Life Sciences 232 (2019) 116597

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

LncRNA SNHG3 regulates laryngeal carcinoma proliferation and migration by modulating the miR-384/WEE1 axis

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ARTICLE INFO

Keywords:
SNHG3
miR-384
WEE1
Migration
Laryngeal carcinoma

ABSTRACT

LncRNA SNHG3 (SNHG3) is involved in tumor development and progression, but little is known about how SNHG3 functions in laryngeal carcinoma (LC). Real time-PCR (RT-PCR) was used to estimate the expression of SNHG3 in LC tissues and cell lines TU212, TU686, and Hep-2. Cell viability, migration, and invasion were evaluated. Our results showed increased SNHG3 in LC tissues and cell lines. Loss of function of SNHG3 reduced cell viability, migration, and invasion of TU212 and TU686 cells. Western blot analyses demonstrated that the protein levels of MMP2 and MMP9 decreased after SNHG3 silencing. Additionally, bioinformatics software predicted that SNHG3 could sponge miR-384 at the 3′-UTR with complementary binding sites, which was validated by a dual-luciferase reporter assay. RT-PCR analysis revealed that knockdown of SNHG3 upregulated miR-384 expression and that overexpression of miR-384 decreased SNHG3. Furthermore, a dual-luciferase reporter assay showed that miR-384 could bind to the 3′-UTR of WEE1, and inhibition of miR-384 markedly increased WEE1 expression. The mRNA and protein levels of WEE1 were downregulated upon deletion of SNGH3. Suppression of WEE1 partly abolished the tumorigenic migration and invasion potential of the miR-384 inhibitor in migration and invasion. Inhibition of miR-384 partially reversed the biological activities of SNHG3 in TU212 and TU686 cells. Collectively, our results indicate that SNHG3 regulated LC cell migration and invasion via the miR-384/WEE1 axis.

1. Introduction

Laryngeal cancer (LC) is a common malignant tumor of the head and neck. Its main pathological type is squamous cell carcinoma. Major risk factors for LC include smoking, drinking, environmental factors, radioactivity, viral infection, and microelement deficiency [1,2]. LC ranks as the 21st most common cancer, with an incidence rate of 1.86/100,000 [3]. Current treatment strategies include primary radiation therapy and surgical resection of the tumor. In the early stages, the cure rate for LC is 80% to 90%, which drops to 60% in the later stages [4]. Early diagnosis and treatment thus are crucial to preserve voice function of the larynx and reduce complications after operation [5]. To that end, understanding key molecules associated with the progression of LC will help identify efficient therapeutic strategies.

LncRNAs are a class of non-coding RNA with a length > 200 nucleotides. Though it was previously thought that lncRNAs had no biological function, it has been reported that they serve as essential regulators in chromatin remodeling, transcriptional regulation, and post-transcriptional processing [6]. For example, the lncRNA SNHG3 is associated with the development and progression of various tumors. SNHG3 upregulation enhances migration and invasion in osteosarcoma cells via the miRNA-151a-3p/RAB22A axis [7]. SNHG3 also is strongly overexpressed in lung adenocarcinoma, where it promotes the proliferation and cell cycle of A549 and NCI-H1299 cells [8]. However, the roles of SNHG3 in LC progression have not been elucidated.

In the present study, we found that SNHG3 was prominently enhanced in LC tissues and cell lines. Silencing of SNHG3 inhibited cell survival, migration, and invasion, as well as protein levels of MMP2 and MMP9. Furthermore, we demonstrated that SNHG3 regulated LC cell migration and invasion via the miR-384/WEE1 axis.

2. Material and methods

2.1. Human tissue specimens

A total of 18 samples of LC tissues and paired adjacent non-cancerous laryngeal tissues were collected from our hospital during surgical resection. Patients received no systemic or local treatment

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https://doi.org/10.1016/j.lfs.2019.116597
Received 26 April 2019; Received in revised form 17 June 2019; Accepted 21 June 2019
Available online 22 June 2019

before their operations. The excised tissues were immediately preserved in liquid nitrogen and held at −80 °C. Routine pathological examination confirmed tumor and non-tumor tissues. All patients signed informed consents. The Institute Research Ethics Committee of The First Affiliated Hospital of Zhengzhou University approved this study.

2.2. Cell line culture

293T cells, human bronchial epithelial cells 16HBE, TU212 and TU686 were obtained from the Cell Center of Life Science of the Chinese Academy of Science (Shanghai, China). 16HBE cells were grown in Dulbecco's Modified Eagles Medium (HyClone, South Logan, UT, USA). TU212 and TU686 cells were maintained in RPMI-1640 medium (Gibco, Carlsbad, CA, USA). Both media were filled with 10% FBS (Hyclone) and 1% penicillin/streptomycin. Cells were cultured in a humidified incubator with 5% CO_2 and 95% air at 37 °C.

