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miR-6838-5p acts as a tumour suppressor by inhibiting IGF1R levels in non-small cell lung cancer

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Abstract

Introduction and Objective. Non-small Cell Lung Cancer (NSCLC) destroys lung tissue, causing respiratory failure and even multi-system damage. There is an urgent clinical need for targeted drugs for the early diagnosis of NSCLC. miR-6838-5p is aberrantly expressed in a variety of cancers but its role in NSCLC is unclear. The aim of the study is to evaluate the diagnostic and prognostic value of miR-6838-5p in NSCLC.

Materials and Method. The study included 87 patients with NSCLC and 87 healthy individuals as control. Human normal lung epithelial cells (16HBE) and lung cancer cell lines (A-549/H1299/H1944/NCI-H460/NCI-H1975) were cultured for relevant testing. RT-qPCR was employed to assay miR-6838-5p and insulin-like growth factor 1 receptor (IGF1R) levels. Receiver operating characteristic (ROC) curves and Kaplan-Meier curves were used to assess clinical value. Cell counting kit-8 (CCK-8), flow cytometry, and transwell assays were employed to examine the biological functions of lung cancer cells. IGF1R was identified as downstream of miR-6838-5p by luciferase reporter gene assay.

Results. miR-6838-5p level was clearly down-regulated in NSCLC patients. miR-6838-5p demonstrates significant diagnostic value for NSCLC, and patients with high expression of miR-6838-5p exhibit improved prognostic survival rates. And it is closely associated with NSCLC proliferation and migration. IGF1R is a target of miR-6838-5p and up-regulated in lung cancer cell lines. Furthermore, up-regulation of IGF1R partially restored the inhibitory effects of miR-6838-5p over-expression on proliferation and migration, as well as the promotion of apoptosis.

Conclusions. miR-6838-5p is downregulated in NSCLC and may suppress its malignant progression by inhibiting IGF1R levels. This may provide an effective target for clinical diagnosis and prognosis.

Key words

apoptosis, NSCLC, IGF1R, cell viability, migration, miR-6838-5p

INTRODUCTION

Lung cancer has a great morbidity and mortality rate. Non-small Cell Lung Cancer (NSCLC) accounts for about 85% of diagnosed lung cancers and is one of the main subtypes [1]. Only a fraction of patients can be diagnosed early (stage I or II) and have the tumour surgically removed, at which point the five-year survival rate is around 90%. More than 60% of patients are diagnosed at an advanced stage (Stage III or IV), which can no longer be removed surgically, and have a five-year survival rate of only 36% [2, 3]. As early as 2020, the Nelson study published a large randomized lung cancer screening trial that highlighted the importance of early lung cancer diagnosis [4]. Currently, chemotherapy remains the primary of treatment for lung cancer, but drug resistance resulting from long-term use of tumour-targeting drugs is also a major obstacle to prognosis [5]. With the development of molecular biology today, human beings have studied the pathogenesis of lung cancer more and more thoroughly. Therefore, finding more accurate and reliable markers will greatly improve the prognosis of NSCLC.

MicroRNAs (miRNAs) regulate a range of biological behaviours such as tumour cell proliferation and apoptosis [6]. Several miRNAs have been established as oncogenes or tumour suppressors with potential as diagnostic markers for lung cancer. For example, over-expression of miR-941 promotes proliferation, invasion and resistance to apoptosis of lung adenocarcinoma cells and is an oncogenic factor [7]. miR-126-3p and miR-210-3p can evaluate the clinicopathological characteristics of NSCLC [8]. miR-6838-5p has been shown to participate in the regulation of multiple cancers. It is down-regulated in hepatocellular carcinoma and attenuates the malignant features of hepatocellular carcinoma (HCC) after up-regulation [9]. Similarly, it

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plays a role as a cancer inhibitor in cervical cancer [10]. Additionally, miR-6838-5p is involved in the development and progression of various cancers, including thyroid cancer, pancreatic cancer, and nasopharyngeal carcinoma [11–13]. Regrettably, the role of miR-6838-5p in NSCLC has not been identified.

Therefore, the current study evaluates the diagnostic and prognostic value of miR-6838-5p levels in NSCLC through clinical trials, and investigated the effects of miR-6838-5p on the proliferation, apoptosis, and migration capabilities of lung cancer cells via *in vitro* cellular experiments.

