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High Expression of Serine Hydroxymethyltransferase 2 Indicates Poor Prognosis of Gastric Cancer Patients

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: Serine hydroxymethyltransferase (SHMT) is the enzyme that catalyzes the reversible conversion of serine to glycine and tetrahydrofolate-bound one-carbon unit. Upregulation of SHMT2 has been observed in a variety of cancers, but the expression profile and clinical value of SHMT2 in gastric cancer (GC) are still unknown.

Material/Methods: In this study, SHMT2 expression was assessed in 130 patients with GC by immunohistochemistry (IHC). mRNA of SHMT2 in GC tissues and normal gastric epithelium was compared with qRT-PCR results. The correlations between SHMT2 and the clinicopathologic factors were analyzed with the chi-square test. Univariate analysis with Kaplan-Meier method was used to estimate the correlations between survival rate and clinicopathologic factors, including SHMT2. The independent prognostic biomarkers were confirmed by multivariate analysis using the Cox-regression hazard model. The function of SHMT2 in progression of GC was assessed by *in vitro* experiments.

Results: The percentages of low and high expression of SHMT2 were 46.92% and 53.08%, respectively. SHMT2 mRNA in GC tissue was significantly higher than mRNA in the patient-paired adjacent tissues. In the clinical analysis, SHMT2 expression was notably associated with positive lymphatic invasion. High SHMT2 was also demonstrated to independently predict poor prognosis of GC. After silencing SHMT2, we proved that SHMT2 can promote proliferation and invasion of GC cells.

Conclusions: High SHMT2 promoted progression and was an independent prognostic biomarker of GC, suggesting that SHMT2 detection would be helpful for stratification of high-risk patients and thus directing personalized treatment.

MeSH Keywords: Aminomethyltransferase • Lymphatic Metastasis • Prognosis • Stomach Neoplasms

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Background

Gastric cancer (GC) is an aggressive and common malignancy ranking 5th in morbidity and 3rd in cancer-associated deaths throughout the world, with over 1 million new cases and an estimated 783 000 deaths in 2018 [1]. GC imposes a severe burden on global health finance, especially East Asia and particularly in China. The most radical treatment of GC is surgery. The postoperative 5-year overall survival rate is 90% for early-stage patients and just 10% for those in advanced stage [2]. Patients with advanced GC are generally treated with surgery followed by chemotherapy [3], but relapse and metastasis are common. Therefore, effective biomarkers that can identify patients at high risk are urgently needed.

Serine hydroxymethyltransferase (SHMT) is the enzyme that catalyzes the reversible conversion of serine to glycine and tetrahydrofolate-bound one-carbon unit. Upregulation in the synthesis and consumption of serine and glycine was observed in transformed cells and cancers [4–6]. In the human genome, there are 2 kinds of SHMT proteins – SHMT1 and SHMT2 [7] – with different functions and expression profiles. SHMT1 is a cytoplasmic isozyme involved in the *de novo* synthesis of thymidylate, and SHMT2 is expressed in mitochondria and regulates the synthesis of mitochondrial thymidine monophosphate (dTMP) [8]. It is interesting to note that SHMT2 and its downstream mitochondrial enzyme – 5,10-methylenetetrahydrofolate dehydrogenase (MTHFD2) – is significantly overexpressed in a variety of cancers, including colorectal, brain, central nervous system (CNS), kidney, and bladder cancers [9–11]. However, the expression profiles of SHMT2 in GC are still unknown.

In the present study, we assessed SHMT2 expression in 130 GC patients by immunohistochemistry (IHC), and 15 fresh GCs and their patient-paired normal tissues with quantitative real-time polymerase chain reaction (qRT-PCR) for the first time. The clinical value of SHMT2 was assessed by analyzing the association between SHMT2 and other clinicopathologic factors. In addition, the prognostic significance of SHMT2 was investigated using univariate analysis (log-rank test) and multivariate analysis (Cox regression model).

