Lupine Online Journal of Pharmacology & Clinical Research

DOI: 10.32474/LOJPCR.2023.03.000158

ISSN: 2644-1373

Research Article

Using Bioinformatic Analysis to Identify FK506 Binding Protein 4 as a Novel Prognostic Factor in Lung Adenocarcinoma

Huiquan Gu[1#], Yanjiao Xie[2#], Fangyu Wang[1], Hanqiang Zhang[3], Longyu Yao[3], Weimin Chen[1*] and Qiang Liu[1*]

[1]*Department of Pharmacology, Hainan Medical University, China*

[2]*Department of Pharmacy, Hainan Provincial People's Hospital, China*

[3]*Department of First Clinical College, Hainan Medical University, China*

***Corresponding author:** Weimin Chen, **Email:744526211@qq.com,** Department of Pharmacology, Hainan Medical University, Haikou, China and

Qiang Liu, **Email: hy0207044@hainmc.edu.cn** Department of pharmacology, Hainan medical university, Haikou, China

#The authors contributed the same work to this paper, and they are the co-first authors.

Received: June 12, 2023 **Published:** June 20, 2023

Abstract

Objective: Lung adenocarcinoma (LUAD), the most common cause of cancer death in humans, urgently requires specific biomarkers for diagnosis, and treatment. FK506 Binding Protein 4(FKBP4) has been observed to be overexpressed in a variety of cancers, but its role in LUAD is unknown. We aimed to evaluate the role of FKBP4 in LUAD tumorigenesis and prognosis.

Methods: The Cancer Genome Atlas (TCGA) database was used to estimate the differential expression of FKBP4 in LUAD and normal tissues. Multiple approaches were used for assessing the association between FKBP4 and clinicopathological parameters. Kaplan–Meier and Cox regression analyses were conducted to elucidate prognosis value of FKBP4. Gene set enrichment analysis (GSEA) was performed for focusing on biological pathways, and single sample GSEA (ssGSEA) was utilized for exploring the association of FKBP4 with infiltration of immune cells.

Results: FKBP4 mRNA level was significantly elevated in cancerous tissues than that in adjacent normal lung tissues. The clinical relevance analysis showed FKBP4 was positively related to the advance of TNM stages, higher pathologic stage, poor tumor status, and worse treatment response. Higher FKBP4 expression predicted dismal overall survival and disease-specific survival. Cox analysis revealed high FKBP4 expression represented an independent prognostic factor. GSEA analysis exhibited enrichment of cell cycle checkpoints, G2/M checkpoints, mitotic G1-G1/S phases, glucose metabolism, glycolysis pathway, and HIF-1α (hypoxia-inducible factor 1α) pathway in FKBP4 high-expression phenotype. Immune infiltration analysis showed FKBP4 contributed to Th1/Th2 balance disorder.

Conclusions: Abnormal expression of FKBP4 predicts a dismal prognosis in LUAD and might regulate the tumor progression by cell cycle checkpoints, glycolysis pathway and Th1/Th2 balance. Our study suggests that FKBP4 can be used as a biomarker to determine prognosis and a potential immunotherapeutic target for LUAD.

Keywords: FKBP4; lung adenocarcinoma; TCGA; prognosis; functional analysis; lupine publishers; lupine publisher's group

Introduction

Lung cancer remains the largest contributor to cancer-related mortality, with an estimated 228,820 new cases only in 2020 in the United States [1,2]. Non-small cell lung cancer (NSCLC) represents approximately 85% of all lung malignancies along with three major

histologic categories, in which LUAD followed by squamous cell carcinoma (LSCC) has become the most common subtype [3]. NSCLC patients, absence of early characterized clinical manifestations, are always diagnosed at an advanced stage for the first time [4]. Unfortunately, in the last century, platinum-based chemotherapy as a widely used method for advanced NSCLC patients only maintains their median survival for 8 months [5]. However, with the development of detection technology, molecular targeting drugs based on genetic changes such as mutation, fusion, amplification have revolutionized LUAD treatment and become standard first-line therapy [6,7]. The guidelines for this heterogeneous disease suggest that all advanced adenocarcinoma patients should be tested for oncogenic drivers to guide appropriate genetic treatment [8].

Nonetheless, numerous molecular targets have not been detected to date [9]. Therefore, it is compelling to infer novel biomarkers for stratification patients into differential risk, response or outcome. FK506 Binding Protein 4 (FKBP4, also known as FKBP52 or FKBP59) belongs to a member of the immunophilin family, and it was discovered in 1985 at that time called EC1 [10]. Serving as a significant regulator of steroid hormone receptor signaling, FKBP4 dysregulation might contribute to various disorders, including endometriosis [11], male urethra morphogenesis [12], and stress-related diseases [13]. Recently, the role of FKBP4 in cancer progression has attracted an emerging attention. Previous study has demonstrated that FKBP4 acts as heat-shock protein 90 (HSP90) associated co-chaperone is down regulated in colon tumor compared with normal colon tissue [14]. Interestingly, we observed the opposite conclusion in the endocrine-related carcinoma. Elevated FKBP4 expression is positively related to worse progression and prognosis in breast cancer [15], which is mediated by interacting with PI3K and promoting Akt/mTORC2 signaling [16]. A similar phenomenon has been observed in prostate cancer.

