

## Original Article

# MicroRNA-130a reduces drug resistance in breast cancer

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**Abstract:** Objective: Although the advent of chemotherapy has made some progress in the comprehensive treatment of breast cancer, drug resistance of tumor cells remains to be one of the main challenges for the treatment of breast cancers. Several microRNAs have been implicated in the resistant process, but the role of miR-130a in drug resistance in breast cancer remains unclear. The present study aims to investigate the role and mechanisms of miR-130a in drug resistance in breast cancer cells and tissues. Patients and methods: miR-130a mimics was used to up-regulate miR-130a expression in Doxorubicin-resistant MCF-7/Adr breast cancer cell line, followed by MTT assay and colony formation to determine cell viability and relative colony number. The relationship between the expression of miR-130a and drug resistance was detected by in situ hybridization in the formalin-fixed paraffin-embedded (FFPE) tissues from 50 breast cancer patients before and after Epirubicin-based neoadjuvant chemotherapy. Results: Up-regulation of miR-130a level in MCF-7/Adr cells decreased the cell viability and colony number, and reversed Doxorubicin resistance of MCF-7/Adr cells. In breast cancer tissue from patients, the miR-130a level was lower before neoadjuvant chemotherapy than that after neoadjuvant chemotherapy ( $P < 0.05$ ). Moreover, a significant increase in the expression of miR-130a was observed in breast tumor tissues from patients sensitive to neoadjuvant chemotherapy compared to the patients who were resistant to neoadjuvant chemotherapy ( $P < 0.05$ ). Conclusion: We concluded that miR-130a might weaken drug resistance of human breast cancer cells, and act as an important factor in prediction of therapeutic responses in chemotherapy of breast cancer.

**Keywords:** MicroRNA, doxorubicin, chemotherapy, resistance, breast cancer

## Introduction

With advances in science and technology, there are more innovations in the approach to management of patients with breast cancer. Epirubicin-based neoadjuvant chemotherapy that is designed to be used prior to surgical removal of tumor has received significant attention [1, 2]. There is now sufficient evidence that the Epirubicin-based neoadjuvant chemotherapy leads to complete pathologic response, and the patient will enjoy a better outcome. However, drug resistance has emerged as a major obstacle to successful treatment of breast cancer [3].

Doxorubicin, a Topoisomerase II catalytic inhibitor, is a broad spectrum antibiotic used in the treatment of cancers, including breast cancer [4, 5]. Epirubicin is a semisynthetic L-arabino derivative of Doxorubicin, and an anthracycline drug used for chemotherapy. It can be used in

combination with other medications to treat breast cancer. Epirubicin, like Doxorubicin, exerts its antitumor effects by complex with DNA, resulting in damage to DNA and interference with the synthesis of DNA, RNA, and proteins [6]. Epirubicin and Doxorubicin are the two most common chemotherapy drugs used in the treatment of breast cancer. Recently, Epirubicin is favored over Doxorubicin, the most popular anthracycline in neoadjuvant chemotherapy regimens of breast cancer as it appears to cause fewer side-effects [7, 8].

MicroRNAs (miRNAs) are non-encoding, single-stranded RNAs of about 18 to 22 nt in length that can regulate target gene expression by binding to specific mRNAs or by regulating protein translation processes in specific mRNAs [9]. A large number of studies have shown that miRNAs are closely related to the development of tumors, the relationship between miRNAs and the sensitivity of tumor cells to chemother-

apeutic drugs has also been widely recognized [10, 11]. Mutations, abnormal expression, and abnormal processing of miRNA affect the normal function of miRNAs, leading to abnormal expression levels of target genes. If such target genes are associated with the drug sensitivity of tumor cells, the sensitivity of tumor cells to therapeutic drugs will be changed [12, 13].

The miR-130 family includes miR-130a and miR-130b, which are located on chromosomes 11 and 22, respectively, and are highly homologous miRNAs. In recent years, it has been reported that miR-130a plays an important role in the proliferation, apoptosis, metastasis and tumor resistance of various tumor cells, such as osteosarcoma [14], gastric cancer [15], liver cancer [16], and breast cancer [17, 18]. However, the role of miR-130 in chemotherapy resistance of breast cancer remains unclear.

