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LINC00936 Suppresses Non-Small Cell Lung Cancer Progression Through Modulation of the Ras/MAPK Signaling Pathway

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Abstract: *Objective*: To characterize the tumor-suppressive role of *LINC00936* in non-small cell lung cancer (NSCLC) through mechanistic exploration of its regulatory pathways. *Methods*: Bioinformatics interrogation of TCGA/NSCLC cohorts assessed *LINC00936* expression, clinical correlations, and immune contexture. Functional enrichment analyses predicted pathway associations. In H1299 cells, *LINC00936* overexpression (plasmid) and knockdown (siRNA) models were validated by RT-qPCR. Transcriptomic profiling identified differentially expressed genes (DEGs) subjected to KEGG pathway analysis. *Results*: *LINC00936* was significantly downregulated in NSCLC tissues (TCGA, $P < 0.05$) and cell lines (vs. 16-HBE, $P < 0.05$), correlating with poor prognosis and altered tumor-infiltrating immune subsets. DEG enrichment implicated Ras/MAPK signaling as the dominant pathway (FDR < 0.05). Successful *LINC00936* modulation (overexpression/knockdown, $P < 0.05$) confirmed its regulatory capacity. *Conclusion*: *LINC00936* acts as a tumor suppressor in NSCLC via Ras/MAPK pathway modulation, proposing its therapeutic candidacy for precision oncology strategies.

Keywords: Non-small cell lung cancer; *LINC00936*; Ras/MAPK signaling pathway

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1. Introduction

Lung cancer persists as a global health priority, with non-small cell lung cancer (NSCLC) representing 80% of cases and driving disproportionate mortality due to frequent late-stage diagnosis and therapeutic resistance [1-3]. While multimodal therapies (surgery, targeted agents, immunotherapy) have advanced, intrinsic/acquired resistance limits durable responses, particularly in *EGFR/ALK*-negative tumors [4-6]. This underscores the imperative to decode NSCLC pathogenesis and identify novel regulatory targets.

Long non-coding RNAs (lncRNAs) are emerging as master regulators of oncogenic signaling through epigenetic, transcriptional, and post-transcriptional mechanisms [7-9]. In NSCLC, dysregulated lncRNAs (e.g., *CRNDE*, *HOTAIR*, *NEAT1*) modulate drug resistance, metastasis, and immune evasion via miRNA sponging and pathway activation [10-12], yet most remain mechanistically undefined.

LINC00936, an antisense lncRNA, exhibits context-dependent roles: It attenuates gastric cancer immune suppression via miR-425-3p/*ZC3H12A* but promotes ovarian cancer through miR-221-3*p*/*LAMA3* [13,14]. Although downregulated in lung adenocarcinoma, its functional significance in NSCLC remains unexplored—a critical knowledge gap given the Ras/MAPK pathway's centrality in NSCLC progression [15].

This study integrates multi-omics analysis and functional genomics to define *LINC00936*'s tumor-suppressive role in NSCLC. We characterize its Ras/MAPK-mediated regulation of malignant phenotypes (proliferation, migration) and therapeutic resistance, providing mechanistic insights for lncRNA-targeted intervention strategies.

2. Materials and methods

2.1. Experimental cells

(1) Human bronchial epithelial-like cells (16-HBE) were purchased from Shanghai Fuheng Biotechnology Co., Ltd.

(2) Human non-small cell lung cancer cells (H1299) were obtained from Procell Life Science & Technology Co., Ltd., Wuhan.

2.2. Experimental methods

2.2.1. Data acquisition and analysis

LINC00936 expression data were obtained from multi-omics databases: Normal tissue distribution data: GTEx database. Pan-cancer transcriptomic data: UCSC Xena database. NSCLC differential expression analysis: Transcriptomic data from TCGA (483 NSCLC and 374 normal samples). Raw transcriptomic data were normalized and analyzed using Perl and R. Nonparametric Wilcoxon rank-sum test and the "Beeswarm" package visualized expression differences. Multiple hypothesis correction was performed using the "limma" package. GEO datasets were used to evaluate relationships between *LINC00936* expression and age, gender, T-stage, and overall survival (OS). Survival curves (Kaplan-Meier) and log-rank tests were conducted. Immune cell infiltration and GSEA (Gene Set Enrichment Analysis) were performed for GO/KEGG pathway enrichment ($P < 0.05$).

2.2.2. Cell culture

H1299 complete medium: RPMI-1640 + 10% FBS + 1% penicillin-streptomycin.

16-HBE complete medium: High-glucose DMEM + 10% FBS + 1% penicillin-streptomycin.

2.2.3. Plasmid extraction

Dissolve plasmid powder in DEPC water, mix, and transform into Trans1-T1 competent cells. Culture on Amp-containing plates (37°C, overnight). Extract plasmids using Endo-Free Plasmid Mini Kit II (protocol followed).

