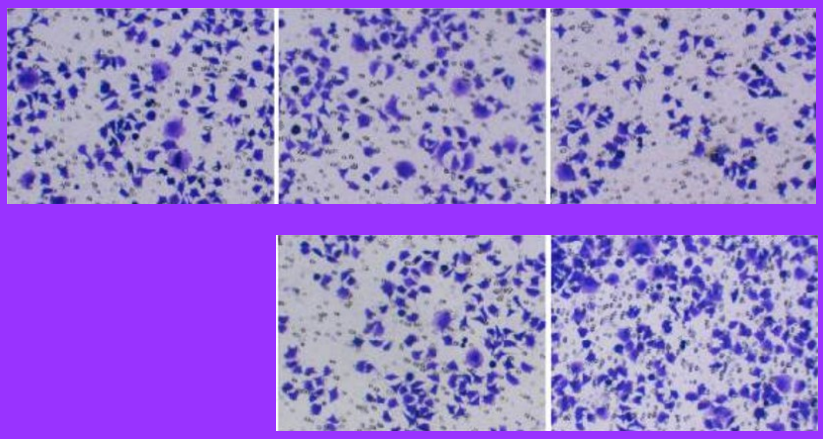

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microRNA-370-5p inhibits non-small cell lung cancer cell proliferation and migration and promotes apoptosis by targeting KPNA3

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Abstract

This study aimed to investigate the biological function of microRNA-370-5p (miR-370-5p) in non-small cell lung cancer (NSCLC) and its regulatory relationship with KPNA3. The expression levels of miR-370-5p and KPNA3 were examined in 72 NSCLC tissue samples and matched adjacent non-tumor tissues, as well as in cell lines (BEAS-2B, A549, H1299, and H460). A549 cells were transfected with miR-370-5p mimic, miR-370-5p inhibitor, or KPNA3 overexpression plasmids. Cell viability was assessed using the CCK-8 assay, migration was measured by Transwell assays, and apoptosis was evaluated via flow cytometry. Dual-luciferase reporter assays confirmed the direct binding between miR-370-5p and KPNA3. miR-370-5p was down-regulated, whereas KPNA3 was upregulated in NSCLC tissues and cells. Overexpression of miR-370-5p inhibited cell proliferation and migration and increased apoptotic rates, while inhibition of miR-370-5p inhibition exerted opposite effects. KPNA3 overexpression partially reversed the effects of miR-370-5p, indicating that KPNA3 functions as a downstream effector of miR-370-5p. miR-370-5p suppresses NSCLC cell growth and migration while promoting apoptosis by directly targeting KPNA3.

Introduction

Lung cancer remains the leading cause of cancer-related death worldwide, with an estimated 2.5 million new cases and 1.8 million deaths in 2022 (Bray et al., 2024). Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer diagnoses (Hu et al., 2021) and is characterized by aggressive biological behavior. Many patients present with advanced or metastatic disease and experience poor long-term survival (Chang et al., 2020). Established risk factors for NSCLC include active cigarette smoking, exposure to secondhand smoke, and occupational and environmental carcinogens such as radon, asbestos, and ambient air pollution. Additionally, inherited genetic susceptibility further modifies individual risk (Thandra et al., 2021). Although therapeutic advances—particularly targeted therapies and immunotherapies—have led to incremental improvements in short-term outcomes, population-based data indicate that the overall 5-year survival rate for patients with NSCLC, especially those with advanced disease, remains unsatisfactory (Chang et al., 2020, Siegel et al., 2024), highlighting the urgent need for more effective management strategies.

Accumulating evidence highlights the essential regulatory role of microRNAs (miRS) in the initiation and progression of NSCLC (El Founini et al., 2021, Lobera et al., 2023, Samson and Parvathi, 2023). Among these, miR-370 and its mature form miR-370-5p have been

increasingly recognized as potential tumor suppressors (Feng et al., 2022, Ji et al., 2022, Ye et al., 2023). Studies have demonstrated that miR-370-5p exerts anti-tumor effects in NSCLC by inhibiting cell proliferation, inducing cell-cycle arrest through p21 activation, and suppressing migration and invasion in A549 cells (Li et al., 2017). Additionally, miR-370 has been shown to restrain NSCLC progression by directly targeting oncogenic molecules such as TRAF4, thereby impairing tumor growth and metastatic potential (Chen et al., 2015). These findings suggest that loss or down-regulation of miR-370-5p may contribute to malignant behavior in NSCLC through the deregulation of multiple downstream oncogenic pathways.

