

Retraction

Retracted: lncRNA NUTM2A-AS1 Targets the SRSF1/Trim37 Signaling Pathway to Promote the Proliferation and Invasion of Breast Cancer

Computational and Mathematical Methods in Medicine

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This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

- (1) Discrepancies in scope
- (2) Discrepancies in the description of the research reported
- (3) Discrepancies between the availability of data and the research described
- (4) Inappropriate citations
- (5) Incoherent, meaningless and/or irrelevant content included in the article
- (6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

In addition, our investigation has also shown that one or more of the following human-subject reporting requirements has not been met in this article: ethical approval by an Institutional Review Board (IRB) committee or equivalent, patient/participant consent to participate, and/or agreement to publish patient/participant details (where relevant).

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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- [1] X. Ning, J. Zhao, F. He, Y. Yuan, B. Li, and J. Ruan, "lncRNA NUTM2A-AS1 Targets the SRSF1/Trim37 Signaling Pathway to Promote the Proliferation and Invasion of Breast Cancer," *Computational and Mathematical Methods in Medicine*, vol. 2022, Article ID 3299336, 8 pages, 2022.

Research Article

lncRNA NUTM2A-AS1 Targets the SRSF1/Trim37 Signaling Pathway to Promote the Proliferation and Invasion of Breast Cancer

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Object. Proliferation and invasion are typical characteristics of breast cancer (BC) cells. Long noncoding RNA NUTM2A-AS1 has been shown to be dysregulated in tumors. This research was to explore the effect of NUTM2A-AS1 on the proliferation and invasion of BC cell lines. **Method.** Using the tumor database (TCGA) and analysis platform (GEPIA), NUTM2A-AS1 expression in breast cancer cases was compared with the normal cases. In addition, Kaplan-Meier curve of overall survival according to the various levels of NUTM2A-AS1 was assessed. Then, we constructed a knockdown plasmid of NUTM2A-AS1 and successfully reduced the expression function of NUTM2A-AS1 in BC cells. **Results.** We found NUTM2A-AS1 could promote the malignant phenotype of proliferation and invasion of BC. In terms of mechanism research, NUTM2A-AS1 was mainly located in the cytoplasm of BC cells, which indicated that NUTM2A-AS1 may achieve its function through transcriptional or posttranscriptional regulation pathways. While knocking down NUTM2A-AS1, we detected several major molecules of the trim family. The results showed that only trim37 mRNA was significantly affected, and protein detection also showed that knockdown NUTM2A-AS1 expression could reduce the expression of trim37. The results of RIP experiments suggested that NUTM2A-AS1 played a key role by combining with SRSF1 and affecting the interaction between SRSF1 and trim37 mRNA. The stability test of mRNA also confirmed that during the knockdown of NUTM2A-AS1, the mRNA stability of trim37 decreased significantly, but this downward trend could be reversed by overexpressed SRSF1. The above results suggested that NUTM2A-AS1 could maintain the stability and expression of trim37 through SRSF1 pathway. The results of rescue experiment showed the overexpression of trim37, while knocking down NUTM2A-AS1 could reverse the decrease of proliferation and invasiveness of BC cells induced by NUTM2A-AS1 knockdown. **Conclusion.** Therefore, trim37 is seen as a necessary target for NUTM2A-AS1 to exert the biological function of BC. Additionally, NUTM2A-AS1 is to regulate the malignant phenotype of BC through NUTM2A-AS1/trim37 pathway.

1. Introduction

The far more prevalent malignancy identified among the females is breast carcinoma [1]. Even though initial treatment has advanced significantly and the fatality rate has dropped over time, the long-term prognosis is still deserving of consideration given the high prevalence of cancer deaths [2]. According to the 2020 Global Cancer Statistical Report, the number of new cases of breast cancer has surpassed that of lung cancer, ranking first in the incidence of female cancer [3]. In 2019, there were 268,600 additional metastatic breast occurrences and 48,100 ductal neoplasia in situ occur-

rences with 41,760 deaths [4]. There are many options for breast cancer treatment. Most women undergo surgery for breast cancer and many also receive additional treatment after surgery, such as chemotherapy, hormone therapy, or radiation. Chemotherapy might also be used before surgery in certain situations. Though great strides have been made in the therapeutic applications, the clinical course still requires care given the high targeted therapy fatality. Because the mechanistic explanation of breast cancer is unknown, more research into novel genes linked to oncogenesis and clarification of the mechanistic explanation is still required [5].

