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LncRNA AC093850.2 predicts poor outcomes in patients with triple-negative breast cancer and motivates tumor progression by sponging miR-4299

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Background: Accumulating evidence displays that non-coding RNAs (ncRNAs) are involved in the progression of triple-negative breast cancer (TNBC). This study aimed to investigate the role of lncRNA AC093850.2 in TNBC. Methods: The AC093850.2 levels were compared using RT-qPCR in TNBC tissues and corresponding normal tissues. The Kaplan-Meier curve method was conducted to assess the clinical significance of AC093850.2 in TNBC. Bioinformatic analysis was used to predict potential miRNA. Cell proliferation and invasion assays were carried out to explore the function of AC093850.2/miR-4299 in TNBC. Results: lncRNA AC093850.2 expression is raised in TNBC tissues and cell lines, which is related to the shorter overall survival of patients. AC093850.2 is directly bound to miR-4299 in TNBC cells. Downregulation of AC093850.2 reduces tumor cell proliferation, migration, and invasion abilities, while miR-4299 silence attenuated AC093850.2 silencing induced inhibition of cellular activities in TNBC cells. Conclusion: In general, the findings suggest that lncRNA AC093850.2 was closely related to the prognosis and progression of TNBC by sponging miR-4299, which might be a prognosis predictor and potential target for treating TNBC patients.

Keywords: AC093850.2, triple-negative breast cancer, miR-4299, prognosis, progression

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Abbreviations: GEPIA, Gene Expression Profiling Interactive Analysis; lncRNA, long non-coding RNA; miRNA, microRNA; ncRNAs, non-coding RNAs; ST6GALNAC4, alphaN-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-*N*-acetylgalactosaminide alpha-2,6-sialyltransferase 4; TNBC, triple-negative breast cancer

INTRODUCTION

The incidence and mortality of breast cancer have obvious regional variations around the world (Azamjah *et al.*, 2019). In recent years, the incidence of breast cancer in China has been increasing year by year, and women tend to be younger (Li *et al.*, 2016). The etiology of breast cancer is complex and closely related to a variety of genetic and non-genetic factors (Cappetta *et al.*, 2021). Studies have manifested that being unmarried, childless, on high-fat diet, obese, having multiple x-rays and obvious benign breast diseases are all risk factors for the occurrence of breast cancer (Rojas & Stuckey, 2016; Sun *et al.*, 2017). Currently, surgical resection and chemotherapy are the main treatments for breast cancer. However, breast cancer has the characteristics of being highly metastatic and spreads easily through lymphatic metastases (Kim, 2021). Breast cancer patients are prone to recurrence after surgical treatment, and the quality of life is also low, which seriously affects the clinical effect of breast cancer prevention and treatment. Among the subtypes of breast cancer, triple-negative breast cancer (TNBC) has a higher risk of recurrence and metastasis (Yin *et al.*, 2020). Due to the obvious heterogeneity of TNBC and the lack of expression of ER, PR, and HER-2, the clinical treatment is more difficult, so the survival rate of TNBC patients is not significantly improved (Yin *et al.*, 2020). Therefore, it is of great significance to explore effective methods and strategies for improving the prevention and treatment of breast cancer.

