Article

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Interaction between miR-140 and HDAC4 in Gastric Cancer Metastasis

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Background: miRNAs are involved in the process of tumorigenesis and metastasis as tumor suppressor genes or oncogenes. This work aims to explore the effect of miR-140 in the proliferation and invasion as well as metastasis of gastric cancer cells, as well as to provide new target for the diagnosis and therapy for gastric cancer.
Methods: miR-140 mimics and miR-140 inhibitors were transfected to the SGC-7901 gastric cancer cells, the expression of miR-140 and histone deacetylase4 (HDAC4) in human gastric cancer and normal gastric tissues was evaluated by quantitative reverse transcription-PCR (qRT-PCR), the HDAC4 protein level was evaluated by western blot method. The effects of miR-140 upregulation and downregulation on the invasion and metastasis ability of SGC-7901 cells were investigated by Transwell cell model. The samples were classified into control group by adding lipofectamine 2000, negative control group by adding miRNA unrelated sequence and lipofectamine 2000, miRNA up-regulated transfection group by adding miR-140 mimics and lipofectamine 2000 were added, as well as miRNA down-regulated transfection group by adding miR-140 inhibitors and lipofectamine 2000.
Results: The effects of up and down regulation of miR-140 on the invasion and metastasis ability of SGC-7901 cells were determined by Transwell chamber model. The expression of miR-140 in gastric cancer cells was significantly lower than that of normal gastric tissue ($p < 0.05$). The invasion and metastasis ability of SGC-7901 cells in miR-140 mimics and miR-140 inhibitor groups were significantly lower and higher when compared with negative control (NC) and control groups, respectively. HDAC protein was significant up-expressed in miR-140 inhibitor group when compared with NC and control groups. All these differences were of statistical significance ($p < 0.05$).
Conclusion: The expression level of miR-140 are associated with the invasive and metastatic properties of gastric cancer cells, which may serve as new target for the clinical treatment of gastric cancer.

Keywords: gastric cancer; miR-140; HDAC4; SGC-7901; invasion; metastasis

Background

Gastric cancer as common malignant tumor ranks third in terms of the mortality among all cancers, threatening to raise health risks, the invasion and metastasis of gastric cancer cells pose main difficulty in improving the therapy [1]. The past years has witnessed revolutionary progress for the exploration of invasion and metastasis in more details, while the underlying mechanism remains ambiguous [2]. All these issues necessitate the research on prevention and therapy of such metastasis to finally improve the prognosis of patients with gastric cancer. To this end, a growing number of reports indicate that microRNAs (miRNA) are closely related with tumor, which regulate the proliferation and apoptosis, as well as the invasion, metastasis and drug resistance of gastric cancer cells [3]. The altered expression of miRNA has been identified to exert promoted and/or suppressed effects on various tumors, indicating that miRNA indeed participate in the pathological mechanisms of tumors [4].

Previous reports have revealed that the missing of miR-15a, miR-16-1, miR-34a and miR-145 are related with the occurrence of chronic lymphocytic leukemia, colorectal cancer, gastric cancer, breast cancer, etc. [5]. The overexpression of miR-192 regulated by cancer-suppressed gene P53 can contribute to the cells cycle arrest of tumor and therefore suppress tumor cells proliferation, the down regulation of miR-192 and miR-215 are correlated with the occurrence of colorectal cancer and multiple myeloma [6–8]. Besides, the overexpression of miR-21, miR-17-92cluster, miR-221 and miR-222 are also proved to promote the occurrence of colorectal cancer, gastric cancer, liver cancer, pancreatic cancer, etc [5]. The anomaly of miR-10b, miR-451a and miR-21 are also closely related with tumor metastasis [9]. The above-mentioned cases signify that miRNA can serve as the marker and target candidate for tumor metastasis.

Specifically, miR-140 finds important role in the hyperplasia and development of the cartilage among the large

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Table 1. Correlation between miR-140 relative expression and clinical pathological features of gastric cancer. The data was presented by median (25th percentile to 75th percentile).

