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RESEARCH ARTICLE

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A long non-coding RNA LNBC3 facilitates non-small cell lung cancer progression by stabilizing BCL6

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Abstract

Background: The non-small cell lung cancer (NSCLC) is a common malignancy worldwide. Numerous reports have shown the critical role of long non-coding RNAs (lncRNAs) in NSCLC. However, the role of a novel lncRNA named LNBC3 is still unknown.

Methods: By lncRNA profiling, novel lncRNAs related to NSCLC were identified. LNBC3 expression was quantified by qRT-PCR. Migration and viability assays were performed to evaluate the function of LNBC3 in vitro. In vivo xenograft model was conducted to determine the oncogenic functions of LNBC3. RNA immunoprecipitation (RIP) followed by mass spectrometry (MS) was utilized to identify BCL6 as LNBC3 binding target.

Results: LNBC3 is markedly overexpressed in tumor tissues and NSCLC cell lines. Higher LNBC3 levels correlated with advanced TNM stages, larger tumor size, and metastasis. LNBC3 promoted NSCLC migration and viability. The in vivo experiments demonstrated that xenograft tumor growth and proliferation were facilitated with increasing LNBC3 levels. The antisense oligonucleotides (ASOs) targeting LNBC3 substantially inhibited lung cancer progression. Mechanistic studies showed that LNBC3 could interact with BCL6 leading to BCL6 stabilization through reduced proteasomal degradation.

Conclusions: Collectively, our data have identified a novel lncRNA LNBC3 in NSCLC progression. The LNBC3-BCL6 axis might be a potential target for pharmaceutical intervention.

KEYWORDS

antisense oligonucleotides, B-cell lymphoma 6, BCL6 on chromosome 3, non-small cell lung cancer

1 | INTRODUCTION

Lung cancer represents a serious disease, and the mortality rates rank the second among all tumors worldwide.[1] The non-small cell lung cancer (NSCLC) accounts for ~85% cases among all lung cancer patients.[2] Histological subtypes of NSCLC primarily contain lung adenocarcinoma (LUAD, around 40 ~ 50%) and lung squamous cell carcinoma (LUSC, around 20%-30% of cases).[3] Although much

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progress has been made on chemotherapy, radiotherapy, and immunotherapy, the NSCLC patients suffer from a low 5-year survival rate.[4] Therefore, identifying the mechanism underlying NSCLC progression is strongly required.

Genomic studies have uncovered complex landscape on transcriptome and identified more sophisticated structure.[5] Specifically, only a small fraction of (<2%) human genome is capable of encoding protein whereas the remaining parts consist of numerous non-coding RNAs.[6] The long non-coding RNAs (lncRNAs) represent series of transcripts (>200 nucleotides in length) with no or minimal protein coding abilities.[7] LncRNAs can play various roles in multiple biological processes such as transcription, translation, or post-translational modification.[8] For example, Lu et al recently found that the lncRNA TBILA can advance NSCLC development by increasing the expression of germinal center-associated lymphoma (HGAL).[9] Yin et al showed that the lncRNA AFAP1-AS1 could suppress p21 protein expression and its higher expression predicts a poor prognosis in NSCLC.[10] Instead, lncRNA MEG3 can raise the expression of p53 and induce apoptosis to inhibit NSCLC progression.[11] However, the role of lncRNA during NSCLC progression is still largely obscure.

By RNA-sequencing strategy, we have identified a novel intergenic lncRNA ENSG00000261159 as an oncogenic lncRNA in lung cancer and we termed it as lncRNA regulating BCL6 on chromosome 3 (LNBC3). We found that LNBC3 is significantly upregulated in lung cancer compared with normal adjacent tissues. LNBC3 also possesses in vivo and in vitro oncogenic effect on lung cancer progression. Mechanistic work argues that LNBC3 interacts with B-cell lymphoma 6 protein (BCL6) and increases its stability to promote NSCLC progression. The antisense oligonucleotides (ASOs) specifically targeting LNBC3 substantially inhibited lung cancer progression suggesting that LNBC3 could possibly serve as a therapeutic target. These data suggest that the novel lncRNA LNBC3 could function as an oncogenic factor and a target for anti-cancer therapy.

2 | MATERIALS AND METHODS

2.1 | Cells, lentiviral constructs, and reagents

The normal WI-38 and lung cancer H1299, A549, 95D, and H838 cells were cultured in Dulbecco's modified Eagle's medium (DMEM, Sigma) with 7% fetal bovine serum (FBS) and 100 μg/mL streptomycin (Sigma). All cell lines were obtained from the Shanghai Cell Biology Institute. Puromycin was used for lentiviral selection for 36 hours. The LNBC3 was first cloned followed by insertion into pWPXL vector (Abcam) to generate pWPXL-LNBC3 vector (ie, LNBC3). The supernatants were harvested and moved to a syringe filter. Empty pWPXL was used as the control group (control). The short hairpin RNA (ShRNA) for LNBC3 (ShLNBC3) and a scramble non-targeting control (ShCtrl) were obtained from GeneChem (Shanghai). Transfection was done using Lipofectamine 3000. See Table S1 for sequences.

