Associations of tumor suppressor SPARCL1 with cancer progression and prognosis (Review)

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Abstract. SPARC-like protein 1 (SPARCL1), a member of the family of secreted proteins which is acidic and rich in cysteine, is a potential tumor suppressor gene in most types of tumor. A systemic review and bioinformatics analysis was carried out to determine the associations between SPARCL1 and tumor progression and clinical factors. Downregulation of SPARCL1, thought to be regulated by epigenetic modifications including DNA methylation, serves important functions in tumor progression and development, with its regulatory functions on cell viability, migration, invasion, cell adhesion and drug resistance. Downregulation of SPARCL1 was markedly associated with a poor overall survival rate of patients with one of ≥7 solid tumors and predicted increased mortality in patients with one of ≥4 distinct tumor types. The present review indicated that SPARCL1 may be a therapeutic target for cancer treatment and a biomarker to determine prognosis.

Contents

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1. SPARC-like protein 1 (SPARCL1) is a potential tumor suppressor gene

SPARCL1, a member of the family of secreted proteins that are acidic and rich in cysteine in the cellular matrix. Originally termed SC1, SPARCL1 was first cloned from the rat central nervous system and encodes an extracellular matrix glycoprotein, similar to osteonectin/basement membrane protein 40/secreted protein acidic and rich in cysteine (SPARC) (1). Subsequently, Schraml *et al* (2) and Girard *et al* (3) cloned the aforementioned gene from endothelial cells in non-small cell lung cancer and high endothelial venules in human tonsil lymphatic tissues, and termed it MAST9 and hevin, respectively. The mRNA of the gene is 3 kb in length and the theoretical molecular mass of the encoded protein, SPARCL1, is ~75 kDa. However, the protein expressed *in vitro* reveals molecular masses of ~75 and 150 kDa, suggesting that SPARCL1 protein may form a homodimer *in vitro* (4).

SPARC is a tumor suppressor gene in cancer, and it has been demonstrated to be involved in the regulation of tumor progression and drug resistance (5,6). SPARCL1 exhibits 62% identity with SPARC and the two proteins share three conservative structural domains (3), indicating functional similarity. SPARCL1 is localized on human chromosome 4, which contains a number of additional known tumor suppressor genes. Thus, SPARCL1 is considered to be a potential tumor suppressor gene and participates in tumor occurrence and development, by regulating tumor cell viability and differentiation (4). SPARCL1 may, additionally, be a potential oncogene and participates in tumor occurrence and development, by regulating tumor cell viability and affecting the production of tumor blood vessels (7).

In the present review, the mRNA expression of SPARCL1 in tumors was analyzed using Oncomine (www.oncomine.org/resource/login.html) (8). As presented in Fig. 1, of the ~20 different types of solid tumors included in the Oncomine database, SPARCL1 was downregulated >2-fold in the majority of tumors analyzed, with the exception of liver cancer, lymphoma and sarcoma, where SPARCL1 was upregulated. The downregulation of SPARCL1 was marked in bladder, breast, cervical, rectal, lung and ovarian cancer. Thus, it may be inferred that SPARCL1 is a tumor suppressor gene in cancer.

2. DNA methylation may be an important mechanism that contributes to the downregulation of SPARCL1

As presented in Table I, SPARCL1 is upregulated in liver cancer (7); however, SPARCL1 is markedly downregulated in prostate (9), lung (10), ovarian (11) and a number of other types of cancer. These results are consistent with Fig. 1. Downregulation of SPARCL1 in tumors may result from the epigenetic mechanisms, including DNA methylation, because SPARCL1 is not a classical tumor suppressor gene exhibiting a deletion or mutation. Isler *et al* (10) used microsatellite analysis, quantitative polymerase chain reaction and sequence analysis of all exons, including the intron-exon junctions and a portion of the putative promoter region, but did not identify a mutation or deletion that may be responsible for the downregulation of SPARCL1. This was indicative of other regulatory mechanisms resulting in the differential expression of SPARCL1 in tumors, including epigenetic modification. A previous study revealed that DNA methylation is the reason for the downregulation of SPARCL1 in pancreatic, ovarian and lung cancers (Table I), and demethylation of the gene partially reversed the abnormal expression in pancreatic cancer (12).

