

Original Article

Downregulation of miR-130a contributes to cisplatin resistance in ovarian cancer cells by targeting X-linked inhibitor of apoptosis (XIAP) directly

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MicroRNAs (miRNAs) are short, highly conserved small non-coding RNA molecules, which post-transcriptionally regulate genes expression and play crucial roles in diverse biological processes. Recent studies have shown that dysregulation of miRNAs might modulate the resistance of cancer cells to chemotherapeutic agents. To investigate the possible role of miR-130a in the development of cisplatin resistance in human ovarian cancer cell line A2780, we evaluated the expression of microRNA-130a (miR-130a) in the cells by the quantitative real-time reverse transcription-polymerase chain reaction. The results showed that miR-130a was significantly down-regulated in cisplatin-resistant ovarian cancer cells. MTT assay and flow cytometry (FCM) results showed that over-expression of miR-130a regulated apoptotic activity, and thereby cisplatin chemosensitivity, in ovarian cancer cells. Furthermore, we found that miR-130a can directly target XIAP, and participate in the regulation of apoptosis. The up-regulation of miR-130a led to a significant decrease in the XIAP mRNA levels and protein levels. XIAP plays an important role in cisplatin resistance in ovarian cancer cell line A2780. Our findings suggested that miR-130a could play a role in the development of cisplatin resistance in ovarian cancer cell line A2780, at least in part by modulation of apoptosis via targeting XIAP.

Keywords ovarian cancer; cisplatin resistance; miR-130a; XIAP

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Introduction

Ovarian cancer remains the most lethal gynecologic malignancy and the fourth most common cause of death due to

cancer among women. The standard treatment of advanced ovarian cancer is cytoreductive surgery followed by a combination platinum-based chemotherapy [1]. Cisplatin is one of the most effective cell cycle non-specific drugs for the treatment of ovarian cancer, and the mechanism involved in the process of its cytotoxicity includes survival inhibition and apoptosis [2]. Despite high responses to initial cytoreductive surgery and platinum-based chemotherapy, more than 75% of ovarian cancer patients ultimately die from recurrence and the development of drug resistance [3]. As a consequence, the 5-year survival rate of patients with advanced-stage epithelial ovarian cancer is only 30% [4]. To improve chemotherapy response, it is crucial to develop novel therapeutic strategies that overcome cancer drug resistance. However, the molecular mechanism involved in the development of chemoresistant disease remains unclear.

Several mechanisms are involved in development of cisplatin resistance including inactivation of apoptosis pathways [5,6], increased inactivation of platinum compounds by glutathione [7], a decreased accumulation in cells [8], and alterations in DNA repair activity. MicroRNAs (miRNAs) are endogenously encoded small non-coding RNAs and function as post-transcriptional regulators by binding to complementary sites in the 3'-untranslated regions (3'-UTRs) of the target mRNAs [9]. Owing to the wide range of target genes, miRNAs are likely to be involved in most biological processes, including cisplatin resistance. Ectopic expression of miR-214, miR-376c, and miR-125b has been reported to enhance cisplatin resistance in ovarian cancer cell lines, through repression of phosphatase and tensin homolog (PTEN), activin receptor-like kinase 7 (ALK7) and BCL2-antagonist/killer 1 (BAK1), respectively [10–12]. In contrast, overexpression of let-7i gives rise to an increase in cisplatin sensitivity in ovarian cancer cell lines [13]. These studies together highlight the need to study

miRNAs that are involved in chemoresistance in ovarian cancers. However, whether other unknown miRNAs are involved in the cisplatin resistance in ovarian cancer is still largely unknown.

