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MiR-153 inhibits migration and invasion of human non-small-cell lung cancer by targeting ADAM19

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ABSTRACT

MiR-153 was reported to be dysregulated in some human cancers. However, the function and mechanism of miR-153 in lung cancer cells remains unknown. In this study, we investigated the role of miR-153 in human non-small-cell lung cancer (NSCLC). Using qRT-PCR, we demonstrated that miR-153 was significantly decreased in clinical NSCLC tissues and cell lines, and downregulation of miR-153 was significantly correlated with lymph node status. We further found that ectopic expression of miR-153 significantly inhibited the proliferation and migration and invasion of NSCLC cells *in vitro*, suggesting that miR-153 may be a novel tumor suppressor in NSCLC. Further integrated analysis revealed that ADAM19 is as a direct and functional target of miR-153. Luciferase reporter assay demonstrated that miR-153 directly targeted 3′UTR of ADAM19, and correlation analysis revealed an inverse correlation between miR-153 and ADAM19 mRNA levels in clinical NSCLC tissues. Knockdown of ADAM19 inhibited migration and invasion of NSCLC cells which was similar with effects of overexpression of miR-153, while overexpression of ADAM19 attenuated the function of miR-153 in NSCLC cells. Taken together, our results highlight the significance of miR-153 and ADAM19 in the development and progression of NSCLC.

1. Introduction

Lung cancer was one of the most malignant cancers and the leading cause of cancer-related deaths worldwide [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer and the 5-year survival rate for NSCLC patients at later stages is only 5–20% [2]. However, the molecular mechanisms underlying the development of NSCLC are currently still poorly understood. Thus, a better understanding of these molecular mechanisms will be useful to develop novel therapeutic targets and improve the current therapeutics [3].

MicroRNAs (miRNAs) represent a class of small non-coding regulatory RNA molecules, approximately 19–25 nucleotides, which can downregulate gene expression by binding to a complementary sequence in the 3′UTR of target mRNAs to either degrade these mRNAs or inhibit them from being translated into proteins [4,5]. MiRNAs are involved in the regulation of many key biological processes including cell proliferation, differentiation and migration [6]. Mounting evidence has revealed that dysregulation of miRNAs occurs in a variety of cancers. Previous studies reported that miR-153 is involved in the progression of many kinds of cancers, including glioblastoma [7], ovarian [8], oral [9], colorectal [10] and prostate cancer [11]. Ectopic expression of miR-153 significantly inhibited oral tumor cell metastasis by direct targeting SNAI1 and ZEB2 [9] and was tumor suppressive in glioblastoma stem cells [7], while upregulation of miR-153 promotes cell proliferation via downregulation of the PTEN tumor suppressor gene in prostate cancer [11] and supports colorectal cancer progression [10]. Recently, Yuan et al. found that miR-153 produced anti-tumor activity by suppressing AKT expression in lung cancer [12]. However, the roles of miR-153 in NSCLC remain poorly understood.

In the present study, we found that miR-153 was significantly downregulated and the expression of miR-153 was inversely correlated with clinical NSCLC lymph node metastasis. Ectopic expression of miR-153 inhibited cell proliferation and cell migration and invasion in NSCLC cells. Furthermore, we found that ADAM19 is one of direct target genes of miR-153, and confirmed that miR-153 exerts its effect on the inhibition of cell migration and invasion by downregulating ADAM19 in NSCLC cells. Our findings suggest that miR-153 may function as a tumor suppressor in NSCLC.

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Table 1
The relationship between miR-153 expression and clinicopathologic features in NSCLC.

Characteristic	Case number	miR-153 expression			*P* value
		Median	25%	75%	
Age					0.3288
⩾62	21	0.0956	0.0321	0.2717	
<60	20	0.0719	0.0325	0.1303	
Gender					0.3985
Man	26	0.0833	0.0343	0.1688	
Woman	15	0.0666	0.0321	0.2650	
Smoking history					0.4783
Yes	27	0.0733	0.0325	0.1667	
No	14	0.0695	0.0335	0.2650	
Histology					0.1775
Adenocarcinoma	22	0.0616	0.0335	0.1667	
Squamous carcinoma	19	0.0956	0.0270	0.3632	
Stage					0.1064
I + II	27	0.0866	0.0320	0.2693	
III + IV	14	0.0616	0.0343	0.1236	
Lymph node status					0.0108
No	25	0.0988	0.0716	0.2784	
Yes	16	0.0323	0.0217	0.0666	

