Current Science
CS 5 (6), 5417-5428 (2025)
Received 17 Oct 2025 | **Accepted 07 November** 2025 | **Online Available 14 November** 2025
https://doi.org/10.52845/CS/2025-5-6-11

Current Science

Current Science

OPEN ACCESS

ISSN (O) 2795-8639

Original Article

Upregulation of PLOD2 is Associated with Tumor Progression and Immune Infiltration in Clear Cell Renal Cell Carcinoma

Shaojun Chen[1]*, Jianqing Ye[1]

[1]Department of Urology, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200092, China

***Corresponding Author: Shaojun Chen**

Abstract:

Objective: Renal cell carcinoma (RCC) is the most common malignant renal tumors in adults. PLOD2 is overexpressed in different human cancers and closely related to a poor prognosis. Here, we aimed to explore the expression of PLOD2 in ccRCC and its roles in tumor progression and immune infiltration based on various database.

Methods: PLOD2 expression levels in different human cancers and its correlation with immune infiltration in ccRCC were determined by using TIMER 2.0 database. GEPIA database was used to evaluate PLOD2 expression and its prognostic significance in ccRCC. The UALCAN database was used to evaluate the association between PLOD2 expression and clinicopathologic features in ccRCC patients. The correlation between PLOD2 expression and immunomodulators in cancers was determined by using the TISIDB database. The differential expressed genes (DEGs) in PLOD2 high expressed group and PLOD2 low expressed group were explored from TARGET database.

Results: PLOD2 is upregulated in multiple human cancers including ccRCC. PLOD2 upregulation is associated with advanced clinical characteristics and poor prognosis in ccRCC. Moreover, overexpression of PLOD2 is correlated with several chemokine expression and immune cells infiltration in ccRCC.

Conclusions: Upregulation of PLOD2 is associated with tumor progression and immune infiltration in ccRCC. PLOD2 may may serve as a novel therapeutic target in the treatment of ccRCC.

Keywords: renal cell carcinoma, PLOD2, tumor progression, immune infiltration.

1. Introduction

Renal cell carcinoma (RCC), originating from the proximal tubular cells of the renal unit, is the most common malignant renal tumors in adults [1]. The incidence of RCC is steadily increasing in recent years. According to available cancer statistics in 2022, RCC is the sixth most frequently diagnosed cancer in males and the ninth in females [2]. Clear cell renal cell carcinoma (ccRCC, KIRC) is the most common histological subtype, which account for approximately 75% of all RCC and is the main cause of kidney cancer deaths [3]. Radical nephrectomy (RN) and nephron-sparing surgery (NSS) are the recommended treatment for localized RCC [4]. As RCC does not respond to conventional chemotherapeutic agents or radiotherapy, the systemic targeted therapy and immunotherapy are the remaining treatment option for metastatic RCC patients [5]. However, nearly 30% of RCC patients have metastatic disease at initial presentation and recurrence occurs in about 30% of patients following surgical resection of the primary tumor [6]. As a result, it is crucial to identify novel molecules involved in RCC progression so as to improve the prognosis of RCC patients.

Procollagen-lysine, 2-oxoglutarate 5-dioxygenase

2 (PLOD2) is a member of PLOD family (PLOD1, PLOD2, and PLOD3) which play pivotal roles in mediating the formation of stabilized collagen cross-links [7]. PLOD2, regulated by HIF-1α, TGF-β and microRNA-26a/b, is overexpressed in different human cancers and closely related to a poor prognosis [8]. For instance, it was reported that the expression of PLOD2 in hepatocellular carcinoma (HCC) tissues was higher than that in adjacent tissues, and increased PLOD2 expression was often found in advanced tumors and was correlated with poor prognosis in HCC patients [9]. PLOD2 expression was also elevated in colorectal carcinoma (CRC), and its higher expression was associated with poorer survival. Overexpression of PLOD2 facilitated CRC proliferation, invasion, and metastasis in vitro and in vivo [10]. Moreover, Wang et al. showed that PLOD2 was high-expressed in osteosarcoma (OS) and promoted OS migration, invasion and angiogenesis in vitro and facilitated OS metastasis and angiogenesis in vivo [11]. A recent literature demonstrated that PLOD2 was induced under hypoxic conditions and strongly associated with poor prognosis in ccRCC patients. PLOD2 depletion reduced proliferation and migration of ccRCC cells in vitro and in vivo [12]. However, the clinical significance of PLOD2 in ccRCC progression and its roles in immune infiltration of ccRCC tumor microenvironment still remains unclear.

In this study, we assessed the expression of PLOD2 and its prognostic significance in a variety of human cancers including KIRC/ccRCC using the Tumor Immune Estimation Resource (TIMER) and Gene Expression Profiling and Interactive Analysis (GEPIA) databases. We also investigated the relationship between PLOD2 expression and clinical features and immune infiltration in KIRC based on TISIDB and UALCAN database. In addition, differential expression genes (DEGs) between PLOD2 high and low expression groups were analyzed originating from the TARGET database. We found that PLOD2 was overexpressed in KIRC and associated with tumor progression and poor prognosis. PLOD2 upregulation was closely correlated with immune infiltration and chemokines expression in KIRC.

2. Materials and Methods

2.1 TIMER Database Analysis

TIMER (https://cistrome.shinyapps.io/timer/) is an online resource for systematic analysis of gene expression and immune infiltration across diverse cancer types. We used TIMER 2.0 database to assess the expression pattern of PLOD2 in various human cancers and the relationship between PLOD2 expression and the level of immune infiltration in KIRC. $p<0.05$ was considered as statistically significant.

