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Original Article

Impact and underlying mechanisms of *miR-1271* on cisplatin resistance in the human ovarian cancer cell line SKOV3/DDP

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Abstract: Despite progress in chemotherapeutic treatment of human ovarian cancer, drug resistance is still an obstacle. MicroRNAs [miRNAs] have been shown to play vital roles in tumorigenesis and tumor progression, and influence cisplatin [DDP]-induced apoptosis. To investigate the possible role of *miR-1271* in the development of DDP resistance in human ovarian cancer, we examined its effect in the human ovarian SKOV3/DDP cell line. We found that *miR-1271* was downregulated in DDP-resistant SKOV3/DDP cells, and that down-regulation of *miR-1271* was concurrent with overexpression of its target antiapoptotic gene X-linked inhibitor of apoptosis protein [XIAP] in SKOV3/DDP cells, compared with the parental SKOV3 cell line. Furthermore, diminished activity of XIAP 3'-untranslated region [3'UTR] luciferase-linked reporter constructs in SKOV3/DDP cells suggested that XIAP was the direct target of *miR-1271*. Overexpression of *miR-1271* inhibited the expression of XIAP and sensitized SKOV3/DDP cells to DDP-induced apoptosis. In conclusion, our findings indicate that *miR-1271* may increase DDP resistance in human ovarian cancer cell lines and participate in the modulation of apoptosis via targeting XIAP.

Keywords: *miR-1271*, XIAP, cisplatin resistance, ovarian cancer, SKOV3/DDP cells

Introduction

Ovarian carcinoma is the most common gynecological malignancy and is one of the five leading causes of cancer-related deaths among women [1, 2]. Most patients diagnosed with ovarian carcinoma are at an advanced stage, resulting in a dismal prognosis and the high death rate [3].

MicroRNAs [miRNAs] are a family of small, non-coding RNAs which can post-transcriptionally repress target gene expression by recruiting an RNA-induced silencing complex to imperfectly bind to the 3' untranslated region [3'-UTR] of the target mRNA [4, 5]. It has been demonstrated that miRNAs are involved in multiple vital biological processes [6]. In 2005, Cimmino and colleagues reported the mechanism of decreasing expression of BCL2, post-transcriptionally regulated by *miR-15* and *miR-16*, suggesting the important function of miRNAs in the intrinsic apoptosis pathway [7]. Previous studies have also indicated that aberrant expression of miRNAs plays a critical role in carcinogenesis [8, 9]. For instance, *miR-1271* was shown to inhibit the proliferation and invasion of tumor cells by targeting various effectors in different cancers [10-14]. In addition, miR-1271 was identified to repress the expression of Glypican-3 which is the most abnormally expressed genes in hepatocellular carcinoma [15]. There are at least twenty-two miRNAs differentially expressed in ovarian cancer [16]. Interestingly, *miR-1271* also participates in the regulation of insulin resistance leading to type 2 diabetes [17].

Currently, cisplatin [DDP] is an indispensable drug for the chemotherapeutic treatment of cancer, including ovarian carcinoma. Cisplatin has ability to crosslink with the purine bases on the DNA, interfere with DNA repair and causing DNA damage, subsequently inducing apoptosis

in cancer cells [18]. However, resistance to DDP inevitably develops in ovarian cancer cells. Despite new treatment approaches, early diagnosis and the prognosis for ovarian cancer have not significantly improved. Recently, numerous studies have demonstrated that multiple microRNAs are strongly related to the chemoresistance phenotype of tumor cells, including *miR-1271*, *miR-143*, *miR-20a*, *miR-181b* and *miR-21* [3, 19]. These findings suggest that better characterization of the molecular mechanism underlying DDP resistance will provide new insights into the treatment of ovarian tumors [2, 16, 20].

As predicted by bioinformatics software, we found that *miR-1271* interacts with the X-linked inhibitor of apoptosis protein [XIAP] in ovarian carcinoma. XIAP is an important member of the family of inhibitor of apoptosis proteins. Up-regulation of the XIAP gene has been shown to decrease the sensitivity of lung tumor cells to chemotherapy drugs, resulting in chemotherapy drug resistance in lung cancer [4, 5]. In this study, we examined the role of *miR-1271* and XIAP in mediating DDP resistance in ovarian carcinoma and their underlying mechanisms in the human ovarian cancer cell line SKOV3/DDP.

