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Original Paper

MicroRNA-361-5p Inhibits Cancer Cell Growth by Targeting CXCR6 in Hepatocellular Carcinoma

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Key Words
CXCR6 • MiRNA-361-5p • Hepatocellular carcinoma • Tumor suppressor

Abstract
Background/Aims: A growing body of evidence supports the notion that MicroRNAs (miRNAs) function as key regulators of tumorigenesis. In the present study, the expression and roles of miRNA-361-5p were explored in hepatocellular carcinoma (HCC). ***Methods:*** Quantitative real-time PCR was used to detect the expression miR-361-5p in HCC tissues and pair-matched adjacent normal tissues. MTT and BrdU assays were used to identify the role of miR-361-5p in the regulation of proliferation and invasion of HCC cells. Using bioinformatics analysis, luciferase reporter assays and Western blots were used to identify the molecular target of miR-361-5p. nude mice were used to detect the anti-tumor role of miR-361-5p *in vivo*. ***Results:*** miR-361-5p was down-regulated in HCC tissues in comparison to adjacent normal tissues, due to hypermethylation at its promoter region. Overexpression of miR-361-5p suppressed proliferation and invasion of HCC cells. Chemokine (C-X-C Motif) receptor 6 (CXCR6) was identified as a target of miR-361-5p. Indeed, knockdown of CXCR6 photocopied, while overexpression of CXCR6 largely attenuated the anti-proliferative effect of miR-361-5p. More importantly, *in vivo* studies demonstrated that forced expression of miR-361-5p significantly inhibited tumor growth in the nude mice. ***Conclusion:*** Our results indicate that miR-361-5p acts as a tumor suppressor and might serve as a novel therapeutic target for the treatment of HCC patients.

Introduction

Hepatocellular carcinoma (HCC), which accounts for 70% – 85% of primary liver cancer cases [1], has become one of the most common malignancies and a leading cause of cancer-related death worldwide [2]. Environmental and genetic risk factors for HCC include chronic

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infection with hepatitis B or C virus, excessive alcohol consumption, obesity, hepatosteatosis and hereditary hemochromatosis [2]. Recent studies have shown that abnormal expression of oncogenes or tumor suppressors, and dysregulation of signaling pathways play key roles in the development of HCC [3-5]. Therefore, understanding the potential mechanisms underlying HCC initiation and/or progression might provide novel and effective therapeutic strategies.

MicroRNAs (miRNAs), a class of small non-coding RNAs, function as critical gene regulators in cancer development via suppressing the expression of target genes by translational inhibition or destabilization of messenger RNAs (mRNAs) [6, 7]. For instance, several miRNAs were deregulated in HCC tissues and found to get involved in various cellular processes, such as cell proliferation, apoptosis, invasion, metastasis and angiogenesis[8-12].

In this study, we found that expression level of miR-361-5p was significantly decreased in human HCC tissues. *In vitro* and *in vivo* studies further demonstrated that miR-361-5p inhibited cell proliferation and growth by directly targeting CXCR6. Altogether, our data suggest that miR-361-5p may serve as a crucial tumor suppressor and is associated with HCC progression.

Materials and Methods

Clinical specimens

30 pairs of human HCC samples and matched adjacent non-tumorous tissues were collected from the surgical specimen archives in our department. All human samples were obtained with informed consent. This study was approved by the Ethical Review Committee of Henan Provincial People's Hospital, 7 Weiwu Road, Zhengzhou, Henan, China.

Cell Culture

The HCC cells (HepG2 and Hep3B) were purchased from The Cell Bank of Type Culture Collection of Chinese Academy of Sciences (CAS, Shanghai, China). Cells were maintained at 37°C in an atmosphere of 5% CO_2 in DMEM medium (Gibco, Shanghai), supplemented with 10% fetal bovine serum, penicillin (100 IU/ml) and streptomycin (100 mg/ml) (Gibco). MiR-361-5p mimics and antisense oligos were purchased from Ambion Company (CA, USA). Non-targeting control mimics (5'-CAG GUC AUA GGC AUA CCGU-3', Cat No.4464058, Ambion Company) or an inhibitor (5'-ACC UUA GCA GGA UUA CUAG-3', Cat No. 4464077, Ambion Company) was employed as negative controls.

