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MicroRNA-18a-5p targets Sec61 translocon alpha 1 subunit to repress hepatocellular carcinoma cell growth before chromradiotherapy

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► ***Original article***

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Keywords: *MicroRNA-18a-5p; Sec61 translocon alpha 1 subunit; hepatocellular carcinoma.*

ABSTRACT

Background: Hepatocellular carcinoma (HCC) cell development was investigated in relation to the regulation of Sec61 translocon alpha 1 subunit (SEC61A1) by microRNA (miR)-18a-5p. ***Materials and Methods:*** After collection of clinical samples, the transfection of interfering vectors of miR-18a-5p or SEC61A1 was into HCC cells to figure out their roles in development of HCC. The Pearson test and starBase analyzed the association and target prediction of miR-18a-5p. Subsequently, through the dual luciferase reporter experiment, SEC61A1 can be regulated via miR-18a-5p. The salvage experiment revealed that miR-18a-5p influence the degradation process of Hepatocellular carcinoma through combining SEC61A1. ***Results:*** In HCC cells, we found that SEC61A1 was elevated and miR-18a-5p was downregulated. HCC cells deteriorating was considerably slowed down by the enhanced miR-18a-5p level. The outcomes demonstrated that miR-18a-5p can interact and regulate SEC61A1. Additionally, the effects of earlier therapy on HCC cell proliferation can be restored by overexpressing SEC61A1. ***Conclusion:*** Overall, in HCC cells and tissues miR-18a-5p was significantly downregulated, and inhibited the proliferative ability of HCC cells by targeting SEC61A1.

INTRODUCTION

Primary hepatocellular carcinoma (HCC) ranks six[th] in incidence among all malignancies and hits prevailing reason of cancer deaths [1-3]. In China, people aged 50 years or above are at high risk of HCC [4]. Hepatitis B and C viruses are available to lead to HCC [5]. The emergence of HCC is a long-term course. For instance, the progression of cirrhotic masses becomes huge being considered as HCC [6]. In the early stage of HCC, the efficacy of treatment methods of local ablation, liver transplantation and tumor resection are fairly optimistic, but the elevation of recurrence rate is in 5-year [7]. MicroRNA (miRNA) affects tumorigenesis via modulating gene, so targeted miRNA is prospective in tumor therapy.

MiRNA is crucial members of the non-coding RNA family [8] and can modulate its expression [9]. Reduced miR-18a-5p has been shown to inhibit tumor growth in ovarian cancer [10, 11]. Moreover, inhibition of miR-18a-5p in HCC can be used to limit the proliferation of cancer cells [12]. However, the specific downstream mechanism of it in HCC is been hardly studied.

Sec61 translocon alpha 1 subunit (SEC61A1) encoding the α-subunit of Sec61 complex is in charge of proteins translocating and integrating into the endoplasmic reticulum membrane [13, 14]. Moreover, Sec61 channels is conducive to cellular calcium homeostasis. The term Sec61 channel disease covers a family of genetic or acquired diseases that exert impacts on Sec61 subunits. The association of Sec61 function was with a wide range of related diseases covering autosomal dominant polycystic liver disease (SEC63 [15], SEC61B [16] and diabetes mellitus (DNAJC3 [17]. Lately, it has been demonstrated that the elevation of SEC61A1 is in colon cancer, boosting cell growth in colon adenocarcinoma [18]. Furthermore, the acceleration of SEC61A1 is in nasopharyngeal carcinoma (NPC) and HCC, facilitating cancer cell development [19, 20]. But the mechanism by which SEC61A1 enhanced tumor progression was not quite clear.

Our research discovered that miR-18a-5p targets SEC61A1 to inhibit HCC cancers. In the hepatocellular carcinoma models decreased of miR-18a-5p and increased of SEC61A1 provides more insight into the biological functions and possible processes of miRNA. The outcomes of the research may help clarify a better understanding of miR-18a-5p's function and offer fresh perspectives on targeted treatments for the disease.

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MATERIALS AND METHODS

Human sample data

From March 2015 to April 2018, the participation of 40 patients with HCC in Ningbo Yinzhou No.2 Hospital was in the study. Thirteen female and twenty-seven male patients, ranging in age from 28 to 80 years, with a mean age of 47.36±10.30 years. The diagnosis of all patients who did not receive any chemotherapy or radiotherapy prior to surgery was via pathology. Samples of HCC and para-cancerous normal tissues were taken from patients and preserved in liquid nitrogen. The provision of each participant was written informed consent. The authorization of adoption of human clinical tissues was via the ethics committee of our institution.

