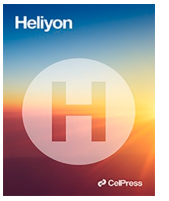
Heliyon 10 (2024) e35265

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Pan-cancer analysis reveals *GGPS1* plays an important role in tumorigenesis in multiple tumor types

Lisha Wei

School of Marine and Biological Engineering, Yancheng Teachers University, Yancheng, Jiangsu, China

ARTICLE INFO

Keywords:
Geranylgeranyl diphosphate synthase 1
Pan-cancer analysis
Tumorigenesis

The deletion of geranylgeranyl diphosphate synthase 1 (*GGPS1*) has been reported to inhibit the proliferation of multiple cells. Although emerging evidence has demonstrated a correlation between *GGPS1* and cancer, no pan-cancer analysis has been conducted to date. This study explored the potential tumorigenesis of *GGPS1* using data from the cancer genome atlas human clinical database. *GGPS1* expression was considerably upregulated at both the RNA and protein levels in several cancer types, especially in breast carcinoma (BRCA), (liver) hepatocellular carcinoma (LIHC/HCC) and lung adenocarcinoma (LUAD). Amplification is the most common form of genetic alteration observed in invasive BRCA, ovarian epithelial tumor and HCC. Additionally, elevated *GGPS1* expression was markedly related to poor patient prognosis and overall survival in several cancer types including LIHC. *GGPS1* expression was also linked to cancer-associated fibroblasts (CAFs) infiltration in several cancer types, such as BRCA and LUAD. Moreover, GGPPS-interacting proteins and *GGPS1*-correlated genes in cancers were functionally enriched in terpenoid backbone biosynthesis, steroid biosynthesis, and metabolic pathways. These results indicate that *GGPS1* may play a role in promoting the tumorigenesis and tumor development, particularly in BRCA and LUAD, and may play a role in steroid biosynthesis and metabolic pathways.

1. Background

Tumors are multifactorial diseases associated with high mortality rates. Understanding the mechanisms of tumorigenesis and tumor development is essential for identifying potential targets for tumor prevention and treatment. Online public oncology databases, such as the cancer genome atlas (TCGA), contain a wealth of information suitable for pan-cancer analysis of the association between genes and tumors [1–3].

Geranylgeranyl diphosphate synthase (GGPPS) is a key enzyme in the mevalonate (MVA) pathway and is responsible for the condensation of 15-carbon farnesyl pyrophosphate into 20-carbon geranylgeranyl pyrophosphate (GGPP) [4]. GGPP belongs to the isoprene hydrophobic groups that can covalently bind to conserved cysteine residues (such as CAAX and CCXX) at the C-terminus of proteins through transferase catalysis. This modification increases the lipophilicity of the substrate, enabling the protein to interact and bind to the membrane of other proteins [5]. However, it generally does not affect the stability and activity of the proteins [6].

We previously found that *Ggps1* knockout inhibits the proliferation of young vascular smooth muscle cells and causes apoptosis in mice [7]. Additionally, other studies have found that GGPPS/*GGPS1* expression is involved in the occurrence of hepatocellular carcinoma (HCC) [8] and tumor metastasis of in lung adenocarcinoma (LUAD) [9]. These findings suggested that GGPPS may be involved in cancer progression and is a potential target of cancer treatment.

E-mail address: weils@yctu.edu.cn.

https://doi.org/10.1016/j.heliyon.2024.e35265
Received 5 April 2024; Received in revised form 24 July 2024; Accepted 25 July 2024
Available online 26 July 2024

However, more evidences is required to determine whether *GGPS1* is worth further studying for its role in tumors. Therefore, we conducted a pan-cancer analysis of *GGPS1* using clinical data from sources such as TCGA database. We evaluated RNA expression, protein expression, gene alteration, and immune infiltration. We enriched pathways from *GGPS1*-correlated genes in cancers and GGPPS-interacting proteins from experiments to investigate the correlation and potential molecular mechanism of *GGPS1* in the pathogenesis and clinical prognosis of various cancers.

2. Materials and methods

2.1. Gene expression analysis

The "Gene_DE" module in tumor immune estimation resource, version 2 (TIMER2) [10–12] [cited 2022 Jun 29] was used to evaluate the RNA expression of *GGPS1* in tumor and adjacent normal tissues among diverse tumor subtypes from the TCGA database. The University of Alabama at Birmingham cancer data analysis portal (UALCAN) [cited 2022 Jun 29] provided a protein expression level analysis option using data from the clinical proteomic tumor analysis consortium (CPTAC) [13,14]. Protein expression of human GGPPS (NP_001032354) in diverse tumor and normal tissues was observed. Immunohistochemistry staining images of *GGPS1* in breast carcinoma (BRCA), LUAD, liver cancer, colon adenocarcinoma (COAD), prostate cancer, and normal tissues were obtained from the human protein atlas (HPA) database [cited 2024 Jun 29]. The default conditions of the respective websites were used to generate the results.

2.2. Survival prognosis analysis

The "Survival Map" module under "Survival Analysis" in gene expression profiling interactive analysis 2 (GEPIA2) [15], was used to analyze the correlation of *GGPS1* expression and patient prognosis, including overall survival (OS) and disease-free survival (DFS) across all TCGA tumors. The relevant thresholds were set as follows: significance level at "0.05", "median" for group cutoff, and "50 %" for both cutoff-high and cutoff-low. Cancers with a significant correlation ($p < 0.05$) in OS and DFS were marked with a black dark frame. Kaplan-Meier curves were plotted for cancers with these significant correlations. All other conditions used to output the results were set to the default parameters of the GEPIA2 sites.

