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ABOUT COVER

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World Journal of Gastrointestinal Oncology (*World J Gastrointest Oncol*, *WJGO*, online ISSN 1948-5204, DOI: 10.4251) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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ORIGINAL ARTICLE

Basic Study

Clinicopathological significance of human leukocyte antigen F-associated transcript 10 expression in colorectal cancer

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Abstract

BACKGROUND

Colorectal cancer (CRC) is a common malignancy of the gastrointestinal tract. The worldwide mortality rate of CRC is about one half of its morbidity. Ubiquitin is a key regulatory factor in the cell cycle and widely exists in eukaryotes. Human leukocyte antigen F-associated transcript 10 (FAT10), known as diubiquitin, is an 18 kDa protein with 29% and 36% homology with the N and C termini of ubiquitin. The function of FAT10 has not been fully elucidated, and some studies have shown that it plays an important role in various cell processes.

AIM

To examine FAT10 expression and to analyze the relationship between FAT10 expression and the clinicopathological parameters of CRC.

METHODS

FAT10 expression in 61 cases of CRC and para-cancer colorectal tissues was measured by immunohistochemistry and Western blotting. The relationship between FAT10 expression and clinicopathological parameters of CRC was statistically analyzed.

RESULTS

Immunohistochemical analysis showed that the positive rate of FAT10 expression in CRC (63.93%) was significantly higher than that in tumor-adjacent tissues (9.84%, $P < 0.05$) and normal colorectal mucosal tissue (1.64%, $P < 0.05$). Western blotting also indicated that FAT10 expression was significantly higher in CRC than in tumor-adjacent tissue ($P < 0.05$). FAT10 expression was closely associated

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with clinical stage and lymphatic spread of CRC. FAT10 expression also positively correlated with p53 expression.

CONCLUSION
FAT10 expression is highly upregulated in CRC. FAT10 expression is closely associated with clinical stage and lymphatic spread of CRC.

Key words: Colorectal cancer; Ubiquitin; Ubiquitin-like proteins; Human leukocyte antigen F-associated transcript 10; p53

Core tip: Colorectal cancer (CRC) is a common malignancy of the gastrointestinal tract. Genetic studies have demonstrated that the development of CRC is a complex process involving the activation of proto-oncogenes, inactivation of tumor suppressor genes, gene mutations, and dysregulation of apoptosis-related genes. Human leukocyte antigen F-associated transcript 10 (FAT10) is a regulatory protein of the ubiquitin-like modifier family that regulates various cell processes including mitosis, chromosome stability, apoptosis, immune control, and 26S-proteasome-mediated protein degradation. Our study investigated FAT10 expression in tumor and tumor-adjacent tissues of CRC patients and analyzed the relationship between FAT10 expression and the clinicopathological parameters of CRC.

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INTRODUCTION

Colorectal cancer (CRC) is a common malignancy of the gastrointestinal tract. In China, the incidence of CRC ranks fifth in men and fourth in women among all malignant tumors, and its mortality ranks fifth[1-9]. The worldwide mortality rate of CRC is about one half of its morbidity. Although the treatment of this malignancy has improved, its prognosis is still not satisfactory. The etiology and pathogenesis of CRC are related to environmental (mainly diet, such as fat and animal protein) and genetic factors. Genetic factors contribute to the development of CRC in many ways. It is well known that CRC is commonly seen in patients with familial adenomatous polyposis and Lynch syndrome, although the incidence in patients with other polyp types is low. Genetic studies have demonstrated that the development of CRC is a complex process involving the activation of proto-oncogenes, inactivation of tumor suppressor genes, gene mutations, and dysregulation of apoptosis-related genes.

Ubiquitin, a polypeptide containing 76 amino acid residues, is a key regulatory factor in the cell cycle and is widely expressed in eukaryotes[10-13]. In recent years, a growing number of ubiquitin-related low-molecular-weight proteins, known as ubiquitin-like proteins, have been identified and are associated with a variety of cell processes[14-16]. So far, two ubiquitin-like protein families, ubiquitin-like modifiers (UBLs) and ubiquitin-domain proteins, have been identified[17-19].

