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Original Article

Decreased expression of serglycin is associated with poor prognosis in gastric cancer

Hui-Ju Wang[1,2,3], Ying-Yu Ma[1,2], Li Li[1,2], Qi Zhang[4], Xiang-Lei He[5], Ke-Tao Jin[6], Xiao-Zhou Mou[1,2], Xiang-Min Tong[1,2], Dong-Sheng Huang[1,2]

[1]Clinical Research Institute, Zhejiang Provincial People's Hospital, Hangzhou 310014, Zhejiang, China; [2]Key Laboratory of Cancer Molecular Diagnosis and Individualized Therapy of Zhejiang Province, Hangzhou 310014, Zhejiang, China; [3]Key Laboratory of Gastroenterology of Zhejiang Province, Hangzhou 310014, Zhejiang, China; [3]Department of Urology, [5]Department of Pothology, Zhejiang Provincial People's Hospital, Hangzhou 310014, Zhejiang, China; [6]Department of Gastrointestinal Surgery, Shaoxing People's Hospital, Shaoxing Hospital of Zhejiang University, Shaoxing 312000, China

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Abstract: Background and aim: Serglycin, a major intracellular proteoglycan, was originally discovered in several hematopoietic cell types. It has been found to over-expressed in several cancers, including multiple myeloma, acute myeloid leukemia, and nasopharyngeal, hepatocellular, breast cancer. However, there is few report of serglycin in gastric cancer. The aim of this study is to investigate the expression of serglycin and its relationship with clinical pathological characters in gastric cancer. Methods: Serglycin mRNA level was determined by quantitative real-time RT-PCR in 89 pairs of matched gastric tumorous tissues and adjacent non-tumorous mucosal tissues. Serglycin protein expression was analyzed by immunohistochemistry in 165 clinically characterized gastric cancer cases and 24 non-tumorous gastric mucosal tissues controls. Results: The mRNA and protein expression of serglycin was significantly decreased in gastric tumor tissues compared with the non-tumorous mucosal tissues. Low expression of serglycin mRNA was associated with depth of invasion and distant metastasis. Low expression of serglycin protein correlated with differentiation, depth of invasion, lymph node metastasis, distant metastasis and TNM stage. A cumulative five-year survival rate of patients with low expression of serglycin was significantly lower than those with high serglycin expression. Conclusions: Decreased expression of serglycin was associated with poor prognosis in gastric cancer.

Keywords: Serglycin, gastric cancer, metastasis

Introduction

Gastric cancer is one of the most common cancers and the second leading cause of cancer-related death worldwide. There are over 900,000 new cases of gastric cancer and 700,000 gastric cancer-related deaths per year in the world [1]. Notably, China alone accounts for 42% of all gastric cancer cases worldwide. There are approximately 400,000 new cases of gastric cancer and 300,000 deaths every year in China [2]. Gastric cancer has no apparent symptoms in early stage. Therefore, most patients are not diagnosed until the disease is advanced. Tumor invasion and metastasis are the primary causes for treatment failure or death among patients with advanced gastric cancer.

Serglycin, a major intracellular proteoglycan, was originally discovered in several hematopoietic cell types, such as mast cells, macrophages, CTLs, Neutrophils, and platelets. It is composed of a core protein, which is 158 aa in length and riches in Ser-Gly dipeptide repeats, with glycosaminoglycan (GAG) covalently attached to it [3, 4]. The GAG chain of Serglycin tremendously varies between different cell types. In connective tissue type mast cell, the GAG chain of serglycin is heparin, while the GAG chains of serglycin in mucosal type MCs are CS-E and CS-4 [5-8]. In macrophages, the GAG types of serglycin are CS-E and CS-4 [9]. In CTLs, the GAG chains of serglycin are CS-E, CS-diB, and CS-4 [10-12]. In neutrophils and platelets, the GAG chain of is serglycin CS-4 [13-15]. Serglycin with different GAG

chain expressed by different cells plays different physiological function, such as promoting storage of proteases, histamine, serotonin, granzyme B, elastase, and regulating apoptosis, cytokine secretion and contraction of CD8+ T cell. Besides, serglycin are also expressed in some non-hematopoietic cell types, including endothelial cells, chondrocytes, pancreatic acinar cell, and smooth muscle cells [16-19].

