

Correlation between GDF15, MMP7 and gastric cancer and its prognosis

L. LU^{1,2}, G.-O. MA^{1,3}, X.-D. LIU^{1,2}, R.-R. SUN^{1,4}, Q. WANG^{1,4},
M. LIU^{1,2}, P.-Y. ZHANG^{1,4}

¹First College of Clinical Medicine, Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China

²Xuzhou City Hospital of TCM, Xuzhou, Jiangsu, China

³Jiangsu Province Hospital of TCM, Nanjing, Jiangsu, China

⁴Xuzhou Central Hospital, Xuzhou, Jiangsu, China

Lei Lu and Guquan Ma contributed equally to this work

Abstract. – **OBJECTIVE:** To explore the correlation between GDF15, MMP7 and gastric cancer and its prognosis.

PATIENTS AND METHODS: Thirty-six cases of gastric cancer admitted to our hospital from February 2014 to February 2015 were included in the observation group. Thirty-two healthy people were selected during the same period as the control group. The levels of MMP7 and GDF15 mRNA in the observation group before and after treatment and in the control group were detected by fluorescence quantitative PCR. The expressions of GDF15 and MMP7 proteins were detected by enzyme-linked immunosorbent assay and Western-blotting analysis. The expression of GDF15 and MMP7 in gastric carcinoma were tested by immunohistochemistry assay.

RESULTS: Compared with the control group, the levels of GDF15 and MMP7 mRNA in the observation group were significantly increased in gastric cancer tissue before treatment ($p < 0.05$). After treatment, there was no significant difference in the expressions of GDF15 and MMP7 mRNA in patients with significant improvement and the control group ($p > 0.05$). Immunohistochemistry and Western blot results found that levels of GDF15 and MMP7 proteins in the observation group before treatment (14.28 ± 1.03 ; 9.06 ± 0.82 g/l) were significantly higher than that in the control group (1.05 ± 0.21 ; 0.94 ± 0.12 g/l). And there were no significant differences between patients with significant improvement (1.64 ± 0.18 ; 1.03 ± 0.22 mg/l) and the control group ($p > 0.05$), while the levels in patients with no significant improvement (12.04 ± 1.01 ; 8.21 ± 0.65 mg/l) were significantly higher than that in the control group. Immunohistochemical results showed that the number of GDF15 and MMP7 positive cells in patients with significant improvement (10.32%; 9.01%) were significantly lower than that before treatment or in patients with no significant improvement (85.43%; 90.27%).

CONCLUSIONS: There were significant correlations between GDF15, MMP7 and the incidence of gastric cancer. Levels of GDF15 and MMP7 in patients were significantly correlated with the degree of rehabilitation after treatment.

Key Words:

GDF15, MMP7, Gastric cancer, Postoperative rehabilitation, Relevance.

Introduction

Statistical data show that, as one of the most common malignant tumors in the digestive system, the incidence rate of gastric cancer has increased year by year in recent years¹. By 2015, the total number of patients with gastric cancer in China is about 485 thousand and is growing at a rate of nearly 2.63% per year. The mortality rate of gastric cancer in China is about 230.21/100,000 per year². Therefore, the research on the pathogenesis of gastritis has become an important direction of medical research^{3,4}. Pathological analysis⁵ showed that 93.3% of the gastric cancer is adenocarcinoma; therefore, early detection and early treatment are the most effective methods for the diagnosis and treatment of gastric cancer. However, since the pathogenesis and early detection of gastric cancer are not clear, there are no specific therapeutic drugs for the treatment at present. Also, as cancers are very easy to relapse after treatment, it is very important to find a marker associated with the pathogenesis and treatment of gastric cancer. It has been showed that tumor cells could be widely transferred in the human body; thus, research on the mechanism of tumor cell and cancer cell metastasis has been