Material and Methods

Specimens and follow-up

The primary cohort consisted of 364 patients who underwent radical surgery and were pathologically diagnosed as having GC at the Sixth People's Hospital of Qingdao and the Yidu Central Hospital of Weifang from 2008 to 2016. From the primary cohort, a final cohort comprising 130 cases was enrolled using the following inclusion criteria: (1) no preoperative chemotherapy or radiotherapy before radical surgery, (2) available follow-ups and tissues for IHC, (3) no severe complication and a follow-up >3 months, and (4) no other malignancies. The final cohort was composed of 49 female patients and 81 male patients, with an average follow-up of 46.6 months. Moreover, 15 cases of GC and their patient-paired normal tissues were obtained during the operation and stored in liquid nitrogen and used for mRNA extraction. The study was approved and supervised by the Ethics Committees of the Sixth People's Hospital and Yidu Central Hospital. All the specimens were collected with written consent of the patients. The TNM stage in this study was determined according to the 8th American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging system.

IHC

The expression and location of SHMT2 were estimated with IHC by the streptavidin peroxidase complex method according to the method described in a previous study [12]. In brief, after being deparaffinized and rehydrated with xylene and graded alcohol, tissues were incubated in boiled 0.01 M citrate buffer (pH=6.0) for the best antigen retrieval. We used 3% H_2O_2 to inactivate the endogenous peroxidase. Following the blockage of unspecific binding by 5% bovine serum albumin (BSA), tissues were incubated in primary antibody of SHMT2 at 1: 100 (Abcam, Cambridge, MA, USA, cat. no. EPR3198) at 1: 100 dilution at 4°C overnight. After rinsing in phosphate-buffered saline 3 times, tissues were incubated in HRP-labeled secondary antibody (ZSBio, Beijing, China) at room temperature for 30 min. Finally, the complex reagent of streptavidin peroxidase (ZSBio, Beijing, China) was used, and 3,3'-diaminobenzidine solution (ZSBio, Beijing, China) was applied for final visualization of the antigen.

Evaluation of IHC result

The IHC results were semi-quantified by calculating IHC score according to the method described in a previous study [13]. The IHC score were evaluated by 2 senior pathologists blinded to the clinical data. The IHC score consisted of 2 aspects: the percentage of positive cells and the staining intensity. The scores for positive cell percentage were set as: 0 points represents <10% positive cells; 1 point represents 10–25% positive cells; 2 points represents 25–50% positive cells, and 3 points represents >50% positive cells. The scores for staining intensity were set as: 0 points represents the negative staining, 1 point represents weak staining, 2 points represents the moderate staining, and 3 points represents strong staining. The final IHC scores were the product of the score (positive cell percentage) multiplied by the score (staining intensity), ranging from 0 to 9. The cut-off was set as the point

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with highest sum of specificity and sensitivity in the receiver operating characteristic curve [14], and this was used to separate the final cohort into subgroups with high SHMT2 and low SHMT2 expression. In our study, the cut-off of SHMT2 was 3.5, meaning that patients with scores ≥4 were defined as SHMT2 high expression and those with scores ≤3 were defined as SHMT2 low expression.

Cell culture

The gastric cancer cell line MKN-28 was purchased from Shanghai Cell Bank (Shanghai, China). MKN28 cells were cultured in RPMI-1640 medium (HyClone, USA) supplemented with 10% fetal bovine serum and 100 U/ml penicillin and 100 ug/ml streptomycin (HyClone, USA) in 5% CO_2 resuscitation.

