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Effects of miR-873 Targeted Regulation of FGF5 on Gastric Cancer and Its Related Mechanism

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Abstract

Objective: To clarify the role of miR-873 targeted regulation of FGF5 in gastric cancer (GC) and its related mechanism.
Methods: Cancer tissues and adjacent tissues of 54 patients with GC who came to our hospital for surgery from March 2018 to April 2019 were collected. QRT-PCR technique was used to detect mRNAs in tissues and cells, Western Blot (WB) was used to determine epithelial-mesenchymal transformation (EMT) and related apoptotic proteins, MTT to measure cell activity, and flow cytometry (FC) to monitor cell apoptosis.
Results: MiR-873 was statistically down-regulated in GC tissues, and was statistically inhibited in GC cells KATO III ($P<0.01$). The proliferation ability was statistically lower in miR-873-inhibitor group than in miR-NC group, and that of miR-873-mimics group was higher compared with siRNA-NC group ($P<0.05$). The apoptosis rate was notably lower in miR-873-inhibitor group than in NC group ($P<0.001$), and that in miR-873-mimics group was statistically lower compared with miR-NC group ($P<0.001$). Transfection of pmirGLO-FGF5 MUT and miR-873 mimics had no effect on cell luciferase activity. Compared with NC group, miR-873-minics and miR-873-inhibition groups had statistically lower FGF5 expression. pcDNA3.1-FGF5 group presented statistically higher and statistically lower apoptosis rate than siRNA-NC group ($P<0.001$). FGF5 up-regulation led to statistically up-regulated β-catenin, c-myc, vimentin, Snail and N-cadherin, and statistically inhibited Bax, Caspase-3 and E-cadherin, while simultaneous miR-144-3p overexpression reversed the EMT progression caused by up-regulation of FGF5.
Conclusion: MiR-873 is a potential therapeutic method for GC by regulating FGF5 to inhibit the proliferation and EMT of GC cells.
Keywords: miR-873, FGF5, gastric cancer, EMT, apoptotic protein, proliferation

Introduction

Gastric cancer (GC) is the world's four major malignant tumors, and one of the most common malignant tumors of the digestive system in the gastrointestinal tract. With the development of society and economy, the incidence of GC shows an emerging trend at younger ages due to the influence of people's unfavorable life and diet habits (Chen et al.,2020; Yin et al.,2020; Nan et al.,2020). Surgical resection, chemical and radiotherapy are currently the primary means of treatment for GC. Although the morbidity and mortality have been reduced to a certain extent, for lymph node metastasis and drug resistance in patients with advanced GC, the prognosis is still poor, which is a public problem threatening human health around the world (Mao et al.,2020; Lu et al.,2020). MicroRNAs (miRNAs) are now acknowledged to be essential in the development and progression of GC (Chen et al.,2020; Li et al.,2020; Ebrahimi et al.,2020).

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MiRNAs regulate many characteristics of cancer, such as proliferation, migration and apoptosis (Zhang et al.,2020).

The abnormal expression of miRNA has been confirmed in many different types of cancers (Satapathy et al.,2019). Recent reports revealed the abnormally expressed miR-873 in cancer and that it plays a critical tumor inhibitory role in the development of endometrial cancer by directly targeting hepatoma-derived growth factor (HDGF), which can be used to prevent the invasion of endometrial cancer(Wang and Zhu,2019; Ma et al.,2020). In addition, accumulating evidence demonstrates that miR-873 plays an anticancer role in various types of cancers, such as cervical cancer, colorectal cancer and non-small cell cancer (Yi-Haiet al.,2020; Fu et al.,2020). However, the function and mechanism of miR-873 in GC progression have not been fully elucidated. Therefore, this paper aims to provide a new theoretical basis for the diagnosis and treatment of miRNA targeted therapy in molecular biology.

By detecting miR-873 mRNA expression in GC, we explore through which targeting protein miR-873 promotes the progress of GC, with a view to finding reliable tumor markers and potential drug targets for clinical diagnosis and prognosis of GC.

