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LncRNA FAM66C predicts poor prognosis in patients with lung adenocarcinoma and regulates cell proliferation and metastasis via miR-339-3p

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Abstract

Background As one of the tumors with the highest fatality rates in the world, LUAD has a high risk of concealment, recurrence, and metastasis, which has turned into a significant issue in the medical community. To find possible treatment targets for LUAD, the study investigated the relationship between FAM66C and the prognosis of LUAD as well as the mechanism by which it interacts with miR-339-3p.

Methods Tissue samples and clinicopathological data were collected from 117 LUAD patients. Polymerase chain reaction assay was used to find FAM66C and miR-339-3p expression in LUAD tissues. Utilizing CCK-8, Transwell, and flow cytometry, the relationship between LUAD cell proliferation, migration, apoptosis, and FAM66C expression was assessed. The dual luciferase reporter gene assay was utilized to investigate the interaction between miR-339-3p and FAM66C. The prognostic potential and connection of FAM66C with clinicopathology were evaluated using the Chi-square test, Kaplan-Meier, and multivariate Cox regression analysis.

Results FAM66C expression was drastically reduced and miR-339-3p expression was upregulated in LUAD cells and tissues. There was a negative correlation between FAM66C and miR-339-3p. FAM66C inhibits the expression of miR-339-3p, and miR-339-3p can reverse the inhibitory impact of FAM66C on LUAD cells. FAM66c expression was substantially associated with clinical TNM stage and lymph node metastases When FAM66C expression is low, the prognosis of LUAD patients is bad.

Conclusions In conclusion, lower FAM66C expression can be utilized to predict the poor prognosis of LUAD, and FAM66C is negatively linked with miR-339-3p, which can influence cancer cell development by modulating miR-339-3p expression.

Keywords LUAD, FAM66C, miR-339-3p, Prognosis, Cellular processes

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Introduction

Lung cancer has a high morbidity and mortality rate, and lung adenocarcinoma (LUAD) is the most frequent subtype, accounting for up to 40% of lung cancer [1–3]. Early on, LUAD is extremely covert and challenging to find. In the late stage, due to LUAD's malignant characteristics of high recurrence and metastasis, even after surgery, radiation, and other relevant treatments, the 5-year survival rate is poor [4]. Therefore, a significant challenge in current research is the need to identify ever-more-effective biomarkers to enhance the prognosis of LUAD patients.

Long non-coding RNA (lncRNA) is crucial for gene transcription, coding, translation, modification, and other regulatory activities. lncRNA engages in multiple biological processes that are associated with cancer cells, which can either slow or speed up the evolution of cancer cells [5, 6], including cervical cancer [3], breast cancer [7], prostate cancer [8]. Multiple lncRNAs have also been found to play key regulatory roles in the proliferation and metastasis of LUAD cells, influencing cancer progression. Through the reverse control of hsa-mir-22-3p, lncRNA DGCR5 influences the growth of LUAD tumors [9]. Down-regulation of LINC01614 lowered glutamine transporter expression and glutamine consumption in LUAD cells, inhibiting LUAD cell growth [10]. A bad prognosis for LUAD is linked to RP11-10A14.5, which can encourage the growth of LUAD cells [11]. However, the pathogenesis of LUAD is complex and an effective therapeutic target has yet to be found. Therefore, this experiment aims to mine new lncRNAs and explore tits roles in LUAD, with a view to providing a basis for the study of the pathogenesis of LUAD.

FAM66C has eight exons and is found on chromosome 12. FAM66C has been linked in studies to the emergence of several malignancies [12–15]. FAM66C was found to be involved in regulating the development of pancreatic cancer by negatively regulating miR-574-3p [14]. FAM66C has been found to be abnormally expressed in glioblastoma and plays an important role in the regulation of hypoxia-related pathways [16]. However, the mechanism of FAM66C in LUAD has not been reported so far. Therefore, this study took FAM66C as the target and carried out related experiments. Advancements in bioinformatics have unveiled the role of lncRNAs as competing endogenous RNAs (CeRNAs), which can sponge miRNAs to regulate the expression of target genes, thereby playing a pivotal role in tumor progression [17]. Research has shown that miR-339-3p serves as a diagnostic and prognostic biomarker for non-small cell lung cancer [18]. Furthermore, miR-339-3p has been found to be targeted and regulated by lncRNAs in multiple cancer types, influencing the malignant behavior of cancer cells. For instance, lncRNA SNHG11 promotes the development of colorectal cancer by mediating the miR-339-3p/SHOX2 axis [19], while lncRNA KCNQ1OT1 facilitates the progression of retinoblastoma by inhibiting miR-339-3p that targets KIF23 [20]. Silencing of LINC00665 inhibits the in vitro growth of cutaneous melanoma and induces apoptosis via the miR-339-3p/TUBB pathway [21]. However, the precise mechanism of miR-339-3p in LUAD remains elusive, and further investigation is required to explore its potential association with FAM66C. This research aims to explore the influence of FAM66C expression on LUAD, evaluate its prognostic significance, and dissect the interplay between FAM66C and miR-339-3p in regulating LUAD cells, ultimately seeking new therapeutic avenues and molecular targets for more effective LUAD treatment.