qRT-PCR

SHMT2 mRNA in GCs and paired normal tissues was estimated by qRT-PCR referring to a previous study [15]. In brief, total mRNAs were extracted with Trizol reagent (Thermo Fisher, Waltham, MA, USA) according to the manufacturer's instructions, and reverse transcription was performed using a QuantiTect Reverse Transcription Kit (Qiagen, Venlo, Netherlands). The StepOnePlus™ RT-PCR system (Thermo Fisher, Waltham, MA, USA) was used for quantitative real-time PCR with SYBR Green qPCR Master Mix (Thermo Scientific, Waltham, MA, USA). GAPDH was used as a control to standardize SHMT2, and results were calculated by $2^{-\Delta\Delta}$Ct method. The primer sequence of SHMT2 and GAPDH was as follows:
SHMT2, forward: 5'-CGAGTTGCGATGCTGTACTT-3';
reverse: 5'-CTGCGTTGCTGTGCTGAG-3';
GAPDH, forward: 5'-GGGAAGGTGAAGGTCGGAGTC-3',
reverse: 5'-CCATGGGTGGAATCATATTGGAA-3'

RNA knockdown

The RNA knockdown of SHMT2 was performed by transfection of siRNA. Two independent siRNAs and a scrambled siRNA of SHMT2 were purchased from Santa Cruz Biotech. Transfection of siRNA was performed using Lipofectamine 2000 according to the user guide.

Proliferation assay

CCK8 assay was used to detect the influence of SHMT2 on proliferation. In brief, cells transfected with SHMT2 siRNAs or scrambled siRNA were plated into 96-well plates (5×10^3 cells/well) and cultured for 0 to 72 h. After incubation, CCK8 (Dojindo, Japan) was used to incubate cells at 37°C for 2 h. The optical density at 450 nm was detected using a spectrophotometer (Molecular Devices Company, San Jose, CA, USA).

Table 1. Basic information on the patients with GC.

Variables	Number	Percentage
Sex		
Female	49	37.69%
Male	81	62.31%
Age		
≤60	44	33.85%
>60	86	66.15%
Tumor size (cm)		
≤5 cm	51	39.23%
>5 cm	79	60.77%
Histopathological grade		
I	33	25.38%
II+III	97	74.62%
T stage		
T1+T2	19	14.62%
T3+T4	111	85.38%
Lymphatic invasion		
Negative	32	24.62%
Positive	98	75.38%
Distant metastasis		
Negative	120	92.31%
Positive	10	7.69%
TNM stage		
I–II	47	36.15%
III–IV	83	63.85%
SHMT2		
Low	61	46.92%
High	69	53.08%

SHMT2 is the abbreviation of serine hydroxymethyltransferase 2.

Invasion assay

Pre-coated 8.0-μm pore Transwell chambers (BD Biosciences, Franklin Lakes, NJ, USA) were used to evaluate the invasion ability of MKN28 cells. After starvation in serum-free medium for 6 h, 10^4 cells were plated into each upper chamber. The lower chambers contained medium with 5% FBS to facilitate the invasion of cells. After incubation for 12 h, cells in the lower surface were fixed with methanol and stained with 0.1% crystal violet (Beyotime, Beijing, China). The invaded cells were counted using a microscope.