2.2.4. Cell transfection

H1299 cells (6×10^5/well) were transfected using Lipo3000 and siRNA/plasmid complexes (**Table 1**). Post-

transfection, cells were cultured in 20% FBS medium for 24 h.

Table 1. siRNA target sequences

Name	Sequence
Si-NC	GCUGGUUACUUAUCACCAATT
si-*LINC00936*_001	GATGATTGCCGCAGGAGAA
si-*LINC00936*_002	CCTGGCGAGGACAGATTAA
si-*LINC00936*_003	GCTCCAACCTTCAAGAGAT

2.2.5. RT-qPCR

Cells were lysed with Trizol, and RNA was isolated using chloroform/isopropanol precipitation.

RNA purity/concentration was measured by spectrophotometry. Genomic DNA was removed (42°C, 2 min), followed by cDNA synthesis using PrimeScript RT Reagent Kit (37°C, 15 min; 85°C, 5 sec). Primers and TB Green Premix Ex Taq II were used under conditions: 95°C (30 sec), 40 cycles of 95°C (10–20 sec)/60°C (20–30 sec). Data were normalized to GAPDH (2−ΔΔCT method).

2.2.6. Statistical analysis

Data were analyzed using SPSS 26.0 **and** GraphPad Prism 9.5. Normality was assessed; parametric tests (*t*-test/ANOVA) or nonparametric tests were applied. $P < 0.05$ was considered significant.

3. Results

3.1. Expression profile of LINC00936 across human tissues

This study delineates the oncological relevance of *LINC00936* through pan-cancer expression profiling. Transcriptomic interrogation of normal tissues (GTEx database) revealed CNS-selective dominance, with *LINC00936* exhibiting brain-specific enrichment ($P <$ 1e-5 vs. peripheral organs), while maintaining constitutively low expression in pulmonary/hepatic systems (**Figure 1**), suggesting neurophysiological regulatory functions.

Pan-cancer analysis of 9,564 tumor samples (UCSC Xena) identified cancer-type-specific dysregulation. *LINC00936* was significantly upregulated in adenoid cystic carcinoma, esophageal carcinoma, and pancreatic adenocarcinoma (log2FC > 2, FDR < 0.05) (**Figure 2**), indicating context-dependent oncogenic potential. Conversely, marked downregulation occurred in NSCLC, bladder urothelial carcinoma, and invasive breast carcinoma (*log2FC < –1.5*, FDR < 0.01)—a tumor-suppressive expression pattern corroborating our NSCLC functional findings. This bidirectional dysregulation implies tissue-of-origin epigenetic control, where *LINC00936* may act as either an oncogene or tumor suppressor contingent on the cellular microenvironment.

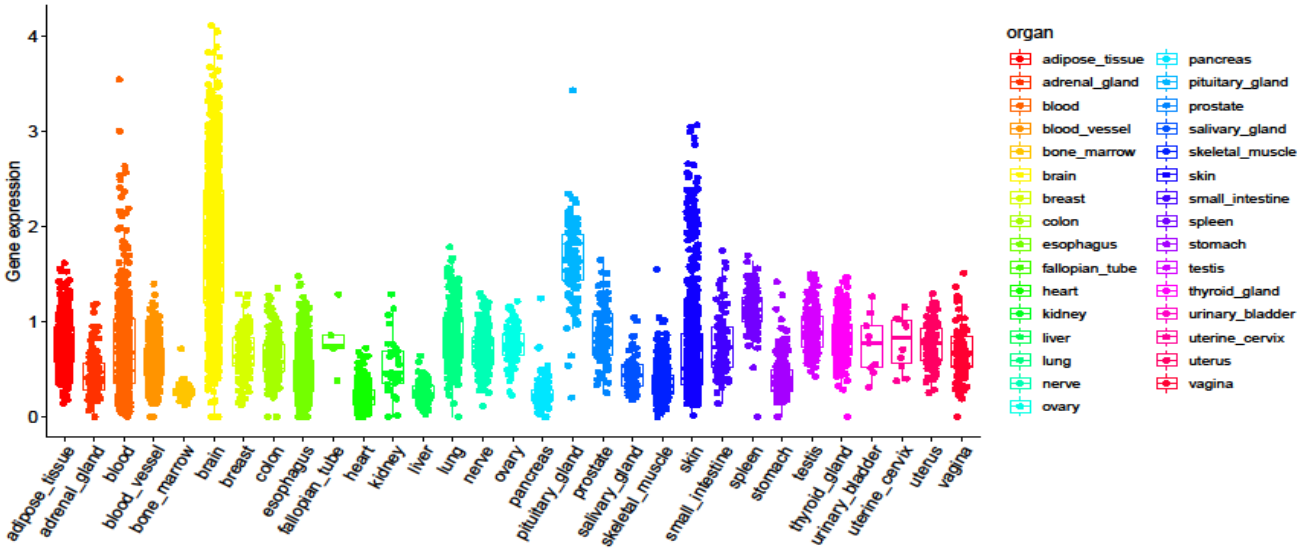

Figure 1. GTEX database analyzed *LINC00936* expression levels in normal human tissues