Materials and methods

Clinical specimens

This study subject was a total of 117 patients chosen to enroll from Huzhou Jiaotong Hospital from 2017 to 2018. Except for LUAD, all patients in the research satisfied surgical criteria, had no significant illness or malignancy, and had never undergone previous anti-cancer therapy. The Ethics Committee at Huzhou Jiaotong Hospital approved and supervised the conduct of this study. All patients were aware of the study purpose and provided informed permission. The paired tumors and normal tissue samples required for the study have been validated by at least two pathologists. Simultaneously, to better understand the postoperative conditions of all patients in the study, patients were observed for 3 to 60 months via telephone follow-up, regular review, and other means.

qRT-PCR

Total RNA was obtained using the Trizol technique (15596026; Thermo Fisher Scientific, Carlsbad, USA). RNA with an OD260/OD280 ratio between 1.8 and 2.0 was initially selected by NanoDrop ND-1000 spectrophotometer (NanoDrop Technology, Wilmington, Delaware, USA) to guarantee that the extracted RNA can be efficiently reverse-transcribed using PrimeScript RT Enzyme Mix I kit (TaKaRa DRR047A, China) into cDNA. PCR was performed using SYBR Green Premix Ex Taq II (RR820A, Takara, Dalian, China) according to the instructions, with the following reaction conditions: pre-denaturation at 95 ℃ for 30 s, denaturation at 95 ℃ for 5 s, and annealing at 60 ℃ for 30 s, for a total of 35 cycles. Applied Biosystems 7300 system (Applied Biosystems, Foster city, CA).) was used to perform it. After that, $2^{-\Delta\Delta ct}$ method was used to calculate the relative expression with GAPD and U6 serving as the internal reference for FAM66C and MiR-339-3p, respectively. Five replicates were set up for each experimental group.

Cell culture and cell transfection

Human lung cancer cells (A549, PC-9, H-2009, H1299) and normal human bronchial epithelial cells (HBE) were obtained from the American Type Culture Collection (ATCC, USA). Firstly, the frozen cells were thawed at room temperature and then inoculated in DMEM medium (Gibco BRL, Rockville, MD, USA) supplemented with 10% FBS and 0.1% penicillin-streptomycin for culture. They were placed in a 37 °C CO_2 incubator. When the cell proliferation density reached about 80%, subculturing was carried out, and close attention was paid to the cell growth environment, and the medium was replaced regularly.

The two groups of cancer cells were divided into blank control groups (CK), FAM66C overexpression group (oe-FAM66C) and its negative control group (oe-NC), oe-FAM66C + miR-339-3p overexpression group (oe-FAM66C + miR-339-3p mimics) and its negative control group (oe-FAM66C + miR-NC). The Lipofectamine 2000 (11668027; Invitrogen, Carlsbad, USA) transfection reagent was used to transfect plasmids into each group of cancer cells respectively. They were incubated in the incubator for 48 h, and then the expression of FAM66C and miR-339-3p was detected to screen the successfully transfected cells. Five replicates were set up for each experimental group.

CCK8 assay

An experiment was conducted to explore the impact of FAM66C and miR-339-3p expression on cancer cell proliferation, employing the CCK-8 assay kit. Successfully transfected and well-maintained cells in each group were seeded into 96-well plates at a density of 1×10^5 cells per well and incubated in a cell culture incubator set at 37 °C with 5% CO_2. At specific time points (0, 24, 48, and 72 h), 10μL CCK-8 reagent (WST-8, Dojindi Labs, Kumamoto, Japan) was introduced into each well and gently mixed. The plates were further incubated for 4 h to ensure complete reaction between the reagent and cells. Subsequently, the optical density of each well was measured using a spectrophotometer (MultiskanGo, Thermo Scientific, Waltham, MA, USA) at a wavelength of 450 nm (OD_{450}). By comparing the OD_{450} values between the experimental groups and the control groups, the proliferation status of LUAD cells was assessed. Five replicates were set up for each experimental group.

Transwell assay

To investigate the effects of FAM66C and miR-339-3p on the migration and invasion abilities of LUAD cancer cells, a Transwell experiment was devised. First, subject the cells in each group to starvation treatment to synchronize the cell cycle. Then, digest the cells with trypsin, remove the culture medium by centrifugation, wash the cells 1–2 times with serum-free medium, and resuspend the cells in serum-free medium to adjust the cell density to an appropriate level. Take an appropriate amount of cell suspension and inoculate it in the upper layer of the Transwell chamber (#PICM01250, EMD Millipore, Billerica, MA, USA), while adding serum-containing medium to the lower layer as a chemotactic factor. For the invasion experiment, pre-coat the Matrigel matrix gel on the membrane of the Transwell chamber to mimic the extracellular matrix. After incubation at 37 °C for 24 h, remove the upper layer cells with a cotton swab and stain the lower layer with 0.1% crystal violet for 30 min. Use an optical microscope (Eclipse E600, Nikon, CA, USA) to count and examine the migrating and invading cells. Five replicates were set up for each experimental group.

