Original Article

The prognostic biomarker TPGS2 is correlated with immune infiltrates in pan-cancer: a bioinformatics analysis

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Background: Tubulin polyglutamylase complex subunit 2 (TPGS2) is an element of the neuronal polyglutamylase complex that plays a role in the post-translational addition of glutamate residues to C-terminal tubulin tails. Recent research has shown that TPGS2 is associated with some tumors, but the roles of TPGS2 in tumor immunity remain unclear.

Methods: The research data were mainly sourced from The Cancer Genome Atlas. The data were analyzed to identify potential correlations between *TPGS2* expression and survival, gene alterations, the tumor mutational burden (TMB), microsatellite instability (MSI), immune infiltration, and various immune-related genes across various cancers. The Wilcoxon rank-sum test was used to identify the significance. A log-rank test and univariate Cox regression analysis were performed to assess the survival state of the patients. Spearman's correlation coefficients were used to show the correlations.

Results: *TPGS2* exhibited abnormal expression patterns in most types of cancers, and has promising prognostic potential in adrenocortical carcinoma and liver hepatocellular carcinoma. Further, *TPGS2* expression was significantly correlated with molecular and immune subtypes. Moreover, the single-cell analyses showed that the expression of *TPGS2* was associated with the cell cycle, metastasis, invasion, inflammation, and DNA damage. In addition, the immune cell infiltration analysis and gene-set enrichment analysis demonstrated that a variety of immune cells and immune processes were associated with *TPGS2* expression in various cancers. Further, immune regulators, including immunoinhibitors, immunostimulators, the major histocompatibility complex, chemokines, and chemokine receptors, were correlated with *TPGS2* expression in different cancer types. Finally, the TMB and MSI, which have been identified as powerful predictors of immunotherapy, were shown to be correlated with the expression of *TPGS2* across human cancers.

Conclusions: *TPGS2* is aberrantly expressed in most cancer tissues and might be associated with immune cell infiltration in the tumor microenvironment. *TPGS2* could serve not only as a biomarker for predicting clinical outcomes, but also as a promising biomarker for evaluating and developing new approaches to immunotherapy in many types of cancers, especially colon adenocarcinoma and stomach adenocarcinoma.

Keywords: Tubulin polyglutamylase complex subunit 2 (TPGS2); pan-cancer; tumor microenvironment (TME); biomarker; immunotherapy

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Introduction

At present, cancer is a leading cause of disease morbidity and mortality worldwide. Unfortunately, the number of newly diagnosed cases continues to grow (1,2). Current mainstream treatment modalities, including surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy, still do not provide a satisfactory prognosis for cancer patients (3). This pan-cancer study sought to apply diagnostic and therapeutic applications in gastric cancer to a broad range of tumors with characteristics of similarity. The identification of common key genes between different types of cancers can help in cancer diagnosis and treatment (4,5).

The application of immunotherapy has opened up a new era in tumor treatment, and it has achieved encouraging results in the treatment of several tumors (including lung cancer, melanoma, and liver cancer), greatly improving the prognosis of patients (6,7). Many immune checkpoint inhibitors (ICIs), such as programmed cell death protein 1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) inhibitors, have been established as routine treatments for many types malignancies; however, their clinical efficacy is limited (8,9). Given the complexities in the efficacy of immunotherapy, it is of great significance to explore new and more effective immune biomarkers.

The tumor microenvironment (TME) refers to the pericellular environment including immune cells, blood vessels, extracellular matrices, fibroblasts, mast cells, and various signaling molecules around the tumor (10,11). In recent years, the important role of the TME in tumorigenesis and development has been recognized. Tumor proliferation, infiltration, and metastasis depend not only on the tumor cells but also on the regulation of various cellular and signaling molecules in the TME (12). T cells, which are crucial in the anti-tumor immune response, have been relatively well studied among adaptive immune cells (13,14). Conversely, the second adaptive immune cell population (i.e., B cells) in the TME has not been well characterized.

However, in the last 5 years, several studies have reported an association between the presence of B cells in the TME and improved clinical outcomes (15-20). B cells can resist tumors by producing tumor-specific antibodies under certain conditions, but specific B cell subsets and antibody specificity can also suppress anti-tumor immunity and promote tumor growth (21). Meanwhile, infiltrating B cells are an important component of tertiary lymphoid structures (TLSs) in tumor tissues (15). Many studies have shown that the number and proportion of stromal cells and immune cells in tumor tissues are closely related to clinical features and prognosis (22-28). A thorough understanding of the TME is essential for accurate evaluation and treatment. To improve prognosis, more targeted molecules need to be identified for cancer diagnosis and treatment and to assess patient prognosis.

Few relevant studies have been conducted on tubulin polyglutamylase complex subunit 2 (*TPGS2*). We obtained partial information on *TPGS2* from the Entrez Molecular Sequence Database Entrez (https://www.ncbi.nlm.nih.gov/search/), which showed that *TPGS2* encodes a protein that is an element of the neuronal polyglutamylase complex, which plays a role in the post-translational addition of glutamate residues to C-terminal tubulin tails, and alternatively spliced transcript variants encoding multiple isoforms have been observed for this gene. *TPGS2* also appears to be associated with tumors and the TME (29,30).

In our preliminary analysis, we confirmed that *TPGS2* has a special role in cancer immunity. Based on this finding, we then performed the pan-cancer analysis to explore the expression, prognostic function, and immune role of *TPGS2* in various cancers. We comprehensively analyzed the relationship between *TPGS2* expression and patient prognosis in 33 types of cancer. Additionally, we further evaluated the association between *TPGS2* and tumor-infiltrating immune cells. Our findings revealed that *TPGS2* has a potential role in the development and progression of cancers; thus, *TPGS2* may serve as a potential prognostic and immunotherapeutic biomarker. We present this article in accordance with the REMARK reporting checklist (available at https://tcr.amegroups.com/article/

Highlight box

Key findings

- Tubulin polyglutamylase complex subunit 2 (TPGS2) is a potential prognostic and immunotherapeutic biomarker in many types of cancers, especially colon adenocarcinoma and stomach adenocarcinoma.

What is known and what is new?

- *TPGS2* has been found to be associated with some tumors.
- *TPGS2* plays a crucial role in tumor immunity.

What is the implication, and what should change now?

- *TPGS2* is a promising tumor immune target, and more research on *TPGS2* and tumor immunity should be conducted.

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Methods

The research data were downloaded from The Cancer Genome Atlas (TCGA), Genotype-Tissue Expression (GTEx), Cancer Cell Line Encyclopedia (CCLE), and Human Protein Atlas (HPA). databases. Data were downloaded for the following tumors: adrenocortical carcinoma (ACC), bladder urothelial carcinoma (BLCA), breast carcinoma (BRCA), cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), cholangiocarcinoma (CHOL), colon adenocarcinoma (COAD), lymphoid neoplasm diffuse large B-cell lymphoma (DLBC), esophageal carcinoma (ESCA), glioblastoma multiforme (GBM), head and neck squamous cell carcinoma (HNSC), kidney chromophobe (KICH), kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP), acute myeloid leukemia (LAML), brain low-grade glioma (LGG), liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), mesothelioma (MESO), ovarian serous cystadenocarcinoma (OV), pancreatic adenocarcinoma (PAAD), pheochromocytoma and paraganglioma (PCPG), prostate adenocarcinoma (PRAD), rectum adenocarcinoma (READ), sarcoma (SARC), skin cutaneous melanoma (SKCM), stomach adenocarcinoma (STAD), testicular germ cell tumor (TGCT), thyroid carcinoma (THCA), thymoma (THYM), uterine corpus endometrial carcinoma (UCEC), uterine carcinosarcoma (UCS), and uveal melanoma (UM or UVM). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Data source and processing

The gene expression and clinical data of normal human tissues and cancer tissues were downloaded from the GTEx database and TCGA by UCSC Xena (https://xenabrowser.net/) (31). For a multidimensional demonstration, the expression of *TPGS2* was analyzed in various cancer cell lines with data from the CCLE. The transcripts per million (TPM) format and the $\log_2$(TPM+1) format were used for the expression profiles and subsequent analyses. Statistical significance was defined as follows: P<0.05, P<0.01, and P<0.001.

IHC of TPGS2

The protein expression of the tumor tissues and normal tissues from the HPA (http://www.proteinatlas.org/) database was applied to verify the protein expression levels of *TPGS2* (32). Data from the HPA database were also used to confirm the intensity of TPGS2 in immunohistochemical staining in six normal and cancer tissues, including LIHC, LUSC, COAD, STAD, PRAD, and TGCT.

Genomic alterations analysis of TPGS2

The cBioPortal (http://www.cbioportal.org) is a multipurpose cancer genomics database that can recognize the molecular information of cancer tissues and comprehend the associated genetics, epigenetics, gene expression, and proteome information (33,34). The cBioPortal was used to display the alteration frequency (including mutation, structural variation, amplification, deep deletion, and multiple alterations) across cancers, and the results were visualized in bar plots. We also obtained a landscape map of the gene mutation sites, a correlation diagram of the copy number alterations (CNAs) and *TPGS2* expression, and Kaplan-Meier curves of the pan-cancer data using the cBioPortal webtool.

Prognostic analysis

The UCSC Xena database was used to download the related prognostic data, including overall survival (OS), progression-free survival (PFS), and disease-specific survival (DSS) data. Next, we plotted the Kaplan-Meier model and univariate Cox regression results to assess the prognosis of various cancers. The *TPGS2* expression median of each cancer was used to divide patients into high- and low-expression subgroups. Next, the Kaplan-Meier method was used to compute the log-rank P value and hazard ratio (HR) with a 95% confidence interval (CI). The "survival" package (3.2-10) was used for the statistical analysis of the survival data, and the "survminer" package (0.4.9) was used for the visualization.

Single-cell analysis of TPGS2

The Cancer Single-cell State Atlas (CancerSEA), a specialized single-cell sequencing database, provides various functional data on cancer cells at the single-cell level (35). The average correlations between the *TPGS2* expression and functional states in different cancers were summarized and presented in a heatmap. The correlations between *TPGS2* expression and several tumor functions

were investigated using single-cell sequencing data. The *TPGS2* expression profiles of single cells are shown in the t-distributed stochastic neighbor embedding (t-SNE) diagrams.

