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Research Article

microRNA-217 suppressed epithelial-to-mesenchymal transition through targeting PTPN14 in gastric cancer

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Background: Gastric cancer (GC) is the one of most common malignancies and its mechanism of metastasis remains unclear. The study was designed to investigate the effects of microRNA-217 on epithelial-to-mesenchymal transition. **Methods:** The expression levels of miR-217 in GC were assayed by real-time qPCR. Metastasis and invasion of cancer cell were assayed by transwell chamber. Double luciferase reporter gene was used to verify the target regulatory relationship between microRNA-217 and tyrosine–protein phosphatase non-receptor type 14 (PTPN14) on gastric cell lines. Epithelial-to-mesenchymal transition (EMT) markers were assayed by Western blot. **Results:** We found that miR-217 had a low level expression in gastric tumor tissues of 40 patients with GC, and a lower expression in the gastric tumor tissues of the patients with GC metastasis. Moreover, miR-217 markedly suppressed the metastasis and invasion of gastric cancer cell line *in vitro*. Furthermore, miR-217 inhibited the expression of PTPN14 by directly targeting its 3′UTR. Moreover, the down-regulation of PTPN14 reduced the metastasis and invasion, whereas up-regulation of PTPN14 led to the enhanced metastases and invasion of gastric cells. miR-217 induced the down-regulation of PTPN14 and inhibited the EMT in gastric cancer cells. **Conclusion:** miR-217 inhibited the EMT through directly targeting to the 3′UTR of PTPN14.

Background

Gastric cancer (GC) is one of the most common cancers [1]. More than 90 percent of mortality in patients with GC is caused by distal metastasis [2,3]. Regrettably, there are no effective treatments for the cure of patients with GC metastasis. Consequently, an in-depth investigation of the molecular mechanisms underlying metastasis is urgent to develop more effective treatments.

MicroRNAs (miRNAs) is a group small non-coding RNAs, inhibiting gene expression. A large number of evidence revealed that miRNAs played an important role in cell proliferation, differentiation, apoptosis, migration and invasion in tumor development [4–8]. Under the molecular mechanisms, epithelial-to-mesenchymal transition (EMT) promotes invasion and migration. EMT is a complex process, showing a loss of E-cadherin expression and gain in the expression of the mesenchymal markers fibronectin, such as zinc finger E-box binding homeobox 1 (ZEB1), resulting in cancer progression and metastasis [10,11]. Compelling evidence indicated that miR-200 family regulates EMT process through targeting ZEB1 and ZEB2, which repressed E-cadherin [9]. Increasing evidence indicated that down-regulation of miR-217 was strongly associated with tumor migration and invasion, such as hepatocellular carcinoma [12]. However, the molecular mechanism of miR-217-induced EMT in GC metastasis is largely unclear. In the present study, we confirmed that miR-217 was decreased in gastric cancer tissues of patients with GC, and up-regulation of miR-217 reduced the migration and invasion of gastric cancer cells

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Table 1 Characterization of the patients with GC

Variable	Gastric cancer, $N = 40$ (%)
Gender	
Male	26 (65)
Female	14 (35)
Age	
Median (range)	52 (34–71)
≥55	24 (60)
<55	16 (40)
Tumor location	
Body	20 (50)
Antrum	13 (33)
Cardia	7 (17)
Histology	
Adenocarcinoma	36 (90)
Mucinous adenocarcinoma	4 (10)
TNM stage	
I	3 (7)
II	11 (28)
III	16 (40)
IV	10 (25)
Lymph node status	
Metastasis	29 (73)
No metastasis	11 (27)

through directly binding to tyrosine–protein phosphatase non-receptor type 14 (PTPN14)-3′UTR, and miR-217-induced the down-regulation of PTPN14 suppressed the EMT in gastric cancer cells.

Materials and methods

Participants and samples

All samples were collected according to the protocols approved by the Ethics Review Board at Zhongnan Hospital of Wuhan University (Ethics No. 201511). Forty patients with GC, including 29 patients with GC metastasis and 11 patients without GC metastasis, were recruited from 2012 to 2014 (Table 1). Written consents were obtained from all participants.

Cell culture

Gastric cell lines including GES-1, BGC-823 and SGC-7901, and HEK293T cell were obtained from ATCC. GES-1 and BGC-823 were cultured in DMEM, and SGC-7901 and HEK293T were cultured in 1640 medium (HyClone) supplemented with 10% FBS at 37°C in 5% CO_2, respectively.

Quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR)

Trizol reagent (Invitrogen) was used to extract total RNAs from the frozen tissues. For PTPN14 mRNA amplification, the reverse transcription reaction was carried out using PrimeScriptTMRT reagent Kits (TaKaRa) at 37°C for 15 min followed by 85°C for 5 min. SYBR®Green Realtime PCR Master Mix was used to perform the PCR reactions at 95°C for 2 min followed by 40 cycles of 95°C for 10 s, 60°C for 10 s and 72°C for 20 s. GAPDH served as an endogenous control. The primers are as follows: GAPDH-F: 5′ GGTGAAGGTCGGAGTCAACGG 3′; GAPDH-R: GAGGTCAATGAAGGGGTCATTG; PTPN14-F: 5′ GTGGACGAACCAAAAGCCAC 3′; PTPN14-R: 5′ GCCCAGACAAAAGGTGCTTG 3′.

Cell migration and invasion assays

After transfection BGC-823 and SGC-7901 cells (5×10^5 cells/ml) with miR-217 control (100 nM), miR-217 mimics (100 nM), si-PTPN14 (100 nM) or PTPN14 vectors (200 ng) for 24 h, the migration and invasion assays were carried out by using QCMTM Laminin Migration Assay (ECM220) and Cell Invasion Assay kit (ECM550) according to

the manufacturer' protocols, respectively. Finally, absorbance was obtained at 570 nm for migration or 560 nm for invasion.

Vector construct and oligonucleotide transfection

For Luciferase assay, the DNA oligonucleotides, which contained the wild-type PTPN14-3′UTR (nt) or mutant PTPN14-3′UTR (nt), were inserted into *Spe* I and *Hind* III restriction enzyme digestion sites. The luciferase report vectors were constructed via the synthesized DNAs and a pMIR-REPORT™ Luciferase vectors. The mutant PTPN14-3′UTR served as a control. The sequences were shown in Table 1.

For PTPN14 vector, human full open reading frame of PTPN14 was transcribed, and amplified, and then the amplified DNAs were inserted into *Spe* I and *Hind* III restriction enzyme digestion sites of pcDNA3.1 vectors (Invitrogen) [13].

MiR-217 control, mimics and inhibitors were purchased from GenePharm (Shanghai GenePharma Co.Ltd., China), and si-PTPN14 was obtained from RIBOBIO (Guangzhou RIBOBIO Co.Ltd., China). Transfections were carried out by using Lipofectamine 2000 (Invitrogen). A final 100 nM of miR-146 NC, mimics, inhibitors, or si-PTPN14, and 200 ng/ml of PTPN14 vectors were used to transfect into BGC-823 and SGC-7901 cells.

Luciferase assay

HEK293T cells were transfected with DNA oligonucleotides containing wide-type PTPN14-3′UTR or mutant PTPN14-3′UTR and Renilla luciferase (pRL-TK, Promega) using Lipofectamine 2000 (Invitrogen). Then, the cells were transfected with miR-217 control (100 nM) or mimics (100 nM), respectively, for 24 h. The cells were lysed using dual luciferase reporter assay system, and the fluorescence activity was measured using GloMax 20/20 Luminometer.

Western blot assay

SDS-PAGE gels (8–12%) were prepared to perform the Western blot assays. The proteins in gels were transferred on PVDF membranes using 200 mA for 90 min, followed by the PVDF membranes were blocked by 3% BSA. The proteins of PTPN14, ZEB1 and E-cadherin were detected with anti-PTPN14 mouse monoclonal antibody, anti-ZEB1 mouse monoclonal antibody and anti-E-cadherin rabbit antibody. GAPDH proteins served as an internal control. All antibodies were purchased from Cell Signaling Technology. The membranes were next incubated with HRP-conjugated secondary antibody (Zhongshan Biotechnology, China). The proteins were detected using SuperSignal® West Dura Extended Duration Substrate kit (Thermo).

Statistical analysis

All statistical analyses were performed using SPSS 13.0 software and graphs were generated using GraphPad Prism 6.0 (Graghpad Software Inc, California). The differences between two groups were determined using Two-tailed Student's *t*-test. Pearson's correlation was used to analyze the relationship between the expressions of miR-217 and PTPN14 mRNA in GC tissues. A P value of less than 0.05 was considered statistically significant.

