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ORIGINAL RESEARCH

Pan-Cancer Analysis of the Prognostic and Immunotherapeutic Value of PDGFB

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Introduction: Cancer is a widespread epidemic that affects millions of individuals across the world. Identifying novel cancer targets is crucial to developing more effective cancer treatments. Platelet-derived growth factor-B (PDGFB) plays a critical role in various tumor processes, including angiogenesis and lymphatic metastasis. However, there is a lack of research on the role of PDGFB in these processes.

Methods: To address this issue, we conducted a comprehensive analysis utilizing multiple online databases to investigate the expression, prognostic, tumor stemness, and immunological effect of PDGFB. In addition, clinical samples were validated using immunohistochemistry.

Results: Our findings revealed that PDGFB was highly expressed in a diverse range of cancer types, and its expression and genetic modifications were significantly associated with clinical outcomes in certain tumors. In general, high expression of PDGFB in tumors is associated with poor prognosis. Surprisingly, PDGFB was found to be highly expressed in renal clear cell carcinoma but was associated with good prognosis. In contrast, PDGFB was low expressed in lung carcinoma, but its expression was found to improve patient survival. These findings demonstrate the complex role of PDGFB in different cancer types. The study also demonstrated that PDGFB was linked to RNA and DNA stemness in 15 and 36 tumor types, respectively, and had a positive association with tumor lymphocyte infiltration. Notably, PDGFB was found to be associated with immune modulators. PDGFB, which is involved in various immune responses, influences the malignant characteristics of various cancer types and controls immune cell infiltration. We confirmed that PDGFB positively correlated with CD8 and PDL1 expression in lower grade glioma.

Conclusion: This study concludes that PDGFB may serve as a potential prognostic marker and a potential targetable pathway in cancer immunotherapy. Overall, the study sheds new light on the role of PDGFB in cancer and highlights its potential clinical significance.

Keywords: PDGFB, pan-cancer, prognosis, immune cell infiltration, biomarker

Introduction

Cancer is a pervasive global public health issue, bringing suffering and hardship to numerous individuals and families.[1] The escalating rate of newly diagnosed cases and the inadequacy of effective therapies magnify this challenge. While traditional cancer treatments such as chemotherapy, surgery, radiotherapy, immunotherapy, and targeted therapy have shown varied outcomes, they are hindered by drug tolerance and adverse reactions.[1] Therefore, there is an essential need to discover and develop additional treatments and biomarkers to aid in the diagnosis and treatment of cancer and enhance the quality of life for those affected by it.

Oncogenesis, the process through which normal cells transform into cancer cells, is driven by genetic mutations that disrupt the normal cell cycle, leading to uncontrolled cell growth and division. These mutations can result from various factors, including environmental toxins, radiation exposure, and genetic predisposition. Understanding oncogenesis is crucial for comprehending the development and progression of cancer and for devising new treatments and therapies to combat this disease effectively.[2,3] The Platelet-Derived Growth Factor (PDGF) family comprises five distinct disulphide-linked dimers, encoded by four separate genes, which exert their biological effects through binding to two receptor

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tyrosine kinases, PDGF receptors alpha and beta. With roles in cell proliferation, differentiation, migration, tissue repair, and regeneration, the PDGF family's intricate interplay underscores the complexity of PDGF signaling, which is tightly regulated in a spatiotemporal manner. Deciphering the mechanisms governing PDGF signaling holds promise for developing novel therapeutic strategies for various diseases, including cancer, fibrosis, and cardiovascular disorders. The PDGF genes are located on different chromosomes in humans, with PDGFA on chromosome 7, PDGFB on chromosome 22, PDGFC on chromosome 4, and PDGFD on chromosome 11; the corresponding locations in mouse chromosomes are 5, 15, 3 and 9, respectively.[4,5] These genes control various biological events related to tumorigenicity, invasion, distant metastasis, promoting angiogenesis, cell proliferation, and migration.[6] PDGFB has been implicated in numerous benign and malignant tumors, such as meningothelioma, glioblastoma, breast carcinoma, pancreatic neoplasms, prostatic neoplasms, esophageal squamous cell carcinoma, ovarian neoplasms, and liver neoplasms.[7–14] Tumor tissue frequently harbors elevated levels of inflammatory cells, including tumor-associated macrophages (TAMs), which facilitate tumor cell invasion, intravascular infiltration, and metastasis. PDGF-BB has been shown to induce high expression levels of IL-33 in pericytes and stromal cells, thereby recruiting substantial numbers of TAMs in response to the IL-33–ST2 receptor interaction. This recruitment subsequently enhances the infiltration of tumor cells into the circulation.[15] Interactions between tumors and immune cells are considered critical factors influencing tumor escape, progression, and therapeutic response. The adaptive immune microenvironment pre-existing against tumors encompasses various components, including antigen processing mechanisms (eg, human leukocyte antigen, HLA), immune checkpoints and modulators, effector cells such as CD8+ T lymphocytes, and regulatory cells like regulatory T cells (TREGs).[16] A comprehensive understanding of the tumor microenvironment (TME) may facilitate deeper insights into the mechanisms underlying tumor development and enhance therapeutic efficacy. Given the important role of PDGFB in TME, the relationship between PDGFB and tumor immunity deserves special attention.

In our current study, we observed that PDGFB is highly expressed in many tumor types. Furthermore, we identified a positive correlation between the expression of PDGF-BB and various immune cell infiltrates across a diverse range of tumors. Additionally, we found a significant positive correlation between PDGFB and several immune checkpoint proteins, including PD-1, PDCD1LG2, CTLA4, and CD274. Therefore, comprehensive, pan-cancer studies are crucial to comprehensively understand the relationship between PDGFB expression and prognosis and immune cell infiltration in various cancers, as well as to identify new therapeutic targets for this devastating disease.

Materials and Methods

PDGFB Expression Analysis

In order to comprehensively investigate the expression of PDGFB in various cancer types, we performed analyses using three reliable online databases: UALCAN,[17] TIMER[18] and GSCA[19] databases. Individual tumor samples are in the Supplementary Table 1. The expression of PDGFB in each cancer type was assessed, taking into account the available gene expression data. Additionally, we examined the relationship between PDGFB expression and cancer subtype or stage, which was done through the utilization of GSCA[19] and UALCAN databases.

Survival Analysis

In this study, we aimed to investigate the potential association between PDGFB expression and the prognosis of patients with 33 different types of cancer. To achieve this, we utilized the GSCA platform, which allowed us to combine mRNA expression data with clinical survival data based on specimen barcodes. We categorized tumor samples into high and low expression groups using median mRNA values and subsequently analyzed the survival time and status within these groups using R-pack survival. To further explore the association between PDGFB expression and overall survival, we utilized various online databases, including Kaplan-Meier plot, GEPIA, UALCAN, and TISIDB. Kaplan-Meier plot,[20] GEPIA,[21] UALCAN, and TISIDB[22] databases were employed to assess the correlation between overall survival and PDGFB expression.

Genomic Instability

The current investigation utilized SangerBox, an online data analysis tool, to analyze the relationship between PDGFB expression and genomic instability in diverse cancer types. SangerBox is an extensive and freely accessible online platform that allows for the exploration of TCGA data. The research aimed to investigate the potential associations between PDGFB gene expression and DNAss as well as RNAss in various cancers. The study utilized sophisticated statistical techniques to analyze large genomic data sets and drew upon the latest research methodologies in the field of genomics.

PDGFB-Related Gene Enrichment Analysis

The present study aimed to elucidate the functional role of PDGFB gene through enrichment analysis. Initially, the GEPIA tool's "similar gene detection" module was employed to extract 100 genes that exhibited an expression pattern similar to PDGFB from the TCGA dataset. Subsequently, gene ontology (GO) and pathway analyses were performed to gain insights into the biological processes and molecular pathways associated with PDGFB. The results were visualized using a heat map generated by an online platform (https://www.bioinformatics.com.cn).

PDGFB gene enrichment analysis was carried to explore the PDGFB function. Firstly, the GEPIA "similar gene detection" module was performed to extract 100 PDGFB-correlated gene from the TCGA datasets that had the most similar expression pattern to PDGFB. Then, GO and pathway analysis were conducted. Heatmap was plotted by https://www.bioinformatics.com.cn.