Human leukocyte antigen F-associated transcript 10 (FAT10), also known as diubiquitin, belongs to the UBL family. FAT10 is an 18-kDa protein with 29% and 36% homology with the N and C termini of ubiquitin, respectively. It is located on chromosome 6 and was originally thought to be a gene of the major histocompatibility complex. Although the function of FAT10 has not been fully elucidated, some studies have shown that it plays an important role in various cell processes[20].

This study investigated FAT10 expression in tumor and tumor-adjacent tissues of CRC patients by immunohistochemistry and Western blotting and analyzed the relationship between FAT10 expression and the clinicopathological parameters of CRC.

MATERIALS AND METHODS

Tissue sample collection

Sixty-one surgical samples were collected from patients who underwent surgery for CRC at our hospital between March 2010 and March 2011. None of the patients underwent preoperative radiotherapy or chemotherapy. There were 38 men and 23 women, with a median age of 67 years (range, 39–97 years). The median tumor size was 50 mm (range, 25–110 mm). Of all patients included, 46 had highly differentiated tumors, 15 had lowly differentiated tumors, 22 had stage I/II disease, 39 had stage III/IV disease, 38 had lymph node metastasis, and 23 had no lymph node metastasis. Tumor-adjacent samples were collected 2 cm away from the tumor, and normal colorectal mucosal samples were collected from surgical margins (> 5 cm away from the tumor). All samples were immediately preserved in liquid nitrogen for further use. Institutional review board approval of Central Hospital Affiliated to Shenyang Medical College was obtained for this study.

Immunohistochemical staining and evaluation

Tissue samples were fixed in neutral buffered formalin solution, embedded in paraffin, and cut into 4-μm sections. The sections were dewaxed in xylene, hydrated in a graded ethanol series, and subjected to immunohistochemical staining for FAT10 using the streptavidin–peroxidase method. Mouse anti-FAT10 monoclonal antibody (dilution, 1:200; Santa Cruz Biotechnology, Santa Cruz, CA, United States) was used as a primary antibody. Following diaminobenzidine staining, yellowish-brown granules present in the nucleus were regarded as positive signals. Five high-power (400×) fields with the most strongly positive signal were selected to count the number of positive cells among 200 tumor cells. The percentage of immunoreactive cells was scored as follows: no staining, 0; 1%-10% staining, 1; 11%-50%, 2; 51%-80%, 3; and 81%-100%, 4. Staining intensity was scored on the following 0-3 scale: negative, 0; light yellowish-brown, 1; yellowish-brown, 2; and brown, 3. Immunoreactive score (IS; 0-7) was calculated as the sum of the score of the percentage of immunoreactive cells and the score of staining intensity. Samples with IS < 4 were considered negative, while those with IS ≥ 4 were considered positive.

Western blotting

Tissue samples were washed in pre-cooled phosphate-buffered saline three times and lysed in a nondenaturing tissue lysis buffer containing protease inhibitors to extract total proteins. Cell lysate proteins were resolved by polyacrylamide gel electrophoresis and electrophoretically transferred to polyvinylidene difluoride membranes. The membranes were blocked with 5% normal fetal bovine serum at room temperature for 2 h, incubated with mouse anti-FAT10 monoclonal antibody (dilution, 1:400; Santa Cruz Biotechnology) or anti-β-actin antibody (dilution, 1:200; Zhongshan Golden Bridge, Beijing, China) at 4°C overnight, washed with Tween Tris Base Buffer Solution (commonly known as TTBS) three times, and then incubated with a horseradish-peroxidase-labeled secondary antibody (dilution, 1:400; Zhongshan Golden Bridge) at room temperature for 2 h. After the membranes were washed three times with TTBS, the proteins were detected by enhanced chemiluminescence. Images were obtained using the EC3 Imaging System, and the bands were semiquantitatively analyzed using ImageJ software to calculate the relative expression of FAT10 to β-actin. The experiment was repeated at least three times, with mean values calculated for further analysis.

