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A Systems Biology Approach Unveils a Critical Role of DPP4 in Upper Gastrointestinal Cancer Patient Outcomes

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Abstract

Gastrointestinal (GI) cancers comprise of cancers that affect the digestive system and its accessory organs. The late detection and poor prognosis of GI cancer emphasizes the importance of identifying reliable and precise biomarkers for early diagnosis and prediction of prognosis. The membrane-bound glycoprotein dipeptidyl-peptidase 4 (DPP4), also known as CD26, is ubiquitously expressed and has a wide spectrum of biological roles. The role of DPP4/CD26 in tumor progression in different types of cancers remains elusive. However, the link between DPP4 and tumor-infiltrating cells, as well as its prognostic significance in malignancies, still require further investigation. This study was intended to elucidate the correlation of DPP4 expression and survival along with prognosis, followed by its associated enriched molecular pathways and immune cell marker levels in upper GI cancers. Results demonstrated a strong correlation between increased DPP4 expression and a worse prognosis in esophageal and gastric cancer and the co-expressed common genes with DPP4 were associated with crucial molecular pathways involved in tumorigenesis. Additionally, DPP4 was shown to be significantly linked to several immune infiltrating cell marker genes, including Macrophages (M1, M2 and Tumor Associated Macrophages), neutrophils, Treg, T-cell exhaustion, Th1 and Th2. Overall, our findings suggest that DPP4 may serve as a substantial prognostic biomarker, a possible therapeutic target, as

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well as it can play a critical role in the regulation of immune cell invasion in patients with gastroesophageal (esophageal, gastroesophageal junction and gastric) cancer.

Keywords

DPP4; integrated analysis; GI cancer; gastroesophageal cancer; gastroesophageal junction; prognosis

I. INTRODUCTION

Gastrointestinal (GI) cancers affect the digestive system and its associated organs. Colorectal, gastric, and esophageal cancers are the most common GI malignancies.[1] The American Cancer Society (www.cancer.org) reports that GI malignancies have the greatest prevalence (193,350 males and 149,690 females) and are the second leading cause of mortality (99,940 males and 71,980 females) (after lung cancer) in the United States.[2] In general, cancers affecting the gastrointestinal tract and digestive organs, including the pancreas, liver, and gallbladder, are responsible for higher mortality rates compared to other systems of the body.[3,4]

In recent years, biomarkers have become more essential in evaluating and treating patients with gastrointestinal cancer. Carcinoembryonic antigen (CEA), which is found to be expressed in embryonic tissue and colorectal cancers, is the most common biomarker used in clinical practice to predict the outcome of disease.[5] Microsatellite instability (MSI) analysis, as well as BRAF and KRAS mutation analyses, are being employed in the evaluation of CRC patients.[6] The variability in clinical responses to CRC treatment necessitates the development of novel predictive and prognostic molecular classifiers that can assist in identifying the most suitable treatment options for each patient. These classifiers should consider the patient's prognosis and expected reaction to chemotherapeutic agents, thereby ensuring optimal treatment outcomes. HER2 status is typically determined using Formalin-Fixed Paraffin-Embedded (FFPE) samples from the esophagus or gastric tumor patients, and it is known that the expression levels of HER2 can alter as a result of therapeutic intervention or disease progression.[7] Although CEA and CA19–9 are the commonly used prognostic markers presently, they are ineffective in detecting early gastric cancer.[8,9] The only biomarker for pancreatic cancer that has been approved by the US Food and Drug Administration (FDA) so far is CA 19–9. However, 10%–13% of patients diagnosed with pancreatic cancer, it was found that CA 19–9 has a sensitivity of 70%–80% and a specificity of 82%–90%.[10,11]

Even though there has been a rapid advancement in GI cancer diagnostics and anti-cancer treatments in recent years, poor patient survival is still a matter of concern. In this regard, it is highly crucial to further explore the molecular mechanisms of such malignancies and investigate the prospective biomarkers (alone or in combination) for early detection, precise prognosis, and specific therapeutic targets for cancer treatment.

Dipeptidyl-peptidase 4 (DPP4) also known as cluster of differentiation 26 (CD26) is a multifunctional type II transmembrane glycoprotein capable of cleaving N-terminal

dipeptides from polypeptides having proline or alanine in the penultimate position.[12,13] DPP4 exists in membrane-bound and soluble isoforms. DPP4 has a transmembrane protein domain associated with the cell membrane and cytoplasmic domain at N-terminus. The extracellular domain of DPP4 is composed of glycosylated, cysteine-rich, and catalytic domains. The catalytic efficacy and dimerization are associated with the C-terminal loop of DPP4.[14] On the contrary, in bodily fluids, a soluble variant, sCD26/sDPP4, can be detected, which is thought to be cleaved off the membrane by matrix metalloproteases and kallikrein-related peptidase 5.[15,16] It has been reported that the possible sources of sDPP4 might include bone marrow-derived cells, adipocytes, vascular smooth muscle cells, and skeletal muscle cells.[17–19] Moreover, the ability to estimate the levels and activity of sDPP4 in serum or plasma makes it an intriguing prospective biomarker.

