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miR-188-5p Suppresses Gastric Cancer Cell Proliferation and Invasion via Targeting ZFP91

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MicroRNAs (miRNAs) have been demonstrated to be essential regulators in the development and progression of various cancers. The role of miR-188-5p in gastric cancer (GC) has not been determined. In this study, we found that the expression of miR-188-5p was downregulated in GC tissues compared with adjacent normal tissues. The lowly expressed miR-188-5p was significantly associated with lymph node metastasis and advanced TNM stage. Moreover, overexpression of miR-188-5p significantly inhibited GC cell proliferation, migration, and invasion but promoted cellular apoptosis. Mechanistically, we identified transcription factor ZFP91 as a target gene of miR-188-5p in GC. We found that miR-188-5p overexpression significantly inhibited the expression of ZFP91 in GC cell lines. There was an inverse correlation between the expression of miR-188-5p and ZFP91 in GC tissues. We found that restoration of ZFP91 in miR-188-5p-overexpressed MGC-803 and SGC-7901 cells promoted cell proliferation, migration, and invasion. Finally, we also showed that overexpression of miR-188-5p inhibited tumor growth in vivo. Taken together, our findings indicated that miR-188-5p serves as a tumor suppressor in human GC by targeting ZFP91, suggesting that miR-188-5p might be a promising therapeutic target for GC treatment.

Key words: miR-188-5p; Gastric cancer; Proliferation; Metastasis; ZFP91

INTRODUCTION

Gastric cancer (GC) is the second most common cause of cancer-related mortality, causing 736,000 deaths per year[1]. The incidence is declining, but the mortality rate is high, making it still a major healthcare issue[2]. Although surgery is still the main treatment for GC, the recurrence rates are very high[3,4]; thus, it is critical to determine the mechanism for the incidence of GC.

Originally discovered in *Caenorhabditis elegans*, microRNAs (miRNAs) are found in most eukaryotes, including humans[5,6]. Reports say that miRNAs account for 1%–5% of the human genome[7] and regulate gene expression through RNA silencing and posttranscriptional regulation[8,9]. Cancer, as a multistep process, requires dysregulation of genes involved in cell proliferation and differentiation[10]. Genes linked with cancer development are characterized as oncogenes and tumor suppressors. Overexpression of oncogenes promotes tumor development[11]. Conversely, tumor suppressor gene expression suppresses tumor formation[12]. Recently, miRNA dysregulation has been found in most tumors examined[13], and miRNAs have also been recognized to function in tumor formation[14,15]. Reports have shown that let-7s acts as a tumor suppressor since it suppresses tumor growth by binding and destabilizing HMG2A, while miR-21 functions as an oncogene since it represses the suppressor genes mapsin, programmed cell death 4 (PDCD4), tropomyosin 1 (TPM1), and phosphatase and tensin homolog (PTEN) to promote tumor progression[16,17].

Previous studies indicate that miR-188-5p serves as a tumor suppressor gene in prostate cancer[18], hepatocellular carcinoma[19], and acute myeloid leukemia[20]. However, whether miR-188-5p plays a role in GC remains to be explored. In this study, we found that miR-188-5p was downregulated in GC. Furthermore, we found that overexpression of miR-188-5p significantly inhibited GC cell proliferation, migration, and invasion both in vitro and in vivo. Mechanistically, miR-188-5p binds to the 3′-UTR of zinc finger protein 91 (ZFP91) to regulate tumor progression. Overexpression of ZFP91 rescued the proliferation, migration, and invasion of GC cells. In all, our study demonstrates that miR-188-5p suppresses GC progression through inhibition of ZFP91.

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MATERIALS AND METHODS

Patient Samples

Fifty-one GC tissue specimens were obtained from Jiaxing First Hospital (Zhejing Province, P.R. China). All patients were not treated with radiation therapy and chemotherapy prior to surgery. Clinical stages were classified according to the World Health Organization criteria and stored in liquid nitrogen or −80°C. All studies were approved by the Institutional Review Board of Jiaxing First Hospital. Written informed consent was obtained from all participating patients.

Cell Culture

Gastric normal cell line GES-1 and cancer cell lines MGC-803, SGC-8901, MKN-28, MKN-45, and BGC-823 were cultured in RPMI-1640 (Invitrogen, Thermo Fisher Scientific, Waltham, MA, USA) supplemented with 10% FBS and 2 mM glutamine, and 100 µg/ml streptomycin and penicillin (Thermo Fisher Scientific). Cells were routinely incubated at 37°C with 5% CO_2.