Features	Number	miR-140 relative expression	Z value	*p* value
Average expression			4.214	<0.001
Up expression	9	1.56 (1.21–1.67)		
Down expression	31	0.23 (0.15–0.48)		
Gender			–1.259	0.213
Male	23	0.43 (0.20–0.79)		
Female	17	0.69 (0.49–0.78)		
Age			3.100	0.002
≤55	12	1.00 (0.86–1.26)		
>55	28	0.67 (0.31–0.88)		
Tumor size (cm)			4.129	<0.001
≤3.5	16	0.88 (0.66–1.04)		
>3.5	24	0.44 (0.31–0.59)		
Histological differentiation			1.210	0.232
High	18	0.83 (0.52–1.00)		
Low	22	0.63 (0.40–0.79)		
Invasion depth at different stages			3.972	<0.001
T1–T3	13	0.92 (0.79–1.01)		
T4	27	0.38 (0.16–0.63)		
Lymph node metastasis at different N stages			4.018	<0.001
N0	9	1.07 (0.98–1.28)		
N1–N3	31	0.30 (0.12–0.49)		

family of micro RNAs. The differential expression of miRNA between epithelial ovarian cancer and normal ovarian tissue screened by microRNA chip technique indicated that the expression of miR-140 in ovarian cancer experienced significant decrease [10]. While the opposite case revealed by the comparison between primary type-II glioma and spontaneously progressed secondary type-IV malignant glioma, where the expression of miR-140 got increased when glioma developed from type II to type IV [11]. It has been verified in the 3T3 cells of mice that histone deacetylase4 (HDAC4) constituted the target gene of miR-140, and miR-140 promoted the development of chondrocyte by suppressing HDAC4 expression [12].

Along with the emerging progress of miRNA and particularly miR-140, the underlying mechanism of miR-140 in the occurrence and development processes of gastric cancer remains largely unexplored. In this work, we aimed to verify that miR-140 can effectively suppress the metastasis process of gastric cancer and serve as target for such therapy in clinic.

Materials and Methods

Sample Source

The 40 patients admitted to the Department of Surgical Oncology in The Third Affiliated Hospital of Qiqihar Medical University during June 2018 and June 2020 were confirmed as gastric cancer cases by pathology department, followed by pathological examination and excision of gastric cancer tissue. The normal gastric tissue which was away from gastric tumor (>10 cm) was selected as control. The samples were extracted and rinsed with saline to remove the mucosal tissue and store in liquid nitrogen. The tumor-node-metastasis (TNM) staging of tumor followed the criteria of the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (UICC/AJCC) TNM pathological staging (The Seventh Version), the clinical data of involved patients are listed in Table 1. Sample collection was approved by the Medical Ethics Committee of Qiqihar Medical University (ethics certification number: QMU-AECC-2021-243) and all patients signed the informed consent.

The human gastric cancer cells SGC-7901 cell line was purchased from the Cell Resource Center in Shanghai Institute of Biological Sciences (China) and maintained in dulbecco's modified eagle medium (DMEM, purchased from Gibco Co., Ltd., USA) containing 10% fetal bovine serum (FBS) to carry out normal culture in 5% CO_2 incubator at 37 °C. The transfection reagent liposome Oligofectamine and Lipofectamine 2000, miR-140 mimics and miR-140 inhibitor and their unrelated sequences (TGA ACAGATAAGGGTTTAA, CAGATAAGGGTTTAAATGT, GATAAGGGTTTAAATGTGA) were all purchased from Invitrogen Co., Ltd., USA. Transwell chamber was purchased from Corning Co., Ltd., USA. Note that both mycoplasma detection and STR identification were carried out, which proved that the SGC-7901 cells used in this work were not contaminated by mycoplasma or cross-contaminated cells.