Results

MiR-217 decreased in GC tissues

To determined miR-217 expression, we analyzed the miR-217 expression in the GC tissues with or without metastasis, and the matched normal tissues. The results showed that the miR-217 expression was markedly decreased in GC tissues with or without metastasis when compared with the control tissues, and miR-217 expression in the metastatic GC tissues was much lower than that in the non-metastatic GC tissues (Figure 1A). The miR-217 expression was also decreased in the tumor tissues of TNM stage II, III and IV, and the lowest expression of miR-217 was found in the tumor tissues of TNM stage IV (Figure 1B). We next selected gastric cell lines of GES-1, BGC-823 and SGC-7901 cells to analyzed miR-217 expression. As shown in Figure 1C, the lowest expression of miR-217 was found in SGC-7901 cells, and the miR-217 expression in BGC-823 cells was significantly lower than that in the GES-1 cells. These results suggested that miR-217 was decreased in GC cells, and associated with tumor metastasis in patients with GC.

MiR-217 inhibited metastasis of GC cells *in vitro*

GC cell line BGC-823 and SGC-7901 were transferred with miR-217 controls or mimics for 24 h, followed by the assays of migration and invasion. As shown in Figure 2, miR-217 mimics significantly reduced the metastasis and

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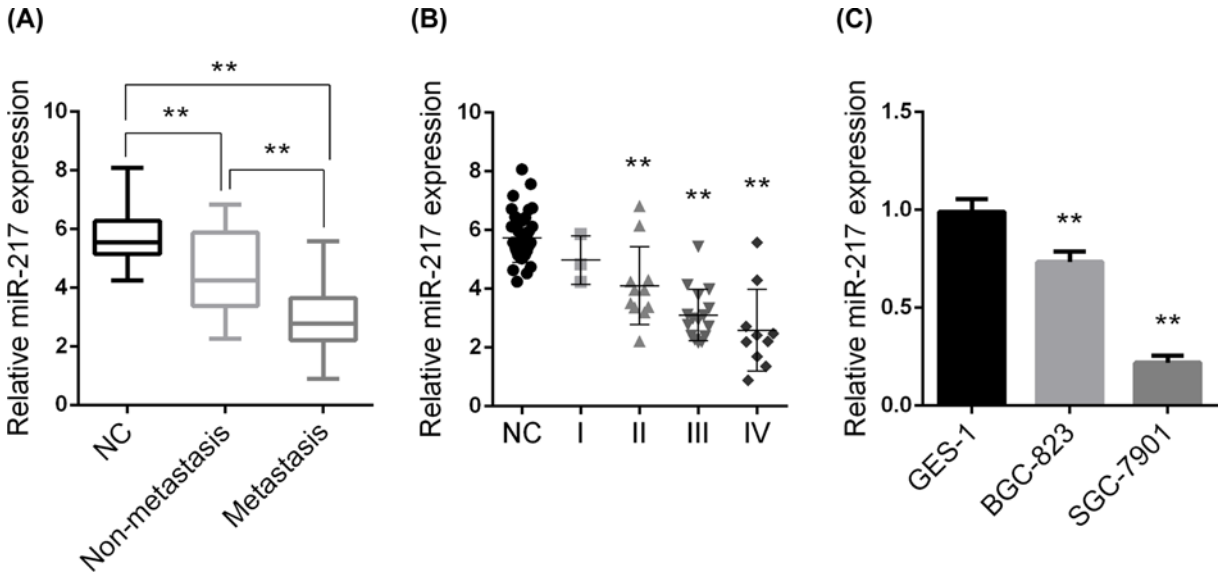

Figure 1. MiR-217 was decreased in tumor tissues of patients with GCmetastasis, and GC cell lines

Quantitative RT-PCR analysis of miR-217 expression. (**A**) Box plots showed miR-217 expression in 40 pairs of gastric tumor tissues of patients with or without GC metastasis. (**B**) Scatter dot plots showed miR-217 expression in tumor tissues of the 40 patients at different TNM stages. (**C**) Bar showed miR-217 expression in gastric cell lines of GES-1, BGC-823 and SGC-7901; **, $P < 0.01$.