Reverse Transcription Quantitative Polymerase Chain Reaction (RT-qPCR)

Total RNAs were extracted using TRIzol® reagent (Invitrogen; Thermo Fisher Scientific, Inc.) according to the manufacturer's protocol. Total RNA was reverse transcribed into cDNA using the PrimeScript™ RT reagent kit with gDNA Eraser (Takara Biotechnology Co., Ltd., Dalian, P.R. China), and 1 µg of total RNA was reverse transcripted for each sample. PCR was done on an Applied Biosystems RT-PCR machine (Foster City, CA, USA), and all results were normalized to U6 snRNA or GAPDH mRNA expression.

CCK-8 Proliferation Assays

Cells (1×10^3 per well) were seeded in 96 wells. Forty-eight and 72 h later, cellular proliferation was evaluated using Cell Counting Kit-8 assay (CCK-8; Dojindo Molecular Technologies, Inc., Kumamoto, Japan) according to the manufacturer's protocol. The absorbance was measured at a wavelength of 450 nm using a Multiskan™ GO Microplate Spectrophotometer (Thermo Fisher Scientific, Inc.).

Apoptosis Analysis

7-Aminoactinomycin D (7-AAD staining) was used to analyze the apoptosis of cancer cells. Briefly, the cells were stained for 30 min at room temperature in the dark with 5 µl of 7-AAD and then analyzed by FACSCalibur (Becton-Dickinson, San Jose, CA, USA).

Migration and Invasion Assays

Migration was measured using 6.5-mm Transwell inserts with 8.0-µm pore polycarbonate membranes (Costar; Corning Incorporated, Corning, NY, USA). Cell invasion assay was performed with 6.5-mm Transwell inserts with 8.0-µm pore polycarbonate membranes (Costar; Corning Incorporated). Briefly, 2×10^5 transfected and nontransfected cells were suspended and seeded into the upper chambers of the inserts, while the culture medium was added to the lower chambers. Twenty-four hours later, cells on the upper surface of the membrane were removed, but cells in the lower membrane were fixed with 100% methanol at room temperature for 20 min and stained with crystal violet. Cells were observed using an optical microscope (Olympus Corporation, Tokyo, Japan) and counted in five random fields from each well. The average number of migrated or invaded cells was calculated.

Tumor Growth In Vivo

Six-week-old male nude mice were used for tumor growth and metastasis assays. For tumor grow assays, the mice were subcutaneously injected with 1×10^6 cells overexpressing miR-188-5p or control ($n=6$ mice/group), and tumor volume was monitored and calculated at 1, 2, 3, and 4 weeks after injection. At 4 weeks postinjection, all mice were sacrificed and the tumors were removed. All animal experiments were approved by the ethics committee of Jiaxing First Hospital.

Statistical Analysis

All data were analyzed with Student's *t*-test for pairwise comparisons. A value of $p<0.05$ was considered to indicate a statistically significant difference. Data are presented as mean ± standard deviation (SD) of at least three independent experiments. Statistical analysis was performed with SPSS.

RESULTS

miR-188-5p Was Downregulated in GC Tissues

To explore the role of miR-188-5p in GC, we examined miR-188-5p expression level in GC tumor tissues ($n=51$) and nontumor tissues ($n=51$) by RT-qPCR. Results showed that miR-188-5p was downregulated in GC tumor tissues compared with adjacent nontumor tissues (Fig. 1A). The expression of miR-188-5p was downregulated in the advanced clinical stages of GC (Fig. 1B) and was much lower in metastasic GC tissues (Fig. 1C). In addition, miR-188-5p expression was downregulated in all the GC cell lines we checked compared with the normal gastric epithelial cell line GES-1 (Fig. 1D). These results show that miR-188-5p is downregulated in GC tissues, indicating that miR-188-5p plays a suppressing role in GC progression.