In this study, we detected the dysregulated miRNAs in the cisplatin-resistant ovarian cancer cells and compared with the parent cells. We observed that miR-130a was down-regulated in cisplatin-resistant ovarian cancer cell line A2780/DDP, and the X-linked inhibitor of apoptosis (XIAP) was confirmed to be a direct target gene of miR-130a. Overexpression of miR-130a could suppress XIAP expression and sensitize A2780/DDP cells to cisplatin. In XIAP siRNA pre-treated A2780/DDP cells, the overexpression of miR-130a could not modulate the cisplatin sensitivity. Taken together, miR-130a plays a critical role in regulating cisplatin sensitivity through suppression of XIAP expression, and it may serve as a potential target for overcoming cisplatin resistance in human ovarian cancer.

Materials and Methods

Cell culture

Human ovarian cancer cell line A2780 and its cognate cisplatin-resistant A2780/DDP cell line were conserved in our laboratory and maintained in RPMI-1640 (Invitrogen, Carlsbad, USA) supplemented with 10% fetal bovine serum (Invitrogen), 100 IU/ml of penicillin, 100 µg/ml of streptomycin (Beyotime Institute of Biotechnology, Haimen, China), and different concentration of cisplatin (Hisun Pharmaceutical, Hangzhou, China) as indicated. Cells were cultured at 37°C in a humidified atmosphere containing 5% CO₂.

Quantitative reverse transcription-polymerase chain reaction

Total RNA was extracted using TRIzol reagent (Invitrogen). For the detection of miR-130a level, the stem-loop quantitative reverse transcription-polymerase chain reaction (qRT-PCR) was performed as described previously [14]. SYBR Premix Ex Taq™ Kit (TaKaRa, Dalian, China) was used following the manufacturer's instructions, and the qRT-PCR was performed and analyzed by CFX-96 Real-Time PCR Detection System (Bio-Rad, Hercules, USA). PCR cycles were as follows: 95°C for 3 min, followed by 35 cycles of 95°C for 30 s, 58°C for 30 s, 72°C for 30 s. *XIAP* mRNA levels were detected as described previously [15]. *GAPDH* and *U6* were used as internal controls.

MTT [3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide] assay

The logarithmically growing ovarian cancer cells (3×10^4 cells) were plated in 96-well plates with 0, 20, 40, 60, 80, or 100 µM of cisplatin. At 48 h after cisplatin treatment,

MTT was added into cells to a final concentration of 0.5 mg/ml. Four hours later, the reduced insoluble MTT was removed and the formazan was dissolved in 150 µl dimethyl sulfoxide. The absorbance of each well was determined at 490 nm using quantitative reverse transcription-polymerase chain reaction iMark Microplate Spectrophotometer (Bio-Rad, Hercules, USA).

MicroRNA transfection

MiR-130a mimics and negative control (NC) were chemically synthesized by HouzaiBio (Nanjing, China). RNA oligonucleotides were transfected into cells at a final concentration of 50 nM using Lipofectamine 2000 (Invitrogen) according to the manufacturer's protocol.

Western blot analysis

Western blot analysis was conducted as previously study [16,17]. Briefly, 50 µg total proteins from samples was separated on 10% sodium dodecyl sulfate polyacrylamide gel electrophoresis gels and transferred to PVDF membranes (Millipore Corp., USA). Membranes were blocked overnight with 5% non-fat dried milk, and then incubated with antibodies to XIAP (1 : 1000; Santa Cruz, Santa Cruz, USA), GAPDH (1 : 1000; Cell Signaling, Beverly, USA) overnight at 4°C. After being washed with PBST (phosphate buffered saline with Tween 20) for three times, the membranes were incubated with horseradish peroxidase-linked secondary antibody and visualized with ECL chemiluminescence kit. GAPDH was used as loading control. The bands were quantified using ImageJ software.