Cell culture

HCC cell lines (HepG2, Huh-7, SMMC-7721, HHCC, PLC), and the normal hepatocyte line (HL-7702) were cultured in 1640 medium. These included 10% FBS, 1% penicillin, and 0.1 mg/mL streptomycin (GIBCO BRL, MD). The cultures were conducted at Huiying Biological Technologies, China. And no keratinocytein serum medium (BD Biosciences, San Jose, CA) containing bovine pituitary gland extract separately.

Cell transfection

The establishment of sh-NC and SEC61A1, oe-NC and SEC61A1 plasmids were commissioned (Sangon Biotech, China) in line with the known SEC61A1 sequence in NCBI. MiR-18a-5p or NC inhibitor , along with MiR-18a-5p or NC mimic (all RiboBio Co., Ltd.) were adopted from Guangzhou, P.R. China. Following the directions provided by the manufacturer, the Lipofectamine 2000 reagent (Invitrogen, USA) was used to transfect the cells.

RT-qPCR

Total RNA has been obtained from tissues, cells, and exosomes using the TRIzol procedure (16096020, Thermofisher, NY, USA). To detect mRNA expression, the reversed transcription of RNA was into cDNA employing cDNA synthesis kit (Vazyme, China).

The detection of miR-18a-5p, SEC61A1, *Bax* and *Bcl-2* was via adopting a PrimeScript RT-PCR kit (Vazyme, China), and the normalization of results was through exerting *GAPDH* with *U6* as loading controls. Analysis of the data was via the $2^{-\Delta\Delta Ct}$ method (table 1).

Western blot

This skill contains fractionation of proteins on SDS -PAGE, electroblot onto PVDF membranes (Thermofisher, USA), and then incubation with anti-SEC61A1 (Abcam, USA) [21]. The Bio-Rad imaging equipment (BioRad, USA) was used to image the protein bands, and Quantity One v4.6.2 software was used to analyze the protein bands' gray values. As a loading control, GAPDH (Abcam, USA) was used.

Table 1. Genes primers.

name	5'– 3' sequences
MiR-18a-5p	F: GATAGCAGCACAGAAATATTGGC
	R: TGGTGTCGTGGAGTCG
SEC61A1	F: GATTGT CCCCAAGTGTCCAT
	R: TGTTTGTGCTTCCAACCAGA
Bax	F: GATCGAGCAGGGCGAATG
	R: CATCTCAGCTGCCACTCG
Bcl-2	F: ATCCAGGACAACGGAGGCTG
	R: CAGATAGGCACCCAGGGTGA
U6	F: CTCGCTTCGGCAGCACA
	R: AACGCTTCACGAATTTGCGT
GAPDH	F: CGGAGTCAACGGATTTGGTCGTAT
	R: AGCCTTCTCCATGGTGGTGAAGAC

Cell proliferation with the cell counting kit-8 (CCK-8)

Onto 96-well plates, logarithmic phase cells were planted (1×10^3 cells/well) and cultivated for 0, 12, 24, and 48 hours with CCK-8 (Dojindo, Japan) reagent (1/10 of the total volume). A microplate reader was used to measure the density of each well at 450 nm.

Plate cloning

Six hundred cells per well of 6-well plates were seeded with logarithmic phase cells until the cell copied was visible in the culture dish. Meanwhile the cells were fixed after adding 5 mL of acid/methanol (1:3), and counting of more than 50 cloned cells was under a low magnification microscope after staining with appropriate amount of Giemsa stain (MCE, USA).

Flow cytometry for cell apoptosis

The FACSCalibur flow cytometer and Annexin V-FITC/PI Kit were utilized to measure the alterations in apoptosis (C1062M, Beyotime, China). To summarize, transfected ESCC cells were collected, twice washed in PBS, and then resuspended in PBS at a density of 105 cells/mL. Annexin V, tagged with FITC, and PI were then added, and the mixture was cultivated for 15 minutes without exposure to light. Finally, FACSCalibur flow cytometer was used to analyze the apoptosis of ESCC cells in each group.

Plate scratch for cell migration

The detection of the cell migratory capacity was via scratch test. The culture of HepG2 cells (5×10^5/mL) was in 12-well plates. Then, the scratch of traumatic surface was on the plate with a pipette tip (200 μL) to determine the size of the traumatic surface, which was then photographed with a microscope to contrast with cell motility. Inverted optical microscope CKX41 (Olympus Corporation) was for image acquisition.

Transwell assay for cell invasion

Matrigel gel (BD, USA) was mixed with a serum-free solution and extended to the Transwell

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chambers' upper compartment surface. Meanwhile, seeding of the cells was into the base of Tanswell chambers in a gel-like manner, and then the culture of Transwell chambers was in well plate's containing 10% FBS medium. After 48 h, the Transwell chambers were removed, and the cells inside the chambers and the residual Matrigel gel were wiped, paraformaldehyde was fixed on the cells passing through the bottom back of the chambers, crystal violet was stained, and the cells were counted via microscopy and analyzed for graphs.