2. Materials and methods

2.1. Patient samples and cell lines

A total of 41 pairs of human NSCLC tumor tissues and their matched normal tissues (at least 5 cm away from primary tumor) were obtained from Xiangya Hospital. None of the NSCLC patients had received radiation therapy or chemotherapy before the surgery, and the tissues were immediately snap-frozen in liquid nitrogen and stored at −80 °C until used. The clinicopathologic information of the patients obtained from patient records was summarized in Table 1. The study was approved by Ethics Committee of Central South University. Five NSCLC cell lines (A549, H157, H460, H358, SK-MES1) and a normal lung bronchus epithelial cell line BEAS-2B were purchased from American Type Culture Collection and cultured in DMEM (Thermo Scientific HyClone, Beijing, China) supplemented with 10% fetal bovine serum, 100 U/ml penicillin, and 100 mg/ml streptomycin (Invitrogen, Carlsbad, CA, USA). All cells were incubated in 5% CO_2 humid atmosphere at 37 °C.

2.2. RNA isolation and quantitative real-time PCR (qRT-PCR)

Total RNA was extracted using Trizol reagent (Invitrogen, USA). The relative expressions of miR-153 were measured using All-in-One™ miRNA qRT-PCR Detection Kit (GeneCopoeia), and snRNA U6 was used as an endogenous control. The specific primers for miR-153 and U6 were purchased from Guangzhou RiboBio (Guangzhou RiboBio Co., Ltd., Guangzhou, China). The relative expressions of ADAM19 were detected by SYBR green qPCR assay (BioRad, USA), and β-actin was used as an endogenous control. Primers used for ADAM19 and β-actin are as follows: ADAM19, 5′-CTGAAGGCTGTGGGAAGAAG-3′ (forward), 5′-AGCTACCACAGG ACCCACAC-3′ (reverse); β-actin, 5′-AGTGTGACGTGGACATCCGCAA AG-3′ (forward), 5′-ATCCACATCTGCTGGAAGGTGGAC-3′ (reverse). qRT-PCR was performed on the ABI 7500 thermocycler (Applied Biosystems, USA). The relative expression levels were calculated using the $2^{-\Delta\Delta ct}$ method.

2.3. Plasmid constructions, miRNA mimics and siRNAs

The coding sequence of ADAM19 was amplified and cloned into pcDNA3.1 vector to generate ADAM19 expression vectors, and the empty pCDNA3.1 vector was used as control. Primers used for ADAM-9 coding sequence are as follow: 5′-GAGCCTGGATGGACAA GAGGAA-3′ (forward) and 5′-CTAGATTTTCGAGCTAATCATC-3′ (reverse). The wild-type 3′UTR of ADAM19 (WT) was amplified with the following primers: 5′-CTCGAGACCGTCCACTGTGCGT-3′ (forward) and 5′-GCGGCCGCACTAACAAGGAAAAAAGGCAC-3′ (reverse). Endonuclease (XhoI/Not I) restriction sites were incorporated in primers to facilitate ligation into the psiCheck-2 reporter vector (Promega, Fitch-burg, WI, USA). Site-directed mutagenesis of the miR-153 seed sequence in the 3′UTR of ADAM19 (Mut) was performed using the QuikChange™ Site-Directed Mutagenesis Kit (Stratagene, La Jolla, CA, USA). miR-153 and scramble mimics and corresponding inhibitor were purchased from RiboBio (Guangzhou, China). ADAM19 specific small interfering RNAs (si-ADAM19) and the control shRNA (si-control) were purchased from GeneChem (Shanghai, China).

2.4. Lentivirus infection and transfection

Lentiviruses containing pre-miR-153 (Lv-miR-153) and negative control (Lv-NC) were purchased from GeneChem Company (Shanghai, China). Cells were cultured to about 70% of the plates and then added by a concentration of 5.0×10^4 TU/well Lv-miR-153 or Lv-NC, and qRT-PCR was performed to determinate

