


Analysis of TRIM27 prognosis value and immune infiltrates in hepatocellular carcinoma

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Abstract

Up-regulation of tripartite motif-containing 27 (TRIM27) in varieties of tumors found that TRIM27 advanced tumor metastasis and invasion. Nevertheless, the relation of TRIM27 and immune infiltration in hepatocellular carcinoma (HCC) and the prognostic value of TRIM27 expression is unknown. We assessed TRIM27 association with immune infiltrates and the prognostic value of TRIM27 in HCC. From the Cancer Genome Atlas, we obtained TRIM27 transcriptional expression profiles of HCC and normal tissues. Using the Human Protein Atlas to evaluate the expression TRIM27, protein-protein interaction (PPI) networks were produced using the STRING database. Functional enrichment analysis was performed by using the clusterProfiler package. The tumor immune estimation resource was used to determine the relation of TRIM27 expression and immune infiltrates. We found that the expression of TRIM27 was up-regulated in HCC tissues compared with adjacent normal tissues. High TRIM27 expression correlated with high pathologic stage and high TNM stage. The receiver operating characteristic curve of TRIM27 area was 0.946. Kaplan–Meier analyses showed poor prognosis in HCC patients with high expression of TRIM27. Correlation analysis suggested that the expression of TRIM27 was related to immune infiltrates and tumor purity. This study indicated in HCC up-regulated the expression of TRIM27 is correlated to poor survival and immune infiltration. TRIM27 is an underlying target of immune therapy and is an underlying biomarker for poor prognosis in HCC.

Keywords

Biomarker, tripartite motif-containing 27, hepatocellular carcinoma, immune infiltrates, prognosis

Introduction

Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer.¹ The treatment methods for HCC patients have improved and include systemic therapy, trans-hepatic arterial chemotherapy, liver transplantation, and surgical resection. Nevertheless, the 5-year survival of patients with HCC is nonetheless unfavorable, second lowest only to pancreatic carcinoma.² Early-stage patients may benefit from surgical resection, while chemotherapy is the first choice for patients with advanced and unresectable disease.³ Patients in early stage may obtain benefit from excision, whereas for advanced and unresectable disease patients, chemotherapy is the first choice. Advanced HCC

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patients with early intrahepatic recurrence after surgery⁴ present poorer prognoses, especially in the presence of vascular invasion.⁵ Recent studies have reported that the use of immunotherapy for patients with liver cancer is especially promising.⁶⁻⁹ Therefore, identifying prognostic biomarkers and therapeutic targets of HCC immunotherapy is essential.

The tripartite motif (TRIM) protein family members are individualized by the existence of three domains: a coiled-coil region, a domain containing B-box domains and a RING finger domain; the TRIM proteins C-terminal region is highly variable.¹⁰ The TRIM27 protein, a member of the TRIM family, is appeared in most human organs.¹¹ Recent studies have found a cancer-promoting role of TRIM27 in various cancer types, including lung cancer, endometrial cancer, and breast cancer.¹²⁻¹⁴ These evidences are consistent with the correlation between TRIM27 expression and the natural history of cancer, indicate the role of this gene and its coded outcomes in cancer development. Nevertheless, in HCC, the TRIM27 prognostic value and its expression has not been fully elucidated. In addition, in HCC, the relationship between TRIM27 and tumor immune infiltration remains indistinct.

In our study, we assessed the expression of TRIM27 in a variety of human cancers. We discovered that TRIM27 is up-regulated in HCC, and the up-regulation of TRIM27 is related to adverse clinical features and risk factors in HCC patients. We found that TRIM27 overexpression is correlation with poor survival of HCC patients. This study ulteriorly found in HCC the TRIM27 diagnostic and prognostic value and the relationship between immune infiltrates and TRIM27.

Materials and methods

The cancer genome atlas dataset analysis

We downloaded from The Cancer Genome Atlas (TCGA) database (<https://genome-cancer.ucsc.edu/>) about TRIM27 corresponding clinical information and transcriptional expression data. After normalizing the data, analyze the differential expression of TRIM27 was used by the R package limma (3.6.3).¹⁵

The Human Protein Atlas (HPA)

The HPA (<https://www.proteinatlas.org/>) includes protein expression data from tumor tissues and normal tissues.^{16,17} We contrasted TRIM27 protein expression in HCC tissue and normal liver tissue by the HPA, the expressions of cancers/pericarcinomas with similar ages and the same location and quantity.

