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Linc00152 knockdown inactivates the Akt/mTOR and Notch1 pathways to exert its anti-hemangioma effect

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ABSTRACT

Aims: Infantile hemangioma (IH) is one of the most common benign vascular tumors occurred in infants. Linc00152 is a kind of long non-coding RNAs (lncRNAs) and acts as a tumor oncogene. Recent study reported that Linc00152 is highly expressed in clinical IH tissues. However, the exact biological roles have not yet been investigated. The aim of the present study was to investigate the oncogenic roles of Linc00152 in IH and the underlying mechanism *in vitro*.

Main methods: The expressions of Linc00152 in IH tissues and hemangioma-derived endothelial cells (HemECs) were determined using quantitative real time-PCR (qRT-PCR) analysis. The expressions of Akt/mTOR and Notch1 pathways related proteins were detected using western blot analysis. Cell proliferation was assessed by detecting Ki67 expression and CCK-8 assay. Cell apoptosis was evaluated by detecting apoptotic rate, caspase-3/7 activity, and Bcl-2 and Bax expression.

Key findings: The results demonstrated Linc00152 was up-regulated in clinical IH tissues and HemECs. Knockdown of Linc00152 in HemECs suppressed the activation of Akt/mTOR and Notch1 signaling pathways and caused reduction in cell proliferation and Ki67 expression in HemECs. Besides, Linc00152 knockdown resulted in a significant increase in apoptotic rate, caspase-3/7 activity, and Bax expression level, as well as a decrease in Bcl-2 expression level. However, the effects of Linc00152 knockdown on cell proliferation and apoptosis were mitigated by overexpression of Akt or Notch1.

Significance: Knockdown of Linc00152 suppressed HemECs proliferation and induced apoptosis *via* inhibiting Akt/mTOR and Notch1 signaling pathways.

1. Introduction

Infantile hemangioma (IH) is one of the most common benign vascular tumors of childhood, occurring in approximately 3 to 10% of infants [1]. IH usually appears in premature and low birth weight infants, and develops within the first weeks or months of life [2]. In addition to premature and low birth weight, chorionic villous sampling, amniocentesis, chorangioma, pre-eclampsia, and placental anomalies are the main documented risk factors for IH [3]. Early lesions may resemble a red scratch or patch, a white patch, or a bruise that mainly occur on the head and neck in females [4]. The vast majority of IH is not associated with any complications and spontaneously regresses over time. However, large IH may lead to tissue or organ damage, and become life threatening in some cases [3]. Better understanding of the pathogenesis may contribute to explore effective therapy for IH. The tumor is characterized by the increased number of unique endothelial cells that constitute blood vessels [2,5]. Herein, endothelial cells might be new therapeutic targets for the treatment of IH.

The AKT/mTOR pathway is a frequently hyperactivated signaling cascades and impacts on cell proliferation, apoptosis, and differentiation in human malignancies [6,7]. It has been reported that the Akt/mTOR has been regarded as one of the most attractive targets for the development of antineoplastic agents [8]. The Notch pathway is a highly conserved and widely used mechanism controlling cell fate in metazoans [9]. Interaction of Notch receptors with its ligands results in proteolytic cleavage of the Notch intracellular domain that enters the nucleus and engages other DNA-binding proteins, thereby regulating expression of Notch target genes, such as *HES* and *HEY*, which are

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involved in cell proliferation, differentiation, and apoptosis [10,11]. Previous studies have demonstrated that Akt/mTOR and Notch1 signaling pathways are implicated in IH [12,13]. Therefore, the inhibition of the Akt/mTOR and Notch1 pathways is of therapeutic interest for the treatment of IH.

Long non-coding RNAs (lncRNAs) are a group of transcripts with > 200 nucleotides without the ability to translate into protein [14]. LncRNAs have been proven to be implicated in most biological events, such as epigenetics, transcription, and post-transcription [15]. The biological roles of lncRNAs are mediated by the interaction with various molecules, including related DNA, RNA, microRNA (miRNA), or proteins [14]. Therefore, dysregulation of lncRNAs are associated with a wide range of diseases, such as cancer, cardiovascular disease and neuro-degeneration disease [15]. Linc00152 is a kind of lncRNAs and acts as a tumor oncogene in many cancers, such as glioblastoma [16], papillary thyroid carcinoma (PTC) [17], colorectal cancer [18], and ovarian cancer [19]. A recent study has demonstrated that Linc00152 is highly expressed in clinical IH tissues [20]. However, the exact biological roles have not yet been validated. Therefore, we aimed to investigate the roles of Linc00152 in IH and the potential mechanism *in vitro*.