2.3. Cell transfection

SiRNA targeting SNHG3 (siSNHG3) and its negative control (siNC); the miR-384 mimic, inhibitor, and its negative control (miR-NC); and WEE1 (siWEE1) and its negative control (siCtrl) were obtained from GenePharma Co. (Shanghai, China). All were transfected into TU212 and TU686 cells using Lipofectamine 3000 (Invitrogen, Carlsbad, CA, USA) in accordance with the manufacturer's protocols.

2.4. Cell viability

A CCK-8 assay (Dojindo, Kumamoto, Japan) was applied to estimate the viability of the LC cell lines. Briefly, the medium was discarded and incubated at 37 °C for 2 h with 110 μL of medium containing 10 μL of CCK-8 reagents. The optical density of each well was recorded using a microplate reader at 450 nm.

2.5. Transwell assays

The migration and invasion of LC cell lines were measured by Transwell assay. For migration, cells were collected at 48 h post-transfection, suspended in serum-free RPMI 1640, and then seeded into the upper chamber of a 24-well Transwell plate (Corning, NY, USA). The lower chamber was filled with complete medium. Cells were fixed and stained, and the numbers of migrative cells were counted from random fields. Similar to the migration assay, excluded cells were seeded onto a Matrigel-coated upper chamber for the invasion assay.

2.6. QRT-PCR

Total RNA was collected from tissues and cells using TRIzol Reagent (Invitrogen) according to manufacturer guidelines. RNA was reverse-transcribed into cDNA using a Reverse Transcription Kit (Takara Bio, Shiga, Japan). Target primers were amplified using a SYBR Green Master Mix Kit (Takara Bio) on the ABI Prism 7300 system (Applied Biosystems). The relative expression of target RNAs or genes was counted using the $2^{-\Delta\Delta Ct}$ method and normalized to U6 or GAPDH.

2.7. Western blot analysis

Total protein from tissues and cells was isolated using lysis buffer (Beyotime, Beijing, China). Equal amounts of protein (50 μg) were separated using SDS-PAGE and then transferred onto a nitrocellulose membrane at 200 mA for 1.5 h at 4 °C. The blots were blocked with 5% non-fat milk at room temperature for 1 h and then incubated overnight with primary antibodies anti-MMP2, anti-MMP9, and anti-β-actin (all from Abcam, Cambridge, MA, USA) and anti-WEE1 (Cell Signaling Technology, Beverly, MA, USA). Subsequently, the blots were disposed with HRP-conjugated antibody for 1 h at normal temperature. The protein band signals were visualized using a ChemiDoc detection system. Optical density values were quantified suing ImageJ software.

2.8. Dual luciferase reporter analysis

The StarBase v2.0 (http://starbase.sysu.edu.cn/starbase2/index.php) database was used to search for a potential target of miR-384 in human. It predicted that SNHG3 could sponge miR-384 at the 3′-UTR. Using PCR, we amplified the putative miR-384 target binding sites in SNHG3 and the SNHG3 mutant binding sequence. We then subcloned into a pmirGLO Reporter plasmid (Promega, Madison, WI, USA) to construct the wild-type SNHG3 3′-UTR (SNHG3 wt) and mutant SNHG3 3′-UTR (SNHG3 mut). The miR-NC or miR-384 mimic was co-transfected for 48 h with SNHG3 wt or SNHG3 mut in 293T cells. Dual-luciferase reporter assays (Promega) were conducted according to the manufacturer's instructions.

TargetScan (http://www.targetscan.org/) predicted that miR-384 could bind to the 3′-UTR of WEE1. Likewise, the wild-type WEE1 (WEE1 wt) 3′-UTR and mutant WEE1 (WEE1 mut) 3′-UTR fragments were cloned into the pmirGLO vector. 293T cells were co-transfected for 48 h with miR-NC or miR-384 mimic and WEE1 wt or WEE1 mut, followed by dual-luciferase reporter assays (Promega) in accordance with the manufacturer's protocols.

2.9. Statistical analysis

All experiments were performed at least three times. Data shown are represented as mean ± SD. The SPSS 11.0 software package was used for statistical analysis. A *t*-test was applied to compare two groups, and a one-way ANOVA to compare multiple groups. $P < 0.05$ indicated statistical significance.

3. Results

3.1. SNHG3 was upregulated in laryngeal carcinoma tissues and cell lines

SNHG3 mRNA levels were determined in LC tissues and cell lines. As evident in Fig. 1A, the mRNA level of SNHG3 increased more in the tumor group than the normal group. Additionally, compared with the 16HBE group, SNHG3 expression was strongly overexpressed in TU212, TU686, and Hep-2 cells, with the highest expression in TU212 and the lowest in TU686 cells (Fig. 1B).