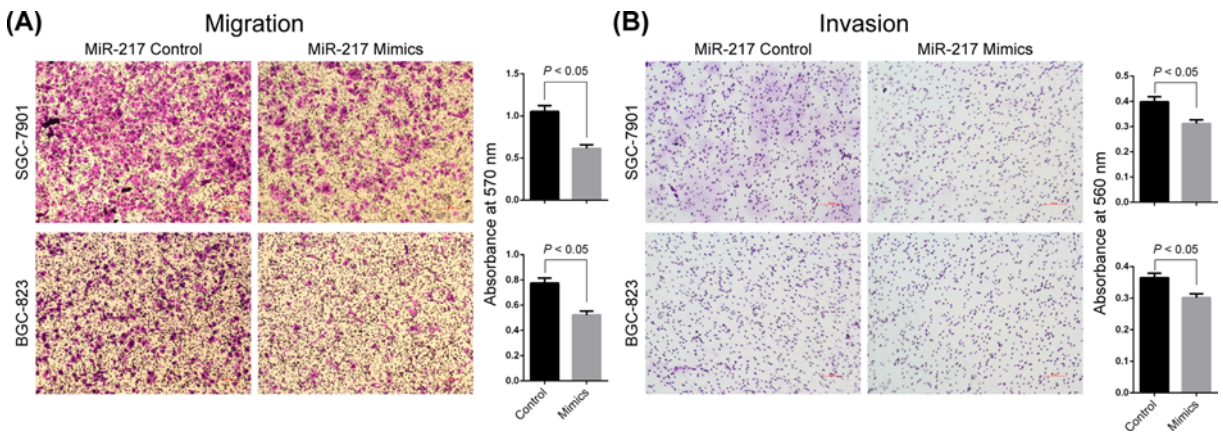

Figure 2. MiR-217 suppressed the migration and invasion of GC cells *in vitro*

BGC-823 and SGC-7901 cells (5×10^5) transfected with miR-217 control (100 nM) or miR-217 mimics (100 nM) for 24 h were used to perform the migration (**A**) and invasion (**B**) assays. Histogram showed the values of absorbance at 570 nm for migration and at 560 nm for invasion.

invasion of BGC-823 and SGC-7901 cells ($P < 0.05$). These data suggested that miR-217 inhibited GC cell metastasis and invasion.

PTPN14 is a novel target of miR-217

Identification of miR-217 target associated with GC metastasis is required for determination of the function of miR-217 in GC metastasis. Therefore, we searched for its potential target genes using prediction algorithms such as MICRORNA.ORG and MIRDB. Interestingly, PTPN14, strongly associated with promoting EMT, is a potential target of miR-217. We next constructed vectors containing the wild-type 3′UTR or mutant 3′UTR of PTPN14 mRNA (Figure 3A). For the luciferase assays, the wild-type or mutant vector and miR-217 control or mimics were cotransfected into HEK293T cells, respectively. The results showed that miR-217 mimics markedly reduced the relative luciferase activity in HEK293T cells transfected with wild-type 3′UTR of PTPN14 ($P < 0.01$), while did not changed