2.2 GEPIA Database Analysis

GEPIA database (https://gepia.cancer-pku.cn/) is an interactive web server to analyze cancer gene expression profile and survival prognosis based on TCGA and the Genotype-Tissue Expression (GTEx) project. Here, we used GEPIA database to determine the expression of PLOD2 in different cancer tissues and the prognostic value of PLOD2 in KIRC, including overall survival (OS) and disease-free survival (DFS). $p<0.05$ was considered as statistically significant.

2.3 UALCAN Database Analysis

The UALCAN database (http://ualcan.path.uab.edu) is a reliable web portal to provide information on gene expression and its association with clinicopathologic features in cancer patients. We used this database to validate the expression level of PLOD2 in KIRC and evaluate its expression between different subgroups based on cancer stage, tumor grade and nodal metastasis status.

2.4 TISIDB Database Analysis

The TISIDB database (http://cis.hku.hk/TISID) is

an online portal for analyzing immune cell infiltration and immunomodulation in cancers. Additionally, it provides the analysis of gene expression between different clinical features. In this study, we used TISIDB database to evaluate the relationship between PLOD2 expression and clinical features in different cancer types and immunomodulators in KIRC.

2.5 Differential Expression Genes (DEGs) between PLOD2 High and Low Expression Groups

The gene expression and clinical data of KIRC patients were obtained from the TARGET database (https://ocg.cancer.gov/programs/target). A total of 71 KIRC patients were divided into PLOD2 high group (n=36) and PLOD2 low group (n=35). Package limma was used to determine the DEGs between the two groups. KEGG and GO (gene ontology) analyses were performed using the package cluster Profiler and ggplot2. $p<0.05$ or $FDR<0.05$ is considered significant (enrichment score with −log10 (P) of more than 1.3).

3. Results

3.1 Pan-Cancer Analysis of PLOD2 Expression in Human Cancers.

We firstly assessed the expression pattern of PLOD2 mRNA in different human cancers and paired normal tissues by using TIMER 2.0 database (https://cistrome.shinyapps.io/timer/). The results showed that PLOD2 was upregulated in multiple human cancer tissues including KIRC (figure. 1A). Then, we also used the GEPIA database (https://gepia.cancer-pku.cn/) to validate the findings from the TIMER database. We found that the mRNA level of PLOD2 was significantly higher in most human tumors compared to adjacent normal tissues including KIRC (figure. 1B). Moreover, box plots of the GEPIA database displayed the overexpression of PLOD2 in various cancer tissues (figure. 1C). These results indicate that PLOD2 is upregulated in most human cancers and may act as an oncogene.

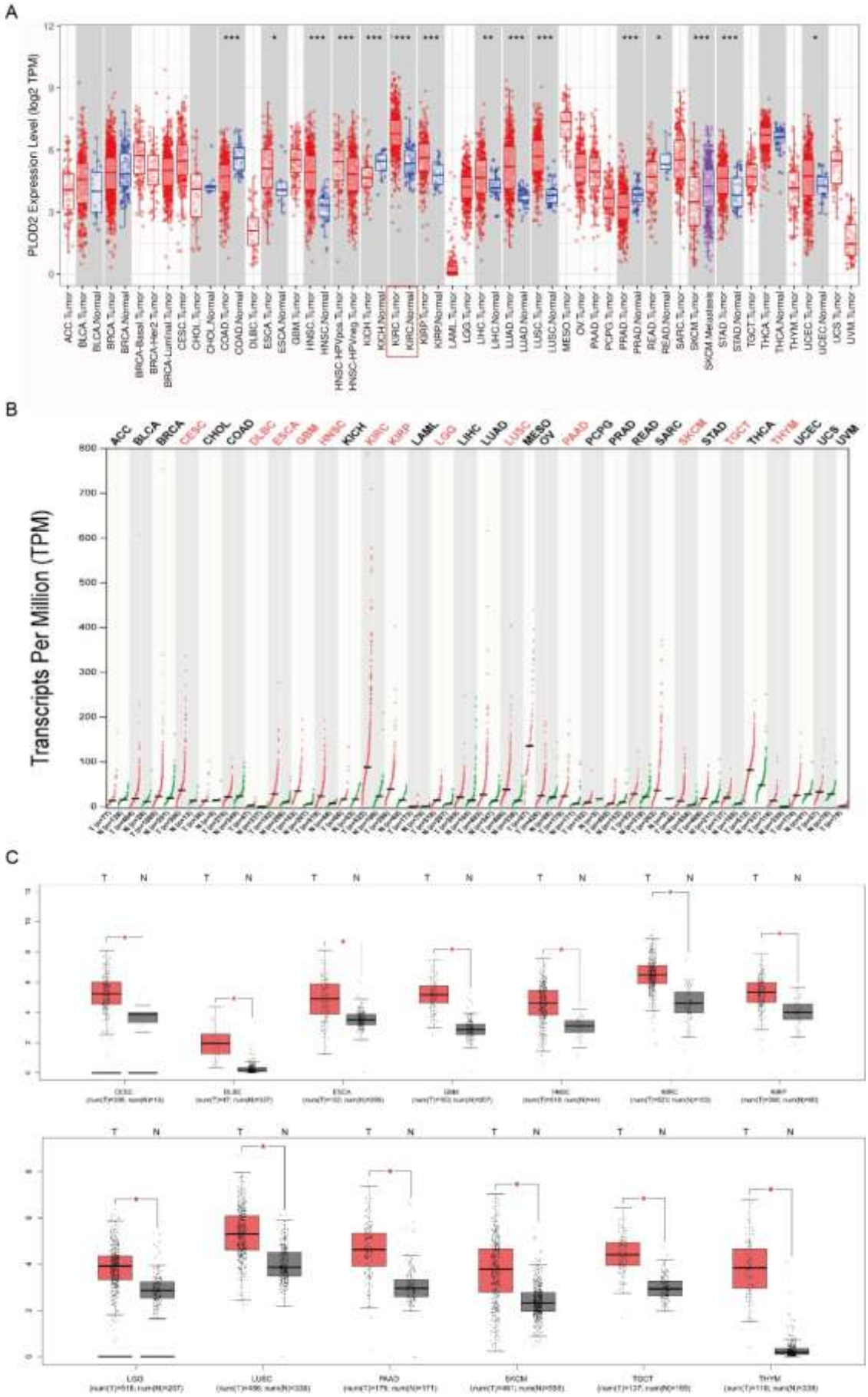

Figure1. Pan-cancer analysis of PLOD2 expression in human cancers. (A) Expression pattern of PLOD2 in various human cancers compared to adjacent normal tissues derived from the TIMER 2.0

