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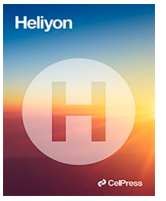

Research article

High expression levels of S1PR3 and PDGFRB indicates unfavorable clinical outcomes in colon adenocarcinoma

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ABSTRACT

Background: Studies verified that sphingosine kinase 1 (SPHK1)/sphingosine 1-phosphate receptors (S1PRs) and platelet-derived growth factor receptors (PDGFRs) play important roles in tumor occurrence and progression. However, the expression and clinical value of SPHK1/S1PRs and PDGFRs in colon adenocarcinoma (COAD) remains unclear. This study aimed to explore the expression of SPHK1/S1PRs and PDGFRs in COAD and further investigate their roles in predicting the prognosis of patients with COAD.

Methods: SPHK1/S1PRs and PDGFRs expression in tissues from patient with COAD were analyzed using The Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx) databases. Kaplan–Meier survival analysis was used to evaluate the prognostic roles of SPHK1/S1PRs and PDGFRs in patients with COAD. Spearman's correlation analysis was performed to assess the relationship between SPHK1/S1PRs and PDGFRs in COAD. Then, $\chi 2$ test was performed to analyze the correlation between SPHK1/S1PR3/PDGFRB and clinicopathological characteristics of the patients. Additionally, possible signaling pathways co-regulated by S1PR3 and PDGFRB were predicted using Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) functional enrichment analyses. Least absolute shrinkage and selection operator (LASSO) regression was used to identify hub genes that co-regulated S1PR3 and PDGFRB expression. A prognostic model based on hub genes was constructed for patients with COPD. Finally, the relationship between the hub genes and tumor immune cell infiltration was investigated.

Results: The expression levels of SPHK1 and PDGFRB were significantly upregulated in COAD patient tissues ($P < 0.001$ and $P < 0.001$, respectively). Moreover, Kaplan–Meier analysis showed that patients with COAD with high expression levels of SPHK1 and S1PR3 had shorter overall survival (OS) than those with low expression levels ($P = 0.013$ and $P = 0.005$, respectively). Spearman's correlation analysis verified a strong positive correlation ($P < 0.001$, $r = 0.790$) between the expression of S1PR3 and PDGFRB. In addition, we found that high SPHK1 and PDGGRB expression levels were associated with perineural invasion ($P < 0.001$ and $P = 0.011$, respectively). High expression of S1PR3 and PDGGRB was prominently associated with N stage ($P = 0.002$ and $P = 0.021$, respectively). High levels of SPHK1, S1PR3, and PDGFRB were associated with lymph node invasion. ($P = 0.018$, $P = 0.004$, and $P = 0.001$, respectively). GO and KEGG results revealed that S1PR3 and PDGFRB may participate in COAD cell extracellular

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matrix organization and cellular signal transduction. Five hub genes, SFRP2, GPRC5B, RSPO3, FGF14, and TCF7L1, were identified using LASSO regression. Survival analysis showed that the OS in the high-risk group was remarkably shorter than that in the low-risk group. The results indicated that tumor immune cells were significantly increased in the high-risk group compared to those in the low-risk group.

Conclusions: S1PR3 and PDGFRB may be important markers for predicting lymphatic metastasis and poor prognosis in patients with COAD. The underlying mechanisms may involve immune cell infiltration.

1. Introduction

Colon cancer has the fifth highest incidence and mortality rate among all cancers, and is one of the most common malignancies in the world [1,2]. Colon adenocarcinoma (COAD) is the most common and aggressive type of colon cancer [3]. Despite improvements in radical resection and chemotherapy, the 5-year overall survival (OS) rate in patients remains unsatisfactory [4]. Clinical evidence shows that the 5-year OS rate of patients with stage III/IV is only 12.5 % [5]. Lymphatic node invasion, which is more common in COAD than vascular invasion, is responsible for the low OS rate, as it is associated with poor prognosis [6]. Therefore, exploring the mechanism underlying lymphatic metastasis may help improve the prognosis of patients.

SPHK1 converts sphingosine to sphingosine 1 phosphate (S1P) and is an important regulator of cancer development and metastasis [7]. S1P binds to S1PRs, which play a vital role in cancer lymphangiogenesis and lymphatic metastasis [8]. Recent studies have shown that SPHK1 promotes colon cancer cell proliferation and migration by upregulating S1PR1 expression [9]. However, the clinical significance of SPHK1/S1PRs in COAD remains unknown.