Real-Time PCR Test

Followed by the culture of SGC-7901 cell line, lipofectamine 2000 (Sangon Biotech Co., Ltd., Shanghai, China) was applied to transfect miR-140 mimics and miR-140 inhibitors into SGC-7901 cells to trigger up and down regulations of miR-140, respectively. The samples were designed into four groups as follows: (1) Control group: only added with lipofectamine 2000. (2) Negative Control (NC) group: miRNA unrelated sequence and lipofectamine 2000 were added. (3) miRNA up-regulated transfection group: miR-140 mimics and lipofectamine 2000 were added. (4) miRNA down-regulated transfection group: miR-140 inhibitors and lipofectamine 2000 were added.

The total RNA in gastric cancer and normal gastric tissue samples were extracted by TRIzol Kit (Takara Bio Inc., Shiga, Japan) after 24 h transfection. By using 10 ng total RNA as the template, the reverse transcriptional reaction was applied according to the instructions on TaqMan® MicroRNA Reverse Transcription Kit (Applied Biosystems, Thermo Fisher Scientific Inc., Waltham, USA). The reverse transcription parameters are listed in **Supplementary Table 1**, the reaction was maintained at 16 °C for 30 min, followed by 42 °C for 30 min and 85 °C for 5 min, which was finally stored at 4 °C. Then, miR-140 specific reverse transcription primer and cDNA Synthesis Kit (Ambion, Austin, USA) were used to synthesize cDNA, which was carried out by Stratagene Mx3005P (Agilent, Santa Clara, USA) and the parameters are listed in **Supplementary Table 2**. PCR primers of miR-140 and internal reference U6 were designed by Invitrogen Co., Ltd. (**Supplementary Table 3**). specifically, the reaction was initiated at 95 °C for 10 min to allow denaturation, followed by maintaining at 95 °C for 15 s and 60 °C for 60 s, a total of 40 cycles were carried out. Then, the system was kept at 72 °C for another 10 min. Three compound tubes were adopted for each sample. The primer sequences of miR-140 are 5′- TGCGGCAGTGGTTTTACCCTATG -3′ (Sence) and 5′- CCAGTGCAGGGTCCGAGGT -3′ (Anti-sence). For that of U6, they were 5′- ATTGGAACGATACAGAGAAGATT -3′ (Sence) and 5′- GGAACGCTTCACGAATTTG -3′ (Anti-sence). Quantitative reverse transcription-PCR (qRT-PCR) analysis was carried out on ABI7000 (Agilent Co., Ltd., SantaClara, USA). The comparison between the expression of miR-140 and U6 helped to obtain ΔCT, which was then compared with that of NC group. The obtained results were calculated based on $2^{-\Delta\Delta CT}$ method and presented by relative quantity (RQ) of miR-140 in gastric cancer and normal gastric tissue samples.

For the evaluation of HDAC4 mRNA level in the transfected cells, the cells were collected after 24 h transfection to extract total RNA. The total RNA (10 μg) was applied as the template to carry out one-step transcription according to the instructions on RT-PCR Kit (Platinum SYBR Green PCR Kit, Invitrogen, USA), and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as reference. The analysis was also completed by Stratagene Mx3005P (Agilent, Santa Clara, USA), and the parameters are listed in **Supplementary Tables 4,5,6**. The reaction condition was as follows: maintaining at 50 °C for 2 min, followed by denaturation at 95 °C for 2 min, maintaining at 95 °C for 15 s and 60 °C for 30 s, with a total cycle number of 50.

