Identification Of PPIA As A Prognostic Biomarker Of Lung Adenocarcinoma From Bioinformatics Analysis

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Abstract

Background: We aim to investigate the expression of the peptidylprolyl isomerase A (PPIA) gene in lung adenocarcinoma (LUAD), and to investigate the diagnostic, prognostic value and correlation with immune infiltrates of PPIA in LUAD.

Methods: Transcriptional expression profiles of PPIA between LUAD tissues and normal tissues were downloaded from the Cancer Genome Atlas (TCGA). The PPIA protein expression was assessed by the Clinical Proteomic Tumor Analysis Consortium (CPTAC). Receiver operating characteristic (ROC) curve was used to differentiate LUAD from adjacent normal tissues. Kaplan-Meier method was conducted to assess the effect of PPIA on survival. Protein-protein interaction (PPI) networks were constructed by the STRING. Functional enrichment analyses were performed using the "ClusterProfiler" package. The relationship between PPIA mRNA expression and immune infiltrates was determined by tumor immune estimation resource (TIMER) and tumor-immune system interaction database (TISIDB).

Results: The expression of PPIA in LUAD tissues was significantly upregulated than those in adjacent normal tissues. High PPIA mRNA expression was associated with lymph node metastases and high TNM stage. The ROC curve analysis showed that PPIA had an AUC value of 0.804 (95% CI: 0.764-0.843). Kaplan-Meier survival analysis showed LUAD patients with high-PPIA had a worse prognosis than those with low-PPIA (mOS: 42.2 months VS 87.2 months, $P=0.001$). Correlation analysis indicated PPIA mRNA expression was correlated with immune infiltrates. PPIA expression had correlations with CD4+ T cell ($r = -0.29$, $P = 5.51e-11$), macrophage M1 ($r = 0.106$, $P = 1.84e-02$), and B cell ($r = -0.181$, $P = 5.40e-5$).

Conclusion: Our research showed that PPIA could be used as a prognostic biomarker. Up-regulation of PPIA expression is significantly related to poor prognosis and immune infiltration of LUAD and may be a potential therapeutic molecular target for LUAD patients.

1. Introduction

Lung cancer is the leading cause of cancer-related death worldwide [1]. Due to diagnosis and treatment in advanced stages, it metastasizes rapidly and shows a high recurrence rate. Despite numerous therapies being constructed to combat lung cancer, lung cancer is still a harmful tumor, especially with low survival rate [2]. Lung cancer is divided into small cell lung cancer and non-small cell lung cancer. Among them, LUAD is a type of non-small cell lung cancer, accounting for the largest proportion, about 70%, and with the poor prognosis [3]. Although medicine is developing rapidly, numerous studies have shown that surgery, chemotherapy, molecular targeted therapy and immunotherapy, these treatments have improved patient survival rate and reduced patient suffering, but the prognosis of LUAD is still unsatisfactory [4]. Therefore, it is urgent to explore more new and effective biomarkers for early diagnosis and accurate prognosis prediction.

PPIA also called cyclophilin A (CYPA) or rotamase A, a member of the ubiquitous peptidyl-prolyl cis-trans isomerase (PPIase) family, was initially purified from bovine thymocytes and identified as the primary

cytosolic binding protein of the immunosuppressive drug cyclosporin A (CsA) [5]. Moreover, this enzyme has been shown to be a key molecule in multiple biological functions, including molecular chaperoning, protein folding, protein trafficking, immune modulation, and cell signaling [6]. Studies have also reported that PPIA is involved in several diseases, including kawasaki disease[7], amyotrophic lateral sclerosis[8], atherosclerosis, myocardial infarction[9], severe sepsis [10], vascular smooth muscle cell disease [11], rheumatoid arthritis and HIV infection [12]. Moreover, several studies have shown that PPIA is expressed in some cancers, including lung cancer, nasopharyngeal carcinoma[13], gastric adenocarcinoma[14], thyroid carcinoma[15], neuroblastoma[16], ovarian cancer[17], pancreatic cancer[18], breast cancer, colorectal cancer[19-20], melanoma[21], liver hepatocellular carcinoma[22]. Many researchers have assessed PPIA function in cancer. It has been suggested that PPIA plays an important role in the whole pathological process of cancer development. High expression levels of PPIA were associated with decreased overall survival in liver hepatocellular carcinoma, colorectal cancer, low-grade glioma, acute myeloid leukemia. However, in gastric adenocarcinoma, high expression levels of CypA are positively correlated with invasiveness and distant metastasis. Therefore, both low and high expression of PPIA are associated with tumor prognosis.