Cell Viability and Proliferation Analysis

The cell viability was determined by assaying the reduction of 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) to formazan. For BrdU analysis, a cell proliferation enzyme-linked immunosorbent assay (BrdU kit; Beyotime, Shanghai) was used to analyze the incorporation of BrdU during DNA synthesis following the manufacturer's protocols.

RNA extraction AND Real-time Quantitative PCR

Total RNA was extracted using the miRNA Isolation Kit (Ambion, Grand Island, NY, USA) according to the manufacturer's instructions. Expression levels of miR-361-5p were measured using Taqman MicroRNA Assays (Applied Biosystems, Shanghai, China). Quantitative real-time PCR was performed by using an Applied Biosystems 7300 Real-time PCR System and a TaqMan Universal PCR Master Mix (Applied Biosystems). Expression of miR-361-5p (5'-AAT AGT CTT AGA GGT CCC CATG-3') was normalized to that of the U6 snRNA (5'-GAC CTT AGC AAT AGC ATT GGCA-3').

Western Blots

Protein extracts were equally loaded onto 10% SDS polyacrylamide gels, electrophoresed, and transferred to nitro cellulose membranes (Amersham Bioscience). After blocking with 5% non-fat milk in PBS, the membranes were probed with antibodies against CXCR6 (ab8023, rabbit polyclonal antibody) (Abcam, Cambridge, Massachusetts, USA) and β-actin (sc-47778, mouse monoclonal antibody) (Santa Cruz

Company), followed by horseradish peroxidase-conjugated secondary antibodies (Santa Cruz Company). The signals were detected by chemiluminescent substrate kit (Millipore Company, Bedford, MA, USA).

Luciferase Reporter Assays

The 3'-untranslated region of human CXCR6 gene (NCBI gene ID: 10663) from +1141 bp to +1920 bp was amplified by RT-PCR using primers as follows: Forward: 5'- GAA TTT GCA AGT CAT GGC TGT-3', Reverse: 5'-ATT ACT AGC ATA TGA GTT TCATA-3'. The mutant construct was also generated by replacing the 3'-UTR with custom made synthetic whole 3'-UTR DNAs with mismatched seed region mutations. Renilla and firefly luciferase activities were measured by the Dual-Luciferase Reporter system (Promega, Madison, USA). All the transient transfections were performed using Lipofectamine 2000 (Invitrogen, Carlsbad, USA), according to the manufacturer's instructions.

MeDIP-qPCR assays

5 mg of genomic DNA from HCC or normal tissues was fragmented to a size of 200 - 500 bp using a Covaris machine and immunoprecipitated with 5mC antibodies (Eurogentec, Liege, Belgium). Immunoprecipitated DNA was recovered with proteinase K digestion followed by column based-purification (DNA wizard, Promega, Fitchburg, WI). Recovered DNA fractions were diluted 1:100 and measured by quantitative real-time PCR using an ABI PRISM 7000 sequence detector system (Applied Biosystems, Carlsbad, CA, USA). Regions of miR-361-5p promoter were amplified using primers listed as follows: Forward: 5'-AGC CAT TGA CTA GCC ATTCC-3', Reverse: 5'-GCC TTA GCA TGA CGC CATGT-3'.

Mouse Experiments

Male BALB/c nude mice aged 5 weeks were purchased from Shanghai Laboratory Animal Company (SLAC, Shanghai). 5.0 x 10^6 HepG2 cells stably expressing miR-361-5p mimics or negative control were injected subcutaneously to the skin under the front legs of the nude mice. The mice were observed over 4 weeks for tumor formation. Mice were then sacrificed and the wet weights of each tumor were determined.

Statistical Analysis

The data shown represent the mean ± standard error (SE) values of at least three independent experiments. Comparisons between groups were analyzed by the t-test and X^2 test. A value of $P < 0.05$ was considered statistically significant.

Results

Down-regulation of miR-361-5p in HCC tissues

To investigate the role of miR-361-5p in the pathogenesis of HCC, its expression levels were analyzed by quantitative real-time PCR in HCC tissues and pair-matched adjacent normal tissues. As shown in the Fig. 1A, miR-361-5p was significantly down-regulated in cancer tissues (Fig. 1A). Previous studies have shown that the aberrant expression of miRNAs in human HCC may be regulated by DNA methylation alterations [13, 14]. We therefore dissected the DNA methylation patterns in the 5'-regulatory regions of miR-361-5p. By methylated DNA immunoprecitation followed by quantitative PCR analysis (MeDIP-qPCR), we found that the captured methylation at the miR-361-5p promoter was enhanced in HCC tissues (Fig. 1B). Besides, administration of 5-aza-cytidine (5-AZA), an inhibitor of DNA methylation, significantly increased the expression of miR-361-5p in HepG2 and Hep3B cells (Fig. 1C and 1D). Thus, our results indicate that down-regulation of miR-361-5p in HCC tissues, at least in part, due to epigenetic mechanisms involving DNA methylation.

