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STMN1 in colon cancer: expression and prognosis in Chinese patients

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Abstract. – OBJECTIVE: To study the stathmin (STMN1) expression in colorectal cancer and tumor-adjacent normal tissue and discuss its prognostic significance in colon cancer.

PATIENTS AND METHODS: STMN1 was tested with qRT-PCR in 30 samples of fresh colon cancer tissue and tumor-adjacent issue, and with immunohistochemical SP method in 105 samples of fresh colon cancer tissue and tumor-adjacent issue to analyze the association between its expression and clinical pathological parameters. Clinical data was combined to study the relationship between STMN1 expression and 5-year survival rate. Univariate analysis and Cox multivariate regression were performed to study the correlation between STMN1 expression and prognosis.

RESULTS: The mRNA and protein level of STMN1 were significantly higher in colon cancer samples than tumor-adjacent normal tissues ($p<0.05$). STMN1 expression was independent of patient age, gender or location, but significantly related to lymph node metastasis and TNM staging ($p<0.05$). Survival analysis by Kaplan-Meier method showed that STMN1 expression was significantly related with the survival of colon cancer patients. The median survival time of STMN1-positive patients (37.5 months) was significantly shorter than STMN1-negative patients (57.1 months, $p<0.05$). Cox multivariate regression indicated that STMN1 is independent prognostic factors predicting the development, invasion and metastasis of colon cancer ($p<0.05$).

CONCLUSIONS: STMN1 overexpression in colon cancer is independently associated with improved survival and significantly related to the development of the disease. Our findings suggest that presence of a STMN1-prognosis interaction that potentially determines clinical outcome.

Key Words:
STMN1, Colon cancer, Immunohistochemistry, qRT-PCR, Prognosis.

Introduction

STMN1 (stathmin or oncoprotein-18) is a gene that is transcriptionally repressed by functional p53, a tumor-suppressor protein that regulates many cellular processes through gene transcription. It is the founding member of a family of proteins that play critically important roles in the regulation of the microtubule cytoskeleton. It destabilizes microtubules and reorganizes cytoskeleton, and functions in the formation of the corticospinal tract[1,2]. The microtubule-depolymerizing activity of STMN1 is regulated by phosphorylation to allow microtubule polymerization and assembly of the mitotic spindle.

STMN1 was first identified as a cellular phosphoprotein overexpressed in leukemia[3] and was associated with laryngeal squamous cell carcinoma[4], breast cancer[5], small cell lung cancer[6], and ovarian carcinoma[7]. STMN1 is phosphorylated in response to epidermal growth factor in colon carcinoma cells[8]. Recently it was reported that STMN1 overexpression was also associated with survival in colorectal cancer patients[9]. However, for now, few studies have been conducted about the prognostic significance of STMN1 expression in colon cancer. To reveal possible prognostic values and pathological roles of stathmin1 in colon cancer, we examined the expression of stathmin1. In this study, we collected tumor and tumor-adjacent tissue sample from 150 patients of stage I-V colon cancer to examine STMN1 expression with real-time PCR and immunohistochemistry and study the effect of tumoral STMN1 expression on prognosis and patient survival.

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Patients and Methods

Tissue Specimens

30 samples of freshly resected colon cancer tissue were collected from colon cancer patients receiving radical resection in the First Central Hospital of Baoding from 2014 to October 2014, among which 10 were of TNM I/II stage and 20 were of TNM III/IV stage. 30 samples of tumor-adjacent colonic mucosa 5 cm above resected tumor margin as a negative control. Samples were protected in liquid nitrogen till use.