The luciferase activity assay

The steps were referred to a former study. The association of miR-18a-5p and SEC61A1 has been clarified. The pmirGLO vector was constructed with the 3′ UTR of the Wt or Mut SEC61A1 mRNA in order to create vectors. Subsequently, the HCC cell line was transfected together with the plasmid vector and miR-18a-5p or NC mimics. A luciferase assay method was used to measure the cells' luciferase activity after twenty-four hours [22].

Statistical analysis

All the information was processed through the statistical software SPSS 21.0. A t-test was utilized for assessing the HCC and normal tissues, whilst an independent sample t test was employed to contrast the other groups. The groups were compared collectively using a one-way ANOVA. After the ANOVA analysis the Tukey's post hoc test was run. The Bonferroni post hoc test and repeated measurement of ANOVA were used to assess the results across groups at various time periods. In clinical samples, miR-18a-5p's Pearson correlation analysis revealed a connection with SEC61A1. The measurement information was presented as mean ±SD. P<0.05 was regarded as a sign of significant differences.

RESULTS

MiR-18a-5p is silenced and correlates with prognosis in HCC

MiR-18a-5p was determined, testifying the decline in HCC (figure 1A, B). Among them, the most dramatical decline was in the HepG2 cell line, so the selection of HepG2 cell line was for the follow-up experiment. Furthermore, the association of miR-18a-5p was manifested with vascular infiltration, tumor node metastasis (TNM) stage, tumor size and number via analyzing clinicopathological information tables (table 2), and elevation of miR-18a-5p had a higher survival prognosis rate (figure 1C).

Augmentation of miR-18a-5p suppresses HCC cell progression

After miR-18a-5p was knock-downed, its impact on the progress of HCC cells was investigated. The effects on HepG2 cells following treatment with NC or miR-18a-5p mimic, or inhibitor were time-dependent (figure 2A); It indicated that raising miR-18a-5p accelerated Bax, inhibited Bcl-2, and retarded the development of HCC cells (figure 2B-G). Conversely, every outcome on miR-18a-5p's silencing was positive.

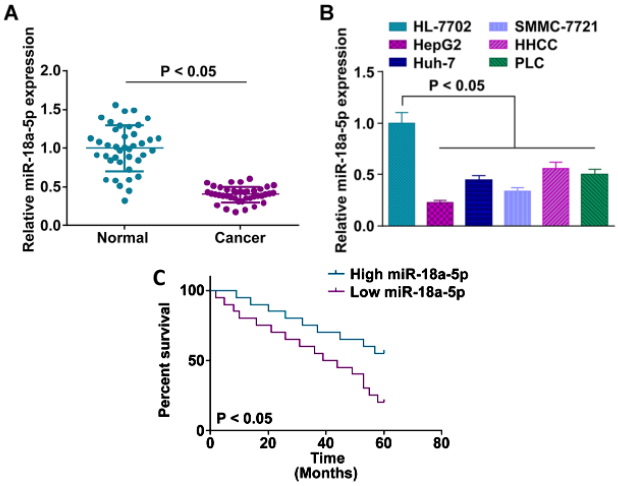


Figure 1. Silence of miR-18a-5p is in hepatocellular carcinoma tissues or cells. **A;** qRT-PCR was utilized to assess miR-18a-5p in HCC or normal tissues. **B;** qRT-PCR was utilized for investigating miR-18a-5p in HCC along with normal cells. **C;** A survival prognosis curve was created for groups. The figures contained measurement data. (n = 3), P<0.05.

Table 2. Demographic characteristics and clinicopathological features of patients with HCC (n = 40).

Parameter	Case	MiR-18a-5p expression		*P*
		Low (n = 20)	High (n = 20)	
Age (y)				0.5273
50 or less	21	12	9	
50 or more	19	8	11	
Gender				0.3406
Male	22	9	13	
Female	18	11	7	
Vascular invasion				0.3406
No	17	4	13	
Yes	23	16	7	
TNM Stage				0.0038
I + II	20	5	15	
III	20	15	5	
Tumor size (cm)				0.0002
5 or less	16	2	14	
5 or more	24	18	6	
Tumor number				0.0079
Single	25	8	17	
Multiple	15	12	3	

MiR-18a-5p targets SEC61A1

The detection of SEC61A1 in HCC tissues and cells manifested the elevation versus normal tissues (figure 3A, B). A speculation that miR-18a-5p had a targeting with SEC61A1 was manifested. The association of miR-18a-5p with SEC61A1 in clinical samples was analyzed adopting Pearson test, which testified a negative correlation between them (figure 3C). For further validation, the prediction of targeting

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binding site of miR-18a-5p with SEC61A1 was via starBase, while the targeting between them was verified (figure 3D, E). Next SEC61A1 expression in HCC cells was examined in the back of regulation of miR-18a-5p, detecting that elevation or silence of miR -18a-5p could restrain or facilitate SEC61A1 in HepG2 cells (figure 3F).