In breast cancer, the inhibition of the activity of cyclophilin A can block the prolactin receptor-mediated signaling and inhibit the occurrence and metastasis of tumors[19]. Boulos et al found that at high PPIA levels, the protein interacts with the proline-containing peptide in the transmembrane domain of CD147, thereby stimulating human pancreatic cancer cell proliferation[18]. While the protein of PPIA considered in Brandon A. Howard's study were overexpressed in the vast majority of NSCLCs, they were not found to be of prognostic significance[23]. But other studies demonstrated that PPIA overexpression stimulates cancer cell growth in NSCLC, with cancer cell growth inhibited by PPIA knockdown[24]. PPIA promoted LUAD metastasis via p38 MAPK[25]. Current research shows that PPIA may inhibit H₂O₂-induced oxidative damage and apoptosis of LUAD cells through the PI3K/Akt/mTOR signaling pathway. The cytoprotective effect of PPIA seems to depend on its PPIase activity[26]. Other study indicated that PPIA as one of the factors of antitumor host defense that can effectively control the initial stages of tumor and metastases formation by regulating the action of MMPs (matrix metalloproteinases) and changing the tumor microenvironment[27]. Therefore the question remains unanswered as to whether PPIA could serve as a prognostic factor and potential target for therapy in the future. However, in the present study, we explored the significance of PPIA in LUAD, explored the potential diagnostic and prognostic value, and analyzed a link between PPIA expression and immune cell infiltration in patients with LUAD, and provide evidence for PPIA as a prognostic factor of LUAD and a potential target for future treatment.

2. Materials And Methods

TCGA Datasets

Transcriptional expression data of PPIA and corresponding clinical information were downloaded from TCGA official website (<https://portal.gdc.cancer.gov/>). The datasets were utilized to observe the mRNA

and protein levels of PPIA in human pan-cancer. 38 cancer types and normal group were included. The RNA-Seq gene expression data with workflow type of FPKM was transformed into TPM format and log2 conversion for further study. Since all the data were downloaded from TCGA Datasets, this study did not need approval from the Ethics Committee.

RNA-Sequencing Data of PPIA in LUAD

The RNA-Seq expression data of PPIA in LUAD was also downloaded from TCGA. Therefore, 535 LUAD and 59 adjacent normal tissue data were retained. The samples selected contained PPIA gene expression data and associated clinical information, including age, gender, smoker condition, T stage, N stage, M stage and tumor location. The mRNA expression data were characterized by mean $\pm$ SD.

Protein-Protein Interaction (PPI) Networks and Functional Enrichment Analysis

STRING is an online database for the retrieval of interacting genes (<http://string-db.org>). In this study, we conducted STRING to search co-expression genes and construct PPI networks with an interaction score >0.4 . Gene ontology (GO) enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses of co-expression genes were performed by the “ClusterProfiler” package and visualized by the “ggplot2” package.

Tumor Immune Estimation Resource (TIMER) Database

TIMER is a comprehensive online resource for systematic analysis of immune infiltrates across various cancer types (<https://cistrome.shinyapps.io/timer/>). In this study, we performed TIMER to determine the relationship between PPIA expression in LUAD and six immune infiltrates (B cells, CD4⁺ T cells, CD8⁺ T cells, neutrophils, macrophages and dendritic cells).

Tumor-Immune System Interaction Database (TISIDB)

TISIDB is an online web integrated repository portal for tumor immune system interaction (<http://cis.hku.hk/TISIDB/>). In this study, we performed TISIDB to determine the expression of PPIA and tumor-infiltrating lymphocytes (TILs) across human cancers. Based on the gene expression profile, the relative abundance of TILs was inferred by using gene set variation analysis. The correlations between PPIA and TILs were measured by Spearman's test.

PrognScan Database

PrognScan database is a powerful online platform to evaluate the correlation between gene expression and survival across various types of cancers (<http://dna00.bio.kyutech.ac.jp/PrognScan/index.html>). In this study, we performed PrognScan database to analyze the correlation between PPIA expression and overall survival in LUAD with two different datasets (jacob-00182-CANDF, jacob-00182-MSK).