miR-361-5p inhibits cancer cell proliferation and growth

Next, we set out to evaluate the biological function of miR-361-5p in HCC progression. miR-361-5p mimics, antisense or negative control (NC) were transfected into HepG2 cells, followed by MTT and BrdU incorporation assays. As a result, miR-361-5p overexpression reduced (Fig. 2A-2B), whereas silencing miR-361-5p expression promoted the growth rates

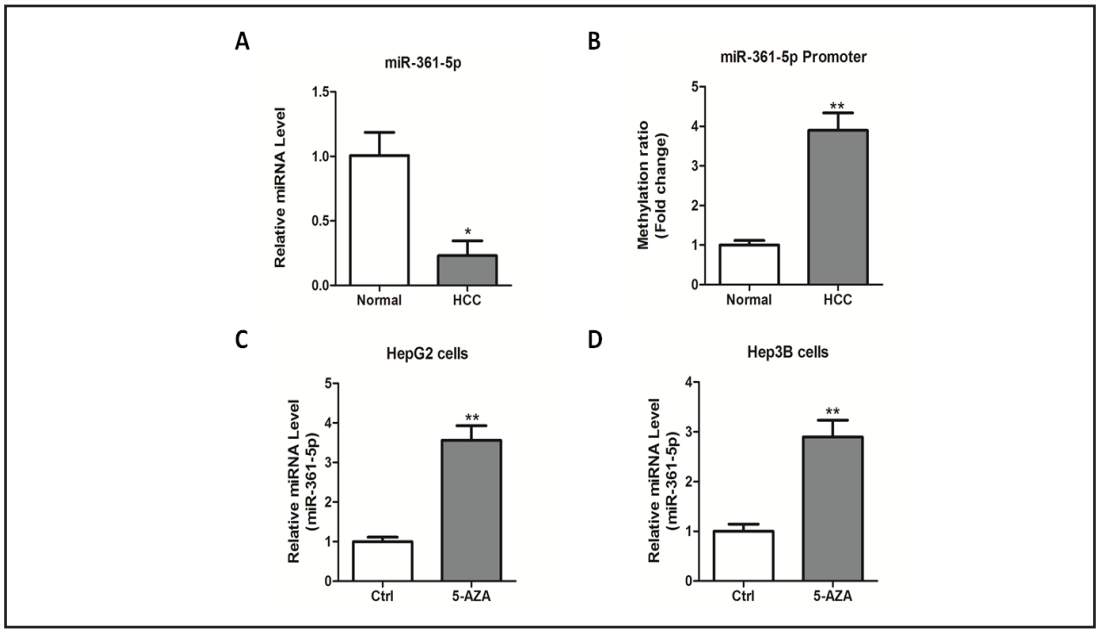

Fig. 1. Expression levels of miR-361-5p in HCC tissues. (A) miR-361-5p expression was determined by quantitative real-time PCR in human HCC tissues and adjacent noncancerous tissues (Normal). n = 30. (B) Promoter-specific methylation levels. Methylated DNA in miR-361-5p promoter was immunoprecipitated and followed by quantitative PCR analysis (MeDIP-qPCR). The ratio of methylated DNA levels in HCC and normal tissues is presented. n = 10. (C-D) Relative expression levels of miR-361-5p in HepG2 and Hep3B cells after 30 hr treatment with 5-AZA or vehicle control (Ctrl). The data represent the mean ± standard error (SE) values of four independent experiments. * $P < 0.05$, ** $P < 0.01$ between two groups.

