MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2020; 26: e922672
DOI: 10.12659/MSM.922672

Received: 2020.01.07
Accepted: 2020.04.04
Available online: 2020.05.12
Published: 2020.07.05

Suppression of Long Non-Coding RNA Metastasis-Associated Lung Adenocarcinoma Transcript 1 (MALAT1) Potentiates Cell Apoptosis and Drug Sensitivity to Taxanes and Adriamycin in Breast Cancer

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Source of support: Departmental sources

Background: The long non-coding RNA (lncRNA) metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is expressed highly in various types of tumors. Moreover, the tumor-initiating role of MALAT1 has been probed in the context of breast cancer. This study was set to investigate the regulatory role of MALAT1 on the chemosensitivity of breast cancer cells to taxanes (Tax) and adriamycin (Adr).

Material/Methods: Following the measurement of MALAT1 expression in patients with breast cancer by means of qRT-PCR, the connection between the MALAT1 expression pattern and the prognosis of breast cancer patients as well as the molecular typing of breast cancer patients was analyzed using Kaplan-Meier survival analysis and receiver operating characteristic (ROC) curves. Next, the analysis between the expression of MALAT1 and the clinical symptoms of breast cancer patients was carried out. Subsequently, we generated taxane-resistant MCF-7 cells (MCF-7/Tax) and purchased Adr-resistant MCF-7 cells (MCF-7/Adr). Finally, the proliferation, apoptosis and drug resistance of resistant and parental cells were evaluated after transfection of silencing MALAT1 into these cells.

Results: MALAT1 was highly expressed in the breast cancer tissues. Moreover, patients with relative overexpression of MALAT1 had worse prognosis. MALAT1 expression was remarkably promoted in MCF-7/Tax and MCF-7/Adr cells, whose sensitivity to Tax and Adr was enhanced following MALAT1 knockdown.

Conclusions: MALAT1 was elevated in breast cancer tissues and MCF-7-resistant cells, relative to corresponding controls and downregulation of MALAT1 inhibited the growth and chemoresistance of breast cancer cells to Tax and Adr.

MeSH Keywords: Drug Resistance • Inflammatory Breast Neoplasms • MCF-7 Cells • RNA, Long Noncoding • Rotaxanes

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/922672

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Background

Breast cancer represents one of the most prevalent malignant neoplastic diseases in female population with over 1 300 000 newly diagnose annually worldwide and more than 450 000 cases of deaths annually [1]. Even though the molecular mechanisms of breast cancer have been broadly explored over the ten years, many unresolved issues still exist in clinic, such as overdue diagnosis, recurrence and metastasis [2]. Treatment schemes are consisted of surgery, radiotherapy, and systemic treatment; and paclitaxel and docetaxel, the 2 main taxanes (Tax), are among the most frequently employed cytotoxic drugs for breast cancer [3]. Tax plays a significant role in the treatment of breast cancer at both early and advanced stages [4]. As standard chemotherapies to stabilize microtubules, the clinical effects of Tax are frequently restricted by drug resistance and neurotoxicity [5]. Adriamycin (Adr) is another important and frequently applied chemotherapy agent in the treatment of breast cancer, with 2 key mechanisms: DNA damage and generation of reactive oxygen species [6].

A group of transcripts, long noncoding RNAs (lncRNAs), is universally transcribed in the genome, and the mutations and dysregulations of which are correlated to varied human disorders [7]. The metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), consisted of over 8700 nt, was revealed to be a prognostic biomarker for metastasis in non-small cell lung cancer at early-stage [8]. MALAT1 has been implicated in the initiation, development, and progression of tumors such as breast cancer [9]. In addition to tumor initiation, the crucial role of MALAT1 in nasopharyngeal carcinoma cell resistance to radiotherapy has been reported previously, where silencing of MALAT1 elevated radiotherapy sensitivity *in vitro* and *in vivo* [10]. On top of that, the knockdown of MALAT1 was related to the potentiated sensitivity of hepatocellular carcinoma cells to various chemotherapeutic agents [11]. Also, MALAT1 diminished the sensitivity of glioma cells towards temozolomide by mediating ZEB1 [12]. In the same vein, MALAT1 expression was linked to poor response to oxaliplatin-based chemotherapy for patients with colorectal cancer at advanced stage as well as lung cancer patients [13,14]. Nevertheless, inadequate knowledge is available now regarding how MALAT1 disturbs the sensitivity of breast cancer cells to Tax and Adr. In this report, the function of MALAT1 in breast cancer cells resistance to Tax and Adr and its association with prognosis of breast cancer were identified.