2.3. Genetic alteration analysis

In cBioPortal website [16,17] [cited 2022 Jun 29], the "TCGA Pan Cancer Atlas Studies" under "Quick select" section was used to obtain alteration frequency of *GGPS1*. The results of the mutation, amplification, deep deletion, and multiple alterations were observed in the "Cancer Types Summary" module across all TCGA tumors. In "Mutations" module, the number of *GGPS1* alterations was observed along with the exon pattern. Additionally, "Survival" module under "Comparison/Survival" section revealed the survivorship curves for TCGA cancer cases with or without *GGPS1* genetic alteration in OS, progression free survival (PFS), disease-specific survival (DSS), and DFS. All other conditions used to output the results were set to the default conditions of the cBioPortal sites.

2.4. Immune infiltration analysis

The "Immune" module under "Gene" section of the TIMER2 website was used to analyze the correlation between *GGPS1* expression and immune infiltration. Cancer-associated fibroblasts (CAFs) were selected to assess infiltration levels and obtain a related heatmap using EPIC, MCPCOUNTER, XCELL, and TIDE for immune infiltration estimations. The *GGPS1* expression and infiltration levels in esophageal carcinoma (ESCA), head and neck squamous cell carcinoma (HNSC), and HNSC-HPV (human papillomavirus)- were visualized as scatter plots. The *p*-values for purity and infiltration levels were obtained using the purity-adjusted Spearman's rank correlation test.

2.5. GGPS1-related gene enrichment analysis

To identify GGPPS-interacting proteins, we searched for "GGPPS" as the protein name and "*Homo sapiens*" as the organism on the search tool for the retrieval of interacting genes/proteins (STRING) website [18] [cited 2022 Jun 29]. The following parameters were configured under "Settings" mudule: "full STRING network" for network type; "evidence" for meaning of network edges; "Experiments" for active interaction sources; "low confidence (0.150)" for minimum required interaction score; "no more than 50 interactors" for max number of interactors to show; and "interactive svg" for network display options. We obtained a networkof GGPPS and the top 50 GGPPS-interacting proteins.

The "Similar Gene Detection" module under "Similar Genes" section in GEPIA2 website provided *GGPS1*-correlated genes with similar expression patterns across cancer types and tissues. Moreover, the "Gene_Corr" module of TIMER2 was used to create a heatmap depicting the relationship between *GGPS1* and several genes, such as component of oligomeric golgi complex 2 (COG2), SCY1-like pseudokinase 3 (SCYL3), signal recognition particle 9 (SRP9), translin associated factor X (TSNAX), and zinc finger and BTB domain containing 41 (ZBTB41) in various cancers.

We used Venny2.1 (https://bioinfogp.cnb.csic.es/tools/venny/index.html) to generate an interactive Venn diagram composing of GGPPS-interacting proteins and *GGPS1*-correlated genes in various cancers from the TCGA database. We entered the combined

proteins into the OmicShare website (https://www.omicshare.com/tools/Home/Task/index) for Kyoto encyclopedia of genes and genomes (KEGG) pathway enrichment. The first 20 signaling pathways were depicted.

3. Results

3.1. Gene expression analysis data

We compared the RNA expression differences of *GGPS1* between cancer tissues and adjacent normal tissues in various cancers using the TCGA data in the TIMER2 website. The results revealed that the RNA expression levels of *GGPS1* in the tumor tissues of BRCA, cholangiocarcinoma, COAD, ESCA, glioblastoma multiforme, HNSC, kidney chromophobe, kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP), LIHC, LUAD, lung squamous cell carcinoma (LUSC), skin cutaneous melanoma (SKCM), stomach adenocarcinoma (STAD), and thyroid carcinoma were significantly ($p < 0.001$) higher than that of corresponding normal tissues (Fig. 1A).

We used the UALCAN website to further evaluate the total GGPPS protein expression in cancer samples compared to normal tissues based on the CPTAC database. The results indicated significant upregulation of GGPPS protein expression in BRCA, KIRC, LUAD, pancreatic adenocarcinoma, HNSC, and HCC ($p < 0.0001$) compared to that in normal tissues (Fig. 1B). These results were consistent with the RNA expression results. However, GGPPS protein expression decreased in colon cancer ($p < 0.05$), which was inconsistent with the RNA results (Fig. 1B). The RNA expression compensates for the increase when protein expression decreases. Therefore, we speculated that this inconsistency may be due to negative feedback regulation. We further evaluated GGPPS protein expression in BRCA, LUAD, liver cancer, COAD, prostate cancer, and normal tissues using immunohistochemical results from the HPA database. GGPPS protein expression was detected in normal prostate tissue but not liver, breast, colon, and lung tissues. The results indicated that the GGPPS protein expression levels in the BRCA, LUAD, liver cancer, COAD and prostate cancer were increased compared to adjacent normal tissue (Fig. 1C). This suggests that high *GGPS1* expression may be involved in the tumorigenesis of various cancers, especially BRCA, LUAD and liver cancer.

3.2. Survival analysis data

To determine whether *GGPS1* expression level was related to patient prognosis, cancer cases from the TCGA database were divided into high- and low-expression groups based on a 50 % cutoff of *GGPS1* expression. As depicted in Fig. 2A and B, high *GGPS1* expression was significantly linked to poor OS in several cancers: adrenocortical carcinoma (ACC)(hazard ratio [HR] > 1; $p = 0.0052$); LIHC (HR > 1; $p = 0.0021$); and uveal melanoma(HR > 1; $p = 0.026$). Similarly, it was associated with poor DFS in ACC (HR > 1; $p = 0.0002$); bladder urothelial carcinoma (HR > 1; $p = 0.03$), cervical squamous cell carcinoma (HR > 1; $p = 0.0064$); and KIRP (HR > 1; $p = 0.026$). Additionally, low *GGPS1* expression was associated with the poor prognosis of OS (HR < 1; $p = 0.0033$) and DFS (HR < 1; $p = 0.0041$) for KIRC (Fig. 2A and B). These findings suggest a significant association between *GGPS1* expression and cancer prognosis, with high *GGPS1* expression predicting poor outcomes across various cancer types.

