MicroRNA-383-5p inhibits the proliferation and promotes the apoptosis of gastric cancer cells by targeting cancerous inhibitor of PP2A

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Received December 4, 2019; Accepted March 20, 2020

DOI: 10.3892/ijmm.2020.4603

Abstract. The aberrant expression of microRNA (miRNAor miR)-383-5p has been found in numerous types of cancer. However, the function of miR-383-5p in gastric cancer (GC) remains elusive and requires further investigation. In the present study, the level of miR-383-5p and cancerous inhibitor of PP2A (CIP2A) in GC cell lines was determined by reverse transcription-quantitative PCR analysis. GC cell proliferation, apoptosis and cell cycle distribution were determined by the MTT assay and flow cytometry, respectively. The mRNA target of miR-383-5p was identified by dual luciferase activity assay. It was observed that the expression of miR-383-5p was lower and that of CIP2A was higher in GC cells compared with the GES-1 normal human gastric epithelial cell line. Transfectoin with miR-383-5p mimic significantly inhibited GC cell proliferation, while it promoted cell apoptosis and G_0/G_1 arrest by targeting CIP2A. Taken together, the findings of the present study demonstrate that miR-383-5p inhibits GC cell proliferation and promotes apoptosis and G_0/G_1 arrest by targeting CIP2A, indicating that targeting miR-383-5p may hold promise as a future therapeutic strategy for patients with GC.

Introduction

GC is the fourth most frequent type of cancer worldwide, and it is characterized by a high mortality rate (1). GC is one of the most serious public health concerns globally, particularly in China (2). Despite the recent advances in the treatment of GC, the prognosis of patients with advanced GC remains poor. Consequently, the investigation and development of novel therapeutic strategies for GC is of utmost importance.

MicroRNAs (miRNAs or miRs) are a type of small non-coding RNAs, which function by negatively regulating the expression of mRNAs by base pairing with their 3'-untranslated region (UTR) (3,4). miRNAs play a key role in the proliferation, apoptosis, metastasis and metabolism of cancer cells (5). The aberrant expression of miRNAs has been observed in various types of cancer, such as breast cancer (6), osteosarcoma (7) and GC (8). In 2018, miR-383-5p was found to act as a tumor suppressor in hepatocellular carcinoma (9). Since then, several studies on the function of miR-383-5p have been published in several cancer types. For example, miR-383-5p has been shown to suppress the proliferation and metastasis of breast cancer cells (10). LINC01128 has also been shown to promote the development of cervical cancer by sponging miR-383-5p (11). RP11-284F21.9 induces the development of oral squamous cell carcinoma by sponging miR-383-5p (12). Moreover, the decreased expression of miR-383-5p has been shown to lead to the proliferation and migration of GC cells (13), and miR-383-5p has been reported to suppress the development of GC by targeting HDAC9 (14).

Cancerous inhibitor of PP2A (CIP2A) was first confirmed to be a tumor-associated auto-antigen in GC and liver cancer (15), the overexpression of which was identified in various types of cancer, such as lung (16), cervical (17) and prostate (18) cancers, as well as GC (19). miR-383-5p has been proven to regulate the development of lung cancer by targeting CIP2A (20). However, to date, at least to the best of our knowledge, there is no study available on the association between miR-383-5p and CIP2A in GC. Thus, the aim of the present study was to investigate whether miR-383-5p regulates the development of GC by targeting CIP2A.

Materials and methods

Cell culture. The 293T cell line, the normal human gastric epithelial cell line GES-1, and two GC cell lines (AGS and HGC-27) were purchased from the American Type Culture Collection. The cells were cultured in Dulbecco's modified Eagle's medium (Invitrogen; Thermo Fisher Scientific, Inc.), supplemented with 5% fetal bovine serum (Invitrogen; Thermo

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Key words: microRNA-383-5p, gastric cancer, cancerous inhibitor of PP2A

Fisher Scientific, Inc.), in a humidified incubator with 95% air and 5% CO_2.

pcDNA treatment. The full length of CIP2A was amplified from the cDNA of GES-1 cells and cloned into the pcDNA3.1 plasmid to construct pcDNA3.1-CIP2A. The cells were then transfected with pcDNA3.1 or pcDNA3.1-CIP2A (2 μg) using Lipofectamine 2000 (Invitrogen; Thermo Fisher Scientific, Inc.) according to the manufacturer's instructions. At 48 h following transfection, the cells were collected for use in the subsequent experiments.

Transfection with miR mimic. miR-NC mimic and miR-383-5p mimic were synthesized by Ambion (Thermo Fisher Scientific, Inc.). miR-NC mimic (100 nM) or miR-383-5p mimic (100 nM) were transfected into cells using Lipofectamine 2000 (Invitrogen; Thermo Fisher Scientific, Inc.) according to the manufacturer's instructions, followed by incubation at 37˚C. At 48 h following transfection, the cells were collected for use in the subsequent experiments.

miR target prediction. TargetScan 7.1 database (http://www.targetscan.org/vert_71/) was used to identify the potential target mRNAs of miR-383-5p.