3. SPARCL1 contributes to tumor development and progression

There have been a limited number of studies on SPARCL1, but the gene has been identified to be markedly associated with tumor development and progression. SPARCL1 contributions to tumor cell viability (13), migration and invasion (12-16) and exhibits an anti-adhesive effect (12,16). In addition, SPARCL1 may be involved in the regulation of drug resistance in cancer. It has been identified that SPARCL1 is a recombinant gene in the extracellular matrix of osteosarcoma in children and is involved in the mechanism of multiple drug resistance (17). A previous study used comprehensive bioinformatics analysis to identify that the SPARCL1 gene was involved in the regulation of drug resistance in ovarian cancer (18).

The association between SPARCL1 and tumor progression was investigated using Coremine Medical (http://www.coremine.com/medical). As presented in Fig. 2, using SPARCL1 and cancer as key words, SPARCL1 was identified to be associated with diagnosis, prognosis, recurrence, invasiveness, metastasis and drug resistance of cancer (Fig. 2A). In addition, the associations identified in the present review, between SPARCL1 and invasiveness, metastasis and drug resistance of cancer, were consistent with previous studies (Table I)(9-16,18-26). Furthermore, analysis indicated that SPARCL1 may participate in cancer development and progression, in 9 biological processes ($P<0.001$) including cell viability, cell cycle, migration and adhesion (Fig. 2B), which is consistent with previous studies (Table I). In addition, SPARCL1 and cancer were annotated with DNA methylation, supporting the hypothesis that DNA methylation may be an important mechanism which contributes to the downregulation of SPARCL1.

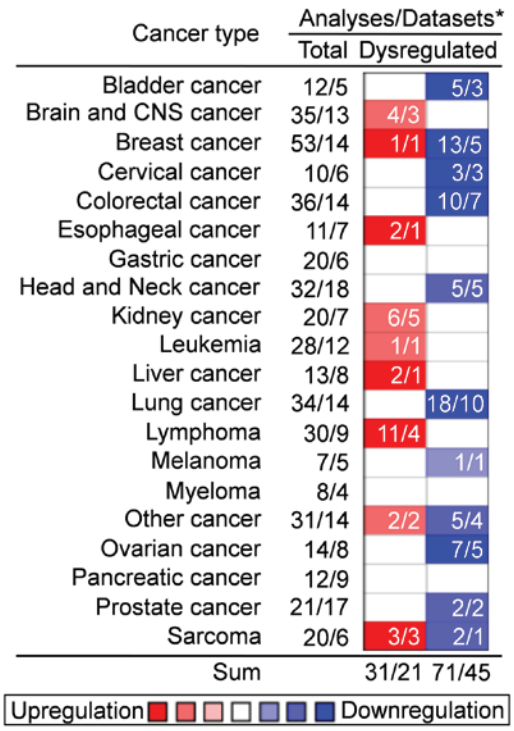

Figure 1. On the basis of the microarray data retrieved from Oncomine, SPARCL1 is differentially expressed in almost all tumors and a marked downregulation of SPARCL1 is observed in the majority of tumors. SPARCL1, SPARC-like protein 1; CNS, central nervous system; *total number of analyses in total number of datasets.

4. Downregulation of SPARCL1 is associated with poor prognosis in cancer

Previous studies indicate that downregulation of SPARCL1 is markedly associated with poor prognosis and therefore the gene may be a prognostic marker in cancers. In prostate cancer, the downregulation of SPARCL1 has been markedly associated with biochemical recurrence, metastatic disease and poor overall survival (OS) time (19). Patients with stage II/III colorectal cancer who possessed increased p53 and decreased SPARCL1 expression levels exhibited ~50% decreased 3-year survival compared with controls (27). Furthermore, in gastric cancer, silenced expression of SPARCL1 predicted a poorer prognosis (23).

On the basis of The Cancer Genome Atlas (TCGA) (24) cohort data, the associations between SPARCL1 and cancer prognosis were analyzed. The expression value of SPARCL1 and the corresponding clinical data of each type of cancer in the TCGA cohort was retrieved from the cBioPortal database (cbioportal.org) (28). Expression values of SPARCL1 were divided into high and low expression using the median as the threshold value in a Kaplan-Meier estimator analysis, in accordance with a previous study (29). As presented in Table II and Fig. 3, downregulation of SPARCL1 was markedly associated with poor OS time in liver cancer (242 samples) and lung cancer (324 samples), and markedly associated with poorer disease-free survival and OS time in glioma (311 samples).

The association between SPARCL1 and OS time in lung cancer was additionally validated using Kaplan-Meier estimator analysis, which selected thousands of samples of

Table I. Summary on the SPARCL1 correlated with tumor progression and development.