Moreover, high expression levels of serglycin have been detected in several malignant haematopoetic and solid tumors, including multiple myeloma (MM), acute myeloid leukemia, nasopharyngeal, hepatocellular and breast cancer [19-23]. The serglycin is the major proteoglycan of multiple myeloma cells [19]; it can inhibit the classical and lectin pathways of complement, thus to protect myeloma cells during immunotherapy and promote survival of malignant cells [24]. Serglycin also confers hematologic tumor cells the resistance against chemotherapy drugs [25]. Besides, serglycin also implicates in the promotion of aggressive phenotype of tumor cells; tumor cells with high serglycin expression showed a much higher vitality of proliferation, migration, invasion and metastasis, and were correlated with poor prognosis [21, 23, 26].

However, no data about serglycin in gastric cancer has been reported so far. In this study, we analyzed the expression of serglycin by RT-qPCR and immunohistochemistry in surgically resected human primary gastric cancer tissues, and investigated the association of serglycin expression with clinicopathological parameters. This study might allow us to gain further insight into the biological function of serglycin in cancers.

Materials and methods

Patients and tissue samples

All of the human tissues were obtained from gastrectomy specimens of patients with primary gastric cancer at Zhejiang Provincial People's Hospital, Hangzhou, China. This study was approved by the Ethics Committee of Zhejiang Provincial People's Hospital, Hangzhou, China. Written informed consent was provided by the patients.

Eighty-nine pairs of matched fresh gastric tumorous and adjacent non-tumorous mucosal tissues were obtained from January 2012 to December 2012. After surgical removal, tissues were frozen immediately in liquid nitrogen and stored at -80°C for further analysis.

165 cases of paraffin-embedded gastric tumorous tissues were obtained from January 2006 to December 2007. The patient cohort consisted of 117 males and 48 females, with a median age of 65.3 years (range: 35-82) at the time of surgery. Patients with advanced-stage disease underwent routine chemotherapy after surgery, but no radiation treatment was given to any patients included in our study. All patients had follow-up records for over 5 years and the follow-up deadline was December 2012. The survival time was calculated from date of surgery to follow-up deadline or date of death, which was caused mainly by carcinoma recurrence or metastasis. Twenty-four non-cancerous human gastric mucosal tissues were obtained from gastrectomies of adjacent gastric cancer margins >5 cm. We followed up all patients by consulting their case documents and through telephone. All tissues were used for tissue microarray (TMA) construction, as previously described [27].

Quantitative real-time RT-PCR

qRT-PCR was performed to determine the mRNA level of serglycin. Briefly, total RNA was extracted from 89 pairs of matched gastric tumorous and adjacent non-tumorous mucosal tissue specimens using Trizol (Invitrogen, Carlsbad, CA) according to the manufacturer's instructions. cDNA synthesis was carried out with the PrimeScript 1st Strand cDNA Synthesis kit (Takara, Dalian, China), using 1 μg of total RNA as the template and Oligo dT primer under 65°C, 5 min, 42°C, 60 min and 70°C, 10 min of reverse transcription. The resulting cDNA was amplified by qPCR using specific primers with SYBR Premix Ex Taq (Takara, Dalian, China). GAPDH was used as an internal control. Primers for serglycin were 5'-TTGCCCTCATCCTGGTTCTG-3' (sense) and 5'-TTGTTGGATTCACCTGGAAGTAG-3' (antisense); Primers for GAPDH were 5'-TGAAGGTCGGAGTCAACGG-3' (sense) and 5'-CTGGAAGATGGTGATGGGATT-3' (antisense). PCR parame-