Gene set enrichment analysis (GSEA)

A GSEA was conducted using the "clusterProfiler" package (3.14.3), and "ggplot2" (3.3.3) was used to graph the results (36,37). The reference gene set was c5.bp.v7.2.symbols.gmt (Gene Ontology), which was derived from the website of the Molecular Signatures Database (MSigDB, https://www.gsea-msigdb.org/gsea/index.jsp). It is generally accepted that the threshold of significant enrichment is a false discovery rate (FDR) <0.25 and a P adjusted value <0.05.

Immune cell infiltration analysis and TME

The immune cell infiltration analysis was largely performed using the Tumor Immune Estimation Resource (TIMER) (38). The *TPGS2*-associated immune cell infiltration correlations were downloaded from the TIMER 2.0 database (http://timer.cistrome.org/). Finally, we visualized the statistical Spearman correlations between *TPGS2* messenger RNA (mRNA) expression and 20 immune cell subsets.

Correlation analysis of the TMB, MSI, and immune regulators

A Spearman correlation analysis of immune regulators and *TPGS2* expression was performed to investigate the correlation between *TPGS2* and the reported biomarkers of cancer immunotherapy, including immunostimulators, immunoinhibitors, the major histocompatibility complex (MHC) genes, chemokines, and chemokine receptors, for various cancer types. A Spearman correlation analysis was also conducted to analyze the relationship between the tumor mutational burden (TMB) (39), microsatellite instability (MSI), and *TPGS2* expression (40) across various cancers.

Statistical analysis

The Wilcoxon rank-sum test was used to evaluate the statistical significance of and compare the *TPGS2* expression levels between tumor and normal tissues. The survival analysis was performed using the Kaplan-Meier method (log-rank test) and a univariate Cox regression analysis was also conducted. A Spearman correlation analysis was conducted to evaluate the correlations between *TPGS2* and other factors, such as immune cell infiltration, the TMB, and MSI. A P value <0.05 was considered statistically significant.

Results

Expression of TPGS2 in cancer tissues

First, we integrated the mRNA expression levels of normal tissues in the GTEx database. The results showed that *TPGS2* was highly expressed in the normal tissues of TGCT, BLCA, and OV, and most lowly expressed in LIHC (*Figure 1A*). According to the tumor cell data from the CCLE, compared to the other tumor cells, *TPGS2* was the most highly expressed in small cell lung cancer and CESC, and the most lowly expressed in chronic lymphocytic leukemia (*Figure 1B*). We then combined the data from TCGA and GTEx databases to reflect the expression levels of *TPGS2* mRNA in various malignancies (*Figure 1C*). The results showed that *TPGS2* mRNA was more highly expressed in 22 kinds of tumors (BRCA, CESC, CHOL, COAD, DLBC, ESCA, GBM, HNSC, LGG, LIHC, LUAD, LUSC, OV, PAAD, PCPG, READ, SKCM, STAD, THCA, THYM, UCEC, and UCS) than their respective normal tissues. Conversely, *TPGS2* was more lowly expressed in five tumors (ACC, KIRC, LAML, PRAD, and TGCT) than their normal tissues. Further, *TPGS2* mRNA was significantly more highly expressed in BLCA, CHOL, COAD, ESCA, HNSC, LIHC, LUSC, STAD, and UCEC cancer tissues than matched normal tissues, and more highly expressed in KICH and PRAD tumor tissues (*Figure 1D*).

Moreover, we evaluated the protein expression of *TPGS2* between normal and tumor tissues using the HPA database. As *Figure 2* shows, compared to the weak staining of TPGS2 in the normal liver, lung, colon, and stomach tissues, stronger staining was observed in the LIHC, LUSC, COAD, and STAD tissues (*Figure 2A-2D*). Normal prostate and testes tissues had medium TPGS2 staining, while their tumor tissues had weaker staining (*Figure 2E,2F*). Thus, the immunohistochemistry (IHC) results re-confirmed our previous analyses. These results indicated that *TPGS2* is aberrantly expressed across human cancers, and we speculated that *TPGS2* may be able to inform the prognosis and treatment of various cancers.

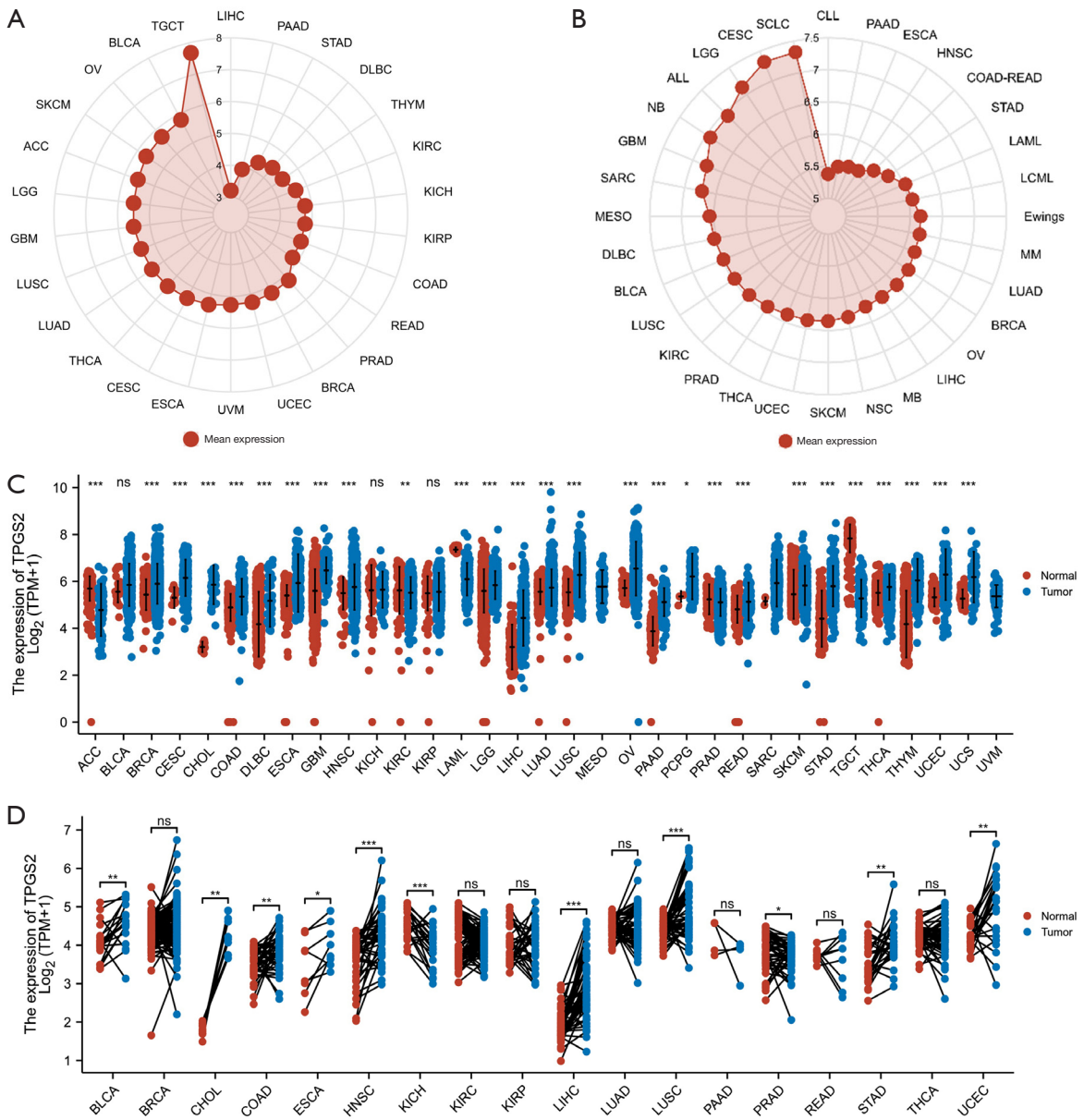

Figure 1 *TPGS2* mRNA expression levels in pan-cancer. (A) *TPGS2* expression levels in normal tissues from the GTEx; (B) *TPGS2* expression levels in tumor cells from the CCLE; (C) *TPGS2* expression difference between tumor tissues from TCGA and normal tissues from the GTEx; (D) *TPGS2* expression difference between tumor tissues and matched normal tissues from TCGA. ns, no significance; *, P<0.05; **, P<0.01; ***, P<0.001. *TPGS2*, tubulin polyglutamylase complex subunit 2; TPM, transcripts per million; mRNA, messenger RNA; GTEx, Genotype-Tissue Expression; CCLE, Cancer Cell Line Encyclopedia; TCGA, The Cancer Genome Atlas.

Association with molecular and immune subtypes

To explore the associations between *TPGS2* expression and molecular and immune subtypes across human cancers, we performed a further analysis by the tumor-immune system interaction database (TISDB). As *Figure 3A-3F* show, *TPGS2* expression was significantly associated with the molecular stages of many cancers, such as BRCA, COAD, HNSC, LGG, LUSC, and PCPG. To explore the relationship between *TPGS2* and cancer immunity, we analyzed the correlation between the immune subtypes and *TPGS2* expression, and found that the expression of *TPGS2*