Materials and methods

Reagents and devices

The DDP-resistant human ovarian cancer cell line SKOV3/DDP and its parental SKOV3 cell line were both purchased from Shanghai Integrated Biotech Solutions Co., Ltd. (Shanghai, China). Bovine calf serum (BCE) and RPMI 1640 medium were obtained from Gibco® (Grand Island, NY, USA). Dimethyl sulfoxide (DMSO) and methyl thiazolyl tetrazolium (MTT) were purchased from Sigma (St. Louis, MO, USA). DDP was purchased from Simcere (Nanjing, China). Luciferase Reporter Gene Assay Kit was from Promega (Madison, WI, USA). The XIAP gene 3'UTR-luciferase reporter plasmid was constructed by Shanghai Integrated Biotech Solutions. The *miR-1271* mimics were purchased from Shanghai GenePharma Co., Ltd. ANNEXIN V-FITC apoptosis detection kit was from Millipore (Bedford, MA, USA). Trizol reagent and transfection reagent Lipofectamine 2000 was from Invitrogen (Carlsbad, CA, USA). XIAP antibodies and GAPDH antibodies were from Santa Cruz Biotechnology (Santa Cruz, CA, USA). The TaqMan Universal PCR Master Mix, TaqMan® MicroRNA Reverse Transcription Kit, U6 TaqMan® MicroRNA Assays and hsa-*miR-1271* TaqMan® MicroRNA Assays were all supplied by ABI (Foster City, CA, USA). The primers for reverse transcription and PCR were obtained from RiboBio Co., Ltd. (Guangzhou, China). Finally, the flow cytometer was from BD Corporation and the fluorescence quantitative PCR instrument (7300HT) was purchased from ABI.

Cell cultures and transfection

Ovarian cancer SKOV3 cell lines were cultured in RPMI 1640 medium supplemented with 10% BCE at 37°C in a humidified incubator with 5% CO_2. The ovarian cancer SKOV3/DDP cell line was incubated in RPMI 1640 medium containing 1 μg/ml DDP and 10% BCE and passaged using 0.25% trypsogen. For treatments, 6×10^5 SKOV3/DDP cells were cultured in microplates for 24 h, then transfected with 100 nM *miR-1271* mimics or 100 nM *miR-1271* mimic controls. All transfections were performed using Lipofectamine 2000 according to the manufacturer's protocol.

Quantitative real-time reverse transcription-PCR (qRT-PCR)

Total RNA was extracted with Trizol Reagent from SKOV3 and SKOV3/DDP cells in the logarithmic phase of growth. First strand cDNA was synthesized using the TaqMan® MicroRNA Reverse Transcription Kit in a 15 μl reaction. The reaction consisted of 0.15 μl of 100 mM/L dNTPs, 1 μl reverse transcriptase, 1.50 μl buffer, 0.19 μl RNase inhibitor, 3 μl of 5 × RT Primer, 4.16 μl nuclease-free water and 5 μl total RNA sample. The incubation time was 30 min at 16°C, followed by 30 min at 42°C and 5 min at 85°C.

Aliquots of 1.33 μl from each cDNA reaction served as templates in 20 μl qRT-PCR reactions containing 10 μl of 2 × Universal PCR Master Mix, 1 μl Taq polymerase and 7.67 μl nuclease-free water. PCR cycles consisted of 95°C for 10 min followed by 40 cycles of 95°C for 15 s and 60°C for 1 min. The expression of miRNA was normalized to U6 RNA. ABI 7300 System SDS Software v1.3.1.21 was used to quantify cDNA. Ct was recorded to perform quantitative analy-