In contrast, karyopherin family proteins, which mediate the nuclear transport of key transcription factors and signaling molecules, have been implicated in tumorigenesis and cancer progression in several malignancies (Chen et al., 2024, Hu et al., 2025). KPNA3 has been associated with the malignant progression of various cancers. In triple-negative breast cancer (TNBC), KPNA3 promotes epithelial–mesenchymal transition (EMT) and enhances invasive capacity by facilitating the nuclear transport of key signaling factors (Choi et al., 2023). Its oncogenic role has also been observed in colorectal cancer, where KPNA3 overexpression accelerates tumor cell proliferation and invasion (Chen et al., 2020). Nevertheless, its functional role in NSCLC remains insufficiently characterized and has not yet been systematically explored. This knowledge gap underscores the need to further investigate whether dysregulated miRs, including miR-370-5p, contribute to NSCLC progression by influencing KPNA3. Clarifying these potential interactions could provide new insights into NSCLC pathobiology and offer promising molecular targets for therapeutic intervention.

Materials and Methods

Study subjects

Seventy-two patients with NSCLC who underwent surgical treatment at the Qingpu Branch of Zhongshan Hospital, Fudan University, between December 2018 and December 2020 were enrolled. Tumor tissues and matched adjacent non-tumor tissues (located ≥ 3 cm from the lesion) were collected during surgery and immediately preserved. All specimens were pathologically verified. Inclusion criteria: NSCLC confirmed by histopathology; no history of other malignancies; and no prior anti-cancer treatment before enrollment. Exclusion criteria: Presence of any additional malignant tumors; refusal to provide tissue samples for research; and lung lesions originating from non-primary metastatic tumors.

Cell culture

The NSCLC cell lines A549, H1299, and H460, along with the bronchial epithelial cell line BEAS-2B, were obtained from the American Type Culture Collection (ATCC, USA). Cells were cultured in DMEM (Thermo Fisher Scientific, USA) supplemented with 10% fetal bovine serum (Gibco, USA) and standard concentrations of penicillin (100 U/mL) and streptomycin (100 µg/mL). Cultures were maintained under routine conditions-namely a humidified atmosphere with CO_2 at 37°C. Passaging was performed when the cell monolayer reached approximately 80% confluence (Zhang et al., 2022).

Cell transfection and experimental grouping

Synthetic miR-370-5p mimic, inhibitor, and their respective negative controls (NCs) were obtained from RiboBio (Guangzhou, China). The KPNA3 overexpression construct (pcDNA3.1-KPNA3, abbreviated as pc-KPNA3) and the empty pcDNA3.1 vector were purchased from GenePharma (Shanghai, China). Once the cells reached approximately 80% adherence, they were detached using trypsin and prepared for transfection. Lipofectamine 2000 (Invitrogen, USA) was used according to the manufacturer's instructions. Subsequent assays were performed 48 hours post-transfection (Zhang et al., 2019).

Cells were allocated into the following groups: Blank, mimic NC, miR-370-5p mimic, inhibitor NC, miR-370-5p inhibitor, miR-370-5p mimic + pcDNA3.1, and miR-370-5p mimic + pc-KPNA3.

RT-qPCR

Total RNA from cultured cells and tissue samples was isolated using TRIzol reagent (Invitrogen, USA). RNA quantity and purity were evaluated immediately after extraction. Reverse transcription was performed with the PrimeScript™ RT reagent kit (Takara, China), and the resulting cDNA was stored at −20°C until analysis. Primer sequences of miR-370-5 and KPNA3 were designed (Table I) and synthesized by Genechem (China). Quantitative PCR was carried out on an ABI

Table I

Primer sequence for genes

Gene		Primer sequence (5′-3′)
miR-370-5p	F	5′-GCAGGTCACGTCTCTGC-3′
	R	5′-TGGTGTCGTGGAGTCG-3′
KPNA3	F	5′-ACAGTGGAACTGCGGAAGAAC-3′
	R	5′-TCAATCGGTGGATTTCTGTCAC-3′
U6	F	5′-CTCGCTTCGGCAGCACA-3′
	R	5′-AACGCTTCACGAATTTGCGT-3′
GAPDH	F	5′-TCCCATCACCATCTTCCA-3′
	R	5′-CATCACGCCACAGTTTTCC-3′

F: Forward; R: Reverse; GAPDH: glyceraldehyde-3-phosphate dehydrogenase

7500 real-time PCR system (ABI, USA) using Power SYBR™ Green PCR Master Mix (Thermo Fisher Scientific). U6 served as the internal reference for miR-370-5p, while GAPDH was used for KPNA3 normalization. Relative gene expression levels were calculated using the 2-ΔΔCt method (Sun et al., 2022).

