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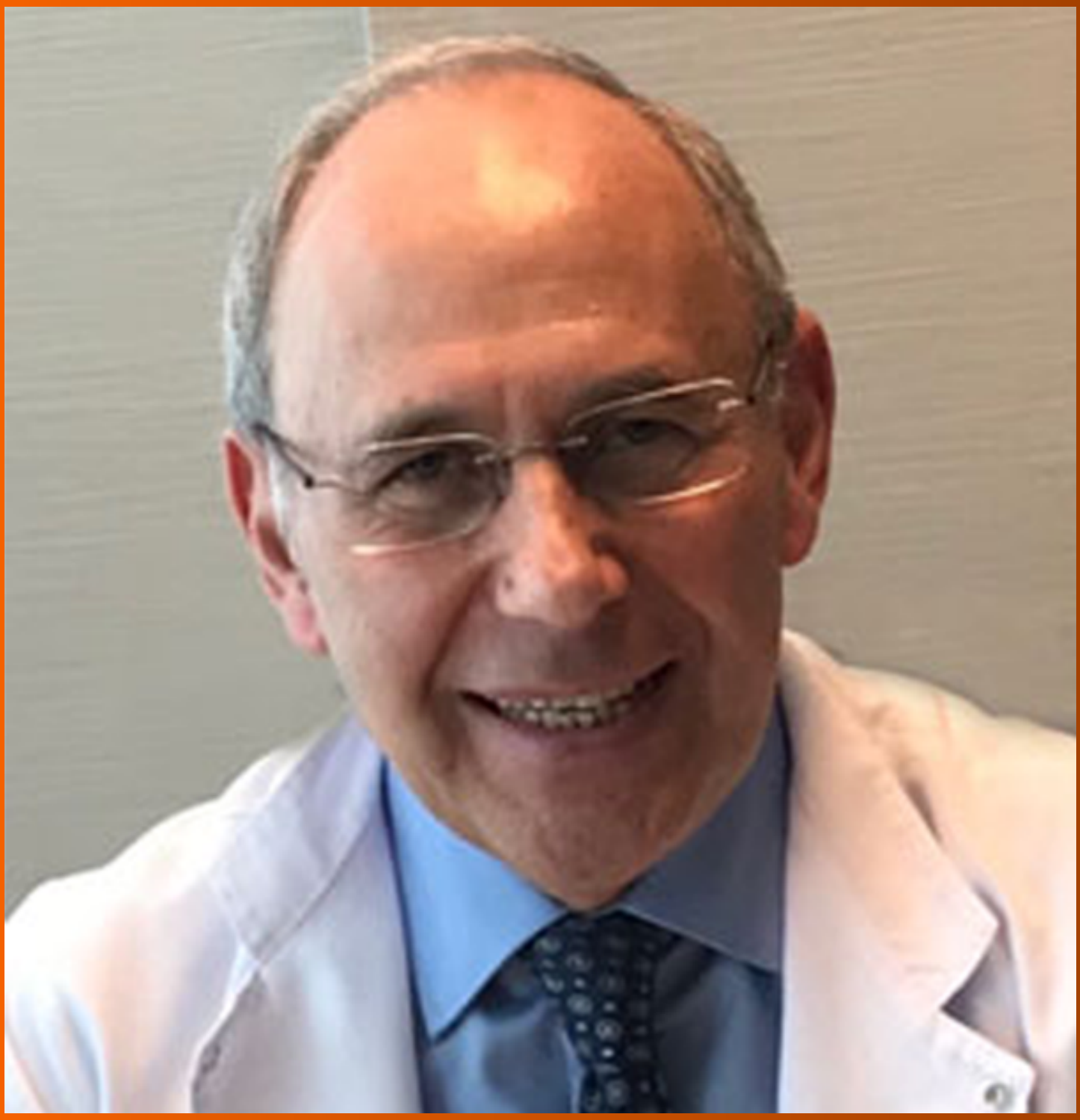

