

High expression of SH2B adaptor protein 1 (SH2B1) indicates poor prognosis in colorectal cancer

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SH2B1, an adaptor protein associated with obesity, is closely related to the occurrence and development of a variety of tumors. To investigate the clinical significance of SH2B1 in colorectal cancer (CRC), expression of SH2B1 in colorectal normal tissues, adenomas, paracarcinoma tissues, carcinoma tissues, and metastatic tissues from 1003 CRC patients was detected by immunohistochemistry (IHC). The prediction power of SH2B1 for CRC prognosis was evaluated by Kaplan-Meier survival analysis and Cox regression model. Results revealed the expression of SH2B1 in carcinoma tissues was significantly higher than that in other tissues. High expression of SH2B1 was an independent risk factor for both disease-free survival (DFS) and disease-specific survival (DSS) and predicted unfavorable prognosis of CRC as well as poor chemotherapeutic response. Conclusively, SH2B1 can serve as an effective predictor for CRC survival and chemotherapeutic outcomes.

Key words: SH2B1, tumorigenesis, prognosis, colorectal cancer

SH2B1 (SRC homology 2 [SH2] B adaptor protein 1), located on chromosome 16p11.2, is an important body weight regulation protein. SH2B1 controls body weight by regulating signaling molecules related to fat storage, sugar utilization, energy balance, and body weight [1]. So, its deficiency can lead to stunting and obesity [2, 3]. Apart from the metabolic function, SH2B1 has been proved to be highly expressed in a variety of cancer cells, such as esophageal cancer, lung cancer, gastric cancer, and colorectal cancer (CRC) [4–8]. And its clinical significance on tumor progression and prognosis has been reported in some cancers, especially in lung cancer [9]. However, few studies were executed on the significance of SH2B1 in CRC. SH2B1 was found to be highly expressed in CRC cell lines *in vitro* and its overexpression was related to CRC cell progression [8, 10]. The objective of this study was to indicate the expression of SH2B1 in different tumor tissues from CRC patients and to clarify if SH2B1 expression in tumor tissues is prognostic and/or predictive for CRC. This study should be helpful for the prediction and targeted treatment of CRC.

Patients and methods

Patients and specimens. Pathologically proven formalin-fixed paraffin-embedded (FFPE) tissues containing

adenoma (n=33), paracancerous (n=38), and cancerous (n=1003) tissues were obtained from the surgically removed specimens of 1003 CRC patients, who received surgical resection at the Shanghai Hospital between January 2006 and November 2011. Patients who received preoperative chemotherapy or radiation were excluded from this study. Each patient's clinical characteristics including age, sex, tumor location, number of resected lymph nodes, differentiation grade, TNM staging (according to the American Joint Committee on Cancer Staging System, 7th edition), adjuvant chemotherapy, serum carcinoembryonic antigen (CEA), and carbohydrate antigen 199 (CA199) levels were collected. Moreover, FFPE tissues of CRC liver metastases (n=17) and normal colorectal specimens (n=36) were collected in the hospital. The follow-up examination of the 1003 CRC patients, containing the chest CT scans, abdominal ultrasonography, pelvic MRI/CT, colonoscopy, serous CEA, and CA199, was carried out every 6 to 12 months. A telephone interview was conducted every 6 to 12 months to gain information about the condition of the patients. This study was approved by the Institutional Review Committee of Shanghai Hospital. All participants signed a written informed consent form, giving permission for the biomaterials to be used in the study.

Immunohistochemistry. Tissue microarrays (TMAs) containing the FFPE specimens were constructed by a commercial agent (Outdo Biotech, Shanghai, China). The examination of immunohistochemistry (IHC) was processed as previously described [11]. Rabbit anti-human SH2B1 polyclonal antibody (1:1,000, HPA076175, Sigma-Aldrich Co.) and secondary antibodies from the Elivision™ super HRP (Mouse/Rabbit) IHC Kit (kit-9922, Maxvision, Foshan, China) were used for incubation following the manufacturer's guidelines. For the minimum intra assay variation, the same individual researcher stained all slides.