2. Materials and methods

2.1. Clinical samples

The present study was approved by the Research Ethics Committee of the Henan Provincial People's Hospital. All participants or guardians have signed the informed consents. Hemangioma tissues and the matched adjacent normal tissues were collected from 12 patients (8 female and 4 male; age range, 2 months to 4 years old; average age, 13.6 months) who underwent surgical resection for the treatment of hemangioma at the Henan Provincial People's Hospital. The stage of hemangioma was divided into proliferating phase hemangioma ($n = 9$) and involuting phase hemangioma ($n = 3$). The obtained samples were immediately frozen in liquid nitrogen and stored at −80 °C until use.

2.2. Cell culture and treatments

The hemangioma-derived endothelial cells (HemECs) and human umbilical vein endothelial cells (HUVECs) were purchased from the Institute of Biochemistry and Cell Biology (Shanghai, China). The HemECs and HUVECs were cultured in Dulbecco's modified Eagle's medium (DMEM; Invitrogen, Carlsbad, CA, USA) supplemented with 10% heat-inactivated FBS (Invitrogen) and 0.1% penicillin/streptomycin (Invitrogen). Cells were grown in a humidified condition with 5% CO_2 at 37 °C.

2.3. Quantitative real time-PCR (qRT-PCR)

Total RNAs were extracted from frozen tissues and HemECs using RNA isolation kit (Takara Bio, Inc., Shiga, Japan) as described by the manufacturer's protocol. The cDNA was then synthesized from 2 μg total RNA using a cDNA synthesis Kit (Takara). The qRT-PCR was performed using SYBR Green PCR Master Mix (Takara) on Applied Biosystems ABI 7500 (Applied Biosystem, Foster, CA, USA). The housekeeping gene GAPDH was used as internal control. The $2^{-\Delta\Delta CT}$ method was used to calculate the expression levels of target gene. The specific primers used in the study were obtained from Sangon Biotech (Shanghai, China), the sequences were listed as follows: Linc00152, F 5′-TGGA ACCA GGCC CCAG GGAA TCTT CAGC TGCA-3′; and R 5′-ACAT AGAG ACTG GCCA GACA AATG GGAA ACCG ACC-3′. GAPDH, F 5′-ACAG TCAG CCGC ATCT TCTT-3′; and R 5′-CTGG AAGA TGGT GATG GGAT-3′.

2.4. Cell transfection

Specific small interfering RNA (siRNA) oligo targeting Linc00152 and control siRNA were obtained from GenePharma (Shanghai, China). Akt and Notch1 overexpressing plasmids (pcDNA-Akt and pcDNA-Notch1) and control plasmid (pcDNA) were purchased from Ribobio Co. (Guangzhou, China). HemECs were plated in 6-well plates and grown to 60% confluence. Subsequently, the siRNA oligo or plasmid were transfected into HemECs using siRNA-mate (GenePharma) or Lipofectamine 2000 (Invitrogen) respectively according to the manufacturer's instructions.

2.5. Western blot

The whole lysates of HemECs were prepared with radioimmunoprecipitation assay (RIPA) lysis buffer (Applygen Technologies Inc., Beijing, China) containing protease inhibitors (Sigma-Aldrich, St. Louis, MO, USA). Equal amounts of proteins (50 μg) were separated by 10% SDS-PAGE, followed by transfer to nitrocellulose membrane. After blocking in the 5% non-fat milk in TBST buffer, the membranes were probed with the primary antibodies against Ki67, Notch1, Hes1, Hey1, Bcl-2, Bax (Abcam, Cambridge, MA, USA); Akt, p-Akt (Invitrogen), mTOR, p-mTOR, and β-actin (Sigma-Aldrich) overnight at 4 °C. Subsequently, the membranes were incubated with corresponding secondary antibody (Sigma-Aldrich) for 1 h at room temperature. The obtained bands were visualized using an enhanced chemiluminescence (ECL) detection kit (Thermo Fisher Scientific, Waltham, MA, USA).

2.6. Cell proliferation assay

Cell proliferation of HemECs was determined using the Cell Counting Kit-8 (CCK-8; Dojindo Molecular Technologies, Kumamoto, Japan) following the manufacturer's instructions. Briefly, HemECs were seeded in 96-well plates at a density of 5×10^3/well and subjected to different transfection. After transfection for 48 h, 10 μl of CCK-8 solution was added to each well, followed by incubation for 2 h in a humidified incubator. Finally, the absorbance at 450 nm was determined using a microplate reader (Bio-Tek, Winooski, VT, USA).