Western blot analysis

Proteins from cultured cells were harvested using RIPA buffer (Beyotime). Protein concentration was quantified with a BCA assay (Beyotime) according to the supplied protocol. Equal amounts of lysates (30 µg per sample) were resolved on 10% SDS–polyacrylamide gels and transferred onto PVDF membranes (Sigma, USA) using a semi-dry transfer system. Membranes were blocked at room temperature with 5% skim milk (Beyotime) before overnight incubation at 4°C with primary antibodies—KPNA3 (1:1000, Bethyl Laboratories, USA) and GAPDH (1:5000, Proteintech). After three washes with TBST, membranes were incubated with HRP-conjugated goat anti-rabbit secondary antibody (1:1000, Abcam) for 1 hour at room temperature. Following additional washes, bands were visualized using an enhanced chemiluminescent reagent (Beyotime). GAPDH served as the loading control, and densitometric measurements were obtained using ImageJ (Zhao et al., 2021).

CCK-8 assay

Cells in the exponential growth phase were rinsed with PBS and detached from culture flasks using a mild trypsin treatment. The resulting suspension was gently triturated to obtain a single-cell suspension, which was then counted and diluted to approximately 2×10^4 cells/mL. Approximately 2×10^3 cells were distributed into each well of a 96-well microplate. Cell viability was assessed using the CCK-8 reagent (Dojindo, Japan). At the indicated time intervals (0, 24, 48, and 72 hours), 10 µL of the reagent was added to each well, followed by a 1-hour incubation. Optical density at 450 nm was measured using a microplate reader to quantify metabolic activity (Xu et al., 2025).

Flow cytometry

Cells harvested during exponential growth were gently detached using EDTA-free trypsin (Bioss, China), collected into flow cytometry tubes, and pelleted by centrifugation. After discarding the supernatant, the cells were rinsed three times with chilled PBS and resuspended to obtain a uniform suspension. Apoptotic events were quantified using an annexin V-FITC/PI dual-staining kit (Beyotime). For staining, 5 µL Annexin V-FITC and 10 µL PI were added to the cell suspension and incubated for 15 min at room temperature in the dark. Samples were subsequently analyzed on a flow cytometer (BD Biosciences, USA) (Shen et al., 2021).

Transwell assay

Cell motility was assessed using a Transwell migration system (Becton Dickinson, USA). Post-transfection cells in the logarithmic growth phase were harvested, washed twice with serum-free medium, resuspended, and counted. A total of 5×10^4 cells were seeded into the upper chamber containing serum-free medium, while the lower chamber was filled with 500 µL RPMI-1640 supplemented with 20% FBS as a chemoattractant. The inserts were incubated at 37°C for 24 hours. After incubation, non-migrated cells on the upper membrane surface were gently removed. The chambers were rinsed with PBS, and migrated cells on the underside of the membrane were fixed with 4% paraformaldehyde for 10 minutes and stained with crystal violet. Images were captured using a light microscope, and migrated cells were quantified with ImageJ (Liao and Peng, 2020).

Dual luciferase reporter gene assay

The potential interaction between miR-370-5p and the 3′ UTR of KPNA3 was initially predicted using the targetScan database (https://www.targetscan.org/vert_72/). Based on the predicted binding motif, DNA fragments containing the wild-type KPNA3 3′UTR sequence were synthesized and inserted downstream of a luciferase reporter to generate the KPNA3-WT construct. A corresponding mutant reporter (KPNA3-MUT), in which the predicted miRNA binding site was specifically altered, was generated in parallel. A549 cells in logarithmic growth phase were seeded into 96-well plates, and when the monolayers reached approximately 70% confluence, reporter constructs (WT or MUT) were co-transfected with either the miR-370-5p mimic or the matched NC using Lipofectamine 2000. After 48 hours of incubation, cells were lysed and subjected to a dual-luciferase readout. Firefly luciferase activity was normalized to Renilla activity (Wang et al., 2024).

Statistical analysis

All analyses were performed using SPSS 25.0 (IBM, USA) and Graphad Prism 9.5 (GraphPad Software, USA). Numerical data were assessed for normality and homogeneity of variance prior to statistical testing. Data are presented as mean ± SD. Comparisons between two groups were conducted using independent-sample t-tests, while comparisons among multiple groups were evaluated using one-way ANOVA, followed by Tukey's post-hoc test for pairwise comparisons when appropriate.