Material and Methods

Ethics statement

This study was carried out under the agreement of the Institutional Review Board of Zhuji Central Hospital. Each participant provided a written informed consent.

Table 1. The clinicopathological features of patients with breast cancer.

Variables	Group	Cases (n)
Age (years)	<65	38
	>65	42
Clinical stage	I/II	34
	III/IV	46
Differentiation level	Low	21
	Median	31
	High	28
Tumor size	<3 cm	33
	>3 cm	47
Lymph node metastasis	Yes	32
	No	48
ER	Positive	56
	Negative	24
PR	Positive	47
	Negative	33
HER-2	Positive	52
	Negative	28

ER – estrogen receptor; PR – progesterone receptor; HER-2 – human epidermal growth factor receptor 2.

Patients and samples

Eighty breast cancer patients enrolled from September 2012 to June 2013 at Zhuji Central Hospital were included, and samples were obtained of their cancer tissues and normal tissues adjacent to cancer (at least 5 cm from cancer tissues). The enrolled participants were aged between 49 to 79 years (mean age, 64.9±7.3 years). The clinical baseline information and molecular typing of patients are presented in Table 1. All study patients were followed every 3 months for 5 years. We restricted the enrollment criteria to female patients who had been histologically diagnosed with breast cancer as their first primary tumor. Only patients without surgery, radiation therapy, and chemotherapy were included. Patients with chronic system disorders and other malignant tumors were excluded from the study.

Cell culture and treatment

Breast cancer MCF-7 cells were obtained from American Type Culture Collection (Manassas, VA, USA). Taxane-resistant MCF-7 (MCF-7/Tax) cells were obtained by the exposure of the parent MCF-7 cells to gradient concentrations of drugs (Sigma-Aldrich, St Louis, MO, USA). All cells were maintained in Roswell Park Memorial Institute-1640 medium added with 10% fetal bovine

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serum, 100 units/mL penicillin and 100 mg/mL streptomycin (Invitrogen, Carlsbad, CA, USA) with 5% CO_2 at a temperature of 37°C. MCF-7 cells resistant to adriamycin (Adr) were purchased from KeyGene (KeyGene, Rockville, MD, USA).

Lentivirus-carrying siRNA-MALAT1 or siRNA scramble control (scramble) was packaged into human embryonic kidney 293T cells using a lentiviral packaging kit (Open Biosystems, Inc., Huntsville, AL, USA) as per the manufacturer's instructions. MCF-7/Tax cells were infected with lentivirus to construct stable cell lines.

Quantitative real-time (RT)-PCR assay

TRIzol (TransGen Biotech, Beijing, China) was utilized to extract total RNA from the cells. Subsequently, RNA was reversely transcribed into cDNA with the help of a TransScript All-in-One First-Strand cDNA Synthesis Kit (TransGen Biotech). The Bestar® SYBR GreenqPCR Master Mix kit was applied for quantitative real-time polymerase chain reaction (qRT-PCR). Specific experimental steps were carried out in accordance with the previous literature [15]. Primers for qPCR are as follows: GAPDH forward primer:
5'-CTCCTCCTGTTCGACAGTCAGC-3';
GAPDH reverse primer: 5'-CCCAATACGACCAAATCCGTT-3';
MALAT1 forward primer: 5'-CATTCGCTTAGTTGGTCTAC-3';
MALAT1 reverse primer: 5'-TTCTACCGTTTTTAGCTTC-3'.

Cell Counting Kit-8 (CCK-8) experiment

MCF-7 cells were plated in a 96-well plate in triplicate at 8×10^3 cells each well. Four hours later, Tax (serial dilution, from 0 to 10 μM, Sigma-Aldrich Company) was added and incubated for another 72 hours.

Apoptosis detection by flow cytometric analysis

Apoptotic cells were evaluated by flow cytometry as previously described [16].

