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Original Research Article

LINC00173 mediates albumin paclitaxel resistance in breast cancer cells by regulating β-catenin expression

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Abstract

Purpose: *To study the effect of LINC00173 on albumin paclitaxel resistance in breast cancer cells, and the underlying mechanism.*
Methods: *Albumin paclitaxel-resistant SK-BR-3/nab-P cell line was established using human breast cancer cell line SK-BR-3. The cells were transfected to obtain LINC00173 over-expression group, LINC00173 low-expression group and control group. The expression level of LINC00173, and proliferative, invasive and migration ability of cells were measured, and the effect of LINC00173 on albumin paclitaxel resistant cells was determined. The levels of β-catenin, P-glycoprotein (P-gp) and cyclinD1 were assayed.*
Results: *With increase in albumin paclitaxel concentration, cell viability in the three groups decreased markedly and reached the lowest level at a concentration of 100 μM. Relative to control group, the invasion, migration and population of cell colonies in low LINC00173-expression group were markedly increased, while those in the LINC00173 over-expression group were significantly decreased ($p < 0.05$). Moreover, compared with the control group, the expressions of β-catenin, P-gp and Cyclin D1 in the low LINC00173-expression group were increased, while those in the LINC00173 over-expression group decreased markedly.*
Conclusion: *Up-regulation of LINC00173 expression suppressed the proliferation and invasiveness of drug-insensitive mammary tumor cells by suppressing β-catenin, and increasing the sensitivity of drug-resistant breast cancer cells to albumin paclitaxel. This finding may be beneficial for the development of new anti-breast cancer drugs.*

Keywords: *LINC00173; β-catenin; breast cancer; albumin paclitaxel; drug resistance*

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INTRODUCTION

Breast cancer is one of the most common malignant tumors in women. Statistics have revealed that in 2020, the population of breast cancer patients worldwide exceeded 2.1 million, and more than 650,000 died from the disease [1]. In recent years, the incidence of breast cancer has been on the increase, especially amongst the younger population, resulting in serious impact on patients and their families. At present,

the major treatment strategies for breast cancer are surgery, radiotherapy and chemotherapy.

Paclitaxel is a frequently-used chemotherapy drug in clinical practice, and albumin paclitaxel, a new formulation with stronger anti-tumor activity, is produced via freeze-drying, using human serum albumin as carrier and stabilizer [2]. However, the emergence of chemotherapeutic drug resistance is still an important cause of chemotherapy failure. Therefore, it has become the focus of medical researchers to investigate the mechanism involved in albumin paclitaxel resistance and find ways to mitigate it.

Studies have found that the occurrence of drug resistance in tumor cells is closely associated with abnormal expression of long non-coding RNA (LncRNA) [3]. This is a long-chain non-coding RNA which mediates the pathogenesis of tumors through multiple signaling pathways [4]. In addition, LINC00173 is a type of LncRNA, but its role in breast cancer resistance has been rarely reported. In this study, through suppression of the expression of LINC00173, the role of LINC00173 in albumin paclitaxel resistance in breast cancer cells, and the underlying mechanism were investigated.

METHODS

Materials

Breast cancer tissues and adjacent normal tissues were randomly sampled from 26 breast carcinoma subjects who were operated on at Affiliated Hospital of Chengde Medical College.

Inclusion criteria

Patients diagnosed with breast cancer for the first time, and who had not been treated with chemotherapy or any other therapy, as well as patients who signed informed consent, were included in the study. The study received approval from the Ethics Authority of out institution, and it was carried out in line with Helsinki declaration [5]. The approval No. is 20200981. Human breast cancer cell SK-BR-3 (Shanghai Fuxiang Biotechnology Co. Ltd.) was used.

Main equipment and reagents

The instruments and reagents used, and their suppliers (in brackets) were: ultra-low temperature refrigerator (Zhongke Meiling Low Temperature Technology Co. Ltd, model: DW-HL398); real-time fluorescence quantitative PCR tester (Jijing Tianjin Mould Co. Ltd, Model: StepOne); Electron microscope (Kunshan Xuncai Instrument Technology Co. Ltd, Model: LV-150N); HT-600B electric thermostatic incubator (Shanghai Zhetu Scientific Instruments); TCL-17M centrifuge (Shanghai Luxiangyi Centrifuge Instruments); fetal bovine serum (Shanghai Jianglin Biotech); 2.5U trypsin (Shanghai First Biochemical Pharmaceutical Co. Ltd); reverse transcription kit (Shanghai Yucan Biotech), and albumin paclitaxel (Shiyao Group Ouyi Pharmaceutical Co. Ltd; batch number: 20193044, specification: 100 mg).

