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ORIGINAL RESEARCH

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CELSR1 enhances doxorubicin resistance by activating the WNT/PCP signaling pathway in breast cancer cells

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Abstract

Doxorubicin (Dox) is a widely used chemotherapy drug to inhibit the growth and survival of human breast cancer (BC) cells. Presently, there is a pressing need for the development of new therapeutic strategies to enhance Dox efficacy by overcoming the resistance exhibited by breast cancer cells. Cadherin EGF LAG seven-pass G-type receptor 1 (CELSR1), belonging to the Flamingo subfamily, has been implicated in the progression of various tumors. However, the specific role and mechanisms of CELSR1 in the resistance of breast cancer to drug treatments have yet to be fully understood. This study aims to clarify the role of CELSR1 in conferring resistance to doxorubicin in breast cancer. Our findings demonstrate that CELSR1 expression is elevated in breast cancer tissues. Silencing of CELSR1 significantly reduced the proliferation and motility of breast cancer cells. Moreover, the ablation of CELSR1 decreased the resistance of breast cancer cells to doxorubicin treatment. At the molecular level, CELSR1 was found to activate the Wnt/Planar Cell Polarity (WNT/PCP) signaling pathway in breast cancer cells. In conclusion, CELSR1 plays a crucial role in promoting the migration of breast cancer cells and in enhancing their resistance to doxorubicin through the activation of the WNT/PCP pathway.

Keywords

Breast cancer (BC); Cancer multidrug resistance; Doxorubicin (Dox); CELSR1; WNT/PCP pathway

1. Introduction

Breast cancer (BC) is one of the most common cancers worldwide, significantly impacting women's health [1]. Despite advancements in therapeutic interventions, BC remains the second leading cause of cancer-related deaths [1, 2]. The incidence and mortality associated with breast cancer are increasing in China, representing approximately one-tenth of the global annual new cases and deaths [3]. Current therapeutic strategies for BC include surgery, radiation, chemotherapy, hormone therapy and targeted therapy. Treatment selection is based on the specific characteristics and stage of the cancer. However, the development of drug resistance, especially to chemotherapy, presents a substantial challenge. Mechanisms of drug resistance in BC typically involve changes in drug targets, upregulation of efflux pumps, alterations in DNA repair mechanisms, disruption of apoptosis pathways, and activation of cell survival signals, highlighting the need for continued research to identify effective treatment strategies [4]. Doxorubicin (Dox) is a widely utilized chemotherapy agent that inhibits the growth and survival of breast cancer cells [5]. Approaches to address Dox resistance include altering the therapeutic regimen, increasing drug dosage, and employing combination therapies [6]. However, the development of intrinsic and acquired resistance to Dox is a common obstacle in breast cancer treatment, often leading to disease recurrence [5]. Inflammation has been identified as a significant factor in the progression of breast cancer, contributing to the development of drug resistance. Persistent inflammation can foster a tumor microenvironment that promotes cancer cell survival and proliferation, thereby diminishing the effectiveness of therapeutic agents and facilitating resistance [5]. Therefore, exploring new therapeutic strategies to improve the efficacy of Dox by overcoming breast cancer cell resistance is imperative.

CELSR1, a component of the Flamingo subfamily [7], also participates in the Planar Cell Polarity (PCP) pathway [8]. Existing literature has documented the elevated expression of CELSR1 across various cancers, including glioma, lung cancer, colorectal cancer and skin cancer, in facilitating tumor cell migration and invasion by activating pathways such as WNT/PCP (Wnt/Planar Cell Polarity) [9, 10]. Specifically, circ_CELSR1 has been shown to enhance paclitaxel resistance in ovarian cancer by modulating the miR-149-5p/salt-inducible kinase 2 (SIK2) axis [9]. In the context of glioma, CELSR1 acts as an oncogene, promoting cell growth and motility, a process mediated by miR199a-5p [11]. Furthermore, CELSR1 has been implicated in the increased invasion of lung adenocarcinoma by promoting tumor cell migration and enhanc-

ing endothelial cell permeability [12]. Given its regulatory role in WNT/PCP signaling, CELSR1 is considered a promising target for developing innovative cancer therapies [12]. Nonetheless, the specific role and mechanism of CELSR1 in conferring drug resistance in breast cancer remain to be elucidated, highlighting the need for additional research in this area.

