Clinical significance of mitochondrial transcription factor A expression in patients with colorectal cancer

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Abstract. Mitochondrial transcription factor A (mtTFA) is necessary for both the transcription and maintenance of mitochondrial DNA (mtDNA). The present study investigated the relationship between clinicopathological factors, prognosis and the immunohistochemical expression of mtTFA in the tumors of patients diagnosed with primary colorectal cancer (CRC). Surgical specimens from 105 colorectal patients were immunohistochemically stained using a polyclonal anti-mtTFA antibody. The relationships among the mtTFA expression, clinicopathological factors and prognosis were evaluated. A total of 47 (44.8%) of the 105 patients with CRC were determined to have positive mtTFA expression. The positive expression of mtTFA significantly correlated with lymph node metastasis, distant metastasis and advanced TNM staging. On the other hand, negative mtTFA expression showed a tendency to correlate with high Ki-67 index. The survival of patients with positive mtTFA expression was significantly worse than that of patients with negative mtTFA expression. The positive mtTFA expression appears to be a useful marker for tumor progression and poor prognosis in patients with CRC.

Introduction

Colorectal cancer (CRC) is one of the most deadly types of cancer in the world. In 2008, CRC was estimated to be the most frequent cause of cancer-related death in females and the third most frequent cause of cancer-related deaths in males in Japan (1). Although there have been recent advances in chemotherapy, the overall survival of metastatic CRC is still low, and the prognosis still remains relatively poor. Therefore, the identification of prognostic factors that are characteristic of CRC patients at high risk for recurrence and that can predict chemosensitivity are needed.

Mitochondrial transcription factor A (mtTFA) is a member of the high mobility group (HMG)-box protein family (2) and stimulates the transcription of mitochondrial genes by binding to the mitochondrial displacement loop (D-loop) region (3,4). mtTFA is involved in not only the transcription, but also in the replication of mitochondrial DNA (mtDNA), the recognition of mtDNA damage, as well as in the stabilization and, indirectly, in the repair of mtDNA (5).

Mutations of the D-loop region in cancer cells are very common (6). This region regulates the transcription and replication of mtDNA (4) and instability in the mtDNA region may be involved in carcinogenesis (7,8). Several reports have identified mutations of mtDNA in various types of cancer cells, including those of the breast, esophagus, stomach, colorectum, prostate, pancreas and liver (6,8-15). Although mtDNA mutations occur at a high frequency in human tumors, it has been unclear whether these mutations alter tumor cell behavior.

Several studies have also shown that the expression of mtTFA increases the amount of mtDNA in human cells (16,17). The mtDNA copy number is suggested to be increased by a feedback mechanism that compensates for defects in the respiratory system (18). Maintenance of mtDNA copy number and expression are considered to be essential for preservation of mitochondrial function and cell growth via the regulation of mtTFA (16,19).

A few clinical studies have examined the status of the mtTFA expression in the cancer tissues (19,20). A 2-fold increase in mtTFA content was shown in endometrioid adenocarcinoma samples compared to the proliferative control endometrial samples (19). The mtTFA expression in endometrioid adenocarcinomas was significantly associated with the surgical stage, myometrial invasion, lymphovascular space invasion, cervical invasion, and lymph node metastasis (20). Moreover, the 10-year overall survival rate of the patients with mtTFA-positive endometrioid adenocarcinoma was

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significantly worse than that of patients with mtTFA-negative endometrioid adenocarcinoma by a univariate, but not a multivariate survival analysis (20).

The significance of mtTFA expression in CRC has not been evaluated in detail. Therefore, the present study investigated the relationship between clinicopathological factors, prognosis and the immunohistochemical expression of mtTFA in tumors of patients diagnosed with primary CRC.

Patients and methods

Patients. A total of 105 patients with primary colorectal cancer who underwent surgery at the Department of Surgery 1, University Hospital of Occupational and Environmental Health, Japan, from 1997 to 2000 were recruited for this study. The clinical data of these patients is summarized in Table I. Informed consent was obtained from all patients prior to the study. No patients had received chemotherapy or radiotherapy before surgery. The clinicopathological findings were determined according to UICC tumor-node-metastasis (TNM) classifications (21).

Table I. Characteristics of all patients.