3.3. Genetic alteration analysis data

To determine how *GGPS1* changes at the genetic level in diverse types of cancer, we used the cBioPortal website to evaluate the genetic alteration status of *GGPS1* based on data from the TCGA database. The results revealed that amplification was the most common alteration observed in most cancers. The frequency of amplification was up to 10 % in BRCA (Fig. 3A), indicating an increased number of *GGPS1* DNA copies in the genome. Additionally, this likely explains the upregulation of *GGPS1* protein and RNA expression in BRCA.

Mutations were as the primary alteration type in endometrial carcinoma (up to 3 % alteration frequency), mature B-cell neoplasms, and COAD (Fig. 3A). We further evaluated the mutation types, mutation sites and case numbers based on 10 953 patients/10 967 samples from 32 studies. We identified only 47 variants (Fig. 3B). These results suggest that mutations are a relatively uncommon type of genetic alteration in cancer. Additionally, we explored the correlation between *GGPS1* genetic alterations and clinical survival prognosis based on TCGA database. However, no statistically significant differences between *GGPS1* genetic alterations and the survival across various cancers were observed (Fig. 3C).

3.4. Immune infiltration analysis data

Immune invasion into the tumor microenvironment (TME) is an critical feature associated with tumor development. CAFs are involved in regulating the function of various tumor infiltrating immune cells [19]. TIMER2.0 was used to generate a heatmap table of the Spearman's correlations between the *GGPS1* expression and the abundance of CAFs in the 59-cell hierarchy across all cancer types. The EPIC, MCPCOUNTER, XCELL, and TIDE algorithms were used to assess immune infiltration. The cor less than 0.2 indicated that no correlation between tumor purity and *GGPS1* expression. In other words, the tumor purity didn't influence the correlation between *GGPS1* expression and immune infiltration of CAFs. The results showed that *GGPS1* expression was slightly positively correlated with CAF infiltration in BRCA, ESCA, HNSC, HNSC-HPV-, LUSC, and STAD (Cor >0.2; $p < 0.05$) (Fig. 4A and B).