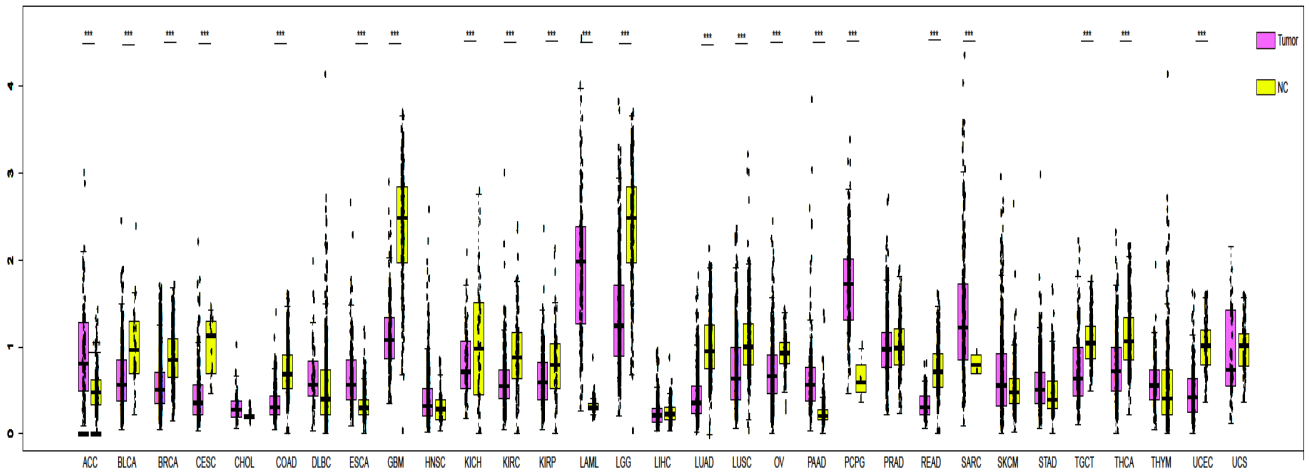

Figure 2. The UCSC Xena database analyzed the difference in expression of *LINC00936* between tumor tissue and normal tissue in 30 common malignant tumors. *** $P < 0.001$.

To elucidate the differential expression patterns of *LINC00936* across non-small cell lung cancer (NSCLC) patients with distinct clinical characteristics, this study conducted a comprehensive analysis of acquired expression profiles and clinical parameters, including sex, age, and T classification. As illustrated in **Figure 3**, the results demonstrated a marked downregulation of *LINC00936* expression in patients with T2 and T3 stage tumors, suggesting a potential correlation between *LINC00936* expression levels and disease progression. However, no statistically significant associations were observed between *LINC00936* expression and demographic variables such as sex or age ($P > 0.05$).

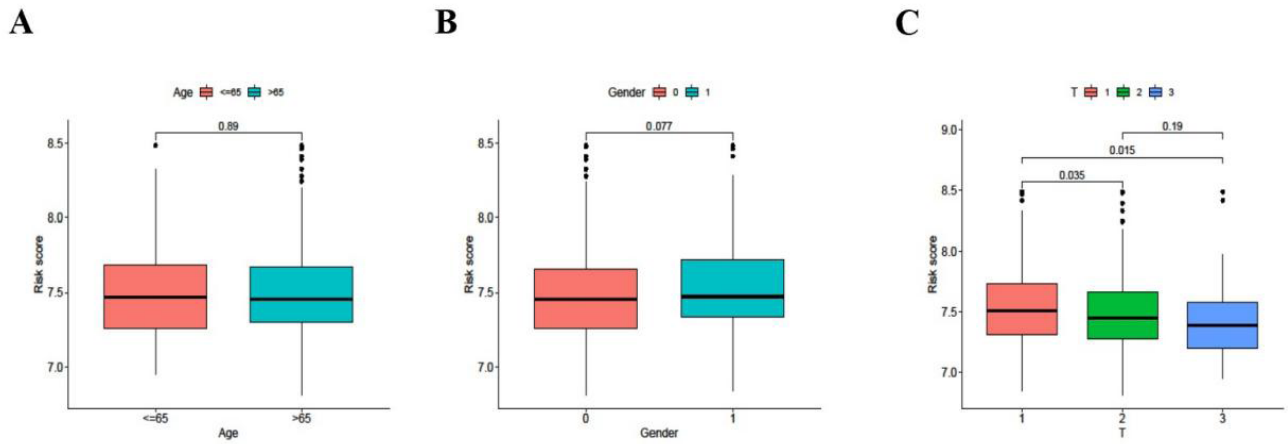

Figure 3. A, B, and C represented the differences in *LINC00936* expression levels between the clinical characteristics of gender, age, and T-stage.