The functions of non-coding RNA (ncRNA) genes have attracted more attention in normal physiological functions and pathological processes (Panni *et al.*, 2020). ncRNAs are a general term for RNA that are not participating in protein-coding, such as long non-coding RNA (lncRNA) and microRNA (miRNA) (Yang *et al.*, 2020; Zhao *et al.*, 2020). With the continuous in-depth study of ncRNA, it was unexpectedly discovered that the mutation or differential expression of ncRNA is related to the occurrence and progression of many diseases (Anastasiadou *et al.*, 2017). Currently, the role of lncRNA in the process of cell proliferation, differentiation, and disease occurrence has received more and more attention (Mori *et al.*, 2018; Romano *et al.*, 2017). LncRNAs are relatively non-conservative in evolution and can regulate cellular activities at multiple levels, including chromatin modification, transcriptional level, and post-transcriptional level regulation (Barreca *et al.*, 2021). The abnormal lncRNA expression can not only affect tumor growth and metastasis but also serve as indicators for clinical detection and treatment (Schmitt & Chang, 2016; Wang *et al.*, 2017). Several lncRNAs are reported to be involved in the progression of breast cancer, such as NR2F1-AS1 (Zhang *et al.*, 2020), H19, and NEAT1 (Müller *et al.*, 2019). LncRNA AC093850.2 expression was increased in lung adenocarcinoma (Qiu *et al.*, 2015) and gastrointestinal esophageal cancer (Su *et al.*, 2022). A previous study reported that AC093850.2 has prognostic significance for breast cancer based on Gene Expression Profiling Interactive Analysis (GEPIA) (Zhang *et al.*, 2019), while its involvement in TNBC is elusive.

Herein, we investigated the role of AC093850.2 in the progression of TNBC. The expression of AC093850.2 was increased in TNBC tissues. miR-4299 functions as a suppressive miRNA in some types of cancer, such as lung cancer (Yang *et al.*, 2018). We observed that AC093850.2 functioned as the sponge of miR-4299 to regulate the progression of TNBC. Thus, the increased expression of

AC093850.2 may serve as a prognostic marker for TNBC patients and be a novel potential therapeutic target.

MATERIALS AND METHODS

Specimen source

A total of 135 cases of TNBC tissues and corresponding paracentral tissue specimens were collected from Weifang People's Hospital from January 2014 to December 2016 and stored in liquid nitrogen until use. All patients signed the informed consent. This study was approved by the Ethics Committee of Weifang People's Hospital. The inclusion criteria: 1) patients were first onset and initial operation; 2) patients were pathologically diagnosed as TNBC; 3) patients have a complete medical history and five-year follow-up information. The median age of patients was 50.5 years, ranging from 29 to 82 years.

Cell lines and transfection

TNBC cell lines (BT549, MDA-MB-231, and HCC1937), other subtypes of breast cancer cell lines (SKBR3, MCF7, BT474), and normal breast epithelial cell line MCF-10A were acquired from ATCC and were stored in our laboratory. Cells were cultured in a DMEM medium (Gibco) containing 10% FBS (Hyclone) in a 5% CO_2 incubator at 37°C, and the medium was changed every 48–72 h. The cells in good conditions were cultured in 6-well plates until the logarithmic growth period.

MDA-MB-231 and HCC1937 cells were used for cell transfection. The AC093850.2 siRNA (si-AC093850.2), siRNA NC, miR-4299 mimic, mimic negative control (mimic NC), miR-4299 inhibitor (inhi-miR-4299), inhibitor NC were obtained from GenePharma (Shanghai, China). These vectors were transfected or co-transfected into TNBC cells using Lipofectamine 2000 reagent.

RNA isolation and RT-qPCR

Total RNA was prepared from tissue specimens and cell lines using a pre-cooled Trizol isolation kit (Invitrogen) and cDNA synthesis was performed using a Transcriptor First Strand cDNA Synthesis Kit (Roche, Mannheim, Germany) for lncRNA and a miRVana miRNA isolation kit (Applied Biosystems) for miRNA. Then cDNA was amplicated by RT-qPCR using an SYBR Green PCR Kit (TaKaRa) for lncRNA or miRCURY LNA miRNA SYBR Green PCR kit (Qiagen) for miRNA. GAPDH and U6 were used as normalization controls. The relative levels of lncRNA and miRNAs were calculated by the comparative Ct method.

MTS assay for cell proliferation

Cell proliferation rate was evaluated using an MTS assay. The cells (3000 cells/well) were incubated in 96-well plates at 37°C. After 24, 48, and 72 h of incubation, the MTS reagent (Promega) was added to the well in a dark environment and incubated in the incubator for 2 h. After incubation, the absorbance value (OD value) of each well was detected at 490 nm by the microplate reader (BioRad).

