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Original Article

Low expression of 2'-5' oligoadenylate synthetase 1 predicted poor prognosis in colorectal cancer

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Abstract: 2'-5' oligoadenylate synthetase 1 (OAS1) is an IFN inducible enzyme and can activate RNaseL, degrade cellular RNA and inhibit protein synthesis. Except anti-virus infection, OAS1 is involved in cell growth, differentiation, apoptosis and migration in several cancers. The purpose of this study was to clarify the role of OAS1 in progression of colorectal cancer (CRC) and to examine whether OAS1 can be used as a prognostic marker for CRC. 135 CRC patients who underwent surgical resection were investigated. The expression of OAS1 was evaluated by immunohistochemical staining to analyze the relationship between OAS1 protein expression and clinicopathological parameters. OAS1 was mainly localized in the nucleus of normal colorectal mucosa and tumor cells, scarcely in the cytoplasm. High expression of OAS1 was only detected in 31.1% of cases. Low expression of OAS1 was significantly correlated with poor pathologic differentiation, lymph node metastasis, distant metastasis, and advanced TNM stages ($P<0.05$ for each). Patients with high OAS1 expression had a significantly better 5-year overall survival rate ($P=0.001$). The same results were found in different groups of patients with G2/G3, lymph node metastasis, TNM stage III/IV, and without distant metastasis ($P<0.05$ for each). Moreover, multivariate analysis showed that OAS1 expression proved to be an independent prognostic factor ($P=0.039$). Patients with high expression of OAS1 exhibited better prognosis than those with low expression of OAS1. Thus, OAS1 could be a useful prognostic marker and potential therapeutic target for CRC patients.

Keywords: OAS1, colorectal cancer, immunohistochemistry, prognosis

Introduction

Colorectal cancer (CRC) is the third commonly diagnosed malignant tumor and the fourth common cause of cancer death throughout the world [1]. Despite advances in treatment, CRC still has a high mortality rate due to the high metastatic potential [2, 3]. Nowadays, the prognosis of CRC patients is usually judged by the conventional classification [AJCC/UICC Tumor-Node-Metastasis (TNM) classification]. However, patients of the same stage frequently have dramatically different outcomes. The development and progression of a carcinoma is closely related to neoplastic cells as well as tumor-associated immune response or tumor immune microenvironment [4]. The inactivation of immune sensors and effectors can predispose to inflammation and tumorigenesis, even tumor metastasis [5-7]. That is also closely associated with the tumor prognosis and overall survival [8]. Therefore, a more comprehensive understanding of immune sensors or effectors in the CRC immune microenvironment is essential and is benefit to early diagnosis and more effective treatment strategies for CRC.

As a pleiotropic cytokine, interferon (IFN) plays an important role in the innate and adaptive immune system of cancer development and anti-cancer immune responses [9]. IFNs induce transcription of a family of 2'-5' oligoadenylate synthetase (OAS) genes. In humans, the OAS family is composed of OAS1, OAS2, OAS3 and OASL, mapping to chromosome 12q24.1-q24.2 [10]. 2'-5' OAS (excluding OASL) recognizes double-stranded RNA (dsRNA), and catalyzes the oligomerization of ATP to form 2-5 oligoadenylates (2-5A) which in turn activates RNaseL to degrade both cellular and viral RNA [11]. The OAS proteins are involved in anti-virus infection, inhibiting protein synthesis, differentiation and

apoptosis of tumor cells [12-14]. OAS3 has been described to inhibit cell growth in breast cancer [15]. In addition, IFN regulated OAS family is obviously associated with tumor metastasis [16-18]. These observations implicate that the OAS family counteracts tumor progression.

OAS1 has two spliced forms in humans that produce two proteins (40 and 46 kDa) that differ in their C-termini by 18 and 54 amino acids, respectively. Overexpression of OAS1 in prostate cancer induces apoptosis and affects cell cycle through increasing p53, BAX and p21 expression [19]. Evidence has also demonstrated that proapoptotic activity of OAS1 isoform 9-2 (p48) is interacting with Bcl-2 and Bcl-xL [20, 21].

Nevertheless, so far, no information is available for the expression status of OAS1 in CRC. Thus, the aim of this study was to investigate the expression and function of OAS1 in CRC.