considered important for the treatment of the cancers⁶⁻⁸. Matrix metalloproteinases (MMP) have been shown to promote cancer cells metastasis in the human body by the degradation of adhesion between cells such as extracellular matrix and related adhesion molecules, etc.⁹. In recent years, it has been shown that MMP plays an important role in the spread of cancer cells in breast cancer and other cancers, but there are few reports about the correlation between MMP and gastric cancer¹⁰⁻¹². Growth differentiation factor 15 (GDF15), an important member of the TGF- β family, has been shown to be closely related to the metastasis of tumor cells¹³. For example, a study showed that the expression of GDF15 in colon cancer was significantly higher than that in the normal population, and it gradually decreased with the improvement of colon cancer¹⁴. But there are few studies exploring the correlation between GDF15 and gastric cancer¹⁵. In this study, we first investigated the correlation between GDF15, MMP7 and gastric cancer and its prognosis to provide theoretical and experimental basis for the diagnosis and treatment of gastric cancer.

Patients and Methods

Patients

Thirty-six cases of gastric cancer (21 males, age = 47.2 ± 10.3 years) admitted to our hospital from February 2014 to February 2015 were included in the observation group. Thirty-two healthy people (16 females, age = 42.1 ± 11.5 years) were selected as the control group during the same period. Inclusion criteria: (1) patients diagnosed with gastric cancer; (2) without other cancers; (3) ages ranged from 30 to 60 years.

Exclusion criteria: (1) suffering from other inflammation; (2) suffering from other tumors and cancers; (3) less than 30 years or older than 60 years. Informed consent was obtained from the individuals enrolled in the study which has been approved by the Institution Ethics Committee of Xuzhou Central Hospital.

RNA Kit (TAKARA, China); GDF-15 and MMP7 gene primers were synthesized by Suzhou Genewiz Biological Engineering Co., Ltd. (Shanghai, China); primary and secondary antibodies GDF-15 and MMP7 primary antibody was goat anti-rabbit antibody (ABM, Winnipeg, Manitoba, Canada) and the secondary antibody was rabbit anti-rat antibody which was labeled by HRP (Ke-qing Biological Company, Suzhou, China).

Instruments: low temperature high-speed centri-

fuge (Thermo, Darmstadt, Germany); super-clean bench (Suzhou Purification Equipment Co., Ltd, Suzhou); PCR instrument (Thermo, Darmstadt, Germany); micro nucleic acid quantitative measurement instrument (Thermo, Darmstadt, Germany); microplate reader (Thermo, Germany); transmembrane apparatus (Thermo, Darmstadt, Germany); protein electrophoresis apparatus (Beijing Liuyi Biotechnology Co., Ltd, China).

Methods

Fluorescence Quantitative PCR

RNA extraction: In this study, RNA was extracted according to the TAKARA RNA Extraction Kit specification⁹ (Dalian, China).

Fluorescence Quantitative PCR

To detect the mRNA expression of GDF15, MMP7 and GAPDH genes in different samples, we used SYBRGREEN1 dye method, and specific experimental protocol was referred to the instructions. All primers used were synthesized by Suzhou Genewiz Biological Engineering Co., Ltd., and the sequences are shown in Table I.

Enzyme-linked Immunosorbent Assay

The experimental protocol was performed according to previous study¹⁶.

Western Blotting Analysis

The experimental protocol was performed according to previous study¹⁷.

Immunohistochemistry

The experimental protocol was performed according to previous study¹⁸.

Statistical Analysis

Statistical analysis was performed using SPSS 14 software (SPSS Inc., Chicago, IL, USA). Classification data was compared with Chi-square test. $\alpha=0.05$, $p<0.05$ was considered statistically significant. $\alpha=0.01$.