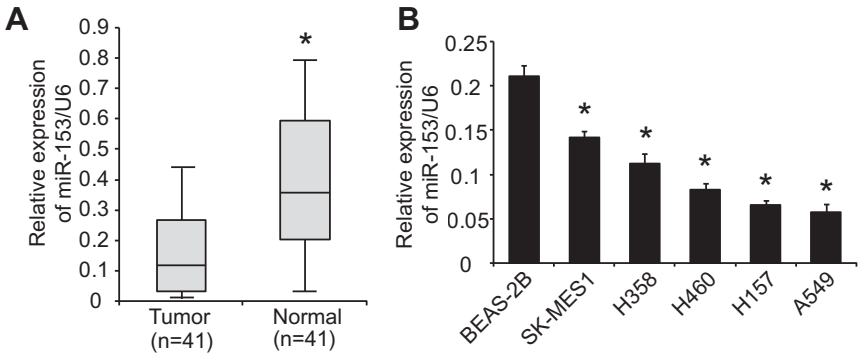

Fig. 1. MiR-153 is down-regulated in NSCLC tissues and cell lines. (A) The relative expression levels of miR-153/U6 snRNA were evaluated by qRT-PCR in 41 paired NSCLC tissues (tumor) and adjacent normal tissues (normal). (B) The relative miR-153 expression levels in five NSCLC cell lines (SK-MES1, H358, H460, A549, H157) and the normal cell line BEAS-2B. *$P < 0.05$.

expression levels of miR-153 after being infected for 5 days. Lipofectamine 2000 Reagent (Invitrogen, Carlsbad, CA) was used for cell transfection following the manufacturer's protocol.

2.5. Cell proliferation, migration and invasion assays

Cell proliferation was evaluated by MTT assay. Cells were allowed to grow in 96-well plates with 3000 cell per well, and incubated for 24, 48 and 72 h, then MTT (10 mg/ml) was added to the cells and incubated for 3 h. The reaction was then terminated by removal of the supernatant followed by adding 200 μl of DMSO. After 2 h incubation, the optical density at 570 nm of each well was measured with a microplate reader (Bio-Rad). Cell migration was assessed by wound healing assays. Cells were seeded in six-well plates and cultured to 100% confluence. Wounds were generated in the cell monolayer using a pipette tip. The cells were then cultured for 48 h and the wound closure was assessed by Scion Image Software (Scion Corporation, Frederick, MD). Cell invasion was assessed by transwell with Matrigel (BD Bioscience). 1×10^5 cells in 200 μl of serum-free media were added into the

