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CircPSMC3 Suppresses Migration and Invasion of Non-Small Cell Lung Cancer Cells via miR-182-5p/NME2 Axis

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Background: CircPSMC3 has been reported to play important roles in the occurrence and development of cancer. However, the role of circPSMC3 in NSCLC (non-small cell lung cancer) and the underlying mechanisms remain unclear.

Material/Methods: The expression of circPSMC3 in NSCLC tissues was measured through qRT-PCR (quantitative real-time polymerase chain reaction). The effect of circPSMC3 on the invasion and migration of NSCLC cell line H1299 was determined through transwell invasion assay and wound healing assay. Dual-luciferase reporter assay was performed for exploring the regulatory interaction between circPSMC3, miR-182-5p, and NME2.

Results: Compared with adjacent normal tissues, the expression of circPSMC3 in NSCLC tissues was decreased. Lower circPSMC3 expression was closely associated with lymph node metastasis and higher TNM stage in NSCLC patients. Biological function analysis suggested that circPSMC3 inhibits the invasion and migration of H1299 cells through upregulating the expression of NME2. Mechanistically, circPSMC3 sponges miR-182-5p to suppress the invasion and migration of NSCLC cells via upregulating NME2 expression.

Conclusions: CircPSMC3 inhibits the invasion and migration of NSCLC cells through the miR-182-5p/NME2 signaling pathway.

MeSH Keywords: **Carcinoma, Non-Small-Cell Lung • Genes, Tumor Suppressor • MicroRNAs**

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Background

Lung carcinoma is one of the most lethal malignancies [1]. Among all lung carcinoma cases, NSCLC (non-small cell lung cancer) accounts for about 85% [2]. Despite great progress in treatment of NSCLC, the 5-year survival rate of NSCLC remains less than 5% [3], primarily due to metastasis. Approximately 60% patients with NSCLC have had metastasis at their first diagnosis [4]. Notably, metastasis is considered to be inevitable during the progression of NSCLC [5]. Therefore, it is extremely urgent to investigate the genetic regulatory networks related to NSCLC metastases.

Circular RNAs (circRNAs) form covalently closed loops, and are a type of non-coding RNA, without polyadenylation tails and 5' to 3' polar [6]. circRNAs can be transcribed from both exons and introns of parent genes [7]. Recently, circRNAs have been reported to play important roles in the progression and development of cancer [8]. In fact, dysregulation of circRNAs has already been found in many types of cancers [9]. Emerging evidence shows that circRNAs can sequester and sponge miRNAs to regulate gene transcription to participate in cancer development [10]. For instance, circPSMC3 levels are low in gastric cancer and inhibit the metastasis and proliferation of gastric cancer via sponging miR-296-5p to upregulate the expression of PTEN [11]. circPSMC3 suppresses the migration and invasion of hepatocellular carcinoma cells through upregulating RBM5 [12]. Moreover, circPSMC3 can induce cell apoptosis and suppress cell proliferation among nasopharyngeal carcinoma through downregulating the expression of ROCK1 [13]. However, the roles of circPSMC3 in the occurrence and progression of NSCLC remain unclear.

In the present study we investigated the role of circPSMC3 in lung cancer, and assessed the relationship between the circPSMC3 expression and TNM stage and lymph node metastasis in NSCLC patients. We further explored the molecular mechanisms of circPSMC3 in suppressing lung cancer, and analyzed the role of circPSMC3 in upregulating NME2 expression, which is inhibited by miR-182-5p in lung cancer.

Material and Methods

NSCLC tissues

The Research Ethic Committee of Zhuji People's Hospital (Zhuji, Zhejiang, P.R. China) approved the present study (No. 20170128), in which 103 pairs of NSCLC and normal tissues were collected from the Department of Cardiothoracic Surgery, Zhuji People's Hospital. All patients gave written informed consent.

Cell culture

GLC-82 cells were obtained from the Chinese Academy of Sciences (Shanghai, China). The cell lines H1299 (ATCC® CRL-5803), A549 (ATCC® CRM-CCL-185), H157 (ATCC® CRL-5802), and H358 (ATCC® CRL-5807) were purchased from ATCC® (Maryland, USA). The culture conditions of NSCLC cells lines were: DMEM (HyClone), 10% FBS (fetal bovine serum, Gibco), 37°C, and 5% CO_2.