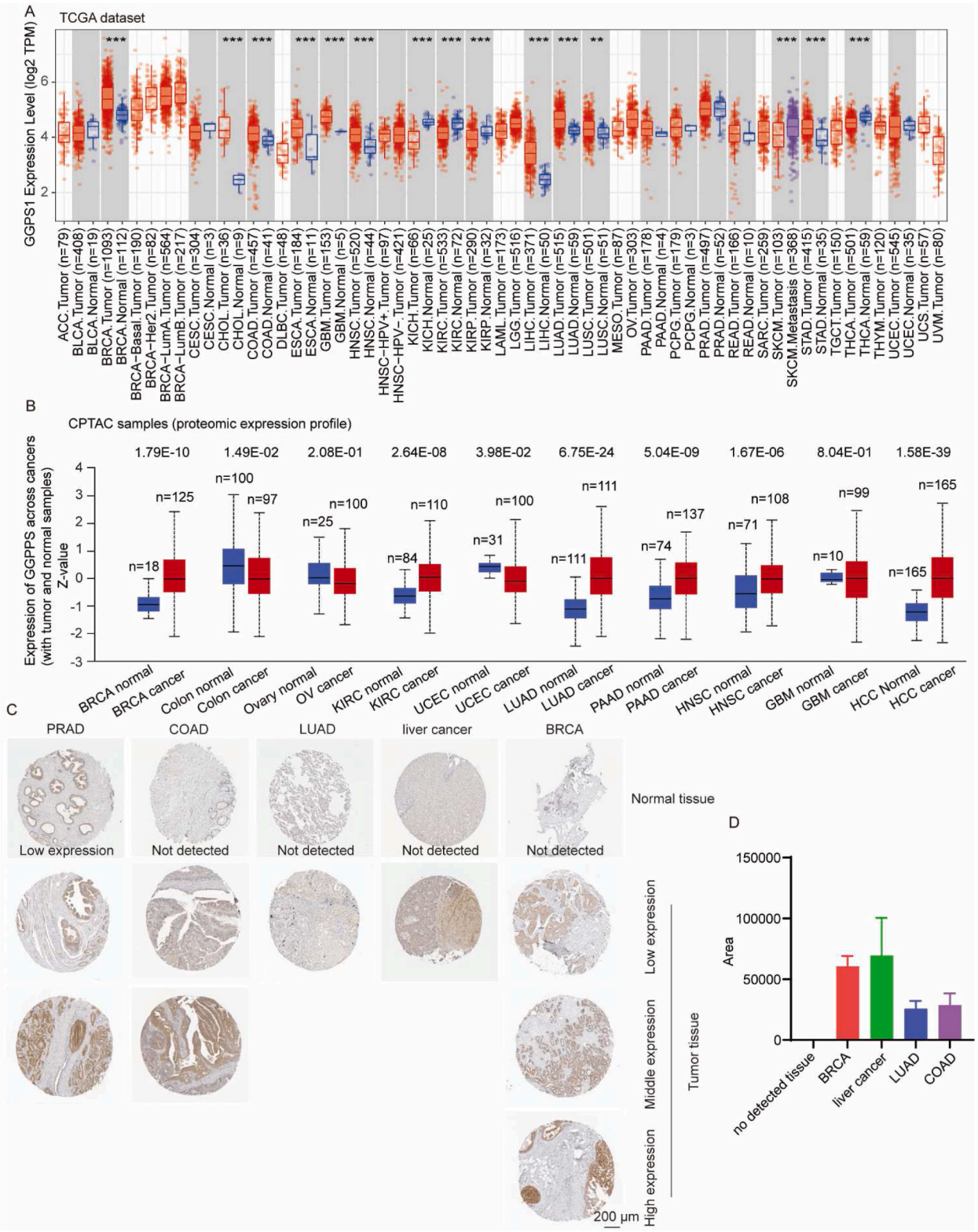


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Fig. 1. Expression level of *GGPS1* gene in diverse tumors **A)** Expression status of the geranylgeranyl diphosphate synthase 1 *(GGPS1)* gene in diverse cancer types or specific subtypes analyzed usingTIMER2. The statistical significance computed using the Wilcoxon test is annotated by the number of stars. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$. **B)** Analysis of the expression level of GGPPS total protein between normal and cancer tissues based on the CPTAC dataset. The p values were calculated using one-sided Fisher's exact test. **C)** Immunohistochemistry staining image of *GGPS1* in LUAD, BRCA, COAD, liver cancer, and prostate cancerwere obtained from the HPA database. Scale bar: 200 μm. **D)** Quantitative histogram of **C**. n = 5~11.

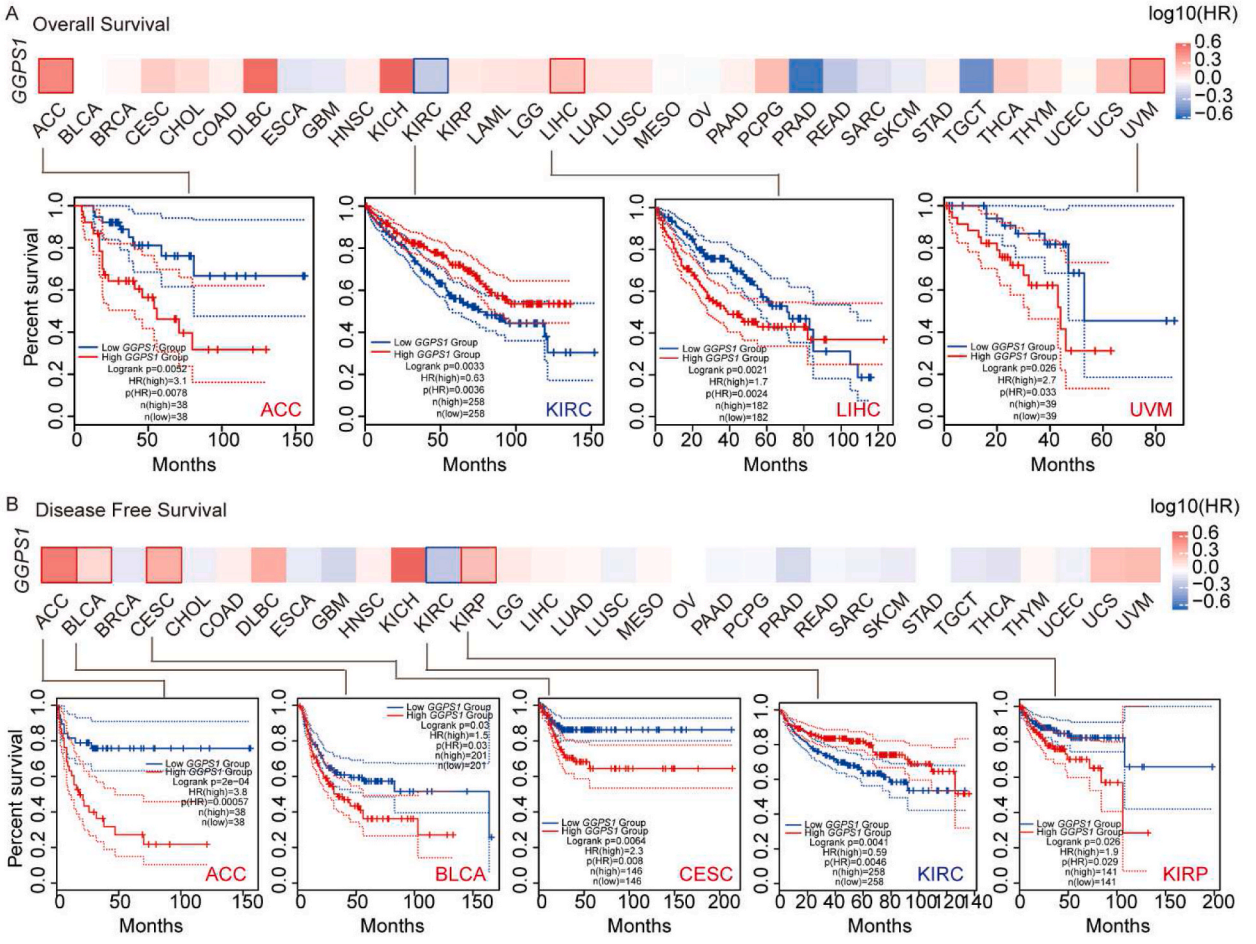

Fig. 2. Correlation between *GGPS1* gene expression and survival prognosis of cancers in TCGA **A)** Overall survival (OS) and **B)** disease-free survival (DFS) analyses of diverse tumors in the cancer genome atlas (TCGA) based on *GGPS1* expression using GEPIA2 tool. Red label indicates positively correlation of *GGPS1* expression to hazard ratio (HR). Blue label indicates negatively correlation. The cancers with significant correlation ($p < 0.05$) between *GGPS1* expression and patient prognosis of OS and DFS in survival map are marked with black dark frame. Kaplan-Meier curves depict survival outcomes of these cancers. p values estimated using Mantel–Cox test. HR calculated based on Cox proportional hazards Model. HR > 1 represents high *GGPS1* expression with reduced survival rate. HR < 1 represents high *GGPS1* expression with increased survival rate.

