Original Article

Prognostic roles of the expression of sphingosine-1-phosphate metabolism enzymes in non-small cell lung cancer

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Background: Sphingosine-1-phosphate (S1P), a bioactive lipid, is generally increased in human non-small cell lung cancer (NSCLC). Evidence has shown that the levels of enzymes in S1P metabolism were associated with clinical outcomes in patients with NSCLC. Nevertheless, the roles of mRNA expression of major enzymes (*SPHK1*, *SPHK2* and *SGPL1*) in S1P metabolism for predicting outcomes in NSCLC patients have not been determined.

Methods: "The Kaplan-Meier plotter" (the KM plotter) is an online database which contains gene expression and clinical data of 1,928 NSCLC patients. In this study, we analyzed the relationship between mRNA expression of major enzymes in S1P metabolism and overall survival (OS) in 1,926 NSCLC patients with the KM plotter. Further analyses stratified by smoking history, non-metastasis patents, clinical stages, negative surgical margin, chemotherapy and radiotherapy were also performed.

Results: High *SPHK1* mRNA expression [hazard ratio (HR) 1.47, 95% confident interval (CI): 1.28–1.68, P=2.6e-08] was significantly correlated to worse OS, but high *SPHK2* (0.66, 95% CI: 0.59–0.75, P=1.9e-10) or *SGPL1* (HR 0.64, 95% CI: 0.55–0.75, P=8.7e-09) mRNA expression was in favor of better OS in NSCLC patients.

Conclusions: The mRNA expression of *SPHK1*, *SPHK2*, and *SGPL1* is potential predictor of outcomes in NSCLC patients.

Keywords: Sphingosine-1-phosphate (S1P); RNA, messenger; carcinoma; non-small cell lung cancer (NSCLC)

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Introduction

Lung cancer is one of the most common and deadly tumors, contributing to 1.8 million new cancer cases and 1.6 million cancer-related deaths worldwide every year (1). Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, and accounts for 85% of all lung cancer (2). Lung adenocarcinoma (Ade) and lung squamous cell carcinoma (SCC) are major types of NSCLC, representing almost 50% and 35% of NSCLC cases, respectively. Despite progress in treatments for NSCLC, most patients present with advanced stage and a poor five-year survival rate (3). Thus, further exploration of the potential prognostic biomarkers

and therapeutic targets in NSCLC is still a priority.

Sphingosine-1-phosphate (S1P) is a bioactive lipid generated from sphingosine by phosphorylation catalyzed by two distinct sphingosine kinase isoforms, SPHK1, and SPHK2 (4). S1P can be reversibly dephosphorylated by S1P phosphatases and lipid phosphate phosphatases or irreversibly degraded by S1P lyase (SGPL1) (4,5). S1P exerts most of its effects by autocrine or paracrine. Intracellular S1P is transported out by ATP-binding cassette transporters (ABC transporters) and spinster homolog 2 (Spns2) and binds to five membrane G-protein-coupled receptors, S1PR1-5 (4). The intracellular effects of S1P are independent of S1PRs (6). S1P plays pivotal roles in many physiological processes, including cell growth, migration, autophagy, angiogenesis, and survival (6). Previous studies have linked aberrant S1P signaling to tumor progression, invasion, metastasis, chemo- and radio-resistance in NSCLC (4,7,8). It was reported that the levels of sphingosine kinases were correlated with clinical outcomes of NSCLC patients (9,10). However, the prognostic roles of mRNA expression of *SPHK1*, *SPHK2* and *SGPL1* in NSCLC patients have not been determined.

The "Kaplan-Meier plotter" (KM plotter) is a widely used online database, which contains data from Cancer Biomedical Informatics Grid (caBIG), the Gene Expression Omnibus (GEO), and The Cancer Genome Atlas (TCGA) lung cancer datasets. Gene expression and clinical data are integrated simultaneously by a PostgreSQL server (11). The KM plotter has been used for identifying genes as potential prognostic markers or drug targets in various cancers, including gastric cancer (12,13), liver cancer (13), breast cancer (14-18), ovarian cancer (19-21), and NSCLC (22-24). In this study, we employed the KM plotter to analyze the prognostic roles of *SPHK1*, *SPHK2*, and *SGPL1* mRNA expression in NSCLC patients.