There is FKBP4 amplification in castration resistant prostate cancer (CRPC) patients, which is related to poor survival [17]. In agreement with prostate cancer, FKBP52 is found to be obviously higher expression in hepatocellular carcinoma (HCC) compared with controls and considered as a diagnostic biomarker of early stage hepatocarcinoma [18]. Regarding the potential mechanism of FKBP4 in several tumor evolutions, we further aimed to explore its role in the progression of LUAD. In this study, we found that there are apparent differences in FKBP4 mRNA levels between LUAD tissues and surrounding normal lung tissues. Subsequently, to evaluate whether FKBP4 could serve as a biomarker for diagnosis and prognosis, we stratified LUAD patients into low- and high-expression groups based on the median value of FKBP4 expression and undertook a retrospective cohort study. We also sought to elucidate the underlying mechanisms by using Gene set enrichment analysis (GSEA) and single sample GSEA (ssGSEA).

Materials and Methods

RNA-Sequencing Data

We downloaded the gene expression data and relevant clinical information for LUAD patients from publicly available TCGA website (https://portal.gdc.cancer.gov/).Then, RNA-Sequencing data with fragments per kilobase per million (FPKM) values were converted to transcripts per million reads (TPM) for comparison gene expression level between different samples. We ultimately selected FKBP4 to further analyze its diagnostic capacity in the cohort (513 LUAD samples and 59 adjacent normal lung samples).

GSEA Gene Enrichment Analysis

To explore the biological pathways involving the FKBP4 gene, GSEA [19] was utilized to investigate the important biological processes between the matrix of high-and low- FKBP4 expression group and previously defined gene sets (c2.cp.v7.0.symbols.gmt). With 1000 permutations, a false discovery rate (FDR) < 0.25 and adjusted P< 0.05 were considered as statistically significant enriched.

Association of FKBP4 with Immune Cell Infiltration

We also examined FKBP4 and immune infiltration levels based on in the literature [20], Spearman correlation analysis was conducted to predict the association between FKBP4 and the immune cell infiltration levels. The P value < 0.001 was indicated a significant difference.

Statistical Analysis

All data analyses and visualizations were done through R software version 3.6.3. Wilcoxon signed rank sum test and Wilcoxon rank sum test were performed to examine the levels of FKBP4 in paired and unpaired samples. Kruskal-Wallis rank sum test, Wilcoxon rank sum test and logistic regressions were performed to analyze the association between FKBP4 and clinicopathological parameters. We selected overall survival (OS) and disease-specific survival (DSS) as the study outcomes, and Kaplan-Meier curve was plotted to estimate the prognostic situation of FKBP4 with the R package survminer (https://CRAN.R-project.org/package=survminer). Univariate and multivariate Cox proportional hazard regression models were performed to examine independent prognostic factors. The P value < 0.05 was taken to denote statistically significant.

Results

The expression of FKBP4 was significantly up-regulated and used as a diagnostic biomarker in LUAD We retrieved the FKBP4 expression data from the TCGA database, then we observed FKBP4 was significantly over-expression in cancerous tissues than surrounding normal lung tissues (Figure 1A, P<0.001). Meanwhile, of the 57 paired samples, FKBP4 showed roughly the same trend: FKBP4 was highly expressed in cancerous samples and lowly expressed in normal samples (Figure 1B, P<0.001). Moreover, we performed ROC curve to assess FKBP4 diagnostic accuracy, the area under the curve (AUC) was 0.870 indicating that FKBP4 might predict whether or not a patient eventually develops LUAD (Figure 1C, CI:0.841-0.899).

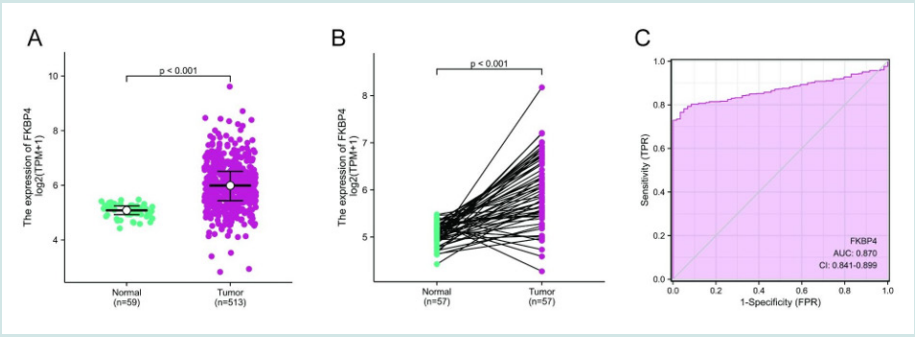

Figure 1: Differential gene expression level and Receiver-operating Characteristic (ROC) curve analysis.
(A) The expression of FKBP4 was significantly upregulated in LUAD compared with normal tissues.
(B) The expression of FKBP4 was significantly upregulated in LUAD compared with adjacent normal tissues.
(C) The FKBP4 for discriminating tumor from non-tumor patients was regarded as a diagnostic biomarker. FPR, False Positive Rate; TPR, True Positive Rate; AUC, area under curve.