3.5. Enrichment analysis of GGPS1-related functional pathways

To elucidate the mechanism of action of *GGPS1* in cancer development, we utilized the GGPPS-interacting proteins obtained from experiments and *GGPS1*-correlated genes in cancers to conduct functional enrichment analysis. Fifty GGPPS-interacting proteins were screened using STRING (Fig. 5A). The top 100 proteins sharing similarly expression patterns with *GGPS1* in cancers were screened using the GEPIA2 tool (Fig. 5B). One common gene, the protein geranylgeranyltransferase type I beta subunit (*PGGT1B*), was found among the GGPPS-interacting proteins and *GGPS1*-correlated genes (Fig. 5C). *PGGT1B,* which encodes encodes a prenylation-catalyzing enzyme (geranylgeranyltransferase type I; GGTase I), is responsible for transferring GGPP to substrate proteins and is involved in inflammation and metabolic processes [20,21]. We used the 149 genes to conduct functional enrichment analysis on the OmicShare website. The results highlighted that the top Kyoto encyclopedia of genes and genomes (KEGG) pathways were related to metabolic pathways, ranking second only to terpenoid backbone and steroid biosynthesis.

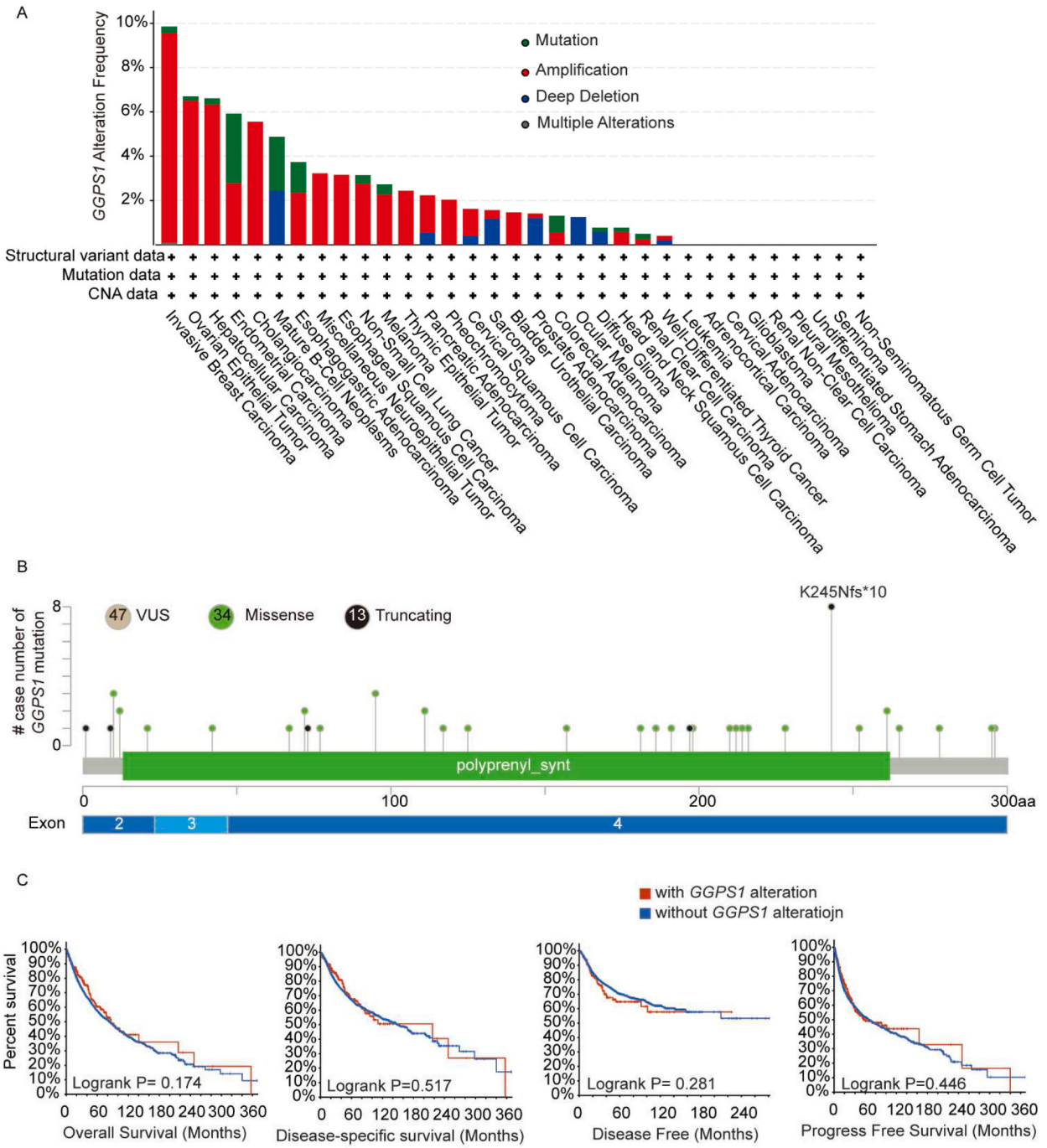

Fig. 3. Mutation features of *GGPS1* in different tumors based on TCGA **A)** The alteration frequency with mutation types and **B)** mutation sites of *GGPS1* gene in diverse cancers analyzed based on TCGA in the cBioPortal website. **C)** The correlation between *GGPS1* genetic alteration and OS, DSS, DFS, and PFS analyzed in cBioPortal website. CNA: copy number alterations. VUS: variants of uncertain significance. *p* values were estimated using Mantel–Cox test.