RT-qPCR

RNAs extraction and RT-qPCR were conducted as described elsewhere [1]. TRIzol reagent from TaKaRa (Japan) was used for extraction of RNAs. RT-qPCR was performed using SYBR Premix Ex Taq II (Takara, Japan). Experiments were conducted according to the manufacturer's instructions. The primers of circPSMC3 were:
Reverse: 5'-GTGTTGGGCTGGAAGCCATC-3';
Forward: 5'-GTTTAGGGTCCCTGCCCTTTG-3'.
The primers of circPSMC3 and GAPDH were from Sangon Biotech (Shanghai, China).

Wound healing assay

H1299 and H157 cells were seeded in 6-well plates. Marker was conducted on the back of 6-well plates, with a 0.5~1-cm horizontal line across the 6-well plate. When cell confluence reached 80%, a scratch was made using 10-μL pipette tips, and scratched the horizontal line for annotating the image and measuring the distance. Then, the linear wound was photographed at 0 h and 48 h using microscopy. Image J software was used to measure the width of the scratch. Experiments were repeated 3 times.

Transwell invasion assay

H1299 and H157 cells (5×10^4) were seeded in upper chambers with 2% FBS medium, and 10% FBS medium was added to the lower chamber (24-well plates). Hanging cell culture inserts, with 8 μm pore size (PIEP12R48, Millipore), were used for the upper chambers in 24-well plates. After 24 h, cells that transmigrated through the upper chamber were fixed with 4% paraformaldehyde and stained with crystal violet. Representative images were photographed at 24 h using microscopy.

Western blot analysis

H1299 and H157 cells were collected at indicated times. Then, extracted proteins were separated using SDS-PAGE. Separated proteins were transferred onto PVDF membrane (Millipore, USA), which were then cultured with 5% non-fat milk in TBST for 1 h. The protein of interest was incubated with NME2 primary antibody (Abcam, USA) at 4°C for 12 h, and continued

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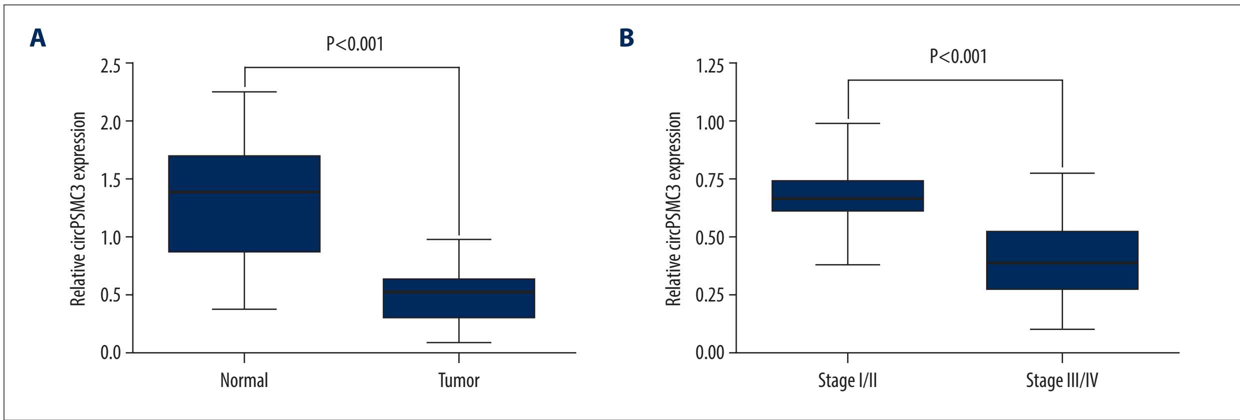

Figure 1. CircPSMC3 expression was decreased in NSCLC. (**A**) The expression of circPSMC3 was assessed in NSCLC tissues and corresponding normal tissues using qRT-PCR. n=103. (**B**) The expression of circPSMC3 was analyzed in patients with stage I/II (n=39) and with stage III/IV (n=64).

Table 1. Relationship between circPSMC3 level and clinicopathologic characteristics in patients with NSCLC.