This study aims to delineate the role of CELSR1 in breast cancer Dox resistance and hypothesize that CELSR1 promotes breast cancer cell migration and contributes to Dox resistance via the WNT/PCP pathway. Comprehensive investigations encompassing bioinformatic analysis were conducted to explore CELSR1-related signaling pathways, cell culture and transfection for manipulating CELSR1 expression, immunoblot assays to detect changes in protein expression, cell counting kit-8 (CCK-8) assays for assessing cell viability, colony formation assays to evaluate proliferative capacity, transwell assays for migration and invasion analysis, and apoptosis assays to quantify cell death, aiming to provide an in-depth understanding of CELSR1's functionality in breast cancer cells and its potential viability as a therapeutic target.

2. Materials and methods

2.1 Bioinformatic analysis

The GEPIA database (http://gepia.cancer-pku.cn/) was used to analyze CELSR1 expression in BC tissues from the The Cancer Genome Atlas (TCGA) database.

2.2 Cell culture and transfection

The human breast epithelial cell line MCF-10A and two types of BC cells, MCF-7 (HTB-22) and MDA-MB-231 (HTB-26), were purchased from the American Type Culture Collection (ATCC) and cultured in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% fetal bovine serum (FBS). The cells were incubated at 37 °C in an atmosphere containing 5% CO_2, and the experiments were performed as previously described [8].

For gene silencing experiments, CELSR1-specific siRNAs (Riobio) were transfected into BC cells using Lipofectamine® 3000 (L3000150, Invitrogen, Massachusetts, MA, USA). A mixture of 10 μL of siRNAs and 3 μL of Lipofectamine® 3000 was prepared and incubated for 20 minutes before being introduced into the cells. Four hours post-transfection, the culture medium was replaced and the BC cells were treated with dox (Dox, 1.0 μmol/L, catalog number 246-818-3, Merck, New Jersey, USA) for 24 hours.

2.3 Immunoblot assay

The protein concentration was quantified using the Bicinchoninic Acid (BCA) method as previously described [9]. Briefly, the cells were separated using 10% Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis (SDS-PAGE) and transferred onto the Polyvinylidene Difluoride (PVDF) membranes. The proteins were blocked with 5% milk, and then the corresponding primary antibodies including CELSR1 (ab225889; 1:500, Abcam, Cambridge, England, UK), Wnt5a (ab235966; 1:500), Ror2 (ab309483; 1:500), c-Jun (ab40766; 1:1000) and Glyceraldehyde 3-Phosphate Dehydrogenase (GAPDH, ab8245; 1:3000) were added. GAPDH was used as the internal reference. Lastly, the membranes were incubated with secondary antibodies for another 1 hour and the signals were then detected.

2.4 CCK-8 assay

The assay was conducted as previously described [9]. Briefly, BC cells were plated onto 96-well plates for 24 h, followed by incubation with CCK-8 (C0038, Beyotime, Beijing, China) for 4 hours and the Optical Density (OD450) value was measured using a microplate reader (Epoch 2, BD, Becton, Dickinson and Company, Franklin Lakes, NJ, USA).

2.5 Colony formation assay

The assay was performed in alignment with the methodology outlined in a previous study [10]. BC cells were seeded into 6-well plates at a density of 1000 cells per well and cultured for 14 days. Subsequently, the cells were fixed with paraformaldehyde (PFA) for 20 minutes and stained with 0.1% crystal violet (P0033, Beyotime, Beijing, China) for another 20 minutes before being photographed.

2.6 Transwell assay

The transwell assay was performed following the protocol described in a previous study [8]. BC cells were allowed to migrate through the transwell membrane for 24 hours, then the cells that invaded the upper chamber were fixed and stained with 2% crystal violet. Images of the stained cells were captured using a fluorescence microscope (A1, Zeiss, Oberkochen, Germany).

2.7 Apoptosis assay

The cells were fixed with 70% ethanol at −20 °C for 2 hours. Then, the cells were stained with propidium iodide (PI) and Annexin-V and analyzed using a FACSCalibur flow cytometer (FACSCalibur, BD, Franklin Lakes, NJ, USA).