In the present study, we investigated the expression of miR-130a in Doxorubicin-resistant MCF-7/Adr breast cancer cell line. Furthermore, we used mimics to up-regulate miR-130a expression level. We found that up-regulation of miR-130a level in MCF-7/Adr cells decreased the cell viability and colony formation. Then, we detected the expression of miR-130a by *in situ* hybridization using FFPE tissues from 50 breast cancer patients before and after Epirubicin-based neoadjuvant chemotherapy. We found that the miR-130a level before Epirubicin-based neoadjuvant chemotherapy was lower than that after Epirubicin-based neoadjuvant chemotherapy. A significant increase in the expression of miR-130a was observed in tumor tissue samples sensitive to Epirubicin-based neoadjuvant chemotherapy compared with those that were resistant to Epirubicin-based neoadjuvant chemotherapy. As a whole, miR-130a might play a role in prediction of therapeutic responses in Epirubicin-based chemotherapy of breast cancer.

### Materials and methods

#### *Clinical information and tissue specimens*

50 paired breast cancer tissues from patients before and after getting Epirubicin-based neoadjuvant chemotherapy were collected at the First Affiliated Hospital of Anhui Medical University (Hefei, Anhui, China) between 2012 and 2017. All tissue diagnoses were confirmed by permanent histology. All the patients have

received Epirubicin-based neoadjuvant chemotherapy due to advanced breast cancer. All tissue samples were incubated for 10 hours in 10% neutral-buffered formalin before being embedded in paraffin. A protocol for the use of tissue samples from patients and follow-up study was approved by the Institutional Review Boards of the First Affiliated Hospital of Anhui Medical University. Every patient had signed a consent form.

#### *In situ hybridization*

Formalin-fixed (10%) paraffin-embedded sections are cut onto microscope slides at 4  $\mu$ m thickness. Sections were deparaffinized in xylene, rehydrated in a graded series of ethanol solutions, and then incubated with 3% hydrogen peroxide for 10 min at room temperature, digested with pepsin for 25 min at 37°C, and rinsed with phosphate-buffered saline (PBS) three times (5 min/wash). A total of 50  $\mu$ l of pre-hybridization solution (provided with antibodies) was placed on each section, and the sections were incubated at 37°C for 4 h. Subsequently, the pre-hybridization solution was removed and then replaced with 50  $\mu$ l of hybridization solution with probes (synthesized by Boster Biotech Co., China), incubated at 37°C for 16 h. Then, the slides were washed with 2  $\times$  sodium chloride-sodium citrate (SSC) three times (5 min/wash), 0.5  $\times$  SSC three times (5 min/wash), and 0.02  $\times$  SSC three times (5 min/wash) at 37°C. The sections were blocked with serum-blocking solution for 30 min at 37°C and incubated with mouse anti-digoxin antibodies (AR0147; ready-to-use; Boster Biotech Co., China) for 60 min at 37°C. Later, the sections were washed with PBS three times (5 min/wash) and were incubated with streptavidin-biotin-peroxidase complex solution (provided with antibodies) for 20 min at 37°C, washed with PBS three times (5 min/wash), further incubated with biotin-peroxidase solution (provided with antibodies) for 20 min at 37°C and washed with PBS three times (5 min/wash). At last, the sections were stained with 3, 3'-diaminobenzidine (DAB) solution for 5 min and counterstained with hematoxylin solution for 3-5 min at room temperature. All the materials were autoclaved and treated with 0.1% diethylpyrocarbonate-double distilled water (DEPC-ddH<sub>2</sub>O) for 24 h, and all solutions were prepared with 0.1% DEPC-ddH<sub>2</sub>O at room temperature or without probes for the negative control samples.

Scoring was determined by the cytoplasm staining intensity of tumor cells as described: no staining = 0; weakly stained = 1; moderately stained = 2; strong stained = 3. Furthermore, according to the percentage of tumor cell over the sections (< 10% = 1; 10%-25% = 2; 25%-50% = 3; > 50% = 4). The final staining scores were determined as intensity × percentage to produce a final score of 0-12. The final staining scores < 5 were considered to be low expression, the final staining scores ≥ 5 were considered to be high expression.

### *Cell lines and cell culture*

Human breast cancer cell line MCF-7/ADR was obtained from KeyGENE (Nanjing, China). Doxorubicin was purchased from Beyotime (Shanghai, China). The cell lines were maintained in RPMI-1640 (Gibco, USA) supplemented with 10% fetal bovine serum (Gibco, USA), 1% penicillin sulfate (KeyGENE, China) and 1% streptomycin sulfate (KeyGENE, China), and incubated at 37°C in 5% CO<sub>2</sub>.

### *Transfection of miR-130a mimics*

MiR-130a level was up-regulated in MCF-7/ADR cells using miR-130a mimics synthesized by Genepharma (Shanghai, China). Cells were plated in six-well plates and cultured to a density of 60%; Then, Lipofectamine 2000 and miR-130a mimics were added into the culture medium to enhance the transfection according to the manufactures instruction. The transfection efficiency of miR-130a was confirmed using qRT-PCR after 24 hours.