GEPIA database analysis

GEPIA (<http://gepia.cancer-pku.cn/>) is a network tool based on TCGA and Genotype Tissue Expression data for normal and cancer gene expression profiles and interactive analysis.¹⁸ Survival analysis of HCC patients was performed by GEPIA, including analyses of disease-free survival (DFS) and overall survival (OS). Log-rank p value $<.05$ was considered as statistically significant.

Protein-protein interaction networks and functional enrichment analysis

Online database of STRING version 11.0 (<https://www.string-db.org/>) to search for interacting genes to construct PPI networks.¹⁹ We performed a STRING search for co-expressing genes of TRIM27 and constructed a PPI network with an interaction score >0.4 . Gene Ontology (GO) enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis of co-expressing genes were performed using the “clusterProfiler” package and visualized by the “ggplot2” package.^{20,21}

The tumor immune estimation resource database

Tumor immune estimation resource database (<https://cistrome.shinyapps.io/timer/>) is an online resource for the systematic analysis of immune infiltration in various cancer types.²² We used TIMER to determine the relationship between the expression level of TRIM27 and the level of immune cell infiltration in HCC. p value $<.05$ was considered as statistically significant.

Statistical analyses

All statistical analyses were performed with R (V 3.6.3) (<https://www.r-project.org/>) and R package ggplot2 (V 3.3.3) was used to visualize expression differences. The differences between HCC tissues and adjacent normal tissues were determined by Mann–Whitney U -test and Paired t -test. Using the ROC package Kaplan–Meier to perform ROC curve in order to detect the cutoff value of TRIM27. To evaluate the effect of TRIM27 on survival through log-rank tests with the survminer package (<https://CRAN.R-project.org/package=survminer>).

Results

TRIM27 expression pattern in pan-cancer and up-regulated mRNA and protein expression of TRIM27 in HCC patients.

We assessed TRIM27 mRNA expression pattern in different cancer types using TCGA. As shown in Figure 1(a),