Data analysis

The Kolmogorov-SmiRnov was applied to test whether data were normally distributed or not. Data were displayed as mean±standard deviation (SD). Multigroup comparisons were conducted using one-way analysis of variance (ANOVA) with Sidak's post hoc test, and *t*-test was carried out for intergroup comparisons using SPSS21.0 (SPSS, IBM, Armonk, NY, USA). Kaplan-Meier analysis was utilized to compare the survival of breast cancer patients. Log-rank test was applied for univariate analysis. Predictive efficacy of MALAT1 on the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2) subtype of breast cancer patients was calculated using the receiver operating characteristic (ROC) curve. Significance was accepted for 2-sided $P<0.05$.

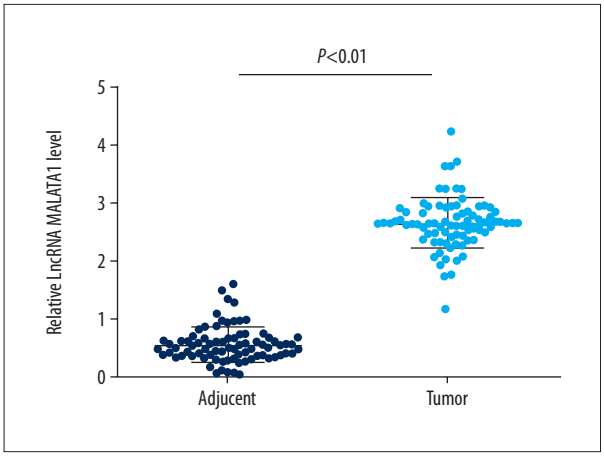

Figure 1. MALAT1 is upregulated in breast cancer tissues determined by qRT-PCR. Totally, 80 breast cancer patients were recruited. MALAT1 – metastasis-associated lung adenocarcinoma transcript 1; qRT-PCR – quantitative real-time polymerase chain reaction.

Results

MALAT1 was expressed highly in breast cancer tissues

The expression of MALAT1 within tissues from 80 breast cancer patients were examined, and MALAT1 was markedly elevated in tumor tissues versus adjacent tissues (Figure 1). The association between the MALAT1 expression pattern and the baseline characteristics of breast cancer patients was analyzed. The median expression of MALAT1 was 2.48. Therefore, patients with MALAT1 expression lower than 2.48 was allocated into the low expression group, and patients with MALAT1 expression greater than 2.48 were allocated into the high expression group. In breast cancer, the expression of MALAT1 was related to the clinical stage, lymph node metastasis, and tumor differentiation. The expression of MALAT1 decreased with the increase in the clinical stage of breast cancer; the expression of MALAT1 in patients at stage III+IV was significantly enhanced relative to patients at stage I+II ($P<0.05$). The MALAT1 expression was profoundly promoted in patients with poor differentiation relative to those with high differentiation ($P<0.05$), and MALAT1 expression in patients with lymph node metastasis was significantly promoted relative to those free of lymph node metastasis ($P<0.05$). Additionally, we hardly observed the correlation between MALAT1 expression and age and tumor size of patients with breast cancer. And we found that patients with high expression of MALAT1 were associated with molecular

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Table 2. The association between MALAT1 expression and clinicopathological variables in breast cancer patients.

Variables	Case (n)	MALAT1 expression		*P* value
		Poor (n=40)	High (n=40)	
Age				0.823
≤65 years	38	20 (50.0)	18 (45.5)	
>65 years	42	20 (40.0)	22 (54.5)	
Tumor size				0.999
≤3 cm	33	16 (40.0)	17 (42.5)	
>3 cm	47	24 (60.0)	23 (57.5)	
Clinical stage				0.012
I+II	34	11 (27.5)	23 (57.5)	
III+IV	46	29 (72.5)	17 (42.5)	
Lymph node metastasis				<0.001
No	48	32 (87.5)	13 (32.50)	
Yes	32	8 (12.5)	27 (67.50)	
Differentiation				<0.001
Low/Median	52	16 (40.0)	36 (90.0)	
High	28	24 (60.0)	4 (10.0)	
ER				0.027
Positive	56	33 (82.50)	23 (57.50)	
Negative	24	7 (17.50)	17 (42.50)	
PR				<0.001
Positive	47	33 (82.50)	14 (35.00)	
Negative	33	7 (17.50)	26 (65.00)	
HER				0.034
Positive	52	31 (77.50)	21 (52.50)	
Negative	28	9 (22.50)	19 (47.50)	

MALAT1 – metastasis-associated lung adenocarcinoma transcript 1; ER – estrogen receptor; PR – progesterone receptor; HER-2 – human epidermal growth factor receptor 2.

typing in breast cancer patients, and patients with negative ER/HER-2/PR exhibited higher expression of MALAT1 (Table 2).