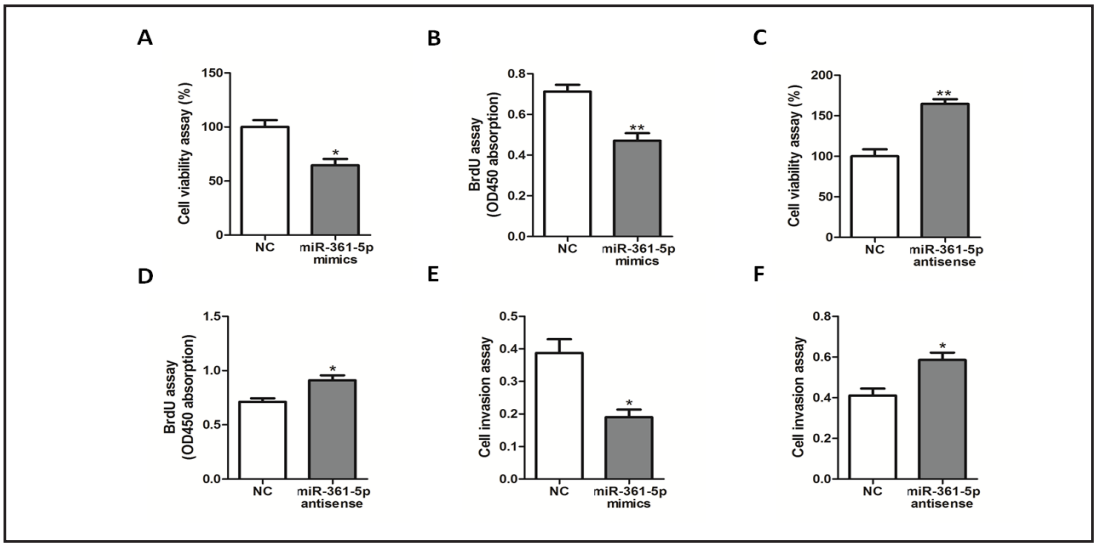

Fig. 2. miR-361-5p inhibits cell proliferation, migration and invasion. (A-B) The cell viability (A) and proliferative potential (B) were determined in HepG2 cells transfected with miR-361-5p mimics or negative control (NC). (C-D) The cell viability (C) and proliferative potential (D) were determined in HepG2 cells transfected with miR-361-5p antisense or negative control (NC). (E-F) The cell invasion abilities were determined in HepG2 cells transfected with miR-361-5p mimics (E), antisense (F) or negative control (NC). * $P < 0.05$, ** $P < 0.01$ between two groups. All the data represent the mean ± standard error (SE) values of four independent experiments.

and proliferation in both cells (Fig. 2C-2D). Moreover, cell invasion ability was also inhibited or enhanced by miR-361-5p mimics or antisense, respectively (Fig. 2E-2F). Similar results

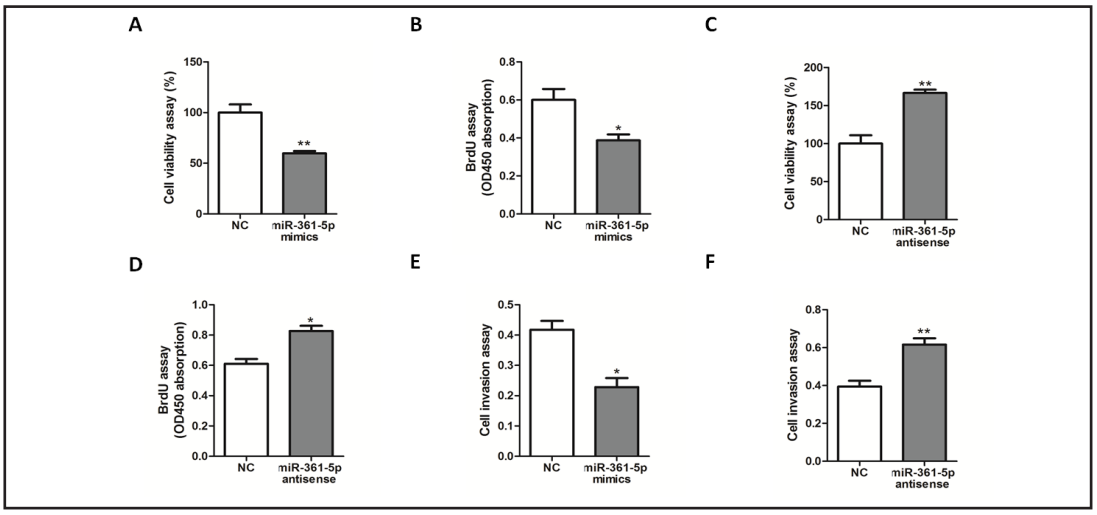

Fig. 3. miR-361-5p inhibits cells proliferation, migration and invasion in Hep3B cells. (A-B) The cell viability (A) and proliferative potential (B) were determined in Hep3B cells transfected with miR-361-5p mimics or negative control (NC). (C-D) The cell viability (C) and proliferative potential (D) were determined in Hep3B cells transfected with miR-361-5p antisense or negative control (NC). (E-F) The cell invasion abilities were determined in Hep3B cells transfected with miR-361-5p mimics (E), antisense (F) or negative control (NC). * $P < 0.05$, ** $P < 0.01$ between two groups. All the data represent the mean ± standard error (SE) values of four independent experiments.