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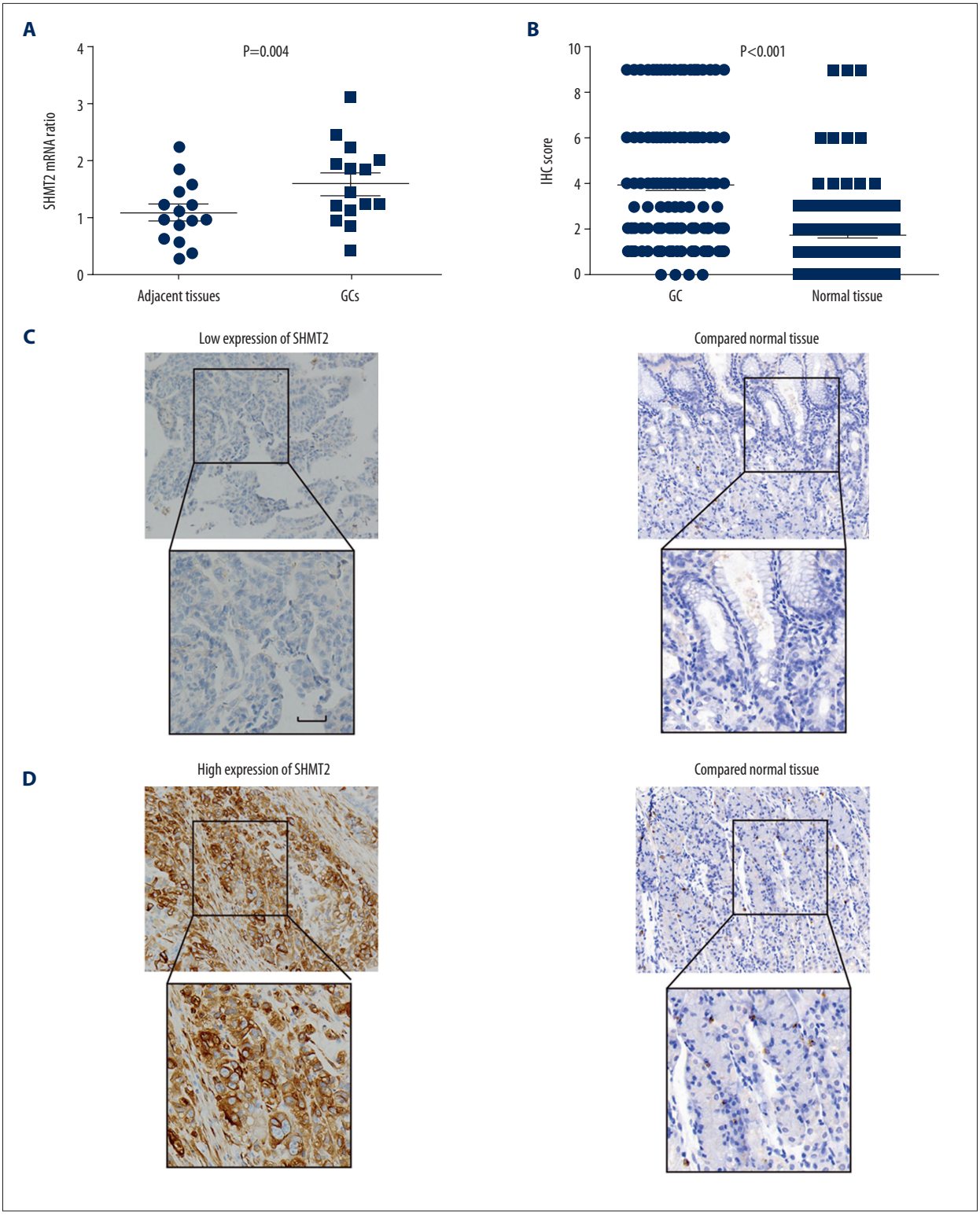

Figure 1. Expression of SHMT2 in gastric cancer tissues and normal gastric tissues. (**A**) The mRNA level of SHMT2 in GCs and paired normal gastric tissues was evaluated with qRT-PCR. The P value was evaluated with the paired *t* test. (**B**) The IHC scores of GC tissues were higher than the scores of adjacent normal tissues. The P value was evaluated with the paired *t* test. (**C, D**) Representative images of low (**C**) and high (**D**) immunohistochemical staining of SHMT2 in GC tissues and paired normal tissues. Scale bar: 50 um.

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Table 2. The association between SHMT2 and clinicopathologic factors.

Variables	SHMT2		P*
	Low	High	
Sex			
Female	21	28	0.587
Male	40	41	
Age			
<60	22	22	0.711
≥60	39	47	
Tumor size			
≤5 cm	29	22	0.068
>5 cm	32	47	
Histopathological grade			
I	20	13	0.068
II+III	41	56	
T stage			
T1+T2	10	9	0.626
T3+T4	51	60	
Lymphatic invasion			
Negative	20	12	0.042
Positive	41	57	
Distant metastasis			
Negative	56	64	0.839
Positive	5	5	
TNM stage			
I–II	29	18	0.149
III–IV	32	51	

SHMT2 is the abbreviation of serine hydroxymethyltransferase 2.
* Calculated by the χ^2 test.