Clinicopathological characteristics	Number	circPSMC3 expression		*P* value
		Low	High	
Age (years)				
≥60	59	38	21	0.874
<60	44	29	15	
Gender				
Male	65	45	20	0.244
Female	38	22	16	
Tumor size (cm)				
≥3	69	47	22	0.352
<3	34	20	14	
Differentiation				
Well and moderate	57	40	17	0.224
Poor	46	27	19	
TNM stage				
I/II	39	20	19	0.022*
III/IV	64	47	17	
Lymph node metastasis				
Yes	67	49	18	0.019*
No	36	18	18	

TNM – tumor node metastasis. * $P<0.05$ represents statistical difference.

to be incubated with secondary antibodies (HRP-labeled secondary antibodies, Sigma, USA) for 2 h at 37°C. The reaction was visualized using ECL (Millipore, USA).

Dual-luciferase reporter assay

H1299 cells were cultured in 96-well plates. When H1299 cell confluence reached 40%, reporter plasmids and miR-182-5p-mimic were simultaneously transfected into H1299 cells with Lipofectamine 2000. After 48 h, based on Luciferase® Reporter Assay protocol (Promega), luciferase experiments were carried out to measure the Renilla and firefly luciferase activities. Then, the ratio of the Renilla/firefly luciferase activities was further calculated.

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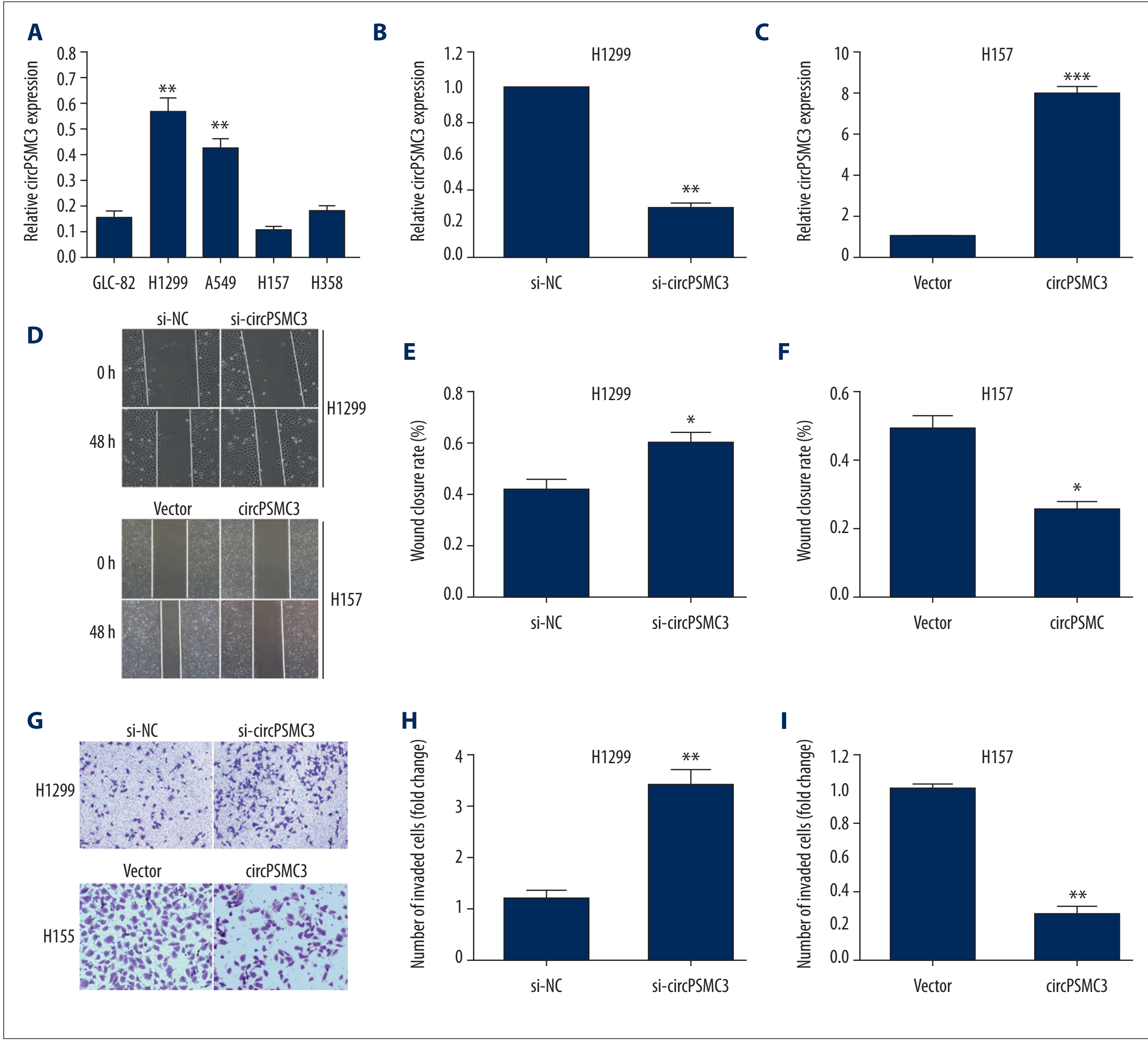