3.2. Knockdown of SNHG3 inhibited cell migration and invasion

TU212 and TU686 cells were incubated with siSNHG3, and a qRT-PCR analysis suggested that siSNHG3 strongly inhibited SNHG3 (Fig. 2A). A CCK-8 assay showed a marked reduction in the proliferation capabilities of TU212 and TU686 cells after SNHG3 suppression (Fig. 2B). We detected decreased protein levels of MMP2 after SNHG3 silencing (Fig. 2C). Depression of SNHG3 also inhibited expression of MMP9 (Fig. 2D).Downregulation of SNHG3 prominently reduced the numbers of migrative cells (Fig. 2E) and invasive cells (Fig. 2F). These data show that SNHG3 knockdown blocked the migration and invasion of TU212 and TU686 cells.

3.3. SNHG3 functioned as a sponge for miR-384

To understand the potential mechanisms of SNHG3 in the migration and invasion of LC cell lines, we examined the relationship between miR-384 and SNHG3. The bioinformatics Starbase v2.0 (http://starbase.sysu.edu.cn/starbase2/index.php) database revealed that miR-384 had a complementary sequence to SNHG3. Fig. 3A shows the binding sites between miR-384 and SNHG3. The luciferase reporter assay confirmed the binding interaction between miR-384 and SNHG3 in 293T cells (Fig. 3B). Also, a qRT-PCR analysis demonstrated that

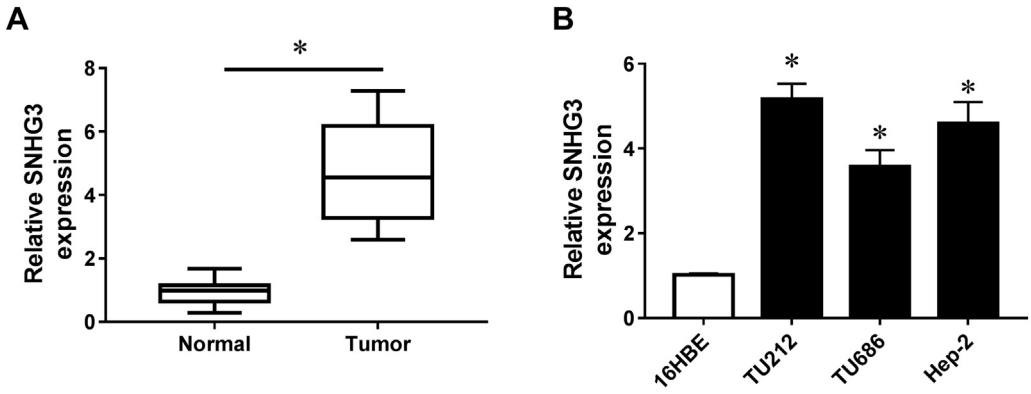

Fig. 1. The upregulation of SNHG3 was observed in laryngeal carcinoma tissues and cell lines. (A) Relative expression of SNHG3 in the laryngeal carcinoma tissues (Tumor) and paired adjacent noncancerous laryngeal tissues (Normal) via RT-PCR analysis. (B) The expression of SNHG3 in human bronchial epithelial 16HBE cells and laryngeal carcinoma TU212, TU686, and Hep-2 cells was detected by RT-PCR. Data are presented as the mean ± SD. *$P < 0.05$ versus the Normal or 16HBE group.

deletion of SNHG3 prominently enhanced expression of miR-384 (Fig. 3C). Overexpression of miR-384 significantly reduced SNHG3 levels in LC cell lines (Fig. 3D). These findings indicate that SNHG3 acted as a molecular sponge to regulate miR-384 in LC cell lines.

3.4. MiR-384 and SNHG3 regulated WEE1

A bioinformatic analysis by TargetScan (http://www.targetscan.org/) predicted WEE1 as a target of miR-384. Fig. 4A shows its binding sites. Moreover, a luciferase reporter assay demonstrated that upregulation of miR-384 decreased WEE1 wt activity but had no effect on WEE1 mut in 293T cells (Fig. 4B). Inhibition of miR-384 dramatically increased the mRNA (Fig. 4C) and protein (Fig. 5D) levels of WEE1 in LC cell lines. We also evaluated the effects of SNHG3 silencing on WEE1 expression and found that mRNA (Fig. 4E) and protein (Fig. 4F) levels of WEE1 increased significantly after SNHG3 silencing. These results reveal that WEE1 was a direct target of miR-384 and that it was regulated by SNHG3 in LC cell lines.