DPP4 exerts biological activity through a multitude of pleiotropic effects, which include protease activity, adenosine deaminase (ADA) association,[20] extracellular matrix interaction,[21] viral entry,[22] and modulation of multiple physiological mechanisms like immunomodulation, adhesion, migration, invasion and apoptosis. Additionally, DPP4 interacts with fibronectin and collagen proteins,[23] and involves in adhesion, migration, invasion, and metastasis. DPP4 is also an important immunoregulatory factor, serving as a biomarker for T cell activation[24] and as an integral element of other signaling pathways, such as the serine protease fibroblast activated protein-alpha (FAP-α), the chemokine receptor CXCR4, and others.[25–27] DPP4 regulates various biological mechanisms, thus its aberrant expression can modulate cancer progression.

DPP4 has been linked to tumor growth in several studies, although its expression and function in various forms of cancer remain unclear.[28] Moreover, DPP4 also seems to have different impacts on the type of cancer cells and tumor microenvironments. Multiple studies reveal that DPP4 functions as a tumor suppressor, as evidenced by melanoma, non-small cell lung cancer (NSCLC), ovarian cancer, endometrial carcinoma, and prostate cancer.[28–33] In contrast, research on colorectal cancer, malignant mesothelioma, hematological malignancies, and Ewing sarcoma indicates that DPP4 expression is correlated with a more carcinogenic nature.[34–37] In these circumstances, the current study highlights all recent findings related to DPP4 on the aberrant expression in upper GI cancers and conjectured development of DPP4 as a potential biomarker and therapeutic target for upper GI and associated cancer diagnosis and prognosis.

II. MATERIALS AND METHODS

A. DPPR Expression in Human Cancers

Gene Expression Profiling Interactive Analysis (GEPIA, http://gepia.cancer-pku.cn/) was used to determine the mRNA expression patterns of DPP4 in different human cancers. This analysis included *P* values less than 0.01 and |Log2FC| larger than 1. GEPIA analyzes the data of RNA sequencing from The Cancer Genome Atlas (TCGA) and the Genotype-Tissue Expression (GTEx) datasets to confirm the differential expression of genes in different types of tumors.

B. Prognostic Potential of DPP4

The Kaplan-Meier (KM) plotter (http://kmplot.com/analysis/) was used to analyze the prognostic value of DPP4 expression.[38] The KM plotter incorporates gene chip and RNA-seq data from the TCGA, the Gene Expression Omnibus (GEO), and the European Genome-phenome Archive (EGA), and it investigates gene expression and patient survival in twenty-one distinct cancer types. We may assess the prognosis of patients in various subgroups, different disease factors, treatment modalities, and data sets by adjusting the parameters. In the KM plotter, cancer patient samples were allocated into two groups based on the median levels of mRNA expression. The survival of the low- and high-expression groups is examined using the K-M survival plot.

C. DPP4 Co-Expressed Genes

LinkedOmics is a web-based platform (http://linkedomics.org/) that incorporates multi-omics data from 32 TCGA cancer types. The DPP4 co-expressed genes in ESCA and STAD were determined by LinkFinder module, by selecting the RNA-seq datasets (HiSeq RNA) and Spearman's correlation test, which were represented in the form of volcano plots. The genes co-expressed with DPP4 with an adjusted P value (< 0.01) were screened out. The common DPP4-correlated genes in ESCA and STAD were used for pathway enrichment analysis using Metascape online tool by selecting (KEGG pathway, WikiPathways, Canonical Pathways and PANTHER pathway) and a P value cutoff 0.05.

D. Correlation of DPP4 Expression with Immune Marker Sets

GEPIA was also used to evaluate the gene expression correlation for provided sets utilizing TCGA data (P-value less than 0.05). In this study, the correlation module assisted in determining how DPP4 expression correlated with various immunological infiltrating cell marker sets, including macrophages (M1, M2), tumor associated macrophages (TAMs), neutrophils, different T-helper cells, Tregs, and exhausted T cells. Previous reports and the CellMarker database (http://biocc.hrbmu.edu.cn/CellMarker/) included these gene markers as examples of representative markers.[39,40]

E. Statistics Analysis

Publicly available databases were used to examine DPP4 expression levels and prognostic values in different cancers. The GEPIA database produced expression data that was scaled by a factor of log2 (TPM+1). Using the default database settings, the survival data from the Kaplan–Meier plotter were assessed using the hazard ratio (HR) and Cox P or P-values from a log-rank test. Spearman's correlation coefficient was used to identify the genes that were co-expressed with DPP4. The Metascape software was used to conduct pathway analysis, and a P value < 0.05 was considered statistically significant. The association between DPP4 and immune cell marker genes was investigated using Spearman's correlation in GEPIA.

III. RESULTS

A. Differential Expression of DPP4 in Various Human Cancers

As per GEPIA database, the expression of DPP4 (Fig. 1) was found to be upregulated in Esophageal carcinoma (ESCA), Kidney renal papillary cell carcinoma (KIRP), Acute Myeloid Leukemia (LAML), Liver Hepatocellular Carcinoma (LIHC), Lung adenocarcinoma (LUAD), Pancreatic adenocarcinoma (PAAD), Prostate Adenocarcinoma (PRAD), Stomach adenocarcinoma (STAD), Thyroid carcinoma (THCA), and Thymoma (THYM). However, the level of DPP4 expression observed was found to be downregulated in Breast invasive carcinoma (BRCA), Kidney Chromophobe (KICH), Lung squamous cell carcinoma (LUSC), and Skin Cutaneous Melanoma (SKCM). Among 10 different cancers associated with high DPP4 expression, we found around 30% of the cancers were associated with GI malignancies. Therefore, we focused on determining the DPP4 expression in GI cancers.