Figure 2. CircPSMC3 inhibits the invasion and migration of NSCLC cells. (**A**) The expression of circPSMC3 was assessed among several NSCLC cell lines by qRT-PCR. ** P<0.01. (**B**) The expression of circPSMC3 in H1299 cells transfected with si-circPSMC3 or si-NC was measured via qRT-PCR. ** P<0.01. (**C**) The expression of circPSMC3 in H157 cells transfected with circPSMC3 or vector was measured via qRT-PCR. ** P<0.01. (**D–I**), Si-circPSMC3 were transfected into H1299 cells and CircPSMC3 was transfected into H157 cells. The cell migration ability was observed by wound healing assay (**D–F**). ** P<0.01. Cellular invasion ability was tested by transwell invasion assay (**G–I**). ** P<0.01.

Statistical analysis

Data analysis was performed using GraphPad Prism 6. The unpaired t test and Pearson correlation analysis were used, with P<0.05 set as the level of statistical significance.

Results

CircPSMC3 expression was decreased in NSCLC cells and was associated with TNM stage and lymph node metastasis

circPSMC3 expression is reported to be reduced in gastric cancer [11], but circPSMC3 expression in NSCLC tissues is unknown. Therefore, to assess circPSMC3 expression in NSCLC, qRT-PCR was carried out to assess its expression in 103 pairs of NSCLC tissues and corresponding normal tissues. As shown

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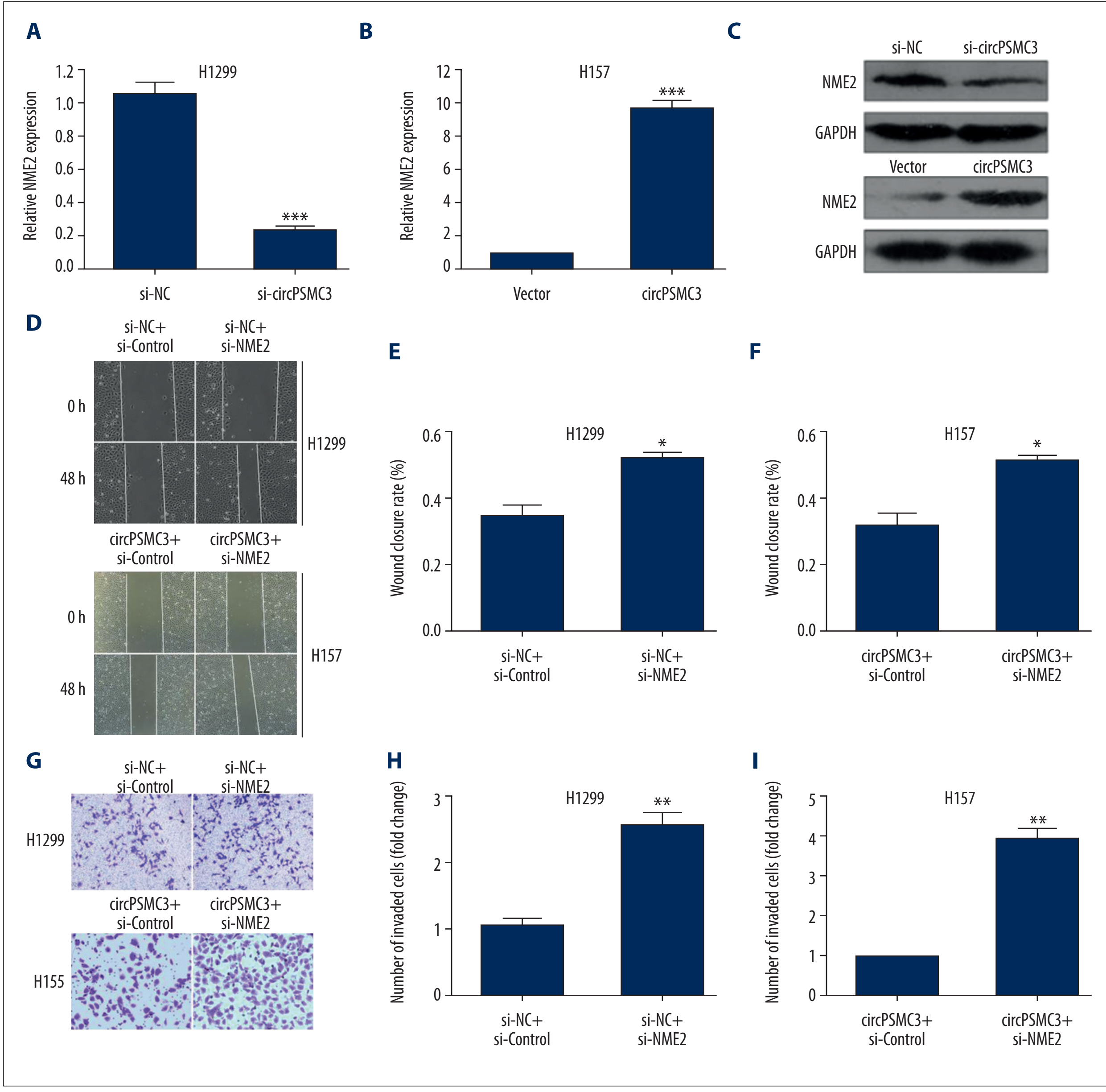