were also observed in Hep3B cells (Fig. 3A-3F), suggesting that miR-361-5p might be a tumor suppressor in HCC.

miR-361-5p inhibits CXCR6 expression by targeting its 3'-UTR

Next, we predicted potential direct targets of miR-361-5p by miRWalk 2.0 programs (http://www.umm.uni-heidelberg.de/apps/zmf/mirwalk/) [15], and found that several genes harbored a potential miR-361-5p binding site (Data not shown). However, only the gene named chemokine (C-X-C Motif) receptor 6 (CXCR6) was reported to be involved in the tumorigenesis (Fig. 4A). Therefore, real-time PCR and western blots analysis were performed to test whether miR-361-5p could regulate CXCR6. As expected, mRNA and protein levels of CXCR6 were reduced in HepG2 cells with miR-361-5p overexpression (Fig. 4B-4C). Moreover, inhibition of miR-361-5p resulted in an increased expression of CXCR6 (Fig. 4D-4E). To verify that CXCR6 is a direct target of miR-361-5p, the full-length 3'-untranslated region (3'-UTR) of CXCR6 gene was cloned into the downstream of the Renilla luciferase gene. As shown in the Fig. 3F, overexpression of miR-361-5p led to a reduction of luciferase activity when the reporter construct contained the wild-type 3'-UTR (Fig. 4F). However, mutation of the miR-361-5p target site abrogated miR-361-5p-mediated reduction in luciferase activity (Fig. 3F).

CXCR6 mediates the tumor-suppressive function of miR-361-5p

To further confirm the functional connection between miR-361-5p and CXCR6, HepG2 cells were transfected with small interfering RNA (siRNA) oligos targeting CXCR6 or negative control (NC), to knockdown endogenous CXCR6 expression (Fig. 5A-5B). As expected, deletion of CXCR6 inhibited cell viability, proliferation and invasion in HepG2 cells (Fig. 5C-5E). On the other hand, overexpression of CXCR6 largely abrogated the anti-proliferative roles of miR-361-5p (Fig. 6A-6D), underlining the specific importance of the CXCR6 for miR-361-5p action in the tumorigenesis.

miR-361-5p suppresses tumor growth in vivo

Finally, to explore the potential tumor suppressing effects of miR-361-5p *in vivo*, HepG2 cells were transfected with lentiviruses containing miR-361-5p mimics or negative control.