2.2 | Human sample collection

The lung cancer samples were harvested from the primary sites in patients from January 2017 to July 2018. Notably, the samples were frozen immediately and stored at a −80°C refrigerator. Totally, 108 specimens were collected. Experimental procedures related to human samples were approved by Human Research Ethics Committee (HREC) at Second Hospital of Shanxi Medical University and in accordance with the 1975 Declaration of Helsinki.

2.3 | Antisense oligonucleotides (ASOs)

Totally, seven ASOs were designed and obtained from GeneChem. The sequences were shown in Table S1. An ASO without targeting effect was used as the control. To deliver ASO, 2×10^5 A549 cells were loaded into a 12-well plate and transfected with 0.5 μg ASOs and 0.8 μL Lipofectamine 2000. For in vivo free uptake, 2×10^5 cells were loaded into 12-well plate and transfected with indicated ASOs with different concentrations without Lipofectamine 2000. ASO delivery in vivo was conducted by intraperitoneal injection at 30 mg/kg with PBS as the control.

2.4 | Western blot

Proteins were extracted by RIPA lysis buffer (Beyotime). Samples were then separated by 8% sodium dodecyl sulfate-polyacrylamide gels (SDS-PAGE) followed by transfer onto nitrocellulose membrane. BCA Protein Assay Kit (Pierce) was used to quantify the concentration. Phosphate-buffered saline (PBS)/Tween-20 together with non-fat milk (4%) were used for blockage. Primary antibodies were incubated overnight. Secondary antibody was loaded at room temperature. Densities for protein bands were analyzed by ImageJ software.

2.5 | Statistical analysis

Statistics were calculated using SPSS (version 16, SPSS, Inc). Data were shown as mean ± SD. Mann-Whitney test was used for comparison between two groups and one-way ANOVA for comparison among multiple groups followed by LSD *post hoc* test. At least three replicates were done. $P < .05$ was statistically significant.

3 | RESULTS

3.1 | LNBC3 is upregulated in NSCLC

To unravel novel lncRNAs related to NSCLC, we performed RNA-sequencing on NSCLC samples and normal adjacent tissues (NATs; Figure 1A). The volcano plot was shown to identify differentially expressed lncRNAs (Figure 1B, dark purple points). Among the 64