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WJGO

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CASE REPORT

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ABOUT COVER

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ORIGINAL ARTICLE

Observational Study

Clinical significance of expression of fibrous sheath interacting protein 1 in colon cancer

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Abstract

BACKGROUND

The occurrence and development of colon cancer are complex, involving a variety of genetic changes, such as mutation and activation of oncogenes, inactivation of tumour suppressor genes, and aberrant proliferation and apoptosis regulation mechanisms. Fibrous sheath interacting protein 1 (*FSIP1*) is a newly discovered oncogene that is frequently activated in a variety of tumours such as breast cancer and bladder cancer. However, the clinical significance of FSIP1 in colon cancer is unclear. In this study, we analysed the clinical significance of expression of FSIP1 in human colon cancer, aimed to clarify the biological role of FSIP1 in the development and progression of colon cancer.

AIM

To investigate the clinical significance of expression of FSIP1 in colon cancer.

METHODS

From March 2011 to March 2014, 302 specimens of tumour tissues and paracancerous tissues were obtained from patients pathologically diagnosed with colon cancer at Shengjing Hospital of China Medical University. Immunohistochemistry was used to detect FSIP1 expression in colon cancer tissues and adjacent normal tissues. Spearman correlation coefficient and Cox regression analyses were used to determine the relationship between FSIP1 expression and clinicopathological factors and prognosis, as well as the impact on survival.

RESULTS

Compared with its expression in adjacent normal tissues, FSIP1 was expressed at higher levels in colon cancer tissues. Spearman correlation analysis showed that high expression of FSIP1 was positively correlated with clinicopathological stage,

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lymph node metastasis, and poor prognosis in colon cancer; it was negatively correlated with the degree of tumour differentiation. Cox regression analysis showed that high FSIP1 expression was an independent risk factor for the prognosis of colon cancer patients.

CONCLUSION
High expression of FSIP1 may be one of the important factors affecting the clinical outcome of colon cancer patients and leading to poor prognosis.

Key words: Colon cancer; Fibrous sheath-interacting protein 1; Expression; Prognosis; Clinical significance; Survival

Core tip: This study examined the expression of fibrous sheath interacting protein 1 (FSIP1) in 302 patients with colon carcinoma and analysed the follow-up data. The results showed that FSIP1 expression was not correlated with sex, age, tumour size, or other factors but was positively correlated with tumour pathological T/N stages and negatively correlated with tumour differentiation. Univariate and multivariate Cox regression analyses and survival analysis showed that high expression of FSIP1 was an independent risk factor for poor prognosis, and overall survival was worse in the FSIP1-high expression group than in the FSIP1-low expression group. So we speculate that FSIP1 plays a role in the carcinogenesis of colon cancer.

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INTRODUCTION

Colon cancer is one of the most common malignant tumours of the digestive system. Approximately 1.2 million patients worldwide are diagnosed with colorectal cancer each year, and more than 600000 patients die directly or indirectly from colorectal cancer. In China, colon cancer accounts for approximately 12%-15% of malignant tumours. At present, approximately 130000 people are newly diagnosed with colon cancer every year in China, and the proportion of patients that are younger than 30 years old can reach 15%[1-6], which is a serious threat to the lives and health of Chinese people.

The main treatment for colon cancer is surgical resection supplemented with postoperative chemotherapy and radiotherapy. However, the early detection rate of colon cancer in China is low, and the treatment effect on invasive or metastatic colon cancer is poor. Therefore, the biological characteristics of invasion and metastasis of malignant tumours are important factors affecting prognosis and are also key to tumour treatment. The occurrence and development of colon cancer are complex, involving a variety of genetic changes, such as mutation and activation of oncogenes, inactivation of tumour suppressor genes, and aberrant proliferation and apoptosis regulation mechanisms.

