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# Inhibitory effects of miRNA-200c on chemotherapy-resistance and cell proliferation of gastric cancer SGC7901/DDP cells

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**[Abstract] Background and Objective:** miRNA-200c can not only inhibit the aggressiveness of cancer cells but also increase the sensitivity of cells to antitumor drugs. However, some mechanisms are still unclear. Recent researches revealed that E-cadherin is more than an inhibitor of metastasis, and it also plays important roles in reversing drug resistance. We had previously found that miRNA-200c could not only induce the expression of E-cadherin but also increase the sensitivity of gastric cancer SGC7901/DDP cells to cisplatin (DDP). This study aimed to explore the effects of miRNA-200c on biological characteristics of SGC7901/DDP cells and the roles of E-cadherin in the regulatory pathway of miRNA-200c. **Methods:** SGC7901/DDP cells and its parental cell line SGC7901 cells were transfected with miRNA-200c precursor (Pre-200c) and E-cadherin siRNA, respectively. Real-time RT-PCR was used to detect miRNA-200c expression after transfection with Pre-200c in SGC7901/DDP cell line. Drug sensitivities to DDP, 5-fluorouracil (5-FU), paclitaxel, and adriamycin (ADR) after transfection were tested using MTT assay. The proliferation of SGC7901/DDP cells was also detected after transfection. The protein changes of E-cadherin, Bax, and Bcl-2 after transfection were detected by Western blot. **Results:** The miRNA-200c expression in SGC7901/DDP cells after transfection of Pre-200c was  $7.128 \pm 0.159$  times of that in negative control ( $P < 0.05$ ). The  $IC_{50}$  of DDP, 5-FU, paclitaxel, and ADR in Pre-200c-transfected group were significantly lower than that in negative control group ( $P < 0.05$ ). Compared to the control group, cell proliferation was significantly decreased ( $P < 0.05$ ). The relative protein expressions of E-cadherin and Bax in Pre-200c-transfected group were significantly higher than those in negative control group ( $P < 0.05$ ), whereas Bcl-2 was significantly lower than that in control ( $P < 0.05$ ). Additionally, E-cadherin protein expression was significantly inhibited after transfected with E-cadherin siRNA in SGC7901 cells. The Bax protein expression was significantly down-regulated by E-cadherin siRNA ( $P < 0.05$ ), whereas the Bcl-2 expression was significantly up-regulated ( $P < 0.05$ ). **Conclusion:** miRNA-200c can indirectly regulate apoptosis through E-cadherin in SGC7901/DDP cells, which may be a possible mechanism of miRNA-200c in reversing drug resistance and inhibiting proliferation.

**Key words:** miRNA-200c, proliferation, drug-resistance, Bax, Bcl-2, E-cadherin

microRNA (miRNA) is a class of single-strand non-coding RNA (21–25 nucleotides). Studies have suggested that miRNAs control the expression of 1/3 of all human genes and are involved in a series of biological processes. miRNAs can function as oncogenes or tumor

suppressor genes during tumorigenesis and cancer progression, and are thus closely related to cancer diagnosis, proliferation, metastasis, clinical stages and prognosis<sup>[1]</sup>. With the growing knowledge of the relation between miRNAs and cancer, it is also shown that the sensitivity of cancer cells to anticancer drug is affected by miRNAs<sup>[2]</sup>.

miRNA-200c is a member of miRNA-200 family, which includes miRNA-200a, miRNA-200b, miRNA-200c, miRNA-141, and miRNA-429. Previous studies showed that miRNA-200c inhibits cancer epithelial-to-mesenchymal