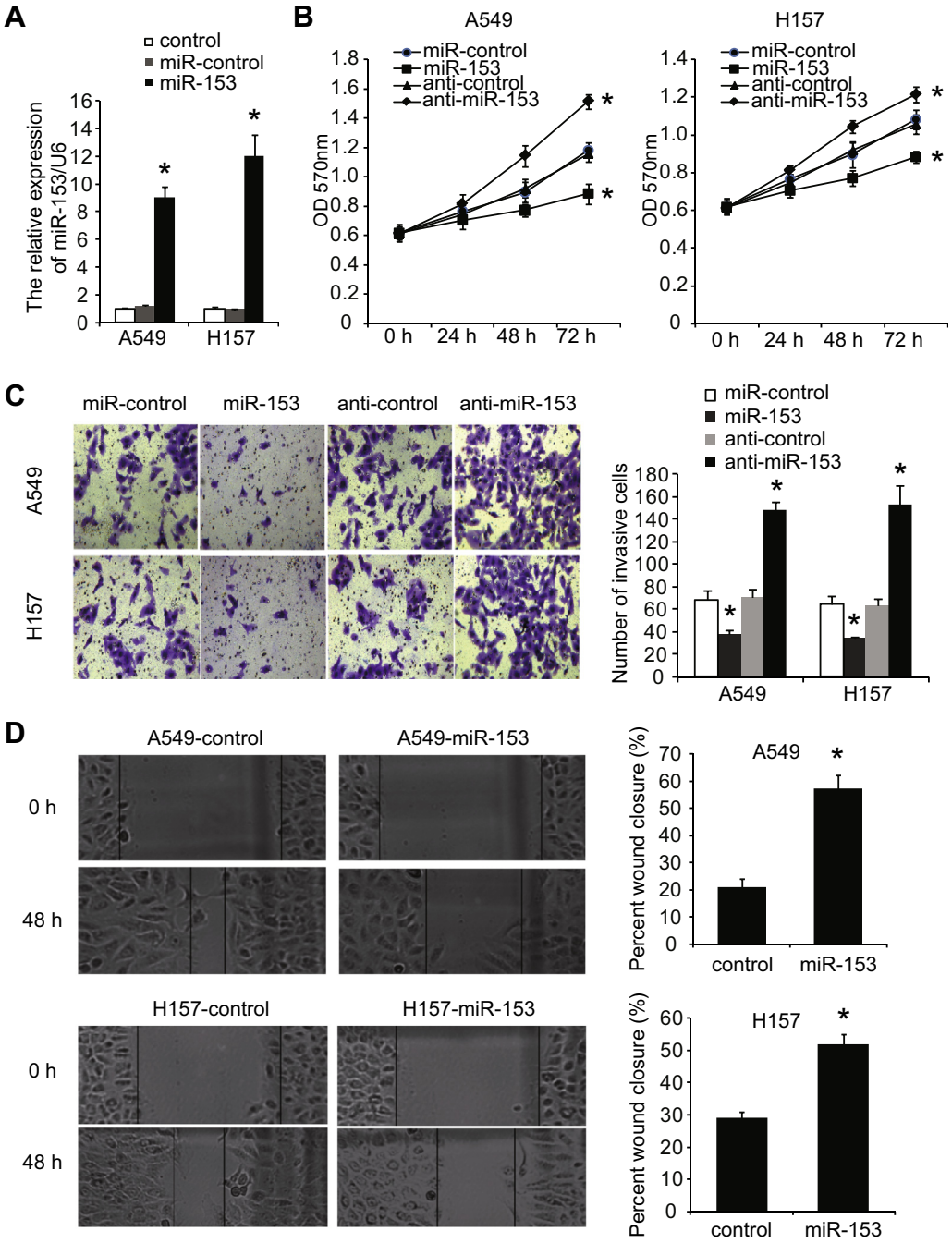

Fig. 2. MiR-153 inhibits the proliferation and migration and invasion of NSCLC Cells *in vitro*. (A) A549 and H157 cells were infected with miR-153 or miR-control lentivirus, and the expression of miR-153 was analyzed by qRT-PCR. The endogenous miR-153 in A549 and H157 cells was silenced with anti-miR-153 mimics, and the effects of miR-153 on cell proliferation, migration and invasion were determined using MTT assay (B), transwell assays with matrigel (C) and wound healing assays (D), respectively. $^*P < 0.05$.

upper chamber of an insert precoated with Matrigel with the lower chamber filled with DMEM with 10% fetal bovine serum. After incubation for 48 h, the non-invading cells remaining on the upper surface of the membrane was removed, and the invaded cells through the membrane were fixed and stained with 0.1% crystal violet, imaged and counted under a microscope (Olympus, Tokyo, Japan).

2.6. Western blotting

Cells were lysed using protein extraction reagent RIPA (Beyotime) supplemented with protease inhibitors, quantified by the BCA method (Beyotime, Jiangsu, China), and 50 μg protein extractions were separated by 12% SDS–PAGE, transferred to nitrocellulose membranes (Whatman, Maidstone, UK) and incubated with specific primary antibodies against ADAM19 (Abgent, Inc., San Diego, CA, USA) and β-actin (Santa Cruz Biotechnology Inc., CA, USA) overnight at 4 °C. Then the membranes were washed and probed with HRP-conjugated secondary antibodies. Signals were visualized with Enhanced Chemiluminescence Plus Kit (GE Healthcare).

2.7. Statistical analysis

Each experiment was repeated at least three times and data were expressed as the mean ± SD. Statistical significance between two groups was analyzed using Student *t*-test. The correlation between miR-153 and ADAM19 expression was analyzed using Spearman's correlation analysis. $P < 0.05$ was considered statistically significant.

3. Results

3.1. MiR-153 is down-regulated in NSCLC tissues and cell lines

We evaluated the expression levels of miR-153 by qRT-PCR in 41 paired NSCLC tissues and adjacent normal tissues. As shown in Fig. 1A, the expression levels of miR-153 were significantly