Methods

The online public database, KM plotter (11), was used to analyze the association between specific gene mRNA expression and overall survival (OS). The KM plotter is an integrated platform identifying NSCLC patients with simultaneously available microarray gene expression data and published clinical characteristics, including survival, from TCGA lung cancer datasets, GEO, and caBIG (25). Currently, 1,928 NSCLC patients' gene expression profiles and survival data are available for analysis in the KM plotter. The follow-up times span of were 20 years. SPHK1, SPHK2, and SGPL1 were entered into the database to obtain KM survival plots (http://kmplot.com/analysis/index.php?p=service&cancer=lung). The number-at-risk was indicated below the main plot. Affymetrix IDs were 219257_s_at (SPHK1), 40273_at (SPHK2), and 212322_at (SGPL1). Auto- selected best cutoff value checkbox was selected for gene mRNA expression to divide patients into high expression and low expression groups. All possible cutoff values between the lower and upper quartiles were computed, and the best performing threshold was used as a cut-off. If the gene had multiple chipsets, the user-selected probe set was selected for analysis. Histology, grade, stage, gender, and smoking history were selected for the Cox multivariate analysis. Hazard ratio (HR) with 95% confidence intervals (CI) and log rank P were automatically calculated by the KM plotter.

Results

The mRNA expression of three major S1P metabolism enzymes (SPHK1, SPHK2 and SGPL1) in NSCLC patients can be found in the KM plotter database (www.kmplotter.com). The KM survival curves were drafted for all NSCLC patients (n=1926), Ade patients (n=720), and SCC patients (n=524), who were followed up for 20 years.

For SPHK1, the Affymetrix ID is 219257_s_at. High *SPHK1* mRNA expression was significantly associated with worse OS in all NSCLC patients (HR 1.47, 95% CI: 1.28–1.68, P=2.6e-08) (*Figure 1A*) and Ade patients (HR 0.73, 95% CI: 0.56–0.94, P=0.014) (*Figure 1B*), but not in SCC patients (HR 1.32, 95% CI: 0.95–1.84, P=0.094) (*Figure 1C*).

For SPHK2, the Affymetrix ID is 40273_at. High *SPHK2* mRNA expression was significantly linked to better OS in all NSCLC patients (HR 0.66, 95% CI: 0.59–0.75, P=1.9e-10) (*Figure 2A*) and Ade patients (HR 0.53, 95% CI: 0.42–0.67, P=6.5e-08) (*Figure 2B*), but not in SCC patients (HR 1.18, 95% CI: 0.91–1.53, P=0.21) (*Figure 2C*).

For SGPL1, the Affymetrix ID is 212322_at. High *SGPL1* mRNA expression was significantly associated with better OS in all NSCLC patients (HR 0.64, 95% CI: 0.55–0.75, P=8.7e-09) (*Figure 3A*), Ade patients (HR 0.45, 95% CI: 0.34–0.6, P=2.3e-08) (*Figure 3B*), and SCC patients (HR 0.76, 95% CI: 0.6–0.97, P=0.024) (*Figure 3C*).

We further assessed the prognostic value of these enzymes in S1P metabolism with other pathological features and clinical treatments: smoking history, metastasis patients, clinical stages, negative surgical margin, chemotherapy, and radiotherapy. *Table 1* shows that high *SPHK1*, and *SGPL1*

