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Identification of LOXL3-Associating Immune Infiltration Landscape and Prognostic Value in Hepatocellular Carcinoma

Ning Wang (wn20121004@126.com)
Tianjin Third Central Hospital https://orcid.org/0000-0003-3103-4636
Xue Zhou
Tianjin Haihe Hospital
Fei Tang
Tianjin Third Central Hospital
Xue Wang
Tianjin Third Central Hospital
Xiaowei Zhu
Tianjin Third Central Hospital

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Abstract

Hepatocellular carcinoma (HCC), the most common type of hepatic malignancies, remains a global health challenge with multiple aetiologies and low five-year survival rate. In recent years, breakthroughs in the field of tumor immunotherapy with immune checkpoint inhibitors (ICIs) have made a therapeutic revolution, which has been shown to improve the prognosis of patients with HCC. Immune infiltrates represent a major component of tumor microenvironment (TME), and play an essential role in both tumor progression and therapeutic response. The major unmet challenge in tumor immunotherapy is exploring the intrinsic and extrinsic mechanisms of TME promoting the management of HCC. Lysyl oxidase like 3 (LOXL3) participates in the remodeling of extracellular matrix (ECM) and the cross-linking of collagen and elastic fibers. It has been reported that LOXL3 is associated with the development and tumorigenesis of multiple types of cancer. In this study, we first found that LOXL3 gene was upregulated in tumor tissues compared with the normal tissues. Furthermore, LOXL3 expression is positively correlated with the infiltration of multiple immune cells and the expression of immune checkpoint genes in HCC. Meanwhile, high LOXL3 expression predicted poor outcomes of the patients with HCC. Functional enrichment analysis suggested that LOXL3 was mainly linked to extracellular structure and matrix organization, cell–cell adhesion, and T cell activation. This is the first comprehensive study to indicate that LOXL3 is correlated with immune infiltrates and may serve as a novel biomarker predicting prognosis and immunotherapy in HCC.

Introduction

Liver cancer remains a major global healthcare challenge with the increasing worldwide incidence of more than 1 million cases in 2025 [1]. Hepatocellular carcinoma (HCC) is the most important subtype, accounting for approximately 90% of all cases of primary liver cancer, with bad prognosis because of tumor aggression and relapse. There are several main factors expanding the risk of HCC, mostly including hepatitis B or C virus (HBV or HCV) infection, alcohol abuse, nonalcoholic fatty liver disease (NAFLD), metabolic syndrome and obesity [2]. At present, some advances have been made in the traditional treatments for HCC, including surgical resection, chemotherapy and radiotherapy. Owing to the strong and extensive resistance of HCC to cytotoxic chemotherapy, efforts to improve treatment options have focused on the combination of transarterial chemoembolization (TACE) with anti-angiogenic agents, which has become an effective strategy to improve the HCC patients' prognosis [3].

Given the crucial effects of immune system on cancer development and progression, it will promote the progression of new immunotherapeutic strategies [4]. Hepatocellular carcinoma is a complex ecosystem consisting of many non-neoplastic cells, mainly immune-related cells. Malfunction of tumor-immune system interaction, including impaired antigen recognition and immunosuppressive tumor microenvironment, contributes to tumor escape from the immune surveillance [5, 6]. Notably, immunotherapy and especially immune checkpoint inhibitors, including programmed death receptor 1 (PD-1) and programmed death receptor ligand 1 (PD-L1) inhibitors have made a revolutionized

breakthrough in the treatment of liver cancer. Combination therapy of the anti-PDL1 antibody atezolizumab and vascular endothelial growth factor (VEGF)-neutralizing antibody bevacizumab possess strong anti-tumor effect, which is expected to become the standard of care as a first-line treatment of HCC [7]. However, only some patients present a good response to this treatment. This has aroused our interest in exploring the potential molecular mechanisms underlying the regulation of tumor immune microenvironment and response to immunotherapy, which contributes to promoting the management of HCC.

Lysyl oxidase like 3 (LOXL3), a member of the lysyl oxidase (LOX)-like proteins family, mainly participates in the remodeling of extracellular matrix and the cross-linking of collagen and elastic fibers [8, 9]. It has been reported that LOX family, including LOXL3, correlates with multiple kinds of cancer cell proliferation, migration, invasion, and metastasis [10, 11]. On the one hand, one study has found that LOXL3 is involved in the migration and angiogenesis of tumor-associated pericytes in the tumor microenvironment [12]. Moreover, LOXL3 was associated with intratumoral, and peritumoral inflammation in breast cancer [13]. On the other hand, aberrant expression of LOXL3 correlated with distant metastasis of gastric cancer [14] and colorectal cancer [15]. Furthermore, overexpression of LOXL3 has been linked to poor prognosis in patients with ovarian cancer [16].

In this study, we first compared the expression level of LOXL3 in tumor tissue and normal tissue, and synthetically evaluated the correlation between LOXL3 expression and immune cells infiltration in HCC. Meanwhile, the correlation analysis of LOXL3 with immune checkpoint genes was performed. In addition, we investigated the relationship between LOXL3 expression and the prognosis of patients with HCC. This is the first comprehensive assessment of the potential value of LOXL3 gene in HCC from tumor immunotherapy and prognosis aspects.

Materials And Methods

2.1. Data collection and processing

The RNA-sequencing data and corresponding clinical information of patients with HCC was extracted from the TCGA data portal (https://portal.gdc.cancer.gov/). The extracted data was normalized and processed by log2 transformation.

2.2. Gene expression analysis

TIMER database was first applied to analyze the expression level of LOXL3 gene between tumor and adjacent normal tissues across multiple cancer types or specific tumor subtypes (https://cistrome.shinyapps.io/timer/). Furthermore, we used the Genotype-Tissue Expression (GTEx) database (https://www.gtexportal.org/home/index.html) and Cancer Cell Line Encyclopedia (CCLE) database (https://portals.broadinstitute.org/ccle) to obtain data on LOXL3 gene expression in 31 normal

tissues and 21 tumor cell lines respectively. In addition, we observed LOXL3 expression level between cancer and normal tissues using the integrated datasets combined TCGA with GTEx databases. We also investigated the LOXL3 expression in different pathological stages (stage I, stage II, stage III, and stage IV) of HCC using Gene Expression Profiling Interactive Analysis (GEPIA) (http://gepia.cancer-pku.cn/) [17]. Moreover, the distribution and subcellular localization of LOXL3, as well as the expression in hepatocellular carcinoma were identified through Immunohistochemistry (IHC) using the Human Protein Atlas (THPA) (https://www.proteinatlas.org/).

2.3. Immune related analysis of LOXL3 expression

TIMER is a comprehensive resource database for the systematic study of 6 immune cell infiltrates, including B cells, $CD4^+$ T cells, $CD8^+$ T cells, neutrophils, macrophages, and myeloid dendritic cells, in multiple cancer types [18]. The correlation analysis between LOXL3 expression and immune infiltrations was performed using the Spearman correlation test. To further determine the estimation of immune infiltration, we performed MCP-counter[19, 20] and Xcell [21] algorithm analysis using the "ImmuneConv" software package. For detecting the interaction between tumor and immune system, TISIDB database (an integrated repository portal) was utilized to explore the immune-related analysis of LOXL3 expression, including tumor infiltrating lymphocytes (TILs), chemokines (or receptors), immune subtypes and molecular subtypes in HCC (http://cis.hku.hk/TISIDB/) [22]. In addition, we evaluated the correlation between LOXL3 expression and the Immune/Stromal Scores and immune checkpoint genes level by Spearman and Pearson correlation analysis, respectively.