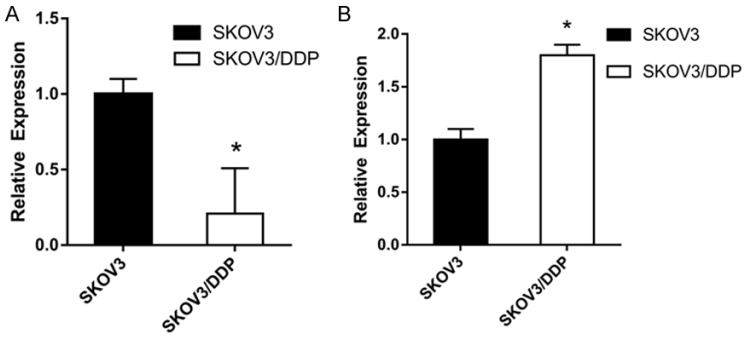

Figure 1. A. Detected by the qRT-PCR, *miR-1271* was significantly downregulated in the DDP-resistant human ovarian cancer cell line SKOV3/DDP, compared with the parental SKOV3 cell line. The downregulated fold change was 4.7 ± 0.3 fold [**P* < 0.01]. B. The results of western blots showed that the antiapoptotic protein XIAP was significantly upregulated in DDP-resistant SKOV3/DDP cells compared with the parental SKOV3 cell line [**P* < 0.01].

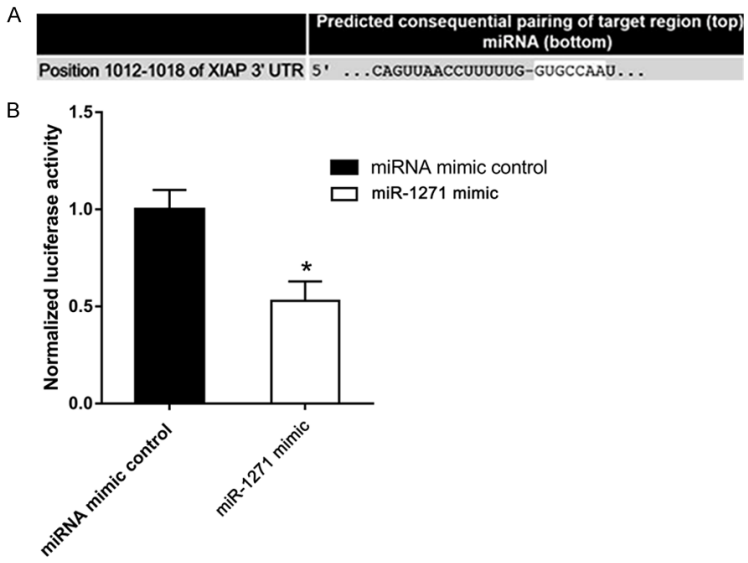

Figure 2. XIAP is targeted by *miR-1271*. A. Complementary sites predicted by TargetScan. Sites in the 3'UTR region of XIAP from nt 1012 to 1018 were fully complementary to *miR-1271.* B. Luciferase assays to determine activity of the XIAP 3'UTR-luciferase reporter construct. The activity in the control group was set at 1. A significant decrease in relative luciferase activity was noted when pGL3-XIAP-3'-UTR was co-transfected with the *miR-1271* mimic but not with the miRNA mimic control [**P* < 0.01].

sis of *miR-1271* expression by the $2^{-\Delta\Delta Ct}$ method.

MTT assay

MTT assay of transfected cells was performed according to the manufacturer's protocol. Treated cells were seeded in 96-well plates at a concentration of 8×10^3 cells per well. DDP was added 12 h later at concentrations of 0.02 μg/ml, 0.2 μg/ml, 2 μg/ml and 20 μg/ml based on the peak concentration of DDP in the plasma of patients. After 48 h incubation, 20 μl of fresh MTT solution (5 mg/ml) was added to each well and incubated for 4 h. The supernatant was then discarded and 150 μl of DMSO was added followed by shock for 10 min. Finally, the absorbance at 490 nm was measured by a microplate reader. We used SPSS software (IBM Corp., Armonk, NY, USA) to calculate the half-maximal inhibitory concentration of DDP in SKOV3/DDP cells after transfection with *miR-1271*.