Cellular apoptosis rate assay

To precisely evaluate the apoptotic status of cancer cells in each treatment group, the following experiment is performed. During cell staining, take 100 μL of the aforementioned cell suspension, add 5 μL of Annexin V-FITC, mix well, and incubate in the dark for 15 min. Subsequently, add 5 μL of propidium iodide (PI) staining solution, mix well again, and continue incubating in the dark for another 5 min (Annexin V-EGFP/PI Kit, CA1020-50T; Solebo Technology Co., Ltd., Beijing, China). After that, transfer the stained cell suspension to the sample tube of the flow cytometer (BD FACSCalibur™, USA). The flow cytometer is used for excitation and detection. Annexin V-FITC is excited by a 488 nm laser to detect green fluorescence, and PI is excited by a 561 nm laser to detect red fluorescence. Finally, the proportion of apoptotic cells is calculated to assess the apoptotic status of cancer cells. Five replicates were set up for each experimental group.

Dual-luciferase reporter assay

To investigate the targeted binding relationship between FAM66C and miR-339-3p, a dual-luciferase reporter gene assay was designed. Firstly, the potential binding site of the 3' untranslated region (3'UTR) sequence of the FAM66C gene with miR-339-3p was predicted using the lncRNASNP2 website (http://bioinfo.life.hust.edu.cn/lncRNASNP#!/). Primers were then designed to amplify fragments containing and excluding this binding site. These fragments were subsequently cloned into the luciferase reporter gene vector (pGL3-Basic vector, Promega, Fitchburg, WI, USA), creating wild-type (WT-FAM66C) and mutant-type (MT-FAM66C) recombinant reporter gene plasmids, respectively. After enzyme digestion, ligation, transformation, screening of positive clones and sequencing verification. Cells in logarithmic growth phase were seeded into culture plates and transfected with the vectors along with blank control, negative