2.8 Statistical analysis

GraphPad Prism (GraphPad Software, Inc., San Diego, CA, USA) version 5.0 software was utilized for statistical analysis. Data are presented as mean ± standard deviation (SD). Differences among groups were evaluated using one-way analysis of variance (ANOVA) followed by Tukey's Honestly Significant Difference (HSD) test. The assignment of groups was blinded until after the statistical analysis was completed. $p < 0.05$ was considered statistically significant.

3. Results

3.1 Overexpression of CELSR1 in BC

To elucidate the role of CELSR1 in breast cancer (BC), we assessed its expression levels using the GEPIA database. Notably, CELSR1 expression in 1085 tumor tissues was significantly elevated compared to that in 291 normal tissues

(Fig. 1A). Further analysis of protein levels of CELSR1 was conducted in the human breast cell line MCF-10A and two types of BC cells, MCF-7 and MDA-MB-231. The findings confirmed elevated expression of CELSR1 in BC cells (Fig. 1B), indicating that CELSR1 is highly expressed in human BC.

3.2 Depletion of CELSR1 suppressed the growth and motility of BC cells

CELSR1 siRNAs were initially transfected into BC cell lines, MCF-7 and MDA-MB-231. Immunoblot assays demonstrated that siCELSR1 transfection significantly reduced CELSR1 levels in both MCF-7 and MDA-MB-231 cells (Fig. 2A). Cell viability assays (CCK-8) revealed that CELSR1 depletion led to a decrease in cell viability, as evidenced by reduced OD450 values at 24, 48 and 72 hours (Fig. 2B). Moreover, colony formation assays showed that CELSR1 depletion resulted in a lower number of colonies in both MCF-7 and MDA-MB-231 cells (Fig. 2C). The inhibition of CELSR1 also reduced BC cell invasion capabilities (Fig. 2D). Collectively, these results indicate that the knockdown of CELSR1 inhibited the growth and motility of BC cells.

3.3 CELSR1 ablation restrained the Dox-resistance of BC cells

Following this, the impact of CELSR1 ablation on the resistance of BC cells to Dox was assessed. Upon treating MCF-7 and MDA-MB-231 cells with Dox, the effects of CELSR1 ablation on cell growth were examined using CCK-8 assays, and it was observed that CELSR1 ablation significantly inhibited the growth of Dox-treated MCF-7 and MDA-MB-231 cells (Fig. 3A). Furthermore, FCM assays demonstrated that CELSR1 knockdown increased the apoptosis rate of MCF-7 and MDA-MB-231 cells following Dox treatment (Fig. 3B). Hence, it is inferred that CELSR1 ablation mitigated the resistance of BC cells to Dox.

3.4 CELSR1 promotes WNT/PCP pathway in BC cells

Lastly, the mechanism via which CELSR1 influences the Dox resistance in BC was examined. Immunoblot assays revealed that CELSR1 knockdown resulted in reduced expression of Wnt5a, Ror2 and c-Jun, all of which are key regulators of the WNT/PCP pathway, in both MCF-7 and MDA-MB-231 cells (Fig. 4). This finding confirms the involvement of CELSR1 in modulating the WNT/PCP signaling pathway in BC cells, indicating that CELSR1 activation of this pathway is a contributing factor to Dox resistance.

