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Research article

Combination of theoretical analysis and experiments: Exploring the role of *PLA2G7* in human cancers, including renal cancer

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ABSTRACT

Background: The pivotal role of phospholipase A2 group VII (*PLA2G7*) has been identified in specific human cancers, such as prostate cancer, diffuse large B cell lymphoma, and melanoma. Given *PLA2G7*'s significant involvement in established tumors, exploring its role in other cancers is highly relevant.

Methods: In this study, we acquired and analyzed data from The Cancer Genome Atlas database, the UCSC XENA website, and other online platforms including Gene Set Cancer Analysis, cBioPortal, Tumor Immune Estimation Resource, and TISIDB to investigate *PLA2G7*'s role in human cancers, including renal cancer. Furthermore, *in vitro* experiments, including immunofluorescence, western blotting, and CCK-8 assays, were conducted to elucidate *PLA2G7*'s role in renal cancer. Finally, the relationship between *PLA2G7* and various drug sensitivity was explored.

Results: Our findings demonstrate that *PLA2G7* is highly expressed and may serve as a valuable candidate biomarker in pan-cancer. *PLA2G7* exhibits distinct alteration frequencies across human cancers and is correlated with tumor mutation burden, tumor microenvironment, DNA stemness score, RNA stemness score, tumorigenesis, tumor immunity, and microsatellite instability in pan-cancer. Immunofluorescence and western blotting revealed a relative high level of *PLA2G7* protein in renal cancer cell lines (ACHN and 786-O), predominantly localized in the cytoplasm. Treatment with a *PLA2G7* gene inhibitor (darapladib) significantly decreased the viability of ACHN and 786-O cell lines. Additionally, we observed an association between *PLA2G7* mRNA levels and various drug sensitivity.

Conclusions: Our study suggests that *PLA2G7* has the potential to serve as a valuable biomarker and therapeutic target for cancer, particularly in the context of renal cancer.

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1. Introduction

Cancer remains a formidable global health challenge due to its clandestine onset, marked heterogeneity, frequent recurrence, and resistance to therapy [1–6]. Despite relentless endeavours by scientists and advancements in radiotherapy, targeted therapy, and immunotherapy [7–9], the prognosis for patients with cancer remains grim [10]. Notably, renal cell carcinoma, a prevalent cancer type, sees 25–30% of patients diagnosed at an advanced stage, resulting in a dismal 5-year survival rate [11]. Hence, it is imperative to explore more effective diagnostic, prognostic, and therapeutic targets. Recently, the rapid evolution of bioinformatics has facilitated scientist to explore more potential valuable genes, which can be used for diagnosis, prognosis, and therapy [12,13].

Phospholipase A2 group VII (*PLA2G7*) is a phospholipase involved in the hydrolysis of platelet-activating factor and truncated phospholipids synthesized through oxidation [14]. Recent studies have identified *PLA2G7* as a potential prognostic biomarker in prostate cancer, diffuse large B cell lymphoma (DLBC), and melanoma [14–16]. For instance, Zheng et al. discovered that, besides its potential as a DLBC biomarker, silencing *PLA2G7* expression in DLBC cell lines (DB and SU-DHL-2) impeded proliferation and migration while inducing apoptotic death. Similarly, treatment with the specific *PLA2G7* inhibitor (darapladib) yielded comparable results, underscoring *PLA2G7*'s vital role in DLBC. Additionally, recent literature has revealed that heightened *PLA2G7* expression and generation characterize cachexia-inducing cancer cell lines. Patients with colorectal and pancreatic cancer with cancer cachexia exhibit elevated circulating *PLA2G7* levels [17], indicating a robust association between *PLA2G7* and human cancers. However, despite limited reports delving into the biological function of *PLA2G7* in specific human cancers, its role in pan-cancer remains unexplored, highlighting a gap in current knowledge.

In this investigation, our hypothesis posited that *PLA2G7* could function as a potential biomarker and therapeutic target across various cancers. Consequently, we sought to delineate the role of *PLA2G7* in pan-cancer by leveraging multiple databases, R software, and *in vitro* experiments. Our objective was to contribute to the identification of additional cancer biomarkers and therapeutic targets. Our exploration encompassed the examination of *PLA2G7*'s expression profile in human cancers and corresponding normal tissues. Additionally, we investigated the diagnostic and prognostic value of *PLA2G7* in pan-cancer. Furthermore, we scrutinized the associations between *PLA2G7* and tumor immunity, mismatch repair (MMR), and its DNA methylation profile in human cancers. Subsequently, our focus shifted to unraveling the significant role of *PLA2G7* in renal cancer. We anticipate that our findings will broaden perspectives on precision tumor diagnosis and treatment strategies.

2. Materials and methods

2.1. PLA2G7 expression profile in different cancer and normal tissues

The RNAseq data for *PLA2G7* in pan-cancer were acquired from The Cancer Genome Atlas (TCGA) (http://portal.gdc.cancer.gov/), and analyzed using R software v3.6.3. Furthermore, the assessment of *PLA2G7* protein levels in both pan-cancer and normal tissues was conducted through the University of Alabama Cancer Data Analysis Portal at Birmingham (UALCAN, http://ualcan.path.uab.edu/index.html) [18,19].

2.2. Diagnostic, prognostic, and clinicopathological features of PLA2G7 in different cancer types

Data pertaining to diagnostic, prognostic, and clinicopathological features of *PLA2G7* in diverse cancer types were sourced from the UCSC XENA website (https://xenabrowser.net/datapages/) [20]. To assess the diagnostic value of *PLA2G7* in human cancers, the "pROC" R package was employed. The diagnostic accuracy, as reflected by the area under the curve (AUC), was categorized as minimal (0.5–0.7), good (0.7–0.9), and excellent (>0.9). Prognostic evaluation, including progression-free interval (PFI), overall survival (OS), and disease-specific survival (DSS), along with an analysis of clinicopathological features, was conducted using R software.

2.3. PLA2G7 mutation profile in human cancers

The mutation profile of *PLA2G7* in human cancers was examined using the cBioPortal online portal (https://www.cbioportal.org/) [21,22] Additionally, the SangerBox website (http://sangerbox.com/) was utilized to assess mutation information associated with *PLA2G7* in various cancer types [23]. Furthermore, the cBioPortal database was employed to explore the relationship between *PLA2G7* gene mutation profiles and clinical outcomes in patients with different cancer types.

2.4. PLA2G7 expression and its association with tumor immunity

To examine the correlation between *PLA2G7* expression and different immune subtypes across various cancer types, the TISIDB online platform [24]. Additionally, the TISIDB website was employed to investigate the relationship between *PLA2G7* expression and various immunomodulators, including immuno-inhibitors, immunostimulators, major histocompatibility complex (MHC), and chemokines.

The "Gene" module in TIMER (https://cistrome.shinyapps.io/timer/) was then employed to explore the association between *PLA2G7* expression and the level of immune infiltration across diverse cancer types [25,26].

2.5. Association of PLA2G7 expression with multiple immune checkpoint (ICP) genes, microsatellite instability (MSI), tumor mutational burden (TMB), stemness score, and tumor microenvironment (TME) in different cancers

The connections between *PLA2G7* and ICP genes, MSI, stemness score, and TMB were examined using SangerBox. Subsequently, the relationship between *PLA2G7* expression and StromalScore and ImmuneScore was also investigated through SangerBox. The findings were then visually presented in a radar chart using R software.

2.6. Correlations between DNA methylation, MMR gene mutation, and PLA2G7

Five MMR genes (*MLH1*, *PMS2*, *MSH2*, *EPCAM*, and *MSH6*) and four DNA methyltransferases (*DNMT1*, *DNMT3B*, *DNMT3A*, and *DNMT2*) obtained from prior literature [27] were analyzed for their correlations with *PLA2G7* using Gene Expression Profiling Interactive Analysis (GEPIA, http://gepia.cancer-pku.cn/index.html) [28]. The results were visualized in a heatmap using R software. Subsequently, the "Mutation" module of the Gene Set Cancer Analysis (GSCA, http://bioinfo.life.hust.edu.cn/GSCA/#/) was employed to investigate the connection between *PLA2G7* mRNA levels and its methylation profile [29].

2.7. PLA2G7 co-expression networks in kidney renal clear cell carcinoma (KIRC)

To identify *PLA2G7* co-expression genes in KIRC, the LinkedOmics portal (http://linkedomics.org/login.php) was employed for this analysis [30]. Subsequently, we further investigated *PLA2G7* co-expression genes using Gene Set Enrichment Analysis (GSEA) to explore their associations with biological processes, cellular components, molecular functions, and KEGG pathways.

2.8. Cell culture

Human renal carcinoma cell lines, including 786-O, ACHN, and 769-P, were purchased form IMMOCELL, Xiamen, China. and cultured in RPMI-1640 medium (Gibco, Billings, MT, USA) supplemented with fetal bovine serum and penicillin-streptomycin. The cells were maintained in a 5% CO_2 humidified atmosphere at 37 °C, and the culture medium was replaced twice daily.

2.9. Immunofluorescence and western blotting assay

Immunofluorescence staining was conducted using previously reported methods [31]. The primary antibody *anti-PLA2G7* (Abcepta, San Diego, CA, USA) was employed for immunofluorescence labeling. For western blotting, protein extraction from cells was performed when the cell density of 786-O, ACHN, and 769-P reached 90%. Proteins were separated using a 10% SDS–PAGE gel and subsequently electrically transferred to a PVDF membrane ((0.2 μm pore size), under an under a voltage of 100V. After blocking with 5% skim milk at room temperature for 1 h, the membranes were incubated with primary antibodies (*anti-PLA2G7* and *anti-GAPDH*, diluted at a ratio of 1:1000) at 4 °C overnight. This was followed by a 1-h incubation with the corresponding secondary antibodies at room temperature.

2.10. Cell counting kit-8 (CCK-8) assay

The renal cancer cell lines (786-O and ACHN) were initially seeded in a 96-well plate at a density of 2×10^3 in 100 μL and cultured for 24 h. Following this, the medium was aspirated, and various concentrations of darapladib solutions (0, 1.5625, 3.125, 6.25, 12.5, and 25 μM) were added to each well and cultured for 3 days. Subsequently, the viability of the cells was assessed using the CCK-8 reagent (Yeasen, Shanghai, China), and the experiment was conducted three times.