Figure 3. CircPSMC3 can inhibit the migration and invasion of NSCLC cells by regulating NME2. (**A–C**) Si-circPSMC3 was transfected into H1299 cells. CircPSMC3 was transfected into H157 cells. RT-qPCR (**A, B**) and Western blot (**C**) were used to measure NME2 protein and mRNA expression. *** $P<0.001$. (**D–I**) Si-NME2 or si-Control was transfected into H1299 and H157 cells transfected with si-NC. Cell migration ability was assessed via wound healing assay (**D–F**). Cellular invasion ability was tested through transwell invasion assay (**G–I**). ** $P<0.01$; * $P<0.05$.

in Figure 1A, circPSMC3 expression was lower in NSCLC tissues than in adjacent normal tissues. Moreover, our results showed that circPSMC3 expression was obviously downregulated among patients with stage III/IV compared to those with stage I/II (Figure 1B). In addition, lower circPSMC3 expression was closely associated with lymph node metastasis and higher TNM stage in NSCLC patients (Table 1). These results indicate that circPSMC3 expression is decreased in NSCLC and is associated with metastasis of NSCLC.

CircPSMC3 suppressed the invasion and migration of NSCLC cells

To investigate the roles of circPSMC3 in the invasion and migration of NSCLC cells, the expression of circPSMC3 was assessed in several NSCLC cell lines (GLC-82, H1299, A549, H157, and H358) via qRT-PCR. As shown in Figure 2A, there was higher circPSMC3 expression in H1299 than in the other 4 NSCLC cell lines. Therefore, H1299 cells were selected to

