LINC01605 promotes aerobic glycolysis through lactate dehydrogenase A in triple-negative breast cancer

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Abstract
Breast cancer is the most prevalent cancer diagnosed in women and the major malignancy that threatens women health, thus we explored the role of long noncoding RNA LINC01605 in triple-negative breast cancer (TNBC). We collected tissue samples from TNBC patients and cultured breast cancer cells to detect LINC01605 levels by RT-PCR. We then constructed LINC01605 knockdown and LINC01605 overexpressed TNBC cell lines, cell proliferation was measured by CCK-8 and colony formation assays, cell migration and invasion were measured by Transwell assay, and aerobic glycolysis of cells was detected. Furthermore, a downstream target gene was found, and its role was confirmed by mouse allogeneic tumor formation. It discovered that LINC01605 expression was significantly increased in TNBC patients, and its high expression predicted a low survival prognosis for TNBC patients. Stable knockdown of LINC01605 remarkably inhibited cell proliferation, migration, and invasion, as well as aerobic glycolysis by inhibiting lactate dehydrogenase A in TNBC cell lines. Notably, knockdown of LINC01605 suppressed in vivo tumor formation and migration in TNBC transplanted mice. In conclusion, targeting long noncoding RNA LINC01605 might serve as a therapeutic candidate strategy to treat patients with TNBC.

KEYWORDS
aerobic glycolysis, breast cancer, LDHA, LINC01605, TNBC

1 | INTRODUCTION
Breast cancer occurs in the breast tissue due to the uncontrolled growth of the breast cells. Breast cancer is the most prevalent cancer diagnosed in women and also the major malignancy that threatens women’s health, accounting for 25% of all cancer incidences. Although breast cancer can occur in both men and women, it is far more common and harmful to women. Globally, millions of women develop breast cancer and more than 400,000 women die of breast cancer every year. Due to the substantial support for breast cancer awareness and research on the mechanism of breast cancer, helping create advances in the diagnosis and treatment of breast cancer,

Abbreviations: ceRNA, competing endogenous RNA; ECAR, extracellular acidification rate; HER2, human epidermal growth factor receptor 2; IncRNA, long noncoding RNA; LDHA, lactate dehydrogenase A; miR/miRNA, microRNA; TNBC, triple-negative breast cancer.

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breast cancer survival rates have increased, and the number of deaths associated with this disease is steadily declining.

Epidemiological data have indicated that the cumulative exposure of estrogen for a long time, such as early premature menopause, delayed menopause, and hormone replacement therapy, caused genetic and epigenetic changes that are important factors in inducing breast cancer. Approximately 70% of patients with breast cancer are clinically positive for estrogen receptor. 3–5 But approximately 10%–20% of breast cancer patients are diagnosed with TNBC, which is characterized by no expression of the three markers in breast cancer, namely estrogen receptor, progesterone receptor, and HER2. 6–9 Unlike hormone receptor-positive or HER2-positive breast cancer, TNBC is often accompanied by lymph node metastasis and higher breast cancer grades. 10 Additionally, until now, effective targeted drugs for TNBC have been relatively scarce, because hormone therapies target one of these three receptors. Therefore, compared to other breast cancer subtypes, TNBCs often require combination therapies with more toxic chemotherapy. However, drug resistance is prone to appear after surgical intervention and approximately 40%–80% of patients will relapse within 3 years 11–14; therefore, it has important theoretical and clinical significance to explore the detailed mechanism of TNBC. In recent years, increasing evidence showed that noncoding RNAs play an important role in the development of tumor, 15 and also participate in the regulation of tumor metabolism. 16,17 Therefore, in our study, we explored the role and mechanism of noncoding RNA LINC01605 in TNBC.

2 | MATERIALS AND METHODS

2.1 | Human specimens

Breast cancer tissues were collected from the patients with their written consent. The study was approved by the Department of General Surgery, Hainan General Hospital.

2.2 | Establishment of stable cell clones

The knockdown of LINC01605 was achieved using shRNA, which was wrapped with lentivirus purchased from GenScript. The cells were infected with the lentivirus according to the manufacturer’s instructions. The cells were selected by puromycin (1 μg/ml) for 2 weeks.