Statistical analysis

All data were analyzed with SPSS 22.0 software (IBM cooperation, Chicago, USA). The chi-square test was used to evaluate the correlation between the SHMT2 expression and the clinicopathologic factors. The Kaplan-Meier method was performed to create a survival curve and the log-rank test was used to evaluate the difference between variable clinicopathologic factors and the survival rates. Multivariate analysis with Cox regression model was carried out for identification of independent prognostic factors. P values less than 0.05 were defined as statistically significant.

Table 3. Prognostic significance of clinicopathologic factors including SHMT2 was analyzed with univariate analysis.

Variables	5-year survival rate	P*
Sex		
Female	28.6	0.333
Male	33.3	
Age		
<60	25	0.577
≥60	34.9	
Tumor size(cm)		
≤5	51	0.001
>5	19	
Histopathological grade		
I	48.5	0.001
II	29.3	
III	6.7	
T stage		
T1	83.3	0.001
T2	53.8	
T3	29.4	
T4	15.4	
Lymphatic invasion		
Negative	46.9	0.018
Positive	27.6	
Distant metastasis		
Negative	34.2	<0.001
Positive	0	
TNM stage		
I	60	<0.001
II	45.9	
III	24.7	
IV	0	
SHMT2		
Low	49.2	<0.001
High	15.9	

SHMT2 is the abbreviation of serine hydroxymethyltransferase 2.
* Calculated by log-rank test.

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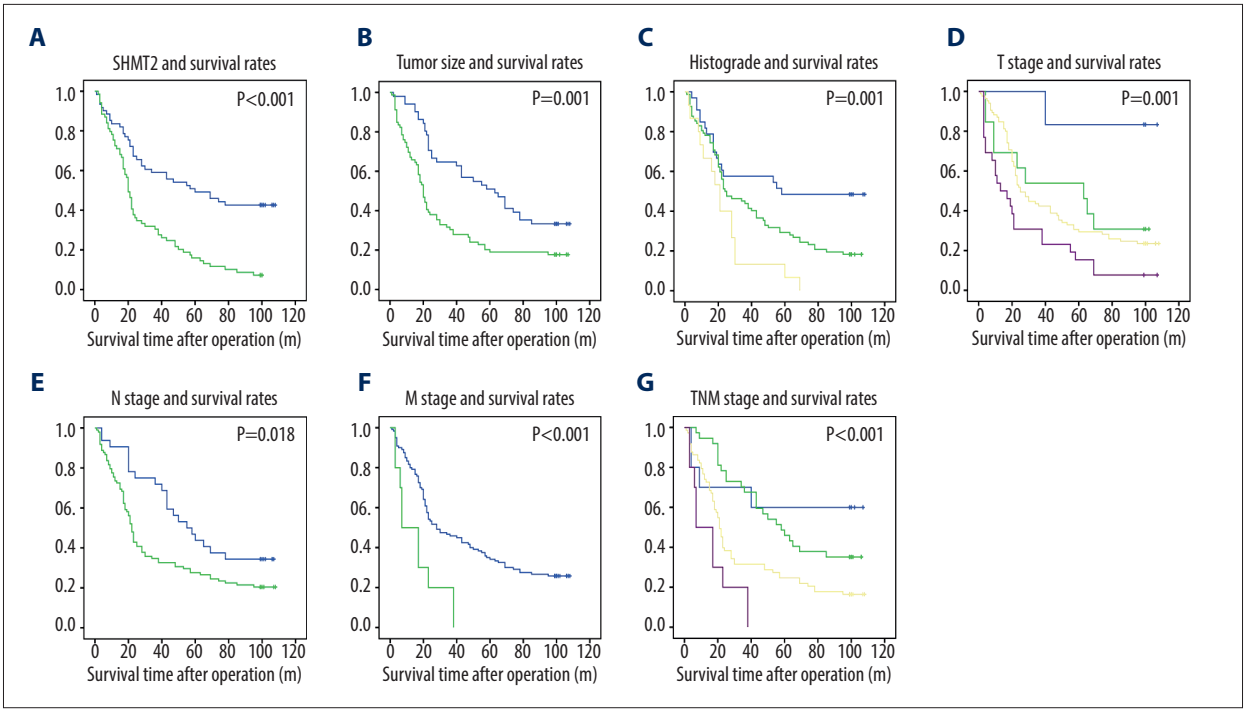