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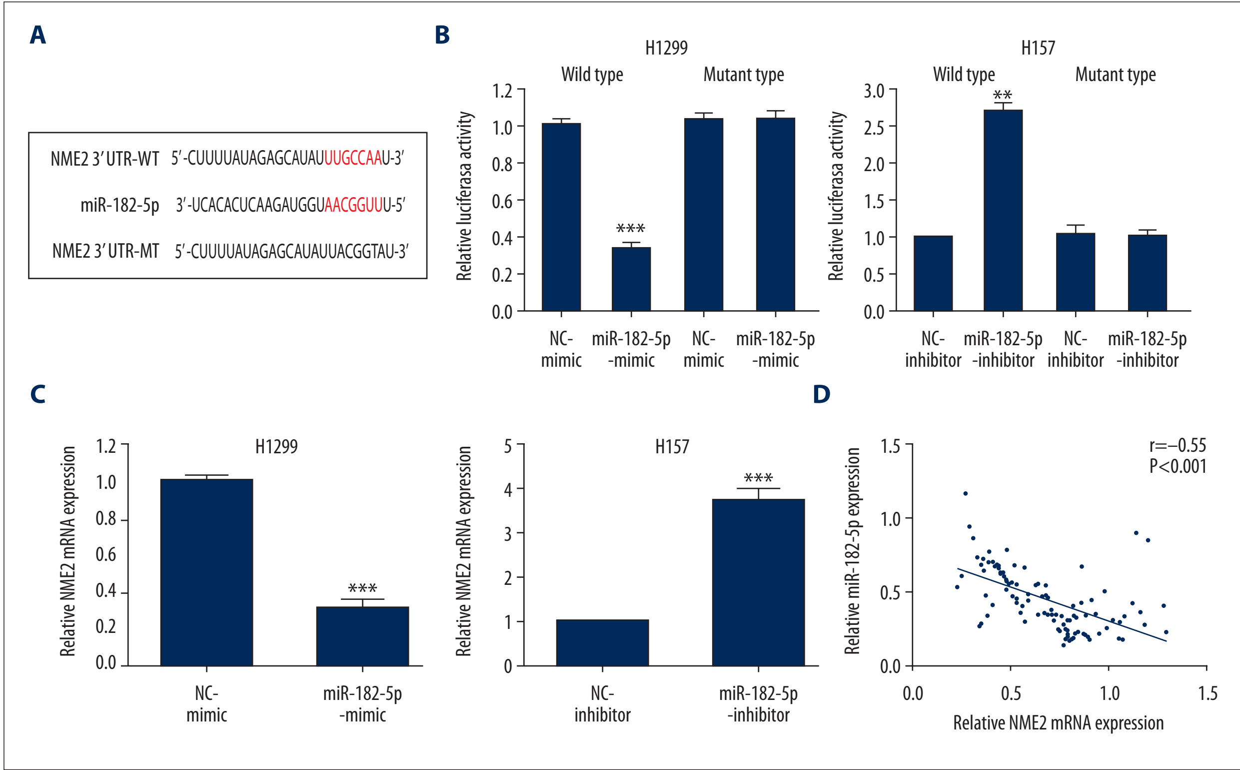

Figure 4. NME2 is a target gene of miR-182-5p. (**A**) The predicted binding site of miR-182-5p in NME2. (**B, C**) miR-182-5p-mimic was transfected into H1299 cells. miR-182-5p inhibitor was transfected into H157 cells. The relative luciferase activity was measured (**B**). RT-qPCR was used to detect NME2 mRNA expression (**C**). *** *P*<0.001. (**D**) The relationship between NME2 and miR-182-5p in NSCLC tissues was explored using Pearson correlation analysis.

be transfected with si-circPSMC3 for further function analysis. H157 cells were assessed for circPSMC3 overexpression. Si-circPSMC3 transection and circPSMC3 overexpression efficiency were measured via qRT-PCR (Figure 2B, 2C). Silenced circPSMC3 promoted the invasion and migration of H1299 cells, and the opposite was found in H157 cells (Figure 2D–2I). These observations indicate that circPSMC3 inhibits the invasion and migration of NSCLC cells.

CircPSMC3 inhibited the invasion and migration of NSCLC cells by regulating NME2

NME was the first suppressor gene reported to be associated with metastasis. NME overexpression can merely inhibit tumor metastasis without affecting primary tumor size [14]. NME2 (nucleoside diphosphate kinase 2), among 10 genes of the NME family, is the most studied in metastasis. In lung cancer, NME2 expression is negatively correlated with tumor stage [15,16]. To investigate the effect of circPSMC3 on NME2 expression, the NME2 mRNA and protein expression was detected in H1299 cells transfected with si-circPSMC3, as well as H157 cells with circPSMC3 overexpression. As shown in Figure 3A–3C, silenced circPSMC3 inhibited NME2 expression at protein and mRNA levels. To further explore the roles of NME2 in the invasion and migration of NSCLC cells, transwell invasion assay and wound healing assay were conducted in H1299 and H157 cells transfected with si-NC and si-NME2. We showed that silencing of NME2 blocked the inhibitory effects of circPSMC3 on the invasion and migration of H1299 cells, and the opposite was found in H157 cells (Figure 3D–3I). In conclusion, circPSMC3 can inhibit the invasion and migration of NSCLC cells via upregulating NME2.