B. mRNA Expression Levels of DPP4 in Gastrointestinal Cancers

GEPIA database was also used to further confirm the mRNA expression of DPP4 between cancer and normal tissues in GI cancers (0.01 *P* value cutoff). The mRNA expression of DPP4 was found to be significantly upregulated in STAD, ESCA and PAAD and non-significantly high in COAD tissues (Fig. 2).

C. Prognostic Potential of DPP4 in Gastrointestinal Cancers

To investigate if there is a link between DPP4 expression and patient survival rates in ESCA, STAD, and PAAD, the KM plotter was used in conjunction with the differential expression of DPP4 in various cancers. According to KM plotter, upregulated expression of DPP4 was associated with reduced overall survival (OS) in ESCA (Log-rank $p = 0.033$, HR = 2.7; Fig. 3A), STAD (Log-rank $p = 0.057$, HR = 1.48; Fig. 3B) and PAAD (Log-rank $p = 0.28$, HR = 0.79; Fig. 3C). Altogether, these results suggest that the DPP4 can be a promising prognostic biomarker in GI malignancies.

D. Genes Co-Expressed with DPP4 in ESCA and STAD

LinkedOmics database identified the genes co-expressed with DPP4 in ESCA and STAD based on its strong prognostic significance in these two forms of cancer. About 19,829 genes in ESCA and 20,226 in STAD were shown to have correlation (positive and negative) with DPP4 and represented by the volcano plots (Fig. 4A and 4B). The co-expressed genes with DPP4 in ESCA and STAD were identified by Spearman's correlation test and further screened with a threshold of *P* value ($p < 0.01$). A total of 10,476 genes were found to be unique in both the cancers. The genes associated with DPP4 in ESCA and STAD were intersected to identify the genes that are expressed commonly. A total of 2,528 (24.13%) common genes were associated with DPP4 in both types of cancers (Fig. 4C). This suggests that both ESCA and STAD are closely associated in terms of 24.13% genes in common. Further pathway enrichment analysis was carried out using the genes that were shown to be commonly correlated.

E. DPP4-Associated Gene Functional Enrichment

To determine the functions of the DPP4 co-expressed genes, the common correlated genes among ESCA and STAD were used to perform the pathway enrichment analysis in Metascape. The DPP4 co-expressed genes were significantly enriched in nuclear receptors meta-pathway, O-linked glycosylation of mucins, regulation of lipid metabolism by PPAR alpha, RHO GTPase cycle, Neutrophil degranulation, SUMOylation of intracellular receptors, PPAR signaling pathway and vitamin D receptor pathway (Fig. 5A). Moreover, Metascape was employed for visualizing the pathways. Each node is characterized by an enriched term and is colored based on the cluster-ID (Fig. 5B and 5C). Altogether, the enrichment analysis revealed that the genes co-expressed with DPP4 were significantly correlated with the pathways involved in cancer progression.

F. Association between DPP4 Expression and Immune Cell Marker Genes

We proceeded further to investigate the correlation between DPP4 and the representative marker genes of different immune infiltrating cells like tumor associated macrophages (TAM) and neutrophils, through GEPIA database (Table 1). Additionally, functional T cells were examined, including numerous types of T-helper cells as well as Tregs and exhausted T cells. The findings revealed that DPP4 had a substantial correlation with most immunological markers in both ESCA and STAD. The results revealed a positive correlation among DPP4 expression and immune cell gene markers, such as M2 macrophage marker (MS4A4A), TAM marker (CD68), neutrophil marker (CEACAM8 and CCR7), Treg marker (CCR8 and FOXP3), exhaustion markers of T cell, i.e., PDCD1 (PD-1) and TIM-3 (HAVCR2), Th1 marker (STAT4) and Th2 marker (STAT5A) and a negatively correlation with M1 marker (IRF5) in both ESCA and STAD. As a result of these observations, it is hypothesized that DPP4 plays a crucial role in immunologic evasion and immunologic tolerance in the tumor microenvironment.

IV. DISCUSSION

The present study revealed that DPP4 is involved in malignancies associated with the upper GI (esophageal, gastric, and gastroesophageal junction), which is extremely intriguing. In the current work, we analyzed the expression profile and prognostic efficacy of DPP4 across human malignancies by integrating public datasets. DPP4 was differentially expressed in tumor tissues when compared with normal tissues. Based on the GEPIA database, we found that DPP4 was highly expressed in in Esophageal carcinoma, Kidney renal papillary cell carcinoma, Acute Myeloid Leukemia, Liver Hepatocellular Carcinoma, Lung adenocarcinoma, Pancreatic adenocarcinoma, Prostate Adenocarcinoma, Stomach adenocarcinoma, Thyroid carcinoma, and Thymoma. However, the level of DPP4 expression was lower in Breast invasive carcinoma, Kidney Chromophobe, Lung squamous cell carcinoma, and Skin Cutaneous Melanoma. DPP4 overexpression was found to be linked with approximately 30% of GI cancers. Therefore, we particularly focused on GI cancers (ESCA, STAD, PAAD, and COAD). As GI malignancies are the primary cause of cancer mortality, we investigated the critical role of DPP4 in GI cancer patient outcomes. Furthermore, we also confirmed that the DPP4 mRNA expression was significantly elevated in STAD, ESCA, and PAAD. Overexpression of DPP4 has been observed in a variety of