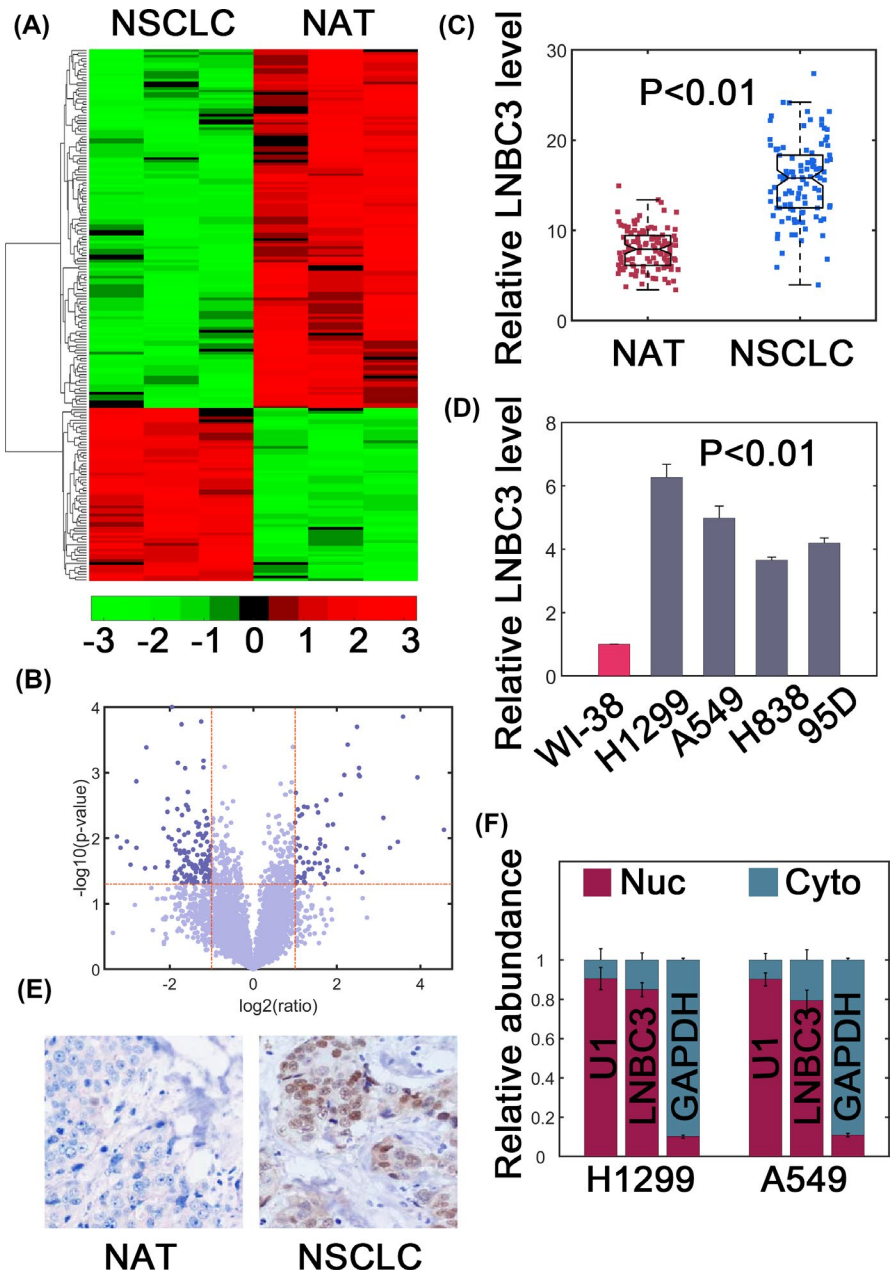

FIGURE 1 Identification of lncRNA LNBC3 in NSCLC. A, Heatmap representation of lncRNA-seq in normal adjacent tissues (NATs) and NSCLC tissues. B, Volcano plot was used to determine the differentially expressed lncRNAs. N = 64 lncRNAs were significantly upregulated. C, Relative LNBC3 expression in normal and NSCLC. D, Relative LNBC3 expression in WI-38 and NSCLC cell lines. $^{**}P < .01$. E, In situ hybridization (ISH) in NSCLC tissues and NATs. F, Subcellular localization of LNBC3. Nuc: nuclear; Cyto: cytoplasm. $^{**}P < .01$

significantly increased transcripts, we noted there were two novel lncRNAs (Figure 1B, Table S2). Since lncRNA LNBC3 (ENSG00000261159) is upregulated in higher fold, we chose it for further assay. The lncRNA LNBC3 is an intergenic transcript with 811 nt in length. LNBC3 was located on chromosome 3 with one transcript (www.ensembl.org). Evaluating the coding potential via (http://lilab.research.bcm.edu/cpat/index.php) showed that it has a low coding probability (0.0100785). LNBC3 was significantly upregulated in NSCLC tissues compared with normal adjacent tissues (NATs, Figure 1C, $P < .01$). Meanwhile, NSCLC cell lines displayed higher LNBC3 expression compared with the normal WI-38 cell line (Figure 1D). Higher LNBC3 expression was significantly associated with TNM stages, tumor size, and metastasis (Table S3). However, it was not significantly associated with age, gender, and histology (Table S3). In situ hybridization (ISH) also confirmed that LNBC3 was markedly stained in NSCLC tissues (Figure 1E). Subcellular localization data showed that LNBC3 was primarily distributed in nucleus (Figure 1F). These results suggested that LNBC3 was upregulated in NSCLC and correlated with malignant phenotypes.

3.2 | LNBC3 advances NSCLC progression

To further investigate the effect of LNBC3, we silenced or overexpressed LNBC3 in H1299 and A549 cells and the results showed that the shRNA and lentiviral constructs targeting LNBC3 could significantly altered LNBC3 levels (Figure 2A,B). CCk-8 viability assays were performed and data suggested that lowering LNBC3 may decrease NSCLC cell viability whereas increasing LNBC3 abundance greatly advanced the viability (Figure 2C,D). We also conducted migration assay and the results showed that overexpressing LNBC3