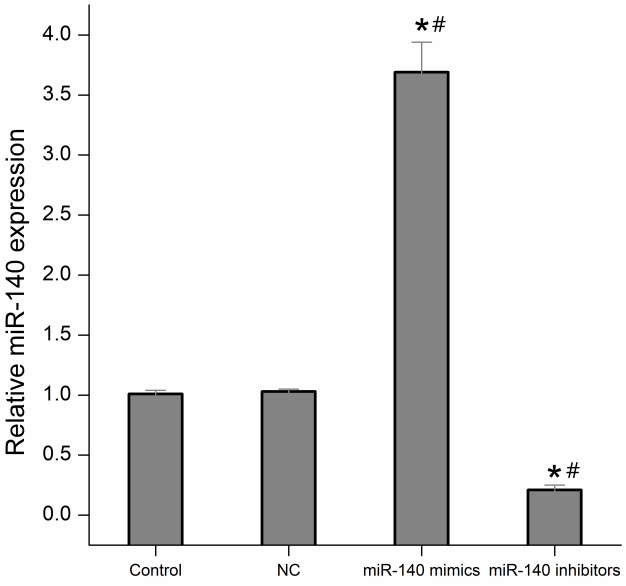

Fig. 1. Relative quantity of miR-140 in SGC-7901 cells of difference groups. The results are presented by mean ± SD. n = 6, * represents $p < 0.05$ when compared with control group and # represents $p < 0.05$ when compared with NC group.

Expression of HDAC4 Protein by Western Blot (WB) Test

The HDAC4 antibody (sc-46672) was purchased from Santa Cruz Biotechnology Co., Ltd. (Santa Cruz, USA), with a dilution factor of 1:1000. the β-action antibody (TA-09) was obtained from ZSGB-BIO Co., Ltd. (Beijing, China), with a dilution factor of 1:1000. The far-infrared secondary antibody (IRDye 680RD) was purchased from LI-COR Inc. (Lincoln, USA) with a dilution factor of 1:8000. The total protein was extracted by radio immunoprecipitation assay (RIPA) buffer after 48 h transfection of SGC-7901 cells in each group. The total protein was then subjected to sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) for 2 h and transferred onto polyvinylidene fluoride (PVDF) membrane, which was then sealed and incubated with HDAC4 overnight at 4 °C. After tris-buffered saline & Polysorbate 20 (TBST) rinsing, the far-infrared fluorescence secondary antibody was added and incubated for 2 h, and imaging system (9120, LI-COR Inc., Lincoln, USA) was employed for imaging. The RQ of HDAC4 protein in each group was analyzed by Gel-Pro Analyzer software (Version 6.0, Bethesda, Rockville, USA).

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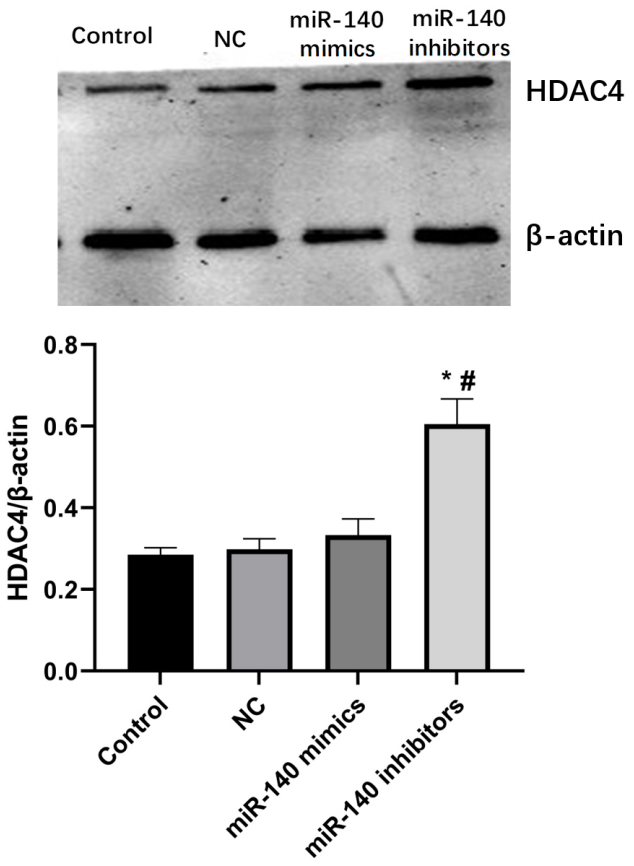

Fig. 2. Effect of miR-140 on HDAC4 expression in the SGC-7901 cells of each group (Western blot results). The results are presented by mean ± SD. n = 6, * represents $p < 0.05$ when compared with control group and # represents $p < 0.05$ when compared with NC group.