Luciferase reporter gene assay. The wild-type (WT) or mutant-type (MT) 3'-UTR of CIP2A were constructed by RiboBio and inserted into the pmiR-REPORT vector (Ambion; Thermo Fisher Scientific, Inc.), which was then transfected into cells using Lipofectamine 2000 (Invitrogen; Thermo Fisher Scientific, Inc.) according to the manufacturer's instructions, and incubated at 37˚C. At 48 h following transfection, the luciferase activity was determined by the Dual Luciferase Reporters Assay System (Promega Corporation) on a LuminoskanTM Ascent Microplate Luminometer (Thermo Fisher Scientific, Inc.). The luciferase activity was normalized to *Renilla* luciferase activity.

Reverse transcription-quantitative PCR (RT-qPCR) analysis. Total RNA was extracted using TRIzol reagent (Invitrogen; Thermo Fisher Scientific, Inc.) according to the manufacturer's instructions. Reverse transcription was conducted at 42˚C for 15 min followed by incubation at 85˚C for 5 sec using the TaqMan Reverse Transcription kit (Applied Biosystems; Thermo Fisher Scientific, Inc.) according to the manufacturer's instructions. RT-qPCR was conducted using the Applied Biosystems 7300 Real-Time PCR system (Applied Biosystems; Thermo Fisher Scientific, Inc.) with the TaqMan Universal PCR Master Mix (Thermo Fisher Scientific, Inc.). The primers used were as follows: CIP2A forward, 5'-AATTTAGTAAAGACCCTGATCTG-3' and reverse, 5'-CAGATCAGGGTCTTTACTAAATT-3'; GAPDH forward, 5'-GGAGCGAGATCCCTCCAAAAT-3' and reverse, 5'-GGCTGTTGTCATACTCTCATGG-3'; miR-383-5p forward, 5'-TCGGTGTTAGTGGAAGACTAGAC-3' and reverse, 5'-GTCTAGTCTTCCACTAACACCGA -3'; U6 forward, 5'-GTGCTCGCTTCGGCAGCACAT-3' and reverse, 5'-AATATGGAACGCTTCACGAAT-3'. The thermocycling conditions were as follows: Initial denaturation at 95˚C for 2 min, and 40 cycles of 95˚C for 15 sec and 64˚C for 30 sec. GAPDH was used as an endogenous control for CIP2A. U6 was used as an endogenous control for miR-383-5p. The relative expression levels were calculated using the $2^{-\Delta\Delta cq}$ method (21).

Western blot analysis. Total protein lysates were prepared by radioimmunoprecipitation assay (RIPA) lysis buffer (Sigma-Aldrich; Merck KGaA) at 4˚C. The protein concentration was determined using a bicinchoninic acid kit (Pierce; Thermo Fisher Scientific, Inc.). Protein samples (20 μg) were separated by 10% SDS-PAGE and transferred onto PVDF membranes. The PVDF membranes were then blocked by 5% BSA (Sigma-Aldrich; Merck KGaA) at room temperature for 1 h, probed with primary antibodies to CIP2A (dilution 1:1,000; #14805), p21 (dilution 1:1,000; #2947), CDK4 (dilution 1:1,000; #12790), Cyclin D1 (dilution 1:1,000; #55506), Bcl-2 (dilution 1:1,000; #4223), BAX (dilution 1:1,000; #5023), β-actin (dilution 1:1,000; #4970) which were purchased form Cell Signaling Technology at 4˚C overnight and horseradish peroxidase-conjugated secondary antibody (dilution 1:1,000; #7074, Cell Signaling Technology) at room temperature for 2 h. Finally, the bands were visualized by the enhanced chemiluminescence detection reagent using the ChemiDoc XRS system (Bio-Rad Laboratories, Inc.).

Cell proliferation assay. Cell proliferation was assessed by MTT assay (Sigma-Aldrich; Merck KGaA) as advised in the manufacturer's manual. Cells ($3x10^3$/100 μl) were plated into each well of the 96-well plates and cultured at 37˚C for 3 days. Subsequently, the dye solution (15 μl) was added to each well and incubated at 37˚C for a further 4 h. Stop solution (100 μl) was then added to each well. The colorimetric absorbance was recorded with the SpectraMax Plus (Molecular Devices LLC) at 570 nm.

Cell cycle analysis. Cells ($1x10^6$) were collected and fixed by 70% ice-cold ethanol at 4˚C overnight. The cells were then re-suspended in PBS (1 ml) supplemented with bovine pancreatic RNase A (100 μg/ml, Sigma-Aldrich; Merck KGaA) and 40 μg/ml propidium iodide (PI; Sigma-Aldrich; Merck KGaA) for 30 min at 4˚C. Subsequently, cell cycle analysis was carried out on a Becton-Dickinson FACSCalibur cytometer (BD Biosciences) and analyzed by ModFit software version 3.2.1 (Verity Software House).