Quantitative evaluation of SH2B1 immunostaining. Stained TMA slides were scanned by the Servicebio system (digital scanning via Panoramic MIDI; 3Dhistech, Budapest, Hungary), and the CaseViewer software was used to evaluate the images under bright-field microscopy at a resolution

of $\times 200$. H-score method was used for the quantification of SH2B1 expression. Immunostaining intensity of SH2B1 protein in a fixed field was assessed as negative (0), weakly positive (1+), moderately positive (2+), and strongly positive (3+). The percentage of epithelial cells at each staining intensity level was measured by the Image-Pro Plus 6.0 software (Media Cybernetics, Inc., Rockville, MD, USA). Five fields were selected randomly and the H-score was calculated by multiplying the average percentage of positive cells by the corresponding staining intensity.

Statistical analysis. Pearson χ^2 test and independent Student t-test (for continuous variables) were used for the descriptive summary of the clinicopathological features. An independent sample t-test was used to compare the differences in IHC score of SH2B1 between different tissues. The optimal cut-off value of the IHC score was identified

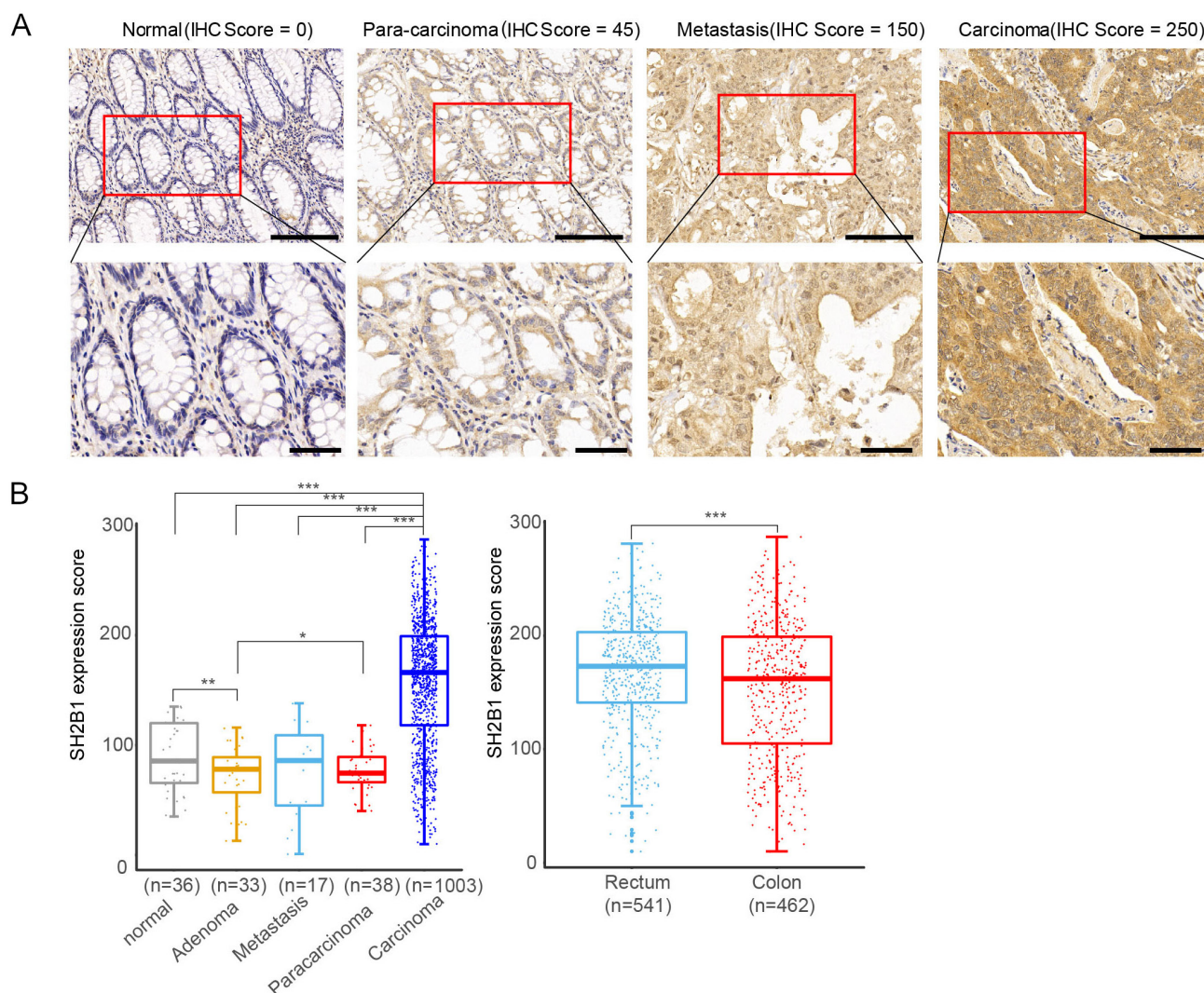


Figure 1. Expression pattern of SH2B1 protein in different tissues of CRC patients. A) Representative immunostainings of SH2B1 in colorectal normal tissues, adenomas, paracarcinoma, carcinoma, and metastatic tissues. Bar, 50 μ m. B) Comparisons of epithelial SH2B1 expression in different tissues. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

by the Maxstat package for the stratification of subgroups. Kaplan-Meier analysis with log-rank test was performed to estimate disease-free survival (DFS) and disease-specific survival (DSS). Cox proportional hazards models were used to estimate the hazard ratios (HRs) and their 95% confidence intervals (CIs). All statistical analyses were performed by SPSS 21.0 and R 3.5.1. A p-value <0.05 was considered statistically significant.