MATERIALS AND METHOD

NSCLC patients and samples. The study was approved by the Ethics Committee of the Third People's Hospital for Yuhang Province, China (Approval No. 2017134, dated 17 May 2017). Participating patients provided signed informed consent in accordance with the Declaration of Helsinki.

The study included 87 NSCLC patients in the research group and 87 healthy individuals as the control group. All 87 patients in the research group were diagnosed and treated between February 2018 – February 2020 at the above-mentioned hospital. Inclusion criteria for the study group: 1) CT scan nodules highly suspicious of lung cancer; 2) diagnosis of NSCLC confirmed by post-operative pathology; 3) patients with complete medical records. Exclusion criteria: 1) patients with severe coronary heart disease, haematopoietic system disease, mental illness, active tuberculosis; 2) pregnant and lactating women. Tumour staging was based on the staging guidelines of the Union for International Cancer Control (UICC). All patients signed an informed consent form. In addition, 5 ml of venous blood were drawn from each subject and serum was separated by centrifugation at room temperature, and stored at -80 °C for subsequent experiments. Haemolyzed samples were discarded and replaced with new specimens. Frozen serum samples must not undergo more than three freeze-thaw cycles.

Prognosis follow-up. Patients underwent five years of prognostic follow-up via online consultations or Outpatient Clinic visits. Survival status was documented and death indicating the endpoint event.

Cell culture. Human normal lung epithelial cells (16HBE) and lung cancer cell lines (A-549/H1299/H1944/NCI-H460/NCI-H1975) were purchased from the Shanghai Academy in Shanghai, China, and cultured in DMEM medium including 10% FBS with 1% penicillin/streptomycin (CHI Scientific, Jiangsu, China). Culture environment – 37 °C and 5% CO_2.

Cell transfection. A-549 and H1299 were inoculated into 96-well plates and transfection was started after culture incorporation to 70%. The mimic NC/miR mimic/inhibitor NC/miR inhibitor/pcDNA3.1-NC/pcDNA3.1-IGF1R were designed and synthesised by MedChem Express LLC (Shanghai, China). The above plasmids were transfected into A-549 and H1299 cells by Lipofectamine 3000 (Invitrogen, USA). After 24h of transfection, the experiment was continued to the next step.

qRT-PCR. Total RNA from subject serum was extracted by TRIzol (Invitrogen, USA) and reverse-transcribed to cDNA by the Primescript RT reagent (TaKaRa, Japan). The reaction system was configured according to SYBR Green qPCR Mix (Shanghai, China) and qRT-PCR was performed on a LightCycler 480 System (Roche Diagnostics). GAPDH served as insulin-like growth factor 1 receptor (IGF1R) control, and U6 as miR-6838-5p control. Relative levels were analyzed by $2^{-\Delta\Delta Ct}$. The primer sequences are as follows: miR-6838-5p: F: 5'-AAGCAGCAGTGGCAAGACTC-3', R: 5'-CTCTACAGCTATATTGCCAGCCAC-3'. IGF1R: F: 5'-AGTATGGAGGGGC CAAGCTA-3'; R: 5'-CAACCCTCCCACGATCAACA-3'.

Cell proliferation. The transfected cells (4×10^3/well) were incubated for 24h and cell proliferation was ascertained with CCK-8 assay (Solarbio, China). After adding 10 µL of CCK-8 solution to the cell suspension, it was gently mixed and incubated at 37 °C for 1 h. Finally, the absorbance at 450 nm was detected at the indicated time.

Apoptosis rate. After 48 h of transfection, the apoptosis rates of A-549 and H1299 cells were measured on a flow cytometer (San Jose, CA, USA) according to the Annexin V-FITC/PI Kit (Solarbio, China). In short, the suspended cells in the mixed buffer were gently mixed with a pipette, and the cell concentration adjusted to 1×10^5 cells/mL. Subsequently, the FITC-labeled reagent and PI staining solution were added in sequence, and the mixture shaken gently. After incubating in the dark for 1 h, flow cytometry acquisition proceeded, followed by data analysis.