Transwell assays

For migration and invasion assays, a 24-well Transwell chamber (8 μm core; Corning, NY) was adopted to carry out the experiments. The membrane in the upper chamber of the transwell was precoated with Matrigel (BD), which was used for the evaluation of the invasion abilities of tumor cells. The migration assay does not need to be precoated with Matrigel. The serum-free medium was used to incubate the cells (1×10^5 cells) in the top chamber, and a 600 μl culture medium with 10% FBS was included in the lower chamber. The invading and migrating cells were fixed, stained, and counted with a microscope (Olympus).

Dual-luciferase reporter assay

The 3'UTR of AC093850.2 fragment with miR-4299 binding sites was inserted into the pmirGLO dual-luciferase vector (Promega) and named as AC093850.2 3'-UTR WT. The mutant 3'UTR of AC093850.2 was subcloned into pmirGLO and named as AC093850.2 3'UTR MUT. The WT or MUT fragment was co-transfected with miR-4299 mimic, or mimic NC into TNBC cells for 48 h. The luciferase activities were detected using a Dual-luciferase reporter assay kit (KeyGen, China).

Statistical analysis

Results were acquired from at least three independent experiments and were presented as mean ± S.D. The significance was assessed by the SPSS and GraphPad Prism software using the χ^2 test, Student's *t*-test, or one-way ANOVA. The survival rates and clinical prognostic value were evaluated by the Kaplan-Meier method and multivariate Cox regression analysis. The difference was considered statistically significant when $P<0.05$ for all statistical analyses.

RESULTS

High AC093850.2 expression was related to clinicopathological parameters and shorter overall survival

The expression of AC093850.2 was monitored using RT-qPCR in 135 pairs of tissue specimens. AC093850.2

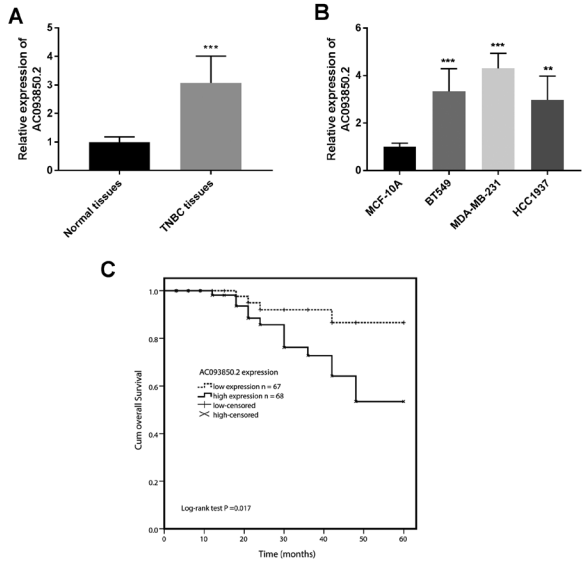

Figure 1. Increased expression of AC093850.2 was related to the shorter overall survival of TNBC patients.
(**A**) The expression level of AC093850.2 in paired tumor tissues and normal tissues was analyzed by RT-qPCR. ***$P<0.001$. (**B**) The expression level of AC093850.2 in TNBC cell lines was measured by RT-qPCR. **$P<0.01$, ***$P<0.001$. (**C**) The Kaplan-Meier curve was conducted to assess the survival outcome of AC093850.2 in TNBC (log-rank test, $P=0.017$).

Table 1. Association of LncRNA AC093850.2 expression and clinicopathological parameters of TNBC patients