2.4. Survival prognosis analysis

To investigate the prognostic value of LOXL3 gene in patients with HCC, survival analysis such as OS (overall survival) and DSS (disease specific survival) was performed. RNA-sequencing data and corresponding clinical information of patients with HCC were visualized with gene distribution and Kaplan-Meier curves. The patients were divided into the high and low risk groups according to the median expression level of LOXL3.

2.5. Protein–protein interaction analysis

The LOXL3-binding proteins could be obtained in a protein–protein interaction (PPI) network via the STRING website (https://string-db.org/) with the corresponding settings performed, including meaning of network edges (“evidence”), active interaction sources (“Experiments”), minimum required interaction score [“Low confidence (0.150)”], and max number of interactors to show (“no more than 50 interactors”).

2.6. Functional enrichment analysis

All samples were divided into two groups based on the median expression level of LOXL3 mRNA, and “Limma” package was utilized to detect differences in genes expression. Set the threshold for the screening of differentially expressed genes (DEGs), including adjusted $P < 0.05$ and $|\log_2 (\text{Fold Change})| >$

1. The adjusted *P*-value was applied to correct the false positive results. To better investigate the biological function of LOXL3, “ClusterProfiler” package was adopted to perform Gene Ontology (GO) and Kyoto encyclopedia of genes and genomes (KEGG) analysis, and the results were visualized.

2.7. MMR gene mutation analysis.

Recent studies have revealed much about dysfunction of DNA mismatch repair system (MMRs) that could result in tumorigenesis [23]. We obtained the mutation levels of MMR genes such as MLH1, MSH2, MSH6, PMS2, and EPCAM from TCGA database. Pearson's correlation analysis was conducted to identify the relationship between LOXL3 expression and MMR gene mutation levels.

2.8. DNA methylation analysis.

DNA methylation is a form of DNA modification, which can induce genetic changes without altering the DNA sequence. It has been suggested that DNA methylation is implicated in tumorigenesis and tumor development [24]. Here, we analyzed the correlation between LOXL3 and four DNA methyltransferase, including DNMT1, DNMT2, DNMT3A, and DNMT3B, in HCC.

2.9. Statistical analysis

The relationship between continuous variables was identified using Spearman’s correlation analysis. The survival analysis of patients with different expression levels of LOXL3 gene in HCC was performed by Kaplan-Meier curves using log-rank test. All R packages were operated using R software version v4.0.3, and $P < 0.05$ was viewed as the cut-off criterion.

Results

3.1. Gene expression analysis of LOXL3 in HCC

We first utilized the GTEx and CCLE databases to observe LOXL3 gene expression in 31 normal tissues (Fig. S1a) and 21 tumor cell lines (Fig. S1b) respectively. Furthermore, TIMER database analysis indicated that the expression of LOXL3 was significantly higher in HCC than that in normal liver tissues based on TCGA database (Fig. 1a). And the gene expression analysis based on the integrated dataset combined TCGA with GTEx database also showed LOXL3 was significantly upregulated in HCC with the corresponding normal tissues as controls (Fig. 1b, c). Additionally, LOXL3 was associated with pathological stages in patients with HCC (Fig. 1d). According to the THPA database, the protein expression level of LOXL3 in HCC tumor tissues was higher than that in normal tissues by IHC staining (Fig. 1e).

3.2. Correlation analysis of LOXL3 expression with immune infiltration levels in HCC

Tumor immunotherapy efficacy mainly depends on the tumor immune microenvironment determined by the density, composition, functional state and organization of tumor-infiltrating components [25]. Tumor

infiltrating lymphocytes were viewed as the independent predictor in cancers [26, 27]. We, therefore, focused attention on detecting the association between LOXL3 expression and the infiltration levels of immune cells in HCC. As shown in Fig. 2a, the expression level of LOXL3 negatively correlated with the purity of tumor, and positively correlated with the infiltration of various immune cells such as $CD8^+$ T cells, $CD4^+$ T cells, B cells, neutrophil cells, macrophage cells, and myeloid dendritic cells in HCC based on the TIMER database. To further verify this trend, we applied the MCP-counter and xCell algorithm to evaluate the immune infiltration level in HCC, respectively. The results indicated that high LOXL3 expression was significantly associated with most of immune infiltrate cells in HCC (Fig. 2b, c). In addition, we obtained the landscape of correlation between LOXL3 expression and 28 TILs among different types of cancer based on TISIDB database (Fig. 3a). Notably, most of the tumor-infiltrating immune cells were positively correlated with LOXL3 expression in HCC (Fig. 3b–m) (cor > 0.5 displayed).

3.3. Correlation analysis of LOXL3 expression with chemokines, chemokine receptors, immune and molecular subtypes in HCC

To further explore the influence of LOXL3 on tumor immune microenvironment, we detected the association of LOXL3 expression with chemokines/chemokine receptors. Intriguingly, we found that LOXL3 expression was positively correlated with many chemokines/chemokine receptors, which suggested that high LOXL3 expression may contribute to the migration of immune cells in TME (Fig. 4a, b). In addition, we obtained the distribution of LOXL3 expression across immune and molecular subtypes (Fig. 4c, d).

3.4. Correlation analysis of LOXL3 expression with immune checkpoint genes and Immune/Stromal Score in HCC

ICIs, an innovative approach in the field of cancer immunotherapy, raise a promising application prospect for improving the outcomes of patients with liver cancer [28-30]. Currently, the challenge is to screen out potential populations who would benefit from immunotherapy. Therefore, identifying biomarker that can effectively predict the efficacy of immunotherapy has become particularly important. We attempted to evaluate the correlation between the expression of LOXL3 and immune control genes based on the data obtained from TCGA. Interestingly, LOXL3 expression positively associated with most of the immune checkpoint markers in HCC (Fig. 5a). Meanwhile, the Immune Score, Stromal Score and ESTIMATE Score calculated through the ESTIMATE algorithm were used to identify and quantify the immune and matrix components in HCC. As per the results, LOXL3 expression was remarkably positively correlated with Immune Score, Stromal Score and ESTIMATE Score in HCC (Fig. 5b-d), which indicated that tumor tissues with high LOXL3 expression possessed a higher degree of immune cell infiltration.

3.5. Correlation analysis of LOXL3 with patients' prognosis in HCC

We assessed the expression distribution and the prognostic value of LOXL3 in patients with HCC based on TCGA database. The patients were divided into the high and low expression groups by the median value of LOXL3 expression. Synthetically considering the risk curve and the survival status, we observed

that the mortality in the high expression group was significantly increase compared with the low expression group in HCC. Moreover, Kaplan-Meier survival analysis indicated that high LOXL3 expression was significantly related to the poor prognosis of patients with HCC (OS, $P = 0.00251$; DSS, $P = 0.0235$) (Fig. 6).

