

Long Noncoding RNA *PART1* Promotes Hepatocellular Carcinoma Progression via Targeting miR-590-3p/*HMGB2* Axis

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Introduction: In East Asia, hepatocellular carcinoma (HCC) is one of the most commonly diagnosed cancer types. Long noncoding RNA (lncRNA) prostate androgen-regulated transcript 1 (*PART1*) was reported to play crucial roles in regulating cancer progression. However, roles and mechanisms of action of *PART1* in hepatocellular carcinoma (HCC) still remain unknown.

Methods: Quantitative real-time polymerase chain reaction (RT-qPCR) method was used to detect the *PART1* expression level in HCC cells. Cell proliferation, colony formation, and transwell invasion assays were performed to investigate the biological roles of *PART1* on HCC cell behaviors. Bioinformatic analysis methods were performed to analyze connections of microRNA-590-3p (miR-590-3p) with *PART1* or high mobility group box 2 (*HMGB2*) in HCC. Moreover, expression levels of *PART1*, miR-590-3p, and *HMGB2* in HCC tissues and normal tissues were analyzed at ENCORI.

Results: *PART1* expression was found to be significantly upregulated in HCC tissues and cells. Functionally, silencing of *PART1* significantly suppressed HCC cell proliferation, colony formation and invasion in vitro, while forcing *PART1* exerts opposite biological effects. Mechanically, miR-590-3p/*HMGB2* axis was downstream target of *PART1*, and silencing of miR-590-3p or forcing of *HMGB2* could rescue the stimulation effects of *PART1* overexpression on HCC cell behaviors.

Discussion: Our results provided evidence that *PART1* serves as oncogenic lncRNA through sponging miR-590-3p to upregulate *HMGB2* expression in HCC.

Keywords: *PART1*, miR-590-3p, *HMGB2*, ceRNA, hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) is the main subtype of liver cancer with a poor prognosis.^{1,2} The infection of hepatitis B virus (HBV) is the main cause for the development of HCC.² The long-term overall survival of HCC remains undesired even with the recent appearance of tumor targeted therapeutic agents.³

Long noncoding RNA (lncRNA) is a type of noncoding RNA with the length of over 200 nucleotides.⁴ The importance of lncRNA in regulating multiple cancer progressions including HCC has been recognized.^{5–7} Hence, investigating acting mechanisms of lncRNAs in HCC could provide novel therapeutic targets for HCC.

PART1, located at chromosome 5q12 60,487,713–60,547,657, is a lncRNA that is firstly identified to be overexpressed in prostate cancer.⁸ Liu et al showed that high *PART1* level was closely correlated with prognosis of laryngeal squamous cell

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carcinoma cancer patients and could be used as prognostic biomarkers and therapeutic targets.⁹ Hu et al revealed *PART1* was overexpressed in bladder cancer, and silencing of *PART1* inhibits cancer cell growth through promoting apoptosis.¹⁰ Recently, Zhu et al investigated the functions of *PART1* in non-small-cell lung cancer and found *PART1* could promote cancer development via regulating Janus kinase and signal transducer and activator of transcription proteins pathway.¹¹ A recent study indicated that *PART1* could be used as a predictor for overall survival and recurrence-free survival of HCC patients.¹² However, biological roles and underlying mechanisms of *PART1* in HCC remain poorly investigated.

High mobility group box 2 (*HMGB2*) is found highly expressed in cancers and functions as an oncogene.^{13–15} For instance, *HMGB2* could regulate gastric cancer progression under the regulation of lncRNA and miRNA.^{13,14} Also, there are several targets for *HMGB2* including *LDHB* and *FBP1* have been found in cancers.¹⁵

This work was conducted to investigate the roles of *PART1* in HCC by analyzing how it influences cancer hallmarks. We also investigate miRNA between *PART1* and *HMGB2* to understand the mechanisms of *PART1* in HCC.