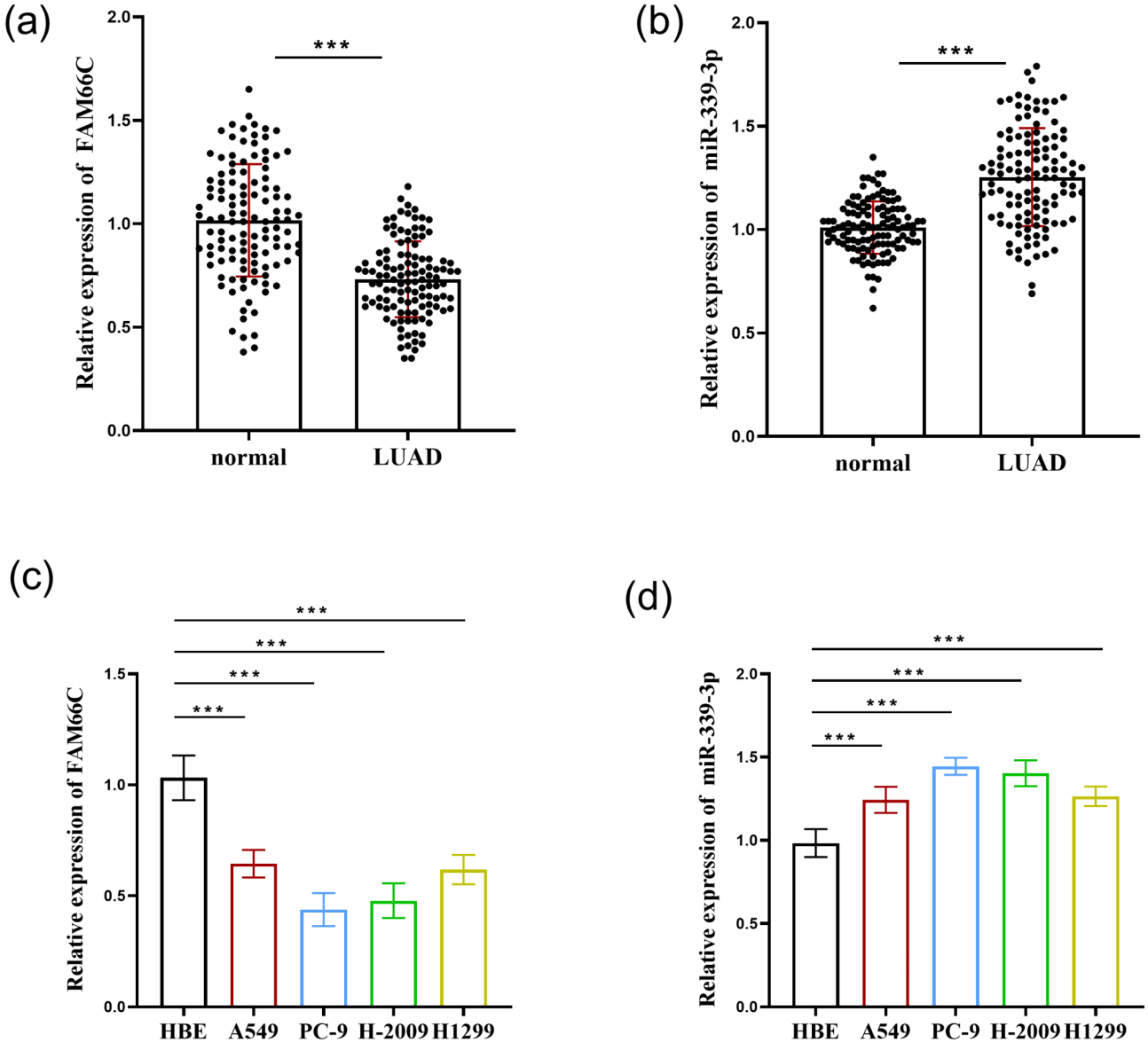


Fig. 1 FAM66C expression in LUAD from collected tissues (**a**) compared with normal tissues. miR-339-3p expression in LUAD compared with normal tissues (**b**). FAM66C (**c**) and miR-339-3p expression in LUAD cells (**d**). ***$P < 0.001$, compared with normal tissues and normal cells

control, miR-339-3p mimics, or inhibitors, using transfection reagents. After a certain period of culture, luciferase activity detection was performed. During detection, cells were lysed, and luciferase substrates were added to measure both firefly and Renilla luciferase activities, from which relative luciferase activities were calculated. Five replicates were set up for each experimental group.

Statistical analysis

GEPIA and Starbase databases were used to analyze the expression of FAM66C in LUAD. The experimental data were expressed as mean ± standard deviation for all data, which were gathered from at least three replicated trials and analyzed with SPSS 26.0 and GraphPad Prism 7.0 software. The multi-group comparisons was done using one-way ANOVA followed by the Turkey post hoc-test and two-group was performed using student's t-test. Using Pearson analysis, the expression correlation between miR-339-3p and FAM66C was assessed. Using the chi-square test, the link between FAM66C and the clinicopathological characteristics of LUAD patients was evaluated. Multivariate Cox regression analysis was used to evaluate the prognostic factors and Kaplan-Meier log-rank tests were used to analyze the correlation between FAM66C expression and the survival time of patients, Log-rank $P < 0.05$ indicates a statistically significant difference in survival time between the two groups. $P < 0.05$ was used to determine statistical significance.