The PDGFRs family is essential for physiological processes such as the migration and tube formation of endothelial cells, which contribute to angiogenesis and lymphangiogenesis [10]. Previous studies have verified that PDGFR, which is abnormally expressed in various tumors, is associated with cancer metastasis and cancer-related angiogenesis [11]. PDGFRA and PDGFRB are classic proto-oncogenes that encode receptor tyrosine kinases that respond to platelet-derived growth factor (PDGF) [12]. A previous study showed that PDGFRA was upregulated in oral squamous cell carcinoma and breast cancer, and was positively associated with cancer metastasis and poor prognosis [13,14]. Simultaneously, high PDGFRB expression was negatively correlated with the prognosis in gastric cancer. Another study revealed involvement of PDGFRB in promoting angiogenesis and modulating the tumor immune microenvironment [15]. However, the expression and clinical significance of PDGFRA/PDGFRB in COAD requires further research.

In this study, we explored the expression of SPHK1/S1PRs and PDGFRs in the tissues of patients with COAD using the cancer genome atlas (TCGA) and genotype-tissue expression (GTEx) databases. Kaplan–Meier survival analysis and log-rank tests were used to investigate the role of SPHK1/S1PRs and PDGFRs in predicting the prognosis of patients with COAD. Moreover, the relationship between the expression of SPHK1/S1PRs/PDGFRs and the clinical characteristics of patients with COAD was analyzed. The possible correlation between SPHK1/S1PRs and PDGFRs in COAD was evaluated. Additionally, we analyzed the potential biological functions and signaling pathways co-mediated by S1PR3 and PDGFRB in COAD using Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) functional enrichment analyses. Hub genes co-regulated with S1PR3 and PDGFRB were identified using LASSO regression, and a prognostic model based on hub genes was constructed for patients with COAD. Finally, the ssGSEA algorithm was used to investigate the levels of immune cell infiltration in patients with COAD.

2. Materials and methods

2.1. Patient information

TCGA, GTEx, and Gene Expression Omnibus (GEO) databases were used to explore the gene expression profiles of SPHK1/S1PRs and PDGFRs in 349 patients with COAD and 290 healthy controls. The patients with COAD were divided into high and low expression groups based on the median values of SPHK1, S1PR3, and PDGFRB expression. Subsequently, the detailed clinical information of the patients was retrieved for further analysis. The Human Protein Atlas (http://www.proteinatlas.org) database was used to detect the tissue expression and localization of SPHK1 and PDGFRB.

2.2. Correlation between SPHK1/S1PRs and PDGFRs in COAD

To investigate the correlation of SPHK1/S1PRs and PDGFRs in COAD, Spearman's correlation analysis was performed. Kaplan–Meier survival analysis was used to investigate the prognostic roles of SPHK1/S1PRs and PDGFRs in overall survival (OS).

2.3. GO and KEGG function analysis

The genes co-regulated by S1PR3 and PDGFRB were identified using the criteria $r > 0.6$ or $p < 0.01$. Subsequently, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) functional enrichment analyses were performed to investigate the possible biological functions of S1PR3 and PDGFRB co-regulation in COAD.

2.4. Construction of risk scoring and survival time model

LASSO regression was used to investigate the risk stratification of patients with COAD. The risk score was as follows: SFRP2*0.0067+GPRC5B*0.1926-RSPO3*0.0881+FGF14*0.4365+TCF7L1*0.1473. After calculating the risk score, patients were divided into low- and high-risk groups based on the median risk score. Cox regression analysis was used to perform survival analysis of patients with COAD in both groups.

2.5. Identification of immune cells in patients with COAD

Single-sample gene cluster enrichment analysis (ssGSEA) is an extension of the GSEA method. R packages (GSVA, GSEABase, and limma) were used to calculate the content of 24 types of immune cells in the high- and low-risk groups.

2.6. Statistical analysis

All statistical analyses were performed using SPSS software (version 22.0; IBM SPSS, Chicago, IL, USA) and R software 3.5.3. A *t*-test was used to explore the difference in SPHK1/S1PRs and PDGFR expression between patients with COAD and healthy controls. Kaplan–Meier survival curves were used to investigate the overall survival (OS) of patients with COAD. The relationship between the expression levels of SPHK1, S1PR3, PDGFRB and clinicopathological characteristics of the patients with COAD was analyzed using a $\chi 2$ test. The correlation between S1PR3 and PDGFRB expression in COAD tissues was calculated using Spearman's correlation. Statistical significance was set at $P < 0.05$.

3. Results

3.1. The expression levels of SPHK1 and PDGFRB were significantly upregulated in tissues from patients with COAD

The TCGA and GTEx databases were used to explore the expression of SPHK1/S1PRs and PDGFRs in tissues from patients with COAD. The results showed that the mRNA expression levels of SPHK1 and PDGFRB were significantly increased in the patients with COAD ($P < 0.001$ and $P < 0.001$, respectively). In contrast, compared with the healthy control group, the mRNA expression levels of S1PR1 and PDGFRA were significantly downregulated in the patients ($P < 0.001$ and $P < 0.001$, respectively) (Fig. 1). No differences were observed in the expression of S1PR2 or S1PR3 between the two groups. The expression levels of these proteins in tumor tissues and paired normal adjacent tissues from patients with COAD were verified using the GEO database (GSE44076). Representative images revealed that PDGFRB and SPHK1 protein expression was increased in patient tissues (Fig. 2).