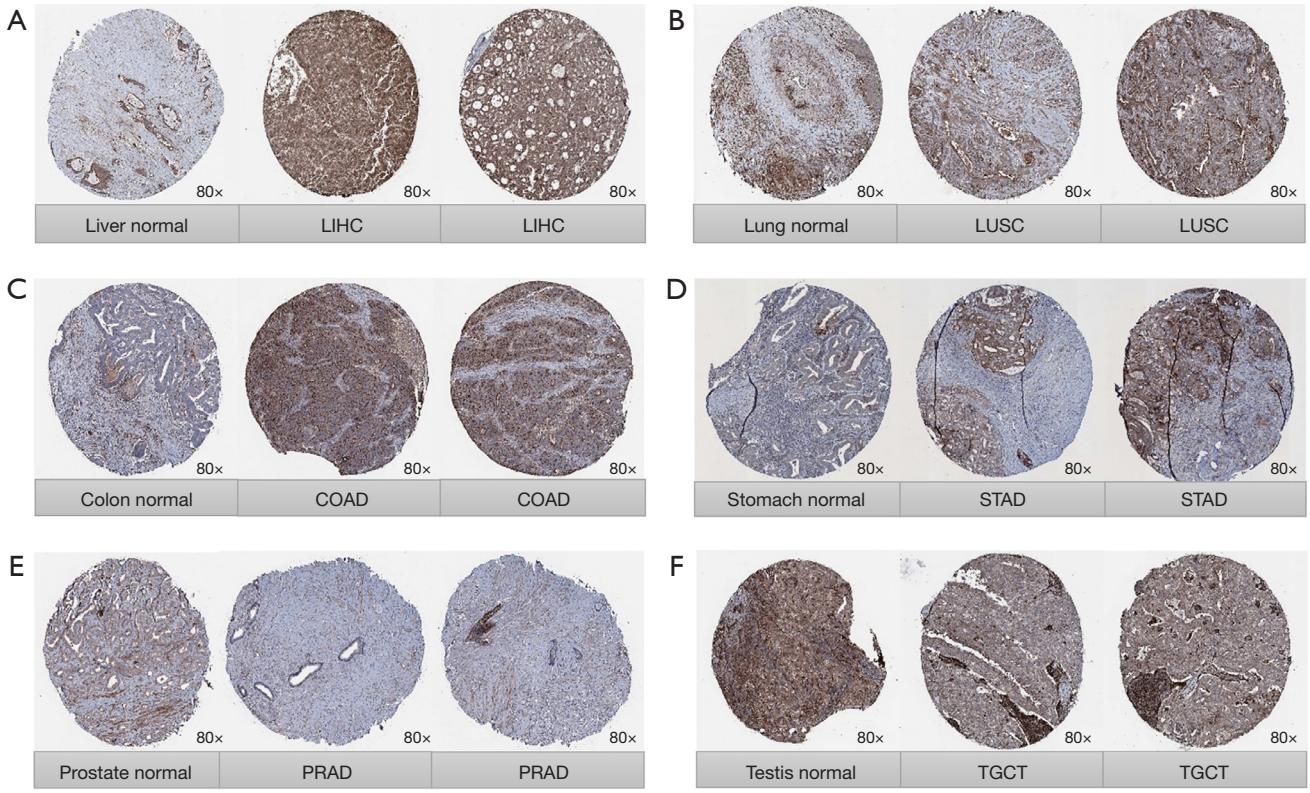

Figure 2 IHC results for various normal and tumor tissues from the HPA. The staining of the TPGS2 protein in (A) liver and LIHC tissues (https://www.proteinatlas.org/ENSG00000134779-TPGS2/pathology/liver+cancer); (B) lung and LUSC tissues (https://www.proteinatlas.org/ENSG00000134779-TPGS2/pathology/lung+cancer); (C) colon and COAD tissues (https://www.proteinatlas.org/ENSG00000134779-TPGS2/pathology/colorectal+cancer); (D) stomach and STAD tissues (https://www.proteinatlas.org/ENSG00000134779-TPGS2/pathology/stomach+cancer); (E) prostate and PRAD tissues (https://www.proteinatlas.org/ENSG00000134779-TPGS2/pathology/prostate+cancer); and (F) testis and TGCT tissues (https://www.proteinatlas.org/ENSG00000134779-TPGS2/pathology/testis+cancer). All images have a magnification of ×80. LIHC, liver hepatocellular carcinoma; LUSC, lung squamous cell carcinoma; COAD, colon adenocarcinoma; STAD, stomach adenocarcinoma; PRAD, prostate adenocarcinoma; TGCT, testicular germ cell tumor; IHC, immunohistochemistry; HPA, Human Protein Atlas; TPGS2, tubulin polyglutamylase complex subunit 2.

was significantly related to immune subtypes in many cancers, including BRCA, KIRC, LIHC, STAD, OV, and SARC (*Figure 3G-3L*). These results indicated that TPGS2 has potential prediction and treatment functions in pan-cancer.

Genetic alteration of TPGS2

Given the abnormal expression of *TPGS2* observed in cancer, we sought to examine whether genetic alterations in *TPGS2* caused this change. Therefore, we conducted a genetic alteration analysis of *TPGS2* using the cBioPortal database with data from TCGA, and PanCancer Atlas. As *Figure 4A* shows, PAAD had the highest alteration rate (6%) with "amplification" and "deep deletion" as the primary types. Conversely, the "deep deletion" type of the CNAs was the primary altered type in the ESAD cases, which had an alteration frequency of ~4%. Notably, the main genetic alteration in UCEC and SKCM was "mutation" (*Figure 4A*). As *Figure 4B* shows, after examining putative CNAs from the significant targets in cancer (GISTIC) module, the CNAs were closely related to the mRNA expression of *TPGS2*.

Clinical prognostic significance of TPGS2

To examine the prognostic role of *TPGS2* across human cancers, prognostic indicators in 33 cancers were

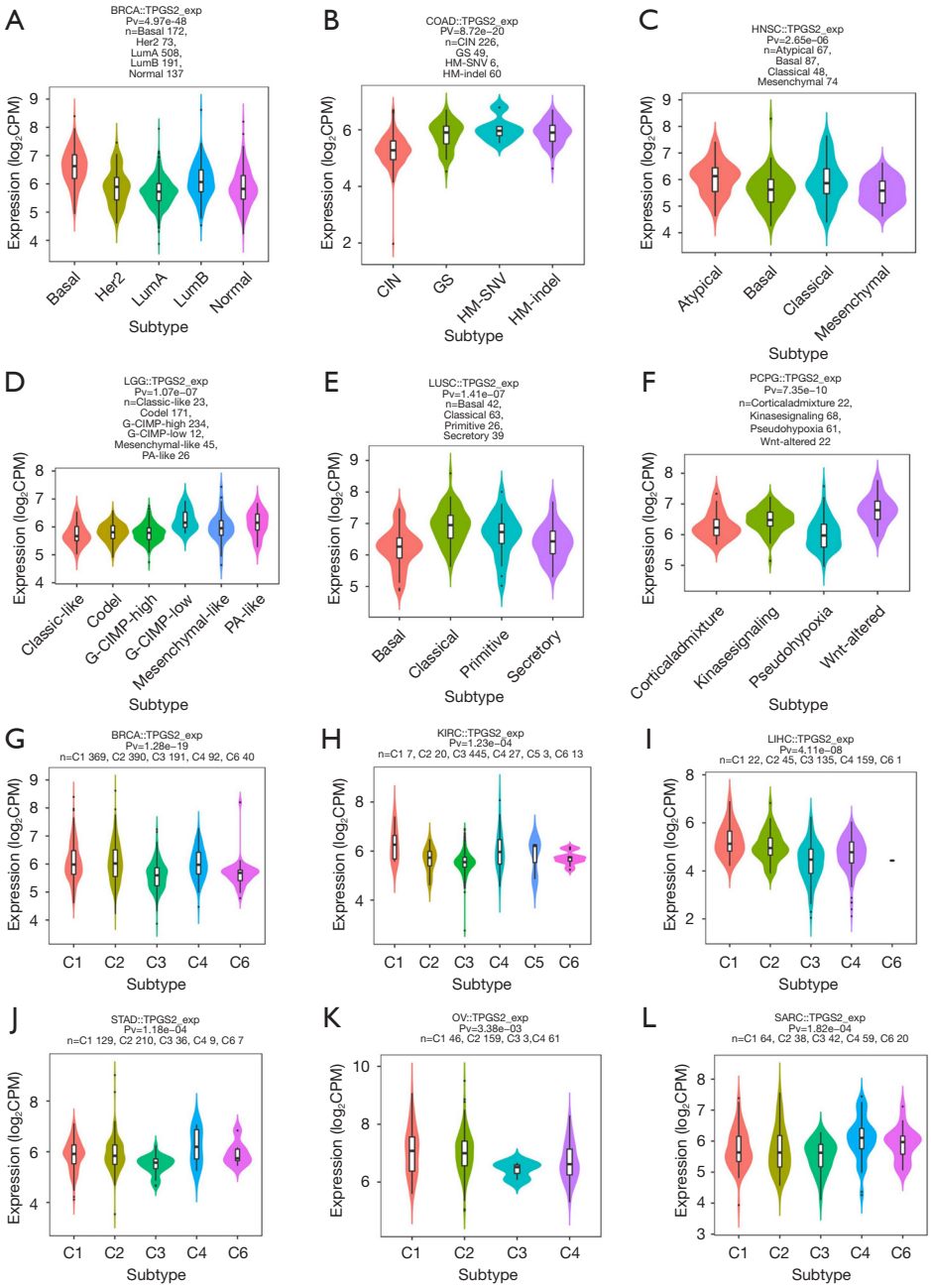

Figure 3 Distribution of *TPGS2* expression across the molecular subtypes of BRCA (A), COAD (B), HNSC (C), LGG (D), LUSC (E), and PCPG (F); associations between *TPGS2* expression and the main immune subtypes of BRCA (G), KIRC (H), LIHC (I), STAD (J), OV (K), and SARC (L). CPM, counts per million reads; *TPGS2*, tubulin polyglutamylase complex subunit 2; BRCA, breast carcinoma; COAD, colon adenocarcinoma; HNSC, head and neck squamous cell carcinoma; LGG, low-grade glioma; LUSC, lung squamous cell carcinoma; PCPG, pheochromocytoma and paraganglioma; KIRC, kidney renal clear cell carcinoma; LIHC, liver hepatocellular carcinoma; STAD, stomach adenocarcinoma; PRAD, prostate adenocarcinoma; OV, ovarian serous cystadenocarcinoma; SARC, sarcoma; C1, wound healing; C2, IFN-gamma dominant; C3, inflammatory; C4, lymphocyte depleted; C5, immunologically quiet; C6, TGF-b dominant.