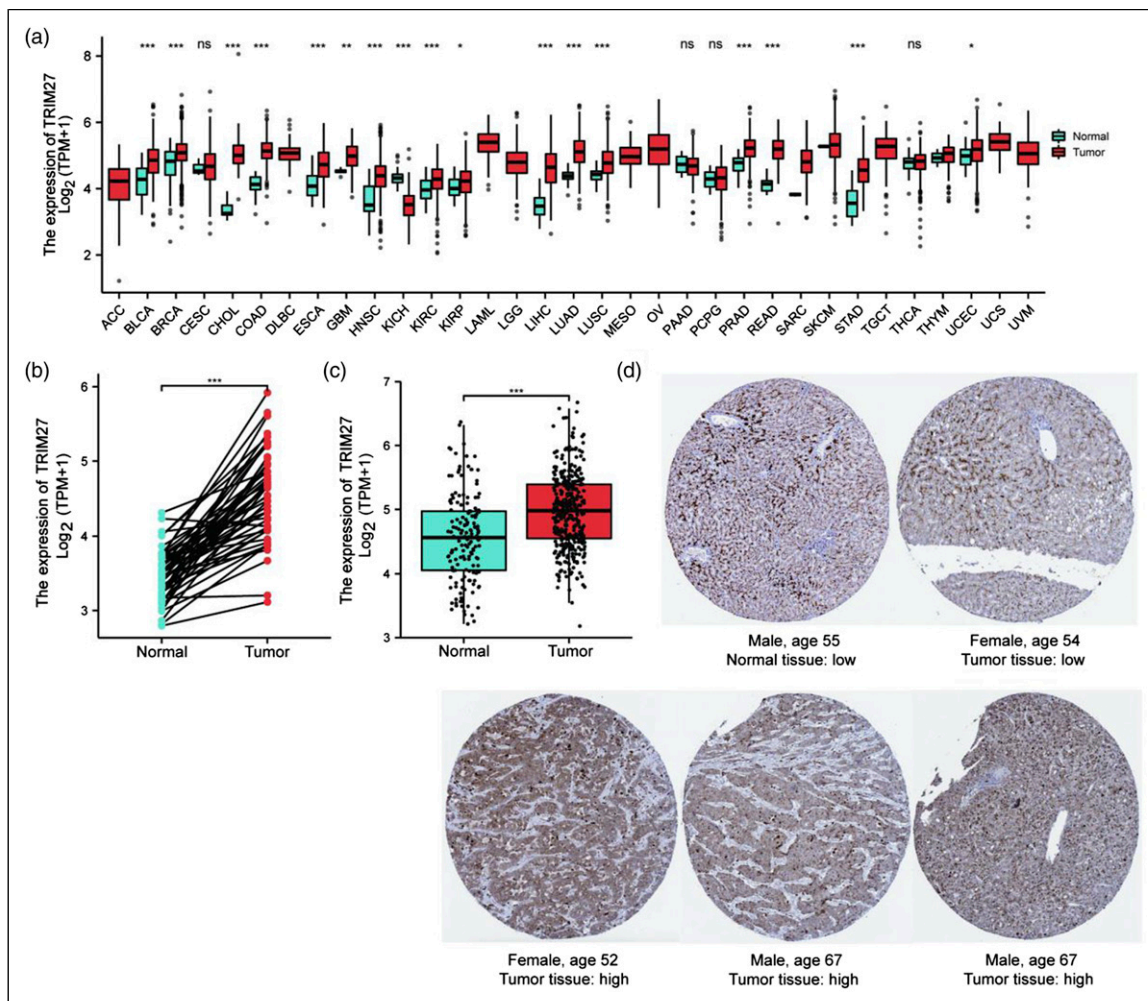


Figure 1. Expression pattern of TRIM27 in Pan-cancer perspective and the mRNA and protein expression of TRIM27 in hepatocellular carcinoma. (a) The mRNA expression of TRIM27 was up-regulated in 16 of 33 cancer types compared with normal tissues. (b) The mRNA expression levels of TRIM27 in 50 hepatocellular carcinoma and matched-adjacent normal samples. (c) The mRNA expression levels of TRIM27 in 374 hepatocellular carcinoma samples and 50 normal samples. (d) The protein levels of TRIM27 based on Human Protein Atlas. Normal tissue, <https://www.proteinatlas.org/ENSG00000204713-TRIM27/tissue/liver#img>; Tumor tissue, <https://www.proteinatlas.org/ENSG00000204713-TRIM27/pathology/liver+cancer#img>. (*** $p < .001$, ** $p < .01$, * $p < .05$).

in 16 of the 33 cancer types, markedly up-regulated of TRIM27 mRNA in tumor tissues compared with that in non-tumor tissues. Using data from TCGA and HPA to analyze the expression of TRIM27 showed that TRIM27 is more expressed in liver tumors than in hepatocyte. As shown in Figure 1(b), paired data analyses indicated that the mRNA expression of TRIM27 in HCC tissues was higher than that expression in adjacent normal hepatocyte ($p < .001$). Analysis of unpaired data also indicated that the mRNA expression of TRIM27 was more up-regulated in HCC tissues than that expression in adjacent normal hepatocyte (Figure 1(c), $p < .001$). HPA indicated that immunohistochemical staining of TRIM27 protein

was higher in HCC tissues than that expression in normal hepatocyte (Figure 1(d)). These results revealed in HCC tissues that expressions of TRIM27 are up-regulated both in the mRNA and protein.

Relationships between the mRNA expression of TRIM27 and the characteristics of clinical and pathological in HCC patients

We next evaluated the correlation between TRIM27 mRNA expression with clinicopathological features in

HCC patients from TCGA. Up-regulated expression of TRIM27 was associated with high T stage ($p = .001$) and high pathological stage ($p = .001$). Also, we observed no significant correlation between TRIM27 expression and other clinicopathological features, such as M stage ($p = 1.000$), N stage ($p = .361$), age ($p = .232$), body mass index ($p = .463$), gender ($p = .658$), AFP ($p = .445$), and Ishak fibrosis score ($p = .240$), as shown in Table 1. These results indicated that TRIM27 is associated with high TNM stage and high pathological stage. Therefore, TRIM27 may serve as a biomarker for poor prognosis in HCC.

ROC curve evaluation of TRIM27 to distinguish HCC samples from normal samples

We conducted ROC curve analysis of the distinction of HCC samples and normal samples for investigating the value of TRIM27 expression. And the results indicated that the AUC value of TRIM27 is 0.946 (95% CI: 0.923–0.970) (Figure 2(a)). With a cutoff value of 3.786, the specificity and sensitivity of TRIM27 are 91.4 and 88.0%, respectively. These findings showed that a promising biomarker of TRIM27 to distinguishing HCC tissues from normal tissues.

Table 1. Clinical characteristics of the hepatocellular carcinoma patients (TCGA).