human malignancies, including those of the prostate, thyroid, and esophagus.[41–45] Recent research suggests that detecting CD26 levels in serum may be an early detection biomarker for gastric cancer.[46] Similarly, a previously published article observed that pancreatic ductal adenocarcinoma (PDAC) tissues have elevated DPP4-like enzyme activity.[47] In fact, individuals with metastatic colorectal cancer have significantly greater levels of soluble CD26.[36] Using the KM plotter database, we observed that elevated expression of DPP4 was significantly related to a poorer prognosis in ESCA and STAD (Fig. 3). These data imply that DPP4 may be an effective biomarker for ESCA and STAD prognosis.

Furthermore, LinkedOmics platform was used to determine the genes co-expressed with DPP4 in both ESCA and STAD. The common DPP4-correlated genes in ESCA and STAD were used for pathway enrichment analysis by Metascape. The pathway enrichment analysis of common DPP4-correlated genes in ESCA and STAD revealed that the DPP4 co-expression genes were significantly involved in pathways that play a crucial role in carcinogenesis. Infection with *Helicobacter pylori* bacteria promotes gastritis, ulcers of stomach and duodenum, and gastric cancer, and mucin O-glycosylation protects the epithelial membrane of the stomach against these diseases.[48] Mucin expression in the normal epithelium is lost during gastric carcinogenesis.[49] The nuclear receptor superfamily includes three ligand-inducible transcription factors called peroxisome proliferator-activated receptors (PPARs). The function of PPARs as tumor suppressors or inducers is dependent on the milieu in which they are expressed; nonetheless, PPAR alpha expression has been associated to cell proliferation and survival in several malignancies.[50] However, there are very few or no studies related to the role of PPAR alpha in ESCA and STAD. While the overexpression of PPAR gamma has been associated with Barrett's esophagus and esophageal adenocarcinoma.[51] Moreover, PPAR also plays an important function in pathogenesis of gastric carcinoma and is upregulated in gastric adenocarcinoma.[52,53] Rho GTPase dysregulation is linked to oncogenic alterations, cell survival and tumor metabolism, metastasis and chemoresistance.[54] In general, Rho GTPases are overexpressed in various cancers, including esophageal and gastric.[55] The importance of SUMOylation in human cancer has increasingly become apparent. The SUMO pathway may enhance cell proliferation, apoptosis resistance, and metastasis by altering proteins involved in carcinogenesis.[56] Previous research found that silencing the SUMO-1 gene enhanced the apoptotic rate of gastric cancer cells.[57] Furthermore, the interaction of circulating vitamin D with the vitamin D receptor (VDR) contributes to the regulation of cell differentiation, apoptosis and, cancer cell growth inhibition.[58] Some research suggests that Vitamin D and VDR may help with early detection or alternative therapy options for esophageal cancer; however, most studies have been ambiguous and contradictory.[59] Similarly, while several studies have linked vitamin D to stomach cancer, the precise role and mechanism of vitamin D during carcinogenesis is unknown. The higher consumption of vitamin D was shown to be related with an increased risk of gastric cancer[60] or in certain cases had no connection with gastric cancer.[61] Overall, we observed that the aberrant expression of DPP4 co-expresses a plethora of genes which are involved in the crucial molecular pathways governing gastroesophageal (esophageal, gastroesophageal junction, and gastric) carcinogenesis. Gastroesophageal (esophageal, gastroesophageal junction, and

gastric) cancer remains a significant clinical problem with an increasing rate of incidence and is associated with poor prognosis.

Additionally, to explore the role of DPP4 in regulating tumor immunology in both ESCA and STAD, the relationships between DPP4 expression and marker genes specific to immune cells were determined. DPP4 expression was found to be correlated with immune cell gene markers, suggesting its role in ESCA and STAD tumor immunology. M1 macrophages play a crucial role in suppressing cancers by impeding tumor cell development within the tumor microenvironment.[62] However, as cancer cells proliferate, the M2-like population expands significantly.[63] M2-like macrophages are known to aid cancer cells in metastasis, angiogenesis, and proliferation via several anti-inflammatory pathways.[63,64] According to a recent study on NSCLC, DPP4 inhibitor, anagliptin suppressed the macrophage differentiation and M2 macrophage polarization to exert its anti-tumor effects.[65] There is a possibility that this effect may apply to tumors arising from different tissues. In our study, the gene marker of M1 macrophage (IRF5) was negatively correlated, while the M2 macrophage marker (MS4A4A) was positively correlated with both ESCA and STAD. This finding suggests the relevance of high DPP4 expression in promoting M2 macrophage polarization, which might contribute to ESCA and STAD carcinogenesis. Interestingly, according to GEPIA, the TAM marker CD68 was positively associated with both ESCA and STAD cancer. TAM polarization is known to contribute to immunosuppression, invasion, and metastasis in several malignancies.[66,67] Our findings revealed the potential contribution of DPP4 to TAM polarization, indicating that DPP4 might be involved in the immunosuppression in ESCA and STAD. Neutrophils play an essential role in the infiltration of inflammatory cells in malignancies and may suppress the antitumor immune response mediated by CD8+ T cells.[68] As per GEPIA, we found a significant correlation between DPP4 and markers of neutrophil i.e., CEACAM8 and CCR7 in ESCA and STAD, which might affect tumor immunity through neutrophils. DPP4 also played a crucial role in Treg activation. The overexpression of DPP4 revealed a positive correlation with the expression of CCR8 and FOXP3 (Treg markers) in both ESCA and STAD. Interestingly, markers of T cell exhaustion PDCD1 (PD-1) and TIM-3 (HAVCR2) were both positively correlated with DPP4 expression in ESCA and STAD. The Treg cell marker FOXP3 has been shown to prevent attack of cytotoxic T cells on tumor cells, and TIM-3 is a critical protein found on the exhausted T cells surface.[69,70] Based on these findings, it was revealed that DPP4 expression might have had a significantly strong link with immune tolerance of tumor cells. Moreover, our results demonstrated the relationship between DPP4 expression and T helper cells, such as Th1 and Th2. GEPIA analysis showed the Th1 marker (STAT4) and Th2 marker (STAT5A) were significantly positively correlated with DPP4 in ESCA and STAD. As a result, DPP4 gene expression in ESCA and STAD may be implicated in the regulation of T-cell responses. Overall, our data suggested that DPP4 expression had a significant effect on immune infiltration and tumor-immune interaction in both ESCA and STAD. Understanding the role of DPP4 in ESCA and STAD might be very crucial in its involvement in gastroesophageal (esophageal, gastroesophageal junction and gastric) cancers.