Figure 2. The correlation between survival rates and SHMT2 expression, tumor size, histopathological grade, T stage, lymphatic invasion, distant metastasis, and TNM stage. The overall survival rates were stratified into groups according to the SHMT2 expression (**A**), tumor size (**B**), histological grade (**C**), tumor filtration (**D**), lymphatic invasion (**E**), metastasis (**F**) and TNM stage (**G**).

Results

The expression of SHMT2 in gastric cancers and normal gastric tissues

The mRNA expression of SHMT2 in GCs and patient-paired normal tissues were compared by qRT-PCR. In the 15 pairs of GC tissues and corresponding adjacent tissues were collected, the SHMT2 mRNA in GCs was substantially higher than in patient-paired normal gastric tissues (Figure 1A), which suggested that SHMT2 may participate in the oncogenesis of GC. The expression and subcellular location of SHMT2 were then investigated by IHC. In the stained 130 cases of GC and adjacent tissues, GCs had significantly higher IHC score than in adjacent tissues (Figure 1B). As an essential enzyme that catalyzes the reversible conversion of serine to glycine, the SHMT2 was mainly expressed in the cytoplasm of GC tissues. The 130 cases were divided into different subgroups according to the expression level of SHMT2. The percentage of low and high expression of SHMT2 accounted for 46.92% and 53.08%, respectively (Table 1). The representative IHC images of low and high SHMT2 expression were shown in Figure 1C and 1D.

SHMT2 expression was notably associated with positive lymphatic invasion

The association between all the clinicopathologic factors and SHMT2 expression was analyzed with the chi-square test (Table 2). SHMT2 expression was shown to be significantly associated with lymphatic invasion. Patients with high SHMT2 expression had high risk of positive lymphatic invasion (P=0.042), indicating the possible role of SHMT2 in GC invasion. Moreover, patients with high SHMT2 seemed to be more likely to have larger tumor size (P=0.068) and advanced histological grade (P=0.068), although the differences were not statistically significant. These results all suggest that SHMT2 is involved in progression of GC.

SHMT2 expression is correlated with low survival rates

The associations among SHMT2 expression, clinicopathologic factors, and survival time were further evaluated with univariate analysis (Table 3). The 5-year survival rates of high-SHMT2 patients was 15.9%, which was remarkably lower than for patients with low SHMT2 expression (49.2%, P<0.001) (Figure 2A). Moreover, large tumor size (P=0.001), high histological grade (P=0.001), more severe tumor filtration (P=0.001), positive lymphatic invasion (P=0.018), positive metastasis (P<0.001), and

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Table 4. Multivariate analysis.

Variables	HR	95%CI	P*
Tumor size (cm)			
≤5	1		
>5	1.22	0.75–1.97	0.419
Histopathological grade			
I	1		
II	1.45	0.82–2.57	0.197
III	3.45	1.60–7.44	0.002
T stage			
T1+T2	1		
T3+T4	1.86	0.93–3.69	0.078
Lymphatic invasion			
Negative	1		
Positive	1.23	0.73–2.05	0.441
Distant metastasis			
Negative	1		
Positive	2.52	1.25–5.07	0.010
SHMT2			
Low	1		
High	2.52	1.60–3.95	<0.001

SHMT2 is the abbreviation of serine hydroxymethyltransferase 2.
* Calculated by Cox regression model.

advanced TNM stage (P<0.001) were all correlated with unfavorable prognosis (Figure 2B–2G).