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transition (EMT) and metastasis by negatively regulating zinc finger E-box binding homeobox 1 (ZEB1) and indirectly up-regulating E-cadherin<sup>[3,4]</sup>. In addition, miRNA-200c directly regulates the expression of TUBB3 and ERRFI-1, which accounts for the increase of cancer cell sensitivity to paclitaxel and epidermal growth factor inhibitor, respectively<sup>[5,6]</sup>. Besides the involvement of target genes of miRNA-200c in the drug-resistance of cancer cells, miRNA-200c also increases the sensitivity of breast cancer MDA-MB-231 cells to adriamycin (ADR)<sup>[7]</sup>. After transfection with miRNA-200c, cell proliferation is inhibited and the expressions of pro-apoptotic related genes are up-regulated, whereas those of pro-survival genes are down-regulated. However, the signaling pathways resulting in the increased drug-sensitivity are not fully understood. Furthermore, miRNA expression profiling assay showed that miRNA-200c is down-regulated in some drug-resistant cancer cell lines<sup>[8,9]</sup>. Therefore, the mechanism of miRNA-200c in cancer drug-resistance needs further study.

After reviewing literatures, we found that E-cadherin, a downstream target protein of miRNA-200c, is related to cancer drug-resistance. This finding provides a theoretical basis for revealing the mechanism of reversing drug-resistance by miRNA-200c. E-cadherin belongs to the adhesion molecule family, which mediates homotypic cell adhesion and inhibits cancer cell metastasis. Recent studies demonstrated that the expression of E-cadherin in some drug-resistant cancer cells is significantly down-regulated or lost<sup>[10,11]</sup>. E-cadherin not only functions as a metastasis inhibitor but also plays a role in the reversal of cancer drug-resistance. Several studies showed that E-cadherin increases the sensitivity of cancer cells to cytotoxic drugs [such as methotrexate, etoposide, cisplatin (DDP), and so on] and epidermal growth factor inhibitor. E-cadherin negatively regulates Bcl-2 expression and thus reverses the resistance to chemotherapeutic drugs<sup>[12]</sup>. Therefore, we hypothesize that the regulation of apoptotic proteins by E-cadherin is a key step in the multiple biological regulations by miRNA-200c, and this subject needs to be further explored.

DDP, 5-fluorouracil (5-FU), paclitaxel, and ADR are major drugs currently used for gastric cancer chemotherapy. SGC7901 cells are originated from human gastric adenocarcinoma and are widely used in China for in vitro studies of gastric cancer. We have prepared a DDP-resistant cell line SGC7901/DDP by intermittent induction. SGC7901/DDP cells can grow in mediums containing 1 mg/L DDP. In our previous study, we found that the expression level of miRNA-200c is significantly lower in SGC7901/DDP cells than in SGC7901 cells<sup>[13]</sup>. Overexpression of miRNA-200c not only up-regulates the expression of E-cadherin but also increases the sensitivity of SGC7901/DDP cell to DDP. To further investigate the

biological effects and molecular mechanisms of miRNA-200c in SGC7901/DDP cells, we explored in the present study the function of miRNA-200c in drug-resistance and proliferation of SGC7901/DDP cells. Western blot was used to detect the protein expression of E-cadherin, Bax, and Bcl-2 after miRNA-200c transfection. In addition, we knocked down E-cadherin expression in SGC7901 cells using small interfering RNA (siRNA) and determined drug-resistance and cell proliferation, as well as the expression levels of Bax and Bcl-2. We aimed to delineate the function of E-cadherin in miRNA-200c regulated sensitivity of cancer cell to anticancer drugs.

## Materials and Methods

### Reagents and cell culture

Fetal calf serum (FCS) and RPMI-1640 medium were purchased from Gibco; Lipofectamine 2000 and Trizol were from Invitrogen; antibodies against E-cadherin, Bcl-2, Bax, and  $\beta$ -actin were from Santa Cruz; IRDye™700/800 fluorescent second antibody was from LI-COR Biosciences; siPOR™ NeoFX™ Transfection Agent, miRNA-200c Precursor sequence, and Negative Control #1 sequence were from Ambion; E-cadherin siRNA sequence and negative control sequence were synthesized by Shanghai GenePharma Co., Ltd. The E-cadherin siRNA sequence was 5'-CAGACAAAGACCAGGACUA-3'; The negative control sequence was 5'-UUCUCCGAACGUGUCACGU TT-3'. Odyssey two-color infrared imaging system was from LI-COR Biosciences. Human DDP-resistant and non-resistant gastric cancer lines (SGC9701/DDP and SGC9701) were stored in our lab. Cells were cultured in RPMI-1640 medium containing 10% FCS at 37°C with 5% CO<sub>2</sub>. Drug-resistant cells were cultured in the medium supplemented with 1 mg/L DDP.