Reverse Transcription-Polymerase Chain Reaction (RT-PCR)

The expression levels of LINC00173 in mammary carcinoma tissue and adjoining healthy tissue were determined using real-time quantitative PCR method. Total RNA was extracted from the breast cancer tissues and adjacent normal tissues of breast cancer patients using lysing with chloroform at room temperature. The RNA concentration was measured, followed by reverse-transcription to cDNA. Then, real-time quantitative PCR procedure was consistent with PCR reaction conditions (pre-denaturation at 95℃ for 10min, 95℃ for 15 sec, 60℃ for 30 sec, 72℃ for 34 sec, and 40 cycles as reaction parameters). The total reaction volume was 20 μL, and the final concentration of each primer was 0.3 μM. The RT-PCR was carried out on ice. The reaction conditions were as shown in Table 1. The primer sequences are shown in Table 2.

Cell culture

The SK-BR-3 albumin paclitaxel-resistant cell line SK-BR-3/nab-P was generated, and SK-BR-3 cells were incubated in DMEM containing 15 μg of albumin paclitaxel. When the cells attained 85 % confluence, they were digested with trypsin, and sub-cultured. A suspension of cells in good logarithmic growth state was subjected to centrifugation. The resultant liquid layer was discarded, while the cells were dispensed in complete medium, and further cultured.

Table 1: Reaction process conditions

Total RNA	**0.1 ng - 0.5 μg (2 μg)**
Oligo (dT) primer	1 μL
DEPC H_2O	11 μL
5 x Reaction Buffer	4 μL
RNAase Inhibitor (20 U/μL)	1 μL
10 mM dNTP Mix	2 μL
RT (200 U/μL)	1 μL
Final volume	20 μL

Table 2: Primer sequences used

Gene		Primer sequences (5' 3')
LINC00173	F	GGAATGTTGCGATCCTCTGC
	R	CAGCCATGTCTGAGAGGTGA
β-catenin	F	GTGGGGCGCCCCAGGCACCA
	R	CTCCTTAATGTCACGCACGAT
P-gp	F	GTACCCATCATTGCAATAGC
	R	CAAACTTCTGCTCCTGAGTC
cyclinD1	F	ACCTGAGGAGGCCGAAPAAC
	R	GCTTCGATCTGTTCCTCTCA
GAPSH	F	CAGCCTCAAGATCATCAGCA
	R	TGTGGTCATGAGTCCTTCCA

Cell transfection

Cells in good growth condition were inoculated in 96-well plates and cultured in cell incubators until the cell density reached about 70 %. Then, LINC00173 over-expression plasmid, LINC00173 interference plasmid and blank plasmid were transfected into the cells, and the cells were cultured for 12 h. Thereafter, the culture medium was replaced with complete medium containing serum, and culturing was continued for 48 h. Logarithmic phase cells were cultured at appropriate density in an incubator. The LINC00173 over-expression group, LINC00173 low-expression group and control group had 6 repeated wells each.

Determination of expression levels of LINC00173

The expression levels of LINC00173 in the control group, low-LINC00173 expression group and LINC00173 over-expression group were measured with RT-PCR method. The experimental procedure used was the same as indicated earlier.

Cell proliferation

Cell proliferation was assessed with CCK-8 method. After transfection, cells that grew to logarithmic growth stage and in good growth state were sub-cultured and inoculated in well plates (20000 cells per well), followed by culturing. At 0, 12, 24 and 36 h, 15 μL of CCK-8 reagent was dispensed into every well, followed by 4 h-incubation in a dark chamber, and absorbance measurement at 470 nm in a spectrophotometer.

Determination of the effect of LINC00173 on albumin paclitaxel-resistant cells

The CCK-8 method was used to determine the effect of LINC00173 on albumin paclitaxel-resistant cells. Cell suspension was inoculated in 96-well plates (150 μL per well). Different concentrations of albumin paclitaxel (0.01, 1 and 100 μM) were dispensed into different wells, followed by 24 h-culturing. Thereafter, percentage cell survival was measured in each group.