2.11. Drug sensitivity

The association between *PLA2G7* mRNA level and the sensitivity of drugs obtained from the Cancer Therapeutics Response Portal was investigated using the GSCA website through its "drug" module.

2.12. Statistical analysis

Statistical analysis of the data obtained from the online websites or databases mentioned above was automatically computed. Differences between groups were assessed using the Student's *t*-test. Statistical significance was defined as a *P*-value or false discovery rate less than 0.05.

3. Results

3.1. Most cancer tissues express PLA2G7 at high levels

Table S1 displays the abbreviations and full names of multiple human cancers. The findings indicate elevated *PLA2G7* mRNA levels in KIRC, BRCA, ESCA, CESC, HNSC, KICH, BLCA, KIRP, STAD, LUAD, PRAD, and LIHC, while THCA and PAAD exhibit lower *PLA2G7*

mRNA levels (Fig. 1A). Subsequently, we assessed *PLA2G7* mRNA expression profiles in various cancer types and paired normal tissues. Fig. 1B illustrates that, in comparison to paired normal tissues, higher *PLA2G7* mRNA levels were observed in BRCA, ESCA, BLCA, HNSC, KIRP, KIRC, KICH, LIHC, STAD, PRAD, and LUAD. Conversely, *PLA2G7* mRNA levels were lower in THCA compared to nearby normal tissues.

After evaluating *PLA2G7* mRNA levels across different human cancer types, we examined PLA2G7 protein levels using the UALCAN online tool. The results revealed higher PLA2G7 protein levels in KIRC and PAAD (Fig. 1D and F) but lower levels in BRCA and LUAD

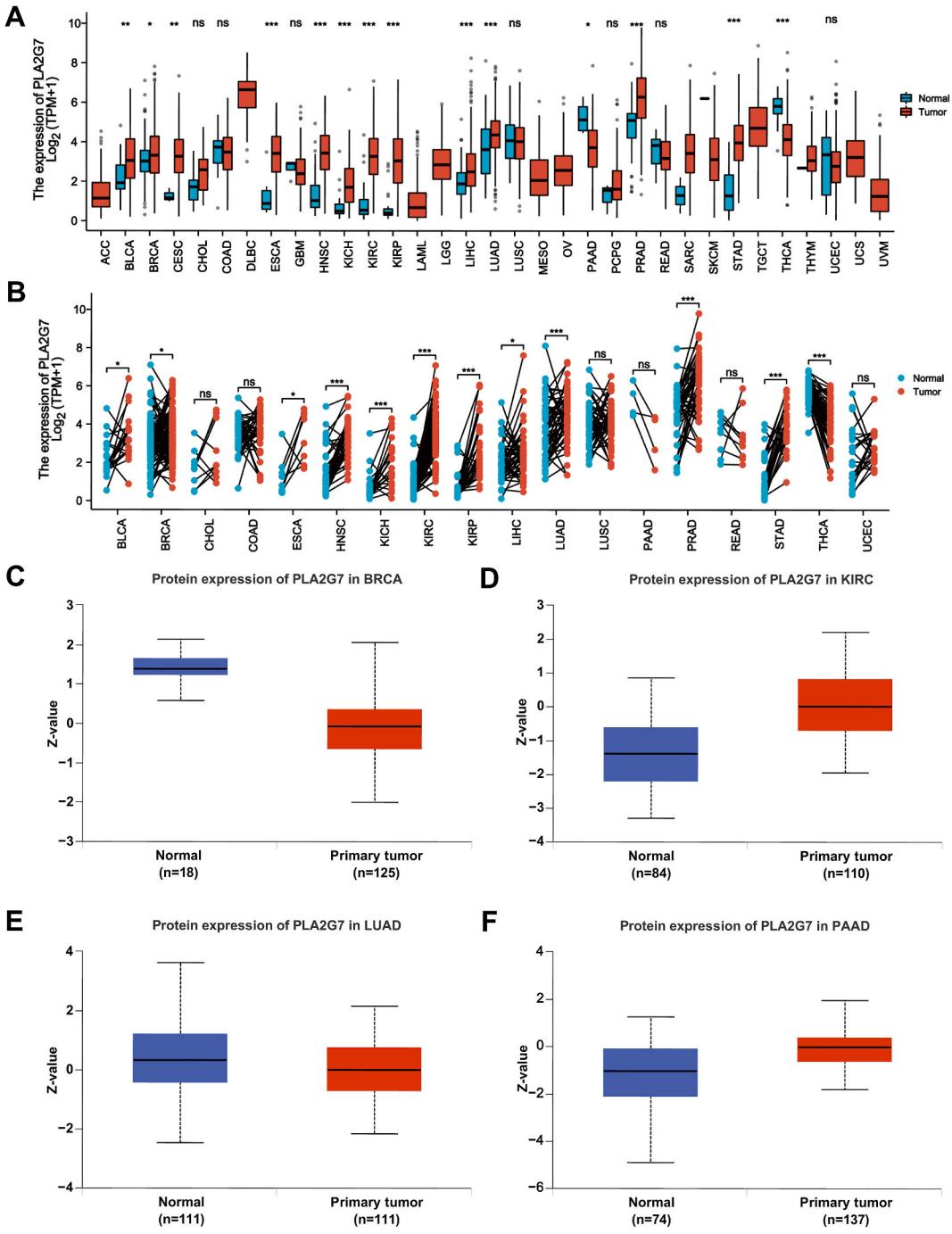

Fig. 1. *PLA2G7* expression profiles. (A) Analysis of *PLA2G7* mRNA levels across multiple cancer types and unpaired normal tissues based on TCGA. (B) Pan-cancer analysis of *PLA2G7* mRNA expression profile in various cancer tissues and paired normal tissues based on TCGA. (C–F) The UALCAN website displays the variations in the expression profiles of PLA2G7 protein across multiple cancer and normal tissues. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ns: no significance.

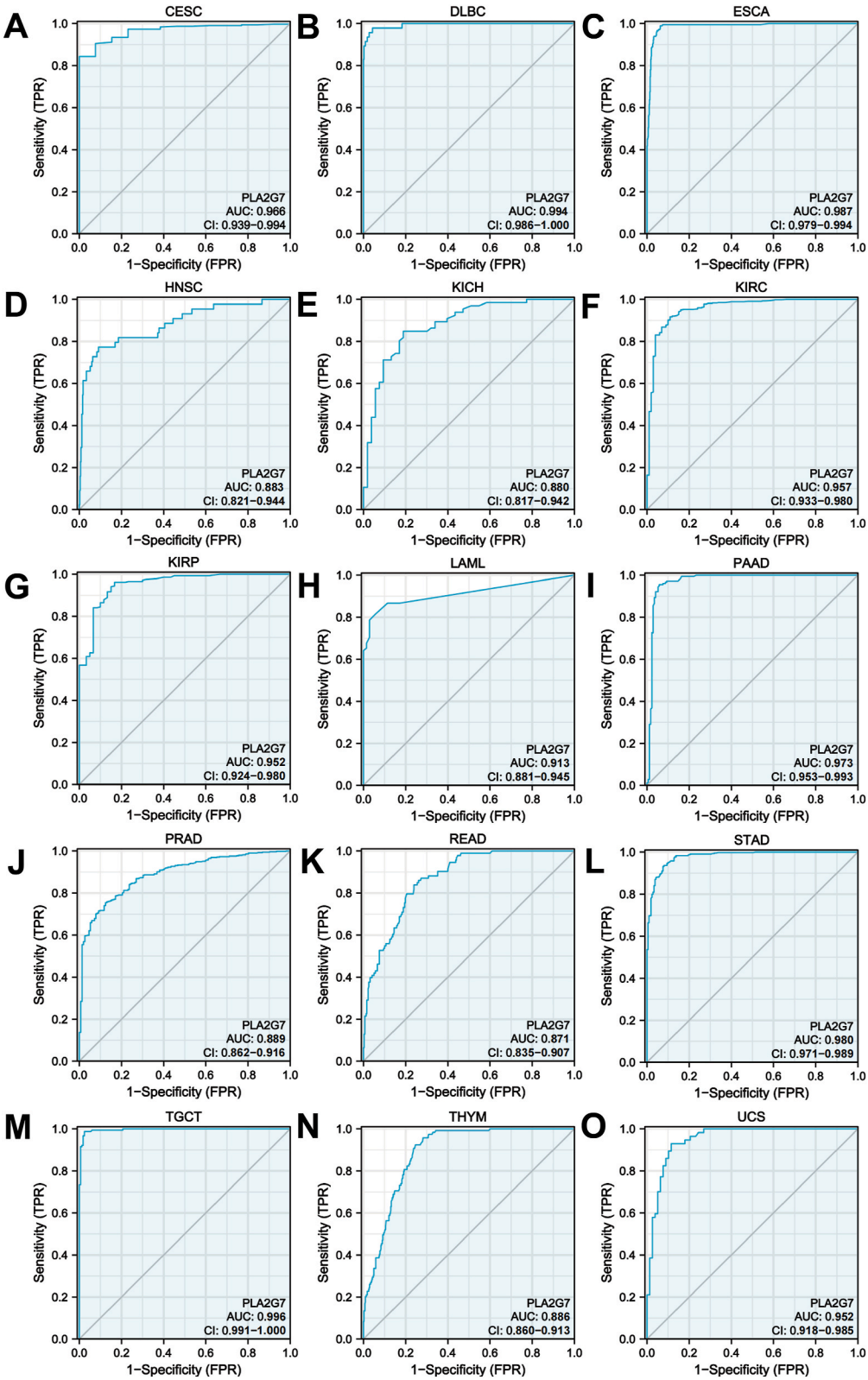

Fig. 2. ROC curves assessing the sensitivity of *PLA2G7* in diagnosing various human cancers.

(Fig. 1C and E).