2.7. Flow cytometry

Cell apoptosis of HemECs was determined by flow cytometry using an annexin V-FITC/PI double staining kit (BD Biosciences, Franklin Lakes, NJ, USA). Briefly, HemECs were resuspended in binding buffer to reach a final concentration of 1×10^6 cells/ml. Subsequently, annexin V-FITC and PI were added to the cells for staining. After gently mixture and incubation for 15 min at room temperature in the dark, the cells were analyzed using the FACSCalibur system (BD Biosciences).

2.8. Detection of caspase-3/7 activity

The activity of caspase-3/7 was measured using Caspase-Glo® 3/7 assay system (Promega, Madison, WI, USA) as described by the manufacturer. Briefly, HemECs were seeded on a 96-well plate at a density of 5×10^4 cells/well and subsequently transfected with siRNA or plasmids. After 48 h, the Caspase-Glo reagent was added to the cells and incubated for 30 min at room temperature. The caspase-3/7 activity was read using the Glomax®-96 microplate illuminometer (Promega).

2.9. Statistical analysis

The analysis of statistical differences was performed using SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, USA) with Student's *t*-test (between two groups) or one-way ANOVA (among more than two groups).

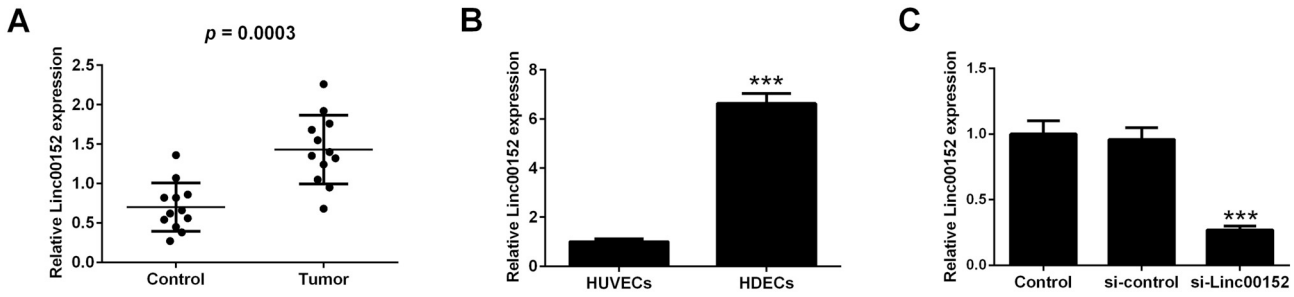

Fig. 1. Linc00152 is significantly up-regulated in IH tissues and HemECs. (A) Expressions of Linc00152 in 12 IH tissues and corresponding adjacent normal tissues. (B) Expressions of Linc00152 in HUVECs and HemECs. (C) Linc00152 siRNA (si-Linc00152) or control siRNA (si-control) was transfected into HemECs, Linc00152 expression was detected using qRT-PCR after 48 h transfection. ***indicated $p < 0.001$ *vs.* HemECs transfected with si-control. HUVECs, human umbilical vein endothelial cells. HemECs, hemangioma-derived endothelial cells.

All data are shown as means ± SD from three independent experiments. Statistical significance was determined at $p < 0.05$.

3. Results

3.1. Linc00152 is up-regulated in IH tissues and HemECs

A previous study suggested that Linc00152 was up-regulated in IH tissues [20]. To confirm it, the expressions of Linc00152 in 12 IH tissues and corresponding adjacent normal tissues were determined by qRT-PCR. The results showed that Linc00152 expression in the IH tissues was higher than that in the adjacent normal tissues (Fig. 1A). The Linc00152 expressions in HUVECs and HemECs were also determined. We found that the expression of Linc00152 in HemECs was higher than that in HUVECs (Fig. 1B). To evaluate the roles of Linc00152 *in vitro*, si-Linc00152 or si-control was transfected into HemECs. The knockdown efficiency was verified using qRT-PCR experiment. The expression of Linc00152 was markedly decreased after si-Linc00152 transfection (Fig. 1C).

3.2. Knockdown of Linc00152 suppresses the Akt/mTOR pathway

In order to evaluate the effect of si-Linc00152 on Akt/mTOR pathway, the expressions of Akt, p-Akt, mTOR, and p-mTOR were detected using western blot. As shown in Fig. 2, the expression levels of p-Akt and p-mTOR were decreased in HemECs transfected with si-Linc00152 compared with si-control group. However, the Akt and mTOR expressions were not changed. The results indicated that Linc00152 knockdown suppressed the Akt/mTOR pathway.