4. Discussion

Recent reports have highlighted that the MVA pathway is involved in several aspects of tumorigenesis including the control of cell proliferation, survival, invasion and metastasis [22–24]. Our findings also demonstrated that the RNA and protein expression of *GGPS1* was significantly upregulated in most tumors, including BRCA, LUAD, PAAD and GBM. Amplification was also the primary *GGPS1* genetic alteration pattern in BRCA and HCC samples. Additionally, high *GGPS1* expression was significantly correlated with the poor

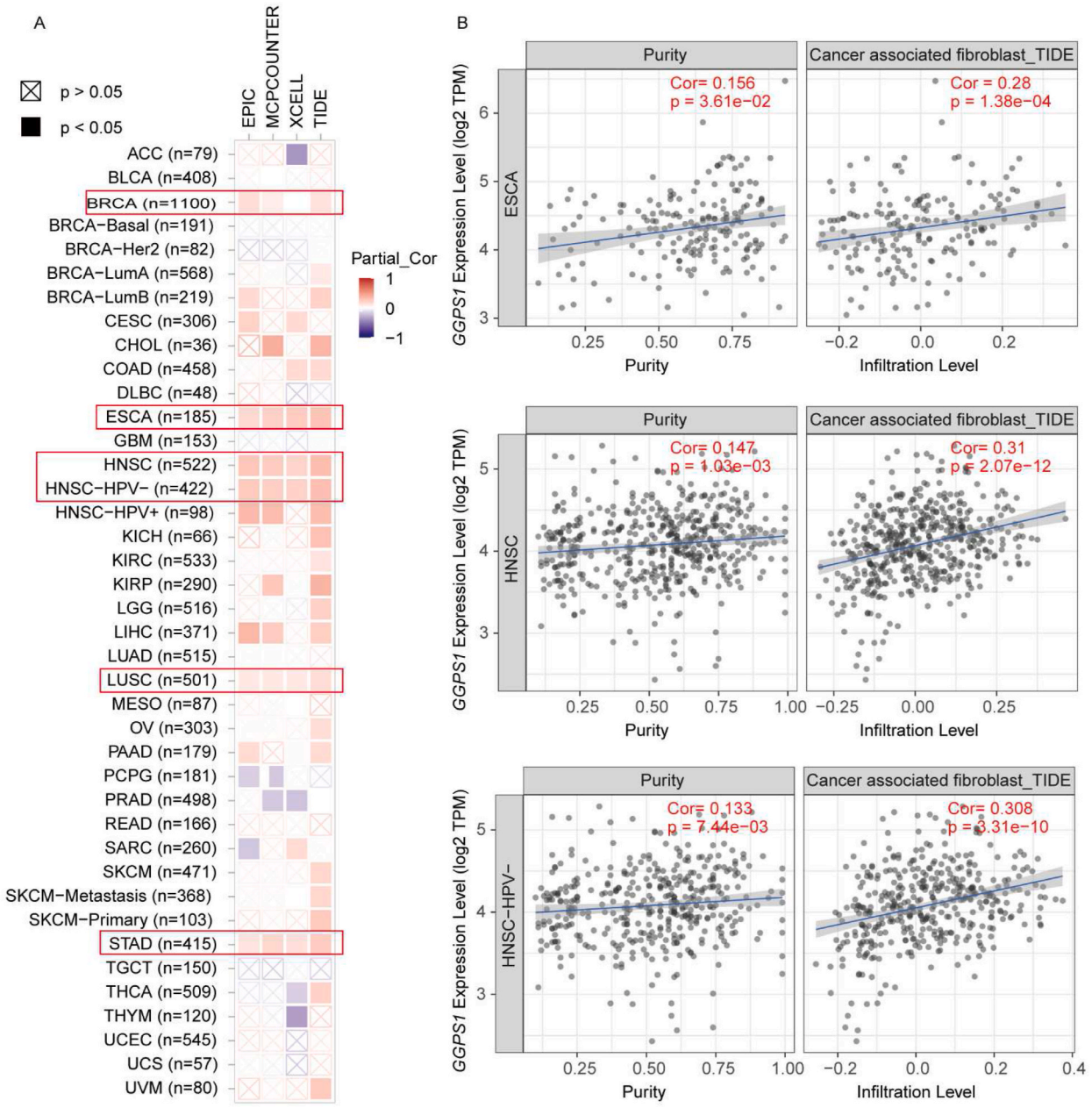

Fig. 4. Correlation analysis between *GGPS1* expression and immune infiltration of CAFs **A)** Correlation analysis between *GGPS1* expression and immune infiltration of CAFs using EPIC, MCPCOUNTER, XCELL, and TIDE for immune infiltration estimations across all types of cancer based on TCGA database. Red label indicates positive correlation ($p < 0.05$, Cor >0). Blue label indicates negative correlation ($p < 0.05$, Cor >0). Gray label indicates not significant correlation ($p > 0.05$). **B)** Correlation of *GGPS1* expression with tumor purity (the proportion of cancer cells in a sample) (left) and with the infiltration level of CAFs in ESCA, HNSC, HNSC-HPV estimated by TIMER (right) were shown as scatter plot. Cor: The Spearman's rank correlation coefficients.