database (https://cistrome.shinyapps.io/timer/). **(B)** Expression profiles of PLOD2 in multiple cancers and paired normal tissues based on the GEPIA database (https://gepia.cancer-pku.cn/). **(C)** Box plots displaying the expression of PLOD2 in different cancers and normal tissues obtained from the GEPIA database. *p < 0.05, **p < 0.01, ***p < 0.001.

3.2 PLOD2 is Closely Correlated with Clinical Characteristics in KIRC

We used TISIDB database (http://cis.hku.hk/TISID) to analyze the correlation between PLOD2 and clinical characteristics in various cancer types. We discovered that KIRC is the most correlated cancer with PLOD2 regard to OS (Figure 2A), stage (Figure 2B), and tumor grade (Figure 2C) among all cancer types. Moreover, we found that upregulation of PLOD2 expression was significantly associated with shorter OS (Figure 2D), advanced clinical stage (Figure 2E) and higher tumor grade (Figure 2F) in KIRC.

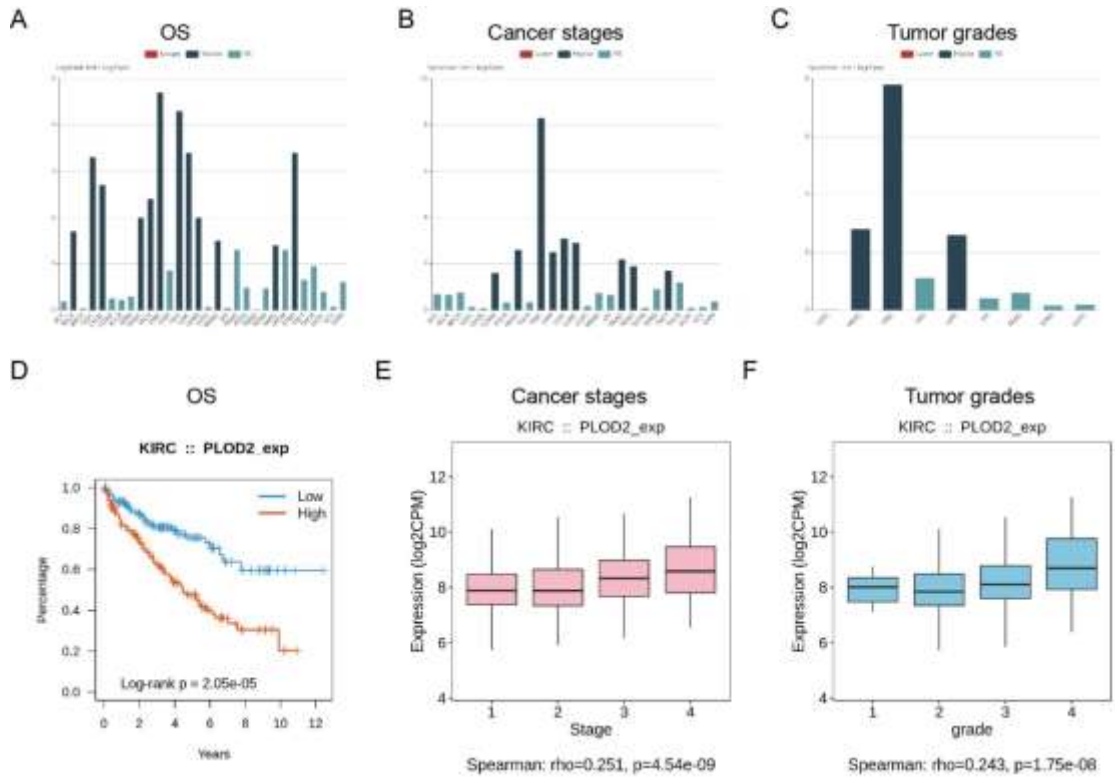

Figure2. PLOD2 is closely correlated with clinical characteristics in KIRC. (A-C) The association between PLOD2 expression and patients' overall survival (OS) **(A),** cancer stage **(B)** and cancer grade **(C)** in various cancers by using the TISIDB database (http://cis.hku.hk/TISID). (D-F) Correlation between the expression of PLOD2 and OS **(D),** stage **(E)** band grade **(F)** of KIRC.

3.3 Upregulation of PLOD2 is Associated with Tumor Progression and Poor Prognosis in KIRC

The UALCAN database (http://ualcan.path.uab.edu) was used to evaluate the expression level of PLOD2 in KIRC and its association with clinicopathologic features in KIRC patients. We found that PLOD2 was upregulated in KIRC tumor tissues when compared with normal kidney tissues (figure. 3A). Meanwhile, the overexpression of PLOD2 was positively correlated with cancer stage, tumor grade and nodal metastasis in KIRC (figure. 3B-D). In

addition, we analyzed the prognostic significance of PLOD2 in KIRC by using GEPIA database. Data showed that high level of PLOD2 predicted both shorter overall survival (OS) and disease-free survival (DFS) in KIRC patients (figure. 3E, F).