Materials and Methods

Cell Culture

HCC cells (SMMC-7721 and Huh7) and normal hepatic cell line LO2 were purchased from Cell Bank of Chinese Academy Sciences. Cells were cultured with DMEM supplemented with 10% FBS (Gibco, Thermo Fisher Scientific, Inc., Waltham, MA, USA) in a 37°C humidified incubator contains 5% CO₂.

Cell Transfection

Small interfering RNA against *PART1* (si-*PART1*, 5'-GCAAUGAAAGCUACCAAU-3'), against *HMGB2* (si-*HMGB2*, 5'-AAGACCAUGUCUGCAAAGGAG-3'), negative control (si-NC, 5'-UUCUCCGAACGUGUCACGUTT-3'), miR-590-3p mimic (5'-UAAUUUUAUGUAUAAGC UAGU-3'), and matched negative control (mi-NC, 5'-AUUAUGUACGGAUUAUUAUA-3') were purchased from GeneChem (Shanghai, China). pcDNA3.1 contains sequence of *PART1* (p*PART1*) was obtained from GenePharm. Lipofectamine 2000 (Invitrogen, Thermo Fisher Scientific, Inc.) was used for cell transfection.

Cell Proliferation Assay

Cells were seeded into 96-well plate at density of 2×10^3 cells/well and incubated for 0, 24, 48, and 72 h. Cell counting kit-8 (CCK-8) reagent (Beyotime, Haimen, Jiangsu, China) was added to the plate and further incubated for four hours. Optical density was observed at the wavelength of 450 nm using a microplate reader.

Colony Formation Assay

Six hundred cells were incubated in a six-well plate and allow to grow for 14 days. Colonies were fixed with methanol, stained with crystal violet, and counted under a microscope. Colony numbers were calculated using formula: colonies from five independent fields/5.

Transwell Invasion Assay

We seeded 5×10^4 cells in serum-free DMEM on upper chamber of Matrigel coated insert. The lower chamber was filled with DMEM containing FBS. After 24 h incubation, invaded cells were fixed with paraformaldehyde, stained with crystal violet, and washed with PBS. Invaded cell numbers were counted under an optical microscope.

Quantitative Real-time Polymerase Chain Reaction (RT-qPCR)

TRIzol reagent (Beyotime) was used to isolate RNA sample from cultured cells. Then, RNA was reverse transcribed into complementary DNA using PrimeScript RT kit (Takara, Dalian, Liaoning, China). RT-qPCR was conducted at ABI 7500 system (Foster City, CA, USA) using SYBR Green (Takara). Relative gene expression level was calculated with 2^{-ΔΔCt} method. Primers used were: *PART1*: 5'-AAGG CCGTGTCAGAACTCAA-3' (forward) and 5'-GTTTTC ATCTCAGCCTGGA-3' (reverse); *HMGB2*: 5'-GGGGAA GAAAAAGGACCCCA-3' (forward) and 5'-GCTGACTGC TCAGACCACAT-3' (reverse); *GAPDH*: 5'-AACGTGT CAGTGGTGGACCTG-3' (forward); and 5'-AGTGGGT GTCGCTGTTGAAGT-3' (reverse); miR-590-3p: 5'-GCGC TAATTTTATGTATAA-3' (forward); and 5'-GTGCAGG GTCCGAGGT-3' (reverse); U6 snRNA: 5'-CTCGCTT CGGCAGCACA-3' (forward) and 5'-AACGCTTCAC GAATTTGCGT-3' (reverse).

Immunoblotting Assay

Total proteins from cells were extracted using RIPA lysis buffer (Beyotime) and quantified with BCA kit (Beyotime). Twenty-five micrograms of protein sample

was separated at 10% sodium dodecyl sulphate polyacrylamide gel electrophoresis and transferred to PVDF membrane. Then the membrane was incubated with primary antibodies (anti-*HMGB2*: ab124670, anti-*GAPDH*: ab181602, Abcam, Cambridge, MA, USA). PVDF membrane was further incubated with horseradish peroxidase-conjugated secondary antibodies (ab6721, Abcam). Band signal was detected with BeyoECL kit (Beyotime).