### Cell transfection

SGC7901/DDP cells in logarithmic growth phase were trypsinized with 0.25% trypsin, then suspended in RPMI-1640 containing 10% FCS and seeded in 6-well plates ( $3 \times 10^5$  cells/well). Transfection of miRNA-200c Precursor (Pre-200c) and its negative control sequence were performed according to the manual provided with the siPOR™ NeoFX™ Transfection Agent. SGC7901 cells were seeded into 6-well plates ( $4 \times 10^5$  cells/well). After 24 h, E-cadherin siRNA and the negative control siRNA were transfected using Lipofectamine 2000. The transfected cells were used for cell proliferation, MTT drug-sensitivity and Western blot experiments.

### **Real-time RT-PCR to detect the expression of miRNA-200c**

The total RNA was extracted from SGC7901/DDP cells at 24 h after transfection with Pre-200c or the negative control sequence, followed by real-time RT-PCR. Briefly, cDNA were synthesized using a miRNA-200c specific primer in reverse transcription system. The reaction condition was as follows: 16°C 30 min, 42°C 42 min, 85°C 5 min. Quantitative detection of RT products was performed using specific sense- and anti-sense primers of miRNA-200c and Sybergreen I dye. The PCR reaction condition was as follows: 95°C for 5 min; 40 cycles of 95°C for 10 s, 60°C for 20 s, 72°C for 20 s, and 78°C for 20 s to obtain fluorescence intensity. U6 was used as an internal control. The sequence of specific primer for miRNA-200c was 5'-GTCGTATCCAGTGGCTGTCTGTGAGTCGGCAA-TGCACTGGATACGACTCCATC-3'; the sequence of sense primer of miRNA-200c was 5'-GGTAATACTGCCGGGTA-AT-3'; the sequence of anti-sense primer of miRNA-200c was 5'-CAGTGCGTGTCTGTGAGT-3'. The data were analyzed using  $2^{-\Delta\Delta C_t}$  method:  $\Delta C_t = (\text{miRNA-200c})C_t - \text{U6C}_t$ ,  $\Delta\Delta C_t = (\text{miRNA-200c})\Delta C_t - (\text{control})\Delta C_t$ .

### **Detect the sensitivity of transfected SGC7901/DDP cells to chemotherapeutic drugs by MTT assay**

At 24 h after transfection of Pre-200c, SGC7901/DDP cells were trypsinized using 0.25% trypsin, then suspended in RPMI-1640 medium containing 10% FCS and seeded in 96-well plates ( $7 \times 10^3$  cells in 100  $\mu\text{L}$  medium/well). Upon attachment of the cells, different concentrations of DDP, 5-FU, paclitaxel, and ADR were added in triplicate wells of the plates. Control wells and zero adjusted wells were also set. After 48 h, 20  $\mu\text{L}$  fresh MTT reagent (5  $\mu\text{g}/\mu\text{L}$ ) was added into each well and the cells were cultured at 37°C in 5%  $\text{CO}_2$  for another 4 h. The medium was discarded carefully and 150  $\mu\text{L}$  DMSO was added and vortexed for 10 min. Absorbance at 490 nm was measured in an ELISA reader. The mean absorbance of triplicate wells was set as A value of each group. The cell inhibition rate of each drug group =  $(A \text{ value of control group} - A \text{ value of drug group}) / A \text{ value of control group} \times 100\%$ . The 50% inhibition concentration ( $\text{IC}_{50}$ ) was calculated according to the cell inhibition curve.