Results

Elevated SH2B1 expression in the cytoplasm of CRC epithelial cells. To gain insights into the expression pattern of SH2B1 in different colorectal tissues, IHC analysis was performed to detect SH2B1 protein expression in colorectal normal tissues, adenomas, paracarcinoma, carcinoma, and metastatic tissues. SH2B1 was mainly expressed in the cytoplasm of epithelial cells. Different SH2B1 expression levels and the corresponding IHC scores are shown in

Figure 1A. The IHC score of epithelial SH2B1 expression was significantly higher in colorectal carcinoma tissues than in the other tissues ($p < 0.001$; Figure 1B). SH2B1 expression differences were also significant between colon and rectal carcinoma tissues ($p < 0.001$; Figure 1B).

Associations between the cytoplasm SH2B1 and patient features. 1003 CRC patients were classified into two subgroups according to the IHC scores: high expression (IHC score ≥ 116) and low expression (IHC score < 116). Then the associations of SH2B1 expression with the clinicopathological characteristics of CRC patients were analyzed. As shown in Table 1, high expression of SH2B1 was associated with poor tissue differentiation ($p < 0.001$), and this phenomenon existed in rectal cancer and colon cancer ($p < 0.001$), respectively. Apart from tissue differentiation, SH2B1 expression was also related to the number of resected lymph nodes ($p = 0.038$), but the phenomenon only existed in colon cancer ($p = 0.039$). According to the results, it's inferred that SH2B1 may contribute to the progression of CRC.

Table 1. Characteristics of patient with CRC dichotomized by SH2B1 expression.