Targets Prediction Using Bioinformatic Tool

miRNA target for *PART1* was analyzed at LncBase V 2.0. Target gene for miRNA was analyzed at TargetScan. miR-590-3p and *HMGB2* were selected for further analysis using these two bioinformatic tools.

Luciferase Reporter Assay

pmiR-Report luciferase vector contains wild-type (wt) sequence of *PART1* or *HMGB2* was named as wt-*PART1*/*HMGB2*. Mutant luciferase vectors were constructed using site-direct mutagenesis kit (Takara) and named as mt-*PART1*/*HMGB2*. Cells were transfected with luciferase reporter vectors and miRNAs using Lipofectamine 2000. After 48 h transfection, relative luciferase activity was measured using Dual-luciferase reporter assay kit (Promega, Madison, WI, USA).

Expression Level of *PART1*, miR-590-3p, and *HMGB2* in HCC Tissues Was Detected at ENCORI

Expression levels of *PART1*, miR-590-3p, and *HMGB2* in HCC tissues and normal tissues were analyzed at ENCORI website.

Silencing of *PART1* Hinders HCC Progression

BALB/c nude mice were used to detect the roles of *PART1* on HCC progression in vivo. Study protocol was approved by the Ethics Committee of Affiliated Hospital of Youjiang Medical University for Nationalities and performed in accordance with National Guidelines for Experimental Animal Welfare issued by the Ministry of Science and Technology, China. Cells transfected with *PART1* knockdown (sh-*PART1* (5'-ACCTCATGCAGCTTGACTGTGATTCATCAAGAGTGAATCACAGTCAA-GCTGCATTT-3') or sh-NC (5'-ACCTCGTACGATTGCGCTCTTAATTCAAGAGATTAAGACGCGCAATCG-TACTT-3')) or stable *PART1* overexpression were injected

into the flank of nude mice. Tumor width and length were measured every seven days to calculate tumor volume. After four weeks, the mice were killed to measure tumor weight. Furthermore, RNA samples were extracted from these tissues to measure the relative gene expression level.

Statistical Analysis

GraphPad Prism 8.0 (GraphPad Inc., San Diego, CA, USA) was used to analyze data obtained from three independent experiments. Differences were calculated using one-way ANOVA and Tukey's post hoc test or Student's *t*-test. Data were presented as mean \pm SD. *P*-value < 0.05 was an indicator for significant difference.

Results

PART1 Expression was Elevated in HCC

ENCORI analysis showed *PART1* was significantly elevated in HCC tissues compared with normal tissues (Figure 1A). Moreover, RT-qPCR analysis result demonstrated *PART1* was upregulated in HCC cells in comparison with normal cells (Figure 1B).

Knockdown of *PART1* Suppresses HCC Cell Proliferation, Colony Formation, and Migration

Introduction of si-*PART1* significantly decreased *PART1* expression in HCC cells (Figure 2A). CCK-8 assay revealed knockdown of *PART1* inhibits HCC cell proliferation rate (Figure 2B). Colony formation assay confirmed the results of CCK-8 assay (Figure 2C). Moreover, decreased invasion ability was observed in HCC cells with si-*PART1* transfection (Figure 2D).

Overexpression of *PART1* Promotes HCC Cell Proliferation, Colony Formation, and Migration

In addition, gain-of-function experiments were conducted to investigate the roles of *PART1*. Transfection of p*PART1* significantly increased the levels of *PART1* in HCC cells (Figure 3A). CCK-8 and colony formation assays confirmed *PART1* overexpression promotes HCC cell growth (Figure 3B and C). Moreover, invasive cell numbers were significantly increased after *PART1* overexpression (Figure 3D).