1 Materials and methods

Fifty-four cases of cancer tissues and adjacent tissues were collected from 54 GC patients who came to our hospital for surgery from March 2018 to April 2019. Inclusion and exclusion criteria: Inclusion criteria: Patients diagnosed with GC by pathology, cytology and imaging (Chiriatti et al.,2020), and had not received relevant diagnosis and treatment in other hospitals, with complete cases. All tissue samples sampled were frozen in liquid nitrogen and stored at -80°C until needed. Exclusion criteria: Patients who had received preoperative chemical/radiotherapy, with severe liver and kidney dysfunction, coagulation dysfunction, cognitive impairment or communication impairment, or those who did not cooperate with the examination were excluded. All the participants volunteered to participate in the experiment and signed informed consent, and cooperated with medical staff to complete the relevant diagnosis and treatment. All the patients were not allergic to the drugs used during surgery, and this study has been approved by the hospital Medical Ethics Committee.

1.1 Main instruments and reagents

Human GC cells KATO III (stem cell bank reserve) and human gastric mucosa normal epithelial cells HFE-145 (BNCC100415, BNCC338003) were bought from BeNa Culture Collection. ABI Stepone Plus Real-Time PCR System, Trizol Extraction Kit, Annexin V/PI Apoptosis Detection Kit (Invitrogen, Carlsbed, CA, United States). SYBR Green PCR Master Mix (Applied Biosystems, Waltham, MA, United States). MTT kit (Beyotime Biotechnology, Shanghai, China, C0009). BCA Protein Kit, Multiskan™ GO Full Wavelength Microplate Reader (Thermo Fisher Scientific Technology, China). FACSCanto flow cytometer (Becton Dickinson, Franklin Lakes, NJ, United States). DR5000 UV-visible spectrophotometer (BioRad, Hercules, United States). The design and synthesis of all primer sequences were conducted by Sangong Bioengineering, Shanghai, China.

1.2 Detection methods

(1) Cell culture and transfection experiments

Cell experiment: KATO III cells were transfected into DMEM supplemented with 10% fetal bovine tissue and penicillin-streptomycin mixed solution, and cultured in a cell incubator with 5% CO2 and 37℃ constant temperature and saturated humidity. Small interfering (si-FGF5-#1, si-FGF5-#2, si-FGF5-#3) and control siRNA (si-NC) obtained from Shanghai GenePharic (Pudong, Shanghai, China), were transfected by LipofectamineTM 2000 following the manufacturer's guidelines. For FGF5 overexpression, its coding sequence (CDS) was amplified and inserted into pcDNA3.1 vector (pcDNA3.1-FGF5), as well as miR-873 targeted inhibition sequence (miR-873-inhibitor), miR-873 mimic sequence (miR-873-mimics), and miR negative control (miR-NC) (Guangzhou, Guangdong, China). The cells were transfected with Lipofectamine 2000 kit (Invitgen, Carlsbad, CA, United States).

(2) QRT-PCR detection

QRT-PCR was employed to detect mRNA expression in tissues and cells. According to the operation instructions of Trizol reagent, the total tissue RNA was extracted and dissolved in 20 μL

DEPC, and then reversely transcribed using a reverse transcription kit. The reaction system was as follows: M-MLV: 1 μl, Olig (d T): 1 μl, RNase inhibitor: 0.5 μl, d NTPs: 1 μl, and RNAse free water was added to a total volume of 15 μl. After that, it was incubated for 60 min at 38 ° C before taking 1 μl of it and treating it at 85℃ for 5s. The synthesized DNA was used as a template for qRT-PCR amplification, with the reaction system prepared as follows: 10×PCR buffer: 2.5 μl, d NTPs: 1 μl, upstream and downstream primers: 1 μl each, Taq DNA Polymerase: 0.25 μl, and dd H2O was added to make up for 25 μl. Reaction conditions: 95 ° C, 15 min; 95 ° C, 15 s; 58 ° C, 30 s; totaling 35 cycles; At last, the extension was performed at 72 ° C for 15 min. Three duplicate holes were set for each sample and the experiment was repeated three times. After the reaction, the amplification curve and fusion curve of real-time PCR was confirmed, and the relative quantities of target genes were calculated according to the result parameters. The relative quantification of target genes was worked out by 2-△Ct.