Fibrous sheath-interacting protein 1 (FSIP1), also known as 17-β-hydroxysteroid dehydrogenase X (HSD10), is encoded by the *HSD17B10* gene located at the human 15q14 locus (GenBank ID: 161835). The FSIP1-encoding gene is highly conserved, and its protein product is a mitochondrial enzyme that catalyses the oxidation of various fatty acids, alcohols, and steroids, precisely regulates chromosome segregation, and maintains microtubule system stability. Missense or silent mutations in the FSIP1-encoding gene may be associated with degenerative diseases such as Alzheimer's disease and aspirin-intolerant asthma[8,9]. FSIP1 is also involved in the early development of spermatogonia, and the transcription of its family member FISP2 begins in the late development of spermatogonia and is related to the assembly of skeletal proteins in sperm flagellar cells[10,11]. In the field of oncology, single nucleotide polymorphisms in *FSIP1*, including GG homozygous and AG heterozygous variants, are associated with a risk of arsenic exposure-related bladder cancer compared with

the AA homozygous wild type[12]. High expression of FSIP1 is also associated with malignant biological behaviour and poor prognosis in bladder cancer, and this process may be related to the PI3K/Akt pathway[13,14]. FSIP1 may also be involved in the synthetic lethality of paclitaxel drugs in non-small-cell lung cancer; FSIP1 knockdown promotes the formation of multipolar spindles, prolongs the mitotic cycle, and sensitizes cells to the micronucleation effect of paclitaxel[15]. Liu *et al*[16] found that FSIP1 expression was related to the biological behaviour of breast cancer cells and the prognosis of breast cancer. In normal tissues, FSIP1 is minimally expressed except for in the testes. By investigating the relationship between FSIP1 and the development, progression, and clinicopathological factors of colon cancer using immunohistochemistry, we verified the abnormal expression of FSIP1 in colon cancer with a large sample of tissues and analysed the correlation between FSIP1 expression and pathological factors and prognosis in colon cancer patients. This study aimed to clarify the biological role of FSIP1 in the development and progression of colon cancer and open a new path for its clinical diagnosis, treatment, and prognosis evaluation.

MATERIALS AND METHODS

General information

Pathological histological sections of tumour tissues and paracancerous tissues were obtained from 302 patients who were diagnosed by pathology and underwent radical resection of colon cancer from March 2011 to March 2014 at the General Hospital of Shengjing Hospital of China Medical University. The relevant clinical information of the patients was collected, including sex, age, tumour size, T stage, N stage, and degree of differentiation. The inclusion criteria were as follows: (1) All patient tumour tissue specimens were identified as primary colon cancer by pathological examination; (2) All patients did not receive anti-tumour treatment before surgery, such as radiotherapy, chemotherapy, and targeted therapy; (3) Patients had no distant metastasis (M0), and the surgical margin was negative (R0); and (4) Patients were healthy in the past and did not have other tumours, severe chronic diseases, or immune system diseases. Patients were followed for at least 5 years to record recurrence and survival.

Immunohistochemistry detection and scoring

Tissue specimens were fixed with 4% paraformaldehyde, embedded in paraffin, and sectioned. Conventional dewaxing and hydration were carried out. The sections were immersed in sodium citrate antigen repair solution and heated at high pressure for 15 min; then 3% hydrogen peroxide solution was added and incubated at room temperature for 10 min. After that, 5% bovine serum albumin solution was added and incubated at room temperature for 1 h. Rabbit polyclonal FSIP1 antibody (1:500 dilution, Santa Cruz Biotechnology, Santa Cruz, CA, United States) was added and incubated overnight at 4 °C. The sections were washed three times with phosphate buffer saline (PBS), and horseradish peroxidase-labelled goat anti-rabbit secondary antibody (1:5000 dilution, Biyuntian Biotechnology Co., Ltd., China) was added and incubated for 1 h at room temperature. Horseradish peroxidase-conjugated goat anti-rabbit secondary antibody was added (1:5000 dilution, Beyotime Biotechnology Co., Ltd., China) and incubated for 1 h at room temperature. The sections were washed three times with PBS, and the DAB staining solution was used to develop colour (Fuzhou Maixin Biotech. Co., Ltd., China). Haematoxylin staining solution was used for counterstaining. Then, the sections were dehydrated, cleared, and sealed with a neutral gum. The staining solution with the primary antibody was replaced with PBS in the negative control. Samples were observed under a microscope. All slides were independently examined blindly by two pathologists. Each slide was scored for FSIP1 staining in five randomly selected views. Cytoplasmic or membrane staining was considered positive for FSIP1 expression. The proportion of positive cells and the intensity of staining were determined using a semi-quantitative scale. The proportion of positive cells was graded as follows: < 25%, 1 point; 25%-50%, 2 points; 51%-75%, 3 points; and > 75%, 4 points. The staining intensity was graded as follows: No colouring, 0 points; light yellow, 1 point; and brown yellow, 2 points. The staining intensity score was multiplied by the score of the positive cell proportion to determine whether FSIP1 expression was negative (total score < 4) or positive (total score ≥ 4).