3.2. *PLA2G7* as a potential biomarker for pan-cancer

The receiver operating characteristic (ROC) analysis of *PLA2G7* in different human cancers is depicted in Fig. 2 and S1, showing the AUC values. *PLA2G7* demonstrated robust accuracy in diagnosing diverse human cancers, with notable AUC values for HNSC (0.883), KICH (0.880), PRAD (0.889), READ (0.871), BRCA (0.701), BLCA (0.732), COAD (0.819), CHOL (0.710), LGG (0.811), UCEC (0.832), OV (0.790), LIHC (0.799), and SKCM (0.849). Remarkably, *PLA2G7* exhibited excellent accuracy in diagnosing CESC (0.966), DLBC (0.994), ESCA (0.987), KIRC (0.957), KIRP (0.952), LAML (0.913), PAAD (0.973), STAD (0.980), TGCT (0.996), and UCS (0.952). Next, we explored the prognostic significance of *PLA2G7* in human malignancies. Results indicated that high *PLA2G7* expression correlated with better OS in CESC (Hazard ratio [HR] = 0.59, $P = 0.027$) and SKCM (HR = 0.74, $P = 0.026$). Conversely, patients with UVM and high *PLA2G7* expression had poorer OS (HR = 3.2, $P = 0.01$) (Fig. 3A–C). Patients with high *PLA2G7* expression in CESC (HR = 0.55, $P = 0.031$), KIRP (HR = 0.44, $P = 0.042$), and SKCM (HR = 0.73, $P = 0.031$) showed improved DSS. Additionally, those with UVM and high *PLA2G7* expression exhibited better DSS (HR = 3.49, $P = 0.009$) (Fig. 3D–G). Furthermore, enhanced *PLA2G7* expression in CESC was associated with better PFI (HR = 0.61, $P = 0.039$) (Fig. 3H). Finally, we investigated the link between *PLA2G7* expression and various clinicopathologic stages in pan-cancer. As illustrated in Fig. 4, *PLA2G7* was prominently expressed in various advanced tumors, including BLCA, ESCA, HNSC, STAD, etc. These findings suggest that *PLA2G7* could serve as a promising diagnostic

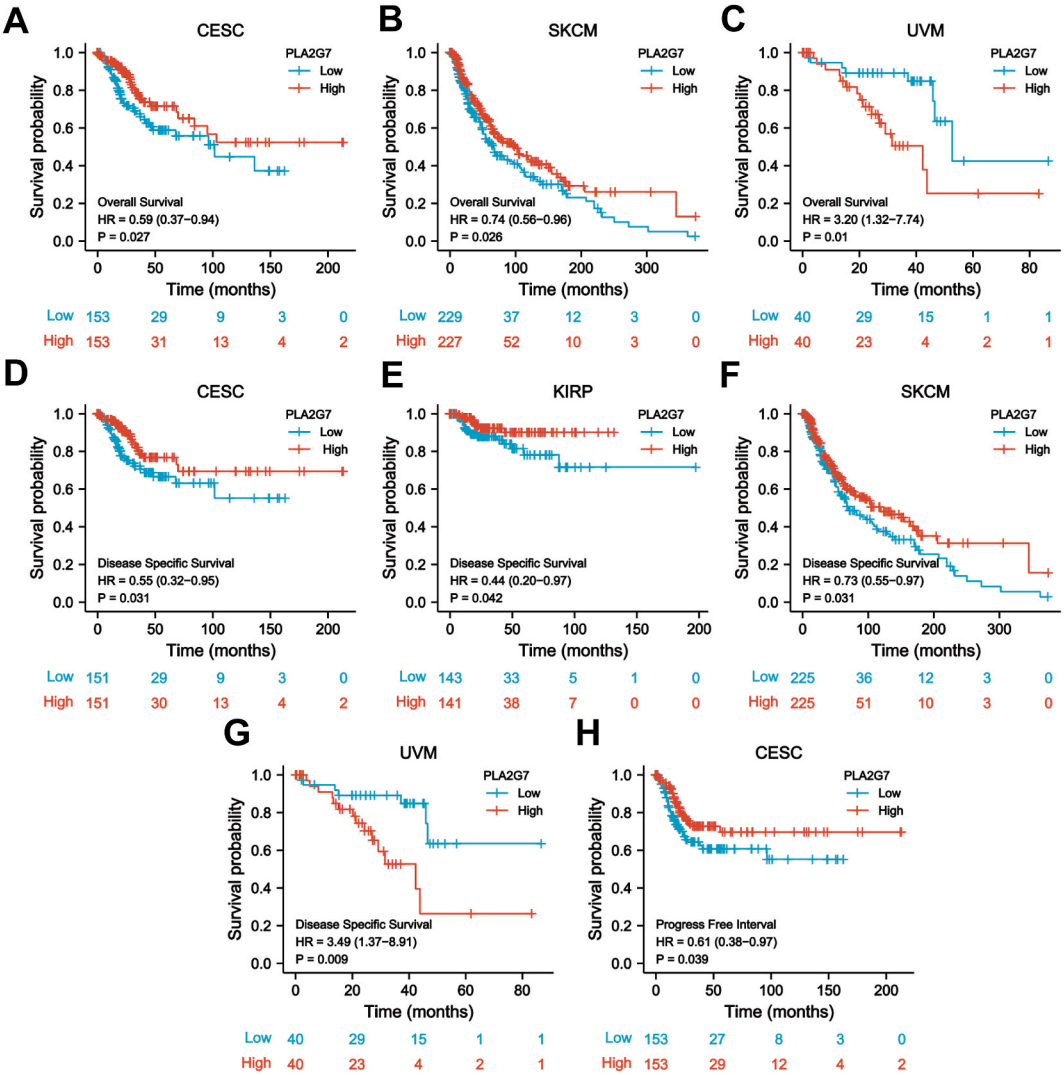

Fig. 3. Clinical outcomes in pan-cancer correlated with *PLA2G7* expression. (A–C) Association between *PLA2G7* expression and overall survival (OS) in human cancers. (D–G) Association between *PLA2G7* expression profile and disease-specific survival (DSS) in various human cancers. (H) Association between *PLA2G7* expression and progression-free interval (PFI) in CESC.

and prognostic biomarker across various human cancers.

3.3. PLA2G7 genetic alteration profile in human cancer

The *PLA2G7* mutation status in various cancer types was explored through the cBioPortal website. In Fig. 5A, it is evident that *PLA2G7* exhibits different alteration frequencies across human cancers. Notably, SKCM demonstrated the highest mutation frequency (>6%) for *PLA2G7*, whereas no mutations were detected in LAML, CHOL, KICH, PCPG, TGCT, THYM, and THCA, with "amplification" being the most prevalent mutation type. Additionally, we further analyzed the specific types of *PLA2G7* mutations using mutation data from 19 cancers obtained from the SangerBox website. The findings revealed that "missense mutation" was the predominant type of *PLA2G7* mutation (Fig. 5B). Prior literature has established that both "amplification mutation" and "missense mutation" can contribute to tumorigenesis by altering the amino acid sequence. Consequently, *PLA2G7* may play a role in tumorigenesis in human cancer. Finally, the relationship between *PLA2G7* gene mutation status and clinical outcomes in multiple human cancers was investigated using the cBioPortal tool. The results indicated that patients with LIHC, KIRP, and STAD with PLA2G7 mutation experienced poorer clinical outcomes (Fig. 5D–F), while those with HNSC and *PLA2G7* mutation exhibited better OS (Fig. 5C). These findings suggest that *PLA2G7* may be involved in tumorigenesis and further validate its potential as a viable prognostic biomarker in human cancers.

3.4. PLA2G7 and tumor immunity

We initially constructed a protein-protein interaction network between *PLA2G7* and its 10 inter-acting proteins (*APOE*, *APOB*, *GHRL*, *PLA2G10*, *LPCAT2*, *LPCAT1*, *PAFAH1B1*, *PLA2G1B*, *APOA1*, and *APOA5*) using the STRING website (Fig. S2A) before conducting GO enrichment analysis. As depicted in Fig. S2B, *PLA2G7* and its interacting proteins were associated with "immune system

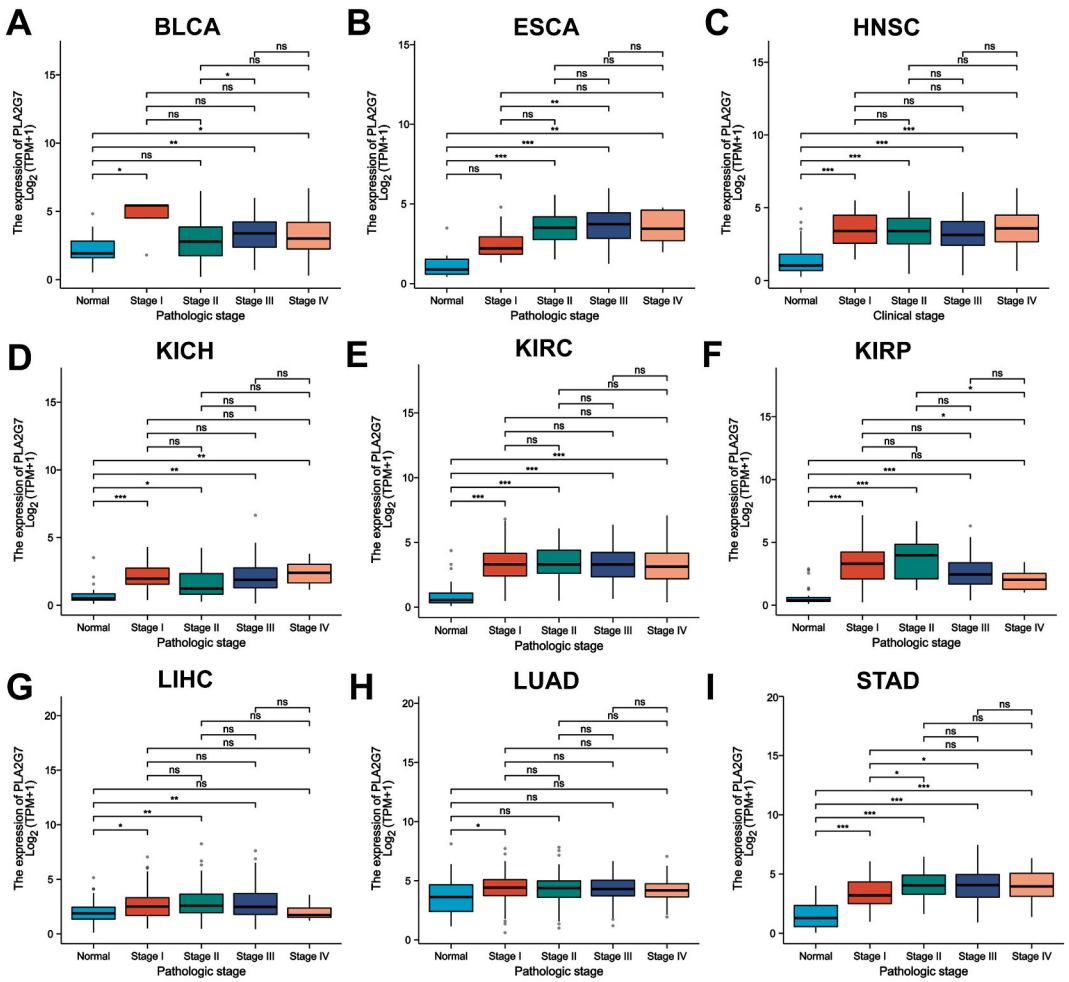

Fig. 4. Associations between *PLA2G7* expression and various tumor stages in human cancers. (A–I) Correlations between *PLA2G7* expression and different tumor stages in BLCA, ESCA, HNSC, KICH, KIRC, KIRP, LIHC, LUAD, and STAD, respectively. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ns: no significance.

