European Review for Medical and Pharmacological Sciences 2020; 24: 9343-9352

Long non-coding RNA LINC00858 promotes cells proliferation and invasion through the miR-153-3p/Rabl3 axis in hepatocellular carcinoma

W.-Y. QI[1], X.-B. MAO[2], Y.-B. HE[3], C.-H. XIAO[4]

[1]Office of Internal Medicine, Nursing Department, Jiangxi Health Vocational College, Nanchang, China
[2]The First Department of Hepatobiliary Surgery, Affiliated Hospital of North Sichuan Medical College, Nanchong, China
[3]Operating Room, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China
[4]Department of Hepatobiliary Surgery, the Fifth Medical Centre of Chinese PLA General Hospital, Beijing, China

Wenyan Qi and Xingbo Mao contributed equally to this work

Abstract. – OBJECTIVE: Long non-coding RNA (lncRNA) LINC00858 is a cancer-associated lncRNA frequently dysregulated in many types of human cancers. In the current study, we aimed to explore the role of LINC00858 in hepatocellular carcinoma (HCC).

PATIENTS AND METHODS: The relative expression levels of LINC00858 in HCC samples and adjacent non-tumor samples were determined by qRT-PCR. Loss-of-function assay was performed to examine the function of LINC00858 in HCC *in vitro*. Bioinformatic analysis and the following Luciferase activity reporter assay were utilized to explore the downstream molecules of LINC00858. CCK-8 assay was performed to detect cell proliferation of HCC cells. Transwell assay was performed to evaluate the invasive ability of HCC cells.

RESULTS: Our results showed that LINC00858 was highly expressed in both HCC tissues and cell lines. Knockdown of LINC00858 inhibited the proliferation and invasion of HCC cells. Moreover, LINC00858 was found to act as a sponge of miR-153-3p, which directly bound to Rabl3 and regulated the Rabl3 expression. Furthermore, inhibition of miR-153-3p counteracted the effects of LINC00858 knockdown on proliferation and invasion of HCC cells. In addition, the overexpression of Rabl3 rescued the effects of miR-153-3p on cell proliferation and invasion of HCC cells.

CONCLUSIONS: In summary, these findings showed that LINC00858 exerted an ontogenetic role in HCC via regulating miR-153-3p/Rabl3 axis. Thus, LINC00858 might be utilized as a therapeutic target for the treatment of HCC.

Key Words:
Hepatocellular carcinoma (HCC), Long non-coding RNA (lncRNA), LINC00858, MiR-153-3p, Rabl3.

Introduction

Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer that frequently appears in patients with cirrhosis[1]. HCC is ranked as the sixth most common cancer with increasing incidence in the world[2]. Although major progresses have been made in prevention, diagnosis, and treatment of HCC, it remains the third leading cause of cancer death[3]. Therefore, it is of great significance to study the underlying mechanisms of HCC progression for improving HCC treatment.

The development of HCC has been found to be closely related to the presence of chronic liver disease and associated with a complex multistep process[4]. During the process, an accumulation of genetic alterations in passenger and driver genes has been observed[5,6]. Long non-coding RNAs (lncRNAs) are group of noncoding RNAs which have more than 200 nucleotides in length without coding ability[7]. They can modulate the functions of target microRNAs (miRNAs) *via* acting as a competitive endogenous RNA (ceRNA)[8]. In recent years, lncRNAs have been reported[9,10] to play important roles in lots of diseases, especially in cancers.

Corresponding Author: Chaohui Xiao, MD; e-mail: xiao_oncol@126.com

LncRNA LINC00858 is a cancer-associated lncRNA that has been found to be frequently dysregulated in many types of human cancer. LINC00858 is highly expressed in primary colon cancer tissues and correlates with poor differentiation, advanced TNM stages, and lymph node metastasis[11]. LINC00858 plays an important role in colorectal cancer and serves as a novel prognostic factor and therapeutic target[12]. LINC00858 silencing significantly represses osteosarcoma cells proliferation and invasion *in vitro* and inhibits the tumor growth *in vivo*[13]. These findings suggest that LINC00858 exerts oncogenic role in those cancers. However, the role of LINC00858 in HCC has not been investigated.

In the present study, we explored the expression levels of LINC00858 in HCC clinical samples and the potential mechanism. The results indicated that LINC00858 expression was upregulated in HCC tissues and exerted an oncogenic role in HCC.

Patients and Methods

Human Tissue Samples

A total of 19 patients who were pathologically diagnosed as HCC at the Fifth Medical Centre of Chinese PLA General Hospital (Beijing, China) were enrolled in the present study. HCC-containing tissues and adjacent non-tumor tissues were collected from the patients during the surgical resection. All patients did not receive any adjuvant therapy before surgery. All patients signed the informed consent before the study. All procedures in the present study were reviewed by the Ethics Committee of the Fifth Medical Centre of Chinese PLA General Hospital and have been approved.

Cell Culture

Normal liver cell line (HL-7702 cells) and the human HCC cells (Hep3B, HuH-7, HCCLM3, BEL-7405 and SK-HEP-1 cells) were obtained from the Shanghai Institute of Biochemistry and Cell Biology (Shanghai, China). The cells were maintained in the RPMI-1640 medium (Invitrogen, Carlsbad, CA, USA) containing 10% fetal bovine serum (FBS; Invitrogen, Carlsbad, CA, USA) with 100 U/ml penicillin and 100 μg/ml streptomycin at 37°C.

Cell Transfection

Small hairpin RNA (shRNA) of LINC00858 (sh-LINC00858) and negative scramble shRNA (sh-NC) were subcloned into the lentiviral shRNA expression vector PGMLV (Genomeditech, Shanghai, China). Hep3B and BEL-7405 cells were infected with the sh-LINC00858 or sh-NC according to the manufacturer's protocol. Stably transfected cells were selected by puromycin.

To construct Rab-like 3 (Rabl3)-overexpressing plasmid (pcDNA3.0-Rabl3), the fragment of Rabl3 was amplified and cloned into pcDNA3.0 vector. MiR-153-3p mimics, negative control mimics, miR-153-3p inhibitor, negative control inhibitor were obtained from GenePharma (Shanghai, China). Cell transfection was performed using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA).

qRT-PCR

Total RNA was extracted from the liver samples and cultured cells using TRIzol reagent (Invitrogen, Carlsbad, CA, USA). Then, the extracted RNA was reverse transcribed into cDNA using the M-MLV Reverse Transcriptase kit (Toyobo, Osaka, Japan). After that, the cDNA was then used for real-time PCR analyses with a SYBR Premix ExTaq II kit (Toyobo, Osaka, Japan). U6 was used as the internal control. The relative expression of target genes was calculated using $2^{-\Delta\Delta Cq}$ method.