Results

Expression of GDF15 and MMP7 mRNA in Gastric Cancer Patients and healthy People

In this study, we took tissue samples of normal population and gastric cancer patients, and extracted total RNA as template. The levels of GDF15 and MMP7 mRNA in different samples

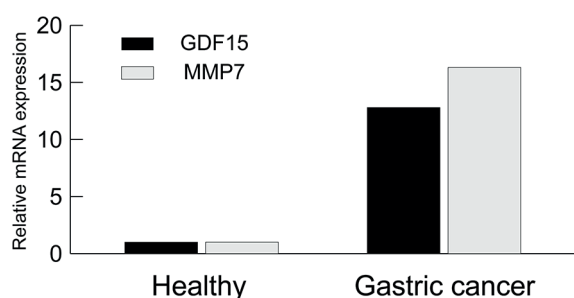
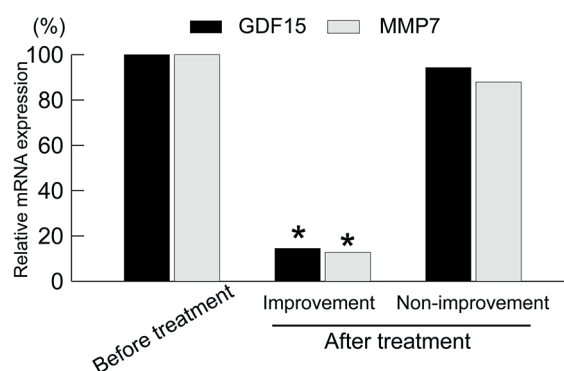
Table I. Primers for fluorescence quantitative PCR.

Primer	Sequence
GDF15-F	GTGCTAGCTAGGAGCTAGCTACG
GDF15-R	CGTGATCGGCTAGCTAGCTAGC
MMP7-F	CGTAGCTAGCTACGTACGATAGC
MMP7-R	CGTAGCTAGCTAGATCGATAGCTA
GAPDH-F	CGTAGGGCTAGCTAGCTAGATAC
GAPDH-R	CGTAGCTGAGAGTTAGCTAGCATC

were determined by fluorescence quantitative PCR method. The results are shown in Figure 1. Compared with the control group, levels of GDF15 and MMP7 mRNA in tissue samples from patients with gastric cancer were relatively high. The expression of GDF15 mRNA in gastric cancer tissue was 12.8 times higher than in the control group. The expression of MMP7 mRNA in gastric cancer tissue was 16.3 times higher than in the control group. The results showed that there were significant differences in the expression of GDF15 and MMP7 in normal and gastric cancer tissue samples ($p < 0.05$), suggesting that there is a certain correlation between GDF15, MMP7, and gastric cancer.

Expression of GDF15 and MMP7 mRNA in Gastric Cancer Patients After Treatment

We extracted total RNA from the pathological tissue of patients with gastric cancer before and after treatment. The levels of GDF15 and MMP7 mRNA in pathological tissue in gastric cancer patients before and after treatment were measured, and the results were shown in Figure 2. In patients with significant improvement after treatment, compared to before treatment, expression levels of GDF15 and MMP7 mRNA decreased significantly ($p < 0.05$), which were 14.5% and 12.8% of

**Figure 1.** Expression of GDF15 and MMP7 mRNA in gastric cancer patients and healthy people (“*” indicated a significant difference between groups).**Figure 2.** Expression of GDF15 and MMP7 mRNA in gastric cancer patients after treatment (“*” indicated a significant difference between groups).

the levels before treatment, respectively. But in patients with gastric cancer who had no significant improvement after treatment, expression levels of GDF15 and MMP7 mRNA didn't differ from those before treatment ($p > 0.05$), which were 94.3% and 87.9% of the levels before treatment, respectively. The results showed that there was a certain correlation between the expression of GDF15 and MMP7 mRNA and rehabilitation status of patients with gastric cancer after treatment.

Expression of GDF15 and MMP7 Proteins in Gastric cancer patients and Healthy People

In the present study, we took total proteins extracted from different samples. The levels of GDF15 and MMP7 proteins in different samples were determined by ELISA, and the results were shown in Figure 3. As can be seen from Table II, level of GDF15 protein in the observation group before treatment (14.28 ± 1.03 mg/l) was significantly higher than that in the control group (1.05 ± 0.21 mg/l) ($p < 0.05$). And level of MMP7 protein in the observation group before treatment (9.06 ± 0.82 mg/l) was significantly higher than that in the control group (0.94 ± 0.12 mg/l) ($p < 0.05$).