SHMT2 independently predicts prognosis of GC

All the significant prognostic valuables in the log-rank test were entered into the Cox regression hazard model for identification of prognostic factors (Table 4). TNM stage was ruled out because of its natural interaction with other factors. In the multivariate analysis, SHMT2 was confirmed as an independent prognostic biomarker of GC (P<0.001), which suggested that high SHMT2 expression can predict poor prognosis by itself. The hazard ratio of SHMT2 was 2.52, indicating that the possibility of cancer-associated death of high-SHMT2 patients was approximately 2.5 times higher compared with those who had low SHMT2 expression. In addition, positive distant metastasis (HR=2.52, 95% CI=1.25–5.07, P=0.010) and high histological grade (HR = 3.45, 95% CI 1.60–7.44, P=0.002) were also independent prognostic factors of GC.

SHMT2 promotes proliferation and invasion of GC cells

Function assays were performed to evaluate the effect of SHMT2 on GC cells. Two independent siRNAs of SHMT2 was transfected into GC cell MKN28 for SHMT2 knockdown (Figure 3A). After successful knockdown, MKN28 was cultured for 3 days and the proliferation was detected by CCK-8 assay. Consequently, SHMT2 knockdown significantly decreased the proliferation of MKN28 (Figure 3B). Transwell assay was carried out to evaluate the influence of SHMT2 on GC invasion (Figure 3C). Silencing SHMT2 also notably attenuated the invasion of GC cells. All of the above results indicate an important role of SHMT2 in GC cell progression.

Discussion

The folate-dependent one-carbon (1C) metabolism is essential in progression and representative metabolic change in cancer growth and proliferation, just like enhanced glucose uptake

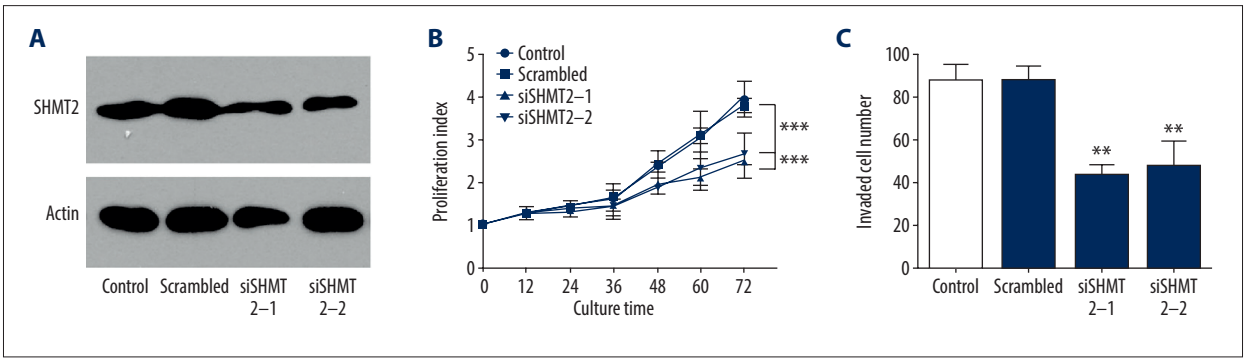

Figure 3. SHMT2 promoted the proliferation and invasion of GC cells. (**A**) Successful knockdown of SHMT2 in MKN-28 cells by siRNA was detected with Western blot. (**B**) CCK-8 assay was used to detect the proliferation of MKN-28 cells. SHMT2 knockdown notably attenuated the proliferation of MKN-28 cells. (**C**) Cell invasion was detected by Matrigel Transwell assay. SHMT2 knockdown decreased the invasion of MKN-28 cells.

