

MECP2 expression in gastric cancer and its correlation with clinical pathological parameters

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Abstract

This study is to investigate the expression of methyl CpG binding protein 2 (MECP2) in gastric cancer (GC) and its clinical significance.

Expression of MECP2 was analyzed in 69 cases of GC tissues and 12 paracancerous tissues, either by qRT-PCR at the mRNA level or by Western blot and immunohistochemistry at the protein level. The correlation of MECP2 expression with clinicopathological parameters was analyzed in the 69 GC patients, and validated in data from the TCGA database. The effect of MECP2 expression on survival was also investigated.

MECP2 was significantly increased at both mRNA and protein levels in GC compared with paracancerous tissues. MECP2 positive expression was significantly correlated with the TNM stages, histological types, and lymph node metastasis status, but was not correlated with sex or age. Significantly shorter overall survival and disease-free survival was observed in MECP2 positive GC cases compared with the MECP2 negative cases. Univariate and multivariate analyses showed that gender, histological type, lymph node metastasis, and MECP2 expression were independent prognostic factors of GC.

The dysregulated expression of MECP2 in GC and its correlation to clinicopathological parameters indicate that MECP2 may regulate the development of GC.

Abbreviations: GC = gastric cancer, GSTP1 = glutathione S-transferase P, Gtl2/Dlk1 = gene-trap locus 2/Delta like noncanonical notch ligand 1, HDACs = histone deacetylase, MECP2 = methyl CpG binding protein 2, MEG3 = maternally expressed 3, qRT-PCR = quantitative real-time PCR, Sin3A = Sin3 transcription regulator family member A, TSSC3 = tumor suppressing subtransferable candidate 3.

Keywords: clinical pathology, gastric cancer, MECP2

1. Introduction

Gastric cancer (GC), which has high incidence in China, is characterized by high morbidity, high mortality, and low survival rate.^[1] Due to inadequate early screening methods for GC, most patients are in late stages when diagnosed.^[2] Although the clinical treatment of GC has been developed in the past few years, the 5-year survival rate of patients is not significantly improved.^[3] Therefore, GC is one of the most difficult-to-treat malignancies that threaten human health.^[1]

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Investigation on the molecular mechanisms underlying GC development will provide a strong theoretical basis for its diagnosis and prognosis.

Methyl CpG-binding protein 2 (MECP2), located on the long arm region2, band 8 of X chromosome (Xq28),^[4] is mutated or dysregulated in many nervous system diseases.^[5] As a methylation binding protein, MECP2 plays important roles in epigenetics.^[6] After gene promoter is methylated, MECP2 binds to the methylated region and forms complex with Sin3 transcription regulator family member A (Sin3A) and histone deacetylase (HDACs), inhibiting gene transcription.^[7] MECP2 is found to be related with many kinds of cancers including breast cancer and hepatic cancer.^[8] For example, maternally expressed 3 (MEG3), a homologous of mouse Gene-trap locus 2/Delta like noncanonical notch ligand 1 (Gtl2/Dlk1) gene imprinting molecule that inhibits GC cell proliferation, is downregulated by MECP2.^[9] MECP2 could also promote the proliferation of hepatic cancer cells by suppressing glutathione S-transferase P (GSTP1) expression.^[10] In osteosarcoma cells, MECP2 binds to the promoter region of the tumor suppressing subtransferable candidate 3 (TSSC3) gene and leads to its silencing, and knockdown of MECP2 expression results in increased of apoptosis as well as inhibition of proliferation, migration, and invasion.^[11] In colorectal cancer, MECP2 is important for the proliferation of cancer cells, and MECP2 also plays roles in the resistance to chemotherapeutic agents. However, the role of MECP2 in GC was rarely reported, and its biological functions in GC is still not clear. The development of GC is closely correlated with gene methylation and high methylation levels are found in the promoter of multiple tumor suppressor genes, leading to the occurrence of cancer.^[12]

In this study, the expression levels of MECP2 in GC and its correlation with clinicopathological factors were analyzed. Our results will provide important basis for analyzing the biological functions and clinical significance of MECP2 in GC.