2.3 | Reverse transcription–PCR

Total RNA was extracted from patients’ tissue or breast cancer cells using TRIzol reagent (Invitrogen), then reverse transcribed into cDNA by PrimeScript RT reagent Kit (Takara). Polymerase chain reaction was carried out using a SYBR Green Real-time PCR Master Mix in an ABI PCR system (Applied Biosystems). The quantitative value was expressed using the 2−ΔΔCT method and normalized to GAPDH.

2.4 | Cell proliferation assay

Breast cancer cells in the logarithmic phase of growth were digested and seeded into a 96-well plate at the density of 1000 cells/well. After 96 h, cell proliferation was determined using CCK-8 (Dojindo Laboratories) in accordance with the manufacturer’s instructions.

2.5 | Colony formation assay

Cells were seeded into 6-well plates at a density of 5000 cells/well, and 2 weeks later, visible colony was formed. Medium was removed following three-time wash with PBS, then cells were fixed in 4% paraformaldehyde for 1 h and stained with 0.1 mg/ml crystal violet solution. After washing, stained colonies were photographed using microscope (Leica). More than 50 cells were determined as a colony, and total number of colonies was counted.

2.6 | Transwell migration assay

Cells were digested and seeded at a density of 50,000 cells/chamber into Transwell chamber which is a 6.5-μm chamber with an 8-μm pore, and placed in the upper of 24-well plates. The lower chamber was filled with medium and 10% FBS (HyClone Laboratories). After incubation for 1 day, the migratory cells under the chamber surface were fixed in 4% paraformaldehyde, stained with 0.1 mg/ml crystal violet solution, counted under microscope with five random fields for each chamber.

2.7 | Transwell invasion assay

Cells were plated at a density of 1 × 10⁶ cells/chamber into 10% Matrigel (BD Biosciences) coated chamber, which were plated in the upper of 24-well plates. The lower chamber was also filled with medium containing FBS. After incubation for 24 h, invasive cells on the lower membrane surface were fixed, stained, and counted using Transwell migration assay.

2.8 | Analysis of glucose uptake and ECAR

Cells were treated with 10 mM fluorescent 2-DG analog 2-NBDG for 1 h, and glucose uptake was determined by flow cytometry (BD Biosciences) after washing twice with PBS. For the analysis of lactate production, cells were digested and seeded into XF 96-well plate in...
Pyruvate-free DMEM overnight. One hour before measurement, medium was changed to XF medium, and 10 mM glucose, 1 mM ATP synthase inhibitor oligomycin, and 50 mM glycolysis inhibitor 2-DG were added at indicated times, according to the manufacturer’s instructions. Lactate production in the medium was measured using Seahorse XF glycolytic rate assay kit by a Seahorse Bioscience XF96 analyzer. The ECAR was analyzed.

2.9 | Western blot analysis

Protein was extracted from breast cancer cells and western blot analysis was carried out as previously described. The LDAH and β-actin Abs were purchased from Abcam.

2.10 | Measurement of mRNA decay

When seeded cells were adhesive to 6-well plates, actinomycin D (10 μg/ml) was added to the medium, then RNA was extracted at 0, 2, 4, 6, and 8 h after adding actinomycin D.

2.11 | In vivo mouse xenograft experiment

Animal experiments were carried out under the guidelines of the Department of General Surgery at Hainan General Hospital, and all animal procedures were approved by the same department. Female nude mice were purchased from GemPharmatech.

MDA-MB-231 cells with or without LINC01605 knockdown were suspended in DMEM. Single cell suspension (5 × 10⁶) was mixed with 0.15 ml Matrigel (50% v/v, Corning Matrigel), and subcutaneously injected into both sides of the breast of 4-week-old nude mice. Tumor volume was measured every 4 days using the formula: π/6 × length × width × thickness (mm³). Tumors were collected on day 30, weighed, and cut into halves. One half was used to extract RNA, and the other half was fixed in formalin following embedding in paraffin.

2.12 | Immunohistochemistry

Five micrometer thick sections from paraffin-embedded tissue underwent antigen retrieval by Diva Declonaker RTU (Biocare Medical) for 10 min at room temperature, then incubated with primary anti-LDHA or Ki-67 (Abcam) for 1 h, followed by the incubation of secondary Ab (Invitrogen). Sections were washed and slides were photographed using a microscope (Leica) as previously described. ¹⁸

2.13 | Hematoxylin–eosin staining

One million MDA-MB-231 cells with or without LINC01605 knockdown in 100 μl PBS were injected into 4-week-old nude mice through the tail vein. After 1 month, mice were killed and lungs were collected, fixed in 4% formalin, embedded in paraffin, and cut into 5-μm thick sections. Lung sections were then stained with H&E as previously described. ¹⁹

2.14 | Statistical analysis

Data were analyzed using Student’s t-test or the one- or two-way ANOVA method followed by a post-hoc test by Prism 7.0, and are represented as mean ± SD. Kaplan–Meier analysis was applied using SPSS.