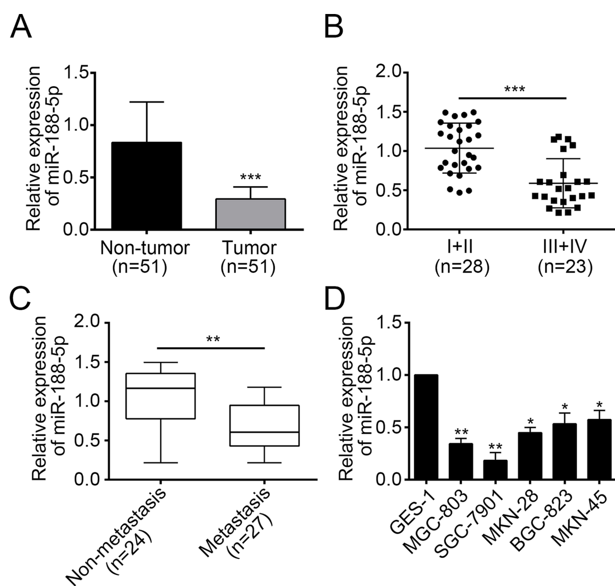

Figure 1. MicroRNA-188-5p (miR-188-5p) was downregulated in gastric cancer (GC) tissues. (A) Reverse transcription quantitative polymerase chain reaction (RT-qPCR) results indicated that the expression of miR-188-5p in GC tissues was downregulated compared with matched adjacent normal tissues. (B) Relative expression level of miR-188-5p in patients at different clinical stages. (C) Relative expression level of miR-188-5p in metastatic or nonmetastatic GC tissue. (D) Relative expression level of miR-188-5p in GC cell lines relative to the normal human gastric epithelial cell line GES-1. *$p<0.5$, **$p<0.01$, and ***$p<0.001$ by two-tailed Student's t-test. All data presented are shown as means±standard deviation (SD) collected from three independent experiments.

Overexpression of miR-188-5p Reduced Cell Proliferation, but Enhanced the Apoptosis

To explore the role of miR-188-5p on GC progression, we overexpressed miR-188-5p in MGC-803 and SGC-7901 cell lines. Results showed that miR-188-5p was successfully overexpressed in these cell lines (Fig. 2A). To reveal the function of miR-188-5p on GC, proliferation assay was first analyzed. As shown in Figure 2B, proliferation of MGC-803 and SGC-7901 was significantly suppressed 48 and 72 h after miR-188-5p mimic transfection. Colony formation assay also showed a significant reduction in colony numbers, which is consistent with the CCK-8 proliferation assays (Fig. 2C). To further evaluate the effect of miR-188-5p on cell proliferation, the cell cycle of miR-188-5p-overexpressed MGC-803 and SGC-7901 cell lines was analyzed by flow cytometry, and the results showed that more cells were stagnated at the G_0/G_1 phase compared with control transfected cells (Fig. 2D). Overexpression of miR-188-5p induced the apoptosis of MGC-803 and SGC-7901 cells (Fig. 2E). These results indicate that overexpression of miR-188-5p results in inhibitory effects on GC progression; thus, miR-188-5p functions as a tumor suppressor of GC.

Overexpression of miR-188-5p Inhibited Cell Migration and Invasion

Studies have shown that miR-188-5p suppresses the metastasis of hepatocellular carcinoma[19] and prostate cancer[18]. To determine whether miR-188-5p also regulates