3.3. Knockdown of Linc00152 suppresses the Notch1 pathway

Next, we investigated the effect of si-Linc00152 on Notch1 pathway by detecting the expressions of Notch1, Hes1, and Hey1 using western blot. The results in Fig. 3 showed that Linc00152 knockdown resulted in significant reduction of Notch1, Hes1, and Hey1 expressions in HemECs, indicating that Linc00152 knockdown suppressed the Notch1 pathway.

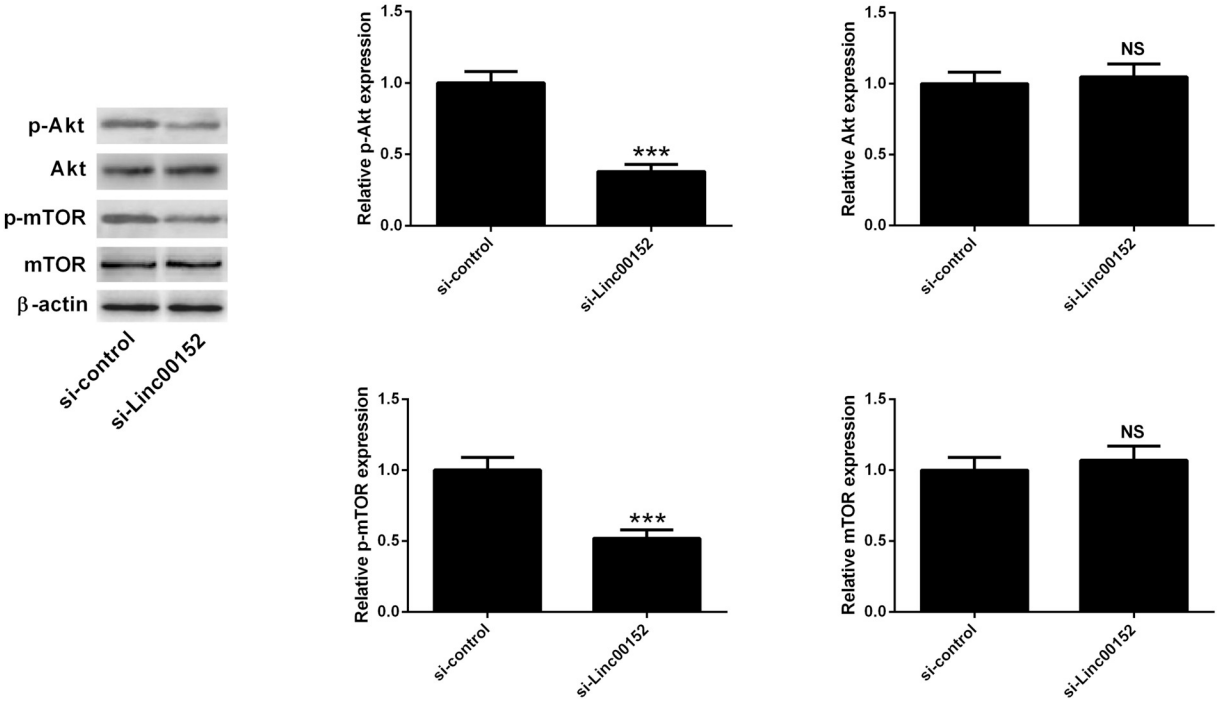

Fig. 2. Effect of Linc00152 knockdown on the Akt/mTOR pathway. In order to evaluate the alternation of Akt/mTOR pathway, the expressions of Akt, p-Akt, mTOR, and p-mTOR were detected using western blot after 48 h transfection. ***indicated $p < 0.001$ *vs.* HemECs transfected with si-control. NS, not significant. HemECs, hemangioma-derived endothelial cells.