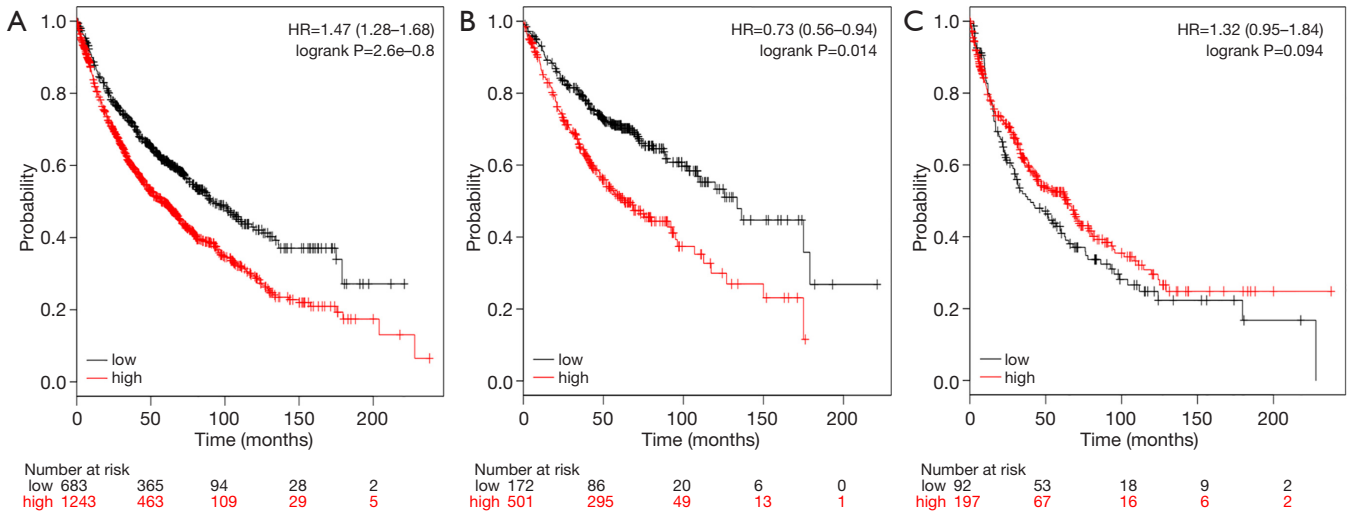

Figure 1 The prognostic role of *SPHK1* mRNA level in NSCLC patients. The Affymetrix ID is 219257_s_at. The Kaplan-Meier survival curves are drafted for (A) all NSCLC patients (n=1,926), (B) Ade patients (n=720), and (C) SCC patients (n=524). NSCLC, non-small cell lung cancer; Ade, adenocarcinoma; SCC, squamous cell carcinoma.