Materials and methods

Patients and tissue samples

The study was approved and monitored by the ethics committee of Sir Run Run Shaw Hospital, Zhejiang University (Hangzhou, China). A total of 135 patients who underwent surgical resection for primary sporadic CRC from March 2004 to October 2006 at Sir Run Run Shaw Hospital were investigated in this study. Patients who received chemotherapy or radical therapy prior to surgery were excluded. Related clinicopathological parameters including age, gender, tumor location, histopathological grading, depth of invasion, lymph node metastasis, distant metastasis and TNM stages were collected from medical charts or pathology reports. Histopathological grading was determined according to the World Health Organization (WHO) classification guidelines [22]. The depth of invasion, lymph node metastasis, and distant metastasis were classified according to the 7th edition of the International Union Against Cancer (UICC) tumor node metastasis (TNM) classification [23]. The subject population comprised 79 male and 56 female patients with a median age of 62.84 years (range, 28-89 years). 9 normal colorectal mucosa biopsy samples, obtained from the healthy volunteers who underwent enteroscopy for routine screening, were used as normal controls. All patients were followed up for a period of 60 months or until death, the mean follow-up time was 44.13 months (range, 1-60 months). Thirty-eight patients died of CRC during the follow-up period.

Immunohistochemistry

The ChemMate™ EnVision™ detection kit (Dako, Carpinteria, CA, USA) was used for immunohistochemistry (IHC) according to the manufacturer's recommended procedure. All tissue samples were fixed with 10% formaldehyde, embedded in paraffin and sectioned into 4-um-thick slices. After dewaxed with dimethylbenzene and rehydrated with a series of graded ethanol, the sections were placed in 0.01 M citrate buffer (pH 6.0) and subjected to pressure cooker treatment for an antigen retrieval process. The endogenous peroxidase activity was blocked by immersing the slides in a 3% hydrogen peroxidase-methanol solution for 15 min at room temperature. The sections were incubated with preimmunized goat serum for 30 min, and then incubated overnight at 4°C with anti-OAS1 antibody (dilution: 1:200; HPA003657, Sigma-Aldrich Co, St. Louis, MO, USA). The slides processed without the primary antibody was used as a negative control. Then the ChemMate EnVision/HRP, Rabbit/Mouse (ENV) reagent was used to the sections as a secondary antibody, followed by application of ChemMate DAB+ Chromogen included in the kit. The slides were counterstained with hematoxylin and examined under a light microscope equipped with a camera.

Evaluation of OAS1 expression

The immunostaining was evaluated by two independent investigators who were unaware of the clinicopathological outcomes of the patients. Expression of OAS1 was scored based on the intensity of staining and proportion of positive cells. The intensity of staining was scored as follows: 0, negative; 1, weakly positive; 2, positive; and 3, strongly positive. The proportion of positive cells was scored as follows: 0, 0-5%; 1, 5%-25%; 2, 25%-50%; 3, 50%-75%; 4, 75%-100%. The two scores were summed to obtain an immunoreactivity score (IRS) value ranging from 0 to 7. To examine the association of the OAS1 expression level with the clinicopathological features, the patients were divided into two groups according IRS: low expression (0-3) and high expression (4-7).