Colony formation assay

Cell suspension was inoculated in 6-well plates (200 cells/well), and maintained in a cell incubator for 7 days. The supernatant was discarded when the cells showed visible colony. The cells were fixed in formaldehyde solution for 10 min, stained with crystal violet, rinsed in tap water, air-dried at room temperature, and photographed.

Cell invasion assay

Cell invasion ability was determined with Transwell cell invasion procedure. The basement membrane was coated with Matrigel and air-dried overnight at 4 °C. Then, serum-deficient medium (200 μL) was dispensed into the upper compartment, while the lower compartment contained 400 μL of whole medium. Cell suspension (150 μL) was inoculated into the upper chamber at a density of 20,000 cells per well, and the cells were cultured in a cell incubator for 24 h. The chamber was taken out, air-dried under laboratory conditions, dyed with crystal violet (0.2%), rinsed with tap water, and examined under a microscope.

Determination of migratory potential

Migratory potential was assessed with scratch migration method. The cells were plated at an appropriate density and cultured in an incubator for 48 h. A micropipette with a 150-μL tip was used to scratch the cells as vertically as possible. An appropriate amount of pre-heated sterile phosphate buffer was added to each well to wash away loose cells from the scratch. Then, the plates were cultured in RPMI1640 culture medium in an incubator for 48 h. Changes in cell migration ability in each group were examined under a microscope, and photographed.

Immunoblotting assay

β-Catenin, P-glycoprotein (P-gp) and cyclin D1 levels were determined with western blot assay. Total protein was extracted from SK-BR-3/PR cells via lysis, and after centrifugation, protein content was determined with BCA method, followed by SDS-PAGE and transfer to PVDF membranes which were sealed and subjected to overnight incubation at 4 °C with the appropriate 1° antibodies. Thereafter, the membrane was

washed with TBST, and incubated with HRP-conjugated 2º immunoglobulin for 60 min under laboratory conditions. The target bands were scanned and subjected to analysis using gel imaging protocol.

Statistics

Results are presented as mean ± SD. In this study, LINC00173 expression level, cell proliferation, invasion, migration ability and other measurement data in breast cancer tissue, adjacent normal tissue and cells of each group were consistent with normal distribution. Comparison amongst multiple groups was performed using means of single-factor multiple-sample mean, while two-group comparison was conducted with independent sample *t*-test. The SPSS version 24.0 software was applied for all statistical evaluations. Values of $p < 0.05$ indicated significant differences.

RESULTS

LINC00173 levels in breast carcinoma tissue and adjacent healthy tissue

The expression level of LINC00173 in breast carcinoma was markedly reduced, relative to that in adjoining healthy tissue ($p < 0.01$; Table 3).

Table 3: LINC00173 levels in breast carcinoma and adjoining healthy tissues

Group	LINC00173
Adjacent normal tissue	1.12±0.10
Breast cancer tissue	0.72±0.07
t	16.709
P-value	<0.001

Results are presented as mean ± SD (n = 26)

LINC00173 expression levels in the cell groups

Compared with the control group, the expression level of LINC00173 was markedly decreased in the low-LINC00173 expression group, but it was markedly increased in the LINC00173 over-expression group ($p < 0.05$; Table 4).

Table 4: LINC00173 expression levels in each group of cells

Group	LINC00173
Control	1.01±0.01
LINC00173 low-expression	0.36±0.04[a]
LINC00173 over-expression	11.52±3.54[ab]
F	56.35
P-value	<0.001

[a]$P < 0.05$, vs control; [b]$p < 0.05$, vs LINC00173 low-expression group

Proliferative capacity of cells

There were no marked variations in cell proliferation potential amongst the three groups at the outset ($p > 0.05$). However, from 12 to 36 h, cell proliferation capacity in the low-LINC00173 expression group was markedly elevated, while cell proliferation in the LINC00173 over-expression group was significantly reduced, when compared with control ($p < 0.05$; Table 5).

Effect of LINC00173 on albumin paclitaxel-resistant cells

No marked changes in cell viability were seen in the three groups in the absence of albumin paclitaxel ($p > 0.05$). However, with increase in albumin paclitaxel concentration, cell viability was markedly decreased in the three groups, reaching the lowest level at albumin paclitaxel concentration of 100 µM. The results are shown in Table 6.

Cell invasion

Relative to the control group, cell invasion in the low-LINC00173 expression group was markedly increased, but it was markedly decreased in the LINC00173 over-expression group ($p < 0.05$; Figure 1).

