5*-related partners

In an attempt to investigate the potential enrichment of particular molecular mechanisms in tumorigenesis, we attempted to screen out targeting *UBR5*-binding proteins and *UBR5* expression-related genes using STRING and GEPIA2. Fig. 6a showed the interaction network of 50 *UBR5*-binding proteins supported by experimental evidence. There were significant positive correlations between the expression level of *UBR5* and that of cell division cycle and apoptosis regulator 1 (*CCAR1*) (R = 0.56), Arginine/serine-rich coiled-coil 2 (*RSRC2*) (R = 0.52), Suppressor of mek1 (*SMEK1*) (R = 0.52), Ubiquitin specific peptidase 7 (*USP7*) (R = 0.52) and Zinc finger protein 7 (*ZNF7*) (R = 0.68) genes (all P < 0.001; Fig. 6b). As shown in Fig. 6c, the heatmap also revealed that the above-mentioned genes were positively correlated with *UBR5* in the majority of types of tumor. An intersection analysis of 50 *UBR5*-binding proteins and 100 *UBR5* expression-related genes showed one common member, namely, SRSF1 (Fig. 6d). In addition, the KEGG data suggested that “spliceosome” and “ubiquitin mediated proteolysis” pathways were involved in cancer progression. (Fig. 6e).

Discussion

It is understood that *UBR5* is a tumor-related gene that affects the biological behavior of tumors in many aspects,