3 | RESULT

3.1 | LINC01605 level was associated with TNBC

To assess the role of LINC01605 in TNBC, we first measured LINC01605 expression in patients with TNBC. LINC01605 level was increased in TNBC cancer tissue in comparison with normal tissue in patients (Figure 1A). Next, we revealed that LINC01605 expression was much higher in some TNBC-derived epithelial cells, namely MDA-MB-231, SUM159, BT549, and MDA-MB-468, than in normal epithelial cells from breast, including MCF-7, T47D, BT474, and SKBR3 (Figure 1B). For the following studies, we chose three breast cancer cells that had higher expression of LINC01605, which were MDA-MB-231, SUM159, and BT549. In addition, the Kaplan–Meier analysis showed that LINC01605 expression is correlated with both overall survival and relapse-free survival of breast cancer patients (Figure 1C,D). Overall, LINC01605 expression was associated with TNBC patients.

3.2 | LINC01605 promoted proliferation, migration, and invasion of TNBC cells in vitro

To further explore the role of LINC01605 in TNBC, we established cell lines that stably knocked down LINC01605 in three TNBC cell lines (Figure 2A). The proliferation of breast cancer cells detected by CCK-8 assay (Figure 2B) and cell colony formation (Figure 2C) was significantly reduced after LINC01605 knockdown in MDA-MB-231, SUM159, and BT549 cells. Moreover, LINC01605 KD cells displayed remarkably decreased abilities of migration (Figure 2D) and invasion (Figure 2E) compared to normal TNBC cells. Therefore, LINC01605 knockdown significantly reduced proliferation, migration, and invasion of breast cancer cells, which suggested that LINC01605 promoted the abilities of migration, proliferation, and invasion in breast cancer cells.

Furthermore, we established cell lines that stably overexpressed LINC01605 in three TNBC cell lines (Figure 3A). The proliferation of breast cancer cells detected by CCK-8 assay (Figure 3B) and cell colony formation (Figure 3C) were significantly increased after
LINC01605 overexpression in MDA-MB-231, SUM159, and BT549 cell lines. Moreover, cells with LINC01605 overexpression displayed remarkably increased abilities of migration (Figure 3D) and invasion (Figure 3E) compared to normal TNBC cells. Therefore, LINC01605 knockdown significantly reduced proliferation, migration, and invasion of breast cancer cells and LINC01605 overexpression significantly increased proliferation, migration, and invasion of breast cancer cells, which suggested that LINC01605 promoted the abilities of migration, proliferation, and invasion in breast cancer cells.

3.3 | LINC01605 enhanced aerobic glycolysis in breast cancer cells

In recent years, studies have shown that LINC01605 can function as ceRNA, and this study found that LINC01605 can regulate cell metabolism. Next, we evaluated the role of LINC01605 in the aerobic glycolysis and metabolism of breast cancer cells. Glucose uptake was significantly decreased in LINC01605-KD breast cancer cells compared to breast cancer cells (Figure 4A). Moreover, lactate production in breast cancer cells was also remarkably reduced after knockdown of LINC01605 (Figure 4B). Glucose uptake and lactate production were increased in breast cancer cells with LINC01605 overexpression compared to breast cancer cells (Figure 4C,D). Not surprisingly, ECAR, which indicates the glycolytic rate of cells, was also significantly downregulated in LINC01605-KD breast cancer cells and upregulated in LINC01605 overexpressed breast cancer cells in comparison with breast cancer cells (Figure 4E,F). Taken together, these data suggested that LINC01605 enhanced aerobic glycolysis in breast cancer cells.