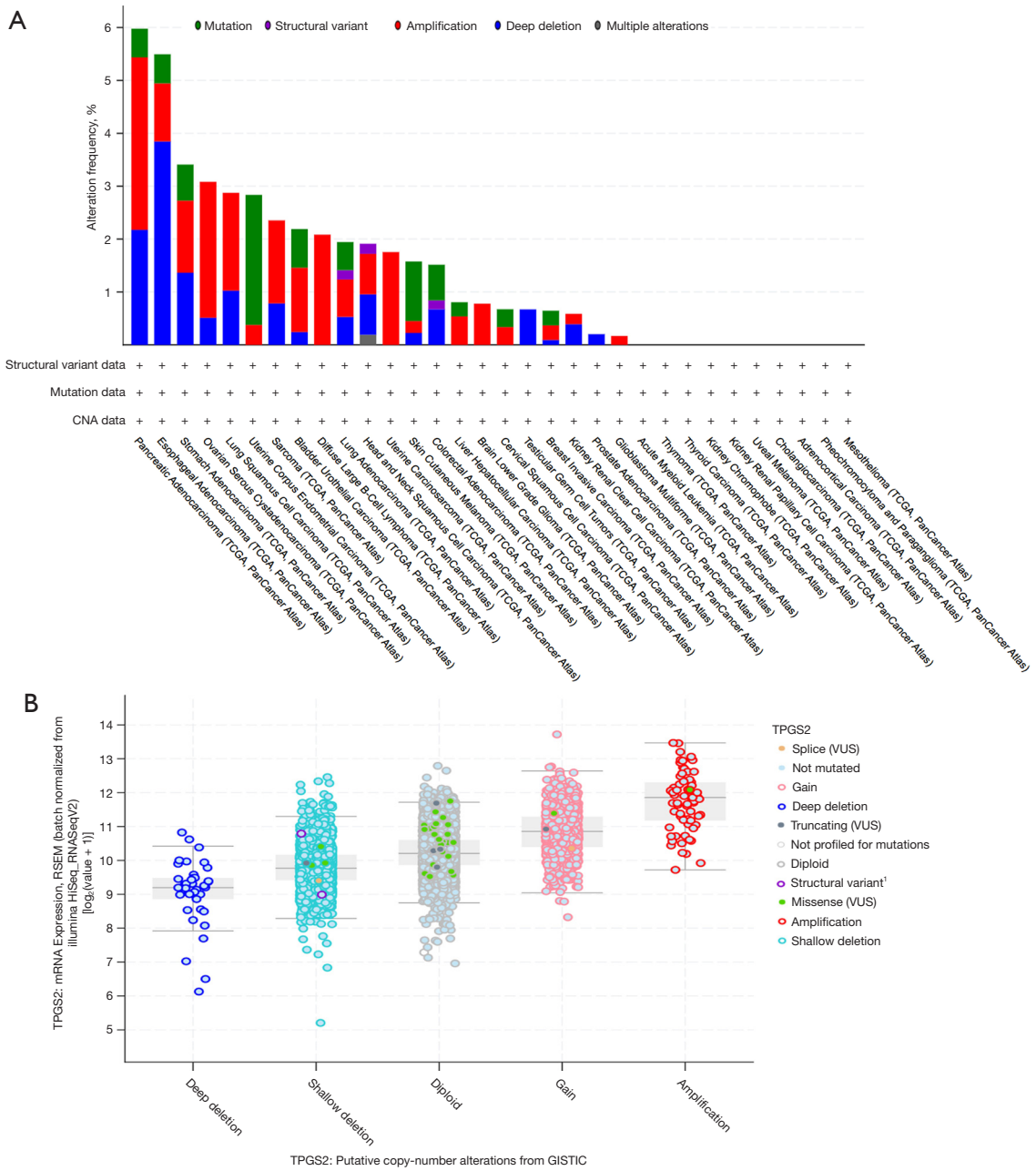

Figure 4 Relationship between *TPGS2* expression and gene alterations. (A) The genetic alteration types and frequency of *TPGS2* in various cancers; (B) the association between CNA and the RNA expression of *TPGS2*. [1], structural variants are shown instead of CNA when a sample has both. *TPGS2*, tubulin polyglutamylase complex subunit 2; CNA, copy number alterations; TCGA, The Cancer Genome Atlas; VUS, variants of uncertain significance.

investigated using the Kaplan-Meier method and a univariate Cox regression analysis. The results showed that *TPGS2* was highly correlated with the prognosis of most cancers. As *Figure 5A* shows, the univariate Cox regression analysis of OS suggested that the high expression of *TPGS2* was a risk factor for the poor prognosis of ACC, BLCA, LGG, LIHC, MESO, SARC, STAD, and UCS, while it was a protective factor for OV and THYM. The results of the Kaplan-Meier OS analysis, which were basically consistent with the results of the univariate Cox regression analysis,

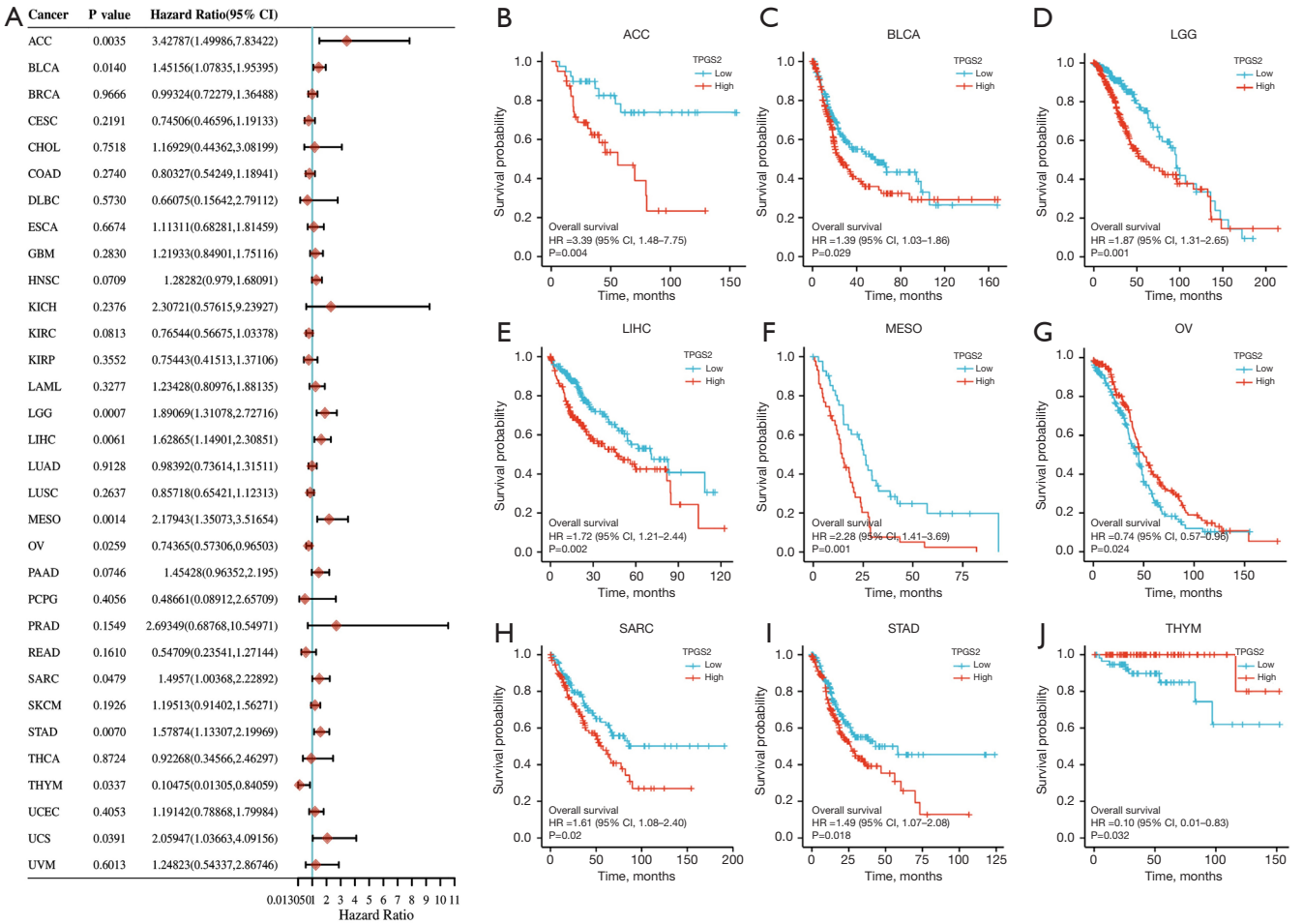

Figure 5 Relationship between *TPGS2* expression and OS. (A) Forest map showing the univariate Cox regression analysis results for *TPGS2* in pan-cancer samples from TCGA. (B-J) Kaplan-Meier curves for nine significant cancers. HR, hazard ratio; CI, confidence interval; ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; LGG, low-grade glioma; LIHC, liver hepatocellular carcinoma; MESO, mesothelioma; OV, ovarian serous cystadenocarcinoma; SARC, sarcoma; STAD, stomach adenocarcinoma; THYM, thymoma; *TPGS2*, tubulin polyglutamylase complex subunit 2; OS, overall survival; TCGA, The Cancer Genome Atlas.

showed that the high expression of *TPGS2* was significantly correlated with a poor prognosis in SARC, MESO, LIHC, LGG, BLCA, and ACC, but was significantly correlated with a better prognosis in OV and THYM (*Figure 5B-5J*). The results of the Cox regression analysis of PFS revealed that *TPGS2* was a risk factor in ACC, HNSC, MESO, and UCS (*Figure 6A*). The results of the Kaplan-Meier analysis showed that patients with high *TPGS2* expression had poorer PFS than those with low *TPGS2* expression in ACC, CHOL, HNSC, LIHC, SARC, and UCS, but had better PFS in PCPG, LUCA (*Figure 6B-6I*). Additionally, the results of the Cox regression analysis of DSS revealed that *TPGS2* acts as a risk factor for ACC, LGG, LIHC, MESO, PAAD, and SARC, but acts as a protective factor for OV (*Figure 7A*). Further, the results of the Kaplan-Meier analysis of DSS showed that a high expression of *TPGS2* was associated with a worse prognosis in ACC, LGG, LIHC, MESO, PAAD, and SARC (*Figure 7B-7H*). Overall, *TPGS2* expression was significantly associated with prognostic parameters in many cancers.