Characteristic	Low expression of TRIM27	High expression of TRIM27	p
<i>n</i>	187	187	
T stage, <i>n</i> (%)			
T1	109 (29.4%)	74 (19.9%)	0.001**
T2	33 (8.9%)	62 (16.7%)	
T3	38 (10.2%)	42 (11.3%)	
T4	6 (1.6%)	7 (1.9%)	
N stage, <i>n</i> (%)			
N0	123 (47.7%)	131 (50.8%)	0.361
N1	3 (1.2%)	1 (0.4%)	
M stage, <i>n</i> (%)			
M0	132 (48.5%)	136 (50%)	1.000
M1	2 (0.7%)	2 (0.7%)	
Pathologic stage, <i>n</i> (%)			
Stage I	103 (29.4%)	70 (20%)	0.001**
Stage II	31 (8.9%)	56 (16%)	
Stage III	38 (10.9%)	47 (13.4%)	
Stage IV	3 (0.9%)	2 (0.6%)	
Gender, <i>n</i> (%)			
Female	63 (16.8%)	58 (15.5%)	0.658
Male	124 (33.2%)	129 (34.5%)	
Age, <i>n</i> (%)			
≤60	95 (25.5%)	82 (22%)	0.232
>60	92 (24.7%)	104 (27.9%)	
BMI, <i>n</i> (%)			
≤25	87 (25.8%)	90 (26.7%)	0.463
>25	86 (25.5%)	74 (22%)	
AFP (ng/ml), <i>n</i> (%)			
≤400	113 (40.4%)	102 (36.4%)	0.445
>400	30 (10.7%)	35 (12.5%)	
Fibrosis Ishak score, <i>n</i> (%)			
0	43 (20%)	32 (14.9%)	0.240
1/2	15 (7%)	16 (7.4%)	
3/4	11 (5.1%)	17 (7.9%)	
5/6	35 (16.3%)	46 (21.4%)	

** $p < .01$.

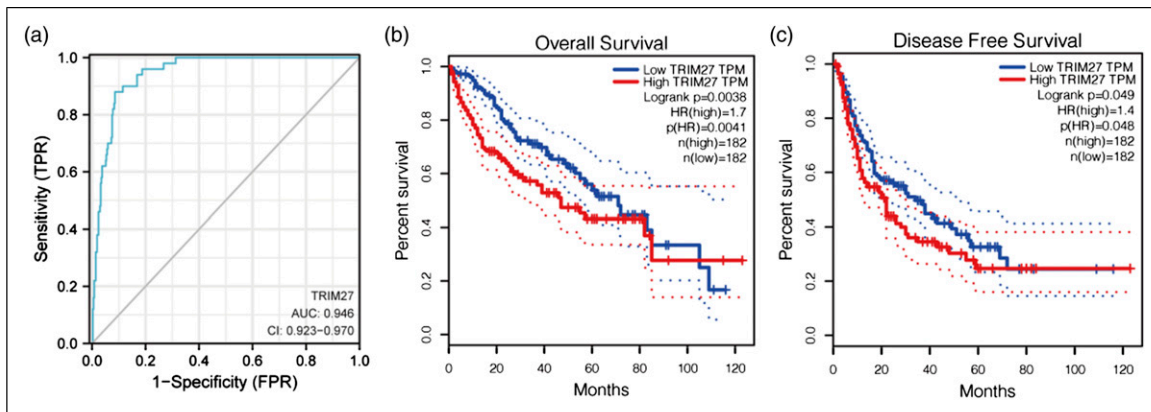


Figure 2. ROC and Kaplan–Meier curves for TRIM27. (a) ROC curve for hepatocellular carcinoma patients based on TRIM27 expression. Kaplan–Meier survival curves indicated that hepatocellular carcinoma patients with high TRIM27 mRNA expression had a shorter OS (b, $p = .0038$) or RFS (c, $p = .049$) than those with low-level of TRIM27.

TRIM27 prognostic values in HCC

Using HCC samples from the GEPIA database, we conducted survival analysis of TRIM27 expression including two prognostic indicators of OS and RFS. In OS analysis, increased TRIM27 expression in HCC was significantly shorter, as shown in Figure 2(b) ($p < .01$). In RFS analysis, increased TRIM27 expression in HCC had an unfavorable prognosis (Figure 2(c), $p < .05$). These findings suggest TRIM27 may be an unfavorable prognostic biomarker for HCC patients.

PPI networks and functional annotations

We construct the PPI network and function annotations conducted by GO analyses, STRING database and KEGG. Figure 3(a) shows TRIM27 network and 10 co-expression genes of TRIM27. Changes in TRIM27 biological processes were related to mitotic nuclear division, nuclear division, and organelle fission, as shown in Figure 3. The relationships between TRIM27 expression and expressions of the 10 co-expressed genes in HCC from TCGA are shown in Figure 3(c)–(i).