OS and DFS outcomes in cancers, such as HCC. The *GGPS1* expression was significantly and positively correlated with CAFs in several tumors including BRCA. However, GGPPS protein expression was decreased in a few cancers, such as colon cancer and UCEC. The inconsistent of GGPPS expression revealed the complexity of tumor formation. The specific reasons need to be studied in the future.

GGPPS is a key enzyme in the MVA pathway, suggesting that the GGPPS expression/MVA pathway is highly associated with cancers progression and patient prognosis in several tumors types, such as BRCA, HCC and LUAD. Statins, which are mevalonate synthesis inhibitors, are potential drugs for cancer treatment [25]. However, the relationship between *GGPS1* expression and cancer requires further investigation. GGPPS deletion caused cell death through eicosanoids metabolism disorders and inflammation accumulation [7]. Inflammation within the TME is regarded as a cancer marker and has been studied as a key target for cancer treatment in recent

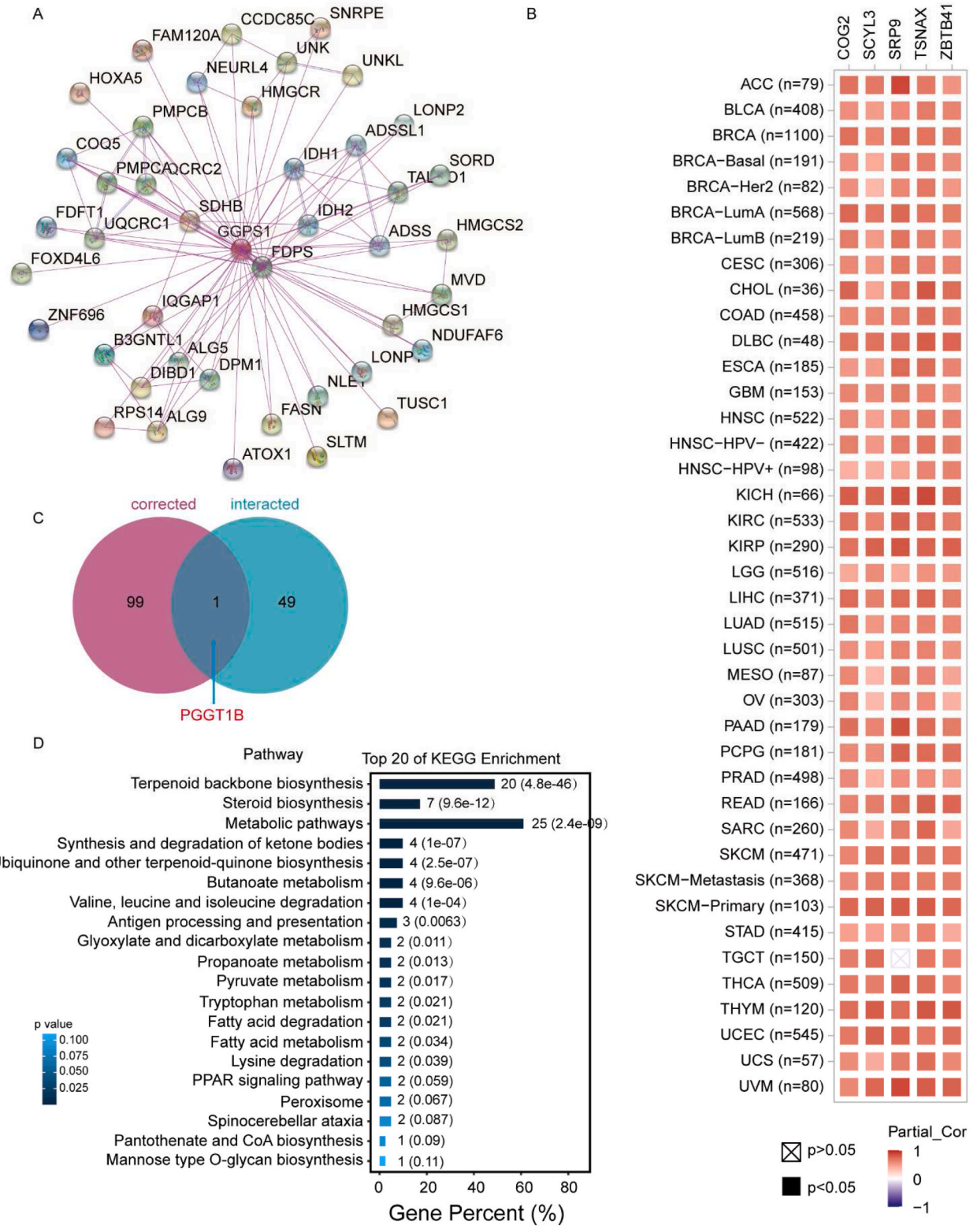

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Fig. 5. *GGPS1*-related gene enrichment analysis **A)** Co-expression network of 50 genes interacting with GGPPS obtained from the STRING tool. **B)** Top 100 *GGPS1*- correlated genes in TCGA projects obtained using GEPIA2. The top genes whose expression are associated with *GGPS1,* including COG2, SCYL3, SRP9, TSNAX, and ZBTB41 are displayed as heatmap. The Spearman's rank correlation coefficients were calculated. **C)** Correlation of *GGPS1*-interacting proteins and correlated genes are presented as a Venn-diagram. **D)** Top 20 signaling KEGG pathways analyzed using OmicShare based on the GGPPS-interacting proteins and *GGPS1*-correlated genes.

years. We applied multiple algorithms (EPIC, XCELL, TIDE and MCPCOUNTER) and observed a statistically significant positive correlation between *GGPS1* expression and CAFs in BRCA, ESCA, HNSC, HNSC-HPV-, LUSC, and STAD tumors.

