HDAC10 expression is associated with DNA mismatch repair gene and is a predictor of good prognosis in colon carcinoma

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Abstract. Despite increasing evidence of the involvement of histone deacetylase (HDAC)10 in cancer tumorigenesis, the potential role of HDAC10 in colon cancer remains unclear. Oncomine database analysis revealed that HDAC10 mRNA was significantly upregulated in colon cancer. In an independent cohort, consistent with mRNA expression levels, constitutively high HDAC10 expression was observed in the cytoplasm and nucleus compared with in adjacent normal tissues (cytoplasm, 93.12±12.98 vs. 31.65±26.50%; nucleus, 84.16±19.23 vs. 68.64±19.00%). Cytoplasmic HDAC expression correlated with gender (r=0.265; P<0.05), lymph node metastasis (N stage; r=0.256; P<0.05) and distant metastasis (M stage; r=0.331; P<0.05) in paracarcinoma tissues. Cytoplasmic HDAC10 expression in tumors was not associated with the four DNA mismatch repair genes examined, but was negatively correlated with mutL homolog 1 (MLH1) (r=-0.244; P<0.05), mutS homolog (MSH)2 (r=-0.410; P<0.01) and MSH6 (r=-0.240; P<0.05) in paracarcinoma tissues. Similarly, nuclear HDAC10 expression was negatively correlated with MLH1 expression (r=-0.288; P<0.05). The findings of the current study suggest that HDAC10 expression is associated with good prognosis in colon cancer tissues and poor prognosis in paracarcinoma tissues with a potential involvement in DNA mismatch repair.

Introduction

Histone deacetylases (HDACs) was the name originally given to a family of proteins responsible for deacetylation of histone proteins, which were later shown to be also involved in the deacetylation of non-histone proteins (1,2). HDACs are divided into four classes based on structure: Class I including HDAC1, HDAC2, HDAC3 and HDAC8; class II, which is further divided into class IIa (HDAC4, HDAC5, HDAC7 and HDAC9) and class IIb (HDAC6 and HDAC10); class III comprising SIRT1 to SIRT7; and class IV, consisting of only HDAC11. While HDAC6 is a well-investigated class II HDAC, little is known about HDAC10.

HDAC10 has been reported to be involved in homologous recombination (3), melanogenesis (4), cells autophagy (5-7), cell cycle regulation (8), DNA mismatch repair (9) and cancer progression (10-16). While HDAC10 was reported to suppresses the proliferation and invasion of clear cell renal cell carcinoma (13), it was also demonstrated to promote cell proliferation via AKT phosphorylation in lung cancer (15). Based on these contradictory observations, we hypothesized that the function of HDAC10 in cancer is more complex and may be dependent on the type of tissue.

Colorectal carcinoma is among the five most commonly diagnosed cancers accounting for over 50% of the top five cancers all cases in China (17). Owing to the high risk of relapse and metastasis, the treatment for advanced colon cancer poses a significant challenge. Thus, it is crucial to discover new and competent therapeutic targets for colon cancer, thereby enabling the discovery of new diagnostic and therapeutic drugs.

To date, the expression of HDAC10, especially the prognostic role and its association with clinicopathological features in colon cancer has not been investigated. In this study we analyzed 100 colon cancer specimens in a tissue microarray (TMA) to assess HDAC10 expression and to evaluate the clinical significance of HDAC10 in colon cancer.

Patients and methods

Patients. A total of 100 colon cancer patients (54 male, 45 female and one missed gender information) aged between 24 and 90 were recruited in this study. All patients underwent surgery during July 2006 to May 2007 and received no prior extra therapy. Of these, 6 were cTNM stage I, 54 were cTNM stage II, 35 were cTNM stage III, and 3 were cTNM stage IV according to AJCC. Following surgery, a long-term follow-up was implemented for all patients up to July 2015. During the follow-up time, 61 patients died of colon carcinoma with a median overall survival time of 26 months. Detailed patient information is listed in Table I.

Immunohistochemistry. Colon adenocarcinoma TMA (HColA180Su09) containing 100 tumor tissues and 80 paired

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Table I. Clinical parameters of colon carcinoma patients.