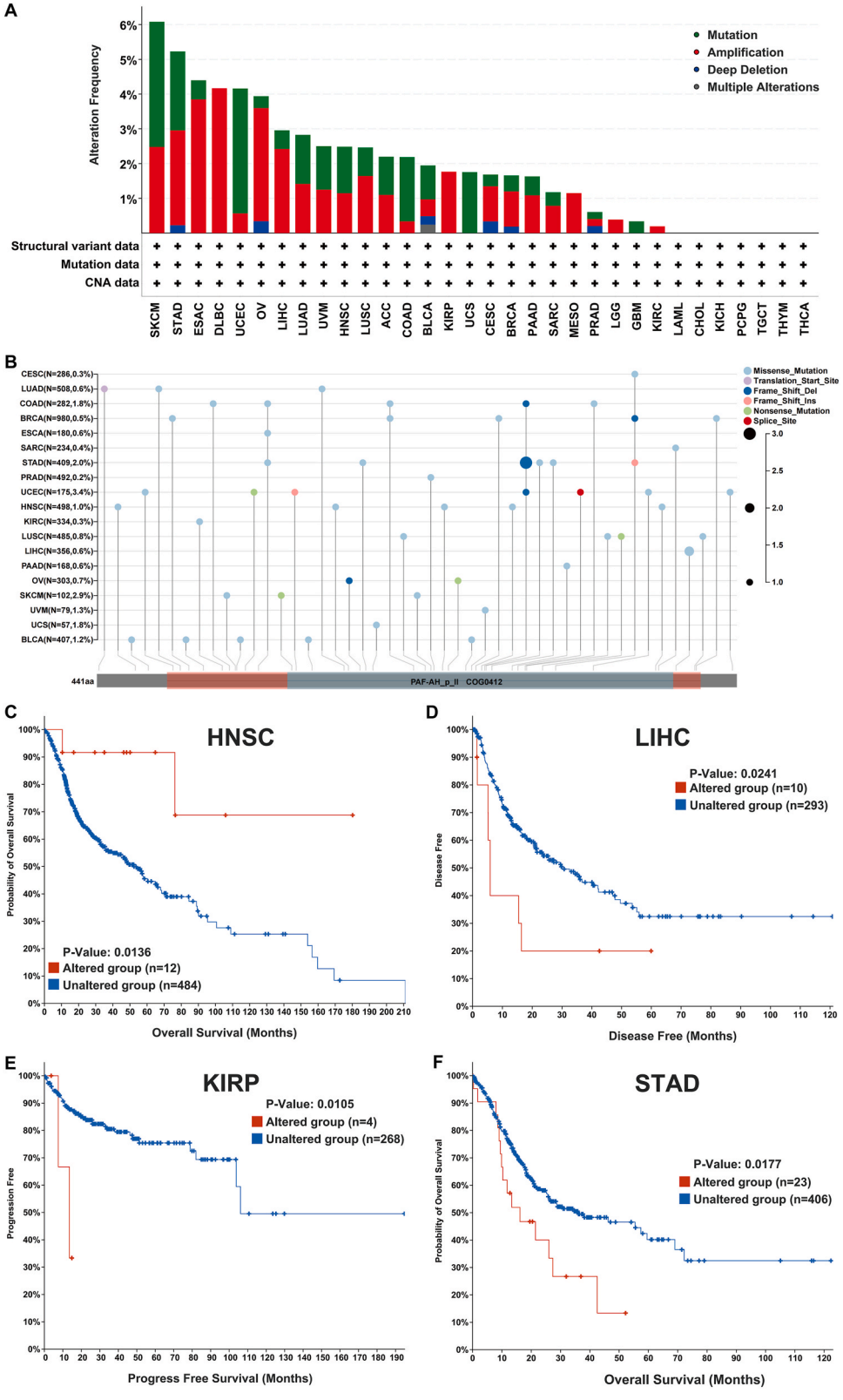

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Fig. 5. Mutation profile of *PLA2G7* in pan-cancer. (A) Frequency of *PLA2G7* alterations in different human cancer types. (B) Mutation information of *PLA2G7* in human cancers. (C) Association between *PLA2G7* gene mutation status and overall survival (OS) in HNSC. (D) Association between *PLA2G7* gene mutation status and disease-free survival in LIHC. (E) Association between *PLA2G7* gene mutation status and progression-free survival in KIRP. (F) Association between *PLA2G7* gene mutation status and OS in STAD.

process," "positive regulation of response to stimulus," and "regulation of immune system process." Furthermore, we investigated the link between *PLA2G7* expression and several immune subtypes in pan-cancer using the TISIDB web tool. The findings revealed that *PLA2G7* expression was associated with various immune subtypes in STAD, BLCA, CESC, BRCA, LUAD, LUSC, MESO, as well as SARC (Fig. 6). Detailed information regarding *PLA2G7* expression and different immune subtypes in other human cancers is presented in Fig. S3. These outcomes suggest that *PLA2G7* plays a role in tumor immunity.

3.5. *PLA2G7 is linked to different ICP genes and immunomodulators in pan-cancer*

Correlations between *PLA2G7* and various immunomodulators (including immuno-inhibitors, immunostimulators, MHC molecules, receptors, and chemokines) were examined using the TISIDB website. The results revealed that *PLA2G7* was positively related to most immunoinhibitors in pan-cancer, particularly in CESC, COAD, HNSC, and TGCT (Fig. 7A). Regarding immunostimulators, *PLA2G7* also exhibited a positive correlation with most immunostimulators across human cancers, notably in BLCA, HNSC, LUSC, and TGCT (Fig. 7B). *PLA2G7* showed a positive relationship with most MHC molecules in pan-cancers such as LUSC, TGCT, and UVM (Fig. 7C). Similarly, chemokines tended to exhibit a positive correlation with *PLA2G7* in most human cancers (Fig. 7D), along with receptors (Fig. 7E). Subsequently, we explored the relationship between *PLA2G7* and different ICP genes in multiple cancer types. As depicted in Fig. 8, most ICP genes showed a positive correlation with *PLA2G7* in human cancers. These findings suggest that *PLA2G7* may play a role in the regulation of tumor immunity and could serve as a potential target for immunotherapy.

3.6. *PLA2G7 is associated with ESTIMATE, TMB, MSI, and stemness scores in human cancers*

Previous literature has established that TMB and MSI in the TME are associated with antitumor immunity and can predict the response to immunotherapy [32,33]. Therefore, we explored the correlations between *PLA2G7* and TMB as well as MSI. As depicted in Fig. 9A, *PLA2G7* was negatively related to MSI in TGCT, HNSC, LUSC, LGG, and STAD, while positively associated with MSI in COAD. Regarding TMB, our findings suggest a negative relationship between *PLA2G7* and TMB in THCA and LIHC, while a positive relationship was observed between *PLA2G7* and STAD, BLCA, COAD, LAML, BRCA, and SARC (Fig. 9B). Subsequently, we analyzed the relationship between *PLA2G7* and two ESTIMATE scores (ImmuneScore and StromalScore) in pan-cancer. As shown in Fig. 9C and D, *PLA2G7* was negatively or positively associated with ImmuneScore and StromalScore in most cancer types. Furthermore, *PLA2G7* was negatively or positively related to DNA stemness score and RNA stemness score in pan-cancer (Figs. S4A–B).

3.7. *Link between PLA2G7 and immune cell infiltration in pan-cancer*

The association between *PLA2G7* expression and six immune infiltration cells was examined using the TIMER website. The results

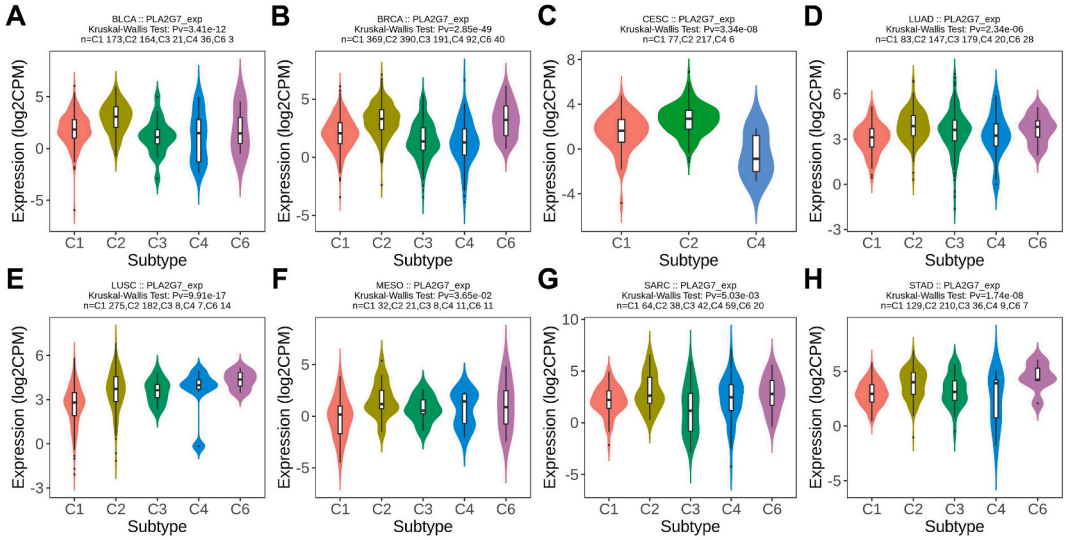

Fig. 6. The link between *PLA2G7* expression and different immune subtypes in pan-cancer. (C1–C6 represented wound healing, IFN-gamma dominant, inflammatory, lymphocyte depleted, immunologically quiet, and TGF-β dominant, respectively).