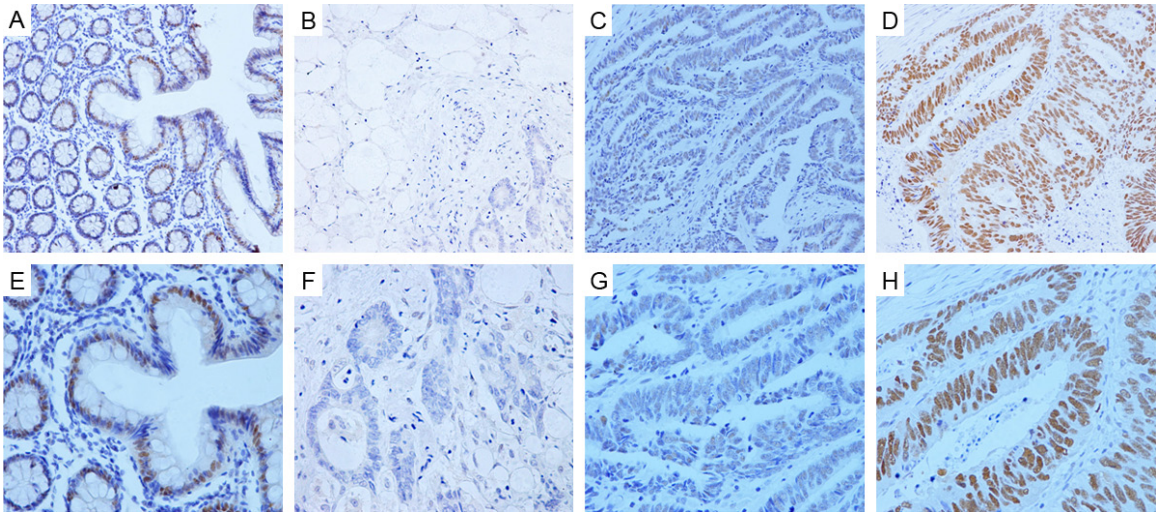

Figure 1. Representative immunohistochemical staining of OAS1 in normal colorectal mucosa and colorectal cancer tissues (Original magnification, A-D: × 200; E-H: × 400). Strong OAS1 expression was shown in nuclei of normal colorectal mucosa tissues (A, E). Different levels of OAS1 expression was observed in cancer cells: undetectable or weak (B, F), moderate (C, G), and strong (D, H).

Statistical analysis

All statistical analysis was performed using the SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA). The two-tailed Chi-square and Fisher's exact test were used to analyze the relationship between OAS1 protein expression with various clinicopathological parameters. The survival rates were estimated using the Kaplan-Meier method, and the differences were compared by the log-rank test. Prognostic factors were examined by univariate and multivariate analysis (Cox proportional hazards regression model). The estimated relative risks of dying were described as adjusted hazard ratios (HRs) with 95% confidence intervals (95% CIs). $P<0.05$ was considered to indicate statistical significance.

Results

Expression of OAS1 in normal colorectal mucosa and colorectal cancer

OAS1 immunostaining was localized predominantly in the nucleus, scarcely in the cytoplasm or cytomembrane. The positive rate of OAS1 expression in CRC tissue (31.1%, 42/135) was significantly lower than in normal colorectal mucosa (100%, 9/9) ($P<0.001$). The representative immunostaining images were shown in **Figure 1**.

Correlation between OAS1 expression and clinicopathological parameters in patients with colorectal cancer

The correlations between the OAS1 protein expression and the clinicopathological parameters of CRC patients were summarized in **Table 1**. OAS1 expression was not found to be associated with gender, age, tumor location, or depth of invasion ($P>0.05$). However, OAS1 expression was significantly correlated with histopathological grading: 39.7% of G1 tumors exhibited a high expression vs. 32.4% and 4% for G2 and G3 tumors, respectively ($P=0.004$). The positive rate of OAS1 expression was significantly lower in CRC patients with lymph node metastasis (22.9%) than in cases without metastasis (40%) ($P=0.0032$). Similarly, the expression of OAS1 in CRC patients with distant metastasis (13.3%) was significantly lower than that without distant metastasis (36.2%) ($P=0.017$). Additionally, OAS1 expression was significantly associated with TNM stages ($P=0.016$), and the positive rate of OAS1 expression was remarkably decreased in CRC patient at different TNM stages (I, 55%; II, 36.1%; III, 28.6%; IV, 13.3%).

Low expression of OAS1 indicated poor survival in CRC patients

The 5-year overall survival rate was significantly lower in patients with low-expression of OAS1

Table 1. Relationship between OAS1 expression and clinicopathological parameters in 135 colorectal cancer patients