Luciferase reporter assay

As predicted by bioinformatic software Target Scan (http://www.targetscan.org), we found possible target genes of *miR-1271* and hypothesized that the XIAP gene may contain similar target sequences. To test this, SKOV3/DDP cells were seeded in 24-well plates at a density of 1.5×10^5 cells per well. Subsequently, 200 ng XIAP 3'UTR-luciferase reporter plasmid and 60 pmol *miR-1271* mimic or 60 pmol *miR-1271* mimic control and 80 ng Renilla reference plasmid were co-transfected into cells. After 24 h, cells were tested for luciferase activity.

Western blot

After transfection for 72 h, total proteins from SKOV3/DDP and parental cells were isolated. Briefly, proteins were separated by 10% SDS-PAGE and transferred onto a nitrocellulose membrane. Sections were blocked for 2 h by 10% skim milk, followed by the addition of XIAP antibody and overnight incubation at 4°C. GAPDH was used as an internal control. Image J software was used to quantify the densities of protein bands related to XIAP expression differences.

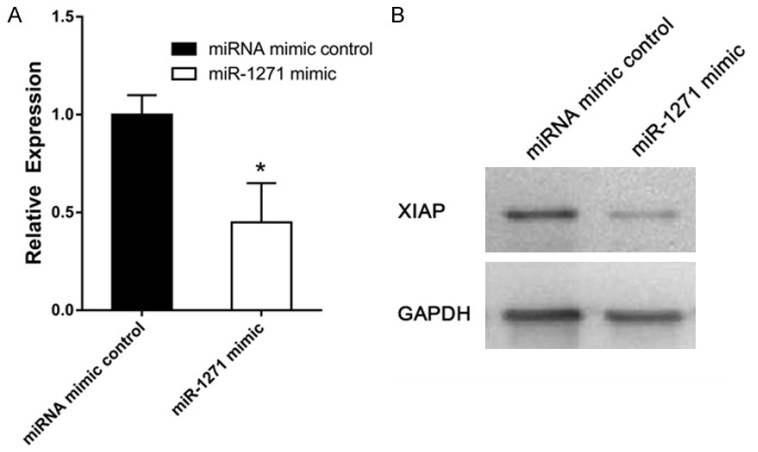

Figure 3. In SKOV3/DDP cells, quantified western blot analysis of XIAP protein expression levels showed that 72 h after transfection, XIAP protein levels in *miR-1271* mimic-transfected cells were significantly decreased compared with miRNA mimic control-transfected cells [*$P < 0.01$].

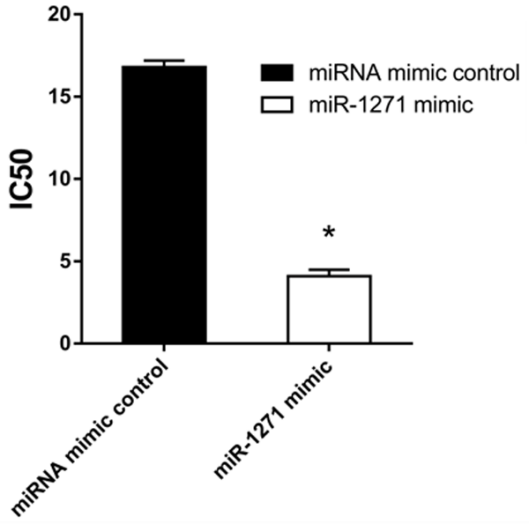

Figure 4. In vitro drug sensitivity analysis of SKOV3/DDP cells using MTT assays showed that cells transfected with the *miR-1271* mimic exhibited greatly enhanced sensitivity to DDP compared with those transfected with the miRNA mimic control. The IC50 of DDP for *miR-1271* mimic-transfected cells was 4.1 ± 0.4 μg/ml compared to 16.8 ± 0.4 μg/ml for miRNA mimic control-transfected cells [*$P < 0.01$].

Apoptosis assay

Apoptotic cells were detected using the ANNEXIN V-FITC apoptosis detection kit. After transfection for 24 h with *miR-1271* mimics or mimic control, SKOV3/DDP cells were incubated for 48 h with a final concentration of 10 μg/ml of DDP. Cells were then trypsinized and the percentage of apoptotic cells was determined by flow cytometer.