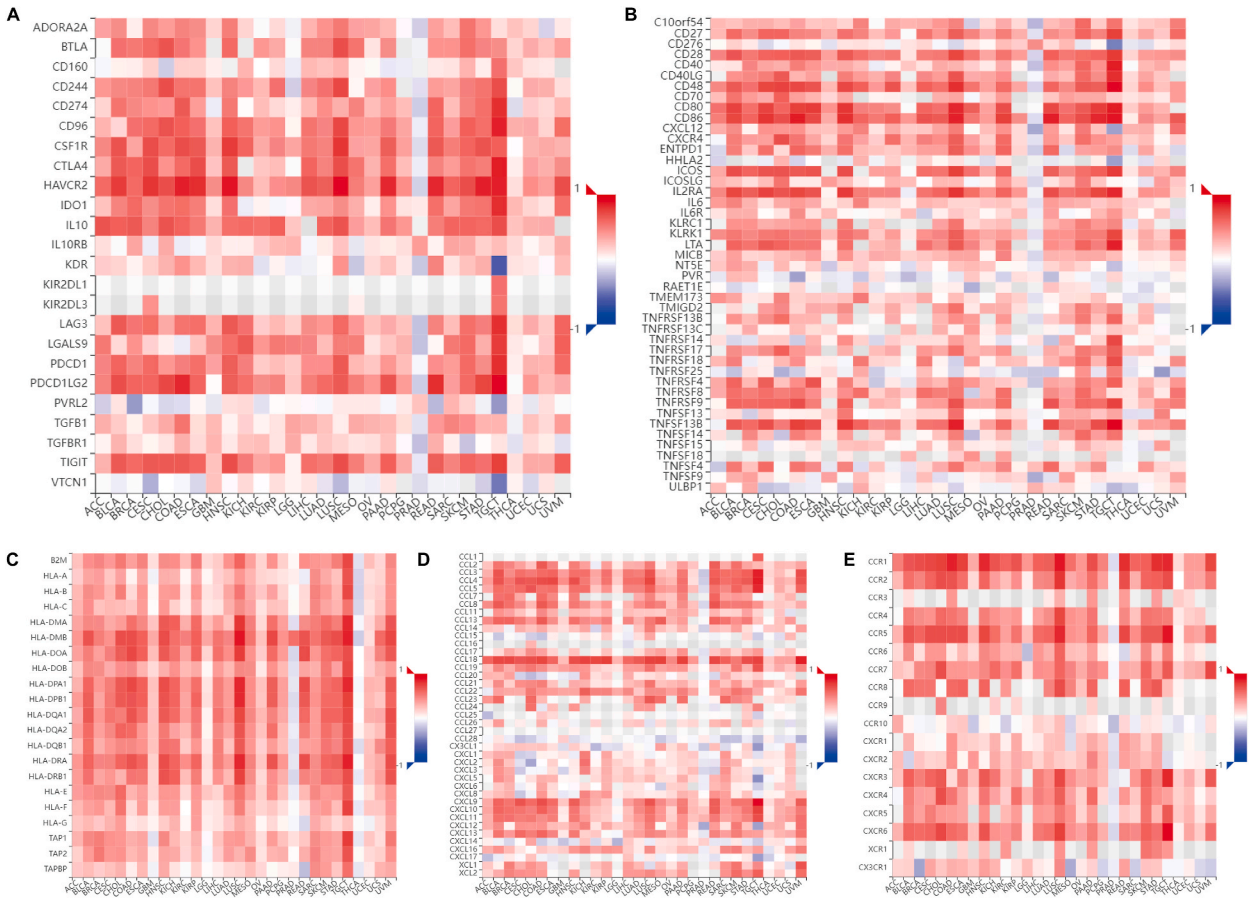

Fig. 7. The link between *PLA2G7* and different immunomodulators in human cancers. (A–E) The link between *PLA2G7* and various immunostimulators, immuno-inhibitors, MHC molecules, chemokines, and receptors in pan-cancer.

demonstrated that *PLA2G7* expression was correlated with $CD4^+$ T cells, B cells, and $CD8^+$ T cells in 25, 23, and 19 human cancers, respectively. Additionally, *PLA2G7* expression was linked to macrophages, neutrophils, and dendritic cells in 24, 29, and 29 human cancers. Notably, as depicted in Fig. 10 and Fig. S5, *PLA2G7* expression was associated with all six immune infiltration cells in 16 tumor types, including KIRC, KIRP, LIHC, LUAD, and LUSC.

3.8. Link between PLA2G7 and MMR genes and DNA methylation in human cancers

Several studies have highlighted the significant roles of MMR genes and DNA methylation in tumorigenesis [34]. We next explored the potential mechanism of *PLA2G7* in tumorigenesis. The results demonstrated that *PLA2G7* was partially or fully related to MMR genes in most cancer types. For example, *PLA2G7* was linked to all MMR genes in COAD, PRAD, and THCA (Fig. 11A). Subsequently, we determined the association between *PLA2G7* and four DNA methyltransferases in human cancer. As shown in Fig. 11B, similar to MMR genes, *PLA2G7* was also related to some or all DNA methyltransferases in most human cancers. For instance, *PLA2G7* was associated with all DNA methyltransferases in BRCA, LIHC, READ, TGCT, and THCA. The relationship between *PLA2G7* mRNA levels and *PLA2G7* gene methylation in pan-cancer was also explored. Fig. 11C and Fig. S6 demonstrated that *PLA2G7* mRNA levels negatively correlated with *PLA2G7* gene methylation in various cancers, including BRCA, CESC, UVM, and KIRP. Finally, the GSCA online tool was employed to ascertain the relationship between *PLA2G7* gene methylation and patients' clinical outcomes in pan-cancer. Figs. S7A and B illustrated that patients with low *PLA2G7* gene methylation levels had poorer OS in THYM and UVM. For disease-free interval (DFI), patients with low *PLA2G7* gene methylation levels had poorer DFI in BRCA (Fig. S7C), while those with low *PLA2G7* gene methylation levels exhibited better DFI in CESC and STAD (Figs. S7D–E). As shown in Figs. S7F–H, patients with low *PLA2G7* gene methylation levels had poorer progression-free survival (PFS) in BRCA, THYM, and UVM, while a poorer DSS was found in patients with low *PLA2G7* gene methylation levels in LUSC and UVM (Figs. S7I–J). These results indicate that *PLA2G7* may promote tumorigenesis through MMR and DNA methylation, and patients with different *PLA2G7* gene methylation levels have different clinical outcomes in specific cancer types, suggesting that *PLA2G7* has value as a biomarker in pan-cancer.

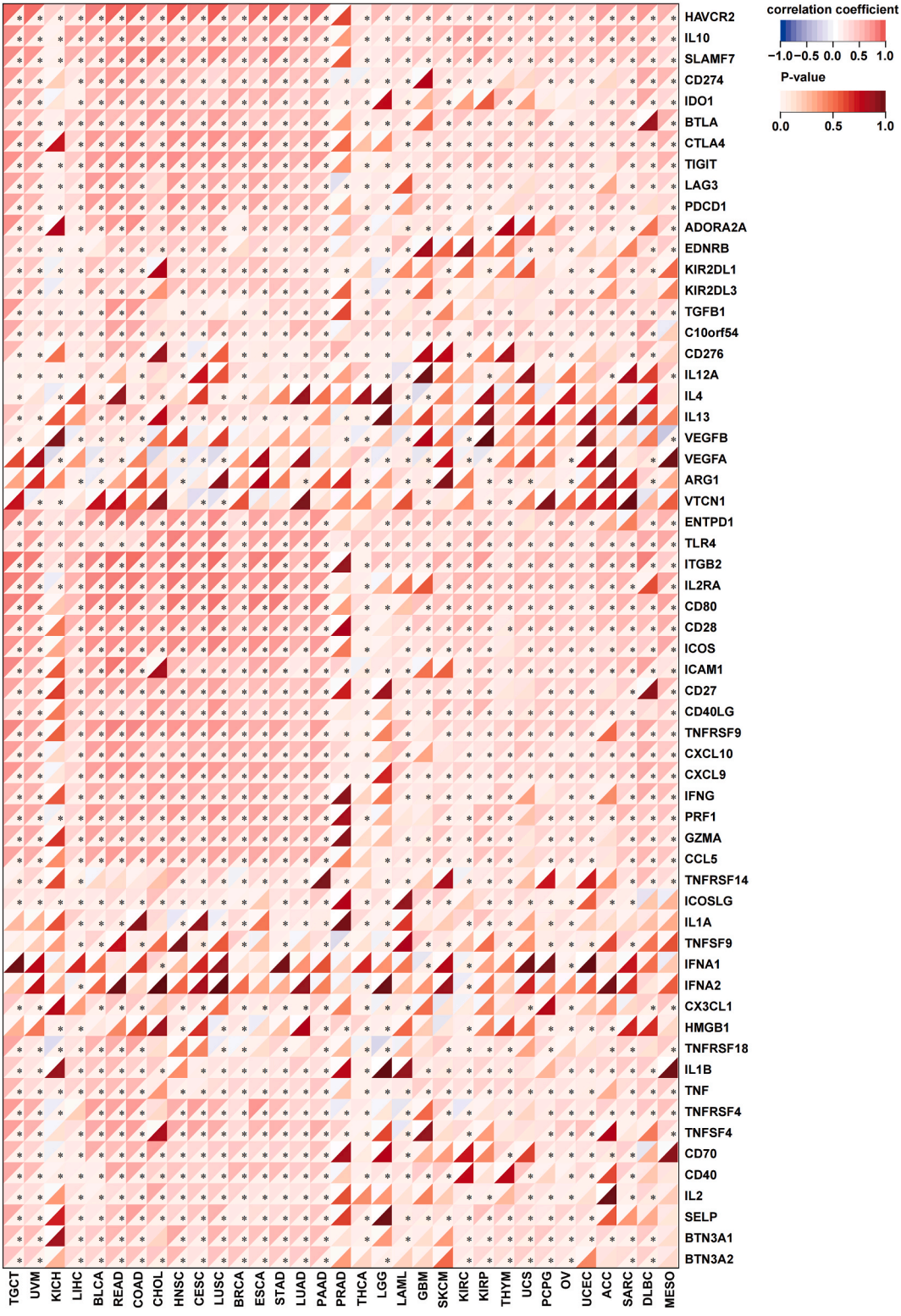

Fig. 8. The link between *PLA2G7* and different ICP genes in human cancers.