orrelation of FKBP4 Expression Levels with Clinicopathological Features

The baseline clinical characteristics of LUAD patients were presented in Table 1. First, a total of 513 cases were included, among which 257 cases categorized as low expression of FKBP4, and 256 cases categorized as high expression of FKBP4. Then, clinical parameters in low- and high-FKBP4 expression cohorts were compared. For the LUAD patients, T stage, M stage, pathologic stage, primary therapy outcome, gender, race, TP53 status were significantly associated with FKBP4 expression level (P<0.05), while other characteristics were not significantly related to FKBP4 expression (Table 1). Otherwise, we also used Kruskal-Walli's rank sum test and Wilcoxon rank sum test to validate whether higher the gene expression level denoted worse performance. Results revealed that FKBP4 expression level was directly associated with the advance of TNM stages, higher pathologic stage, poor tumor status, worse treatment response (Figure 2, P<0.05). Subsequently, univariate logistic regression analysis showed that upregulated FKBP4 level was significant associated with tumor size (Odds Ratio [OR]=2.48 (1.70-3.65) for T2&T3&T4 vs. T1), lymph node invasion (OR=1.53 (1.06-2.23) for N1&N2&N3 vs. N0), distant metastasis (OR=3.09 (1.27-8.67) for M1 vs. M0), pathologic stage (OR=1.89 (1.33-2.70) for Stage II &Stage III &Stage IV vs. Stage I), primary therapy outcome (OR=1.81(1.17-2.82) for PD&SD &PR vs. CR), and TP53 status (OR=1.92 (1.35-2.74) for Mut vs. WT) (Table 2, all P<0.05). In short, all of the above results indicated that high expression of FKBP4 is associated with poor outcomes.

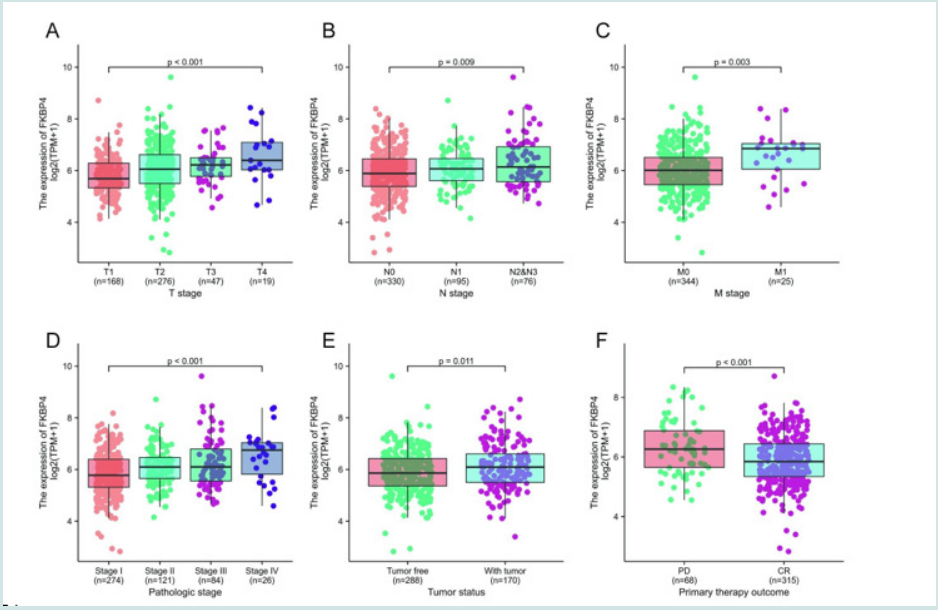

Figure 2: Correlation analysis between FKBP4 and clinical characteristics in LUAD.
(A) for clinical T stage; (B) for clinical N stage; (C) for clinical M stage; (D)for pathologic stage; (E)for tumor status; (F) for primary therapy outcome (PD,progressive disease; CR, complete remission).

Table 1: The correlations between low and high expression of FKBP4 and clinicopathological characteristics in LUAD patients from TCGA.

Characters	Level	Low expression of FKBP4	High expression of FKBP4	P
N		**257**	**256**	
T stage (%)	T1	109(42.7%)	59(23.1%)	<0.001
	T2	126(49.4%)	150(58.8%)	
	T3	16(6.3%)	31(12.2%)	
	T4	4(1.6%)	15(5.9%)	
N stage (%)	N0	176(70.7%)	154(61.1%)	0.116
	N1	40(16.1%)	55(21.8%)	
	N2	32(12.9%)	42(16.7%)	
	N3	1(0.4%)	1(0.4%)	
M stage (%)	M0	170(96.6%)	174(90.2%)	0.024
	M1	6(3.4%)	19(9.8%)	
Pathologic stage (%)	Stage I	157(62.1%)	117(46.4%)	0.002
	Stage II	51(20.2%)	70(27.8%)	
	Stage III	38(15.0%)	46(18.3%)	
	Stage IV	7(2.8%)	19(7.5%)	
Primary therapy	CR	177(79.4%)	138(68.0%)	0.016
Outcome (%)	PD	24(10.8%)	44(21.7%)	
	PR	3(1.3%)	3(1.5%)	
	SD	19(8.5%)	18(8.9%)	
Gender (%)	Female	156(60.7%)	120(46.9%)	0.002
	Male	101(39.3%)	136(53.1%)	
Race (%)	Asian	2(0.9%)	5(2.3%)	0.036
	Black or African American	35(15.1%)	17(7.9%)	
	White	195(84.1%)	192(89.7%)	
Tumor status (%)	Tumor free	155(66.5%)	133(59.1%)	0.122
	With tumor	78(33.5%)	92(40.9%)	
TP53 status (%)	Mut	101(39.5%)	140(55.6%)	<0.001
	WT	155(60.5%)	112(44.4%)	
KRAS status (%)	Mut	63(24.6%)	76(30.2%)	0.193
	WT	193(75.4%)	176(69.8%)	

Table 2: Univariate logistic regression analysis of the relation between FKBP4 and clinicopathological features.