TPGS2 expression patterns in single-cell analyses and related-functional status

Due to the complexity of tumor cells, the new technique of single-cell transcriptome sequencing is increasingly

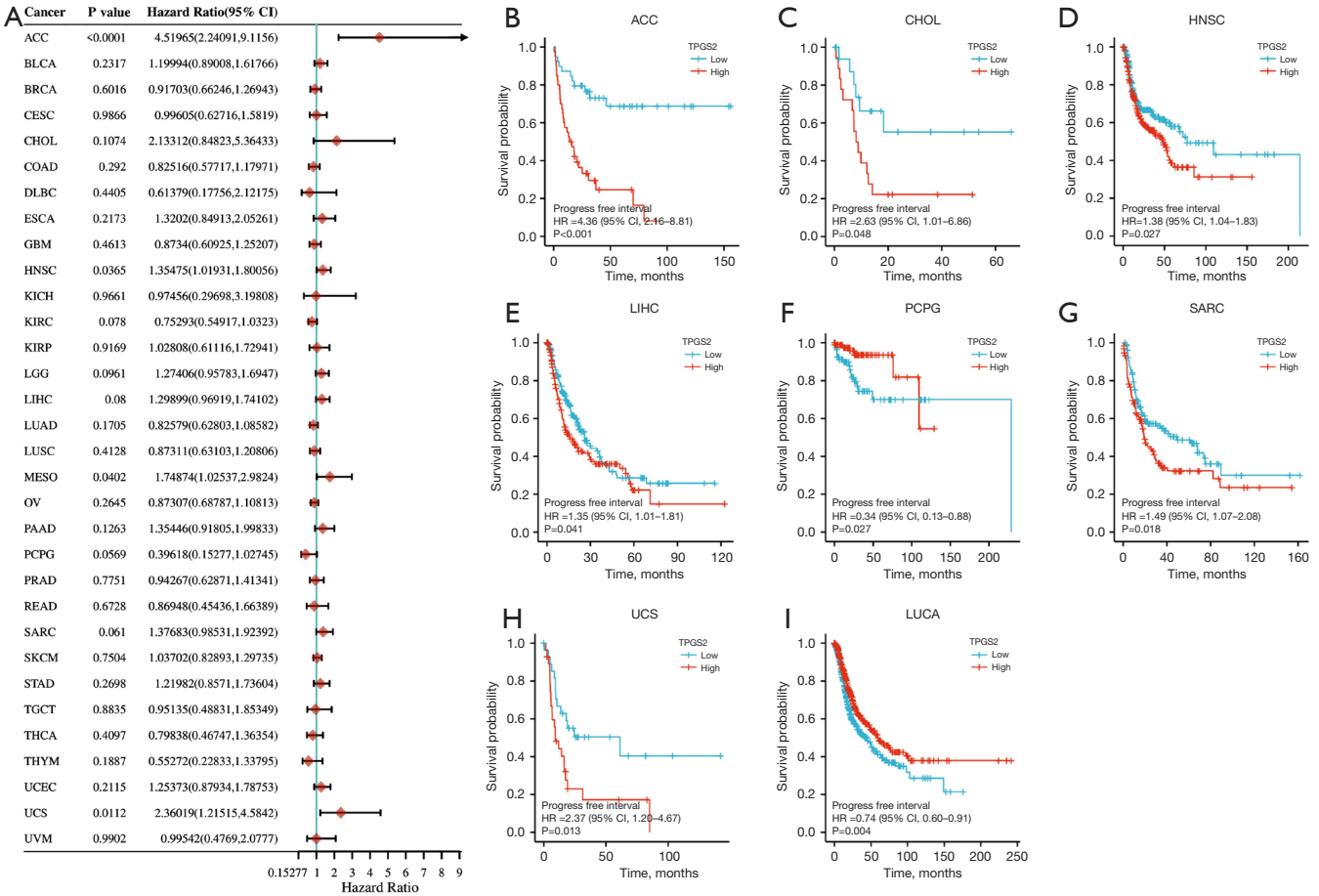

Figure 6 Relationship between *TPGS2* expression and PFI. (A) Forest map showing the univariate Cox regression analysis results for *TPGS2* in pan-cancer samples from TCGA. (B-I) Kaplan-Meier curves for eight significant cancers. HR, hazard ratio; CI, confidence interval; PFI, progress free interval; *TPGS2*, tubulin polyglutamylase complex subunit 2; ACC, adrenocortical carcinoma; CHOL, cholangiocarcinoma; HNSC, head and neck squamous cell carcinoma; LIHC, liver hepatocellular carcinoma; PCPG, pheochromocytoma and paraganglioma; SARC, sarcoma; UCS, uterine carcinosarcoma; LUCA, lung carcinoma; TCGA, The Cancer Genome Atlas.

being used to analyze a variety of cancer cells, immune cells, endothelial cells, and stromal cells. To explore the expression of *TPGS2* in single-cell analyses in pan-cancer and its relationship with tumor functional status, we obtained tumor single-cell data on *TPGS2* from the CancerSEA.

As *Figure 8A* shows, we found that many types of cancers, including UM, non-small cell lung cancer (NSCLC), and high-grade glioma (HGG), were associated with most tumor functional states. We also analyzed expression distribution with t-SNE plots, and the correlation between *TPGS2* expression and functional states in different cancers based on the CancerSEA database, and found that *TPGS2* expression in UM was significantly associated with DNA repair, DNA damage, apoptosis, metastasis, invasion, and quiescence (*Figure 8B*); acute myelocytic leukemia (AML) was closely associated with invasion and differentiation (*Figure 8C*); retinoblastoma (RB) was correlated with differentiation and angiogenesis (*Figure 8D*); chronic myeloid leukemia (CML) was closely associated with proliferation (*Figure 8E*); and NSCLC was associated with epithelial-to-mesenchymal transition (*Figure 8F*). The t-SNE plots showed the expression distribution of *TPGS2* in UM, AML, RB, CML and NSCLC cells (*Figure 8G-8K*). In the plots, every point represents a single cell, and the color of the point represents the expression level of *TPGS2* in the cell. The results suggest *TPGS2* might play an important role in some functional states, and most of the

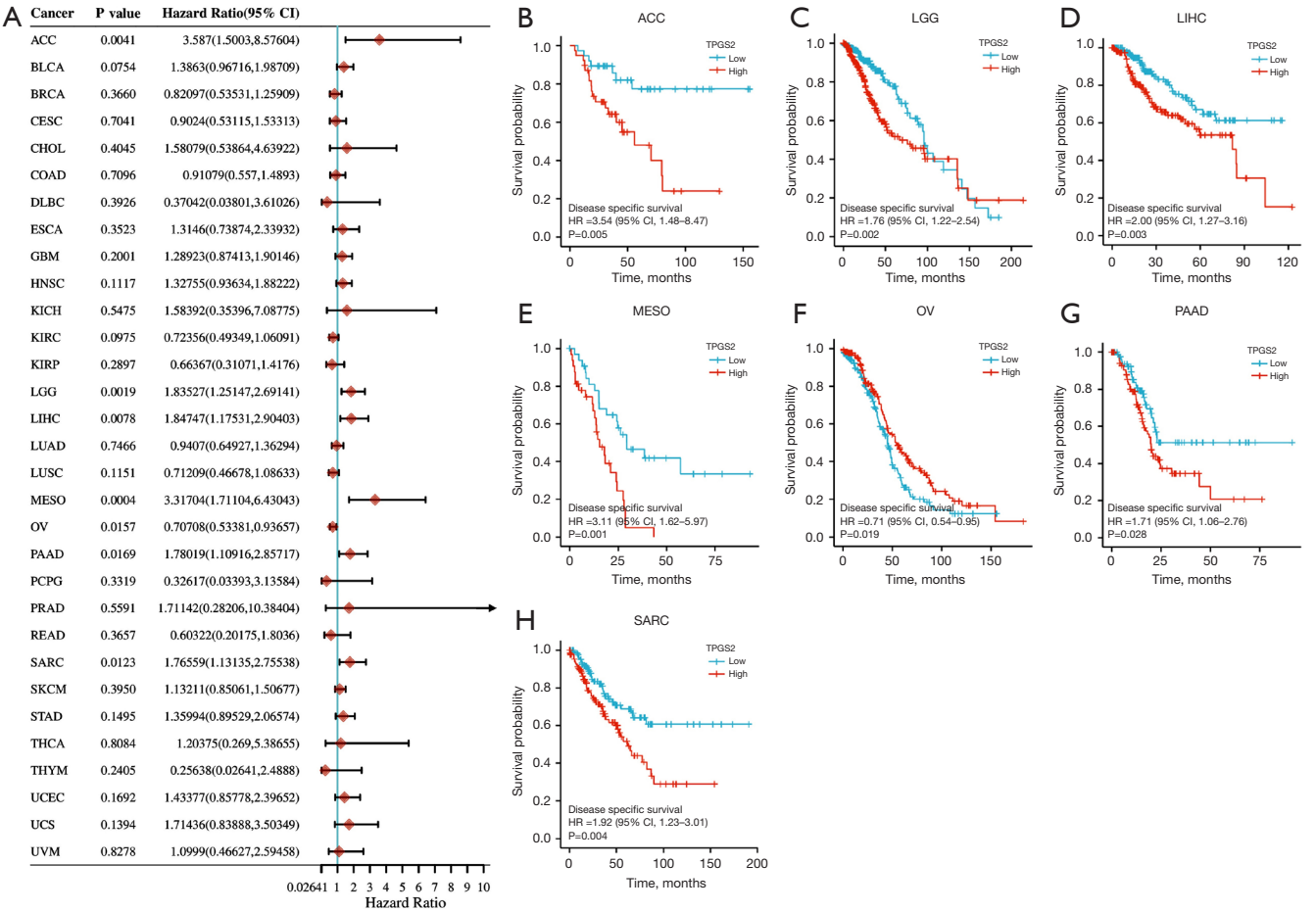

Figure 7 Relationship between *TPGS2* expression levels and DSS. (A) Forest map showing the univariate Cox regression analysis results for *TPGS2* in pan-cancer samples from TCGA. (B-H) Kaplan-Meier curves for seven significant cancers. HR, hazard ratio; CI, confidence interval; DSS, disease-specific survival; *TPGS2*, tubulin polyglutamylase complex subunit 2; ACC, adrenocortical carcinoma; LGG, low-grade glioma; LIHC, liver hepatocellular carcinoma; MESO, mesothelioma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; SARC, sarcoma; TCGA, The Cancer Genome Atlast.

functional states have been linked to the occurrence and progression of cancers.