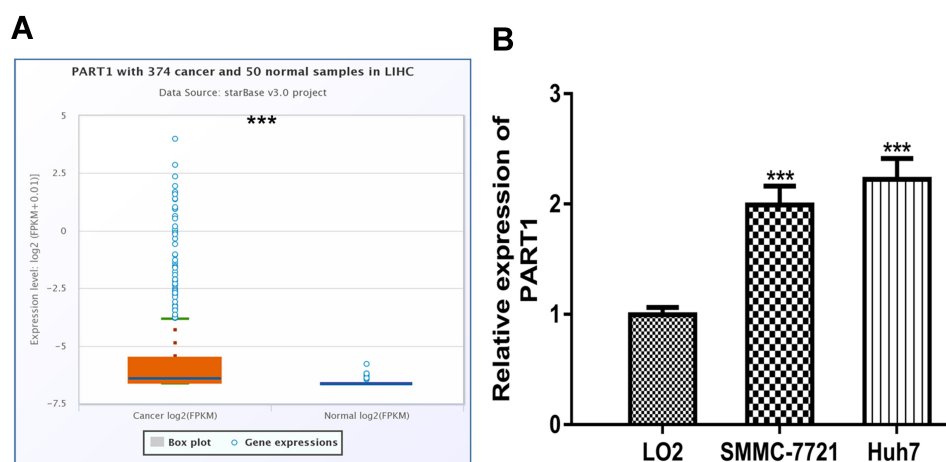


Figure 1 Expression of *PART1* in HCC. **(A)** Expression of *PART1* in HCC tissues and normal tissues. **(B)** Expression of *PART1* in HCC cell lines and normal cell line. * $P < 0.001$. *PART1*: prostate androgen-regulated transcript 1.

Abbreviation: HCC, hepatocellular carcinoma.