3.6. Functional enrichment analysis of LOXL3

To further clarify the potential biological function and mechanism of LOXL3, we performed DEGs analysis to identify the altered genes, and conducted KEGG and GO for Functional enrichment analysis. The samples of HCC were divided into the high and low LOXL3 expression groups through processing the transcriptome data from TCGA. Furthermore, DEGs were obtained from the two groups with the criteria settings of $|\log_2 FC|>1$, adjusted $P<0.05$. The volcano plot displayed that 875 genes were differentially expressed containing 794 upregulated genes and 81 downregulated genes (Fig. 7a). Corresponding hierarchical clustering analysis for these differential genes was exhibited using heatmap (Fig. 7b). In addition, the results of KEGG pathway enrichment analysis of upregulated DEGs were mainly involved in rheumatoid arthritis, phagosome, tuberculosis, staphylococcus aureus infection, and cell adhesion molecules (CAMs) (Fig. 7c). Meanwhile, we performed GO enrichment analysis of upregulated DEGs, which indicated that most of these genes were mainly linked to the events such as extracellular structure organization, extracellular matrix organization, regulation of cell–cell adhesion, positive regulation of cell adhesion, T cell activation, and leukocyte cell–cell adhesion (Fig. 7d).

Next, we screen out the targeting LOXL3-binding proteins with a visual PPI network by means of the STRING database. As shown in Fig. 8a, a total of 14 LOXL3-binding proteins were detected from the “experiments” active interaction sources of STRING. And we screened out the common members such as LTBP1 and LAMA2 through comparing LOXL3 expression-correlated DEGs with LOXL3-interacted genes (Fig. 8b). Corresponding genes information mentioned above has been provided in the Supporting Information materials. Additionally, we observed the expression of LOXL3 was significantly positively correlated with that of LTBP1 ($r = 0.496$, $P = 1.8e{-}24$) and LAMA2 ($r = 0.479$, $P = 1.16e{-}22$) (Fig. 8c).

3.7. Correlation analysis of LOXL3 with DNA damage repair and DNA methylation in human pan-cancer.

MMRs and DNMTs are involving in the DNA damage repair and DNA methylation, respectively. For investigating the potential role of LOXL3 in tumorigenesis, the correlation of LOXL3 expression with MMR gene mutation levels and the expression of DNMTs was analyzed. The landscape of correlation of LOXL3 expression with five MMR genes (MLH1, MSH2, MSH6, PMS2, and EPCAM) and four DNA methyltransferase (DNMT1, DNMT2, DNMT3A, and DNMT3B) in human cancers was exhibited, respectively (Fig. S2 and S3).

Discussion

Recent years have seen increasingly significant progress in the precision medicine and immunotherapeutic approaches to hepatocellular carcinoma. With receiving satisfactory therapeutic

effects of immune checkpoint inhibitors in different cancer types, a great deal of researches about ICIs were performed in patients with HCC [31]. According to the latest National Comprehensive Cancer Network (NCCN) guidelines in hepatobiliary cancers, several clinical trials that target anti-PD-1 antibody are underway, including nivolumab, ipilimumab, and pembrolizumab [32]. A phase 3 clinical trial has reported that atezolizumab combined with bevacizumab achieved better overall and progression-free survival compared with sorafenib in unresectable HCC [33]. Although immune checkpoint inhibitors have applied during the treatment of HCC, a major challenge that how to accurately screen patients who will benefit best from immunotherapy is urgently needed to be studied. Therefore, it is crucial to investigate the mechanism of interaction between tumor cells and immune microenvironment, which is of great significance to the development of tumor immunotherapy.

Since researches are limited with regard to the biological function of LOXL3 in cancers, especially in hepatocellular carcinoma, the comprehensive bioinformatics analysis was applied to investigate LOXL3-associated immune infiltration landscape, prognostic impact and potential regulatory mechanisms in HCC. In our study, we uncovered that LOXL3 was upregulated in HCC tissues compared with normal tissues and correlated with poor prognosis of patients with HCC. Moreover, LOXL3 expression positively correlated with infiltrating levels of multiple immune cells and mRNA expression levels of immune checkpoint genes in HCC. In addition, functional enrichment analysis demonstrated that the biological function of LOXL3 was mainly involved in extracellular structure organization, extracellular matrix organization, regulation of cell–cell adhesion, positive regulation of cell adhesion, T cell activation, and leukocyte cell–cell adhesion. To sum up, we found clear evidence supporting the correlation between LOXL3 and immune checkpoint therapy in HCC.

Tumor heterogeneity relies on the tumor microenvironment, including cancer cells, various kinds of immune cells and the surrounding stroma, which closely associates with patients' response to immunotherapy and the prognosis in multiple cancers [34]. There are multiple cellular and molecular mechanisms to evade and/or resist immune attack promoting the generation and development of tumors. TME tends to reflect high immunosuppression and drug resistance, leading to unsatisfactory responses to immunotherapy. Accumulating evidence indicated that the efficacy of immune checkpoint blockade (ICB) is determined by a fully functional antitumor immune response that is usually restricted in most tumors. Additionally, the central issue of ICB lies in restoring the function of T cell to eliminate tumors, and T cell fate is largely determined by T cell metabolism, which can influence the effects of anti-tumor immunotherapy [35]. The high LOXL3 expression in tumor tissues accelerated immune cells infiltration, which would initiate the immune response exerting the antitumor efficiency. Meanwhile, confronting immune attack caused by TILs, tumor cells could upregulate the expression of immune checkpoint genes with the purpose of inhibiting T cell activity resulting in immune escape, which also explains the consistent correlation between LOXL3 and immune checkpoint genes. This mechanism mentioned above is known as "adaptive immune resistance" [36].

In conclusion, the findings of our study demonstrated that LOXL3 expression correlated with the poor outcomes of patients with HCC. Additionally, the comprehensive analysis of LOXL3-associating immune infiltration landscape could lay the groundwork for further researches on the potential mechanism underlying the interaction between tumor cells and immune microenvironment during immunotherapy. It is reasonable to assume that LOXL3 may serve as a novel immune infiltration-associated biomarker predicting prognosis and response to immunotherapy, which will promote the progression of new immunotherapeutic strategies.

Abbreviations

CAMs, cell adhesion molecules; CCLE, cancer cell line encyclopedia; CI, confidence interval; DEGs, differentially expressed genes; DSS, disease specific survival; ECM, extracellular matrix; FC, fold change; FDR, false discovery rate; GEPIA, gene expression profiling interactive analysis; GO, Gene Ontology; GTEx, genotype-tissue expression; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; ICB, immune checkpoint blockade; ICIs, immune checkpoint inhibitors; IHC, Immunohistochemistry; KEGG, Kyoto encyclopedia of genes and genomes; LOX, lysyl oxidase; LOXL3, lysyl oxidase like 3; MMRs, mismatch repair system; NAFLD, nonalcoholic fatty liver disease; NCCN, national comprehensive cancer network; OS, overall survival; PD-1, programmed death receptor 1; PD-L1, programmed death receptor ligand 1; PPI, protein–protein interaction; TACE, transarterial chemoembolization; TCGA, the cancer genome atlas; THPA, the human protein atlas; TIMER, tumor immune estimation resource; TME, tumor microenvironment; VEGF, vascular endothelial growth factor.