Cell apoptotic analysis. Cell apoptosis was determined using the Annexin V-fluorescein isothiocyanate (FITC) apoptosis kit (Merck KGaA) according to the manufacturer's instructions. Cells were incubated in ice-cold 1X binding buffer (500 μl) containing Annexin V-FITC (2.3 μl) for 10 min at 4˚C, followed by incubation at room temperature for 10 min in the dark. Subsequently, the cells were re-suspended in ice-cold 1X binding buffer (500 μl) supplemented with PI (5 μl), and incubated at room temperature for 15 min. The signals of Annexin V-FITC and PI were detected using a flow cytometer (FACSCalibur™; BD Biosciences).

Statistical analysis. All experiments were performed at least 3 times. The values are expressed as the means ± standard error of the mean. Differences between 2 groups were analyzed using an unpaired Student's t-test, while differences

among 3 groups were analyzed by one-way analysis of variance followed by Newman-Keuls test. Values of $P<0.05$ were considered to indicate statistically significant differences.

Results

miR-383-5p expression is decreased in GC cell lines. The expression level of miR-383-5p was assessed in GC cell lines. RT-qPCR analysis revealed that the miR-383-5p expression level was significantly lower in the GC cell lines (AGS and HGC-27) compared with the GES-1 normal gastric epithelial cell line (Fig. 1), which were then used in the subsequent experiments.

miR-383-5p directly targets CIP2A. Using the online open access database, TargetScan 7.1 (http://www.targetscan.org/vert_71/), CIP2A was selected as a candidate target mRNA for miR-383-5p. The potential CIP2A 3'-UTR fragments (WT and MT) are presented in Fig. 2A. In the 293T cell line, miR-383-5p mimic induced a significantly lower luciferase activity in the WT CIP2A 3'-UTR luciferase reporter plasmid, whereas no significant alteration was detected in the luciferase activity of the MT plasmid (Fig. 2B).

CIP2A expression is increased in GC cell lines. The expression of CIP2A in the GC cell lines, AGS and HGC-27, was then investigated by RT-qPCR analysis and western blot analysis. It was observed that the expression of CIP2A at the mRNA (Fig. 3A) and protein (Fig. 3B and C) level was significantly higher in the AGS and HGC-27 GC cells compared with that in the normal gastric epithelial cell line, GES-1.

Transfection of miR-383-5p mimic and pcDNA3.1-CIP2A. RT-qPCR and western blot analysis were used to verify the transfection of miR-383-5p mimic and pcDNA3.1-CIP2A in the GC cell lines, AGS and HGC-27. For miR-383-5p, the cells were divided into 3 groups, including the control, miR-NC mimic and miR-383-5p mimic groups. The results demonstrated that the miR-383-5p level was significantly increased by transfection with miR-383-5p mimic, indicating the successful transfection of miR-383-5p mimic in the AGS and HGC-27 GC cells (Fig. 4A); furthermore, the CIP2A protein level was significantly decreased by transfection with miR-383-5p mimic in the AGS and HGC-27 GC cells (Fig. 4B and C).

For pcDNA3.1-CIP2A, the cells were divided into 3 groups, including the control, pcDNA3.1 and pcDNA3.1-CIP2A groups. The CIP2A protein level was significantly increased by transfection with pcDNA3.1-CIP2A in the AGS and HGC-27 GC cells (Fig. 4D and E), indicating the successful transfection of pcDNA3.1-CIP2A in AGS and HGC-27 GC cells.

miR-383-5p inhibits the proliferation of GC cells by targeting CIP2A. When investigating the role of miR-383-5p in human GC cell proliferation by MTT assay, compared to transfection with miR-NC mimic, transfection with miR-383-5p mimic was shown to significantly decrease AGS and HGC-27 cell proliferation, which was reversed by transfection with pcDNA3.1-CIP2A (Fig. 5A and B). p21 was negatively correlated with cell proliferation, for example,

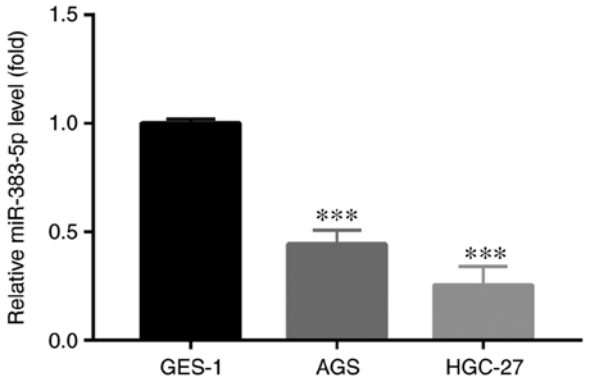

Figure 1. Expression of miR-383-5p in GC cell lines. The miR-383-5p expression level was assessed by reverse transcription-quantitative PCR analysis. ***P<0.001 vs. GES-1. GC, gastric cancer.