Clinical factors	No. of patients
Gender	
Male	54
Female	45
Age	
≤60	21
>60	73
Tumor size	
≤5 cm	55
>5 cm	43
Pathological grade	
1	2
2	48
3	50
T stage	
T1+T2	7
T3+T4	89
N stage	
N0	60
N1	27
N2	11
M stage	
M0	97
M1	3
cTNM stage	
1	6
2	54
3	35
4	3
Tumor location	
Right	61
Left	38

adjacent tissues was obtained from Shanghai Outdo Biotech Co., Ltd. (Shanghai, China) for standardization. Deparaffinization of the TMA was performed by xylene and graded alcohol following incubation at high temperature for an hour. After antigen retrieval by EDTA and blocking with goat serum, the TMA was incubated with the primary anti-HDAC10 antibody (24913-1-AP) obtained from ProteinTech Group, Inc. (Chicago, IL, USA) at a dilution of 1:2,500 at 4˚C overnight, and subsequently incubated with horse radish peroxidase (HRP) labeled secondary-antibody (K8000; Dako; Agilent Technologies, Inc., Santa Clara, CA, USA) for 30 min. Diaminobenzidine (DAB) and hematoxylin redyeing were performed for visualization. Three random fields having more than 100 cells were visually analyzed and scored by pathologists. The colon cancer patients were divided into three subgroups based on differences in HDAC10 expression as follows: 0-60%, low expression; 61-90%, median expression; 91-100%, high expression. The expression of mutL homolog 1 (MLH1) (1:5,000, sc-56160; Santa Cruz Biotechnology, Inc., Dallas, TX, USA), mutS homolog (MSH)2 (1:100, sc-56163; Santa Cruz Biotechnology, Inc.), MSH6 (1:5,000, 66172-1-Ig; ProteinTech Group, Inc.) and PMS2 (1:1,500, sc-618; Santa Cruz Biotechnology, Inc.) was also detected in these patients with the same protocol. The specificity of the anti-HDAC10 antibody used in the present study was validated by Wang *et al* in a previous study (18).

Statistical analysis. The difference in HDAC10 expression between colon adenocarcinoma and adjacent tissues was evaluated by paired t-test. Spearman's rank correlation coefficient and two-tailed test were performed to evaluate the correlation between HDAC10 expression and clinical parameters. Pearson analysis was performed to assess the association between HDAC10 and MLH1/MSH2/MSH6/PMS2 expression. Based on HDAC10 and clinical parameters, overall survival curves were drawn according to the Kaplan-Meier method and log-rank test. Subsequently, COX multivariate regression survival analysis was performed to determine the independent prognostic marker. All statistical analyses were conducted using SPSS 17.0 software (SPSS, Inc., Chicago, IL, USA), with $P<0.05$ being considered significant.

Results

Evaluation of HDAC10 mRNA expression in colon carcinoma. The HDAC10 mRNA expression level in colon adenocarcinoma was investigated in the Oncomine database. As depicted in Fig. 1, HDAC10 mRNA expression in colon adenocarcinoma tissues was found to be significantly upregulated both in the Kaiser colon statistics involving 41 colon carcinoma tissues and 5 normal tissues (fold change=1.103, $P<0.05$; Fig. 1A) as well as in the TCGA colorectal database containing 101 colon adenocarcinoma tissues and 19 normal colon tissues (fold change=1.656, P=1.07e-7; Fig. 1B).

HDAC10 expression is high in colon carcinoma. To investigate HDAC10 expression in colon adenocarcinoma, two-step immunohistochemistry was performed on the TMA. As shown in Fig. 2, constitutively high HDAC10 expression was visualized both in the cytoplasm and nucleus in most colon cancer tissues when compared with the adjacent normal tissues. Subsequently, HDAC10 expression in colon cancer was systemically investigated by statistical analysis with the adjacent normal tissue as a control (cytoplasm, 93.12±12.98 vs. 31.65±26.50%; Fig. 2C; nucleus, 84.16±19.23 vs. 68.64±19.00%; Fig. 2D). The results indicated significantly elevated expression of HDAC10 protein at the tissue level. Regardless of the location, HDAC10 expression did not show a significant correlation with the tumor tissue when compared with the adjacent normal tissue (Table I). Interestingly, HDAC10 expression in the nucleus was associated with its cytoplasmic expression, both in the tumor tissue as well as in the adjacent normal tissue (Table II).

