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Original Article

Downregulation of long non-coding RNA MT1DP correlates with poor prognosis in colorectal cancer

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Abstract: Background: Accumulated evidence has shown that long non-coding RNAs (lncRNAs) are emerging as key molecules in human malignancies. The lncRNA metallothionein 1D, pseudogene (MT1DP) was recently identified as a tumor suppressor in liver cancers. However, its expression pattern and clinical performance in colorectal cancer (CRC) have not been addressed. Methods: Our investigation was carried out on 78 cases of CRC tissues and matched adjacent normal tissues. The expression levels of MT1DP were determined by quantitative real-time PCR. Subsequently, its clinical values in CRC were further evaluated. Results: MT1DP expression was significantly downregulated in 55 of 78 CRC tissues (70.5%, P<0.001). The area under curve (AUC) of the ROC was 0.714; 95% confidence interval (CI) was 0.636-0.783, the sensitivity was 88.46% and the specificity was 51.28%. Moreover, low level of MT1DP expression in CRC was closely correlated with TNM stage (P=0.020) and distant metastasis (P=0.005). In addition, low MT1DP expression had a poorer overall survival (OS) and disease-free survival (DFS) rates in CRC patients (P=0.002 and 0.006, respectively). Additionally, univariate and multivariable Cox regression analyses further identified that downregulated MT1DP might act as an independent prognostic factor for OS and DFS of CRC patients. Conclusions: Low expression of MT1DP is involved in CRC progression and could be a novel biomarker of diagnostic and prognostic evaluation of CRC patients.

Keywords: Colorectal cancer, lncRNA, MT1DP, prognosis

Introduction

Colorectal cancer (CRC) remains a major health problem and represents the third in the cancer morbidity and the second in the cancer mortality worldwide, with more than 1 million individuals being diagnosed and 0.6 million succumb to the disease worldwide annually [1]. Despite scientific efforts and significant advances in surgical resection, radiotherapy and chemotherapy, the overall long-term survival rate of CRC patients has not changed dramatically in the past decades. On the other hand, although a variety of molecular markers, which are involved in the development of CRC, have been identified, their pathophysiological mechanisms remain largely elusive [2-4]. Therefore, new approaches, including the exploration of novel sensitive, specific biomarkers and therapeutic targets, are urgently needed to improve the early diagnosis, prognosis prediction and monitor response to treatment for this deadly disease.

Long noncoding RNAs (lncRNAs) represent a new class of non-protein-coding RNAs which have a length of more than 200 nucleotides and conventionally cannot be translated into proteins. When it comes to the structural similarity to mRNA, both kinds of RNAs are marked by 5' cap and 3' poly A. However, it has a diverse subcellular location and plays important roles in many aspects of biological processes, such as chromosome imprinting, histone modifica-

Table 1. Relationship of MT1DP expression with clinicopathological characteristics in CRC patients

Variables	Number of cases	MT1DP expression		*P*-value
		High (n=39)	Low (n=39)	
Age (years)				0.365
≤59	39	22	17	
>59	39	17	22	
Gender				0.610
Male	57	27	30	
Female	21	12	9	
Tumor size (cm)				0.103
≤4	30	19	11	
>4	48	20	28	
Tumor location				0.640
Colon	49	26	23	
Rectum	29	13	16	
Tumor differentiation				0.147
Well/moderately	47	27	20	
Poorly	31	12	19	
TNM stage				0.020
I-II	31	21	10	
III-IV	47	18	29	
Distant metastasis				0.005
Absence	56	34	22	
Presence	22	5	17	

tion, cell differentiation, cell cycle regulation and cytoplasmic transport, etc. Accumulated evidence has shown that deregulated expression of lncRNAs is closely correlated with the diversity of diseases, including human malignancies [5, 6]. Aberrant expressions of certain lncRNAs are associated with tumor growth and metastasis in CRC, and some of them have been implicated positive value in diagnosis and prognostication [7-9]. For example, lncRNA-CCAT1 [10], HOTAIR [11], UCA1 [12] and MALAT1 [13], etc. are upregulated in CRC tissues, in contrast, lncRNA-LET [14], MEG3 [15], GAS5 [16] and LOC285194 [17], etc. are downregulated in CRC tissues. However, the relationship of specific lncRNAs expression with malignant progression or prognosis, as well as detailed molecular mechanisms in CRC, remains to be further evaluated.