Western Blot

Total protein of Hep3B and BEL-7405 cells was respectively extracted using Radio-Immunoprecipitation Assay (RIPA) extraction reagent (Invitrogen, Carlsbad, CA, USA). Proteins were separated using 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) at 90 V for 30 min and 110 V for 70 min, followed by transferring to polyvinylidene difluoride membranes (Millipore, Billerica, MA, USA). The membranes were blocked with 5% bovine serum albumin (BSA) and incubated with the specific primary antibodies against Rabl3 or β-actin (Abcam, Cambridge, MA, USA) diluted in 5% BSA overnight at 4°C. On the second day, horseradish peroxidase (HRP)-conjugated secondary antibody (Abcam, Cambridge, MA, USA) was added to the membranes. The protein signals were finally visualized using a chemiluminescence reagent (Millipore, Billerica, MA, USA).

Cell-Counting Kit-8 (CCK-8) Assay

The proliferation ability of Hep3B and BEL-7405 cells was detected using the CCK-8 assay (Dojindo Laboratories, Kumamoto, Japan). Appropriately, 6000 cells per well were plated in 96-well plates and cultured for 0, 24, 48, and 72 h. Then, 10 μl CCK-8 solution was added to each

well, followed by an incubation for 4 h. Cell proliferation ability was determined by detecting the absorbance at 450 nm using a microplate reader (Bio-Rad, Hercules, CA, USA).

Transwell-Invasion Assay

The Matrigel precoated upper chambers of transwell (Millipore, Billerica, MA, USA) were added with 2×10^4 cells in 200 µl Dulbecco's Modified Eagle's Medium (DMEM) serum-free medium. While 800 µl DMEM medium containing 10% FBS were added into the lower chambers. After culturing for 24 h, the cells on the upper surface of the inserts were wiped with a cotton swab. The invaded cells on the lower surface of the inserts were stained with 0.1% crystal violet for quantification under an inverted phase-contrast microscope (200×).

Luciferase Reporter Assay

Full sequence of LINC00858 (LINC00858-WT), mutant type (LINC00858-MUT), Rabl3 wild-type 3'-UTR (Rabl3-WT) and mutant 3'-UTR (Rabl3-MUT) were cloned and inserted into the PGL3-control vector. Hep3B cells were co-transfected with LINC00858-WT/LINC00858-MUT or Rabl3-WT/Rabl3-MUT and miR-153-3p mimics/control mimics. After 48 h the Luciferase activity was measured using Dual-Luciferase reporter assay kit (Beyotime Biotechnology Co., Shanghai, China).

Tumor Growth in Nude Mice

Twenty female nude BALB/7 mice (six weeks old; Beijing Weitong Lihua Laboratory Animal Co, Ltd. Beijing, China) were randomly divided into two groups. For the xenograft implantation experiment, approximately 2×10^6 shRNA-LINC00858 infected Hep3B cells and shRNA-NC infected Hep3B cells were subcutaneously implanted into both flanks of mice in control group (n = 6) and shRNA-LINC00858 group (n = 6), respectively. After 5 weeks, the tumors in the mice were harvested and weighted. All animal experiments were approved by the Animal Care and Use Committee of the Fifth Medical Centre of Chinese PLA General Hospital and conducted in accordance with the Institutional Animal Care and Use Committee guidelines.

Statistical Analysis

Data were analyzed by GraphPad prism 8.0 version (La Jolla, CA, USA) and presented as the mean ± standard deviation (SD). The comparisons of LINC00858 and miR-153-3p expression in HCC samples and the matched normal samples were performed using the Student's *t*-test. Comparisons of tumor growth in control group and shRNA-LINC00858 group were performed using the Student's *t*-test. Comparisons among more than two groups were performed using one-way analysis of variance (ANOVA). A p-value < 0.05 indicated a statistically significant result.

Results

The Expression of LINC00858 is Upregulated in HCC Tissues and Cell Lines

In order to validate the role of LINC00858 in HCC, we assessed the LINC00858 expression levels in HCC samples and adjacent non-tumor tissues. The results from qRT-PCR showed that HCC samples showed higher levels of LINC00858 compared to the adjacent non-tumor tissues (Figure 1A). Additionally, LINC00858 was highly expressed in human

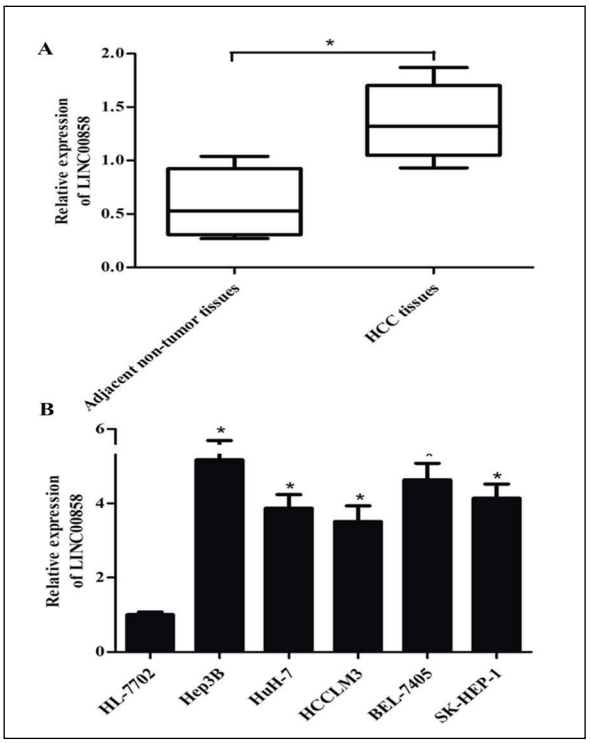

Figure 1. Differential expression levels of LINC00858 in HCC tissues and cell lines. The relative expression levels of LINC00858 were determined by qRT-PCR. **A,** LINC00858 expression levels in HCC samples and adjacent non-tumor samples. **B,** LINC00858 expression levels in normal liver cell line (HL-7702 cells) and human HCC cells (Hep3B, HuH-7, HCCLM3, BEL-7405 and SK-HEP-1 cells). The data were compared to the HL-7702 cells. *p < 0.05 was considered statistically significant.