3.2. High SPHK1 and S1PR3 expression levels predicted poor prognosis in patients with COAD

Subsequently, the effects of SPHK1/S1PRs and PDGFRs on the OS of patients with COAD were evaluated using Kaplan–Meier

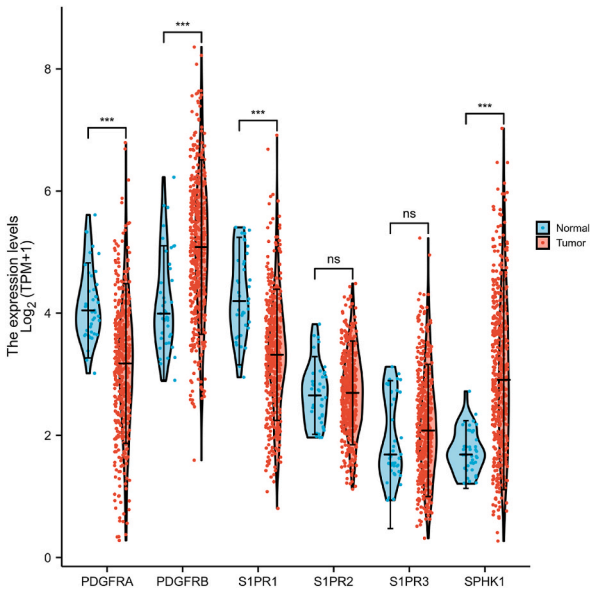

Fig. 1. SPHK1 and PDGFRB were increased in tissues from patients with COAD. The mRNA expression levels of SPHK1, S1PRs, PDGFRA and PDGFRB in patient tissues versus normal samples from the TCGA and GTEx database were analyzed. ***$P < 0.001$.

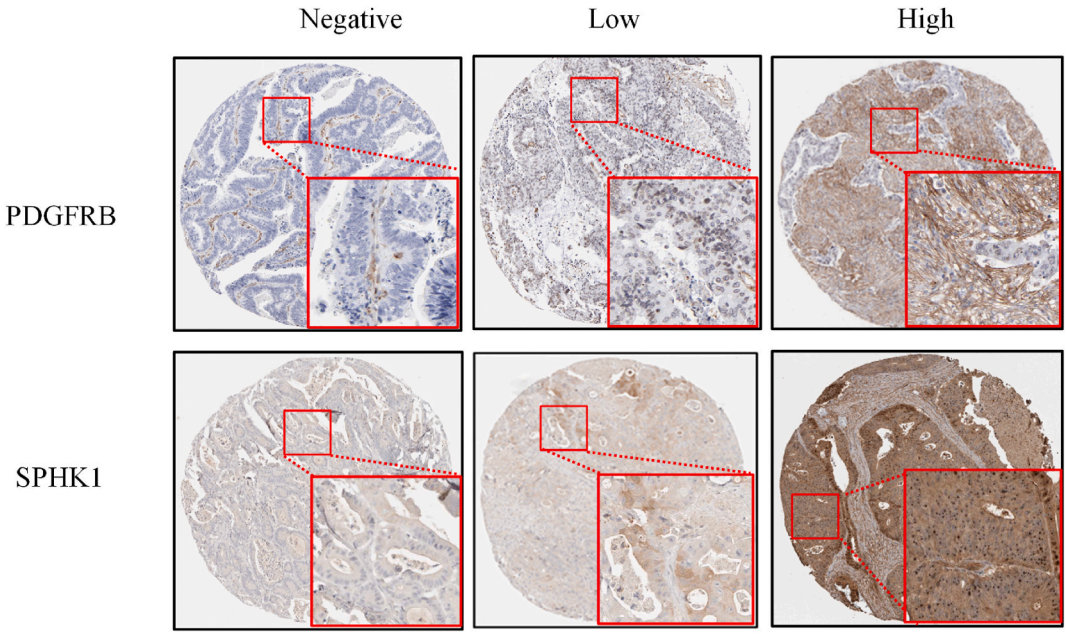

Fig. 2. Immunohistochemical staining of PDGFRB and SPHK1 in tissues from healthy controls and patients with COAD in the Human Protein Atlas database. The low and high correspond to the weak and strong intensity of immunohistochemical staining, respectively.