A novel lncRNA in liver cancer, metallothionein 1D pseudogene (MT1DP), has recently been found to inhibit liver cancer cell growth by acting as a tumor suppressor. Mechanistic analysis revealed an autoregulatory feedback that both Runt related transcription factor 2 (Runx2) and Yes associated protein (YAP) could negatively regulate MT1DP through promoter binding. Moreover, MT1DP inhibited cell proliferation and transformative phenotype of liver cancer cells through reducing protein synthesis of FoxA1, which could enhance YAP transcription by facilitating open chromatin around CREB binding region within the YAP promoter [18]. However, the relationship between MT1DP expression and its potential clinicopathologic role in CRC remains unclear. In the present investigation, we aimed to explore the expression pattern of MT1DP in CRC tissues and adjacent normal specimens. In addition, the association of MT1DP expression with clinicopathological characteristics and prognosis value in patients with CRC was also investigated.

Materials and methods

Patients and tissue samples

A total of 78 paired human CRC tissues and adjacent normal tissues were recruited in this study. The pathological type of them is all the adenocarcinoma. None of the patient received preoperative treatment, such as radiotherapy or chemotherapy. The adjacent normal tissues from the CRC site is defined as 5 centimetres from the tumor margins. The tissues were immediately frozen in liquid nitrogen after surgical removal and stored at -80°C for further analysis. The diagnosis of all CRC patients was pathologically confirmed. Histological differentiation and distant metastasis were classified according to the World Health Organization classification criteria. Clinical stage was evaluated on the basis of the TNM classification system. The detailed clinical characteristics of the patients were listed in **Table 1**. The follow-up data were obtained by reviewing the out-patient charts and contacting the patients by telephone or mail. Overall survival was calculated from the date of the initial surgical operation to the date of death or last date of follow-up. This project protocol was approved by the Ethics Committee of Nanjing Medical University and Medical Association of Jiangsu Province. All patients have signed informed consent forms.

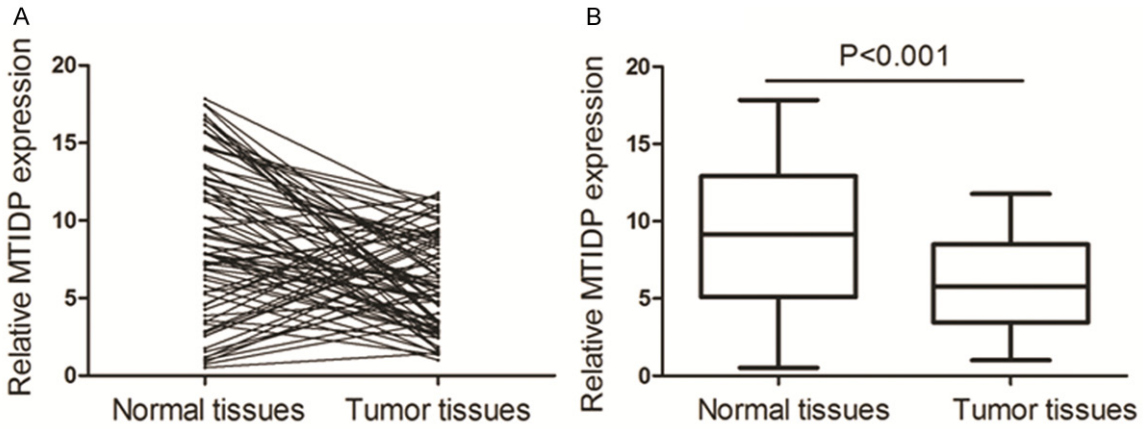

Figure 1. MT1DP expression pattern in CRC tumor tissues. A. Comparison of MT1DP expression levels between CRC tumor tissues and matched adjacent normal tissues by qRT-PCR analysis. GAPDH was used as an internal control. B. Statistical analysis indicates significant differences in MT1DP level between paired samples determined using the Wilcoxon matched-pairs test, P<0.001.

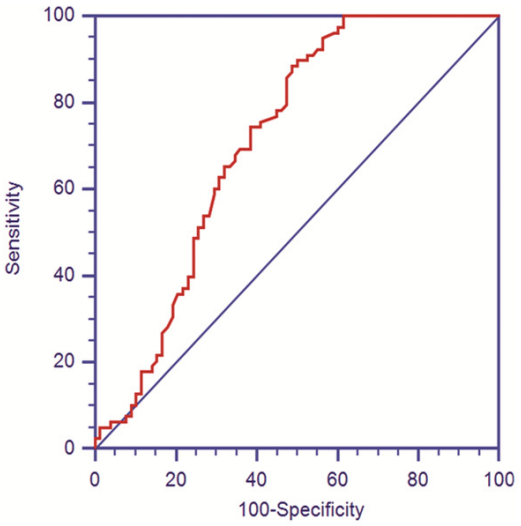

Figure 2. ROC curve analysis based on MT1DP expression in tumor tissues and adjacent normal tissues of CRC patients. The area under the ROC curve (AUC) indicates the diagnostic power of MT1DP expression for CRC.