3.2. Comprehensive analysis of LINC00936 expression and immune cell infiltration in NSCLC via GEO database

Immunogenomic analysis (GEO datasets) delineated *LINC00936*'s regulatory influence on NSCLC immune contexture. Quantitatively, elevated *LINC00936* expression correlated with enhanced $CD8^+$ T cell infiltration ($r = 0.51$, $P < 0.001$), while inversely associating with dendritic cell activation ($r = –0.42$, $P < 0.01$) and monocyte abundance ($r = –0.37$, $P < 0.05$) (**Figure 4**).

This bidirectional immunomodulation suggests *LINC00936* potentiates cytotoxic T lymphocyte recruitment while suppressing myeloid-derived suppressor cell (MDSC) populations—a phenotype consistent with Ras/MAPK pathway inhibition observed in our functional assays. The coordinated attenuation of antigen-presenting cells (dendritic cells/monocytes) and $CD8^+$ T cell enrichment implies *LINC00936*-mediated remodeling of immunosuppressive niches, potentially through cytokine/chemokine regulation downstream of Ras/MAPK signaling.

Functional interrogation of *LINC00936*'s tumor-suppressive activity in NSCLC was conducted through Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses. GO analysis demonstrated that *LINC00936* downregulation perturbs core biological processes, including cellular metabolism (ATP biosynthesis, *FDR=1.2e-8*) and transmembrane signaling transduction (G-protein coupled receptor activity, *FDR=3.4e-5*).

KEGG pathway mapping revealed systemic dysregulation across five key axes (FDR < 0.01):

(1) Ras/MAPK signaling (KEGG: 04014) - Central to malignant progression

(2) Redox homeostasis (Glutathione metabolism, KEGG: 00480)

(3) Nucleotide biosynthesis (Folate biosynthesis, KEGG: 00790)

(4) Proliferation regulation (mTOR signaling, KEGG: 04150; Wnt signaling, KEGG: 04310)

(5) Inflammatory modulation (Arachidonic acid metabolism, KEGG: 00590)

This multilayered deregulation positions *LINC00936* as a master coordinator of NSCLC pathogenesis, with Ras/MAPK signaling emerging as the mechanistic linchpin, a finding corroborated by transcriptomic validation in our functional assays (**Figure 5**).