Correlation between HDAC10 expression and clinical parameters. HDAC10 expression in colon adenocarcinoma tissues showed no significant correlation with any clinicopathological factors, apart from a link between cytoplasmic HDAC expression and gender ($r=0.265$, $P<0.05$). Intriguingly however,

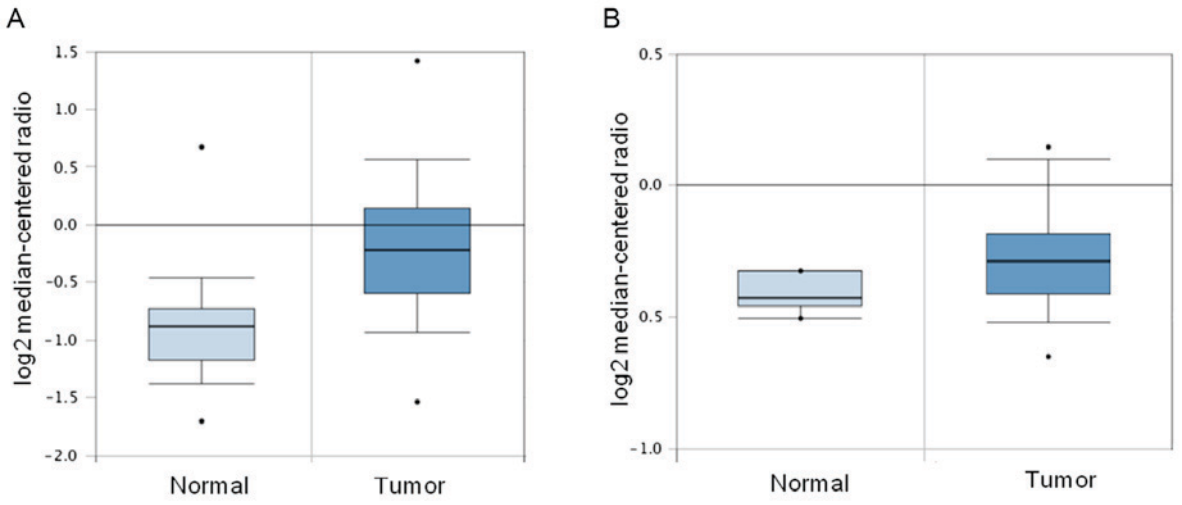

Figure 1. Oncomine database for HDAC10 mRNA expression in (A) TCGA colorectal database and (B) Kaiser Colon study. HDAC10, histone deacetylase 10.