Tumor type	SPARCL1 expression	Biological function	Molecular mechanism	Mechanism of gene expression
Prostate cancer	Downregulation (9)	Inhibition of cell migration and invasion (14)	Affects migration by regulating RhoC (19); inhibition of the assembly of focal adhesions (20)	-
Colorectal cancer	Downregulation (13,21)	Inhibition of cell proliferation, growth and invasion (13)	Affects tumor cell differentiation through EMT (13)	-
Hilar cholangiocarcinoma	Downregulation (15)	Inhibition of cell migration (15)	Inhibition of the expression of MMP-9, MMP-2, vimentin and fibronectin (15)	-
Gastric cancer	Downregulation (22,23)	-	Inactivation of its tumor suppressor functions (22)	Loss of heterozygosity (23)
Pancreatic cancer	Downregulation (12)	Inhibition of tumor cell proliferation and invasion (12)	Anti-invasive effects (12)	DNA methylation (12)
Ovarian cancer	Downregulation (11)	Associated with multiple drug resistance (18)	Interaction with drug resistance-related proteins including PTEN (18)	DNA methylation (24)
Lung cancer	Downregulation (10)	Decrease in luciferase activity (10)	-	DNA methylation (25)
Glioma	Downregulation (16)	Associated with cell cycle (16)	Anti-adhesion (16)	-
Liver cancer	Upregulation (7)	-	-	-
Uterine leiomyoma	Upregulation (26)	-	-	-

SPARCL1, SPARC-like protein 1; MMP, matrix metalloproteinase; PTEN, phosphatase and tensin homolog.

Table II. Association between SPARCL1 expression and prognosis in glioma, lung cancer and liver cancer.

		DFS (median)				OS (median)			
				95% confidence interval				95% confidence interval	
Disease type	Group	Estimate	Standard error	Lower boundary	Upper boundary	Estimate	Standard error	Lower boundary	Upper boundary
Glioma	L	37.900	3.983	30.093	45.707	62.900	12.971	37.476	88.324
	H	62.000	10.173	42.061	81.939	98.200	19.627	59.731	136.669
	Total	43.500	4.524	34.633	52.367	87.400	10.232	67.346	107.454
Lung cancer	L					42.500	3.920	34.818	50.182
	H					60.100	12.425	35.747	84.453
	Total					49.200	3.705	41.938	56.462
Liver cancer	L					40.400	9.142	22.483	58.317
	H					80.700	10.853	59.428	101.972
	Total					55.600	8.087	39.749	71.451

SPARCL1 expression and survival data in The Cancer Genome Atlas cohort were used for the analysis. Expression values of a gene were divided into high and low expression using the median as a cut-off. H, high expression; L, low expression; DFS, disease-free survival; OS, overall survival.

Table III. Association between SPARCL1 expression and vital status of patients with different tumors, in accordance with The Cancer Genome Atlas cohort.

		SPARCL1 expression		
Patient's vital status	No. of patients	Low (%)	High (%)	P-value
Glioma of lower grade	528			0.001
Deceased	134 (25.4%)	84 (62.7)	50 (37.3)	
Alive	394 (74.6%)	180 (45.7)	214 (54.3)	
Lung adenocarcinoma	516			0.001
Deceased	187 (36.2%)	111 (59.4)	76 (40.6)	
Alive	329 (63.8%)	146 (44.4)	183 (55.6)	
Hepatocellular carcinoma	372			0.024
Deceased	130 (34.9%)	75 (57.7)	55 (42.3)	
Alive	242 (65.1%)	110 (45.5)	132 (54.5)	
Cervical adenocarcinoma	305			0.076
Deceased	73 (23.9%)	43 (58.9)	30 (41.1)	
Alive	232 (76.1%)	109 (47.0)	123 (53.0)	
Subcutaneous melanoma	470			0.42
Deceased	222 (47.2%)	100 (45.0)	122 (55.0)	
Alive	248 (52.8%)	135 (54.4)	113 (45.6)	
Acute myeloid leukemia	173			0.916
Deceased	114 (65.9%)	57 (50.0)	57 (50.0)	
Alive	59 (34.1%)	29 (49.2)	30 (50.8)	
Lymphoma	27			1
Deceased	6 (22.2%)	3 (50.0)	3 (50.0)	
Alive	21 (77.8%)	11 (52.4)	10 (47.6)	
Prostate adenocarcinoma	497			0.339
Deceased	10 (2.0%)	7 (70.0)	3 (30.0)	
Alive	487 (98.0%)	242 (49.7)	245 (50.3)	
Sarcoma	261			0.666
Deceased	99 (37.9%)	51 (51.5)	48 (48.5)	
Alive	162 (62.1%)	79 (48.8)	83 (51.2)	
Esophageal carcinoma	184			0.981
Deceased	77 (41.8%)	38 (49.4)	39 (50.6)	
Alive	107 (58.2%)	53 (49.5)	54 (50.5)	