Declarations

Ethics approval

This article is not involved in any studies with human participants or animals performed by any of the authors.

Consent to participate

Not applicable.

Consent for publication

All authors consent to the publication of this research.

Availability of data and material

All data is available under reasonable request.

Competing interests

The authors have declared no competing interests.

Funding

Not applicable.

Authors' contributions

Ning Wang and Xue Zhou contributed to the study conception, design, and visualization. Fei Tang and XiaoWei Zhu performed data analysis and figure generation. Xue Wang contributed to collection and integration of data. Ning Wang wrote the manuscript.

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Code availability

Not applicable.

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Figures

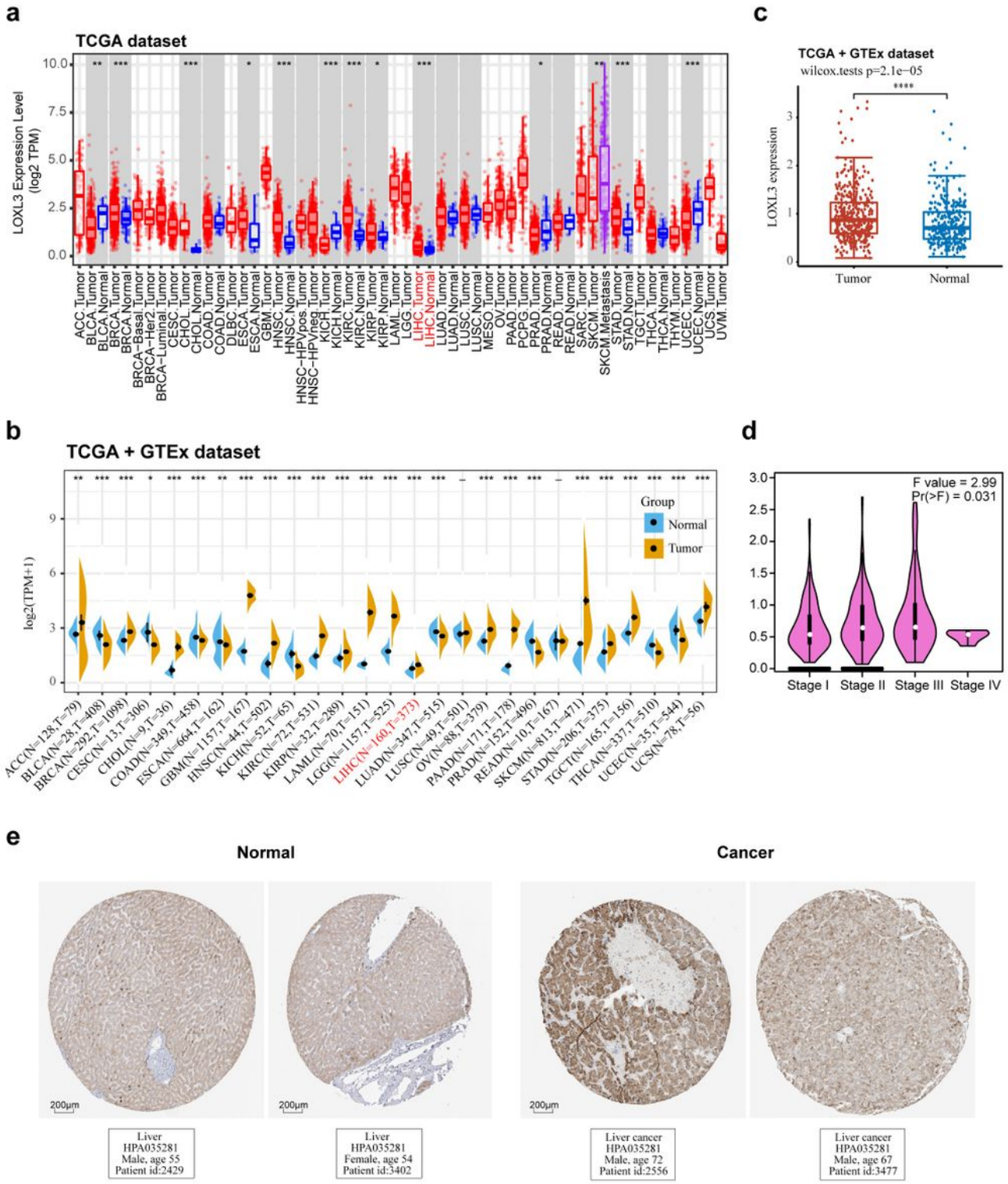

Figure 1

The expression level of LOXL3 gene in tumor. (a) LOXL3 expression in different cancer types based on TIMER database. (b) LOXL3 expression in different types of tumor tissue and normal tissue based on TCGA and GTEx database. (c) LOXL3 expression in HCC matched TCGA normal and GTEx data. (d)

LOXL3 expression in different pathological stages (stage I, stage II, stage III, and stage IV) in HCC based on GEPIA database. (e) Representative IHC images and detailed information on the expression of LOXL3 in HCC tumor tissues and normal tissues based on the THPA database. *P < 0.05, **P < 0.01, ***P < 0.001, and ****P < 0.0001.