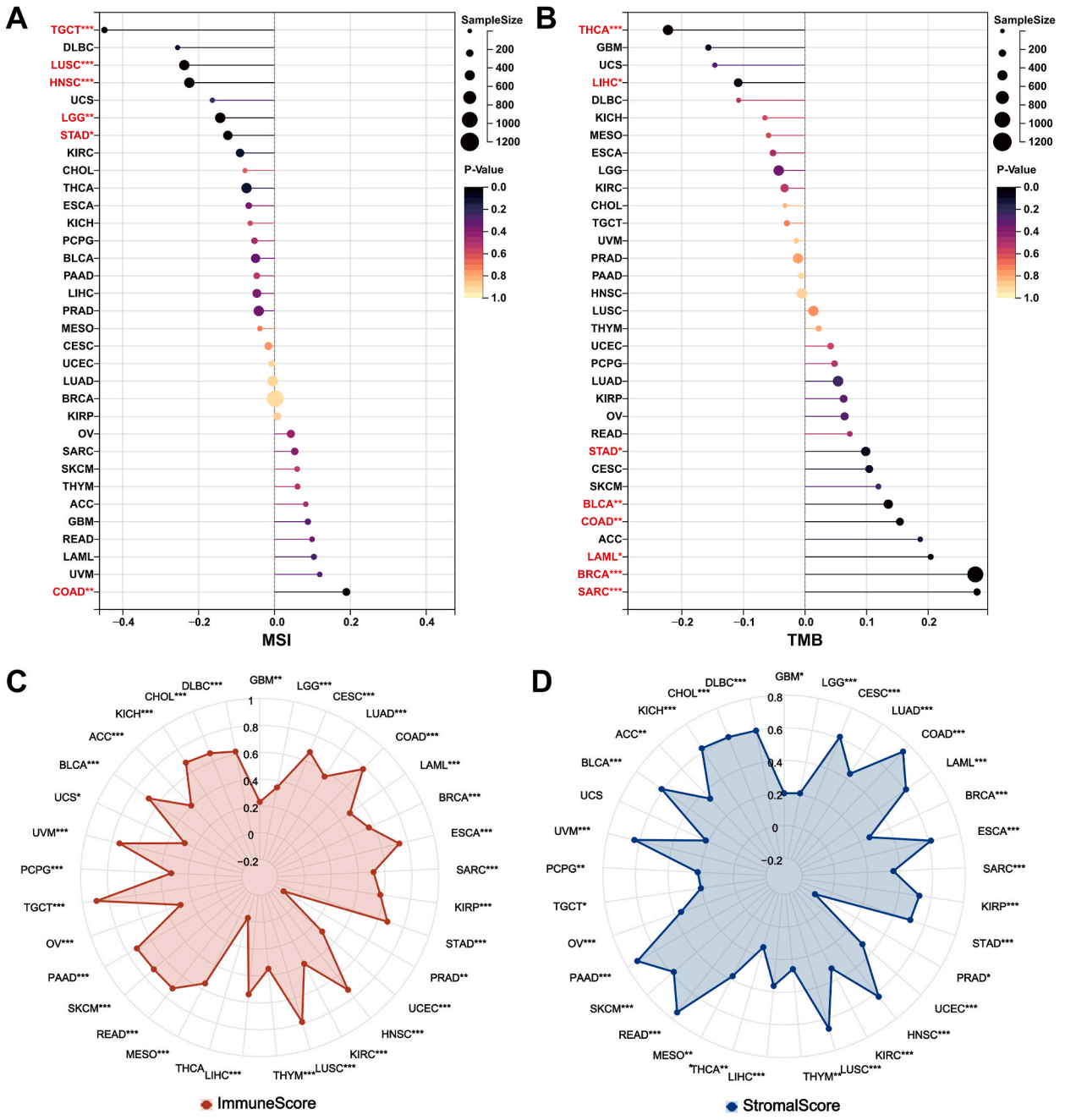

Fig. 9. Correlations of *PLA2G7* expression profile and MSI, TMB, and two ESTIMATE scores in cancers. (A–B) The link between *PLA2G7* expression and MSI as well as TMB in human cancers. (C–D) The link between *PLA2G7* and two ESTIMATE scores (ImmuneScore and StromalScore) in various cancer types. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

3.9. *PLA2G7 co-expression genes correlate with the immune response in KIRC*

We investigated the link between *PLA2G7* and diagnosis, prognosis, and immunity in human cancers. Utilizing the LinkedOmics online tool, we constructed *PLA2G7* co-expression networks to study its potential function in KIRC. This marks the first examination of *PLA2G7* function in KIRC. The results revealed that 3618 genes (represented as red dots) and 2806 genes (represented as green dots) were significantly linked to *PLA2G7* in KIRC, either positively or negatively (Fig. 12A). Subsequently, heat maps were generated to illustrate the top 50 genes that were positively or negatively linked to *PLA2G7* in KIRC (Fig. 12B and C). The details of the co-expression genes are presented in Supplementary Tables 2 and 3 Notably, *CCL18*, *GM2A*, and *CHRNA1* were strongly associated with *PLA2G7* expression ($r = 0.736$, 0.701, 0.678, and $P = 7.74E\text{-}92$, 4.45E-80, 5.10E-79, respectively). Furthermore, GSEA using the

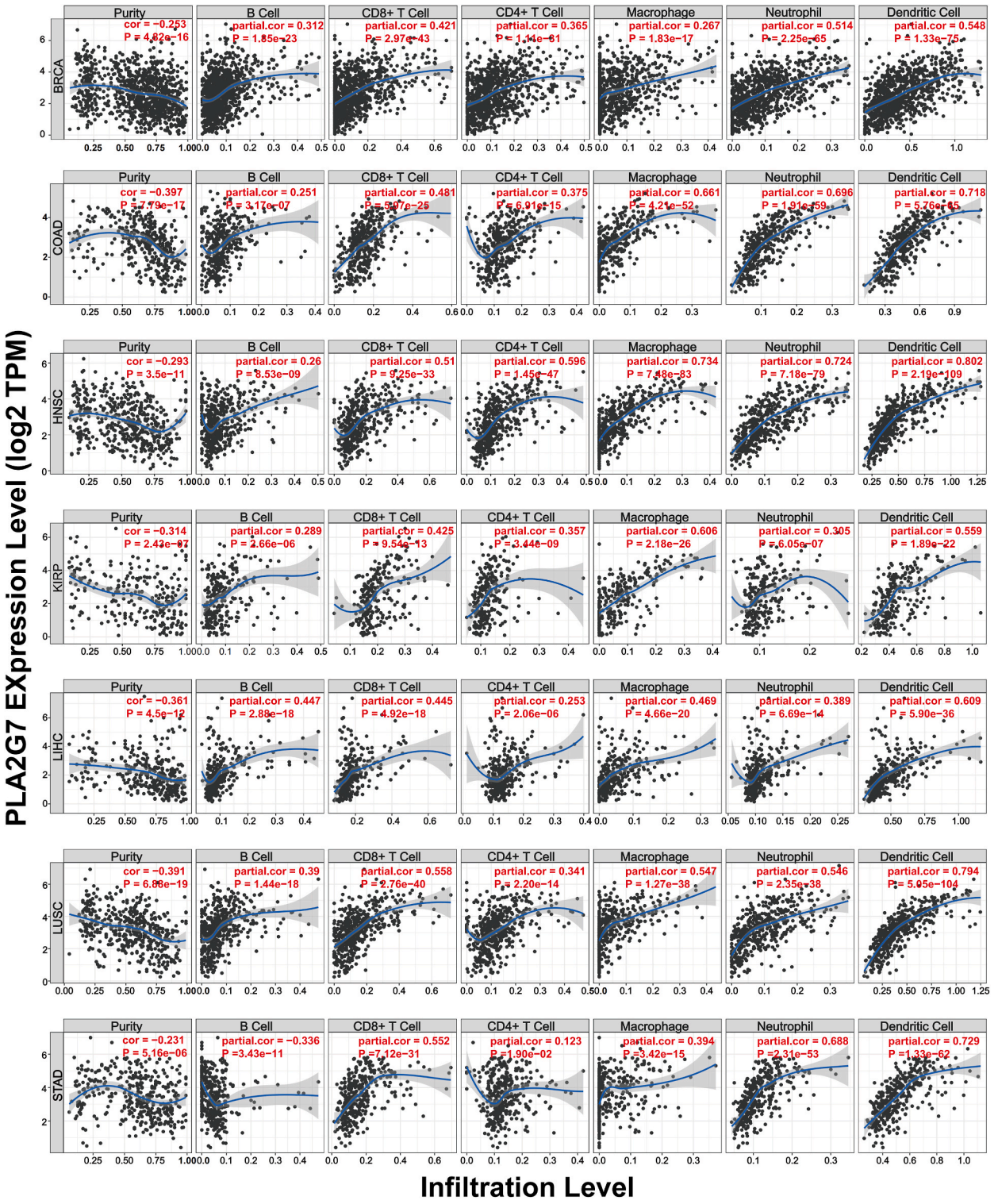

Fig. 10. The link between *PLA2G7* expression and six immune infiltration cells ($CD8^+$ T cells, $CD4^+$ T cells, dendritic cells, B cells, neutrophils, and macrophages) in COAD, BRCA, HNSC, KIRP, LUSC, LIHC, and STAD.