Statistical Analyses

All statistical analyses were performed with R (V3.6.3 <https://www.r-project.org/>) and R package ggplot2 was used to visualize expression differences. Paired t-test and Mann-Whitney U-test were used to determine the differences between LUAD tissues and adjacent normal tissues. ROC curve was performed to detect the cutoff value of PPIA using the pROC package. Kaplan-Meier and log-rank tests were conducted with the survminer package (<https://CRAN.R-project.org/package=survminer>) to assess the effect of PPIA on survival.

3. Results

PPIA Is Upregulated in Pan-Cancer and LUAD According to Public Databases

To determine whether PPIA is involved in human cancers, we first analyzed the expression of PPIA in different types of cancers via utilizing the TIMER 2.0 database. We observed that PPIA expression was significantly higher in most human cancers compared with the corresponding normal tissues (all $P < 0.05$) according to the TIMER 2.0 d (**Figure 1a**). Then, further analysis of PPIA mRNA expression was carried out for

57 tumor tissues and paired adjacent nontumor tissues of LUAD patients in the TCGA database. The LUAD tissues displayed a significantly higher PPIA mRNA expression level than the adjacent non-tumor tissues by paired data analysis (**Figure 1b**, 7.394 ± 0.207 vs 7.899 ± 0.539 , $P < 0.001$). What is more, Unpaired data analyses showed that the mRNA expression levels of PPIA in LUAD ($n = 535$) were significantly higher than those in normal tissues ($n = 59$) (**Figure 1c**, 7.394 ± 0.205 vs 7.899 ± 0.559 , $P < 0.001$). These results indicated that the mRNA expression of PPIA was abnormally expressed across different cancer types, and also the mRNA of PPIA are upregulated in LUAD tissues. From the perspective of PPIA expression, PPIA has a certain specificity for LUAD diagnosis. The specificity of PPIA for LUAD diagnosis at the level of regulatory mechanisms will be explored in our future work.

Relationships Between PPIA mRNA Levels and Clinical Pathological Characteristics of LUAD Patients

To evaluate the association between the mRNA expression of PPIA and clinical pathological characteristics of LUAD samples, we performed Mann-Whitney U-test and logistic regression analysis. As shown in **Figures 2a-i**, higher expression levels of PPIA were observed in patients with high TNM stage, and patients with lymph node metastases. However, no statistically significant correlation were found between the expression levels of PPIA and other clinical characteristics, such as age, smoker, gender, T stage, M stage, and anatomic subdivision (right vs. left, peripheral vs. central). Taken together, these results suggested that PPIA is correlated with lymph node metastases and high TNM stage [all $p < 0.05$], further suggesting PPIA may act as a biomarker of poor prognosis for LUAD.

High PPIA Expression Is Related to Poor Survival in Patients With LUAD

To investigate the value for PPIA to distinguish LUAD samples from normal samples, we performed a ROC curve analysis. As showed in **Figure 3a**, the ROC curve analysis showed PPIA had an AUC value of

0.804(95% CI: 0.764-0.843).At a cutoff of 7.655, PPIA had sensitivity and specificity of 91.5%, 67.7%,respectively.These findings indicated that PPIA could be a promising biomarker to differentiate LUAD tissues from normal tissues.

To explore the relationship between PPIA mRNA expression and OS in LUAD patients, Kaplan-Meier curves and Prognoscan database were performed. As shown in

Figure 3b, the OS of LUAD patients with high level of PPIA was significantly shorter than those with low level of PPIA(DOS:42.2monthsVS 87.2months;HR:1.74,95%CI:1.29-2.33, $P=0.001$).As shown in subgroup analysis (**Figure 3c-q**),high expression of PPIA was correlated with poor overall survival in different clinical characteristics factors,such as age,gender, pathological stage,M stage,N stage,T stage,smoke status,year of smoke,and anatomic neoplasm subdivision(all $P<0.05$).

Further,we implemented univariate and multivariate analyses on 535 LUAD patients collected from the TCGA database to investigate the impact of the different clinical characteristics and PPIA expression on survival.Univariate analysis revealed four vital predictors of survival including pathological stage (HR:2.664,95% CI:1.960-3.621, $p<0.001$),T stage (HR:2.317, 95% CI:1.591-3.375, $p<0.001$),N stage (HR:2.601, 95% CI:1.944-3.480, $p<0.001$),and PPIA expression (HR:1.718,95% CI:1.283-2.302, $p<0.001$).Multivariate analysis turned out that the high T stage(HR:1.619,95% CI: 1.004-2.610, $P=0.048$),high N stage(HR:1.952,95% CI: 1.312-2.904, $P<0.001$), high PPIA mRNA(HR:1.512,95%CI:1.062-2.154, $P=0.022$) expression were crucial independent predictor of a poor OS in LUAD (**Table 1**).These data indicated that high mRNA expression of PPIA is a biomarker of poor prognosis in LUAD.