Characteristics	Total (N)	Odds Ratio (OR) in FKBP4 expression	P value
T stage (T2&T3&T4 vs. T1)	510	2.48(1.70-3.65)	<0.001
N stage (N1&N2&N3 vs. N0)	501	1.53(1.06-2.23)	0.024
M stage (M1 vs. M0)	369	3.09(1.27-8.67)	0.019
Pathologic stage (Stage II &Stage III &Stage IV vs. Stage I)	505	1.89(1.33-2.70)	<0.001
Primary therapy outcome (PD&SD&PRvs. CR)	426	1.81(1.17-2.82)	0.008
Tumor status (With tumor vs. Tumor free)	458	1.37(0.94-2.01)	0.101
TP53 status (Mut vs. WT)	508	1.92(1.35-2.74)	<0.001
KRAS status (Mut vs. WT)	508	1.32(0.90-1.96)	0.161

FKBP4 was used as an Independent Prognostic Factor in LUAD

To evaluate the prognostic implications of FKBP4, we carried out Kaplan-Meier survival analysis and Cox regression analysis, with prognosis data from a Cell article [21]. We assumed only significant risk factors identified in univariate regression analysis were incorporated into the multivariate regression model. As shown in the Figure 3, higher FKBP4 expression predicted dismal OS (hazard ratio [HR]=1.75, 95% confidence interval [CI]:1.30-2.35, P<0.001) and poor DSS (HR=1.81, 95% CI:1.24-2.64, P=0.002). The univariate analysis revealed that FKBP4 associated essentially with T stage (HR:1.668; 95%CI:1.184-2.349; P=0.003), N stage (HR:2.606; 95%CI:1.939-3.503; P<0.001), M stage (HR:2.111; 95%CI:1.232-3.616; P=0.007), pathologic 165 stage (HR:2.975; 95%CI:2.188-4.045; P<0.001), primary therapy outcome (HR:2.818; 166 95%CI:2.004-3.963; P<0.001), tumor status (HR:6.211; 95%CI:4.258-9.059; P<0.001) and FKBP4 (HR:1.750; 95%CI:1.303-2.349; P<0.001). Multivariate analysis provided that primary therapy outcome (1.977, 1.257-3.111, P=0.003), tumor status (6.093, 3.603-10304, P<0.001), and high expression of FKBP4 (1.911, 1.193-3.062, P=0.007) were independent prognostic factors (Table 3).

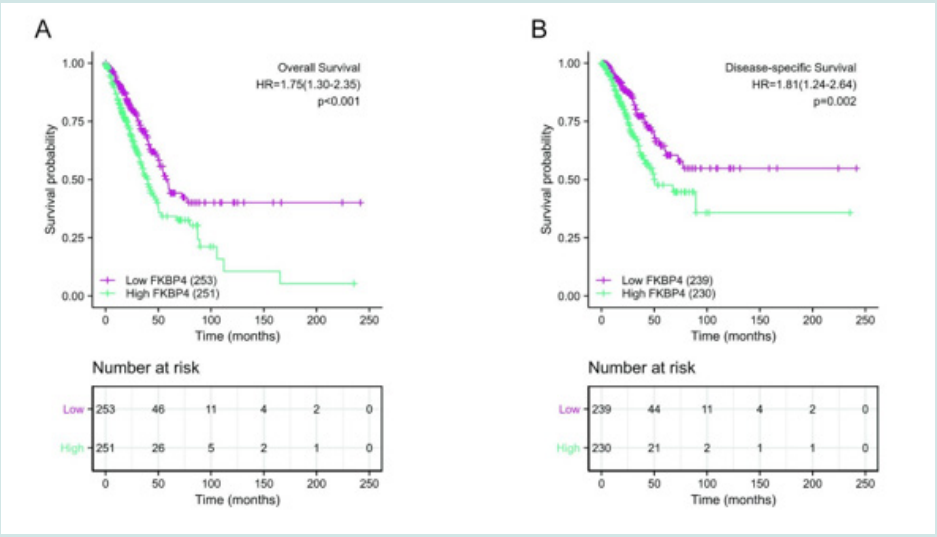

Figure 3: The Kaplan-Meier survival curve for differential expression levels of FKBP4 mRNA (low vs. high) in LUAD patients. (A) The overall survival (OS) curve. (B) The disease-specific survival (DSS) curve.

Table 3: Cox regression analyses of overall survival in lung adenocarcinoma patients.

Characteristics	Total	Univariate analysis		Multivariate analysis	
	(N)	HR (95% CI)	P value	HR (95% CI)	P value
T stage (T2&T3&T4 vs.T1)	501	1.668(1.184-2.349)	0.003	1.21(0.697-2.101)	0.498
N stage (N1&N2&N3 vs.N0)	492	2.606(1.939-3.503)	<0.001	1.521(0.749-3.087)	0.246
M stage (M1 vs. M0)	360	2.111(1.232-3.616)	0.007	0.909(0.389-2.123)	0.825
Pathologic stage (Stage II&Stage III& Stage IV vs.Stage I)	496	2.975(2.188-4.045)	<0.001	0.887(0.406-1.938)	0.763
Primary therapy outcome(PD&SD&PR vs. CR)	419	2.818(2.004-3.963)	<0.001	1.977(1.257-3.111)	0.003
Gender (Male vs. Female)	504	1.06(0.792-1.418)	0.694		
Age (>65 vs. <=65)	494	1.228(0.915-1.649)	0.171		
Race (White vs. Asian&Black or African American)	446	1.422(0.869-2.327)	0.162		
Tumor status (With tumorvs. Tumor free)	450	6.211(4.258-9.059)	<0.001	6.093(3.603-10.304)	<0.001
TP53 status (Mut vs. WT)	499	1.254(0.936-1.680)	0.13		
KRAS status (Mut vs. WT)	499	1.087(0.779-1.517)	0.623		
FKBP4 (High vs. Low)	504	1.75(1.303-2.349)	<0.001	1.911(1.193-3.062)	0.007