NME2 is a target gene of miR-182-5p

According to the predication of TargetScanHuman software (*http://www.targetscan.org/*), there is a binding site of miR-182-5p in NME2 (Figure 4A). Then, the relative luciferase activity was measured using reporter plasmids cloned with miR-182-5p binding sequences in NME2 3'-UTR wildtype and mutant counterparts. As shown in Figure 4B, the relative luciferase activity was obviously decreased in H1299 cells transfected with miR-182-5p-mimic, and the opposite was found in H157 cells transfected with miR-182-5p inhibitor. Moreover, miR-182-5p remarkably downregulated NME2 expression in H1299 and H157 cells (Figure 4C). To explore the relationship between NME2 and miR-182-5p, Pearson correlation analysis was performed. The results showed that there was negative

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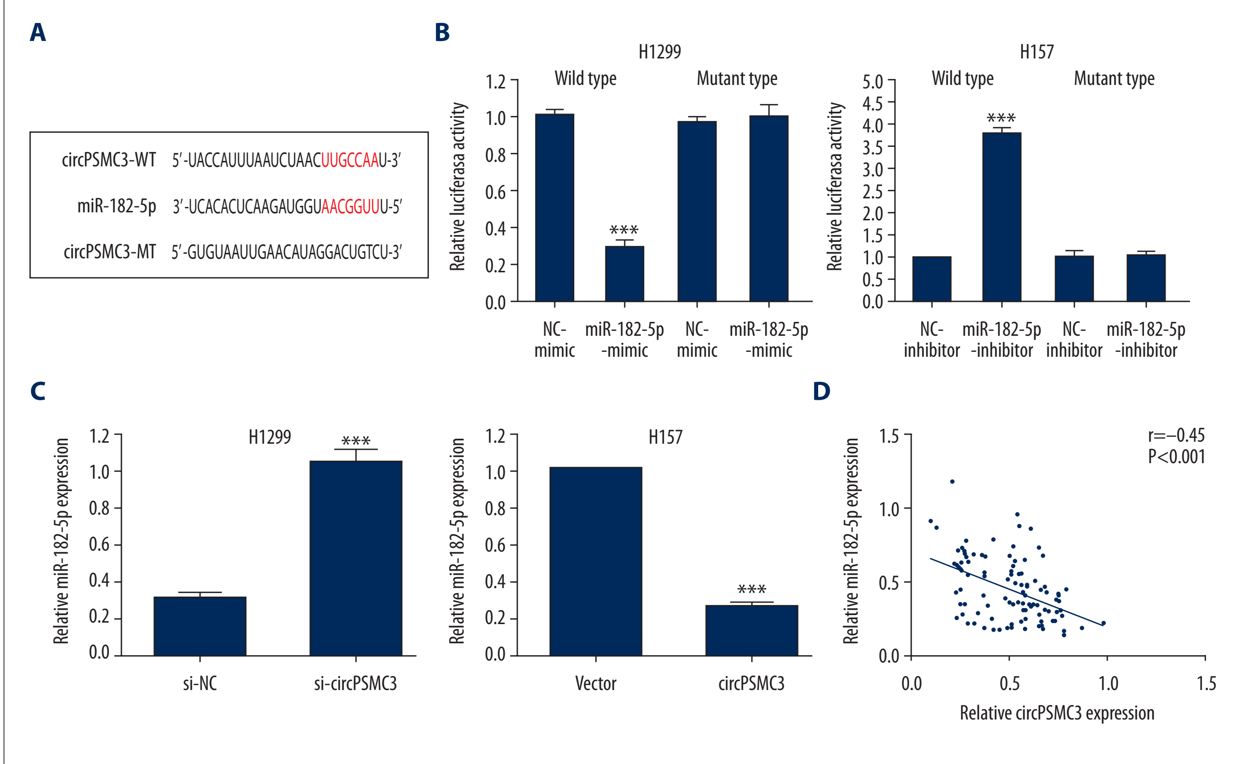

Figure 5. CircPSMC3 can sponge miR-182-5p in NSCLC cells. (**A**) The predicted binding site of miR-182-5p in circPSMC3. (**B**) miR-182-5p-mimic was transfected into H1299 cells. miR-182-5p inhibitor were transfected into H157 cells. The relative luciferase activity was detected. *** *P*<0.001. (**C**) Si-circPSMC3 was transfected into H1299 cells. CircPSMC3 was transfected into H157 cells. RT-qPCR was used to detect miR-182-5p expression. *** *P*<0.001. (**D**) Pearson correlation analysis was used to explore the relationship between circPSMC3 and miR-182-5p in NSCLC tissues.

relationship between NME2 and miR-182-5p in NSCLC tissues (Figure 4D). Taken together, these results suggest that NME2 is a target gene of miR-182-5p.