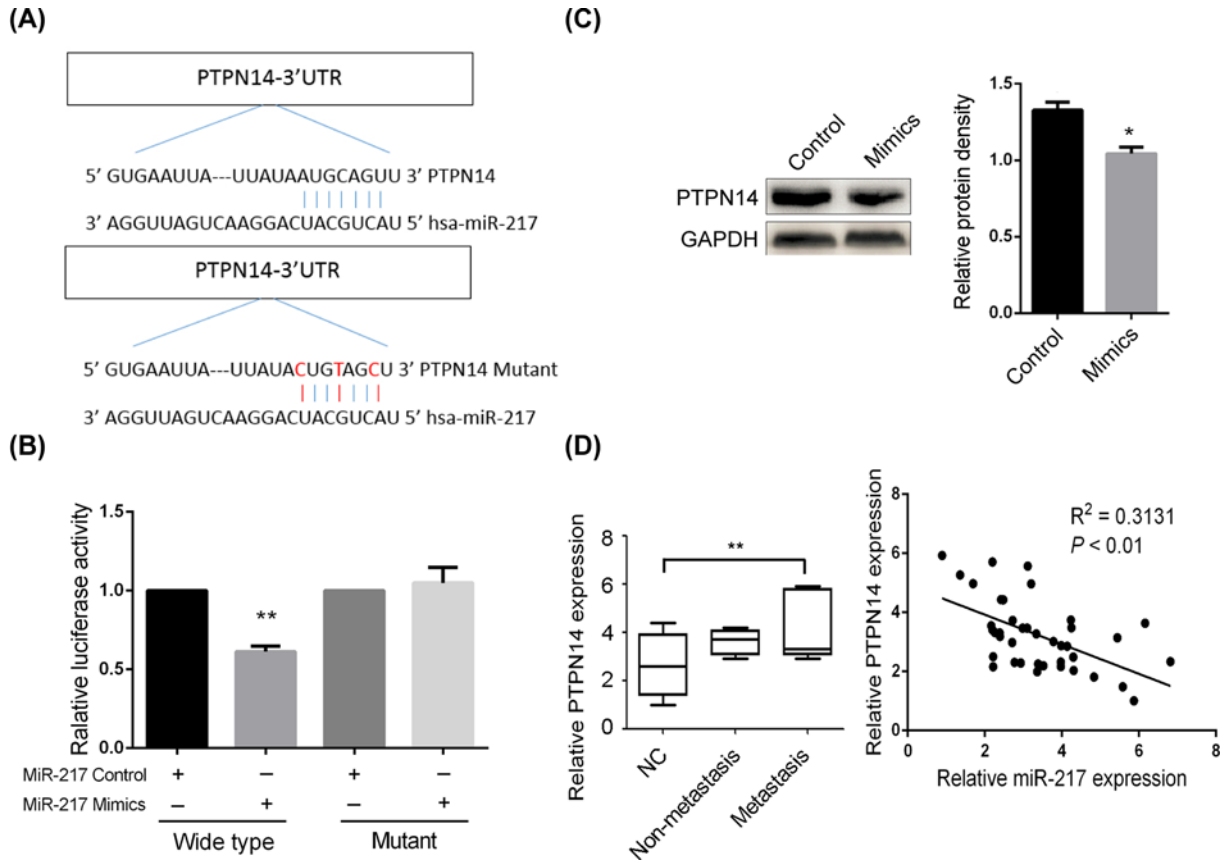

Figure 3. PTPN14 is a novel target of miR-217

(**A**) Prediction algorithms showed that miR-217 targets the binding site of PTPN14 and the binding site mutant. (**B**) Luciferase assay showed miR-217 mimics significantly reduced the luciferase activity in HEK293T cells after cotransfection with the wild-type luciferase reporter vectors (0.8 μg) and miR-217 mimics (100 nM), while the luciferase activity was not changed when the cells were cotransfected with mutant luciferase reporter vectors (0.8 μg) and miR-217 mimics (100 nM). (**C**) Western blotting showed that miR-217 mimics markedly decreased the protein expression of PTPN14. (**D**) Linear regression revealed a strongly negative correlation between the mRNA expressions of PTPN14 and miR-217 in the gastric tumor tissues of the 40 patients; *, $P < 0.05$ and **, $P < 0.01$.

the luciferase activity in HEK293T cells transfected with mutant 3′UTR (Figure 3B). We also confirmed that miR-217 markedly decreased the protein expression of PTPN14 ($P < 0.01$) (Figure 3C).

Next, we further detected mRNA expression of PTPN14 in the 40 pairs of GC tissues, and found PTPN14 increased in GC tissues with metastasis.The results of Pearson's correlation also showed a strongly negative correlation between the expressions of miR-217 and PTPN14 mRNA. (Figure 3D, $P < 0.01$). Together, miR-217 suppressed PTPN14 expression by directly targeting its 3′UTR, and the miR-217 expression was negatively correlated with PTPN14 expression in GC tissues.

The down-regulation of PTPN14 suppressed the metastasis of GC cells

To determine whether PTPN14 is a major target of miR-217, we next determined the role of PTPN14 in modulating the migration and invasion of GC cells using si-PTPN14 and PTPN14 vector. The results showed that si-PTPN14 significantly repressed the protein and mRNA expression of PTPN14, whereas the PTPN14 vector markedly increased the expression of PTPN14 (Figure 4A). Migration and invasion assays showed that the si-PTPN14 markedly reduced the metastasis and invasion of SGC-7901 and BGC-823 cells, whereas the PTPN14 vector significantly enhanced the cell migration and invasion, consistent with miR-217 mimics-induced effects ($P < 0.05$, Figure 4B,C). To further determine miR-217-induced effects through targeting PTPN14, SGC-7901 and BGC-823 cells were cotransfected with miR-217 mimics and the PTPN14 vectors, respectively, for 24 h. As shown in Figure 4D, the inhibitory effects induced