Luciferase assay

The luciferase assay was performed in A2780/DDP cells. To construct *XIAP* 3'-UTR luciferase reporter (*XIAP* 3'-UTR-wild), full length human *XIAP* 3'-UTR was inserted into the *XhoI* and *NotI* sites in the psi-CHECK2 vector (Promega, Madison, USA) downstream from the renilla luciferase coding sequence. Mutations (*XIAP* 3'-UTR-mut) within the putative miR-130a-binding sites were created with a QuikChange site-directed mutagenesis kit (Stratagene, La Jolla, USA). Cells were seeded in 24-well plates, co-transfected with 100 ng luciferase reporter vector and 30 nM miR-130a mimics, incubated overnight. Then, luciferase activity was measured using the Dual-Glo Luciferase assay system (Promega).

Apoptosis assay

The A2780/DDP cells transfected with miR-130a mimics or NC were treated with 10 mM cisplatin for 48 h and then harvested. Apoptosis was evaluated using the FITC Annexin V Apoptosis Detection Kit (BD Biosciences, Franklin Lakes, USA). The percentage of apoptotic cells (AnnexinV-FITC

positive and PI-negative cells) was determined by Flow Cytometry.

siRNA transfection

The sequences of XIAP siRNA were described previously [16]. The transfection was performed using Lipofectamine 2000 (Invitrogen) according to the manufacturer's protocol. The cells were prepared for further analysis 48 h after transfection.

Statistical analysis

All experimental data were shown as the mean \pm standard deviation. Differences between samples were analyzed using the two-tailed Student's *t*-test. $P < 0.05$ was considered statistically significant.

Results

MiR-130a is down-regulated in cisplatin-resistant ovarian cancer cells

Firstly, we compared the cisplatin resistance of the A2780/DDP cell line and the parental A2780 cells using MTT assay. The results showed that A2780/DDP cell line had a significantly higher survival rate than A2780 cells [Fig. 1(A)], which indicated that A2780/DDP cell line was cisplatin resistant. Previous studies have shown that miR-130a is related to drug resistance in cancer cells [17], but the expression of miR-130a in cisplatin resistant ovarian cancer cells was controversial. To identify the role of miR-130a in cisplatin resistance, we measured the expression of miR-130a in A2780/DDP and A2780 cells. qRT-PCR results revealed that miR-130a was significantly down-regulated in A2780/DDP cells compared with A2780 cells [Fig. 1(B)], which indicated that miR-130a might be associated with cisplatin resistance in A2780/DDP cells.

Overexpression of miR-130a sensitizes the A2780/DDP cells to cisplatin

To directly test the relationship between miR-130a and cisplatin resistance, we further investigated the effects of miR-130a on cisplatin-induced cytotoxicity in A2780/DDP cells. The cells were transfected with either miR-130a mimics or NC. qRT-PCR results showed that miR-130a mimics effectively increased the expression level of miR-130a [$P < 0.05$, Fig. 2(A)]. When the transfected cells were incubated with different doses of cisplatin, miR-130a mimics transfected A2780/DDP cells had a significantly lower survival than the NC group [$P < 0.05$, Fig. 2(B)], suggesting that increasing miR-130a expression alters the cisplatin sensitivity in A2780/DDP cells. The flow cytometry assay results revealed that there were more apoptotic cells in the miR-130a transfected groups compared with the NC group [Fig. 2(C,D)]. These findings suggested that miR-130a could increase the cisplatin sensitivity by promoting apoptosis in A2780/DDP cells.

XIAP is a direct target of miR-130a

With the help of Target Scan databases, we found the target site of miR-130a within the *XIAP* 3'-UTR and hypothesized XIAP, an endogenous modulator of apoptosis, to be a potential target gene of miR-130a [Fig. 3(A)]. Next, we used luciferase reporter assay to confirm the direct regulation of XIAP by miR-130a in the cisplatin-resistant ovarian cancer cell lines. The results indicated that overexpression of miR-130a in A2780/DDP cells could suppress the luciferase activity under the control of *XIAP* 3'-UTR-wild luciferase reporter, but had no effect on the *XIAP* 3' UTR-mut luciferase reporter [Fig. 3(A,B)]. Furthermore, western blot analysis showed that the protein level of XIAP in miR-130a mimics transfected A2780/DDP cells was lower than that in NC transfected A2780/DDP cells [Fig. 3(C,D)]. These data indicated that XIAP was negatively regulated by miR-130a.