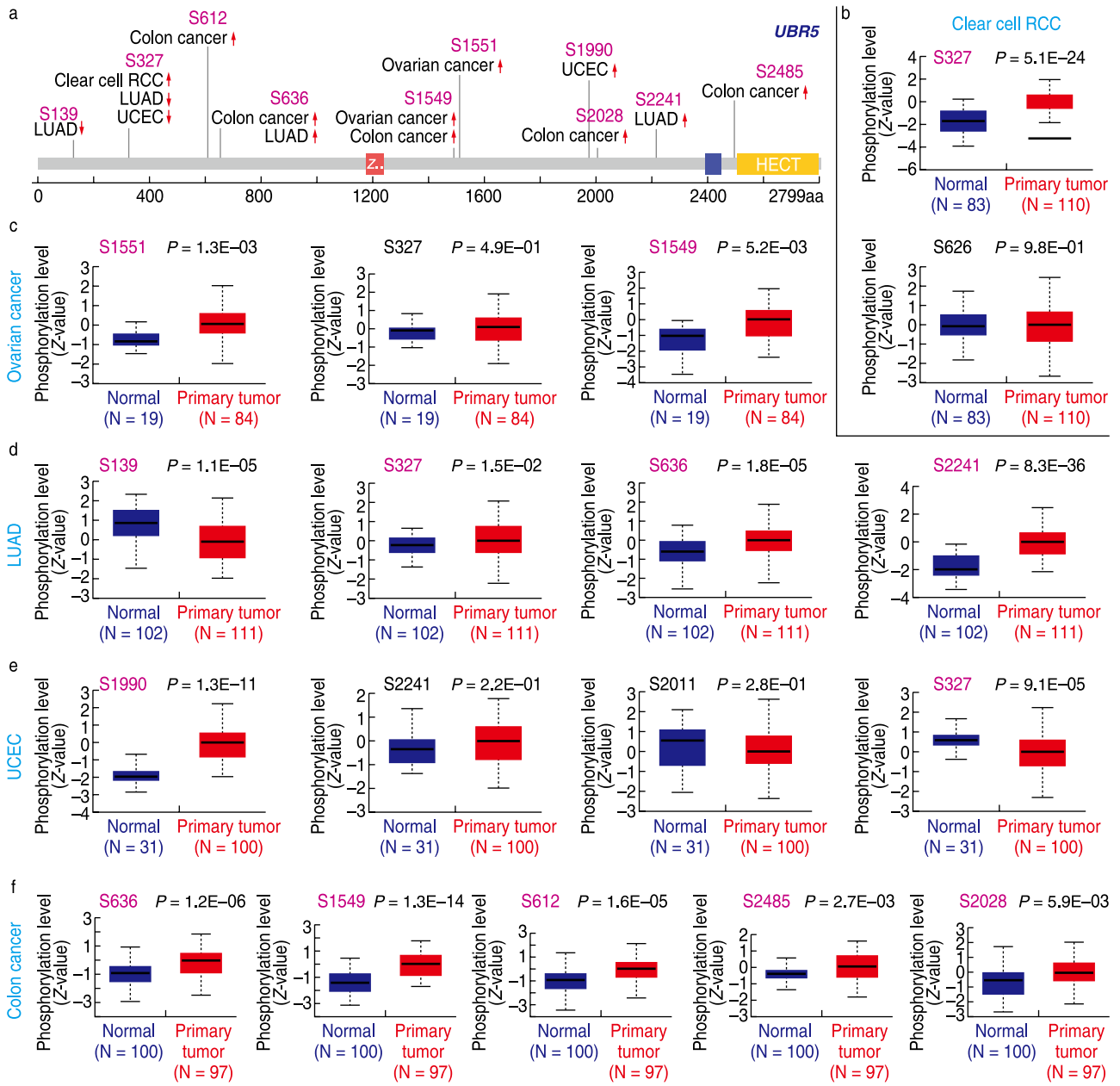


Fig. 4 Phosphorylation analysis of different tumors. (a) Analysis of *UBR5* phosphoprotein expression level based on the CPTAC dataset, S139, S327, S612, S626, S1549, S1551, S1990, S2028, S2241, and S2485; The box plots for different cancers, including clear cell RCC (b), ovarian cancer (c), LUAD (d), UCEC (e) and breast cancer (f), all $P < 0.05$.

such as cell cycle regulation, apoptosis regulation, tumor suppressor gene regulation, invasion and metastasis regulation [23]. Some studies have reported a correlation between the *UBR5* gene, tumor microenvironment, and cancer immunotherapy, suggesting that the gene may modulate tumor progression and provide an immunotherapeutic effect [24–25]. However, the prognostic value and the biological function of the *UBR5* gene in cancer has not been well-characterized. With further investigation into this gene, knowledge regarding its regulatory mechanism in cancer will become increasingly clear, which will aid in the molecular diagnosis and targeted therapy of cancer, as well as improving prognostic assessments in cancer patients. Thus, we present a comprehensive overview of the *UBR5* gene based on data from TCGA, CPTAC and GEO databases.

We first explored expression of the *UBR5* gene and its correlation with the pathological cancer stage. We found that 17 genes were differentially expressed in cancerous tissues compared with the corresponding control tissues