3.4 | Lactate dehydrogenase A was the target of LINC01605

Lactate dehydrogenase A is a key metabolic enzyme that catalyzes the interconversion of pyruvate and L-lactate with concomitant interconversion of NADH and NAD, which plays an important role in anaerobic metabolism. Bioinformatics analysis showed that LINC01605 and metabolism-related gene LDHA had the same miR-34a-5p target site (Figure 5A). Dual luciferase reporter assay experiment had shown that miRNA can inhibit LDHA and LINC01605 (Figure 5B,C). Therefore, we guessed that LINC01605 regulated aerobic glycolysis by LDHA. First, we discovered that the mRNA level of LDHA was reduced after LINC01605 knockdown and increased after LINC01605 overexpression in three breast cancer cell lines (Figure 5D,E). Moreover, the half-life of LDHA was shortened by LINC01605 knockdown and extended by LINC01605 overexpression in three breast cancer cell lines (Figure 5F,G). Protein level of LDHA was also reduced after LINC01605 knockdown and increased after LINC01605 overexpression in breast cancer cells (Figure 5H,I).
This suggested that LINC01605 increased aerobic glycolysis by inhibiting the degradation of LDHA and increasing the expression of LDHA in breast cancer cells.

### 3.5 LINC01605 promoted proliferation and metastasis of TNBC in vivo

To further confirm the role of LINC01605 in TNBC, we implanted normal breast cancer cells or LINC01605-KD cells into female nude mice. Implantated cells formed tumor in mice, however, the tumor volume (Figure 6A) and tumor weight (Figure 6B) were both decreased in the mice implanted with LINC01605-KD cells with a low expression of LINC01605 (Figure 6C). LINC01605-KD cell-formed tumors also had decreased expression of LDHA and Ki-67 (Figure 6D). MDA-MB-231 cells were injected into mice through the tail vein, the mice were killed 1 month later, and lung tissue was collected and examined. Therefore, we also determined lung metastases in these mice and H&E staining showed that LINC01605-KD cell-implanted mice displayed reduced lung metastases (Figure 6E).
We then implanted normal breast cells or LINC01605-OE cells into female nude mice. Implanted cells formed tumors in mice. Tumor volume (Figure 6F) and tumor weight (Figure 6G) were both increased in the mice implanted with LINC01605-OE cells with a high expression of LINC01605 (Figure 6H). LINC01605-OE cell-formed tumors also had increased expression of LDHA and Ki-67 (Figure 6I). MDA-MB-231 cells were injected into mice through the tail vein, and the mice were killed 3 weeks later; lung tissue was collected and examined. Lung metastases were found in five of the six mice in the control group, while lung metastases were detected in all six mice in the LINC01605-OE group. Compared with the control group, each mouse in the overexpression group formed more and larger metastases (Figure 6J). Altogether, LINC01605 promoted TNBC in mice.

3.6 Knockdown of LDHA rescues the phenotype induced by LINC01605 knockdown

To study the function of LDHA in mediating the oncogenic role of LINC01605 in breast cancer cells, here we further knocked down LDHA in LINC01605-OE breast cancer cell lines. As shown in
Figure 7A,B, LINC01605 overexpression stimulated cell viability, whereas knockdown of LDHA in LINC01605-OE cells rescued the promoted effects in breast cancer cells. Likewise, migration and invasion assays showed that cell migration and invasion in LDHA knockdown cells were significantly restored in comparison with LINC01605 overexpression (Figure 7C,D). As shown in Figure 7E-G, LINC01605 overexpression increased cell glucose uptake, lactate production, and ECAR, whereas knockdown of LDHA in LINC01605-OE cells rescued the promoted effects in breast cancer cells. Our results highlighted the predominant role of LDHA downstream of LINC01605 in breast cancer.

4 | DISCUSSION

Our study showed for the first time that IncRNA LINC01605 was correlated with TNBC as well as the survival rate and relapse-free survival of breast cancer patients. Knockdown of LINC01605...
inhibited migration, proliferation, and invasion of breast cancer cells to delay the development of TNBC. Furthermore, we proved that LINC01605 regulated breast cancer by mediating aerobic glycolysis through targeting LDHA.