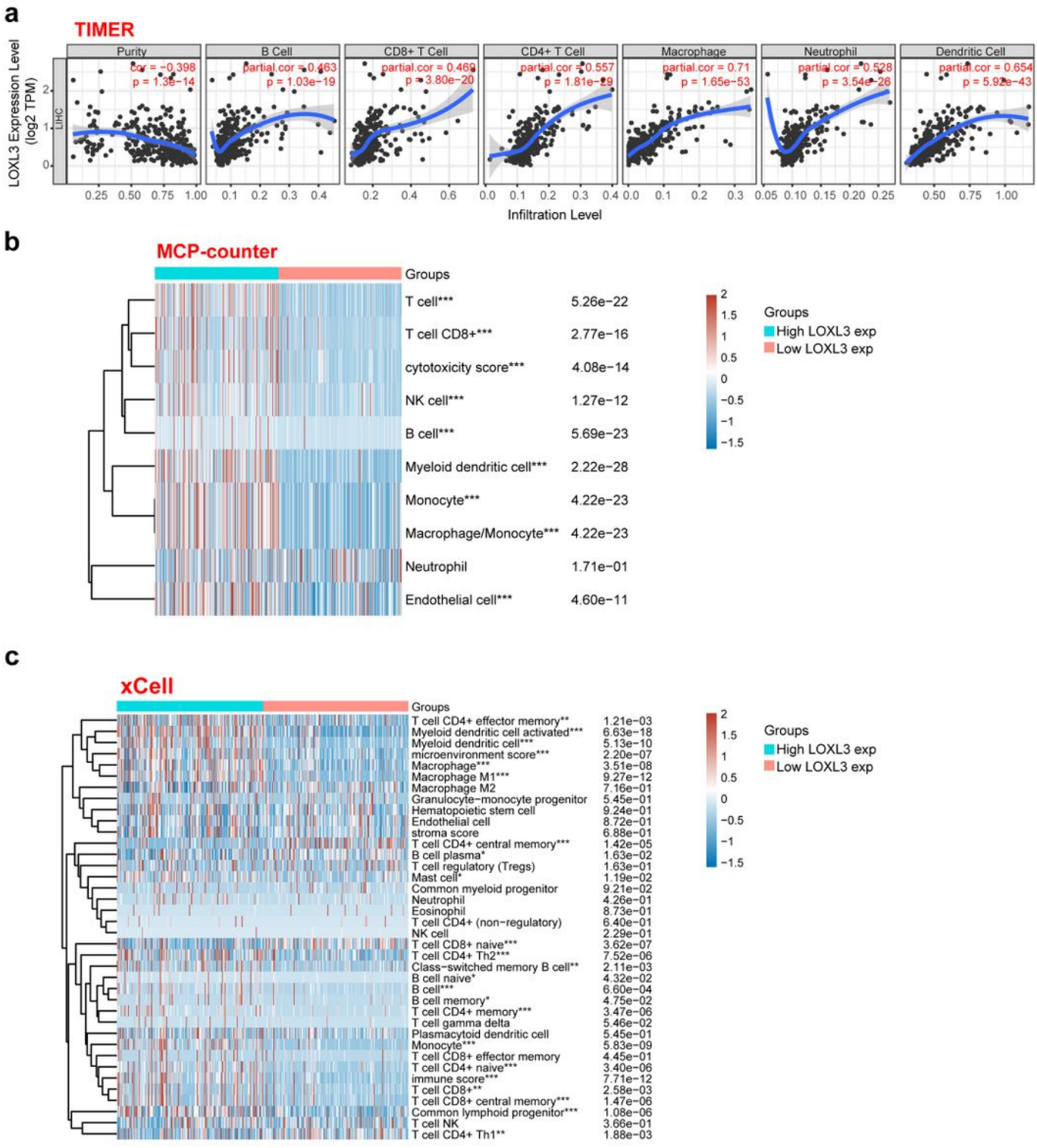

Figure 2

The correlation between LOXL3 expression and immune infiltration levels in HCC. (a) The negative correlation between LOXL3 expression and the purity of tumor and the positive correlation of LOXL3 expression with infiltrating levels of CD8+ T cells, CD4+ T cells, B cells, neutrophil cells, macrophage cells, and myeloid dendritic cells in HCC based on TIMER database. Heatmap of the correlation analysis between LOXL3 expression and immune infiltrations in HCC using (b) MCP-counter and (c) xCell. *P < 0.05, **P < 0.01, and ***P < 0.001.

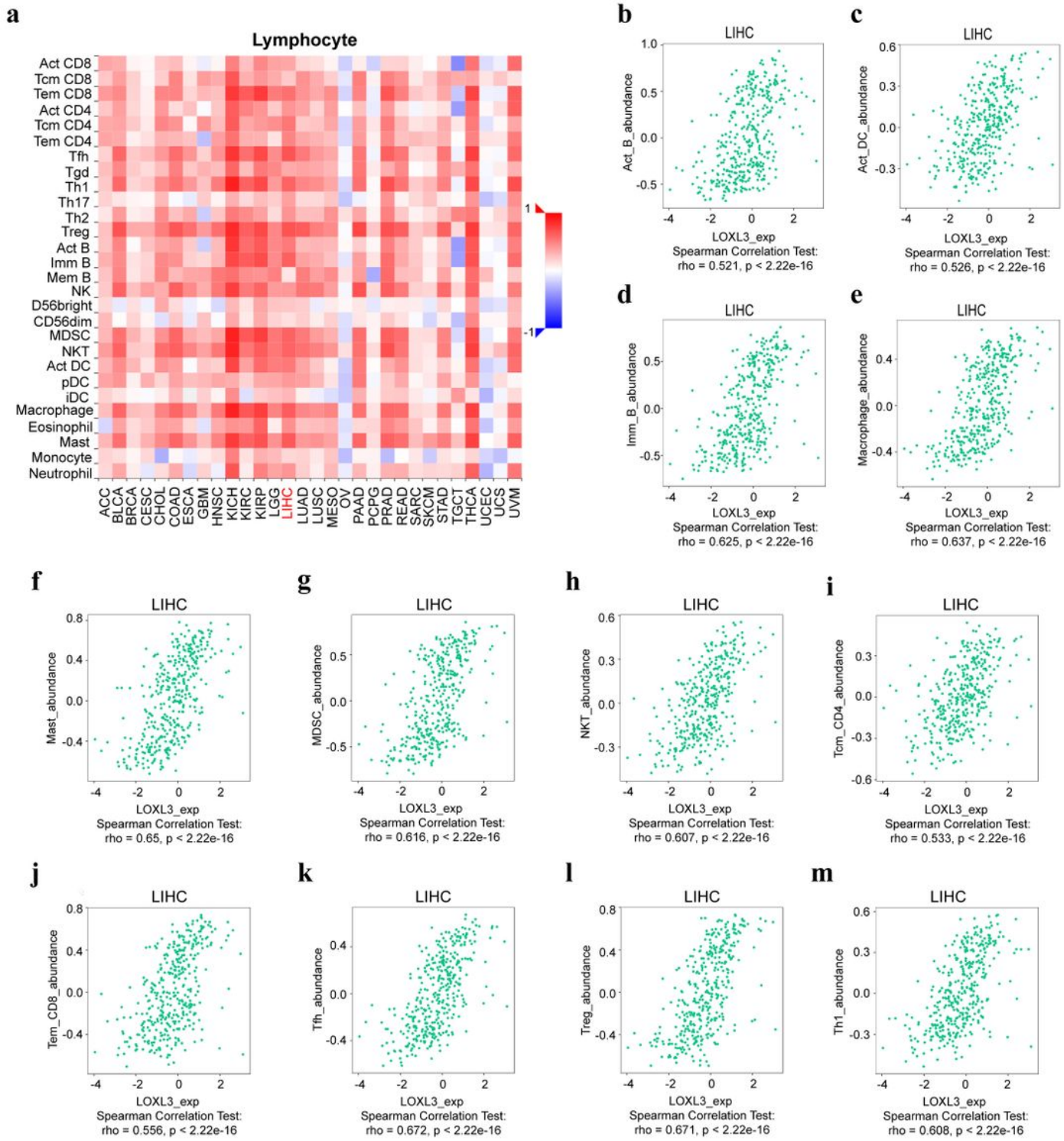

Figure 3

Correlation analysis of LOXL3 expression with TILs in cancer based on the TISIDB database. (a) The landscape of relationship between LOXL3 expression and TILs in multiple types of cancers (red means positive correlation and blue means negative correlation). (b–m) LOXL3 expression was significantly positively associated with the infiltrating levels of act_B, act_DC, Imm_B, macrophage, mast, MDSC, NKT, tcm_CD4, tem_CD8, Tfh, Treg, and Th1 in HCC.