Variables	All (n=1003)			Colon (n=462)			Rectum (n=541)		
	SH2B1 ^L (n=216)	SH2B1 ^H (n=787)	p-value	SH2B1 ^L (n=131)	SH2B1 ^H (n=331)	p-value	SH2B1 ^L (n=85)	SH2B1 ^H (n=456)	p-value
Age, mean±SD	60.83±11.83	61.02±12.65	0.843	60.90±12.64	62.69±14.00	0.203	60.73±10.54	59.81±11.44	0.491**
Sex, n (%)									
Male	121 (56.0)	478 (60.7)	0.210	72 (55.0)	187 (56.5)	0.765	49 (53.4)	291 (63.8)	0.280*
Female	95 (44.0)	309 (39.3)		59 (45.0)	144 (43.5)		36 (31.6)	165 (36.2)	
Differential grade, n (%)									
Well	47 (21.8)	71 (9.0)	<0.001	34 (26.0)	47 (14.2)	<0.001	13 (15.3)	24 (5.3)	<0.001***
Moderate	159 (73.6)	681 (86.5)		90 (68.7)	263 (79.5)		69 (81.2)	418 (91.7)	
Poor	0 (0.0)	26 (3.3)		0 (0.0)	14 (4.2)		0 (0.0)	12 (2.6)	
Missing	10 (4.6)	9 (1.2)		7 (5.3)	7 (2.1)		3 (3.5)	2 (0.4)	
Lymph nodes, n (%)									
<12	163 (75.5)	650 (82.6)	0.038	88 (67.2)	258 (77.9)	0.039	75 (88.2)	392 (86.0)	0.797*
≥12	53 (24.5)	135 (17.2)		43 (32.8)	72 (21.8)		10 (11.8)	63 (13.8)	
Missing		2 (0.3)			1 (0.3)			1 (0.2)	
TNM stage, n (%)									
I	10 (4.6)	128 (16.3)	0.788	3 (2.3)	30 (9.1)	0.568	0 (0.0)	1 (0.2)	0.957***
II	141 (65.3)	364 (46.3)		83 (63.4)	162 (48.9)		75 (88.2)	392 (86.0)	
III	65 (30.1)	295 (37.5)		45 (34.4)	139 (42.0)		10 (11.8)	63 (13.8)	
Chemotherapy, n (%)									
Yes	184 (85.2)	631 (80.2)	0.095	109 (83.2)	258 (77.9)	0.207	75 (88.2)	373 (81.8)	0.149*
No	32 (14.8)	156 (19.8)		22 (16.8)	73 (22.1)		10 (11.8)	83 (18.2)	
Serum CEA, n (%)									
<5 ng/ml	135 (62.5)	485 (61.6)	0.652	79 (60.3)	192 (58.0)	0.651	56 (65.9)	293 (64.3)	0.738*
≥5 ng/ml	81 (37.5)	299 (38.0)		52 (39.7)	139 (42.0)		29 (34.1)	160 (35.1)	
Missing		3 (0.4)						3 (0.7)	
Serum CA199, n (%)									
<37 U/ml	182 (84.3)	674 (85.6)	0.637	108 (82.4)	268 (81.0)	0.713	74 (87.1)	406 (89.0)	0.675*
≥37 U/ml	34 (15.7)	111 (14.1)		23 (17.6)	63 (19.0)		11 (12.9)	48 (10.5)	
Missing		2 (0.3)						2 (0.4)	

Abbreviations: CA199-carbohydrate antigen 199; CEA-carcinoembryonic antigen; CRC-colorectal cancer; SH2B1-Nicotinamide N-methyltransferase; SH2B1L-SH2B1 low expression; SH2B1H-SH2B1 high expression. Notes: * χ^2 or Fisher's exact test, missing values are excluded for all statistic tests; **Student's t-test; ***Mann-Whitney U test (nonparametric), missing values are excluded for all statistic tests

Epithelial SH2B1 expression predicts unfavorable survival of CRC patients. Then, the prognostic value of epithelial SH2B1 expression in CRC was further studied. First, Kaplan-Meier survival analysis was used to estimate the difference of DFS and DSS between the two subgroups, which were stratified by SH2B1 expression level. Kaplan-Meier curves and log-rank tests revealed that high SH2B1 expression was significantly associated with shorter DFS ($p < 0.001$) and DSS ($p < 0.001$) for CRC patients (Figure 2A). And it's consistently remained in colon cancer and rectal cancer (Figures 2B, 2C). Next, univariate Cox analysis was employed to screen factors, which were highly associated with DFS or DSS. As shown in Table 2, the expression of SH2B1 was significantly associated with both DFS ($p < 0.01$) and DSS ($p < 0.001$) of CRC patients; besides, TNM stage, chemotherapy treatment, serum CEA, and CA199 was associated with DFS of CRC patients. Moreover, SH2B1 expression was subjected to multivariate Cox regression analysis, taking TNM stage, chemotherapy treatment, serum CEA, and CA199 as covariates, to further explore the association of SH2B1 expression with DFS and DSS of CRC patients. The results showed that high SH2B1 expression in CRC was an independent risk factor for DFS (HR: 3.188; 95% CI: 1.973–5.149) and DSS (HR: 5.525; 95% CI: 2.480–12.308), as shown in Table 2. What is more, high SH2B1 expression remained the independent risk factor when multivariate Cox regression analysis was carried out respectively in colon cancer and rectal cancer (Supplementary Tables S1 and S2).