HCC cells (Hep3B, HuH-7, HCCLM3, BEL-7405 and SK-HEP-1 cells), especially in Hep3B and BEL-7405 cells, as compared to the normal liver cell line HL-7702 cells (Figure 1B).

LINC00858 Knockdown Inhibits Cell Proliferation and Invasion in HCC

To determine the potential biological functions of LINC00858 *in vitro*, LINC00858 was knocked down in Hep3B and BEL-7405 cells using sh-LINC00858. As shown in Figures 2A and 2B, significant reductions in LINC00858 expression were observed in sh-LINC00858 infected Hep3B and BEL-7405 cells. CCK-8 assay demonstrated that proliferation ability of Hep3B and BEL-7405 cells was markedly reduced by sh-LINC00858 (Figures 2C and 2D). Transwell assay proved that infection with sh-LINC00858 caused significant decreases in invasive ability of Hep3B and BEL-7405 cells (Figures 2E and 2F).

LINC00858 Knockdown Hinders Xenografts Growth In Vivo

Then, we assessed the role of LINC00858 in tumorigenesis *in vivo*, shRNA-NC or shRNA-LINC00858 infected Hep3B cells were subcutaneously implanted into both flanks of mice. We found that the knockdown of LINC00858 suppressed the tumor growth *in vivo* (Figure 3A). The sh-LINC00858 infected Hep3B cells generated smaller tumors in nude mice than

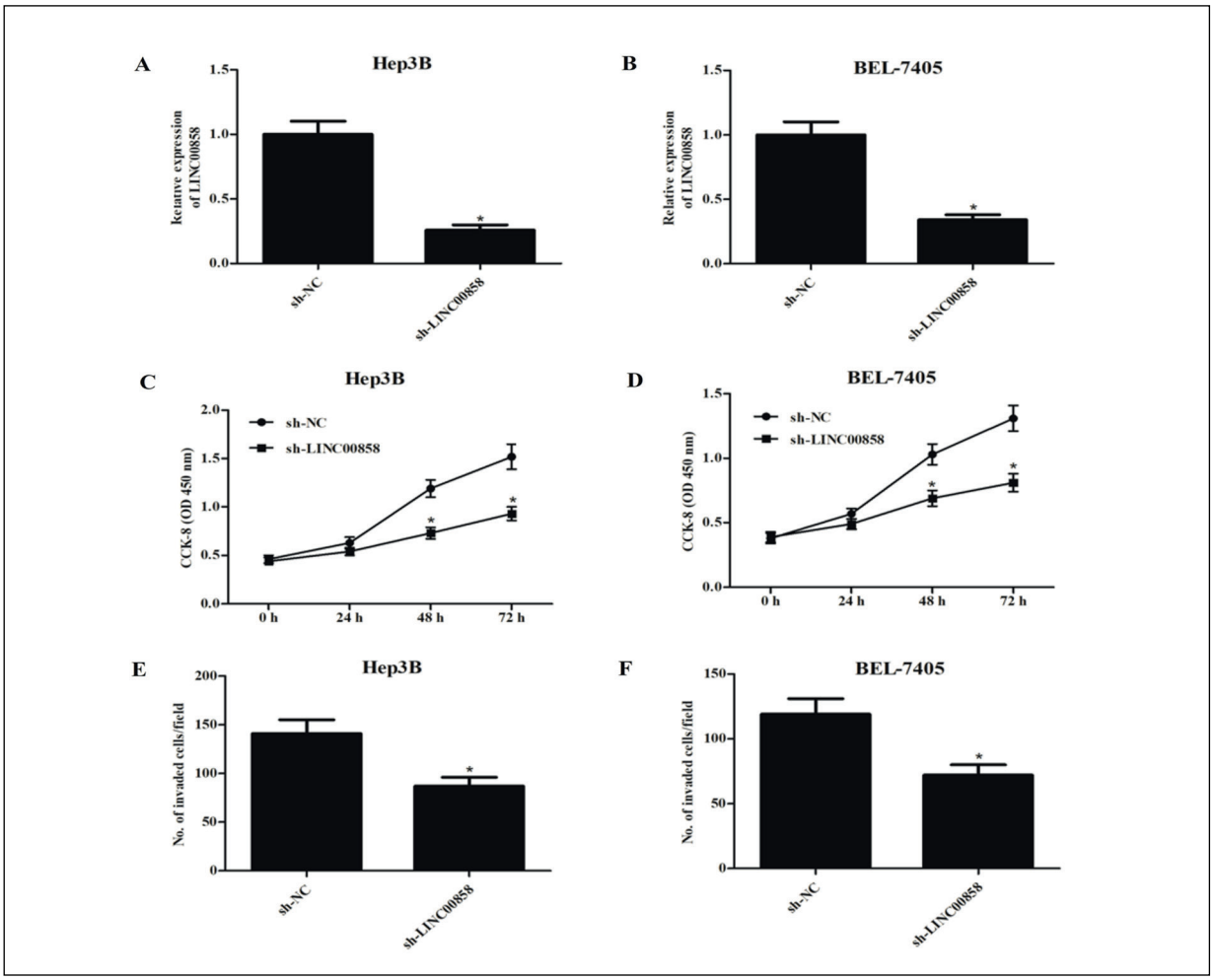

Figure 2. The function of LINC00858 in cell proliferation and invasion of HCC cells. **A,** and **B,** LINC00858 was knocked down in Hep3B and BEL-7405 cells through infection with sh-LINC00858. **C,** and **D,** CCK-8 assay was performed to detect cell proliferation of Hep3B and BEL-7405 cells with different treatments. **E,** and **F,** Transwell assay was performed to evaluate invasive ability of Hep3B and BEL-7405 cells with different treatments. *$p < 0.05$ was considered statistically significant.