2. Materials and methods

2.1. Patients

A total of 69 cases of GC patients who were diagnosed between Mar, 2011, and Sep, 2011, at the Hospital affiliated to Yan'an University were enrolled. There were 47 male and 22 female patients. The average age of patients was 57 (ranging from 20 to 82). The GC cases included 3 cases of well-differentiated GC, 16 cases of middle-differentiated GC, and 50 cases of poorly differentiated GC. The TNM stages were as follows: Stage I, 15 cases; Stage II, 18 cases; Stage III, 3 cases, and Stage IV, 33 cases. Thirty-two cases had lymph node metastasis and 37 cases were without lymph node metastasis. The tumor tissues were collected from 69 GC patients and paracancerous tissues were collected from 12 matched GC patients. All subjects were first diagnosed and confirmed by pathological diagnosis, and without radiotherapy and chemotherapy. Prior written and informed consent were obtained from every patient and the study was approved by the ethics review board of Yan'an University.

2.2. Immunohistochemistry

Immunohistochemical analysis was performed to detect MECP2 expression. Briefly, GC and paracancerous tissues were embedded in paraffin and cut into 5- μ m sections. After rinsing with xylene and hydration with gradient alcohol, antigen retrieval was performed in microwave. The sections were then treated with 30 mL/L H₂O₂ for 15 minutes to inactivate endogenous peroxidase. After washing 3 times with PBS, the primary rabbit antihuman MECP2 antibody (ab137621, Abcam, Cambridge, UK) diluted at 1:200 was added and incubated overnight at 4°C. Following incubation, the goat anti-rabbit secondary antibody conjugated to horseradish peroxidase (Beijing Zhongshan Gold Bridge Biology Company, China) was added and incubated at 37°C for 20 minutes. The DAB reagent was used for color detection. Hematoxylin was used to stain nucleus. PBS was used as a negative control instead of primary antibody. Ten randomly selected fields of view (magnification, \times 400) from each tissue section were observed and 100 cells were counted to analyze their average positive rates. Cells without positive staining or with a positive rate less than 10% were defined as MECP2 negative expression (-). Cells with a positive rate more than or equal to 10% were defined as MECP2 positive expression (+).

2.3. RNA extraction and quantitative real-time PCR (qRT-PCR)

Total RNAs were isolated using the TRIzol isolation reagent (Invitrogen Co., Carlsbad, California) from the tissues according to the manufacturer's instructions. Total RNAs were reverse transcribed into cDNA. The SYBR Premix Ex TaqTMII (TaKaRa Biotechnology [Dalian] Co., Ltd., Dalian, China) was used for qRT-PCR. The reaction mixture was incubated for 1 cycle at 95°C for 1 minutes, followed by 40 cycles at 95°C for 10 seconds and 60°C for 40 seconds. Primers used were as follows: MECP2 forward 5'-GCCGAGAGCTATGGACAGCA-3'; MECP2 reverse 5'-CCAACCTCAGACAGGTTTCCAG-3'; β -actin forward 5'-CCAACCGCGAGAAGATGA-3'; β -actin

reverse 5'-CCAGAGGCGTACAGGGATA-3'. The relative expression levels were evaluated by the 2^{- $\Delta\Delta$ Ct} method. The expression of β -actin was used as the internal control for MECP2 expression.

2.4. Western blotting analysis

Total protein was extracted by the RIPA lysis buffer from GC tissues and paracancerous tissues according to the manufacture's instruction. Samples containing 20 μ g proteins were separated on SDS-PAGE and transferred to PVDF membranes. Membranes were incubated overnight at 4°C with the rabbit anti-human anti-MECP2 antibody diluted at 1: 100 (ab137621, Abcam, Cambridge, UK) or mouse anti-human anti- β -actin antibody diluted at 1:3000 (SC-7963, Santa Cruz Biotechnology, CA). The goat anti-rabbit secondary antibody conjugated to horseradish peroxidase (Beijing Zhongshan Gold Bridge Biology Company, China) was added to incubate for 1.5 hours at room temperature. The membranes were visualized using the enhanced chemiluminescence. The level of β -actin was used as an internal control.