Epithelial SH2B1 expression predicts the prognosis of patients with early-stage CRC. The relationship between SH2B1 expression and DFS/DSS among patients with earlier-stage CRC (stage I/II) and among patients with later-stage CRC (stage III) was studied, respectively. Results showed that high SH2B1 expression was related to poorer DSS and DFS in early-stage CRC patients as well as in stage III CRC patients (all $p < 0.01$, Figure 3A). Similar results were found in colon cancer (all $p < 0.01$, Figure 3B) but not in rectal cancer (Figure 3C).

Epithelial SH2B1 expression predicts benefit from adjuvant chemotherapy for CRC patients. The association between SH2B1 expression and survival outcomes among patients with or without chemotherapy was further studied. In our cohort, almost all the stage III CRC patients (340/360) and stage II CRC patients who were diagnosed with adverse prognostic factors (412/505) received postoperative chemotherapy. For these stage II or stage III CRC patients who received chemotherapy, higher SH2B1 expression indicated shorter DSS and DFS (Figure 4). This result demonstrates that SH2B1 expression may predict the chemotherapeutic response of stage II/III CRC patients.

Discussion

In previous studies, SH2B1 was mainly associated with type 2 diabetes and obesity [12, 13]. It is remarkable that compared with the general population, people with type 2

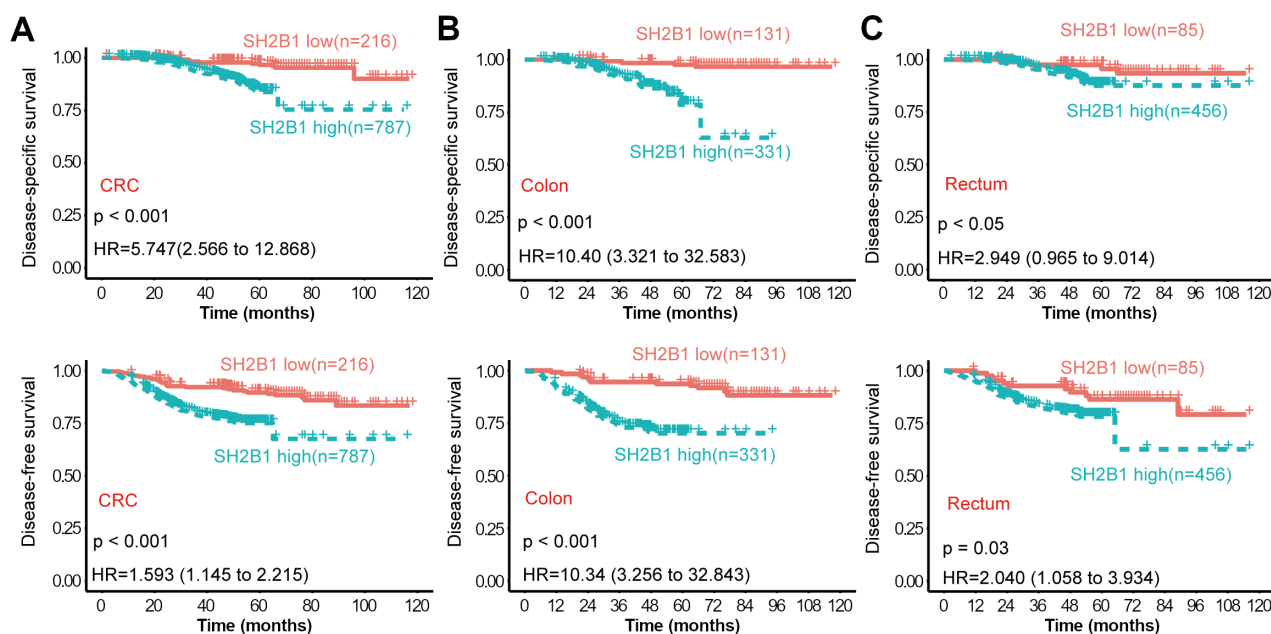


Figure 2. Kaplan-Meier survival curves showing a comparison of DFS and DSS between high and low SH2B1 expression subgroups. A) Comparisons of DFS and DSS between SH2B1-high and SH2B1-low subgroups in CRC patients. B) Comparisons of DFS and DSS between SH2B1-high and SH2B1-low subgroups in colon cancer patients. C) Comparisons of DFS and DSS between SH2B1-high and SH2B1-low subgroups in rectal cancer patients. Log-rank p-values and hazard ratios (HRs) from Kaplan-Meier analysis with the log-rank test are shown.

Table 2. Cox regression analysis of immunohistochemistry SH2B1 expression and clinicopathological covariates in the CRC patients.

Variables	Disease-specific survival				Disease-free survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
SH2B1								
Low vs. High	5.747 (2.566–12.868)	<0.001	5.525 (2.480–12.308)	<0.001	1.593 (1.145–2.215)	0.006	3.188 (1.973–5.149)	<0.001
Sex								