Statistical analysis

Data processing and statistical analyses were performed using SPSS 24.0 software (SPSS Inc., Chicago, IL, United States). The count data are expressed as the mean ± SD, and an independent or paired Student's *t* test was used; the measurement data were

expressed as a rate, and the χ^2 test was used. Survival analysis was performed using the Kaplan-Meier method. Correlations between FSIP1 expression and various clinicopathological factors were identified using Spearman correlation analysis. Univariate and multivariate Cox regression analyses were used to determine the risk factors that influenced patient outcomes. $P < 0.05$ was considered statistically significant.

RESULTS

Differential expression of FSIP1 in colon cancer tissues and adjacent tissues

FSIP1 expression in tissues sections and the clinicopathological data of 302 patients with colon cancer were statistically analysed. It was found that FSIP1 was mainly localized in the cytoplasm, and the expression in colon cancer tissues was significantly higher than that in adjacent tissues, and it was related to the degree of tumour differentiation. (Figure 1).

High expression of FSIP1 is associated with clinicopathological factors in patients with colon cancer

Of all the 302 patients in this group, 203 were negative for FSIP1 expression and 99 had positive FSIP1 expression. FSIP1 expression was not associated with age, sex, or tumour size, whereas positive FSIP1 expression was closely associated with tumour T stage, N stage, and degree of differentiation. That is, patients with positive expression of FSIP1 had worse tumour T and N stages and a lower degree of tumour differentiation than patient with negative FSIP1 expression (Table 1).

Correlation between FSIP1 expression and various clinicopathological parameters

The Spearman correlation coefficient was used to analyse the correlation between FSIP1 expression and various clinicopathological parameters. The results showed that there was no significant correlation between FSIP1 expression and patient sex, age, or tumour size. FSIP1 expression was significantly positively correlated with tumour pathological stage (T stage) and lymph node metastasis (N stage) (Table 2, Spearman correlation coefficient greater than 0, $P < 0.05$). FSIP1 expression was negatively correlated with tumour differentiation (Table 2, Spearman correlation coefficient less than 0, $P < 0.05$).

Relative mortality risk (n = 302) based on univariate and multivariate analyses

The risk factors for death in this group were evaluated by univariate and multivariate Cox regression analyses (Table 3). A total of 92 patients died during the follow-up period. The hazard ratio (HR) of death for FSIP1 expression was 2.933 [95% confidence interval (CI): 2.067-4.559, $P = 0.000$]; after adjusting for the other six baseline factors (age, sex, tumour size, pathological tumour stage, pathological nodal stage, and tumour differentiation), the HR of death for positive expression of FSIP1 was 2.661 (95%CI: 1.979-5.635, $P = 0.001$) according to multivariate regression analysis. There was a significant difference, so positive expression of FSIP1 was an independent risk factor for death in this group of patients.

Kaplan-Meier survival analysis

Patients were grouped according to FSIP1 expression (FSIP1-negative group, $n = 203$; FSIP1-positive group, $n = 99$), and survival analysis was performed according to the follow-up results using the Kaplan-Meier method. The results showed that the overall prognosis of patients in the FSIP1-positive group was significantly worse than that of patients in the FSIP1-negative group (Figure 2, $P = 0.0014$).