105 paraffin embedded samples were provided by Department of Pathology of the First Central Hospital of Baoding and were prepared from surgically removed colon cancer tissue, with 47 samples of distal normal mucosa as a negative control. The corresponding patients of cancer tissue samples include 69 males and 36 females, aged 22 to 79 yrs (medium age: 53.8 yrs). The tumor locations were recorded as follows: 34 cases of sigmoid colon, 33 cases of ascending colon, 15 cases of transverse colon, and 23 cases of descending colon. The negative mucosa control samples were collected from 25 males and 22 females aged 40 to 72 yrs (medium age: 51.7 yrs). General characteristics were comparable between the two groups. The inclusion criteria includes: (1) Patients were diagnosed with primary colon cancer; (2) Patients received an open radical resection of the colon tumor; the tumor was completely removed; the vascular system was treated with the ligation and the procedure has followed the protocol of total mesorectal excision; the bowel was reconstructed with anastomats and muscle layer was reinforced with absorbable line; (3) Patients with history of tumor were excluded; (4) Patients were native to chemotherapy or radiotherapy; (5) Clear pathological diagnosis and complete clinical follow-up data can be provided; (6) The postoperative chemotherapy schedule may include 5-FU/CF, 5-FU/lev, UFt, Xeloda or FOLFOX. Tumor stage and tumor location were recorded according to AJCC (American Joint Committee on Cancer) and TNM.

Follow-up schedule: All patients were followed according to NCCN Guidelines for the treatment of colon cancer: Patients were re-visited every 3 months within 2 years after surgery and every 6 months during 3 to 5 years after surgery.

This study was approved by the Ethics Committees of First Central Hospital of Baoding. Informed consent was obtained from all study subjects.

Reagents and Methods

Immunohistochemistry for STMN1

Immunohistochemistry was performed as the previously established method. The slide was pre-treated with polylysine. Paraffin-embedded samples serial sections (4 μm) were mounted on slices coated with APES (3-aminopropyltriethoxysilan; Sigma-Aldrich, St. Louis, MO, USA). Sections were floated onto slides in a water bath and then dried at room temperature for 48 hours before being stained. Paraffin was removed in xylene and bought to water through graded concentrations of alcohol. Slides were treated with 3% hydrogen peroxide solution at room temperature for 15 minutes to block endogenous peroxidase activity. Slides were then placed in a glass box filled with 0.1 mol/L citrate buffer for 20 minutes at 95°C, followed with rinsing with PBS. Tissue sections were incubated with 10% normal goat serum (ZhongShan Biotech Corp. Beijing, China) in phosphate-buffered saline (30 min). Primary antibody against STMN1 (Rabbit polyclonal to STMN1, 1:50 dilution; Cell Signaling, Danvers, MA, USA) was applied, and the slides were maintained overnight at room temperature. Next, we applied an anti-rabbit IgG antibody (Vector Laboratories, Peterborough, UK) for 30 minutes, followed by an avidin-biotin complex conjugate (ZhongShan Biotech Corp. Beijing, China. 1:1000) for 60 minutes. Slides were developed using diaminobenzidine and methyl-green counterstain. Finally, slides were sealed with neutral gum. Phosphate buffer was used as negative control of primary antibody.

RNA Extraction and Real-time RT-PCR

Cryopreserved colon cancer tissue and tumor-adjacent tissue samples were grinded. 1 mL Trizol was added and the mixture was removed to polypropylene tube to extract total RNA. Sequential RNA extraction was performed as described in the Invitrogen product information. Total RNA was isolated with TRIZOL reagent (Invitrogen, Carlsbad, CA, USA). Expression levels of RNA were analyzed using an ABI PRISM 7500 instrument (Applied Biosystems, Waltham, MA, USA). Briefly, cDNA was prepared in a 20-μL reaction volume using 200 U MuLV (Invitrogen, Carlsbad, CA, USA) reverse transcriptase, 0.5 mg dNTP, 25URNA inhibitory enzyme and specific primers for each RNA. The cycle parameters for the reverse transcription reaction were 95°C for 30 s, 58°C for 30 s, 60°C for 30 s, and a hold at 4°C. All reactions were run in

triplicate. A STMN1 primer (upstream, 5'-AAGAAAGACGCAAGTCCCATG-3'; downstream, 5'-CTTCAGTCTCGTCAGCAGGGT-3') was used, with β-actin as an internal control (upstream primer, 5'-CTTCAGTCTCGTCAGCAGGGT-3'; downstream primer, 5'- AGGGGCCGGACTCGTCATAC-3'). A melting curve was prepared after amplification, and the expression of STMN1 RNA relative to β-actin was determined using the $2^{-\Delta\Delta CT}$ method. The Ct was defined as the fractional cycle number at which the fluorescence passed a fixed threshold.