2.5. Statistical analysis

Data analysis was carried out using the SPSS software 13.0 (IBM Corp, Chicago, IL) and expressed as mean \pm SD. Differences between groups were analyzed using the independent-samples *t* test. Differences among groups were analyzed using the Fisher exact test or chi-square test. Survival of patients was analyzed by the Kaplan–Meier analysis and the difference in survival was analyzed by the log-rank test. Univariate and multivariate analyses was used to analyze the independent factors for prognosis. Each experiment was repeated 3 times, and *P* < .05 was considered as significant.

3. Results

3.1. Expression of MECP2 in GC tissues

To investigate whether MECP2 expression was dysregulated in GC, its expression was analyzed in 21 GC tissues and 12 paracancerous tissues by qRT-PCR, Western blot, and immunohistochemistry. As shown in Fig. 1, the MECP2 mRNA level was

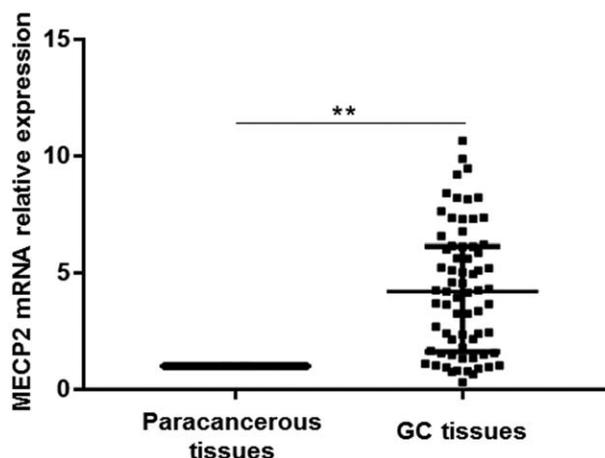


Figure 1. Expression of MECP2 mRNA. MECP2 mRNA expression was analyzed in GC tissues and 12 paracancerous tissues by qRT-PCR. ***P* < .01, independent-samples *t* test. GC = gastric cancer, MECP2 = methyl CpG binding protein 2, qRT-PCR = quantitative real-time PCR.

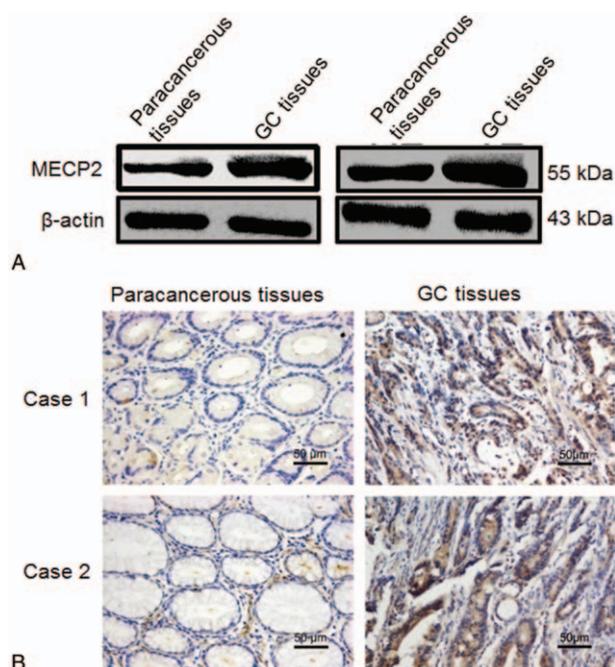


Figure 2. Expression of MECP2 protein. (A) MECP2 protein expression was analyzed in GC and paired paracancerous tissues by Western blot. Expression of β -actin was used as internal control. Representative images from 2 cases were shown. (B) MECP2 expression was analyzed in GC and paired paracancerous tissues by immunohistochemistry. Representative images from 2 cases were shown. MECP2 was stained as brown granules. Original magnification, $\times 400$. GC = gastric cancer, MECP2 = methyl CpG binding protein 2.