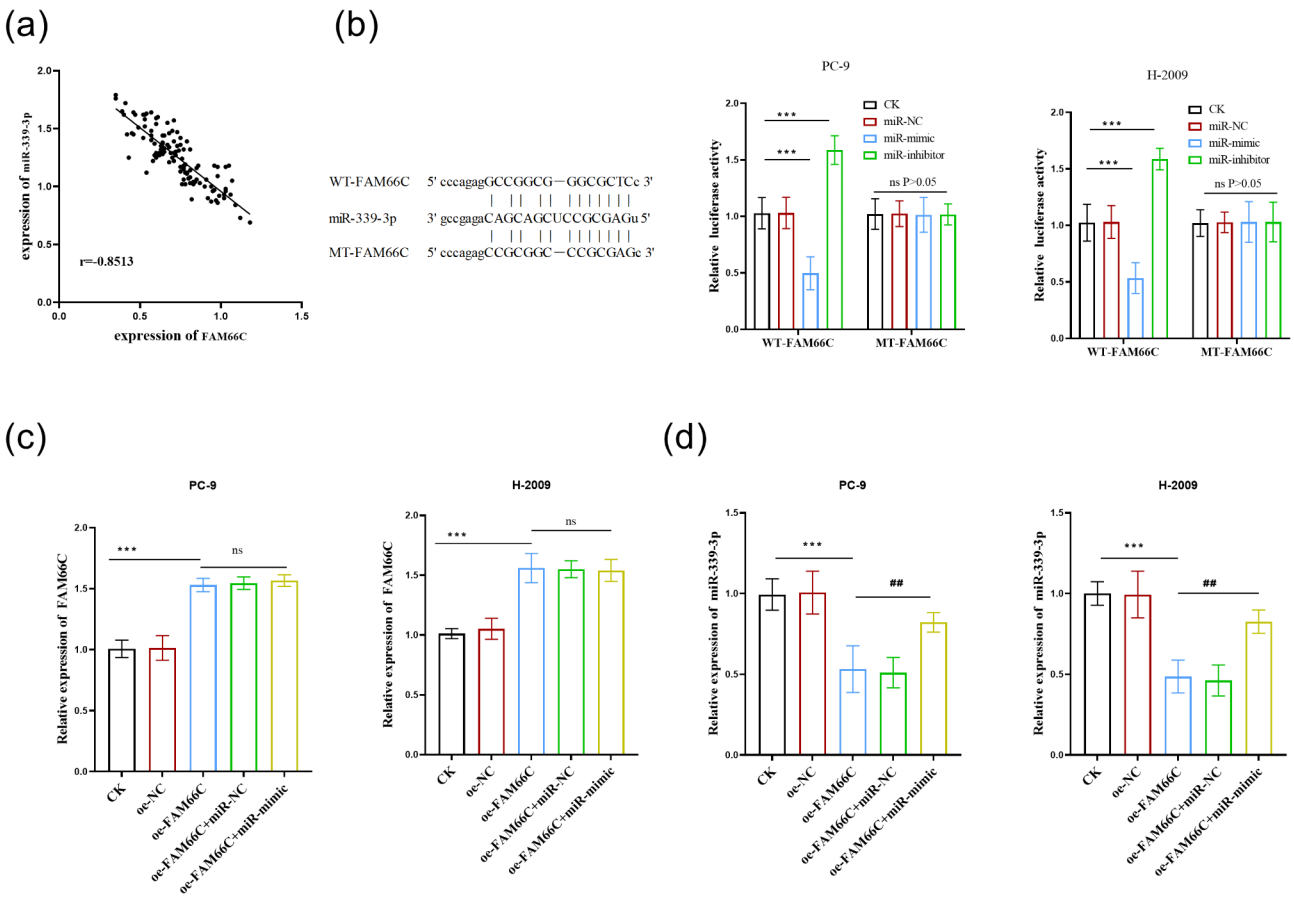


Fig. 2 Correlation between FAM66C and miR-339-3p in LUAD tissues (**a**). The effect of miR-339-3p on the luciferase activity of FAM66C (**b**). Effect of oe-FAM66C transfection on the expression of FAM66C (**c**) and miR-339-3p (**d**) in LUAD cells. ***$P < 0.001$, compared with normal cells or CK group; $^{\#\#}P < 0.01$ compared with the oe- FAM66C group

Results

The expression of FAM66C and mir-339-3p in LUAD tissues and cells

We used qRT-PCR to detect FAM66C expression, which was downregulated in LUAD tissues (Fig. 1a). In addition, it was shown that miR-339-3p expression levels in tumor tissues were upregulated significantly from those in normal tissues (Fig. 1b). When compared to HBE cells, the expression of FAM66 was dramatically down-regulated (Fig. 1c) in LUAD cells A549, PC-9, H-2009, and H1299, while miR-339-3p expression was significantly up-regulated (Fig. 1d).

FAM66C interacts with mir-339-3p in LUAD

The expression of FAM66C and miR-339-3p in LUAD tissues was found to be negatively correlated (Fig. 2a). MiR-339-3p mimics transfected into cells considerably reduced the activity of the WT-FAM66C luciferase, whereas miR-339-3p inhibitors transfected into cells greatly boosted the activity of the WT-FAM66C luciferase (Fig. 2b). As can be seen from Fig. 2c, transfection of oe-FAM66C successfully and effectively upregulated the expression of FAM66C, while overexpression of miR-339-3p did not impact the expression of FAM66C. When FAM66C was overexpressed, the expression of miR-339-3p was downregulated. After transfection with miR-339-3p mimics, it effectively upregulated miR-339-3p on this basis (Fig. 2d).

FAM66C/ miR-339-3p's effect on LUAD cell development

Further analysis of the impact of FAM66C expression on cellular activities revealed that overexpression of FAM66C could significantly inhibit the -proliferation of two types of cancer cells (Fig. 3a). Additionally, as indicated by the Transwell experiment (Fig. S1), the upregulation of FAM66C also exhibited significant inhibition on the migration (Fig. 3b) and invasion (Fig. 3c) of LUAD cells; however, overexpression of FAM66C showed a significant promoting effect on the apoptosis of cancer cells (Fig. 3d). Moreover, it was discovered that overexpression of miR-339-3p could significantly reverse these effects.