DISCUSSION

The occurrence and development of colon cancer involve in a variety of genetic changes. The prognosis of colon cancer also varies widely, depending on factors such as tumour TNM stage, pathological type, and degree of differentiation, in addition to whether an oncogene mutation is involved. Over the years, many scholars have been constantly looking for markers related to the diagnosis and prognosis of colon cancer. Currently, only EGFR/K-ras/BRAF[17-19] and related targeted therapies are commonly accepted for they have some significance in determining treatments and prognosis. Targeted immunotherapy based on immunological checkpoints, such as PD1/PDL1 inhibitors, has also gradually been included in clinical applications in recent years[20,21]. However, the long-term effects lack the support of large-sample multicentre clinical

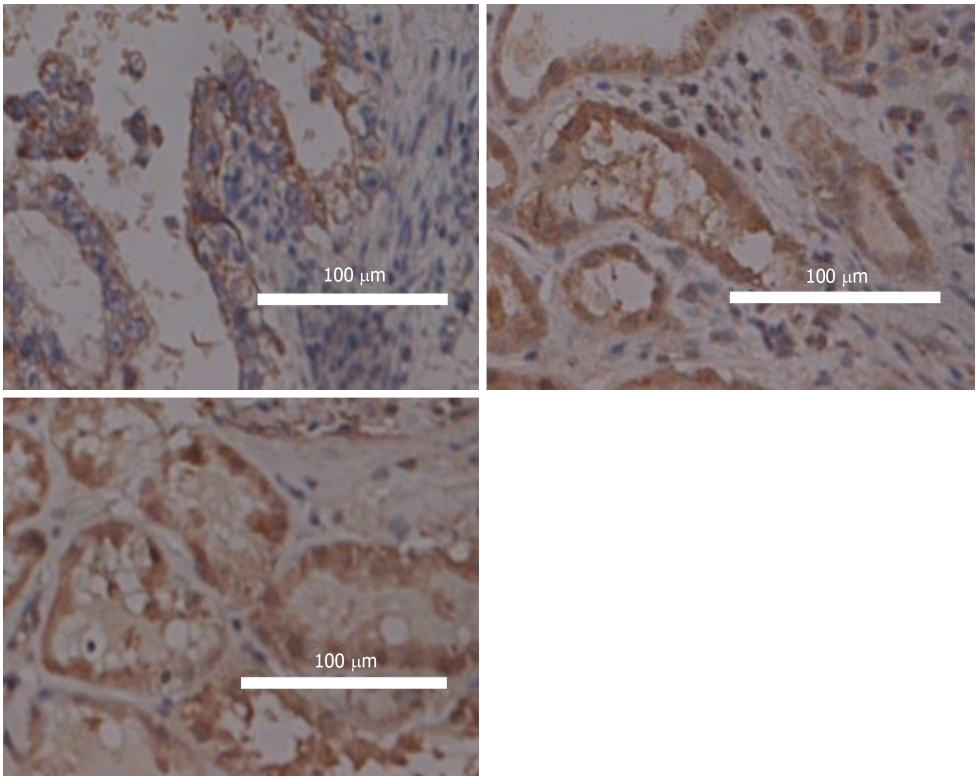

Figure 1 Immunohistochemistry analysis of the expression of fibrous sheath interacting protein 1 in colon cancer specimens. A: Paracancerous tissue; B: Colon cancer (highly differentiated); C: Colon cancer (poorly differentiated).