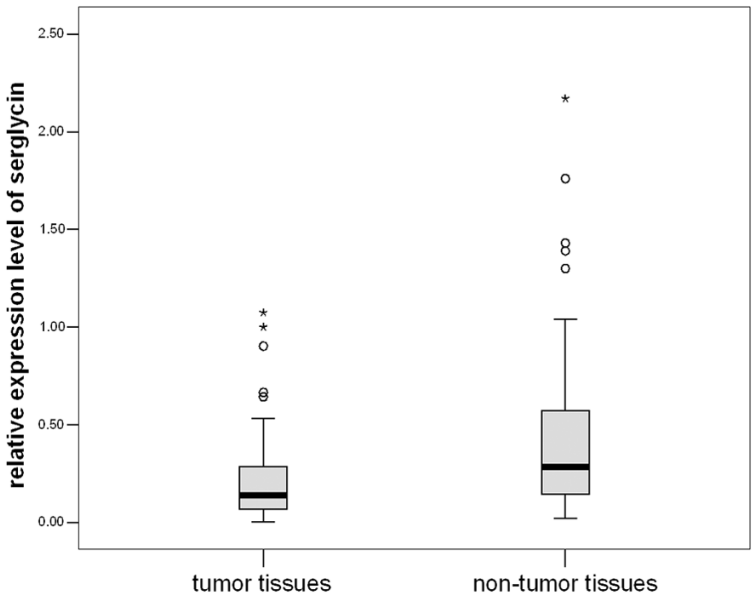

Figure 1. Relative expression of serglycin mRNA in gastric tumor tissues and non-tumor tissues.

Table 1. Relationship between Serglycin mRNA levels and pathological parameters of gastric cancer

Clinical parameters	Numbers	Serglycin mRNA levels	*P*-value
Age (years)			0.918
≥60	51	0.222±0.274	
<60	38	0.216±0.229	
Gender			0.361
Male	55	0.199±0.210	
Female	34	0.251±0.315	
Size			0.913
<5	40	0.216±0.220	
≥5	49	0.222±0.282	
Histologic differentiation			0.087
Well+Moderately	43	0.174±0.174	
Poorly	46	0.261±0.308	
Invasion depth			
T1+T2+T3	28	0.315±0.335	0.048
T4	61	0.175±0.196	
Lymphatic metastasis			0.070
N0+N1	30	0.184±0.183	
N2+N3	59	0.288±0.349	
Distant metastasisa			<0.001
M0	76	0.246±0.265	
M1	13	0.064±0.067	
TNM stages			
I+II	22	0.313±0.367	0.141
III+IV	67	0.188±0.199	

ters were as follows: 95°C for 5 min, followed by 40 cycles of 95°C for 10 s, 60°C for 20 s and 72°C for 20 s. At the end of the PCR cycles, melting curve analysis was performed. The Relative expression of serglycin to GAPDH was calculated using $2^{-\Delta CT}$ method.

Immunohistochemical staining

Immunohistochemical staining was performed by the standard method. Briefly, 5 μm sections from the TMAs were baked at 60°C for 2 h. Then, the sections were de-paraffinized in xylene, rehydrated using a gradient of ethanol concentrations, microwaved in 10 mM citrate buffer for 15 min to retrieve antigen, blocked with 3% hydrogen peroxide for 10 min to inhibit endogenous peroxidase activity and incubated with 10% goat non-immune serum for 20 min to reduce background non-specific staining. After that, the sections were incubated with the rabbit anti-serglycin polyclonal antibody (Abcam, Cambridge, UK) (1:200 dilution) at 4°C overnight, then incubated with biotin-labeled secondary antibody (Invitrogen, Carlsbad, CA) at room temperature for 20 min, followed by incubation with HRP-conjugated streptavidin (Invitrogen, Carlsbad, CA) at room temperature for 20 min. Then, Color development was performed with DAB Substrate Kit (Dako, Glostrup, Denmark). Finally, the sections were counterstained with hematoxylin, dehydrated, cleared and mounted.