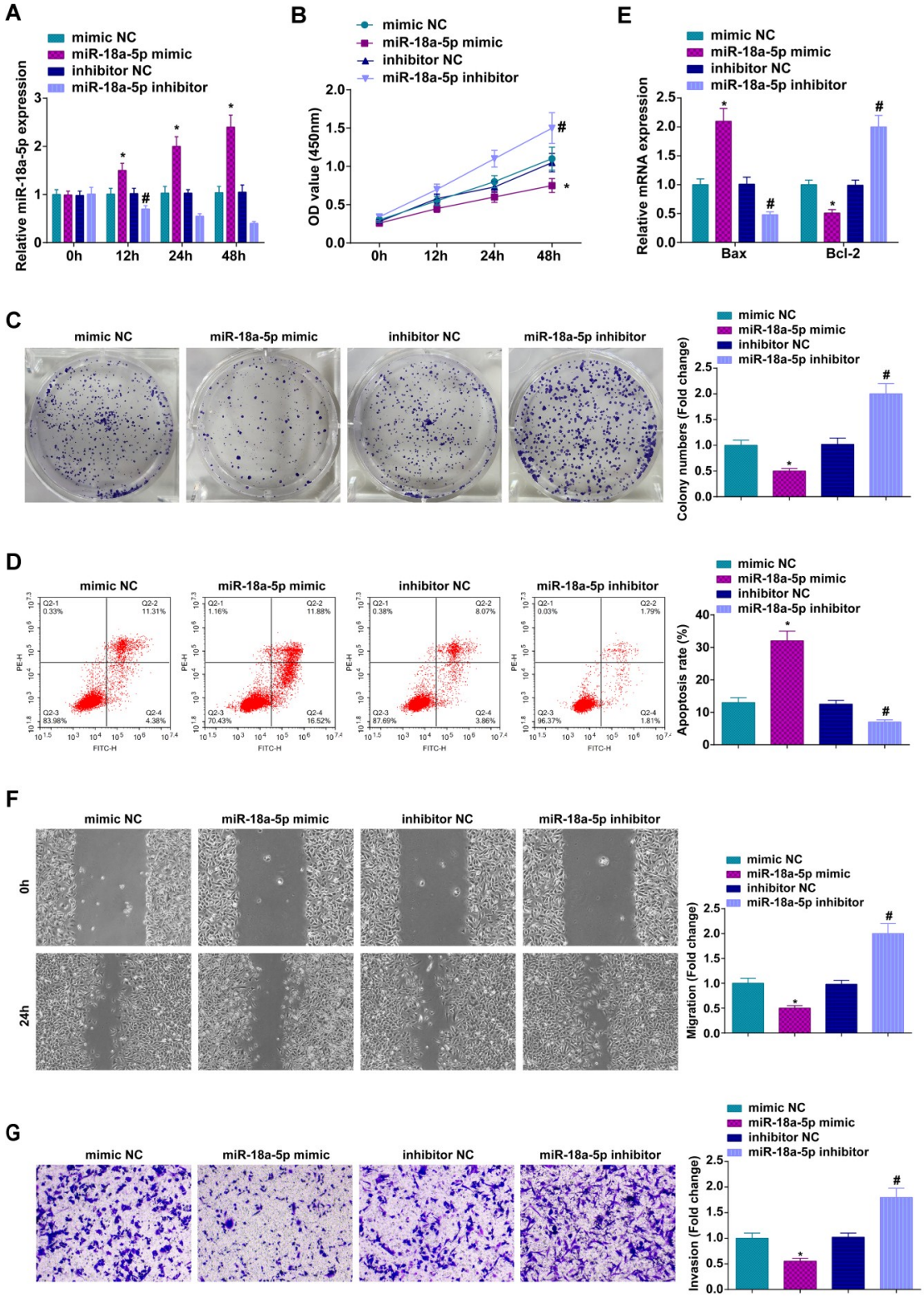


Figure 2. Elevation of miR-18a-5p suppresses hepatocellular carcinoma development. **A;** After treatment in HCC, RT-qPCR was executed to detect miR-18a-5p. **B;** The CCK-8 assay looked at the proliferation of HepG2 cells in various groups. **C;** The plate cloning assay tracked the proliferation of HepG2 cells in various groups. **D;** The flow cytometry assay looked at the apoptosis of HepG2 cells in various groups. **E;** Bax and the expression of Bcl-2 was found by RT-qPCR in several groups. **F;** HepG2 cell movement was identified in several groups using plate scratching. **G;** HepG2 cell invasion was identified in various groups using the Transwell assay. P<0.05 * vs the NC mimic; # vs the NC inhibitor.