Statistical analysis

Statistical analyses were performed using SPSS version 21.0. Data are presented as mean ± SD. The relationship between FAT10 expression and clinicopathological parameters of CRC was analyzed by χ^2 test. Comparisons between groups were evaluated by *t* test, and comparisons among three or more groups were analyzed by analysis of variance, followed by the least significant difference test or Tamhane's test. $P < 0.05$ was considered statistically significant.

RESULTS

High expression of FAT10 in CRC

Immunohistochemical staining showed that positive signals, most of which were weak, were present only in four (6.56%) normal colorectal mucosal tissues and in 11 (18.03%) tumor-adjacent tissues (Figure 1A). According to IS, only one (1.64%) normal colorectal mucosal tissue and six (9.84%) tumor-adjacent tissues were positive for

FAT10. In contrast, 46 (75.41%) CRC tissues were positive for FAT10, of which 39 showed moderately to strongly positive expression (Figure 1B). FAT10 expression was significantly higher in CRC than in normal colorectal mucosa and tumor-adjacent tissues ($P < 0.05$), although there was no significant difference between normal colorectal mucosa and tumor-adjacent tissues ($P > 0.05$; Table 1 and Figure 1C).

Western blotting showed that in 30 pairs of colorectal tissues, FAT10 expression was significantly higher in CRC than in tumor-adjacent tissues ($t = 6.558$, $P = 0.000$; Figure 2).

FAT10 expression positively correlates with clinical stage, lymph node metastasis, and p53 expression in CRC

We assessed the relationship between FAT10 expression and some clinicopathological parameters of CRC, including age, sex, tumor size, clinical stage, tumor differentiation, lymph node metastasis, and p53 expression. FAT10 expression was associated with clinical stage and lymph node metastasis (Table 2). In addition, there was a positive correlation between p53 and FAT10 expression in CRC (Table 3).

DISCUSSION

FAT10 is a regulatory protein of the UBL family that regulates various cell processes including mitosis, chromosome stability, apoptosis, immune control, and 26S-proteasome-mediated protein degradation[21-25]. FAT10 can bind with a mitotic spindle assembly checkpoint protein, mitotic arrest deficiency 2 (MAD2), in a noncovalent manner. MAD2 is responsible for maintaining the integrity of the spindle during mitosis, and dysfunction of MAD2 can lead to chromosome instability, which is an important characteristic of many tumors[22,26,27].

Overexpression of the FAT10 gene has been found in some malignant tumors, including gastrointestinal and gynecological malignancies[28-30]. It is reported that interferon-γ and tumor necrosis factor (TNF)-α can increase the expression of the *FAT10* gene[31-35], while FAT10 expression can be negatively regulated by p53, which plays an important role in regulating the cell cycle[36-38]. FAT10 is abnormally highly expressed in some malignant tumors and highly expressed in premetaphase of the cell cycle; MAD2 dysfunction causes abnormal mitotic division and chromosome instability; and expression of FAT10 is positively regulated by TNF-α (a putative tumor promoter)[32] and negatively regulated by p53 (a guardian of the genome)[37]. These results suggest that FAT10 plays an important role in cell cycle regulation and tumorigenesis.

Our results showed that the positive expression rate of FAT10 protein gradually increased from normal mucosal tissue to tumor-adjacent tissue and CRC. Consistent with this finding, Western blotting indicated that FAT10 protein expression was significantly higher in CRC tissue than in tumor-adjacent tissue. Collectively, these findings suggest that increased FAT10 expression plays an important role in colorectal carcinogenesis.