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and aerobic glycolysis [16,17]. In the most rapidly proliferating cells, such as tumor cells, 1C units generated from serine catabolism in the mitochondria can be exported to the cytosol as formate, and then re-assimilated into folates to support nucleotide synthesis [18–20]. The antagonism of 1C metabolic enzymes has been used in chemotherapy for over 60 years, and since then, the important role of 1C metabolism in tumorigenesis has been extensively studied [21]. Many drugs, including the common clinical agents pemetrexed, 5-fluorouracil, and methotrexate, are therapeutically targeted at 1C metabolism [22]. Between the only 2 SHMT members, expression of SHMT2 is significantly upregulated in a variety of cancers compared with SHMT1 [9,23]. In a previous study, *SHMT2* was identified as a potential cancer driver gene by comparative oncogenomics [9]. Our identification of SHMT2 as a prognostic biomarker in GC is an important addition to the oncogenic study of SHMT2, and provides insight into the significance of SHMT2 as a drug target.

Along with the trend of personalized management, new applications are being tried to treat patients based on the molecular profile of the tumor. For example, a recent clinical trial demonstrated that immune checkpoint blockade therapy can suppress the progression in 12 types of tumors only if they have mismatch repair deficiency [24].

However, the clinical application of molecularly guided personalized treatment in GC remains stagnant. The extensive use of gene sequencing has resulted in discovery of many new biomarkers or genetic alterations of gastric cancer. For example, the Cancer Genome Atlas Research Network has published the results of full genomic profiling of 295 primary gastric adenocarcinomas [25]. Unfortunately, only a few of these genetic findings lead to clinical trials [26]. One reason for this is that final protein expression was not only altered by genetic alteration, but also by other cellular procedures like lncRNA and post-transcriptional modification. One great breakthrough in gastric biomarkers is the discovery of human epidermal growth factor receptor-2(HER2). Approximately 12–20% of gastric adenocarcinomas are HER2-positive [27], and previous studies reported that HER2-positive patients have worse prognoses, necessitating use of Herceptin in the treatment of gastric cancer [28]. Therefore, discovery of effective biomarkers with high potency to be drug targets in gastric cancer is still urgently needed. In our study, we investigated the potential biomarker of GC by IHC, which could directly affect the expression level of the potential biomarkers. This increased the efficiency from biomarker identification to potential drug target.

Most gastric cancers are gastric adenocarcinomas, but are highly heterogeneous with respect to architecture and growth, cell differentiation, histogenesis, and molecular pathogenesis [29]. This heterogeneity makes the investigation of molecular classification based on different biomarkers of genetic amplification essential. In our study, we demonstrated that SHMT2 is an independent prognostic biomarker of GC, with a very remarkably high statistical significance ($P<0.001$). This result indicates that SHMT2 detection after surgery would be helpful for stratification of patients with high risk, and may thus direct personalized treatment. Moreover, the correlation between SHMT2 and GC progression indicated that SHMT2 may be a potential drug target, which may stimulate pharmacological industry interest in SHMT2 and help develop new targeted drugs to treat GC. It is especially important to define the value of SHMT2 as a potential drug target in GC, because small-molecule dual inhibitors of SHMT1/2 have been developed in recent studies [30]. However, the function of the specific inhibitor of SHMT2 in suppressing tumor progression remains unclear, and the potency of SHMT2 inhibitor as a possible clinical drug needs more trials and experiments. Clearly, the clinical effects of the inhibitors need clinical trials because one-carbon donor formate generally rescues cells from SHMT inhibition.

Conclusions

In this study, we assessed the expression of SHMT2 in 130 patients with GC by immunohistochemistry (IHC) and evaluated its clinical and prognostic significance for the first time. Consequently, we showed that SHMT2 expression was notably correlated with lymphatic invasion, and that SHMT2 was an independent prognostic biomarker of GC. Our results suggest that SHMT2 detection would be helpful for stratification of high-risk patients and thus direct personalized treatment. SHMT2 may be a potential drug target of GC, and anti-SHMT2 drugs may be promising in therapy for GC treatment.

Conflicts of interest

None.

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