Evaluation of Cell Invasion and Metastasis Ability by Transwell Test

The SGC-7901 cells after transfection in each group was subjected to Transwell upper chamber enveloped by Matrigel, while the lower chamber was added with 600 uL Roswell Park Memorial Institute-1640 (RPMI-1640) complete cell culture medium containing 20% FBS for 24 h culture. Then, the cells in upper chamber were removed by cotton swab and stabilized by methanol, followed by 15 min staining using 1% crystal violet. Phosphate buffer solution (PBS) was then used to wash the remaining crystal violet for 3 times. The invaded cells were observed by microscope, 5 images were randomly recorded to calculate the invasion rate, where positive cells were stained as violet. The experimental procedures of cell metastasis kept similar with that of cell invasion, except that Matrigel was not used.

Statistical Methods

The statistical analysis was conducted using SPSS 22.0 software (IBM Corp., Armonk, NY, USA). A normality test was conducted on the collected measurement data. If the dataset was found to be non-normally distributed, the median (25th percentile to 75th percentile) was utilized to characterize the dataset. The Wilcoxon rank-sum test was employed to compare two independent samples. Otherwise, measurement data was presented by mean ± standard deviation (mean ± SD) and *t*-test was applied using two independent samples. The comparison among groups adopted analysis of variance (ANOVA) and tukey post-hoc pairwise test. $p < 0.05$ denotes that the difference is of statistical significance.

Results

Correlation between miR-140 Expression in Gastric Cancer and Clinical Pathological Parameters

The 40 gastric cancer patients (male 23, female 17) with average age of 56 (±14) were assessed. It is noticed that miR-140 experienced significant down-regulation in gastric cancer tissue, which accounted for 77.5% of the involved patients, as clearly shown in Table 1. Our results also indicate that the expression level of miR-140 was related with age, tumor size, invasion degree and lymph node metastasis.

RQ of miR-140 after SGC-7901 Cell Transfection by miR-140 Mimics and miR-140 Inhibitors

As clearly shown in Fig. 1, miR-140 was obviously up-regulated and down-regulated after miR-140 mimics and miR-140 inhibitors transfected SGC-7901 cells, respectively. Specifically, the RQ of miR-140 in NC groups was in close proximity to that of control group, which however showed 3.6-fold increase in miR-140 mimics group but 4.8-fold decrease in miR-140 inhibitors group. These differences were of statistical significance ($p < 0.05$), thus indicating the successful transfection of SGC-7901 via miR-140 mimics and miR-140 inhibitors, which up-regulate and down-regulate the expression of miR-140, respectively.

Effect of Regulated miR-140 Expression on the Expression of HDAC4 in SGC-7901 Cells

Enabled by Western blot test, we found that the expression of HDAC4 in SGC-7901 can be regulated by miR-140 expression change. Compared with control group and NC group, the expression of HDAC4 protein was evidently increased in miR-140 inhibitors group. The differences are statistical significance ($p < 0.05$), as shown in Fig. 2. The results indicate that miR-140 mimics do not modulate HDAC protein levels. This lack of effect may be attributed to the sequestration of the miR-140 mimic by specific competing endogenous RNAs (ceRNAs), such as SNHG1 and TMPO-AS1 [13,14]. In addition, the time point of the WB test following transfection could potentially influence the results.