Table II. Expression of GDF15 and MMP7 proteins in gastric cancer patients and healthy people.

Group	Level of GDF15 ($\mu\text{g/l}$)	Level of MMP7 ($\mu\text{g/l}$)
Healthy people	1.05 ± 0.21	0.94 ± 0.12
Gastric cancer patients	$14.28 \pm 1.03^*$	$9.06 \pm 0.82^*$

* p : significant difference.

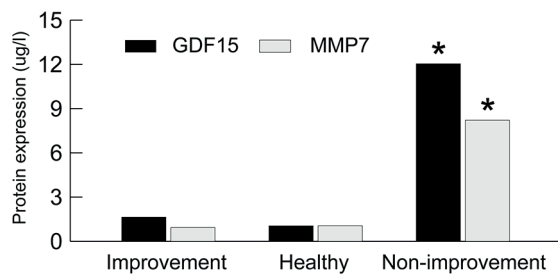


Figure 3. Expression of GDF15 and MMP7 proteins in gastric cancer patients and healthy people (“*” indicated a significant difference between groups).

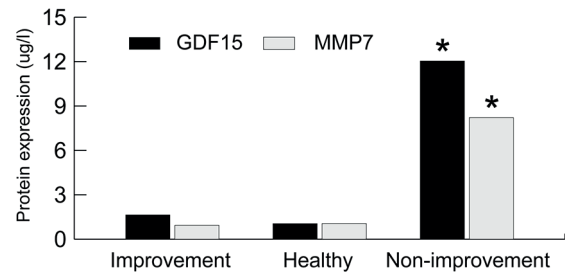


Figure 4. Expression of GDF15 and MMP7 proteins in gastric cancer patients before and after treatment (“*” indicated a significant difference between groups).

Table III. Quantitative determination of GDF15 and MMP7 protein levels in different samples.

Group	N	Patients with no significant improvement		Patients with significant improvement	
			($\mu\text{g/l}$)		($\mu\text{g/l}$)
Healthy people	32	GDF15	MMP7	GDF15	MMP7
		1.37 ± 0.18	1.32 ± 0.11	1.35 ± 0.17	1.21 ± 0.11
Gastric cancer patients	36	14.04 ± 1.26	9.31 ± 0.43	2.23 ± 0.18	0.74 ± 0.16

*p: significant difference.

Expression of GDF15 and MMP7 Proteins in Gastric Cancer Patients after Treatment

In this study, we took total proteins extracted from different samples. The levels of GDF15 and MMP7 proteins in different samples were determined by ELISA, and the results were shown in Figure 4. After treatment, comparison of GDF15 protein levels between patients in the cured observation group (1.64 ± 0.18 g/l) and the control group (1.05 ± 0.21 g/l) revealed no significant differences ($p<0.05$), while the levels in patients with no significant improvement (12.04 ± 1.01 ; 8.21 ± 0.65 g/l) were significantly higher than that in the control group (1.05 ± 0.21 g/l) ($p>0.05$). After treatment, comparison of MMP7 protein levels between patients in the cured observation group (0.94 g/l) and the control group revealed no significant differences ($p<0.05$), while the levels in patients with no significant improvement (8.21 ± 0.65 g/l) were significantly higher than that in the control group ($p>0.05$).

Detection of GDF15 and MMP7 Protein Levels in Different Samples by Western blot Analysis

The levels of GDF15 and MMP7 proteins in patients with gastric cancer and healthy people were detected by Western blot analysis. And