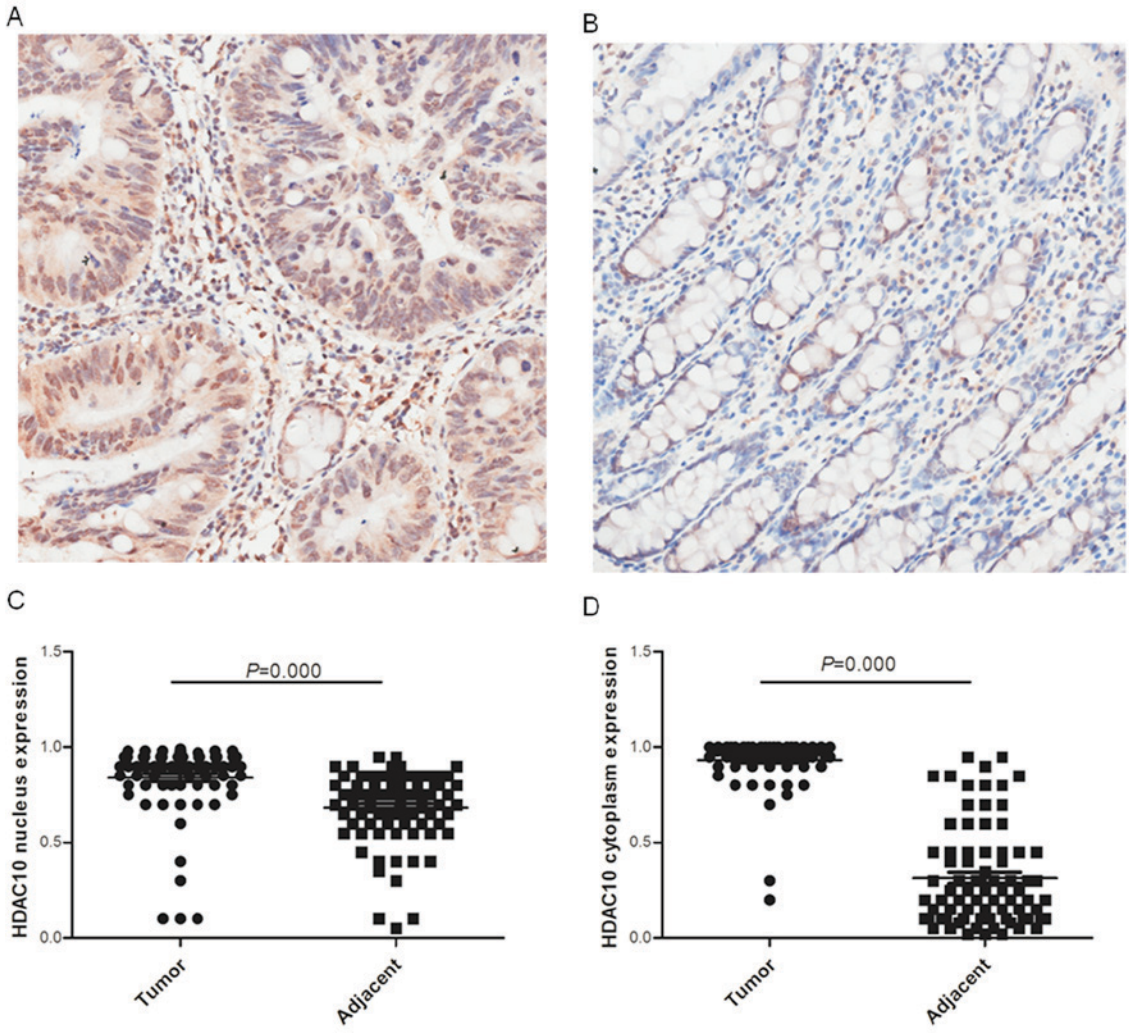

Figure 2. Representative immunohistochemistry images for HDAC10 expression in (A) colon cancer tissues and (B) para-carcinoma tissues (magnification, x200). (C) HDAC10 cytoplasmic expression and (D) nuclear expression were analyzed by paired t-test. P<0.05 was considered to be significant. HDAC10, histone deacetylase 10.

HDAC10 expression in para-carcinoma tissues was highly associated with clinicopathological factors. Cytoplasmic HDAC10 expression was found to be positively correlated with lymph node metastasis (N stage, r=0.256, P<0.05) and distant metastasis (M stage, r=0.331, P<0.05). Detailed results of the correlation analysis are listed in Table III.

Table II. Correlation between HDAC10 expression in tumor and para-carcinoma tissues.

		Cytoplasm		Nucleus	
Location	Tissue	Tumor	Para-carcinoma	Tumor	Para-carcinoma
Cytoplasm	Tumor				
	Pearson correlation	1	0.100	0.227[a]	-0.107
	Sig. (2-tailed)		0.387	0.024	0.356
	Number	98	77	98	77
	Para-carcinoma				
	Pearson correlation	0.100	1	-0.094	0.333[b]
	Sig. (2-tailed)	0.387		0.416	0.003
	Number	77	79	77	79
Nucleus	Tumor				
	Pearson correlation	0.227[a]	-0.094	1	0.037
	Sig. (2-tailed)	0.024	0.416		0.747
	Number	98	77	98	77
	Para-carcinoma				
	Pearson correlation	-0.107	0.333[b]	0.037	1
	Sig. (2-tailed)	0.356	0.003	0.747	
	Number	77	79	77	79

[a]Correlation is significant at the 0.05 level (2-tailed). [b]Correlation is significant at the 0.01 level (2-tailed). HDAC10, histone deacetylase 10.