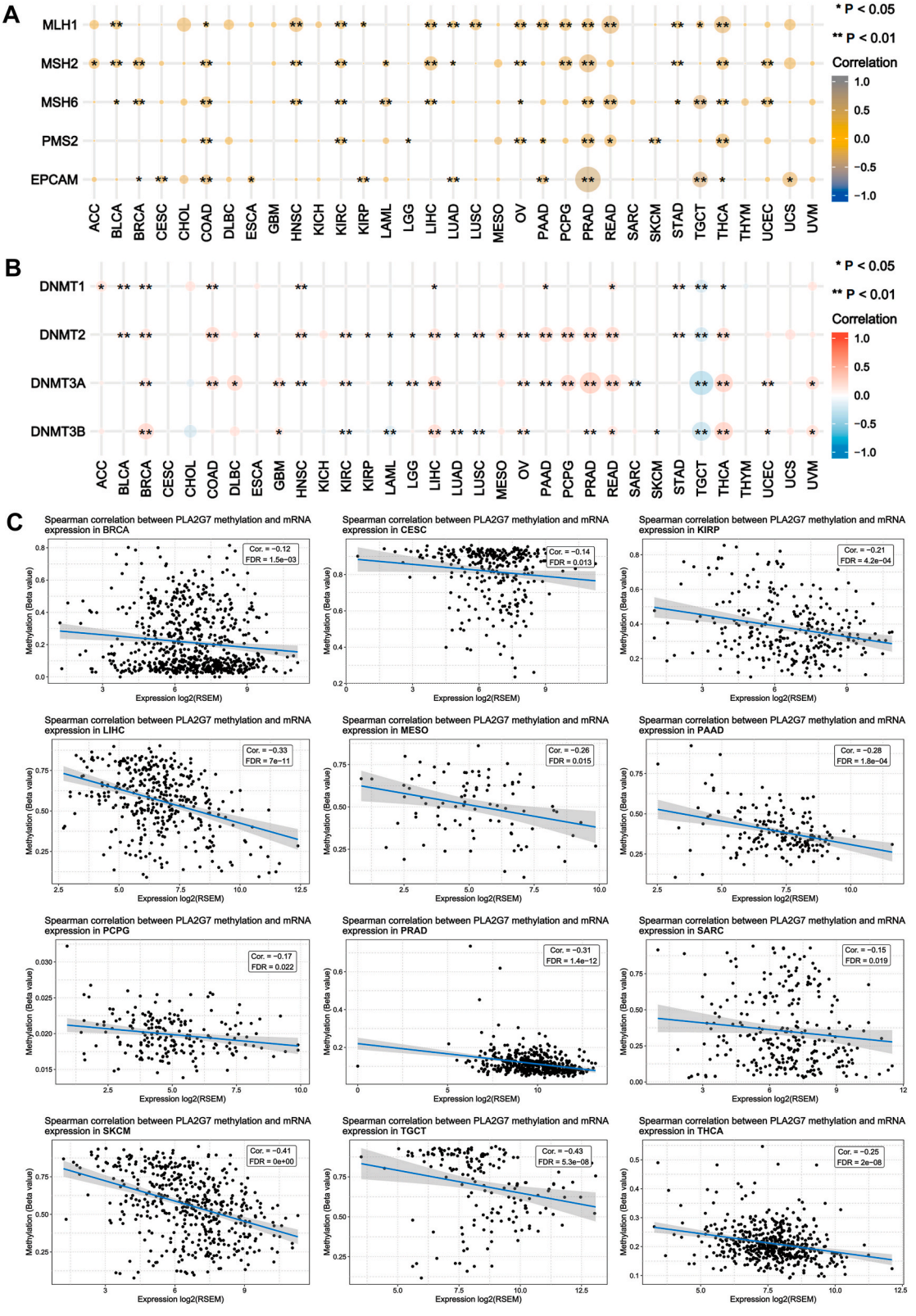

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Fig. 11. The link between *PLA2G7* and MMR and its DNA methylation in different cancer types. (A) Link between *PLA2G7* and five MMR genes (*MLH1*, *MSH2*, *MSH6*, *EPCAM*, and *PMS2*) in various cancer types. (B) Link between *PLA2G7* and four DNA methyltransferases (*DNMT1*, *DNMT3B*, *DNMT2*, and *DNMT3A*) in various cancer types. (C) The link between *PLA2G7* mRNA levels and its gene methylation level in various cancer types. $^{*}P < 0.05$, $^{**}P < 0.01$.

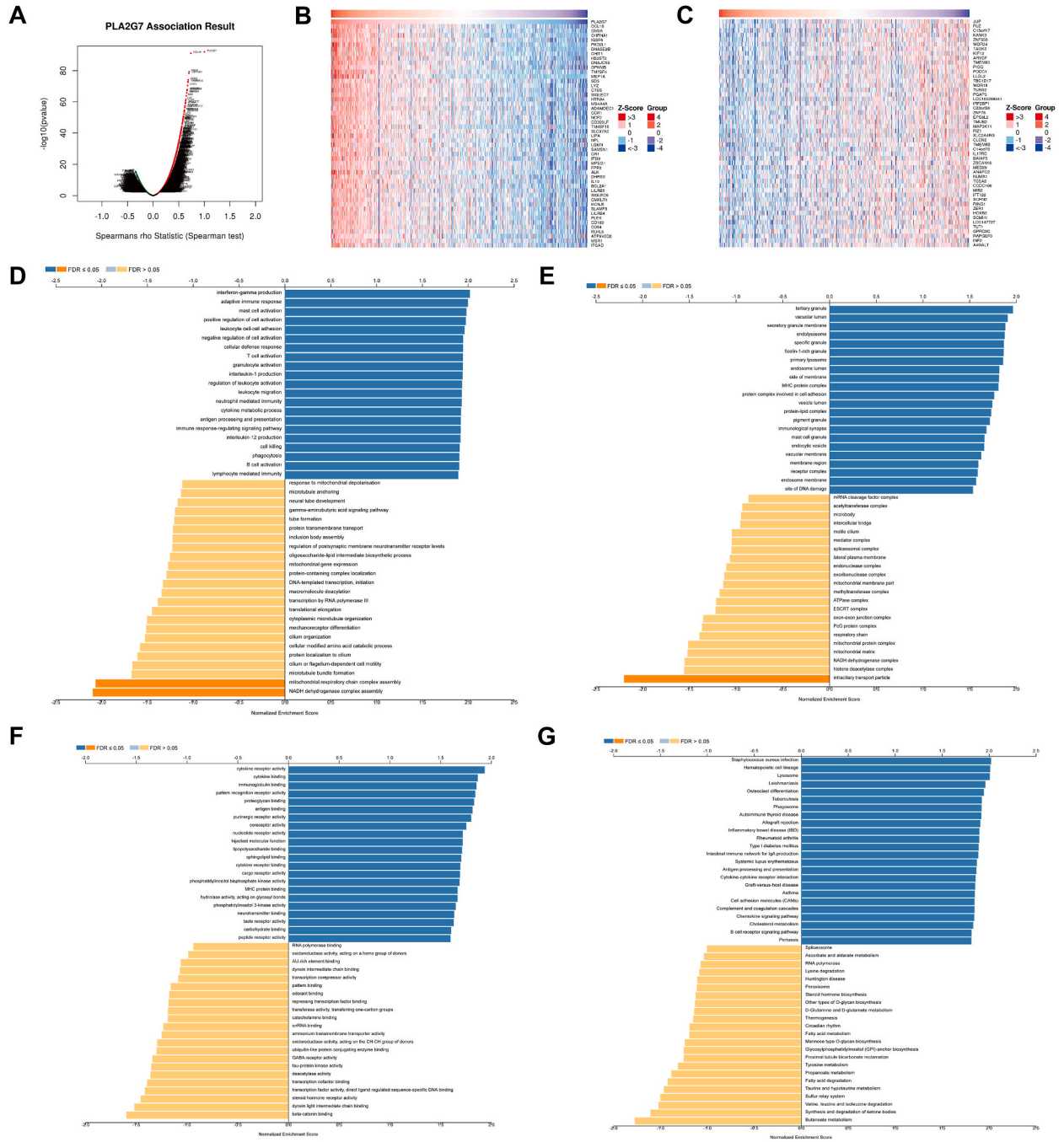

Fig. 12. Enrichment analysis of *PLA2G7* co-expression genes in KIRC investigated through the LinkedOmics website. (A) *PLA2G7* co-expression genes in KIRC. (B–C) Top 50 genes that were either positively or negatively associated with *PLA2G7* in KIRC. (D–F) GO biological process, cellular component, and molecular function analysis of *PLA2G7* co-expression genes in KIRC. (G) KEGG analysis of *PLA2G7* in KIRC.

LinkedOmics online tool indicated that *PLA2G7* co-expression genes primarily participated in immunity-related Gene Ontology (GO) terms, including "immunoglobulin binding," "leukocyte cell-cell adhesion," "adaptive immune response," "T cell activation," and "MHC protein complex" (Fig. 12D–F). Regarding the Kyoto Encyclopedia of Genes and Genomes (KEGG), *PLA2G7* co-expression genes were involved in the "B cell receptor signaling pathway," "*Staphylococcus aureus* infection," and "chemokine signaling pathway" (Fig. 12G). These findings suggest that *PLA2G7* plays a crucial role in KIRC by participating in tumor immunity.