Long noncoding RNA (lncRNA) is a form of RNA that has a sequence of 200 to one million but does not translate for proteins [6]. It is longer continually in the pathological conditions, and its functions are considered as an aggressor or anticancer genes in the negatively or positively feedback system [7]. These nonprotein coding RNAs can regulate chromosome remodeling, transcriptional, genomic reorganization, genetic imprint, cell growth, migratory, cell death, and nucleoplasm transport among other biological functions [8]. Numerous research has demonstrated that lncRNAs serve a complex and extensive role in the emergence and progression of cancer, which is hoped that they will one day be used as an indicator for serious illness and therapy objectives [9].

NUTM2A-AS1 is a 3.7 kb-lncRNA endpoint differentiated triggering discovered in the 19th humanity's chromosome [10]. NUTM2A-AS1 is a cytoplasmic protein that functions in differentiating activation and is required for the mRNA of essential differentiating genes. Once NUTM2A-AS1 is depleted, those certain advancement of the organization genetic traits total absence induction, causing NUTM2A-AS1 deficient epidermis to exhibit unusual terminal distinguishing morphological characteristics, which manifests as genomic skin conditions with aberrant skin integrity, such as hyperkeratosis vulgaris and hyperkeratosis clown [11]. Furthermore, an abundance of researchers has discovered that NUTM2A-AS1 is unusually displayed in various carcinoma and that its interpretation is linked to expansion, cell death, incursion, and metastatic spread, implying that NUTM2A-AS1 might be used as a biosynthetic pathway and therapeutic interventions target [12–14].

Nevertheless, there has been relatively little investigation into the transcription factors and mechanisms of NUTM2A-AS1 in carcinomas. NUTM2A-AS1 is a HER-2-specific lncRNA that is highly increased in mammary carcinoma according to certain research. Knockout NUTM2A-AS1 can inhibit breast tumorigenesis and replication process *in vitro* and promote apoptotic cellular death [15]. NUTM2A-AS1 has exhibited cancer-promoting action. NUTM2A-AS1 was discovered to be highly expressed in carcinoma cells and cell lines, and elevated NUTM2A-AS1 levels were linked to a poor prognosis [16]. As a result, we started looking into the amount of NUTM2A-AS1 production in breast cancer and struggled to find out how NUTM2A-AS1 was engaged in the onset and progression of breast cancer. NUTM2A-AS1 was shown to be highly elevated in mammary carcinoma in this investigation, and the upregulation was linked to the age of onset, tumor volume, and TNM stage. Further research revealed that NUTM2A-AS1 boosted tumor cell growth and migration via modulating its gene encoding trim37. Finally, NUTM2A-AS1 functions as an oncogenic in cancer and could be exploited as a diagnostic and therapy biomarker.

2. Materials and Methods

2.1. Bioinformatics Analysis. The GEPIA (<http://gepia2.cancer-pku.cn/#index>) is an accessible resource that combines data from Cancer-Genome Atlas (TCGA) and Genotype-

Tissue Expression (GTEx) programs for logistic regression and genetic association analysis of patients' outcomes [17]. NUTM2A-AS1 expression in breast cancer cases was compared with the normal cases. In addition, Kaplan-Meier curve of overall survival according to the various levels of NUTM2A-AS1 was assessed.

2.2. Cell Culture. During our research, we used three distinct BC cell lines. Those cells were grown in high-glucose DMEM (GIBCO, Grand Island) with cell-culture mix containing 10% FBS (Sigma-Aldrich, US) at 37 degrees Celsius and 5% CO₂.

2.3. Small Interfering RNA Transfection. The cellular lines were incubated into the six-well plates with a minimum intensity of 2.5×10^5 /well. Both groups were formed the control (sh-NC) and the interfering (sh-NUTM2A-AS1). The transfected reagent was applied to the 6-well plates at the amount recommended in the handbook. The specimens were harvested for further testing after 48-72 hours of cultivation. Real-time PCR and western blot were used to evaluate the production of NUTM2A-AS1 after suppression (RiboBio, China).

2.4. Cell Counting Kit-8 Assay. The CCK-8 test was used to measure cellular proliferation as the manufacturer guidelines (Enzo Life Sciences). 100 μ l of lysis buffer was spread in 96-well plates and grown at 37 and 5% CO₂. At the specified time, 10 mL of CCK-8 solution was added to each well. Simultaneously, the plates were placed in an incubator for 4 hours at 37°C. The fluorescence from each sample was then quantified at 450 nm using only a multifunctional enzymatic tagging device.