Cell migration. After 48 h of transfection, cell migration assays were performed by the transwell chamber (Corning, NY, USA). A-549 and H1299 cells in serum-free medium were inoculated into the upper chamber (1×10^5 cells/well) and medium containing 10% FBS (Solarbio, China) was added to lower chamber. After 24 h of operation, migrated cells were immobilised with methanol, stained with 0.1% crystal violet after 5 min, and then counted using a Leica CME microscope (Leica Microsystems, Wetzlar, Germany).

Dual-luciferase reporter assay. Complementary sequences were predicted by miRDB. The pmirGL vector (Shanghai GenePharma Co., Ltd., China) was used to construct the wild-type (IGF1R-WT) and mutant (IGF1R-MUT) plasmids of IGF1R. IGF1R-WT or IGF1R-MUT were co-transfected with mimic NC, miR mimic or inhibitor NC, and the miR inhibitor into the A549 cell. After 48 h of transfection, cells were lysed and luciferase activity was detected using the dual-luciferase reporter assay system (E2920, Promega, USA).

Statistical analysis. Data were analyzed and graphs were produced using SPSS 27.0 and GraphPad Prism 8.0. The chi-square test was adopted to analyze the correlation between clinicopathological characteristics of NSCLC patients and miR-6838-5p. ROC curve was employed to assess diagnostic ability. Survivability was assessed by Kaplan-Meier. P 0.05 was considered as the difference.

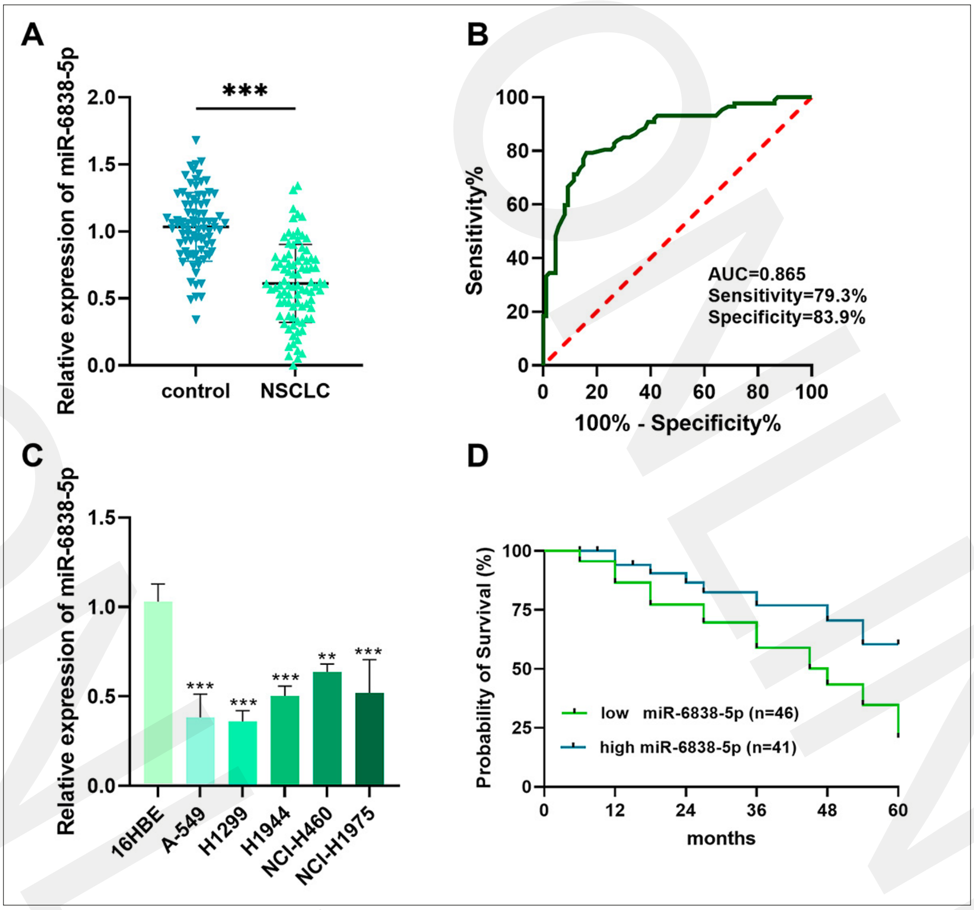

Figure 1. Diagnostic and prognostic value of miR-6838-5p in NSCLC. A) miR-6838-5p levels were down-regulated in NSCLC patients. B) miR-6838-5p has good diagnostic effect on NSCLC. C) Reduced miR-6838-5p levels in 5 lung cancer cell lines. D) High levels of miR-6838-5p showed better prognosis.
**P* < 0.01, ****P* < 0.001