Variable	Cases (n=135)	AC093850.2 expression		*P*-value
		Low (n=67)	High (n=68)	
Age (years)				0.436
≤ 50	70	37	33	
> 50	65	30	35	
Tumor size (cm)				0.048
≤ 2	61	36	25	
> 2	74	31	43	
Pathological stage				0.098
I-II	75	42	33	
III	60	25	35	
Lymph node metastasis				0.007
Negative	75	45	30	
Positive	60	22	38	
TNM stage				0.001
I-II	77	48	29	
III	58	19	39	
Ki67				0.024
≤ 14%	86	49	37	
> 14%	49	18	31	

expression was upregulated in TNBC tissues ($P<0.001$, Fig. 1A). Further, the higher AC093850.2 expression was observed in TNBC cell lines (BT549, MDA-MB-231, and HCC1937) as shown in Fig. 1B ($P<0.01$). The expression of AC093850.2 in other subtypes of breast cancer cells was measured. The expression of AC093850.2 was also increased in other subtypes of breast cancer (SKBR3, MCF7, BT474) ($P<0.01$, Supplementary Fig. 1 at https://ojs.ptbioch.edu.pl/index.php/abp/), but not as high as that in TNBC cells except for SKBR3 cell.

The χ^2 test was used to evaluate whether the expression of AC093850.2 was associated with the clinical characteristics of TNBC patients. The results in Table 1 indicated that high expression of AC093850.2 was related to the aggressive characteristics of TNBC, including positive lymph node metastasis ($P=0.007$), advanced TNM stage ($P=0.001$), larger tumor size ($P=0.048$), and high Ki67 level ($P=0.024$). The data suggest that AC093850.2 was potentially associated with a higher risk of disease, which may be correlated with patients' survival. The clinical analysis verified high AC093850.2 expression in correlation with poor survival data of patients with TNBC (log-rank $P=0.017$, Fig. 1C). These results revealed that AC093850.2 upregulation may participate in the progression of TNBC and be potentially a valuable prognostic predictor for this disease. Moreover, multivariate Cox regression analysis included clinical characteristics and AC093850.2 expression in the evaluation of prognostic-related risk factors in TNBC. The results in Table 2 revealed that age and pathological stage were not independent risk factors for prognosis of patients, while AC093850.2 expression, tumor size, lymph node metastasis, TNM stage, and Ki67 were independent risk factors for the shorter prognosis of TNBC patients.

LncRNA AC093850.2 targeted miR-4299 and regulated its expression

Bioinformatics prediction (LncBase Predicted v.2) showed that AC093850.2 could potentially bind to several miRNAs, including miR-4299. Among these miRNAs, miR-4299 expression was found to be increased in AC093850.2-knockdown TNBC cells, as shown in Fig. 2A ($P<0.001$). The targeting relationship between AC093850.2 and miR-4299 was displayed in Fig. 2B.

Table 2. Multivariate Cox analysis of factors for survival of TNBC patients

Variables	Multivariate Cox analysis		
	HR	95%CI	*P* value
AC093850.2 expression (low *vs* high)	0.226	0.060–0.846	0.027
Age (≤50 *vs* >50 years)	0.447	0.160–1.246	0.124
Tumor size (≤2 *vs* >2 cm)	0.202	0.044–0.920	0.039
Pathological stage (I–II *vs* III)	0.449	0.149–1.349	0.154
Lymph node metastasis (Negative *vs* Positive)	0.177	0.036–0.865	0.032
TNM stage (I–II *vs* III)	0.269	0.083–0.870	0.028
Ki67 (≤14% *vs* >14%)	0.305	0.099–0.939	0.039