Clinicopathological parameters	N (%)	OAS1 expression		X^2	*P*-value
		Low (%)	High (%)		
Total	135	93 (68.9)	42 (31.1)		
Gender					
Male	79 (58.5)	51 (64.6)	28 (35.4)	1.668	0.197
Female	56 (41.5)	42 (75)	14 (25)		
Age					
≥63	68 (50.4)	49 (72.1)	19 (27.9)	0.642	0.423
<63	67 (49.6)	44 (65.7)	23 (34.3)		
Tumor location					
Rectum	81 (60)	51 (63)	30 (37)	3.318	0.069
Colon	54 (40)	42 (77.8)	12 (22.2)		
Histopathological grading					
G1 (Well)	73 (54.1)	44 (60.3)	29 (39.7)	11.132	0.004*
G2 (moderately)	37 (27.4)	25 (67.6)	12 (32.4)		
G3 (Poorly)	25 (18.5)	24 (96)	1 (4)		
Depth of invasion					
pT1/T2	33 (24.4)	20 (60.6)	13 (39.4)	1.398	0.237
pT3/T4	102 (75.7)	73 (71.6)	29 (28.4)		
Lymph nodal status					
N0	65 (48.1)	39 (60)	26 (40)	4.621	0.032*
N1/2/3	70 (51.9)	54 (77.1)	16 (22.9)		
Distant metastasis					
M0	105 (77.8)	67 (63.8)	38 (36.2)	5.688	0.017*
M1	30 (22.2)	26 (86.7)	4 (13.3)		
TNM stage					
I	20 (14.8)	9 (45)	11 (55)	10.317	0.016*
II	36 (26.7)	23 (63.9)	13 (36.1)		
III	49 (36.3)	35 (71.4)	14 (28.6)		
IV	30 (22.2)	26 (86.7)	4 (13.3)		

*Statistically significant (P<0.05).

than in those with high-expression of OAS1 (P=0.001; **Figure 2A**). In 105 patients without distant metastasis, 67 patients with low-expression of OAS1 also had significantly low 5-year overall survival rate than that of patients with high-expression of OAS1 (P=0.01, **Figure 2D**). The result that 5-year overall survival rate was remarkably low in patients with low-expression of OAS1 was also found in some different groups of patients: patients with G2/G3 (P=0.021, **Figure 2B**); patients with lymph node metastasis (P=0.002, **Figure 2C**); patients with TNM stage III/IV (P=0.019, **Figure 2E**). However, that result was not significantly detected in patients with G1, distant metastasis, or TNM stage I/II (P>0.05) (data not shown).

To further substantiate the prognostic value of OAS1 in CRC, univariate and multivariate analysis of survival was conducted, and the results were shown in **Tables 2** and **3**, respectively. Univariate regression analyses revealed that histopathological grading (P=0.001), lymph node metastasis (P=0.001), distant metastasis (P<0.001), TNM stages (P<0.001), and OAS1 expression (P=0.003) significantly affected 5-year overall survival rate of CRC patients. To exclude the interaction of multiple factors, multivariate analysis was performed using the Cox proportional hazards regression model for all of the significant variables examined in the univariate analysis. Comparing to patients with the low-expression of OAS1, a better survival was observed in patients with high-expression of OAS1 (HR: 0.327; 95% CI: 0.114-0.943). Furthermore, other factors failed to demonstrate independence, but OAS1 expression proved to be a significant independent prognostic factor for survival in CRC (P=0.039).

Discussion

In this study, we report the association between OAS1 protein expression and clinicopathological features in CRC for the first time. We found that OAS1 was mainly stained in the nucleus but not the cytoplasm in the colorectal mucosa. However, some researches show OAS1 in Xenopus oocytes is localization in both the cytoplasm and the nucleus, as well as OAS2 in human lymphoblastoid cell [24, 25]. This paradoxical finding supports organ-specificity. Mandal *et al* have reported that immunohistochemical expression of OAS1 is high in the normal prostate but lower in prostate cancer. We consistently found that the OAS1 protein had a