Male vs. Female	0.844 (0.537–1.327)	0.463			0.916 (0.687–1.221)	0.549		
Tumor location								
Colon vs. Rectum	1.204 (0.774–1.872)	0.410			1.139 (0.859–1.509)	0.367		
Differential grade								
(Well+Moderate) vs. Poor	0.854 (0.425–1.716)	0.657			0.939 (0.601–1.453)	0.776		
Lymph nodes, n (%)								
<12 vs. ≥12	1.100 (0.616–1.965)	0.747			1.212 (0.856–1.718)	0.279	2.954 (1.853–4.709)	<0.001
TNM stage								
I+II vs. III	1.593 (1.025–2.475)	0.038			2.507 (1.889–3.327)	<0.001	2.253 (1.690–3.004)	<0.001
Chemotherapy								
Yes vs. No	1.107 (0.611–2.007)	0.737			1.706 (1.104–2.637)	0.010		
Serum CEA (ng/ml)								
<5 vs. ≥5	1.556 (1.003–2.416)	0.051	1.559 (1.000–2.430)	0.05	0.625 (0.472–0.828)	0.001	1.367 (1.014–1.845)	0.041
Serum CA199 (U/ml)								
<37 vs. ≥37	1.549 (0.883–2.716)	0.127			1.970 (1.407–2.756)	<0.001	1.593 (1.112–2.281)	0.011

diabetes have a higher risk of CRC [13–16]. In this study, we demonstrated the associations between the expression of SH2B1 and clinical manifestations in CRC. The results showed that SH2B1 expression was more elevated in CRC tissues comparing with the noncancerous colorectal tissues. SH2B1 expression in CRC was strongly associated with the differentiation grade of cancer tissues, and high SH2B1 expression predicted poor prognosis of CRC patients. In order to eliminate the influence of cancer differentiation grade, which effects the progression of cancer, we balanced this factor in multivariate Cox regression analysis and still found that high SH2B1 expression was associated with unfavorable outcomes in CRC. These results indicate that SH2B1 expression is an independent risk factor of survival for CRC patients. For patients with stage II/III CRC, adjuvant chemotherapy is the common treatment. However, the outcomes are usually unpredictable due to the heterogeneity of the response to chemotherapeutic drugs and the lack of predictive biomarkers relating to chemotherapy. Therefore, our study also focused on the contribution of SH2B1 expression to chemotherapy resistance. It was found

that tumors with high SH2B1 expression were associated with poor survival outcomes in CRC patients with chemotherapy, and this association was weak in patients without chemotherapy. This result suggested that SH2B1 could be a biomarker for the prediction of CRC patients' chemotherapy response.