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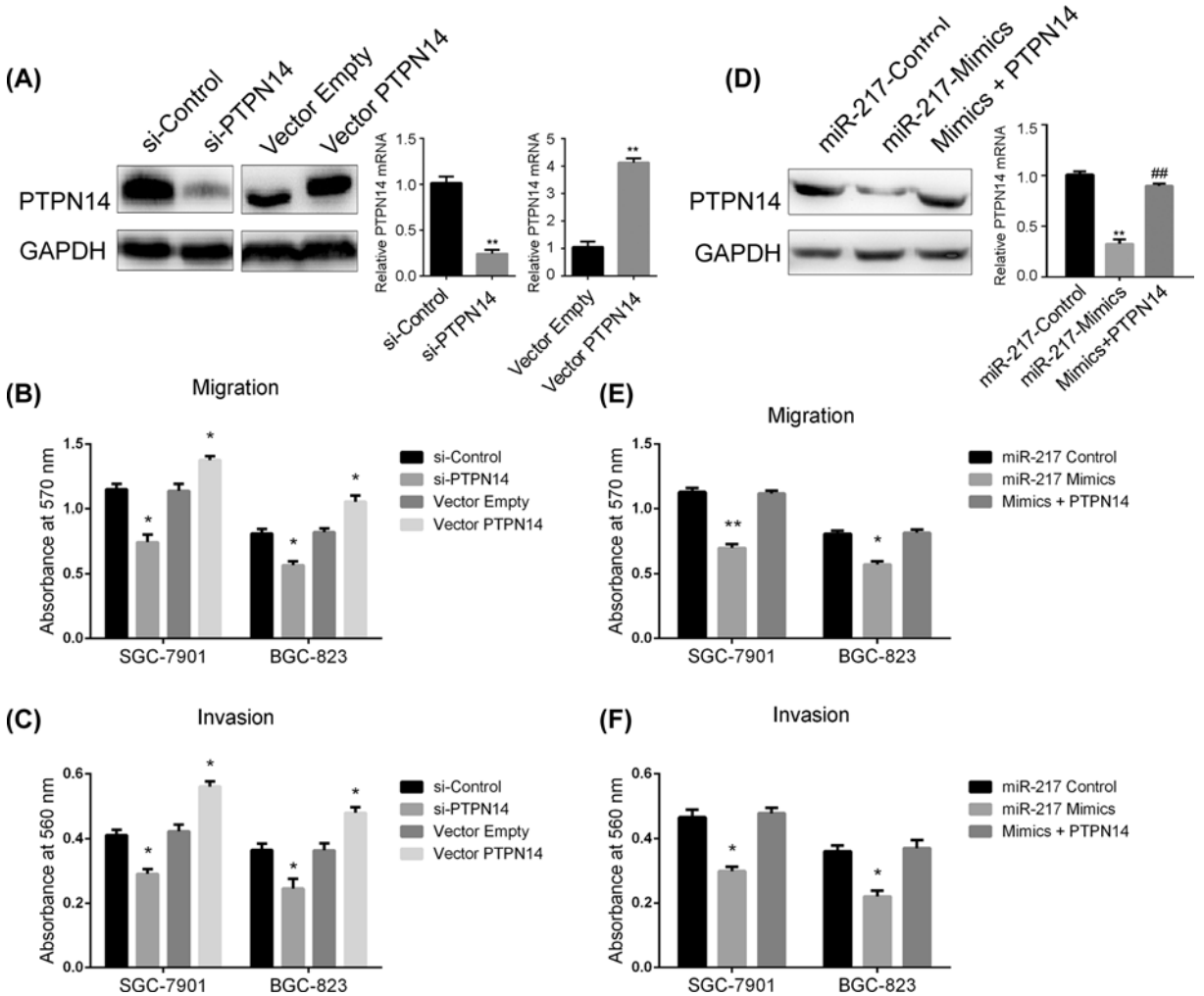

Figure 4. The loss of PTPN14 induced by si-PTPN14 or miR-217 suppressed the migration and invasion of GC cells

(**A**) Western blotting assays real-time PCR showed that the PTPN14 expression was decreased or increased in SGC-7901 cells after transfection with si-PTPN14 (100 nM) or vector PTPN14 (200 ng/ml), respectively. (**B** and **C**) Bar showed that the migration and invasion of SGC-7901 and BGC-823 cells were reduced or enhanced when the cells were transfected with si-PTPN14 (100 nM) or vector PTPN14 (200 ng/ml). (**D**) Western blotting assays and real-time PCR showed that the PTPN14 expression was decreased or reversed after transfection with miR-217 mimics (100 nM) or cotransfection with miR-217 mimics (100 nM) and vector PTPN14 (200 ng/ml), respectively. (**E** and **F**) Bar showed that the migration and invasion of SGC-7901 and BGC-823 cells were reduced or reversed when the cells were transfected with miR-217 mimics (100 nM) or cotransfected with miR-217 mimics (100 nM) and vector PTPN14 (200 ng/ml), respectively. *, $P < 0.05$; **, $P < 0.01$.

by miR-217 mimics were significantly reversed by cotransfecting with miR-217 mimics and PTPN14 vectors. Functional investigation revealed that miR-217 mimics significantly suppressed the cell metastasis and invasion, which were reversed by cotransfecting with miR-217 mimics and PTPN14 vectors ($P < 0.05$ or $P < 0.01$) (Figure 4E,F). These suggested that miR-217 suppressed the metastasis and invasion of GC cells by inducing the loss of PTPN14.