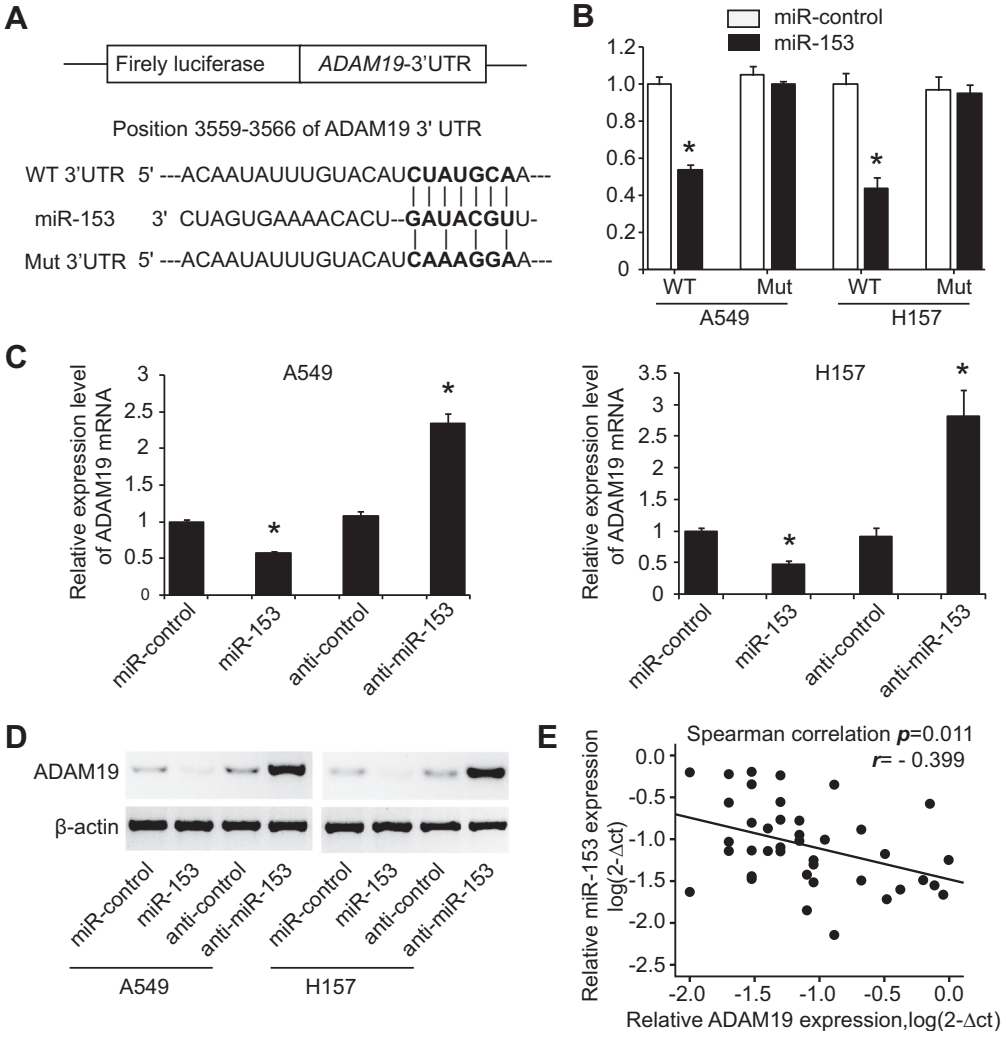

Fig. 3. MiR-153 directly inhibits ADAM19 expression by targeting its 3′UTR. (A) Predicted binding sequences of miR-153 in the 3′UTR of ADAM19. Mutation was generated in the seed region of the 3′UTR of ADAM19 by mutating 3 nt that is recognized by miR-153. A fragment of 3′UTR of ADAM19 containing wild-type (WT) or mutant (Mut) 3′UTR of ADAM19 was subcloned into the luciferase reporter vector. (B) Luciferase assay was performed in A549 and H157 cells cotransfected with miR-153 mimics and a luciferase reporter containing the wild-type (WT) or mutant (Mut) 3′UTR of ADAM19. Luciferase activities were measured 36 h post-transfection. (C and D) The expression of ADAM19 in A549 and H157 cells after 48 h transfection with miR-153 mimics (miR-153), scramble mimics (miR-control) or their inhibitor mimics (anti-miR-153 and anti-control) was measured by qRT-PCR and Western blot. (E) A statistically inverse correlation between miR-153 and ADAM19 mRNA levels in 41 NSCLC tumor tissues by correlation analysis. *$P < 0.05$.

Table 2
The relationship between ADAM19 expression and clinicopathologic features in NSCLC.