Different prognostic role of HDAC10 in colon carcinoma and para-carcinoma. High cytoplasmic expression of HDAC10 in tumor tissues predicted good prognosis in colon cancer patients, with 0% survival in the population with low HDAC10 expression after 8 years of follow-up, in contrast with 29.4% for population with median expression and 43.0% for population with high expression (Fig. 3A). Conversely, cytoplasmic HDAC10 expression in para-carcinoma tissues was associated with poor outcome of patients (43.3 vs. 20.0 vs. 0%, P<0.001; Fig. 3B). Nuclear HDAC10 expression in the tumor tissues did not correlate with overall increased survival of colon cancer patients (28.6 vs. 40.8 vs. 40.5%, P>0.05; Fig. 3C), while high nuclear HDAC10 expression in the para-carcinoma tissues was correlated with increased survival rate (43.5 vs. 38.9 vs. 0%, P<0.001; Fig. 3D). Furthermore, regional lymph node metastasis (N stage, 51.7 vs. 25.9 vs. 9.1%, P=0.000), distant metastasis (M stage, 40.2 vs. 0.0%, P<0.001), tumor location (right vs. left, 31.1 vs. 52.6%, P<0.05) and clinical stage (cTNM, 66.7 vs. 50.0 vs. 22.9 vs. 0.0%, P<0.001) were all correlated with overall survival time. Subsequent multivariate analysis indicated that only cytoplasmic HDAC10 expression was an independent prognostic marker for colon cancer (Table IV).

HDAC10 may be associated with DNA mismatch repair. The implication of HDAC10 in DNA repair pathway via interaction with DNA mismatch repair gene MSH2 in HeLa cells prompted us to explore the possibility that HDAC10 is involved in the progression of colon cancer via its interaction with the DNA mismatch repair genes (9). Four major DNA mismatch repair genes MLH1, MSH2, MSH6 and PMS2 were investigated by immunohistochemistry. Pearson analysis was performed to evaluate the their association with HDAC10. The results, listed in Table V, predicted that cytoplasmic HDAC10 expression in the tumor tissue was not associated with any of the four DNA mismatch repair genes. Instead it showed negative association with MLH1 (r=-0.244, P<0.05), MSH2 (r=-0.410, P<0.001) and MSH6 (r=-0.240, P<0.05) in the para-carcinoma tissues. Similarly, nuclear HDAC10 expression was negatively correlated with MLH1 expression (r=-0.288, P<0.05).

Discussion

To the best of our knowledge, our findings highlight for the first time, the clinical significance of HDAC10 in colon cancer. HDAC10 was demonstrated to be a tumor suppresser in some types of cancer, including clear cell renal cell carcinoma (13), cervical cancer (19), gastric cancer (12,20), and ovarian cancer (16). The function of HDAC10 in lung cancer is a matter of debate (10,15). High HDAC10 expression was associated with good prognosis in non-small cell lung cancer (10) but has been lately demonstrated to promote lung cancer proliferation (15).

Class II HDACs have been reported to be able to shuttle between the nucleus and cytoplasm. In this study, we found similar behavior of HDAC10 expression in colon cancer tissues. Yang *et al* reported that HDAC10 is mainly expressed in the cytoplasm of lung cancer cells but is mainly located in the nucleus of normal lung cells, and suggested different functions of cytoplasmic and nuclear HDAC10 in lung cancer progression (15). The association of cytoplasmic and nuclear HDAC10 expression and clinicophathological and prognostic effect is inconsistent even in colon cancer. Moreover, in tumor tissues HDAC10 acted as a tumor suppressor, but showed quite different effect in adjacent tissues, suggesting that HDAC10 might act as a tumor suppressor in colon cancer tissues but

Table III. Association between HDAC10 and clinical parameters in colon adenocarcinoma.