data. Therefore, markers of broad significance to guide clinical diagnosis and treatment are urgent needed. In the field of tumour biology, FSIP1 is currently considered a cancer antigen that is highly expressed in various tumours, such as breast cancer, lung cancer, and bladder cancer, and is associated with a poor prognosis[9,22,23]. Research on FSIP1 is relatively scarce worldwide. It is currently recognized that FSIP1 is a protein involved in sperm flagella assembly and the assembly of A-kinase anchoring protein 4 (AKAP4). AKAP4 can target cAMP-dependent binding protein kinase A (PKA), forming a complex with it, and anchoring PKA to the fibre sheath; studies have reported that AKAP4 is a substrate for ERK1/2 and a protein that catalyses the switch between cAMP/PKA and PKC/ERK1/2 in human sperm[24,25]. It is well known that PKA and PKC play important roles in tumour proliferation, angiogenesis, drug resistance, biological behaviour, and prognosis in colorectal cancer[24,26-28]. Therefore, FSIP1 is likely to participate in the biological activities of tumour cells, such as proliferation and invasion, through the abovementioned pathways and may also promote tumour angiogenesis and affect prognosis. It has been confirmed that FSIP1 is overexpressed in various breast cancers and is associated with prognosis. High expression of FSIP1 can promote the biological activity of breast cancer cells and reduce the sensitivity of tumours to chemotherapeutic drugs such as paclitaxel, which may be related to FSIP1 binding multidrug resistance protein 1 and making it stable. FSIP1 also regulates the proliferation and invasion of ER+ or HER2+ breast cancer cells by interacting with HER2[22]. It has also been reported that FSIP1 binds to PKA and SRC-3[31] and participates in chromosome segregation[16]. In addition, knockdown of FSIP1 in triple-negative breast cancer promotes autophagy, enhances AMP-activated protein kinase signalling, and reduces mTOR and Wnt/β-catenin pathway effects, thus reducing the sensitivity of tumour cells to chemotherapy drugs[32]. There are also a few reports in other tumours. For example, Sun *et al*[13,14] found that high expression of FSIP1 was positively correlated with a poor prognosis in bladder cancer, and *in vitro* cytological experiments confirmed that knockdown of FSIP1 expression inhibited PI3K/AKT pathway activity and phosphorylation levels in T24 cells, thereby inducing tumour cell apoptosis. However, there is few report on the expression of FSIP1 in colorectal cancer and its relationship with clinicopathological factors and prognosis, as well as its effects on related biological behaviour.

In this study, we examined the expression of FSIP1 in the pathological tissues of 302 patients with colon adenocarcinoma and statistically analysed at least 5 years of

Table 1 Correlation between fibrous sheath interacting protein 1 expression and clinicopathological features (*n* = 302), *n* (%)

Characteristic (%)	FSIP1 negative (*n* = 203)	FSIP1 positive (*n* = 99)	*P* value
Median age	63 ± 17.6	59 ± 20.8	0.521
Sex			
Male	121 (60)	54 (55)	0.438
Female	82 (40)	45 (45)	
Tumor size			0.313
< 5	85 (41)	39 (39)	
5-10	97 (48)	49 (49)	
> 10	21 (5)	11 (12)	
Pathological tumor stage			0.001[1]
T1	89 (44)	30 (30)	
T2	46 (23)	17 (17)	
T3	44 (22)	25 (25)	
T4	24 (11)	27 (28)	
Pathological nodal stage			0.000[1]
N0	65 (32)	20 (20)	
N1	78 (38)	33 (33)	
N2	39 (19)	28 (28)	
N3	21 (11)	18 (19)	
Tumor differentiation			0.000[1]
Well	71 (35)	45 (46)	
Moderate	85 (42)	31 (31)	
Poor	47 (23)	23 (23)	

[1]The results were statistically significant ($P < 0.01$). The results showed that high expression of fibrous sheath interacting protein 1 was positively correlated with colon cancer stage and lymph node metastasis and negatively correlated with tumour differentiation. FSIP1: Fibrous sheath interacting protein 1.