In addition, we analyzed the relationship between FAT10 expression and some clinicopathological parameters of CRC (including age, sex, tumor size, clinical stage, tumor differentiation, lymph node metastasis, and p53 expression). FAT10 expression was associated with clinical stage and lymph node metastasis. FAT10 expression was significantly higher in stage III/IV than in stage I/II CRC, and CRC with lymph node metastasis expressed more FAT10. Moreover, FAT10 expression was positively correlated with p53 expression. These results indicate that FAT10 expression is closely related to the degree of malignancy of CRC and the invasion and proliferation of cancer cells.

In summary, FAT10 is a UBL family member that is closely associated with the development of a wide variety of tumors. This study demonstrated that FAT10 is highly expressed in CRC, and FAT10 expression is closely related to clinical stage and lymph node metastasis. However, our current study is a proof-of-principle, and additional research needs to be performed to confirm our results. Therefore, further exploration of the role of FAT10 in the development of CRC and the underlying mechanisms, especially its relationship with the cell cycle, will be important for understanding the value of FAT10 in CRC diagnosis, prognosis and therapy.

Table 1 Expression of human leukocyte antigen F-associated transcript 10 in colorectal cancer, *n* (%)

Group	Staining score	*P* value	FAT10		*P* value
			Negative (IS < 4)	Positive (IS ≥ 4)	
Normal	0.18 ± 0.72	0.000	60/61 (98.36)	1/61 (1.64)	0.000
Para-cancer	0.64 ± 1.46		55/61 (90.16)	6/61 (9.84)	
Cancer	4.46 ± 2.97		22/61 (36.07)	39/61 (63.93)	

IS: Immunoreactive score; FAT10: Human leukocyte antigen F-associated transcript 10.

Table 2 Relationship between human leukocyte antigen F-associated transcript 10 expression and clinicopathologic parameters of colorectal cancer

Clinicopathologic parameter	*n*	+	-	*P* value
Age, yr				0.095
< 50	8	3	5	
≥ 50	53	36	17	
Gender				0.476
Male	38	23	15	
Female	23	16	7	
Tumor size, mm				0.231
< 50	41	28	13	
≥ 50	20	11	9	
Tumor differentiation				0.325
High	46	31	15	
Low	15	8	7	
Clinical stage				0.000
I/II	22	7	15	
III/IV	39	32	7	
Lymph node metastasis				0.000
No	23	8	15	
Yes	38	31	7	

Table 3 Correlation between human leukocyte antigen F-associated transcript 10 and p53 expression in colorectal cancer

	FAT10 positive	FAT10 negative
p53 positive	30	4
p53 negative	9	18

r = 0.568, P = 0.000. FAT10: Human leukocyte antigen F-associated transcript 10.