Results

Downregulated miR-370-5p expression in NSCLC tissues and cell lines

RT-qPCR was performed to quantify miR-370-5p levels in 72 pairs of NSCLC tissues and their corresponding

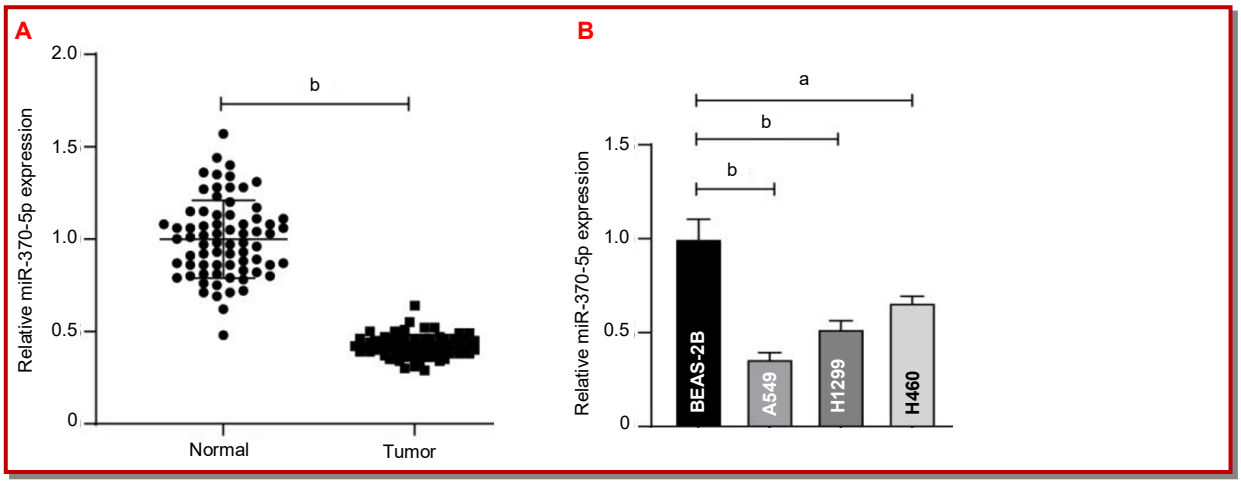

Figure 1: Expression of miR-370-5p in NSCLC tissues and cell lines. A: RT-qPCR analysis of miR-370-5p expression in 72 paired NSCLC tissues (n=72) and adjacent non-tumorous tissues (n=72). B: RT-qPCR detection of miR-370-5p levels in the BEAS-2B cell line and NSCLC cell lines (A549, H1299, and H460). All experiments were performed in triplicate; [a]p<0.01, [b]p<0.001

adjacent non-tumorous samples. miR-370-5p expression was significantly reduced in tumor specimens compared to matched paracancerous tissues (p<0.05; Figure 1A). To further validate these findings *in vitro*, miR-370-5p expression was examined in four NSCLC cell lines using RT-qPCR. Consistent with the tissue results, all NSCLC cell lines (A549, H1299, and H460) exhibited substantially lower miR-370-5p levels than the bronchial epithelial cell line BEAS-2B (p<0.05; Figure 1B).