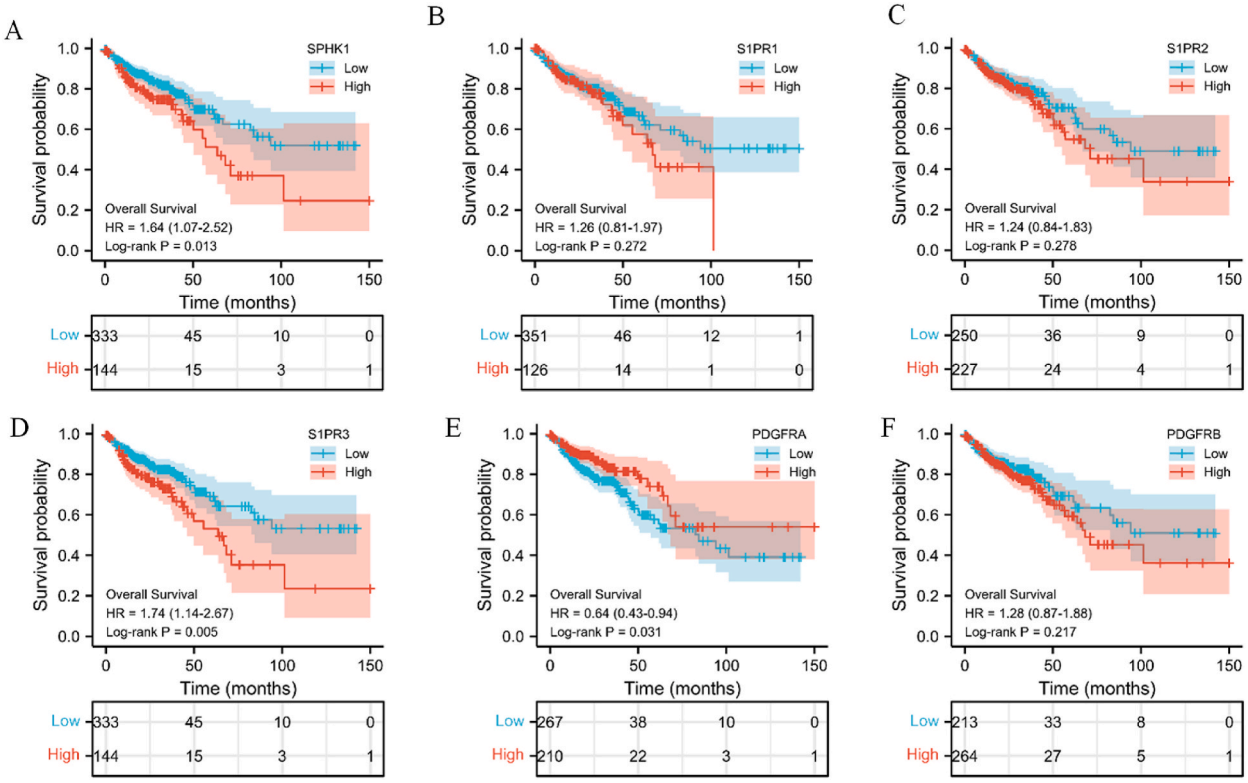

Fig. 3. Kaplan–Meier curves show the OS of patients with COAD with different expression levels of SPHK1, S1PR1, S1PR2, S1PR3, PDGFRA, and PDGFRB.

survival analysis and log-rank tests. The results revealed that patients with COAD with high expression levels of SPHK1 and S1PR3 had shorter OS than patients with low expression levels (P = 0.013 and P = 0.005, respectively), indicating that SPHK1 and S1PR3 may be potential markers for predicting the prognosis of patients with COAD. However, patients with COAD with high PDGFRA expression levels had longer OS than those with low expression levels (P = 0.031) (Fig. 3).

3.3. Correlation between SPHK1/S1PRs and PDGFRs in COAD

Based on these results, we further analyzed the correlation between SPHK1/S1PRs and PDGFRs in COAD. The results of TCGA database analysis showed a strong positive correlation (P < 0.001, r = 0.790) between S1PR3 and PDGFRB expression levels in COAD (Fig. 4) (Table 1).

3.4. High expression of SPHK1, S1PR3, and PDGFRB indicated unfavorable clinical symptoms of patients with COAD

SPHK1 and PDGFRB were highly expressed in patients with COAD. Moreover, increased SPHK1 and S1PR3 expression predicted poor prognosis in patients with COAD. To better understand the associations between the expression levels of the three proteins and clinicopathological parameters of patients with COAD, data from 239 patients with COAD were analyzed in detail. The patients were divided into high- and low-expression groups based on the median values of SPHK1, S1PR3, and PDGFRB expression. As shown in Table 2, there were no significant differences between the expression levels of the three proteins by the patients' age, gender, M stage, and CEA level (all P > 0.05). We found that high SPHK1 and PDGGRB expression levels were strongly related to residual tumors (P = 0.018 and P = 0.045, respectively) and perineural invasion (P < 0.001 and P = 0.011, respectively). In addition, high S1PR3 and PDGGRB expression levels were associated with the N stage (P = 0.002 and P = 0.021, respectively). More importantly, the results verified that high SPHK1, S1PR3, and PDGFRB expression levels were significantly associated with positive lymph invasion (P = 0.018, P = 0.004, and P = 0.001, respectively), suggesting that SPHK1, S1PR3, and PDGFRB synergistically promote lymph node metastasis in COAD.