Functional analysis

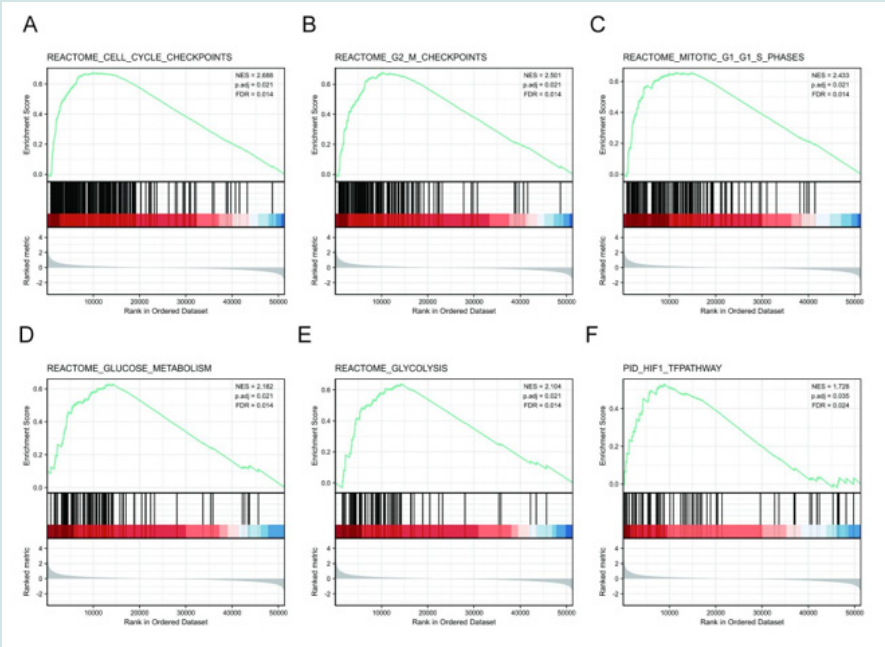

Figure 4: Gene set enrichment analysis (GSEA) on related signaling pathways of FKBP4 in LUAD.
(A) cell cycle checkpoints; (B) G2/M checkpoints; (C) mitotic G1-G1/S phases; (D) glucose metabolism;
(E) glycolysis; (F) HIF-1 (hypoxia-inducible factor 1) pathway. NES, normalized enrichment score; p.adj, adjust P value; FDR: False discovery rate.

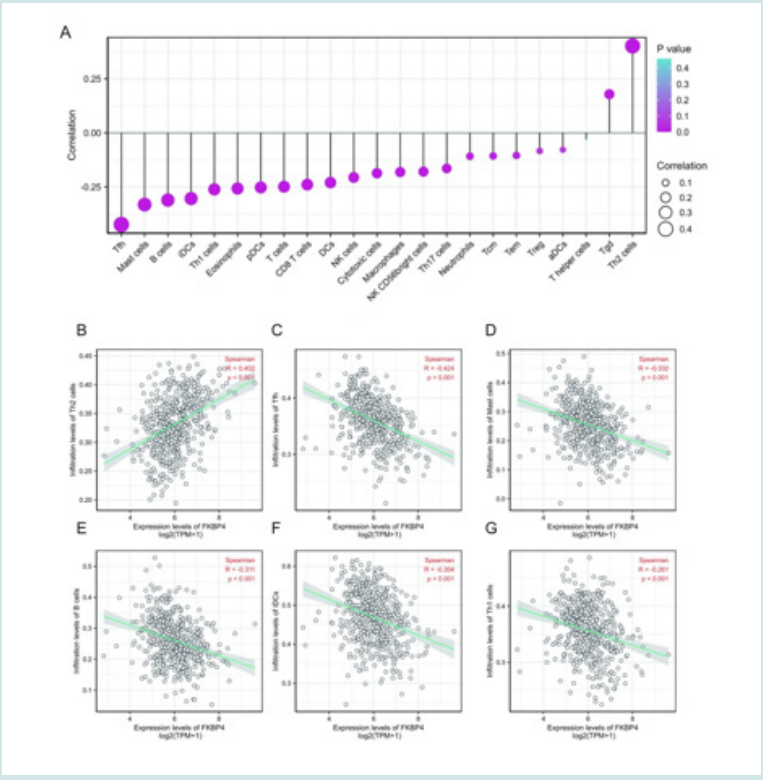

Figure 5: The association between FKBP4 and immune cell infiltration in the tumor environment.
(A) Correlations between FKBP4 expression and the abundance of the immune cell infiltrate. (B) Correlations between the expression levels of FKBP4 and infiltration levels of Th2 cells; (C) Tfh cells; (D) Mast cells; (E) B cells; (F) iDCs cells; (G) Th1 cells. Th2, T helper 2; Tfh, T follicular helper; iDCs, immature Dendritic cells

To gain insight into the functional annotation of differential expression between high - and low- FKBP4 expression cohorts, GSEA was performed to identify altered canonical pathways. We observed that there were 395 statistically significant data sets, including cell cycle checkpoints, G2/M checkpoints, mitotic G1-G1/S phases, glucose metabolism, glycolysis pathway, and HIF-1α (hypoxia-inducible factor 1α) pathway (Figure 4). In addition, to assess the relationship between FKBP4 expression level and immune cell infiltration degree, we performed Spearman correlation analysis by ssGSEA method using GSVA package [22]. Finally, we found that FKBP4 expression level was positively related to the abundances of T helper 2 (Th2), and negatively related to the abundances of T follicular helper (Tfh), mast cells, B cells, immature Dendritic cells (iDCs), Th1 cells, and so on (Figure 5).