Table 1. **MiR-873, FGF5 and their internal reference primer sequences**

Gene	Forward	Reverse
miR-873	5'-GCAGGAACTTGTGAGTCTCCT-3'	5'-GCGAGCACAGAATTAATACGAC-3'
FGF5	5'-CCCGGATGGCAAAGTCAATGG-3'	5'-TTCAGGGCAACATACCACTCCCG-3'
U6	5'-CTCGCTTCGGCAGCACA-3'	5'-AACGCTTCACGAATTTGCGT-3'
GAPDH	5'-CAAAGGTGGATCAGATTCAAG-3'	5'-GGTGAGCATTATCACCCAGAA-3'

(3) Western Blot detection

After lysis, the cells were gathered and transferred to a centrifuge tube, where they were centrifuged at 12000×g and 4℃ for 10min, and the obtained supernatant was collected as a protein sample. The protein concentration was determined by BCA method, and protein samples were diluted with Lysis buffer to prepare a protein of 20mg/ml. After that, 8.00% separation gel and 5.00% laminated gel were prepared for SDS-PAGE electrophoresis, and upon completion, the protein was transferred to a PVDF membrane. Then β-catenin, c-myc (1:1000) primary antibody, and internal reference β-actin (1:3000) were added for overnight sealing at 4 ° C. Next, it was adding with HRP-labeled goat anti-mouse secondary antibody (1: 5000), incubate at 37 ° C for 1 h, and rinse 3 times with TBST for 5 min each. Finally, development was carried out in a dark room, the excess liquid on the membrane was firstly blotted, and then illuminated by ECL to develop. The protein bands were scanned and the grayscale values were analyzed by Quantity One software (Molecular Devices Corp, The Bay Area, CA, United States).

(4) Cell proliferation experiment

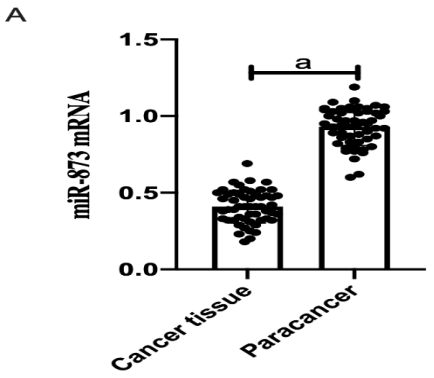
The viability of cells was detected by MTT. Twenty-four hours after transfection, the cells were harvested and adjusted to 5×10^3 cells per well. Then the cells were inoculated on 96-well plates and incubated at 37 ℃ for 24 h, 48 h and 72 h, at which time point, 20 μL MTT solution (5 μ mg/mL) was added for another 4-hour culture at 37 ℃. Finally, 200 μL dimethyl sulfoxide was added to each well, and then the OD value of each group of cells was measured using a spectrophotometer at a wavelength of 570 mm.

(5) Apoptosis experiment

After 48 hours of transfection, the cells were digested with 0.25% trypsin and washed with PBS twice. Then they were resuspended with 100 μL of AnnexinV binding buffer, configured to a 1×10^6 cells/mL suspension, and added with 5 μL Annexin-V/FITC solution for a 15-minute incubationat 4 ℃. Followed by the addition of 5 μL PI staining solution, and then the culture was resumed for 5min at 4 ℃. Cell apoptosis was determined by FC**.** After conducting the experiment three times, the average value was obtained.