3.5. Bioinformatics analysis of S1PR3 and PDGFRB co-regulated genes

In total, 2096 genes related to the prognosis of patients with COAD were selected using univariate Cox regression analysis. There were 1022 genes related to PDGFRB and 668 genes related to S1PR3. After combining these three results, 34 genes were selected as co-regulated (Fig. 5A). To further investigate the role of these 34 genes in COAD, GO and KEGG analyses were performed to predict the potential biological functions and signaling pathways mediated by S1PR3 and PDGFRB. KEGG pathway analysis revealed that the 34 genes were mainly involved in the Wnt signaling pathway and focal adhesion (Fig. 5B). GO term enrichment analysis of the co-regulated genes indicated that the 34 genes were mainly involved in cytoskeletal rearrangements (Fig. 5C). GO and KEGG analyses showed that S1PR3 and PDGFRB may participate in COAD cell cytoskeletal rearrangement and cellular signal transduction.

3.6. Construction of a prognostic model of the S1PR3 and PDGFRB co-regulated genes

Bioinformatics analysis showed that there were 34 genes not only related to the prognosis of COAD patients, but also to the

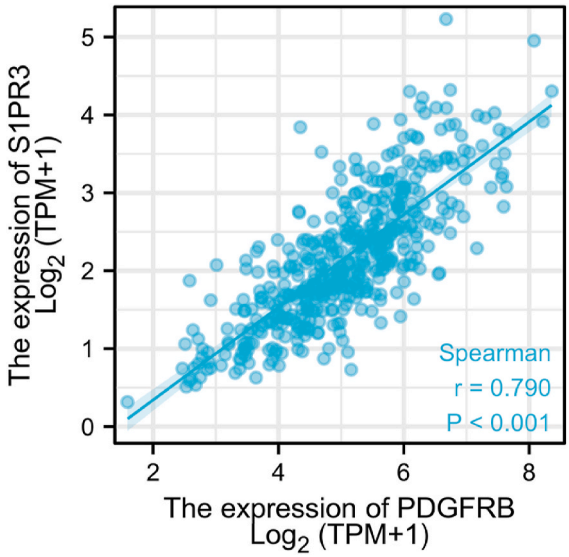

Fig. 4. Correlation between S1PR3 and PDGFRB expression levels in tissues from patients with COAD analyzed from the TCGA and GTEx databases.

Table 1
Correlation between the expression levels of SPHK1/S1PRs and PDGFRs in COAD.

	PDGFRA	*P*	PDGFRB	*P*
SPHK1	0.290	2.71e-11	0.687	2.25e-74
S1PR1	0.710	1.36e-81	0.719	1.66e-84
S1PR2	0.26	2.18e-9	0.607	3.98e-54
S1PR3	0.567	7.90e-46	**0.790**	1.03e-103

Table 2
Correlation between the expression levels of SPHK1, S1PR3, PDGFRB and clinicopathological characteristics of patients with COAD.

Parameters		SPHK1			S1PR3			PDGFRB		
		Low (239)	High (239)	*P*	Low (239)	High (239)	*P*	Low (239)	High (239)	*P*
Age	≥65	93	101	0.514	86	108	0.05	94	100	0.641
	<65	146	138		153	131		145	139	
Gender	Female	113	113	1.000	112	114	0.927	107	119	0.314
	male	126	126		127	125		132	120	
Pathologic stage	I	44	37	0.551	47	34	**0.03**	42	39	0.355
	II	93	94		103	84		100	87	
	III	6	73		57	76		58	75	
	IV	35	31		27	39		42	39	
T stage	T1	5	6	0.639	9	2	**0.017**	7	4	0.535
	T2	46	37		47	36		44	39	
	T3	160	163		161	162		161	162	
	T4	27	33		22	38		26	34	
N stage	N0	149	135	0.100	160	124	**0.002**	154	130	**0.021**
	N1	56	52		47	61		53	55	
	N2	34	52		32	54		32	54	
M stage	M0	171	178	0.641	181	168	0.134	172	177	0.843
	M1	35	31		27	39		34	32	
CEA level	≤5	90	106	0.524	95	101	0.989	93	103	0.943
	>5	54	53		51	56		52	55	
Lymphatic invasion	No	140	126	**0.018**	144	122	**0.004**	146	120	**0.001**
	Yes	68	100		66	102		65	103	
Colon polyps	No	145	117	**0.034**	129	133	0.658	132	130	0.724
	Yes	64	82		76	70		77	69	
Residual tumor	R0	161	185	**0.018**	174	172	1.00	165	181	**0.045**
	R1	2	2		2	2		1	3	
	R2	18	6		12	12		165	181	
Perineural invasion	No	74	61	**<0.001**	59	76	0.375	63	72	**0.011**
	Yes	9	37		16	30		11	35 (	