3.5. Inhibition of WEE1 partly abrogated the effects of miR-384 in LC cell lines

TU212 and TU686 cells were transfected with miR-384 inhibitor and siWEE1. Cell viability, migration, and invasion then were determined. As illustrated in Fig. 5A, loss of function of miR-384 promoted the survival of LC cells, whereas depletion of WEE1 had the opposite effect. Additionally, deletion of miR-384 facilitated the migration (Fig. 5B) and invasion (Fig. 5C) of LC cells, and these effects were partly abolished by WEE1 silencing. MMP2 (Fig. 5D) and MMP9 (Fig. 5E) levels were increased by the miR-384 inhibitor but blocked by downregulation of WEE1. These data indicate that miR-384 silencing contributed to cell migration and invasion by targeting WEE1 in LC cell lines.

3.6. Downregulation of miR-384 partly reversed the biological functions of SNHG3 in LC cell lines

Cell migration and invasion were assayed after transfection with siSNHG3 and miR-384 inhibitor to determine whether SNHG3 exerted its biological functions through miR-384. As shown in Fig. 6A, the miR-384 inhibitor partly abrogated the growth-inhibiting property of SNHG3 knockdown. Similarly, miR-384 silencing abolished the inhibitory effects of SNHG3 deletion on migration (Fig. 6B) and invasion (Fig. 6C). Furthermore, depletion of miR-384 partially reversed the inhibitory functions SNHG3 silencing in MMP2 (Fig. 6D) and MMP9 (Fig. 6E).

4. Discussion

Increasing evidence has shown that alterations in lncRNAs function

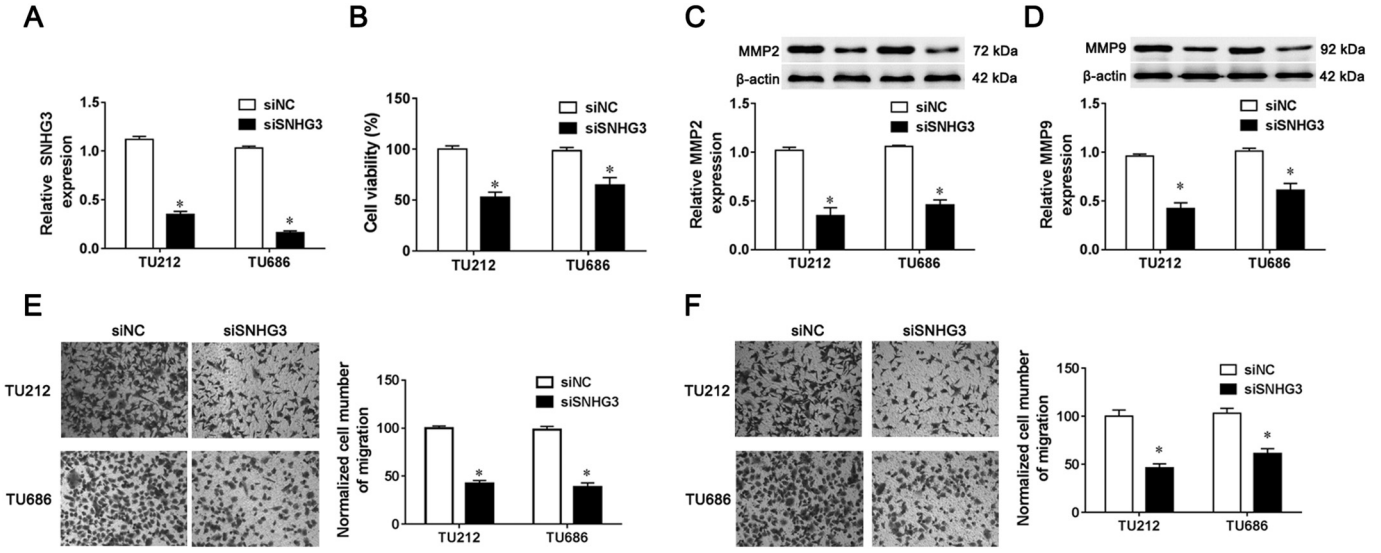

Fig. 2. Knockdown of SNHG3 reduced migration and invasion capacities, as well as MMP2 and MMP9 protein levels. SiSNHG3 and siNC were transfected into TU212 and TU686 cells for 48 h. (A) The relative expression of SNHG3 in TU212 and TU686 cells was determined by RT-PCR. (B) A CCK-8 assay was performed to evaluate cell viability. The protein levels of (C) MMP2 and (D) MMP9 were tested via western blot analysis. A Transwell assay was conducted to estimate the (E) migration and (F) invasion of laryngeal carcinoma cell lines. Data are presented as the mean ± SD. *$P < 0.05$ versus the siNC group.