Statistical analysis

The data were analyzed with SPSS 11.0 software. All experiments were performed three times. All values are presented as means ± SD. The statistical significance of differences between groups was determined by a paired or unpaired Student's t-test. *P* values less than 0.05 were regarded as significant.

Results

Low levels of miR-1271 are inversely correlated with up-regulation of XIAP

qRT-PCR was performed to detect the expression of *miR-1271* in SKOV3/DDP and their parental cells. The results showed that compared to parental SKOV3 cells, *miR-1271* was significantly downregulated 4.7 ± 0.3 fold in ovarian carcinoma SKOV3/DDP cells (**Figure 1A**).

Western blot assays (**Figure 1B**) were used to detect the expression level of XIAP. The results showed that XIAP was significantly overexpressed in SKOV3/DDP cells. These results suggested that *miR-1271* may have a regulatory effect on the expression of XIAP.

XIAP is targeted by miR-1271

Predicted by Target Scan (**Figure 2A**), sites in the 3'UTR of XIAP from nt 1012 to 1018 were fully complementary to *miR-1271*, which suggested that the XIAP gene was a target of *miR-1271*. To verify this prediction, we performed luciferase assays with a luciferase reporter construct linked to the XIAP 3'UTR. Results showed that compared with the control group, luciferase activity was notably reduced when pGL3-XIAP-3'-UTR was co-transfected with the *miR-1271* mimics (**Figure 2B**).

This indicated that *miR-1271* likely regulated XIAP expression through this base paring interaction.

miR-1271 directly represses XIAP expression

To experimentally prove the regulatory effect of *miR-1271*, western blot analysis was used to

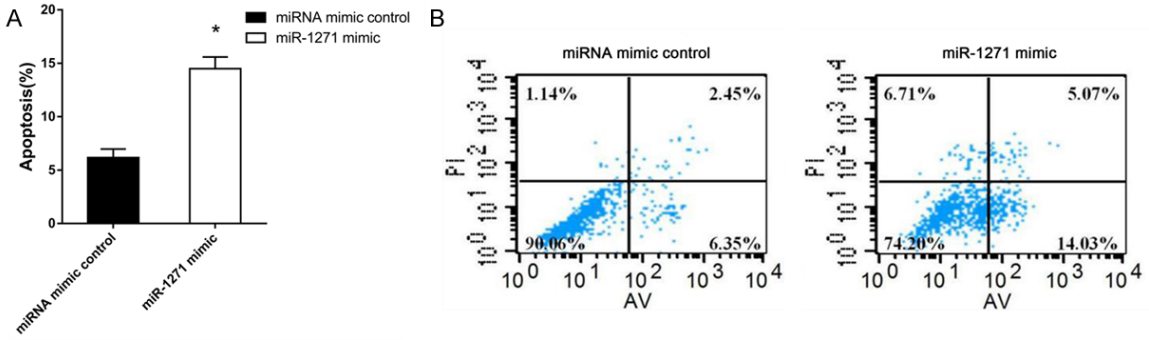

Figure 5. Effect of *miR-1271* overexpression on apoptosis. Apoptosis evaluated by flow cytometry showed a marked increase in apoptosis in *miR-1271* mimic-transfected cells after DDP treatment compared with the miRNA mimic control-transfected cells. The apoptosis rates were 14.54 ± 1.1% and 6.12 ± 0.8%, respectively [*$P < 0.01$].

detect the expression level of XIAP. As shown in **Figure 3**, XIAP expression was notably decreased after transfection of the *miR-1271* mimic. The downregulated fold change was 2.2 ± 0.2 fold. Combined with our previous results, this finding suggested that *miR-1271* directly inhibited XIAP expression via the base-pairing interaction in the XIAP 3'UTR.

miR-1271 sensitized drug-resistant cells to DDP-induced apoptosis

The results of MTT assays showed that in the *miR-1271* mimic group, the IC50 of DDP for SKOV3/DDP cells was 4.1 ± 0.4 μg/ml, while in the *miR-1271* mimic control group, it was 16.8 ± 0.4 μg/ml (**Figure 4**). In addition, as detected by flow cytometry, the apoptotic rate after DDP treatment was 14.54 ± 1.1% in cells transfected with the *miR-1271* mimic, markedly higher than the rate of 6.12 ± 0.8% in the control group (**Figure 5**).