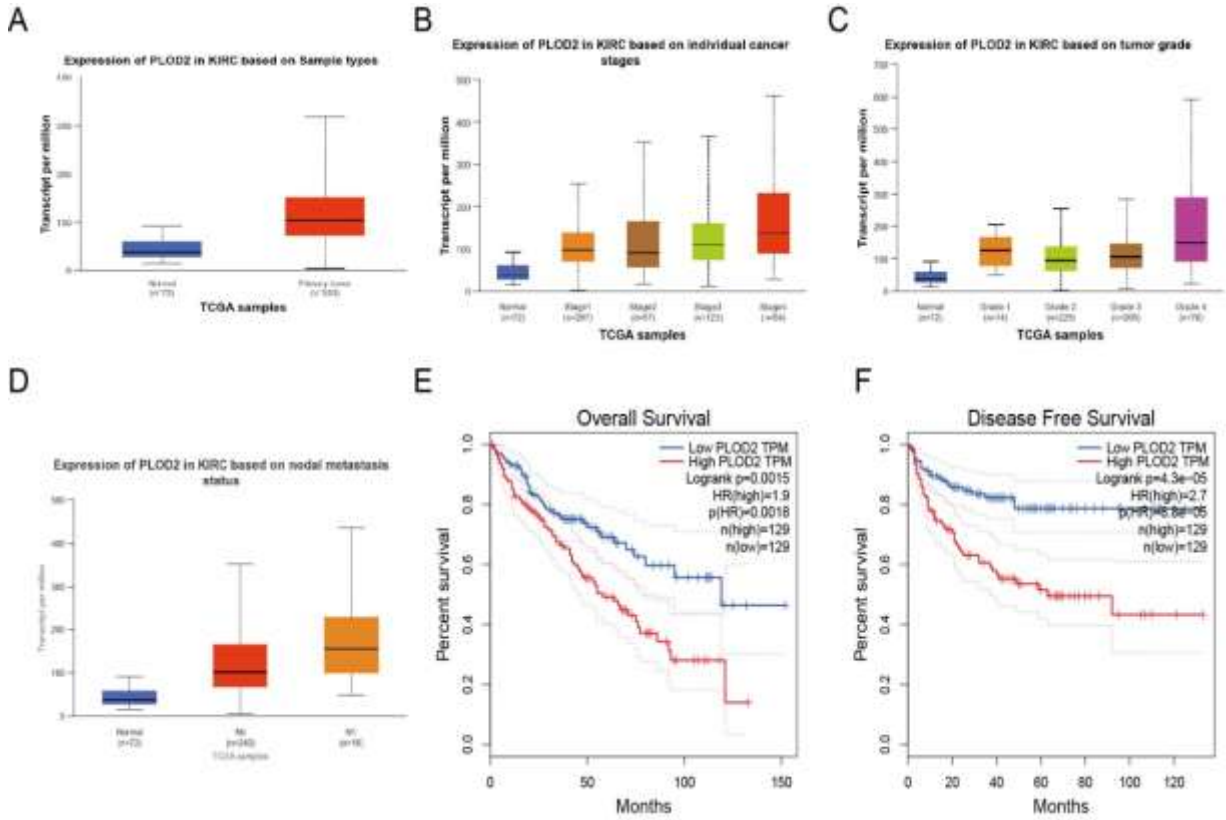

Figure3. Upregulation of PLOD2 is associated with tumor progression and poor prognosis in KIRC. **(A)** Expression of PLOD2 in KIRC tumor tissues and normal kidney tissues derived from the UALCAN database (http://ualcan.path.uab.edu). **(B-D)** The correlations between PLOD2 expression and cancer stage **(B),** tumor grade (C) and nodal metastasis status **(D)** in KIRC derived from the UALCAN database. **(E-F)** The overall survival (OS) and disease free survival (DFS) data of KIRC patients with high or low level of PLOD2 based on GEPIA database.

3.4 PLOD2 Expression is Correlated with Immunomodulators and Chemokines Expression in KIRC

The correlation between PLOD2 expression and immunomodulators in various cancers was determined by using the TISIDB database (http://cis.hku.hk/TISID). We observed that PLOD2 expression was closely correlated with immune cells infiltration in human cancers (figure 4A) and several immune cells infiltrated positively correlated with PLOD2 expression in KIRC (figure 4B-L).