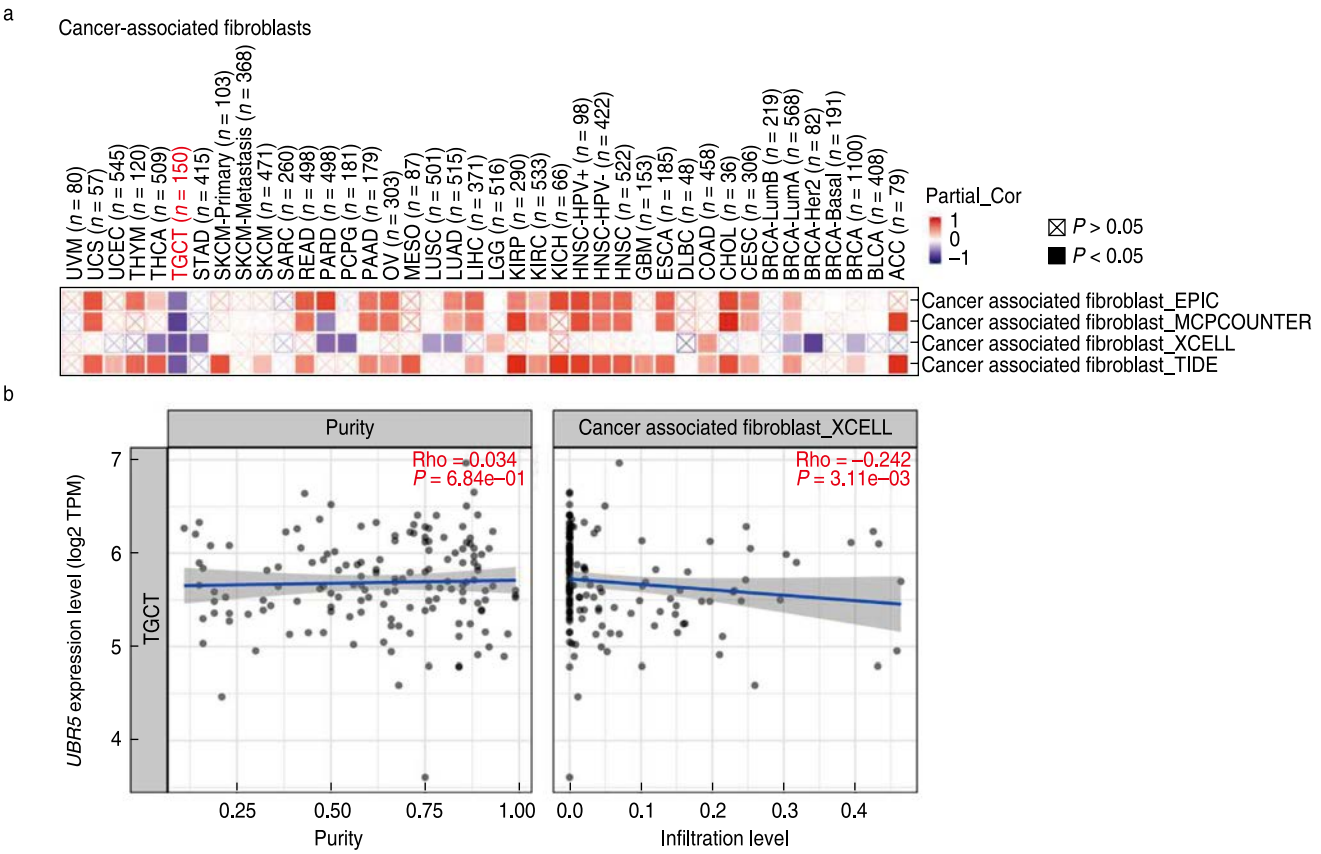
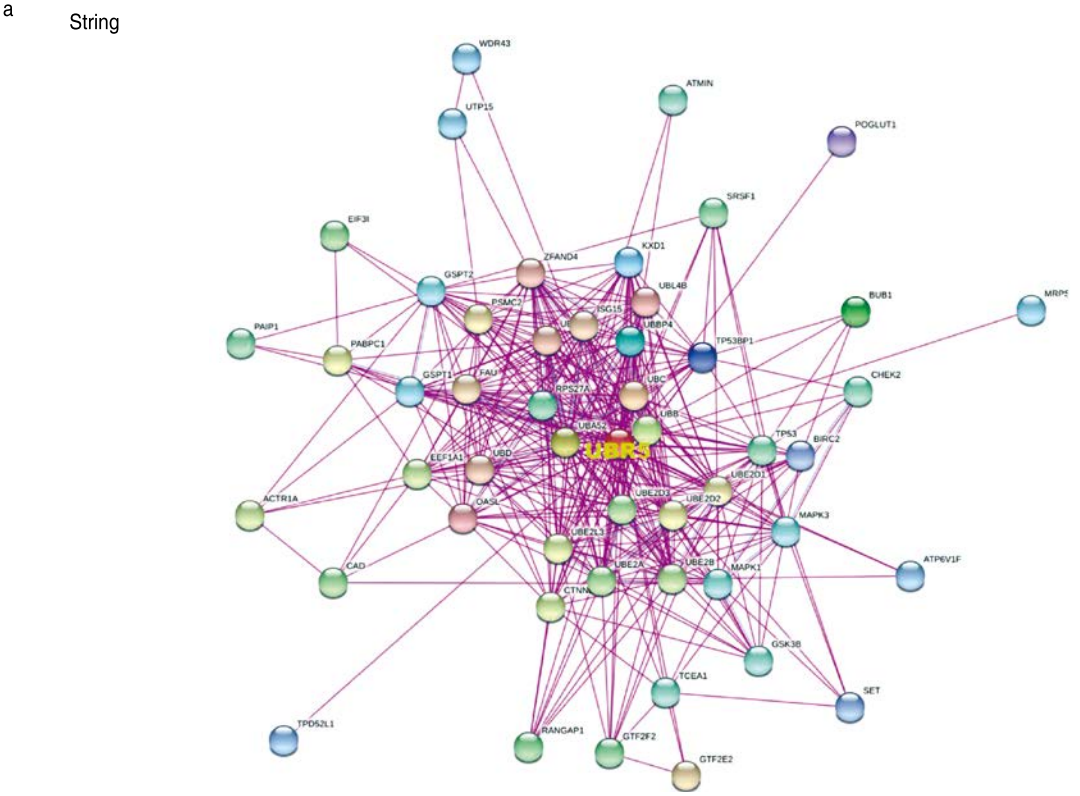