expression levels of PDGFRB and S1PR3. LASSO regression was then used to select 5 hub genes (SFRP2, GPRC5B, RSPO3, FGF14, and TCF7L1) from the 34 genes. The risk score for each patient was calculated using the TCGA cohort. Patients were divided into high- and low-risk groups based on the median risk score. Survival analysis demonstrated that the OS in the high-risk group was shorter than that in the low-risk group (Fig. 6).

3.7. Differences in immune infiltration between the high- and the low-risk groups

High expression of the five hub genes was associated with poor prognosis in patients with COAD. The ssGSEA algorithm was used to further assess the relationship between hub genes and immune cell infiltration. The results showed a significant correlation between the five hub genes (SFRP2, GPRC5B, RSPO3, FGF14, and TCF7L1) and immune cells. Counts of B cells, cytotoxic cells, DC, eosinophils, iDC, Macrophages, Mast cells, Neutrophils, CD56dim cells, NK cells, pDC, T cells, Tcm, Tem, TFH, Tgd, Th1 cells, and Tregs were significantly higher in the high-risk group than in the low-risk group. However, Th17 and Th2 cells were negatively correlated with the risk score (Fig. 7). This suggests that hub genes may be involved in tumor immune cell infiltration.

4. Discussion

COAD is one of the most fatal cancers worldwide. Currently, recurrence and metastasis are the major factors that limit the survival of patients [16]. Despite improvements in targeted therapies, the survival rate of patients remains unsatisfactory [17]. Currently, there is an urgent need to accurately predict the prognosis of patients and develop effective treatments to prevent cancer cell invasion and metastasis. In this study, potential prognostic factors of patients with COAD were analyzed to evaluate their prognostic prediction capability.

Previous studies have shown that SPHK1 and PDGFR are abnormally expressed in many types of cancer and participate in tumor