GSEA

To explore the biological processes related to *TPGS2* expression across human cancers, we performed a differential expression analysis between the top 50% *TPGS2* expression subgroup and the bottom *TPGS2* expression subgroup for each type of cancer. We conducted a GSEA to evaluate the biological processes of 33 types of cancers from TCGA. The results showed that *TPGS2* is likely involved in a great deal of immune regulation-related biological processes, especially immunoglobulin (Ig) production, the humoral immune response mediated by circulating Ig, B cell-mediated immunity, the regulation of the humoral immune response, and the B cell receptor signaling pathway (*Figure 9A-9F*). This provides evidence that *TPGS2* may be involved in the immune response and cancers, which prompted us to explore the role of TPGS2 in the cancer-immune process and immune microenvironment.

Immune cell infiltration analysis

To further explore the role of *TPGS2* in tumor immunity, we explored the correlations between *TPGS2* expression and immune cell infiltration levels across cancers. TIMER 2.0 was used to generate a heatmap associated with a variety

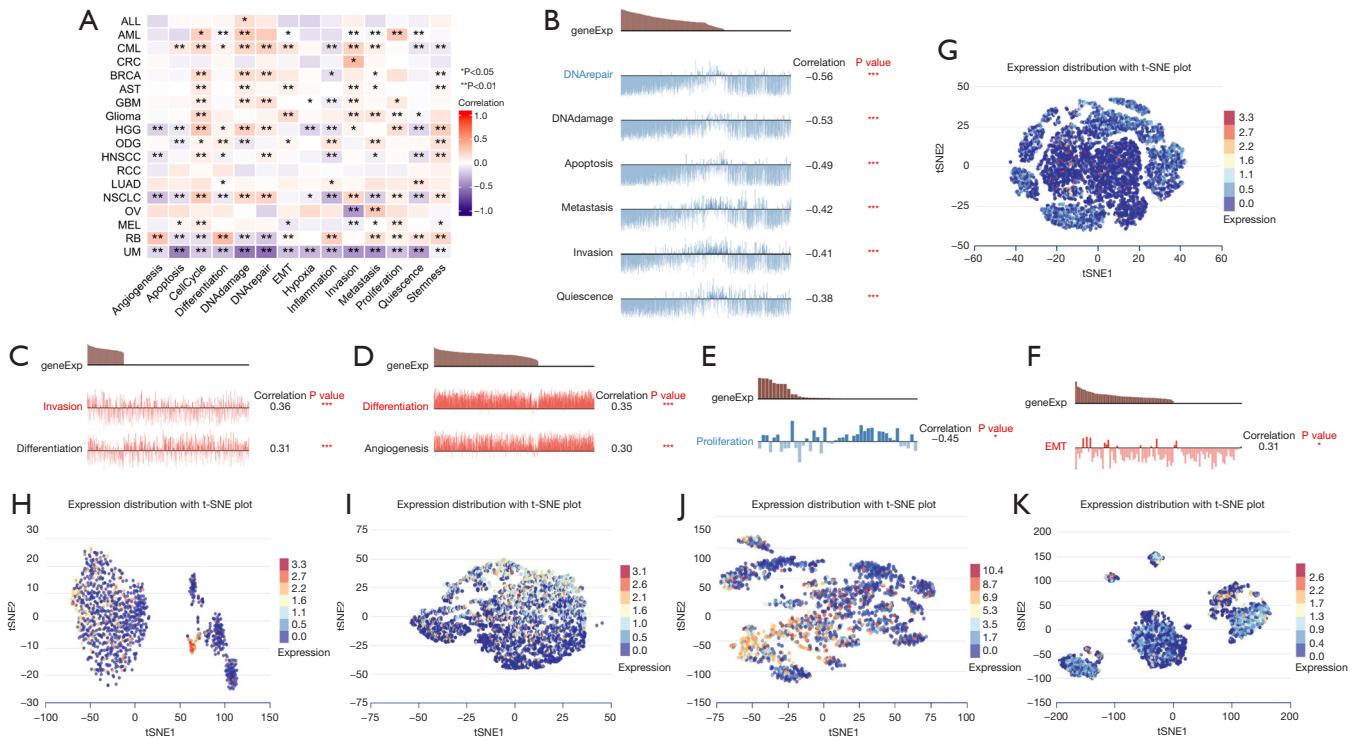

Figure 8 The expression levels of *TPGS2* based on the single-cell analysis. (A) Average correlations between the expression levels of *TPGS2* and functional states in various cancers; (B-F) the relationship between *TPGS2* expression and various functional states in UM, AML, RB, CML, and NSCLC were explored by the CancerSEA; (G-K) the expression distribution of *TPGS2* in cells of UM, AML, RB, CML and NSCLC are displayed in a t-SNE diagram. *, P<0.05; **, P<0.01; ***, P<0.001. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myelogenous leukemia; CRC, colorectal cancer; BRCA, breast carcinoma; AST, astrocytoma; GBM, glioblastoma; HGG, high-grade glioma; ODG, oligodendroglioma; HNSCC, head and neck squamous cell carcinoma; RCC, renal cell carcinoma; LUAD, lung adenocarcinoma; NSCLC, non-small cell lung cancer; OV, ovarian carcinoma; MEL, melanoma; RB, retinoblastoma; UM, uveal melanoma; EMT, epithelial-to-mesenchymal transition; t-SNE, t-distributed stochastic neighbor embedding; *TPGS2*, tubulin polyglutamylase complex subunit 2.

of immune cell infiltration, which was performed on a variety of quantitative immuno-infiltration platforms. The results were then categorized based on different immune score categories (Figures S1-S6). These analyses showed the infiltration levels of cluster of differentiation (CD)8$^+$ T cells, CD4$^+$ T cells, T regulatory cells (Tregs), B cells, neutrophils, macrophages, progenitors, dendritic cells (DCs), mast cells, cancer-associated fibroblasts (CAFs), endothelial cell (endos), natural killer (NK) cells, T cell follicular helper (Tfh) cells, T cell gamma delta (γδT) cells, NK T cells, monocytes, myeloid-derived suppressor cells (MDSCs), and eosinophils (Eos). As *Figure 10* shows, *TPGS2* was positively related to the level of many cells, such as macrophages, CD4$^+$ T cells, CD8$^+$ T cells, B cells, neutrophils, and CAFs. We also found that *TPGS2* had a higher correlation with immune cell infiltration in THYM and HNSC than other tumors, especially in CD4$^+$ T cells, CD8$^+$ T cells, macrophages, and B cells. However, their trend of correlation was slightly different, which might be related to the immune specificity of these cancers.

Co-expression of TPGS2 with immune-associated genes

To further explore the role of *TPGS2* in cancer immunity, we performed a Spearman correlation analysis to reveal the correlation between *TPGS2* expression and immune-related genes (*Figure 11A-11E*). The heatmaps illustrated that the gene encoding immunoinhibitor, immunostimulator, MHC, chemokine, and chemokine receptor proteins were significantly correlated with the expression of *TPGS2* in

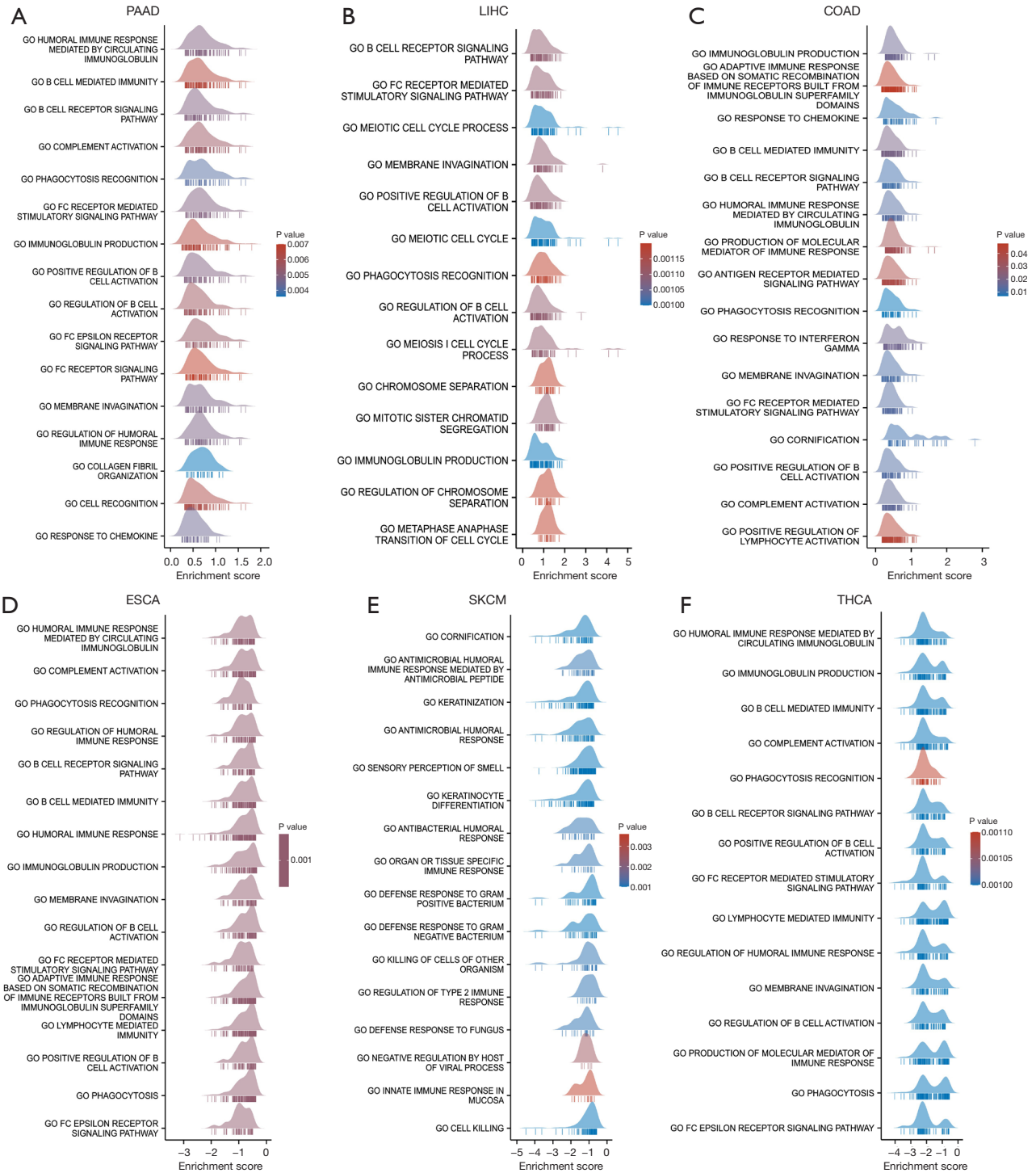

Figure 9 GSEA of *TPGS2* in various cancers. (A-F) Top biological processes of the GSEA in indicated tumor types. GO, Gene Ontology; PAAD, pancreatic adenocarcinoma; LIHC, liver hepatocellular carcinoma; COAD, colon adenocarcinoma; ESCA, esophageal carcinoma; SKCM, skin cutaneous melanoma; THCA, thyroid carcinoma; GSEA, gene-set enrichment analysis; *TPGS2*, tubulin polyglutamylase complex subunit 2.