Characteristic	Case number	ADAM19 expression			*P* value
		Median	25%	75%	
Age					0.5527
⩾62	21	0.1264	0.0431	0.4104	
<60	20	0.1195	0.0409	0.3422	
Gender					0.2935
Man	26	0.0933	0.0343	0.3688	
Woman	15	0.0866	0.0321	0.3251	
Smoking history					0.2043
Yes	27	0.1033	0.0325	0.4267	
No	14	0.0795	0.0335	0.3650	
Histology					0.3104
Adenocarcinoma	22	0.0873	0.0335	0.3753	
Squamous carcinoma	19	0.0916	0.0371	0.3432	
Stage					0.0101
I + II	27	0.0743	0.0312	0.1847	
III + IV	14	0.1797	0.0903	0.5275	
Lymph node status					0.0073
No	25	0.0724	0.0201	0.2304	
Yes	16	0.2223	0.0517	0.7351	

decreased in NSCLC tissues compared with those in adjacent normal tissues. Notably, analysis of the correlation between miR-153 expression levels and clinicopathologic parameters revealed that the downregulation of miR-153 was significantly correlated with lymph node status ($P = 0.0108$), while no significant correlation was found in other parameters (Table 1). In addition, we detected miR-153 expression levels in five NSCLC cell lines and found that the relative expression levels of miR-153 in NSCLC cells were lower than that of the normal cell line BEAS-2B (Fig. 1B). Taken together, these data suggest that decreased expression level of miR-153 may be associated with NSCLC carcinogenesis.

3.2. MiR-153 inhibits the proliferation and migration and invasion of NSCLC cells in vitro

We then investigated the functional roles of miR-153 in NSCLC cells. To do so, we first constructed lentiviral vector expressing miR-153 or miR-control, and infected A549 and H157 cell lines, respectively. Overexpression of miR-153 in these stable infected cells (named A549-miR-153 or H157-miR-153) was confirmed by qRT-PCR (Fig. 2A). Cell proliferation assays revealed that overexpression of miR-153 inhibited the proliferation of A549 and H157 cells (Fig. 2B). In addition, transwell assays with matrigel (Fig. 2C) and wound healing assays (Fig. 2D) showed that ectopic expression of miR-153 in A549 and H157 cells significantly inhibited cell invasion and migration ability, respectively. In contrast, when endogenous miR-153 was silenced with anti-miR-153 mimics, the cell proliferation (Fig. 2B) and invasion (Fig. 2C) and migration (data not shown) was increased. These results suggest that miR-153 is tumor suppressor gene in NSCLC Cells *in vitro*.

3.3. MiR-153 directly inhibits ADAM19 expression by targeting its 3′UTR

To elucidate the molecular mechanism by which miR-153 exerts its inhibitory effect on NSCLC cells, we predicted potential targets of miR-153 using the TargetScan and miRanda tools. Among the predicted candidate targets, we focused on ADAM19 in the study, considering the involvement of ADAM19 in the pathogenesis of many human cancers. To validate if miR-153 was able to directly target 3′UTR of ADAM19, a fragment of wild type or mutant 3′UTR of ADAM19 was cloned into psiCheck-2 reporter vector, respectively (Fig. 3A). Luciferase reporter assays revealed that up-regulation of miR-153 significantly decreased the relative luciferase activity of 3′UTR of ADAM19 in A549 or H157 cells, but had no effect on the mutant 3′UTR of ADAM19 (Fig. 3B). Of note, qRT-PCR and Western blotting analysis revealed that overexpression of miR-153 significantly reduced the expression of ADAM19, and knockdown of miR-153 by inhibitor mimics increased ADAM19 expression in A549 or H157 cells (Fig. 3C and D). In addition, there was a significant inverse correlation between expression levels of miR-153 and ADAM19 mRNAs in NSCLC tissues (Fig. 3E), and the correlation analysis between ADAM19 expression levels and clinicopathologic parameters revealed that the upregulation of ADAM19 was significantly correlated with lymph node status ($P = 0.0073$) and tumor stage ($P = 0.0101$) (Table 2), suggesting upregulation of ADAM19 may be associated with NSCLC metastasis. Taken together, these results suggest that miR-153 suppresses ADAM19 expression by directly targeting its 3′UTR.