RESULTS

miR-6838-5p is down-regulated in NSCLC patients. miR-6838-5p levels in NSCLC patients were clearly lower than control (Fig. 1A), and had good diagnostic ability for NSCLC (AUC=0.865, Sensitivity=79.3%, Specificity=83.9%) (Fig. 1B). miR-6838-5p levels in 16HBE and five lung cancer cell lines were compared. The results consistently showed that miR-6838-5p levels were clearly down-regulated in lung cancer cell lines ($P < 0.001$) (Fig. 1C). Two cell lines exhibiting the lowest levels of miR-6838-5p were selected for subsequent experiments. Patients were categorised into high-expression (n=41) and low-expression (n=46) groups, based on the mean value of miR-6838-5p in their serum. Kaplan-Meier curve showed that high levels of miR-6838-5p had a more favourable prognosis (Fig. 1D). By analyzing the relationship between clinicopathological features and miR-6838-5p levels in NSCLC patients, it was found that miR-6838-5p levels were not related to age and gender ($P > 0.05$), but there was a greater relationship with smoking, tumour size, TNM stage, and lymph node metastasis ($P < 0.05$). This demonstrates that miR-6838-5p levels may have a close relationship with tumour development (Tab. 1).

Effect of miR-6838-5p over-expression on lung cancer cells. It was found that transfection of miR mimic up-regulated miR-6838-5p levels, whereas transfection of miR inhibitor

Table 1. Association between clinicopathological features and miR-6838-5p levels of NSCLC patients

Features	Total	miR-6838-5p		P
	(n=87)	Low(n=46)	High(n=41)	
Age (years)				
<58	45	23	22	0.733
≥58	42	23	19	
Gender				
female	34	20	14	0.373
male	53	26	27	
Smoking				
No	54	25	29	0.116
Yes	33	21	12	
Tumour size				
<3cm	43	17	26	0.014
≥3cm	44	29	15	
Lymph node metastasis				
No	54	22	32	0.004
Yes	33	24	9	
TNM stage				
I-II	47	17	30	0.001
III-IV	40	29	11	

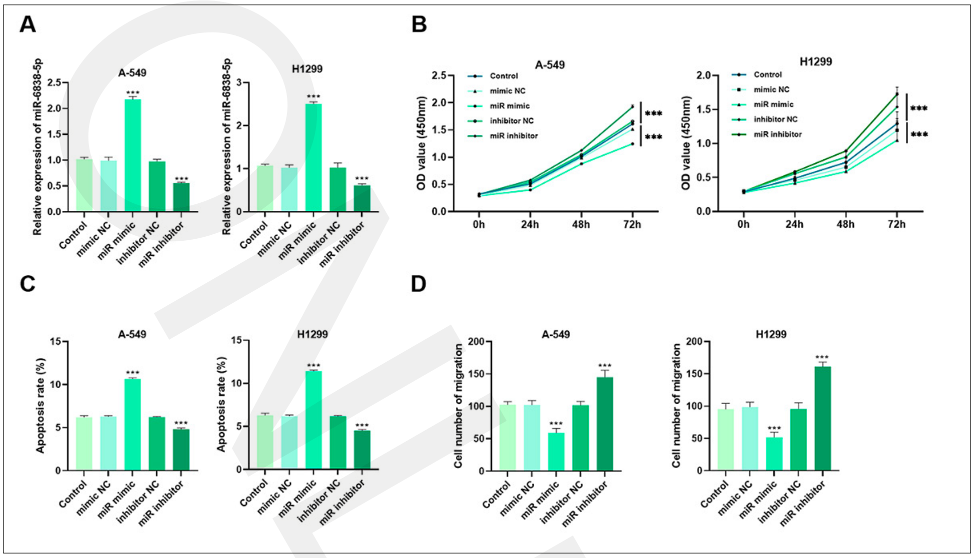

Figure 2. Impact of miR-6838-5p on biological functions of lung cancer cells. A) Increase in miR-6838-5p levels after transfected miR mimic. B, C, D) Over-expression of miR-6838-5p clearly inhibits cell proliferation and migration but promotes apoptosis. (n=3).
***$P < 0.001$ vs control