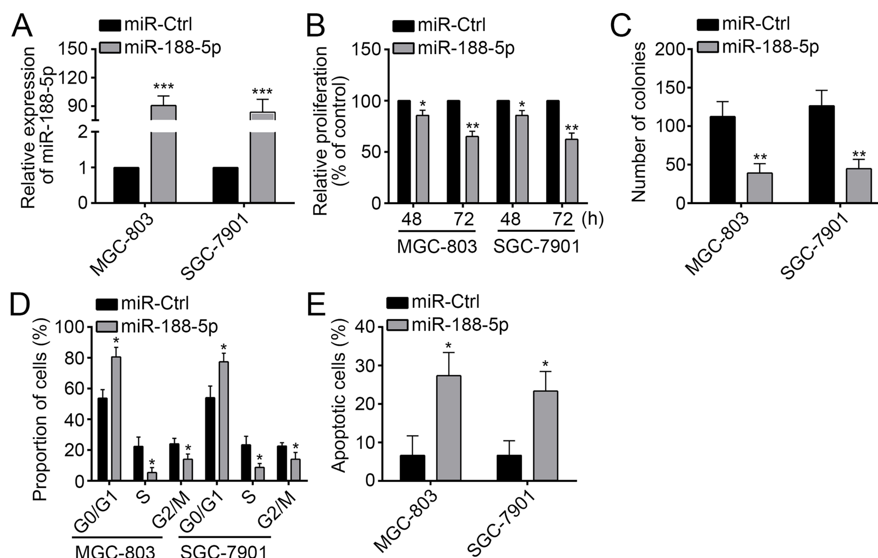

Figure 2. Overexpression of miR-188-5p reduced cell proliferation but enhanced apoptosis. (A) miR-188-5p mimic significantly enhanced the expression of miR-188-5p in MGC-803 and SGC-7901 cells. (B) Graphical representation of cell counting kit-8 (CCK-8) assay in MGC-803 and SGC-7901 cells transfected with miR-188-5p mimic or control for 48 or 72 h. (C) Colony formation assay indicated that overexpression of miR-188-5p significantly suppressed the colony numbers. (D) Cell cycle analysis and (E) apoptosis assay of MGC-803 and SGC-7901 cells transfected with miR-188-5p mimic or control. *$p<0.05$, **$p<0.01$, and ***$p<0.001$ by two-tailed Student's t-test. All data were collected from three independent experiments.

metastasis in GC cancer, we performed Transwell assays with miR-188-5p-overexpressed or control MGC-803 and SGC-7901 cells. Results indicated that miR-188-5p overexpression significantly inhibited the migration and invasion of MGC-803 and SGC-7901 cells (Fig. 3A and B). These data suggest that miR-188-5p inhibits GC cell migration and invasion.

ZFP91 Was a Target of miR-188-5p

miRNAs have long been recognized to regulate gene expression through binding to target gene 3′-UTRs[5]. We found that miR-188-5p had a complementary sequence with *ZFP91* mRNA (Fig. 4A). To validate that ZFP91 is a target of miR-188-5p, the complementary sequence was mutated, and a binding assay was conducted. Luciferase assay results showed that overexpression of miR-188-5p significantly inhibited ZFP91 expression (Fig. 4B), while mutation in the 3′-UTR of ZFP91 blocked the inhibitory effect (Fig. 4B). This indicates that miRNA-188-5p binds to the 3′-UTR of ZFP91. Indeed, when miR-188-5p was overexpressed in MGC-803 and SGC-7901 cells, ZFP91 expression was downregulated (Fig. 4C and D). We also found that there was a negative correlation between miR-188-5p and ZFP91 by Spearman's correlation analysis (Fig. 4E). In contrast with miR-188-5p being downregulated in tumor tissues (Fig. 1A), ZFP91 was overexpressed in tumor tissues (Fig. 4F). All of these tell us that ZFP91 is a target of miRNA-188-5p, and miRNA-188-5p binds to the 3′-UTR to regulate ZFP91 expression.

ZFP91 Restored the Effects of miR-188-5p Mimic on GC Cells

As miR-188-5p is downregulated in GC tumors, while ZFP91 is upregulated in GC tumors, and miR-188-5p regulates ZFP91 expression, we wondered whether miR-188-5p regulates GC progression through ZFP91. ZFP91 expression level was restored in MGC-803 and SGC-7901 cells (Fig. 5A), and this resulted in the rescue of proliferation (Fig. 5B), apoptosis (Fig. 5C), migration (Fig. 5D), and invasion abilities (Fig. 5E). These results show that miR-188-5p inhibits GC progression through