### **Proliferation of SGC9701/DDP cells after transfection**

At 24 h after transfection of Pre-200c, SGC7901/DDP cells were trypsinized using 0.25% trypsin, then suspended

in RPMI-1640 medium containing 10% FCS and seeded in 24-well plates ( $1 \times 10^4$  cells/well). Cells were counted after trypsinization every day at the same time point. Each group contains triplicate wells. The growth curve was then drawn.

### **Detection of protein levels of E-cadherin, Bax, and Bcl-2 by Western blot**

Cells were harvest and washed for 2 times 72 h after transfection of Pre-200c. Cells were lysed using 100  $\mu\text{L}$  lysis buffer at 4°C for 30 min. The lysate was centrifuged for 10 min at  $12\,000 \times g$ . Protein assay was performed using Bradford method. Proteins (50  $\mu\text{g}$ ) were separated by electrophoresis in 12% SDS-PAGE gel and then transferred onto a PVDF membrane. The membrane was blocked with 5% dry milk for 1 h, then incubated overnight with the primary antibody at 4°C. Subsequently, the membrane was incubated with the secondary antibody (1 : 10 000) for 1 h in dark. After extensive wash, the membrane was scanned using the Odyssey two-color infrared imaging system. The value of optical density (OD) was calculated. Protein expression levels were defined as the OD of objective protein / the OD of  $\beta$ -actin.

### **Statistical analysis**

All data are presented as mean  $\pm$  standard deviation. The *t* test was performed to determine differences between groups using SPSS13.0 statistical software.  $P < 0.05$  was considered significant.

## **Results**

### **Expression level of miRNA-200c in SGC7901/DDP cells at 24 h after transfection**

Real-time RT-PCR showed that the  $\Delta C_t$  of miRNA-200c in Pre-200c-transfected SGC7901/DDP cells was  $7.1 \pm 0.2$  times of that in control cells ( $12.66 \pm 0.08$  vs.  $15.49 \pm 0.08$ ,  $P < 0.05$ ).

### **The effect of miRNA-200c on drug resistance of SGC7901/DDP cells**

The  $\text{IC}_{50}$  of DDP, 5-FU, paclitaxel, and ADR were ( $7.52 \pm 0.19$ ) mg/L, ( $7.27 \pm 0.09$ ) mg/L, ( $1.70 \pm 0.33$ ) mg/L, and ( $0.38 \pm 0.05$ ) mg/L, respectively, in Pre-200c-transfected SGC7901/DDP cells, and were ( $12.18 \pm 0.29$ ) mg/L, ( $11.53 \pm 0.60$ ) mg/L, ( $3.14 \pm 0.40$ ) mg/L, and ( $0.72 \pm 0.03$ ) mg/L, respectively, in control cells. The  $\text{IC}_{50}$  of these drugs were significantly decreased after Pre-200c transfection ( $P <$

0.05). The sensitivity of Pre-200c-transfected cells to chemotherapeutic drugs was increased.

### The effect of miRNA-200c on the proliferation of SGC7901/DDP cells

Compared to the negative control, the proliferation of Pre-200c-transfected SGC7901/DDP cells was significantly inhibited since the third day after transfection ( $P < 0.05$ ) (Figure 1).

### The effect of miRNA-200c on the expression of E-cadherin, Bax, and Bcl-2 in SGC7901/DDP cells

The protein levels of E-cadherin, Bax, and Bcl-2 were  $0.47 \pm 0.01$ ,  $0.38 \pm 0.01$ , and  $0.07 \pm 0.01$ , respectively, in Pre-200c-transfected SGC7901/DDP cells, and were  $0.11 \pm 0.00$ ,  $0.11 \pm 0.01$ , and  $0.44 \pm 0.02$ , respectively, in control

cells. The expression of E-cadherin and Bax were significantly increased, whereas the expression of Bcl-2 was significantly decreased after Pre-200c transfection ( $P < 0.05$ ) (Figure 2).