Patients with overexpression of MALAT1 had worse prognosis

Subsequently, we performed Kaplan-Meier survival analysis on the basis of follow-up records, and found that patients with MALAT1 overexpression had a worse prognosis, with a 5-year survival rate of 24.3% and an average survival time of 29.67 months after diagnosis. The 5-year survival rate was 42.5%, and the average survival time after diagnosis was 38.89 months for patients with relatively lower MALAT1 expression ($P<0.05$; Figure 2A). We subsequently analyzed the predictive efficacy of MALAT1 for molecular typing in breast cancer patients using the ROC curve. It was revealed that MALAT1 had a sensitivity of 76.0%, specificity of 63.6%, and area under the curve (AUC) of 0.719 for ER negative patients; sensitivity of 59.3%, specificity of 79.2%, AUC of 0.702 for HER-2 negative patients; and sensitivity of 81.8%, specificity of 70.2%, and AUC of 0.777 for patients with PR negative breast cancer (Figure 2B).

MALAT1 was overexpressed in MCF-1/Tax cells

With the aim of verifying the role of MALAT1 on the resistance of MCF-1 cells to Tax, we constructed an MCF-1/Tax cell line and determined the success construction of the MCF-7/Tax cell line using the CCK-8 cytotoxicity assay (Figure 3A). Then, we tested the MALAT1 expression in MCF-1 and MCF-1/Tax cells by qRT-PCR, and found that the MALAT1 expression in MCF-1/Tax cells was profoundly increased (Figure 3B). In an attempt to assess the regulatory role of MALAT1 on chemoresistance in breast

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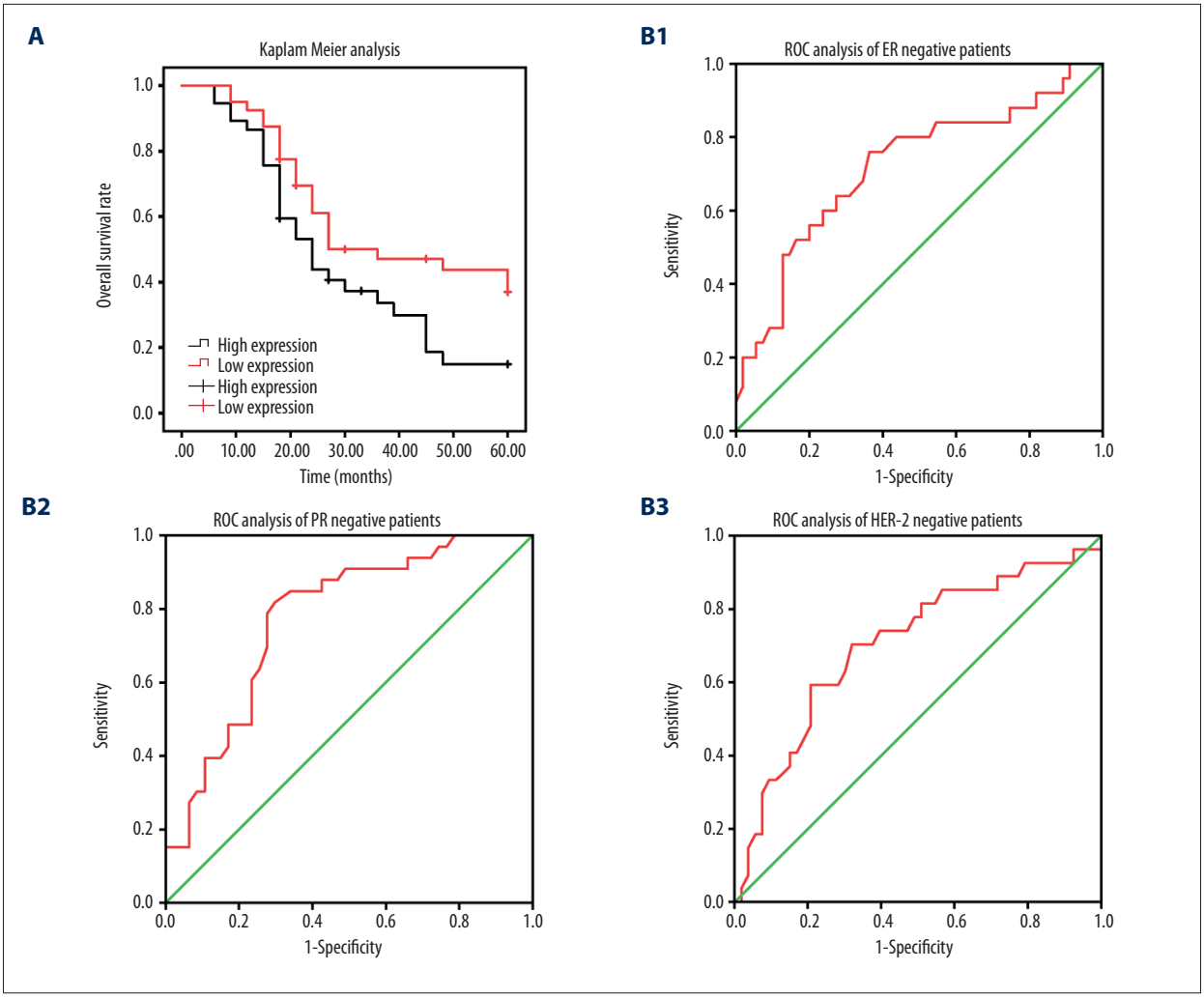