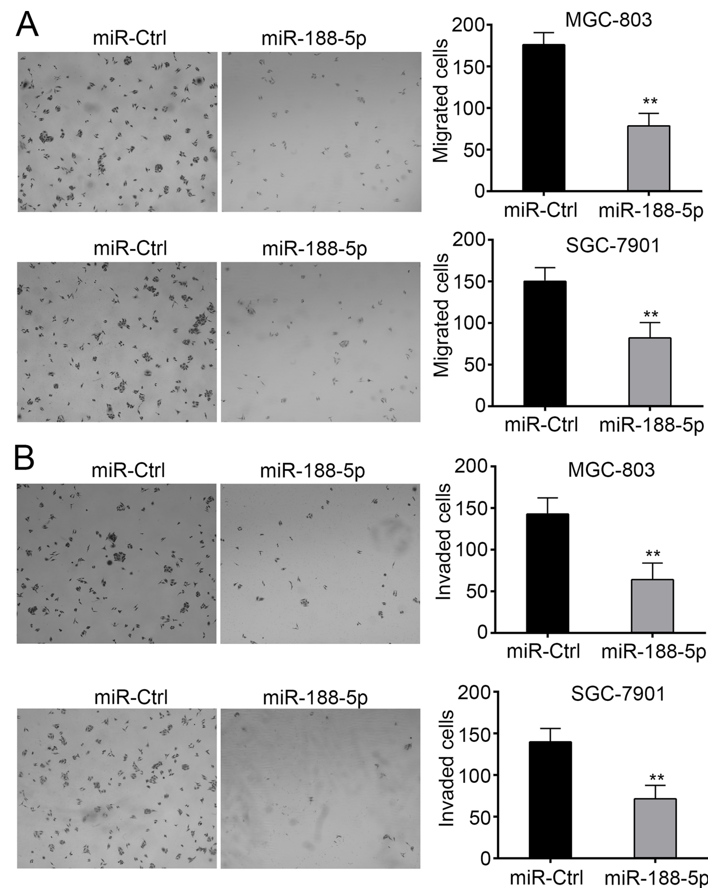

Figure 3. Overexpression of miR-188-5p inhibited cell migration and invasion. Ectopic expression of miR-188-5p in MGC-803 and SGC-7901 cells inhibited (A) cell migration and (B) invasion. $^{**}p<0.01$ by two-tailed Student's *t*-test. All data presented are shown as means ± SD collected from three independent experiments.

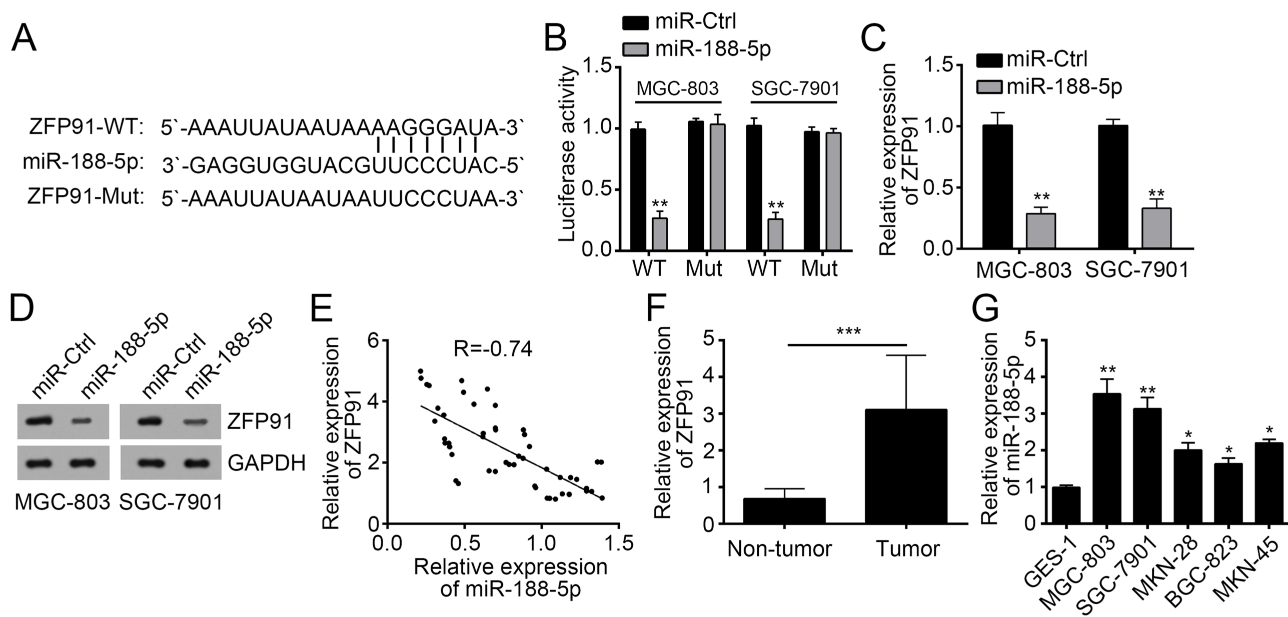

Figure 4. Zinc finger protein 91 (ZFP91) was a target of miR-188-5p. (A) The predicted complementary sequence in the 3′-UTR of ZFP91 mRNA with miR-188-5p. (B) Upregulation of miR-188-5p significantly inhibited the luciferase activity in MGC-803 and SGC-7901 cells, while mutation of the complementary sequence in the 3′-UTR region of ZFP91 mRNA abrogated the inhibitory effect of miR-188-5p. Overexpression of miR-188-5p significantly inhibited the (C) mRNA and (D) protein levels of ZFP91 in MGC-803 and SGC-7901 cells. (E) The correlation between ZFP91 mRNA and miR-188-5p expression in 51 cases of GC specimens was evaluated using Spearman's correlation analysis. (F) Relative expression level of ZFP91 in GC tissues and corresponding normal tissues. (G) Relative expression of ZFP91 in GC cell lines was determined by RT-qPCR. $*p<0.05$, $**p<0.01$, and $***p<0.001$ by two-tailed Student's *t*-test. All data presented are shown as means ± SD collected from three independent experiments.