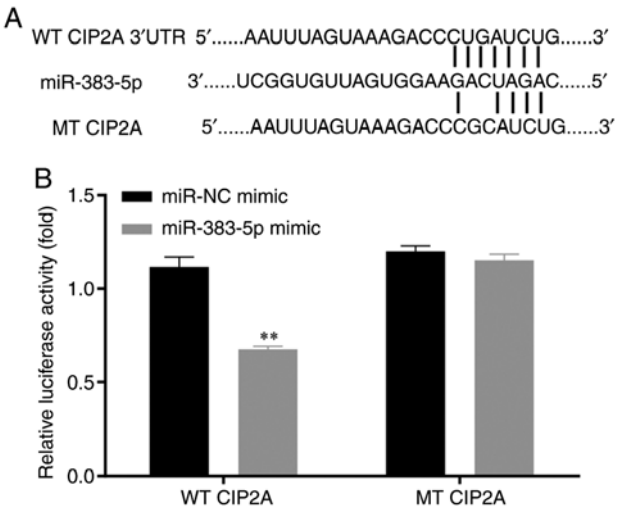

Figure 2. Interaction between miR-383-5p and CIP2A. (A) The potential WT and MT CIP2A 3'UTR fragment and miR-383-5p were investigated. (B) Effects of miR-383-5p mimic on luciferase activity. **P<0.01 miR-383-5p mimic vs. miR-NC mimic. WT, wild-type; MT, mutant type; CIP2A, cancerous inhibitor of PP2A; UTR, untranslated region.

LincRNAFEZF1-AS1 to induced proliferation of GC cells by repressing p21 (22). Western blot analysis was used to assess the protein level of p21. Compared to transfection with miR-NC mimic, miR-383-5p mimic significantly increased the protein level of p21, which was reversed by pcDNA3.1- CIP2A (Fig. 5C and D).

miR-383-5p induces the apoptosis of GC cells by targeting CIP2A. In order to elucidate the potential anti-proliferative mechanisms of action of miR-383-5p in the GC cell lines AGS and HGC-27, cell cycle progression and apoptosis were analyzed by flow cytometry.

Compared to transfection with miR-NC mimic, miR-383-5p mimic significantly increased the proportion of cells in the G_1 phase and decreased the proportion of cells in the S phase, which was reversed by transfection with pcDNA3.1-CIP2A (Fig. 6A-D). Cyclin D1 and CDK4 are associated with the progression of the cell cycle; for example, RN181 regulates the activity of cyclin D1-CDK4, thus controlling the progression from the G_1 to the S phase

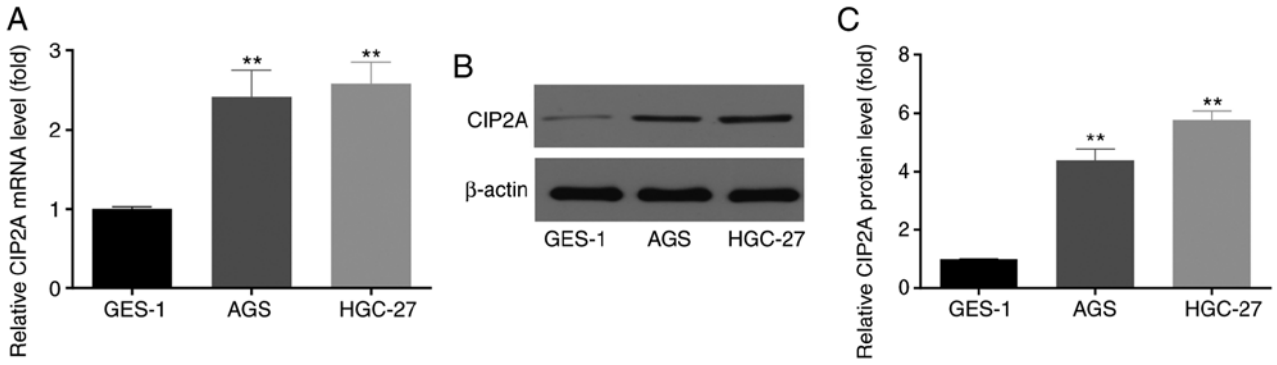

Figure 3. Expression of CIP2A in GC cell lines. (A-C) The CIP2A mRNA and protein expression levels were assessed by reverse transcription-quantitative PCR analysis and western blotting, respectively. **P<0.01 vs. GES-1. CIP2A, cancerous inhibitor of PP2A; GC, gastric cancer.