### *MTT assay*

To measure the cell proliferation, non-transfected MCF-7/Adr cells and miR-130a mimics transfected MCF-7/Adr cells were incubated with 0.5 mg/ml MTT buffer (Thermo Fisher, USA) on a 96-well plate at 37°C for 72 hours. The absorbance at 570 nm was detected at 0 h, 24 h, 48 h, and 72 h using a spectrophotometer (Bio-Rad, USA). Each experiment was repeated at least three times.

The sensitivity of the non-transfected MCF-7/Adr cells and miR-130a mimics transfected MCF-7/Adr cells to Doxorubicin was determined. Cells were seeded into 96-well plates and co-

cultured with Doxorubicin (2 µM). We measured the cell activity by using 0.5 mg/ml MTT buffer at 72 h. Each experiment was repeated at least three times.

### *Soft agar assay for colony formation*

Soft agar colony forming assay was used to evaluate cellular transformation in vitro. 500 cells were seeded into 6-well plates and cultured in common media (1.5 mL, DMEM medium containing 10% FBS and 3% agarose). About 12 days later, colonies that appeared were fixed with pre-cold methanol and stained with 2% Giemsa solution. Experiments were repeated three times.

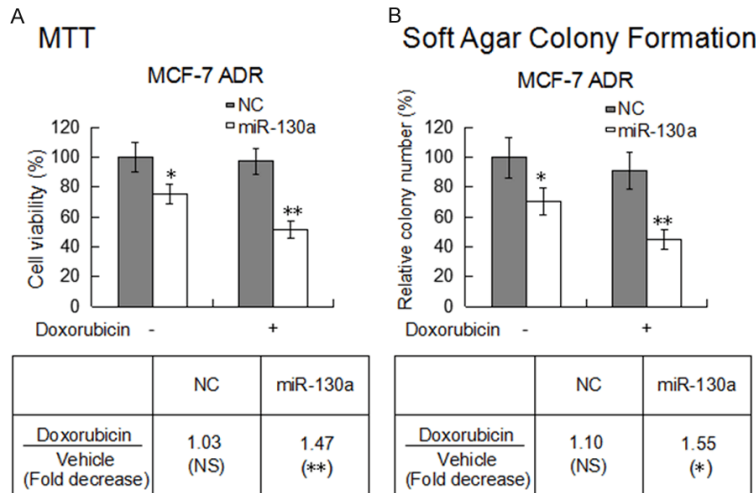
### *Statistical analysis*

Data analysis was performed using the SPSS for Windows (version 18.0; SPSS, Inc., Chicago, IL, USA) statistical software. All data were presented as mean ± standard. For MTT assay and cell colony formation assay, a one-way analysis of variance followed by Bonferroni or Tamhane post hoc tests was used. Pearson's chi-square test was used to analyze the results of the In situ hybridization. A value of *P* < 0.05 was considered statistically significant.