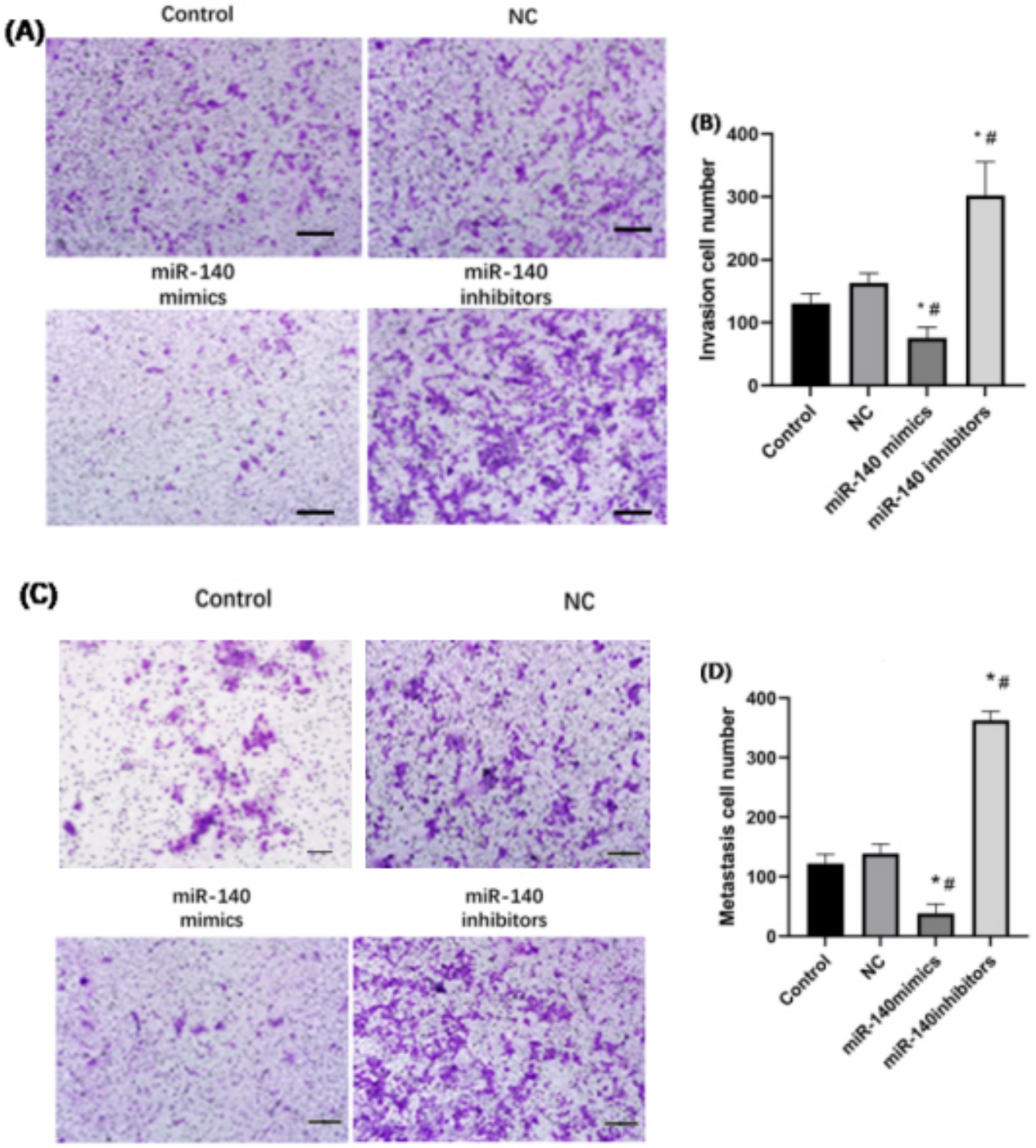

Fig. 3. Effect of up-regulated and down-regulated miR-140 on the (A,B) invasion and (C,D) metastasis ability of SGC-7901 cells (stained by crystal violet, n = 3, * represents $p < 0.05$ when compared with control group and # represents $p < 0.05$ when compared with NC group, scale bars in (A,C) are all 100 μm).