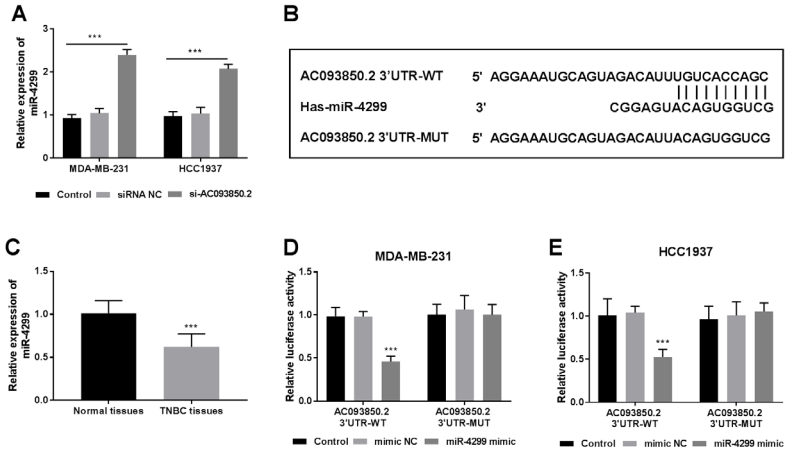

Figure 2. AC093850.2 directly binds to miR-4299 in TNBC cells.
(**A**) miR-4299 was increased in AC093850.2 silenced cells. ***P<0.001. (**B**) Sequencing alignment showed putative binding sites between AC093850.2 and miR-4299. (**C**) The expression of miR-4299 was detected using RT-qPCR in TNBC tissues. ***P<0.001. (**D**) Overexpression of miR-4299 decreased relative luciferase activity of AC093850.2-WT but not AC093850.2-MUT in MDA-MB-231 cells. ***P<0.001. (**E**) Increased expression of miR-4299 reduced relative luciferase activity of AC093850.2-WT but not AC093850.2-MUT in HCC1937 cells. ***P<0.001.

Whereafter, the downregulation of miR-4299 expression in TNBC tissues was observed compared with that in normal tissues (P<0.001, Fig. 2C). The dual-luciferase reporter assay validated the binding relationship between AC093850.2 and miR-4299 and the results demonstrated that the luciferase activity of cells co-transfected with AC093850.2-WT and miR-4299 mimic was decreased (P<0.001), while no significant changes were observed in cells co-transfected with AC093850.2-MUT and miR-4299 mimic (Fig. 2D and 2E). The above results revealed that AC093850.2 targeted and regulated the expression of miR-4299.

Silence of AC093850.2 weakened cell proliferation possibly by regulating miR-4299

After transfection, downregulation of AC093850.2 by si-AC093850.2 reached more than 200% in cells of both TNBC cell lines (P<0.001, Fig. 3A). Silence of AC093850.2 led to the increased expression of miR-4299 in both cell lines, while downregulation of miR-4299 restrained the increased levels of miR-4299 by si-AC093850.2 (P<0.001, Fig. 3A).

Results of cell proliferation experiments indicated that silencing AC093850.2 inhibited proliferation abilities, while knockdown of miR-4299 reversed the inhibitory effect of si-AC093850.2 on the proliferation of cancer cells (P<0.05, Fig. 3B).

Influence of knockdown of AC093850.2 on cellular migration and invasion activities by regulating miR-4299

Following the above cellular experiments, Transwell assays were performed to evaluate the influence of si-AC093850.2 on cell migration and invasion capacities. Silencing of AC093850.2 expression effectively inhibited the migration of cells (P<0.001), whereas the im-

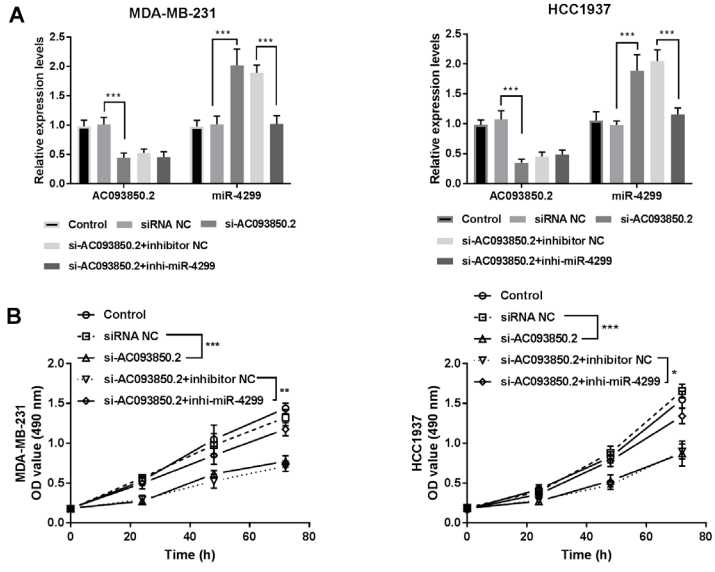

Figure 3. AC093850.2 acts as a ceRNA that regulate cell proliferation by sponging miR-4299.
(**A**) RT-qPCR analysis of AC093850.2 or miR-4299 expression in MDA-MB-231 and HCC1937 cells after transfection. ***P<0.001. (**B**) The proliferation abilities were inhibited by the knockdown of AC093850.2 while reversed by the silence of miR-4299. ***P<0.001.