3.10. *PLA2G7 is mainly distributed in whole cells and influences renal cancer cell proliferation*

After systematically analyzing the involvement of *PLA2G7* in human cancers, we proposed that PLA2G7 is a potential biomarker and therapeutic target for human cancer, including renal cancer. Subsequently, *in vitro* experiments were conducted to validate this hypothesis, using renal cancer as an example. As shown in Fig. 13A, the renal cancer cell lines 786-O and ACHN expressed *PLA2G7* protein, while no obvious *PLA2G7* protein was detected in renal cancer cell line 769-P. Considering the *PLA2G7* protein expression profile of above three renal cancer cell lines, we chose 786-O and ACHN renal cancer cell lines for further study. An immunofluorescence experiment was conducted to explore the distribution of *PLA2G7* in renal cancer cells. Fig. 13B shows that *PLA2G7* was distributed throughout renal cancer cells, particularly in the cytoplasm. Next, a CCK-8 assay was performed to investigate the influence of *PLA2G7* on renal cancer cell proliferation. Fig. 13C illustrates that after inhibiting *PLA2G7* gene expression, the viability of 786-O and ACHN cells was significantly decreased. These results suggest that *PLA2G7* may serve as a promising therapeutic target in renal cancer.

3.11. *PLA2G7 related to Cancer Therapeutics Response Portal (CTRP) drug sensitivity*

We further investigated the relationship between *PLA2G7* mRNA levels and CTRP drug sensitivity. Fig. 14 illustrates that *PLA2G7* mRNA levels were positively or negatively linked to the sensitivity of CTRP drugs, including BCL-2 inhibitor (ABT-199), ATM inhibitor (KU-60019), and Braf/Mapk-targeting compound (GDC-0879), which have been proved having a good anti-tumor effect [35–37]. These findings suggest that *PLA2G7* may guide the use of specific anti-cancer drugs in clinical practice.

4. Discussion

The current trend in tumor treatment emphasizes precision and individualized approaches. Surgical resection combined with chemotherapy is presently the preferred therapeutic strategy for most patients with advanced cancer [38]. Clinical trials are underway to explore immunotherapy as a supplementary curative and palliative treatment, potentially offering a novel strategy for patients with advanced or inoperable disease [39,40]. However, the development of precision and individualized tumor therapy is somewhat constrained by the lack of effective diagnostic and therapeutic targets.

The significance of *PLA2G7* in specific cancer types has only been partially studied to date. For example, recent literature revealed that the downregulation of *PLA2G7* in a breast cancer cell line (HCC1937) promoted proliferation and migration, suggesting a vital role for *PLA2G7* in cancer [41]. Additionally, *PLA2G7* has been implicated in the inflammatory process and associated with tumor immunity. The Lp-PLA2 protein encoded by *PLA2G7* has been demonstrated to be expressed by various immune cells [16,42,43]. These findings prompted us to investigate the link between *PLA2G7* and human cancers. Our findings indicate that *PLA2G7* is relatively highly expressed in various human cancers and may serve as a potential biomarker, including in renal cancer. Furthermore, *PLA2G7* is associated with various immune subtypes, ICP genes, immune infiltration, and immunomodulators in pan-cancer, suggesting its

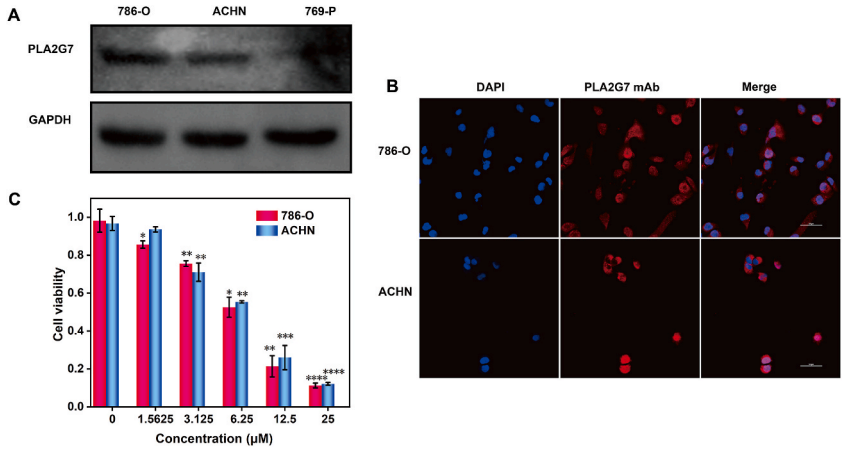

Fig. 13. Biological function of *PLA2G7* in renal cancer. (A) *PLA2G7* protein levels in 786-O, ACHN, and 769-P renal cancer cell lines. (B) Distribution of *PLA2G7* protein in 786-O and ACHN renal cancer cell lines. (C) Viability of 786-O and ACHN renal cancer cell lines explored using CCK-8 assay after treatment with different concentrations of *PLA2G7* gene inhibitor. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$.

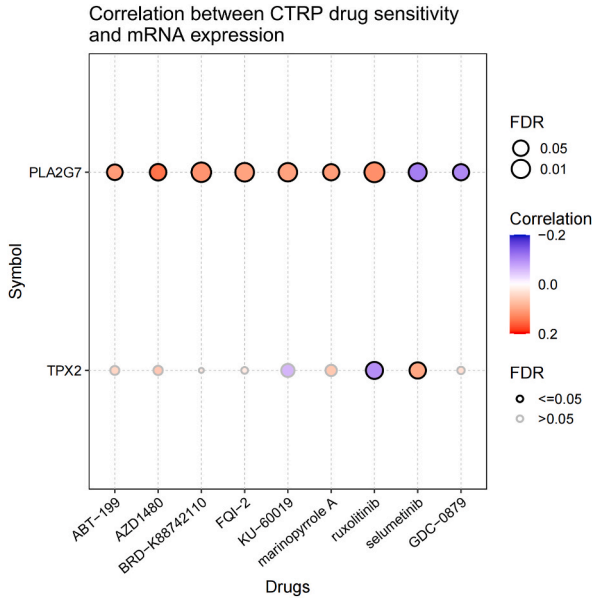

Fig. 14. The link between *PLA2G7* expression and various CTRP drugs from the GSCA website (orange and blue-purple circles indicate positive and negative correlations, respectively). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

relevance to tumor immunity across different cancer types. This association may position *PLA2G7* as a potential target for immunotherapy.

TMB and MSI have been demonstrated to be associated with antitumor immunity and can serve as predictors for immunotherapy response [44–46]. In this study, we investigated the relationship between *PLA2G7* and MSI, as well as TMB, using the SangerBox online tool. Our results revealed that *PLA2G7* was linked to MSI in TGCT, LUSC, HNSC, LGG, and COAD, and it was also associated with THCA, LIHC, STAD, BLCA, COAD, LAML, BRCA, and SARC. Previous studies have established that the TME significantly influences cancer survival, immune evasion, proliferation, clinical prognosis, and metastasis [47,48]. As integral components of the TME, ImmuneScore and StromalScore play crucial roles in the immune metabolism of tumor cells [49]. Our findings indicated a close association between *PLA2G7* and ImmuneScore in 32 cancer types, StromalScore in 32 cancer types, and all tumor-infiltrating lymphocytes in 16 cancer types. These results suggest that *PLA2G7* is intricately linked to the TME and could potentially serve as a target for immunotherapy across various cancer types.

MMR and DNA methylation are pivotal for maintaining genome stability and may serve as novel biomarkers in tumorigenesis [27]. Consequently, we examined the relationship between *PLA2G7* and various MMR genes, along with four DNA methyltransferases in pan-cancer. Our findings revealed a significant association between *PLA2G7* and MMR, as well as DNA methylation, in different cancer types, implying that *PLA2G7* may contribute to tumorigenesis through MMR and DNA methylation mechanisms.

Patients with renal cancer, such as KIRC, often experience poor prognosis, and there is a lack of effective diagnostic and therapeutic targets in clinical practice. Therefore, there is an urgent need to identify potential therapeutic targets for kidney cancer. In our study, we delved into the role of *PLA2G7* in renal cancer to provide a theoretical basis for its treatment. The results of GO enrichment demonstrated that *PLA2G7* and its co-expression genes were associated with the "regulation of immune system process," "immune system process," and "positive regulation of response to stimulus." Additionally, CCK-8 experiments revealed a significant decrease in the cell viability of renal cancer cells after inhibiting the *PLA2G7* gene. Taken together, we propose that *PLA2G7* may be a promising therapeutic target for renal cancer. Finally, we explored the correlations between *PLA2G7* mRNA levels and CTRP drug sensitivity. Our findings suggest that *PLA2G7* may guide the use of specific anticancer drugs in clinical practice.

Bioinformatics has garnered significant attention from scientists in recent years, owing to its large sample size, convenient operation, and high analytical efficiency. It has evolved into a powerful tool for researchers seeking potential disease diagnostic and therapeutic biomarkers. The booming development of bioinformatics is expected to unearth more effective tumor biomarkers and therapeutic targets, including those for renal cancer, over the next five years. This progress is anticipated to drive advancements in precision and individualized tumor treatment.

While this study comprehensively explores the role of *PLA2G7* in human cancers, certain limitations persist. in our study. First, the majority of findings are data-driven, with only a limited number of experiments conducted to validate our analyses. Additionally, our investigation into the proliferation capacity of renal cancer was confined to cellular-level experiments, warranting further validation at the animal level. Second, although we have demonstrated the crucial role of *PLA2G7* in human cancers, including renal cancer, the specific tumor-promoting mechanisms of *PLA2G7* necessitate further elucidation.

5. Conclusions

In summary, our study establishes *PLA2G7* as a promising diagnostic and prognostic biomarker across various cancers, including renal cancer. Furthermore, it emerges as a potential therapeutic target in human cancers, offering a valuable theoretical foundation for advancing cancer treatment strategies.

Data availability statement

The original data of this work can be acquired from the corresponding authors upon reasonable request.

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CRediT authorship contribution statement

Jun Xie: Writing – review & editing, Writing – original draft, Conceptualization. **Li Zhu:** Methodology, Investigation. **Xutao Yang:** Investigation, Data curation. **Fengfei Yu:** Software, Methodology. **Bingfu Fan:** Methodology, Investigation. **Yibo Wu:** Software. **Zonglang Zhou:** Data curation, Conceptualization. **Weiqiang Lin:** Writing – review & editing, Methodology, Conceptualization. **Yi Yang:** Writing – review & editing, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e27906.

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