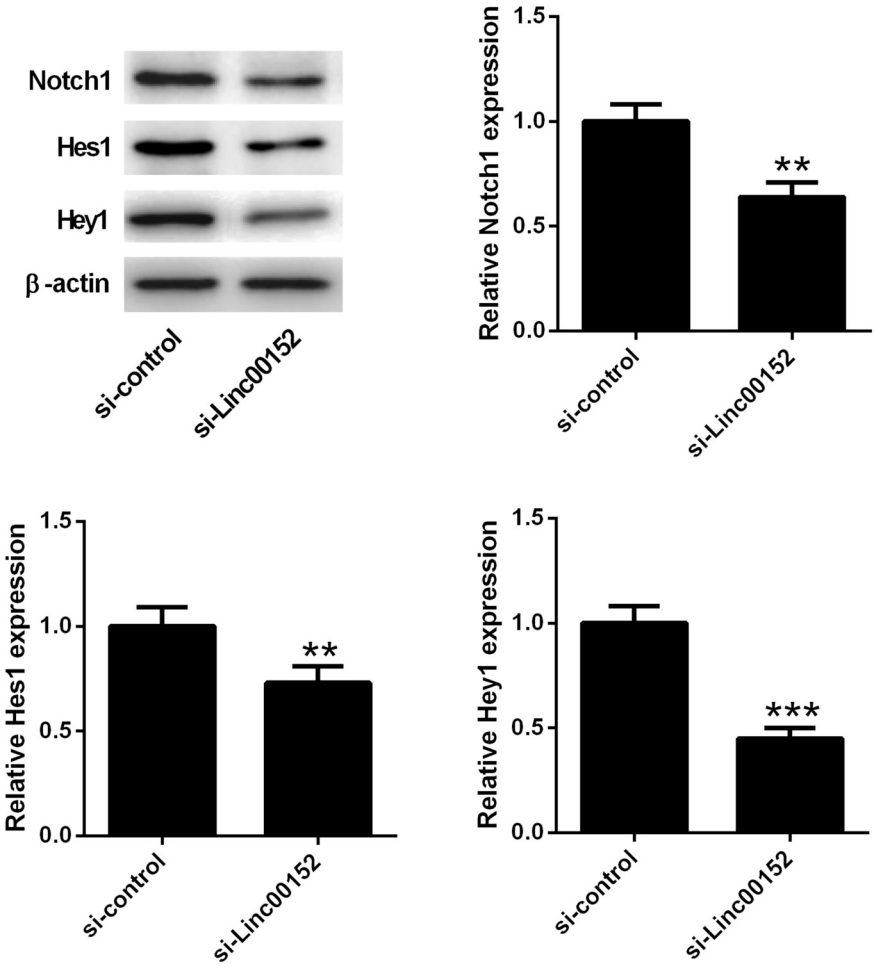

Fig. 3. Effect of Linc00152 knockdown on the Notch1 pathway. The alternation of Notch1 pathway was evaluated by detecting the expressions of Notch1, Hes1, and Hey1 using western blot after 48 h transfection. **indicated $p < 0.01$ *vs.* HemECs transfected with si-control. ***indicated $p < 0.001$ *vs.* HemECs transfected with si-control. HemECs, hemangioma-derived endothelial cells.

3.4. Knockdown of Linc00152 inhibits proliferation and induces apoptosis by the Akt/mTOR pathway in HemECs

HemECs were transfected with pcDNA-Akt or pcDNA. After pcDNA-Akt transfection, the Akt expression was markedly increased (Fig. 4A). CCK-8 assay showed that knockdown of Linc00152 inhibited cell proliferation of HemECs (Fig. 4B). The Ki67 expression was decreased after si-Linc00152 transfection, which confirmed the inhibitory effect of Linc00152 knockdown on cell proliferation (Fig. 4C). However, the effect of Linc00152 knockdown on cell proliferation was attenuated by Akt overexpression (Fig. 4B and C). The apoptotic rate and caspase-3/7 activity were elevated in HemECs transfected with si-Linc00152, indicating Linc00152 knockdown induced apoptosis in HemECs. However, the effect of Linc00152 knockdown on apoptosis was attenuated by Akt overexpression (Fig. 4D and E). Linc00152 knockdown decreased the expression level of anti-apoptotic protein Bcl-2 and increased the expression level of pro-apoptotic protein Bax. Whereas, the effect of Linc00152 knockdown on the expression of Bcl-2 and Bax was attenuated by Akt overexpression (Fig. 4F).

3.5. Knockdown of Linc00152 inhibits proliferation and induces apoptosis by the Notch1 pathway in HemECs

HemECs were transfected with pcDNA-Notch1 or pcDNA and the expression of Notch1 was determined using western blot analysis. As shown in Fig. 5A, the Notch1 expression was increased after pcDNA-Notch1 transfection. Further investigations showed that the inhibitory effects of si-Linc00152 on cell proliferation and Ki67 expression were mitigated by Notch1 overexpression (Fig. 5B and C). The induction effects of apoptotic rate and caspase-3/7 activity caused by Linc00152 knockdown were attenuated by Notch1 overexpression (Fig. 5D and E). Linc00152 knockdown up-regulated Bcl-2 expression and down-regulated Bax expression. However, the effect of Linc00152 knockdown on the expression of Bcl-2 and Bax was attenuated by Notch1 overexpression (Fig. 5F). These data suggested that knockdown of Linc00152 inhibited proliferation and induces apoptosis by the Notch1 pathway in HemECs.