RNA isolation and quantitative real-time PCR (qRT-PCR)

Total RNA was extracted from tissue samples by TRIzol reagent (Invitrogen) following the manufacture's protocol. The concentration and purity of RNA were measured spectrophotometrically at 260 and 280 nm. Only the samples with the OD A260/A280 ratio close to value of 1.8~2.0 were subsequently analyzed. Reverse transcription was performed using the PrimeScript™ First Strand cDNA synthesis kit (Takara, Dalian, China) according to the manufacturer's instructions. qRT-PCR was performed by using SYBR Premix Ex Taq™ II kit (Takara) on the Applied Biosystems 7500 PCR System (ABI, TX, USA). The primers of MT1DP were 5'-ATTTCTGAGGCGAGAGGACT-3' (forward) and 5'-GCAGGAGCAGCAGTTCT TCT-3' (reverse). The primers of GAPDH (internal control) were 5'-AGAAGGCTG GGGCTCATTTG-3' (forward) and 5'-AGGGGCCATCCACAGTCTTC-3' (reverse). The PCR amplification protocol was as follows: 95°C for 5 minutes, 40 cycles of denaturation at 95°C for 30 s, annealing at 58°C for 30 s, and extension at 72°C for 20 s. All reactions were conducted in triplicate. The comparative cycle threshold (CT) method and the equation $2^{-\Delta\Delta CT}$ were applied to quantify the expression level of MT1DP.

Statistical analysis

The significance of differences between groups was estimated by Student's t-test, χ^2 test or Wilcoxon test, as appropriate. A receiver operating characteristic (ROC) curve was established to evaluate the diagnostic value. Survival curve was constructed with the Kaplan-Meier method and compared by the log-rank test. Univariate and multivariate analyses were used on the basis of Cox proportional hazard regression model. All statistical analyses were performed using SPSS 18.0 software (SPSS, Chicago, IL, USA). Two-sided *P*-values less than 0.05 were considered to be statistically significant.

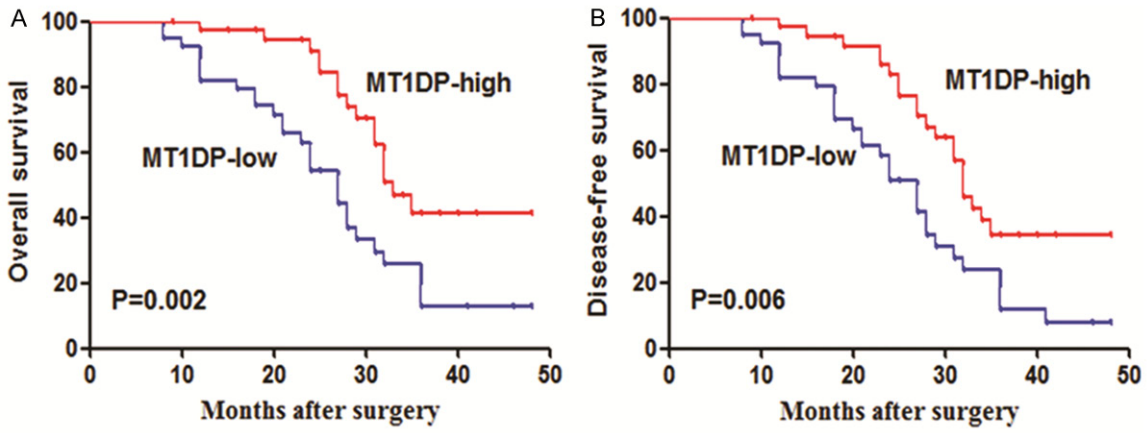

Figure 3. Kaplan-Meier analyses OS (A) and DFS (B) of CRC patients according to MT1DP expression levels. Difference between high-level and low-level groups was calculated by the log-rank test.

Results

MT1DP expression was downregulated in patients with CRC

To investigate whether MT1DP expression was altered in CRC tissues, we detected its expression level by qRT-PCR in 78 paired tumor tissues and adjacent normal tissues. As showed in **Figure 1A**, **1B**, MT1DP expression was obvious decreased in tumor tissues, as compared with the adjacent normal tissues, P<0.001. MT1DP expression was downregulated in 55 of 78 (70.5%) CRC patients, approximately 1.52-folds lower than that in adjacent normal tissues.