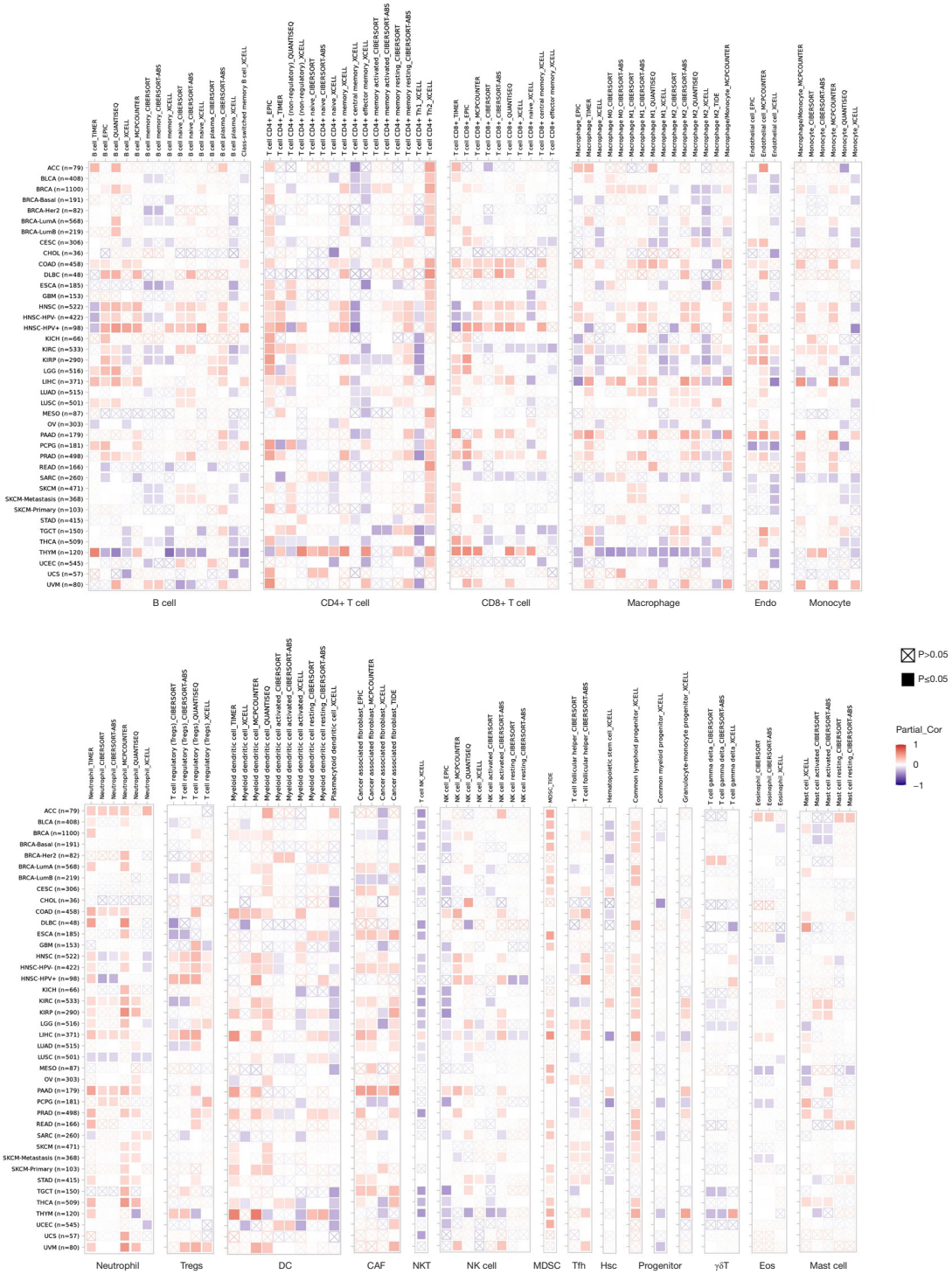

Figure 10 The correlations between *TPGS2* expression and the infiltration levels of B cells, CD4$^+$ T cells, CD8$^+$ T cells, macrophages, Endos, monocytes, neutrophils, Tregs, DCs, CAFs, NK T cells, NK cells, MDSCs, Tfh cells, progenitor, γδT cells, eosinophils (Eos), and mast cells in cancers. Positive correlations in red, and negative correlations blue. *TPGS2*, tubulin polyglutamylase complex subunit 2; Endos, endothelial cells; Tregs, T regulatory cells; DCs, dendritic cells; CAFs, cancer-associated fibroblasts; NK, natural killer; MDSCs, myeloid-derived suppressor cells; Tfh, T cell follicular helper; γδT, T cell gamma delta.

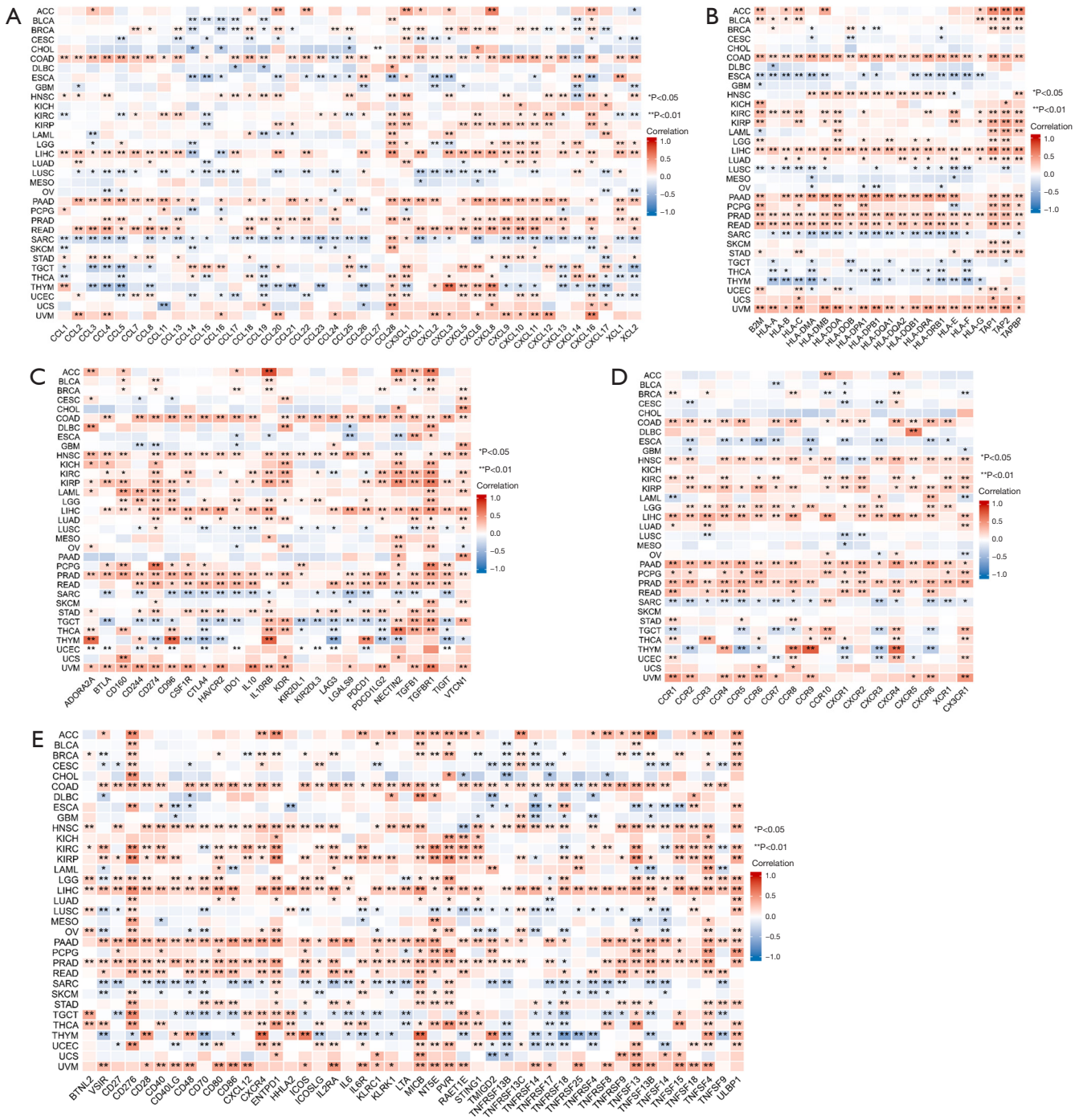

Figure 11 Co-expression between *TPGS2* and immune-associated genes. Co-expression between *TPGS2* and gene encoding chemokines (A), MHCs (B), immunoinhibitors (C), chemokine receptors (D), and immunostimulators (E). *, P<0.05; **, P<0.01. *TPGS2*, tubulin polyglutamylase complex subunit 2; MHC, major histocompatibility complex.