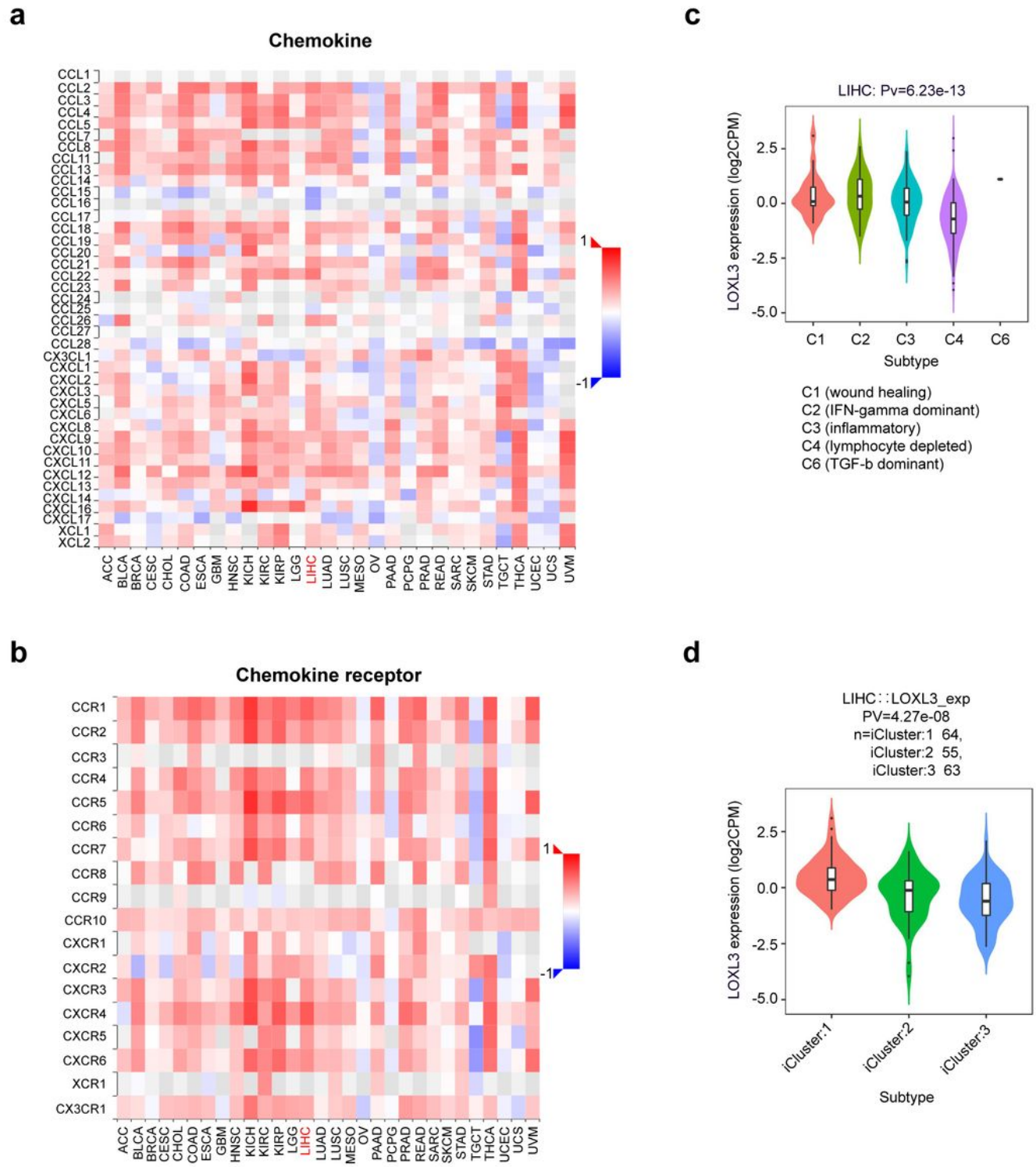

Figure 4

Correlation analysis of LOXL3 expression with chemokines/chemokine receptors, immune and molecular subtypes. (a) Correlation analysis of LOXL3 expression with chemokines in pan-cancer. (b) Correlation analysis of LOXL3 expression with chemokine receptors in pan-cancer. (c) Correlation of LOXL3 expression and immune subtypes in HCC. (d) Correlation of LOXL3 expression and molecular subtypes in HCC.