Expression values of SPARCL1 were divided into high and low expression using the median as the threshold value. Cervical adenocarcinoma is defined as a cervical squamous cell carcinoma and endocervical adenocarcinoma. Lymphoma is defined as a lymphoid neoplasm diffuse large B-cell lymphoma. SPARCL1, SPARC-like protein 1.

ovarian, lung, breast and gastric cancer from microarrays deposited in the TCGA cohort and Gene Expression Omnibus profiles (30). Using the median expression as the threshold value, it was identified that the downregulation of SPARCL1 in lung cancer (3,021 samples) predicted decreased OS time (Fig. 4A), which was consistent with the results based on the TCGA cohort data (Table II and Fig. 3). Furthermore, downregulation of SPARCL1 predicted improved OS time in gastric cancer (1,223 samples) (Fig. 4B), although this result was in contrast with a previous study (23). In addition, in breast cancer (2,627 samples), downregulation of SPARCL1 predicted poorer OS time (Fig. 4C).

SPARCL1 was additionally associated with clinical features of a number of types of tumor. Downregulation of SPARCL1 was associated with increased mortality of patients with glioma, liver and lung cancer ($P<0.05$), and patients with cervical cancer ($P=0.076$; Table III). Furthermore, the downregulation rate of SPARCL1 increased considerably for surviving patients with cervical cancer and downregulation of the gene in ovarian cancer was markedly associated with a lower histological grade ($P<0.05$; Table IV).

5. Conclusions

Previous studies on the association between SPARCL1 and tumor progression are relatively limited. One previous study suggested that SPARCL1 is an oncogene (7), but a number of contradictory studies have identified SPARCL1 as a potential

Table IV. Association of SPARCL1 expression with neoplasm status and neoplasm histological grade in several cancers, in accordance with The Cancer Genome Atlas cohort.

Variables	No. of patients	SPARCL1 expression		P-value
		Low (%)	High (%)	
Glioma of lower grade	442			0.036
With tumor	220 (49.8%)	100 (45.5)	120 (54.5)	
Tumor-free	222 (50.2%)	123 (55.4)	99 (44.6)	
Cervical adenocarcinoma	263			0.013
With tumor	76 (28.9%)	47 (61.8)	29 (38.2)	
Tumor-free	187 (71.1%)	84 (44.9)	103 (50.2)	
Ovarian serous cystadenocarcinoma	476			0.004
Histological grade 2	56 (11.8%)	18 (32.1)	38 (67.9)	
Histological grade 3	420 (88.2%)	220 (52.4)	200 (47.6)	

Expression values of SPARCL1 were divided into high and low expression using the median as the threshold value. Cervical adenocarcinoma is defined as a cervical squamous cell carcinoma and endocervical adenocarcinoma.