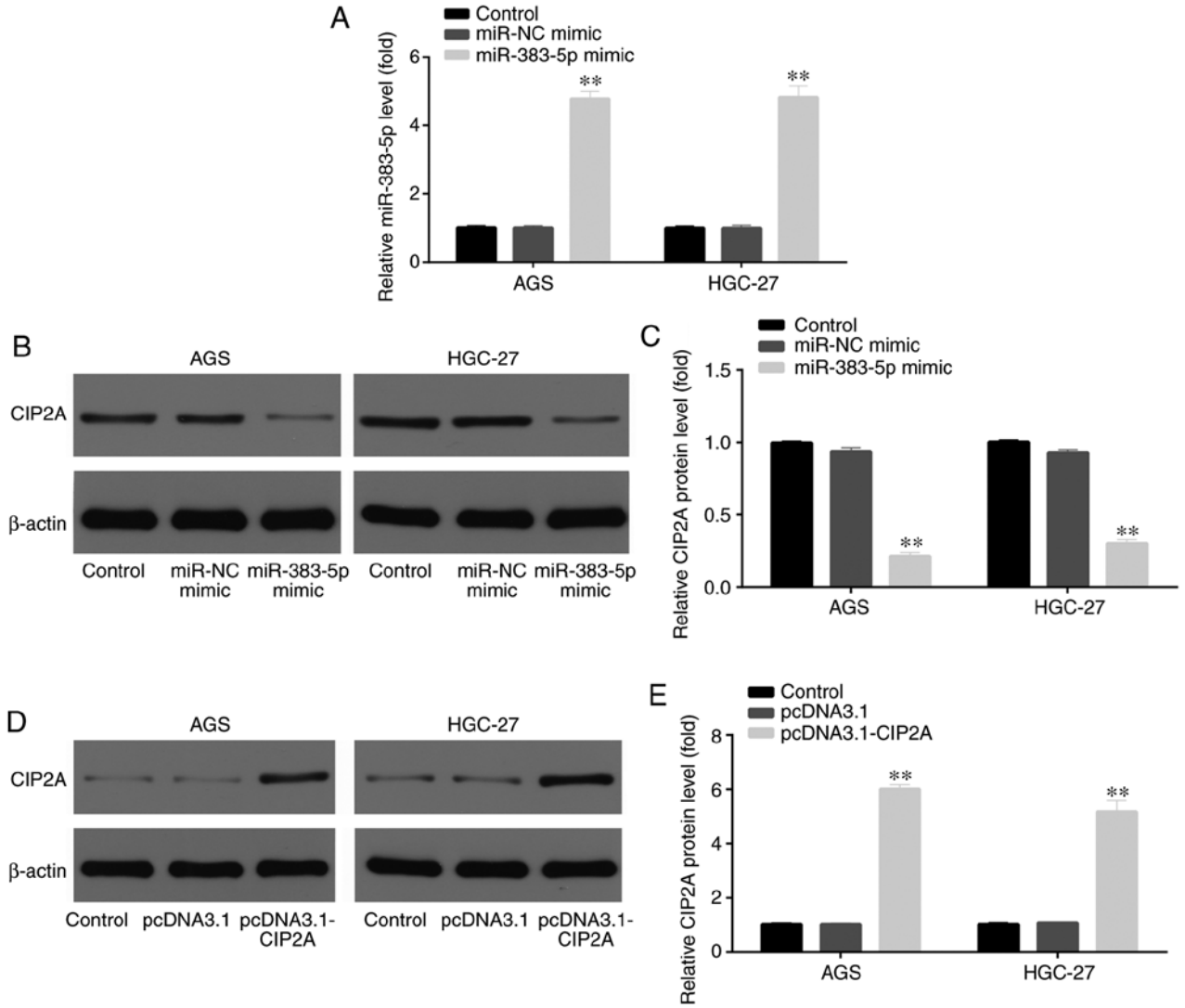

Figure 4. Transfection with miR-383-5p mimic and pcDNA3.1-CIP2A. (A) The miR-383-5p level was assessed by reverse transcription-quantitative PCR analysis. (B-E) The CIP2A protein level was assessed by western blot analysis. **P<0.01 miR-383-5p mimic vs. miR-NC mimic. CIP2A, cancerous inhibitor of PP2A.

in GC cells (23). Furthermore, compared to transfection with miR-NC mimic, transfection with miR-383-5p mimic significantly increased the protein levels of CDK4 and cyclin D1, and this effect was reversed by pcDNA3.1-CIP2A (Fig. 6E-G).

Furthermore, an increased proportion of apoptotic cells was observed in the GC cell lines, AGS and HGC-27, following transfection with miR-383-5p mimic compared to miR-NC mimic, which was reversed by transfection with pcDNA3.1-CIP2A (Fig. 7A and B). The ratio of pro-apoptotic