MiR-370-5p exerts a restraining influence on NSCLC

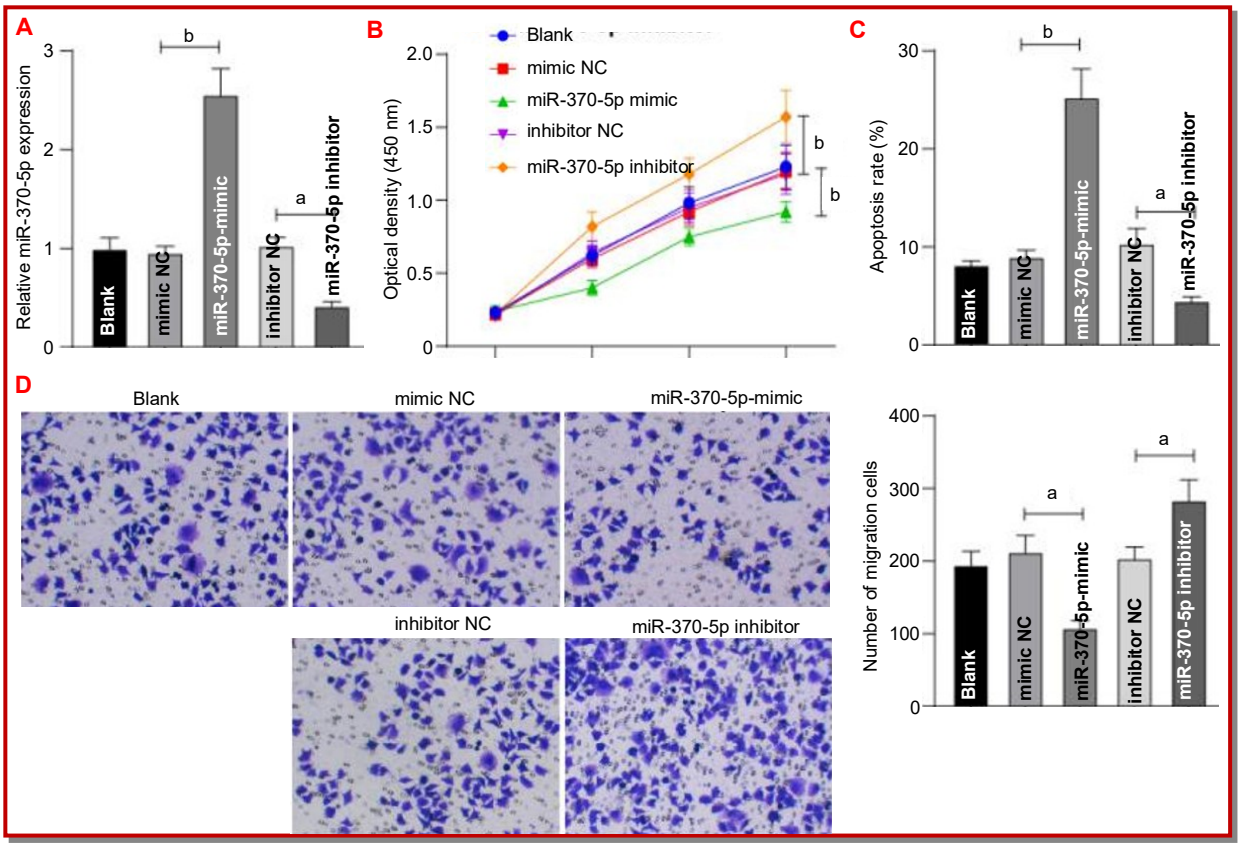

Figure 2: Upregulation of miR-370-5p suppresses NSCLC cell proliferation and migration while promoting apoptosis. A: RT-qPCR analysis of miR-370-5p transfection efficiency; B: CCK-8 assay for cell proliferation; C: Flow cytometric detection of cell apoptosis; D: Transwell assay for cell migration. All experiments were performed in triplicate; [a]p<0.01, [b]p<0.001