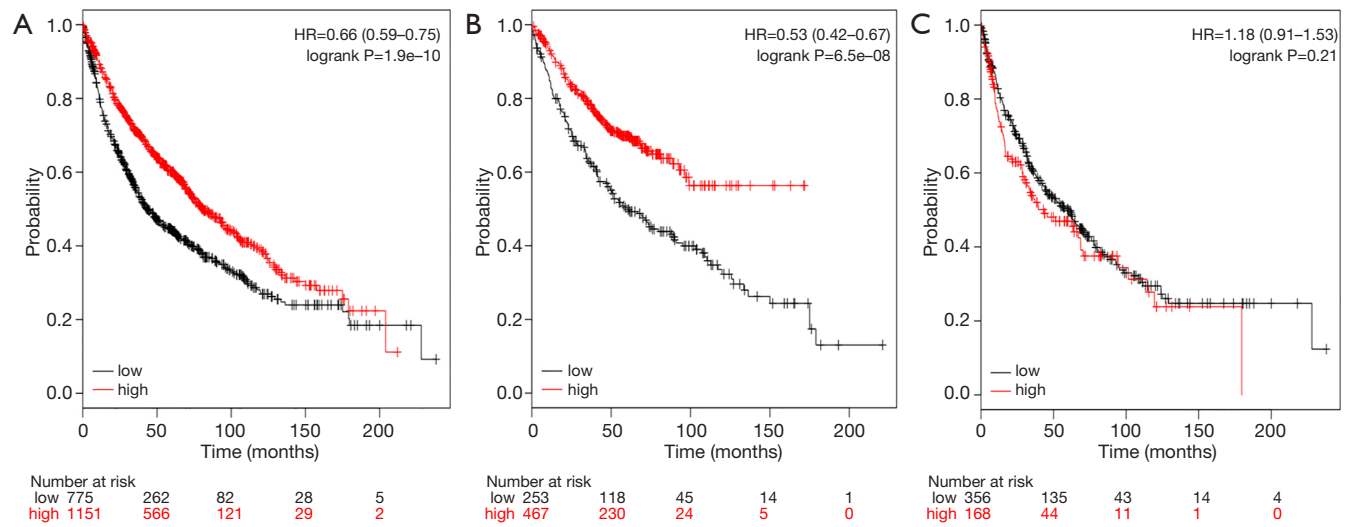

Figure 2 The prognostic role of *SHPK2* mRNA level in NSCLC patients. The Affymetrix ID is 40273_at. The Kaplan-Meier survival curves are drafted for (A) all NSCLC patients (n=1,926), (B) Ade patients (n=720), and (C) SCC patients (n=524). NSCLC, non-small cell lung cancer; Ade, adenocarcinoma; SCC, squamous cell carcinoma.

mRNA expression was correlated with clinical outcomes in NSCLC patients, despite smoking history. High *SPHK2* mRNA expression was only associated with better OS in patients who used to smoke. From *Table 2* and *Table 3*, high *SPHK1*, *SPHK2* and *SGPL1* mRNA expression were associated with OS in patients without metastasis and with negative surgical margins. *Table 4* shows that high *SPHK1* mRNA expression was associated with clinical stage I NSCLC patients. High *SPHK2* and *SGPL1* mRNA expression were correlated with OS in clinical stage I and II NSCLC patients. *Table 5* shows that high *SPHK1* and *SPHK2* mRNA expression was only correlated with OS in patients who did not accept chemotherapy. *Table 6* shows that high *SPHK1* mRNA expression was associated with OS in all patients with or without radiotherapy, while high *SPHK2* mRNA expression was only correlated with OS in

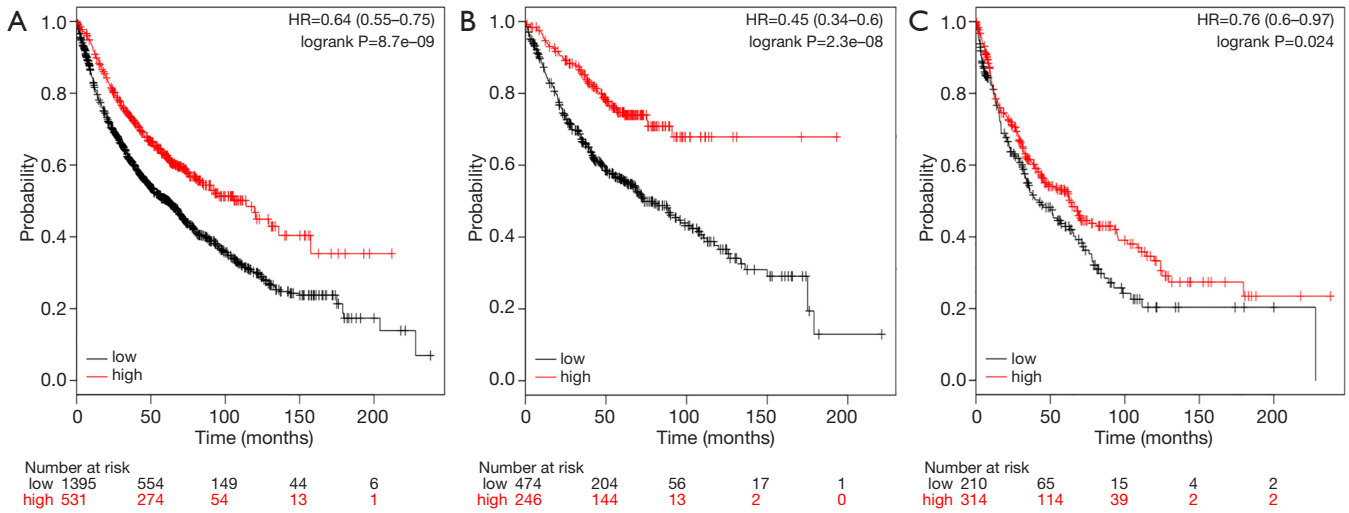

Figure 3 The prognostic role of *SPGL1* mRNA level in NSCLC patients. The Affymetrix ID is 212322_at. The Kaplan-Meier survival curves are drafted for (A) all NSCLC patients (n=1,926), (B) Ade patients (n=720), and (C) SCC patients (n=524). NSCLC, non-small cell lung cancer; Ade, adenocarcinoma; SCC, squamous cell carcinoma.