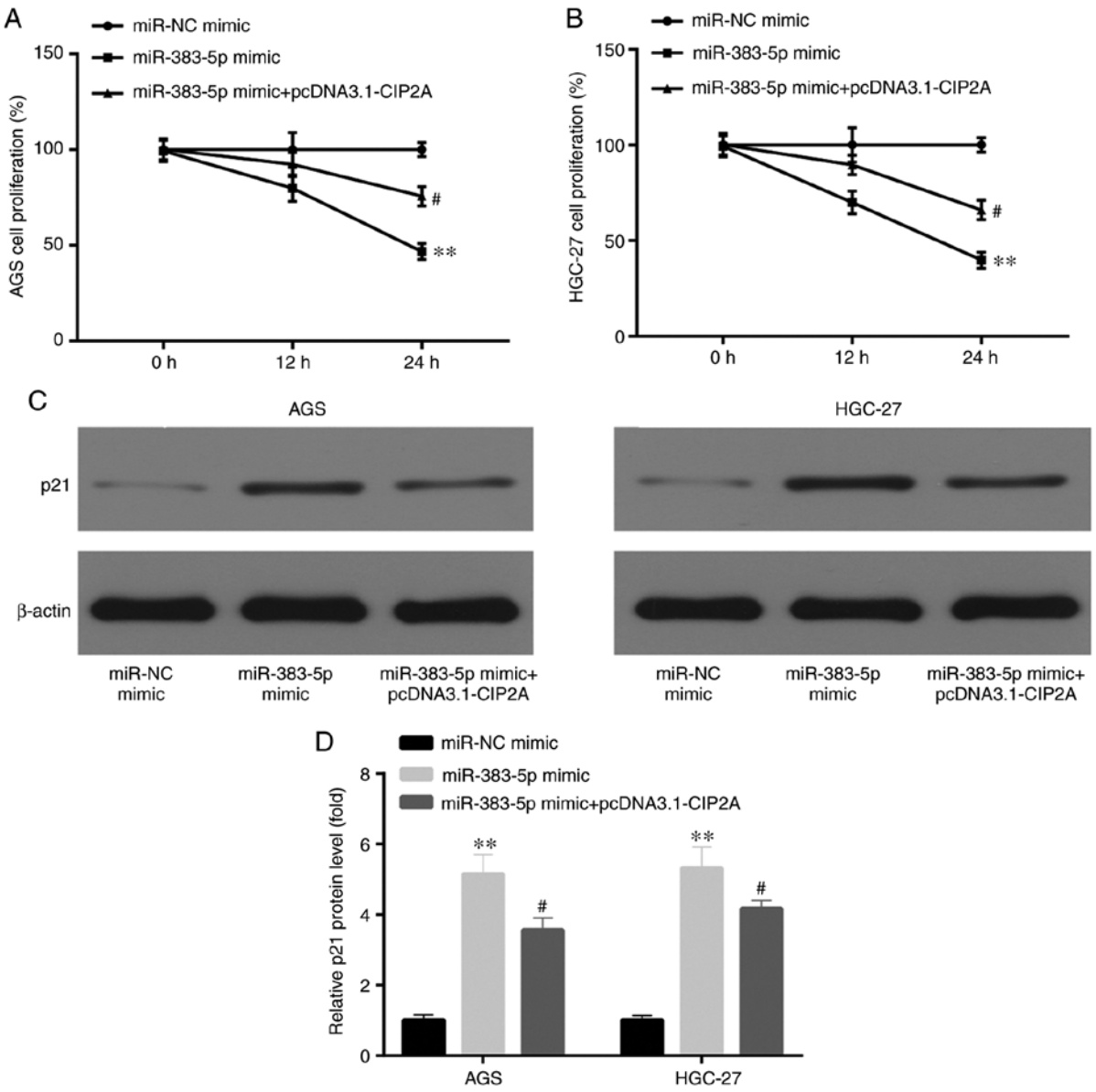

Figure 5. Effects of miR-383-5p on GC cell proliferation. (A and B) Cell proliferation was assessed by the MTT assay. (C and D) The p21 protein level was assessed by western blot analysis. **P<0.01 miR-383-5p mimic vs. miR-NC mimic. #P<0.05 miR-383-5p mimic + pcDNA3.1-CIP2A vs. miR-383-5p mimic. GC, gastric cancer; CIP2A, cancerous inhibitor of PP2A.

BAX to anti-apoptotic Bcl-2 was crucial for the promotion of cell apoptosis (24). In addition, compared to miR-NC mimic, the BAX/Bcl-2 ratio was increased by miR-383-5p mimic, which was reversed by pcDNA3.1-CIP2A (Fig. 7C and D).

Discussion

The dysregulation of miR-383 is associated with various types of cancer, such as hepatocellular carcinoma (25), pancreatic cancer (26) and glioma (27). Consistently, it was observed that miR-383-5p was also significantly decreased in GC cell lines compared with the GES-1 normal gastric epithelial cell line.

miRNAs target different mRNAs to control cancer progression (28,29). For example, the overexpression of miR-383-5p inhibits ovarian cancer cell proliferation by targeting and downregulating tripartite motif-containing 27 (30); miR-383-5p reverses hepatocellular carcinoma cell proliferation by targeting aldo-keto reductase family 1 member B10 (9). The present study demonstrated that miR-383-5p functions as a tumor suppressor by targeting and downregulating CIP2A, which was also proven by a previous study on lung cancer (23).

CIP2A overexpression has been detected in GC tumor samples (19). Consistently, the present study also demonstrated that CIP2A was significantly overexpressed in GC cell lines compared with the GES-1 normal gastric epithelial cell line.