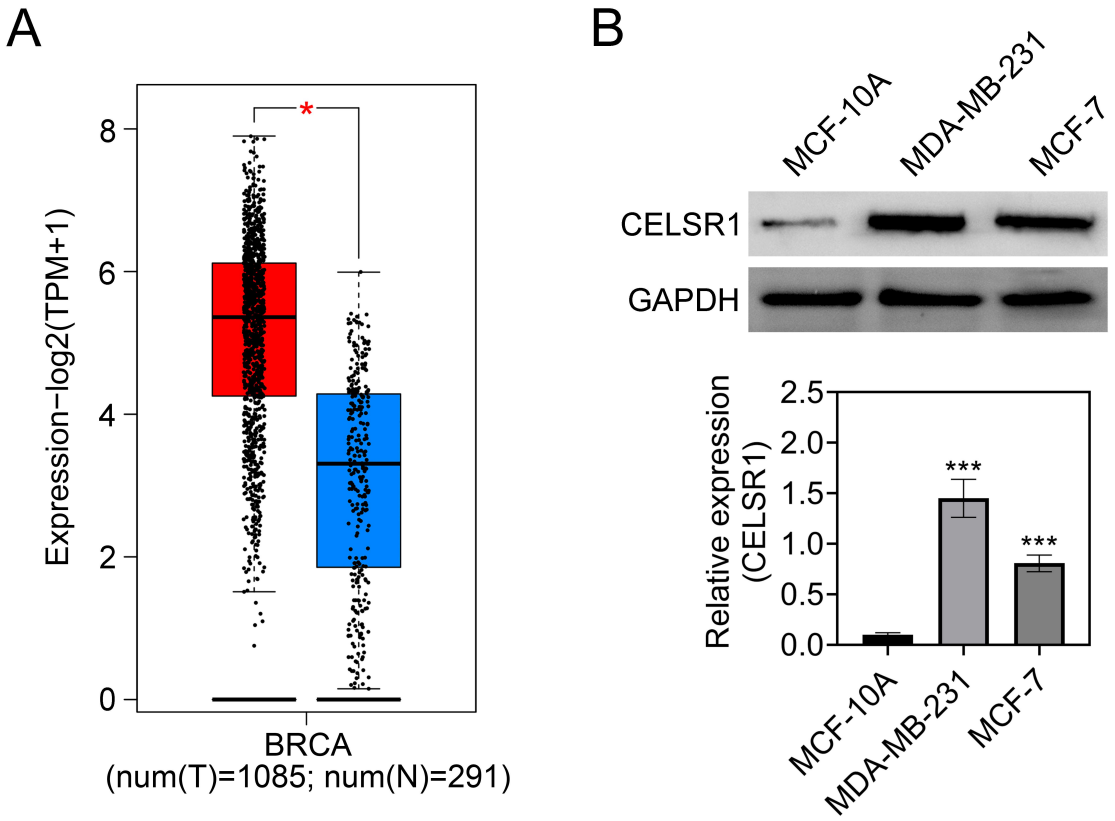

FIGURE 1. Overexpression of CELSR1 in BC cells and tissues. (A) Analysis of the GEPIA database reveals CELSR1 expression levels (transcripts per million) in 291 normal and 1085 breast cancer (BC) tissues. (B) Immunoblot assays demonstrate CELSR1 protein levels in MCF-10A (normal breast epithelial), MCF-7 and MDA-MB-231 (breast cancer) cell lines. *$p < 0.05$, ***$p < 0.001$. TPM+1: Transcripts per million plus one; BRCA: Breast cancer; CELSR1: Cadherin EGF LAG Seven-Pass G-Type Receptor 1; GAPDH: Glyceraldehyde-3-Phosphate Dehydrogenase.