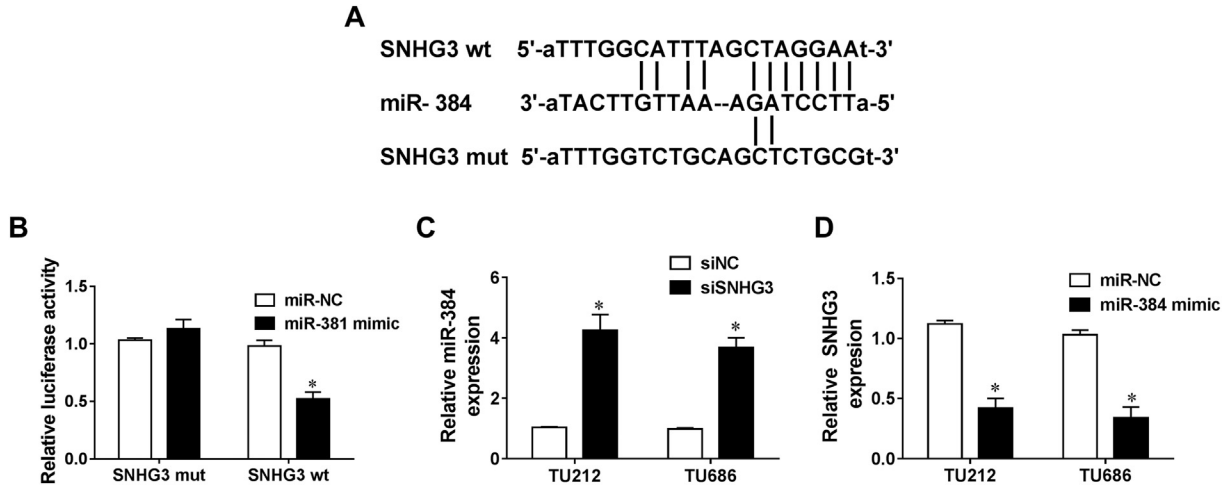

Fig. 3. SNHG3 could sponge miR-483 and negatively regulated miR-384. (A) The binding sites between SNHG3 and miR-483 are shown. (B) 293T cells were transfected with miR-NC (or miR-384 mimic) and SNHG3 wt (or SNHG3 mut) for 48 h, and the relative luciferase activities were evaluated using a dual-luciferase reporter assay. (C) SiNC or siSNHG3 was transfected into TU212 and TU686 cells for 48 h, and the relative expression of miR-384 was measured using RT-PCR. (D) TU212 and TU686 cells were transfected with the miR-NC or miR-384 mimic, and the relative expression of SNHG3 was detected using RT-CPR. Data are presented as the mean ± SD. *$P < 0.05$ versus the siNC or miR-NC group.

as key regulators in the development and progression of various cancers. Once considered to be transcriptional noise in human genomes [9], lncRNAs are now associated with several diseases, especially cancers [10]. Abundant reports confirm that lncRNAs PCAT19, ST7-AS1, and UCA1 influence LC progression [11–13]. Also, SNHG3 is upregulated in osteosarcoma and lung adenocarcinoma [7,8]. Consistent with these findings, we observed that SNHG3 was highly expressed in LC tissues and cell lines.

LncRNA has central role in gene regulation and mediates multiple aspects of cellular behavior, including survival, proliferation, apoptosis