2.5. Western Blot Analysis. The controlled cells (sh-NC) and the interfered cells (sh-NUTM2A-AS1) were harvested. These proteins were purified using RIPA solution under 4°C circumstances. The method described kit (Pierce, Rockford, IL) was used to determine the protein content. The reaction mixture was supplemented with 1*loading buffers in equal parts before being isolated by 4 percent-12 percent SDS-PAGE and electronically coated over PVDF membranes. In room temp, 5% fat-free milk was used to obstruct the cell membrane for 1 hour. The membranes were then treated nightly at 4°C with specific antibodies against NUTM2A-AS1 and Tubulin (Sigma-Aldrich, USA). After rinsing with TBS for 30 minutes, it was prepared by diluting for 1 hour with HRP-labeled goat anti-rabbit IgG. The samples were then measured using Imaging Lab automated gel-analysis software and viewed using fluorescent dyes chemicals.

2.6. Real-Time PCR. RNAiso Plus Kit was applied to extract gross RNA from cells. The RNA was reverse transcribed into cDNA with First Strand cDNA Synthesis Kit (Qiagen, Germany). The cDNA templates were amplified by real-time PCR with Takara SYBR Green PCR Kit. GAPDH was utilizing as internal control. Real-time PCR was conducted via DNA Engine Opticon 2 Real-Time Cycler (MJ Research, Inc.). The relatively fold-change mRNA levels were