In the present study, we utilized a variety of online databases to conduct a thorough bioinformatics investigation of DPP4 expression and the potential mechanisms involved in

various malignancies. This method allows for high sample sizes, cheap cost, and wide-scale genomics and functional investigations. The study we conducted had certain limitations, one of which was that all the information we utilized in our analysis was obtained from publicly available web databases. However, it can serve as a strong platform for future clinical research efforts aimed at providing precise clinical data in a larger sample cohort.

V. CONCLUSIONS

The present study was conducted to comprehend the role of DPP4 in tumor-immune interactions and cancer prognosis. According to the findings of this study, the expression of DPP4 is linked to esophageal and gastric cancer prognosis, as well as the infiltration of immune cells. In summary, DPP4 may serve as a useful biomarker for cancer prognosis as well as a key regulator of immune cell infiltration in patients with esophageal and gastric cancer. Our current study is based on publicly available databases, but further research is required to better understand the function of DPP4 in several pathological aspects of cancer. Additionally, further evaluations will help to establish if DPP4 might be a useful diagnostic and prognostic molecular signature and a potential therapeutic target for gastroesophageal (esophageal, gastroesophageal junction, and gastric) cancers.

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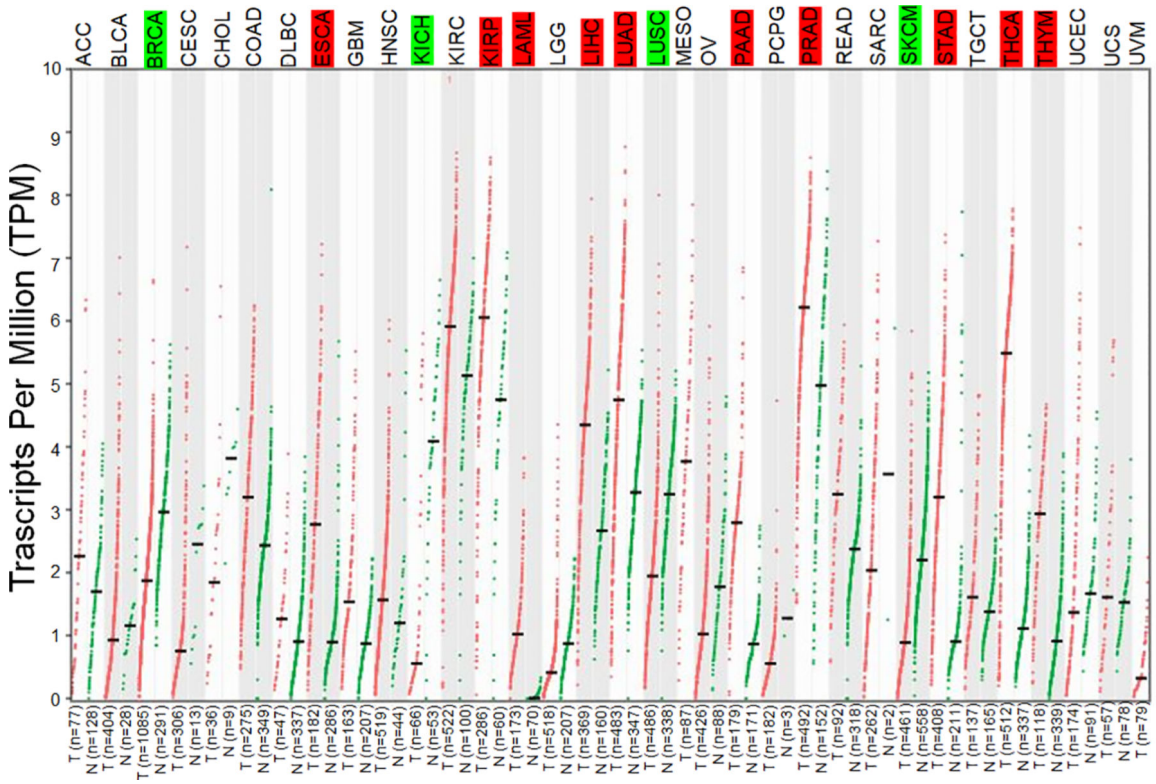

FIG. 1:

The differential expression of DPP4 in human cancers. The comparative data obtained from GEPIA represents expression of DPP4 in various tumor and normal tissues. Red color denotes the tumor tissues and green color denotes normal tissue. For the expression data, log2 (TPM+1) was used as the scaling factor. T, tumor; N, normal.