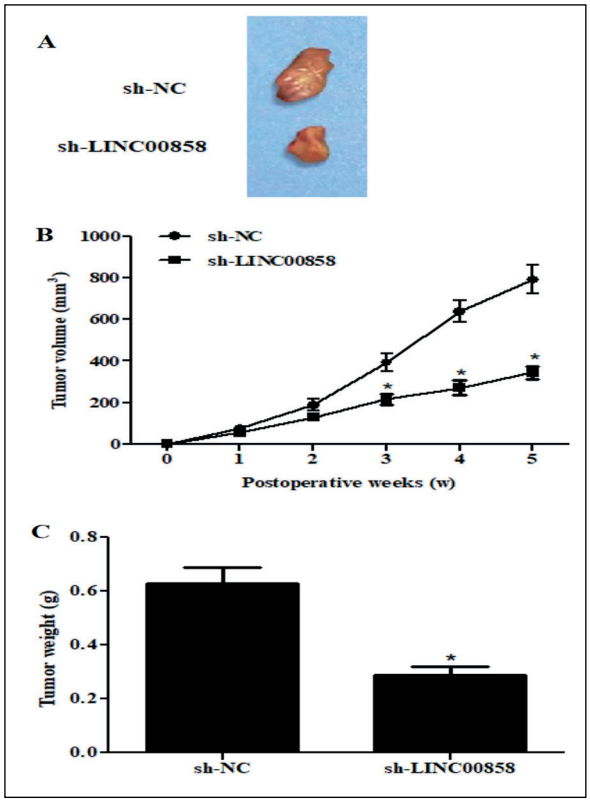

Figure 3. The role of LINC00858LINC00858 in HCC tumorigenesis. The shRNA-NC or shRNA-LINC00858 infected Hep3B cells were subcutaneously implanted into both flanks of mice. **A,** Tumor growth was monitored every three days. **B,** and **C,** Tumor volume and weight were measured after 5 weeks post implantation. *$p < 0.05$ was considered statistically significant.

sh-NC infected Hep3B cells, as evidenced by reduced tumor volume and weight (Figures 3B and 3C).

LINC00858 Directly Interacts With MiR-153-3p in HCC Cells

According to the online software analysis, we found that LINC00858 had binding sites with miR-153-3p (Figure 4A). To further verify the interaction between LINC00858 and miR-153-3p, the Luciferase reporter assay was performed. The results showed that co-transfection with LINC00858-WT and miR-153-3p mimics caused a significant decrease in the Luciferase activity (Figure 4B). Knockdown of LINC00858 resulted in marked increase in miR-153-3p expression in Hep3B cells (Figure 4C). Furthermore, the expression of LINC00858 in HCC tissues was negatively associated with miR-153-3p expression (Figure 4D).

The Expression of MiR-153-3p Is Downregulated in HCC Tissues and Cell Lines

Subsequently, we examined the expression level of miR-153-3p in HCC samples and pair-matched normal samples using qRT-PCR. The results in Figure 5A showed that the expression levels of miR-153-3p were significantly decreased in HCC samples compared to the adjacent non-tumor samples. In addition, miR-153-3p expression levels were significantly downregulated in human HCC cells including Hep3B, HuH-7, HCCLM3, BEL-7405 and SK-HEP-1 cells, as compared to HL-7702 cells (Figure 5B).

MiR-153-3p Inhibitor Counteracts LINC00858 Knockdown on Proliferation and Invasion

Next, we aimed to evaluate the effect of miR-153-3p inhibitor on cell proliferation and invasion in LINC00858 knocked down Hep3B cells. Compared to the LINC00858 knocked down Hep3B cells, miR-153-3p expression was markedly reduced after transfection with miR-153-3p inhibitor (Figure 6A). The sh-LINC00858 caused decreases in cell proliferation and invasion of Hep3B cells were attenuated by miR-153-3p inhibitor (Figures 6B and 6C).

MiR-153-3p Targets Rabl3 in HCC Cells

We also used online software to predict the potential target mRNA of miR-153-3p. As indicated in Figure 7A, miR-153-3p was predicted to bind to the 3'UTR of Rabl3. Luciferase reporter assay showed that Hep3B cells co-transfected with Rabl3-WT and miR-153-3p mimics exhibited decreased Luciferase activity (Figure 7B). Transfection with miR-153-3p mimics significantly reduced Rabl3 protein expression in Hep3B cells (Figure 7C).

Overexpression of Rabl3 Can Partially Rescue the Effect of MiR-153-3p Upregulation on Cell Proliferation and Invasion

We next confirmed the role of Rabl3 in the effect of miR-153-3p through transfection with Rabl3-overexpressing vector. As illustrated in Figure 8A and 8B, Rabl3 expression was increased by pcDNA3.0-Rabl3 in Hep3B cells transfected with miR-153-3p mimics. Transfection with miR-153-3p mimics significantly inhibited the proliferation and invasion of Hep3B