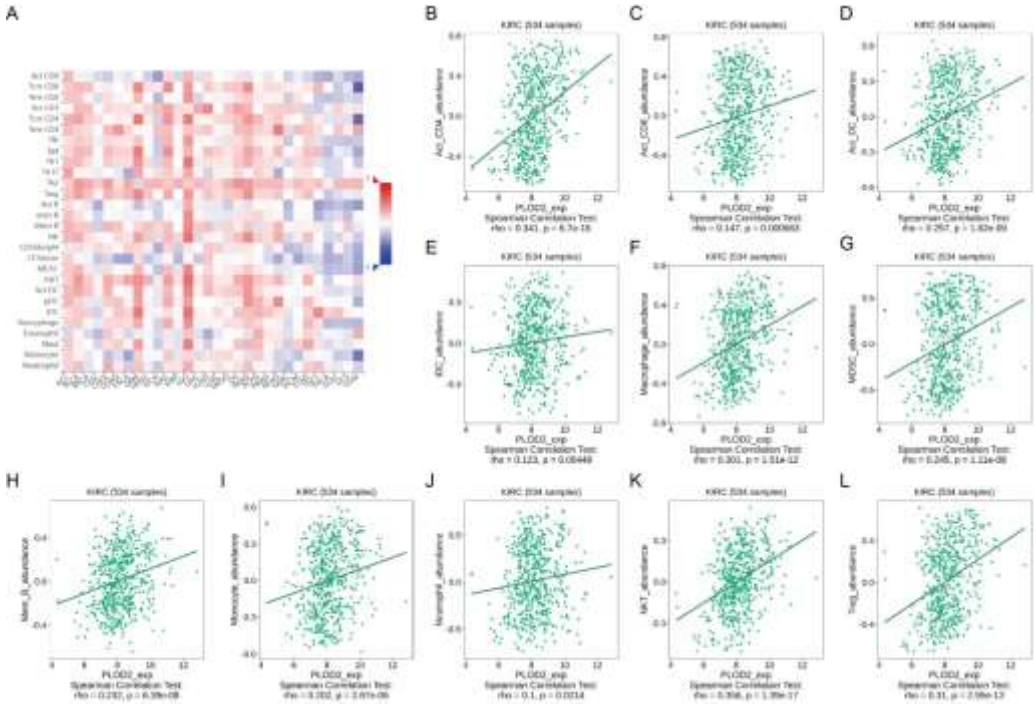

Figure4. Correlation between PLOD2 expression and immunomodulators in KIRC. (A) Correlation analysis between the infiltration of tumor-infiltrating lymphocytes (TILs) and PLOD2 expression in multiple human cancers by using the TISIDB database. **(B-L)** The immune cells positively correlated with PLOD2 expression in KIRC using the TISIDB database.

Additionally, we found that PLOD2 expression was associated with chemokine expression levels in different cancers (figure 5A) and several chemokine expression levels were positively correlated with PLOD2 expression in KIRC (figure 5B-L). These results suggest that PLOD2 may play a pivotal role in tumor immunity.

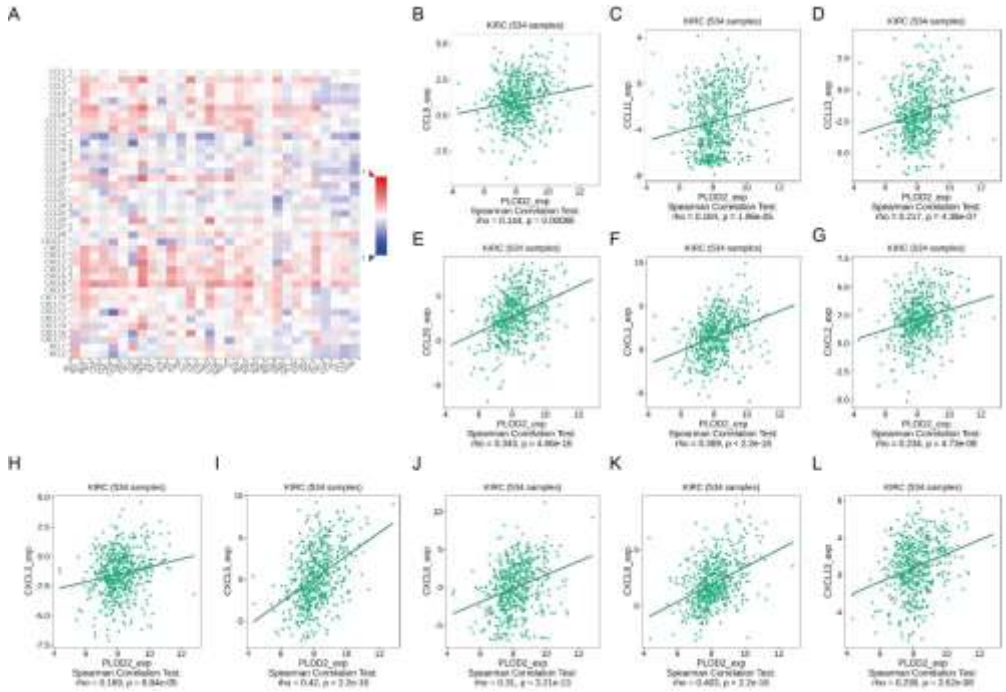

Figure5. Correlation between PLOD2 expression and chemokine expression levels in KIRC. (A)

Correlation between chemokine expression levels and PLOD2 expression in different cancers analyzed by TISIDB database. **(B-L)** Several chemokine expression levels were positively correlated with PLOD2 expression in KIRC based on the TISIDB database.

3.5 PLOD2 Expression is Correlated with Immune Infiltration in KIRC

By using the TIMER 2.0 database, we found that the expression of PLOD2 was significantly negatively correlated with tumor purity while positively correlated with B cells, CD8+ T cells, CD4+ T cells, macrophages, neutrophils, and dendritic cells in KIRC (figure 6A). The SCNA defined using TIMER 2.0 indicated that PLOD2 SCNA (arm-level gain) affected the levels of CD4+ T cells (figure 6B). Moreover, we observed that PLOD2 expression was positively correlated with CD68, CD163, and CD206 (MRC1) expression levels in KIRC based on TIMER 2.0 database (figure 6C-E). These results reveal that PLOD2 is significantly correlated with immune infiltration in KIRC.