significantly increased in GC compared with paracancerous tissues ($P < .01$). Representative results of Western blot in 2 cases showed that the MECP2 protein was upregulated in GC tissues (Fig. 2A). Further, immunohistochemistry in 2 cases showed that the positive expression of MECP2 showed as brown granules, which was mainly observed in the nuclei of GC and paracancerous tissues and was rarely observed in cytoplasm. The MECP2 level was increased in GC tissues compared with that in paracancerous tissues (Fig. 2B), which is consistent with the result of Western blot. Therefore, MECP2 at both mRNA and protein levels are obviously elevated in GC tissues.

To validate the above results, data of MECP2 expression obtained from the TCGA database (<http://xena.ucsc.edu/>) was analyzed. It could be seen that MECP2 expression was increased with poorer differentiated GC types, and its expression was significantly correlated with histological type of GC ($P = .0004$, Fig. 3). These results indicate that MECP2 could potentially regulate GC cell differentiation and proliferation.

3.2. Correlation of MECP2 expression with clinicopathological parameters in GC

Next, we investigate the relationship between MECP2 expression levels and the clinicopathological parameters in the 69 GC patients. As shown in Table 1, we found that MECP2 positive expression as demonstrated by immunohistochemistry was positively correlated with TNM stages and lymph node metastasis status. Namely, the MECP2 positive rate was increased in patients with higher TNM stages, and with lymph node metastasis. In addition, the MECP2 expression was negatively correlated with histologi-

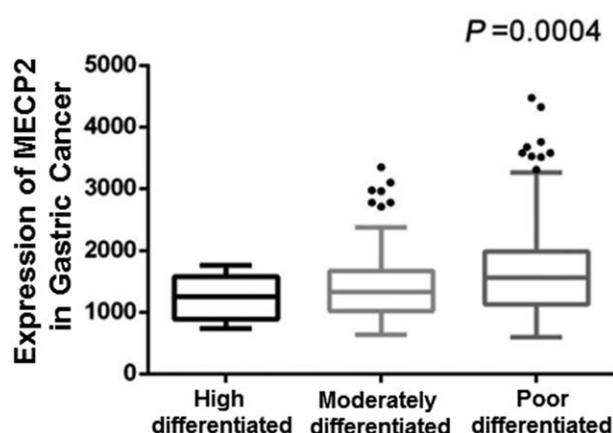


Figure 3. Correlation of MECP2 expression and histological type of GC. MECP2 expression data were retrieved from the TCGA database and the relative expression was shown with different histological types. High differentiated, $n = 12$; moderately differentiated, $n = 146$; poor differentiated, $n = 246$. Data were analyzed by the Fisher or chi-square test. GC = gastric cancer, MECP2 = methyl CpG binding protein 2.

cal type of GC ($P < .05$). However, no correlation was found between MECP2 expression and age or sex ($P > .05$).

3.3. Relationship between MECP2 expression and prognosis of GC patients

To assess the relationship between MECP2 expression and prognosis of GC patients, the Kaplan–Meier survival curve of the 69 GC patients was plotted. The 5-year overall survival rate of the 56 patients with positive MECP2 expression was only 28.6 (16/56), whereas the 5-year survival rate of the 13 MECP2 negative patients was 61.5 (8/13). As shown in Fig. 4A and B, the overall survival and disease-free survival between MECP2

Table 1
Correlation of MECP2 expression with clinicopathological parameters in gastric cancer.