CircPSMC3 can sponge miR-182-5p in non-small cell lung cancer cells

To identify the molecular mechanisms related to circPSMC3-induced NME2 expression, a binding site of miR-182-5p in circPSMC3 was predicted using Starbase software (*http://www.targetscan.org/*) (Figure 5A). Then, the relative luciferase activity was analyzed using reporter plasmids cloned with miR-182-5p binding sequences in circPSMC3 wildtype and mutant counterparts. As shown in Figure 5B, there was distinctly lower relative luciferase activity in H1299 cells transfected with miR-182-5p-mimic compared to H157 cells transfected with miR-182-5p inhibitor. Furthermore, miR-182-5p expression was much higher in the si-circPSMC3 group than in the si-NC group in H1299 cells, and the opposite was found in H157 cells. (Figure 5C). In addition, Pearson correlation analysis showed a negative relationship between circPSMC3 and miR-182-5p in NSCLC tissues (Figure 5D). These results suggest that circPSMC3 sponges miR-182-5p in NSCLC.

Discussion

Despite improvement in understanding the biology of NSCLC, metastasis remains an important challenge for treatment strategies. Therefore, exploring the regulatory mechanism of metastasis in non-small cell lung cancer is vital for developing effective treatment strategies. In the present study, we found that circPSMC3 suppressed the invasion and migration of NSCLC cells via the miR-182-5p/NME2 signaling pathway.

CircRNAs are geared to endogenous non-coding RNAs, and increasing evidence has demonstrated that circRNAs play a crucial role in cancer [17–19]. For example, PVT1 can sponge miR425 to promote the proliferation of gastric cancer cells [20]. Hsa_circ_0005075 also has discrepant expression in hepatocellular cancer, and is correlated with tumor size [21]. In lung cancer, circ-ITCH is overexpressed, and can inhibit the Wnt/β-catenin signaling pathway through serving as miR-7 and miR-214 sponges, which participate in the regulation of metastasis [22]. Moreover, circRNA100876 expression is increased in NSCLC, and higher circRNA100876 level is closely related to the metastasis of lymph nodes and tumor stage [23]. CircPSMC3 inhibits the metastasis and proliferation of gastric

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cancer through sponging miR-296-5p via serving as a competitive endogenous RNA [11]. In addition, circPSMC3 inhibits hepatocellular carcinoma migration and invasion by upregulating RBM5 [12]. Similar to previous findings, we demonstrated that circPSMC3 was reduced in NSCLC, and targeted miR-182-5p to suppress the metastasis of NSCLC. The function of miR-182-5p in cancer has been reported early. miR-182-5p can enhance the invasion, migration, viability, and mitosis of human gastric cells via suppressing RAB27A [24]. Furthermore, miR-182-5p enhances the motility and invasive ability of hepatocellular cancer cells [25]. These previous results are consistent with our present findings.

The NME gene was the first metastasis suppressor to be reported. Some studies have confirmed that NME2 can suppress metastasis through regulating cell adhesion factors, such as vinculin [26]. Others found that NME2 can repress telomerase activity for MDM2 activity inhibition, causing decreased cell motility [16]. In gastric cancer, NME2 can repress metastasis through reducing cell migration and invasion ability [27]. Moreover, NME2 expression is negatively correlated with advanced/metastatic phase in multiple cancers, such as breast cancer and melanoma [28]. To assess the effect of circPSMC3 on NME2 expression, the protein and mRNA expression of NME2 were detected among H1299 cells transfected with si-circPSMC3. Our results showed that circPSMC3 inhibits the invasion and migration of NSCLC cells via upregulating NME2. In addition, NME2 expression was reported to be regulated by miRNAs. NME2 is directly targeted by miR-645, and is involved in modulating cell migration [29], while CARMA3 enhances the motility of lung cancer cells through reducing the expression of NME2 via the NF-κB/miR-182 axis [29]. In the present study, we used TargetScanHuman software to predict the existence of a binding site of miR-182-5p in NME2. The results of luciferase reporter assay showed that NME2 is a target gene of miR-182-5p in NSCLC.

Conclusions

Our results indicated that circPSMC3 expression was decreased in NSCLC tissues compared with adjacent normal tissues. Lower circPSMC3 expression was closely associated with lymph node metastasis and higher TNM stage in NSCLC patients. Most important, the present data shows that circPSMC3 inhibits the invasion and migration of NSCLC cells via the miR-182-5p/NME2 axis.

Conflict of interests

None.

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