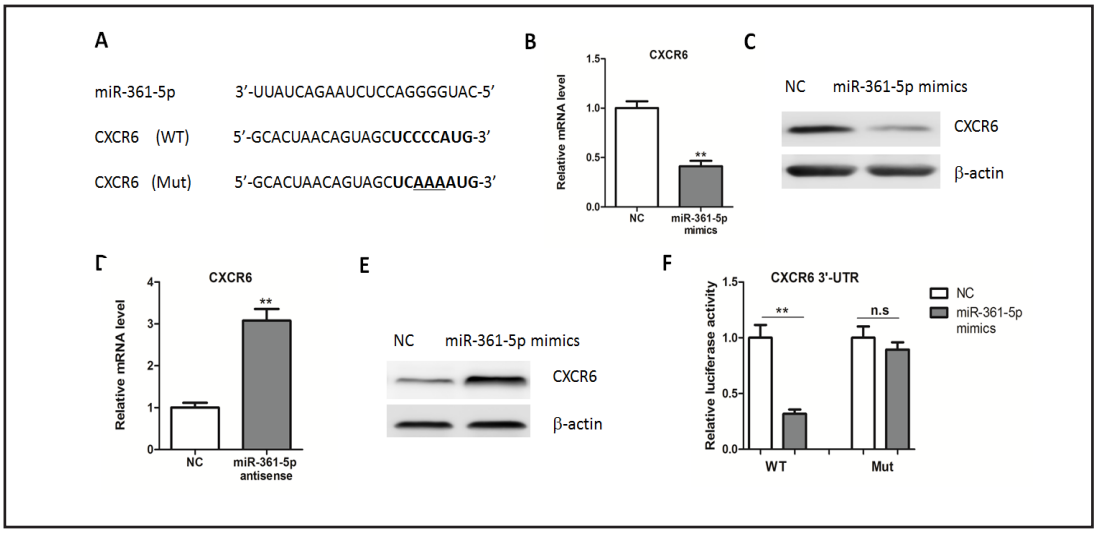

Fig. 4. miR-361-5p negatively regulates CXCR6 expression in HCC cells. (A) Computer prediction of miR-361-5p binding sites in the 3'-UTR of CXCR6 gene. (B-C) Relative mRNA (B) and protein (C) levels of CXCR6 in HepG2 cells transfected with miR-361-5p mimics or negative control (NC). (D-E) Relative mRNA (D) and protein (E) levels of CXCR6 in HepG2 cells transfected with miR-361-5p antisense or negative control (NC). (F) Luciferase reporter assays in HepG2 cells. Cells were transfected with wild-type or mutant 3'-UTR-reporter constructs together with miR-361-5p mimics or negative control (NC). ** $P < 0.01$ between two groups. The data (B, D, F) represent the mean ± standard error (SE) values of three independent experiments.

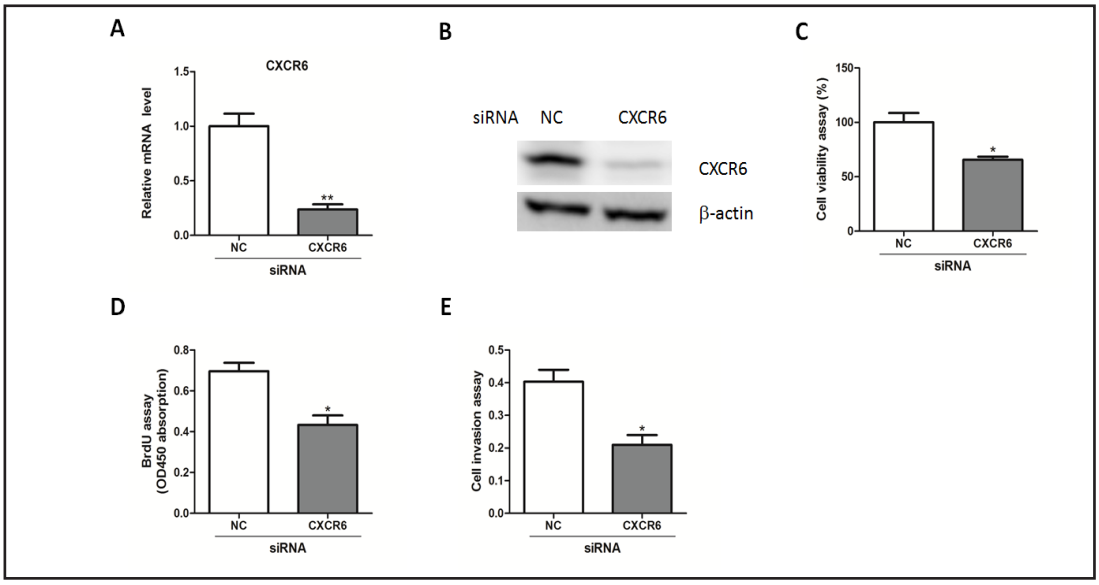

Fig. 5. Knockdown of CXCR6 suppresses HCC cell growth. (A-B) Relative mRNA (A) and protein (B) levels of CXCR6 in HepG2 cells transfected with siRNA oligos targeting CXCR6 or negative control (NC). (C-E) The cell viability (C), proliferation (D) and invasion abilities (E) were determined in HepG2 cells. * $P < 0.05$ between two groups. The data (A, C, D, E) represent the mean ± standard error (SE) values of four independent experiments.

Then these cells were injected subcutaneously to the skin under the front legs of the nude mice. As a result, miR-361-5p overexpression significantly inhibited cancer cell growth in mice, as shown by reduced tumor sizes and weight (Fig. 7A-7B). Consistently, expression levels of CXCR6 were also reduced in tumors by miR-361-5p overexpression (Fig. 7C-7D).