In recent years, SH2B1 has been found to be highly expressed in some cancers and has been demonstrated to be associated with the development of cancers [4–8]. Our results consistently suggested that SH2B1 might play an important role in the progression of CRC. And how does SH2B1 affect tumor progression? There are several views on this issue. First, it has been confirmed that SH2B1 can regulate cell migration, proliferation, and differentiation *in vitro* [10, 17, 18], but the mechanism is still unclear. Second, SH2B1 may be involved in the regulation of oxidative stress, which can promote the development and progress of many aspects of cancer [19, 20]. Third, SH2B1 serves as an adaptor protein involved in cancer development, for example, it increases the risk of cancer by promoting the transmission of leptin [21–23]. Also, SH2B1 may serve as an enhancer of tyrosine

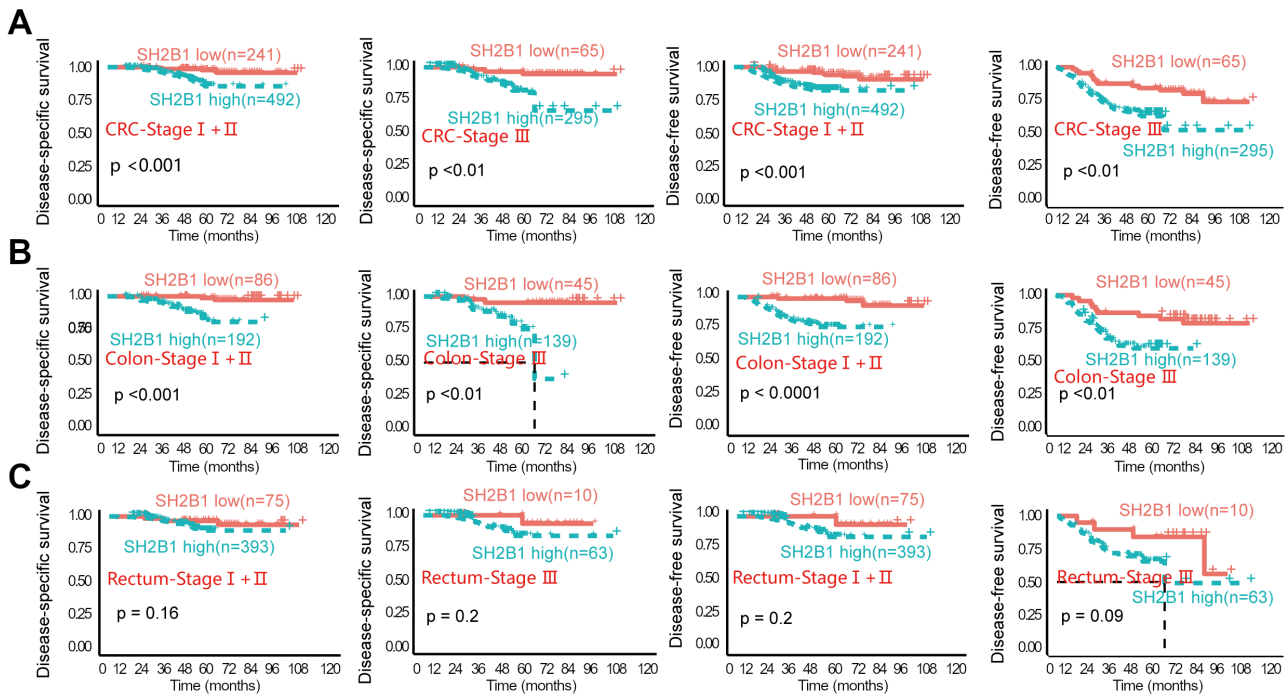


Figure 3. Kaplan-Meier survival curves showing comparisons between high and low SH2B1 expression subgroups in patients with earlier-stage CRC (stage I and II) and in patients with later-stage CRC (stage III). A) Kaplan-Meier survival curves of DFS and DSS between SH2B1-high and SH2B1-low subgroups in CRC patients. B) Kaplan-Meier survival curves of DFS and DSS between SH2B1-high and SH2B1-low subgroups in colon cancer patients. C) Kaplan-Meier survival curves of DFS and DSS between SH2B1-high and SH2B1-low subgroups in rectal cancer patients.