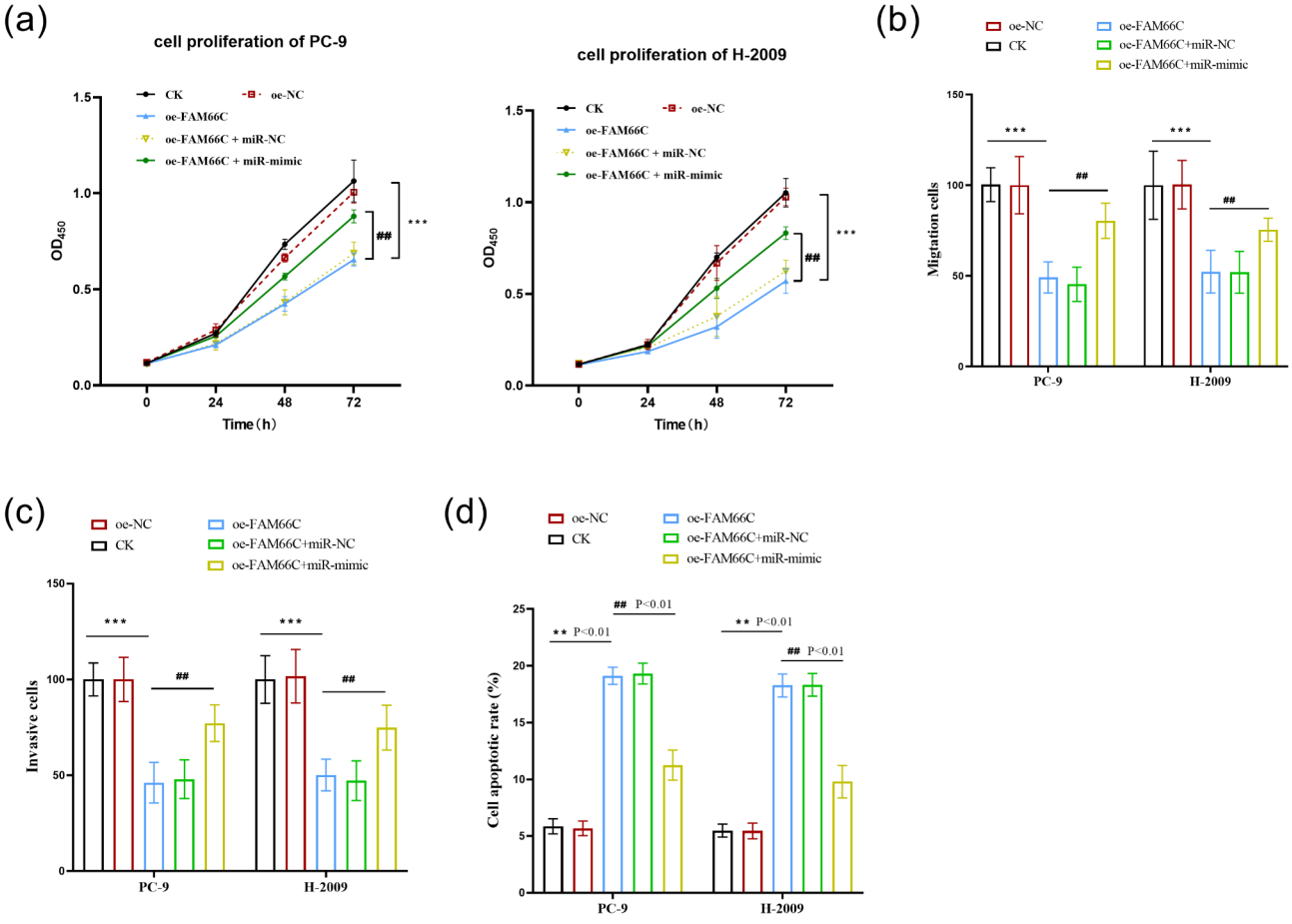


Fig. 3 The effect of FAM66C / miR-339-3p on cell proliferation (**a**), migration (**b**), invasion (**c**) and apoptosis (**d**) of LUAD. ***$P < 0.01$, compared with CK-group; ##$P < 0.01$ compared with the oe-FAM66C group

FAM66C and clinicopathological characteristics of patients, as well as clinical prognosis

The statistical analysis of the clinical information of 117 LUAD patients was performed to investigate the relationship between FAM66C expression and clinicopathology. As shown in Table 1, FAM66C expression levels were not statistically correlated with age ($P = 0.530$), gender ($P = 823$), smoking history ($P = 0.677$), differentiation ($P = 0.332$), or neoplastic stage ($P = 0.054$), that was found to be substantially associated to clinical TNM stage ($P = 0.026$) and lymph node metastases ($P = 0.040$). According to Fig. 4a, Kaplan-Meier curves analysis revealed that FAM66C expression level was significantly correlated with patient survival rate (log rank $P = 0.039$), and the survival rate of the group with high FAM66C expression was significantly higher than that of the group with low FAM66C expression. According to the Cox regression analysis (Fig. 4b), it was discovered that the prognosis of patients was significantly correlated with FAM66C expression, lymph node metastasis, TNM stage, and patient gender ($P < 0.01$).

Discussion

The number of LUAD patients has risen in recent years, owing to increased environmental pollution, changes in people's lifestyles, and other factors. Currently, the primary therapeutic approaches for LUAD are surgical resection, chemotherapy, radiation, and so forth, nevertheless these treatments have limitations in improving patient survival [4]. Thus, there is an immediate necessity to delve into novel therapeutic approaches. The exploration of new targeted biomarkers constitutes a pivotal yet challenging aspect of LUAD research. Accumulating evidence underscores the crucial role of lncRNAs in the development of LUAD [22–24], thereby rendering the investigation of the functions of emerging lncRNAs in this context highly significant.