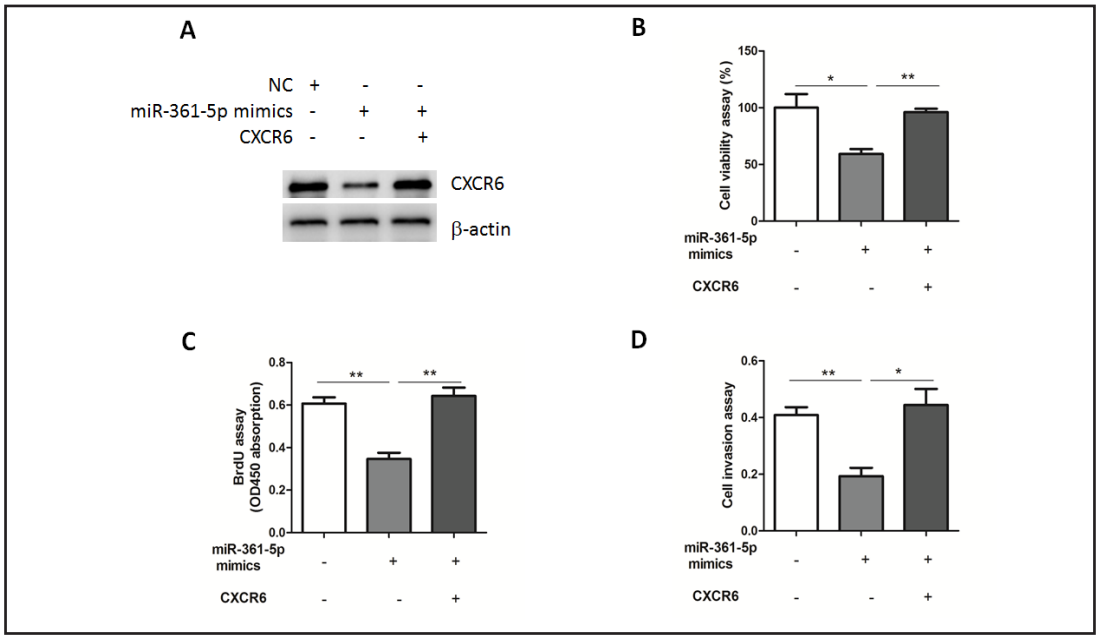

Fig. 6. CXCR6 re-introduction reverses the anti-proliferative roles of miR-361-5p. (A) Representative protein expression of CXCR6 was determined by western blots in HepG2 cells. Cells were pre-transfected with miR-361-5p mimics or negative control (NC) for 24 hr, and then transfected with expression plasmids for CXCR6 or empty vector (EV) for another 30 hr. (B-D) The cell viability (B), proliferation (C) and invasion abilities (D) were determined in HepG2 cells. * $P < 0.05$, ** $P < 0.01$ between two groups. The data (B, C, D) represent the mean ± standard error (SE) values of four independent experiments.