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Decline of SEC61A1 represses HCC cell progression

Moreover, increased miR-18a-5p may inhibit HCC cells' ability to operate biologically, and it may also target SEC61A1, but it was not clear how SEC61A1 regulated HCC cells, thus the successful transfection of si-SEC61A1 and NC and oe-SEC61A1 and NC was verified into HepG2 cells (figure 4A). The results of each experiment testified that silence of SEC61A1 could restrain HepG2 cell development, which was accelerated via elevated SEC61A1 (figure 4B-G). In short, decline of SEC61A1 suppressed HCC cell growth.

Acceleration of SEC61A1 reverses the repression of augmented miR-18a-5p on cellular processes of HCC

To verify that miR-18a-5p targeted SEC61A1 to suppress HCC development, the transfection of miR-18a-5p mimic, oe-SEC61A1 and oe-NC was successfully into HepG2 cells (figure 5A). After augmentation of SEC61A1, CCK-8 assay and the plate cloning assay showed that the HepG2 cell proliferation was increased (figure 5B-C); flow cytometry and *Bax* and *Bcl-2* level alterations indicated that a decrease in apoptosis (figure 5D-E); Increased cell invasion and migration were found using the Transwell test and plate scratching (figure 5F-G).

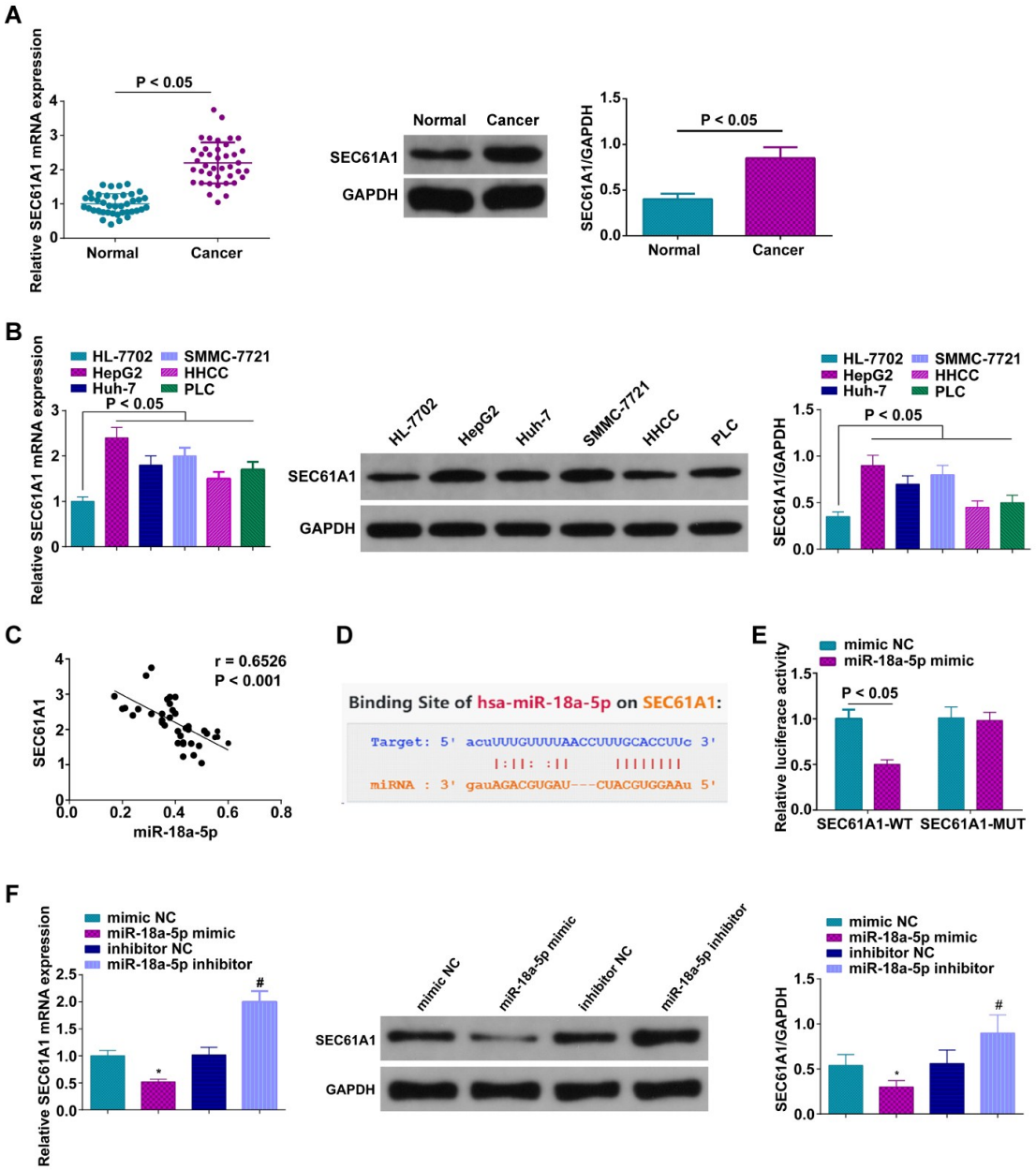


Figure 3. MiR-18a-5p has a targeting relationship with SEC61A1. **A;** Via RT-qPCR and Western blot to test SEC61A1 in HCC and normal tissues. **B;** Via RT-qPCR and Western blot to test SEC61A1 in HCC cells along with normal hepatocyte line. **C;** The connection of SEC61A1 and miR-18a-5p. **D;** targeting sites between SEC61A1 and miR-18a-5p. **E;** Luciferase reporter assay to test a targeting association. **F;** RT-qPCR and Western blot to detect SEC61A1 in HepG2 cells after treatment with miR-18a-5p mimic, mimic NC. P<0.05, * vs the mimic NC; # vs the inhibitor NC.

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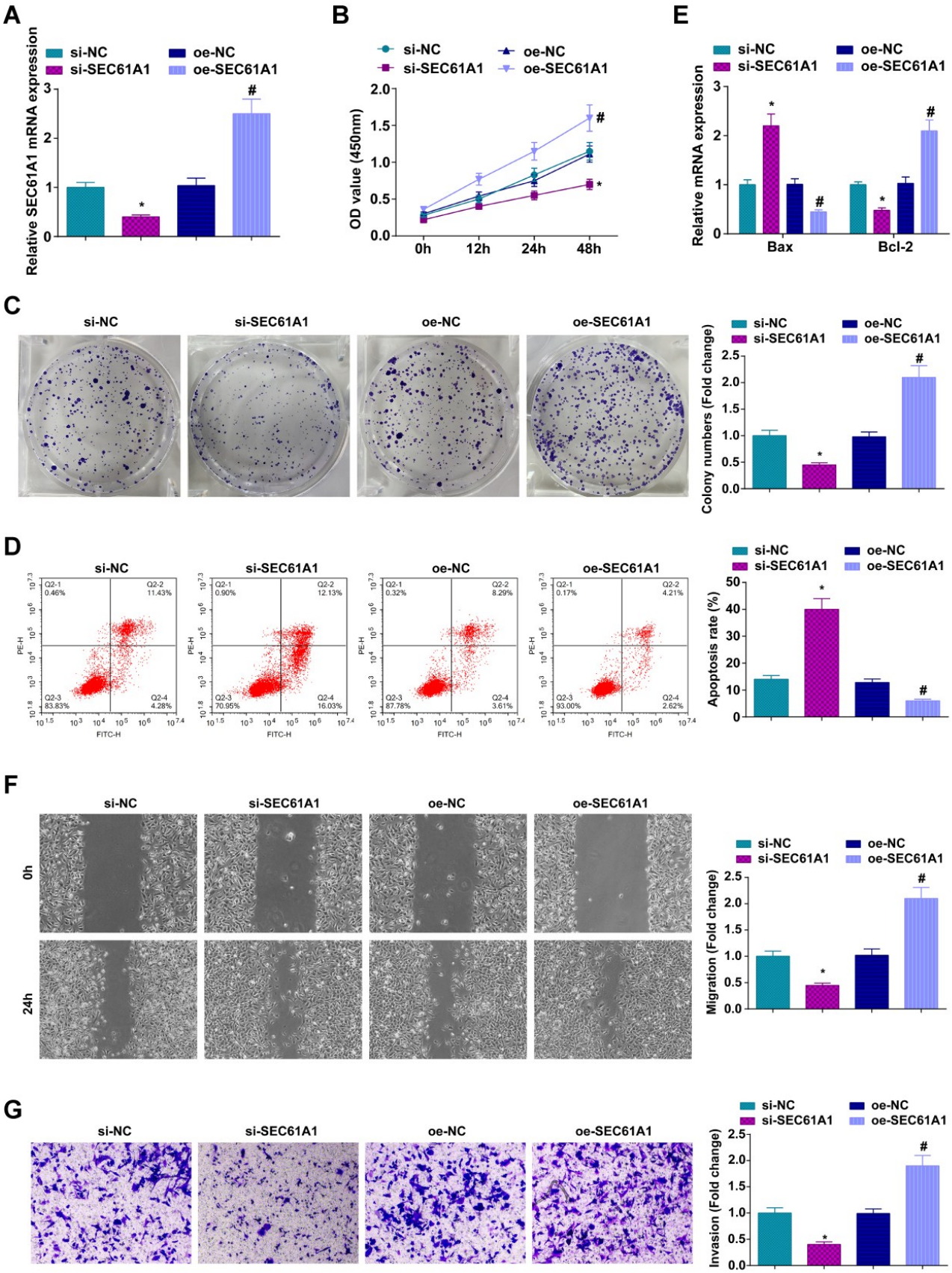