A review of the literature revealed that FAM66C, a lncRNA associated with copper toxicity, exhibits abnormal expression in LUAD, although its specific role in LUAD patients remains unknown. To address this, the present study conducted a study. Initially, bioinformatics database analysis demonstrated that FAM66C expression was downregulated in LUAD tissues, which was further

Table 1 The Association of FAM66C with patients' clinicopathological features

Variant	Cases ($n=117$)	lncRNA FAM66C expression		*P*
		Low ($n=60$)	High ($n=57$)	
Age				0.530
<60	54	26	28	
≥60	63	34	29	
Gender				0.823
Male	71	37	34	
Female	46	23	23	
Smoking history				0.677
Yes	70	37	33	
No	47	23	24	
Differentiation				0.332
Well-moderate	77	37	40	
Poor	40	23	17	
Lymph node metastasis				0.026
Yes	36	24	12	
No	81	36	45	
TNM stage				0.040
I-II	71	31	40	
III	46	29	17	
Neoplasm stage				0.054
T1-T2	76	34	42	
T3-T4	41	26	15	

validated using tissue samples from LUAD patients. Further analysis indicated a significant correlation between FAM66C and TNM staging as well as lymph node metastasis in LUAD patients. Additionally, FAM66C has the potential to serve as a prognostic biomarker for LUAD, with higher expression levels associated with better patient survival rates. Consistent with this, Wang et al. also identified FAM66C as a marker for tumor prognosis in their prognostic prediction model for LUAD [25]. These findings suggest a pivotal role for FAM66C in the progression of LUAD. To further investigate its function in LUAD, preliminary studies were conducted using cancer cells as the research subject.

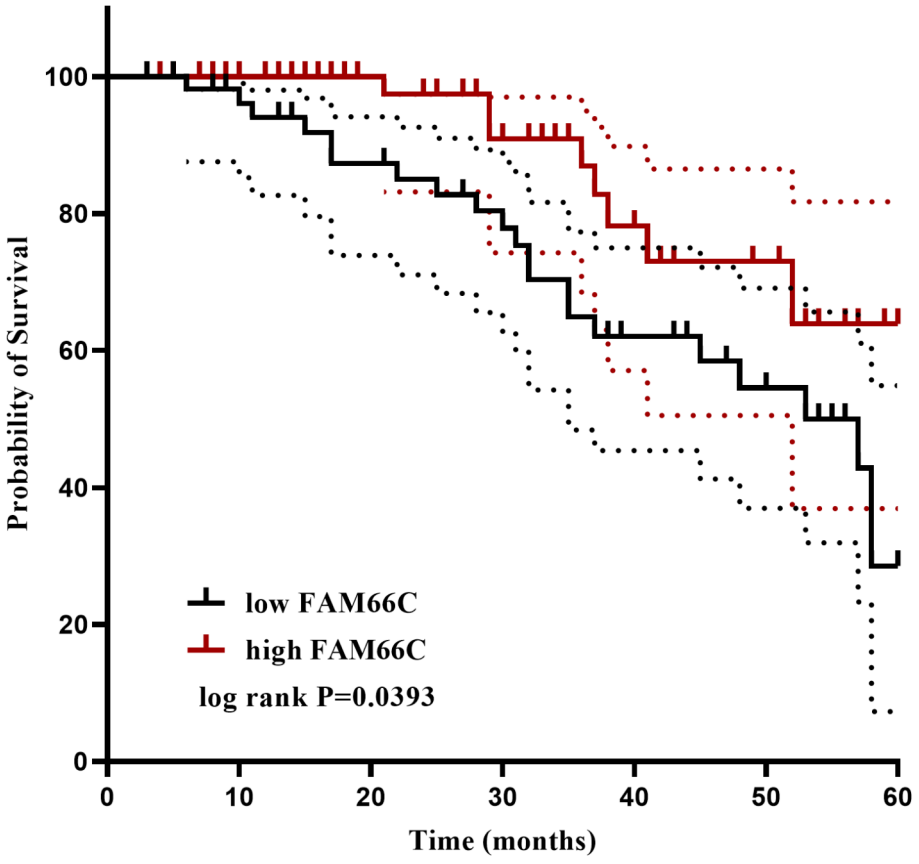
In our study, Overexpression of FAM66C can effectively inhibit the malignant biological behavior of cancer cells. In addition, we further evaluated the potential of FAM66C as a prognostic marker for LUAD. FAM66C was significantly correlated with TNM stage and lymph node metastases of patients, and the higher the expression of FAM66C, the higher the survival rate of patients. Moreover, it was found that FAM66C, lymph node metastasis, TNM stage and patient gender could all be used as biomarkers for LUAD prognosis. In a nutshell, the downregulated expression of FAM66C may be a signal of tumor deterioration and metastasis in patients, which greatly increases the probability of poor prognosis in patients.

Our study found that overexpressing FAM66C effectively inhibits the malignant biological behaviors of LUAD cells. According to studies, FAM66C has a stimulative effect on some cancers, such as FAM66C can enhance the growth of prostate cancer cells by activating EGFR-ERK and inhibiting the proteasome pathway [12], the expression of miR-23b-3p can be negatively regulated by FAM66C, which can activate the glucose degradation of intrahepatic bile duct cancer cells and boost the activity of cancer cells [13]. On the contrary, some tumors are inhibited, for instance, FAM66C suppresses pancreatic cancer development by sponging miR-574-3p [14]. Significantly promoted the progression of glioma cells was the knockout of FAM66C [15]. The aforementioned research indicates that FAM66C plays a crucial regulatory role in tumor development.