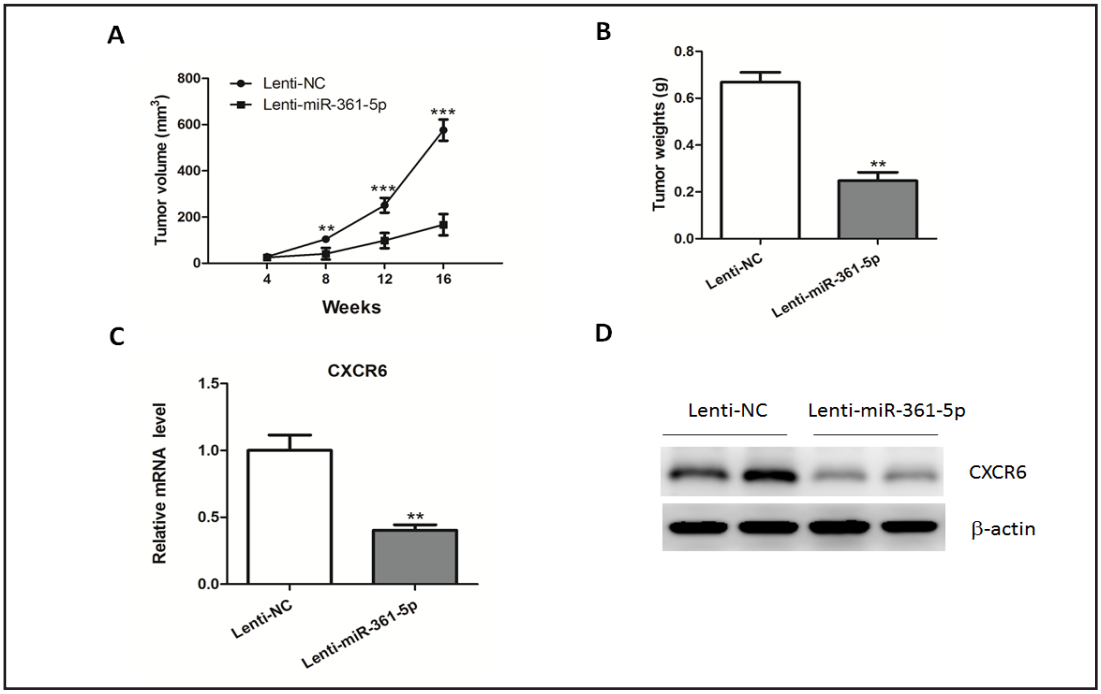

Fig. 7. miR-361-5p inhibits tumor growth *in vivo*. (A-B) HepG2 cells stably transfected with lentviruses containing miR-361-5p mimics or negative control (NC) were injected into nude mice (n=8 for each group) and followed up for tumorigenesis. Growth curve of tumor volumes (A) and tumor weights (B) were taken 4 weeks after injection. (C-D) Relative mRNA (C) and protein (D) levels of CXCR6 in tumors were determined by quantitative real-time PCR and western blots. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ between two groups.

Discussion

Previous studies have shown that miR-361-5p was dys-regulated and played an important role in several types of human cancers. For instance, the expression levels of microRNA-361-5p and its target vascular endothelial growth factor A (VEGFA) were inversely correlated in human cutaneous squamous cell carcinoma [16]. Besides, miR-361-5p was down-regulated and acted as a tumor suppressor in prostate cancer by targeting signal transducer and activator of transcription-6 (STAT6) [17]. Moreover, miR-361-5p was shown to inhibit colorectal and gastric cancer growth and metastasis by targeting staphylococcal nuclease domain containing-1 (SND-1) [18]. However, Wu et al. reported that miR-361-5p could enhance cell proliferation and promote cell invasion in cervical cancer cells through mediation of epithelial-to-mesenchymal transition [19]. Although the reason for this inconsistence remains poorly understood, the roles of miR-361 might be cell- or tissue-specific, which might rely on its down-stream targets.

In the present study, we for the first time, revealed the expression and role of miR-361-5p in the pathogenesis of HCC. We found that miR-361-5p was significantly down-regulated in HCC tissues due to hypermethylation at its promoter region. *In vitro* and *in vivo* studies demonstrated that miR-361-5p inhibited HCC cell proliferation and tumor growth. Mechanistically, CXCR6 was identified as a potential target of miR-361-5p by bioinformatics analysis, luciferase reporter assays and western blots. In addition, the knockdown of CXCR6 phenocopied, whereas restoration of CXCR6 attenuated the anti-proliferative roles of miR-361-5p. Therefore, our results suggest that miR-361-5p might be a novel agent for the treatment of patients with HCC. However, further studies are still needed to explore the relationship between miR-361-5p expression and clinical characteristic and prognosis of patients with HCC.

It has been shown that CXCR6 and its natural ligand CXCL16 were highly expressed in many types of human cancers, including papillary thyroid carcinoma, non-small cell lung carcinoma, gastric cancer and HCC [20-24]. Consequently, up-regulation of CXCR6 contributed to a proinflammatory tumor microenvironment that promoted metastasis and poor patient outcomes in HCC [24]. In agreement, knockdown of CXCR6 inhibited HCC cell invasion *in vitro* and inhibited tumorigenicity, neutrophil recruitment, angiogenesis, and metastasis of hepatoma cells *in vivo* [24]. Nevertheless, the molecular basis for the aberrant expression of CXCR6 in human cancers remains uncovered. Therefore, our results indicate that dys-regulated miRNAs might be an important mechanism for the up-regulation of CXCR6 in HCC.

In summary, our data demonstrate that miR-361-5p inhibits HCC cell proliferation, migration and invasion *in vitro* and suppresses tumor growth *in vivo*, and that CXCR6 is a direct target of miR-361-5p. Strategies designed to up-regulate miR-361-5p or down-regulate CXCR6 expression may provide a venue to ameliorate tumor progression in patients with HCC.

Disclosure Statement

None.

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