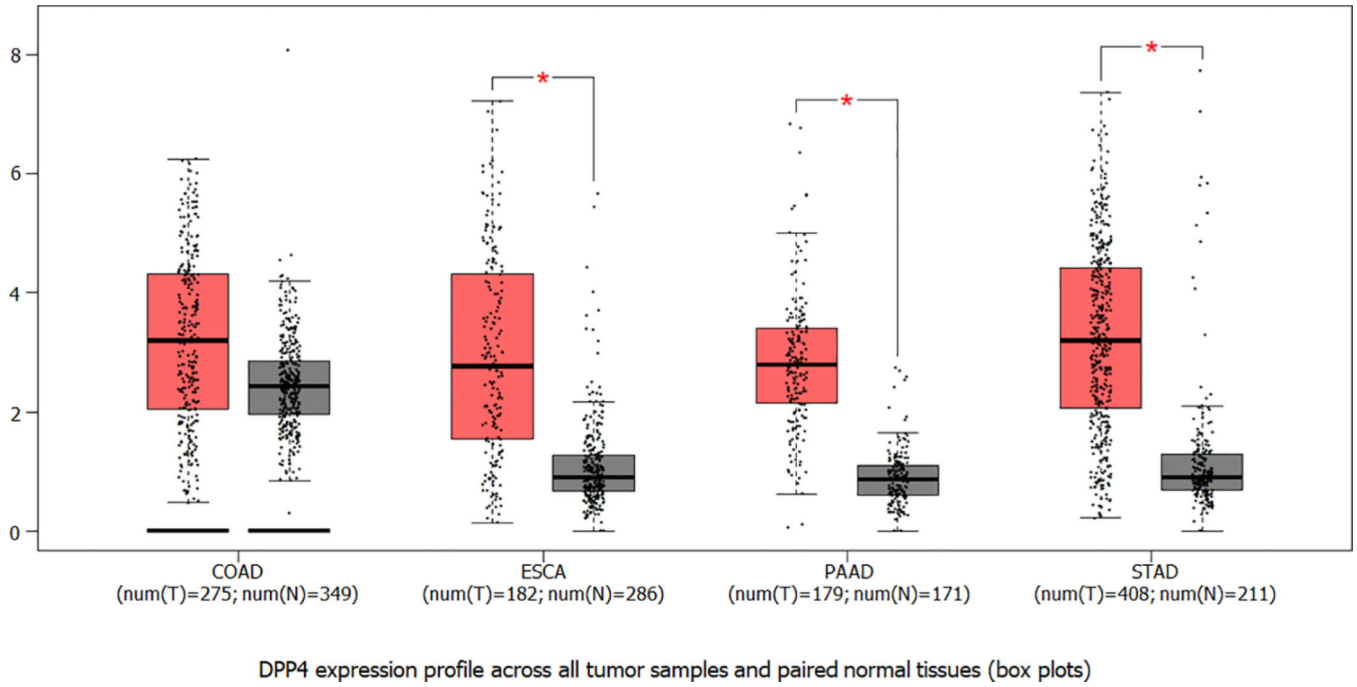

FIG. 2:

The GEPIA boxplot of DPP4 gene expressions in normal and COAD, ESCA, PAAD, STAD cancer tissues. The red box denotes cancer tissue and gray box denotes normal tissues (*P value cutoff 0.01).

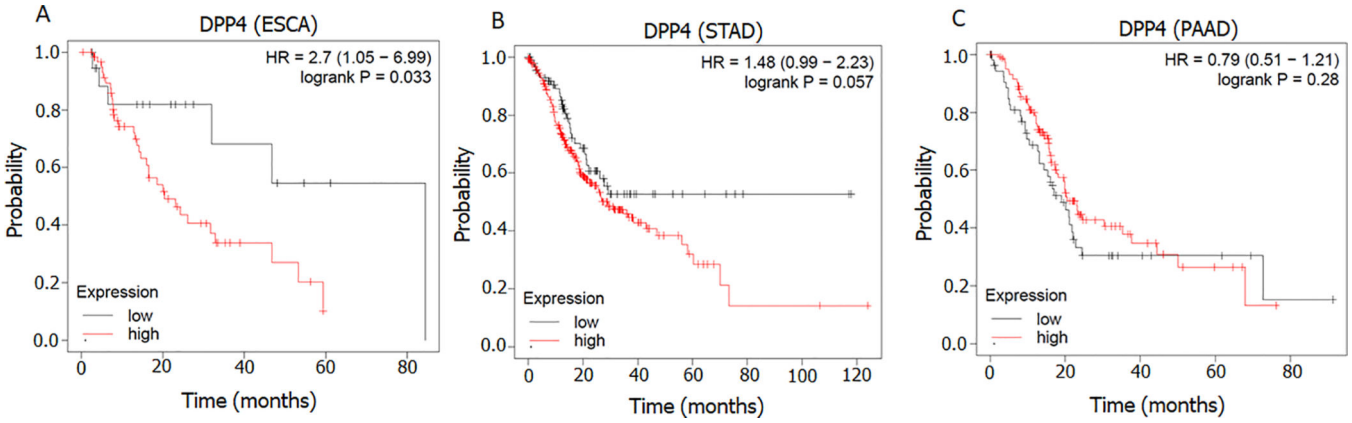

FIG. 3:

Comparison of overall survival with upregulated and downregulated expression of DPP4 in different ESCA, STAD and PAAD using Kaplan–Meier plotter. (A and B) DPP4 overexpression is associated with poor OS prognosis in ESCA and STAD, and (C) DPP4 expression exhibited no association with PAAD prognosis. OS, overall survival; HR, hazard ratio.

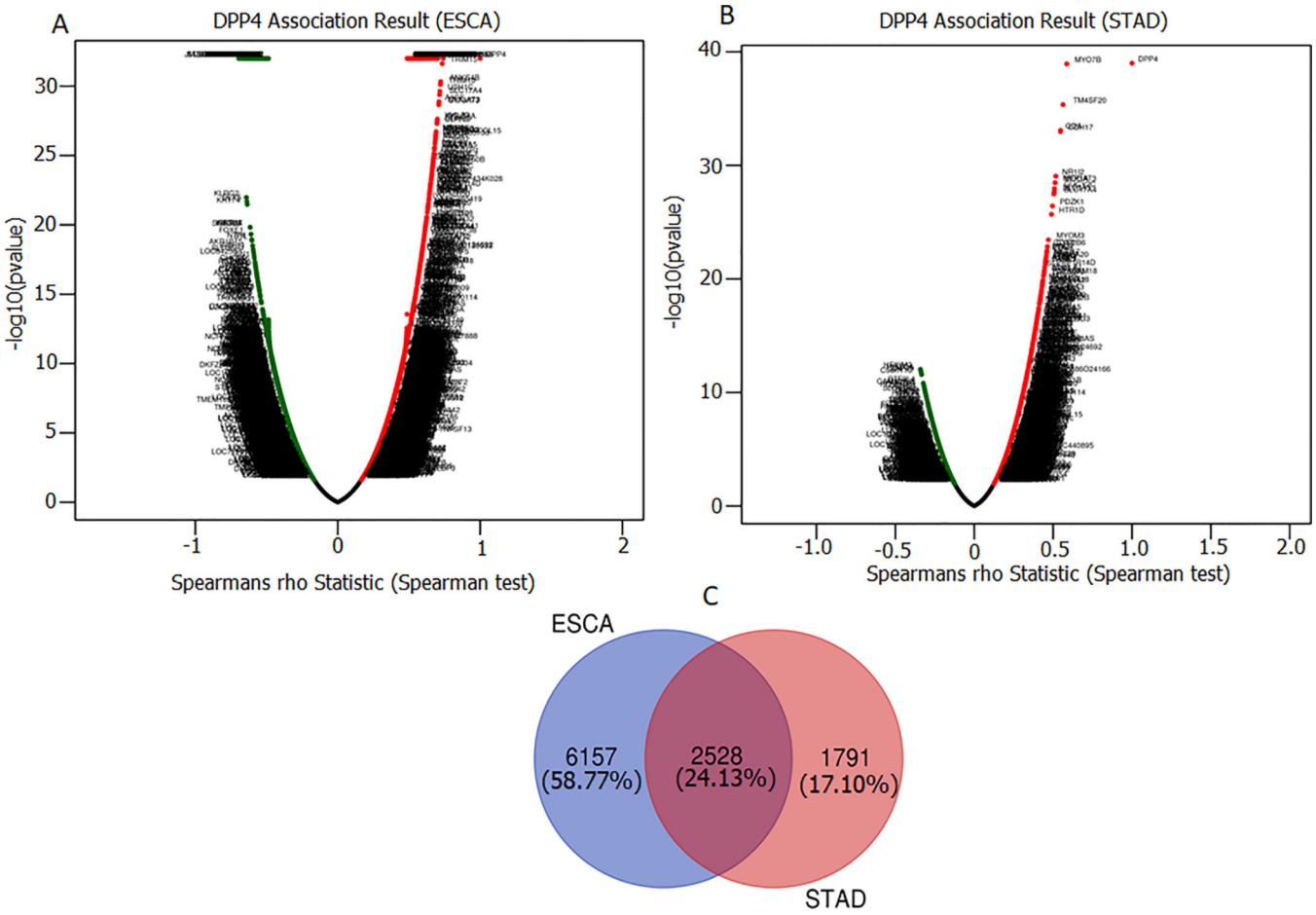

FIG. 4:

DPP4-associated co-expressed genes in ESCA and STAD. (A and B) The DPP4 associated genes were evaluated by Spearman's test in ESCA and STAD. Green dots denote positive and red dots denote negative correlations with DPP4, respectively. (C) Intersection of DPP4 associated genes in ESCA and STAD to determine commonly expressed genes.