Fig. 5 Correlation analysis of *UBR5* in the tumor microenvironment and immune infiltration. (a) Correlation heat map of differentially expressed *UBR5* gene (TIMER2); (b) The correlation between differentially expressed *UBR5* gene and immune cell infiltration (TIMER2).



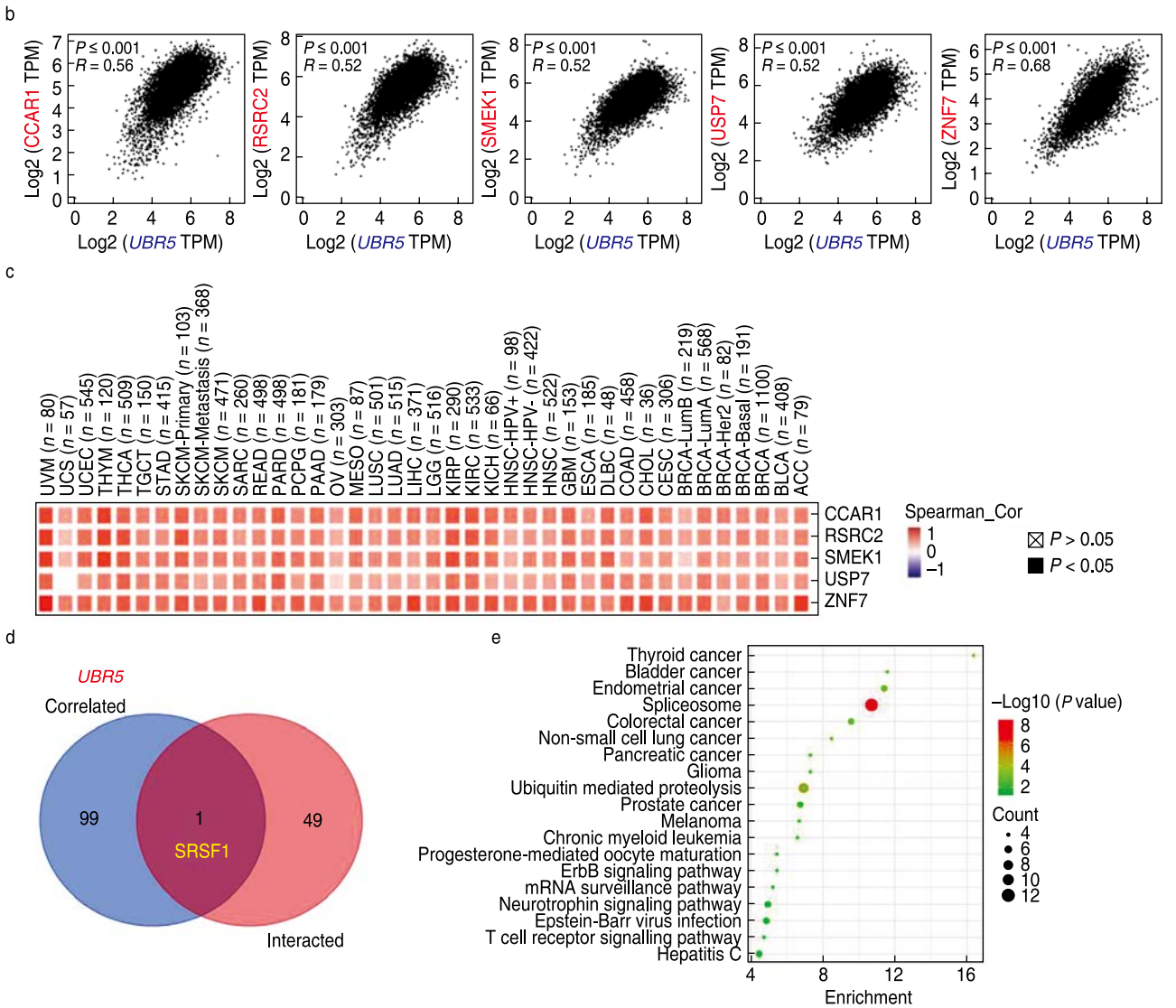


Fig. 6 *UBR5*-related gene enrichment analysis. (a) Interaction network of 50 *UBR5*-binding proteins through STRING tool; (b) *UBR5* expression level was positively correlated with that of CCAR1, RSRC2, SMEK1, USP7 and ZNF7 genes; (c) Correlation heat map of the differentially expressed *UBR5* gene; (d) One common member named SRSF1 was observed through intersection analysis; (e) *UBR5* expression-related genes for enrichment analysis.

(higher expression of BRCA, CHOL, COAD, ESCA, GBM, HNSC, LIHC, LUAD, LUSC, PCPG, PRAD, READ and STAD; lower expression of KICH, KIRC, THCA and UCEC). *UBR5* gene expression in cancerous tissues was further confirmed in studies from GTEx and CPTAC datasets. These data demonstrate that differentially expression of *UBR5* may play a significant role in cancer.

Furthermore, in BRCA, PRAD and READ patients, high expression of *UBR5* were significantly associated with a poor prognosis. Zhang *et al*. found that *UBR5* was overexpressed in gallbladder cancer tumor tissues and was significantly associated with tumor size, histological and tumor differentiation [26]. Yang *et al*. revealed that high expression of *UBR5* was associated with poor overall and disease-free survival in patients with gastric cancer [27]. This analysis demonstrates that *UBR5* may be an important biomarker for predicting the prognosis of patients with cancer.

Since the *UBR5* gene was significantly differentially expressed in cancer tissues, we explored its molecular characteristics. There were frequent genetic alterations in the *UBR5* gene expressed in cancer tissues, with mutation and amplification being the most common. It has been reported that the *UBR5* gene is localized to chromosome 8q22 [28]. Mutation and amplification occur frequently in this region in many types of cancer, including breast cancer, esophageal cancer and mammary ductal carcinoma [29–31]. Tumorigenesis and the progression

of cancer are complex and multi-faceted, and genetic alteration plays an important role in these processes. We found a low to high correlation of prognoses with the differential expression of the *UBR5* gene, suggesting that *UBR5* plays a synergistic role in tumorigenesis and the progression of cancer.