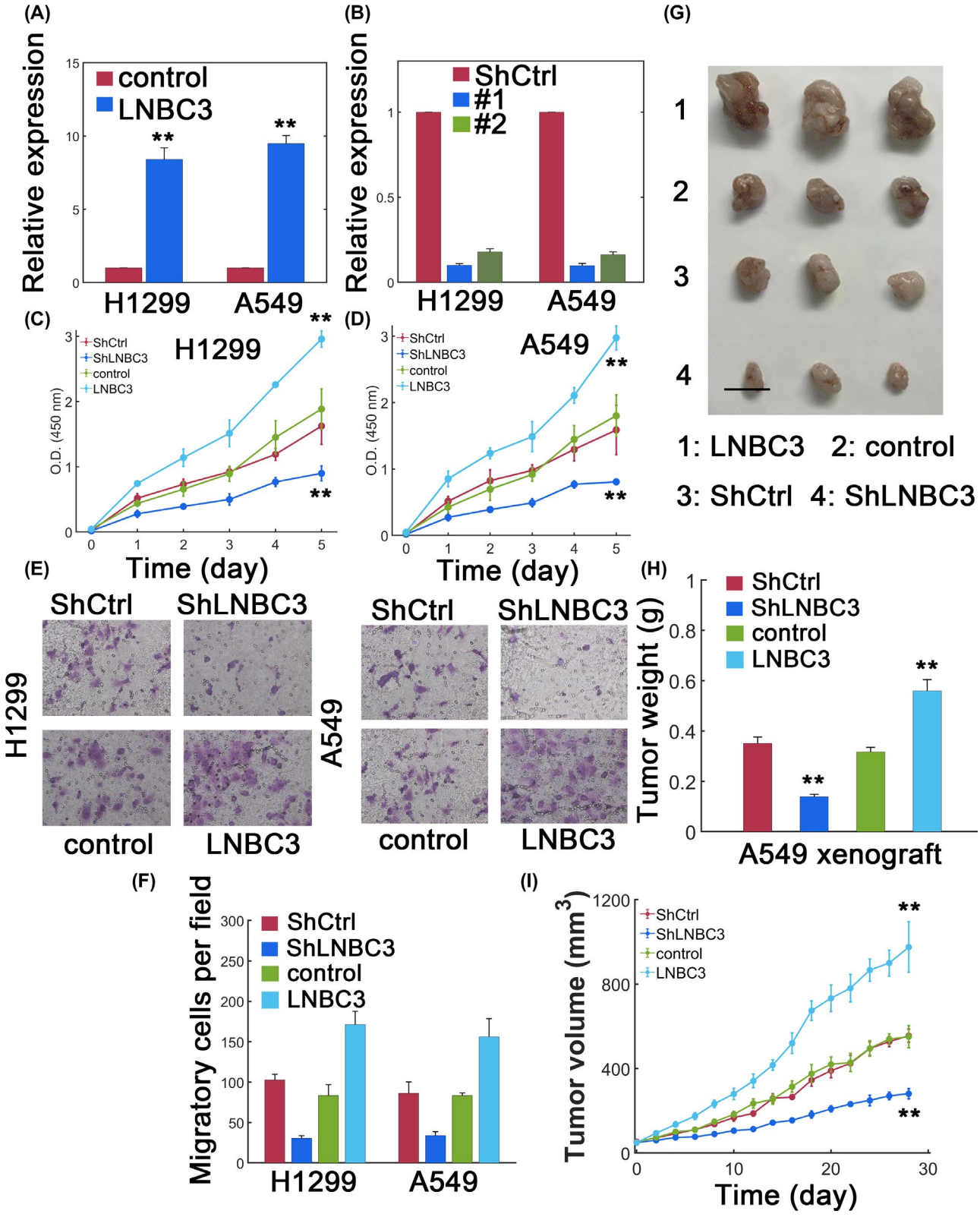

FIGURE 2 LNBC3 inhibits NSCLC in vitro and in vivo. A, The overexpression efficiency with lentiviral LNBC3 transfection. B, Knockdown efficiency with LNBC3 shRNA. Note that shRNA#1 showed higher efficiency and was selected as shLNBC3. C, D, Effect of LNBC3 on viability of H1299 (C) and A549 cells (D) transfected with shRNA scramble control (ShCtrl), ShLNBC3, lentiviral control (control), or lentiviral vector containing LNBC3 (LNBC3). E, Evaluating the effect of LNBC3 on H1299 (left) and A549 (right) cell migration. F, Quantification of migration in (E). G, Xenograft tumor model using A549 cells with LNBC3 knockdown or overexpression. Scalebar: 1 cm. H, Quantification results for (G). I, In vivo tumor growth of A549 xenograft tumor model with different LNBC3 expression status. $^{**}P < .01$