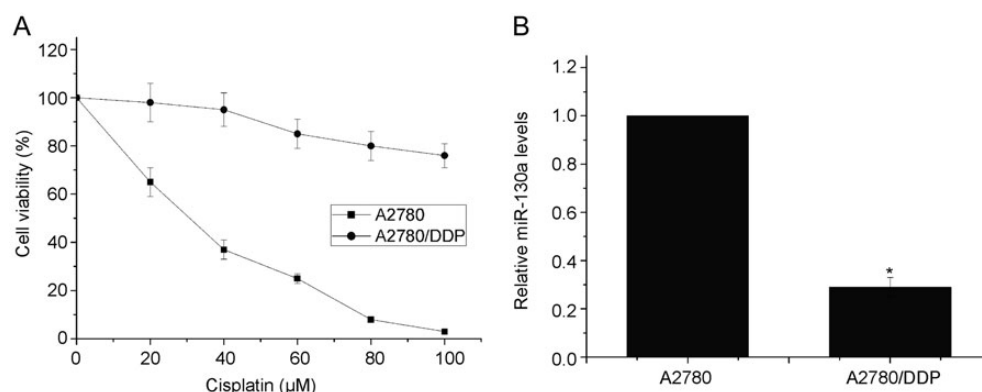


Figure 1 MiR-130a is associated with cisplatin resistance in A2780 cells (A) The sensitivity of A2780/DDP cells and A2780 cells to cisplatin were measured using MTT assay. (B) The miR-130a expression level in A2780/DDP cells and A2780 cells were measured using qRT-PCR. * $P < 0.05$, vs. A2780 cells.