Evaluation of the immunohistochemical staining

The immunohistochemical stain of serglycin was scored by two pathologists independently, based on the intensity and the proportion of positively stained cells. Staining intensity was evaluated with a four-tiered grading system: 0 = negative, 1 = weak, 2 = moderate and 3 = strong. The

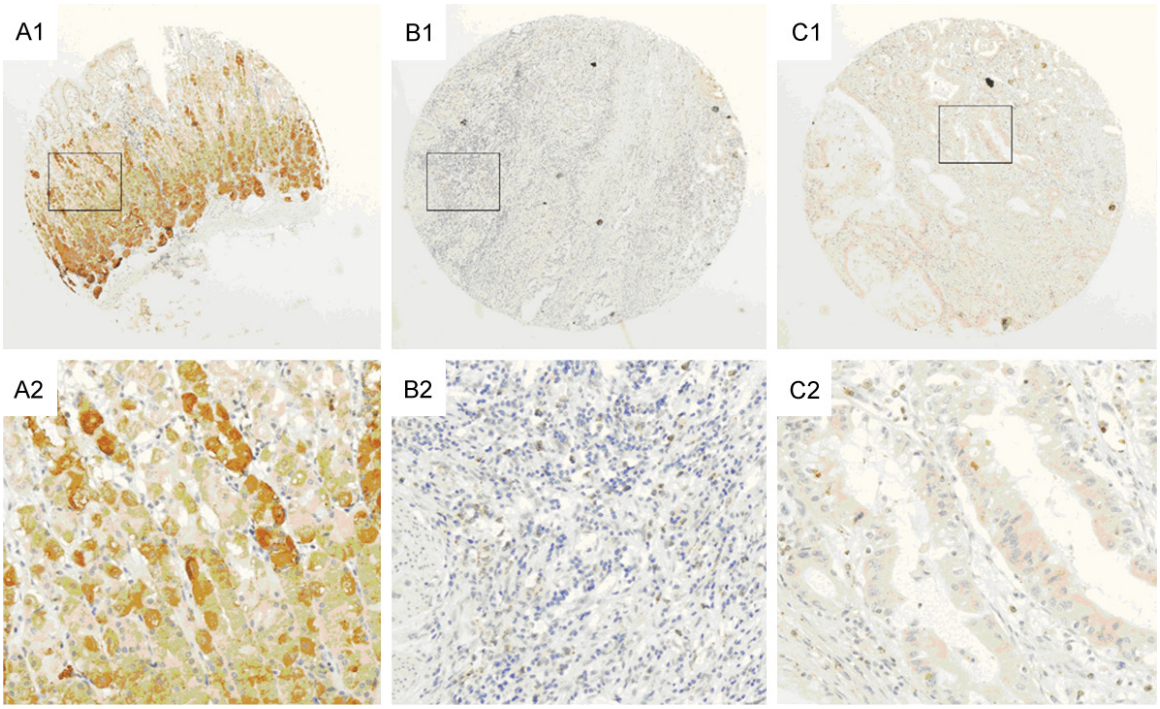

Figure 2. Expression of serglycin in gastric tumor tissues and non-tumorous tissues. A1 (×64), A2 (×320): Strong expression of serglycin in non-tumorous tissues; B1 (×64), B2 (×320), C1 (×64), C2 (×320): Low or absent expression of serglycin in gastric tumor tissues.

percentage of positive cells were scored as follows: 0 for no cell stained, 1 for 1%-25% of cells stained, 2 for 26-50% of cells stained, 3 for 51-75% of cells stained and 4 for more than 75% of cells stained. Scores for intensity and percentage of positive cells were multiplied. Scores ≤3 was used to define tumors with low serglycin expression and scores ≥4 with high serglycin expression.

Statistical analysis

Statistical analysis was performed using Statistical Program for Social Sciences (SPSS) software 13.0 (SPSS Inc., Chicago, IL, USA). The paired-samples *t*-test was used to analyze the differences of serglycin mRNA expression between tumor and non-tumor tissues. Independent-Samples T test and χ^2-tests were applied to assess the statistical significance of the associations between serglycin mRNA/protein expression and clinicopathological parameters, respectively. Survival curves were estimated using the Kaplan-Meier method, and the log-rank test was used to calculate differences between the curves. A *P* value of less than 0.05 was considered statistically significant.