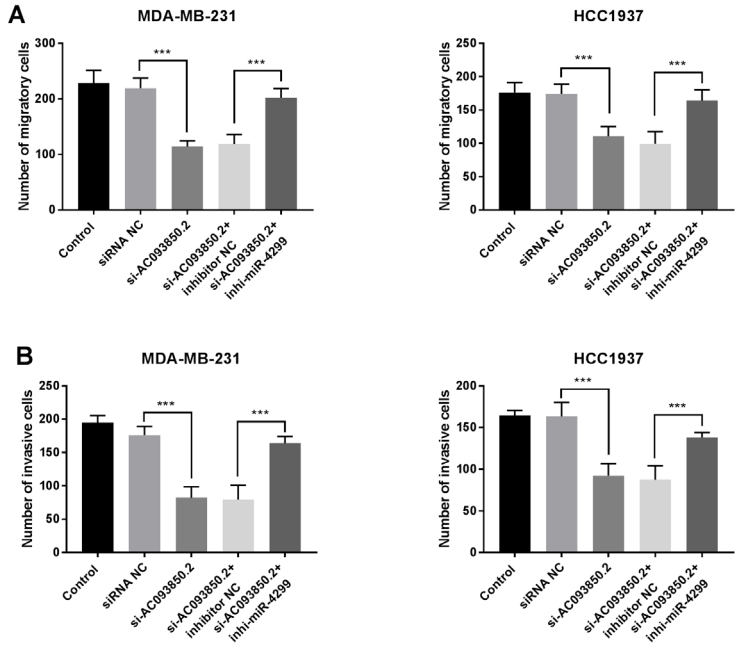

Figure 4. Downregulation of miR-4299 reverses the inhibition of migration and invasion potential in TNBC cells induced AC093850.2 silencing.
(**A**) A Transwell migration assay was conducted to determine the effects of AC093850.2/miR-4299 knockdown on cell migration. ***P<0.001. (**B**) Transwell invasion assay was performed to measure the effects of AC093850.2/miR-4299 silencing on cell invasion capacities. ***P<0.001.

pact of knockdown of AC093850.2 was reversed by a miR-4299 inhibitor (P<0.001, Fig. 4A). Similar results were observed in invasion assays (P<0.001, Fig. 4B). These data suggest that AC093850.2 interference is a towardly strategy to prevent TNBC progression by targeting miR-4299.

DISCUSSION

TNBC is difficult to cure, easy to relapse, and has a high metastasis rate, which has become a major problem in the treatment of breast cancer. Hence, exploring novel prognostic and therapeutic targets is extremely important for improving clinical strategies and outcomes for TNBC patients. Growing studies suggest that lncRNAs involved in tumor prognosis and progression have been identified (Huang *et al.*, 2021; Volovat *et al.*, 2020). For instance, lncRNA HAGLR (Jin *et al.*, 2021), CARMN (Sheng *et al.*, 2021), and Uc003xsl.1 (Xu *et al.*, 2022) were involved in the tumor progression of TNBC and were associated with patients' prognosis. In this study, we clarified the expression levels of AC093850.2 that were remarkably increased in TNBC tissues compared with corresponding paracancerous normal tissues. Similarly, the expression pattern of AC093850.2 was observed in TNBC cell lines. These results speculated that AC093850.2 may be involved in the regulation of the malignant evolution of TNBC. Interestingly, a high expression of AC093850.2 was observed in an HER-positive breast cancer cell line (SKBR3 cell), which imply that AC093850.2 may not have an actual impact only on TNBC. In this study, we mainly investigated the role of AC093850.2 in TNBC.