Analysis of the correlation between TRIM27 expression and immune cell infiltration in HCC

Immune infiltration plays an important part about the formation and evolution of HCC.²³ By the TIMER database, the study next examined the correlation between TRIM27 expression and seven forms of tumor-infiltrating immune cells. The SCNA defined using TIMER included arm-level deletions, diploid/normal, arm-level gain, and high amplification. TRIM27 SCNA (arm-level gain, high amplification) affected the levels of infiltrating B cells, macrophages, and neutrophils (Figure 4(a)). We next evaluated the relationship

between TRIM27 expression and immune cell infiltration level. TRIM27 expression was positively related to macrophage ($r = 0.245$, $p = 4.51e-06$), CD4⁺ T cell ($r = 0.254$, $p = 1.83e-06$), neutrophil ($r = 0.265$, $p = 5.92e-07$), B cell ($r = 0.195$, $p = 2.68e-04$), and dendritic cell ($r = 0.261$, $p = 1.07e-06$) infiltration (Figure 4(b)). These results showed that in HCC, TRIM27 might be a part in immune infiltration.

Correlation between TRIM27 and immune checkpoints in HCC

In tumor immune escape, CTLA-4 and PD-1/PD-L1 are important primary immune checkpoints. Premeditating the latent oncogenic role of TRIM27 in HCC. We next examined the correlation between TRIM27 and CTLA-4 or PD-1, PD-L1 in HCC. TRIM27 expression was positively related to CTLA-4 and PD-1, PD-L1 in HCC, adjusted by purity, as shown in Figure 5(a)–(c). The findings indicate that TRIM27-mediated HCC oncogenic might through tumor immune escape.

Discussion

HCC is a highly malignant disease; the poor overall prognosis of HCC patients is due to disease aggressiveness and frequency of recurrence.²⁴ For patients with tumor of liver, the preferred treatment is operation.²⁵ However, patients received operative resection relapsed within 5 years at a rate of 60%–70%.²⁶ Clarifying the molecular mechanism of HCC oncogenic might supply important thread about the development of efficacious therapeutical aims and identification of the biomarkers of prognostic.^{27,28} In a variety of human cancers, TRIM27