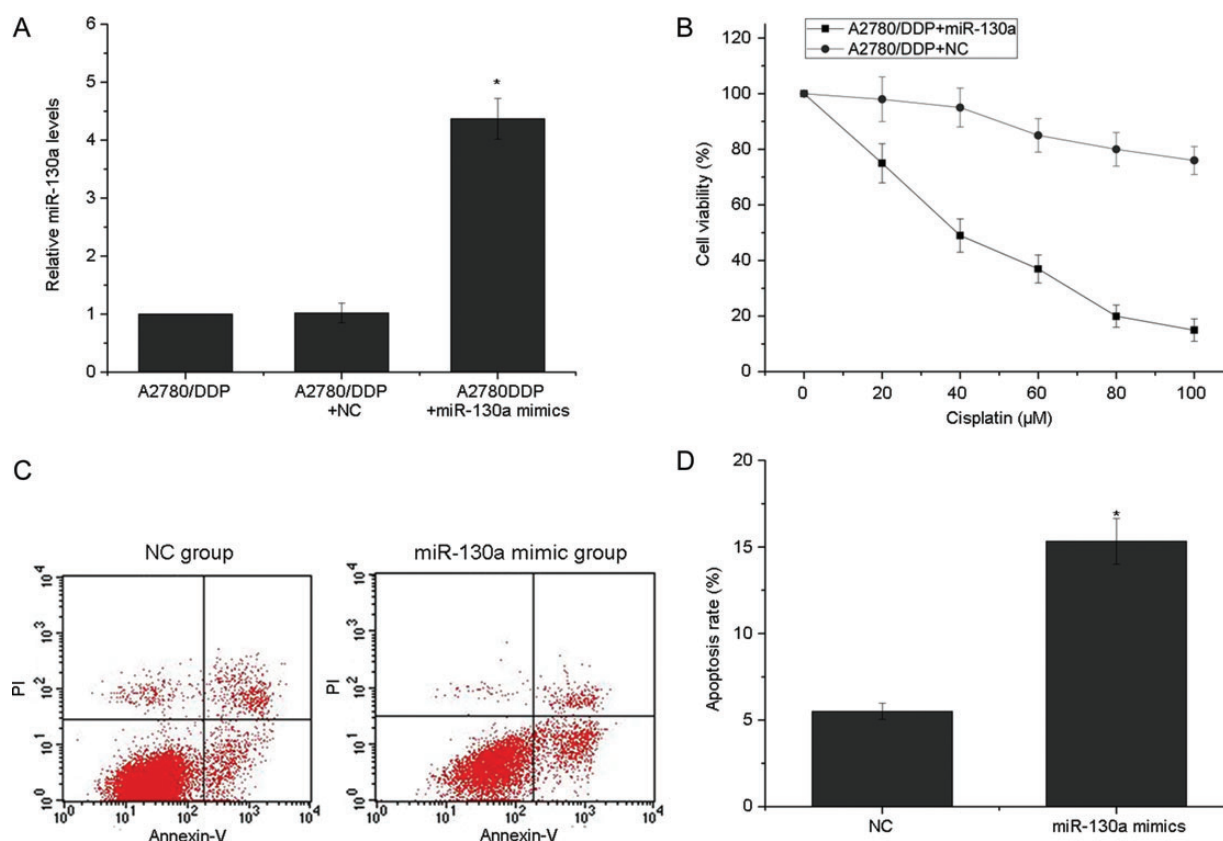


Figure 2 Overexpression of miR-130a sensitizes the A2780/DDP cells to cisplatin (A) The expression of miR-130a was increased after transfection of miR-130a mimics in A2780/DDP cells. (B) The transfection of miR-130a mimics enhanced the cisplatin sensitivity in A2780/DDP cells. (C, D) The transfection of miR-130a mimics enhanced the apoptosis induced by cisplatin in A2780/DDP cells. * $P < 0.05$, vs. NC group.

MiR-130a could regulate cisplatin chemosensitivity in A2780 cells by targeting XIAP

Given that miR-130a showed a low expression level in cisplatin-resistant ovarian cancer cells, we explored if miR-130a could contribute to the cisplatin chemoresistance in ovarian cancer. Previous studies have shown that XIAP is involved in drug resistance in several types of cancer [18,19]; however, its role in cisplatin sensitivity in the A2780 cell line remains unclear. We transfected XIAP siRNA or NC into A2780/DDP cells, followed by treatment with different doses of cisplatin. XIAP siRNA significantly reduced the XIAP expression at protein and mRNA levels [Fig. 4(A–C)]. Furthermore, the A2780/DDP cells that were pre-treated with XIAP siRNA had decreased survival rate compared with NC group [Fig. 4(D)]. More importantly, the XIAP siRNA pre-treated A2780/DDP cells had a similar survival pattern with miR-130a overexpressing A2780/DDP cells. In A2780/DDP cells that were pre-treated with XIAP siRNA, the overexpression of miR-130a could not modulate the cisplatin sensitivity [Fig. 4(D)]. So, we concluded that miR-130a may regulate cisplatin chemosensitivity in ovarian cancer cells by directly targeting XIAP.

Discussion

In this paper, for the first time, we showed that cisplatin-induced drug resistance is associated with the downregulation of miR-130a in the ovarian cancer cell line A2780. MiR-130a may regulate the survival of ovarian cancer cell lines by targeting XIAP expression and causing subsequent changes in apoptosis induced by cisplatin.

Cisplatin is the first-line chemotherapy drug for many malignancies, including ovarian cancer. In advanced ovarian cancer the first-line drugs of chemotherapy are the combination of cisplatin/carboplatin with paclitaxel. With this regimen, around 20% of patients do not respond at the first cycle and are featured by progression upon treatment in the first year and poor outcome [18,19]. The remaining patients relapse after one year from the first cycle of therapy and tend to poorly respond to the additional chemotherapy lines. Therefore, the molecular pathway involved in primary and acquired drug resistance is important. It will help to establish rational therapeutic strategies aiming to circumvent the acquisition of the drug resistance.