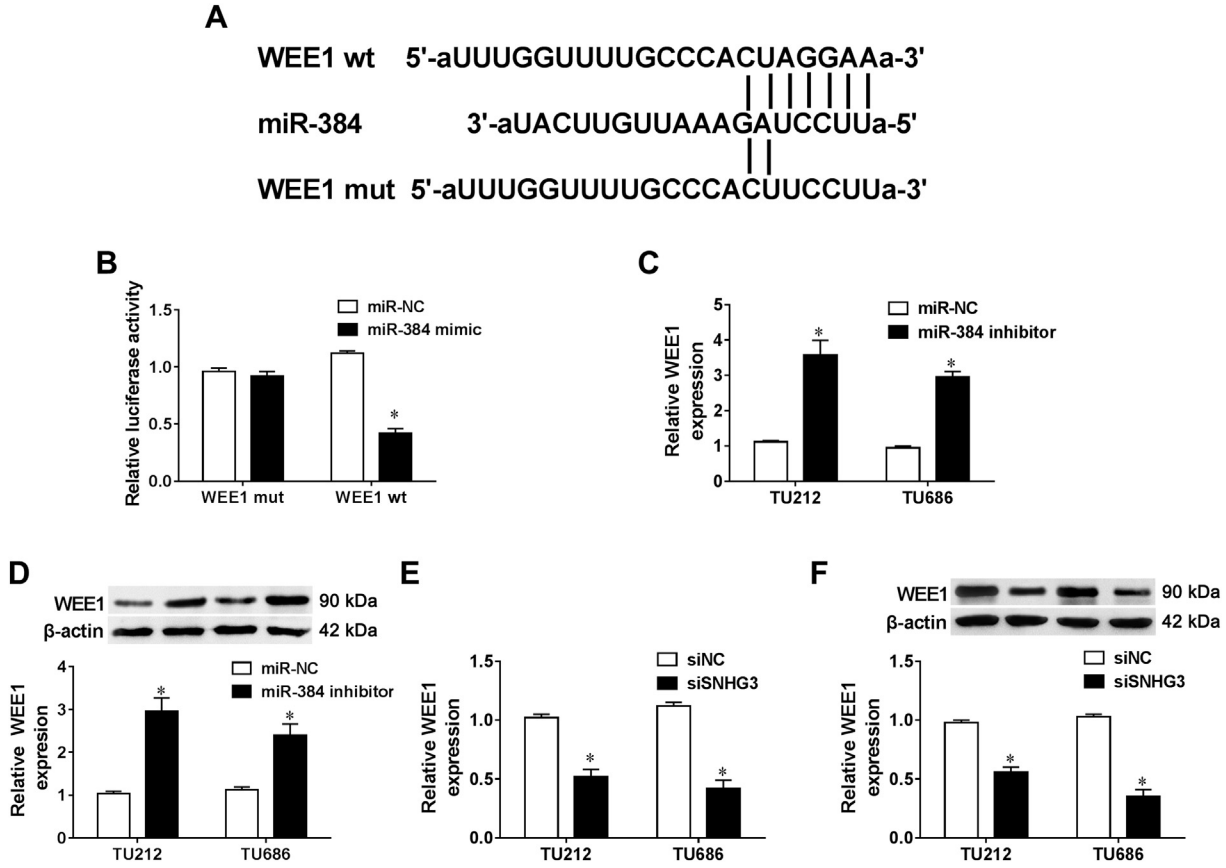

Fig. 4. WEE1 was a target of miR-384 and was positively regulated by SNHG3. (A) The interaction binding sites are displayed. (B) 293T cells were transfected with miR-NC (or miR-483) and WEE1 mut (or WEE1 wt) for 48 h, and a dual-luciferase reporter assay was conducted to evaluate the relative luciferase. TU212 and TU686 cells were incubated with miR-NC or miR-483 inhibitor, and the (C) mRNA and (D) protein levels of WEE1 were tested using RT-CPR and western blot analysis. The siNC or siSNHG3 were transfected into TU212 and TU686 cells for 48 h, and then (E) RT-PCR and (F) western blot assays were conducted to measure the expression of WEE1. Data are presented as the mean ± SD. *$P < 0.05$ versus the miR-NC or siNC group.