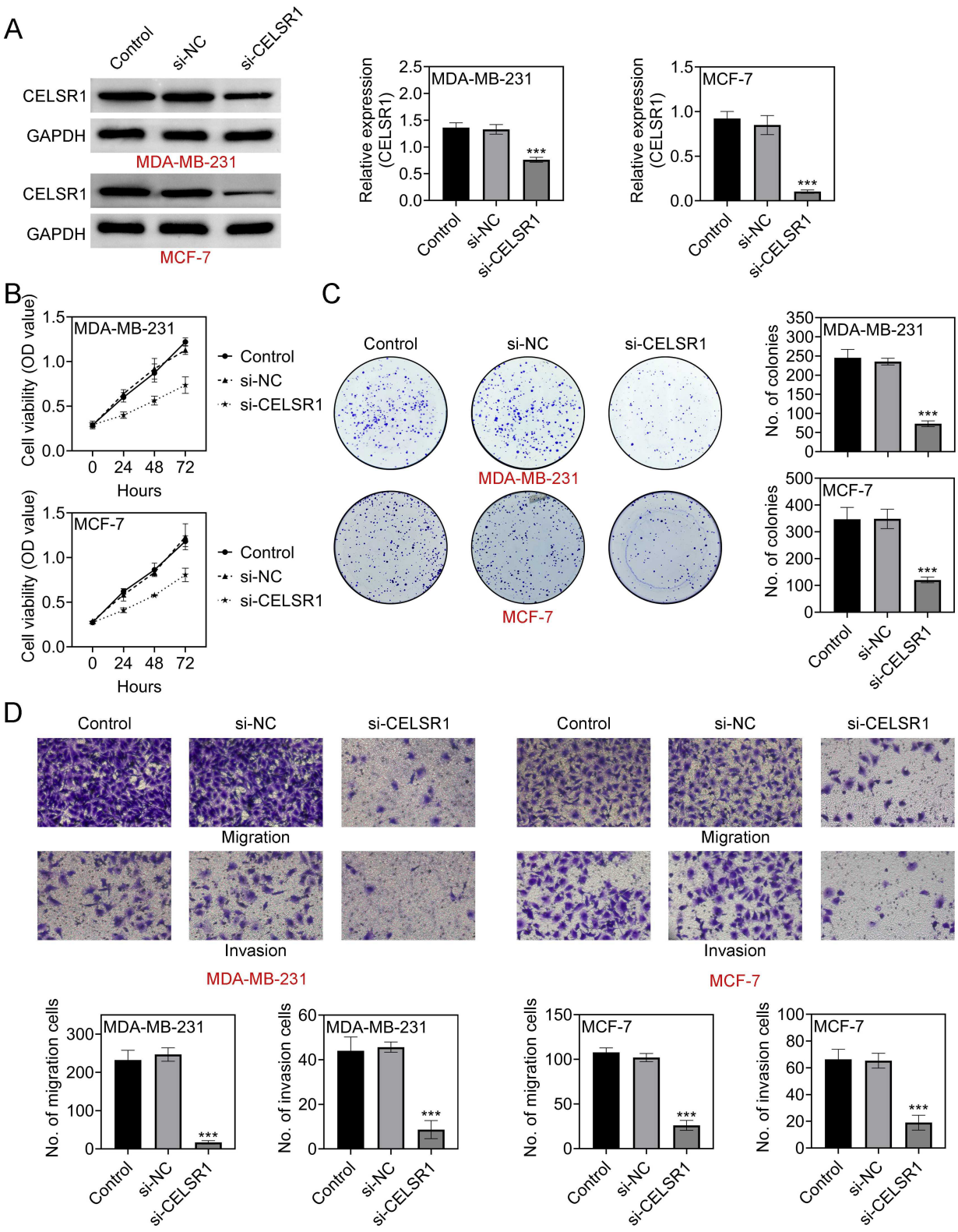

FIGURE 2. The depletion of CELSR1 suppressed the growth and motility of BC cells. (A) Immunoblot analysis of CELSR1 expression in MCF-7 and MDA-MB-231 cells post-transfection for 24 hours, with quantification of relative expression levels. (B) Cell growth of MCF-7 and MDA-MB-231 cells measured by CCK-8 assays at 24, 48 and 72 hours post-transfection, with OD450 values recorded. Six replicates per group were conducted. (C) Colony formation assays assessing the growth of MCF-7 and MDA-MB-231 cells 24 hours post-transfection, including quantification of colony numbers. (D) Transwell assays evaluating the invasion capability of MCF-7 and MDA-MB-231 cells 24 hours post-transfection, with invasive cell numbers quantified and compared. NC: negative control; CELSR1: Cadherin EGF LAG Seven-Pass G-Type Receptor 1; GAPDH: Glyceraldehyde-3-Phosphate Dehydrogenase; OD: Optical Density. ***$p < 0.001$.