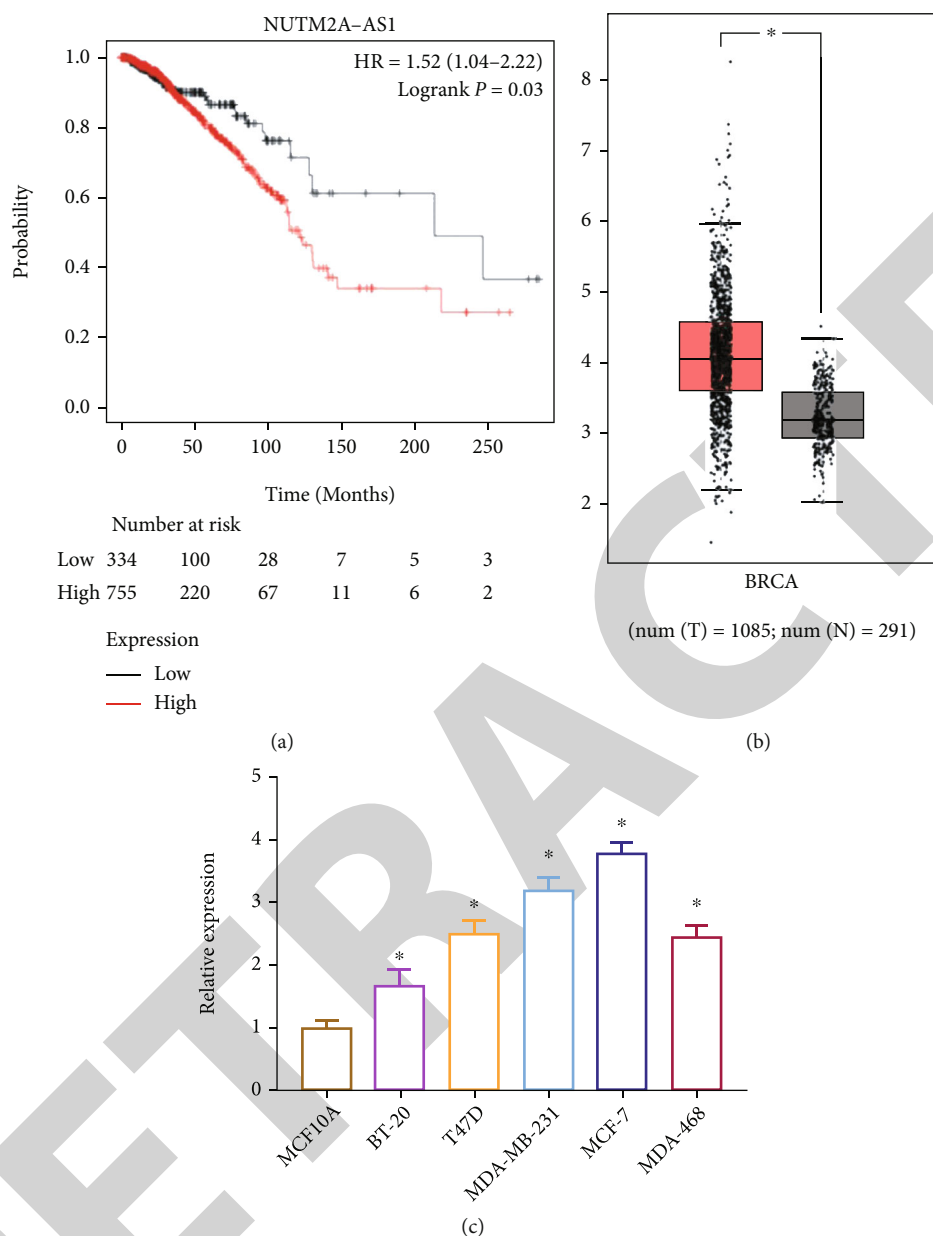


FIGURE 1: (a) The Kaplan-Meier curve of NUTM2A-AS1 in breast cancer samples of TCGA dataset. (b) The levels of NUTM2A-AS1 expression were exhibited between breast cancer and normal specimens. (c) The relative expression of NUTM2A-AS1 in various breast cancer cell lines, including BT-20, T47D, MDA-MB-231, MCF-7, and MDA-468 (* $P < 0.05$).

computed. From Sangon Biotech, GAPDH and NUTM2A-AS1 primers were purchased. The following primer sequences were used for qPCR: GAPDH forward, 5'-TTTG GTATCGTGGGAAGGACTC-3' and reverse, 5'-GTAGAG GCAGGGATGATGTTCT-3'; NUTM2A-AS1 forward, 5'-TACCTCTAGTTCTTCCCAGGC-3' and reverse, 5'-TTTT GCTTTTCTCCTGGCCC-3'.

2.7. Colony-Formation Assay. Mono-cell suspensions were injected into six-well plates in a dose of 2 mL at a concentration of 600 cells/well. For two weeks, the cells were cultured in an atmosphere at 37°C and 5% CO₂. Every other day, a different culture medium was used. When a clone cell cluster

emerged visible to the naked eye, the culture would be stopped. Following that, the cells were rinsed with PBS, fixed in formaldehyde for 15 minutes at 4°C, and then colored with 0.5 percent crystal violet for 20 minutes at room temperature.

2.8. Flow Cytometric Analysis. The samples were inoculated into six-well plates with 2.5×10^5 cells/well. The cells were collected after three-day siRNA transfection. Then, the cells were then settled and cultivated in precooled ice-cold 70 percent ethanol at 4°C instantly at 4°C; rinsed thoroughly and stained with 25 ml of PI (25 ml), 500 ml of buffer (500 ml), and 10 ml of RNase A (10 ml) at 37°C for 30 min at 37°C in a dark-room with cellular cycles and apoptotic kit (Invitrogen).