Diagnostic value of downregulated MT1DP for CRC

To explore whether MT1DP expression can serve as a biomarker to differentiate CRC from normal tissues, a receiver operating characteristic (ROC) curve was then constructed. We found that the area under curve (AUC) of the ROC was 0.714; 95% confidence interval (CI) was 0.636-0.783, the sensitivity was 88.46% (95% CI: 79.2-94.6) and the specificity was 51.28% (95% CI: 39.7-62.8), Youden index (J=0.3974) was maximal, P<0.001, indicating that downregulation of MT1DP might have a potential diagnostic value for CRC (**Figure 2**).

Correlation between MT1DP expression and clinical characteristics of CRC patients

For better understanding of the clinical relevance of MT1DP expression in CRC, correlation between MT1DP expression and clinicopathological characteristics were evaluated. The expression levels of MT1DP were classified as high or low on the basis of the median value, 78 patients were subsequently divided into MT1DP-low group (n=39) and MT1DP-high group (n=39). The results showed that low level of MT1DP expression in CRC was significantly correlated with TNM stage (P=0.020) and distant metastasis (P=0.005). In contrast, there was no association between MT1DP expression and other clinical parameters, such as age (P=0.365), gender (P=0.610), tumor size (P=0.103), tumor location (P=0.640) and tumor differentiation (P= 0.147, **Table 1**). Our data indicate that downregulation of MT1DP can help us predict the tumor stage and judge the progression of CRC.

Association of MT1DP expression with prognosis in CRC patients

To investigate the prognostic value of MT1DP expression in patients with CRC, Kaplan-Meier survival analysis was performed according to the follow-up data. Survival analyses demonstrated significant differences in overall survival (OS) and disease-free survival (DFS) of patients who were divided into two groups based on their MT1DP expression levels. Specifically, CRC patients with low MT1DP expression had poorer OS and DFS rates than those with high MT1DP expression (log-rank test, P=0.002 and 0.006, respectively, **Figure 3A**, **3B**).

In addition, Cox proportional hazards analyses were applied to further evaluate the prognostic

Table 2. Univariate and multivariate regression analyses of clinicopathological parameters associated with prognosis of CRC patients

Variables	Subset	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Overall survival					
Age	≤61 vs. >61	1.355 (0.818-2.244)	0.239	-	-
Gender	Male vs. Female	1.437 (0.861-2.398)	0.165	-	-
Tumor size (cm)	≤4 vs. >4	2.314 (1.428-3.750)	0.001	1.524 (0.921-2.521)	0.101
Tumor location	Colon *vs.* Rectum	1.154 (0.686-1.942)	0.589	-	-
Tumor differentiation	Well + moderately vs. Poorly	1.946 (1.177-3.217)	0.010	1.358 (0.813-2.271)	0.243
TNM stage	I-II vs. III-IV	2.570 (1.570-4.207)	<0.001	2.269 (1.385-3.719)	0.001
Distant metastasis	Absence vs. Presence	3.271 (1.954-5.477)	<0.001	2.891 (1.677-4.985)	<0.001
MT1DP expression	Low vs. High	2.116 (1.294-3.460)	0.003	2.029 (1.221-3.371)	0.008
Disease-free survival					
Age	≤61 vs. >61	1.297 (0.747-2.083)	0.372	-	-
Gender	Male vs. Female	1.326 (0.795-2.219)	0.257	-	-
Tumor size (cm)	≤4 vs. >4	1.935 (1.154-3.201)	0.013	1.488 (0.897-2.445)	0.135
Tumor location	Colon vs. Rectum	1.116 (0.610-1.839)	0.625	-	-
Tumor differentiation	Well + moderately vs. Poorly	1.859 (1.056-3.113)	0.036	1.383 (0.835-2.302)	0.210
TNM stage	I-II vs. III-IV	3.015 (1.836-5.261)	<0.001	2.669 (1.608-4.483)	<0.001
Distant metastasis	Absence vs. Presence	3.925 (2.206-6.782)	<0.001	3.348 (2.067-5.829)	<0.001
MT1DP expression	Low vs. High	2.074 (1.165-3.392)	0.007	1.917 (1.134-3.145)	0.019

HR, hazard ratio; CI, confidence interval.

value of MT1DP expression in CRC. Univariate survival analyses revealed that tumor size, tumor differentiation, TNM stage, distant metastasis and MT1DP expression were significantly associated with OS and DFS of CRC patients (all P<0.05). In contrast, the other clinicopathological parameters, such as age, gender and tumor location were not statistically significant prognosis factors (all P>0.05, **Table 2**). Subsequently, multivariate Cox proportional hazards analyses showed that MT1DP expression, as well as TNM stage and distant metastasis, still maintained their significance as strongly associated with OS and DFS of CRC patients (all P<0.05, **Table 2**), suggesting that MT1DP could be an independent prognostic factor for CRC.