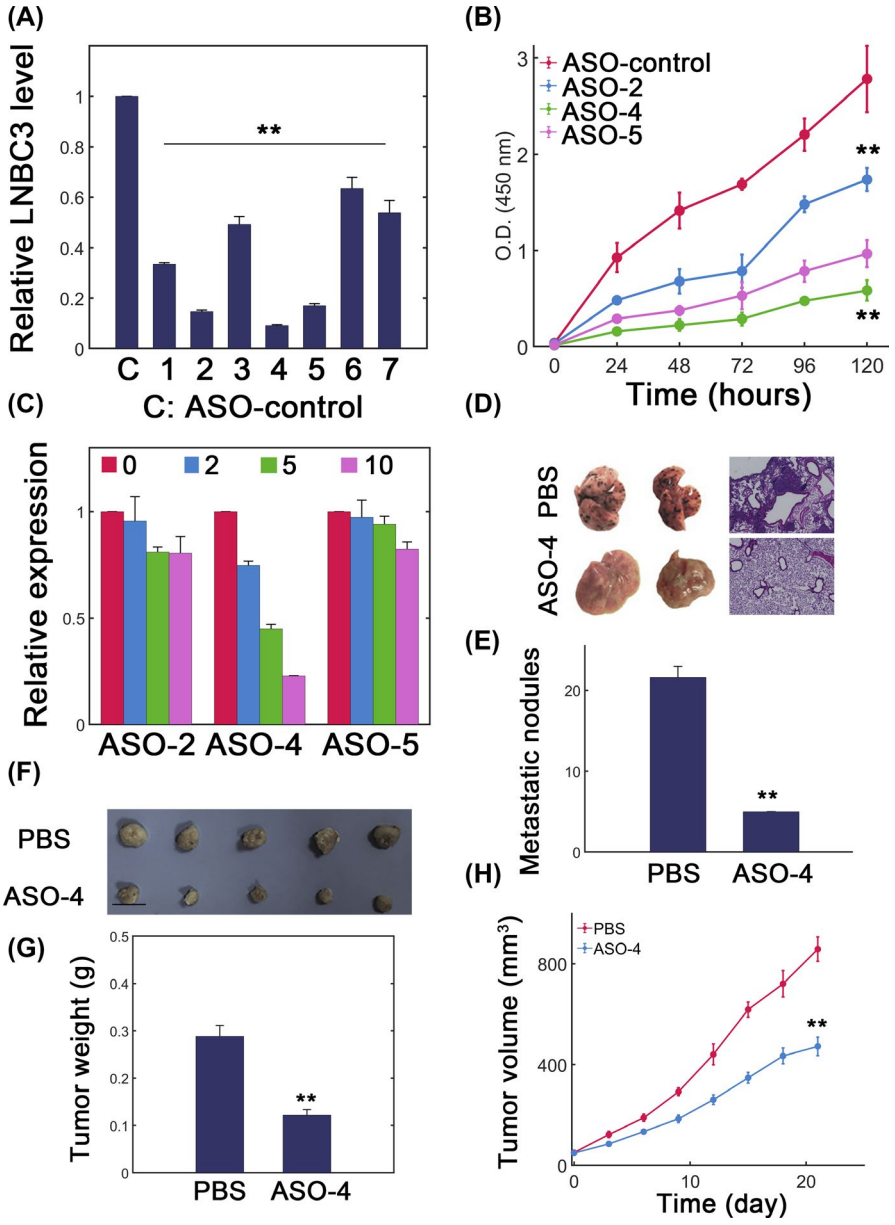

FIGURE 3 Therapeutic potential for LNBC3. A, The qRT-PCR results for relative LNBC3 expression in A549 cells transfected with ASO-control or different ASO constructs. B, The effect of selected ASOs on NSCLC cell viability. C, Free uptake analysis in A549 cells using different concentrations of ASOs (0, 2, 5, and 10 μmol/L). The relative LNBC3 expression was evaluated. D, In vivo metastasis model showed anatomy and H & E staining for lungs. Twenty-one days after implantation, mice were randomly assigned into two groups (PBS and ASO-4). The PBS or ASO-4 treatment was conducted twice a week immediately after the group assignment. E, The number of metastatic nodules was shown for (D). F, Xenograft tumor images for A549 cells treated with PBS or ASO-4. A549 cells were subcutaneously injected into nude mice. After 21 d, all mice were randomly assigned into two groups with similar starting tumor volumes (PBS and ASO-4). Then, PBS and ASO-4 treatment were immediately applied twice a week. G, Statistical results for (F). H, The tumor volumes of A549 xenografts treated with PBS or ASO-4. $^{**}P < .01$

could markedly facilitated the migration of NSCLC cells whereas decreasing LNBC3 inhibited the migration (Figure 2E,F). We further evaluated the in vivo effect of LNBC3. LNBC3 silence reduced in vivo tumor growth whereas LNBC3 overexpression accelerated NSCLC xenograft tumor growth (Figure 2G, quantification was shown in Figure 2H). Consistently, LNBC3 overexpression also increased the tumor volume whereas silencing LNBC3 significantly reduced the tumor growth (Figure 2I). These data suggested that LNBC3 had an oncogenic effect both in vivo and in vitro.

3.3 | Evaluating LNBC3 as a therapeutic target

We next investigated whether LNBC3 could serve as a potential target to eradicate BC using antisense oligonucleotide (ASO). Seven ASOs were designed and the results showed that they all dramatically decreased LNBC3 expression (Figure 3A). Since ASO-2, ASO-4, and ASO-5 displayed higher efficiency compared with the other ASOs, we further evaluated their effects on BC viability. The results showed that ASO-2, ASO-4, and ASO-5 could significantly decrease the viability of A549 cells (Figure 3B). Then, A549 cells were transfected with ASOs without transfection agents to approximate the in vivo status. The results showed that ASO-4 was more effective than the other two ASOs (Figure 3C). Therefore, ASO-4 was selected for further assays. We established an in vivo metastasis model during which we found significantly reduced metastatic nodules in ASO-4-treated group compared with phosphate-buffered saline (PBS)-treated group (Figure 3D,E). PBS or ASO-4 treated groups did not alter the mice body weights significantly (Figure S1A). We further evaluated the biochemical parameters and found that the levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were generally similar across PBS or ASO-4 treated groups