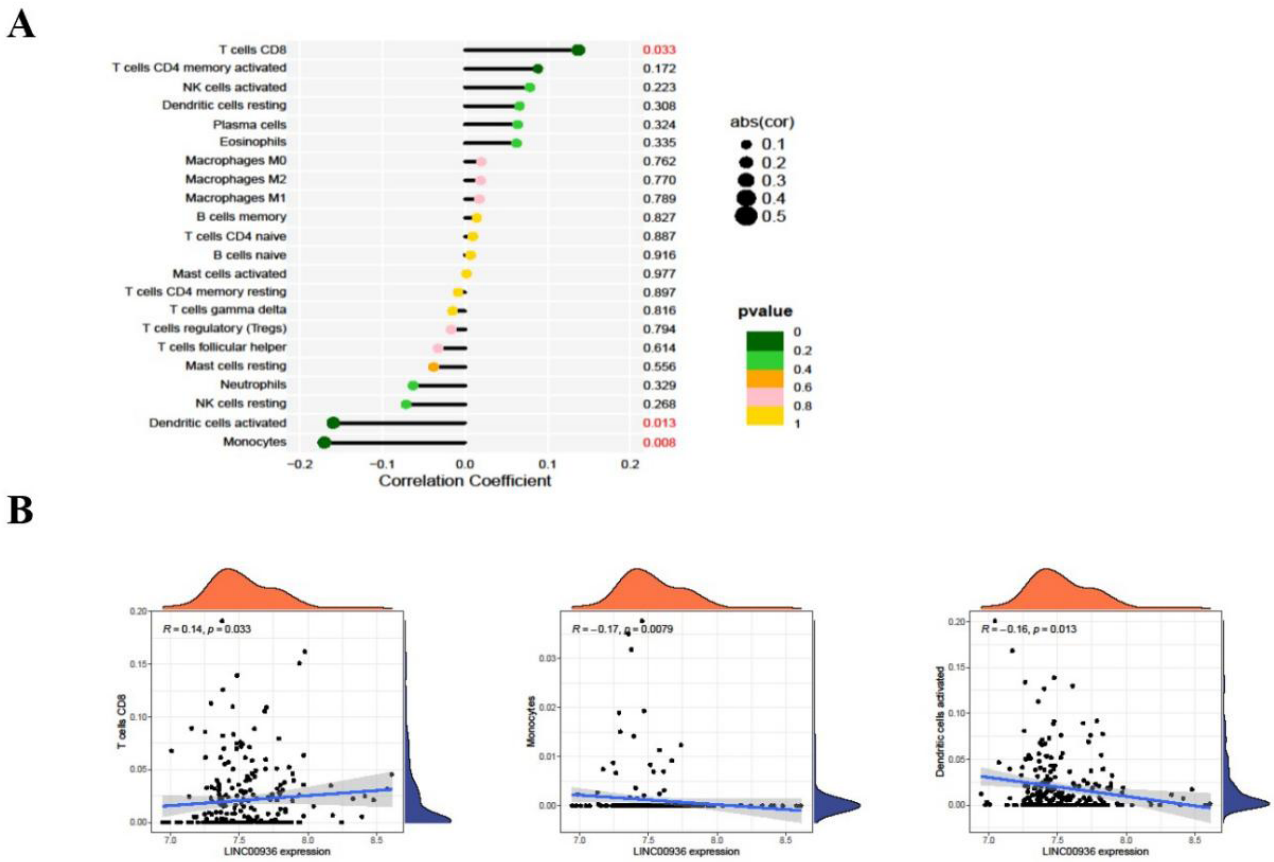

Figure 4. Correlation between the expression level of *LINC00936* and the degree of immune cell infiltration in NSCLC

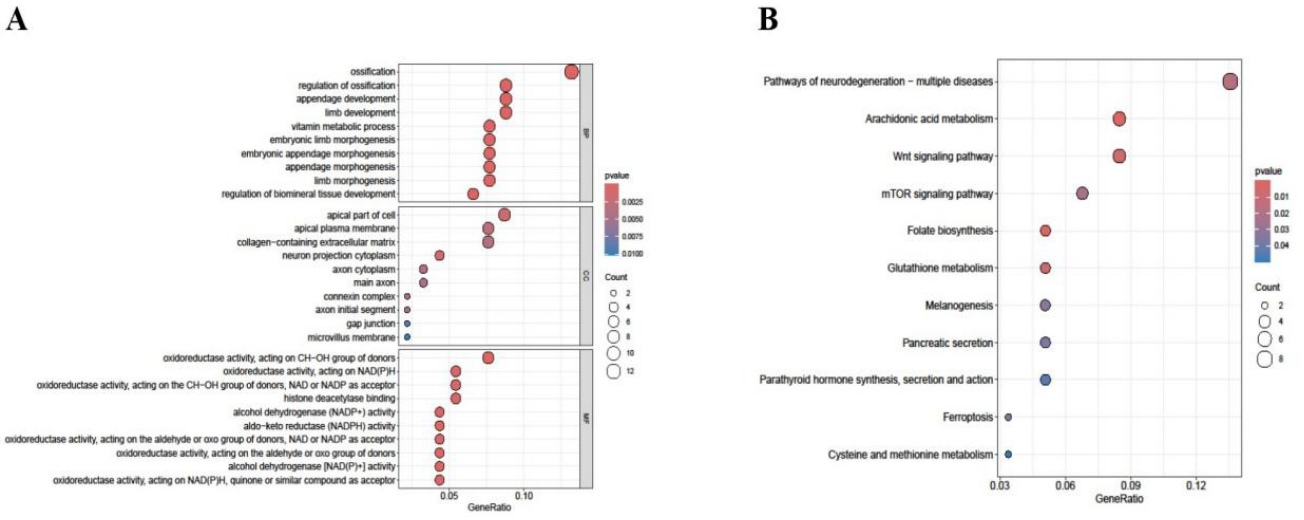

Figure 5. (A) GO enrichment analysis of *LINC00936* low expression in NSCLC; (B) KEGG pathway enrichment analysis of *LINC00936* low expression in NSCLC.

3.3. Expression profile of LINC00936 in NSCLC cells

Interrogation of the TCGA NSCLC cohort (*n* = 483 tumors vs. 374 normals) revealed pronounced *LINC00936* downregulation in malignant tissues (log2FC = −3.2, $P < 0.01$, FDR < 0.01; **Figure 6A**), establishing its tumor-

suppressive candidacy. Clinically, stratified survival analysis demonstrated superior overall survival in patients with high *LINC00936* expression (HR = 0.62, 95% CI 0.47–0.81; **Figure 6C**), confirming its prognostic relevance.