CIP2A and miR-383-5p regulate cell proliferation. For example, CIP2A was shown to induce cell proliferation and protect cells from apoptosis in non-small-cell lung cancer (31,32); furthermore, miR-383-5p reduced cell proliferation in hepatocellular carcinoma (9) and GC (14). Consistently, it was observed that miR-383-5p inhibited GC cell proliferation, and induced p21 expression which was negatively related to cell proliferation (33), by targeting

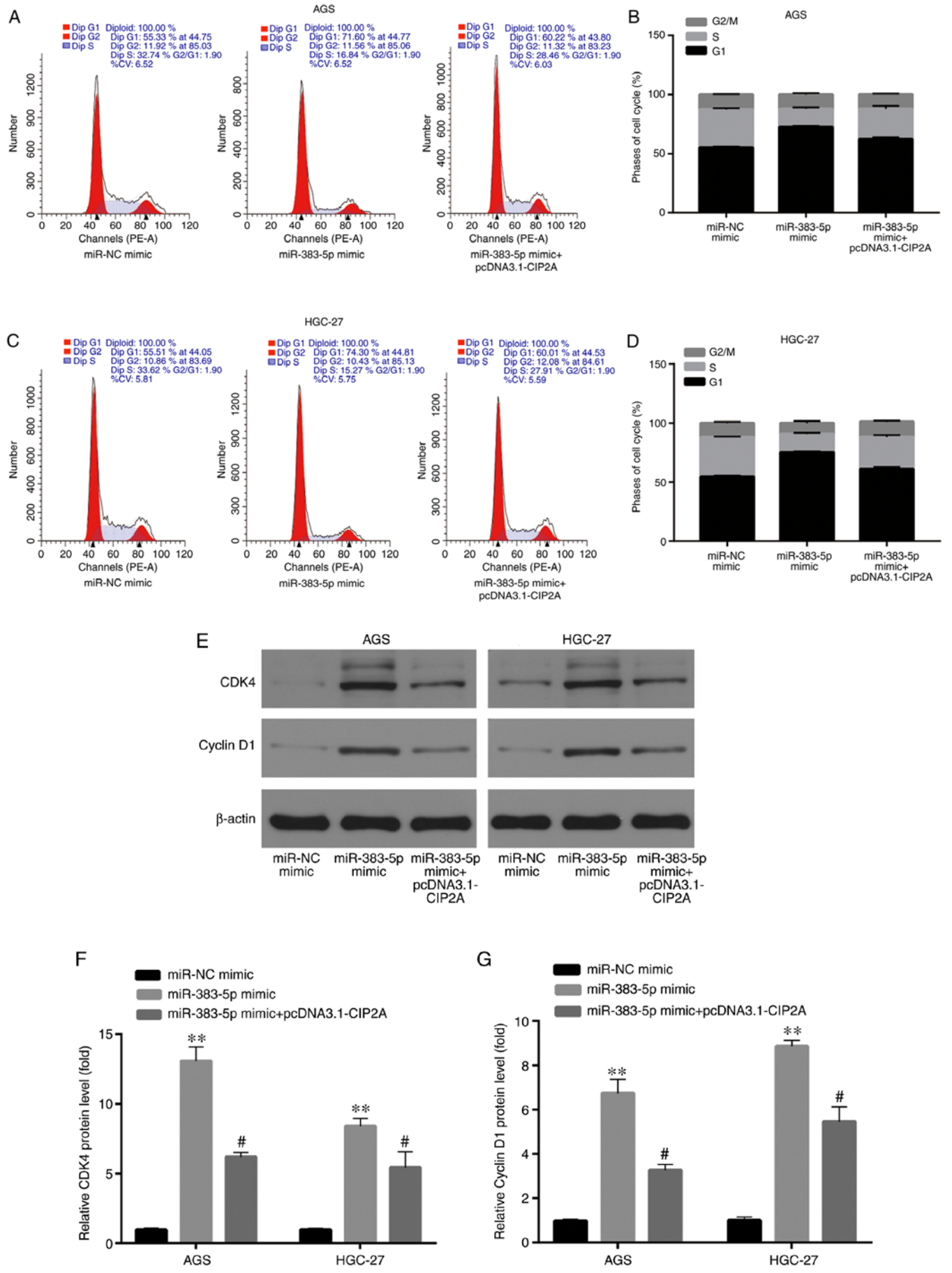

Figure 6. Effects of miR-383-5p on GC cell cycle. (A-D) Cell cycle distribution was assessed by flow cytometry. (E-G) The protein levels CDK4 and cyclin D1 were assessed by western blot analysis. **P<0.01 miR-383-5p mimic vs. miR-NC mimic. $^{\#}$P<0.05 miR-383-5p mimic + pcDNA3.1-CIP2A vs. miR-383-5p mimic. GC, gastric cancer; CIP2A, cancerous inhibitor of PP2A.