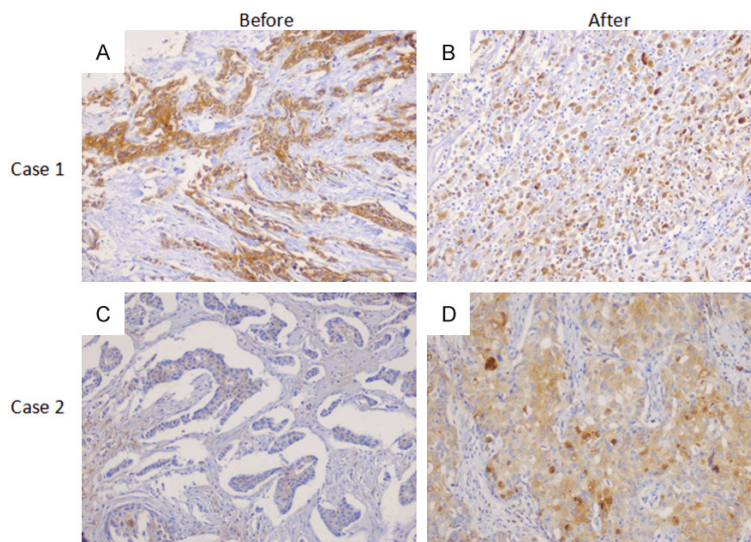
## **Results**

### *Up-regulation of miR-130a reversed doxorubicin resistance of MCF-7/Adr cells and inhibited cell growth*

To analyze the function of miR-130a, we over-expressed miR-130a in MCF-7/Adr cells using miR-130a mimics. MTT assay demonstrated that the proliferation ability of MCF-7/Adr cells was significantly reduced by miR-130a up-regulation compared to the negative control cells (**Figure 1A**). The relative colony number of miR-130a mimics treated MCF-7/Adr cells decreased significantly than the negative control cells (**Figure 1B**). To further analyze the relationship between miR-130a and Doxorubicin resistance, miR-130a mimics treated MCF-7/Adr cells and negative control MCF-7/Adr cells were cultured with Doxorubicin, respectively. The proliferation ability of miR-130a mimics treated cells was remarkably decreased than the negative control after co-cultured with Doxorubicin (**Figure 1A**). The relative colony number of miR-130a



**Figure 1.** A. MTT assay was performed to determine proliferation of miR-130a mimics treated MCF-7/Adr cells compared with negative control before and after co-cultured with Doxorubicin. B. Soft agar colony forming assay was used to evaluate the cellular transformation of miR-130a mimics treated MCF-7/Adr cells and negative control cells before and after co-cultured with Doxorubicin.



**Figure 2.** In situ hybridization was performed to determine the expression level of miR-130a in tissue samples before and after neoadjuvant chemotherapy. Case 1: the expression level of miR-130a in the tumor tissue before neoadjuvant chemotherapy (A) was higher than the level after neoadjuvant chemotherapy (B). Case 2: the expression level of miR-130a in the tumor tissue before neoadjuvant chemotherapy (C) was lower than the level after neoadjuvant chemotherapy (D).

mimics treated MCF-7/Adr cells decreased significantly than the negative control after co-cultured with Doxorubicin (**Figure 1B**). The results demonstrated that overexpression of miR-130a inhibited cell growth and reversed Doxorubicin resistance of MCF-7/Adr cells.

*miR-130a expression levels were up-regulated in breast cancer tissue samples from patients with advanced breast cancer receiving epirubicin-based neoadjuvant chemotherapy*

Neoadjuvant chemotherapy, designed to be used prior to surgical removal of a tumor, has received significant attention. It was applied to treat advanced breast cancer patients usually. We collected 50 paired breast cancer tissues from patients before and after getting Epirubicin-based neoadjuvant chemotherapy to measure the miR-130a expression level (**Figure 2**). We categorized the miR-130a levels as high or low by the final staining score of in situ hybridization. Before chemotherapy, 12 breast cancer patients (24%) had high tissue levels of miR-130a, 38 breast cancer patients (76%) had low tissue levels of miR-130a. After chemotherapy, 27 breast cancer patients (54%) had high tissue levels of miR-130a, 23 breast cancer patients (46%) had low tissue levels of miR-130a (**Table 1**). The analysis demonstrated that the expression level of miR-130a were increased in the tumor samples of patients after neoadjuvant chemotherapy compared to the samples before treatment ( $P < 0.05$ ).

*miR-130a expression levels in breast cancer tissue samples from patients who were sensitive to epirubicin-based*

*neoadjuvant chemotherapy were higher than those who were resistant to epirubicin-based neoadjuvant chemotherapy*

Clinical response to epirubicin-based neoadjuvant chemotherapy of 50 patients was classi-



**Table 1.** Expression of miR-130a in breast cancer tissues before and after chemotherapy

Group	n	miR-130a expression		$\chi^2$	P
		High expression n (%)	Low expression n (%)		
Pre-chemotherapy	50	12 (24.0)	38 (76.0)	9.458	0.002
Post-chemotherapy	50	27 (54.0)	23 (46.0)		

**Table 2.** Relationship between miR-130a expression and the clinical response post-chemotherapy

Group	n	miR-130a expression		$\chi^2$	P
		Low expression n (%)	High expression n (%)		
Chemotherapy-sensitive	32	10 (31.2)	22 (68.8)	7.785	0.005
Chemotherapy-resistant	18	13 (72.2)	5 (27.8)		

**Table 3.** Differences of miR-130a expression change before and after chemotherapy between chemotherapy-resistant and chemotherapy-sensitive groups

Group	n	miR-130a expression change before and after chemotherapy		$\chi^2$	P
		Increased n (%)	Unchanged/Decreased n (%)		
Chemotherapy-sensitive	32	22 (68.8)	10 (31.2)	12.500	0.001
Chemotherapy-resistant	18	3 (16.7)	15 (83.3)		

fied as chemotherapy-resistant (progressive disease) and chemotherapy-sensitive groups (partial response + stable disease). To further analyze the function of miR-130a in therapeutic resistance of breast cancer, we detected the level of miR-130a in the two different groups.