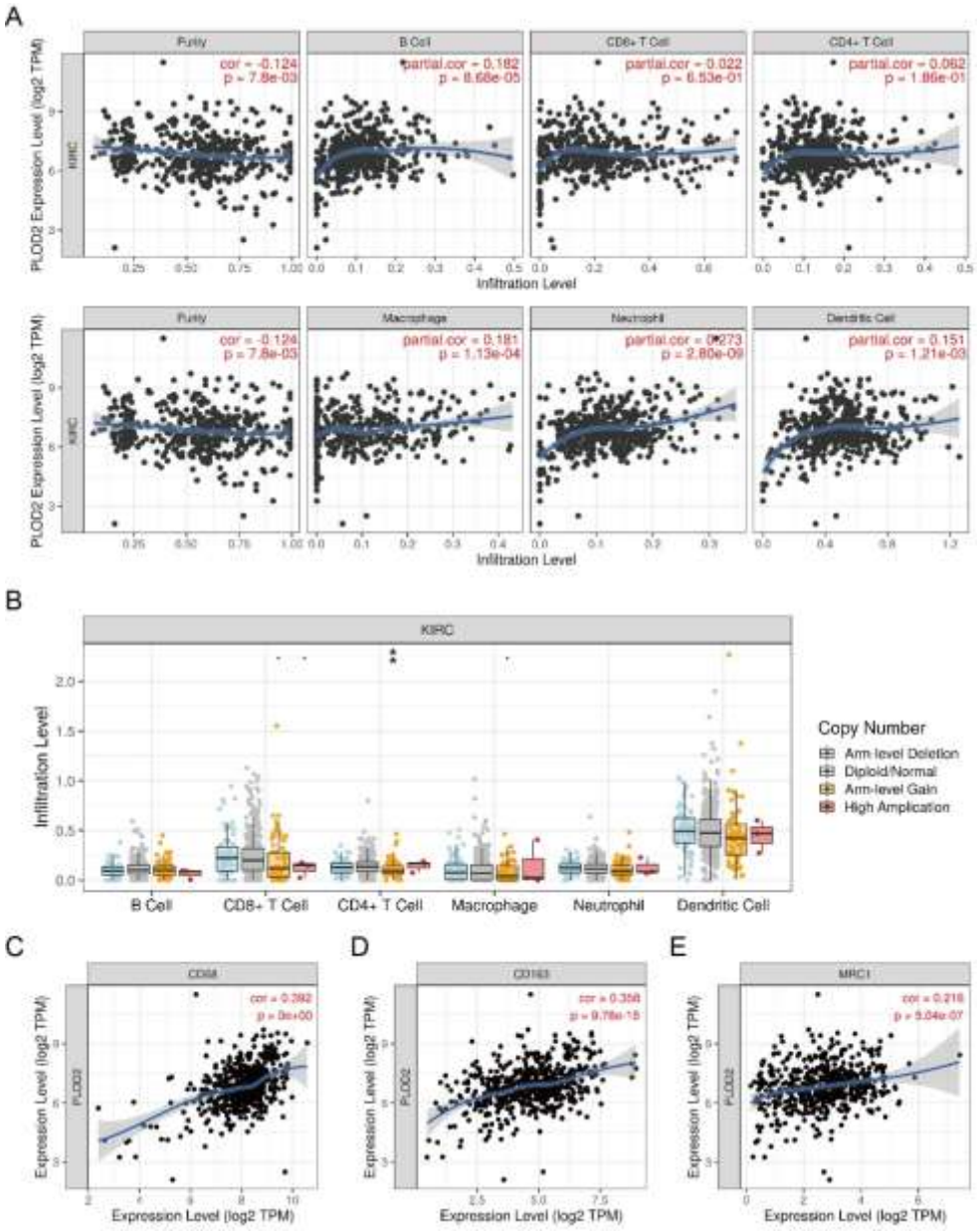

Figure6. Relationship between PLOD2 expression level and immune infiltration in KIRC gain from TIMER 2.0 database. (A) The correlation between PLOD2 expression level and tumor purity, infiltrating

levels of B cells, CD8+ T cells, CD4+ T cells, macrophages, neutrophils, and dendritic cells in KIRC. **(B)** The infiltration level of various immune cells under different copy numbers of PLOD2 in KIRC. (C-E) The correlation between PLOD2 expression and CD68, CD163 and CD206（MRC1）expression levels in KIRC.

3.6 Differential Expressed Genes (Degs) Associated with PLOD2 Expression Level and Functional Enrichment Analysis

We analyzed the differential expressed genes (DEGs) in PLOD2 high expressed group (n=36) and PLOD2 low expressed group (n=35) based on TARGET database. The results of DEGs in two groups were presented in a volcano plot (figure 7A) and heatmap (figures 7B). Then, KEGG pathway enrichment analysis and gene ontology (GO) analysis were performed based on DEGs between PLOD2 high and low expression groups (figure 7C, D). We found that the PI3K-AKT signaling pathway and kidney development were activated in PLOD2 upregulated group.