3.4. ADAM19 is involved in miR-153-suppressed migration and invasion of NSCLC cells

To further determine whether miR-153 exerts its inhibitory effect through downregulation of ADAM19 in NSCLC cells, we firstly knocked down ADAM19 in A549 or H157 cells infected with lentiviral constructs containing ADAM19 specific small interfering RNAs (si-ADAM19) (Fig. 4A). As expected, ADAM19 knockdown significantly inhibited cell migration and invasion of A549 or H157 cells (Fig. 4B), which was similar to the effects of miR-153 overexpression. Next, A549/H157-miR-153 cells were transfected with ADAM19 expression plasmids lacking 3′UTR to rescue ADAM19 expression (Fig. 4A). As shown in Fig. 4C, ADAM19 overexpression significantly attenuated miR-153-induced inhibition on cellular migration and invasion in A549 and H157 cells. Of note, knock down or overexpression of ADAM19 had no significant effect on cell proliferation of A549 or H157 cells (data not shown). Taken together, these results suggest that ADAM19 is a functional target of miR-153, involved in miR-153-suppressed migration and invasion of lung cancer cells.

4. Discussion

A lot of studies have revealed the relationship between dysregulated miRNAs and cancer progression [13–15]. MiR-153 has been reported to be significantly dysregulated in many human cancers [7–11]. In the present study, we investigated the expression patterns of miR-153 in NSCLC clinical samples and identified decreased miR-153 expression as a valid factor associated with lymph node metastasis. In addition, the expression levels of miR-153 in five NSCLC cell lines were also significantly downregulated. These findings suggest that miR-153 may be a tumor suppressor gene in NSCLC.

To validate this hypothesis, we investigated the functional roles of miR-153 in two NSCLC cell lines. Cell proliferation assays demonstrated that overexpression of miR-153 inhibited NSCLC cell proliferation. This was consistent with previous findings that overexpression of miR-153 suppressed glioblastoma (GBM) cell proliferation and GBM stem cell growth [7,16], but inconsistent in prostate cancer in which miR-153 promoted cell cycle transition and cell proliferation [11]. Our transwell assays with matrigel and wound healing assays revealed that ectopic expression of miR-153 in A549 and H157 cells could dramatically inhibit their migration and invasion ability *in vitro*. This finding was consistent with previous study that ectopic expression of miR-153 in