Figure 2. Breast cancer patients with high expression of MALAT1 are associated with worse prognosis as revealed by Kaplan-Meier survival analysis. (**A**) Kaplan-Meier overall survival curves of MALAT1 of breast cancer. (**B1–B3**) ROC analysis of predictive efficacy of MALAT1 and molecular typing in breast cancer patients. MALAT1 – metastasis-associated lung adenocarcinoma transcript 1; ROC – receiver operating characteristic.

cancer cells, we transfected siRNA MALAT1 into MCF-1/Tax cells. Subsequently, the MALAT1 expression in cells was tested by means of qRT-PCR to validate the success of delivery (Figure 3C).

Knockdown of MALAT1 enhanced the chemosensitivity of breast cancer cells towards Tax

Then, we detected the chemoresistance of MCF-7/Tax cells transfected with si-MALAT1 to Tax. CCK-8 results exhibited that the sensitivity of MCF-7/Tax cells to Tax was significantly increased after MALAT1 downregulation (Figure 4A). Subsequently, the apoptosis level of the cells was detected by flow cytometry, and the apoptosis level of the MCF-7/Tax cells that delivered with si-MALAT1 was found to be significantly increased (Figure 4B). Hence, silencing of MALAT1 was accountable for the pro-apoptotic capability of MCF-7/Tax cells.

Knockdown of MALAT1 enhanced the chemosensitivity of breast cancer cells towards Adr

To better clarify the effects of MALAT1 knockdown on breast cancer cell resistance, we purchased MCF-7/Adr resistant cell lines. We first verified that MCF-7/Adr had a higher median inhibition concentration (IC50) value (Figure 5A) for Adr by using CCK-8 kits. Subsequently, we examined the expression of MALAT1 in MCF-7/Adr cells by qRT-PCR. MALAT1 expression in the MCF-7/Adr cells were significantly higher than that in parental MCF-7 cells (Figure 5B). We then transfected siRNA MALAT1 into MCF-7/Adr cells. qRT-PCR showed the successful transfection (Figure 5C). The CCK-8 results showed that the cell sensitivity to Adr was significantly improved after MALAT1 knockdown (Figure 5D). Lastly, the apoptosis level of the cells was detected by flow cytometry, and it was found that the

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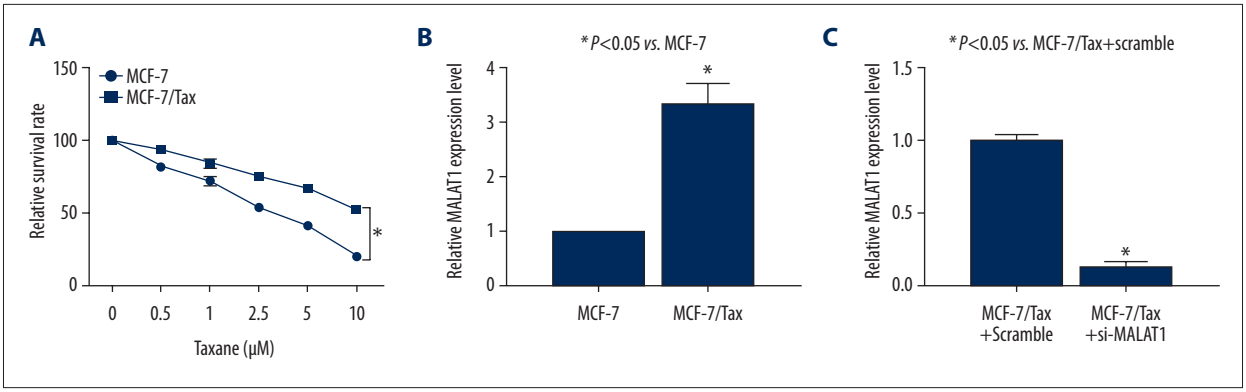