Results

Down-regulated serglycin mRNA in gastric tumor tissues

The expression of serglycin in gastric tumor tissues and corresponding non-tumor tissues was analyzed using qRT-PCR and a total of 89 pairs of matched tissue specimens. Expression levels of serglycin were much lower in gastric tumors than in non-tumor tissues (0.218±0.022 *VS* 0.415±0.0418, *P*<0.05; **Figure 1**). The association of serglycin mRNA level between clinicopathological parameters was also evaluated. T4 or M1 stage tumor tissues showed significantly lower expression of serglycin mRNA than T2, T3 or M0 stage tumor tissues did (0.175±0.196 *VS* 0.315±0.335, *P* = 0.048; 0.064±0.067 *VS* 0.246±0.265, *P*<0.001; **Table 1**).

Down-regulated serglycin protein in gastric tumor tissues

Serglycin was highly expressed in all adjacent non-tumorous mucosal tissue, strong cytoplasmic staining could be seen in cells located at the surface of glandular and foveolar compartment (**Figure 2A**). In tumor tissues, the expres-

Table 2. Relationship between Serglycin expression and pathological parameters of gastric cancer

Clinical parameters	Number	Serglycin expression		*P* value
		High	Low	
Age (years)				0.849
≥60	98	60	38	
<60	67	42	25	
Gender				0.377
Male	122	73	49	
Female	43	29	14	
Size				0.239
<5	112	72	40	
≥5	53	29	24	
Histologic differentiation				0.027
Well+Moderately	73	52	21	
Poorly	92	50	42	
Invasion depth				0.004
T1+T2+T3	104	73	31	
T4	61	29	32	
Lymphatic metastasis				
N0+N1	71	50	21	0.048
N2+N3	94	52	42	
Distant metastasisa				<0.001
M0	147	101	46	
M1	18	1	17	
TNM Stages				0.001
I+II	46	38	8	
III+IV	119	64	55	

sion of serglycin was decreased or even absent (**Figure 2B**, **2C**). The immunostaining of serglycin was detected in 102 of 165 (61.82%) gastric tumor tissues.

Correlation between serglycin protein expression and clinicopathologic parameters

The correlation between expression of serglycin protein and clinical variables is shown in **Table 2**. The serglycin expression level was significantly related to differentiation, depth of invasion, lymph node metastasis, distant metastasis and TNM stage. Expression of serglycin in gastric tumor tissues with poor differentiation, or deep tumor invasion (T3-T4), lymph node metastasis, distant metastasis and high TNM stage was significantly lower than in those with superficial tumor invasion (T1-T2), or without lymph node metastasis and distant metastasis, respectively (**Table 2**). There was no significant correlation between serglycin expression and other clinicopathologic parameters.

Survival analysis

The mean survival time of patients with low serglycin expression was 41.66±2.23 months, which was significantly lower that of patients with high serglycin expression (51.45± 1.30, $P = 0.006$). Low expression of serglycin was associated with poor overall survival when compared to high serglycin expression (**Figure 3**).

Discussion

Proteoglycans are composed of a core protein with several attached glycosaminoglycans, such as hyaluronan, keratan sulfate, heparan sulfate/heparin, chondroitin sulfate/dermatan sulfate. They are the major constituents of extracellular matrices, as well as cell surfaces and basement membranes.

Proteoglycans participated in many normal physiological processes and disease states, including tumorigenesis and progression. Several proteoglycans involved in cancer progression, acting either as promoters or inhibitors, have been identified. For example, versican is highly expressed in most malignancies by the activated peritumoral stromal cells or some cancer cells, and increases the motility, proliferation, invasion and metastasis of cancer cells [28, 29]. Decorin possesses the anti-tumor effect by repressing and attenuating tumor cell survival, growth, migration and angiogenesis [30, 31]. While some other proteoglycans, such as syndecans, may function as a tumor suppressor or promoter according to the different tumor types [32, 33].