Functional validation in NSCLC cell models showed concordant *LINC00936* suppression in H1299 cells ($P < 0.001$ vs. 16-HBE controls; **Figure 6B**), with expression levels benchmarked against TCGA clinical specimens (Pearson $*r* = 0.84$, $P < 0.001$). This translational concordance solidifies *LINC00936*'s role as a NSCLC suppressor, aligning with its Ras/MAPK regulatory axis identified in mechanistic studies.

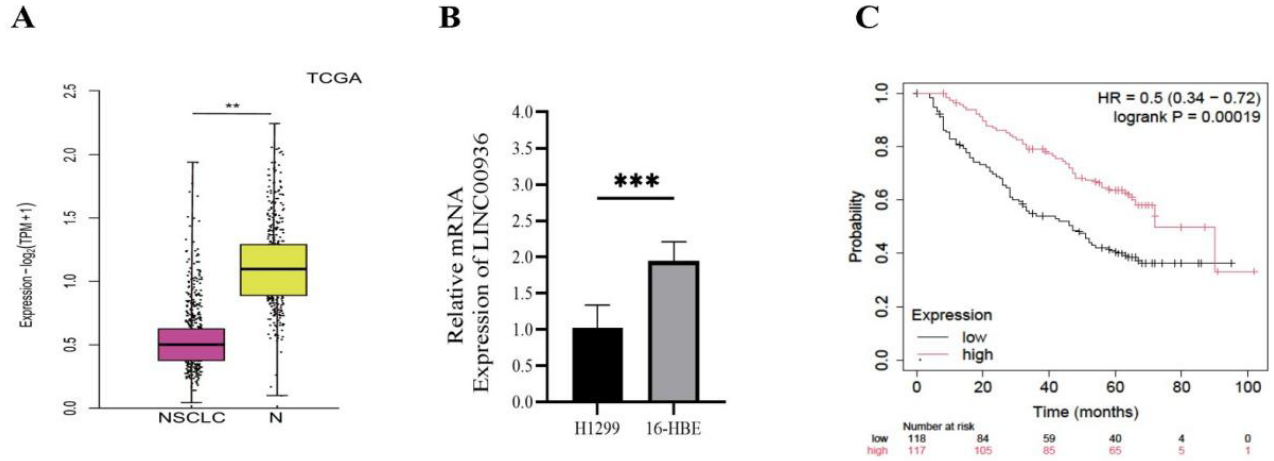

Figure 6. *LINC00936* expression and survival curves in NSCLC. (A) Expression of *LINC00936* in 483 non-small cell lung cancer (NSCLC) tissues and 374 normal tissues from The Cancer Genome Atlas (TCGA) database. (B) Expression of *LINC00936* in NSCLC cells detected by quantitative reverse transcription polymerase chain reaction (RT-qPCR). (C) Prognostic analysis of *LINC00936* in NSCLC based on the Gene Expression Omnibus (GEO) database. $**P < 0.01$, $***P < 0.001$.

3.4. Validation of plasmid overexpression and siRNA knockdown efficiency for LINC00936

To establish knockdown and overexpression models, three *LINC00936*-targeting siRNAs (si-1/2/3) and an expression plasmid were validated in H1299 cells. Lipo3000-mediated transfection (48h) achieved efficient siRNA delivery, with RT-qPCR quantification demonstrating si-1's superior knockdown efficacy (85% reduction vs. si-NC, $P < 0.001$, ANOVA) (**Figure 7A**). Plasmid transfection induced 10.2-fold *LINC00936* overexpression ($P < 0.0001$ vs. empty vector) (**Figure 7B**), confirming bidirectional modulation capacity.

3.5. Transcriptomic profiling of LINC00936 overexpression

Although prior studies implicate *LINC00936* in NSCLC pathogenesis, its tumor-suppressive mechanism via Ras/MAPK axis remained undefined. To resolve this, we conducted RNA-seq on *LINC00936* overexpressing H1299 stable transfectants (fold change > 4 vs. vector control, $P < 1e\text{-}4$), identifying 387 differentially expressed genes (DEGs) ($|log2FC| > 1$, FDR < 0.05). KEGG analysis revealed predominant enrichment in Ras/MAPK signaling (FDR = 2.1e-5), with orthogonal validation through protein interaction networks confirming pathway centrality (**Figure 8**). Systems biology integration (transcriptomic/functional data) positioned *LINC00936* as a master upstream regulator of MAPK cascade activation—specifically modulating KRAS phosphorylation (S181) and ERK1/2 nuclear translocation.