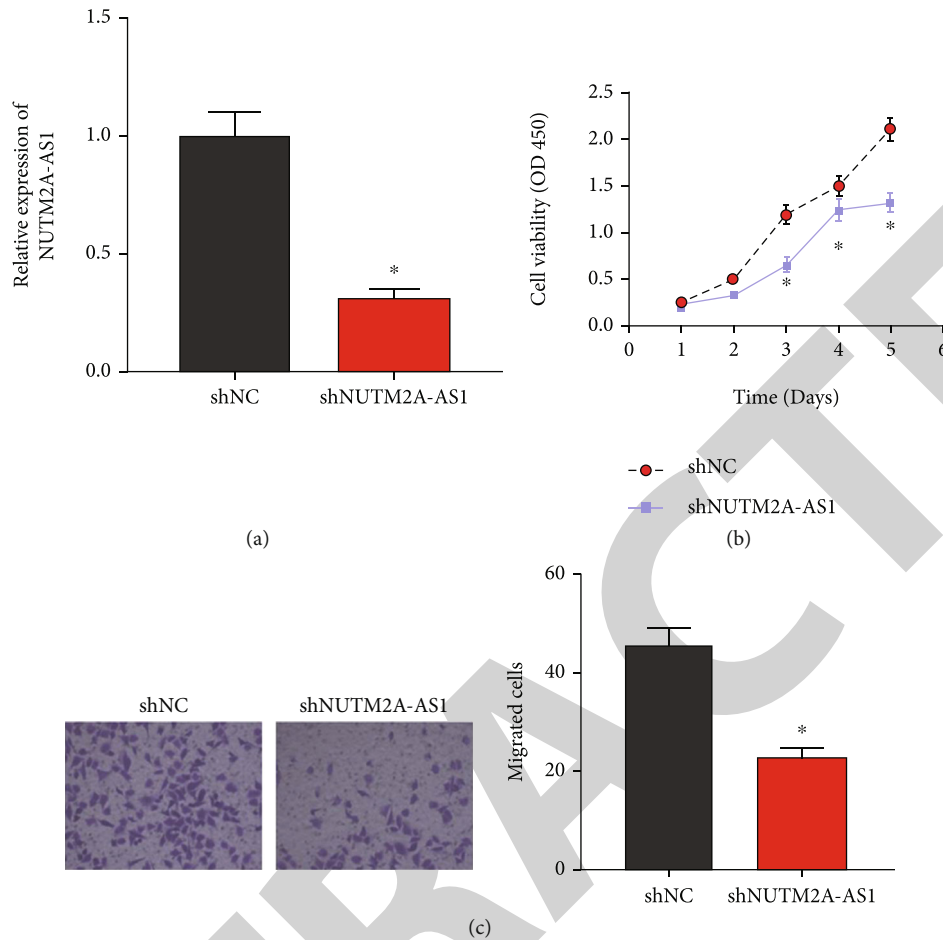


FIGURE 2: (a) The relative levels of NUTM2A-AS1 mRNA in the shNC and sh-NUTM2A-AS1 groups. (b) The cell viability of shNC and sh-NUTM2A-AS1 cells was exhibited. (c) The invasive ability of shNC and sh-NUTM2A-AS1 cells was eliminated.

2.9. *Statistical Analysis.* GraphPad Prism 8.0 software was used for descriptive statistics. These findings were recorded as mean standard deviation. The *t*-test was used to determine the statistical significance of variance. To facilitate comparison from more than two groups, one-way ANOVA was utilized. *P* more than 0.05 was regarded as clinically important.

3. Results

3.1. *Characterization and Expression of NUTM2A-AS1 in BC Tissues and Cells.* To explore whether NUTM2A-AS1 may influence the long-term survivals of BC patients, we searched “GEPIA” and found that high NUTM2A-AS1 levels were involved in the OS of BC patients based on TCGA datasets (Figure 1(a)). For preliminarily exploring whether NUTM2A-AS1, we searched “GEPIA” which showed that NUTM2A-AS1 presented a high expression in BC specimens based on TCGA datasets (Figure 1(b)). In addition, the results of RT-PCR also showed that BC cell lines showed higher NUTM2A-AS1 expression than the normal MCF-10A (Figure 1(c)).

3.2. *NUTM2A-AS1 Can Promote the Proliferation and Invasion of Breast Cancer Cells.* Proliferation and invasion are typical characteristics of breast cancer cells. In order to

explore the effect of NUTM2A-AS1 on the proliferation and invasion of breast cancer cell lines, we constructed a knockdown plasmid of NUTM2A-AS1 and successfully reduced the expression of NUTM2A-AS1 in breast cancer cells (Figure 2(a)). Subsequently, CCK8 experiments showed that the proliferation ability of breast cancer cell lines decreased significantly with the knockdown of NUTM2A-AS1 (Figure 2(b)). Transwell assay also showed that the invasive ability of breast cancer cell lines decreased significantly with the knockout of NUTM2A-AS1 (Figure 2(c)). These results suggested that NUTM2A-AS1 can promote the malignant phenotype of proliferation and invasion of breast cancer.