Correlation Analysis Between PPIA Expression and Immune Cell Infiltration

In LUAD

We analyzed the correlation between PPIA expression and the six types of tumor infiltrating immune cells in the TIMER database.As shown in **Figure 4a**,PPIA expression had correlations with CD4+ T cell ($r = -0.29$, $P = 5.51e-11$),macrophage M1 ($r = 0.106$, $P = 1.84e-02$), and B cell ($r = -0.181$, $P = 5.40e-5$). We also evaluated the correlation between PPIA expression and 73 types of TILs in the TISIDB database. **Figure 4b** shown the relations between expression of PPIA and 73 types of TILs and immunostimulator across human cancers.As shown in **Figure 4c**, the expression of PPIA was correlated with abundance of IL6R($r = -0.312$, $P = 5.49e-13$), CD40LG($r = -0.358$, $P = 3.58e-17$), CD28 ($r = -0.301$, $P = 3.6e-12$), C100f54 ($r = -0.299$, $P = 4.7e-12$),and CD56dim cells ($r = 0.213$, $P = 1.11e-6$). These data indicated that PPIA may play a specific role in immune infiltration in LUAD.

PPI Networks and Functional Annotations

To construct PPI networks and functional annotations, we conducted STRING database,GO,and KEGG analyses.**Figure 5a** showed a network of PPIA and its 10 co-expression genes(CFL1,PFN1,H2AFX,TRIM5,PPP3R1,PPP3CA,PPP3CB,MAPK3,BSG,ITK).As shown in **Figure 5b**,changes in the biological process of PPIA were associated with human immunodeficiency virus 1

infection,T cell receptor signaling pathway,VEGF signaling pathway,Fc receptor signaling pathway,Fc-epsilon receptor signaling pathway and non-canonical Wnt signaling pathway.Functional annotations indicated that these genes were involved in phosphoprotein phosphatase activity,protein serine/threonine phosphatase activity, cell-substrate adherens junction,focal adhesion,sarcolemma and cyclosporin A binding.The correlation analyses between the expression of PPIA and co-expressed genes in LUAD from TCGA were shown in **Figures 5c-l**.

4. Discussion

LUAD is considered the most common type of lung cancer. In recent years, LUAD has made new progress in diagnosis and treatment,but the treatment effect of advanced lung cancer is still limited. Although the combination therapy has been substantively developed,the prognosis of LUAD patients is still very poor,with a 5-year survival rate of <20% [28].At present, it is urgent to determine the prognostic value of key genes in order to better treat advanced lung cancer.PPIA overexpression was considered to play important roles in cancer pathogenesis. Nevertheless, the mechanism of PPIA affecting the biological behavior of LUAD cells has been shown to be different in each study. In this study, the database was used to analyze the specific expression and immune infiltration of PPIA in actual clinical practices, which provided a basis for the possible use of PPIA as a prognostic indicator and a possible therapeutic target for LUAD, as well as a reference for further elucidation of the mechanism of PPIA in LUAD.

PPIA is an enzyme encoded by the PPIA gene on chromosome 7,and four pseudogenes (PPIP2, PPIP3, PPIP4, and PPIP6) are localized on chromosome 14, 10, 18, and 3 respectively[29]. Human PPIA is an18 kDa,165-amino acid long protein found mainly in cytoplasm of all tissues in mammals, whereas other Cyps are found in the endoplasmic reticulum (ER), the mitochondria, or the nucleus [30]. Although PPIA is present intracellularly,PPIA can be secreted from cells in response to inflammatory stimuli such as hypoxia, infection, and other oxidative stresses [31]. In our analysis, intense PPIA expression was observed in most of the LUAD tissues, while limited expression was shown in the peritumoral tissues.The high expression of PPIA was related to the poor survival of LUAD patients,which was consistent with the correlation between the overexpression of PPIA and the overall survival of liver hepatocellular carcinoma and colorectal cancer[21,22].ROC curve analysis indicated that PPIA could be a promising diagnostic biomarker to differentiate LUAD from normal tissues.In addition,the progression of LUAD may be associated with the upregulation of PPIA.Notably,the expression of PPIA was positively correlated with high N stage,high pathological stage.Patients with LUAD with higher expression levels of PPIA exhibited significantly shorter overall survival times.The increased expression of PPIA in LUAD with pathological stage of III/IV and lymph node metastasis further indicates that PPIA may be involved in the progression and malignant transformation of LUAD. In subgroup analyses, patients of LUAD with high PPIA expression had shorter OS than patients with low PPIA levels and were characterized by TNM stage,pathological stage,male and female,whole age,anatomic neoplasm subdivision of left and peripheral,smoke and non-smoke,smoked for less than 40 years.In M0 stage,the OS was shorter in patients with high expression of PPIA, while in the M1 phase, the epitopes of PPIA were not correlated with OS,which may be related to the aforementioned viewpoint that the anti-tumor