### The effect of E-cadherin siRNA on the expression of Bcl-2 and Bax in SGC7901 cells

At 24, 48, and 72 h after E-cadherin siRNA transfection in SGC7901 cells, the expression level of E-cadherin was significantly lower in transfected cells than in control cells ( $0.24 \pm 0.01$ ,  $0.16 \pm 0.01$ , and  $0.12 \pm 0.01$  vs.  $0.53 \pm 0.01$ ;  $P < 0.05$ ) (Figure 3). At 72 h after E-cadherin siRNA transfection, the protein level of Bax was significantly lower in transfected cells than in control cells ( $0.14 \pm 0.01$  vs.  $0.37 \pm 0.02$ ,  $P < 0.05$ ), whereas that of Bcl-2 was significantly higher in transfected cells than in control cells ( $0.33 \pm 0.01$  vs.  $0.11 \pm 0.01$ ,  $P < 0.05$ ) (Figure 4).

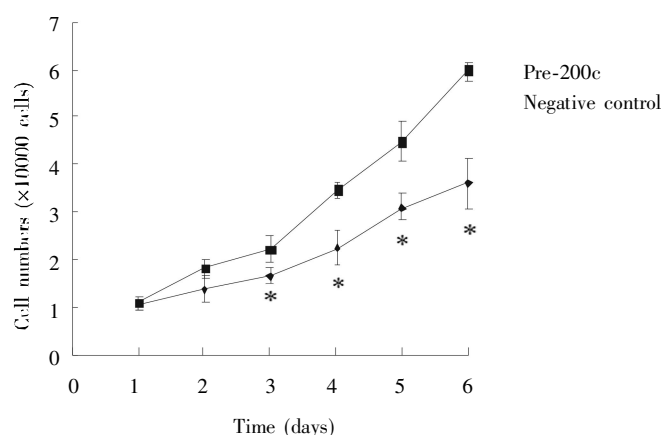


Figure 1 Changes of cell proliferation after transfected with miRNA-200c precursor in SGC7901/DDP cells

\* $P < 0.05$ , Pre-200c-transfected cells vs. negative control cells,  $n = 3$ . Pre-200c significantly inhibited the proliferation of SGC7901/DDP cells since the third day after transfection.

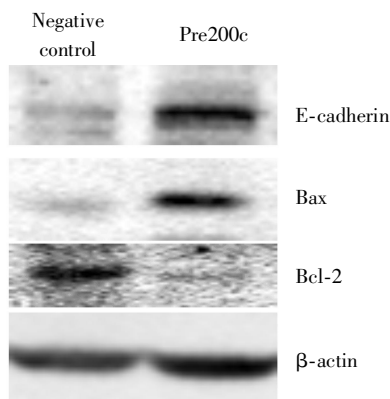
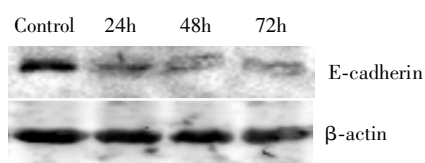


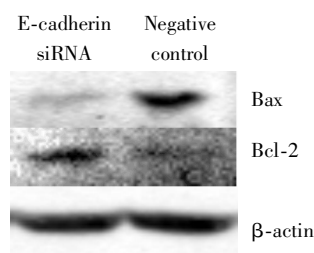
Figure 2 Expression changes of E-cadherin, Bax, and Bcl-2 proteins after transfected with miRNA-200c precursor in SGC7901/DDP cells

After Pre-200c transfection, the expression of E-cadherin and Bax in SGC7901/DDP cells were significantly increased, whereas the expression of Bcl-2 was significantly decreased.



**Figure 3** Changes of E-cadherin protein expression after transfection of E-cadherin siRNA in SGC7901 cells

After E-cadherin siRNA transfection, the protein level of E-cadherin in SGC7901 cells was significantly decreased.



**Figure 4** The Bax and Bcl-2 protein expression changes at 72 h after transfection of E-cadherin siRNA in SGC7901 cells

After E-cadherin siRNA transfection, the protein level of Bax in SGC7901 cells was significantly decreased, whereas that of Bcl-2 was increased.