follow-up data. The results showed that compared with the expression in tumour adjacent tissues, the expression of FSIP1 was significantly increased in colon cancer tissues, and the high expression of FSIP1 was positively correlated with colon cancer stage and lymph node metastasis and negatively correlated with tumour differentiation. Spearman correlation analysis was used to determine the correlation between the expression of FSIP1 and various clinicopathological factors. The results showed that FSIP1 expression was not correlated with sex, age, tumour size, or other factors but was positively correlated with tumour pathological T stage and lymph node metastasis (N stage) and negatively correlated with tumour differentiation. Univariate and multivariate Cox regression analyses and survival analysis showed that high expression of FSIP1 was an independent risk factor for poor prognosis, and overall survival was worse in the FSIP1-high expression group than in the FSIP1-low expression group. The above results indicate that the FSIP1-encoding gene plays a role in promoting the carcinogenesis and progression of human colon cancer and is closely related to the occurrence and development of colon cancer. High FSIP1 expression often indicates more active biological behaviour in tumour cells and poor prognosis. Therefore, we speculate that FSIP1 may become an important molecular marker for the diagnosis, prognosis, and treatment of colon cancer.

However, this study only performed preliminary histological validation in human samples. We look forward to further *in vitro* cell experiments exploring the effects of FSIP1 on many factors of colon cancer cells, such as biological behaviour, epithelial to mesenchymal transition, drug sensitivity, immune tolerance, and the tumour microenvironment, as well as the specific signalling pathways and related interacting proteins. These studies will fully reveal the role of FSIP1 in the development of colon cancer, further enrich the understanding of the molecular mechanism of colon cancer pathogenesis, and provide a theoretical basis and new ideas for future methods for gene detection, diagnosis, prognosis determination, and drug treatment in colon cancer.

Table 2 Correlation between fibrous sheath interacting protein 1 expression and various clinicopathological factors

Clinicopathological parameter	*P* value (Spearman correlation)
Age	0.689 (0.055)
Sex	0.762 (0.047)
Tumour size	0.564 (0.061)
Pathological tumour stage	0.003 (0.476)[1]
Pathological nodal stage	0.001 (0.564)[1]
Tumour differentiation	0.001 (-0.595)[2]

[1]Spearman correlation coefficient greater than 0, $P < 0.05$.
[2]Spearman correlation coefficient less than 0, $P < 0.05$. FSIP1: Fibrous sheath interacting protein 1.

Table 3 Relative mortality risk ($n = 302$) based on univariate and multivariate Cox regression analyses of clinical pathological parameters and high fibrous sheath interacting protein 1 expression

Characteristic	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age		0.899		0.675
≤ 60	1 (Ref)		1 (Ref)	
> 60	0.972 (0.721-1.322)	0.899	1.019 (0.732–1.418)	0.675
Sex		0.674		0.739
Male	1 (Ref)		1 (Ref)	
Female	1.558 (0.731-2.235)	0.674	2.339 (0.610-3.886)	0.739
Tumor size		0.003		0.219
< 5	1 (Ref)		1 (Ref)	
5-10	1.427 (0.973-1.886)	0.043	1.339 (0.921-1.992)	0.198
> 10	1.661 (1.095-2.291)	0.005	1.431 (0.695-1.832)	0.399
Pathological tumor stage		0.000		
T1	1 (Ref)		1 (Ref)	0.000
T2	2.521 (1.567-4.631)	0.001	1.330 (1.009-2.461)	0.002
T3	3.213 (2.288–9.198)	0.000	3.445 (1.925-4.901)	0.000
T4	4.883 (1.528–5.438)	0.000	4.870 (2.062-9.126)	0.000
Pathological nodal stage		0.000		0.000
N0	1 (Ref)		1 (Ref)	
N1	1.916 (1.379-3.221)	0.003	1.687 (1.563-6.019)	0.002
N2	4.422 (1.837-7.622)	0.000	6.819 (3.421-12.567)	0.000
N3	9.230 (4.399-12.257)	0.000	7.909 (3.963-16.878)	0.000
Tumor differentiation		0.000		0.000
Well	1 (Ref)		1 (Ref)	
Mediate	4.696 (1.565-8.912)	0.000	5.229 (4.442-9.887)	0.000
Poor	7.129 (3.126-11.703)	0.000	6.443 (2.126-12.556)	0.000
FSIP1 expression				
Negative	1 (Ref)		1 (Ref)	
Positive	2.933 (2.067-4.559)	0.000	2.661 (1.979-5.635)	0.001