Discussion

Lung cancer is the most frequent cancer and the leading cause of death in cancer. As the most common histologic subtype of NSCLC, LUAD is characterized by uncontrolled malignant growth of cells in the lungs and bronchi. Due to the lack of effective early diagnostic methods, mortality is high in patients with intermediate to advanced stages. As a member of the immunophilic protein family, FKBP4 binds to FK506 but does not trigger immunosuppression due to the unique FK1 structural domain. Current studies on FKBP4 are still limited to promoting the maturation of steroid hormone receptors, influencing protein folding and aggregation, and being involved in the development of endocrine-related tumors related to it [23]. In contrast, the role of FKBP4 in the diagnosis or prognosis of LUAD has rarely been reported. Therefore, further studies on the functional impact of FKBP4 in LUAD are needed. In our study, we discovered that FKBP4 was strongly expressed in tumor tissues and showed good accuracy to distinguish tumor or non-tumor patients by constructing the ROC curve (AUC=0.870).

This meant that people with higher expression of FKBP4 had a greater risk of LUAD. Subsequently, we explored the relationship between FKBP4 and different clinicopathological factors in LUAD patients, and we found the FKBP4 expression level was positively associated with disease progression. In addition, FKBP4 was still an independent prognostic factor for OS. And then, we also try to understand the underlying mechanism by GSEA and ssGSEA. Currently, tumor TNM staging system is a widely used tool for guiding treatment and predicting prognosis. Previous research confirms that larger tumor diameter [24], lymph node involvement [25], and distant spread [26] are associated with worse survival rates. In our study, we found that higher levels of FKBP4 were significantly correlated with higher T stage, N stage, M stage, and pathologic stage. These results of Kruskal-Walli's rank sum test and Wilcoxon rank sum test were consistent with univariate logistic regression analysis. As stated above, High FKBP4 expression was related to poor prognosis.

The prognostic value of FKBP4 was also validated by Kaplan-Meier curves and COX regression, FKBP4 was regarded as an independent prognostic factor. In terms of primary therapy outcome, high expression of FKBP4 predicted disease progression, and patients with low expression of FKBP4 achieved complete remission. Therefore, we inferred that FKBP4 could also be used as a predictor of initial treatment response. Above results indicated that FKBP4 could stratified patients into differential cancer risk, therapy response and long-term prognosis. Elevated FKBP4 expression was associated with dismal clinicopathological features, poor therapy outcome and shorter survival time. In order to explore the potential mechanism of FKBP4, we investigated its biological pathways by GSEA. Enrichment results suggested that high expression of FKBP4 was engaged in the regulation of cell cycle checkpoints, which guaranteed cell duplication and division. Importantly, G2/M DNA damage checkpoint is activated in the early stage of HCC which implies a possible error in the cell cycle [27].

Our study also found the activation of cell cycle checkpoints, which indicated that elevated FKBP4 expression correlated with cell cycle disturbances. Some studies have identified that cell cycle disorder could result in uncontrolled cell growth. It was observed that lncINS-IGF2 increases cell proliferation and migration by facilitating G1/S transition in NSCLC cells [28]. It was also found that promoting faster G1/S cell cycle transition could enhance cell proliferation [29]. Not only G1/S transition, but also G2/M dysregulation contributes to tumor initiation and tumor progression. Emerging research have confirmed inducing G2/M phase arrest could retard cell proliferation [30,31]. Thus, FKBP4 might serve as a potential therapeutic target for cell cycle. Additionally, GSEA verified that high expression of FKBP4 was enriched in glucose metabolism and HIF-1pathway. A study demonstrates that the aberration of glucose metabolism, especially the glycolysis pathway, is regarded as significantly associated with carcinogenesis [32]. Importantly, as compared with healthy cells, lung cancer cells with enhanced aerobic glycolysis led to rapid cell proliferation [33].

Prior studies have found that regulating glycolytic enzymes could effectively reduce tumor formation. It is reported that Hexokinase 2(HK2) is highly expressed in malignant NSCLC tissues with poor survival time30906213 [34] and targeting down-regulation of HK2 expression could inhibit cell viability, reduce anchorage-independent colony formation, and suppress xenografted tumor growth [35]. It is worth mentioning that Pyruvate kinase M2 (PKM2) is also a critical regulator of aerobic glycolysis. The results targeting PKM2 is consistent with HK2 in reducing cell viability, and colony formation [36]. Furthermore, HIF-1α as a master regulator of aerobic glycolysis could upregulate key enzymes such as HK2, PKM2, and pyruvate dehydrogenase kinase 3 (PDK3) [37,38], resulting in accelerated glycolysis. In addition, HIF-1α could induce the vascular endothelial growth factor (VEGF) synthesis, which promotes cancer growth and metastasis [39]. Therefore, we hypothesized that FKBP4 promoted tumor progression via glycolysis and HIF-1α pathway.

More than biological pathway functions, the association between FKBP4 expression and immune cell levels was investigated.