4. Discussion

IH is a vascular tumor of infancy, characterized by a proliferative rapid growth phase [3,21]. A recent study assessed the expression profiles of lncRNAs in IH tissues using microarray analysis. The results suggested that lncRNAs likely regulated several genes with important roles in angiogenesis, and knockdown of lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) induced apoptosis and S-phase cell cycle arrest in HUVECs [20]. Zhao et al. [22] revealed that lncRNA SNHG16 was strongly over-expressed in the proliferating phase

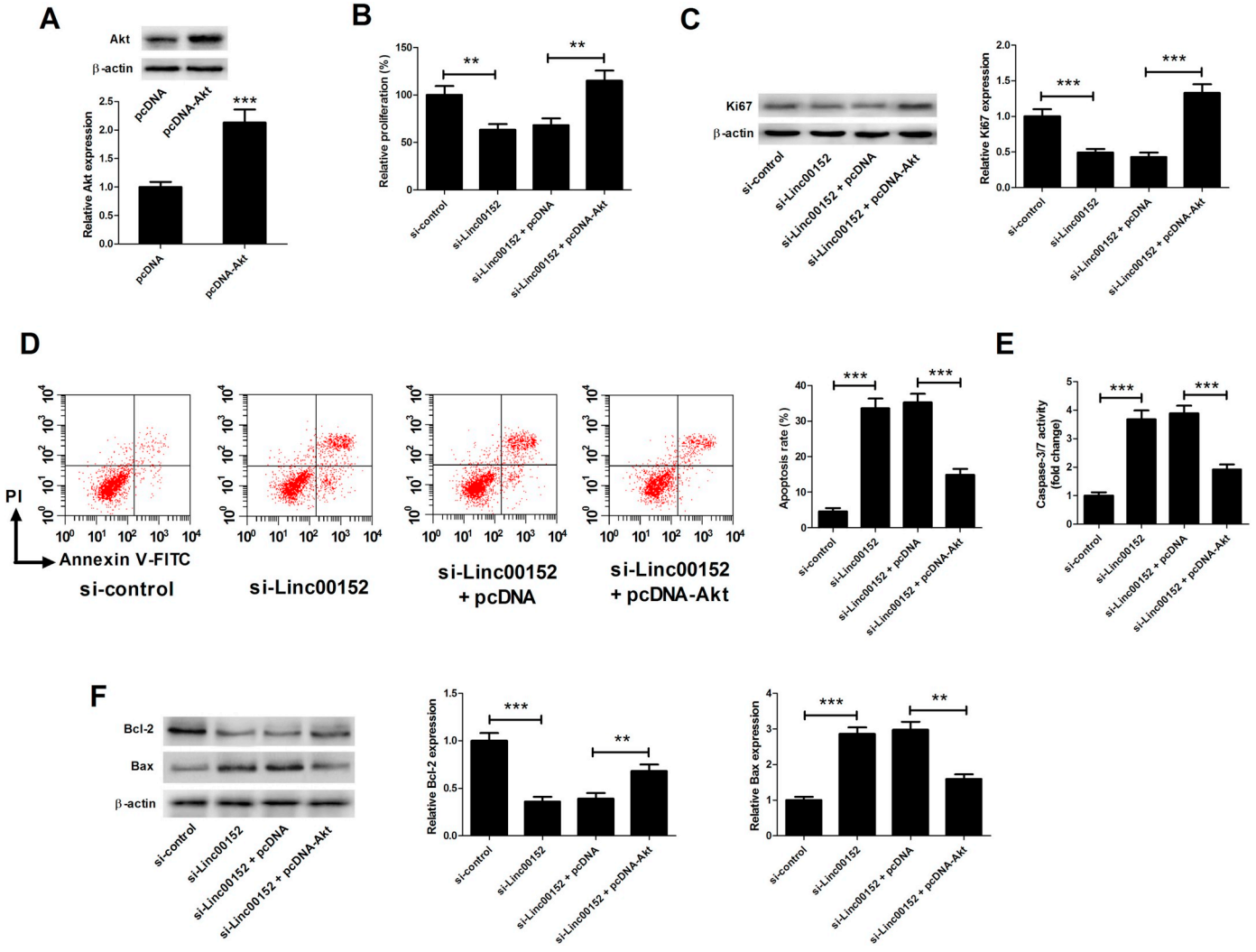

Fig. 4. Roles of Akt/mTOR pathway in si-Linc00152-transfected HemECs. (A) Akt expression was detected using western blot after 48 h transfection with pcDNA-Akt or pcDNA. (B) CCK-8 assay was performed to assess cell proliferation after 48 h transfection. (C) Ki67 expression was detected using western blot after 48 h transfection. (D) Apoptotic rate was examined using flow cytometry after 48 h transfection. (E) Caspase-3/7 activity in HemECs after 48 h transfection. (F) Bcl-2 and Bax expressions were detected using western blot after 48 h transfection. **indicated $p < 0.01$. ***indicated $p < 0.001$. HemECs, hemangioma-derived endothelial cells.

IH tissues and HemECs. Silenced SNHG16 negatively affected proliferation, vasoformation, migration, and invasion of HemECs. Taken together, these findings indicated that lncRNAs might be implicated in the pathogenesis of IH.

Linc00152 is a kind of lncRNA that has been documented serving as an oncogene in multiple cancers. Linc00152 is closely associated with glioma WHO classification and indicates a poor prognosis in patients with glioblastoma [16]. Blocking Linc00152 inhibits proliferation, invasive and migratory capacity, and colony formation of glioblastoma cell lines [16]. Linc00152 expression is significantly increased in PTC tissues and derived cell lines [17]. Knockdown of Linc00152 