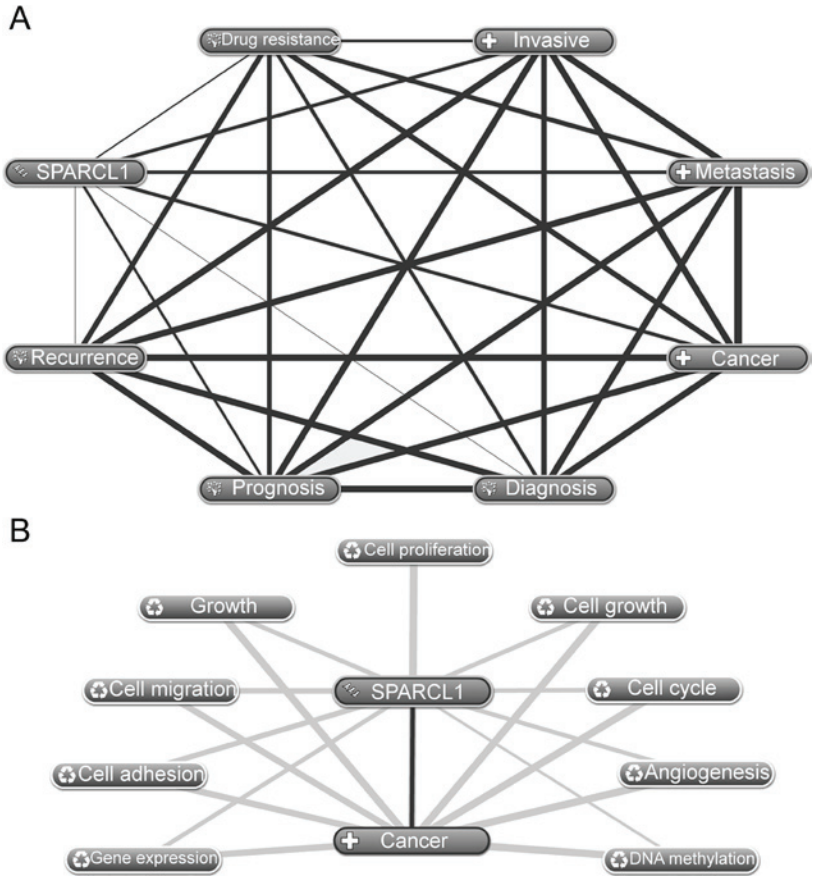

Figure 2. Associations between SPARCL1 and tumors, as analyzed using Coremine Medical. (A) Associations between SPARCL1 and tumor progression and development. (B) Hypothetical pathways/biological processes in which SPARCL1 was involved. SPARCL1, SPARC-like protein 1.

tumor suppressor gene (4,12,13,15). A bioinformatic analysis, on the basis of the data retrieved from Oncomine and the TCGA cohort, was conducted to identify the associations between SPARCL1 and tumor progression. Oncomine included information concerning SPARCL1 expression in almost 20 solid tumors (Fig. 1) and this identified that downregulation of SPARCL1 is prevalent in the majority of tumors, suggesting that SPARCL1 is a tumor suppressor gene.

The present review revealed that the downregulation of the SPARCL1 was markedly associated with poor OS time of ≥7 solid tumors, which included prostate (19), colorectal (27),