properties of CypA may be more effective in the initial stages of cancer development[27].The current results indicated that PPIA may serve as a biomarker for the progress of LUAD. Therefore, in clinical work, LUAD patients with high expression of PPIA have a higher risk of recurrence, and follow-up examinations should be performed more frequently.

Many studies about the possible role of PPIA in human TILs have emerged in recent years. It has been reported that the expression of PPIA may be related to T cell infiltration. In this study, we found that several tumor infiltrating immune cells (CD4+ T cell, B cell, macrophage M1) were correlated with the expression of PPIA in LUAD by using TIMER. We also found that the expression of PPIA was negatively correlated with CD4+ T cells and B cells, and positively correlated with macrophage M1. Among the infiltrated immune cells, CD4+ T cells exhibited the most remarkable correlation with PPIA expression and prognosis of LUAD patients. In liver cancer, PPIA has a strong correlation with the expression of B cells, CD8+ T cells, CD4+ T cells, macrophages, neutrophils and dendritic cells[32]. Different tumors may cause different immune cell infiltration. In addition, the expression of PPIA was negatively correlated with CD28, CD40LG, IL6R, and C10orf54, which was consistent with the expression of CD4+ T cells and B cells. These findings suggest that there is a potential correlation between PPIA and immune infiltration in LUAD. However, further research should be designed to confirm this correlation.

Currently, the signaling pathway of PPIA in tumors had been partially reported. The co-expression analysis in this study showed that the expression of PPIA was significantly correlated with the expressions of BSG, CFL1, H2AX, ITK, PFN1, PPP3R1 and TRIM5. The expression of PPIA directly or indirectly affected the expression of these co-expressed genes. We speculate that these co-expressed genes may be related to the prognosis of LUAD or may be prognostic markers of LUAD, but all of these need further experimental confirmation.

Basigin (BSG), also known as extracellular matrix metalloproteinase inducer or cluster of differentiation 147 (CD147), PPIA/CD147 signaling has been reported to lead to cell migration, proliferation and differentiation [33]. PPIA was reported to interact with BSG, which could lead to decreased activity and proliferation of lymphocytes [34], causing immune inhibition of cancer cells. Studies[35] demonstrated that BSG overexpression was highly associated with poor prognosis of LUAD by stimulating the production of matrix metalloproteinases. This is consistent with our finding that high PPIA expression was positively correlated with high BSG expression and negatively correlated with high immunocyte infiltration, which may be the reason for lower OS compared with patients with low PPIA expression. PPIA could inhibit the activity of interleukin-2 tyrosine kinase (ITK), leading to decreased activation of T cells[36]. This suggests a negative correlation between PPIA and ITK expression, which means that PPIA expression should be negatively correlated with CD4 T cell count, consistent with the results of this study. Disregulation of these genes can lead to changes in PPIA signaling, which can affect the prognosis of tumors by regulating growth, metastatic potential and tumor microenvironment, and can provide targets for tumor treatment.

Notably, there were certain limitations to the present study. The relationship between the expression of PPIA and the prognosis in LUAD and the mechanism of its influence on immune infiltration require further clinical trials. In summary, in this study, we found that PPIA is up-regulated in LUAD and is negatively correlated with prognosis. PPIA may be used as a potential biomarker and therapeutic molecular target for poor prognosis in LUAD, and may play a role in immune infiltration.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare no conflicts of interest.

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Authors' contributions

LL, JLY conceived the study, contributed to the study design, assisted with analysis, and wrote the first draft of the article. ZTC, FL, KC, JYG contributed to data preparation and analysis.