suppresses proliferation, colony formation, migration, and invasion *in vitro*, and impairs tumor growth *in vivo* [17]. A previous study has demonstrated that Linc00152 is increased in 7.84-fold in IH tissues and is closely associated with endothelial dysfunction [20]. Teng et al. [23] reported that Linc00152 exhibited an important role in the improvement of vascular endothelial function through suppressing apoptosis and promoting migration by sponging miR-4767. Therefore, we speculated that Linc00152 might have a potential role in the pathogenesis of IH. Our results showed that Linc00152 was up-regulated in IH tissues and HemECs. Knockdown of Linc00152 in HemECs suppressed cell proliferation and induced apoptosis.

Alterations in several cellular signaling pathways have been linked to the development of IH [24]. The major pathways implicated in IH include the PI3K/Akt/mTOR and Notch signaling pathways [24]. Targeting these pathways is of interest from a therapeutic perspective to reverse, delay or prevent the neovascularization in IH. Linc00152 was previously shown to promote tumor growth through the activation of EGFR-mediated PI3K/Akt pathway in gastric cancer [25]. In addition, Linc00152 knockdown exhibited anti-tumor effects against lung cancer *via* EGFR/PI3K/Akt pathway [26]. Linc00152 promoted gallbladder cancer cell proliferation and metastasis, inhibited apoptosis, and promoted tumor growth *in vivo via* regulating PI3K/Akt pathway [27]. Linc00152 exerted its oncogenic role by acting as a sponge for miR-4775, and cyclin-dependent kinases 6 (CDK6) was confirmed to be a direct target of miR-4775. CDK6 regulates glioma cell proliferation and invasion *via* PI3K/Akt/MAPK and Notch signaling pathways [28]. Linc00152 knockdown suppressed tumor growth and invasion *in vitro* and *in vivo* through miR-612-dependent Akt/NF-κB pathway in glioblastoma [16]. Linc00152 accelerated cell proliferation, metastasis, and