3.3. *NUTM2A-AS1 Can Maintain the Stability of Trim37 through SRSF1.* In order to further explore the biological mechanism of NUTM2A-AS1 regulating the malignant phenotype of breast cancer, we then detected the intracellular localization of NUTM2A-AS1. The results showed that NUTM2A-AS1 was mainly located in the cytoplasm of breast cancer cells (Figure 3(a)), which indicated that NUTM2A-AS1 may achieve its function through transcriptional or posttranscriptional regulation pathways. The Trim family is a potential oncogene that affects the biological function of breast cancer. In order to clarify the effect of

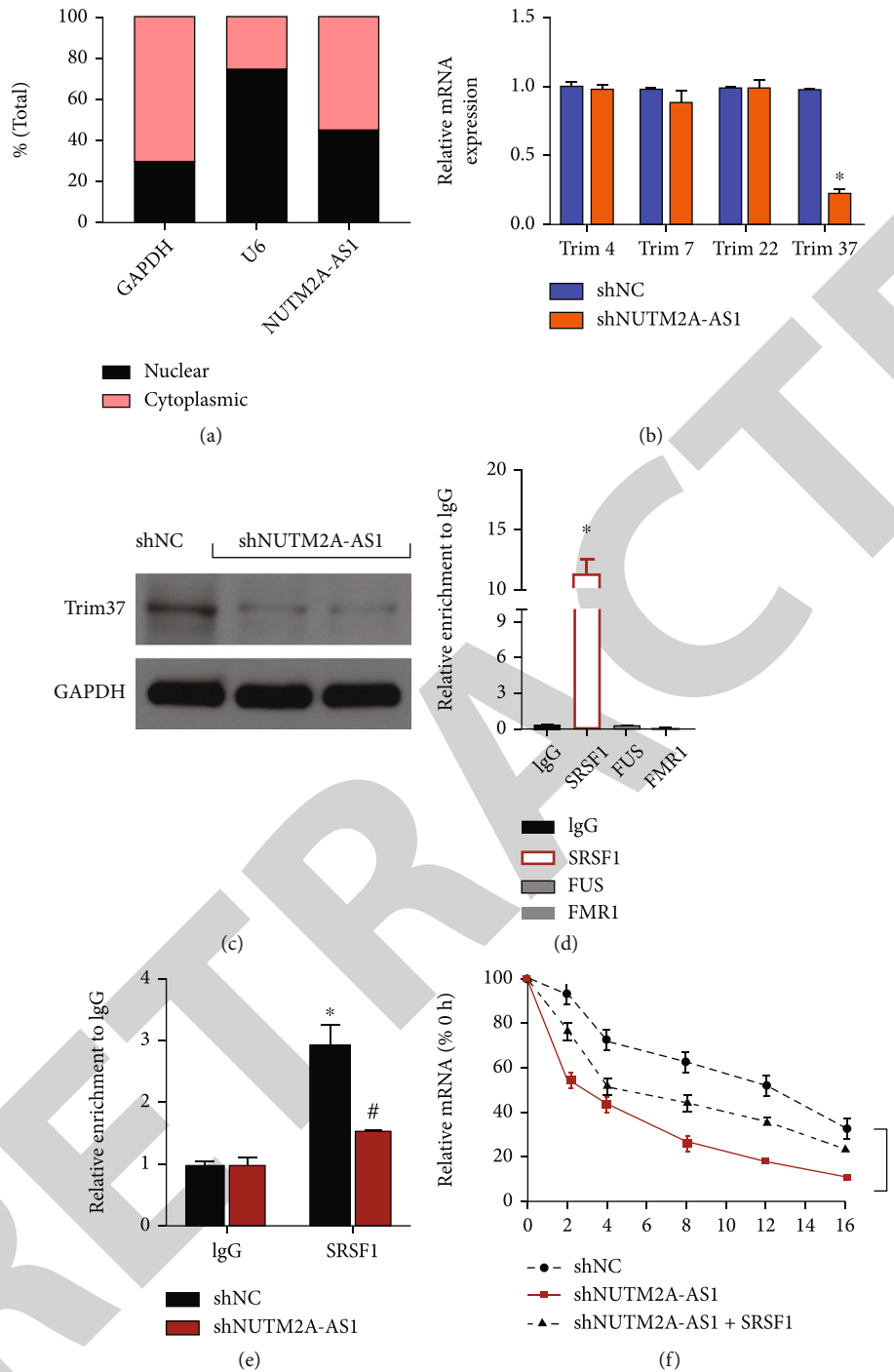


FIGURE 3: (a) NUTM2A-AS1 was mainly located in the cytoplasm of breast cancer cells. (b) The relative mRNA expression of Trim4, Trim 7, Trim22, and Trim 37 under knockdown NUTM2A-AS1. (c) The expression of trim37 was detected by western blot under knockdown NUTM2A-AS1. (d) The interaction between NUTM2A-AS1 and RNA binding protein SRSF1 was detected by RIP assay. (e) The interaction between SRSF1 protein and trim37mRNA was explored by RIP assay. (f) The mRNA stability of trim37 was assessed by mRNA stability test, * $P < 0.05$.