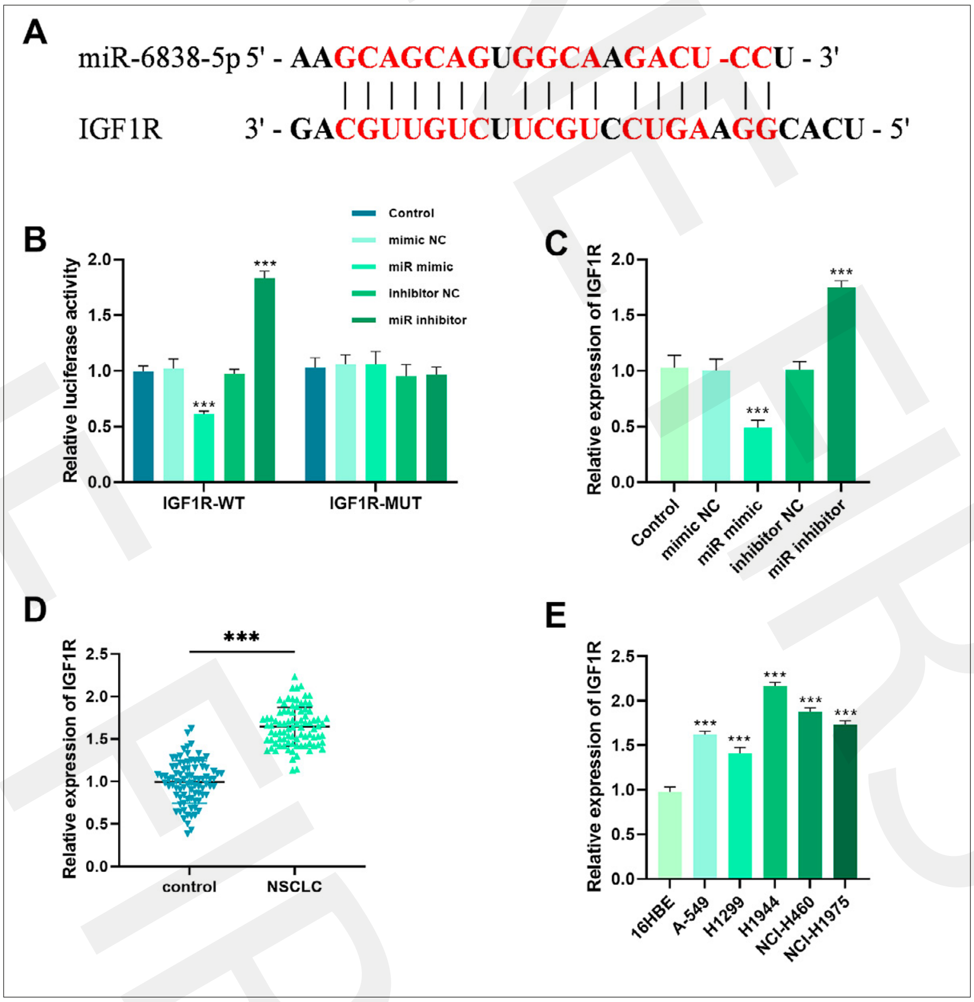

Figure 3. Targeting relationship of miR-6838-5p to IGF1R. A) Complementary sequences. B) Over-expression of miR-6838-5p inhibits IGF1R-WT luciferase activity. C) Inhibition of IGF1R levels by over-expression of miR-6838-5p. D) IGF1R levels were up-regulated in NSCLC patients. E) Up-regulation of IGF1R levels in lung cancer cell. (n=3).
***$P < 0.001$