Pan-cancer analysis of the correlation of the PDGFB expression with tumor cell infiltration and immune modulator genes

We utilized the TIMER database to analyze the expression profiles of PDGFB and immune cell infiltration across multiple cancer types. Furthermore, we examined the correlation between PDGFB expression and immunomodulators using the TISIDB database. The results were visualized using a heat map generated by an online platform (https://www.xiantao.love/products).

Patients and Tissue Specimens

The clinical samples used in this study were obtained from the affiliated hospital of Jiangnan University in China. Formalin-fixed, paraffin-embedded samples from 52 LGG patients were collected between 2012 and 2023 (Supplementary Table 2). It's important to note that all samples were obtained with the explicit consent of the patients, and the study was conducted in accordance with the approval of the ethics committee of the affiliated hospital of Jiangnan University. Our study complies with the Declaration of Helsinki.

Immunohistochemistry Analysis

In this study, the immunohistochemistry assay was performed with minor modifications to a previously described protocol.[23,24] Primary antibodies against PDGFB (1:400, abs, #abs135848), CD8 (1:500, Proteintech, #66868-1-AP), and PD-1 (1:500, Proteintech, #28076-1-AP) were used in the assay.

Statistical Analysis

For the analysis of the differential expression of PDGFB, a p-value was estimated using the *t*-test and was further adjusted by FDR. Survival analysis was conducted using the Cox Proportional-Hazards model and Log rank tests. In terms of expression and subtype, as well as stage analysis, GSCA compared the GSVA score among groups using the Wilcoxon test for two groups and ANOVA test for more than two groups. Trend analysis was performed using the Mann-Kendall Trend Test. In all cases, a p-value of less than 0.05 was considered to indicate statistical significance.

Results

Pan-Cancer Expression Landscape of PDGFB

In this study, the objective was to investigate the role of PDGFB in various types of cancers. Analysis of the GSCA database revealed heterogeneous PDGFB expression across 33 human cancer types. PDGFB was found to be notably upregulated in Bladder urothelial carcinoma (BLCA), Colon adenocarcinoma (COAD), Stomach adenocarcinoma (STAD), Head and Neck squamous cell carcinoma (HNSC), Kidney renal clear cell carcinoma (KIRC), Liver hepatocellular carcinoma (LIHC), and Thyroid carcinoma (THCA)compared to adjacent normal tissues, while it was downregulated in Kidney chromophobe (KICH), Kidney renal papillary cell carcinoma (KIRP), Lung adenocarcinoma (LUAD), and Lung squamous cell carcinoma (LUSC) (Figure 1A). Subsequent validation using the TIMER and UALCAN databases confirmed significant upregulation of PDGFB in BLCA, breast invasive carcinoma (BRCA), COAD, Cholangiocarcinoma (CHOL), HNSC, KIRC, LIHC, THCA, and STAD, while downregulation was observed in KICH, KIRP, LUAD, LUSC, and Uterine Corpus Endometrial Carcinoma (UCEC) (Figure 1B and C). Overall, PDGFB expression was notably elevated in COAD, HNSC, LIHC, KIRC, STAD, and THCA compared to KICH, KIRP, LUAD, and LUSC, suggesting PDGFB's potential as a tumor biomarker.

Further correlation analysis using the GSCA and UALCAN databases demonstrated significant associations between PDGFB mRNA expression and specific cancer subtypes, particularly HNSC, LUSC, STAD, and KIRC (Figure 2A and B), with KIRC showing particularly strong correlation (Figure 2A). Assessment of different cancer stages revealed significant associations between PDGFB mRNA expression and BLCA, COAD, KIRC, READ, THCA, and UVM (Figure 3A). Notably, PDGFB expression displayed positive correlations with pathologic stage in COAD, READ, and UVM, while exhibiting negative correlations with pathologic stage in KIRC (Figure 3B and C).

Survival Analysis

Our investigation involved an in-depth analysis of the potential relationship between PDGFB expression levels and patient prognosis across various types of cancer. This comprehensive analysis encompassed overall survival (OS), disease-free interval (DFI), disease-specific survival (DSS), and progression-free survival (PFS). In terms of OS, PDGFB was identified as a high-risk gene in Glioma (GBMLGG), Brain Lower Grade Glioma (LGG), LUAD, MESO, ALL-R, HNSC, and LUSC, while it was a lower-risk gene in KIRC (Figure 4A). Moreover, high PDGFB expression was linked to poor prognosis in terms of DSS in GBMLGG, LGG, LUSC, LUAD, COAD, STES, COADREAD, MESO, ESCA, and KIRP. However, it was associated with a favorable prognosis in KIRC (Figure 4B). Additionally, high PDGFB expression levels were associated with poor DFS in KIRP and CESC (Figure 4C). Regarding with PFS, high expression of PDGFB was linked to poor PFS in GBMLGG, LGG, UVM, LUSC, CESC, LUAD, COADREAD, and PRAD (Figure 4D).

Consistent with the SangerBox analysis, the TIMER survival analysis indicated that PDGFB serves as a high-risk gene in HNSC, LGG, LUAD, LUSC, and MESO, while being a low-risk gene in KIRC (Figure 5). Further confirmation from KM plot, GEPIA, UALCAN, and TISIDB supported the notion that PDGFB may function as a prognostic marker for multiple tumors. Specifically, it was identified as a high-risk gene in BRCA, CESC, HNSC, LUSC, LUAD, READ, STAD, and THYM, and a low-risk gene in KIRC (Supplementary Figure 1). These robust findings suggest that PDGFB holds promise as a potential prognostic marker across various types of cancer.

Correlation of PDGFB Expression and Tumor Stemness

In our comprehensive analysis across multiple cancer types, we sought to explore the relationship between PDGFB expression and tumor stemness using parameters such as DNAss and RNAss. Our findings revealed a significant association between PDGFB expression and tumor stemness in various tumors (Figure 6). Specifically, we observed a positive association in six tumors, including GBMLGG, LGG, KIRP, KIPAN, PRAD, and THYM, while nine tumors displayed a negative correlation with PDGFB expression, such as GBM, COAD, COADREAD, UCEC, LIHC, THCA, TGCT, PCPG, and BLCA. Additionally, we identified a significant overall association in 36 tumors, with a notable negative association in these tumors, such as GBM, GBMLGG, LGG, CESC, LUAD, COAD, COADREAD, LAML, BRCA, ESCA, STES, SARC, KIRP, KIPAN, STAD, PRAD, UCEC, HNSC, KIRC, LUSC, THYM, LIHC, THCA, MESO, READ, PAAD, OV, TGCT,