	Total	MECP2 positive expression ($\geq 10\%$)	MECP2 negative expression ($< 10\%$)	*P
Age				
<50	18	12	6	.139
≥ 50	51	44	7	
Gender				
Male	47	36	11	.277
Female	22	20	2	
Histological type				
Well-differentiated	3	2	1	.021
Middle-differentiated	16	12	4	
Poorly-differentiated	50	48	2	
TNM stages				
I	15	10	5	.038
II	18	13	5	
III	3	2	1	
IV	33	31	2	
Lymph node metastasis				
Yes	32	31	1	.002
No	37	25	12	

MECP2 = methyl CpG binding protein 2.
* Fisher exact test or chi-square test.

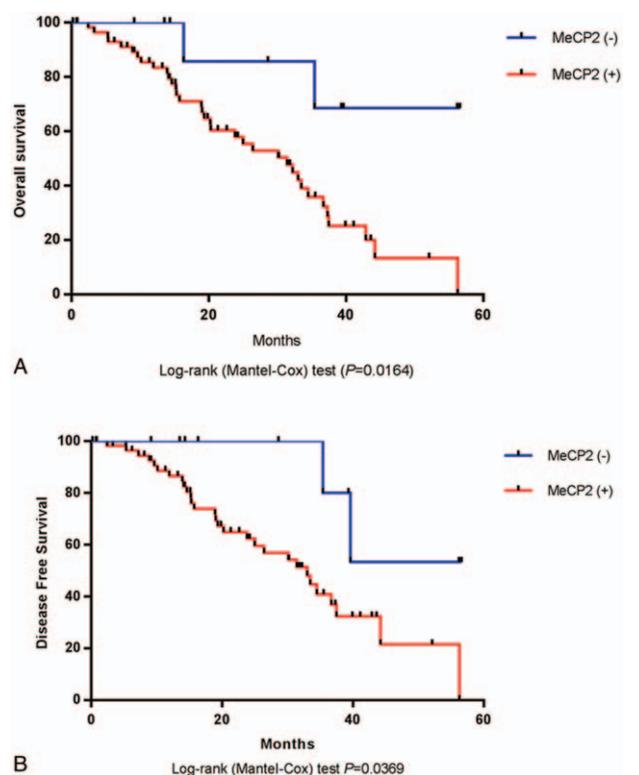


Figure 4. Correlation of MECP2 expression and survival of GC patients. (A) The overall survival of the 69 GC patients with or without MECP2 expression was analyzed by Kaplan–Meier analysis. (B) The disease-free survival of the 69 GC patients with or without MECP2 expression was analyzed by Kaplan–Meier analysis. The log-rank test was used to analyze the difference in survival. GC = gastric cancer, MECP2 = methyl CpG binding protein 2.

positive and negative patients were significantly different ($P = .0164$ and $P = .0369$), suggesting that high MECP2 expression predicts poor prognosis in GC patients. Furthermore, univariate and multivariate analyses showed that gender, histological type, lymph node metastasis, and MECP2 expression were independent factors for GC prognosis (Table 2).

4. Discussion and Conclusion

MECP2 mediates gene transcriptional activation or inactivation, therefore regulating the expression of multiple genes. The role of MECP2 in nervous system diseases is widely reported^[13] and the

expression of many molecules is found to be suppressed by MECP2.^[14] In addition, MECP2 could regulate gene expression in many cancers, leading to changes in cell proliferation, cell cycle, apoptosis, migration, invasion, and other biological functions. However, study on MECP2 in GC is rare. Because that MECP2 is the key molecule bridging DNA methylation and gene suppression, it is of great value to study the correlation of MECP2 with GC.

In this study, we first investigated the expression of MECP2 in 69 cases of GC patients. Results of qRT-PCR showed that MECP2 mRNA was significantly upregulated in GC tissues compared with paracancerous tissues. In line with this, the MECP2 protein was also significantly upregulated in GC as determined by Western blot and immunochemistry. And, MECP2 was principally expressed in the nucleus. These results suggest that accumulation of MECP2 in the nucleus of GC cells is critical for its regulation on gene transcription. In addition, dysregulated MECP2 in GC indicates that it may function as an oncogene to regulate GC development.