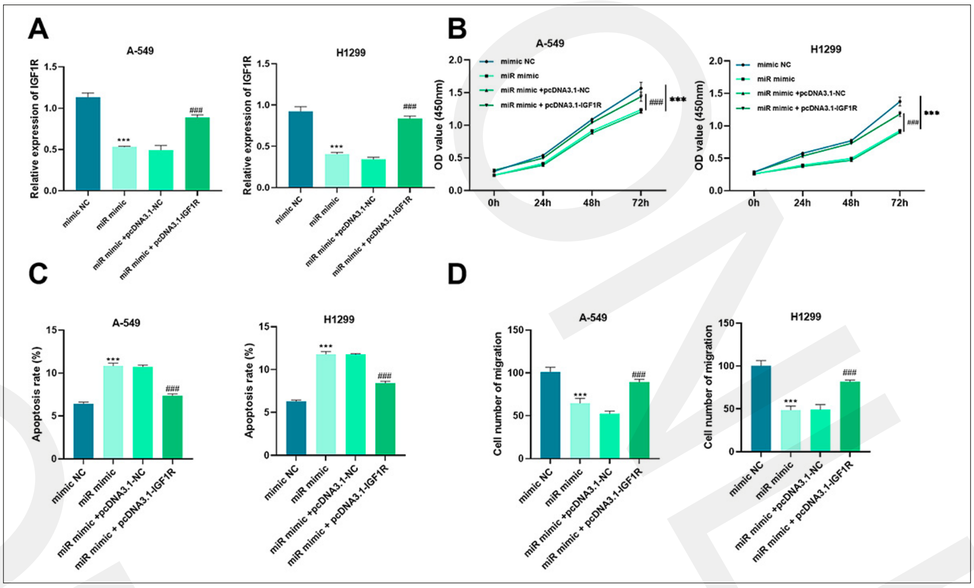

Figure 4. Impact of IGF1R on biological function of lung cancer cells. A) Changes in IGF1R levels after transfection with pcDNA3.1-IGF1R. B, C, D) Up-regulation of IGF1R partially restored the inhibitory effects of miR-6838-5p over-expression on proliferation and migration, as well as the promotion of apoptosis. (n=3).
$^{***}P < 0.001$ vs mimic NC; $^{\#\#\#}P < 0.001$ vs miR mimic)

down-regulated miR-6838-5p levels ($P < 0.05$) (Fig. 2A). Over-expression of miR-6838-5p inhibited lung cancer cell proliferation and accelerated their apoptosis, whereas silencing miR-6838-5p promoted proliferation and inhibited apoptosis ($P < 0.05$) (Fig. 2B, C). By testing the migration ability of A-549 and H1299 cells by transwell it was found that up-regulation or down-regulation of miR-6838-5p inhibited or promoted cell migration ($P < 0.05$) (Fig. 2D).

IGF1R is a direct target of miR-6838-5p. Complementary sequences between IGF1R and miR-6838-5p ($P < 0.05$) were identified (Fig. 3A), and over-expression or silencing of miR-6838-5p either inhibited or promoted IGF1R-WT luciferase activity, but did not affect the activity of IGF1R-MUT luciferase, regardless of changes in miR-6838-5p ($P < 0.05$) (Fig. 3B). Up-regulation of miR-6838-5p suppressed IGF1R levels, and down-regulation of miR-6838-5p had the the opposite effect ($P < 0.05$) (Fig. 3C). IGF1R levels were dramatically elevated in NSCLC patients compared to control ($P < 0.001$) (Fig. 3D). Evidently, Significant upregulation of IGF1R levels was also observed in 5 lung cancer cell lines ($P < 0.001$) (Fig. 3E).

IGF1R over-expression impairs the effect of miR-6838-5p on lung cancer cells. To further explore the action of miR-6838-5p in NSCLC by regulating IGF1R, pcDNA3.1-IGF1R were transfected into A-549 and H1299 cells. The results indicated that transfection of the miR mimic suppresses IGF1R levels. Up-regulation of IGF1R alleviated the inhibitory effect of miR-6838-5p over-expression on IGF1R levels ($P < 0.05$) (Fig. 4A). Transfection of miR mimic inhibits the proliferation and migration of lung cancer cells and accelerates their apoptosis. In addition, up-regulation of IGF1R partially restored the inhibitory effects of miR-6838-5p over-expression on lung cancer cell proliferation and migration as well as the promotion of apoptosis ($P < 0.05$) (Fig. 4B, C and D).