MicroRNAs (miRNAs) are a group of non-coding, single-stranded RNAs which regulate gene expression by targeting

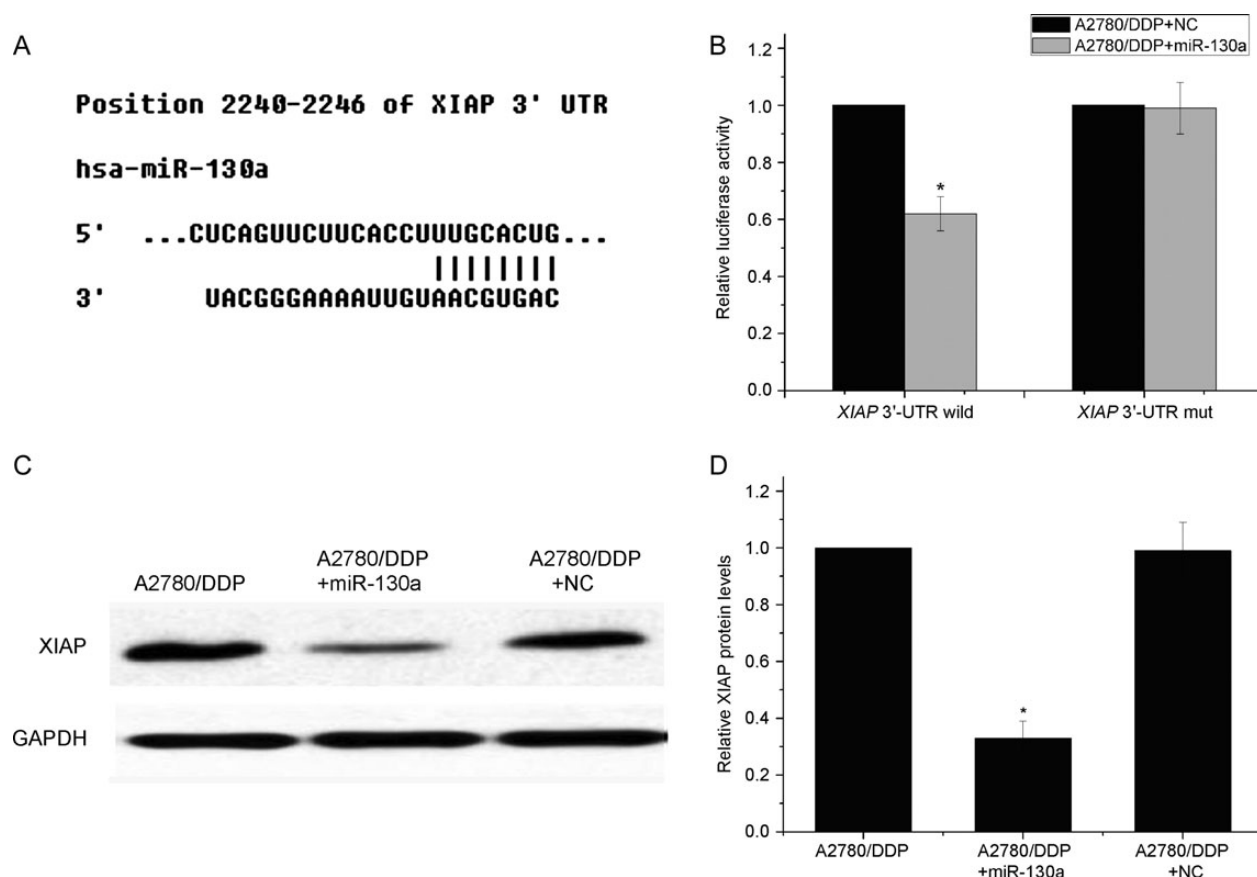


Figure 3 XIAP is a direct target gene of miR-130a (A) XIAP 3' UTR carries a potential miR-130a binding site. (B) Luciferase reporter assay was performed in the cisplatin-resistant A2780/DDP cells. Cells were transfected with the reporter vector with wild-type or mutated XIAP 3'-UTR fragment, along with miR-130a mimics. (C, D) XIAP protein levels were measured by western blot analysis. * $P < 0.05$, vs. NC.

