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Correlation between GDF15, MMP7 and gastric cancer and its prognosis

L. LU[1,2], G.-Q. 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]

[1]First College of Clinical Medicine, NanjingUniversity of Chinese Medicin[illegible]anjing[illegible]ngsu, Ch[illegible]
[2]Xuzhou City Hospital of TCM, Xuzhou, Jiangsu, China
[3]Jiangsu Province Hospital of TCM, Nanjing, Jiangsu, China
[4]Xuzhou 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 G[illegible]F15 mRNA in the observation group before[illegible]ter treatment and in the control group w[illegible]e tected by fluorescence quantitative PCR[illegible]e expressions of GDF15 and MMP7 proteins [illegible] detected by enzyme-linked immunosorbent [illegible]say and Western-blotting analysis. The expre[illegible]sion of GDF15 and MMP7 in [illegible]rcinoma were tested by immunohisto[illegible]ssay.

RESULTS: Compared wi[illegible]e con[illegible] group, the levels of GDF15 and [illegible]7mRN[illegible] servation group were si[illegible]ntl[illegible] gastric cancer tissue[illegible]fore[illegible]t ($p<0.05$). After treatment, th[illegible]as no[illegible]cant difference in the expr[illegible]ons of GDF[illegible]d MMP7 mRNA in patien[illegible]significant i[illegible]ement and the cont[illegible]re[illegible]>0.05). Immunohistochemistry an[illegible]Vester[illegible] results found that levels of G[illegible]F15 and MM[illegible]teins in the observatio[illegible]oup before tre[illegible]t (14.28±1.03: 9.06±0[illegible]g/l) were significantly higher than that i[illegible]e con[illegible] group (1.05±0.21; 0.94±0.12 g/l) [illegible]d the[illegible]ere n[illegible] significant differences b[illegible]n[illegible]ients w[illegible] significant improvement ([illegible]8; 1.03[illegible]2 mg/l) and the con[illegible]roup[illegible]05)[illegible]le the levels in patients [illegible]o sig[illegible]mprovement (12.04±1.01; 8.21[illegible]5 mg/l)[illegible]e significantly higher than that[illegible]the control group. Immunohistochemical[illegible]ved that the number of GDF15 a[illegible]MMP7 p[illegible]itive 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%; 90.2[illegible].

CONCLUSIONS: There[illegible]re significant correlations between GDF15, MMP7 and the incidence of gastric cancer. Levels of GDF15 and MMP7 in patien[illegible]were significantly correlated with the degree[illegible]ehabilitation after treatment.

Key[illegible]
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 years[1]. 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 year[2]. Therefore, the research on the pathogenesis of gastritis has become an important direction of medical research[3,4]. Pathological analysis[5] 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

Corresponding Author: Peiying Zhang, MD; e-mail: zpyxzsy@163.com

considered important for the treatment of the cancers[6-8]. 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 cancer[10-12]. 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 cells[13]. 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 cancer[14]. But there are few studies exploring the correlation between GDF15 and gastric cancer[15]. 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 ma age = 47.2±10.3 years) admitted to our hospit from February 2014 to Februa re inclu- ded in the observation grou irty- healthy people (16 females, age= ±11.5) were selected as the control g uring riod.Inclusion criteria:) pa nosed with gastric cancer; (2) w ut othe rs; (3) ages ranged from 30 to ears.

Exclusion cri suffering fro ther inflammation; (uffe m other tumors and cancers; (3) less than 30 or older than 60 years. In ed consent wa ined from the individ enrolled in the study which has been appro by th titution Ethics Committee of Xu Cent ospital.

RN AKAR China); GDF-15 and MMP7 g mers e synthesized by Suzhou iz Bio gineering Co., Ltd. (Shangha ina); pr y and secondary antibodies GD and MMP7 primary antibody was goat an dy (ABM, Winnipeg, Manitoba, ada) and the secondary antibody was rabbit rat antibody which was labeled by HRP (Keq ological Company, Suzhou, China).

In ments: low temperature high-speed centrifuge (Thermo, Darmstadt, Germany); super-clean bench (Suzhou Purification Equipmen Suzhou); PCR instrument (Therm armst Germany); micro nucleic acid qua tive measurement instrument (Thermo, Dar Germany); microplate reader (Thermo, Germa nsmembrane apparatus (Thermo, rmstadt any) protein electrophoresis atus (Beiji Biotechnology Co., Ltd ma).