MiR-217 inhibited the EMT in GC cells

Compelling evidences indicated that PTPN14 played an important role in EMT. Thus, we detected the protein expressions of E-cadherin and ZEB1 in GC cells after transfection with miR-217 control and mimics. As shown in Figure 5, miR-217 mimics markedly decreased the expression of E-cadherin, whereas significantly increased the expression of ZEB1. To further determine that miR-217 modulated the EMT through targeting PTPN14, we also measured the protein expressions of E-cadherin and ZEB1 in SGC-7901 cells by cotransfecting with miR-217 mimics and PTPN14

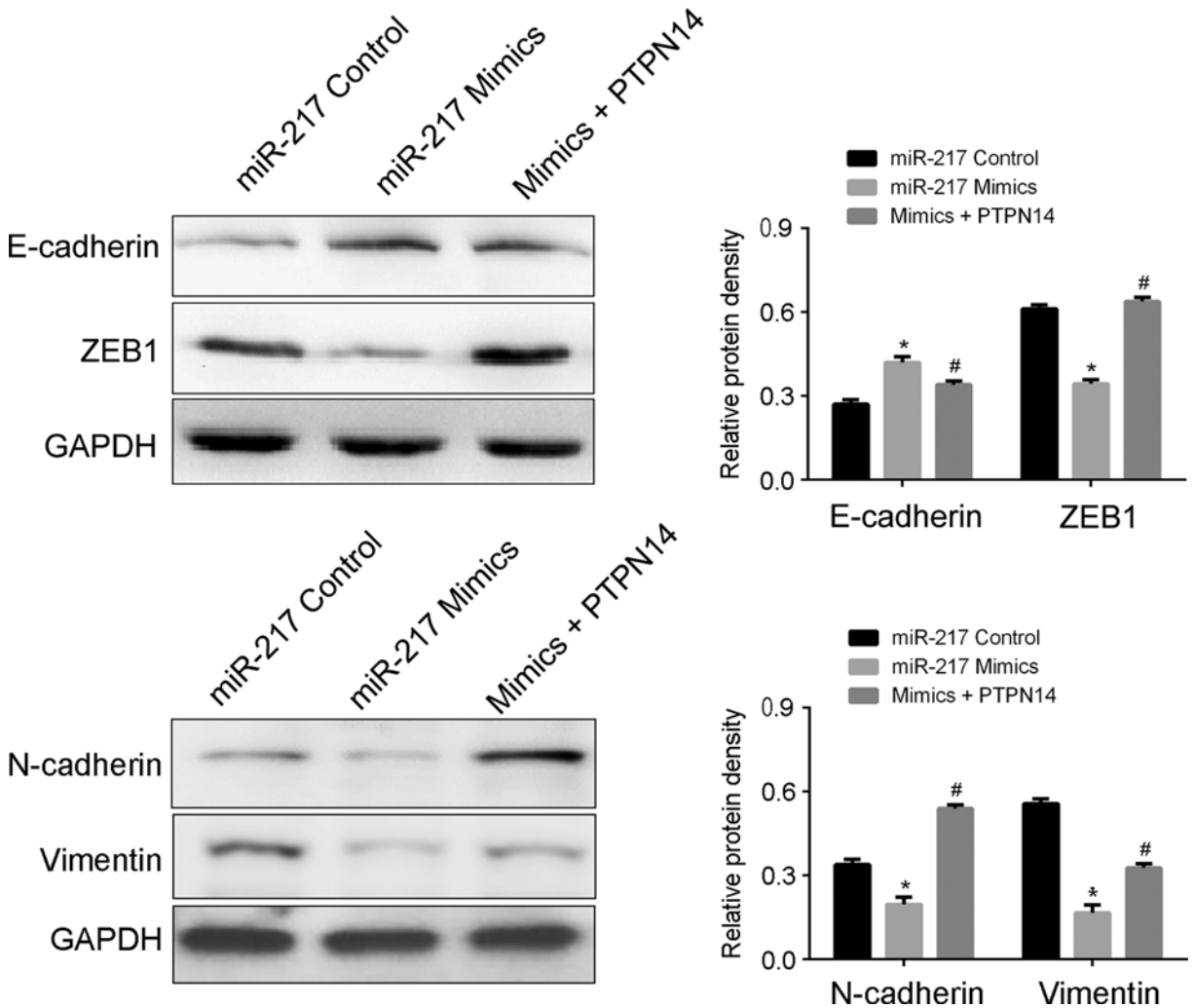

Figure 5. MiR-217 inhibited the EMT in GC cells

Western blotting assays showed miR-217 mimics markedly promoted the expression of E-cadherin, and decreased the expression of ZEB1, N-cadherin and Vimentin in SGC-7901 cells after transfection with miR-217 mimics (100 nM). When SGC-7901 cells were cotransfected with miR-217 mimics (100 nM) and vector PTPN14 (200 ng/ml), the expressions of E-cadherin, ZEB1, N-cadherin and Vimentin were reversed.

vectors. The results showed that the protein expressions of E-cadherin and ZEB1 were reversed. These suggested that miR-217 modulated the EMT in GC cells through targeting PTPN14.

Discussion

MiRNAs play an important role in tumor development and metastasis. In the present study, we found that the expression of miR-217 was decreased in GC tissues, consistent with that in other cancers. For example, Zhao et al. [14] indicated that the decreased expression of miR-217 could regulate KRAS and function as a tumor suppressor in pancreatic ductal adenocarcinoma. Su et al. [12] reported that the miR-217 expression was strongly decreased in metastatic hepatocellular carcinoma (HCC) tissues and highly invasive MHCC-79HHCC cells. Li et al. [15] stated that the lower expression of miR-217 was associated with higher tumor grade and stage in cell renal carcinoma. These data indicated that the down-regulated expression of miR-217 was associated with tumor development and metastasis.

We also found that miR-217 suppressed the function of PTPN14. PTPN14 also known as PEZ, PTP36, is a crucial factor in tumorigenesis, EMT and malignant transformation. Liu et al. [16] indicated that PTPN14 interacted with Yes associated protein (YAP), a transcriptional co-activator in cancers promoting EMT and malignant transformation. Ten years ago, Wang et al. [17] found that PTPN14 mutation in human cancers affected 26% of colorectal cancers and