Cell migration

Figure 2 shows that, compared with the control group, cell migration in the low-LINC00173 expression group was significantly increased, but it was markedly decreased in the LINC00173 over-expression cells.

Table 5: Comparison of proliferative capacity amongst the groups (mean ± SD, n = 6)

Group	Cell proliferation capacity			
	0 h	***12 h***	***24 h***	***36 h***
Control	0.22±0.02	0.61±0.03	1.23±0.07	1.96±0.09
LINC00173 low-expression	0.21±0.02	0.87±0.05[a]	1.51±0.11[a]	2.15±0.08[a]
LINC00173 over-expression	0.23±0.03	0.53±0.03[ab]	1.08±0.06[ab]	1.54±0.10[ab]
F	1.06	132.28	41.62	71.58
P-value	0.371	<0.001	<0.002	<0.001

[a,b]$P < 0.05$, vs control ([a]); vs LINC00173 low-expression ([b])

Table 6: Effect of LINC00173 on albumin paclitaxel resistant cells (*x*±*s*)

Group	Cell viability (%)			
	0	***0.01 μM***	***1 μM***	***100 μM***
Control	100.00±0.01	89.54±0.12	65.83±1.57	15.74±3.33
LINC00173 low-expression	100.00±0.01	94.52±0.53[a]	76.81±1.69[a]	15.76±3.30
LINC00173 over-expression	100.00±0.01	77.39±0.83[ab]	50.56±1.73[ab]	15.71±3.35
F	0.00	1420.02	376.28	0.00
P-value	1.000	<0.001	<0.001	1.000

[a, b]$P < 0.05$, vs control ([a]); vs LINC00173 low-expression ([b])

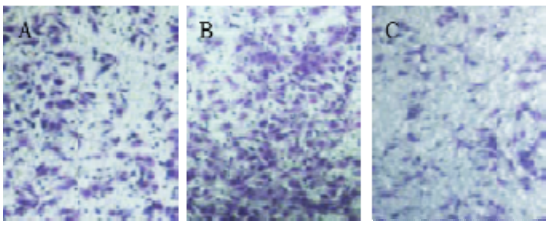

Figure 1: Cell invasion ability in each group of cells. A: Control group; B: low-LINC00173 expression group; C: LINC00173 over-expression group

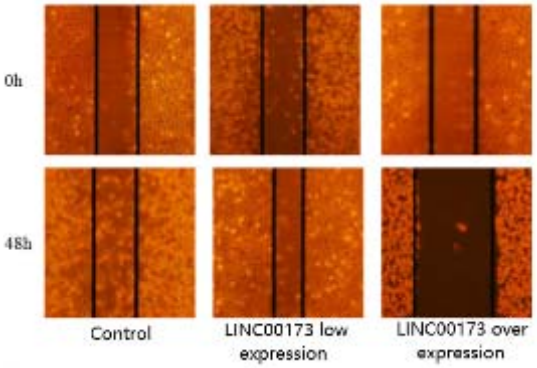

Figure 2: Migration ability in each group of cells

Colony formation potential

The number of cloned cells was markedly higher in low-LINC00173 expression group than in control. In contrast, the population of cloned cells in LINC00173 over-expression cells was decreased markedly. These results are presented in Figure 3.

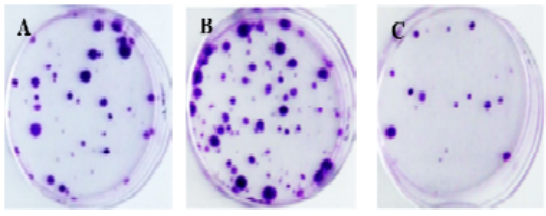

Figure 3: Colony formation ability in each group. A: Control group; B: low-LINC00173 expression group; C: LINC00173 over-expression group

Expression levels of β-catenin, P-gp and Cyclin D1

As shown in Table 7, the protein expression levels of β-catenin, P-gp and Cyclin D1 in the low-LINC00173 expression group were significantly increased, relative to the control group ($p < 0.05$). In contrast, these protein levels were markedly decreased in the LINC00173 over-expression cells.