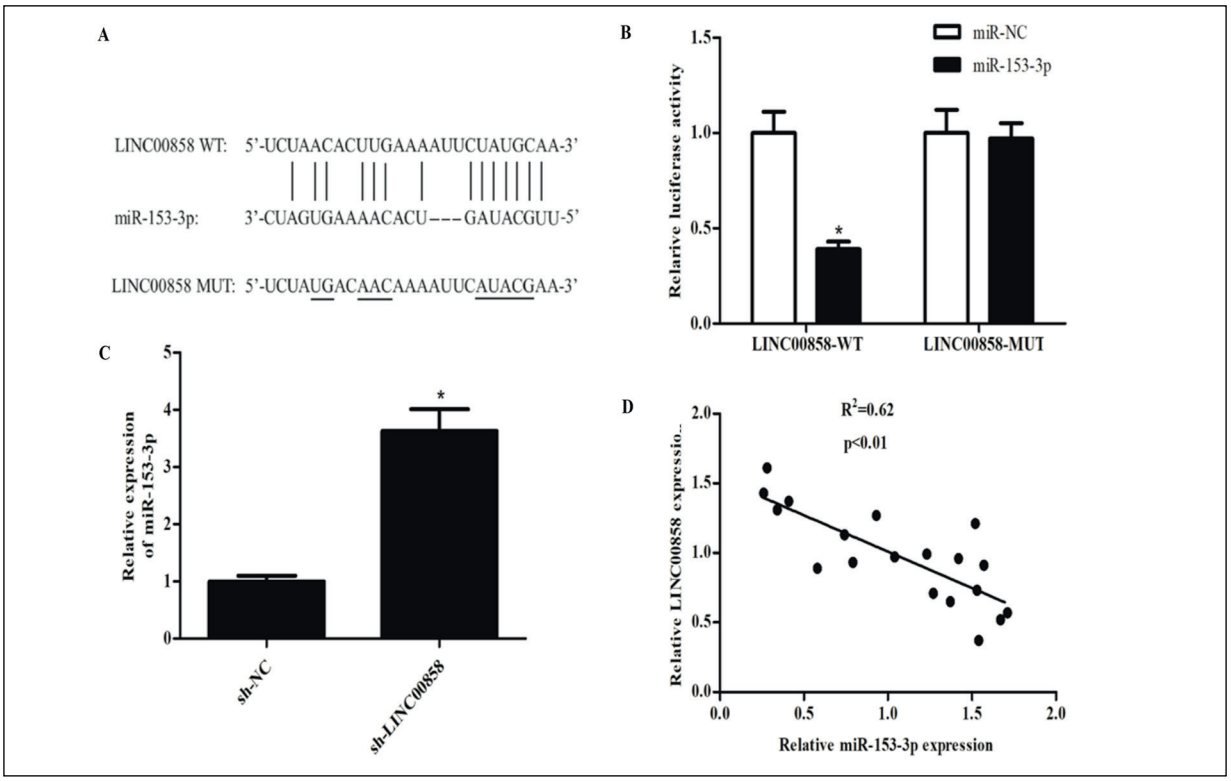

Figure 4. LINC00858 directly interacts with miR-153-3p in HCC cells. **A,** Bioinformatic analysis of the interaction between LINC00858 and miR-153-3p. **B,** Luciferase reporter assay was performed to further verify the interaction. **C,** Role of LINC00858 in the regulation of miR-153-3p expression. **D,** Association between the expression levels of LINC00858 and miR-153-3p in HCC tissues. *$p < 0.05$ was considered statistically significant.

cells. The overexpression of Rabl3 prevented the inhibitory effects of miR-153-3p on the proliferation and invasion of Hep3B cells (Figures 8C and 8D).

Discussion

The functions of the vast majority of lncRNAs remain unknown but increasing lncRNAs have

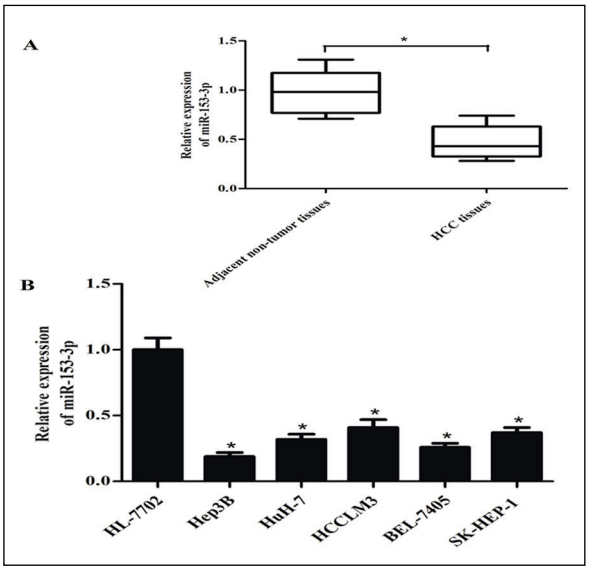

Figure 5. Differential expression levels of miR-153-3p in HCC tissues and cell lines. The relative expression levels of miR-153-3p were determined by qRT-PCR. **A,** MiR-153-3p expression levels in HCC samples and adjacent non-tumor samples. **B,** MiR-153-3p expression levels in normal liver cell line (HL-7702 cells) and human HCC cells (Hep3B, HuH-7, HCCLM3, BEL-7405 and SK-HEP-1 cells). The data were compared to the HL-7702 cells. *$p < 0.05$ was considered statistically significant.

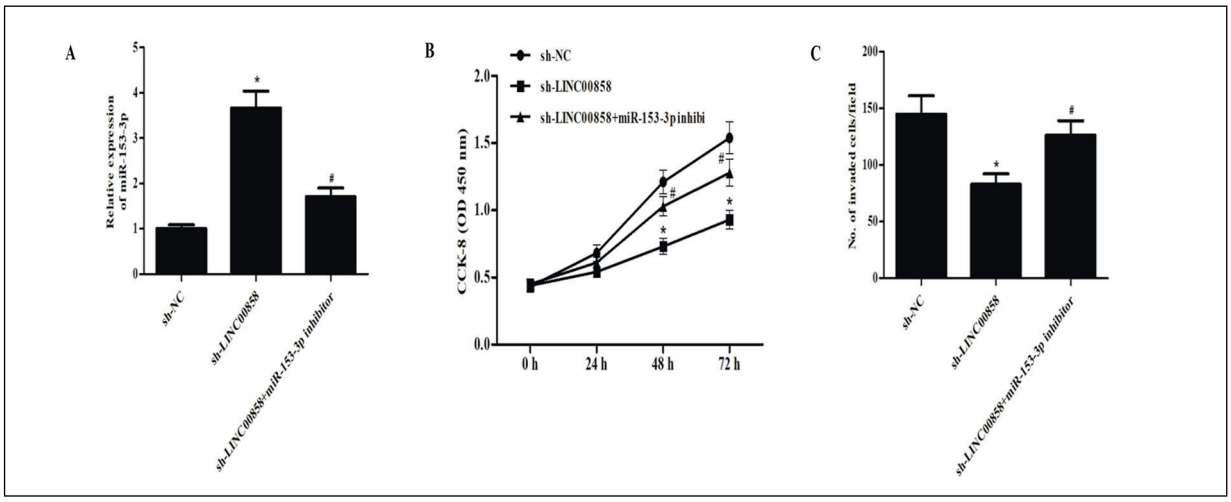

Figure 6. MiR-153-3p inhibitor counteracts LINC00858 knockdown on proliferation and invasion. **A,** MiR-153-3p expression level in Hep3B cells after transfection with sh-LINC00858 and/or miR-153-3p inhibitor. **B,** CCK-8 assay was performed to detect differential cell proliferation of Hep3B cells with different treatments. The data were compared to the sh-LINC00858 infected Hep3B cells. **C,** Transwell assay was performed to evaluate differential invasive ability of Hep3B cells with different treatments. *$p < 0.05$ *vs.* sh-NC group; #$p < 0.05$ *vs.* sh-LINC00858 group.