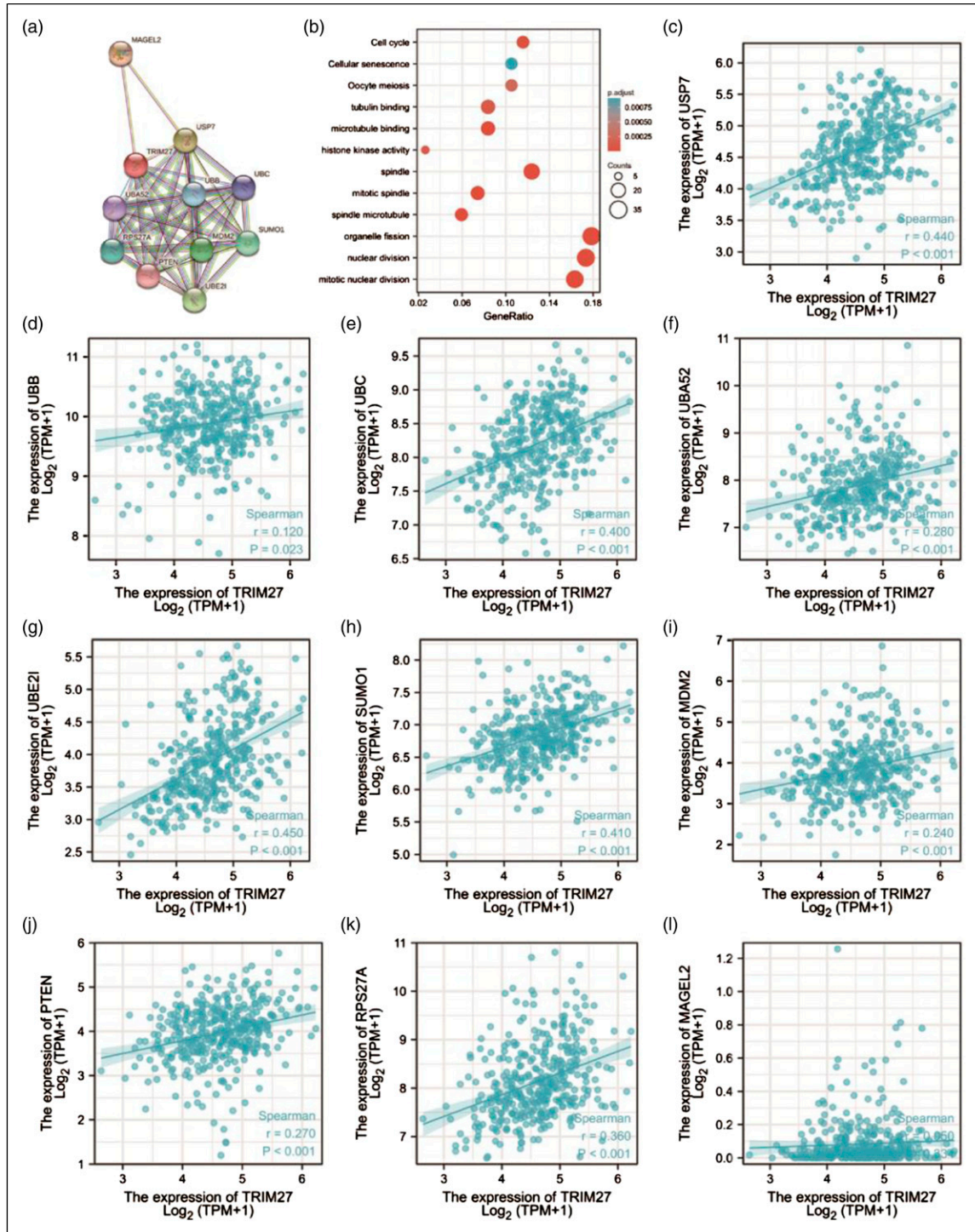


Figure 3. PPI networks and functional enrichment analyses. a) A network of TRIM27 and its co-expression genes. (b) Functional enrichment analyses of 11 involved genes. (c–l) The correlation analyses between the expression of TRIM27 and co-expressed genes in hepatocellular carcinoma.

supplies important thread in the occurrence and progression, including HCC. Nevertheless, knowledge in HCC of TRIM27 expression and prognostic value is still insufficient.

A pan-cancer analysis carried out about the expression of TRIM27 through TCGA data in the study found that TRIM27 expression was increased in HCC tissues. Increased TRIM27 expression was positively correlative to highly pathological