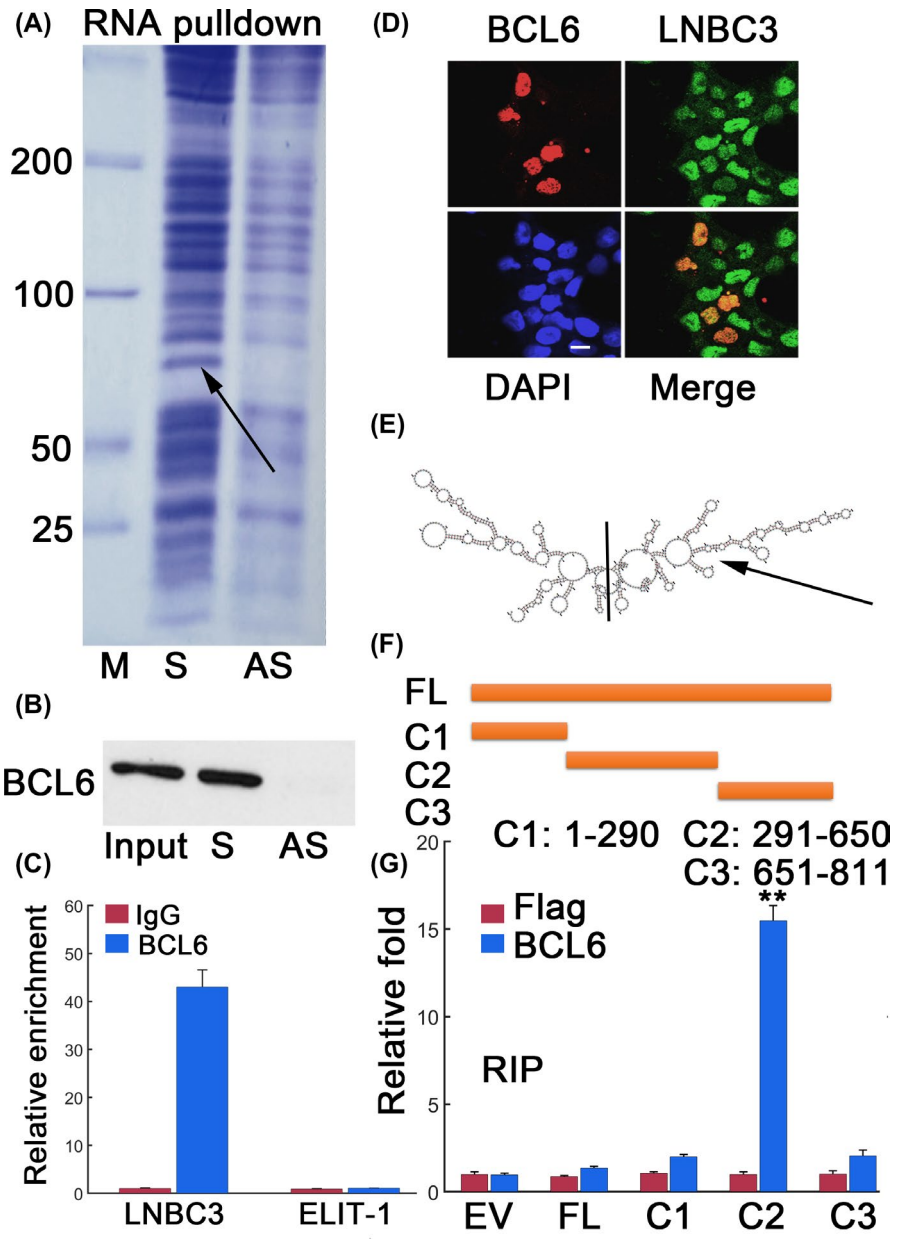

FIGURE 4 Identification of BCL6 as LNBC3 binding protein. A, RNA pull-down assay for sense/antisense LNBC3 transcripts. The arrow indicates the specific band for mass spectrometry. B, Proteins obtained by RNA pull-down were analyzed by specific antibody for BCL6 by immunoblot. C, RNA immunoprecipitation (RIP) for LNBC3. The lncRNA ELIT-1 was used as a negative control. D, Fluorescence in situ hybridization (FISH) data displaying the co-localization of LNBC3 and BCL6. E, The secondary structure of LNBC3 predicted by RNAfold (http://rna.tbi.univie.ac.at//cgi-bin/RNAWebSuite/RNAfold.cgi). The black arrow indicated the domain for BCL6 binding. F, Construction of full length or truncated LNBC3 transcripts. G, RIP followed by qRT-PCR to uncover the domain for LNBC3 binding with BCL6. Fold enrichment data were adjusted by comparing the inputs with Flag-Vec

(Figure S1B). Meanwhile, a xenograft model was conducted and we observed that ASO-4 could markedly decrease tumor growth in vivo (Figure 3F,G). The tumor volume was substantially decreased with ASO-4 treatment compared with PBS control group (Figure 3H). These data demonstrated that LNBC3 might be a potential target for therapeutic intervention via ASOs in NSCLC.

3.4 | BCL6 interacts with LNBC3

To investigate the underlying mechanism of LNBC3 mediated NSCLC progression, we performed RNA pull-down assays. The results showed one specific band (Figure 4A, as indicated by the arrow). The band was then resected for mass spectrometry (MS) assay. Five putative partners were identified (Table S4). Immunoblots confirmed that BCL6 was associated with LNBC3 (Figure 4B). Furthermore, BCL6 was markedly enriched for LNBC3 by RNA immunoprecipitation (RIP, Figure 4C). Fluorescence in situ hybridization (FISH) showed that BCL6 signals indeed overlapped with those for LNBC3 (Figure 4D). To identify the binding regions of LNBC3, we constructed different LNBC3 truncated constructs based on the predicted secondary structure (Figure 4E,F). The results demonstrated that the central domain was required for BCL6-LNBC3 binding (Figure 4G). These results suggested that LNBC3 could bind BCL6 via its central region.