2 Statistical methods

Statistical analysis was carried out by SPSS 20.0 (SPSS, Inc, Chicago, IL, United States). Normally



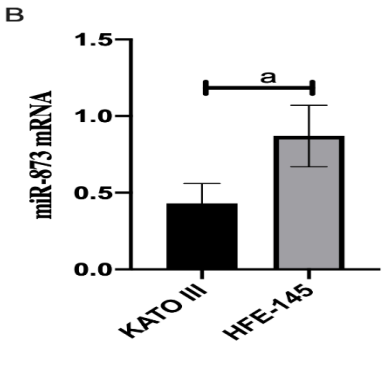
(SPSS, Inc, Chicago, IL, United States). Normally distributed data were described as mean ± standard deviation (mean ± SD). Measurement data were compared by independent sample t-test, multi-time data were compared using repeated measures ANOVA, and Bonferroni method was used for post hoc testing. Mean comparison among multiple groups was conducted using one-way ANOVA, and post hoc tests were performed using the LSD-t method. P<0.05 indicated a statistically significant difference.

3 Results

3.1 miR-873 expression in GC

(1) QRT-PCR quantitative detection of miR-873 expression in GC tissues and cell lines

The results showed that miR-873 expression in GC tissues was statistically down-regulated compared to normal tissues adjacent to cancer, and miR-873 expression in GC cells KATO III was statistically inhibited compared with HFE-145 of human gastric mucosa normal epithelial cells. (Figure 1)



(2) Effects of miR-873 on biological functions of KATO III

MiR-873 was statistically reduced in miR-873-inhibitor compared with miR-NC group, and was statistically upregulated in miR-873-mimics group

as compared to miR-873-inhibitor group (P<0.01). MTT results demonstrated that the proliferation ability was statistically lower in miR-873-inhibitor group than in miR-NC group (P<0.05), and that in miR-873-mimics group was higher compared with siRNA-NC group (P<0.05). As indicated by FC, the apoptosis rate was statistically lower in miR-873-inhibitor group than in NC group (P<0.001), and that in miR-873-mimics group was statistically lower compared with miR-NC group (P<0.001). (Figure 2)

A: MiR-873 was statistically up-regulated in GC tissues; B: Compared with human gastric mucosa normal epithelial cells HFE-145, miR-873 was notably downregulated in GC cells KATO III. Note: an indicated P<0.001.

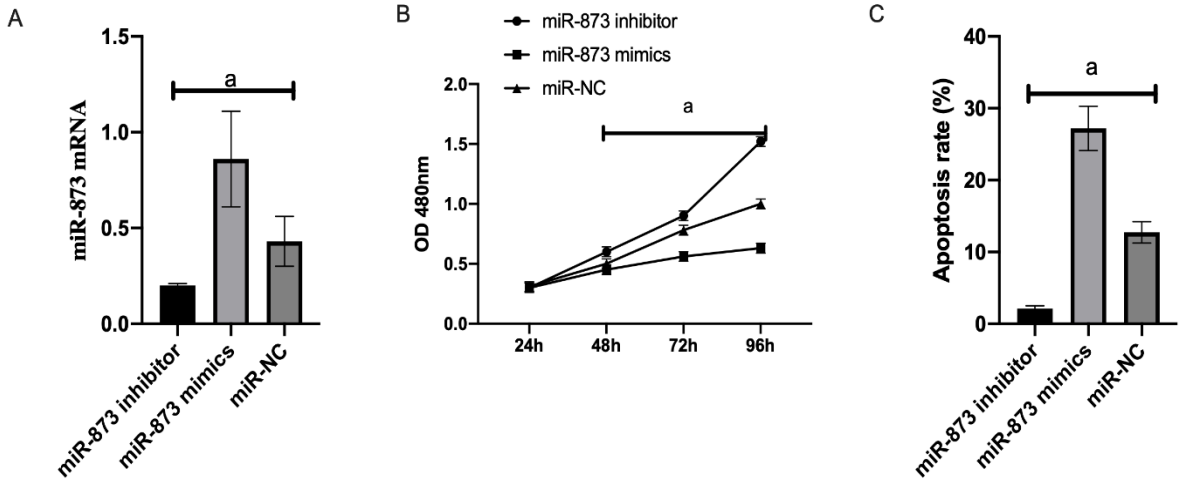


Figure 2. **MiR-873 expression in cells and its effects on cell biological functions**