Methods

Fluorescence antitati PCR

RNA ext n: In this st A was extracted ac the TAKA A RNA Extraction pech 9 (Dalian, China).

Flu nce Quantita PCR

detect the mRNA expression of GDF15, MP7 and GAPDH genes in different samples, used SYBR EN1 dye method, and spe- experiment rotocol was referred to the i ions. A mers used were synthesized by S viz Biological Engineering Co., Ltd., and the sequences are shown in Table I.

linked Immunosorbent Assay

The xperimental protocol was performed according to previous study[16].

Western Blotting Analysis

The experimental protocol was performed according to previous study[17].

Immunohistochemistry

The experimental protocol was performed according to previous study[18].

Statistical Analysis

Statistical analysis was performed using SPSS 14 software (SPSS Inc., Chicago, IL, USA). Classification data was compared with Chi-square test. α=0.05, p<0.05 was considered statistically significant. α=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 that 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 tissues of gastric cancer patients before and after treatment were detected, and the results were shown in Figure 1. 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

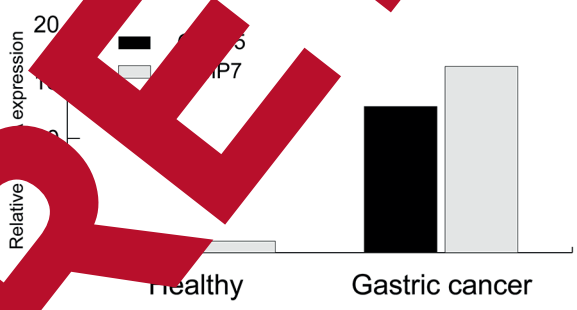

Figure 1. Expression of GDF15 and MMP7 mRNA in gastric cancer patients and healthy people ("*"indicated a significant difference between groups).

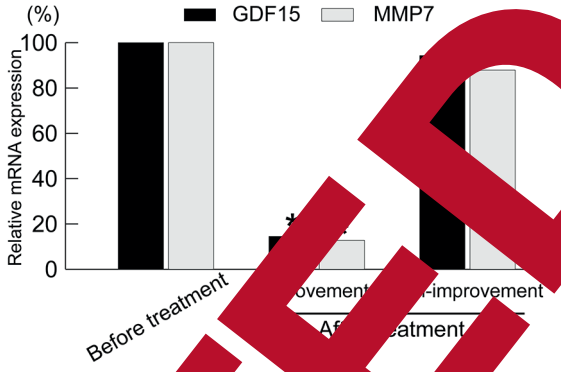

Figure 2. Expression of GDF15 and MMP7 mRNA in gastric cancer patients after treatment (* indicated a significant difference between groups).

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 92.3% and 87.9% of the levels before treatment, respectively. The results showed that there was a 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 (μg/l)	Level of MMP7 (μg/l)
Healthy people	1.05±0.21	0.94±0.12
Gastric cancer patients	14.28±1.03*	9.06±0.82*

*p: significant difference.

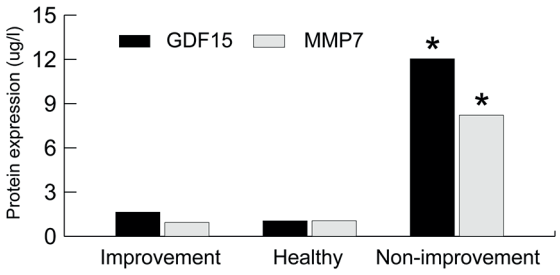

Figure 3. Expression of GDF15 and MMP7 proteins in gastric cancer patients and healthy people ("*"indicated a significant difference between groups).

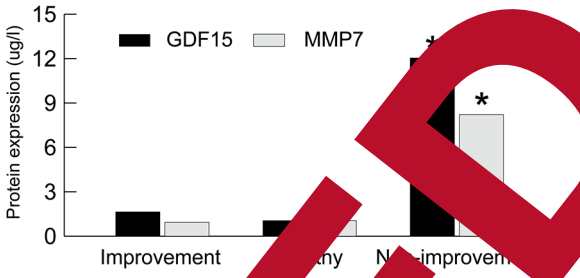

Figure 4. Expression o[illegible]15 and [illegible]7 prote[illegible]s in gastric cancer patients befo[illegible]fte[illegible]tment ("[illegible]icated a significant differen[illegible]etwe[illegible]).