mRNAs for translational repression, mRNA degradation or both. miRNAs play an important regulatory role in pathogenesis of tumor in human involved in cell differentiation, proliferation, migration, metabolism, and apoptosis [20–22]. Thus far, several reports have revealed that miRNAs are involved in the process of cisplatin resistance in multiple tumors. These miRNAs could play a crucial role in drug resistance by targeting their specific genes. For instance, miR-200c expression is down-regulated in human breast cancer cells resistant to doxorubicin MCF-7/Adriamycin. Up-regulation of miR-200c by transfecting miR-200c mimics in breast cancer cells could enhance the chemosensitivity to epirubicin [23]. MiR-93 was significantly up-regulated in cisplatin-resistant ovarian cancer cells, and down-regulating miR-93 sensitized cells to undergo apoptosis [24]. Sorrentino *et al.* [25] reported that six miRNAs (let-7e, miR-30c, miR-125b, miR-130a, and miR-335) are always diversely expressed in all the resistant ovarian cancer cell lines. The miR-30c, miR-130a, and miR-335 are down-regulated in all the resistant cell lines, thereby suggesting their direct involvement in the development of chemoresistance. They also found that down-regulation of miR-130a is associated with increased expression of M-CSF, a common

feature of aggressive disease and chemoresistance in ovarian cancer. But the role of miR-130a in cancer drug resistance remains controversial. Yang *et al.* [26] found that down-regulation of miR-130a could inhibit *MDR1* mRNA and P-gp expression, and overcome the cisplatin resistance in SKOV3/CIS cells. In this study, we found that miR-130a was down-regulated in the cisplatin-resistant A2780/DDP cells when compared with its corresponding cisplatin-sensitive parental cell lines by qRT-PCR. Overexpression of miR-130a enhanced cisplatin chemosensitivity in cisplatin-resistant A2780/DDP cells. This controversial may be due to the different roles of miR-130a in different cell lines. These findings suggested that miR-130a could regulate cisplatin chemosensitivity in ovarian cancer line A2780.

Numerous miR-130a targets have been identified, including Runt-related transcription factor 3 (*RUNX3*) [27], Autophagy Related Protein 2B (*ATG2B*) and DICER1 [28], MAD homolog 4 (*Smad4*) [29], and MET [30]. Of these miR-130a targets, we focused on the XIAP, because it is one of the most potent inhibitors of caspases and apoptosis to date, and is known to be upregulated in various malignancies [31]. XIAP has been shown to be one of the important regulators in cisplatin-induced apoptosis in ovarian cancer cells