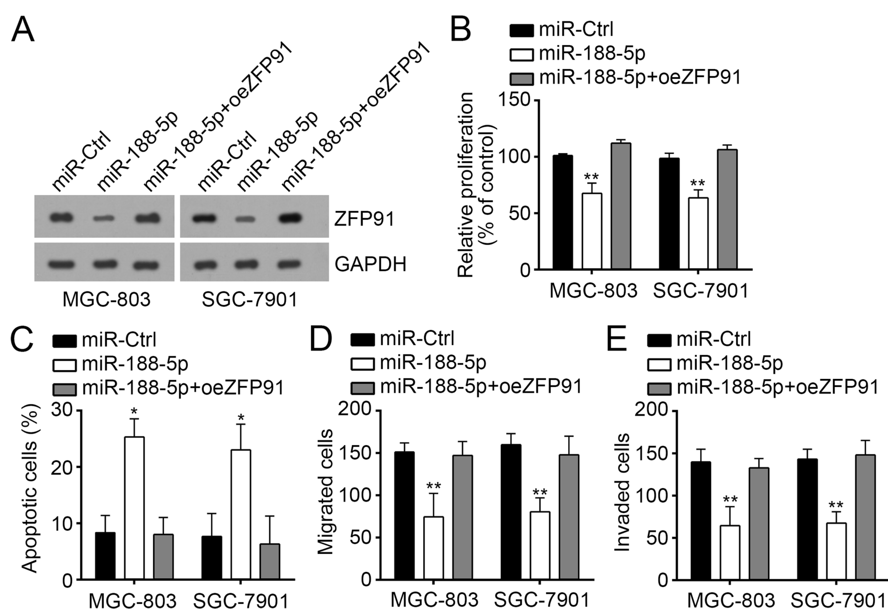

Figure 5. ZFP91 restored the effects of miR-188-5p mimic in MGC-803 and SGC-7901 cells. (A) The protein levels of ZFP91 were restored in cotransfected MGC-803 and SGC-7901 cells. (B) Restoration of ZFP91 rescued the proliferation ability of miR-188-5p-overexpressed MGC-803 and SGC-7901 cells. (C) Restoration of ZFP91 inhibited the apoptosis of miR-188-5p-overexpressed MGC-803 and SGC-7901 cells. Restoration of ZFP91 enhanced the (D) migration and (E) invasion abilities of miR-188-5p-overexpressed MGC-803 and SGC-7901 cells. $*p<0.05$ and $**p<0.01$ by two-tailed Student's *t*-test. All data presented are shown as means ± SD collected from three independent experiments.

ZFP91 in vitro. To demonstrate that miR-188-5p regulates GC progression in vivo, miR-188-5p-transfected SGC-7901 cells were injected into nude mice to observe the rate of tumor growth (Fig. 6). Results show that ZFP91 overexpression (Fig. 6C) rescued the inhibitory effect of miR-188-5p on tumor growth, indicated by rescued tumor volume (Fig. 6A) and tumor weight (Fig. 6B). These results show that miR-188-5p regulates GC progression in vivo. All these results prove that miR-188-5p inhibits GC progression through ZFP91.

DISCUSSION

Though advances in diagnosis and treatment have greatly improved long-term survival for early GC, the prognosis of advanced cancer still remains poor[21]. Early GC has few symptoms, making it very difficult to observe, so the disease is usually in an advanced stage when it is diagnosed[22]. In the past 15 years, researchers have uncovered some molecular mechanisms of invasion and metastasis of GC, but not enough to help develop good treatments for the disease[23]. For advanced cancers, invasion and metastasis are achieved via a multistep progression, including changes in cell adhesion molecules, various growth factors, matrix degradation enzymes, and motility factors[24]. Nowadays, with the tool of genomic science analysis, some detailed mechanisms of GC and its progression have been discovered[25], yet there is still a need for a better understanding of the molecular mechanisms to develop new paradigms and possible improvements in cancer diagnostics and therapeutics. To analyze the mechanisms of tumor progression, gene expression profile analysis is one key approach. In this study, we analyzed miR-188-5p expression in patient tumor samples and adjacent nontumor tissue and found that miR-188-5p was downregulated in tumor tissues.