HDAC10 expression										
Location	Tissue	Gender	Age	Tumor size	Pathological grade	T	N	M	cTNM	Tumor location
Cytoplasm	Tumor									
	Correlation Coefficient	0.194	0.108	0.025	-0.181	-0.030	0.146	0.087	0.101	0.001
	Sig. (2-tailed)	0.057	0.305	0.811	0.074	0.773	0.157	0.395	0.326	0.996
	Number	97	92	96	98	94	96	98	96	97
	Para-carcinoma									
	Correlation coefficient	0.179	0.133	-0.015	-0.095	-0.107	0.256[a]	0.331[b]	0.180	-0.085
	Sig. (2-tailed)	0.118	0.259	0.899	0.403	0.356	0.024	0.003	0.115	0.461
	Number	78	74	78	79	77	78	79	78	78
Nucleus	Tumor									
	Correlation Coefficient	0.265[b]	0.100	0.199	-0.007	0.059	0.073	-0.082	0.065	-0.046
	Sig. (2-tailed)	0.009	0.344	0.052	0.946	0.571	0.477	0.421	0.529	0.655
	Number	97	92	96	98	94	96	98	96	97
	Para-carcinoma									
	Correlation Coefficient	0.119	-0.067	0.045	0.119	-0.090	0.207	0.075	0.122	0.037
	Sig. (2-tailed)	0.301	0.569	0.694	0.298	0.438	0.069	0.510	0.287	0.746
	Number	78	74	78	79	77	78	79	78	78

[a]Correlation is significant at the 0.05 level (2-tailed). [b]Correlation is significant at the 0.01 level (2-tailed). HDAC10, histone deacetylase 10.