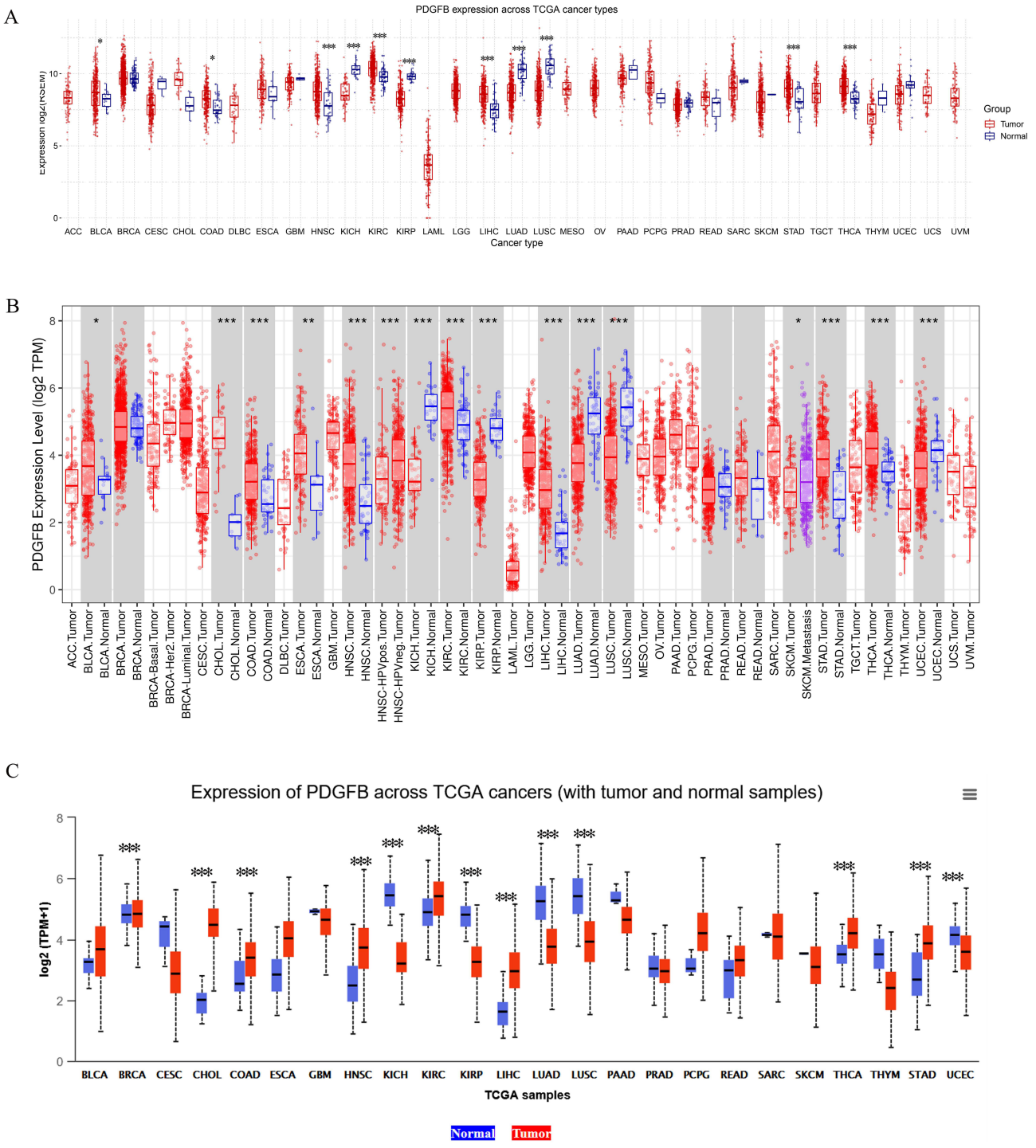

Figure 1 Differential expression of PDGFB in pan-cancer. PDGFB expression in tumor and normal tissues across 33 tumor types by GSCA (**A**), TIMRE (**B**) and UALCAN (**C**). *p<0.05; **p<0.01; ***p<0.001.

PCPG, SKCM, UVM, UCS, BLCA, KICH, CHO, and DLBC. These findings have the potential to pave the way for the development of new therapeutic strategies targeting tumor stemness based on the observed associations.

Functional Enrichment Analysis of PDGFB

Utilizing the TCGA datasets, our gene expression profiling (GEPIA) analysis uncovered the top 100 genes exhibiting expression patterns akin to PDGFB across all tumor types (Supplementary Table 3). This exploration provided valuable

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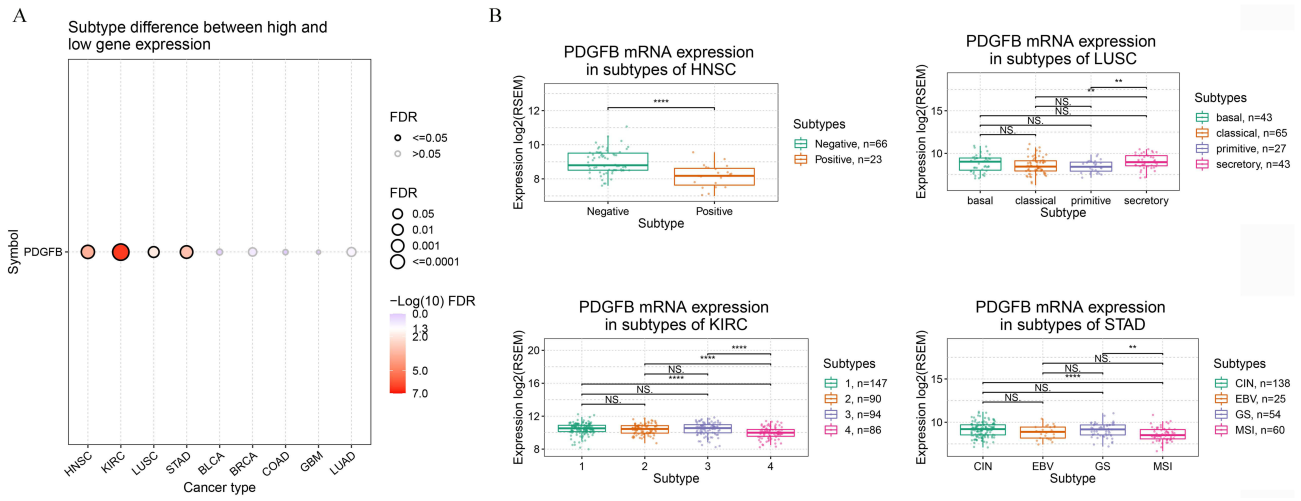

Figure 2 Pan-cancer analysis of the correlation between PDGFB expression and subtype. (**A**) Subtype difference between high and low PDGFB expression. (**B**) PDGFB mRNA expression in subtypes of HNSC, LUSC, KIRC and STAD. **p<0.01; ****p<0.0001.

insights into the underlying mechanisms of PDGFB action in carcinogenesis. In-depth Gene Ontology enrichment analysis of PDGFB unveiled its involvement in diverse biological processes, including angiogenesis, regulation of vasculature development, and epithelial cell migration (Figure 7A). At the cellular level, PDGFB was notably associated with membrane microdomains, specific regions, and rafts (Figure 7B). Its molecular function was primarily linked to growth factor binding, transmembrane receptor protein kinase activity, and protein tyrosine kinase activity (Figure 7C). Pathway analysis indicated PDGFB's participation in several pathways, such as the Rap1, P13K-Akt, Focal adhesion, and MAPK signaling pathways (Figure 7D).

Furthermore, an analysis of PDGFB protein interactions using the STRING tool revealed its multifaceted interaction with various proteins, including PDGFA, PDGFC, PDGFD, PDGFRA, PDGFB, and Vascular endothelial growth factor receptor 2 (KDR) (Figure 7E). Remarkably, PDGFB exhibited a positive correlation with the expression level of KDR (Figure 7F). Given KDR's involvement in the Rap1 signaling pathway, it is plausible that PDGFB may interact with KDR to activate the Rap1 signaling pathway. These findings shed light on the intricate molecular landscape and potential signaling cascades involving PDGFB, offering promising avenues for further research and therapeutic exploration.

PDGFB Expression Positively Correlated With Immune Cell Infiltration and Immunomodulator

Our comprehensive pan-cancer analysis, based on data from the TIMER and TISIDB databases, investigated the correlation between PDGFB expression and the extent of immune infiltration across various cancer types. The results, outlined in Figure 8, unveiled a positive correlation between PDGFB expression and the infiltration levels of CD8+ T cells, CD4+ T cells, B cells, macrophages, neutrophils, and dendritic cells in numerous cancer types. Notably, this association was negative in THYM alone. Additionally, utilizing the TISIDB database, we observed a generally positive relationship between PDGFB gene expression and both immunosuppressive and immunostimulatory genes across different cell types. However, in specific cancers like BRCA, CESC, HNSC, KIRC, LUSC, and THCA, a negative correlation between PDGFB expression and immunosuppressive genes was identified (Figure 9A). Similarly, regarding immunostimulatory genes, a negative correlation was evident in BRCA, CESC, HNSC, TGCT, and THCA (Figure 9B). Furthermore, with regard to MHC molecular gene expression levels, most cell types exhibited a positive correlation with PDGFB, with the exception of BRCA, CHOL, HNSC, LUAD, and THCA, which displayed a negative correlation (Figure 9C). These findings offer valuable insights into the regulatory role of PDGFB in shaping the tumor microenvironment and its potential impact on immune modulation across diverse cancer types.