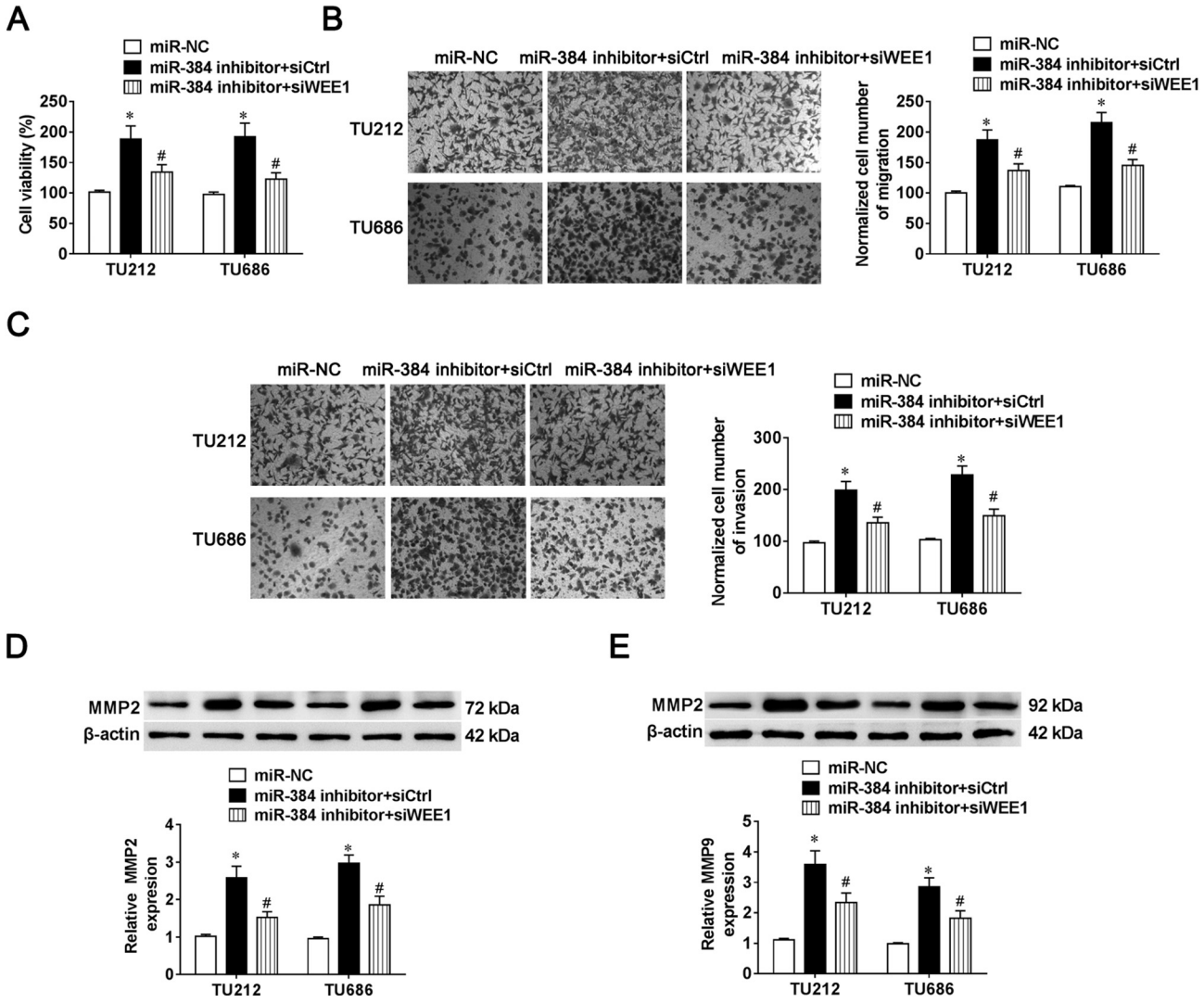

Fig. 5. Inhibition of WEE1 reversed the tumorigenic potential of miR-384 inhibitor. TU212 and TU686 were incubated with a miR-384 inhibitor and siWEE1 for 48 h. (A) Cell viability was measured using a CCK-8 assay. The (B) migration and (C) invasion capacities were tested using a Transwell assay. The protein levels of (D) MMP2 and (E) MMP9 were determined by western blot analysis. Data are presented as the mean ± SD. $^{*}P < 0.05$ versus the miR-NC group; $^{\#}P < 0.05$ versus the miR-384 inhibitor + siWEE1 group.

and invasion [14]. It has been proved that SNHG3 upregulation triggered the proliferation of lung adenocarcinoma cells and repressed cell apoptosis [8]. SNHG3 also displayed promoting survival and anti-apoptotic effect in glioma cells [15]. These findings revealed that SNHG3 contributes to survival of cancer cells. Furthermore, invasion and migration are closely related to the growth and development of tumors, and invasive behavior is intrinsic to tumor metastasis [8]. Before migrating, the cell body must change its shape to link with the surrounding micro-environment [16]. Tumor cells can degrade the matrix by adhering their surface receptors to various components in the extracellular matrix or by secreting protein-degrading enzymes, thus forming a local lysis zone and metastatic pathway for tumor cells. Matrix metalloproteinase upregulation contributes to the breakdown of extracellular matrix and promotes tumor growth [17].

Enhanced expression of SNHG3 contributes to the migration and invasion of osteosarcoma and lung cancer [8,18]. Consistent with these findings, our data confirmed that suppression of SNHG3 reduced cell migration and invasion. A recent report shows that overexpression of SNHG3 facilitates epithelial-to-mesenchymal transition and cell invasion in hepatocellular carcinoma [19]. In breast cancer cells, SNHG3 increases the protein levels of MMP2 and MMP9 [20]. Our study also demonstrated that SNHG3 knockdown substantially decreased MMP2 and MMP2.

Sponging miRNA is a key mechanism of lncRNA-regulating gene expression. In the present work, we found that SNHG3 could sponge miR-384 and that depression of SNHG3 prominently increased miR-384 levels. MiR-384 participates in the occurrence and growth of multiple cancers. Downregulation of miR-384 has been observed in colorectal cancer, breast cancer, and non-small-cell lung cancer, and it acts as a tumor suppressor gene in various cancers by inhibiting cell migration and invasion [21–23]. Our previous study demonstrated that miR-384 was strikingly reduced in LC tissues and cell lines and that it enhanced growth inhibition and apoptosis [24]. We observed that the miR-384 inhibitor partly abrogated the biological functions of SNHG3 silencing, suggesting that SNHG3 knockdown impeded cell migration and invasion by regulating miR-384.