Previous studies have demonstrated that altered miRNA expression is closely associated with cancer[26]. However the functions of miRNA may vary. Studies have shown that several miRNAs can function as oncogenes, while others will function as tumor suppressor genes[16,17,27,28]. In this study, we found that miR-188-5p was downregulated in GC tissues and cell lines. Overexpression of miR-188-5p reduced GC cell colony formation ability and the proliferation of cancer cells. miR-188-5p overexpression inhibited GC cell invasion and migration. These data all indicate that miR-188-5p functions as a tumor suppressor gene for GC. These findings are in accordance with the previously described tumor suppressor role of miR-188-5p in many other cancers[18–20], suggesting that miR-188-5p may be a universal tumor suppressor, making it a promising target for drug development.

Proliferation, invasion, and migration are all hallmarks of cancer[24]. To achieve an advanced stage, proliferation and resistance to apoptosis are indispensable steps. ZFP91 has been reported to promote proliferation in colon cancer[29] and prostate cancer[30]. In our study, we found that ZFP91 is overexpressed in GC, and ZFP91 promotes the progression of GC. When miR-188-5p is expressed, which targets to the 3′-UTR of ZFP91, the proliferation rate is decreased, while the apoptotic rate is increased in GC cell lines. Overexpression of ZFP91 in miR-188-5p overexpressed cell lines rescued the progression phenotype, indicating a tumor-promoting role of ZFP91 in GC.

We also found that miR-188-5p suppresses GC progression through ZFP91. miR-188-5p overexpression

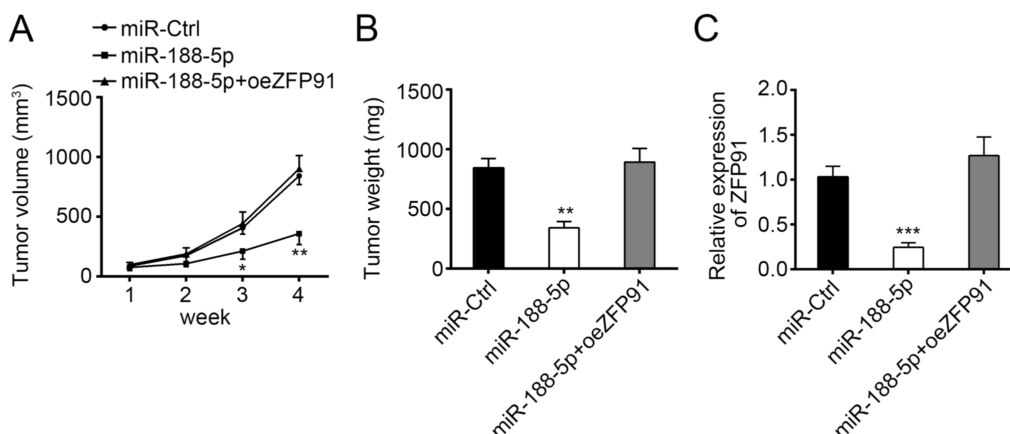

Figure 6. miR-188-5p and ZFP91 showed inverse effects on tumor growth in vivo. (A) The growth curve of tumors in nude mice. SGC-7901 cells were transfected with indicative plasmids and injected into nude mice subcutaneously. $n=6$ for each group. (B) Tumor weight was measured at the endpoint of the experiment. (C) The expression of ZFP91 was analyzed in formed tumor tissues by RT-qPCR. *$p<0.5$, **$p<0.01$, and ***$p<0.001$ by two-tailed Student's t-test. All data presented are shown as means ± SD collected from three independent experiments.

suppressed GC progression, while ZFP91 overexpression blocked the suppressing role. In summary, our research demonstrated for the first time that miR-188-5p functions as a tumor suppressor in GC and explored its functional mechanism. We found that miR-188-5p binds to the 3′-UTR of ZFP91 to inhibit ZFP91 expression, thus leading to proliferation, migration, and invasion inhibition of GC.

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