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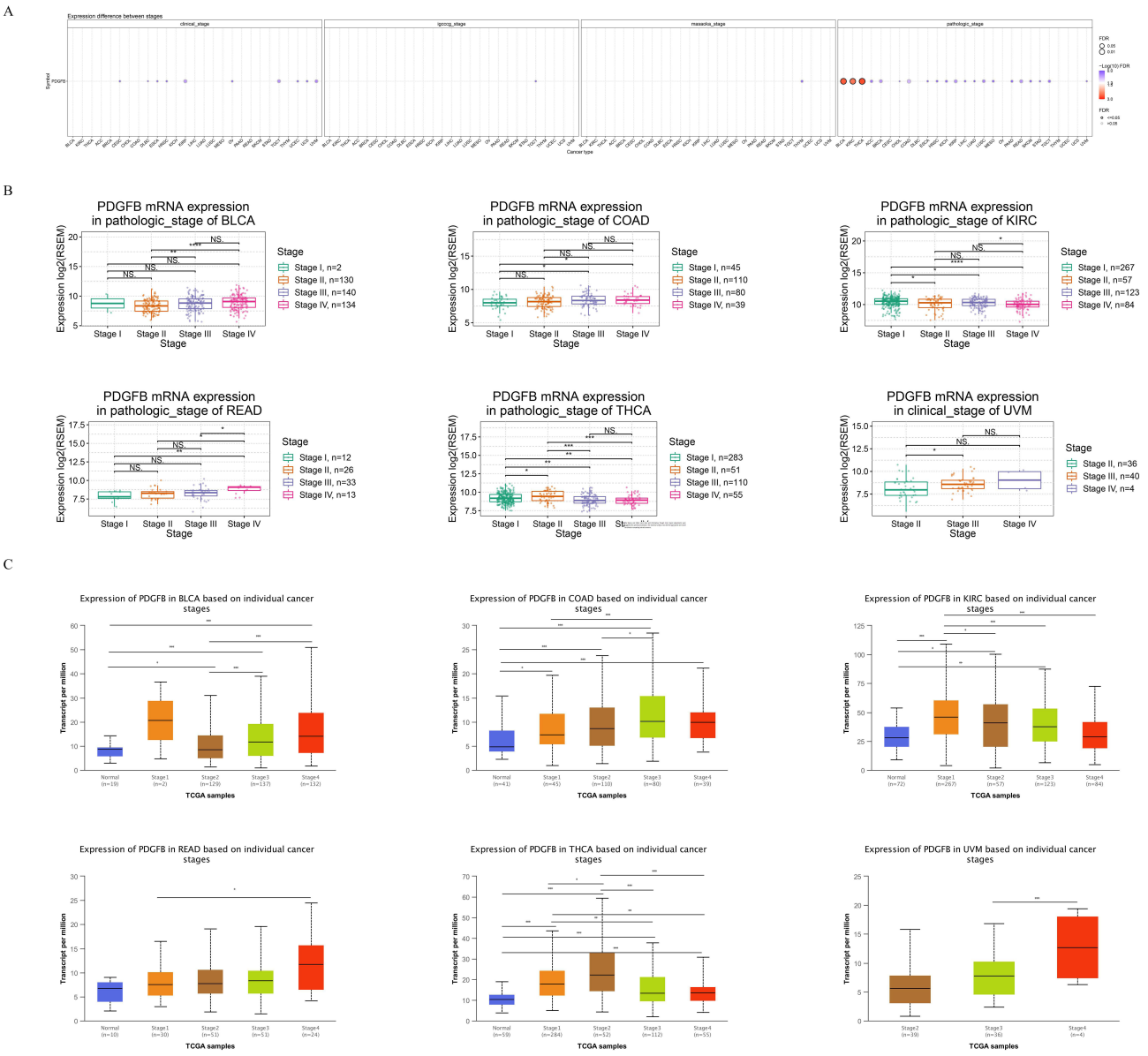

Figure 3 Pan-cancer analysis of the correlation between PDGFB expression and stage. (**A**) PDGFB mRNA expression difference between stages in pan-cancer. (**B**) PDGFB expression in pathologic stage of BLCA, COAD, KIRC, READ, THCA, and clinical stage of UVM from GSCA website. (**C**) PDGFB expression in stage of BLCA, COAD, KIRC, READ, THCA, and UVM from UALCAN website. *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001.

PDGFB Is Associated With Poor Prognosis, Immune Infiltration in LGG

To further verify the expression of PDGFB in LGG, an immunohistochemical (IHC) analysis was performed to measure the level of PDGFB protein expression in 52 randomly selected tumor tissues from LGG patients. The IHC assessment showed that 56% of the tumor tissues exhibited high PDGFB expression, while 44% displayed low expression based on the IHC scoring criteria. Subsequently, we analyzed the correlation between PDGFB expression and immune infiltration, as well as immune checkpoint genes. Using serial sections of specimens from the same patient, we evaluated the immune infiltration and PD-L1 expression. The results indicated that tissues with high PDGFB expression had a significantly higher number of infiltrating CD8+ lymphocytes compared to those with low PDGFB expression. Additionally, a positive correlation was observed between PD-L1 protein expression levels and PDGFB expression levels (Figure 10A and B). To assess the association between PDGFB and patient prognosis in LGG, the tumor tissues were divided into high and low PDGFB expression groups, and the clinical follow-up data of the patients were analyzed using Kaplan-Meier survival

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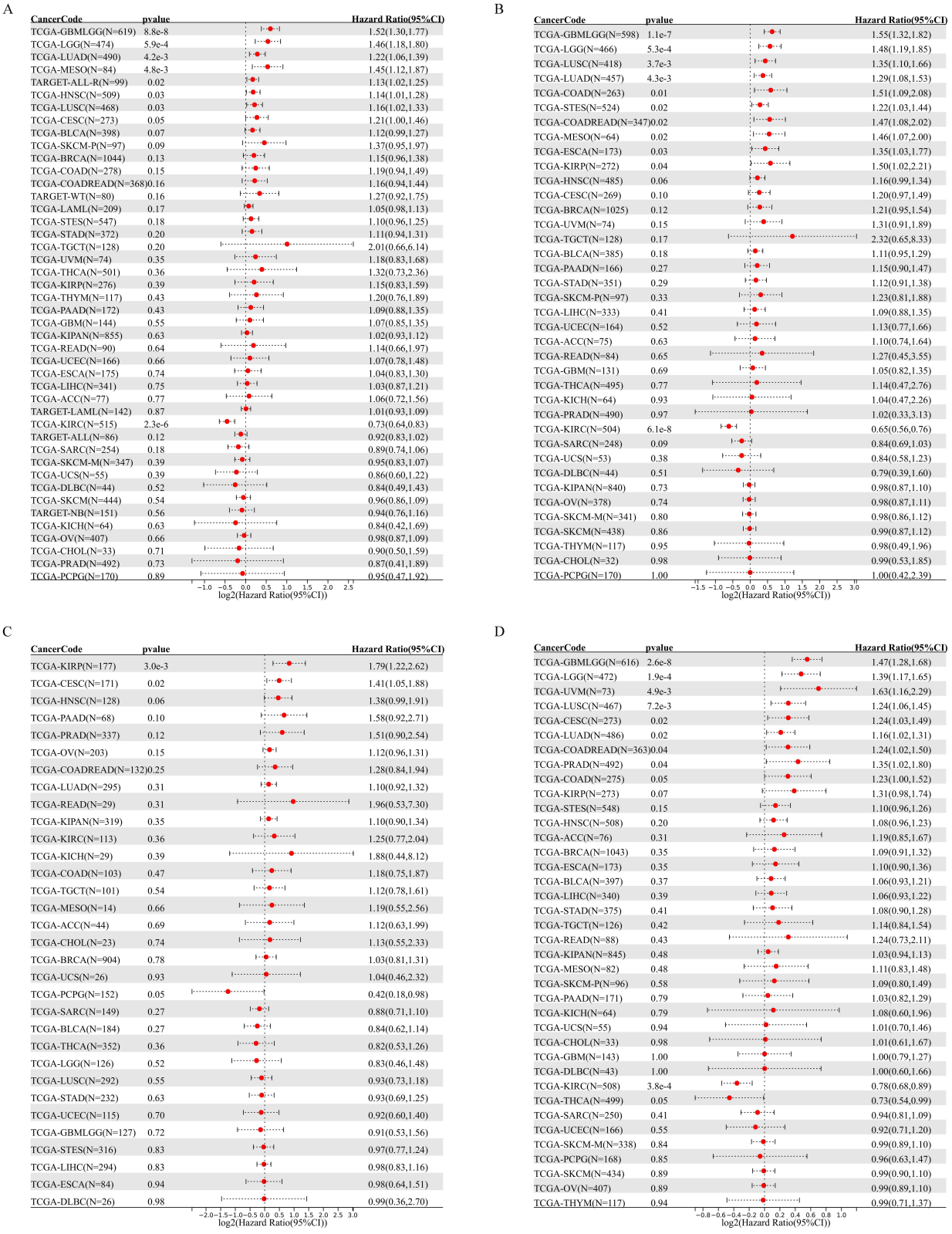

Figure 4 Correlation between PDGFB expression and survival analysis in patients. (**A**) Overall survival map. (**B**) Disease-specific survival. (**C**) Disease-free interval. (**D**) Progression-free interval.