A, MiR-873 expression in each cell line. **B:** MiR-873 expression in KATO III after transfection. **C:** Proliferation of KATO III after transfection. Apoptosis of KATO III after transfection. Note: a indicated P<0.001

3.2 Targeted binding of FGF5 with miR-873

Double luciferase reporter gene was used to detect the luciferase activity of KATO III cells transfected with pmirGLO-FGF5 WT/MUT and miR-873 mimics. The results showed that transfection of pmirGLO FGF5 WT and miR-873 mimics statistically inhibited the luciferase activity of KATO III cells, while transfection of pmirGLO-FGF5 MUT and miR-873 mimics had no effect on luciferase activity of KATO III cells. Compared with NC group, miR-873-minics and miR-873-inhibition groups had statistically lower FGF5 expression. (Figure 3)

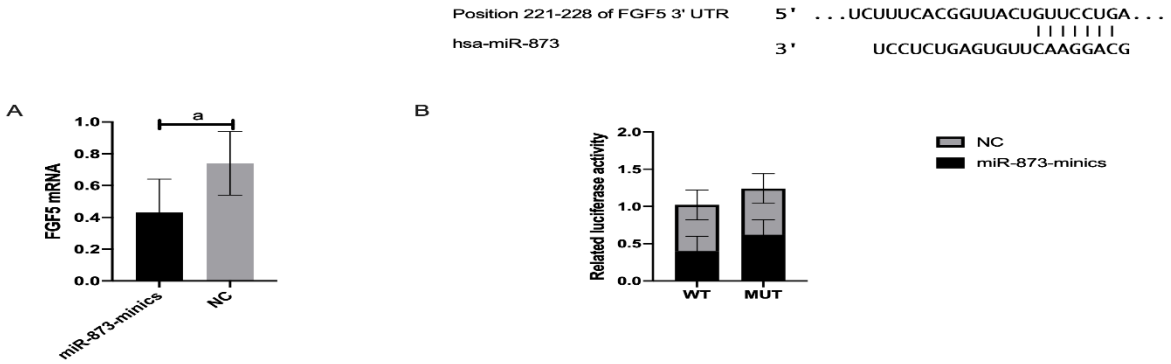


Figure 3. **Targeted binding of FGF5 with miR-873**

A: FGF5 expression in KATO III after transfection. **B:** Luciferase activity of KATO III. Note: a indicated P<0.001.

3.3 FGF5 expression in GC

(1) QRT-PCR quantitative detection of FGF5 expression in GC tissues and cell lines

The results showed that FGF5 expression in GC tissues was statistically up-regulated compared to normal tissues adjacent to cancer, and that in GC cells KATO III was statistically increased compared with HFE-145 of human gastric mucosa normal epithelial cells. (Figure 4)

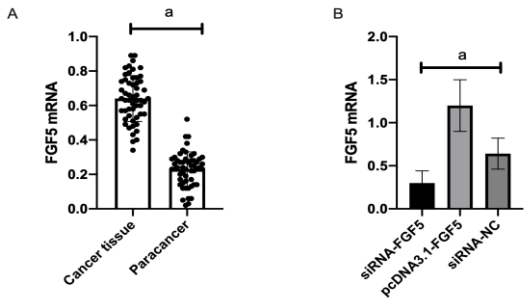


Figure 4. **FGF5 expression in GC**

A: The expression of FGF5 in GC tissues was statistically up-regulated; **B:** Compared with human gastric mucosa normal epithelial cells HFE-145, the expression of FGF5 in GC cells KATO III was statistically increased. Note: an indicated P<0.001.