## Discussion

miRNAs, a class of 21–25 nt single-strand non-coding RNAs, negatively regulate the expression of other genes by interfering mRNA translation and are involved in multiple processes of tumorigenesis and cancer progression.

miRNA-200c belongs to the miRNA-200 family. miRNA-200c inhibits the EMT process of cells<sup>[3]</sup>, tumor invasion and metastasis<sup>[4]</sup>. In addition, miRNA-200c also increases drug sensitivity of cancer cells to paclitaxel, epidermal growth factor inhibitors, and ADR<sup>[5-7]</sup>. After transfecting SGC7901/DDP cells with Pre-200c, we found that the expression of miRNA-200c was significantly increased as shown by real-time PCR analysis and the drug sensitivity of SGC7901/DDP cells to DDP, 5-FU, paclitaxel, and ADR was significantly enhanced. Furthermore, significant growth inhibition was observed in the Pre-200c-transfected SGC7901/DDP cells. Recent studies suggested that miRNA-200c can regulate the expression of proliferation- and apoptosis-related genes<sup>[7]</sup>. Therefore, we hypothesized that the roles of miRNA-200c in the inhibition of gastric cancer cell proliferation and the reverse of drug resistance are related with these genes. In this study, we found that E-cadherin expression was significantly enhanced

in SGC7901/DDP cells after transfection of Pre-200c, which was accompanied by the increase of Bax expression and the decrease of Bcl-2 expression. Influencing the homeostasis of cell apoptosis might be one of the most important mechanisms by which miRNA-200c induces the reversal of cancer cell drug resistance. However, the downstream genes of miRNA-200c that regulate apoptosis-related genes have not been reported.

Recent studies have shown that E-cadherin not only regulates cancer metastasis but also plays an important role in cancer drug resistance. E-cadherin reverses the resistance of cancer cells to chemotherapeutic drugs by negatively regulating the expression of Bcl-2<sup>[12]</sup>. In addition, E-cadherin inhibits cell proliferation by regulating the expression of P27<sup>[14]</sup>. Therefore, E-cadherin may play a key role in the miRNA-200c-induced biological consequences. To further study the function of E-cadherin in the miRNA-200c pathway, we specifically inhibited the expression of E-cadherin by siRNA in SGC7901 cells and found that the expression of E-cadherin was dramatically inhibited. At 72 h after siRNA transfection, the protein level of Bax was significantly lower than that in the control group, whereas the protein level of Bcl-2 was significantly higher than that in the control group. Therefore, miRNA-200c may regulate Bax and Bcl-2 expression via E-cadherin. Whether miRNA-200c inhibits cell proliferation via E-cadherin needs further study.

Understanding how E-cadherin regulates apoptosis- and proliferation-related genes will help to delineate the molecular mechanism of miRNA-200c function. A recent study suggested that E-cadherin increases the expression of tumor suppressor gene PTEN<sup>[15]</sup>, a protein that is abnormally expressed in a variety of cancer cells. PTEN plays a role in cell proliferation, apoptosis, and chemotherapy resistance through the phosphatidylinositol-3 kinase (PI3K)/Akt signaling pathway. PTEN can regulate apoptosis-related genes (such as Bax and Bcl-2) through inhibiting the PI3K/Akt signaling pathway<sup>[16,17]</sup> and increases the sensitivity of cancer cells to various anticancer drugs (DDP, ADR and cetuximab), thus playing an important role in anti-tumor and the reversal of drug resistance<sup>[16,18-22]</sup>. In our previous study<sup>[13]</sup>, we found that miRNA-200c increases PTEN protein expression in SGC7901/DDP cells, suggesting that E-cadherin may regulate proliferation- and apoptosis-related genes through PTEN. We are currently testing this hypothesis.

In summary, we speculate that miRNA-200c indirectly regulates the expression of apoptosis-related genes through E-cadherin. This pathway may serve as an important mechanism by which miRNA-200c induces proliferation inhibition and the reversal of drug resistance. We will further explore how E-cadherin regulates downstream pathways that lead to cell proliferation and apoptosis.

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