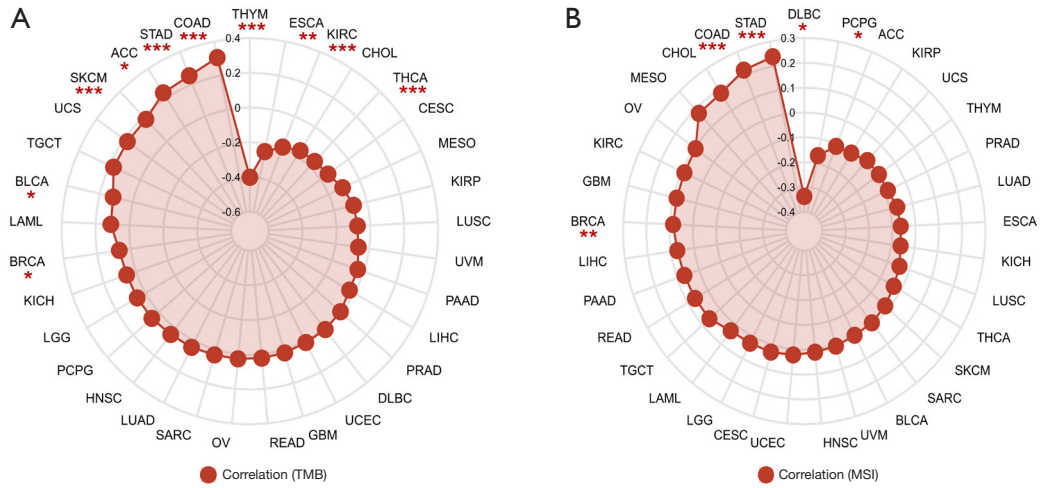

Figure 12 The correlation between *TPGS2* expression and the TMB, and MSI. (A) Radar map showing the correlation between *TPGS2* expression and the TMB. (B) Radar map showing the correlation between *TPGS2* expression and MSI. The red lines represent the correlation coefficients. Spearman correlation test, *, P<0.05; **, P<0.01; and ***, P<0.001. *TPGS2*, tubulin polyglutamylase complex subunit 2; TMB, tumor mutational burden; MSI, microsatellite instability.

most cancers. The correlation analyses revealed strong connections between *TPGS2* and specific cancer types, such as HNSC, LIHC, PAAD, PRAD, SARC, THYM, and UM. Additionally, *TPGS2* was positively correlated with most of the immunomodulatory factors in COAD, HNSC, KIRP, LIHC, PAAD, PRAD, READ, and UVM, but negatively correlated with ESCA and SARC.

TMB and MSI analysis

The TMB and MSI are two well-known biomarkers that predict immune therapy responses across different cancers (41,42). Most scholars believe that patients with a high TMB and MSI have increased response rates to immunotherapy and display better outcomes to immunotherapy treatments. Therefore, we assessed the correlation with TMB and MSI to evaluate the efficacy of *TPGS2* in predicting ICIs therapy outcomes in pan-cancer. As *Figure 12* shows, *TPGS2* expression was positively correlated with the TMB in BRCA, BLCA, ACC, SKCM, STAD, and COAD, and *TPGS2* expression was negatively correlated with the TMB in ESCA, KIRC, THCA, and THYM (*Figure 12A*). Additionally, *TPGS2* expression was positively correlated with MSI in BRCA, COAD, and STAD, and *TPGS2* expression was negatively correlated with MSI in DLBC and PCPG (*Figure 12B*). Thus, our analyses indicate that *TPGS2* could have a potential role in predicting the effectiveness of ICIs in a number of cancers.

Discussion

Currently, many immune checkpoint molecules have been applied to pharmacotherapy, such as CTLA-4, PD-1, PD-L1, T cell immunoreceptors with Ig and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT), and lymphocyte activating 3 (43-47). CTLA-4 and PD-L1/PD-1 have received the greatest attention; thus, anti-PD-1/PD-L1 and anti-CTLA-4 techniques have been applied to the immunotherapy of a number of cancers (46). However, at present, the most serious challenges for such treatments are related to their inapparent efficacy and side effects (48). As a result, there is a pressing need to investigate novel immunological checkpoints and methods to estimate the effects of cancer immunotherapy (48,49). Our results showed that *TPGS2* is a promising biomarker of cancer, which provides a vital clue for further research on the potential role of *TPGS2* in prognosis and tumor immunity.

The analysis of *TPGS2* expression based on the GTEx and TCGA databases revealed that *TPGS2* was abnormally upregulated in 22 cancers and downregulated in five cancers (*Figure 1A*). Moreover, the expression of *TPGS2* was notably downregulated in TGCT tissue compared with normal testicular tissue. Data about RNA was used to cluster genes based on their expression in single-cell types. Based on the single-cell type expression cluster from HPA, we found that *TPGS2* was mainly expressed in spermatids.

Thus, we speculate that the specific expression in normal testicular tissue is connected with the lower expression of *TPGS2* in TGCT. However, it is not yet known why *TPGS2* is unevenly expressed across cancers.

Next, the IHC results from the HPA were consistent with our preliminary conclusions (*Figure 2*). According to the analysis of the association between *TPGS2* and various subtypes, *TPGS2* may be associated with molecular and immune subtypes across human cancers (*Figure 3*). This suggests that *TPGS2* can be used to differentiate among molecular and immune types of tumors. Since most genetic alteration proportions of *TPGS2* in cancers are less than 5%, there appears to be no significant correlation between *TPGS2* expression and genomic alterations (*Figure 4A*).

In addition, we evaluated the clinical prognosis of patients who were grouped according to *TPGS2* expression levels. There were differences among the various survival measures (i.e., OS, PFI, and DSS); however, the expression of *TPGS2* was still significantly associated with survival (*Figures 5*-7). According to the Kaplan-Meier and univariate Cox regression analyses, the upregulated expression of TPGS2 was associated with a poor prognosis in patients with SARC, LIHC, and LGG, while the high expression of TPGS2 was associated with a better OS prognosis in patients with OV and THYM. Thus, TPGS2 is likely to be an important biomarker for predicting the prognosis of cancer patients.

The single-cell analysis showed that *TPGS2* expression was associated with a number of functional states, including the cell cycle, metastasis, invasion, inflammation, DNA damage, and stemness, in various cancers (*Figure 8*). These results suggest that *TPGS2* is associated with multiple cancer functional states in many human cancers.

According to the GSEA, *TPGS2* was closely related to some immune response processes, such as Ig production, B cell-mediated immunity, the humoral immune response mediated by circulating Ig, the regulation of the humoral immune response, and the B cell receptor signaling pathway (*Figure 9*). Therefore, it is very likely that *TPGS2* is involved in the functions related to B cells.

Recently, the importance of B cells has been found in tumor immunity. Since 2020, three research teams from the United States, France, and Sweden have analyzed a large sample of clinical cohort studies, and reported a positive correlation between B-cell infiltration and the formation of TLSs and the response to immunotherapy in a variety of cancer types (50-52). B cells also express a number of checkpoint molecules, including PD-1, PD-L1/2, and CTLA-4B (15). Patients who responded to ICIs therapy were reported that more memory B cells, C-X-C motif chemokine receptor 3+ cells, and germinal center-like B cells were found in their TMEs than patients who did not response to ICIs therapy (52).

In addition, studies (21,53) have shown that the Igs in many antibody-secreting B cells, which mainly secrete IgG and IgA, are tumor-dependent. These Igs are correlated with the tumorigenesis site, and higher proportions of IgG have been observed in thyroid, testicular, and skin tumors, while higher proportions of IgA been observed in kidney, ovarian, pancreatic, and colorectal cancers. This is consistent with our GSEA finding that a higher number of Ig-related biological states were enriched.

Another important finding of our research is that *TPGS2* plays a pivotal role in cancer immunity. In recent years, many studies have shown that the immune status of cancers is closely correlated to the cell composition of and infiltration concentration around the tumor (54-56). *TPGS2* was found to be positively correlated with the infiltrating levels of multiple immune cells, such as macrophages, $CD4^+$ T cells, $CD8^+$ T cells, B cells, and neutrophils (*Figure 10*), which suggests that *TPGS2* is likely to influence development and prognosis of various cancers by affecting the TME.

Pro-inflammatory mediators, including chemokines, cytokines, and prostaglandins, have been found in the TME, which affects tumor initiation, progression, and metastasis (57-59). Our analyses of *TPGS2* expression and pan-cancer immunomodulatory factors suggested that *TPGS2* is co-expressed with genes that encode the immunoinhibitor, immunostimulator, MHC, chemokine, and chemokine receptor proteins, especially in THYM and HNSC (*Figure 11*). These results suggest that *TPGS2* is likely to be involved in the progression and prognosis of cancers by interacting with the TME.

Further, the TMB is a promising prognostic and predictive biomarker for immunotherapy in human cancers (60-63). Research has demonstrated that patients, suffering from melanoma (64,65) or urothelial carcinoma (66,67) with a high TMB achieve better clinical outcomes from ICIs. Similarly, MSI also plays a vital role as a predictive biomarker for tumor immunotherapy (68). The Food and Drug Administration has authorized MSI-high status or deficient mismatch repair as prognostic biomarkers for directing the therapeutic application of ICIs in certain malignancies (69). According to our analyses, the TMB in 10 types of cancers and MSI in five types of cancers were

significantly correlated with the expression of *TPGS2*. Thus, *TPGS2* is likely to act as a predictor of the efficacy of immunotherapy in many cancers.

Wang's study demonstrated that the *cir-TPGS2* (derived from *TPGS2*)–related axis promoted breast cancer cell motility by the TME (30). Another study demonstrated that *TPGS2* could be a potential gene in renal cell carcinoma (29). Together with our findings, such results suggest that *TPGS2* could serve as a potential biomarker in anti-tumor immunity treatments.

However, our research had a number of limitations. First, while we showed that *TPGS2* is a promising predictor of prognosis and immunotherapy in many cancers, the mechanism by which this occurs remains unknown, and we have no evidence of any direct interaction. Second, our data were mainly obtained from open databases, and no clinical cohort was used for verification, which inevitably led to various biases and decreased the credibility of the results. Third, *TPGS2* has rarely been studied in human tumors, and in-depth studies need to be conducted to verify its role in cancer prognosis prediction and immunotherapy. Fourth, our research revealed a promising direction for tumor research in *TPGS2*; however, this study was a descriptive study based on bioinformatics, and the mechanism related to both *TPGS2* and the development and therapy of specific tumors need to be further explored, and experimental verification *in vitro* and *in vivo* is required. In the future, we intend to conduct further experiments to examine the mechanism of *TPGS2* across human cancers.

Conclusions

In summary, we performed a comprehensive pan-cancer analysis that demonstrated that the aberrant expression of *TPGS2* was associated with the prognosis, immune cell infiltration, TME, some immune response processes, and various function states across human cancers. Thus, *TPGS2* could serve not only as a biomarker for predicting clinical outcomes, but also as a promising biomarker for evaluating and developing new approaches to immunotherapy in many types of cancers, especially COAD and STAD.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-113/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-113/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-113/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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