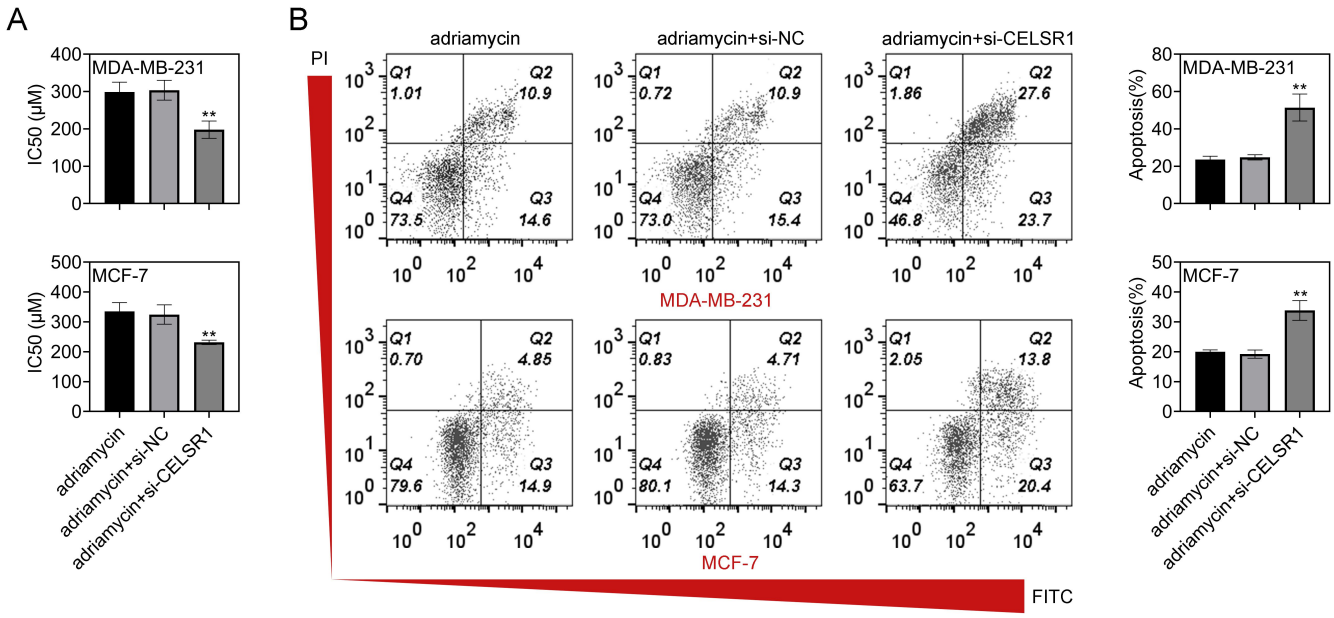

FIGURE 3. CELSR1 ablation restrained the Dox-resistance of BC cells. (A) CCK-8 assays assessing the growth of MCF-7 and MDA-MB-231 cells treated as indicated for 24 hours, with OD450 values measured and compared. Six replicates per group were conducted. (B) Flow cytometry (FCM) analysis of apoptosis in MCF-7 and MDA-MB-231 cells following the specified treatment for 24 hours, with the percentage of apoptotic cells compared. Three replicates per group were performed. NC: negative control; Dox: doxorubicin; IC50: Half Maximal Inhibitory Concentration; PI: Propidium Iodide; FITC: Fluorescein Isothiocyanate; si-CELSR1: Small Interfering RNA targeting Cadherin EGF LAG Seven-Pass G-Type Receptor 1. $^{**}p < 0.01$.

4. Discussion

The development of resistance to Dox, a key chemotherapeutic agent for breast cancer, poses a significant challenge to effective treatment [6]. Resistance mechanisms are complex, involving the overexpression of Adenosine Triphosphate (ATP)-binding cassette (ABC) transporters, alterations in cell death pathways, autophagy, and cell cycle arrest [5]. Triple-negative breast cancer (TNBC), characterized by the absence of estrogen, progesterone, and Human Epidermal Growth Factor Receptor 2 (HER2) receptors, is notably more resistant to chemotherapy, complicating its management [6]. Long-term exposure of TNBC cell lines to Dox has been associated with significant changes in gene expression and mutations, which may contribute to the emergence of drug resistance [6], suggesting potential biomarkers and therapeutic targets for combating resistance in breast cancer. Our present study reveals that CELSR1 may inhibit breast cancer cell migration and counteract Dox resistance, highlighting CELSR1 as a potential target for overcoming resistance to Dox in breast cancer treatments.

CELSR1, a member of the non-canonical cadherin family, plays critical roles in various biological processes, including cell adhesion, polarity and signaling pathways [8, 11, 12]. Its significance is particularly highlighted during developmental stages, notably in the nervous system's development and cell migration [13]. The involvement of CELSR1 in tumorigenesis has begun to draw attention, and research in this area remains in its early stages [11, 14]. It is suggested that CELSR1 may affect tumor cell behavior by modulating cell-cell interactions and various signaling pathways [11, 14]. Additionally, interactions between CELSR1 and immune cells within the tumor microenvironment may influence tumor immune evasion and responses to therapy [15, 16]. In this study, several assays were utilized to confirm CELSR1's role in the proliferation and mobility of breast cancer cells and its impact on resistance to Dox. While these findings shed light on the potential involvement of CELSR1 in breast cancer pathology and treatment resistance, further detailed molecular mechanisms remain to be elucidated. Future research directions should incorporate multidimensional omics approaches to identify downstream targets of CELSR1 and assess its effects on drug resistance in *in vivo* models, such as nude mouse xenografts.