Characteristics	
No. of patients	105
Gender (Male/Female)	59/46
Age (years) (mean ± SD)	65.3±12.1
Site (colon/rectum)	51/54
Tumor size (cm) (mean ± SD)	5.3±2.1
Histological type	
Differentiated	99
Undifferentiated	6
Depth of invasion	
T1/T2/T3/T4	1/19/57/28
Lymph node metastasis (-/+)	50/55
Distant metastasis (-/+)	82/23
TNM stage	
I/II/III/IV	7/31/34/23

Antibody against mtTFA. Regarding the immunohistochemical staining of mtTFA, the anti-mtTFA polyclonal antibody was a kind gift from Dr K. Kohno (Department of Molecular Biology, University of Occupational and Environmental Health, Japan). This antibody was generated by multiple immunizations of a New Zealand white rabbit using synthetic peptides, as previously described (22). This antibody has been published in a previous study (20).

Immunohistochemical staining. Immunohistochemical staining of mtTFA was performed in formalin-fixed 2 μm sections of tissues embedded in paraffin. The 2 μm sections were deparaffinized in xylene and then rehydrated. Endogeneous peroxidase was blocked with 0.3% hydrogen peroxidase in methanol for 10 min. After washing with phosphate-buffered saline (PBS), the sections were preincubated with 10% rabbit serum albumin in PBS for 10 min at room temperature. The slides were then incubated with the mtTFA antibody for 2 h at room temperature (dilution 1:400). Antibody binding was visualized using the EnVision + Dual link system with diaminobenzidine as the chromogen (Dako Cytomation, Kyoto, Japan). The slides were counterstained with methyl green and mounted.

Staining evaluation of mtTFA. Immunostained slides were analyzed independently by 2 authors. Differences were resolved by simultaneous viewing. The expression of mtTFA in the CRC samples was evaluated according to the methods described by Toki *et al* (20). The cases were judged as (-) or (±) when no immunostaining was identified or when only minimal occasional staining (<5%) was present, respectively, and focally positive (+) when staining of at least 5% but less than 50% of the tumor cells, and diffusely positive (++) when at least 50% of the tumor cells showed immunoreactivitiy. Finally, the cases were classified into two groups based on negative (- or ±) or positive (+ or ++) staining.

Immunohistochemical staining of Ki-67 and determination of the Ki-67 index. Immunohistochemical staining of Ki-67 was performed on formalin-fixed 2 μm sections of tissues embedded in paraffin. The 2 μm sections were deparaffinized in xylene and then rehydrated. Endogeneous peroxidase was blocked with 0.3% hydrogen peroxidase in methanol for 10 min. The slides were subjected to a microwave treatment in 10 mM citrate buffer (pH 6.0) for 10 min. After washing with PBS, the sections were preincubated with 10% rabbit serum albumin in PBS for 10 min at room temperature. Immunohistochemical staining for Ki-67 antigen was performed using a monoclonal mouse anti-human Ki-67 antibody Clone MIB-1 (Dako Japan). The slides were then incubated with Ki-67 antibody for 1 h at room temperature (dilution 1:50). After washing with PBS, the slides were treated with an anti-mouse immunoglobulin for 20 min and were then incubated with streptavidin-biotinylated horseradish peroxidase complex (LSAB kit/HRP) (Nichirei, Tokyo, Japan) for 10 min. The slides were incubated in PBS containing diaminobenzidine and 1% hydrogen peroxidase for 10 min, counterstained with Mayer's hematoxylin, and mounted (23).

The proliferative activity of tumor cells was assessed by the Ki-67 index. The Ki-67 index was determined as the percentage of tumor cells showing positive staining of nuclei relative to the total number of tumor cells counted (23).

Clinicopathological assessment. The tumors were staged by two pathologists who had no prior knowledge of the results of the assays, according to the 7th edition of the UICC tumor-node-metastasis (TNM) classifications (21). Clinicopathological factors such as age, gender, tumor size, histological type, depth of invasion, lymph node metastasis, distant metastasis and staging were analyzed for an association with mtTFA expression.

Statistical analysis. The relationships between the parameters were also assessed statistically using the χ^2 test with the StatView-J software package (version 5.0, SAS Institute, Inc., Cary, NC). The Kaplan-Meier method was applied to determine

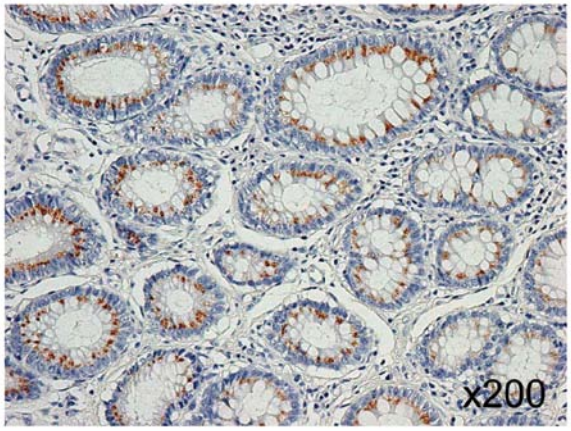

Figure 1. Immunohistochemical staining of mtTFA in normal colonic mucosa.