It is well known that the Th1/Th2 balance is essential for the maintenance of immune responses. However, when this balance is disturbed, a tumor occurs [40]. Prior study found that NSCLC patients have increased expression of Th2 cytokines (IL-4 and IL-10) and decreased expression of Th1 cytokines (IL-2 and INF-γ) in the peripheral blood, whose postoperative IL-4 abnormalities manifest a significantly shorter survival time. In line with this, we found that FKBP4 transcript levels were positively and dramatically correlated with the level of Th2, and negatively correlated with infiltration levels of Th1. Thus, we inferred that patient with high levels of FKBP4 had a Poorer prognosis due to altered Th1/Th2 balance. Although using bioinformatic analysis to identify FKBP4 as a novel prognostic factor, there are still some limitations. First, we only consider data from TCGA for confirming its capacity on stratification patients into differential risk level, response or outcome.

Second, focusing on canonical pathways and immune function might neglect other possible the mechanistic role of FKBP4. Third, external validation of biological experiments was not done. Therefore, we should further validate its capacity in vitro and in vivo and collect patients for a prospective study. Overall, high expression of FKBP4 was significantly associated with LUAD progression, poor survival and immune infiltration, and as a tumor-promoting factor, may promote tumorigenic development by regulating glucose metabolism and the HIF-1 α pathway as well as Th1/Th2 balance in LUAD. This study demonstrates that FKBP4 has the potential to predict the therapeutic effects of LUAD and is expected to be a new cancer marker and target for cancer treatment.

Author Contributions

Qiang Liu and Weimin Chen designed this research. Huiquan Gu and Yanjiao Xie carried out the concrete analysis and wrote the first draw manuscript. Fangyu Wang edited the figures and tables. Hanqiang Zhang and Longyu Yao edited the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The authors sincerely acknowledge Helixlife for the public databases and bioinformatics approaches.

Ethics Approval and Consent to Participant

Not applicable.

Consent for Publication

Not applicable.

Competing Interests

The authors declare that they have no competing interests.

Funding

The research project was partially or fully sponsored by The National Natural Science Foundation of China with grant number (NO.82060851). and The Hainan Medical University Innovative Experimental Projects (NO. HYYS2021A35).

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, et al. (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68(6): 394-424.
2. Siegel RL, Miller KD, Jemal A (2020) Cancer statistics, 2020. CA Cancer J Clin 70(1): 7-30.
3. Herbst RS, Heymach JV, Lippman SM (2008) Lung cancer. N Engl J Med 359(13): 1367-1380.
4. Walters S, Maringe C, Coleman MP, Peake MD, Butler J, et al. (2013) Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-basedstudy,2004-2007. Thorax 68(6): 551-564.
5. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, et al. (2002) Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346(2): 92-98.
6. Vargas AJ, Harris CC (2016) Biomarker development in the precision medicine era: lung cancer as a case study. Nat Rev Cancer 16(8): 525-37.
7. Arbour KC, Riely GJ (2019) Systemic Therapy for Locally Advanced and Metastatic Non-Small Cell Lung Cancer: A Review. JAMA 322(8): 764-774.
8. Ettinger DS, Aisner DL, Wood DE, Akerley W, Bauman J, et al. (2018) NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 5.2018. J Natl Compr Canc Netw 16(7): 807-821.
9. Rodriguez-Canales J, Parra-Cuentas E, Wistuba II (2016) Diagnosis and Molecular Classification of Lung Cancer. Cancer Treat Res 170: 25-46.
10. Nakao K, Myers JE, Faber LE (1985) Development of a monoclonal antibody to the rabbit 8.5S uterine progestin receptor. Can J Biochem Cell Biol 63(1): 33-40.
11. Joshi NR, Miyadahira EH, Afshar Y, Jeong JW, Young SL, et al. (2017) Progesterone Resistance in Endometriosis Is Modulated by the Altered Expression of MicroRNA-29c and FKBP4. J Clin Endocrinol Metab 102(1): 141-149.
12. Chen H, Yong W, Hinds TD Jr, Yang Z, Zhou Y, et al. (2010) Fkbp52 regulates androgen receptor transactivation activity and male urethra morphogenesis. J Biol Chem 285(36): 27776-84.
13. Baker JD, Ozsan I, Rodriguez Ospina S, Gulick D, Blair LJ (2018) Hsp90 Heterocomplexes Regulate Steroid Hormone Receptors: From Stress Response to Psychiatric Disease. Int J Mol Sci 20(1): 79.
14. Garifulin OM, Kykot VO, Gridina NY, Kiyamova RG, Gout IT, et al. (2015) Application of serex-analysis for identification of human colon cancer antigens. Exp Oncol 37(3): 173-180.
15. Xiong H, Chen Z, Zheng W, Sun J, Fu Q, et al. (2020) FKBP4 is a malignant indicator in luminal A subtype of breast cancer. J Cancer 11(7): 1727-1736.
16. Mange A, Coyaud E, Desmetz C, Laurent E, Beganton B, et al. (2019) FKBP4 connects mTORC2 and PI3K to activate the PDK1/Akt-dependent cell proliferation signaling in breast cancer. Theranostics 9(23): 7003-7015.
17. Federer-Gsponer JR, Quintavalle C, Muller DC, Dietsche T, Perrina V, et al. (2018) Delineation of human prostate cancer evolution identifies chromothripsis as a polyclonal event and FKBP4 as a potential driver of castration resistance. J Pathol 245(1): 74-84.
18. Liu Y, Li C, Xing Z, Yuan X, Wu Y, et al. (2010) Proteomic mining in the dysplastic liver of WHV/c-myc mice—insights and indicators for early hepatocarcinogenesis. FEBS J 277(19): 4039-4053.
19. Subramanian A, Kuehn H, Gould J, Tamayo P, Mesirov JP (2007) GSEA-P: a desktop application for Gene Set Enrichment Analysis. Bioinformatics 23(23): 3251-3253.