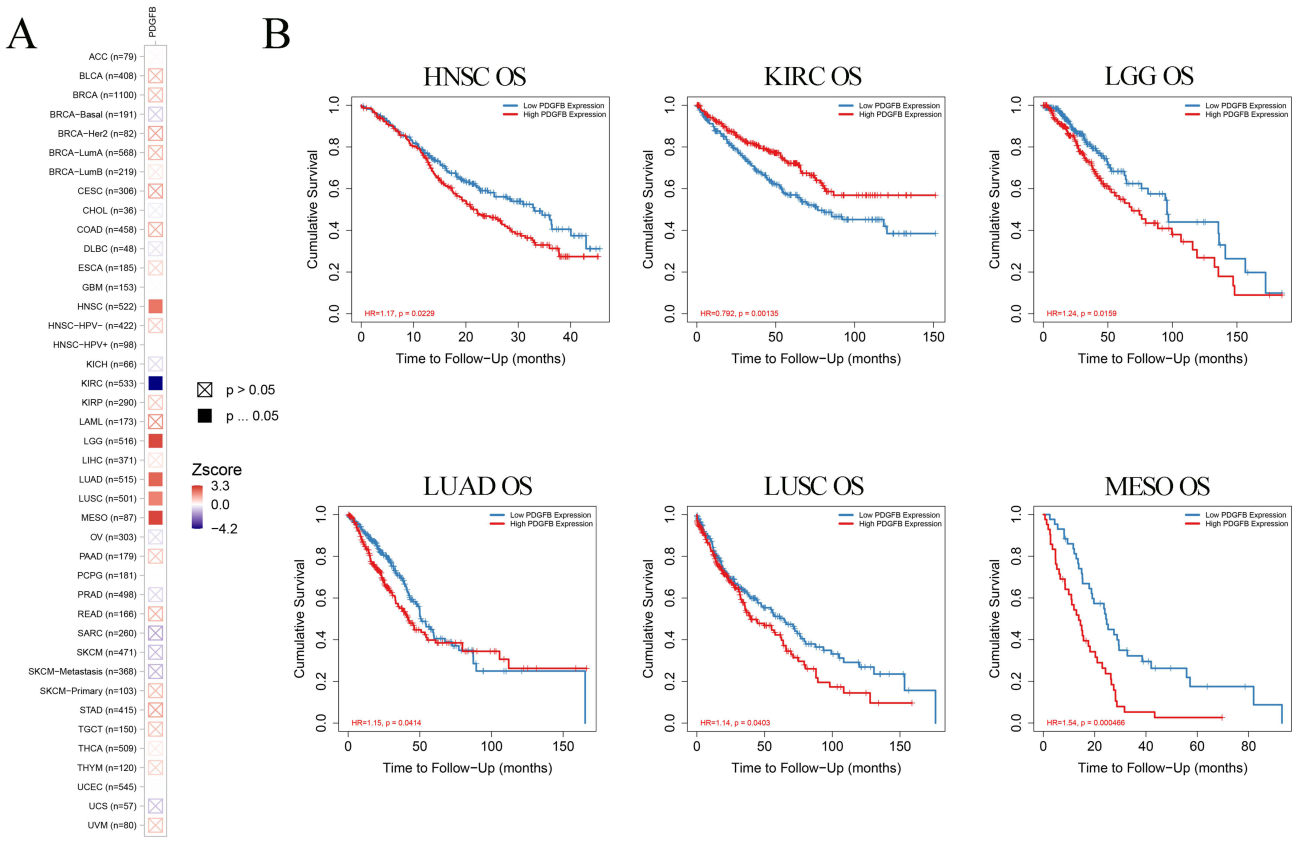

Figure 5 Correlation between PDGFB expression and overall survival from TIMER. (**A**) OS of PDGFB expression in pan-cancer. (**B**) OS of PDGFB expression in HNSC, KIRC, LGG, LUAD, LUSC, and MESO.

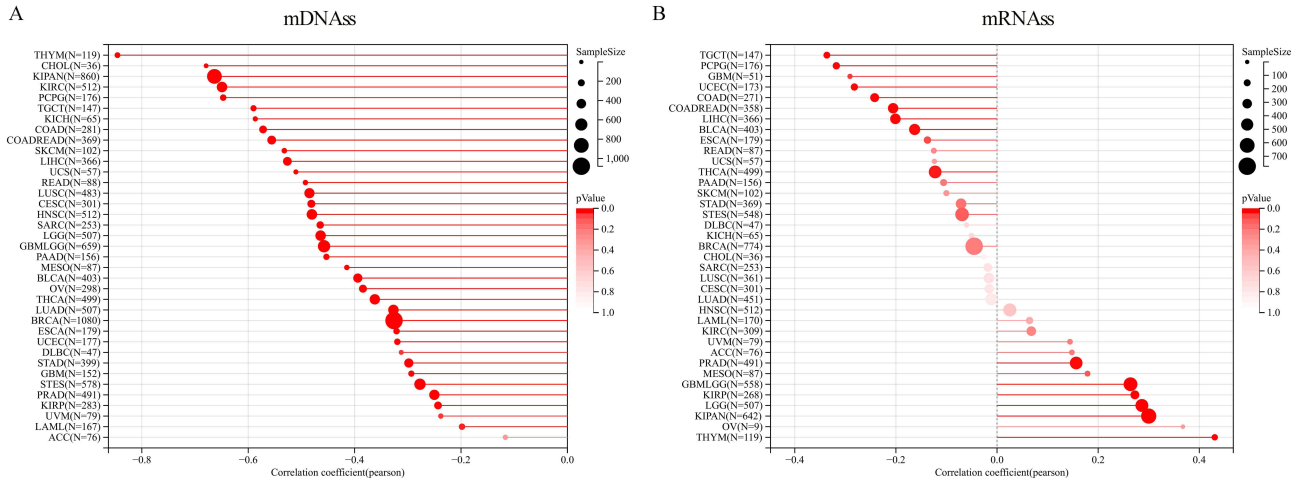

Figure 6 Association of PDGFB with cancer stemness. (**A**) represents mDNAsi, and (**B**) represents mRNAsi. Lollipop charts are displayed where the size of the dots represents the sample size, and the color represents the *p*-value.

analysis and the Log rank test. The findings revealed that high PDGFB expression was associated with a poorer prognosis compared to low PDGFB expression (Figure 10C). These findings offer valuable insights into the role of PDGFB in regulating immune infiltration and checkpoint gene expression in LGG, as well as its potential as a prognostic marker in this disease.

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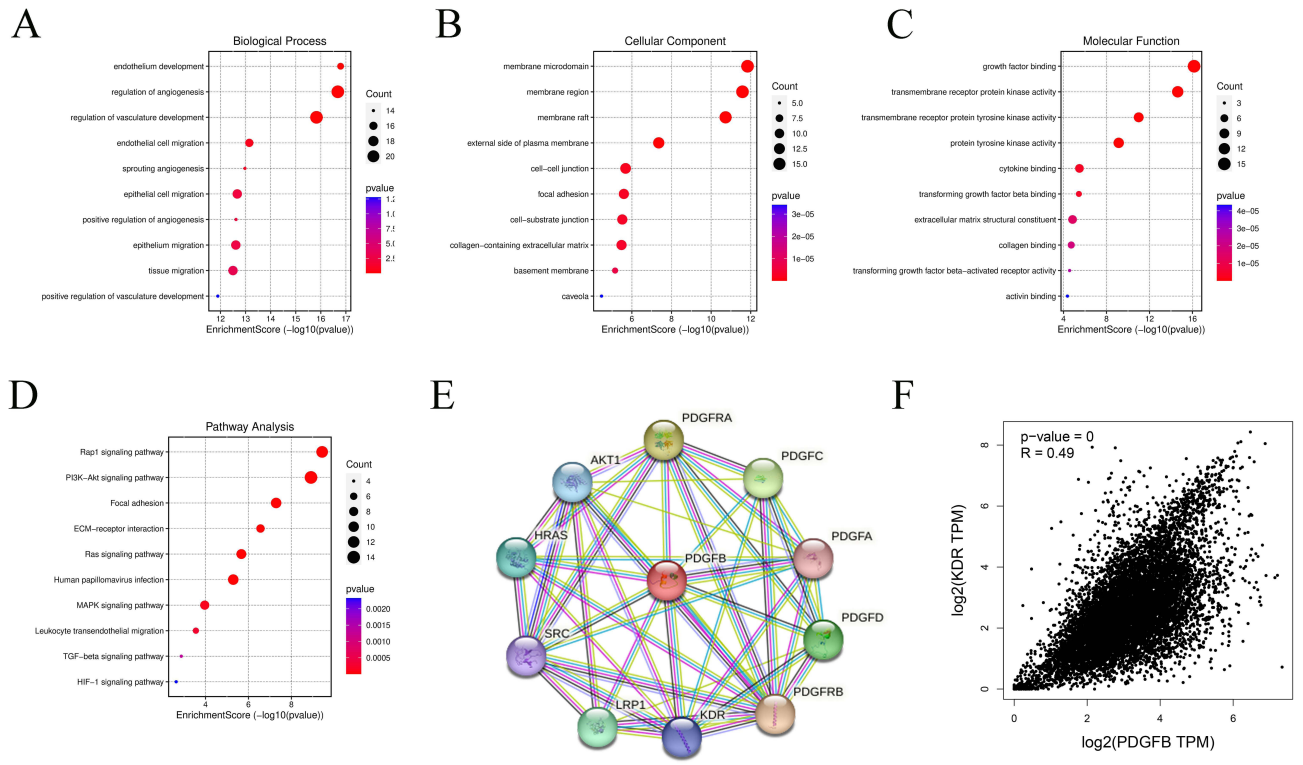