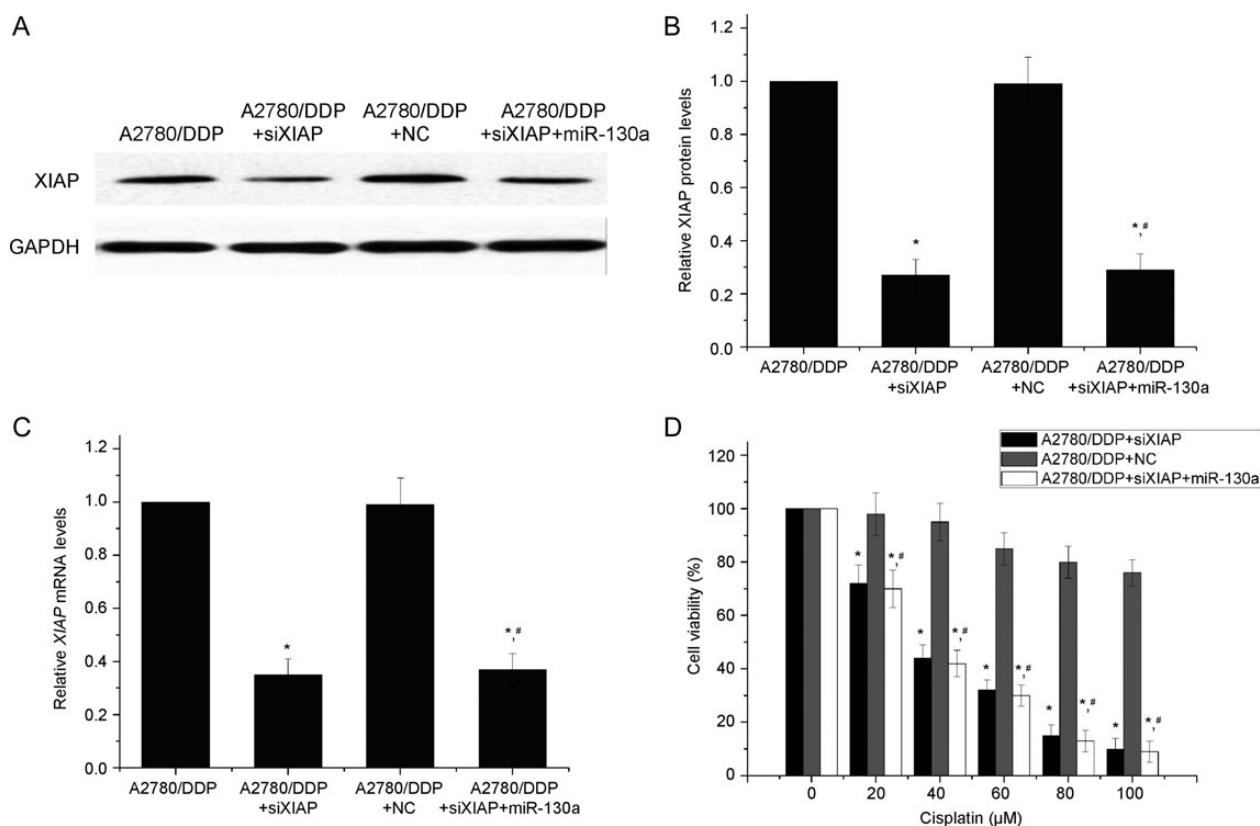


Figure 4 MiR-130a could regulate cisplatin chemosensitivity in A2780 cells by targeting XIAP (A, B) XIAP siRNA inhibited the protein expression of XIAP in A2780/DDP cells. (C) XIAP siRNA inhibited the mRNA levels of XIAP (D) XIAP siRNA enhanced the cisplatin sensitivity in A2780/DDP cells. siXIAP: XIAP siRNA. * $P < 0.05$, vs. NC; ** $P > 0.05$, vs. A2780/DDP + siXIAP group.

[32], and down-regulation of XIAP sensitizes cells to cisplatin [33]. Consistent with these data, here we demonstrated that XIAP was a target of miR-130a, and played a role in cisplatin resistance in the A2780 cell line. Moreover, knock-down of XIAP significantly decreased cell survival and had an overall effect that was similar to miR-130a overexpression. To our knowledge, this is the first report describing an association between miR-130a, XIAP expression, and cisplatin resistance in A2780 cells.

In summary, our results showed that ovarian cancer cells with down-regulated miR-130a expression and increased XIAP protein expression were more resistant to cisplatin than the control cells. These results may help to develop personalized treatment for patients who have abnormal levels of miR-130a or XIAP. Furthermore, the novel miR-130a/XIAP signaling pathway in A2780 cell line may provide drug targets for the sensitization of tumor cells and could be applied to treat cisplatin resistance in ovarian cancer patients.

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