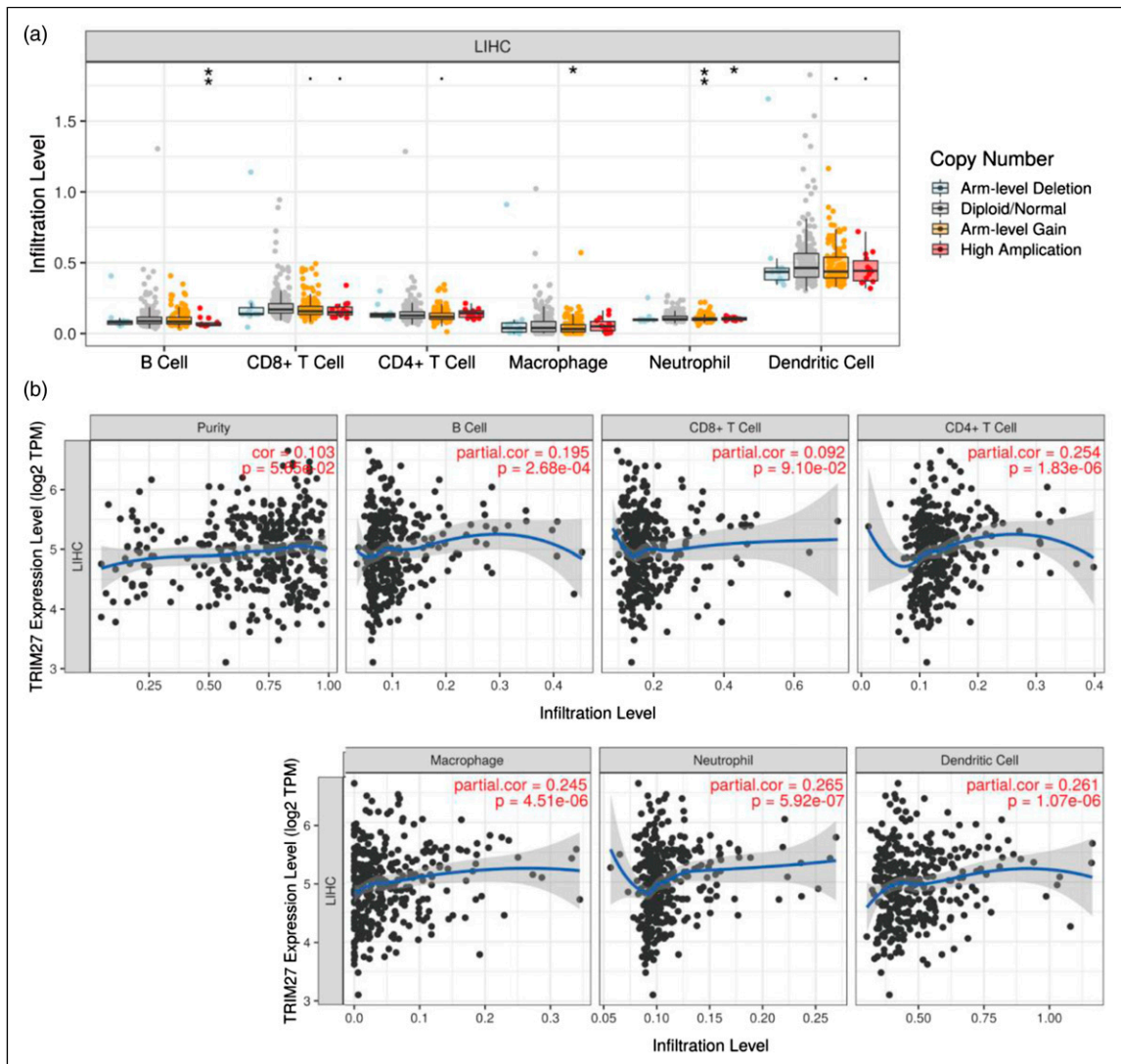


Figure 4. The relationship of immune cell infiltration with TRIM27 level in HCC. (a) The infiltration level of various immune cells under different copy numbers of TRIM27 in HCC. (b) The correlation of TRIM27 expression level with B cell, CD8⁺ T cell, CD4⁺ T cell, macrophage, neutrophil, or dendritic cell infiltration level in HCC.

stage and TNM stage. TRIM27 may be a bright diagnostic biomarker for distinguishing HCC from normal tissues through ROC curve analysis. Through univariate analysis and Kaplan–Meier curve analysis, high TRIM27 expression shows relevance to short OS or RFS; also, TRIM27 might be a latent biomarker toward poorer prognosis in HCC. In conclusion, these findings indicate that TRIM27 may supply important thread in immune infiltration in HCC.

The family of TRIM protein can still be thought to contain various regulative proteins of tumors. TRIM27, part of the TRIM family, exhibits a cancer-promoting role by enhancing tumor proliferation and metastasis in a variety of tumors. Research reported that knockdown TRIM27 remarkably weakened the transitivity and

invasiveness of endometrial cancer cells, and also lowered the integrins b1 and a2 levels.¹³ The mutation of TRIM27 has been reported by Iwakoshi et al. that is contained in the signaling of epidermal growth factor receptor (EGFR) in lung cancer, and TRIM27 can be used as a prognostic factor of EGFR mutations in lung cancer. However, in HCC, TRIM27 expression and prognostic value of TRIM27 have still not been examined. In the study, pan-cancer analysis was performed and these findings were accordant to previous findings on the abnormal expression of TRIM27 mRNA in various cancers. We found that TRIM27 is up-regulated in HCC, and high TRIM27 expression is positively correlated with high pathological staging and TNM staging.

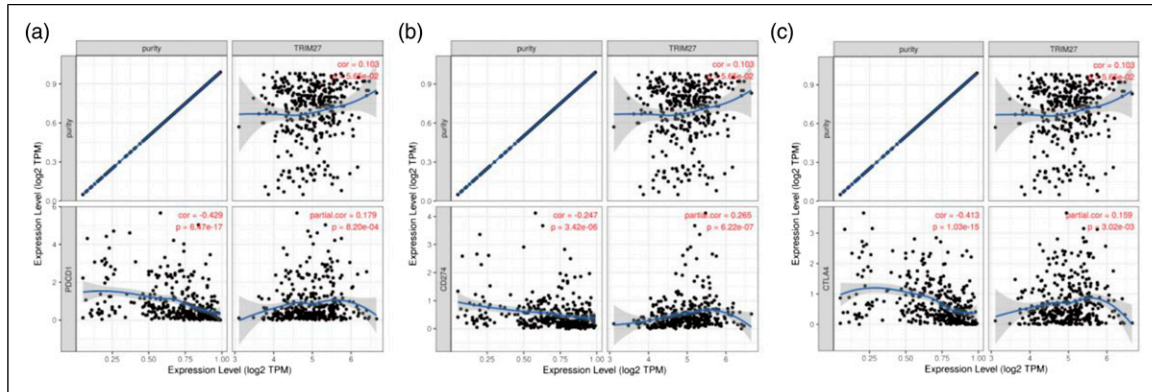


Figure 5. Correlation of TRIM27 expression with PD-1, PD-L1, and CTLA-4 expression in HCC. Spearman correlation of TRIM27 with expression of PD-1 (a), PD-L1 (b), CTLA-4 (c) in HCC adjusted by purity using TIMER.