Figure 7 Functional enrichment analysis of PDGFB in pan-cancer. The Gene Ontology enrichment analysis of PDGFB revealed its role in v biological processes (**A**), cellular component (**B**), molecular function (**C**), and Pathway analysis (**D**). (**E**) The available determined PDGFB-related proteins from the STRING website. (**F**) The correlated between PDGFB and selected binding gene KDR from the GEPIA2 tool.

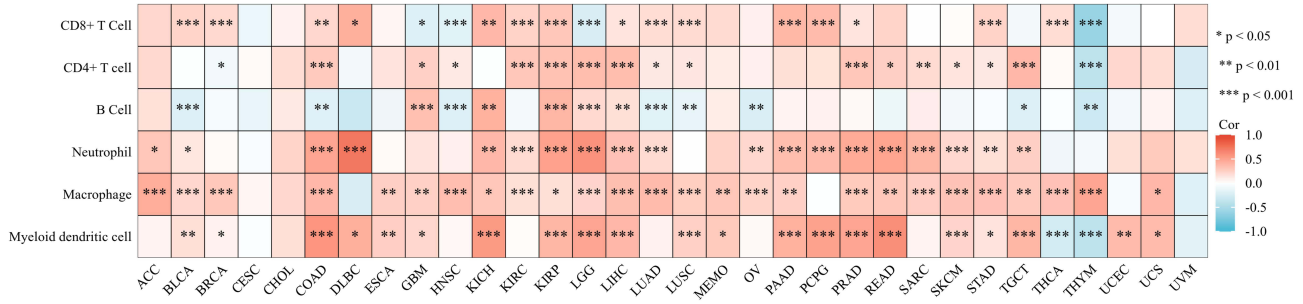

Figure 8 Correlation between PDGFB expression and immune infiltration in pan-cancer. The PDGFB expression significantly correlated with the infiltration levels of various immune cells in the TIMER database. The darker the color, the greater the correlation. *p<0.05; **p<0.01; ***p<0.001.

Discussion

The research on PDGFB has revealed its significant impact on various aspects of cancer biology across different tumor types. PDGF-BB and its receptor, PDGFRβ, have been observed to play pivotal roles in breast cancer progression, influencing autocrine and paracrine processes that regulate cancer growth, metastasis, and angiogenesis. Moreover, the expression of PDGFB has been linked to improved survival in certain breast cancer patients, suggesting its potential as a target for enhancing therapeutic efficacy. Additionally, PDGFB has been associated with diverse functions in different cancers, such as inducing MAPK and Akt phosphorylation in pancreatic cancer cells, promoting mesenchymal stem cell proliferation in prostate cancer, and contributing to resistance to cisplatin in HCC cells under hypoxic conditions.[10–14] Notably, the association of PDGFB with RNA and DNA stemness in multiple tumor types underscores its broader relevance in cancer development and progression.

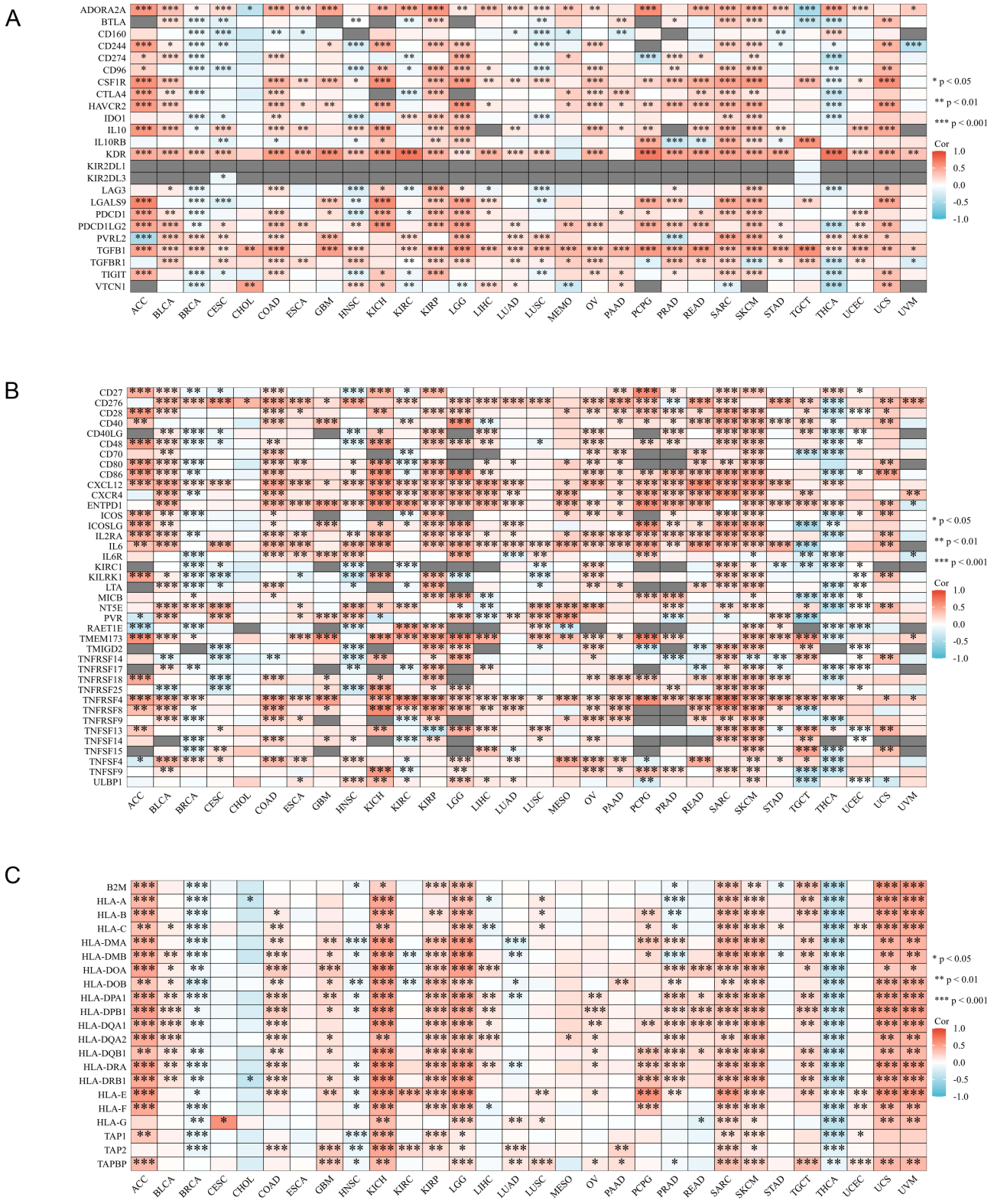

Figure 9 Relationship between three kinds of immunomodulator and PDGFB expression from TISIDB database. Expression correlation between PDGFB and immune stimulators (**A**), immune inhibitors (**B**), and MHC molecules (**C**). *p<0.05; **p<0.01; ***p<0.001.