Our study also showed that expression of MECP2 could be used as an independent prognostic factor for survival in GC patients. By analyzing the 5-year survival of the 69 GC patients, we found that MECP2 negative patients had significantly longer survival time compared with MECP2 positive patients. Importantly, MECP2 expression was significantly correlated with the histological type of GC ($P = .0004$), as analyzed in the 69 cases of GC patients enrolled in our study as well as in 404 cases of GC data from the TCGA database. Additionally, MECP2 expression was increased with the development of TNM stages, or the status of lymph node metastasis. It is well established that gender,^[15] lymph node metastasis,^[16] and histological type^[17,18] are prognostic factors for GC. Consistently, our results further confirmed that gender, histological type, and lymph node metastasis were independent factors for GC prognosis. Furthermore, we found that MECP2 expression was an independent prognostic factor for GC. Thus, our findings suggest that MECP2 may regulate the development of GC and predict the prognosis of GC.

In recent years, it has been found that MECP2 may promote the development of tumor by regulating the expression of tumor-related genes. MECP2 can inhibit the expression of tumor suppressor genes such as P16INK4a, hMLH1, IL-6, TFPI-2, Netrin-4, RASSF1A, mPer1 and mPer2, and regulate the cell cycle, apoptosis, tumor metastasis and tumor angiogenesis and growth in the occurrence and development of skin cancer, endometrial cancer, pancreatic cancer, colon cancer, glioma and other tumors.^[19–22] In osteosarcoma and prostate cancer, MECP2 inhibits apoptosis and thus promotes cell survival by

Table 2

Univariate and multivariate analyses of clinicopathological factors for prognosis prediction of gastric cancer patients.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age, ≥ 50 / < 50 years	1.384 (0.740–2.592)	.309		
Gender, male/female	2.268 (1.193–4.314)	.012	2.990 (1.522–5.872)	.001
Histological types	2.986 (1.555–5.734)	.001	2.224 (1.019–4.854)	.045
TNM stages, III & IV/I & II	1.626 (0.849–3.116)	.143		
Lymph node metastasis, yes/no	8.685 (4.264–17.690)	.000	4.664 (1.699–12.803)	.003
MECP2 expression, positive/negative	16.235 (7.043–37.421)	.000	6.294 (2.181–18.164)	.001

CI = confidence interval, HR = hazard ratio, MECP2 = methyl CpG binding protein 2.

All statistical tests were 2 sided; significance level $P < .05$.

activating Hsp27 expression.^[23] Mex2 regulates FOXF1/Wnt5a/ β -catenin and miR-338/BMI1/P-REX2 signaling pathways to promote the proliferation of gastric cancer cells, as well as MYOD1/caspase-3 pathway to inhibit apoptosis by binding to the promoter of FOXF1, MYOD1, and miR-338, which can inhibit the proliferation of gastric cancer cells.^[24,25] It can also promote the proliferation of gastric cancer cells by promoting the expression of glucose-related gene GANAB^[26] and activating the ERK1/2 signaling pathway.^[27] These data suggest that MECP2 can bind to the methylated CpG sites of tumor suppressor genes or proto-oncogenes and regulate their expression, affecting the occurrence and development of tumor. Therefore, MECP2 may be a key protein for the epigenetic regulation of gastric cancer. However, until now few reports were on the correlation analysis between MECP2 expression and gastric cancer clinicopathological index. The Kaplan–Meier survival curve combined with TCGA analysis showed that the positive expression of MECP2 was closely related with the clinical stage, lymph node metastasis, histological type, and prognosis but not with gender and sex. However, the sample size of this study was relatively small and further study with larger sample size is warranted.

Taken together, dysregulated MECP2 in GC indicates that it may participate in several physiological processes in GC. MECP2 may be used as a potential target for drug development of GC. Our results may be helpful for the early screening, risk evaluation, treatment, and prognosis prediction of GC. Further studies are needed to investigate the role of MECP2 on GC cell growth.

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