Table III. Quantitative determination of GDF15 and MMP7 protein levels in [illegible]es.

Group	N	Patients with no significant improvement		Pa[illegible]with signi[illegible] improve[illegible]nt	(μg/l)
		GDF15	MMP7	DF15	MMP7
Healthy people	32	1.37±0.18	1.32±0.11	5±0.17	1.21±0.11
Gastric cancer patients	36	14.04±1.26	31±0.43	3±0.18	0.74±0.16

*p: significant difference.

Expression of GDF15 and MMP7 P[illegible] in Gastric Cancer Patients after Treatment

In this study, we took total proteins extrac[illegible] from different samples. The level[illegible]f GDF15 a[illegible] MMP7 proteins in different s[illegible]re deter-mined by ELISA, and the r[illegible]s we[illegible]own in Figure 4. After treatment[illegible]parison[illegible]GDF15 protein levels between p[illegible]in th[illegible] vation group (1.64±0.[illegible]g/l)[illegible]ntrol group (1.05±0.21 g/l) reve[illegible]no sign[illegible]differences (p<0.05), while t[illegible]vels in patie[illegible]h no significant impr[illegible](12.04±1.01;[illegible]1±0.65 g/l) were sign[illegible]ntly[illegible]than that in the control group[illegible]09±0.21 g/[illegible]0.05). After treatment, co[illegible]ison of MMP7 p[illegible]levels betwe-en pati[illegible]in the cured observa[illegible]ion group (0.94 g/l) a[illegible]e co[illegible]group revealed no significant dif[illegible]es ([illegible]5), wh[illegible]the levels in patients with [illegible]ant im[illegible]ement (8.21±0.65 g/l) [illegible]sig[illegible]ly hi[illegible]than that in the control [illegible](p>0.0[illegible]

Det[illegible]ion of GDF15 and MMP7 Protein L[illegible]erent Samples by Western [illegible] Analysis

[illegible]he levels of GDF15 and MMP7 proteins in p[illegible]with gastric cancer and healthy people were[illegible]tected by Western blot analysis. And [illegible]were shown in Figure 5. The levels [illegible]GD[illegible]5 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	(%)
		GDF15	MMP7	GDF15	MP7
Gastric cancer patients	36	85.43±2.32	90.27±1.08	10.32±0.12	21

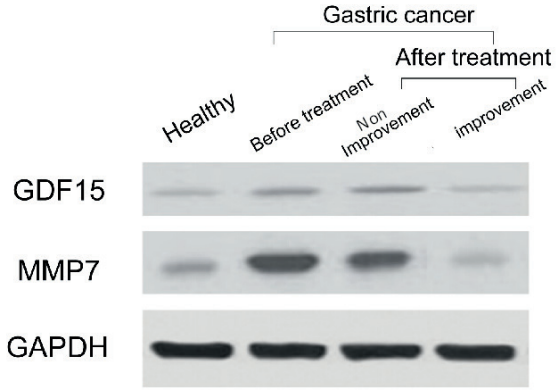

Figure 5. Detection of GDF15 andMMP7 protein levels in different samples by Western blot analysis.

Discussion

As a common digestive disease, the incidence of gastric cancer in China has increased year by year[19]. However, the pathogenesis of gastric cancer, as well as the majority of the signaling molecules and genes involved are still present[20], which leads to the fact that there are no effective methods regarding prognosis and treatment of gastric cancer. And during the metastasis of cancer cells and the enhancement of drug resistance in cancer cells, the efficacy of a large number of chemotherapy drugs declines[21]. In recent years, research studies showed that MMP7 protein is an important member of the MMP family and abnormally expressed in breast cancer, colon cancer and so on[11,22,23]. Further findings indicated that[24], MMP7 protein in cancer tissues and cancer cells promotes the invasion and migration of cancer cells, degradation of cell adhesion between cancer cells. Besides, studies on drug resistance 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 cells[25]. It has been shown that there was 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 homozygous, while in normal population, the main genotype was A/G heterozygous genotype[26], which indicated that the polymorphism of MMP gene may be related to the regulation of cancer cell migration. Research reports[14,27] showed that GDF15, as an important member of 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 cancer[14]. 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