(2) Effects of FGF5 on biological functions of KATO III

We selected KATO III for transfection. Compared with siRNA-NC group, FGF5 was statistically decreased in siRNA-FGF5 group (P<0.01), while was markedly elevated in pcDNA3.1-FGF5 group (P<0.01). MTT results showed that the proliferative capacity of siRNA-FGF5 group was statistically lower compared with siRNA-NC group (P<0.05), and the proliferative capacity of pcDNA3.1-FGF5 group was increased compared with siRNA-NC group (P<0.05). Flow cytometry results exhibited that the apoptosis rate was statistically lower in siRNA-FGF5 and pcDNA3.1-FGF5 groups was group was statistically reduced in comparison with siRNA-NC group (both P<0.001) . (Figure 5)

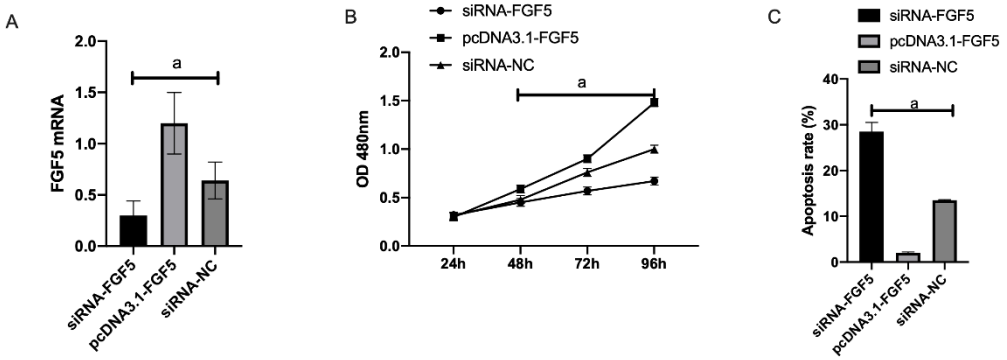


Figure 5. **FGF5 expression in cells and its effects on cell biological functions**

A, FGF5 expression in each cell line. **B:** FGF5 expression in KATO III after transfection. **C:** Proliferation of KATO III after transfection. Apoptosis of KATO III after transfection. Note: an indicated P<0.001.

3.4 In vitro experiments verify that miR-873 inhibits FGF5 and promotes the occurrence and metastasis of GC

Wb showed that, FGF5 up-regulation led to statistically up-regulated β-catenin, c-myc, vimentin, Snail and N-cadherin, and statistically inhibited Bax, Caspase-3 and E-cadherin, while simultaneous miR-144-3p overexpression reversed the EMT progression caused by up-regulation of FGF5. The results showed that miR-873 could inhibit the promotion effect of FGF5 on GC progression. (Figure 6, 7)