Tissue evaluation

Using a light microscope, a visual grading system based on the number of positively stained cells in each tissue sample was used. STMN1 positivity was defined as the presence of light yellow, brownish yellow or brown cytoplasmic particles. Each slide was assigned a score for intensity according to the visual grading system by Sulzers et al[10,11]: Staining was divided into 4 degrees of intensity (1= no yellow particles, 1= light yellow particles, 2= pale brown particles, 3=brown particles) or evaluated by staining pattern: five fields of high power microscopic view were observed for percentage of positive stained cells (0=no positive stained cells, 1=positive stained cells <25%, 2= positive stained cells 25%-50%, 3= positive stained cells ≥ 50%). STMN1 expression was evaluated by the product of staining intensity and percentage of positive stained cells: 0=negative (-); 1-2=weak positive (+); 3-6=positive (++); 7-9=strong positive (+++). If the produce was less than 2 points, then the slide was scored as negative; otherwise, the slide was positive. Two investigators who were blinded to all clinical information scored all specimens. Discrepant scores (about 15% of cases) were resolved by consensus.

Statistical Analysis

SPSS13.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for analysis. The paired *t*-test was used for the comparison between groups. Chi-square test was used to analyze the relationship between STMN1 expression and clinical pathological data. Survival analysis was performed with Kaplan-Meier method, and Log-rank method was used for comparison between groups, with five years survival rate of patients as observation index. Univariate and multivariate analysis were performed with and Cox regression model. All data are presented as the mean ± SE. Differences were considered to be statistically significant at $p<0.05$.

Results

STMN1 RNA level increased significantly in colon cancer specimens. As indicated in Figure 1, 19 out of 30 tested colon samples showed positive STMN1 expression (positive rate, 63.3%, $p<0.01$ compared with normal control). The overexpression rate of STMN1 mRNA in 10 samples of TNM I/II colon cancer and 20 samples of TNM II/IV colon cancer were 40% and 75%, respectively.

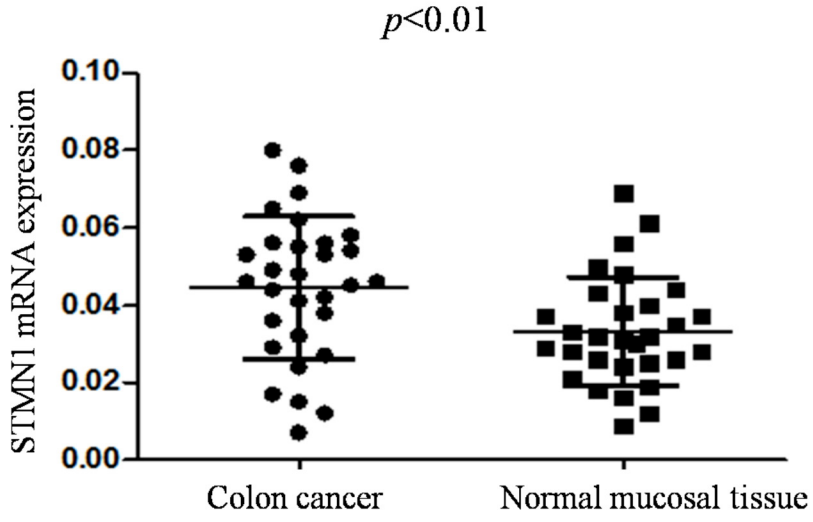

Figure 1. STMN1 mRNA expression in colon cancer and normal muscosal tissue.