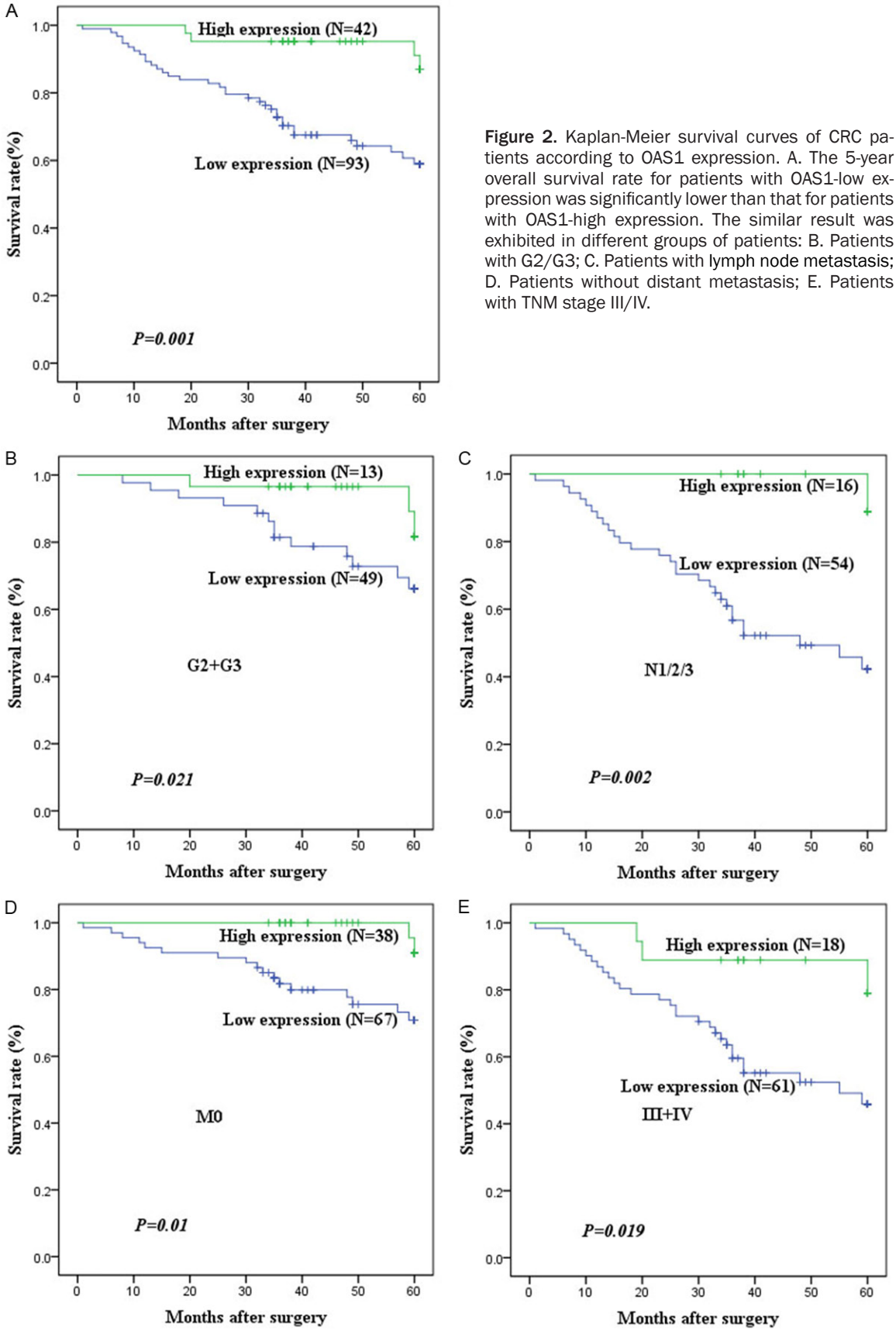

Figure 2. Kaplan-Meier survival curves of CRC patients according to OAS1 expression. A. The 5-year overall survival rate for patients with OAS1-low expression was significantly lower than that for patients with OAS1-high expression. The similar result was exhibited in different groups of patients: B. Patients with G2/G3; C. Patients with lymph node metastasis; D. Patients without distant metastasis; E. Patients with TNM stage III/IV.

Table 2. Univariate survival analyses of various factors in CRC

Characteristics	Categories	HR	95% CI	*P*-value
Gender	Male/Female	0.961	0.502-1.842	0.961
Age	≥63/<63	1.613	0.842-3.092	0.15
Tumor location	Rectum/Colon	1.562	0.825-2.955	0.171
Histopathological grading	Well/moderately/poorly	1.96	1.312-2.927	0.001*
Depth of invasion	T1+T2/T3+T4	1.622	0.714-3.685	0.248
Lymph node metastasis	N0/N1/N2/N3	3.677	1.737-7.784	0.001*
Distant metastasis	M0/M1	5.854	3.054-11.22	<0.001*
TNM stage	I/II/III/IV	2.993	1.950-4.592	<0.001*
OAS1 expression	Low/High	0.211	0.075-0.596	0.003*

HR, hazard ratio; CI, confidence interval. *Statistically significant (P<0.05).