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a smaller fraction of lung, breast and gastric cancers. We also showed that the expression of PTPN14 was increased in GC and involved in GC metastasis. Furthermore, PTPN14 was a novel target of miR-217, highlighting the molecular mechanism underlying the role of miR-217 in GC metastasis.

EMT is a complex process, where many hallmarks were changed, including the decreased expression of E-cadherin (CDH1), and increased expression of vimentin (VIM), ZEB1, Snail Homolog 1(SNAI1) and TWIST1(Twist-related protein 1) [18]. ZEB1 is associated with suppression of E-cadherin and EMT, and also serves as a transcriptional activator directing in part toward mesenchymal genes such as collagens, smooth muscle actin and myosin, vimentin [19–20]. In our study, we used the epithelial marker CDH1, and mesenchymal marker ZEB1 to analyze the EMT in GC cells, and the results confirmed that miR-217-induced loss of PTPN14 suppressed the EMT in GC cells.

Conclusion

We found that the miR-217 expression was decreased in metastatic GC tissues. MiR-217 suppressed the EMT through targeting PTPN14, and further repressed the metastatic ability of GC cells.

Availability of Data and Material

Please contact author for data requests.

Author Contribution

Z.W. conceived and designed the experiments. G.C. and Z.Y. performed the in vitro experiments. M.F. analyzed the data and wrote the paper. Z.W. wrote the manuscript critically. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

All samples were collected from consenting individuals according to the protocols approved by the Ethics Review Board at Zhongnan Hospital of Wuhan University (Ethics No. 201511).

Consent for Publication

Written consents were obtained from all participants.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

Funding

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Abbreviations

CDH, E-cadherin; EMT, epithelial-to-mesenchymal transition; GC, gastric cancer; PTPN14, tyrosine-protein phosphatase non-receptor type 14; SNAI1, Snail Homolog 1; TWIST1, Twist-related protein-1; YAP, Yes associated protein; ZEB1, zinc finger E-box binding homeobox 1.

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