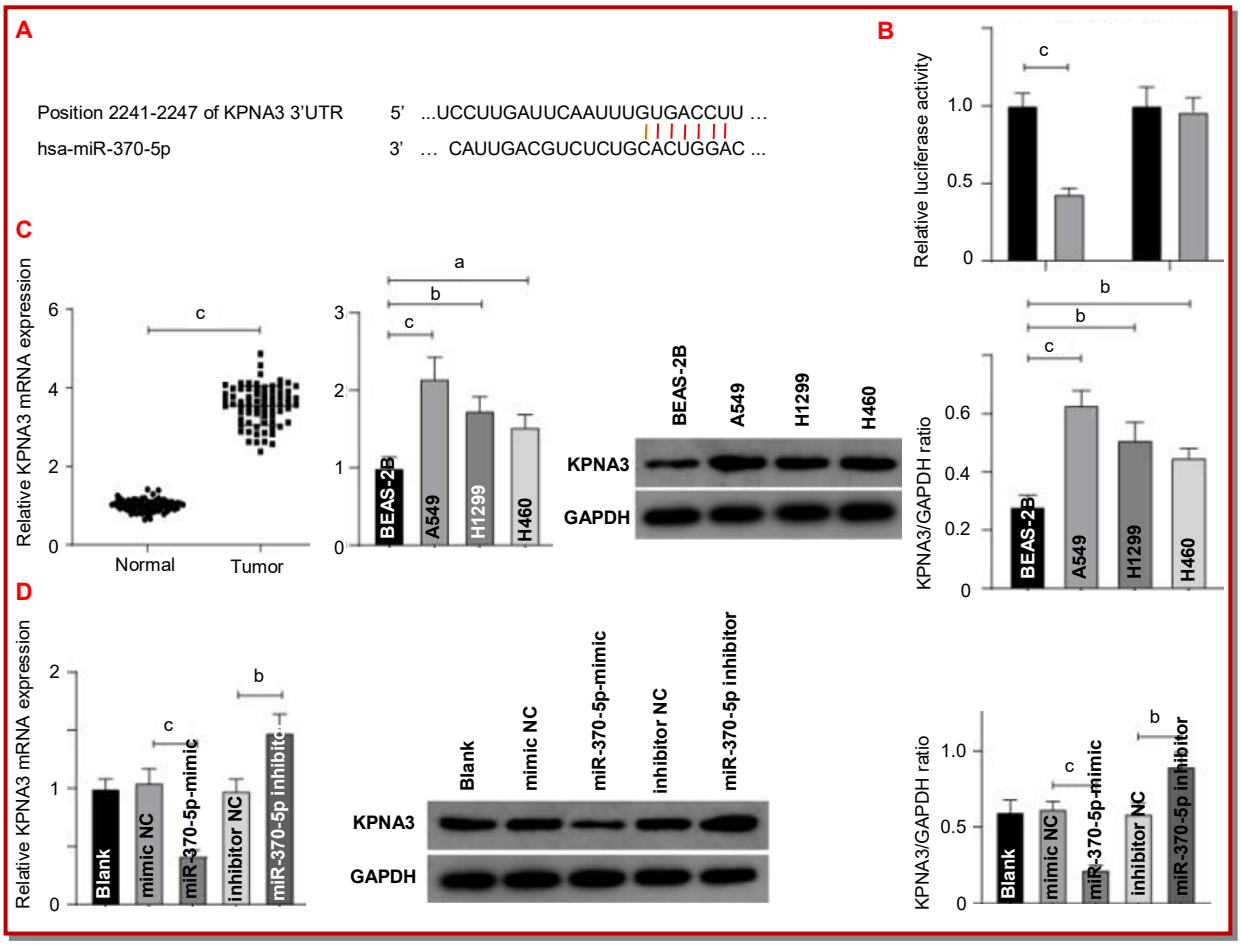

Figure 3: KPNA3 is a direct target of miR-370-5p. A: Prediction of the interaction between miR-370-5p and KPNA3 using the TargetScan database; B: Dual-luciferase reporter assay confirming the binding relationship between miR-370-5p and KPNA3; C: RT-qPCR and Western blot analysis of KPNA3 expression in NSCLC tissues and cell lines; D: RT-qPCR and Western blot detection of KPNA3 expression in cells transfected with miR-370-5p mimic or inhibitor. All experiments were performed in triplicate; $^{a}p<0.05$, $^{b}p<0.01$, $^{c}p<0.001$

cell aggressiveness

To clarify the functional role of miR-370-5p in NSCLC progression, A549 cells were transfected with either a miR-370-5p mimic or inhibitor, and RT-qPCR confirmed efficient transfection (Figure 2A). Cells overexpressing miR-370-5p exhibited a significant decrease in metabolic activity, as measured by CCK-8 assays, whereas reducing its levels produced the opposite effect (Figure 2B). Flow cytometry analysis showed that increasing miR-370-5p levels led to a higher proportion of apoptotic cells, while its inhibition reduced apoptosis (Figure 2C). Similarly, Transwell assays demonstrated that enforced miR-370-5p expression markedly impaired cell motility, whereas silencing it promoted migration (Figure 2D). Collectively, these findings indicate that miR-370-5p exerts a suppressive effect on NSCLC cell aggressiveness by inhibiting proliferation and migration while enhancing apoptotic responses.

KPNA3 is identified as a direct target gene of miR-370-5p

To identify downstream effectors of miR-370-5p, the TargetScan database was queried for predicted miRNA–mRNA interactions, which highlighted KPNA3 as a potential target (Figure 3A). This interaction was experimentally confirmed using a dual-luciferase reporter system: introducing miR-370-5p mimics markedly reduced luciferase activity from the KPNA3 wild-type 3'UTR construct, whereas the mutant construct remained unaffected (Figure 3B). Expression profiling further showed that KPNA3 levels were significantly elevated in NSCLC tissues compared with adjacent non-tumorous samples and were consistently higher in NSCLC cell lines (A549, H1299, H460) relative to BEAS-2B cells (Figure 3C). Moreover, manipulating miR-370-5p abundance in A549 cells produced reciprocal effects on KPNA3 expression: enhanced miR-370-5p sharply decreased KPNA3 mRNA and protein levels, whereas miR-370-5p inhibition resulted in their elevation (Figure 3D). Together, these findings confirm