Serglycin is the dominating intracellular proteoglycans in many immune cells. It is also found over-expressed in MM, AML, nasopharyngeal, hepatocellular and breast cancer, and is considered as a promoter in cancer progression. Serglycin is the major proteoglycan expressed and secreted by MM cells [19]; serglycin knockdown dramatically decreased adhesion of MM cells, inhibited tumor growth in mice, and impaired development of tumor blood vessels [34]. In HCC, increased expression of serglycin

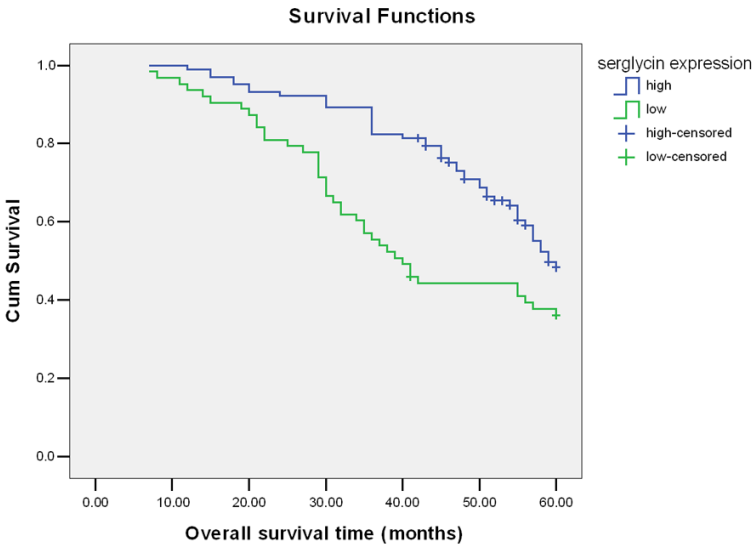

Figure 3. Kaplan-Meier survival curves of gastric cancer patients with different levels of serglycin expression.

was positively associated with HBV infection, GGT level, vascular invasion, advanced BCLC stage and early recurrences [22]. In NPC, high serglycin expression was an unfavorable independent indicator of distant metastasis-free and disease-free survival; inhibition of serglycin expression in highly metastatic NPC cells suppressed cells' invasive motility and metastatic capacity [21]. Besides, elevated expression of serglycin in both HCC and NPC was accompanied by elevated levels of vimentin and absences of E-cadherin, indicating that serglycin may promote tumor metastasis by regulating EMT [21, 22]. Also, serglycin can protect malignant cell during immunotherapy and promote cells' survival by interacting directly with C1q and mannose-binding lectin to inhibit both the classical and lectin pathways of complement [24]. All these studies indicated that serglycin may be a tumor promoter played an important role in tumor metastasis.

The expression and biological function of serglycin in gastrointestinal tract are still unclear. Recently, Anastasia V et al reported that serglycin expression was shown in normal colon tissue and being moderately decreased in colon tumors [35]. It's the first report that the expression of serglycin was decreased in tumor tissues. Interestingly, in our study, we found that the expression of serglycin was highly expressed in normal gastric mucosal tissues, while downregulated or even absent in gastric cancer tissues, and the expression of serglycin was negative correlated with depth of invasion, lymph node metastasis, distant metastasis and TNM stage, which was conversed with the reports of serglycin in most other malignant tumors. Also, it was reported that loss of serglycin may promote primary tumor growth and vessel functionality in the RIP1-Tag2 Mouse Model for Spontaneous insulinoma formation [36]. These findings indicated that serglycin may also have tumorigenesis and tumor develop in gastrointestinal tract.

In summary, our study shows that the expression of serglycin is significantly decreased in gastric tumor tissues, and is associated with poor differentiation, depth of invasion, lymph node metastasis, distant metastasis, advanced TNM stage and poor overall survival. These results suggest that serglycin may function as a tumor suppressor in gastric cancer, and might serve as a therapeutic target in gastric cancer.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Dong-Sheng Huang, Clinical Research Institute, Zhejiang Provincial People's Hospital, No. 158 Shangtang Road, Hangzhou 310014, Zhejiang Province, China; Tel: +86-571-85893027; Fax: +86-571-85891448; E-mail: dshuang@zju.edu.cn

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