MiRNA downregulates the expression of target gene by binding to the 3′-UTR seed region. This classic biological function of miRNA is the basis of the endogenous, competitive RNA molecular network [25]. A dual-luciferase reporter assay illuminated that miR-384 directly targeted WEE1. WEE1 is associated with the cell cycle, apoptosis, invasion, and migration of cancer cells. It is highly expressed in many cancers, including breast cancer, leukemia, melanoma, and brain tumors. Treatment for these cancers often involves DNA damage agents, and

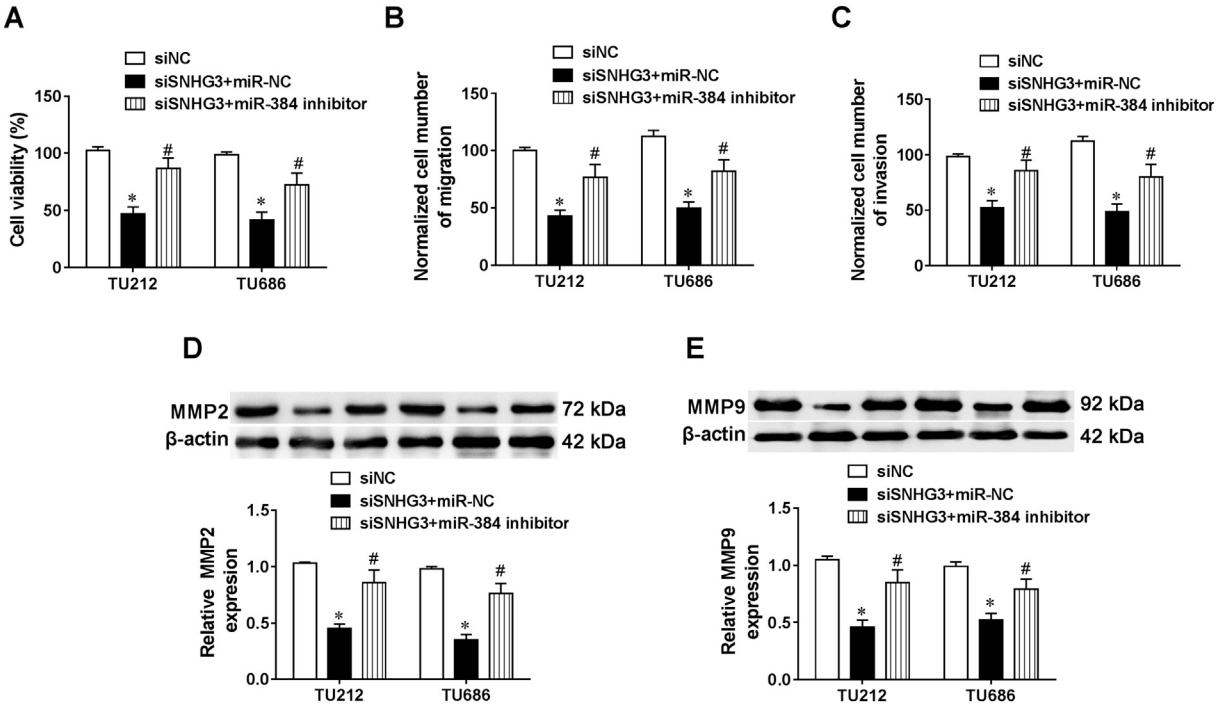

Fig. 6. Downregulation of miR-384 partially abolished the biological activities of SNHG3 in migration and invasion. TU212 and TU686 cells were transfected with siSNHG3 and a miR-384 inhibitor for 48 h. (A) A CCK-8 assay was performed to evaluate cell viability. A Transwell assay was conducted to estimate the (B) migration and (C) invasion of TU212 and TU686 cells. A western blot was used to test the expression of (D) MMP2 and (E) MMP9. Data are presented as the mean ± SD. $^{*}P < 0.05$ versus the siNC group; $^{\#}P < 0.05$ versus the siSNHG3 + miR-384 inhibitor group.

targeted inhibition of WEE1 can improve the efficacy of these treatments [26]. A recent report also revealed that WEE1 is strongly overexpressed in LC tissues and that knockdown of WEE1 promotes growth inhibition and apoptosis [27], suggesting that WEE1 is implicated in LC progression.

In this work, our data indicated that the facilitation roles of the miR-384 inhibitor in cell migration and invasion were partly reversed by silencing WEE1. Furthermore, the miR-384 inhibitor partly abolished the biological activities of SNHG3. These data indicate that SNHG3 regulated cell migration and invasion via the miR-384/WEE1 axis. Collectively, our results showed strong overexpression of SNHG3 in LC cells. SNHG3 regulated WEE1 by sponging miR-384 and then modulating the migration and invasion of TU212 and TU686 cells. These findings demonstrate that SNHG3 may play a key role in identifying efficient therapeutic strategies for laryngeal carcinoma.

Authors' contribution

Liang Wang and Ke Su conceived and designed the study; Liang Wang, Ke Su and Huanhuan Wu conducted the experiments and collected the data; Liang Wang, Ke Su, Huanhuan Wu and Junli Li analyzed the data and interpreted the results; Liang Wang wrote the first draft of the manuscript; Junli Li and Dandan Song revised the manuscript; all authors approved the final manuscript.

Funding statement

None.

Acknowledgement

None.

Declaration of Competing Interest

The authors have no financial conflicts of interest.

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