Figure 4. Silence of SEC61A1 represses progression of HCC cells. **A;** RT-qPCR detected SEC61A1 in HCC cells after treatment of si-NC, si-SEC61A1, oe-NC and oe-SEC61A1. **B;** HepG2 cell proliferation in various groups was assessed using the CCK-8 assay. **C;** HepG2 cell proliferation in various groups was observed using the Plate Cloning Assay. **D;** HepG2 cell apoptosis was identified by flow cytometry in various groups. **E;** Bax and Bcl-2 expression was identified by RT-qPCR in various groups. **F;** HepG2 cell movement was identified by plate scratching in various groups. **G;** HepG2 cell invasion was detected in several groups using the Transwell test. (n = 3), * vs the si-NC group, $P < 0.05$; # vs the oe-NC, $P < 0.05$.

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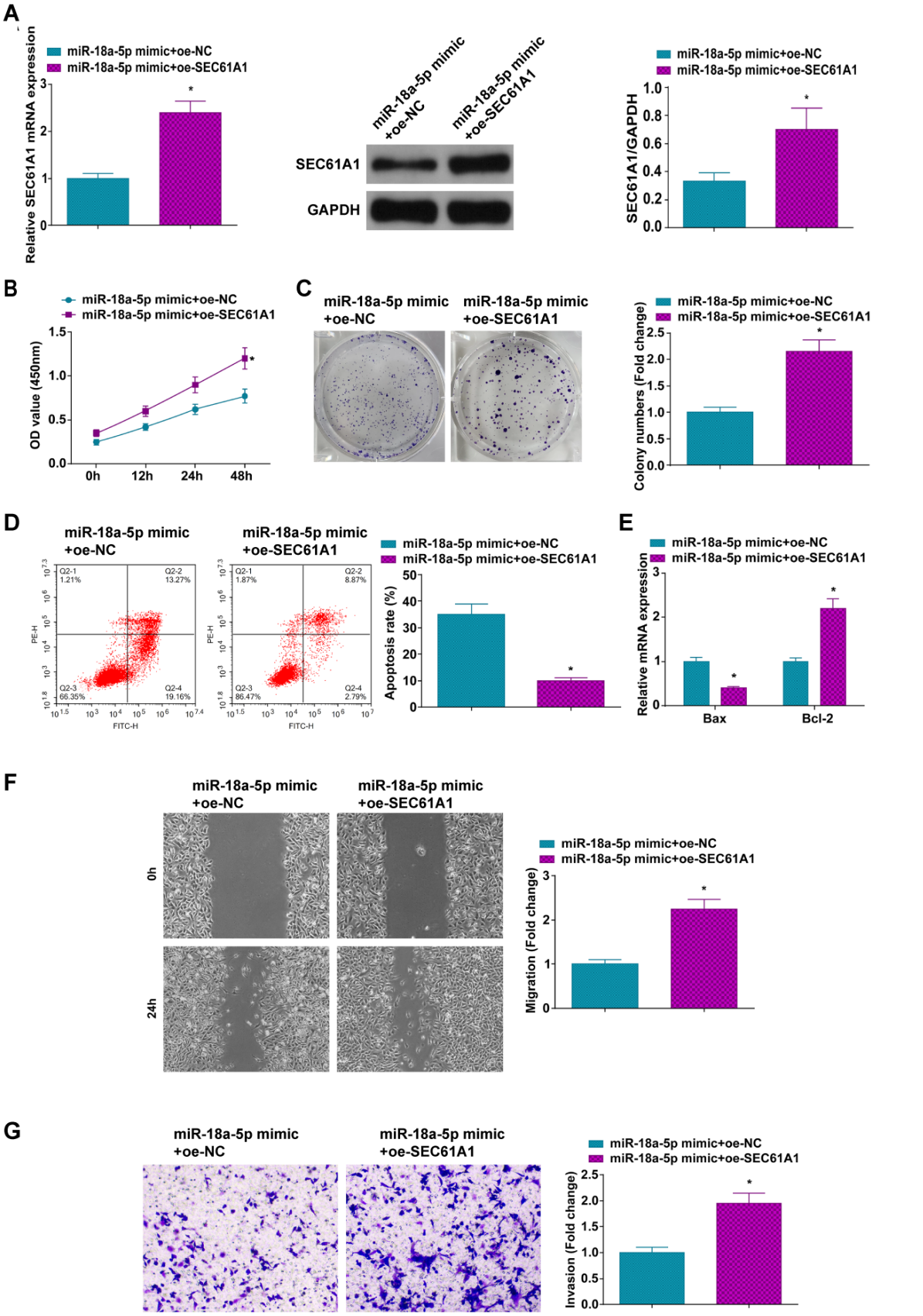