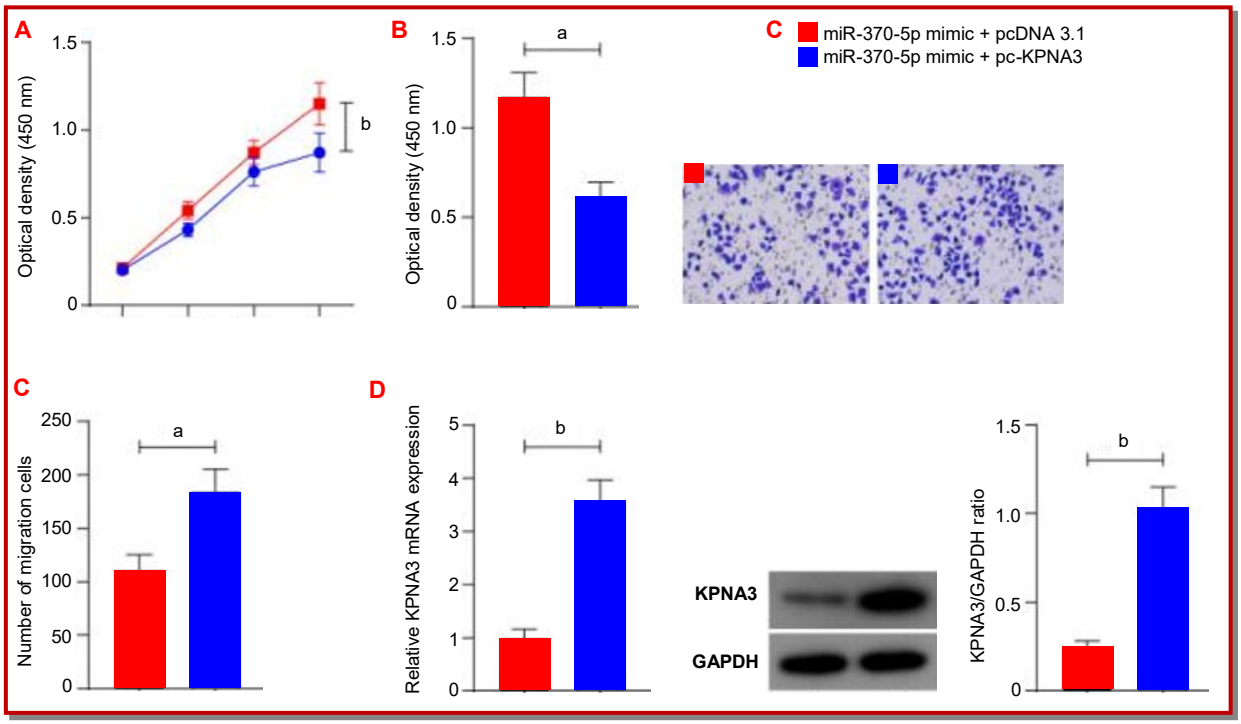

Figure 4: KPNA3 overexpression partially attenuates the inhibitory effects of miR-370-5p on NSCLC. A: CCK-8 assay for cell proliferation; B: Flow cytometric analysis of cell apoptosis; C: Transwell assay for cell migration; D: RT-qPCR and Western blot analysis of KPNA3 mRNA and protein expression in cells co-transfected with miR-370-5p mimic and pc-KPNA3. All experiments were performed in triplicate; $^{a}p< 0.01$, $^{b}p<0.001$

KPNA3 as a direct downstream target negatively regulated by miR-370-5p.

KPNA3 overexpression partially reverses the suppressive effects of miR-370-5p on NSCLC cells.

To determine whether KPNA3 counteracts the inhibitory effects of miR-370-5p in NSCLC, rescue experiments were conducted. Functional assays—including CCK-8 proliferation tests, flow cytometry, and Transwell migration analysis—demonstrated that forced expression of KPNA3 significantly attenuated the antitumor effects induced by miR-370-5p overexpression. Compared with the miR-370-5p mimic + pcDNA3.1 group, cells in the miR-370-5p mimic + pc-KPNA3 group exhibited enhanced proliferative and migratory capacities, accompanied by a reduced apoptotic rate (all $p<0.05$) (Figure 4A–C). Consistently, RT-qPCR and western blot analyses showed that KPNA3 mRNA and protein levels were markedly elevated in the miR-370-5p mimic + pc-KPNA3 group relative to the miR-370-5p mimic + pcDNA3.1 group (Figure 4D).

Discussion

This study demonstrated that miR-370-5p functions as a tumor suppressor in NSCLC by inhibiting cell proliferation and migration while promoting apoptosis. KPNA3 was identified as a direct downstream target of miR-370-5p. Furthermore, forced expression of KPNA3 partially reversed the inhibitory effects induced by miR-370-5p overexpression. These findings suggest that dysregulation of the miR-370-5p/KPNA3 axis plays a critical role in NSCLC progression.