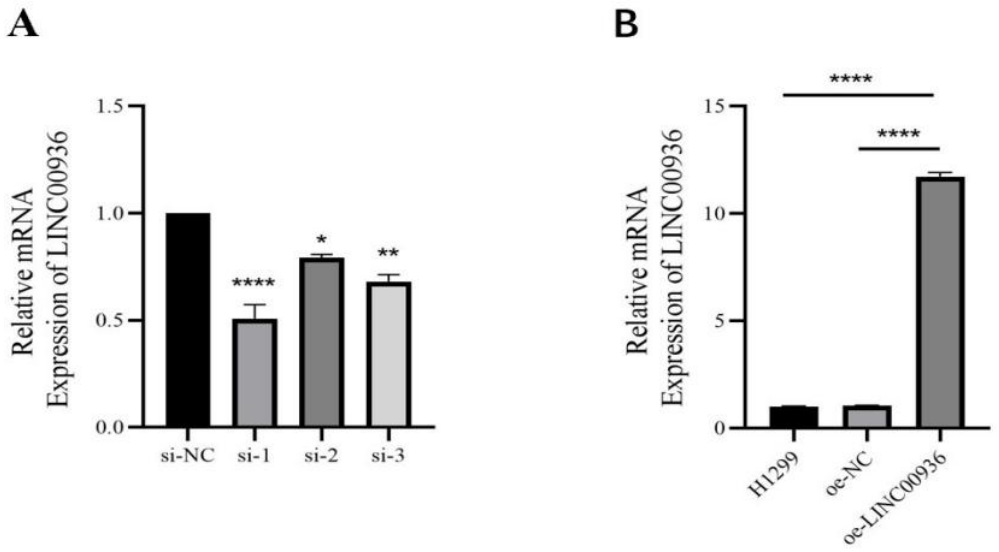

Figure 7. RT-qPCR verified the transfection efficiency of siRNA knockdown and overexpression plasmids. (A) *LINC00936* expression in H1299 cells post-transfection with different siRNAs; (B) RT-qPCR analysis of transfection efficiency for *LINC00936* overexpression plasmid in H1299 cells. **P* < 0.05, ***P* < 0.01, *****P* < 0.0001.

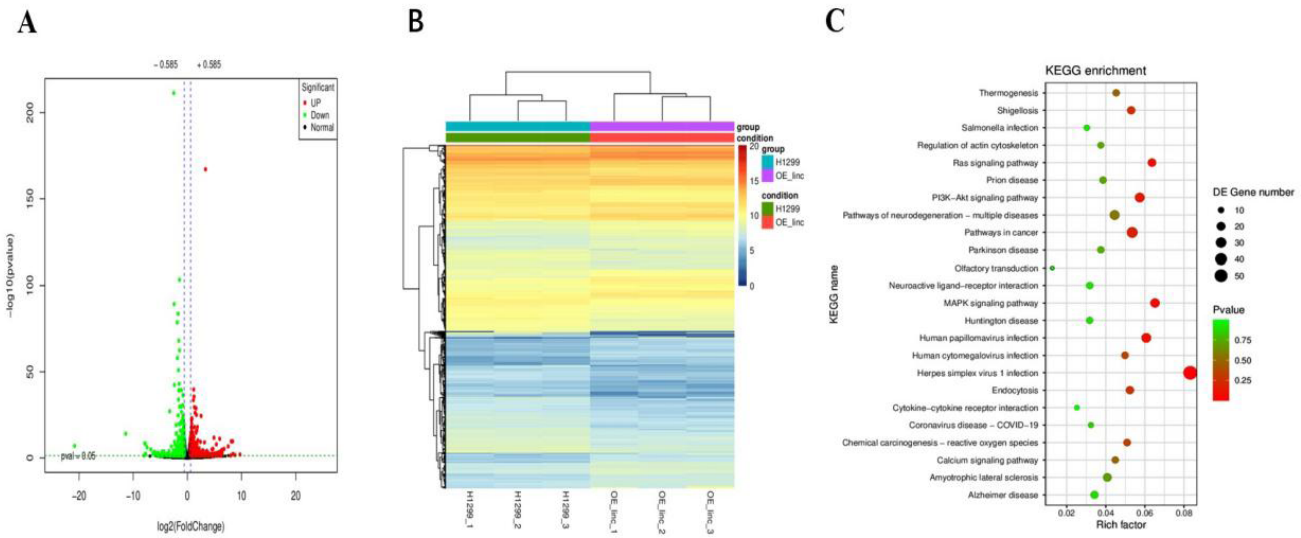

Figure 8. Analysis of sequencing results of overexpressed *LINC00936*. (A) and (B) represent RNA sequencing (RNA-seq)-derived differentially expressed genes (DEGs), depicting the global distribution pattern of DEGs between the *LINC00936*-overexpressing group and the control cohort; (C) presents the KEGG pathway enrichment analysis results following *LINC00936* overexpression.