Long noncoding RNAs are a type of noncoding RNAs with transcriptional length of over 200 nucleotides. Accumulating evidence has indicated that IncRNAs are involved in multiple physiological and pathophysiological processes, especially in tumor progression. Many IncRNAs were proved to be biomarkers of cancers, and IncRNA-based risk scoring systems were used to predict prognosis of alcohol-related hepatocellular carcinoma. Among the IncRNAs involved in the risk scoring systems, LINC01605 is poorly studied, but all the publications about LINC01605 have indicated that it exerted a certain impact on tumor progression. For example, LINC01605 accelerated laryngeal squamous cell carcinoma by targeting miR493-3p. Moreover, LINC01605 aggravated bladder cancer by enhancing MMP9. Therefore, due to its high correlation with tumors, we explored the role of LINC01605 in breast cancer, which had not been studied. After skin cancer, breast cancer is the most common cancer diagnosed in women in the United States, which greatly threatens women’s health. Therefore, we explored the role of LINC01605 in breast cancer, especially TNBC, and our study for the first time discovered the relationship between the high expression of LINC01605 and TNBC.

Aerobic glycolysis is a 10-step reaction wherein oxygen is required to reoxidize NADH and glucose into NAD+ and pyruvate. The energy metabolism of cancer cells is characterized as increased aerobic glycolysis, referred to as the Warburg effect. Otto Warburg first discovered this phenomenon in 1920. Even in an environment with sufficient oxygen, cancer cells still quickly convert oxygen into energy through high glycolytic metabolism. Because high aerobic glycolysis is a hallmark of cancer cell metabolism, targeting it could be a therapeutic strategy for cancer therapy. Therefore, in recent decades, emerging evidence confirmed the role of aerobic glycolysis in breast cancer. Molecular targeted therapies show many advantages for the treatment of various cancers in comparison with traditional chemotherapies. In particular, targeting key enzymes of glycolysis, including hexokinase, pyruvate kinase, and phosphofructokinase, and glucose transporters were all reported as antibreast cancer therapeutic strategies. Furthermore, a wide range of factors that might serve as therapeutic targets suppressed breast cancer by regulating aerobic glycolysis, including betulinic acid, miRNA-186-3p, tumor-derived macrophages, and zoptarelin doxorubicin. Our current study showed that LINC01605 promoted breast cancer by targeting LDHA, which is also a crucial enzyme in aerobic glycolysis. Although this is the first report of the role of LINC01605 in breast cancer by regulating aerobic glycolysis, noncoding RNAs have been extensively explored and proven as key mediators of aerobic glycolysis in breast cancer for a long time.

Here, we showed that LINC01605 targeted mRNA of LDHA to regulate aerobic glycolysis, leading to the accelerated breast cancer. Our data discovered that knockdown of LINC01605 could shorten the half-life of LDHA mRNA, but how LINC01605 affected the mRNA of LDHA still remains unclear. Long noncoding RNAs always act as ceRNA to regulate other RNA transcription by competing for shared miRNAs. A previous publication revealed that LINC01605 promoted laryngeal squamous cell carcinoma by targeting miR-493-3p, and LINC01605 acted as ceRNA with miR-293-3p. Additionally, LDHA and programmed death ligand 1 were completely binding to miRNA-34a to act as ceRNA in TNBC. These publications gave us a hint that LINC01605 might regulate LDHA in a ceRNA way, but the microRNA that was involved in this process was unknown. Therefore, we might further explore the detailed mechanism behind how LINC01605 regulates LDHA, and whether some specific miRNAs are involved.

In summary, our study discovered that LINC01605 was highly expressed in patients with TNBC, and its high expression was also correlated with overall survival rate and relapse-free survival of breast cancer patients, which might suggest that, like other IncRNAs, LINC01605 might also serve as a diagnostic biomarker of TNBC in the clinic. Notably, due to the complexity of TNBC, in that the high expression of the three receptors that were always used as biomarkers of breast cancer cannot be utilized for TNBC, a diagnostic biomarker for TNBC is required. Our study could provide a novel insight into a diagnostic biomarker for TNBC. Furthermore, our data also suggested that LINC01605 might serve as a therapeutic target for patients with TNBC.

Our study indicated that IncNA LINC01605 was correlated with the survival rate and relapse-free survival of TNBC patients. Knockdown of LINC01605 inhibited proliferation, migration, and invasion of breast cancer cells to delay the development of TNBC. Furthermore, we proved that LINC01605 regulated breast cancer by mediating aerobic glycolysis through targeting LDHA. Therefore,
LINC01605 might serve as a potential diagnostic biomarker and therapeutic target for patients with TNBC.

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**DISCLOSURE**

The authors have no conflict of interest.

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