Accumulating evidence indicates that miRs are essential regulators of oncogenic signaling in NSCLC, acting through post-transcriptional repression of multiple target genes (El Founini et al., 2021). The data of this study are consistent with previous findings showing that miR-370-5p exerts antitumor effects in lung cancer. Kim et al. reported that miR-370-5p suppresses proliferation and migration of A549 cells by activating p21, thereby promoting cell-cycle arrest and reducing the invasive potential of NSCLC cells (Li et al., 2017). Similarly, miR-370 inhibits lung cancer cell growth and metastatic behavior through direct repression of SMAD1, further supporting the tumor-suppressive role of this miRNA in pulmonary malignancies (Tang et al., 2022). The results obtained in this study align with and extend these observations by confirming that miR-370-5p is significantly downregulated in NSCLC cells and that its restoration leads to robust antitumor effects.

This study also provides novel insights into the role of KPNA3 in NSCLC. KPNA3 mediates the import of transcription factors and signaling molecules into the nucleus. Aberrant activation of nuclear transport pathways has been increasingly recognized as a hallmark of

cancer progression (Wang et al., 2023). Structural and functional analyses have highlighted that importin-α family members are essential for nuclear trafficking and are implicated in multiple cellular processes relevant to cancer biology, including proliferation, stress response, and transcriptional regulation (Kehlenbach et al., 2023). Similarly, importin-α proteins play a critical role in coordinating the nuclear localization of cargos that govern key oncogenic pathways (Oka and Yoneda, 2018).

Although KPNA3 has not been extensively studied in lung cancer, its oncogenic properties have been documented in other malignancies. KPNA3 promotes EMT and enhances invasion in TNBC by regulating components of the TGF-β and AKT signaling pathways (Choi et al., 2023). This evidence supports the broader hypothesis that dysregulated nuclear transport mediated by KPNA3 may facilitate malignant phenotypes by enabling the nuclear translocation of protumorigenic transcription factors. This study provides the first evidence that KPNA3 is upregulated in NSCLC cells and contributes to tumorigenic behavior. The partial rescue effect observed upon KPNA3 overexpression further confirms its functional relevance downstream of miR-370-5p.

Mechanistically, the miR-370-5p/KPNA3 axis identified in this study is likely associated with alterations in the nuclear trafficking of signaling proteins that promote proliferation and motility. Given the established role of importin-α proteins in the nuclear import of NF-κB, SMADs, STATs, and other transcription factors (Xiao et al., 2000, Leonard et al., 2018), dysregulated KPNA3 expression may enhance oncogenic transcriptional programs in NSCLC. This hypothesis warrants further investigation using transcriptomic and proteomic approaches to identify KPNA3-dependent nuclear cargos in lung cancer cells.

Findings of this study have potential clinical implications. Restoring tumor-suppressive miRNAs or targeting dysregulated nuclear transport proteins represents an emerging therapeutic strategy in cancer. miRNA mimics, including those based on tumor-suppressive miRNAs like miR-370-5p, are currently under exploration in preclinical and early clinical settings. Meanwhile, pharmacologic inhibition of importin-mediated nuclear transport has been proposed as a promising anti-cancer approach. Therefore, the miR-370-5p/KPNA3 signaling axis may serve as a potential molecular target for NSCLC therapy, particularly for tumors exhibiting low miR-370-5p and high KPNA3 expression.

Despite these promising findings, several limitations should be acknowledged. First, this study was conducted entirely *in vitro*, and *in vivo* validation is required to confirm the impact of miR-370-5p modulation on tumor growth and metastasis in animal models. Second, KPNA3 is unlikely to be the sole functional target of miR-370-5p; additional downstream effectors may contribute to the observed phenotypes and should be identified through comprehensive target screening. Third, clinical specimens were not examined, and therefore, the prognostic significance of miR-370-5p and KPNA3 expression in NSCLC patients remains to be determined.

Conclusion

miR-370-5p acts as a potent suppressor of NSCLC cell proliferation and migration and demonstrates that its antitumor effects are mediated, at least in part, through direct targeting of KPNA3. These findings reveal a previously unrecognized regulatory mechanism involving miRNA-dependent modulation of nuclear transport machinery and highlight the therapeutic potential of the miR-370-5p/KPNA3 axis in NSCLC.

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Ethical Issue

Written informed consents were obtained from all patients prior to the study. This study was approved by the Ethic Committee of Qingpu Branch of Zhongshan Hospital, Fudan University.

Conflict of Interest

Authors declare no conflict of interest

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