DISCUSSION

NSCLC poses an existential challenge and economic burden to humans worldwide. Due to environmental pollution and smoking, the incidence of NSCLC has a tendency to to affect younger patients. To make matters worse, half of the patients are diagnosed with advanced stages of the disease and multi-organ metastases. Recently, miRNA-targeted therapies have become an essential tool in the treatment of human tumours [14, 15]. In the current study, miR-6838-5p showed great potential for diagnosis and treatment of NSCLC.

miR-6838-5p has been described as down-regulated in a variety of cancers, thereby disrupting malignant metastasis, inhibiting malignant proliferation and epithelial mesenchymal transition (EMT) in triple-negative breast cancer (TNBC), by negatively regulating WNT3A [16]. miR-6838-5p also inhibits PTPN4 levels, and reduces growth, metastasis and glycolysis in HCC [17]. FGD5-AS1 promotes renewal and metastasis of thyroid cancer (TC) cells by regulating miR-6838-5p [12]. miR-6838-5p plays a similar role in nasopharyngeal carcinoma [11]. In addition, miR-6838-5p is involved in the regulation of myocardial injury and cerebral ischemia reperfusion injury [18, 19].

In the current study, miR-6838-5p appeared clearly down-regulated in NSCLC patients and had good diagnostic ability, and patients with high levels of miR-6838-5p showed better prognosis. Furthermore, the results of clinical analyses revealed a close association between miR-6838-5p and tumour size and stage, as well as metastasis. miR-6838-5p is down-regulated in HCC and also holds significant diagnostic value, which is consistent with the results of the current study [9]. Similarly, miR-4429 was down-regulated in the serum of NSCLC patients and was strongly associated with tumour stage and metastasis [20]. Accordingly, it was hypothesized that miR-6838-5p might affect NSCLC progression by regulating the biological activity of lung cancer cells. This hypothesis was confirmed by *in vitro* cellular experiments which showed that the over-expression miR-6838-5p enhanced the self-renewal capacity and migration of lung cancer cells. Similarly, miR-6838-5p over-expression inhibited the proliferation of breast cancer cells, thereby inhibiting breast cancer progression [21]. Not coincidentally, Zhang et al. verified the inhibitory effect of miR-6838-5p on hepatoblastoma in tumour rat models [22] which suggests that miR-6838-5p plays a role in suppressing cancer factors in NSCLC. The current study experimentally determined the targeting relationship between miR-6838-5p and IGF1R, through which a deeper understanding of the molecular mechanism of NSCLC was obtained. IGF1R has been shown to be aberrantly expressed in a range of cancers and is strongly related to tumour activity [23, 24]. It was observed that IGF1R was positively correlated with NSCLC tumour size, and that NSCLC patients with high IGF1R levels had a poorer prognosis [25]. The current study also demonstrated that IGF1R is over-expressed in NSCLC patients and is a target of miR-6838-5p.

A specific inhibitor against IGF1R (IGF1R-3801–1738) has been devised which is effective in improving the condition of low-risk NSCLC patients, but is ineffective in high-risk patients [26]. In addition, natural IGF1R inhibitors have been isolated that can act against solid tumours such as HCC [27], but their potential in NSCLC remains to be explored. In the presented study, the over-expression of IGF1R partially counteracted the inhibitory effect of miR-6838-5p upregulation on lung cancer cell proliferation and migration, which is consistent with the results of a previous study [28]. Similarly, RBM8A potentiated the malignant phenotype of breast cancer cells through increased IGF1R expression [29]. This suggests that the inhibitory impact of miR-6838-5p on malignant metastasis of NSCLC may be achieved by inhibiting IGF1R levels. In the future, it might be feasible to treat NSCLC by developing a combined inhibitor of miR-6838-5p and IGF1R.

Limitations of the study. The limited clinical sample size may not be sufficient to fully support the experimental findings. In addition, only one downstream pathway of miR-6838-5p was studied, while studies of the up-stream pathway and other down-stream pathways were omitted. For instance, miR-6838-5p interacts with WNT3A to activate the Wnt-β-catenin signalling pathway, thereby suppressing triple-negative breast cancer [16]. The LncRNA CERS6-AS1/miR-6838-5p/FOXP2 pathways can regulate the progression of cervical cancer [10], and may prove highly instructive for investigating the regulation of miR-6838-5p in NSCLC. Future studies will expand the sample size and conduct animal experiments to elucidate how these pathways modulate NSCLC progression.

CONCLUSION

miR-6838-5p may suppress the proliferation and migration of lung cancer cells by inhibiting the level of IGF1R. High expression of miR-6838-5p is associated with favourable prognosis and may serve as a potential diagnostic biomarker and clinical prognostic target for NSCLC.

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