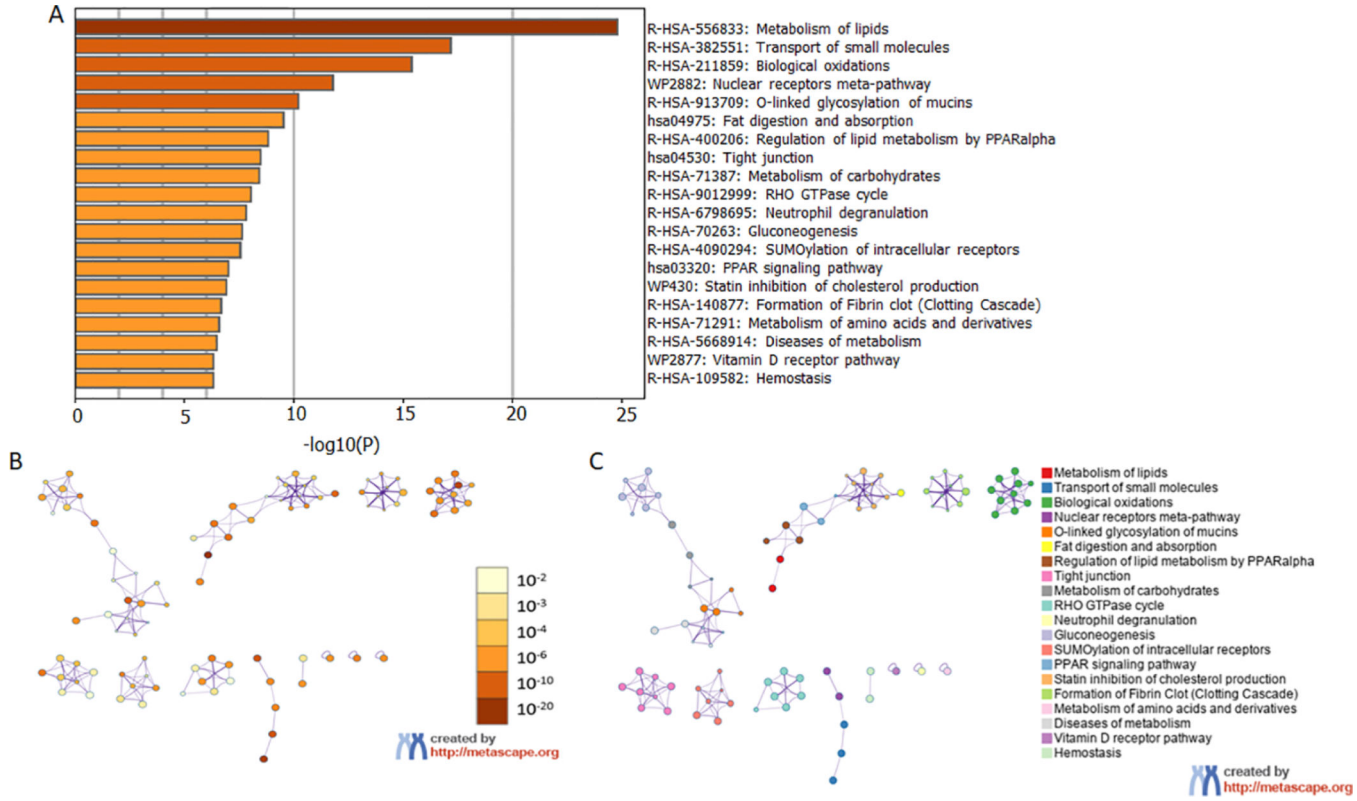

FIG. 5:

Pathway enrichment analysis of genes co-expressed with DPP4 in the Metascape platform. (A) The 20 most enriched biological pathways associated with DPP4 co-expressed genes are represented. (B) The co-expressed genes with DPP4 were depicted by different colors, which reflected different enrichment pathways. (C) Network of the top 20 biological processes enriched colored by cluster ID.

TABLE 1:

Correlations between DPP4 expression and markers genes of immune cells using GEPIA in ESCA and STAD

Description	Gene marker	ESCA				STAD			
		Tumor		Normal		Tumor		Normal	
		R	*P* value	*R*	*P* value	*R*	*P* value	*R*	*P* value
M1	IRF5	−0.059	0.09	0.09	0.76	0.43	***	0.23	0.17
M2	MS4A4A	0.12	***	0.54	0.06	0.16	***	0.26	0.13
TAM	CD68	0.24	***	0.58	0.04	0.59	***	0.58	***
Neutrophils	CEACAM8	0.32	***	0.23	0.44	0.39	***	0.014	0.94
	CCR7	0.22	***	0.26	0.38	0.34	***	0.26	0.12
Treg	CCR8	0.31	***	0.18	0.55	0.58	***	0.12	0.5
	FOXP3	0.26	***	0.33	0.27	0.55	***	0.088	0.61
T cell exhaustion	PDCD1 (PD-1)	0.16	***	0.18	0.55	0.19	***	0.21	0.22
	TIM-3 (HAVCR2)	0.41	***	0.69	0.11	0.48	***	0.35	0.035
Th1	STAT4	0.33	***	0.69	0.009	0.086	0.039	0.47	0.003
Th2	STAT5	0.24	***	0.69	0.011	0.32	***	0.086	0.62

*** $P \leq 0.001$, Spearman's rho.