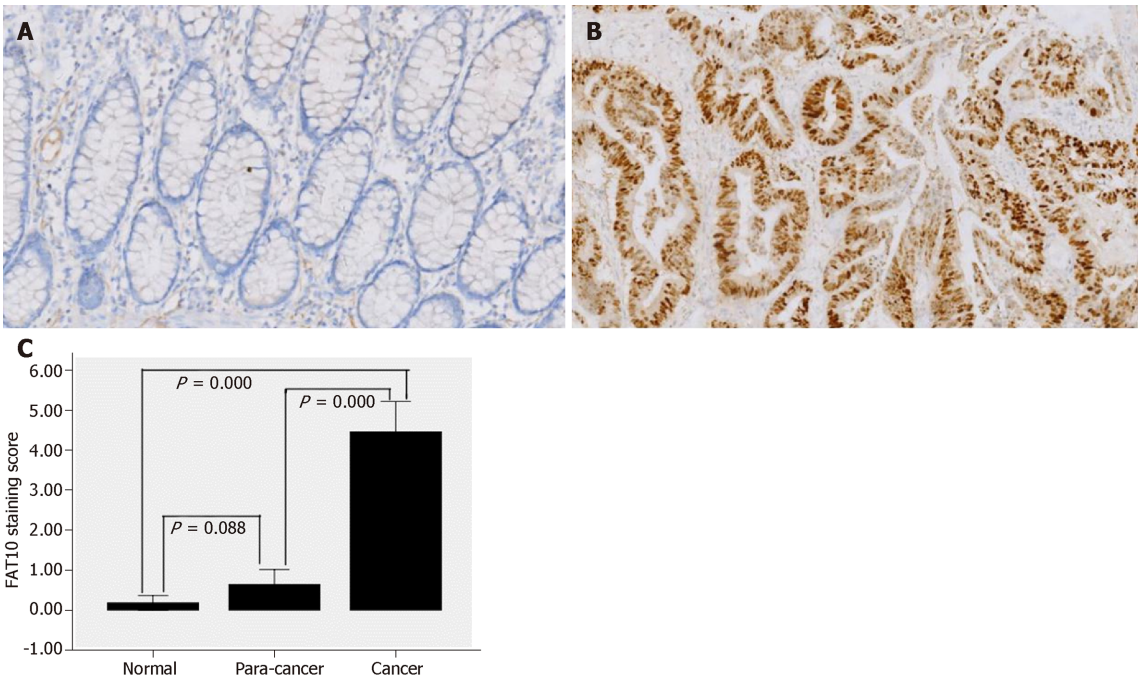

Figure 1 Immunohistochemical staining for human leukocyte antigen F-associated transcript 10 in colorectal tissues (original magnification, 100×). A: Human leukocyte antigen F-associated transcript 10 (FAT10) expression is negative in para-cancer tissue; B: FAT10 expression is strongly positive in moderately differentiated colorectal adenocarcinoma; C: Semi-quantitative analysis of FAT10 expression in normal colorectal mucosal tissue, para-cancer tissue, and colorectal cancer tissue.

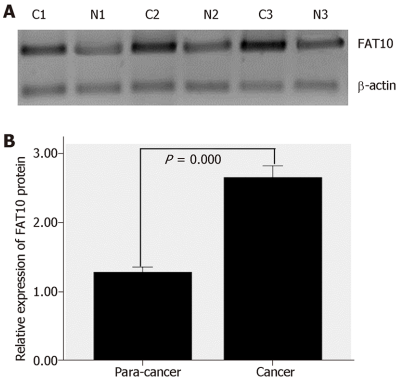

Figure 2 Western blot analysis of human leukocyte antigen F-associated transcript 10 expression in colorectal cancer and para-cancer tissues. A: Western blot analysis; B: Relative expression. FAT10: Human leukocyte antigen F-associated transcript 10.

ARTICLE HIGHLIGHTS

Research background

The worldwide mortality rate of colorectal cancer (CRC) is about one half of its morbidity. Ubiquitin is a key regulatory factor in the cell cycle and widely exists in eukaryotes. Human leukocyte antigen F-associated transcript 10 (FAT10), also known as diubiquitin, is an 18-kDa protein with 29% and 36% homology with the N and C termini of ubiquitin, respectively.

Research motivation

The function of FAT10 has not been fully elucidated, and some studies have shown that it plays an important role in various cell processes.

Research objectives

The objective of this study is to examine FAT10 expression and to analyze the relationship between FAT10 expression and the clinicopathological parameters of CRC.

Research methods

Immunohistochemistry and Western blotting were used to measure FAT10 expression in 61

cases of CRC and para-cancer colorectal tissues. In addition, the relationship between FAT10 expression and the clinicopathological parameters of CRC was statistically analyzed.

Research results

Immunohistochemical analysis showed that the positive rate of FAT10 expression in CRC was significantly higher than in tumor-adjacent tissue and normal colorectal mucosal tissue. Western blotting indicated that FAT10 expression was significantly higher in CRC than in tumor-adjacent tissue. FAT10 expression was closely associated with clinical stage and lymphatic spread of CRC.

Research conclusions

FAT10 expression is highly upregulated in CRC and is closely associated with clinical stage and lymphatic spread of CRC.

Research perspectives

Further exploration of the role of FAT10 in the development of CRC and the underlying mechanisms, especially its relationship with the cell cycle, will be important for understanding the value of FAT10 in CRC diagnosis, prognosis and therapy.

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