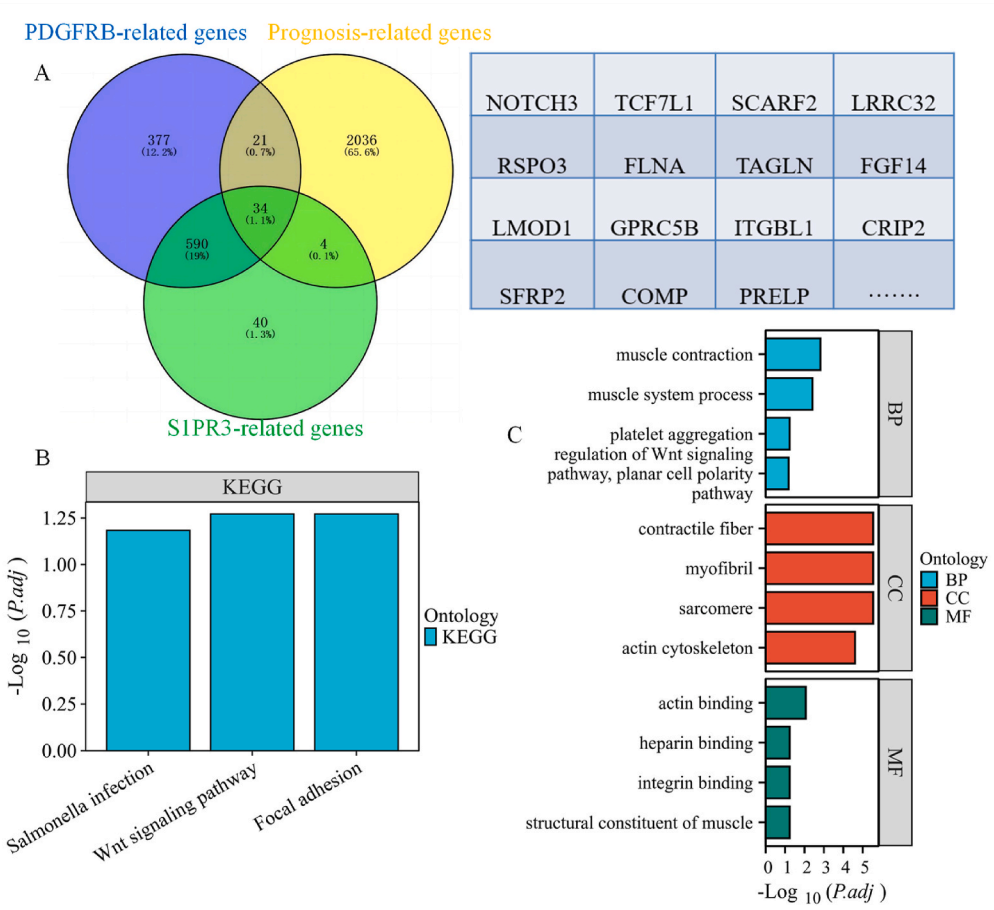

Fig. 5. GO term and KEGG analysis of the co-related genes. (A) Genes selected by combining results of prognosis related genes and S1PR3/PDGFRB related genes in COAD. (B) KEGG enrichment. The length of the bars is proportional to the number of genes. (C) GO term enrichment. The y-axis shows the GO terms of biological process. The length of the bars is proportional to the number of genes. GO, gene ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.

progression, including cancer cell invasion and metastasis [18,19]. SPHK1 has been identified as an oncogene in gastric cancer, suggesting that SPHK1 is a potential biomarker and therapeutic target [20]. S1PRs expression is tissue specific and plays an important role in regulating cell proliferation and metastasis in various cancers [21]. Previous studies have found that PDGFRB plays a crucial role in breast cancer tumorigenesis and metastasis and may be a potential therapeutic target for breast cancer treatment [22]. Therefore, we analyzed TCGA and GTEx databases to evaluate the expression of SPHK1/S1PRs and PDGFR in COAD. Consistent with previous reports on lung and gastric cancer [23,24], our results showed that the mRNA expression of SPHK1 and PDGFRB was significantly upregulated in the COAD group, suggesting that SPHK1 and PDGFRB might play vital roles in COAD development. Further studies revealed that patients with COAD with high SPHK1 and S1PR3 expression had shorter OS than those with low expression, indicating that SPHK1 and S1PR3 are related to poor prognosis. Therefore, SPHK1 and S1PR3 may serve as markers for the diagnosis and prognosis of COAD.

Our previous study verified that S1PR3 and lymphatic endothelial hyaluronic acid receptors (LYVE-1) are co-localized in lymphatic endothelial cells and participate in tumor lymphangiogenesis [25]. PDGFRB and LYVE-1 were confirmed as “partners” involved in the opening of lymphatic intercellular junctions [26]. Combined with the expression level of SPHK1 in COAD and its role in predicting the prognosis of patients with COAD, we hypothesized that SPHK1, S1PR3, and PDGFRB may coordinate COAD progression. The results showed that the expression of SPHK1, S1PR3, and PDGFRB was markedly associated with lymph invasion, indicating that they might synergistically promote COAD lymph node metastasis. A recent study showed that SPHK1 enhanced colon cancer cell proliferation and invasion by upregulating MMP-2/9 expression [27]. SPHK1 promotes colorectal cancer metastasis through the FAK/AKT/MMP pathway [28]. However, the mechanism of SPHK1-induced lymphatic metastasis remains unclear. In this study, high S1PR3 and PDGGRB expression was associated with N stage in patients with COAD. The correlation between SPHK1/S1PRs and PDGFR expression in COAD was analyzed. The results revealed a strong positive correlation between S1PR3 and PDGFRB expression. In addition, S1PR3 and PDGFRB, as receptors on the cell surface, interact with LYVE-1. Therefore, we propose that S1PR3 and PDGFRB colocalize in the cytomembrane and function as complex receptors for binding S1P. This may be the mechanism underlying COAD metastasis.

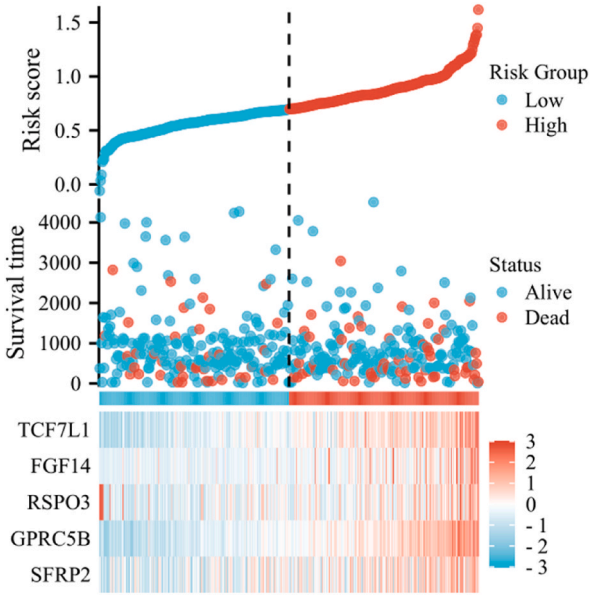

Fig. 6. Construction of risk score and survival time model of patients with COAD in high- and low-risk groups.