Table I. STMN1 expression in colon cancer and normal colonic mucosa tissue

	N	STMN1		χ^2	*p*-value
		Positive	Negative		
Mucosal tissue	47	12	35	6.370	$p<0.05$
Colon cancer	105	66	39		

STMN1 protein expression in cancer tissue was significantly higher than tumor-adjacent tissue (Figure 2A). Positive staining of STMN1 was featured with diffuse yellow to brown staining in the cytoplasm. The positive rate of STMN1 in cancer tissue was 62.9% (66/105), significantly higher than normal colonic mucosa control (25.5%, 12/47), which only shows pale or no brownish staining (Figure 2B, $\chi^2 = 6.37$, $p<0.05$). Statistical analysis of STMN1 expression in colon cancer and normal colonic mucosa tissue is presented in Table I.

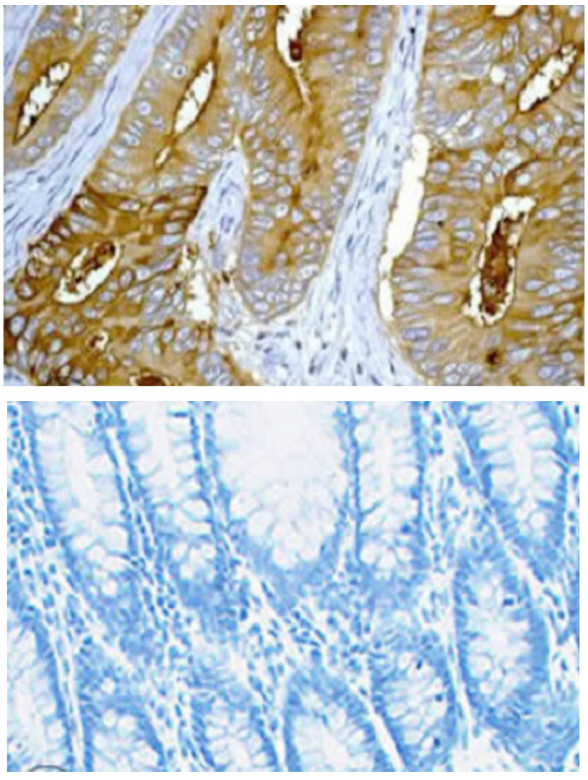

Figure 2. Immunohistochemical staining of stathmin1 in colorectal cancer sections. Anti-stathmin1 antibody was used for immunohistochemical staining in human colon cancer tissues as described in "Materials and Methods" section. (A) STMN1 protein expression in colon cancer. Five random fields were observed in each section at × 400 magnification. (B) Negative control of STMN1 in normal rectal mucosa. Five random fields were observed in each section at × 400 magnification.

STMN1 expression and clinical pathological parameters of 105 patients with colon cancer. STMN1 expression was independent of patients' age, gender, tumor differentiation level or location, but was associated with lymph node metastasis and TNM staging ($p<0.05$, Table II).

Kaplan-Meier analyses were performed to determine and to compare overall and STMN1-specific 5-year survivals. The five-year survival rate of all 105 cases of colon cancer was 48.5% (51/105), among which the survival rates for STMN1-positive and -negative patients were 39% (26/66) and 64% (25/39), respectively; and the medium survival period for STMN1-positive and -negative patients were 37.5 months and 57.1 months, respectively, indicating that the medium survival time for STMN1-positive patients was significantly shorter than STMN1-negative group, with statistical significance analyzed by log-rank test ($\chi^2=7.507$, $p<0.05$; Figure 3).

Analysis of prognostic factor in colon cancer patients. Multivariate Cox proportional hazard model by using variables including age, gender, differentiation, lymph node metastasis, TNM staging, tumor location, and STMN1 expression, which were all identified as prognostically significant by univariate analysis, demonstrated that differentiation, lymph node metastasis and STMN1 are independent predictor for overall survival ($p<0.05$; Table III).