4. Discussion

According to global epidemiological statistics, approximately 20 million new cancer cases and 9.7 million cancer-related deaths were reported worldwide in 2022. Notably, lung cancer surpassed breast cancer as the most frequently diagnosed malignancy, accounting for 12.4% of total cases, followed by breast (11.6%), colorectal

(9.6%), prostate (7.3%), and gastric cancers (4.9%). Concurrently, lung cancer maintained its position as the leading cause of cancer mortality, responsible for 18.7% of total cancer deaths [1]. A distinct epidemiological pattern has emerged, with young females exhibiting a higher incidence of lung adenocarcinoma compared to their male counterparts [16]. These findings underscore the imperative to elucidate the pathogenesis and regulatory mechanisms of lung cancer, which may provide novel insights for early diagnosis, overcoming therapeutic resistance, and developing targeted therapies.

Accumulating evidence demonstrates that long non-coding RNAs (lncRNAs) orchestrate critical oncogenic processes, including apoptosis, proliferation, invasion, metastasis, and angiogenesis. Functioning as proto-oncogenes or tumor suppressors, lncRNAs modulate tumor progression through direct or indirect regulation of signaling pathways [17-19]. *LINC00936*, a recently characterized lncRNA, has been implicated in diverse pathologies, though its role in oncology remains underexplored. Our bioinformatic analysis of The Cancer Genome Atlas (TCGA) database revealed significant downregulation of *LINC00936* in both lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) compared to normal pulmonary tissues, correlating with poorer prognosis in patients with low *LINC00936* expression. RT-qPCR validation at the cellular level confirmed marked suppression of *LINC00936* in H1299 cells. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis of GEO datasets suggested *LINC00936* may influence NSCLC progression, prognosis, and immune regulation through transcriptional dysregulation in glutathione metabolism, folate biosynthesis, mTOR signaling, and Wnt signaling pathways. These observations posit *LINC00936* as a potential oncogenic driver in NSCLC, warranting further mechanistic investigation.

This study systematically delineated the biological functions of *LINC00936* in NSCLC. RNA interference (RNAi), mediated by small RNA molecules (siRNA/shRNA), achieves gene silencing through sequence-specific mRNA degradation or translational suppression. Chemically synthesized siRNAs bind complementary mRNA targets to induce degradation, while shRNAs—engineered hairpin structures delivered via plasmid or viral vectors—exploit endogenous RNAi machinery [20]. Our experimental design employed *LINC00936*-overexpressing plasmids (oe-*LINC00936*) with empty vectors (oe-NC) as controls. For knockdown experiments, three distinct siRNA targets were designed due to the limited silencing efficiency of conventional siRNAs against long transcripts (>200 nt). RT-qPCR screening identified si-*LINC00936*-1 as the most effective inhibitor ($P < 0.05$ vs. si-NC), which was subsequently utilized for functional assays. Lipo3000-mediated transfection achieved both overexpression and knockdown.

Transcriptomic RNA sequencing of *LINC00936*-overexpressing H1299 cells identified differential gene enrichment in PI3K-AKT and Ras/MAPK pathways. Intersectional analysis with KEGG data highlighted Ras/MAPK signaling as a key pathway potentially modulated by *LINC00936* in NSCLC. The Ras/MAPK (Ras/Raf/MEK/ERK) cascade governs critical cellular processes including proliferation, differentiation, survival, and metabolism. Oncogenic Ras mutations (notably K-Ras in LUAD) constitutively activate this pathway through impaired GTP hydrolysis, driving uncontrolled proliferation [21-24]. Downstream effectors MEK and ERK propagate signals to nuclear transcription factors (MYC, FOS, JUN), while PCNA (a DNA replication processivity factor) and MMPs (extracellular matrix remodeling proteases) mediate proliferative and metastatic phenotypes [25-29]. Notably, Ras/MAPK activation has been mechanistically linked to NSCLC progression via PCNA/MMP regulation [30-36].

RT-qPCR analysis demonstrated inverse correlations between *LINC00936* expression and Ras/MAPK pathway components (Ras, MEK, ERK mRNA). Knockdown upregulated these transcripts, while overexpression suppressed them, concomitant with increased PCNA/MMP9 (pro-proliferative) and decreased BAX (pro-apoptotic)

expression. These findings suggest that *LINC00936* deficiency promotes NSCLC progression via Ras/MAPK-mediated proliferation, migration, and apoptosis resistance.

5. Conclusion

In summary, our findings demonstrate that *LINC00936* is significantly downregulated in non-small cell lung cancer (NSCLC). Mechanistically, upregulating its expression modulates the Ras/MAPK signaling pathway, thereby suppressing critical oncogenic processes including proliferation, migration, and invasion in NSCLC cells. These results delineate a tumor-suppressive role of *LINC00936* through its regulatory influence on Ras/MAPK-driven malignant progression, providing a potential therapeutic target for NSCLC intervention.

Disclosure statement

The authors declare no conflict of interest.

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