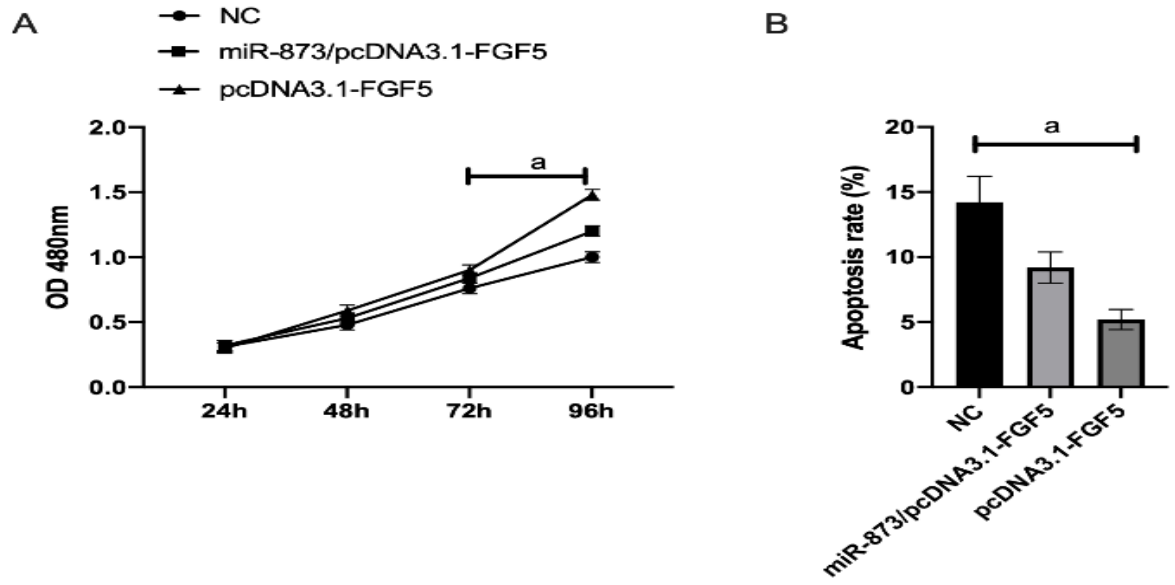


Figure 6. **In vitro experiments verify that miR-873 inhibits FGF5 and promotes the occurrence and metastasis of GC**

A: Proliferation of KATO III. **B:** Apoptosis of KATO III.

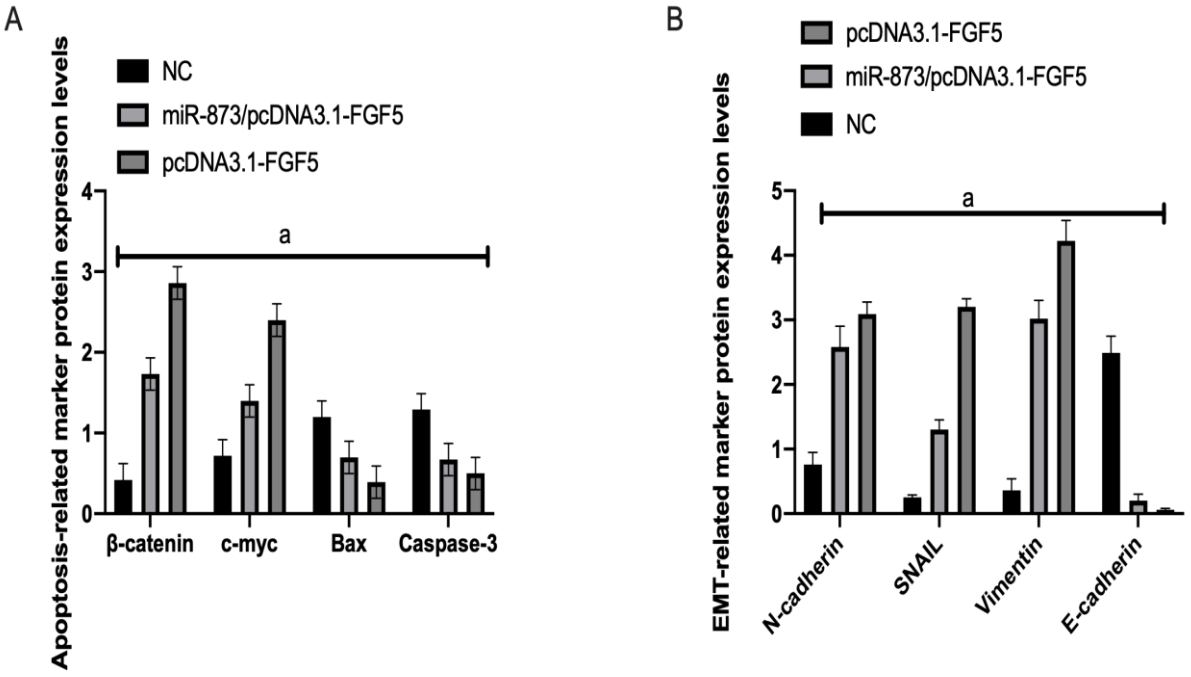


Figure 7. **Apoptosis-related proteins and EMT-related proteins in KATO III**

A: Apoptosis-related proteins in the cytoplasm of KATO III. **B:** EMT-related proteins in the cytoplasm of KATO III.