In breast cancer, the WNT/PCP pathway regulates cell polarity, motility and tissue morphogenesis, and its dysregulation, either through activation or inhibition, can significantly influence the invasive and metastatic abilities of tumor cells [17]. Moreover, the WNT/PCP pathway interacts with other signaling pathways, such as the Transforming Growth Factor Beta (TGF-β), which further impacts the tumor microenvironment and cellular behaviors, highlighting its potential as a novel therapeutic target for breast cancer treatment [18]. Our study's findings support the notion that CELSR1 modulates breast cancer cell growth and motility through the WNT/PCP pathway, underscoring the importance of CELSR1 in the regulation of these processes.

Although there is no research regarding the association between the WNT/PCP pathway and Dox resistance in breast cancer, the critical functions of this pathway in cell polarity, migration, tissue morphogenesis and its potential implications on tumor development suggest a possible indirect impact on chemotherapy sensitivity [18]. For instance, the activation

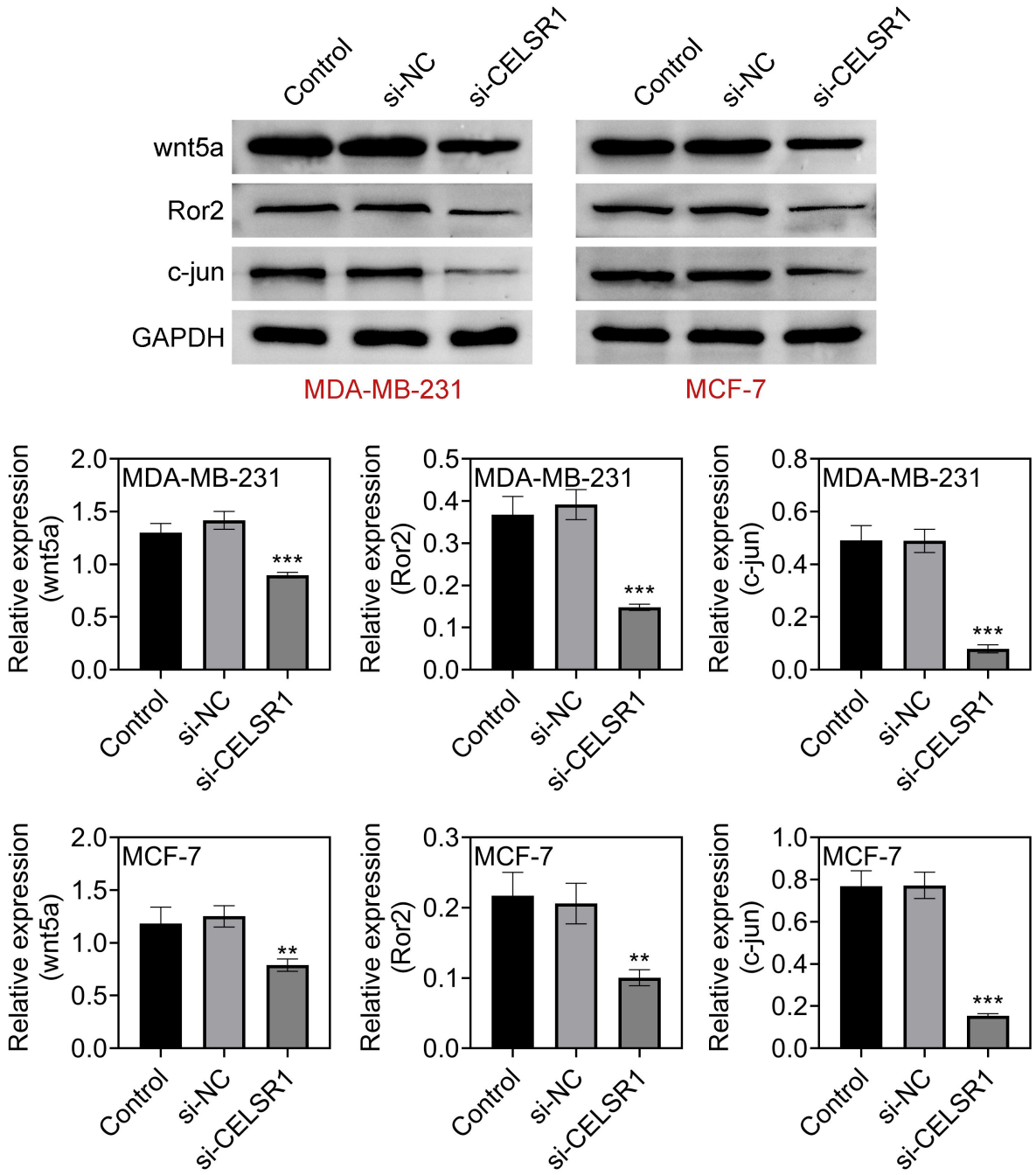

FIGURE 4. CELSR1 promotes WNT/PCP pathway in BC cells. Immunoblot assays showed the expression of Wnt5a, Ror2, and c-Jun in MCF-7 and MDA-MB-231 cells upon the indicated transfection for 24 h. The relative expression of Wnt5a, Ror2 and c-Jun was quantified and compared. Three repeats for each group was performed. NC: negative control; CELSR1: Cadherin EGF LAG Seven-Pass G-Type Receptor 1; GAPDH: Glyceraldehyde-3-Phosphate Dehydrogenase. $^{**}p < 0.01$, $^{***}p < 0.001$.

of the WNT/PCP pathway could theoretically promote tumor cell invasiveness and metastatic potential, attributes that might contribute to the development of resistance against chemotherapeutic agents like Dox [19]. The pathway's influence on breast cancer encompasses the regulation of cell migration, invasion, and properties of cancer stem cells, all of which are factors that contribute to the tumor's aggressiveness and metastatic capability. Moreover, aberrant activation of the WNT/PCP pathway is linked to adverse prognosis and resistance to chemotherapy, highlighting the importance of targeting this pathway as a novel therapeutic approach to curb tumor progression and enhance the efficacy of treatments in breast cancer [19]. Herein, our study provides initial insights suggesting that CELSR1 may mediate Dox resistance in breast cancer cells through its effects on the WNT/PCP pathway, pointing to the need for further investigation into the specific mechanisms at play.