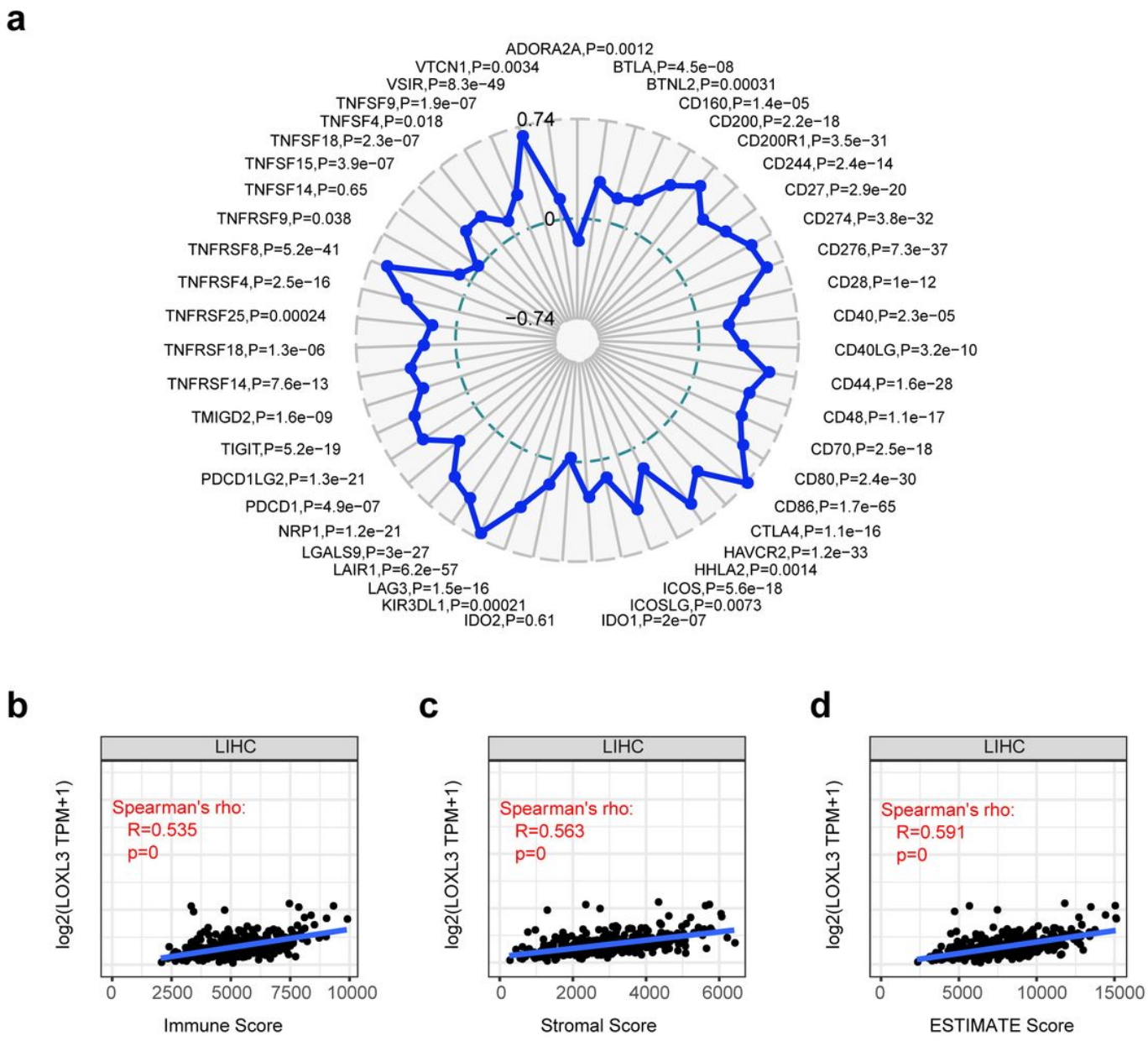

Figure 5

Correlation analysis of LOXL3 expression with immune checkpoint genes, Immune Score, Stromal Score, and ESTIMATE Score in HCC. (a) Correlation analysis of LOXL3 expression with immune checkpoint genes. (b-d) Correlation analysis of LOXL3 expression with Immune Score, Stromal Score, and ESTIMATE Score in HCC.

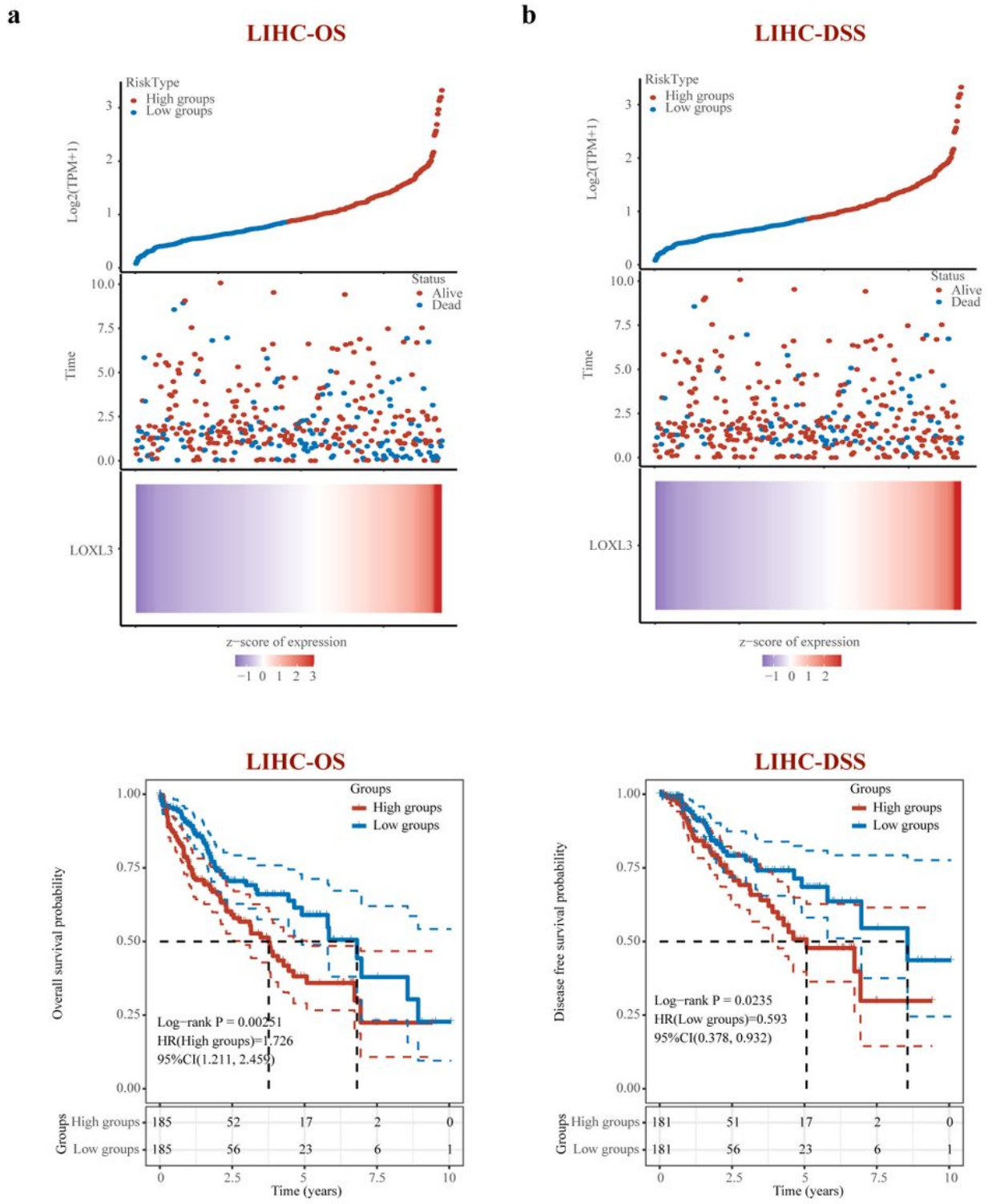

Figure 6

Prognostic analysis of LOXL3 expression on OS, DSS in HCC based on TCGA database. (a) LOXL3 expression distribution, survival status and survival curve on OS. (b) LOXL3 expression distribution, survival status and survival curve on DSS.