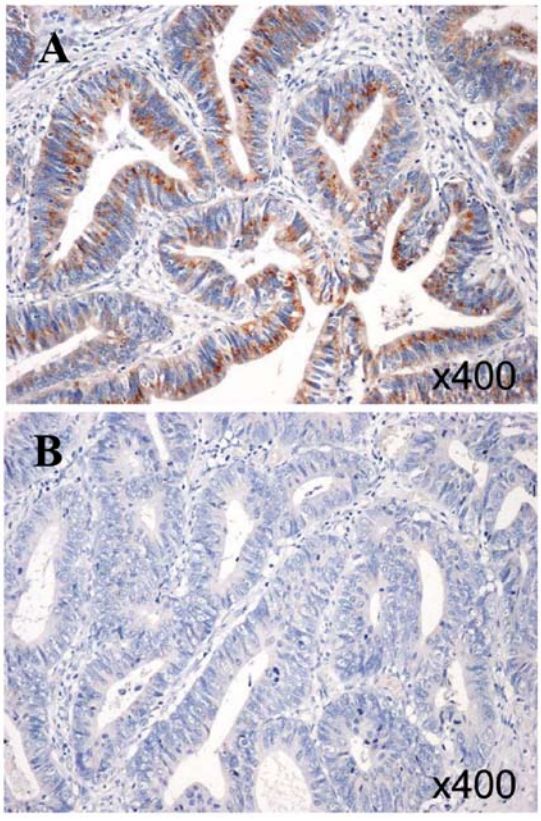

Figure 2. Immunohistochemical staining of mtTFA in colorectal cancer specimens. (A) Positive expression of mtTFA and (B) negative expression of mtTFA.

survival and statistical significance was calculated using the log-rank test. Univariate and multivariate analyses of survival were conducted using the Cox proportional hazards model. Statistical significance was established at the P≤0.05 level.

Results

Table I shows the profiles of the 105 patients diagnosed with primary colorectal cancer recruited for the present study. Immunohistochemical staining of endogenous mtTFA was performed on 105 colorectal cancer specimens. The expression of mtTFA was observed in the cytoplasma of the normal colonic mucosa (Fig. 1). Positive signals for mtTFA were also observed in the cytoplasm of cancer cells (Fig. 2A). The mtTFA expression was graded (-) in 25.7%, (±) in 29.5%, (+) in 19.0% and (++) in 25.7% of all cases, respectively. A total of 47 (44.8%) of the 105 patients with colorectal carcinoma were determined to be positive for mtTFA expression, and 58 (55.2%) were negative for mtTFA staining.

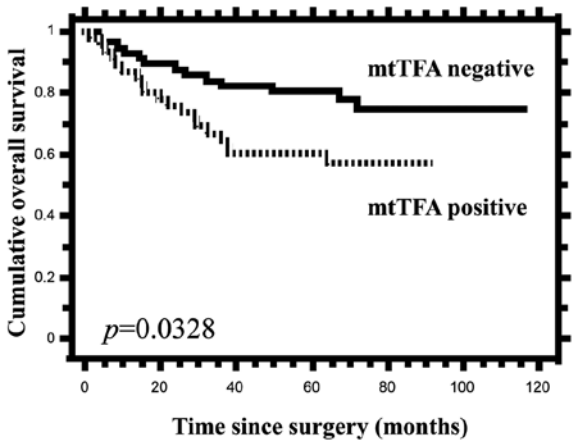

Figure 3. The prognostic significance of mtTFA expression was analyzed using the Kaplan-Meier method in the patients with colorectal cancer (n=105). The patients were divided into negative and positive groups according to the previous classification (20). The patients in the mtTFA-negative group showed a significantly better prognosis in comparison to those in the mtTFA-positive group (P=0.0328)

The mean Ki-67 index was 45.5% (8.8-91.2%). The patients were divided into high and low Ki-67 index groups assessed with the mean value of 45.5% as the cut-off value. The number of patients with high Ki-67 index was 48 and that with low Ki-67 index was 57.