Discussion

In recent years, a great number of biochemical changes that contribute to the development of drug resistance have been revealed with our growing understanding of cancer [21, 22]. Numerous studies have identified that miRNAs are negatively regulated in a variety of cancers [10, 23, 24]. These suggested miRNAs may act as anti-oncogenes [4].

The application of Solexa technology first revealed the human *miR-1271* gene and its location at intron 2 of ADP-ribosylation factor-like 10. Jensen and Covault found that human *miR-1271* is highly expressed in brain tissues, and probably participates in the development of nerve cells [25]. Furthermore, the expression of *miR1271* and host gene is a synergetic process, suggesting a promoter-sharing region. However, *miR-1271* is suppressed in pancreatic cancer, non-small cell lung cancer, ovarian carcinoma and gastric cancer. Functioning as a tumor suppressor gene, *miR-1271* inhibits the synthesis of proteins such as ZEB1, TWIST1, Cyclin G1 and FOXQ1, consequently restraining the proliferation and invasion of tumors [12, 14, 20]. In addition, further studies have demonstrated that *miR-1271* is significantly downregulated in DDP-resistant gastric cancer cells, and overexpression of *miR-1271* has been shown to suppress the proliferation and promote the process of DDP-induced apoptosis by targeting and inhibiting several vital signal pathway-related proteins like IGF1R, IRS1, mTOR and BCL2 [2, 7, 19]. These findings indicated that *miR-1271* is closely associated with the emergence of DDP resistance in tumor cells.

In this study, we firstly found the relationship between *miR-1271* and XIAP in SKOV3 and SKOV3/DDP cells, and results showed a significant decrease in *miR-1271*, which was correlated with overexpression of XIAP. These results indicate that *miR-1271* and XIAP may be related to modulation of drug-resistance phenotype. We then examined whether the resistance could be reversed using MMT assays of SKOV3/DDP cells transfected with *miR-1271* mimics and treated with DDP. Our data suggest that *miR-1271* may regulate the translational control of XIAP. Moreover, by using luciferase reporter assays, we identified binding sites of *miR-1271* in the 3'UTR of the XIAP gene.

As a common chemotherapy drug has been used for almost three decades, DDP has been

shown to restrain a variety of human cancers. However, the occurrence of drug resistance largely weakens the effect of chemotherapeutic treatment, increasing the burden of clinical patients. The mechanism of DDP resistance is quite complicated which involves the interaction of multiple genes. Previous studies indicated that aberrant expression of some miRNAs is relevant to the acquired drug resistance of the tumor. The sensitivity of tumor cells may thus be altered by modulating miRNAs expression levels [3, 23]. Moreover, researchers have discovered that the aberrant expression profiles of miRNAs existed between normal and tumor patients, even between different stages [26-29]. We can postulate that miRA-1271 has promising functions in the clinical detection and treatment. Besides the potential function as an early biomarker for prognosis, miR-1271 may be developed as molecular targeted agents for clinical treatment of diverse cancers.

Current studies involving the upstream regulatory mechanisms underlying dysregulation of *miR-1271* in SKOV3/DDP cells are still limited. Recently, few evidences have shown that miRNA genes may be regulated also by epigenetic mechanisms [28]. We found two CpG islands (chr5: 175815289-175815847 [+]; chr5: 175792356-175793505 [+]) in the *miR-1271* promoter region by searching ENCODE DNA Methylation, and the existence of methylation sites has been detected in various tumor cell lines. We hypothesize that increasing methylation of the *miR-1271* promoter results in the downregulation of *miR1271* in drug-tolerant cells. However, further studies will be required to verify the underlying mechanisms.

In summary, we found in this study that *miR-1271* could sensitize drug-resistant cells and promote apoptosis in ovarian carcinoma by targeting the anti-apoptotic protein XIAP. Our study lays a foundation for a better understanding of the mechanism which will enable miRNA-mediated therapy in cancer treatment.

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Disclosure of conflict of interest

None.

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