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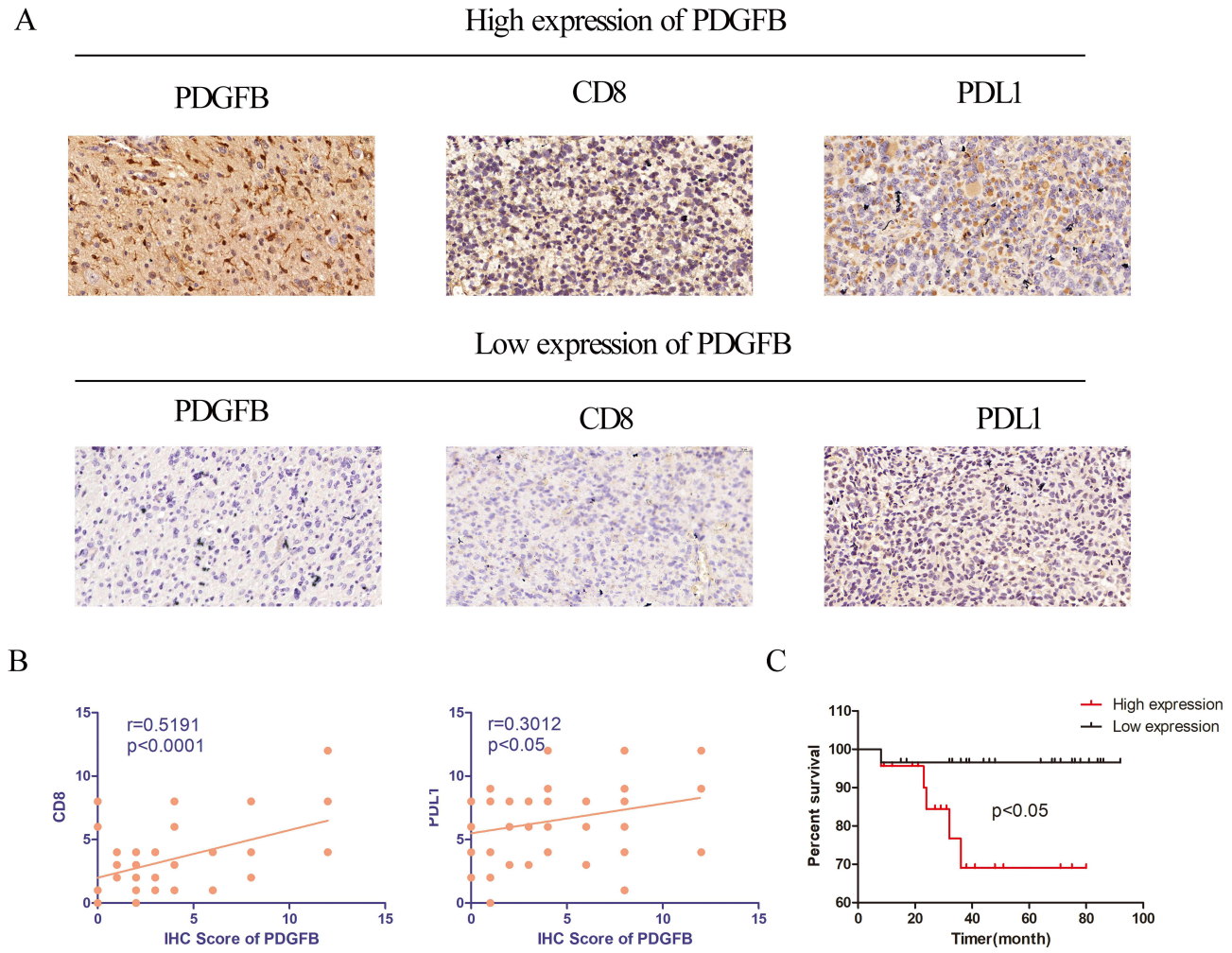

Figure 10 Correlation between PDGFB expression and immune infiltration, as well as prognosis in LGG. (**A**) Representative IHC staining of LGG tissues indicating both PDGFB-high and low expression, with the presence of positively stained CD8 and PD-L1 expression cells. Scale bars, 20um. (**B**) The correlation of PDGFB with CD8 and PD-L1 protein expression were evaluated by Pearson's correlation. (**C**) Kaplan-Meier survival curves for OS of patients with LGG based on the expression status of PDGFB.

Furthermore, the complex interplay between tumor cells and the tumor microenvironment (TME) has been increasingly recognized as a critical factor in cancer development and immune evasion.[25] Studies have been increasingly indicating that components of cancer cells and their related microenvironments may facilitate the immune evasion of tumor cells, leading to tumor growth, recurrence and metastasis.[23,26,27] PDGF-BB, derived from tumors, has been found to modulate key aspects of the TME, such as angiogenesis, lymphangiogenesis, and immune cell migration.[28] Tumor cells, stromal cells and immune cells crosstalk with each other and collectively determine tumor progression. Specifically, our study explored the relationship between PDGFB expression and the tumor immune microenvironment, revealing a significant positive correlation between PDGFB expression and the infiltration levels of six immune cells across different tumor types, except for thymoma. Immunotherapy has significantly transformed the cancer treatment landscape over the past decade. Inhibitors targeting the immune checkpoint proteins CTLA-4, PD-1, and PD-L1 can elicit durable remissions in a subset of patients with metastatic disease.[29] Our study identified a positive correlation between PDGFB and immune checkpoint marker PDCD1, CD244, CD274, PDCD1LG2, CTLA-4 in lower-grade gliomas (Supplementary Figure 2), indicating that PDGFB may represent a promising immunotherapeutic target. This comprehensive analysis also indicated an overall positive association between PDGFB gene expression and both immunosuppressive and immunostimulatory genes across diverse cell types, shedding light on the potential role of PDGFB in shaping the tumor microenvironment and its interaction with the immune system.

Surprisingly, the relationship between PDGFB expression and prognosis revealed unexpected patterns in specific cancers, including KIRC, LUAD, and LUSC. Contrary to conventional assumptions, high PDGFB expression corresponded with a favorable prognosis in KIRC, while low expression was linked to improved prognosis in LUAD and LUSC. These findings underscore the intricate nature of PDGFB's involvement in cancer prognosis and its interplay with the immune system, as evidenced by its correlation with immune checkpoint markers and genes known for their immunosuppressive or immune-boosting effects across different cancer types. In their study, Cao et al highlighted a significant increase in CXCL11 expression in COAD, which correlated with enhanced patient survival, likely attributed to heightened levels of anti-tumor immune cells inhibiting tumor growth and metastasis.[30] Furthermore, in KIRC, PDGFB expression exhibited a negative correlation with immune checkpoint markers such as PD1, TIGIT, CD274, and LAG3, suggesting that elevated levels of PDGFB are associated with an increase in anti-tumor immune cells, ultimately leading to improved survival in patients with renal clear cell carcinoma. Similarly, in lung squamous cell carcinoma, PDGFB showed a negative correlation with immunosuppressive genes and a positive correlation with immune-boosting genes, indicating that high PDGFB expression aligns with a larger presence of immune-boosting cells, resulting in reduced patient survival. Conversely, PDGFB demonstrated positive correlations with both immunosuppressive and immune-boosting genes in lung adenocarcinoma, suggesting that immune activation outweighed immunosuppression, leading to improved survival. This warrants further investigation in future experiments to confirm these predictions.

In conclusion, our comprehensive analysis demonstrated the diverse expression patterns of PDGFB across tumor types and its significant implications for clinical prognosis, DNA methylation, tumor stemness, and immune cell infiltration. This indicates that PDGFB holds promise as a standalone prognostic marker for various tumors, with its expression directly influencing prognosis outcomes. Moreover, the expression of PDGFB is closely associated with immune cell infiltration, and our experiments further confirmed a positive correlation between PDGFB and PDL1. These findings suggest that PDGFB may serve as a promising target for future immunotherapy.