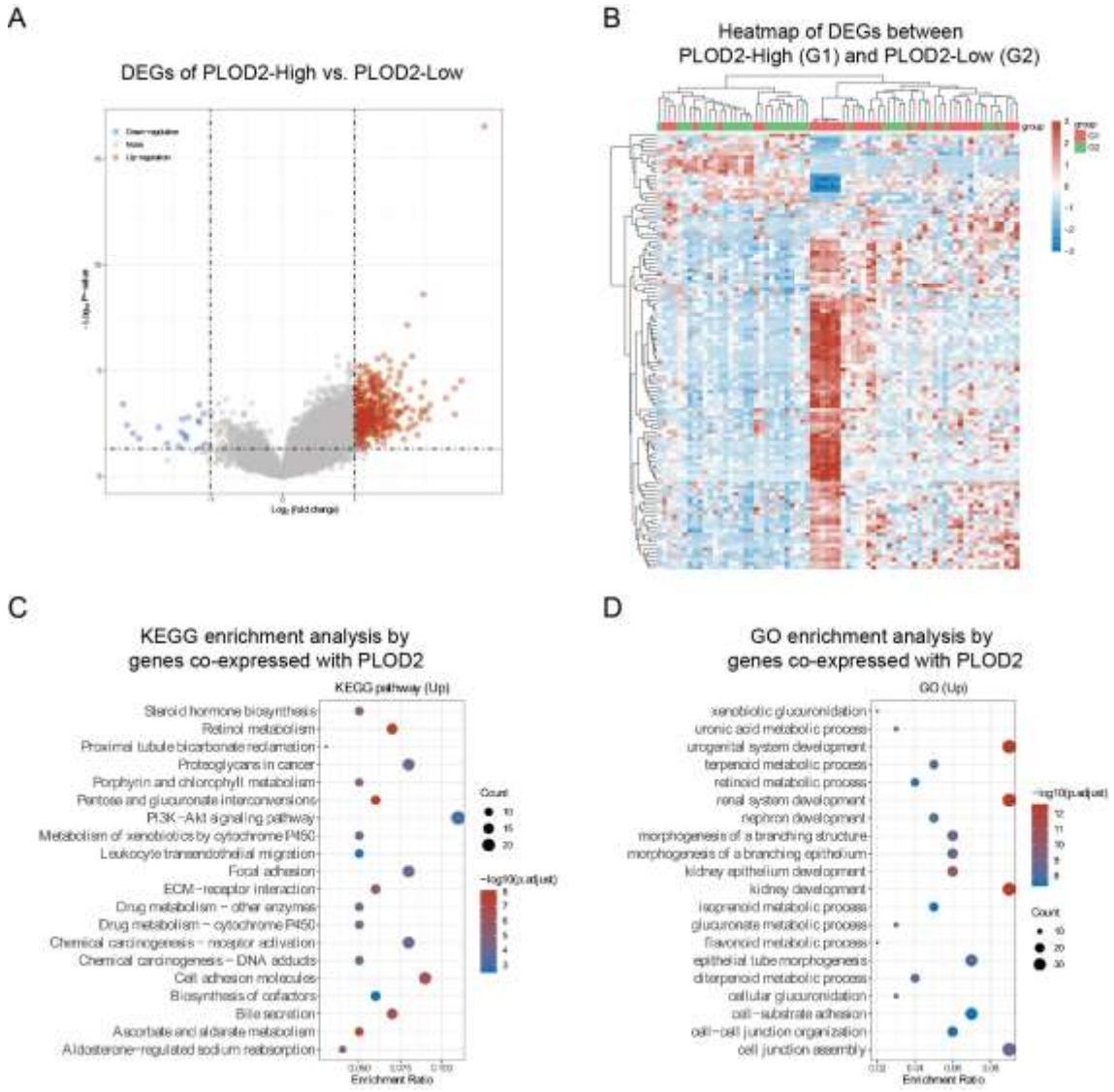

Figure7. Differential expressed genes in PLOD2 high and low expressed groups and functional enrichment with KEGG and GO analysis. (A) The volcano map shows differentially expressed genes (DEGs) related to PLOD2 expression level in KIRC. (B) The heatmap of differential expression gene (DEGs) according to PLOD2 high or low expression in KIRC. (C and D) The KEGG enrichment (C) and

GO enrichment (D) analysis by genes co-expressed with PLOD2. p<0.05 or FDR<0.05 is considered significant (enrichment score with −log10 (P) of more than 1.3).

4. Discussion

It was reported that PLOD family members (PLOD1/2/3) were all upregulated in ccRCC tissues and significantly associated with advanced tumor stage, high pathological grade and poorer prognosis [13]. A published paper demonstrated that PLOD3 expression was enhanced in RCC and PLOD3 knockdown suppressed RCC malignance via inhibiting TWIST1-mediated activation of β-catenin and AKT signaling [14]. Recently, accumulating evidence showed that PLOD2 was increased in RCC and correlated with tumor progression and poor prognosis [12, 15]. Here, we firstly performed the pan-cancer analysis of PLOD2 expression in human cancers. We observed that PLOD2 expression is upregulated in multiple human cancer tissues including KIRC. Then, we found that PLOD2 is closely correlated with advanced clinical features and poor prognosis via TISIDB database and UALCAN database. These indicated that PLOD2 may play a pivotal role in the initiation and progression in RCC.

As we known, clear cell renal cell carcinoma (ccRCC) is one of the most immunologically distinct tumor types due to high response rate to immunotherapies [16]. Immune infiltration is closely associated with clinical outcome in RCC and the tumor-infiltrating immune cells regulate cancer progression and serve as therapeutic targets [17, 18]. A growing number of research proved the regulatory effect of PLOD2 in immune infiltration of various tumors. Wang er al. showed that PLOD2 was high-expressed and associated with poor prognosis and immune cell infiltration in osteosarcoma (OS) [11]. Li et al. reported that PLOD2 expression was significantly upregulated in cervical cancer (CESC). Immune infiltration analysis showed that PLOD2 was highly correlated with B cells, CD4+ T cells, T helper type 2 (Th2) cells, and eosinophils in CESC [19]. In addition, a literature indicated that PLOD2 was correlated with neutrophil infiltration and may serve as a useful therapeutic target in glioblastoma.

In this study, we explored the correlation between PLOD2 and immune infiltration in KIRC. Results obtained from TISIDB database showed that PLOD2 expression is correlated with multiple immunomodulators and chemokines expression in KIRC. By using the TIMER 2.0 database, we found that the expression of PLOD2 was significantly negatively correlated with tumor purity while positively correlated with B cells, CD8+ T cells, CD4+ T cells, macrophages, neutrophils, and dendritic cells in KIRC. Moreover, we observed that PLOD2 expression was positively correlated with CD68, CD163, and CD206 (MRC1) expression levels in KIRC. In addition, the differential expressed genes (DEGs) in PLOD2 high expressed group and PLOD2 low expressed group were exhibited based on TARGET database. These suggest that PLOD2 is closely correlated with immune infiltration in KIRC and may serve as a novel target in the treatment of KIRC.