However, its expression and regulatory functions vary across different tumors, potentially due to the underlying mechanisms of FAM66C action. Our study further delved into the downstream mechanisms of FAM66C, uncovering a binding site between FAM66C and miR-339-3p in databases. miR-339-3p plays a pivotal regulatory role in various cancers, such as modulating the apoptosis of melanoma cells [26] and influencing epithelial-mesenchymal transition in nasopharyngeal cancer cells [27]. Notably, studies have indicated that miR-339-3p is significantly upregulated in LUAD [18], aligning with our findings. This research observed a significant negative correlation between the expression trends of FAM66C and miR-339-3p, and FAM66C negatively regulates the expression level of miR-339-3p. Transfection with miR-339-3p mimics reversed the suppressive effect on tumor cells mediated by upregulated FAM66C. Collectively, these findings imply that FAM66C may participate in the malignant behavior of LUAD cells by sponging miR-339-3p.

Studies have indicated that miR-339-3p inhibits apoptosis in lung vascular endothelial cells by targeting Anxa3 and suppressing the relative expression of proteins associated with the Akt/mTOR signaling pathway. Additionally, Whang et al. demonstrated that overexpression of miR-339-3p regulates TRAF3 expression through the p38 pathway, thereby inhibiting cell apoptosis in caerulein-induced acute pancreatitis [28]. Furthermore, LINC00467 modulates the proliferation and migration of glioblastoma cells via the miR-339-3p/IPK2 axis [29]. Given the significant role of miR-339-3p, it is crucial to explore the specific downstream signaling pathways and molecular mechanisms through which FAM66C and miR-339-3p regulate these cellular processes. Due to time constraints, this study did not delve further into this aspect; however, future research will aim to comprehensively understand the mechanistic links between FAM66C, miR-339-3p, and the progression of LUAD.

(a)



(b)

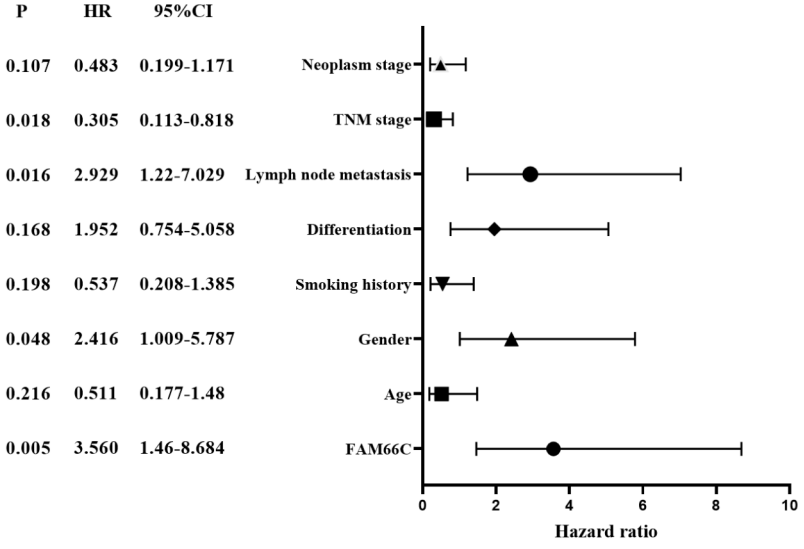


Fig. 4 Kaplan–Meier followed by the log rank test assessed the overall survival rate of patients in 60 months (**a**). Cox regression analysis assessed the prognostic value of clinicopathological features and FAM66C (**b**)

The primary aim of this study was to preliminarily investigate novel molecular mechanisms associated with LUAD and to conduct an initial analysis of their functional roles. However, due to the limitations of time and funds, more multi-level experimental validations were not carried out. Notably, during initial attempts to knock out FAM66C, accurate detection of its expression levels was challenging due to its low baseline expression, making it difficult to observe significant and reliable changes post-knockout. This limitation may stem from the inherent characteristics of the cell lines or the specific biological context of FAM66C in these cancer cells. Future research endeavors will focus on addressing these limitations by conducting more comprehensive experiments, including wound healing, EDU, or plate clone assays, as well as in vivo animal studies, and exploring alternative methods for effective FAM66C knockout and accurate expression measurement. Insights from these studies will be crucial for advancing our understanding of LUAD molecular mechanisms and developing potential therapies.

Conclusion

In summary, FAM66C may serve as a key inhibitor in the progression of LUAD, and its low expression is associated with poor prognosis and accelerated development of the disease. miR-339-3p exhibits a negative correlation with FAM66C and can mediate the effects of FAM66C on LUAD cell proliferation, migration, and apoptosis.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13019-025-03374-1.

Supplementary Material 1: **Figure S1**. Migration and invasion imaging of LUAD cells.

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N/A.

Author contributions
All authors designed this study. X. C, W.H. X, Y. S, A.N. Q and H.L. Q conducted the experiment and analyzed the data. X. C, W.H. X, Y. S, A.N. Q and H.L. Q wrote the manuscript. All authors revised the manuscript. All authors reviewed and approved for publication.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The informed consent was obtained from patients and this study has been approved by the Ethics Committees of Huzhou Jiaotong Hospital.

Consent for publication
N/A.

Competing interests
The authors declare no competing interests.

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