Cancer is associated with substantial changes in the cellular metabolism. Recent studies reported that arachidonic acid (AA) was enhanced in PIK3CA-induced BRCA. PIK3CA-induced tumorigenesis can be rescued by inhibiting cPLA2 synergy and limiting fatty acid intake [26]. AA, synthesized from dietary polyunsaturated fatty acids (PUFA), are the key substrates for eicosanoids metabolism. Bioactive metabolites exert both proinflammatory and anti-inflammatory effects [27]. Multiple studies have reported that eicosanoids metabolism is associated with tumor growth, progression and metastasis [28,29]. Despite the multiplex network of eicosanoid metabolites, there are no well-defined targets for eicosanoids metabolism in cancer treatment. Our previous findings suggested that GGPPS and/or CYB5R3 [7], which are eicosanoid metabolism upregulators, are potentially effective targets for cancer treatment concerning inflammation. Our analysis identified GGTase I as a major downstream target of GGPPS that not only binds to GGPPS but also correlates with *GGPS1* in cancers. GGTase I is responsible for the protein prenylation during the post-translational modification of several target proteins containing CAAX at the C-terminus, especially the geranylgeranylation of small G proteins, such as Rac1(20). This may be the key mechanism through which *GGPS1* and *PGGT1B* are involved in cancer development.

We found that the top KEGG pathways enriched from *GGPS1* interacting proteins and correlated genes were also related to metabolic pathways. These results suggest that eicosanoid metabolism may be an emerging perspective on the effect of GGPPS on cancers. In summary, we revealed a significantly correlation of *GGPS1* and cancer development, clinical prognosis, and immune infiltration across diverse cancer types using a pan-cancer analysis based on a lot of public clinical data. We hypothesize that metabolism, especially eicosanoids metabolism, plays a key role in the involvement of GGPPS in cancer. However, the underlying mechanism requires further studies.

Abbreviations: *GGPS1*: geranylgeranyl diphosphate synthase 1; TCGA: The Cancer Genome Atlas; MVA pathway: mevalonate pathway; FPP: farnesyl pyrophosphate; GGPP: geranylgeranyl pyrophosphate; CPTAC: Clinical Proteomic Tumor Analysis Consortium; HPA: Human Protein Atlas; OS: overall survival; DFS: disease-free survival; DSS: disease-specific survival; PFS: progress-free survival; ACC: adrenocortical carcinoma; BLCA: bladder urothelial carcinoma; BRCA: breast invasive carcinoma; CESC: cervical squamous cell carcinoma; CHOL: cholangio carcinoma; COAD: colon adenocarcinoma; DLBC: diffuse large B cell lymphoma; ESCA: esophageal carcinoma; GBM: glioblastoma multiforme; HNSC: head and neck squamous cell carcinoma; KICH: kidney chromophobe; KIRC: kidney renal clear cell carcinoma; KIRP: kidney renal papillary cell carcinoma; LAML: acute myeloid leukemia; LGG: low-grade glioma; LIHC (HCC): liver hepatocellular carcinoma (hepatocellular carcinoma); LUAD: lung adenocarcinoma; LUSC: lung squamous cell carcinoma; MESO: malignant mesothelioma; OV: ovarian cancer; PAAD: pancreatic adenocarcinoma; PCPG: pheochromocytoma and paraganglioma; PRAD: prostate adenocarcinoma; READ: rectal cancer; SARC: sarcoma; SKCM: skin cutaneous melanoma; STAD: stomach adenocarcinoma; TGCT: testicular germ cell tumors; THCA: thyroid carcinoma; THYM: thymoma; UCEC: uterine corpus endometrial cancer; UCS: uterine carcinosarcoma; UVM: uveal melanoma; EC: endometrial carcinoma; EOC: epithelial ovarian cancer; HNSC-HPV (human papillomavirus)-; COG2: component of oligomeric golgi complex 2; SCYL3: SCY1-like pseudokinase 3; SRP9: signal recognition particle 9; TSNAX: translin associated factor X; ZBTB41: Zinc finger and BTB domain containing 41; KEGG: Kyoto encyclopedia of genes and genomes; TME: tumor microenvironment; CAFs: tumor-associated fibroblasts; PGGT1B: protein geranylgeranyl transferase type I beta subunit; GGTase I: geranylgeranyltransferase type I; AA: arachidonic acid; PUFA: polyunsaturated fatty acids.

Funding

This study was supported by National Natural Science Foundation of China Grants 82200976 (to Lisha Wei).

Data sharing statement

Publicly available datasets were analyzed in this study. These data can be found as follows. The gene expression analysis was available from TIMER2 (http://timer.cistrome.org/), UALCAN (http://ualcan.path.uab.edu/analysis-prot.html) and GEPIA2 (http://gepia2.cancer-pku.cn/#index). Survival prognosis analysis was available from GEPIA2 (http://gepia2.cancer-pku.cn/#index). Genetic alteration analysis was available from cBioPortal (https://www.cbioportal.org/). Immune infiltration analysis was available from TIMER2 (http://timer.cistrome.org/). GGPS1-related gene enrichment analysis was available from STRING (https://string-db.org/), GEPIA2 (http://gepia2.cancer-pku.cn/#index), Venny2.1 (https://bioinfogp.cnb.csic.es/tools/venny/index.html) and OmicShare website (https://www.omicshare.com/tools/Home/Task/index).

Ethics statement

No experiments were performed in this study. Therefore, ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not

required for this study in accordance with the national legislation and the institutional requirements.

CRediT authorship contribution statement

Lisha Wei: Writing – review & editing, Writing – original draft, Visualization, Software, Resources, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

All authors disclosed no relevant relationships.

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