Table 1 Correlation between S1P metabolism enzyme mRNA high expression and different smoking history in NSCLC patients

Gene	Smoking history	Patients	Hazard ratio	95% CI	P value
SPHK1	Yes	820	1.74	(1.33–2.28)	4.5e-05
	No	205	2.41	(1.36–4.24)	0.0018
SPHK2	Yes	820	0.67	(0.54–0.83)	0.00015
	No	205	0.62	(0.35–1.08)	0.0872
SGPL1	Yes	820	0.74	(0.58–0.94)	0.0155
	No	205	0.56	(0.32–0.98)	0.0408

NSCLC, non-small cell lung cancer; S1P, sphingosine-1-phosphate.

Table 2 Correlation between S1P metabolism enzyme mRNA high expression and non-metastasis NSCLC patients

Gene	AJCC stage M	Patients	Hazard ratio	95% CI	P value
SPHK1	0	681	1.43	(1.11–1.84)	0.0047
SPHK2	0	681	0.77	(0.62–0.95)	0.0162
SGPL1	0	681	0.76	(0.59–0.97)	0.0298

NSCLC, non-small cell lung cancer; S1P, sphingosine-1-phosphate; AJCC, American Joint Committee on Cancer.

Table 3 Correlation between S1P metabolism enzyme mRNA high expression and the surgery success of NSCLC patients

Gene	Surgery success	Patients	Hazard ratio	95% CI	P value
SPHK1	Negative margins	726	2.03	(1.62–2.55)	5.8e-10
SPHK2	Negative margins	726	0.57	(0.44–0.72)	3.1e-06
SGPL1	Negative margins	726	0.7	(0.54–0.91)	0.0071

NSCLC, non-small cell lung cancer; S1P, sphingosine-1-phosphate.

Table 4 Correlation between S1P metabolism enzyme mRNA high expression and the clinical stage of NSCLC patients

Gene	Stage	Patients	Hazard ratio	95% CI	P value
SPHK1	I	577	2.14	(1.62–2.82)	3.4e-08
	II	244	0.78	(0.52–1.19)	0.2472
	III	70	1.33	(0.71–2.5)	0.3657
SPHK2	I	577	0.51	(0.39–0.67)	7.3e-07
	II	244	0.56	(0.38–0.82)	0.0023
	III	70	0.64	(0.37–1.1)	0.1048
SGPL1	I	577	0.52	(0.4–0.69)	2.4e-06
	II	244	0.51	(0.34–0.77)	0.00091
	III	70	1.37	(0.8–2.36)	0.2483

NSCLC, non-small cell lung cancer; S1P, sphingosine-1-phosphate.

Table 5 Correlation between S1P metabolism enzyme mRNA high expression and the chemotherapy of NSCLC patients

Gene	Chemotherapy	Patients	Hazard ratio	95% CI	P value
SPHK1	Yes	176	1.47	(0.96–2.24)	0.0758
	No	310	2.06	(1.46–2.89)	2.2e-05
SPHK2	Yes	176	0.73	(0.45–1.16)	0.1814
	No	310	0.63	(0.45–0.88)	0.0065
SGPL1	Yes	176	0.77	(0.5–1.18)	0.2293
	No	310	0.74	(0.5–1.09)	0.1277

NSCLC, non-small cell lung cancer; S1P, sphingosine-1-phosphate.