Figure 3. Tax-resistant MCF-7 cells express higher MALAT1 expression. (**A**) MCF-7 cells were exposed to gradient concentrations of Tax (Sigma-Aldrich, St Louis, MO, USA) to ensure the construction of Tax resistant breast cancer cells by CCK-8 assay. (**B**) The MALAT1 expression in MCF-7 cells and MCF-7/Tax cells measured by qRT-PCR. (**C**) The MALAT1 expression in MCF-7/Tax cells transfected with si-MALAT1 or scramble siRNA measured by qRT-PCR. Data are expressed as mean±SD. One-way ANOVA and Sidak's multiple comparisons test. were used to determine statistical significance, otherwise unpaired *t*-test was used, * *P*<0.05. Three independent experiments were performed. MALAT1 – metastasis-associated lung adenocarcinoma transcript 1; Tax – taxanes; CCK-8 – Cell Counting Kit-8; qRT-PCR – quantitative real-time polymerase chain reaction; SD – standard deviation.

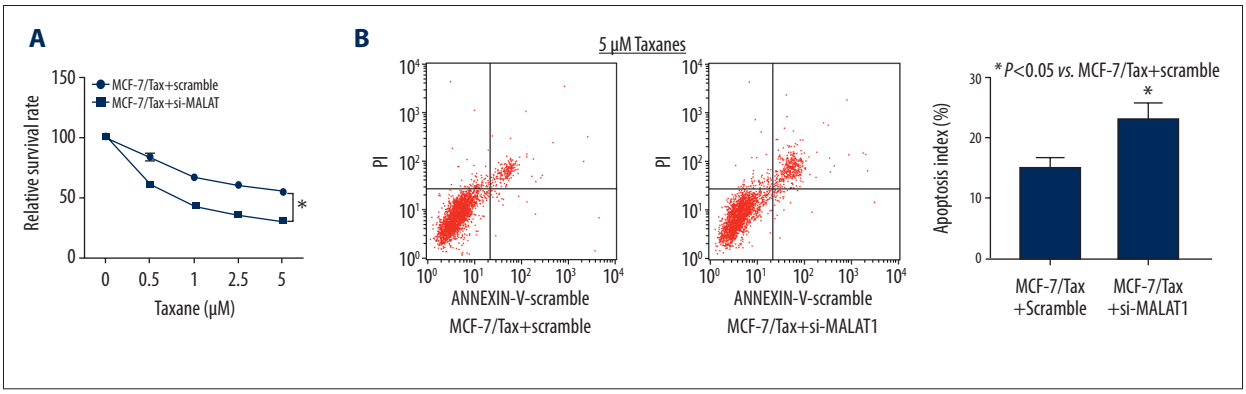

Figure 4. MALAT1 silencing promotes Tax sensitivity of breast cancer cells. (**A**) The cell viability of MCF-7/Tax cells when exposed to gradient concentrations of Tax determined by CCK-8 assays. (**B**) Apoptosis rate of the MCF-7/Tax cells examined by flow cytometry analysis. Data are expressed as mean±SD. One-way ANOVA and Sidak's multiple comparisons test were used to determine statistical significance, otherwise unpaired *t*-test was used, * *P*<0.05. Three independent experiments were performed. MALAT1 – metastasis-associated lung adenocarcinoma transcript 1; Tax – taxanes; CCK-8 – Cell Counting Kit-8; SD – standard deviations.

apoptosis rate of MCF-7/Tax cells with MALAT1 knockdown was significantly increased (Figure 5E).