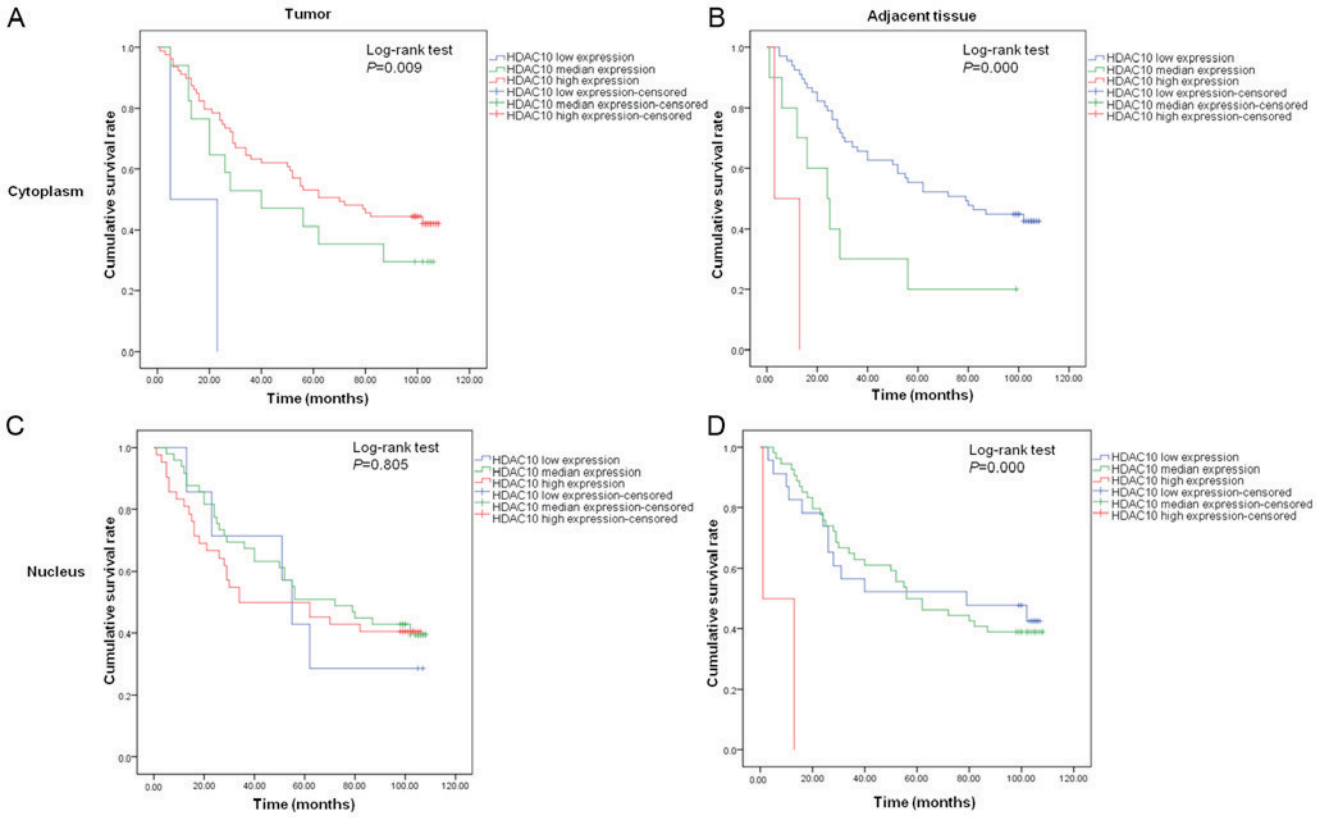

Figure 3. Survival analysis based on HDAC10 expression in different subgroups. (A) Cytoplasmic HDAC10 expression in tumor tissues; (B) cytoplasmic HDAC10 expression in adjacent tissues; (C) nuclear HDAC10 expression in tumor tissues; (D) nuclear HDAC10 expression in adjacent tissues. HDAC10, histone deacetylase 10.

Table IV. Multivariate analysis of factors associated with survival in colon carcinoma.

Factors	Sig.	Exp (B)	95.0% CI for Exp (B)	
			Lower	Upper
N stage	0.928	0.954	0.343	2.657
M stage	0.986	0.981	0.109	8.845
cTNM stage	0.120	2.378	0.798	7.086
Tumor location (right vs. left)	0.469	0.788	0.413	1.503
Cytoplasmic HDAC10 in tumor	0.093	0.539	0.262	1.109
Cytoplasmic HDAC10 in para-carcinoma	0.020	2.896	1.181	7.105
Nuclear HD10 in para-carcinoma	0.974	0.988	0.488	2.000

Table V. Association between HDAC10 expression and expression of DNA mismatch repair genes in colon cancer.

HDAC10 expression					
Location	Tissue	MLH1	MSH2	MSH6	PMS2
Cytoplasm	Tumor				
	Pearson correlation	-0.072	-0.208	-0.071	0.158
	Sig. (2-tailed)	0.530	0.068	0.526	0.165
	Number	79	78	81	79
	Para-carcinoma				
	Pearson correlation	-0.244[a]	-0.410[b]	-0.240[a]	-0.066
	Sig. (2-tailed)	0.038	0.000	0.040	0.580
	Number	72	71	73	72
Nucleus	Tumor				
	Pearson correlation	0.164	0.118	0.230[a]	0.297[b]
	Sig. (2-tailed)	0.148	0.302	0.039	0.008
	Number	79	78	81	79
	Para-carcinoma				
	Pearson correlation	-0.288[a]	-0.126	-0.097	-0.031
	Sig. (2-tailed)	0.014	0.295	0.413	0.798
	Number	72	71	73	72

[a]Correlation is significant at the 0.05 level (2-tailed). [b]Correlation is significant at the 0.01 level (2-tailed). HDAC10, histone deacetylase 10.

may also function as a tumor promoter by promoting tumor metastasis to regional lymph node or to distant tissues.

A growing number of studies point to quite different prognosis of patients between right-sided and left-sided colon cancers (21). The probability of relapse of colon carcinoma in different sides is dependent on different molecular pathways (22). Our observation is consistent with the previous studies that survival of patients with right-sided colon cancer is less than those with left-sided colon cancer.

In summary, our findings suggest that HDAC10 expression in tumor tissues is associated with good prognosis of colon cancers but predicted poor prognostic outcomes in para-carcinoma tissues, probably owing to regulation of the DNA mismatch repair pathway. Further studies by altering the HDAC10 expression in colon cancer cells and normal colon cells to investigate the potential functionin invasion and metastasis is needed to test our notion that HDAC10 has different roles in tumor and para-carcinoma tissues.

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