Table 6 Correlation between S1P metabolism enzyme mRNA high expression and the radiotherapy of NSCLC patients

Gene	Radiotherapy	Patients	Hazard ratio	95% CI	P value
SPHK1	Yes	70	1.86	(1.03–3.37)	0.0364
	No	271	1.55	(1.09–2.21)	0.015
SPHK2	Yes	70	0.6	(0.33–1.1)	0.0971
	No	271	0.67	(0.47–0.95)	0.0251
SGPL1	Yes	70	1.46	(0.8–2.65)	0.2104
	No	271	0.69	(0.44–1.06)	0.0865

NSCLC, non-small cell lung cancer; S1P, sphingosine-1-phosphate.

patients who accepted radiotherapy.

Cox multivariate regression analysis was performed with selected clinical parameters, including cancer grade, stage, gender, and smoking history. However, the full clinical data were only available for 130 SCC patients in the multivariate analysis. In accordance with univariate analysis, neither high SPHK1 expression (HR 0.83, 95% CI: 0.51–1.36, P=0.4636) nor high SPHK2 expression (HR 0.69, 95% CI: 0.41–1.18, P=0.1732) was significantly associated with worse OS in SCC patients. Unexpectedly, high SPGL1 gene expression was associated with worse OS in SCC patients (HR 1.77, 95% CI: 1.03–3.04, P=0.0388).

Discussion

The KM plotter is a widely-used online tool for assessing associations between gene expression and outcomes in patients with different cancers. Numerous genes were identified as prognostic biomarkers and therapeutic targets by the KM plotter, such as *MMP1*, *CBX1*, and *RPS14* in breast cancer (14-16); *E2F2* and *CCNE2* in ovarian cancer (19); *TREM2* in gastric cancer (12); and *Notch1-3* and *HSPB1* in NSCLC (23,24). With this online tool, we propose *SPHK1*, *SPHK2*, and *SGPL1* mRNA levels as potential prognostic predictors for NSCLC patients. For lack of clinical data, whether these mRNA levels are independent prognostic factors in NSCLC is still not determined.

S1P has a pivotal role in cell proliferation, migration, and inflammation. The accumulation of S1P is a balance between the synthesis catalyzed by SPHKs and the catabolism catalyzed by SGPL1 (4,8). Aberrant S1P metabolism and dysregulation of its downstream signals were observed in several tumors including breast, esophageal, prostate, colon, oral cancer, and NSCLC (4,26-30).

SPHK1 was elevated in various types of cancers, contributing to tumor proliferation, invasion and metastasis (31,32). In the human A549 NSCLC cell line, SPHK1 induced cell proliferation and suppressed cell apoptosis through nuclear factor-κB (NF-κB) and intracellular calcium signaling (33). The invasion and migration capacities of NSCLC cell were also enhanced by SPHK1, with the promoted epithelial mesenchymal transition (EMT), activation of the PI3K-Akt pathway, and E-cadherin expression (34,35). In accordance with the experimental results, clinical evidence revealed an approximate 2-fold elevation of *SPHK1* in NSCLC tissue versus normal tissue (10,36). In addition, high SPHK1 expression was markedly associated with advanced clinical staging, tumor-node-metastasis (TNM) classification, and worse OS; and SPHK1 level was identified as an independent prognostic factor for NSCLC patients (10). Consistent with previous studies, our results indicate that high *SPHK1* mRNA expression was significantly associated with worse OS in all NSCLC patients. Moreover, our stratified analysis showed that *SPHK1* mRNA might be more efficient in predicting outcomes in Ade patients than SCC patients.