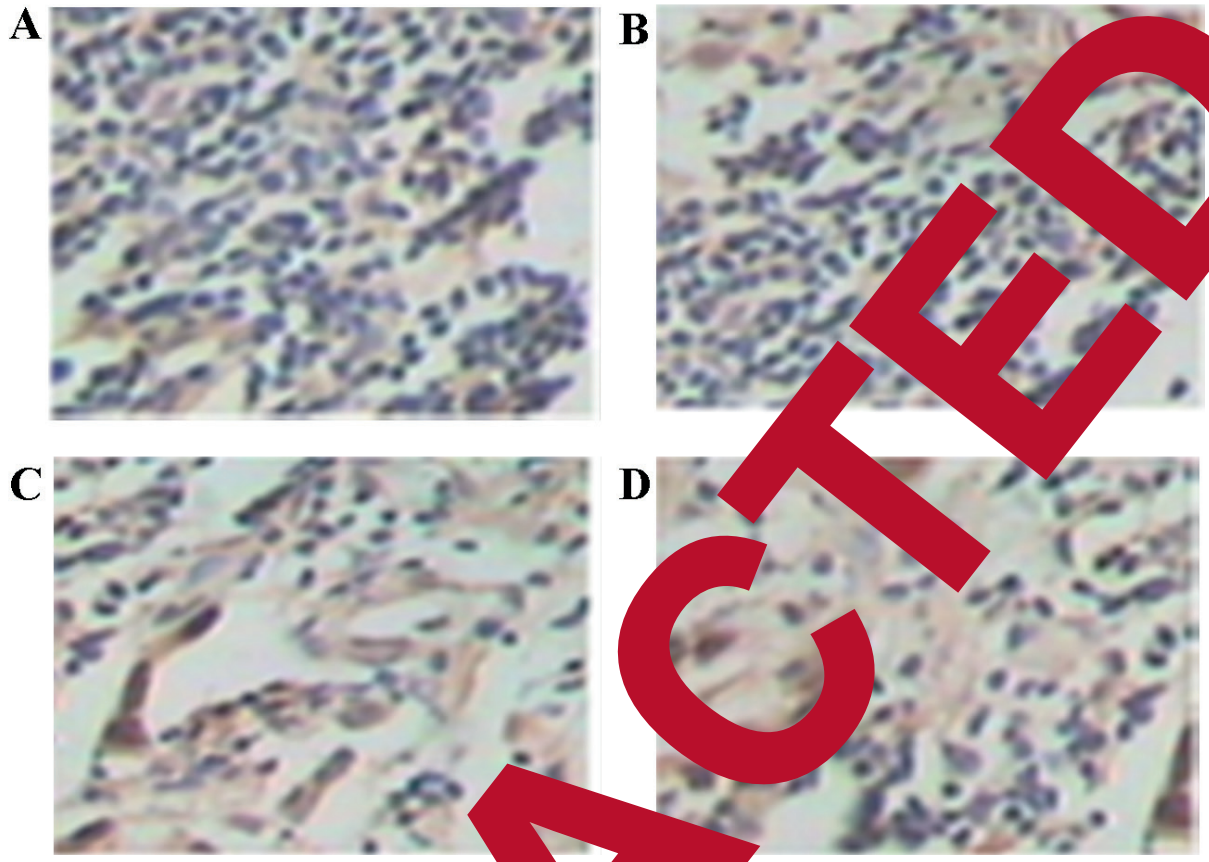

Figure 6. Immunohistochemistry of gastric cancer tis… t… servation group before and after treatment. Panel ***A,*** Tissue sample in patients with gastric cancer; Panel ***B,*** Tissue sa… gastric cancer patient with no significant improvement; Panel ***C,*** Tissue samples in gastric cancer patie… ith significan… ovement; Panel ***D,*** Healthy gastric tissue sample.

MMP7 proteins in the p… were correlated with the de… e o… ation of patients after chemoth… y.

Conflict of i… est

The authors declare no con… interest.

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