To further investigate the association between AC093850.2 and the clinical properties of TNBC, the clinicopathological characteristics of patients were gathered and statistically analyzed. The expression of AC093850.2 affected the tumor size, lymph node metastasis, TNM stage, and Ki67 of TNBC patients. However, TNBC is regulated by a variety of lncRNAs or other genes, and the expression levels of different lncRNAs in TNBC are not the same, and the relationship with the clinical characteristics of TNBC is not the same. For instance, serum lncRNA SUMO1P3 levels were related to positive lymphovascular invasion, lymph node metastasis, or high grade, but not related to tumor size (Na-Er *et al.*, 2021). Herein, further survival analysis revealed that TNBC patients with high AC093850.2 expression had a poor survival outcome. Multivariate Cox regression analysis revealed that AC093850.2 expression is a risk factor for the overall survival of TNBC patients. The clinical prognostic significance of AC093850.2 was reported in esophageal squamous cell carcinoma (Huang *et al.*, 2018). A previous differently identifying RNA expression profiles study indicated that AC093850.2 has a prognostic value for breast cancer (Zhang *et al.*, 2019). Similarly, results in this study validated the prognostic value of AC093850.2 in TNBC using a bunch of TNBC patients. Therefore, AC093850.2 may be an independent prognostic factor for TNBC.

lncRNAs could act as a competitive endogenous RNA to regulate miRNA function. For instance, lncRNA XLOC-006390 as a ceRNA facilitates cervical cancer tumorigenesis by inhibiting miR-331-3p and miR-338-3p (Luan & Wang, 2018). The expression of lncRNA PCED1B-AS1 expression is increased in colorectal adenocarcinoma tissues and knockdown of PCED1B-AS1 suppresses tumor progression by sponging miR-633 (Liu *et al.*, 2022). In this study, we used an online database to identify miRNAs with AC093850.2 binding sites, which showed a binding relationship between miR-4299 and AC093850.2. The expression of miR-4299 was increased in AC093850.2-silenced tumor cells. We also observed that AC093850.2 functions as a sponge for miR-4299 in

TNBC. We also observed that miR-4299 expression was downregulated in TNBC tumor tissues. These data revealed that lncRNA AC093850.2 may act as a ceRNA to regulate tumor progression of TNBC by inhibiting miR-4299 expression.

The role of lncRNAs in tumorigenesis and progression has been widely investigated. Further cellular experiments were conducted to explore the influence of AC093850.2/miR-4299 on the cellular activities of TNBC cells. miR-4299 was downregulated in non-small cell lung cancer tissues and restrained tumor cell proliferation, migration, and invasion by modulating the activation of the PTEN/AKT/PI3K signaling pathway (Yang *et al.*, 2018). The expression of miR-4299 was also decreased in follicular thyroid carcinoma cells and could mediate the invasive properties by targeting ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 4 (ST6GALNAC4) (Miao *et al.*, 2016). The current results revealed that knockdown of AC093850.2 restrained cell viability and migration of TNBC cells, whereas the impact of AC093850.2 knockdown was recovered by miR-4299 inhibitor, indicating that AC093850.2 interference is a towardly strategy to impede TNBC progression by targeting miR-4299.

There are some limitations of this study. This study mainly investigated the role of AC093850.2 in TNBC, but its impact on other subtypes of breast cancer remains to be explored. In future studies, other subtypes of breast cancer patients will be enrolled to explore the clinical role of AC093850.2 in other subtypes of breast cancer. On the other hand, the detailed mechanism of AC093850.2 in TNBC needs to be investigated in the future.

In general, lncRNA AC093850.2 was elevated in TNBC tissues and related to patients' prognosis. AC093850.2/miR-4299 suggests crosstalk between lncRNA and miRNA that might drive TNBC progression. This crosstalk between AC093850.2 and miR-4299 may reveal the mechanism of AC093850.2 in TNBC, which may be a potential target for TNBC treatment and prognosis prediction.

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