Discussion

In this study, we have shown that the recruited Chinese colon cancer patients were featured with STMN1 overexpression, which was a new predictive indicator of poor prognosis and shorter survival rates in colon cancer.

The incidence of colorectal cancer ranks the fourth among malignant tumors, the first cause of death in China's urban residents. The five-year survival of colorectal cancer was over 60% according to Cancer Statistics in 2005[12]. STMN1 (stathmin1) is an unstable microtubule-regulating

Table II. STMN1 expression and clinical pathological parameters of 105 patients of colon cancer.

Clinical pathological parameters	N	STMN1 expression		χ^2	*p*-value
		Positive (%)	Negative (%)		
Age					
<60	67	42	25	0.039	0.578
≥60	38	25	13		
Gender					
Male	69	46	23	1.926	0.165
Female	36	20	16		
Differentiation					
High/medium	43	24	19	2.896	0.089
Low or mucinous adenocarcinoma	62	43	19		
Lymph node metastasis					
Negative	45	24	21	5.872	0.015
Positive	60	42	18		
TNM staging					
I-II	35	19	16	4.447	0.032
III-IV	70	48	22		
Tumor location					
Ascending colon	33	22	11	1.051	0.307
Transverse colon	15	10	5		
Descending colon	23	14	9		
Sigmoid colon	34	20	14		

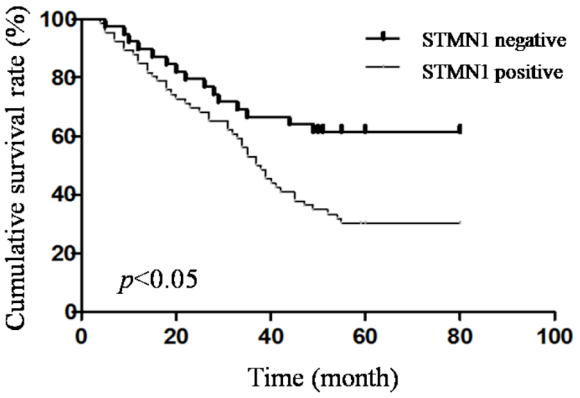

Figure 3. Kaplan-Meier4 curves for cumulative survival rates of patients with colon cancer categorized according to STMN1 states. Five-year survival of STMN1 negative-patients was significantly higher than STMN1-positive patients ($p<0.05$).

protein that was observed with overexpression in carcinogenesis of various cancers, including leukemia, breast cancer, lung cancer, skin squamous cell carcinoma, and ovarian cancer. Ke et al[13] studied the role of stathmin1 in gastric cancer carcinogenesis using immunohistochemistry and RT-PCR and found that stathmin1 mRNA and protein in gastric cancer tissues were both significantly higher than those in adjacent non-tumor tissues, but stathmin1 expression status is not an independent prognostic factor for patients with gastric cancer. Multivariate analysis results indicated that that only lymph node metastasis and TNM stage were the independent prognostic indicators for gastric cancer.

Tan et al[14] performed comparative proteome analysis and identified STMN1 to be highly up-regulated in primary CRC cells, and perturbations in STMN1 levels resulted in significant changes in cell migration, invasion, adhesion, and colony formation. Specifically, STMN1 was found to be highly expressed in primary colorectal tumors and metastatic tissues as compared to the adjacent normal colorectal tissues, which was confirmed in our study with patients' specimens. STMN1 was also implicated in molecular mechanisms regulating trophoblast migration and invasion at the maternal-fetal interface, as reported by Tian et al[15], that STMN1 may play a key role in regulating trophoblast invasion, which may lead to abnormal trophoblast invasion and result in recurrent miscarriage.

Critical role for stathmin1 as the potential therapeutic target has been recognized. Mechanisms for stathmin1 regulation of microtubules and proliferation have been suggested. Machado-Neto et

Table III. Univariate and multivariate analysis about survival rate of 105 patients of colon cancer.