NUTM2A-AS1 on the trim family, we detected several major molecules of the trim family while knocking out NUTM2A-AS1. The results showed that only trim37mRNA was significantly affected (Figure 3(b)). Protein detection also showed that knocking down the expression of NUTM2A-AS1 could reduce the expression of trim37

(Figure 3(c)). lncRNA affected the stability of downstream target gene mRNA through RNA binding protein pathway, which was an important way for lncRNA to realize its function. RIP results showed that there was interaction between NUTM2A-AS1 and RNA binding protein SRSF1 (Figure 3(d)). RIP experiments also showed that there was

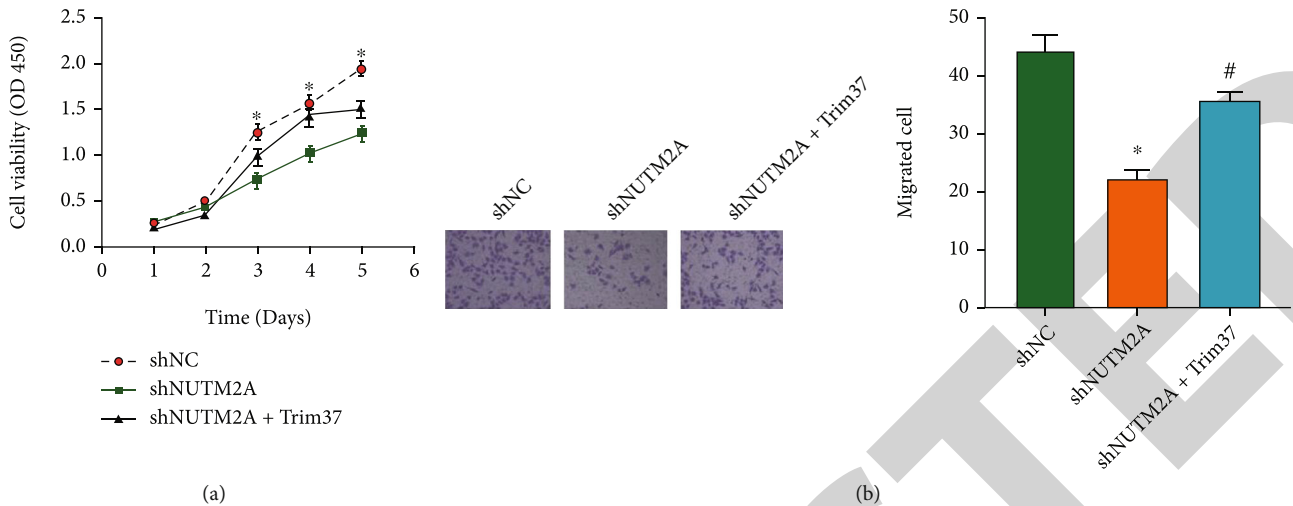


FIGURE 4: (a) The cell viability of breast cancer cells was assessed under knockdown NUTM2A-AS1 and knockdown NUTM2A – AS1 + trim37. (b) The invasiveness of breast cancer cells was assessed under knockdown NUTM2A-AS1 and knockdown NUTM2A – AS1 + trim37.

an interaction between SRSF1 protein and trim37mRNA, but this interaction decreased with the knockdown of NUTM2A-AS1. The above results suggested that NUTM2A-AS1 played a role by binding to SRSF1 and affecting the interaction between the latter and trim37mRNA (Figure 3(e)). mRNA stability test also showed that with the knockout of NUTM2A-AS1, the mRNA stability of trim37 decreased significantly, but this downward trend could be reversed by overexpressed SRSF1 (Figure 3(f)).

3.4. The Recovery Experiment Showed That Overexpression of trim37 Could Reverse the Phenotypic Changes Caused by NUTM2A-AS1 Knockdown. The above results showed that NUTM2A-AS1 could maintain the stability and expression of trim37 through SRSF1 pathway. In order to further clarify whether NUTM2A-AS1 can work through trim37, we designed rescue experiment. The results showed the overexpression of trim37, while knocking down NUTM2A-AS1 could reverse the decrease of proliferation and invasiveness of BC cell line caused by NUTM2A-AS1 knockdown (Figures 4(a) and 4(b)). Trim37 was a necessary link for NUTM2A-AS1 to realize the biological function of breast cancer. NUTM2A-AS1 regulated the malignant phenotype of breast cancer through NUTM2A-AS1/trim37 pathway.