We then focused on protein phosphorylation of *UBR5* in patients with cancer using UALCAN. Phosphorylation is a formidable regulator of many proteins involved in essential intracellular processes. Studies have reported on the possible role of phosphorylation in both protein function and the progression of specific cancers [32]. Phosphorylation may provide key information about the derangements and serve as major targets for therapeutics, which is a rapidly growing area of cancer research [33]. The results showed that S327, S636 and S1549 all exhibited a higher phosphorylation level of *UBR5*. Bethard *et al*. revealed that *UBR5* has 477 potential phosphorylation sites. However, few studies have specifically targeted the identification of these phosphorylation sites [34]. Further laboratory studies to evaluate the potential role of *UBR5* phosphorylation in tumorigenesis are needed.

We also found a negative correlation between *UBR5* expression and immune infiltration of cancer-associated fibroblasts. Evidence indicates that cancer development is a complex process that involves interactions between tumor cells, stromal fibroblasts, and immune cells. Tumor-infiltrating immune cells play a role in the promotion or inhibition of tumor growth [35–37]. This analysis demonstrates the role of *UBR5* in the tumor microenvironment and the promotion or inhibition in different types of cancer.

Additionally, analysis of "protein processing in spliceosome" and "ubiquitin mediated proteolysis" pathways may bring novel insights into the potential association of *UBR5* with etiology or pathogenesis of cancers [38].

In conclusion, we hope these results will be a helpful guide to aid in helping diagnose cancer and to assist in the design of new immunotherapeutic drugs.

Conflicts of interest

The authors indicated no potential conflicts of interest.

Ethics approval and consent to participate

Ethics approval is not applicable because this study did not involve human or animal testing.

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DOI 10.1007/s10330-021-0515-5
Cite this article as: Wang GY, Yin ST, Justice A, *et al*. Effect of *UBR5* on the tumor microenvironment and its related mechanisms in cancer. Oncol Transl Med, 2021, 7: 294–304.