Discussion

Although several kinds of treatments have been developed recently for CRC, poor prognosis continues to be in patients with advanced CRC [19-21]. Thus, clarifying the underlying mechanisms of CRC progression, as well as finding new molecular targets for its diagnosis, prognosis and treatment, will contribute to improve the clinical strategy and outcome of this deadly disease.

Some lncRNAs, acting as oncogenes and tumor suppressors, have potential biological and clinical relevance in CRC, and many of them may potentially be more sensitive and specific for diagnosis and prognosis than the current mRNA or protein biomarkers [22-24].

In the current study, we offered a novel candidate biomarker, namely MT1DP, for diagnosis, prognosis and therapy of CRC. We prospectively investigated MT1DP expression by qRT-PCR in 78 paired tumor samples and adjacent non-tumor tissues, as well as the association of MT1DP with clinicopathological characteristics and prognosis in CRC patients. These qRT-PCR results suggest that MT1DP was frequently downregulated in 55 of 78 (70.5%) CRC patients, approximately 1.52-folds lower than that in adjacent normal tissues. There was no significant downregulated in 29.5% (23 of 78) of CRC patients. A possible explanation for this is that these 23 patients were in the early stages of CRC and they had no distant metastasis. ROC curve showed that the expression level of MT1DP had a potential diagnostic value in CRC. Moreover, it was also found that low expression of MT1DP in CRC was closely associated with TNM stage and distant metastasis, suggesting that MT1DP expression could help us predict

the tumor stage and judge the progression of CRC. Recent researches in liver cancers have shown that MT1DP could inhibit cell proliferation and transformative phenotype of liver cancer cells. Overexpression of MT1DP resulted in reduced cell colony formation in soft agar, but increased apoptosis in liver cancer cells, whereas knockdown of this lncRNA had the opposite effect, indicating that MT1DP acts as a tumor suppressor. Furthermore, MT1DP was revealed as a negative regulator of Alfa-fetoprotein (AFP), a classic liver cancer tumor marker [18]. Our study revealed that MT1DP might play a tumor suppressor role in CRC carcinogenesis.

On the other hand, our Kaplan-Meier analyses also demonstrated that MT1DP expression was significantly associated with OS and DFS of CRC patients. Besides, Univariate and multivariate Cox proportional hazards analyses further revealed that MT1DP could be independent prognostic factors for OS and DFS in CRC patients. Thus, MT1DP might serve to identify high-risk CRC patients who had higher risk of death and might be a useful candidate for receiving more aggressive and more effective treatment. It has been reported that MT1DP acts as a tumor suppressor in liver cancer through a fine-tune mechanism [18]. However, the precise molecular mechanisms underlying the low expression of MT1DP in CRC and its potential functions are still incompletely known. Therefore, further studies should be applied to elucidate the detailed mechanisms of both the causes and effects of altered expression of MT1DP which involved in CRC. Additionally, owing to lncRNAs exert biological functions mainly through regulating expression of some important cancer related genes, and they may regulate genes expression through directly binding proteins [25, 26], microRNAs [27, 28] or mRNAs [29, 30], and altering the activities as well. As a result, potential proteins, microRNAs or mRNAs whose expressions and activities are regulated by MT1DP should also be further evaluated in CRC, and more in-depth recognition of the fine mechanisms will enable us to deeply understand the potential role of MT1DP during CRC carcinogenesis and progression. By now, KRAS, as colorectal cancer mutations, has been comparatively thoroughly researched. It is a pivotal issue for guiding targeted drug therapy. While our present study mainly involves the early diagnoses and prognostic analysis on the CRC patients who haven't received preoperative treatment, such as radiotherapy or chemotherapy. We will certainly carry out further research to determine the relationship between MT1DP level and drug resistance in patients with advanced metastatic colorectal cancer.

Collectively, the results indicate that MT1DP expression is significantly downregulated and associated with poor progression of the majority of human CRC. And MT1DP expression is also identified as an independent prognostic marker for CRC patients. In addition, the study provides evidence that the MT1DP may serve as a diagnostic and prognostic marker in clinical practice. Finally, it may contribute to a better understanding of the pathogenesis of CRC.

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Disclosure of conflict of interest

None.

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