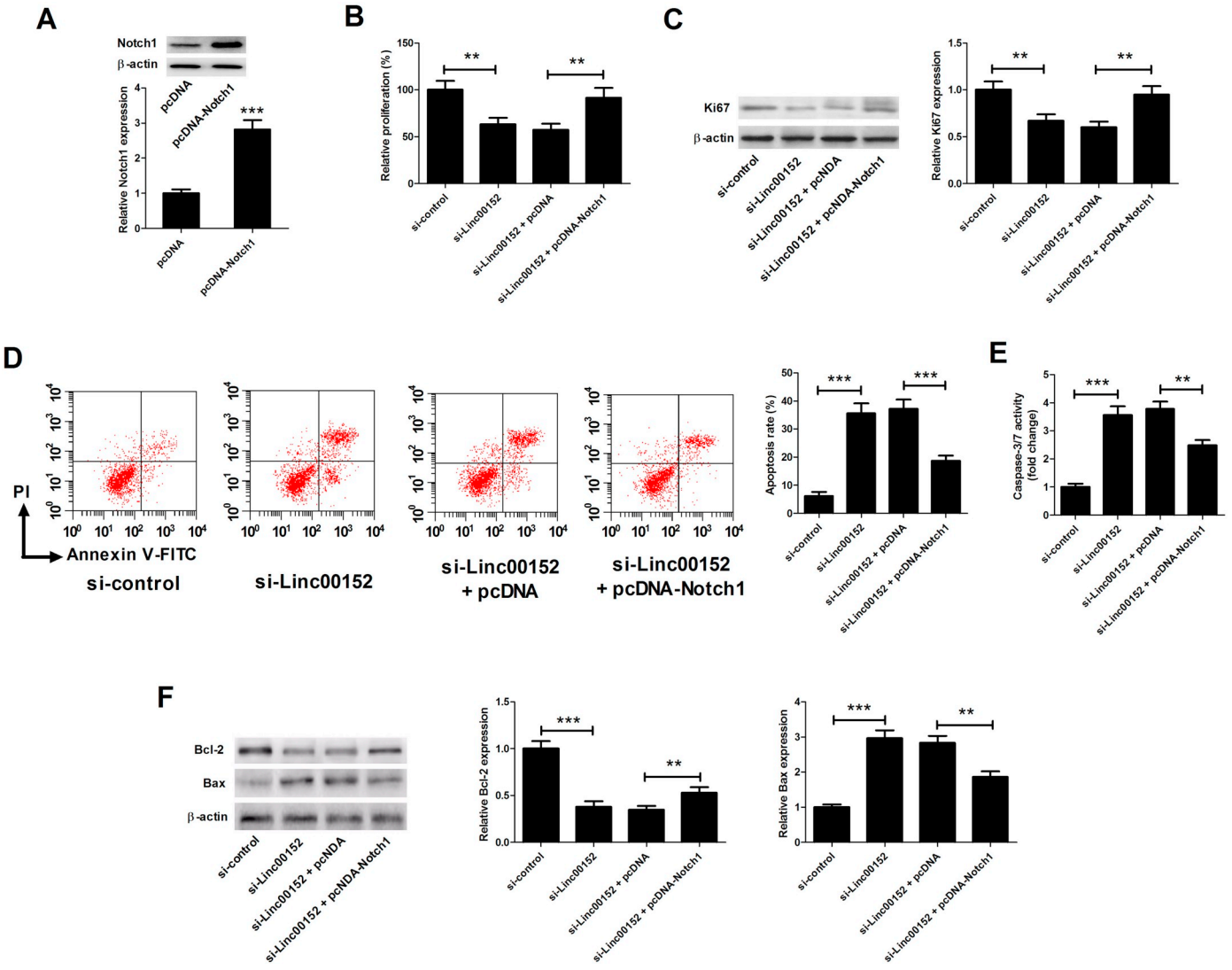

Fig. 5. Roles of Notch1 pathway in si-Linc00152-transfected HemECs. (A) Notch1 expression was detected using western blot after 48 h transfection with pcDNA-Notch1 or pcDNA. (B) CCK-8 assay was performed to assess cell proliferation after 48 h transfection. (C) Ki67 expression was detected using western blot after 48 h transfection. (D) Apoptotic rate was examined using flow cytometry after 48 h transfection. (E) Caspase-3/7 activity in HemECs after 48 h transfection. (F) Bcl-2 and Bax expressions were detected using western blot after 48 h transfection. **indicated $p < 0.01$. ***indicated $p < 0.001$. HemECs, hemangioma-derived endothelial cells.

conferred 5-fluorouracil resistance in colorectal cancer by regulating Notch1 pathway *via* sponging miR-139-5p [18]. Our results showed that Linc00152 knockdown inhibited the Akt/mTOR pathway and Notch1 signaling pathways. Overexpression Akt and Notch1 attenuated the effects of Linc00152 knockdown on cell proliferation and apoptosis.

In conclusion, the current study demonstrated that Linc00152 was dramatically up-regulated in IH tissues and HemECs. Knockdown of Linc00152 in HemECs suppressed cell proliferation and induced apoptosis, which was mediated by the Akt/mTOR and Notch1 signaling pathways. Therefore, it is supposed that Linc00152 might be potential therapeutic target for the management of IH.

Conflict of interest

The authors declare that they have no conflict of interest.

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