Effects of Up-Regulation and Down-Regulation of miR-140 on the Invasion and Metastasis of Gastric Cancer Cells

The metastasis ability of SGC-7901 cells affected by miR-140 was studied by Transwell chamber model test. As shown in Fig. 3A,B, the invasion rate in miR-140 mimics (75.4 ± 17.5) group was obviously decreased compared with that of control (130.8 ± 15.8) and NC (163.6 ± 14.8) groups. The invasion rate in miR-140 inhibitors (302.4 ± 53.2) group was obviously increased compared with that of control (130.8 ± 15.8) and NC (163.6 ± 14.8) groups. As shown in Fig. 3C,D, the transmembrane cell number in miR-140 mimics (38.2 ± 16.0) and miR-140 inhibitors (362.6 ± 15.3) groups were significantly lower and higher

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than that of control (122 ± 15.8) and NC groups (139 ± 15.8), respectively. Such differences in both invasion and metastasis are of statistical significance ($p < 0.05$). The results indicate that the expression level of miR-140 are associated with the invasive and metastatic properties of gastric cancer cells.

Discussion

As described before, miR-140 plays different regulation roles throughout the occurrence and development processes of various tumors. In this work, the combined results reveal that miR-140 in gastric cancer tissue shows evidently lower expression compared to that of normal gastric cancer, which is correlated with tumor size, invasion degree and lymph node metastasis. Generally, larger tumor with higher invasion degree and lymph node staging would result in lower RQ of miR-140, keeping good consistency of the results by Iorio *et al*. [10].

It is generally acknowledged that metastasis constitutes one of the important reasons causing the death of patients with malignant tumor. Song *et al*. [15] revealed that miR-140 showed negative regulation of HDAC4 at protein level in colon cancer cell HCT116 and osteosarcoma cell U-2 OS, and transient transfection of miR-140 may lead to the overexpression of cell cycle regulatory proteins p53 and p21 in HCT116 and U-2 OS cells, thus resulting in the arrest of cell cycles G_1 and G_2 accompanied by evidently suppressed cell proliferation of the two cells. In this work, it was found that the transfected SGC-7901 cells were characterized by significantly decreased metastasis and invasion ability when miR-140 mimics transfection was introduced, while the cells transfected by miR-140 inhibitors showed enhanced metastasis and invasion ability. These results are in line with the previous report that miR-140 can suppress the proliferation and metastasis ability of liver cancer cells and non-small lung cancer cells [16,17].

HDAC refers to one of proteases located in eukaryotic cells with main function of modifying the structure of chromosome and regulating other functional proteins, which shows regulation effect on the development, differentiation and apoptosis of tumor cells, as well guiding function for gene expression. It was reported that HDAC4 showed high expression in breast cancer and endometrial cancer, which can serve as cancer-promoted gene to regulate the proliferation and apoptosis of related tumor as well as the cisplatin resistance. To further probe the potential regulation effect of miR-140 in human gastric cancer via regulating HDAC4 target gene, here we used Western blot to directly evaluate the expression of HDAC4 protein transfected by miR-140 in each group. The HDAC4 was found to show high expression level in miR-140 inhibitor group compare with NC and control groups. Also, the combined findings highlight that HDAC can be potentially used for the therapy of cancer, as evidenced by the wider deployment of common HDAC inhibitor in clinical tumor treatment. One can expect that the development and application of HDAC inhibitor can be extended if the expression status of various proteins in HDAC family can be clearly revealed.

Conclusion

In summary, this work verifies that miR-140 constitutes one of the main factors in terms of regulating the expression of HDAC4 protein in gastric cancer, which shows important role in suppressing the proliferation, invasion and metastasis of gastric cancer cells, thereby providing basis for finding new target in clinical gastric cancer treatment.

Author Contributions

XiaoW dedicated to the guarantor of integrity of the entire study, study design, literature research, data acquisition and manuscript review; XianW performed the study design; SW carried out the study concepts and data analysis; YZ was involved in the experimental studies, manuscript preparation and manuscript editing; FG performed the definition of intellectual content and clinical studies; YS carried out the statistical analysis. All authors have read and approved this article.

Ethics Approval and Consent to Participate

This study is approved by the Animal Ethical Care Committee of Qiqihar Medical University, NO. QMU-AECC-2021-243.

Acknowledgment

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.23812/j.biol.regul.homeost.agents.20253901.7.

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