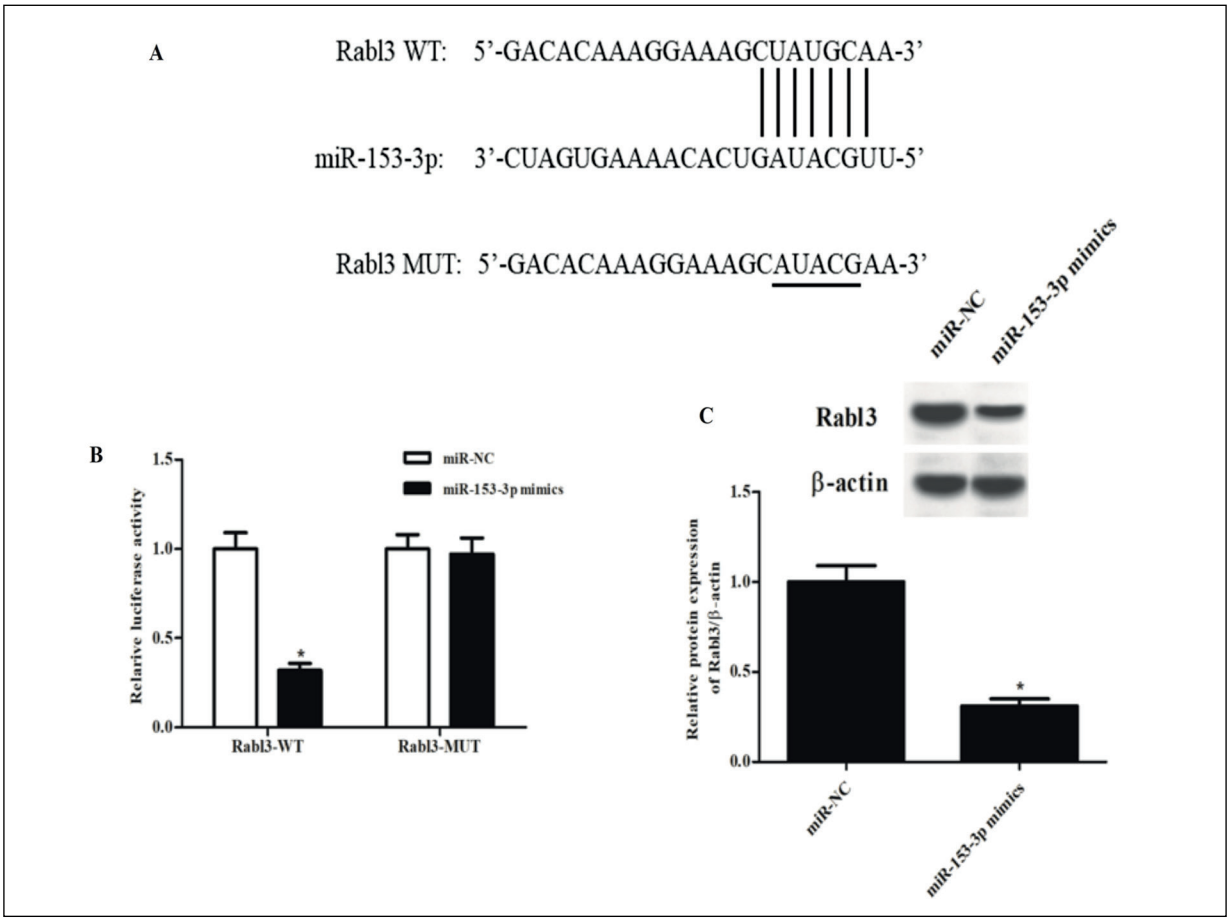

Figure 7. MiR-153-3p targets Rabl3 in HCC cells. **A,** Bioinformatic analysis of the interaction between miR-153-3p and Rabl3. **B,** Luciferase reporter assay was performed to further verify the interaction. The data were compared to control cells. **C,** Role of miR-153-3p in the regulation of Rabl3 expression was evaluated by Western blot. The data were compared to the Hep3B cells transfected with negative control mimics. *$p < 0.05$ was considered statistically significant.