3.5 | LNBC3 reduces the ubiquitination of BCL6

We then investigated whether the LNBC3-BCL6 interaction affected the stability of BCL6. Silencing LNBC3 strongly decreased the protein levels of BCL6 (Figure 5A) whereas overexpressing LNBC3 markedly increased BCL6 abundance (Figure 5B). Treatment

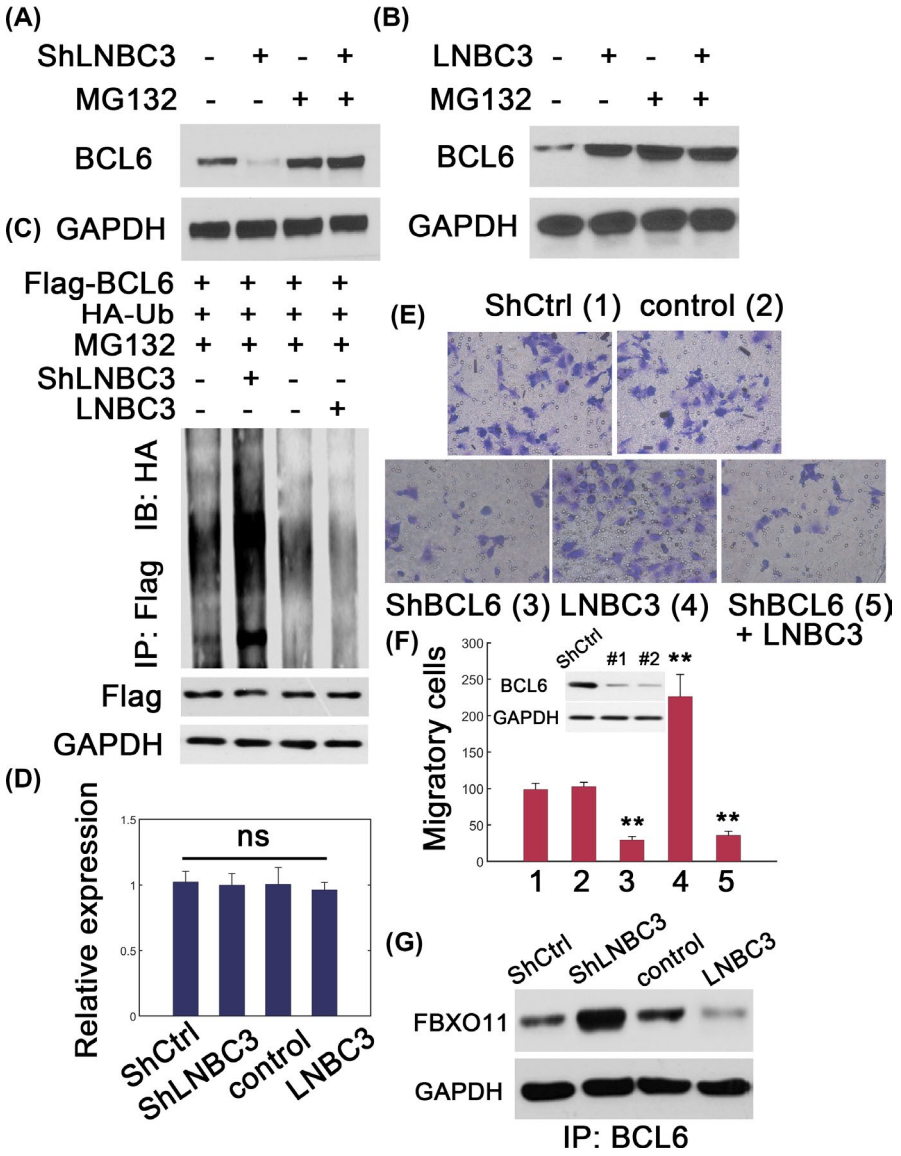

FIGURE 5 LNBC3 destabilizes BCL6 via proteasomal ubiquitination. A, BCL6 expression in A549 cells transfected with ShCtrl or shLNBC3 and treated with DMSO (MG132-) or proteasome inhibitor MG132 (MG132+, 20 mg/mL). B, BCL6 expression in A549 cells with or without lentiviral LNBC3 transfection (LNBC3) treated with either DMSO or MG132. C, Ubiquitination of BCL6 in ShCtrl or shLNBC3 treated A549 cells expressing full-length Flag-tagged BCL6 (Flag-BCL6). D, Relative expression of BCL6 mRNA with LNBC3 knockdown or overexpression. E, Migratory capacity of A549 cells transfected with ShCtrl, empty lentiviral vector (control), ShBCL6, lentiviral LNBC3 vector (LNBC3), or combined lentivirus-mediated LNBC3 overexpression and ShBCL6. The case number was labeled in brackets. F, Quantification of migration assay in (E). The knockdown efficiency of two BCL6 shRNAs was shown as inset. ShBCL6#2 was chosen for higher efficiency. G, Altered FBXO11/BCL6 interaction with LNBC3 knockdown or overexpression. $^{**}P < .01$

of A549 cells with proteasome inhibitor MG132, however, the effect of changing LNBC3 on BCL6 expression was diminished (Figure 5A,B). We noted that the ubiquitination of BCL6 was greatly facilitated by LNBC3 silence (Figure 5C). Meanwhile, overexpressing LNBC3 strongly inhibited ubiquitin ligation toward BCL6 (Figure 5C). LNBC3 knockdown or overexpression did not affect the *BCL6* mRNA levels (Figure 5D). Silencing BCL6 substantially inhibited the migration of A549 cells whereas LNBC3 overexpression advanced A549 migration as expected (Figure 5E,F). However, simultaneous BCL6 silence and LNBC3 overexpression nearly completely abolished the migration promoting effect of LNBC3 (Figure 5E,F). Previous work showed that FBXO11 can target BCL6 for degradation via proteasomal pathway.[12] We further verified whether LNBC3 affected the interaction between FBXO11 and BCL6. Immunoprecipitation results showed that overexpressing LNBC3 significantly decreased the binding FBXO11 with BCL6 whereas LNBC3 silence promoted FBXO11-BCL6 interaction (Figure 5G). These results suggested that LNBC3 could stabilize BCL6 via reducing BCL6 ubiquitination.