4. Discussion

Numerous reports have studied lncRNAs as potential predictive and therapeutic indicators particular to BC patients in latest days [18]. Depending on TCGA databases and RT-PCR findings, the research was successful in determining NUTM2A-AS1, a novel BC-related lncRNA with elevated expression in BC specimens and cell lines. Trim37 has been widely used throughout the therapeutic management of severe BC in recent decades [19]. The level of NUTM2A-AS1 expression was found to be higher in remaining tumor, suggesting that NUTM2A-AS1 may enhance BC cell proliferation. Strong NUTM2A-AS1 expression was linked to dis-

tant metastases, tumor grade, and a poorer negative prognosis according to clinical tests. Multivariate regression also verified NUTM2A-AS1 as a novel potential factor particular to BC. Ultimately, it would be the first research to demonstrate that NUTM2A-AS1 may well be employed as a future therapeutic indicator in BC.

NUTM2A-AS1 is a critical lncRNA for histological fragmentation of body cells [20]. Earlier research has shown that NUTM2A-AS1 plays key experience in several cellular mechanisms' tumorigenic genesis and advancement [21]. NUTM2A-AS1 can reduce cellular invasion and metastasis in malignancy by modulating the miR-544a/FBXW7 pathway [22]. In gastric carcinoma, a great level of NUTM2A-AS1 can stimulate cell growth by altering KLF2 mRNA stabilization [23]. The role and mechanisms of NUTM2A-AS1 in breast cancer were the emphasis of our research. NUTM2A-AS1 production was shown to be increased in tumor samples and cell lines. Moreover, elevated NUTM2A-AS1 translation was related to a greater malignant grade. Previous research has also connected NUTM2A-AS1 to a bad outcome. These findings have suggested that NUTM2A-AS1 can be employed as both a predictive and therapeutic indicator for breast cancer. The functional retraction research was performed to investigate the oncogenic involvement of NUTM2A-AS1 in breast cancer. Upregulation of NUTM2A-AS1 has been shown in vitro to accelerate the multiplication of breast cancer cells, which might impact well be done by maintaining cellular cycle and fate. Simultaneously, the transcription of NUTM2A-AS1 can improve cellular migratory.

We established that NUTM2A-AS1 could control TRIM37 in breast cancer, although the pathway is yet unknown. NUTM2A-AS1 has been shown to connect to SRSF1 in the cytoplasmic via the NUTM2A-AS1 structure and to control the stabilization of downstream mRNA via SMD. SRSF1 can immediately attach to targeting mRNA using UPF1 and the RNA dual formation by targeting mRNA and lncRNA to inhibit fast mRNA disintegration

[24]. Earlier research and current nuclear cytoplasmic separating assays and RNA IP have demonstrated that NUTM2A-AS1 is mostly found in the cytoplasmic breast-cancer cells and plays a role in posttranscriptional transcriptional via partnering through SRSF1 [25]. The integration of SRSF1 and NUTM2A-AS1/TRIM37 was affirmed, which was the interplay between the Alu elements in NUTM2A-AS1 and TRIM37 3-UTR, as well as confirmation that TRIM37 mRNA consistency was directly impacted by NUTM2A-AS1 and SRSF1 expression profiles, which supported our hypothesis that NUTM2A-AS1 mediated SMD may be the pathways of the NUTM2A-AS1-TRIM37 [26]. So many of the foregoing findings have suggested that the “NUTM2A-AS1-SRSF1-TRIM37” pathway may be important in the advancement of breast cancer. Sp1 and H3K27 have been shown to be engaged in the activation of NUTM2A-AS1 transcript. Our research still leaves something to be desired. Further exploration is needed in future *in vivo* experiments. In addition, multicenter large-scale case studies should be conducted in the future.

To summarize, this analysis found a novel mechanism implicated in the development of breast cancer. Our findings emphasize the importance of the NUTM2A-AS1-SRSF1-TRIM37 axis in controlling mammary tumorigenesis and dissemination. Our results emphasize on the mechanistic explanation by which NUTM2A-AS1 regulates mammary tumor progression. NUTM2A-AS1 can be employed as a breast cancer screening marker and therapy target, as well as providing an investigational foundation for diagnosis and management.

Data Availability

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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