CELSR1 overexpression is often correlated with increased invasiveness and adverse prognosis in breast cancer and contributes to tumor proliferation, migration and invasion by activating signaling pathways, notably the WNT/PCP pathway [15]. Furthermore, increased CELSR1 levels are associated

with enhanced resistance of breast cancer cells to chemotherapeutic agents such as Dox, which may result from various mechanisms, including changes in drug internalization, enhanced drug efflux, reduced apoptosis, and heightened activation of DNA repair pathways [17]. CELSR1's influence may extend to altering the responsiveness of breast cancer cells to a range of chemotherapy drugs, affecting the expression of Multidrug Resistance (MDR) proteins and the metabolism of drugs. Beyond its role in breast cancer, CELSR1's impact has been observed in other types of tumors, including lung cancer, colorectal cancer, and glioma [15, 17–19]. Given these findings, CELSR1 emerges as a promising target for therapeutic intervention. Subsequent research and the development of new therapeutic strategies should concentrate on creating CELSR1 inhibitors or modulators to improve chemotherapy efficacy in breast cancer and other malignancies characterized by high CELSR1 expression.

The main limitations include the need for more detailed investigations into the molecular mechanisms and the application of comprehensive omics approaches to verify downstream genes and their impact on drug resistance. Future research should prioritize validating these findings *in vivo*, especially using tumor xenograft models in nude mice, to deepen our understanding of CELSR1's involvement in drug resistance mechanisms. Additionally, examining CELSR1's interactions with the tumor microenvironment, with a particular focus on its role in tumor immune evasion and response to therapy, would offer broader insights.

5. Conclusions

In summary, our findings indicate that CELSR1 plays a significant role in promoting BC cell migration and conferring resistance to Dox, primarily through the WNT/PCP signaling pathway. Therefore, targeting CELSR1 could represent a novel strategy to combat drug resistance in breast cancer.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

LL—designed the study and carried them out. LL, HTL, MHS and AA—supervised the data collection, analyzed the data, interpreted the data. LL and BLM—prepared the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This article does not contain any studies with human participants or animals performed by any of the authors.

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Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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