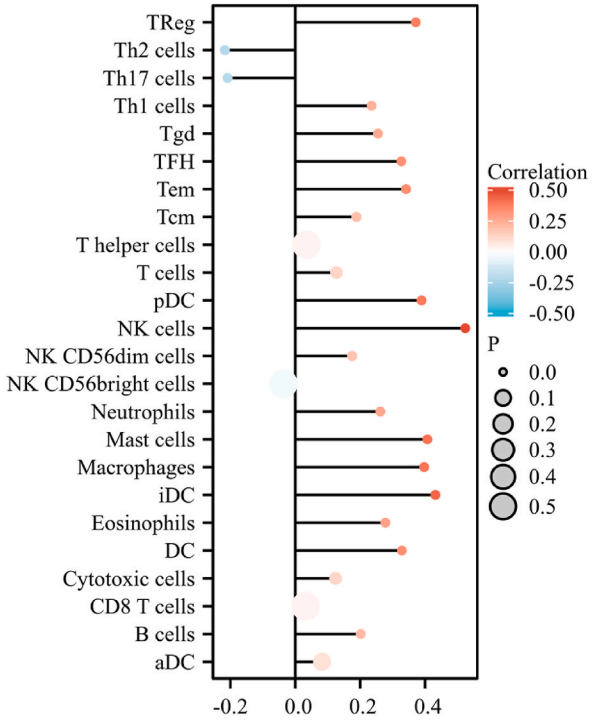

Fig. 7. The correlation of the immune cell infiltration in the high-r and the low-risk groups.

SPHK1 is a synthetase of S1P, an important component of the extracellular matrix in the tumor microenvironment [29]. S1P promotes cancer progression by stimulating lymphatic spread and lymphangiogenesis in breast cancer and esophageal squamous cell carcinoma [30,31]. In the present study, GO and KEGG pathway analyses showed that S1PR3 and PDGFRB were mainly involved in cytoskeletal rearrangement and cellular signal transduction. Then the hub genes regulated by S1PR3 and PDGFRB were further investigated to explore the molecular mechanism underlying COAD metastasis, which might be target genes in applicable to pancreatic cancer therapy. Five hub genes (SFRP2, GPRC5B, RSPO3, FGF14, and TCF7L1) were selected using LASSO regression. SFRP2 is an oncogene in urothelial cells and is associated with lymphatic metastasis and vascular invasion [32]. GPRC5B was reported as a novel

invasion-related gene for prognosis prediction in COAD, and FGF14 promotes tumor aggressiveness in breast cancer [33,34]. These reports indicate that hub genes play important roles in cancer progression. Our results were consistent with those of previous studies. In the present study, survival analysis suggested that the OS in the high-risk group was significantly shorter than that in the low-risk group. A recent study indicated that tumor-associated immune cells, including macrophages, mast cells, and neutrophils, promote lymphangiogenesis and lymphatic metastasis by regulating VEGFC-VEGFR3 signaling in tumor microenvironment [35,36]. T and NK cells promote lymphatic metastasis and invasion in COAD and rectal cancer, respectively [37,38]. In this study, the results of immune cell infiltration showed that NK and T cells were significantly increased in the high-risk group compared to the low-risk group, suggesting that hub genes might recruit T and NK cells for lymphatic metastasis in COAD.

In the TCGA COAD cohort, we found that the expression levels of S1PR3 and PDGGRB were prominently associated with N stage and lymph invasion. Subsequently, SFRP2, GPRC5B, RSPO3, FGF14, and TCF7L1 were screened as hub genes that might participate in COAD development by regulating immune cell infiltration and cancer invasion. However, the function of S1PR3 and PDGGRB in COAD needs further exploration in vivo. Moreover, the role of S1PR3 and PDGGRB in immune cell infiltration and COAD invasion needs to be verified in vitro experiments.

In conclusion, this study demonstrates for the first time that the expression levels of SPHK1 and PDGFRB are significantly upregulated in COAD. High expression of S1PR3 and PDGFRB may be involved in cancer lymphatic metastasis by regulating immune cell infiltration through downstream hub genes. Thus, S1PR3 and PDGFRB may serve as novel markers for predicting COAD prognosis. However, the specific in vitro mechanism remains unclear.

Data availability

Data will be made available on request.

CRediT authorship contribution statement

Mengsi Yu: Writing – original draft, Resources. **Kainan Zhang:** Software, Methodology, Data curation. **Song Wang:** Writing – review & editing.

Declaration of competing interest

The authors have declared that no competing interest exists.

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