Abbreviations

ACC, Adrenocortical carcinoma; BLCA, Bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, Cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL;Cholangiocarcinoma; COAD, Colon adenocarcinoma; DLBC, Lymphoid Neoplasm 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, Brain Lower Grade Glioma; LIHC, Liver hepatocellular carcinoma; LUAD, Lung adenocarcinoma; LUSC, Lung squamous cell carcinoma; MESO, Mesothelioma; OV, Ovarian serous cystadenocarcinoma; PAAD, Pancreatic adenocarcinoma; PCPG, Pheochromocytoma and Paraganglioma; PRAD, Prostate adenocarcinoma; READ, Rectum adenocarcinoma; STRC, Sarcoma; SKCM, Skin Cutaneous Melanoma; STAD, Stomach adenocarcinoma; TGCT, Testicular Germ Cell Tumors; THCA, Thyroid carcinoma; THYM, Thymoma; UCEC, Uterine Corpus Endometrial Carcinoma; UCS, Uterine Carcinosarcoma; UVM, Uveal Melanoma; TME, The tumor microenvironment; OS, overall survival; DSS, disease-specific survival; DFI, disease-free interval; PFI, progression-free interval; PDGFB, Platelet-derived growth factor-B; CTRP, Genomics of Therapeutics Response Portal; TMB, Tumor mutation burden; MSI, Microsatellite instability.

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Disclosure

The authors declare no competing interests in this work.

References

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin*. 2024;74(1):12–49. doi:10.3322/caac.21820
2. Jeggo PA, Pearl LH, Carr AM. DNA repair, genome stability and cancer: a historical perspective. *Nat Rev Cancer*. 2016;16(1):35–42. doi:10.1038/nrc.2015.4
3. Chatterjee A, Rodger EJ, Eccles MR. Epigenetic drivers of tumourigenesis and cancer metastasis. *Semin Cancer Biol*. 2018;51:149–159. doi:10.1016/j.semcancer.2017.08.004
4. Fredriksson L, Li H, Eriksson U. The PDGF family: four gene products form five dimeric isoforms. *Cytokine Growth Factor Rev*. 2004;15(4):197–204. doi:10.1016/j.cytogfr.2004.03.007
5. Uutela M, Lauren J, Bergsten E, et al. Chromosomal location, exon structure, and vascular expression patterns of the human PDGFC and PDGFD genes. *Circulation*. 2001;103(18):2242–2247. doi:10.1161/01.CIR.103.18.2242
6. Heldin CH, Westermark B. Mechanism of action and in vivo role of platelet-derived growth factor. *Physiol Rev*. 1999;79(4):1283–1316. doi:10.1152/physrev.1999.79.4.1283
7. Johnson MD, O'Connell M, Iqbal MA, Williams JP. Radiation effects on human leptomeningeal cell response to cerebrospinal fluid and PDGF-BB. *Int J Radiat Biol*. 2012;88(7):547–555. doi:10.3109/09553002.2012.690929
8. Costa PM, Cardoso AL, Pereira de Almeida LF, Bruce JN, Canoll P, Pedroso de Lima MC. PDGF-B-mediated downregulation of miR-21: new insights into PDGF signaling in glioblastoma. *Human Molecular Genetics*. 2012;21(23):5118–5130. doi:10.1093/hmg/dds358
9. Yi B, Williams PJ, Niewolna M, Wang Y, Yoneda T. Tumor-derived platelet-derived growth factor-BB plays a critical role in osteosclerotic bone metastasis in an animal model of human breast cancer. *Cancer Res*. 2002;62(3):917–923.
10. Kawaguchi J, Adachi S, Yasuda I, et al. UVC irradiation suppresses platelet-derived growth factor-BB-induced migration in human pancreatic cancer cells. *Oncol Rep*. 2012;27(4):935–939. doi:10.3892/or.2011.1612
11. Cheng J, Ye H, Liu Z, et al. Platelet-derived growth factor-BB accelerates prostate cancer growth by promoting the proliferation of mesenchymal stem cells. *J Cell Biochem*. 2013;114(7):1510–1518. doi:10.1002/jcb.24492
12. Matsumoto S, Yamada Y, Narikiyo M, et al. Prognostic significance of platelet-derived growth factor-BB expression in human esophageal squamous cell carcinomas. *Anticancer Res*. 2007;27(4B):2409–2414.
13. Cimpean AM, Cobec IM, Ceausu RA, Popescu R, Tudor A, Raica M. Platelet derived growth factor BB: a"must-have" therapeutic target "redivivus" in ovarian cancer. *Cancer Genomics Proteomics*. 2016;13(6):511–517. doi:10.21873/cgp.20014
14. Lau CK, Yang ZF, Ho DW, et al. An Akt/hypoxia-inducible factor-1alpha/platelet-derived growth factor-BB autocrine loop mediates hypoxia-induced chemoresistance in liver cancer cells and tumorigenic hepatic progenitor cells. *Clin Cancer Res*. 2009;15(10):3462–3471. doi:10.1158/1078-0432.CCR-08-2127
15. Yang Y, Andersson P, Hosaka K, et al. The PDGF-BB-SOX7 axis-modulated IL-33 in pericytes and stromal cells promotes metastasis through tumour-associated macrophages. *Nat Commun*. 2016;7:11385. doi:10.1038/ncomms11385
16. Bai Y, Cao K, Zhang P, Ma J, Zhu J. Prognostic and immunological implications of FAM72A in pan-cancer and functional validations. *Int J mol Sci*. 2022;24(1):375. doi:10.3390/ijms24010375
17. Chandrashekar DS, Bashel B, Balasubramanya SAH, et al. UALCAN: a portal for facilitating tumor subgroup gene expression and survival analyses. *Neoplasia*. 2017;19(8):649–658. doi:10.1016/j.neo.2017.05.002
18. Li T, Fan J, Wang B, et al. TIMER: a web server for comprehensive analysis of tumor-infiltrating immune cells. *Cancer Res*. 2017;77(21):e108–e110. doi:10.1158/0008-5472.CAN-17-0307
19. Liu CJ, Hu FF, Xie GY, et al. GSCA: an integrated platform for gene set cancer analysis at genomic, pharmacogenomic and immunogenomic levels. *Briefings Bioinf*. 2023;24(1). doi:10.1093/bib/bbac558
20. Gyorffy B. Survival analysis across the entire transcriptome identifies biomarkers with the highest prognostic power in breast cancer. *Comput Struct Biotechnol J*. 2021;19:4101–4109. doi:10.1016/j.csbj.2021.07.014
21. Tang Z, Li C, Kang B, Gao G, Li C, Zhang Z. GEPIA: a web server for cancer and normal gene expression profiling and interactive analyses. *Nucleic Acids Res*. 2017;45(W1):W98–W102. doi:10.1093/nar/gkx247
22. Ru B, Wong CN, Tong Y, et al. TISIDB: an integrated repository portal for tumor-immune system interactions. *Bioinformatics*. 2019;35(20):4200–4202. doi:10.1093/bioinformatics/btz210
23. Wang B, Zhao L, Chen D. Coactosin-like protein in breast carcinoma: friend or foe?. *Journal of Inflammation Research*. 2022;15:4013–4025. doi:10.2147/JIR.S362606
24. Wang X, Bai Y, Wang B. Coactosin-like protein 1 (COTL1) could be an immunological and prognostic biomarker: from pan-cancer analysis to low-grade glioma validation. *J Inflamm Res*. 2024;17:1805–1820. doi:10.2147/JIR.S453509
25. Mlecnik B, Bindea G, Pages F, Galon J. Tumor immunosurveillance in human cancers. *Cancer Metastasis Rev*. 2011;30(1):5–12. doi:10.1007/s10555-011-9270-7
26. Wang B, Chen D, Hua H. TBC1D3 family is a prognostic biomarker and correlates with immune infiltration in kidney renal clear cell carcinoma. *mol Ther Oncolytics*. 2021;22:528–538. doi:10.1016/j.omto.2021.06.014
27. Zhang C, Zhang G, Sun N, et al. Comprehensive molecular analyses of a TNF family-based signature with regard to prognosis, immune features, and biomarkers for immunotherapy in lung adenocarcinoma. *EBioMedicine*. 2020;59:102959. doi:10.1016/j.ebiom.2020.102959
28. Shah S, Sizemore GM. Diverse roles of tumor-stromal PDGFB-to-PDGFRbeta signaling in breast cancer growth and metastasis. *Adv Cancer Res*. 2022;154:93–140.
29. Wang SJ, Dougan SK, Dougan M. Immune mechanisms of toxicity from checkpoint inhibitors. *Trends Cancer*. 2023;9(7):543–553. doi:10.1016/j.trecan.2023.04.002
30. Cao Y, Jiao N, Sun T, et al. CXCL11 correlates with antitumor immunity and an improved prognosis in colon cancer. *Front Cell Develop Biol*. 2021;9:646252. doi:10.3389/fcell.2021.646252