SPHK2 is also widely believed to be an oncogene in lung cancer. Inhibition of SPHK2 in A549 human NSCLC cells led to cell apoptosis in previous research (37). Another recent study suggests that SPHK2-generating S1P binds to human telomerase reverse transcriptase in NSCLC cells, promoting telomerase stability, cell proliferation, and tumor growth. The level of SPHK2 was gradually upregulated from normal, metaplasia/dysplasia tissues to NSCLC tissues (9). Additionally, the level of SPHK2 in NSCLC tissues was significantly associated with the proliferative index, lymph node status, histology grade, and

clinical stage (9). High SPHK2 expression was regarded as an independent prognostic factor for worse OS in NSCLC patients (9). Contrary to previous findings, our results show that high *SPHK2* mRNA expression was strongly linked to better OS in NSCLC patients. This diversity can probably be explained by some regulators between *SPHK2* mRNA expression and SPHK2. For example, microRNA promotes target mRNA degradation or silencing by binding to 3'-untranslated regions (38). It was reported that miR-338-3p suppressed NSCLC progression in nude mouse xenograft models by downregulating SPHK2 (39). However, it was observed that miR-338-3p expression was also downregulated in NCCLC. Thus, the regulatory mechanism between *SPHK2* mRNA expression and SPHK2 protein level in NSCLC needs further investigation.

SGPL1, the only enzyme that irreversibly degrades S1P in cells, was suggested as a potential tumor suppressor. SPGL1 deficiency has been shown to lead to increased cell growth, cell proliferation and transformation. Moreover, loss of SGPL1 causes cell resistance to apoptosis induced by chemotherapy, accompanied by a strong increase in Bcl-2 and Bcl-xL protein levels (40). Compared with control animals, mice with intestinal epithelium-specific *Sgpl1* deletion exhibited greater disease activity, cytokine levels, S1P accumulation, tumors, STAT3 activation in a chemically induced tumor model. Mechanically, silencing SPGL1 promoted tumorigenic transformation through a pathway involving extracellular transport of S1P through S1P transporter Spns2, S1P receptor activation, and JAK2/STAT3-dependent pathway (41). Compared with normal tissues, the levels of SGPL1 were lower in human melanoma, colon carcinoma, oral cancer tissues and prostate cancer (27-29). In human prostatectomy specimens, a marked decrease in SPL enzymatic activity was observed in tumor samples, compared with normal tissue. Tissue microarray analysis confirmed that the loss of SPGL1 in human prostate cancer was associated with a higher Gleason score (27). However, the role of SGPL1 in NSCLC remains unclear. Our univariate analysis shows that high *SGPL1* mRNA expression was significantly associated with better survival in all NSCLC patients. However, in our multivariate analysis, SCC patients with high *SGPL1* mRNA expression were associated with worse outcomes, suggesting SGPL1 is not an independent prognostic factor in SCC. Further clinical research is advocated in this area.

Evidence suggests that targeting enzymes in S1P metabolism makes NSCLC cells sensitized to radiation or chemotherapy (6,27). *SPHK1*-overexpressed A549 NSCLC cells had a higher survival rate compared with control cells after treatment of doxorubicin or docetaxel (10). The knocking down of *SPHK1* with small interfering RNA (siRNA) not only inhibited cancer cell proliferation but also sensitized cancer cells to apoptosis induced by doxorubicin or docetaxel (10). SPHK1 inhibitor, in combination with chemotherapy, significantly reduced the tumor size and weight of xenografted NSCLC tumors in mice (10). Notably, SPHK2 was implicated in promoting cell apoptosis and sensitivity to treatment of gefitinib in NSCLC (42). Proposed as a radio-responsive protein, SGPL1 potentiated cell death after ironizing radiation (43). It was also reported that SGPL1 sensitized lung cancer cells to cisplatin, mainly mediated by upregulation of p38 (44). Collectively, these findings indicate that targeting different S1P metabolism enzymes might improve the efficacy of different chemotherapeutic drugs or radiation. The mRNA levels of S1P metabolism enzymes in NSCLC might provide an indication for which chemotherapeutic drugs to choose in clinical practice. The combination of SPHK1 inhibitor and SGPL1 activator would be a new therapeutic strategy for chemo- or chemo-resistant NSCLC.

Conclusions

In NSCLC patients, high *SPHK1* mRNA expression was strongly associated with worse survival. In contrast, high *SPHK2* and *SGPL1* mRNA expression was an indicator of better survival. The combination of SPHK1 inhibitor and SGPL1 activator might be a new therapeutic strategy for patients with NSCLC resistant to chemo- or radio-therapy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest

to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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