In the chemotherapy-sensitive group, 22 breast cancer patients (68.8%) had high tissue levels of miR-130a, and 10 breast cancer patients (31.2%) had low tissue levels of miR-130a. In the chemotherapy-resistant group, 5 breast cancer patients (27.8%) had high tissue levels of miR-130a, and 13 breast cancer patients (72.2%) had low tissue levels of miR-130a (**Table 2**). These data suggested that miR-130a expression levels in the tumor samples of chemotherapy-sensitive group patients were higher than the chemotherapy-resistant group patients ( $P < 0.05$ ).

In the chemotherapy-sensitive group, miR-130a tissue expression level of 22 breast cancer patients (68.8%) post-chemotherapy was increased compared to pre-chemotherapy, and 10 breast cancer patients (31.2%) had unchanged or decreased level. In the chemotherapy-resistant group, miR-130a tissue expression level of 3 breast cancer patients (16.7%) post-chemotherapy was increased compared to pre-chemotherapy, and 15 breast cancer patients (83.3%) had unchanged or decreased

level (**Table 3**). These data indicated that miR-130a levels were significantly reduced after chemotherapy in chemotherapy-resistant group. In contrast, miR-130a levels were increased obviously after chemotherapy in chemotherapy-sensitive group ( $P < 0.05$ ).

These results verified that miR-130a might play an important role in resistance to epirubicin-based chemotherapy of breast cancer.

## Discussion

Nowadays, neoadjuvant chemotherapy is offered to patients with locally advanced breast cancer and also those breast cancer patients who may benefit from size reduction before conservation therapy. However, chemotherapy resistance is one of the reasons for the treatment failure [1, 3]. Therefore, it is important to identify the mechanism of chemotherapy resistance in breast cancer.

More and more evidence indicates that miR-130a is associated with drug resistance and acts as an intermediate in PI3K/Akt/PTEN/mTOR, Wnt/ $\beta$ -catenin and NF- $\kappa$ B/PTEN drug resistance signaling pathways [19-21]. Yang et al [20] found that upregulation of miR-130a might be associated with MDR1/P-gp-mediated drug resistance in SKOV3/CIS cells and play the role of an intermediate in drug-resistance

pathways in PI3K/Akt/PTEN/mTOR and ABC superfamily drug transporters in ovarian cancer cells. Hu et al [21] reported that colon cancer-associated transcript-1 (CCAT1)/miR-130a axis enhanced cisplatin (DDP) resistance of non-small-cell lung cancer (NSCLC) cells by targeting sex-determining region Y-box 4 (SOX4). Although many studies have reported that miR-130a is related to drug resistance in several cancers, studies on miR-130a of drug resistance in breast cancer have not been reported. Miao et al [22] reported that microRNA-130b targets PTEN to mediate drug resistance and proliferation of breast cancer cells via the PI3K/Akt signaling pathway. New evidence has demonstrated that miR-130a plays an important role in diverse physiological processes in breast cancer, including regulating cell growth, metastasis and invasion [23-25]. Kong et al [24] found that miR-130a-3p is down-regulated in human breast cancer tissues and exosomes from circulating blood, and overexpression of miR-130a-3p in breast cancer stem cells inhibits cellular proliferation, migration, and invasion. Taken together, their results demonstrated that lower levels of exosome-derived miR-130a-3p are associated with lymph node metastasis and advanced TNM stage. Their study revealed a tumor-inhibiting function of miR-130a in breast cancer, and these results are consistent with our current findings. Our present study demonstrated that up-regulation of miR-130a reversed Doxorubicin resistance of MCF-7/Adr cells and inhibited cell growth. We also found that miR-130a expression levels were up-regulated in breast cancer tissue samples from patients with advanced breast cancer receiving Epirubicin-based chemotherapy. Moreover, our results indicated that miR-130a expression levels in breast cancer tissue samples from patients who were sensitive to Epirubicin-based chemotherapy were higher than those who were resistant to Epirubicin-based chemotherapy.

In conclusion, we revealed that up-regulated miR-130a expression can enhance the sensitivity of MCF-7/Adr cells to Doxorubicin. Moreover, we found that down-regulation of miR-130a expression might be associated with resistance to Epirubicin-based chemotherapy in breast cancer tissues. More efforts are needed to further delineate the biofunctional roles of miR-130a for reversing Doxorubicin resistance. It

will provide a potential target to overcome drug resistance and improve efficacy of chemotherapy for patients with breast cancer.

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## Disclosure of conflict of interest

None.

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