Based on the evaluation of the mtTFA immnunostaining, the positive expression of mtTFA significantly correlated with lymph node metastasis, distant metastasis and TNM staging. On the other hand, the expression of mtTFA did not correlated with age, gender, site of tumor, tumor size, depth of invasion, histopathological type and Ki-67 index (Table II). However, the low expression of mtTFA tended to correlate with high Ki-67 index (P=0.0772).

Kaplan-Meier analyses for overall survival based on mtTFA expression were also performed (Fig. 3). The median follow-up time was 71.0 months (range 1.4-115.9 months). The survival rate of the patients negative for mtTFA expression was significantly higher than that of patients with positive mtTFA expression (5-year survival rate, 80.5% vs. 60.4%, P=0.0328) (Fig. 3).

A univariate analysis indicated that the TNM stage, lymph node metastasis, distant metastasis, depth of invasion, histological type and mtTFA expression were significant prognostic factors (Table III). However, mtTFA expression was not a significant prognostic factor by the multivariate analysis (Table IV).

Discussion

Our study indicated that mtTFA expression was immunohistochemically detected in 47 (44.8%) of 105 patients with CRC. On the other hand, a previous study indicated that mtTFA

Table II. Association between the expression of mtTFA and clinicopathological factors of all patients with colorectal cancer.

Characteristics	mtTFA expression		P-value
	Negative	Positive	
Age (years)			
Young (≤65)	25	21	
Old (>65)	33	26	0.8713
Gender			
Male	36	23	
Female	22	24	0.1774
Site			
Colon	26	25	
Rectum	32	22	0.3938
Tumor size (cm)			
Small (≤5.3)	36	24	
Big (>5.3)	22	23	0.2572
Histological type			
Differentiated	55	44	
Undifferentiated	3	3	0.7904
Depth of invasion (T)			
≤T3	46	31	
T4	12	16	0.1239
Lymph node metastasis (N)			
(-)	36	14	
(+)	22	33	0.0010
Distant metastasis (M)			
(-)	50	32	
(+)	8	15	0.0256
TNM stage			
I, II,	35	13	
III, IV	23	34	0.0008
Ki-67 index (%)			
Low (≤45.5)	27	30	
High (>45.5)	31	17	0.0772

The patients were divided into positive and negative groups of mtTFA expression. The patients were divided into old and young groups of age assessed with the mean values of 65.3 years as the cut-off value. The patients were divided into big and small groups assessed with the mean value of 5.3 cm in diameter as the cut-off value. The patients were divided into high and low Ki-67 index groups assessed with the mean value of 45.5% as the cut-off value.

Table III. Univariate analysis for clinicopathological factors and the expression of mtTFA in patients with colorectal cancer.

Factor	P-value of univariate analysis
TNM stage (I, II vs. III, IV)	<0.0001
Lymph node metastasis (- vs. +)	<0.0001
Distant metastasis (- vs. +)	<0.0001
T (T1, T2, T3 vs. T4)	0.0003
Histological type (differentiated vs. undifferentiated)	0.0029
mtTFA expression (negative vs. positive)	0.0328
Gender (male vs. female)	0.0936
Site (colon vs. rectum)	0.1642
Size (big vs. small)	0.3086
Age (old vs. young)	0.5735
Ki-67 index (high vs. low)	0.7247

The patients were divided into positive and negative groups of mtTFA expression. The patients were divided into old and young groups of age assessed with the mean values of 65.3 years as the cut-off value. The patient tumors were divided into big and small assessed with the mean value of 5.3 cm in diameter as the cut-off value. The patients were divided into high and low Ki-67 index groups assessed with the mean value of 45.5% as the cut-off value.

expression was immunohistochemically detected in 34.2% of endometrial carcinomas (20). This previous study used the same antibody that we used in the present study (20). Therefore, it appears that there is a difference in the mtTFA expression rate between CRC and endometrial cancer. This difference may be due to the organ specificity of protein expression. Our present study also showed that positive mtTFA expression significantly correlated with lymph node metastasis, distant metastasis and advanced TNM stage in the patients with CRC. The study in endometrial cancer indicated that positive mtTFA expression in endometrioid adenocarcinomas was significantly associated with an advanced surgical stage, myometrial invasion, lymphovascular space invasion, cervical invasion, and lymph node metastasis (20). These data indicate that the mtTFA expression seems to be associated with tumor invasion and metastasis.