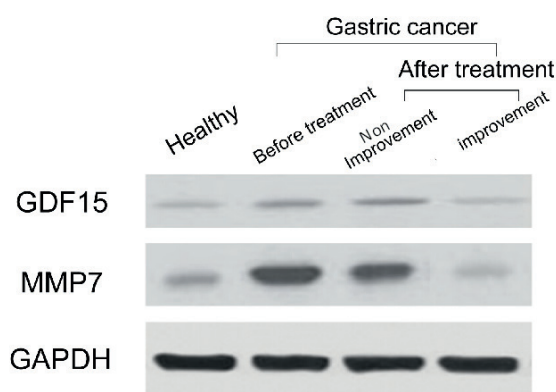
the results were shown in Figure 5. The levels of GDF15 and MMP7 proteins in patients with gastric cancer were both significantly higher than that in healthy people ($p<0.05$), which was consistent with ELISA results. Also, levels of GDF15 and MMP7 proteins in gastric cancer patients with significant improvement after treatment were significantly lower than that in patients with no significant improvement. Quantitative determination of Western blot results showed that the findings above were consistent with ELISA results (Figure 4).

Immunohistochemistry of Gastric Cancer Tissue in the Observation Group Before and after Treatment

In this study, immunohistochemical analysis of the expression of GDF15 and MMP7 in gastric cancer tissue was conducted and showed that (Figure 6), in patients with significant improvement after treatment, the number of GDF15 positive cells (10.32%) in tissue was significantly less than that in patients with no significant improvement (85.43%) ($p<0.05$). Meanwhile, in patients with significant improvement after treatment, the number of MMP7 positive cells (9.01%) was also significantly less than that in patients with no significant improvement (90.27%) ($p<0.05$) (Table IV).

Table IV. The number of positive cells in gastric cancer tissue in the observation group before and after treatment.

Group	N	Patients with no significant improvement	(%)	Patients with significant improvement	(%)
Gastric cancer patients	36	GDF15 85.43±2.32	MMP7 90.27±1.08	GDF15 10.32±0.12	MMP7 9.01±1.21

**Figure 5.** Detection of GDF15 and MMP7 protein levels in different samples by Western blot analysis.

Discussion

As a common digestive disease, the incidence of gastric cancer in China has increased year by year¹⁹. However, the pathogenesis of gastric cancer, as well as many of the signaling molecules and genes involved are not clear at present²⁰, which leads to the fact that there are no effective methods regarding diagnosis and treatment of gastric cancer. And due to the metastasis of cancer cells and the enhancement of drug resistance in cancer cells, the efficacy of a large number of chemotherapy drugs declines²¹. In recent years, research studies showed that MMP-7 protein is an important member of the MMP family and abnormally expressed in breast cancer, colon cancer and so on^{11,22,23}. Further research findings indicated that²⁴, MMP7 protein in cancer tissues and cancer cells promoted the metastasis and migration of cancer cells by degradation of cell adhesion between cancer cells. Besides, studies on drug resistance of cancer cells found that the expression of MMP7 protein was higher in highly resistant cancer cells, and cell migration was significantly increased, suggesting that MMP7 protein enhanced the drug resistance of cancer cells²⁵. It

has been shown that there was a significant correlation between the polymorphism of MMP7 gene and the incidence of colon cancer. For example, there was a significant difference in the genotype frequencies of MMP7-18A/G in colon cancer patients and normal population. In colon cancer patients, the main genotypes were GG/AA homozygous, while in normal population, the main genotype was A/G heterozygous genotype²⁶, which indicated that the polymorphism of MMP7 gene may be related to the regulation of cancer cell migration. Research results^{14,27} showed that GDF15, as an important member of the TGF- β family, expressed higher levels in pancreatic carcinoma and colon carcinoma cells than that in normal cells. Further studies showed that the gene could enter into the surrounding cells through paracrine and autocrine. The level of GDF15 in serum of colon cancer patients was significantly higher than that in healthy people, indicating that GDF15 gene might serve as a marker for the diagnosis of cancer¹⁴. In this study, we first detected the expression levels of GDF15 and MMP7 genes in gastric cancer patients and healthy people. And the results showed that both GDF15 and MMP7 mRNA and protein levels differed significantly in gastric cancer and healthy population. Then the gastric cancer patients were divided into two groups (namely group of patients with significant improvement after chemotherapy) and (group of patients with no significant improvement). We found that GDF15 and MMP7 protein levels decreased significantly in patients who had a significant improvement, but remained high in pre-treatment and patients with no significant improvement.