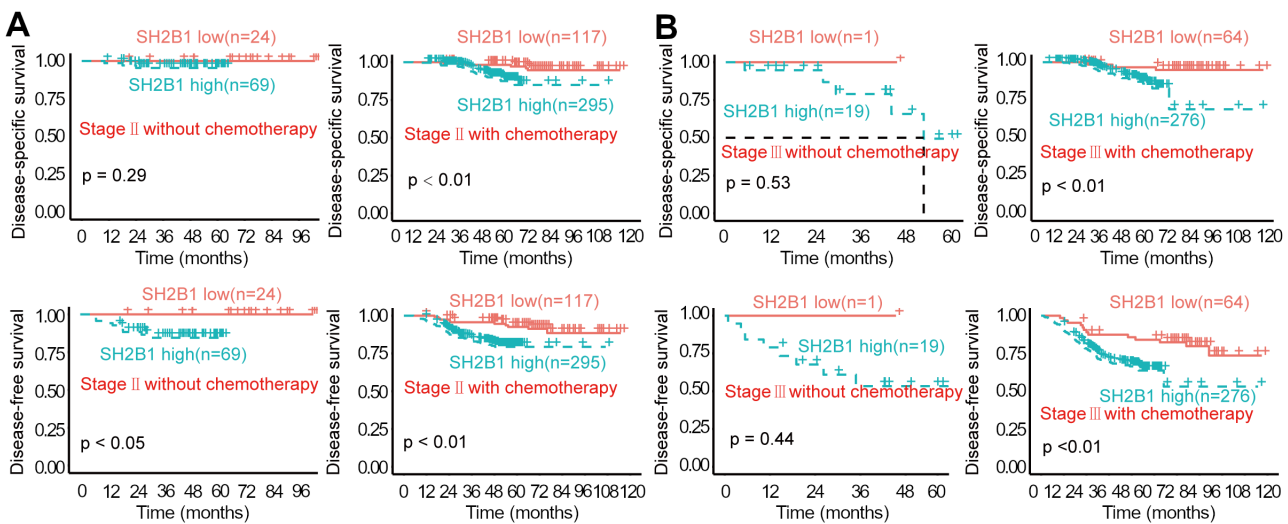


Figure 4. Kaplan-Meier survival curves showing a comparison of DFS and DSS between high and low SH2B1 expression subgroups in stage II/III CRC patients with or without chemotherapy. A) Kaplan-Meier survival curves of DFS and DSS between SH2B1-high and SH2B1-low subgroups in stage II CRC patients with or without chemotherapy. B) Kaplan-Meier survival curves of DFS and DSS between SH2B1-high and SH2B1-low subgroups in stage III CRC patients with or without chemotherapy.

kinase receptors, which participate in tumor progression by enhancing kinase activity [24–26].

In conclusion, our study evaluated the prognostic value of SH2B1 in CRC with a large cohort of CRC patients, and the results showed that SH2B1 could be a prognostic marker

for CRC survival and a potential predictive biomarker for chemotherapy response. Nevertheless, the current study also has a few limitations. First, we cannot rule out the possibility of selection bias because of the loss of follow-ups. Second, some important prognostic factors were not included, such

as microsatellite instability and extramural venous invasion, thus it may lead to an incomplete inclusion of variables in multivariate Cox analysis. Furthermore, the biological function of SH2B1 and its mechanism in CRC progression remains to be studied.

Supplementary information is available in the online version of the paper.

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