The present study indicated that the negative mtTFA expression showed a tendency to correlate with high Ki-67 index (P=0.0772). A previous study indicated that the knockdown of mtTFA expression in a cancer cell line induces p21-dependent G1 cell cycle arrest (24). As the Ki-67 is expressed in all phases of the cell cycle except G0, cancer cells in G1 cell cycle may be accumulated in the patients with negative mtTFA expression. The recent study also indicated that the overexpression of mtTFA enhances the growth of cancer cell lines (24). Therefore, the expression of mtTFA may be associated with cancer cell growth.

There appears to be favorable prognostic significance of negative mtTFA expression in CRC tumors as identified by univariate analysis. However, the significance was not seen by multivariate survival analysis. The study in endometrial cancer patients indicated that the 10-year overall survival rate of the patients with mtTFA-negative endometrioid adenocarcinoma was also significantly better than that of patients with mtTFA-positive endometrioid adenocarcinoma by univariate, but not multivariate survival analysis (20). These data indicate that the

Table IV. Multivariate analysis for clinicopathological factors and the expression of mtTFA in patients with colorectal cancer.

Factor	P-value	Hazard ratio	95% CI
Distant metastasis (- vs. +)	<0.0001	0.142	0.060-0.337
Depth of invasion (T1, T2, T3 vs. T4)	0.0178	0.390	0.179-0.849
TNM stage (I, II vs. III, IV)	0.0348	0.185	0.039-0.886
Histological type (differentiated vs. undifferentiated)	0.3588	0.609	0.211-1.758
mtTFA expression (negative vs. positive)	0.7273	0.872	0.404-1.881

The patients were divided into positive and negative groups of mtTFA expression.

negative mtTFA expression correlates with favorable prognosis by affecting tumor progression.

Several reports have indicated that mtTFA is necessary for both the transcription and maintenance of mtDNA (16,17,25). When the expression of endogenous mtTFA was repressed by RNA interference in HeLa cells, the amount of mtTFA and mtDNA were both decreased (17). On the other hand, overexpression of human mtTFA in mice increases the amount of mtDNA and dramatically ameliorates the cardiac dysfunction caused by myocardial infarction (25). Another study indicated that the constitutive overexpression of human mtTFA in transgenic mice led to elevated total mtTFA levels and correlated well with an increased mtDNA copy number (16). However, it is still unclear whether mtTFA directly affects the amount of mtDNA in cancer cells and what impact such mutations have on the expression and stability of mtDNA.

Changes in mtDNA content have been reported in various cancer types. A low tumor mtDNA content has been found in hepatocellular carcinoma (26), breast cancer (27) and renal cell carcinoma (28). On the other hand, some studies have shown that tumor tissues from patients with thyroid cancer (27), lung cancer (28), malignant head and neck lesions (29) and CRC (30) have an elevated mtDNA content. In esophageal cancer, the mtDNA content has been found to be increased in some tumors and decreased in others (10). No significant correlation between somatic mtDNA mutations and mtDNA content, or between the mtDNA content and metastatic status in esophageal cancer have been observed(10). These studies indicate that there is a discrepancy or that there are variations in the mtDNA status in particular cancers. Since the mtDNA status changes depending on the cellular environment, it may be difficult to evaluate the significance of the mtDNA status.

Some studies have examined the regulatory mechanism responsible for the expression of mtTFA (31-33). An *in vivo* genomic footprinting study suggested that nuclear respiratory factor 2 (NRF-2) and Sp1 are probably involved in the regulation of the mtTFA gene in rat hepatoma (31). The *in vitro* methylation of the NRF-1 binding site suppressed the promoter activity of mtTFA (32). Overexpression of the PGC-1 related coactivator (PRC) in oncocytic tumors induced mitochondrial biogenesis through NRF-1, thus resulting in an increase in mtTFA and mtDNA transcript levels (33). Another study indicated that there is redox regulation of NRF-1 phosphorylation and nuclear translocation by phosphatidylinositol 3,4,5-triphosphate kinase/Akt signaling, that controls mtTFA induction by an antioxidant prosurvival network (34). The regulatory mechanism for mtTFA is not fully understood. However, the regulation of the mtTFA expression may be important because CRC patients with negative mtTFA immunostaining have a favorable prognosis. More extensive studies about the regulation of mtTFA are needed. Additionally, mtTFA preferentially recognized cisplatin-damaged DNA via a physical interaction with p53 and was upregulated by treatment with cisplatin and 5-FU (22). On the basis of this study, the mtTFA expression may affect the chemosensitivity of recurrent or metastatic CRC patients.

In conclusion, we have demonstrated that positive mtTFA immunostaining of tumor specimens may be a useful marker for the progression of the tumors and for a poor prognosis of patients with CRC.

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