Conclusions

There were significant correlations between GDF15 and MMP7 and the incidence of gastric cancer. Moreover, the levels of GDF15 and

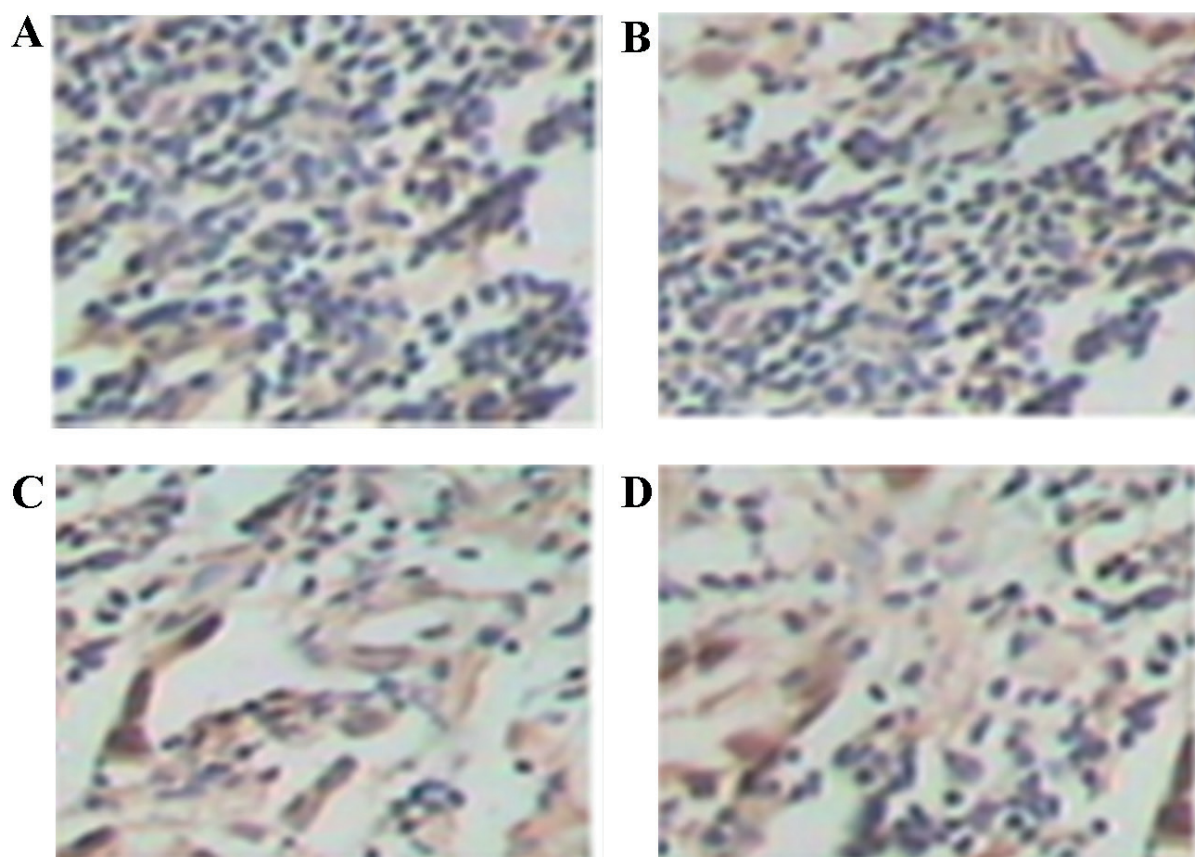


Figure 6. Immunohistochemistry of gastric cancer tissue in the observation group before and after treatment. Panel **A**, Tissue sample in patients with gastric cancer; Panel **B**, Tissue samples in gastric cancer patient with no significant improvement; Panel **C**, Tissue samples in gastric cancer patients with significant improvement; Panel **D**, Healthy gastric tissue sample.

MMP7 proteins in the patients were significantly correlated with the degree of rehabilitation of patients after chemotherapy.

Conflict of interest

The authors declare no conflicts of interest.

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