20. Bindea G, Mlecnik B, Tosolini M, Kirilovsky A, Waldner M, et al. (2013) Spatiotemporal dynamics of intratumoral immune cells reveal the immune landscape in human cancer. Immunity 39(4): 782-795.

21. Liu J, Lichtenberg T, Hoadley KA, Poisson LM, Lazar AJ, et al. (2018) An Integrated TCGA Pan-Cancer Clinical Data Resource to Drive High-Quality Survival Outcome Analytics. Cell 173(2): 400-416.

22. Hanzelmann S, Castelo R, Guinney J (2013) GSVA: gene set variation analysis for microarray and RNA-seq data. BMC Bioinformatics 14: 7.

23. Solassol J, Mange A, Maudelonde T (2011) FKBP family proteins as promising new biomarkers for cancer. Curr Opin Pharmacol 11(4): 320-325.

24. Stojiljkovic D, Santrac N, Stojiljkovic T, Miletic N, Gavrilovic D (2015) Correlation of tumor size as independent factor and disease stage with local recurrence of non-small cell lung carcinoma and its operability. J BUON 20(1): 166-172.

25. Zhang YK, Chai ZD, Tan LL, Wang ZY, Chen ZJ, et al. (2017) Association of lymph node involvement with the prognosis of pathological T1 invasive non-small cell lung cancer. World J Surg Oncol 15(1): 64.

26. Cheng H, Perez-Soler R (2018) Leptomeningeal metastases in non-small-cell lung cancer. Lancet Oncol 19(1): e43-e55.

27. Yin L, Chang C, Xu C (2017) G2/M checkpoint plays a vital role at the early stage of HCC by analysis of key pathways and genes. Oncotarget 8(44): 76305-76317.

28. Gao S, Lin Z, Li C, Wang Y, Yang L, et al. (2019) lncINS-IGF2 Promotes Cell Proliferation and Migration by Promoting G1/S Transition in Lung Cancer. Technol Cancer Res Treat 18: 1533033818823029.

29. Hui L, Zhang S, Wudu M, Ren H, Xu Y, et al. (2019) CBLL1 is highly expressed in non-small cell lung cancer and promotes cell proliferation and invasion. Thorac Cancer 10(6): 1479-1488.

30. Lin SQ, Jia FJ, Zhang CY, Liu FY, Ma JH, et al. (2019) Actinomycin V Suppresses Human Non-Small-Cell Lung Carcinoma A549 Cells by Inducing G2/M Phase Arrest and Apoptosis via the p53-Dependent Pathway. Mar Drugs 17(10): 572.

31. Concato VM, Tomiotto-Pellissier F, Silva TF, Goncalves MD, Bortoleti B, et al. (2020) 3,3',5,5'-tetramethoxybiphenyl-4,4'diol induces cell cycle arrest in G2/M phase and apoptosis in human non-small cell lung cancer A549 cells. Chem Biol Interact 326: 109133.

32. Ding M, Li F, Wang B, Chi G, Liu H (2019) A comprehensive analysis of WGCNA and serum metabolomics manifests the lung cancer-associated disordered glucose metabolism. J Cell Biochem 120(6): 10855-10863.

33. Vander Heiden MG, Cantley LC, Thompson CB (2009) Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science 324(5930): 1029-33.

34. Zhou L, Li M, Yu X, Gao F, Li W (2019) Repression of Hexokinases II-Mediated Glycolysis Contributes to Piperlongumine-Induced Tumor Suppression in Non-Small Cell Lung Cancer Cells. Int J Biol Sci 15(4): 826-837.

35. Yuan J, Peng G, Xiao G, Yang Z, Huang J, et al. (2020) Xanthohumol suppresses glioblastoma via modulation of Hexokinase 2 -mediated glycolysis. J Cancer 11(14): 4047-4058.

36. Suzuki A, Puri S, Leland P, Puri A, Moudgil T, et al. (2019) Subcellular compartmentalization of PKM2 identifies anti-PKM2 therapy response in vitro and in vivo mouse model of human non-small-cell lung cancer. PLoS One 14(5): e0217131.

37. Prigione A, Rohwer N, Hoffmann S, Mlody B, Drews K, et al. (2014) HIF1alpha modulates cell fate reprogramming through early glycolytic shift and upregulation of PDK1-3 and PKM2. Stem Cells 32(2): 364-376.

38. Peng W, Huang W, Ge X, Xue L, Zhao W, et al. (2019) Type Igamma phosphatidylinositol phosphate kinase promotes tumor growth by facilitating Warburg effect in colorectal cancer. EBio Medicine 44: 375-386.

39. Frezzetti D, Gallo M, Maiello MR, D'Alessio A, Esposito C, et al. (2017) VEGF as a potential target in lung cancer. Expert Opin Ther Targets 21(10): 959-966.

40. Li J, Wang Z, Mao K, Guo X (2014) Clinical significance of serum T helper 1/T helper 2 cytokine shift in patients with non-small cell lung cancer. Oncol Lett 8(4): 1682-1686.

DOI: 10.32474/LOJPCR.2023.03.000158