Discussion

Breast cancer stands out as one of the most frequent cancers among Chinese female; cases in China constitute 12.2% of newly diagnosed breast cancer cases in total and 9.6% of deaths from breast cancer globally [17]. As a critical chemotherapeutic agent, Tax has been widely applied to treat numerous kinds of cancers, involving prostate cancer, lung cancer, as well as ovarian cancer, but its clinical efficacy is constrained by the chemoresistance of primary tumor cells during treatment [18]. Adr, a topoisomerase II catalytic inhibitor, is an antibiotic applied in the treatment of various cancers, including breast cancer [19]. In breast cancer, MALAT1 stimulated breast cancer cell migration and invasion by binding to miR-1 [20]. The identical pro-invasive role of MALAT1 has also been identified in triple-negative breast cancer [21]. All these reports demonstrated that the expression pattern of MALAT1 was in a positive correlation with cell proliferation, migration as well as invasion. Besides, the pro-metastatic role of MALAT1 has been established in cancers is principally controlled by governing epithelial-to-mesenchymal transition [22]. While the function of MALAT1 in drug sensitivity to Tax and Adr in breast

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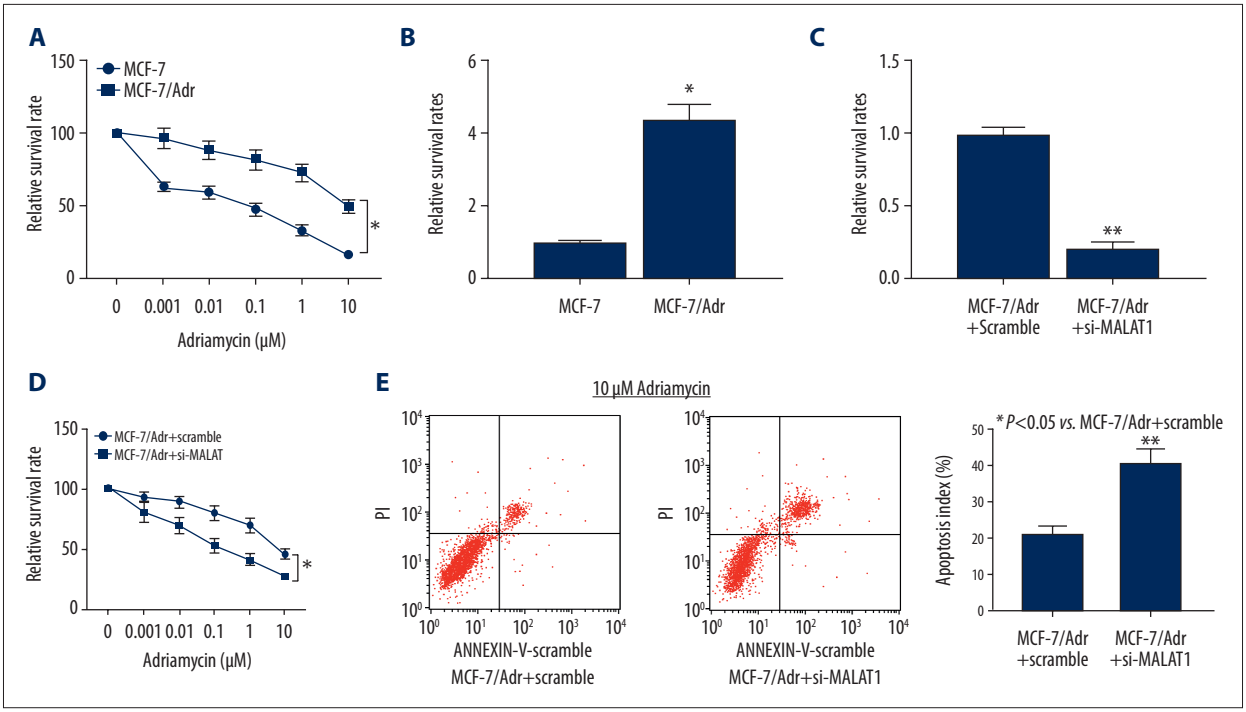