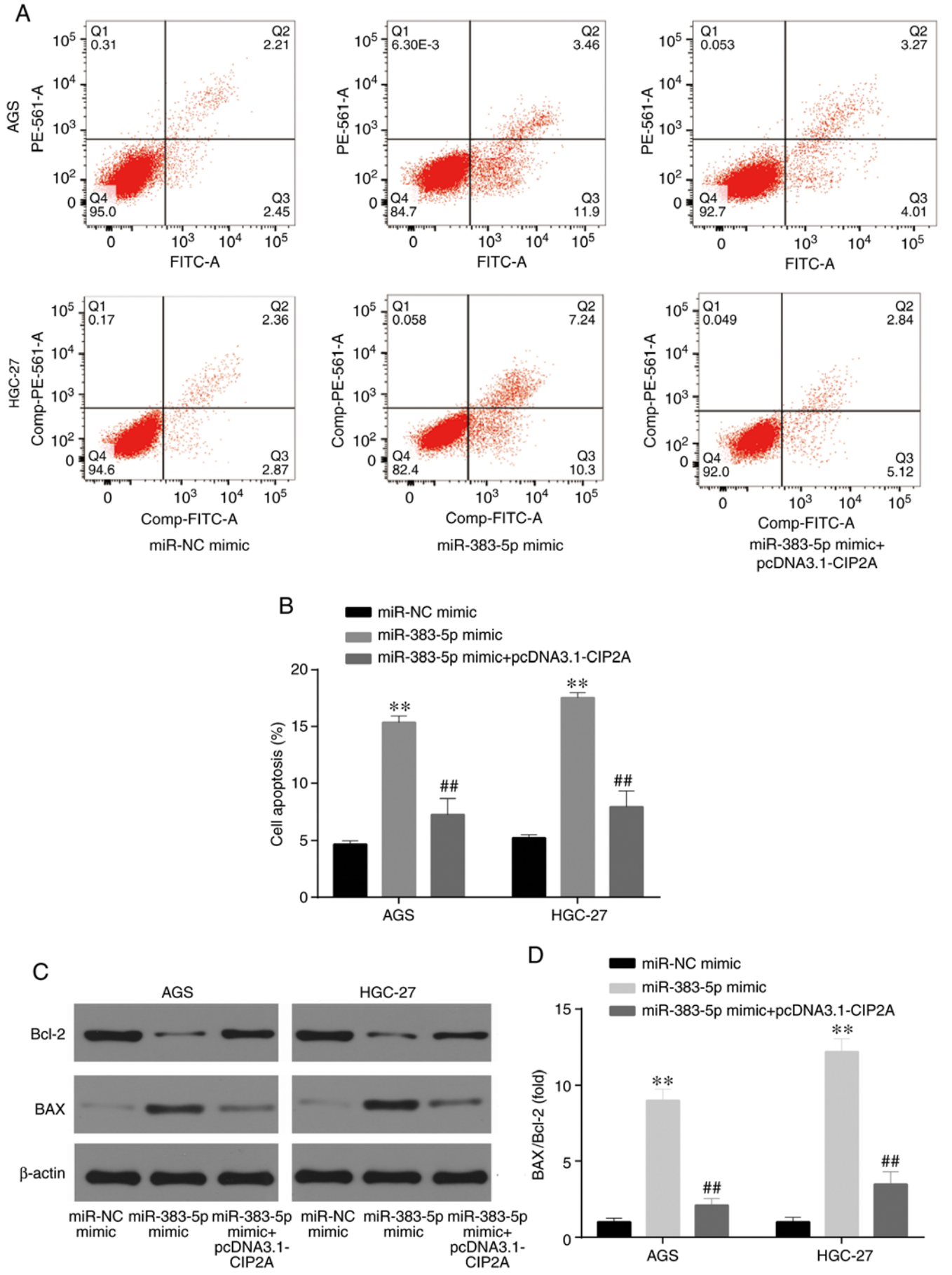

Figure 7. Effects of miR-383-5p on GC cell apoptosis. (A and B) Cell apoptosis was assessed by flow cytometry. (C and D) The protein levels of BAX and Bcl-2 were assessed by western blot analysis. **P<0.01 miR-383-5p mimic vs. miR-NC mimic. $^{\#\#}$P<0.01 miR-383-5p mimic + pcDNA3.1-CIP2A vs. miR-383-5p mimic. GC, gastric cancer; CIP2A, cancerous inhibitor of PP2A; Bcl-2, B-cell lymphoma 2; BAX, Bcl-2-associated X protein.

CIP2A. In addition, miR-383-5p mimic induced G_0/G_1 arrest and CDK4/cyclin D1 expression which was positively related to the cell cycle (34), and increased cell apoptosis and the BAX/Bcl-2 ratio, which was positively associated with cell apoptosis (35,36), by targeting CIP2A. Therefore, on the whole, these findings indicate that miR-383-5p inhibited the proliferation of GC cells by inducing apoptosis and cell cycle arrest in the G0/G1 phase by targeting CIP2A.

The present study clearly demonstrated that the restoration of CIP2A expression abrogated the inhibitory effects of miR-383-5p on GC cell proliferation. Taken together, the findings of the present study demonstrated that miR-383-5p exerts an inhibitory effect on GC by inhibiting CIP2A.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

All the datasets generated and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

XL, JY and QC participated in designing and conducting the experiments; XL, JY and AX analyzed the data; JC conceived the study, supervised the experiments, performed data analysis and wrote the manuscript. All the authors have read and approved the final version of the manuscript for publication.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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