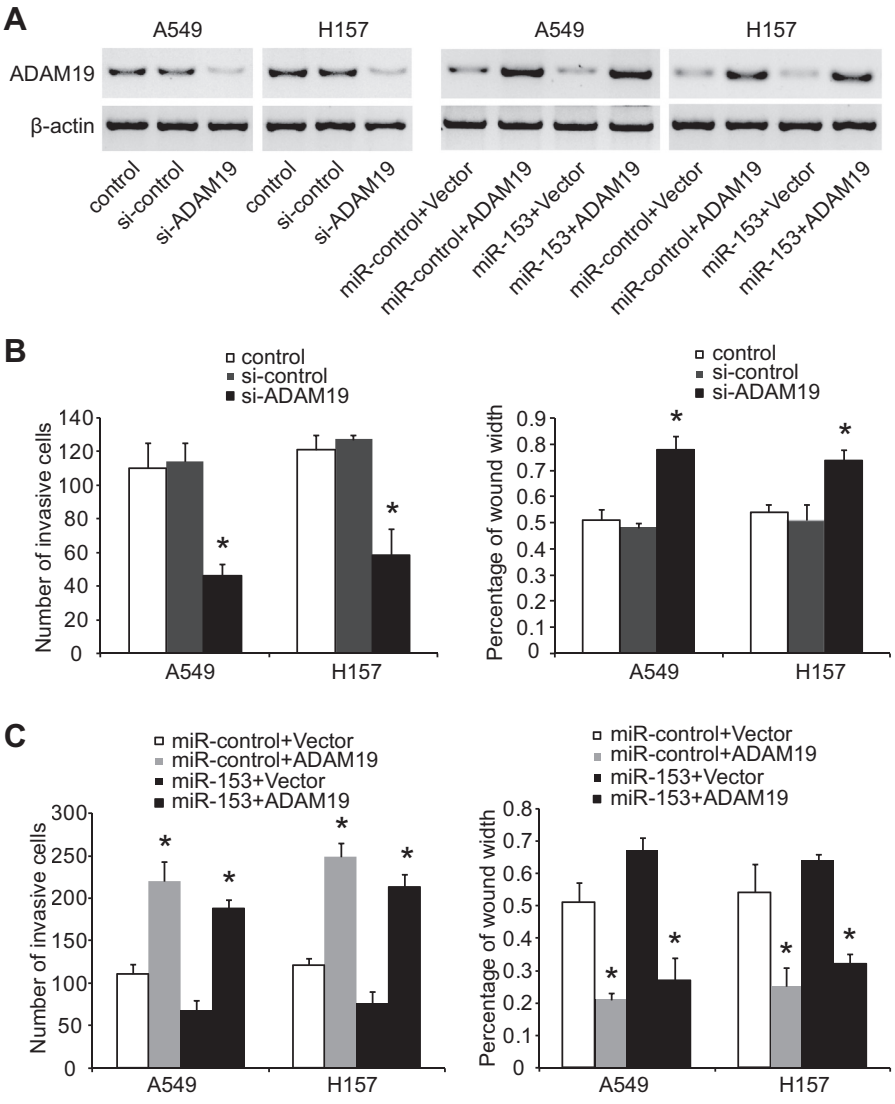

Fig. 4. ADAM19 is involved in miR-153-suppressed migration and invasion of NSCLC cells. A549 or H157 cells were infected with specific small interfering RNAs, si-ADAM19, and miR-153 stably infected A549 or H157 cells were transfected with ADAM19 expression plasmids lacking 3′UTR. (A) The expression of ADAM19 was examined by Western blotting. (B) The effect of ADAM19 knockdown on the cell migration or invasion was assessed by wound healing or transwell with matrigel assay, respectively. (C) The effect of rescued ADAM19 on the cell migration or invasion was assessed by wound healing or transwell with matrigel assay, respectively. $^{*}P < 0.05$.

mesenchymal-like cells resulted in an epithelial morphology change with decreased cellular invasive ability and significantly inhibited tumor cell metastasis in ovarian cancer [8]. However, another study revealed that miR-153 upregulation increased colorectal cancer invasiveness [10]. These data suggest that the roles of miR-153 might vary in different types of cancers. Here, we demonstrated that miR-153 exerted its inhibitory effect on the proliferation and migration and invasion of NSCLC cells.

Since the impact of specific miRNAs on cancer biology depends on their downstream targets. In this study, we further predicted and validated that ADAM19 was a novel direct target of miR-153 by the luciferase reporter assay in A549 and H157 cells. qPCR and Western blot analysis also confirmed that ADAM19 was downregulated by miR-153 upregulation at the mRNA and protein levels. Furthermore, there was a significant inverse correlation between expression levels of miR-153 and ADAM19 mRNAs in clinical NSCLC samples, and high expression of ADAM19 was significantly correlated with NSCLC lymph node status and advanced tumor stages. Functional study revealed that ADAM19 knockdown significantly inhibited cell migration and invasion of A549 or H157 cells, while ADAM19 overexpression attenuated miR-153-induced inhibition on cellular migration and invasion. Therefore, our results suggested that the mechanism of the miR-153-mediated inhibition of the invasion and migration in NSCLC might be through downregulating ADAM19. However, the further molecular mechanism of miR-153-mediated inhibition of the invasion and migration in NSCLC will be investigated in the future.

ADAM19 is a member of a disintegrin and metalloproteinases (ADAMs), which are involved in various biological functions, such as fertilization, embryonic development, cell adhesion, cell migration, cell signaling, proteolytic shedding and proteolysis [17,18]. Dysregulation of many ADAM proteins has been observed in the regulation of growth factor activities and integrin functions, leading to promotion of cell growth and invasion in human tumors [19,20]. ADAM19 is upregulated in human brain tumors such as astrocytoma and glioblastoma and is correlated with the invasiveness of glioma [21]. ADAM19 is also overexpressed in lung cancerous cells [22]. Abnormally high expression of ADAM19 is also

linked to inflammation and fibrosis of the lung [23] and kidney [24]. Thus, targeted inhibition of ADAM19 may be crucial for the treatment of certain types of tumors and inflammatory diseases.

In conclusion, our current findings revealed that miR-153 is frequently downregulated in NSCLC, and demonstrated the biological functions of miR-153 in significantly inhibiting the proliferation and migration and invasion of NSCLC cells. We also identified ADAM19 as a novel target possibly involved in miR-153-mediated migration and invasion suppression for NSCLC, implicating restoration of miR-153 may be a potential therapeutic strategy for NSCLC.

Conflict of interest

The authors declare that they have no conflict of interest.

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