Figure 5. MALAT1 silencing promotes Adr sensitivity of breast cancer cells. (**A**) MCF-7 cells were exposed to gradient concentrations of Adr (Sigma-Aldrich, St Louis, MO, USA) to ensure the construction of Adr resistant breast cancer cells by CCK-8 assay. (**B**) The MALAT1 expression in MCF-7 cells and MCF-7/Adr cells measured by qRT-PCR. (**C**) The MALAT1 expression in MCF-7/Adr cells transfected with si-MALAT1 or scramble siRNA measured by qRT-PCR. (**D**) The cell viability of MCF-7/Adr cells when exposed to gradient concentrations of Adr determined by CCK-8 assays. (**E**) Apoptosis rate of the MCF-7/Adr cells examined by flow cytometry analysis. Data are expressed as mean±SD. One-way ANOVA and Sidak's multiple comparisons test were used to determine statistical significance, otherwise unpaired *t*-test was used, * $P<0.05$, ** $P<0.01$. Three independent experiments were performed. MALAT1 – metastasis-associated lung adenocarcinoma transcript 1; Adr – adriamycin; CCK-8 – Cell Counting Kit-8; qRT-PCR – quantitative real-time polymerase chain reaction; SD – standard deviations.0

cancer remains elusive. This study proposed that knockdown of MALAT1 maybe serve as a capable treatment target by repressing the breast cancer cell resistance to Tax and Adr.

To begin with, the MALAT1 expression was investigated in breast cancer tissues and cells, which established that MALAT1 was overexpressed relative to normal tissues and cells. In consistence with our observations, MALAT1 has also been concluded to be expressed highly in breast cancer tissues, and proliferation, migration, and tube formation was inhibited when shRNA against MALAT1 was stably delivered into MCF-7 cells [23]. More specifically, MALAT1 induced MDA-MB-231 and MDA-MD-435 cell proliferation and invasion through different pathways in breast cancer [24]. MALAT1 is one of the most typical lncRNAs that involve in tumor-initiating activities in several tumors, including osteosarcoma [25], tongue cancer [26], as well as gastric cancer [27]. Besides, higher expression of MALAT1 in breast cancer patients was monitored to be associated with poor prognosis, clinical staging, lymph node metastasis, and tumor differentiation, but not with tumor size and patient age. In bladder cancer, elevated MALAT1 expression was also linked to advanced histological grade, higher tumor stage, as well as lymph node metastasis [28]. Of note, MALAT1 was upregulated in papillary thyroid cancer, which was tightly related to tumor size, lymph node metastasis, and World Health Organization disease stage [29]. Esophageal squamous cell carcinoma patients with a higher MALAT1 expression suffered from a shorter disease-free survival and overall survival versus patients with lower MALAT1 expression, yet showed no correlation between lymph node metastasis and MALAT1 expression, which may by caused by different patient populations [30]. ER, PR, and HER-2 statuses were independent prognostic factors for the overall survival of breast cancer patients [31]. However, we observed in the present study that MALAT1 expression was closely correlated with ER, PR, and HER-2 statuses of breast cancer patients. Therefore, we may conclude that MALAT1 has the potency to exert prognostically significant effects.

Our results also verified that depletion of MALAT1 remarkably repressed resistance of breast cancer to Tax and Adr *in vitro*. Similarly, in colorectal cancer, MALAT1 knockdown culminated in the enhancement of cancer cell sensitivity to 5-flurouracil [32]. Cytarabine treatment was found to induce apoptosis

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of acute myeloid leukemia cells, while MALAT1 silencing in the presence of cytarabine treatment substantially reinforced apoptosis [33], which was in line with our flow cytometric results. Moreover, suppression of MALAT1 promoted the chemosensitivity by suppressing the bladder cancer cells resistance to cisplatin [34]. MALAT1 enhanced prostate cell proliferation and its resistance against Tax [35]. Similarly, overexpression of MALAT1 could significantly strengthen viability and growth of cancer cells as well as the chemoresistance of lung cancer cells to cisplatin, Adr, gefitinib, and Tax [36]. Hence, MALAT1 may be used as a universal player for chemotherapeutic improvement for different drugs in various cancers.

Conclusions

The current study suggests that silencing of MALAT1 could exert suppressive effects on breast cancer cell chemoresistance to Tax and Adr *in vitro*. This discovery might provide prognostic value for breast cancer treatment. Further studies involving animals is essential to verify the significance of MALAT1 in breast cancer treatment and the detailed mechanisms. Since lncRNAs have been identified to be imperative therapeutic targets for breast cancer, it is of great importance to abundantly investigate and recognize the mechanism regarding MALAT1 in chemoresistance.

Availability of data and materials

All the data generated or analyzed during this study are included in this published article.

Conflict of interest

None.

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