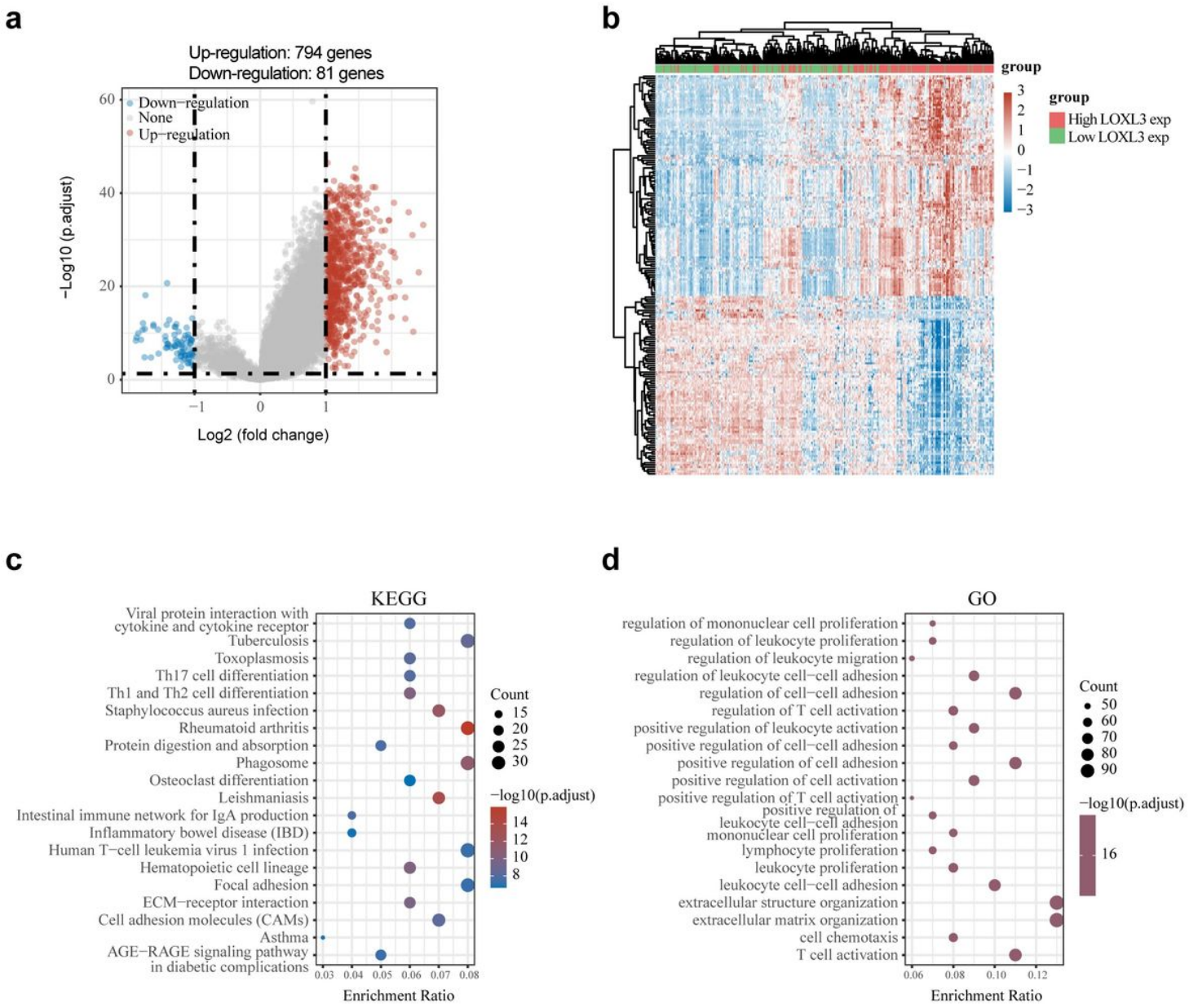

Figure 7

Functional enrichment analysis of LOXL3 expression-correlated DEGs in HCC. (a) Volcano plot of DEGs between samples in HCC with high and low LOXL3 expression. (b) Heatmap of LOXL3 expression-correlated DEGs by clustering analysis. (c) KEGG enrichment and (d) GO enrichment analysis of upregulated DEGs with LOXL3 expression.

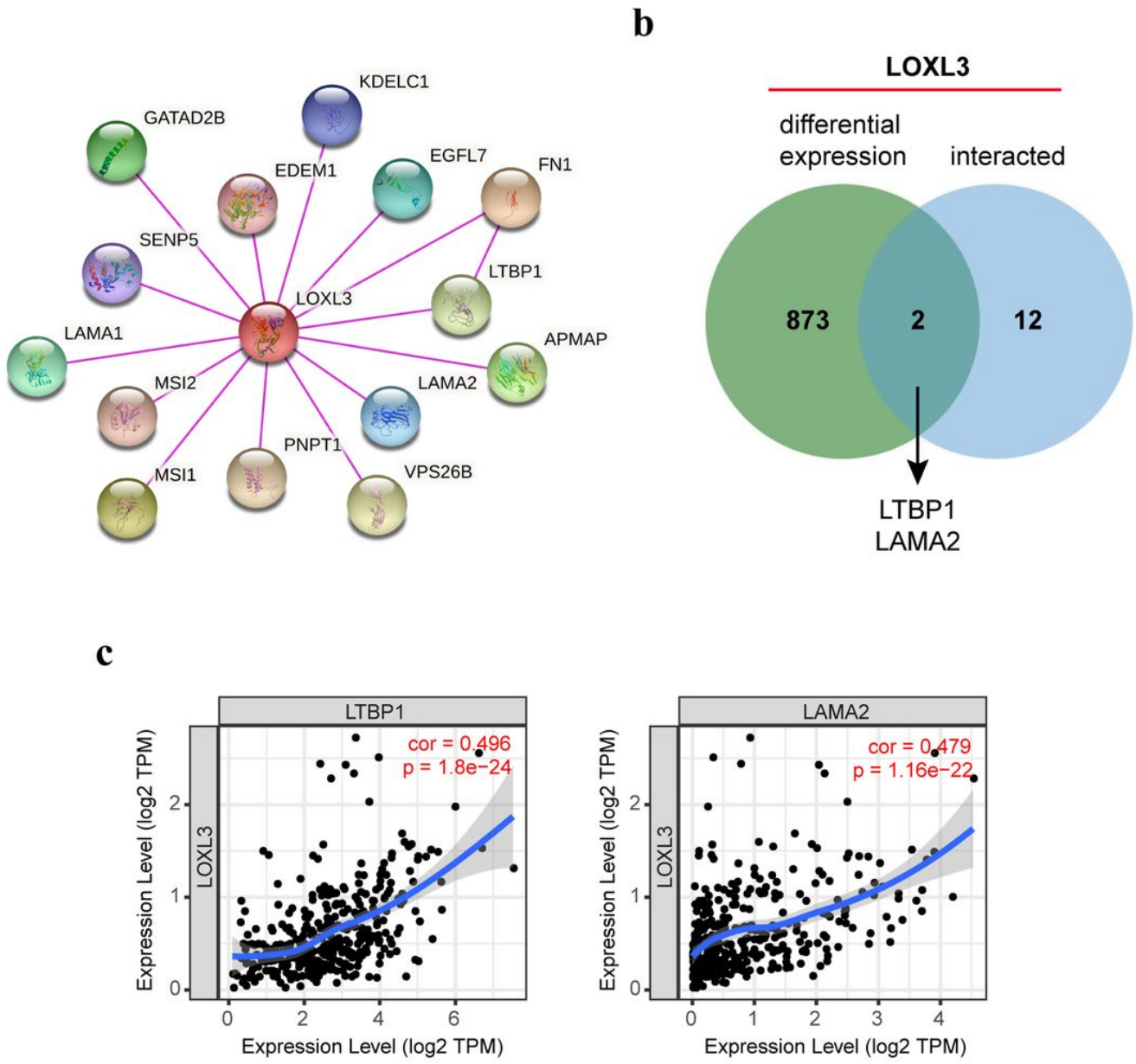

Figure 8

PPI network analysis of LOXL3-related genes. (a) The visualizing interaction network of LOXL3-binding proteins was obtained base on STRING database. (b) An intersection analysis between LOXL3 expression-correlated DEGs and LOXL3-interacted genes. (c) Correlation analysis of LOXL3 with intersection genes, including LTBP1 and LAMA2.

Supplementary Files

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- SupplementaryMaterial.xlsx

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