Figure 5. Elevation of SEC61A1 reverses the suppression of increased miR-18a-5p on biological functions. **A;** Western blot along with RT-qPCR were used to evaluate SEC61A in HCC cells following treatment. **B;** HepG2 cell proliferation was tested in various groups using the CCK-8 assay. **C;** HepG2 cell proliferation was seen in various groups using the plate cloning assay. **D;** HepG2 cell apoptosis was identified in various groups using flow cytometry. **E;** RT-qPCR identified Bax and Bcl-2 in distinct groups. **F;** Plate scratching revealed HepG2 cell movement in various groups. **G;** Transwell assay identified HepG2 cell invasion in distinct groups. (n=3), * vs the miR-18a-5p mimic + oe-NC, P<0.05.

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DISCUSSION

HCC is the third most prevalent cause of cancer-related fatalities and the fifth most common cancer globally, and its frequency is continually rising [23]. Therefore, it is important to explore the pathogenesis of hepatocellular carcinoma. MiRNA exerts critical influence on cell biology, affecting cell development process via regulating many genes [24-29]. MiRNA manifests dynamic shift at different phases of cell development. The augmented miRNA exerts specific functions at certain periods [30]. Greatly different miRNA in normal and tumor tissues could reflect the developmental differentiation of tumors [31, 32], then how to regulate miRNA becomes a new research direction for tumor therapy.

The current literature has confirmed that miR-18a -5p is raised and it can adversely regulate CPEB3, which can accelerate the deterioration of HCC cells. Besides, silence of miR-18a-5p suppresses tumor growth in ovarian cancer [33]. Meanwhile, our results documented that increased levels of miR-18a-5p inhibited the level of proliferation, functioning as an oncogenic factor to prevent HCC from progressing further.

MiR-18a-5p was combination with downstream targeting protein mRNA to affect cell biological functions. The exploration of molecular mechanism of miR-18a-5p was in modulating cell biological functions. The results were testified that it was available to target SEC61A1, which led to decline of HCC cell growth. SEC61A1 encoding the alpha subunit of the heterotrimeric Sec61 complex, is a major sector of the human translocator. This structure is in charge of proteins translocating and integrating into the endoplasmic reticulum membrane. What's more, Sec61 channels is conducive to cellular calcium homeostasis. The Sec61 channel disease covers family of genetic or acquired diseases that exert an impact on Sec61 subunits. The association of Sec61 function is with a wide range of related diseases involving autosomal dominant polycystic hepatocellular disease (SEC63 [15], SEC61B [16]) and diabetes mellitus (DNAJC3 [17]). Lately, it has been indicated that elevation of SEC61A1 in colon cancer accelerates cell development in colon adenocarcinoma]. Furthermore, elevation of SEC61A1 in NPC and HCC boosts cancer cell development. In the study, declined SEC61A1 accelerated Bax and suppressed Bcl-2, leading to diminished malignant growth functions. MiR-18a-5p and SEC61A1 were expected to be new potential therapeutic targets for HCC. Appropriate in vivo tumor studies were not able to be carried out in order to learn more about the signaling of the miR-18a-5p/SEC61A1 signal in solid HCC due to time and financial constraints. Moreover, it was predicted and confirmed that miR-18a-5p would target SEC61A1. One of the research's weaknesses was that other miR-18a-5p downstream targeting genes were not included.

CONCLUSION

MiR-18a-5p by specifically targeting SEC61A1 reduced HCC cell growth. Finding new targeted therapeutics for HCC and extending the potential mechanism of miR-18a-5p in HCC will be made possible by this study. Further research is still needed to fully understand the regulatory networks of SEC61A1 and miR-18a-5p in signal transduction during the progression of HCC.

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***Competing interests*:** The authors have no conflicts of interest to declare.

***Availability of data and materials*:** The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

***Ethical approval*:** All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All subjects was approved by Ningbo Yinzhou No.2 Hospital (201504901A).

***Author contribution*:** Q-L.W., conceived and designed the experiments. Q.C., and M-M.W., contributed significantly to the experiments and arranging data. X-K.M., performed data analyses. Q.C., wrote the draft manuscript. Q-L.W. revised the manuscript. All authors read and approved the final manuscript.

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