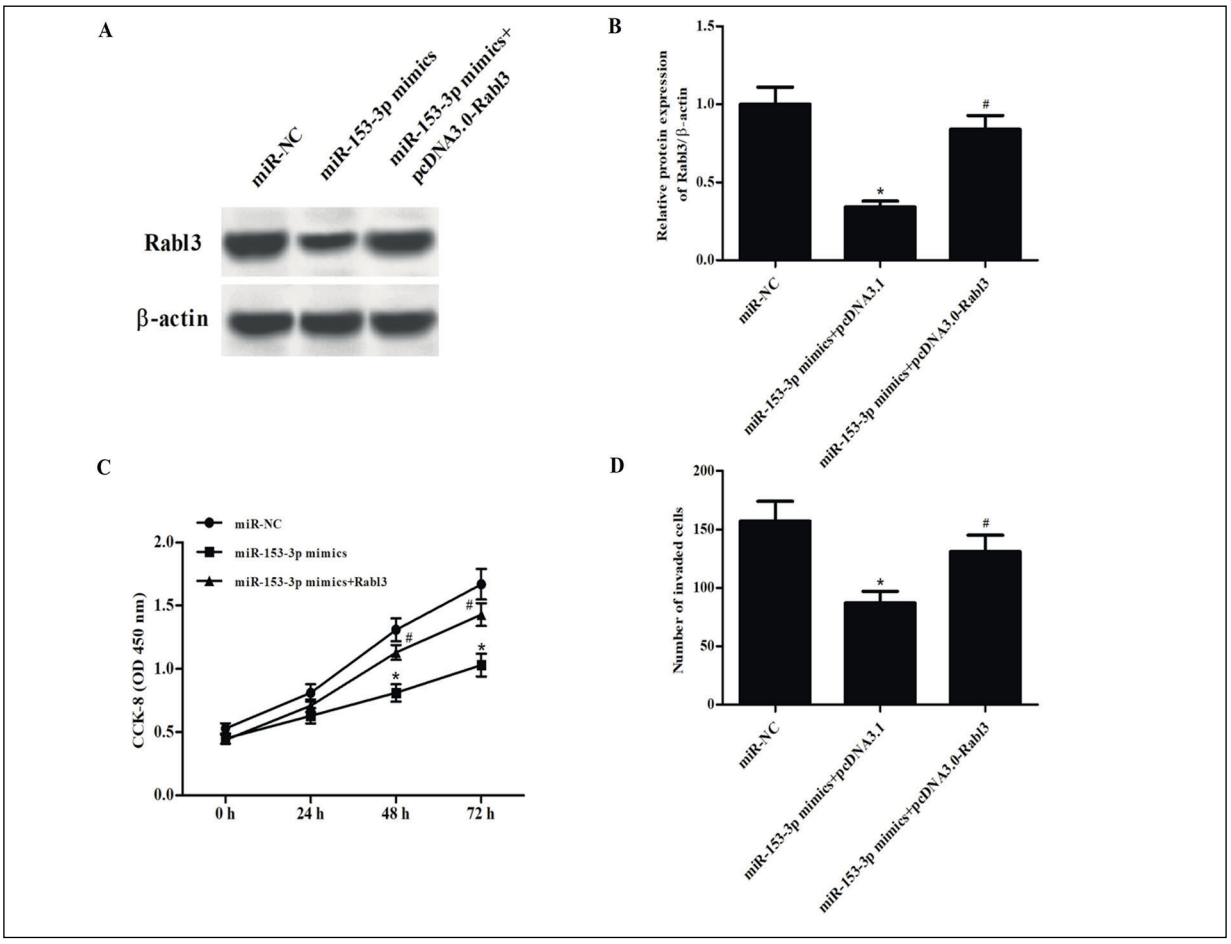

Figure 8. Overexpression of Rabl3 can partially rescue the effect of miR-153-3p upregulation on cell proliferation and invasion. Hep3B cells were co-transfected with miR-153-3p mimics and pcDNA3.0-Rabl3. **A,** The protein expression of Rabl3 was detected using Western blot. **B,** Quantification analysis of Rabl3. **C,** CCK-8 assay was performed to detect differential cell proliferation of Hep3B cells with different treatments. **D,** Transwell assay was performed to evaluate differential invasive ability of Hep3B cells with different treatments. *$p < 0.05$ *vs.* miR-NC group; #$p < 0.05$ *vs.* miR-153-3p mimics + pcDNA3.0.

been found to be implicated in a myriad of biological processes[10]. The common modes of their actions include regulating gene expression in *cis* and in *trans*, regulating protein activity and abundance, and scaffolding of subcellular domains and complexes[14,15]. In addition, lncRNAs also interact with small RNAs, thereby exerting their functions[16]. Recently, many lncRNAs have been found to participate in tumorigenesis by binding to various miRNAs and triggering oncogenic signaling pathways. LINC00858 promotes progress of lung cancer *via* binding to miR-3182 and regulating the expression of miR-3182[17]. LINC00858 promotes cells proliferation, migration and invasion of colorectal cancer cells by acting as a ceRNA of miR-22-3p[12]. LINC00858 functions as a ceRNA for miR-422a to facilitate the cell growth in non-small cell lung cancer (NSCLC)[18]. In the present study, we found that LINC00858 was highly expressed in HCC tissues and cell lines. The knockdown of LINC00858 inhibited cell proliferation and invasion in HCC cells. Furthermore, LINC00858 was found to directly bind to miR-153-3p and suppressed the expression of miR-153-3p in HCC cells.

Interestingly, miR-153-3p is a miRNA that has been demonstrated to have crucial roles in the progression of several cancers[19-21]. MiR-153-3p expression was found to be dysregulated in acute lymphoblastic leukemia and might be a target for the treatment[22]. MiR-153-3p is lowly expressed in ovarian carcinoma tissues and regulates progression of ovarian carcinoma both *in vitro* and *in vivo*[23]. Sun et al[24] reported that miR-153-3p is a potential target to enhance the effect of radio sensitivity on glioma cells. Zeng et al[25] demon-

strated that miR-153-3p might be a potential target in the diagnosis and treatment of malignant melanoma. Our results showed that miR-153-3p expression was downregulated in HCC tissues and cell lines, which were negatively associated with LINC00858. Moreover, inhibition of miR-153-3p counteracted the effects of LINC00858 knockdown on proliferation and invasion of HCC cells. The results indicated that LINC00858 executed its role *via* sponging miR-153-3p in HCC cells. Many miRNAs function as critical roles in tumorigenesis via targeting 3'-UTR of indicated genes[26]. Our bioinformatic analysis showed that Rabl3 might be a target gene of miR-153-3p, which was detected by Luciferase activity reporter assay. We also found that miR-153-3p overexpression significantly inhibited the expression of Rabl3 in HCC cells. The Rabl3 gene belongs to the Rab subfamily, which is the largest group in the Ras superfamily of small GTPases[27]. Genetic and functional studies on Rabl3 have supported its putative roles in cancer development. For example, high expression of Rabl3 is observed in NSCLC and associated with poor survival of patients with NSCLC[28]. Additionally, Rabl3 is expressed at significantly higher rates in HCC tissues compared with adjacent normal hepatic tissues. The rate of positive Rabl3 expression is higher in the HCC tissues of patients with lymph node metastasis, tumor thrombi in the portal vein and an advanced clinical stage, implying that Rabl3 is associated with pathogenesis and poor prognosis in HCC[29,30]. Consistent with the published data, our results showed that Rabl3 expression is increased in HCC samples and negatively related to miR-153-3p expression. Moreover, overexpression of Rabl3 rescued the effects of miR-153-3p on cell proliferation and invasion of HCC cells. These findings indicated that miR-153-3p exerted its role *via* targeting Rabl3.