4 | DISCUSSION

In current work, we have identified a novel oncogenic lncRNA termed LNBC3 in NSCLC. We found that decreasing LNBC3 expression by ASOs may effectively inhibit NSCLC suppression suggesting that LNBC3 could act as a potential target for therapeutic intervention. Mechanistic study demonstrated that LNBC3 could interact with BCL6, a well characterized oncogenic factor and increased the stability of BCL6. Therefore, LNBC3 can possibly facilitate NSCLC development via its modulation on BCL6 turnover. Whether LNBC3 plays an oncogenic role in other types of cancers remains to be determined. Furthermore, lncRNAs can also function as a competitive endogenous RNA to regulate various biological processes.[13] This possibility should be investigated in future.

We have identified that LNBC3 interacts with BCL6 and modulates its protein turnover. Notably, the BCL6 gene covers around 24 kb on chromosome 3q27 and is characterized by an N-terminal BTB/POZ domain.[14] The central region of BCL6 can mediate the

recruitment of MTA3 repressor to abolish a diverse set of target genes.[14,15] Several strategies have been reported to regulate BCL6 function. Acetylation within the BCL6 PEST domain has been shown to diminish BCL6 ability to recruit corepressors.[16] Furthermore, DNA damage can also phosphorylate BCL6 via ATM checkpoint kinase and result in proteasomal degradation of BCL6.[14] The tumor suppressor p53 has been reported as a direct BCL6 target and BCL6 can inhibit apoptosis by decreasing p53 expression.[17] *BCL6* is usually regarded as an oncogene and undergoes rearrangements at chromosome 3q27 especially in diffuse large B-cell lymphoma (DLBCL, ~40%) leading to deregulated BCL6 overexpression.[18] Notably, genomic deletions or somatic mutations depleting CREBBP and EP300 in cancer cells frequently result in decreased histone acetyl transferase (HAT) activity and BCL6 hyperactivation.[19] Given the multiple oncogenic roles of BCL6, increasing BCL6 expression may contribute largely to cancer progression. Our current work has provided additional insight into the post-translational regulation of BCL6 via a new lncRNA LNBC3 in NSCLC. We found that LNBC3 interacts with BCL6 and decreases the ubiquitination of BCL6 possibly via reduced FBXO11-BCL6 binding. Intricate design of antisense oligonucleotides (ASOs) targeting LNBC3 might be a promising way to annihilate LNBC3 levels in NSCLC.

The notion that BCL6 might serve as a target for pharmaceutical intervention is motivated by a recent bioinformatics search.[20] Deb et al have identified that *BCL6* locus may represent a vulnerable point to treat NSCLC downstream of common oncogenes.[20] Previous report has also demonstrated that miR-187-3p mitigates *BCL6* expression and inhibits NSCLC development (eg, A549 and SPC-A1).[21] Therefore, BCL6 represents a novel vulnerability and therapeutic target especially in lung cancer. BCL6 and MYC are putative prognostic factors, and analogous results can also be found in NSCLC.[20] As a result, targeted delivery to inhibit BCL6 expression is strongly required. Since LNBC3 is a novel lncRNA responsible for maintaining BCL6 stability, we sought the possibility of taking LNBC3 as a therapeutic target via regulating BCL6 abundance. We designed specific antisense oligonucleotides, several of which have displayed promising efficiency for *LNBC3* silence. RNA interference has significant drawbacks including low efficiency of cellular uptake and short of stability.[22] The modified ASOs by phosphorothioate can enter cells with high efficiency to eradicate prostate cancer (PC) cells.[23] Specifically, an antisense oligonucleotide IONIS-APO(a)$_{Rx}$ has been used to modulate apolipoprotein to treat calcific aortic valve stenosis in a clinical trial.[24] In current work, designing ASOs targeting LNBC3 has provided an alternative way to inhibit NSCLC progression. Therefore, LNBC3 might be designated as a potential NSCLC-associated transcript to eradicate NSCLC malignancy. Improvement on the uptake efficiency of ASOs targeting LNBC3 with low or minimal toxicity deserves further investigation.

In conclusion, we have identified a novel lncRNA LNBC3 and evaluated its role during NSCLC progression. LNBC3 exerts its oncogenic effect probably by interacting and stabilizing BCL6 in NSCLC. We have used a strategy to efficiently inhibit BCL6 expression via LNBC3-targeted ASOs. Taken together, the LNBC3-BCL6 axis may provide a novel target for therapeutic intervention.

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CONFLICT OF INTEREST

The authors declare no competing interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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