LC, WHL contributed to the interpretation of the results and report finalization. All authors agreed with the decision to submit.

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Table

TABLE 1 | Univariate and multivariate analyses of the correlation of PPIA expression with LUAD patients.

Characteristics	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
T stage(T1&T2 vs T3&T4)	2.317 (1.591-3.375)	<0.001	1.619 (1.004-2.610)	0.048
N stage(N0 vs N1&N2&N3)	2.601 (1.944-3.480)	<0.001	1.952 (1.312-2.904)	<0.001
M stage(M0 vs M1)	2.136 (1.248-3.653)	0.006	1.144 (0.602-2.173)	0.681
Pathologic stage(Stage I,II vs III,IV)	2.664 (1.960-3.621)	<0.001	1.539 (0.933-2.538)	0.091
Gender(Female vs Male)	1.070 (0.803-1.426)	0.642		
Age(<=65 vs >65)	1.223 (0.916-1.635)	0.172		
number_pack_years_smoked(<40 vs >=40)	1.073 (0.753-1.528)	0.697		
Smoker(No vs Yes)	0.894 (0.592-1.348)	0.591		
Anatomic neoplasm subdivision(Left vs Right)	1.037 (0.770-1.397)	0.810		
Anatomic neoplasm subdivision2(Central vs Peripheral)	0.913 (0.570-1.463)	0.706		
PPIA(Low vs High)	1.718 (1.283-2.302)	<0.001	1.512 (1.062-2.154)	0.022

Figures

Figure 1

PPIA expression in normal human tissues, human tumors, and LUAD. **(a)** PPIA expression level among a variety of human cancers in the TIMER database (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$). **(b)** PPIA mRNA expression between pairs of tumors and normal tissues of LUAD patients from the TCGA database. **(c)** PPIA protein expression between primary tumors and normal tissues of LUAD patients from the CPTAC database.

Figure 2

Relationships between PPIA mRNA levels and clinical pathological characteristics. PPIA mRNA expression was significantly correlated with lymph

node metastases**(b)**,high TNM stage**(f)**.However,no statistically significant correlation were found between the expression levels of PPIA and T stage**(a)**,M stage**(c)**,age**(d)**,gender was male**(e)**,smoke condition**(g)**, and anatomic neoplasm subdivision **(h,i)** (ns, no significance, and . *P < 0.05, **P < 0.01, ***P < 0.001).

Figure 3

Prognostic role of PPIA in LUAD patients. **(a)**ROC curves of evaluating the accuracy of PPIA gene. **(b)** Kaplan-Meier curve of the association between PPIA mRNA expression and the prognosis of LUAD patients.High expression of PPIA was correlated with poor overall survival in age**(c/d)**,male**(e)**,female**(f)**,stage in I,II/III,IV**(g/h)**,M0 stage**(i)**,N stage**(j)**,T1,T2/T3,T4 stage**(k/l)**,smoke status**(m/n)**,year of smoke**(o)**,and anatomic neoplasm subdivision**(p/q)**. Hazard ratio (HR),confidence interval (CI),receiver operating characteristic (ROC), area under the curve (AUC). (*p < 0.05, **p < 0.01, ***p < 0.001)

Figure 4

Correlations of PPIA expression with immune infiltration level. **(a)** PPIA expression is positively correlated with macrophages and negatively correlated with CD4+ T cells and B cells in LUAD. **(b)** Relations between the expression of PPIA and TILs across human cancers. **(c)** PPIA was correlated with IL6R, CD40LG, CD28, C10orf54, and CD56dim cells.

Figure 5

PPI networks and functional enrichment analyses. **(a)** A network of LIMK1 and its co-expression genes. **(b)** Functional enrichment analyses of involved genes. **(c-l)** The correlation analyses between the expression of PPIA and co-expressed genes in LUAD. BSG, basigin; PPP3R1, recombinant protein phosphatase 3, regulatory subunit 1; PPP3CB, recombinant protein phosphatase 3 catalytic subunit beta; PPP3CA, recombinant protein phosphatase 3 catalytic subunit, alpha isozyme; PFN1, profilin 1; MAPK3, mitogen-activated protein kinase 3; ITK, IL-2-inducible T cell kinase; H2AX, histone 2AX; CFL1, cofilin-1; TRIM5, tripartite-motif-containing protein 5 isoform.