Conclusions

These findings demonstrated that LINC00858 exerted an ontogenetic role in HCC *via* regulating the miR-153-3p/Rabl3 axis. The results indicated that LINC00858 might be utilized as a therapeutic target for the treatment of HCC.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Massarweh NN, El-Serag HB. epidemiology of hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Cancer Control 2017; 24: 1073274817729245.
2) Tabrizian P, Roayaie S, Schwartz ME. Current management of hepatocellular carcinoma. World J Gastroenterol 2014; 20: 10223-10237.
3) Hartke J, Johnson M, Ghabril M. The diagnosis and treatment of hepatocellular carcinoma. Semin Diagn Pathol 2017; 34: 153-159.
4) Yang S, Yang L, Li X, Li B, Li Y, Zhang X, Ma Y, Peng X, Jin H, Li H. New insights into autophagy in hepatocellular carcinoma: mechanisms and therapeutic strategies. Am J Cancer Res 2019; 9 :1329-1353.
5) Wang L, Wang WL, Zhang Y, Guo SP, Zhang J, Li QL. Epigenetic and genetic alterations of PTEN in hepatocellular carcinoma. Hepatol Res 2007; 37: 389-396.
6) Sun HK, Ihm CH, Kwon KC, Park JW, Kong G. Genetic alterations in hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Cancer Genetics Cytogenetics 2001; 130: 22-28.
7) Lim LJ, Wong SYS, Huang F, Lim S, Chong SS, Ooi LL, Kon OL, Lee CG. Roles and regulation of long noncoding rnas in hepatocellular carcinoma. Cancer Res 2019; 79: 5131-5139.
8) Dey BK, Mueller AC, Dutta A. Long non-coding RNAs as emerging regulators of differentiation, development, and disease. Transcription 2014; 5: e944014-944011-944019.
9) Chen G, Wang Z, Wang D, Qiu C, Liu M, Chen X, Zhang Q, Yan G, Cui Q. LncRNA disease: a database for long-non-coding RNA-associated diseases. Nucleic Acids Res 2013; 1: D983-D986.
10) Chen X, Yan G-Y. Novel human lncRNA-disease association inference based on lncRNA expression profiles. Bioinformatics 2013; 29: 2617-2624.
11) Xu T, Wu K, Zhang L, Zheng S, Wang X, Zuo H, Wu X, Tao G, Jiang B, Zhang L. Long non-coding RNA LINC00858 exerts a tumor-promoting role in colon cancer via HNF4alpha and WNK2 regulation. Cell Oncol 2019; 43: 297-310.
12) Sha QK, Chen L, Xi JZ, Song H. Long non-coding RNA LINC00858 promotes cells proliferation, migration and invasion by acting as a ceRNA of miR-22-3p in colorectal cancer. Artif Cells Nanomed Biotechnol 2019; 47: 1057-1066.
13) Gu Z, Hou Z, Zheng L, Wang X, Wu L, Zhang C. Long noncoding RNA LINC00858 promotes osteosarcoma through regulating miR-139-CDK14 axis. Biochem Biophys Res Commun 2018; 503: 1134-1140.
14) Carmona S, Lin B, Chou T, Arroyo K, Sun S. LncRNA Jpx induces Xist expression in mice using both trans and cis mechanisms. PLoS Genetics 2018; 14: e1007378-e1007398.

15) Ferre F, Colantoni A, Helmer-Citterich M. Revealing protein-lncRNA interaction. Brief Bioinform 2016; 17: 106-116.

16) Guo L, Zhao Y, Yang S, Zhang H, Chen F. An integrated analysis of miRNA, lncRNA, and mRNA expression profiles. Biomed Res Int 2014; 2014: 345605-345616.

17) Xue M, Shi D, Xu G, Wang W. The long noncoding RNA linc00858 promotes progress of lung cancer through miR-3182/MMP2 axis. Artif Cells Nanomed Biotechnol 2019; 47: 2091-2097.

18) Zhu SP, Wang JY, Wang XG, Zhao JP. Long intergenic non-protein coding RNA 00858 functions as a competing endogenous RNA for miR-422a to facilitate the cell growth in non-small cell lung cancer. Aging (Albany NY) 2017; 9: 475-486.

19) Chang AC, Lien MY, Tsai MH, Hua CH, Tang CH. WISP-1 promotes epithelial-mesenchymal transition in oral squamous cell carcinoma cells via the miR-153-3p/Snail axis. Cancers (Basel) 2019; 11: E1903-E1918.

20) Ma H, Tian T, Liu X, Xia M, Chen C, Mai L, Xie S, Yu L. Upregulated circ_0005576 facilitates cervical cancer progression via the miR-153/KIF20A axis. Biomed Pharmacother 2019; 118: 109311-109318.

21) Cheng FH, Zhao ZS, Liu WD. Long non-coding RNA ROR regulated ABCB1 to induce cisplatin resistance in osteosarcoma by sponging miR-153-3p. Eur Rev Med Pharmacol Sci 2019; 23: 7256-7265.

22) Jiang J, Liu Y, Zhao Y, Tian F, Wang G. MiR-153-3p suppresses inhibitor of growth protein 2 expression to function as tumor suppressor in acute lymphoblastic leukemia. Technol Cancer Res Treat 2019; 18: 1533033819852990.

23) Li C, Zhang Y, Zhao W, Cui S, Song Y. MiR-153-3p regulates progression of ovarian carcinoma in vitro and in vivo by targeting MCL1 gene. J Cell Biochem 2019; 120: 19147-19158.

24) Sun D, Mu Y, Piao H. MicroRNA-153-3p enhances cell radiosensitivity by targeting BCL2 in human glioma. Biol Res 2018; 51: 56-81.

25) Zeng HF, Yan S, Wu SF. MicroRNA-153-3p suppress cell proliferation and invasion by targeting SNAI1 in melanoma. Biochem Biophys Res Commun 2017; 487: 140-145.

26) Lu TX, Rothenberg ME. MicroRNA. J Allergy Clin Immunol 2018; 141: 1202-1207.

27) Reiner DJ, Lundquist EA. Small GTPases. WormBook 2018; 2018: 1-65.

28) Zhang W, Sun J, Luo J. High Expression of Rab-like 3 (Rabl3) is associated with poor survival of patients with non-small cell lung cancer via repression of MAPK8/9/10-mediated autophagy. Med Sci Monit 2016; 22: 1582-1588.

29) An J, Liu Z, Liang Q, Pan Y, Li H, Wang R, Jin Y. Overexpression of Rabl3 and Cullin7 is associated with pathogenesis and poor prognosis in hepatocellular carcinoma. Hum Pathol 2017; 67: 146-151.

30) Pan Y, Liu Z, Feng Z, Hui D, Huang X, Tong D, Jin Y. The overexpression of Rabl3 is associated with pathogenesis and clinicopathologic variables in hepatocellular carcinoma. Tumour Biol 2017; 39: 1010428317696230.