Table 7: β-Catenin, P-gp and Cyclin D1 levels in each group of cells

Group	β-catenin	P-gp	Cyclin D1
Control	1.01±0.01	1.00±0.03	1.01±0.02
LINC00173 low expression	1.36±0.03[a]	1.47±0.07[a]	1.58±0.03[a]
LINC00173 over-expression	0.46±0.05[ab]	0.57±0.03[ab]	0.69±0.05[ab]
F	1058.57	544.39	962.68
P-value	<0.001	<0.001	<0.001

[a, b]$P < 0.05$, vs control ([a]); vs LINC00173 low-expression group ([b])

DISCUSSION

Breast carcinoma is the most prevalent malignancy, and a major cause of mortality in females. Chemotherapy is an important treatment strategy for breast cancer. However, research has found that mammary carcinoma cells are increasingly becoming insensitive to anti-tumor drugs, a situation which has significantly reduced the effect of chemotherapy in patients, and increased difficulties in their treatment [6]. The emergence of drug resistance in tumor cells is a complex process which may be the result of multiple mechanisms [7].

The LncRNA is a multifunctional non-coding RNA which is involved in several molecular biological events such as genomic imprinting, chromatin modification and silencing of chromosomes. Moreover, it is vital for initiation and termination of transcription, and intranuclear transport [8]. It has been found that LncRNA is crucial in several pathophysiological functions [9]. However, it is not clear if it is involved in albumin paclitaxel

resistance in breast cancer cells.

With advances in molecular biology, many molecular markers have been discovered. Some scholars have reported that LICN00472 significantly affected the survival of breast cancer [10]. Studies have shown that HOTAIR level in breast cancer is closely related to the metastasis status of patients, and could be used as an important marker of prognosis of breast cancer. In the present study, albumin paclitaxel-resistant SK-BR-3/PR cells were established, and LICN00472 was over-expressed or under-expressed, with the aim of investigating the role of LINC00173 in albumin paclitaxel resistance in breast cancer, and the associated mechanism.

Studies suggest that cell proliferation is important in the sensitivity of cancer cells to chemotherapeutic drugs, and that proliferative cells are more sensitive to chemotherapy than quiescent cells [12]. In this study, it was found that down-regulation of LINC00173 expression significantly enhanced the proliferation ability of SK-BR-3/PR cells and suppressed the sensitivity of drug-resistant cells to albumin paclitaxel. In contrast, up-regulation of LINC00173 expression inhibited the proliferation ability of SK-BR-3/PR cells and increased the sensitivity of drug-resistant cells to albumin paclitaxel.

It may be that the up-regulated expression of LINC00173 reduced the expression of P-gp on the cell membrane and increased the aggregation of drugs within the cells, thereby enhancing their killing effect on tumor cells [13]. In addition, this study has demonstrated that the up-regulation or down-regulation of LINC00173 expression markedly inhibited or promoted the invasion and migration, respectively, of SK-BR-3/PR cells.

Numerous signal routes are implicated in the pathogenesis of mammary carcinoma [14]. The Wnt signal route is extremely conserved, and it is an important route in tumor development [15]. Under normal conditions, the Wnt signal route is closed and β-catenin level is reduced, which make it unable to enter the nucleus to play a role. When the Wnt signaling pathway is activated, the downstream target gene cyclin D1 becomes active, resulting in the occurrence of breast cancer [16,17]. Phospho-acylated glycoprotein (P-gp) is a transmembrane protein which uses the energy released by ATP hydrolysis to actively transport anti-tumor drugs and hydrophobic lipophilic compounds to the outside of cells to enable the cells escape the killing effects of chemotherapy [18].

Studies have found that P-gp expression level is closely related to the resistance of cancer cells to chemotherapeutic drugs [19]. When the transcription of drug-resistant genes is inhibited, their expression levels are significantly reduced and the sensitivity of cells to chemotherapeutic drugs is increased [20]. The data obtained in this investigation suggest that Wnt/β-catenin signal route is implicated in the pathogenesis of albumin paclitaxel resistance, and that LINC00173 regulates the expressions of β-catenin, CyclinD1 and P-gp.

CONCLUSION

The results obtained in this study indicate that the up-regulation of LINC00173 expression may inhibit cell proliferation, invasion and migratory potential of drug-insensitive breast carcinoma cells by suppressing the generation of β-catenin, thereby increasing the sensitivity of the drug-resistant breast cancer cells to albumin paclitaxel. This finding will be beneficial in the development of new anti-breast cancer drugs.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was performed by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Lihui Ma designed the study, supervised the data collection, and analyzed the data. Chunyu Tian interpreted the data and prepared the manuscript for publication. Mengze Xu, Hongxu Zhang, Hancheng Liu, Xinghua Liu supervised the data collection, analyzed the data and reviewed the draft of the manuscript.

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