These findings show in HCC that TRIM27 might serve as a latent biomarker of poorer prognosis. Confirmed the clinical worth of TRIM27 about HCC, we performed ROC curve analysis. These results indicated the potential value of TRIM27 in HCC detection. Our findings showed that TRIM27 might be a potential diagnostic biological marker to distinguish HCC from normal samples. In addition, log-rank test analysis and Kaplan–Meier curve showed a lower survival rate with higher TRIM27 expression in HCC patients. Based on the data, we conclude that TRIM27 may represent a latent biomarker of poorer prognosis of HCC.

Our co-expression analysis showed that TRIM27 expression was significantly correlated with the expressions of ubiquitin specific peptidase 7 (USP7), recombinant small ubiquitin-related modifier protein 1 (SUMO1) and the product of murine double minute 2 gene (MDM2). TRIM27 is an important component of the TRIM27-USP7 complex and participates in cell metabolism. The ubiquitination–deubiquitination cascade mediated by the TRIM27-USP7 complex plays an important role in TNF- α -induced apoptosis.²⁹ Maat et al. proposed a model in which USP7 counteracts the activity of TRIM27 E3 ligase, thereby maintaining the integrity and function of PRC1.1. Inhibiting USP7 may be a promising new strategy for the treatment of acute myeloid leukemia patients.³⁰ TRIM27 is a member of the TRIM family of E3 ubiquitin ligases, MDM2 functioning as an E3 ubiquitin ligase mediated p53 degradation to regulate this critical tumor suppressor.³¹ Current functional information indicates that TRIM27 is associated with a variety of subcellular topologies and processes. Several interactions of TRIM27 with other proteins have been reported including with the E3 SUMO protein ligase PIAS3.^{32,33} We speculate that up-regulation of TRIM27 would affect the entire pathway, and this possibility should be examined in future studies.

A large number of researches have certified that the prognostic and the efficacy of radiotherapy, immunotherapy, and chemotherapy of patients with cancer can be influenced by tumor immune cell infiltration.^{34–36} This study showed that TRIM27 was positively related to a variety of immune cells in HCC, involving macrophage, dendritic cell, CD4⁺ T cell, neutrophil, and B cell. In conclusion, TRIM27 is also remarkably positively related to these biomarkers of infiltrating immune cells. Our data show tumor immune infiltration might partly explain carcinogenic effect of TRIM27 in HCC.

The effect of immune therapy not merely requires the tumor microenvironment sufficient infiltrate by immune cells, but also relies on the full immune checkpoints expression.³⁷ Therefore, this study evaluated correlation between TRIM27 and immune checkpoints. Our findings showed the higher TRIM27 expression was closely related to CTLA-4 and PD-1, PD-L1 in HCC, suggesting that it improved the effect of immune therapy through targeting TRIM27 in HCC.

There are definitely limitations to our study. A database used to confirm the correlation between the expression of TRIM27 and HCC to enlarge the sample size and make sure the accurateness of the experimental outcomes. The data we owned from multiplex databases to narrow the deviation that a single database might cause. Future studies need to carry out related animal and cell experiments, forward to study the potential roles of TRIM in HCC.

Conclusions

We demonstrated that TRIM27 is highly expressed in many types of human cancers including HCC and showed that TRIM27 represents a potential biomarker of poor prognosis to identify HCC patients with adverse clinical outcomes. Our results also showed that TRIM27 may exert its carcinogenic effects by increasing tumor immune cell

infiltration and immune checkpoint expression. These findings should be verified by additional experiments and large-scale clinical trials.

Authors' contributions

WHC, ZY and YL drafted the manuscript and performed the data analysis. YB designed the experiments. LQ and LJ collected the data, which was supervised by YB. All authors have reviewed and approve the final manuscript.

Declaration of conflicting interests

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Data availability statement

Data and material availability can be obtained from corresponding author on request.

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