In conclusion, we found that PLOD2 expression is upregulated in multiple human cancer tissues including KIRC/ccRCC. High expression of PLOD2 is associated with advanced clinical features and poor prognosis in KIRC. PLOD2 is closely correlated with immune infiltration in KIRC. These suggest that PLOD2 plays a pivotal role in the progression of ccRCC and may serve as a therapeutic target in the treatment of ccRCC.

Author contributions

Conceived and designed the study: SJC. Performed the data collecting: SJC, JQY. Analyzed the data: SJC. Writing and revision of

the manuscript: SJC, JQY. All authors contributed to the article and approved it for publication.

Funding

No funding was received.

Conflict of Interests Statement

The authors declared no potential conflicts of interest of this article.

References:

1. Bukavina L, Bensalah K, Bray F, Carlo M, Challacombe B, Karam JA, Kassouf W, Mitchell T, Montironi R, O'Brien T, Panebianco V, Scelo G, Shuch B, van Poppel H, Blosser CD, Psutka SP. Epidemiology of Renal Cell Carcinoma: 2022 Update. Eur Urol. 2022;82(5):529-42.
2. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72(1):7-33.
3. Hsieh JJ, Purdue MP, Signoretti S, Swanton C, Albiges L, Schmidinger M, Heng DY, Larkin J, Ficarra V. Renal cell carcinoma. Nat Rev Dis Primers. 2017;3:17009.
4. Escudier B, Porta C, Schmidinger M, Rioux-Leclercq N, Bex A, Khoo V, Grunwald V, Gillessen S, Horwich A, clinicalguidelines @esmo.org EGCEa. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-updagger. Ann Oncol. 2019;30(5):706-20.
5. Li R, Jiang X, Wang P, Liu X. Prognostic value of neutrophil extracellular trap signature in clear cell renal cell carcinoma. Front Oncol. 2023;13:1205713.
6. Makhov P, Joshi S, Ghatalia P, Kutikov A, Uzzo RG, Kolenko VM. Resistance to Systemic Therapies in Clear Cell Renal Cell Carcinoma: Mechanisms and Management Strategies. Mol Cancer Ther. 2018;17(7):1355-64.
7. Xu Q, Kong N, Zhao Y, Wu Q, Wang X, Xun X, Gao P. Pan-Cancer Analyses Reveal Oncogenic and Immunological Role of PLOD2. Front Genet. 2022;13:864655.
8. Du H, Pang M, Hou X, Yuan S, Sun L. PLOD2 in cancer research. Biomed Pharmacother. 2017;90:670-6.
9. Li K, Niu Y, Li K, Zhong C, Qiu Z, Yuan Y, Shi Y, Lin Z, Huang Z, Zuo D, Yuan Y, Li B. Dysregulation of PLOD2 Promotes Tumor Metastasis and Invasion in Hepatocellular Carcinoma. J Clin Transl Hepatol. 2023;11(5):1094-105.
10. Lan J, Zhang S, Zheng L, Long X, Chen J, Liu X, Zhou M, Zhou J. PLOD2 promotes colorectal cancer progression by stabilizing USP15 to activate the AKT/mTOR signaling pathway. Cancer Sci. 2023;114(8):3190-202.
11. Wang Z, Fan G, Zhu H, Yu L, She D, Wei Y, Huang J, Li T, Zhan S, Zhou S, Zhu Y, Wang Y, Chen X, Zhao J, Zhou G. PLOD2 high expression associates with immune infiltration and facilitates cancer progression in osteosarcoma. Front Oncol. 2022;12:980390.
12. Liu T, Xiang W, Chen Z, Wang G, Cao R, Zhou F, Meng Z, Luo Y, Chen L. Hypoxia-induced PLOD2 promotes clear cell renal cell carcinoma progression via modulating EGFR-dependent AKT pathway activation. Cell Death Dis. 2023;14(11):774.
13. Xu WH, Xu Y, Wang J, Tian X, Wu J, Wan FN, Wang HK, Qu YY, Zhang HL, Ye DW. Procollagen-lysine, 2-oxoglutarate 5-dioxygenases 1, 2, and 3 are potential prognostic indicators in patients with clear cell renal cell carcinoma. Aging (Albany NY). 2019;11(16):6503-21.
14. Xie D, Li J, Wei S, Qi P, Ji H, Su J, Du N, Zhang X. Knockdown of PLOD3 suppresses the malignant progression of renal cell carcinoma via reducing TWIST1 expression. Mol Cell Probes. 2020;53:101608.
15. Chen Y, He Y, Li Z, Zhang N, Zhou C, He X, Xue D. METTL3 facilitates renal cell carcinoma progression by PLOD2 m(6)A-methylation under prolonged hypoxia. Cell Death Dis. 2024;15(1):62.

16. Borcherding N, Vishwakarma A, Voigt AP, Bellizzi A, Kaplan J, Nepple K, Salem AK, Jenkins RW, Zakharia Y, Zhang W. Mapping the immune environment in clear cell renal carcinoma by single-cell genomics. Commun Biol. 2021;4(1):122.
17. Zhang S, Zhang E, Long J, Hu Z, Peng J, Liu L, Tang F, Li L, Ouyang Y, Zeng Z. Immune infiltration in renal cell carcinoma. Cancer Sci. 2019;110(5):1564-72.
18. Wang L, Song L. Identification of immune cell infiltration profiles in renal cell carcinoma and their clinical significance. Medicine (Baltimore). 2023;102(19):e33732.
19. Li G, Wang X, Liu G. PLOD2 Is a Potent Prognostic Marker and Associates with Immune Infiltration in Cervical Cancer. Biomed Res Int. 2021;2021:5512340.