Table 3. Multivariate survival analyses of prognostic factors in CRC

Characteristics	Categories	HR	95% CI	*P*-value
Histopathological grading	Well/moderately/poorly	1.444	0.94-2.218	0.093
Lymph node metastasis	N0/N1/N2/N3	2.396	0.835-6.881	0.104
Distant metastasis	M0/M1	3.645	0.847-15.679	0.082
TNM stage	I/II/III/IV	1.071	0.39-2.938	0.894
OAS1 expression	Low/High	0.327	0.114-0.943	0.039*

HR, hazard ratio; CI, confidence interval. *Statistically significant (P<0.05).

high expression in all of normal colorectal mucosa but only 31.1% of positive rate in CRC.

OAS family, particularly OAS1, has been reported to be involved in tumor progression of several cancer types, such as Lymphoblastic Leukemia, oral cancer, prostate cancer, breast cancer and cervical cancer [12, 13, 15, 26-28]. In our study, OAS1 expression in CRC was significantly associated with histopathological grading, lymph node metastasis, distant metastasis, and TNM stages. Additionally, a lower expression of OAS1 was found in patients with advanced grade, metastasis and TNM stages. Mandal *et al* reported OAS1 expression was decreased progressively with stage in prostate cancer [19]. They also reported that OAS1 protein was not expressed in LNCaP cells, derived from a prostate cancer patient with lymph node metastasis. Transfection of PC3 cells with 2'-5' oligoadenylate suppressed cell migration [18]. These findings agree with our results. In this context, OAS1 may suppress tumor development in CRC, especially tumor metastasis.

Furthermore, the 5-year overall survival rates of the patients with low OAS1 expression are significantly lower than those of the patients with high OAS1 expression. The same results have been significantly found in different patient groups with G2/G3, lymph node metastasis, TNM stage III/IV or without distant metastasis. These data uncovered that OAS1 was frequently downregulated in CRC, and low expression of OAS1 may indicate the poor prognosis in patients with CRC, especially those with advanced stages.

Multiple factors affect the prognosis of CRC. Lymph node metastasis and the tumor-node-metastasis stage are proven to be prognostic markers to aid in the identification of CRC patients [29]. In our study, lymph node metastasis and TNM stages are consistently prognostic factors on univariate analysis, as well as histopathological grading, distant metastasis, and OAS1 expression. Then we show that OAS1 expression was an independent prognostic factor in CRC. High expression of OAS1 was associated with decreased risk of death in CRC patients. These findings may have important clinical significance. OAS1 expression could be used as a useful prognostic factor to predict the survival of postoperative CRC patients.

Similar results about OAS1 biofunctions and related molecular mechanism in cancers have been reported. For instance, Mandal *et al* have

reported that overexpression of OAS1 induces apoptosis and cell cycle arrest; whilst silencing of OAS1 leads to the opposite results in prostate cancer [19]. Transient transfection of OAS into breast cancer cell lines could result in decreased cells proliferation and apoptosis dependent on the OAS/RNaseL pathway mediating with BRCA1 [13]. Molinaro *et al* have reported that RNA fractions can bind to and active OAS in prostate cancer cell lines but can't in normal prostate epithelial cells [30]. Therefore, OAS1 could be a good therapeutic target for CRC treatment to prevent tumor development and progression.

In conclusion, this study reveals that OAS1 is involved in tumor proliferation, differentiation and metastasis in CRC. Low expression of OAS1 could be a predictor for poor overall survival in CRC patients. In addition, OAS1 expression could be an independent prognostic marker for CRC patients. Anyway, further studies about molecular mechanisms of OAS1 in CRC progression are needed for the development of the effective clinical diagnosis and therapeutic strategy.

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Disclosure of conflict of interest

None.

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