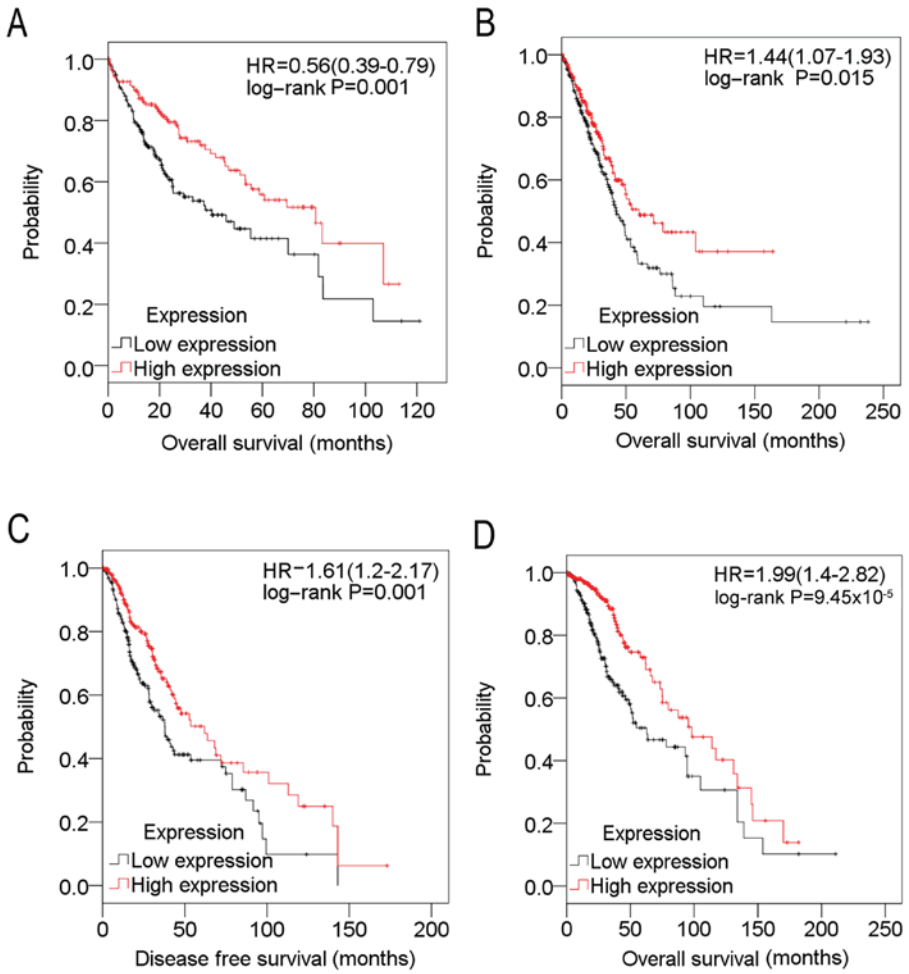

Figure 3. Kaplan-Meier estimator survival plots for SPARCL1 in (A) liver cancer, (B) lung cancer, (C) glioma and (D) glioma, on the basis of data retrieved from The Cancer Genome Atlas cohort. Expression values of SPARCL1 were divided into high (red line) and low (black line) expression using the median as the threshold value. SPARCL1, SPARC-like protein 1; HR, hazard ratio.

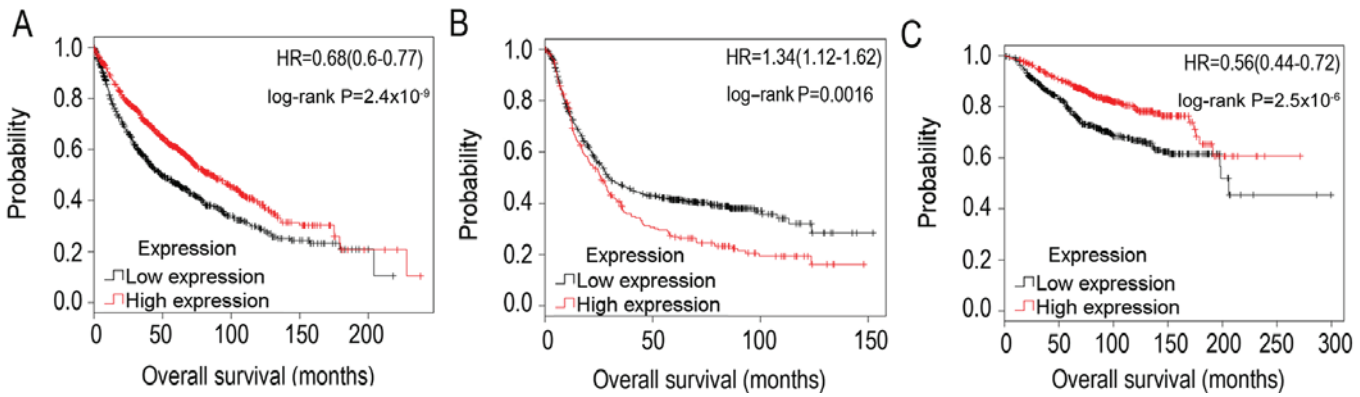

Figure 4. Kaplan-Meier estimator survival plots for SPARCL1 in (A) lung cancer, (B) gastric cancer and (C) breast cancer. Expression values of SPARCL1 were divided into high (red line) and low (black line) expression using the median as the threshold value. SPARCL1, SPARC-like protein 1; HR, hazard ratio.

gastric (23), liver, lung, glioma and breast cancer (Table II; Figs. 3 and 4). In addition, decreased expression of SPARCL1 typically predicted increased mortality in glioma, lung, liver and cervical cancer (Table III). Therefore, SPARCL1 may be a universal prognostic marker of tumors in the clinic.

Previous studies have indicated that SPARCL1 is a tumor suppressor gene and is involved in tumor cell viability (13), migration and invasion (12-16) and cell adhesion (12,16), and is associated with drug resistance of tumors (17,18). Consistent with these studies, bioinformatics analysis in the present review revealed that SPARCL1 was associated with prognosis, invasiveness, metastasis, recurrence and drug resistance of cancer (Fig. 2A). It is hypothesized that SPARCL1 exhibits these aforementioned actions by interactions with a number

of biological processes/signaling pathways including cell adhesion, cell viability, cell cycle and cell migration (Fig. 2B). These results indicate that SPARCL1 serves important functions in tumor progression.

The present review has elucidated the association between SAPRCL1 and cancer. SPARCL1 may be an important tumor suppressor gene in tumor progression and development, and it may be a therapeutic target for cancer treatment and a potential biomarker for prognosis.

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