Clinical pathological parameters	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p*-value
Age	1.225 (1.007-1.491)	0.043	1.518 (0.981-2.349)	0.075
Gender	0.862 (0.497-1.495)	0.597		
Differentiation	1.305 (1.100-1.549)	0.018	1.902 (1.103-3.279)	0.021
Lymph node metastasis	1.991 (1.153-3.437)	0.013	1.979 (0.993-3.230)	0.046
TNM Staging	1.342 (1.058-1.702)	0.015	1.991 (1.011-3.872)	0.044
Tumor location	1.826 (0.947-3.521)	0.072		
STMN1 expression	2.421 (1.302-4.501)	0.005	2.394 (1.156-4.955)	0.019

al[16] found that the JAK/STAT pathway involved in myeloproliferative neoplasms and can be inhibited by ruxolitinib, while stathmin1 silencing induced by ruxolitinib prevented ruxolitinib-induced microtubule instability and increased apoptosis. Transfection with the bi-shSTMN1-encoding expression plasmid (pbi-shSTMN1) markedly reduced CCL-247 human colorectal cancer and SK-Mel-28 melanoma cell growth *in vitro*. Phadke et al[17] generated a novel bifunctional small hairpin RNAs (bi-shRNAs) using the miR30 scaffold that is highly effective for knockdown of human stathmin1 (STMN1) mRNA and reported that treatments with pbi-shSTMN1 inhibited the growth of tumor grafts derived from low-passage primary melanoma and abrogated osteosarcoma tumor graft growth. STMN1 overexpression in human solid cancers was considered to be correlated with their poor prognosis. Akhtar et al[18] also reported that stathmin1 overexpression was common in gastric cancer, and lentivirus mediated RNAi effectively reduced stathmin1 expression in gastric cells, indicating that STMN1 may be a potential therapeutic strategy for gastric cancer. The regulation of STMN1 itself has also been studied, with STAT3[19], p53, TNF-α and heat shock proteins being suggested involved in the regulation of STMN1 transcription and expression[20].

In this study, we studied the STMN1 protein expression in colon cancer tissue with qRT-PCR and immunohistochemistry. Results showed that the positive rate of expression of STMN1 in colon cancer tissue (positive rate of STMN1 mRNA: 63.3%; immunohistochemistry positive rate: 62.9%) was significantly higher than tumor-adjacent tissue, indicating that the STMN1 may be related to poor outcome of Chinese colon cancer patients. We, further, analyzed the relationship between STMN1 and other clinical pathological parameters and found that STMN1 was positively correlated with lymph node metastasis and TNM stage, and was independent of age, sex and degree of differentiation. Kaplan–Meier survival analysis indicated that the five-year survival of patients receiving radical resection of colon cancer but with higher STMN1 expression was significantly higher than STMN1 negative patients (39% vs. 64%), and the medium survival time of STMN1-positive patients was also remarkably shorter than STMN1-negative ones (37.5 months vs. 57.1 months). Our results indicated that STMN1 was predictive of poor prognosis, which was consistent with studies on lung cancer and gastric cancer. Target-specific anti-stathmin effectors, such as ribozymes[21] have been used to silence stathmin *in vitro* and in combination with chemotherapeutic agents where additive synergistic interactions have been demonstrated (i.e., taxanes)[22]. Clinically, the predictive significance of STMN1 suggested that STMN1-positive patients who are more prone to development may receive adjuvant therapy, such as microtubule inhibitor (for example, paclitaxel)[23].

The results of multivariable Cox analysis suggested that among the clinical pathological characteristics, the degree of differentiation, lymph node metastasis and STMN1 expression are indicators affecting prognosis, which was evidenced by following previous studies with CRC patients[14] and gastric cancer patients[13].

Conclusions

STMN1 is extensively involved in occurrence, development, invasion and metastasis of colon cancer, which can be considered as a potential target for genetic therapy. It is likely that clinical opportunities with STMN1 specific drugs may become a future focus of study.

Conflicts of interest

The authors declare no conflicts of interest.

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