The results showed that the hazard ratio of fibrous sheath interacting protein 1 positivity in terms of risk of death was 2.933 (95%CI: 2.067-4.559; $P = 0.001$). After adjusting for other baseline parameters (including age, sex, tumour size, pathological T stage, lymph node metastasis N stage, and tumour differentiation), the hazard ratio of fibrous sheath interacting protein 1 positivity in terms of risk of death changed minimally (hazard ratio = 2.661, 95%CI: 1.979-5.635; $P = 0.001$). CI: Confidence interval; HR: Hazard ratio; Ref: Reference category.

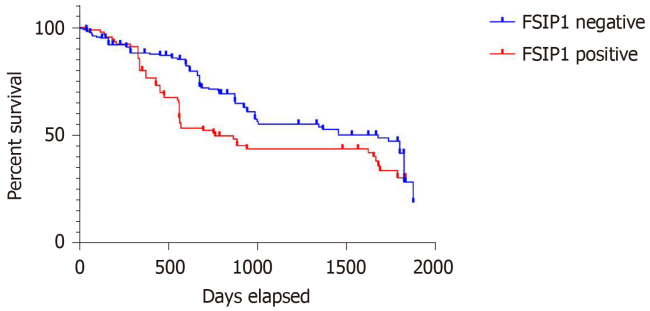

Figure 2 Overall survival curves according to fibrous sheath interacting protein 1 expression (*P* = 0.0014). FSIP1: Fibrous sheath interacting protein 1.

ARTICLE HIGHLIGHTS

Research background

The occurrence and development of colon cancer are complex, involving a variety of genetic changes. Fibrous sheath interacting protein 1 (FSIP1) is a newly discovered oncogene that is frequently activated in a variety of tumours. However, the clinical significance of FSIP1 in colon cancer is unclear. In this study, the authors analysed the clinical significance of expression FSIP1 in human colon cancer, with an aim to clarify the biological role of FSIP1 in the development and progression of colon cancer.

Research motivation

Over the years, many scholars have been constantly looking for markers related to the diagnosis and prognosis of colon cancer. However, only EGFR/K-ras/BRAF and related targeted therapies are commonly accepted. Therefore, markers of broad significance to guide clinical diagnosis and treatment are still urgent needed.

Research objectives

In the study, the authors aimed to clarify the biological function of FSIP1 in the development and progression of colon cancer and its relationship with the clinical parameters.

Research methods

A total of 302 specimens of tumour tissues and paracancerous tissues from patients with a pathological diagnosis of colon cancer were analyzed. FSIP1 expression in colon cancer tissues and adjacent normal tissues was detected by immunohistochemistry. Spearman correlation coefficient and Cox regression analyses were used to determine the relationship between FSIP1 expression and clinicopathological factors and prognosis, as well as the impact on survival.

Research results

Compared with the expression in benign adjacent tissues, the expression of FSIP1 was significantly increased in colon cancer tissues, and the high expression of FSIP1 was positively correlated with colon cancer stage and lymph node metastasis and negatively correlated with tumour differentiation. Spearman correlation analysis was used to determine the correlation between the expression of FSIP1 and various clinicopathological factors. The FSIP1 expression was not correlated with sex, age, tumour size, or other factors but was positively correlated with tumour pathological T stage and lymph node metastasis (N stage) and negatively correlated with tumour differentiation.

Research conclusions

High expression of FSIP1 may be one of the important factors affecting the clinical outcome of colon cancer patients and leading to poor prognosis.

Research perspectives

From the results, the authors speculate that FSIP1 may become an important molecular marker for the diagnosis, prognosis, and treatment of colon cancer. Although this study only performed preliminary histological validation in human samples, we look forward to further *in vitro* cell experiments exploring the effects of FSIP1 on many factors of colon cancer cells.

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