Discussion

In recent years, miRNAs have been shown to be involved in carcinogenesis by influencing the expression of certain cancer-related pathways (Zhang B-Y et al.,2020; Zhou et al.,2020). Dysregulation of miRNA occurs in multiple

malignancies, and participates in cancer progression and is crucial in gene regulation in cancer metastasis, treatment and prognosis (Shi et al.,2020). They are indispensable in various cellular mechanisms. MiR-137 inhibits the migration of prostate cancer cells by targeting LGR4 via the EGFR/ERK signaling pathway (Guan et al.,2019). This study is to investigate the effect of miR-873 on the progression and biological function of GC by regulating FGF5.

In this study, we found through qRT-PCR that miR-873 expression in GC tissues and GC cells KATO III was statistically decreased, and high FGF5 expression was linked with the differentiation of GC patients. By monitoring the contents of two target genes in the serum of the patients and drawing ROC curves, it was found that miR-873 and FGF5 had better diagnostic efficacy in GC. Currently, it has been reported that Mir-873 is inhibited in digestive diseases (Chen Yu et al.,2020). Through TargetScan database analysis, we further found a targeted relationship between FGF5 and miR-873, and between miR-873 and ZEB2, and that miR-873 and FGF5 were correlated with GC differentiation. In addition, FGF5 was observed to be overexpressed in GC tissues and GC cells KATO III. MiR-873-5p inhibits cell migration and invasion of papillary thyroid carcinoma by regulating CXCL16(Wang Zhenglin et al.,2020). MicroRNA-related studies suggest that miR-567 inhibits cell proliferation, migration and invasion by targeting FGF5 in osteosarcoma (Liu et al.,2018). Zhang et al found in their study that miR-145-5p down-regulation improved the survival of retinal ganglion cells by targeting FGF5, thus delaying the progression of diabetic retinopathy (Zhang Jingjing et al.,2019). Combined with the data of this study, we believe that miR-873 is silenced in GC while FGF5 is highly expressed, and miR-873 can affect the progression of GC by targeting FGF5.

Finally, we verified the inhibitory effect of miR-873 targeting FGF5 on EMT of GC cells in vitro. Relevant reports on EMT show that EMT is necessary for the growth and survival of tumor cells (Saxena et al.,2020), while FGF controls the EMT of the stomach and small intestine by regulating cell division (Zhang Jinglin,Zhou Yuhang et al.,2019). In the current study, miR-873 upregulation statistically inhibited FGF5 mRNA expression in GC, and miR-873 overexpression statistically inhibited the proliferation and EMT of colon cancer cells, reversing the inhibition of EMT induced by up-regulation of FGF5. MiR-873-5p, a new regulation of TUSC3 gene in colon cancer, can partially reverse the disease progression caused by the activation of AKT pathway in colon cancer by inhibiting TUSC3 gene (Zhu et al.,2019). Relevant research suggests that miR-873 can target differentiated embryonic chondrocyte-expressed gene 2 (DEC2) to notably inhibit the growth, migration and EMT of esophageal cancer cells (Liang et al.,2018); Cao et al. found that miR-873-5p affected the progression of GC by targeting hedgehog GLI signal (Cao et al.,2016).

Still, there is room for improvement in this study. Animal experiments had not yet conducted, and further research is needed to determine whether miR-873 can affect the occurrence and development of tumors by other means. Therefore, we hope to explore the miRNA regulatory network through bioinformatics analysis in future studies, so as to provide more basis for our experiments.

Taken together, miR-873 is a potential therapeutic method for GC by regulating FGF5 to inhibit the proliferation and EMT of GC cells.

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