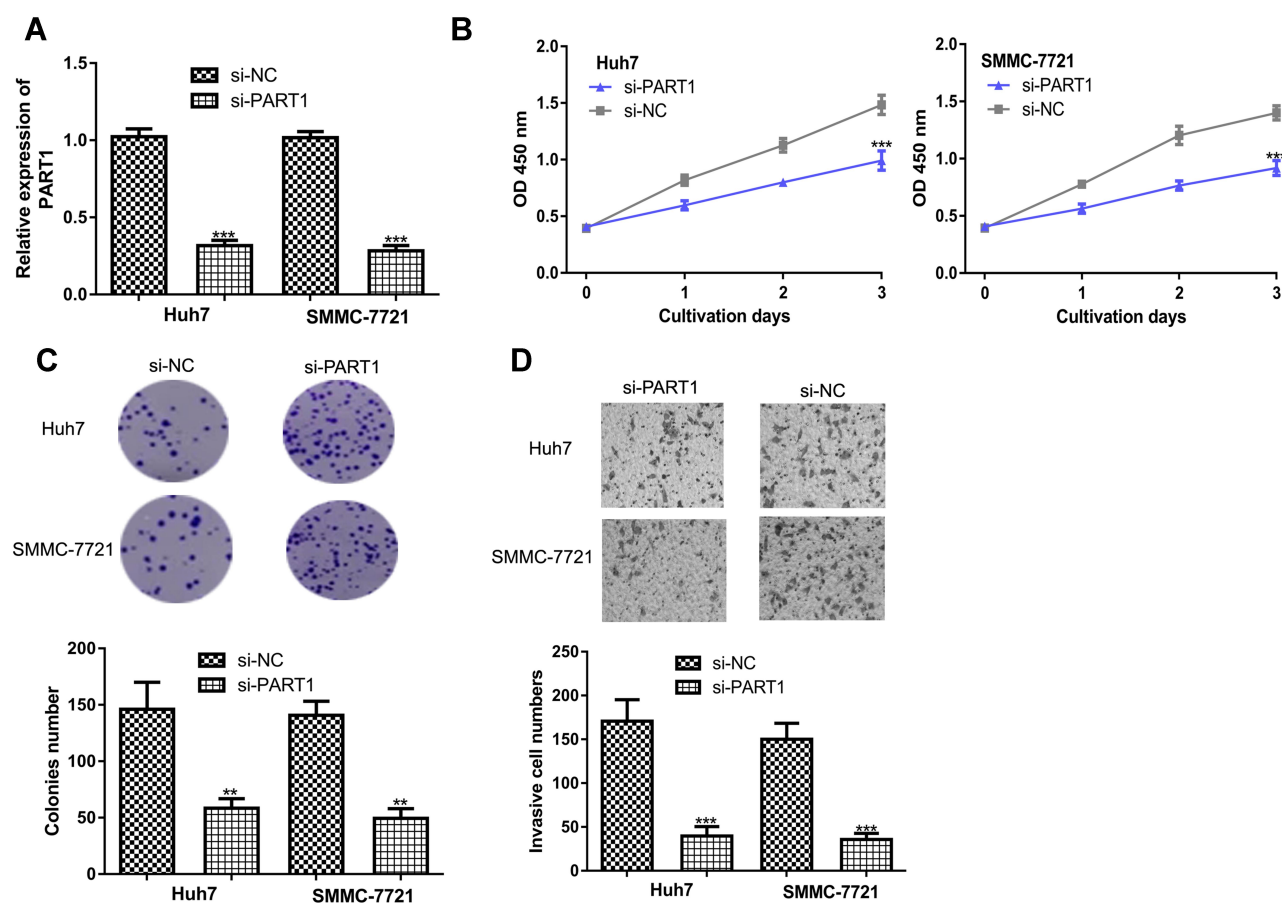


Figure 2 *PART1* knockdown inhibits HCC cell proliferation, colony formation and invasion. **(A)** Transfection efficacy of si-*PART1* and si-NC in HCC cells. **(B)** CCK-8 assay revealed HCC cell proliferation was suppressed by *PART1* knockdown. **(C)** Colony numbers were reduced by *PART1* knockdown in HCC cells. **(D)** Transwell invasion assay found that *PART1* knockdown suppressed invasion of HCC cells. * $P < 0.001$, ** $P < 0.01$.

Abbreviations: *PART1*, prostate androgen-regulated transcript 1; HCC, hepatocellular carcinoma; si-*PART1*, small interfering RNA targeting *PART1*; si-NC, negative control siRNA; CCK-8, cell counting kit-8.

PART1 Regulates miR-590-3p and *HMGB2* in HCC

Growing evidence indicated *PART1* serves as competing endogenous RNA (ceRNA) to sequester miRNA and regulate target gene expression.^{10,11} miR-590-3p was revealed to be the potential target for *PART1* (Figure 4A). miR-590-3p level was found to be decreased in tumor tissues compared with normal tissues (Figure 4B). Moreover, the knockdown of *PART1* significantly increased miR-590-3p levels in HCC cells (Figure 4C). Importantly, forcing miR-590-3p expression reduced relative luciferase activity of HCC cells transfected with wt-*PART1* but not mt-*PART1* (Figure 4D). Moreover, miR-590-3p was found to bind with *HMGB2* through TargetScan analysis (Figure 4E). *HMGB2* level was found to be elevated in HCC tissues compared with normal tissues (Figure 4F). Interestingly, transfection of miR-590-3p mimic decreased *HMGB2*

mRNA levels in HCC cells (Figure 4G). Western blot confirmed that forcing miR-590-3p expression decreased *HMGB2* protein levels in HCC cells (Figure 4H). As expected, forcing miR-590-3p expression inhibited relative luciferase activity of HCC cells transfected with wt-*HMGB2* (Figure 4I).

miR-590-3p and *HMGB2* Mediates the Oncogenic Role of *PART1* in HCC

To further explore the roles of miR-590-3p and *HMGB2* in HCC, rescue experiments were conducted. RT-qPCR showed overexpression of miR-590-3p or knockdown of *HMGB2* partially reversed the effects of p*PART1* on *HMGB2* expression (Figure 5A). CCK-8 assay, colony formation assay, and transwell invasion assay indicated that the stimulation effects of p*PART1* on HCC cells could be abrogated by miR-590-3p overexpression or *HMGB2* knockdown (Figure 5B–D).

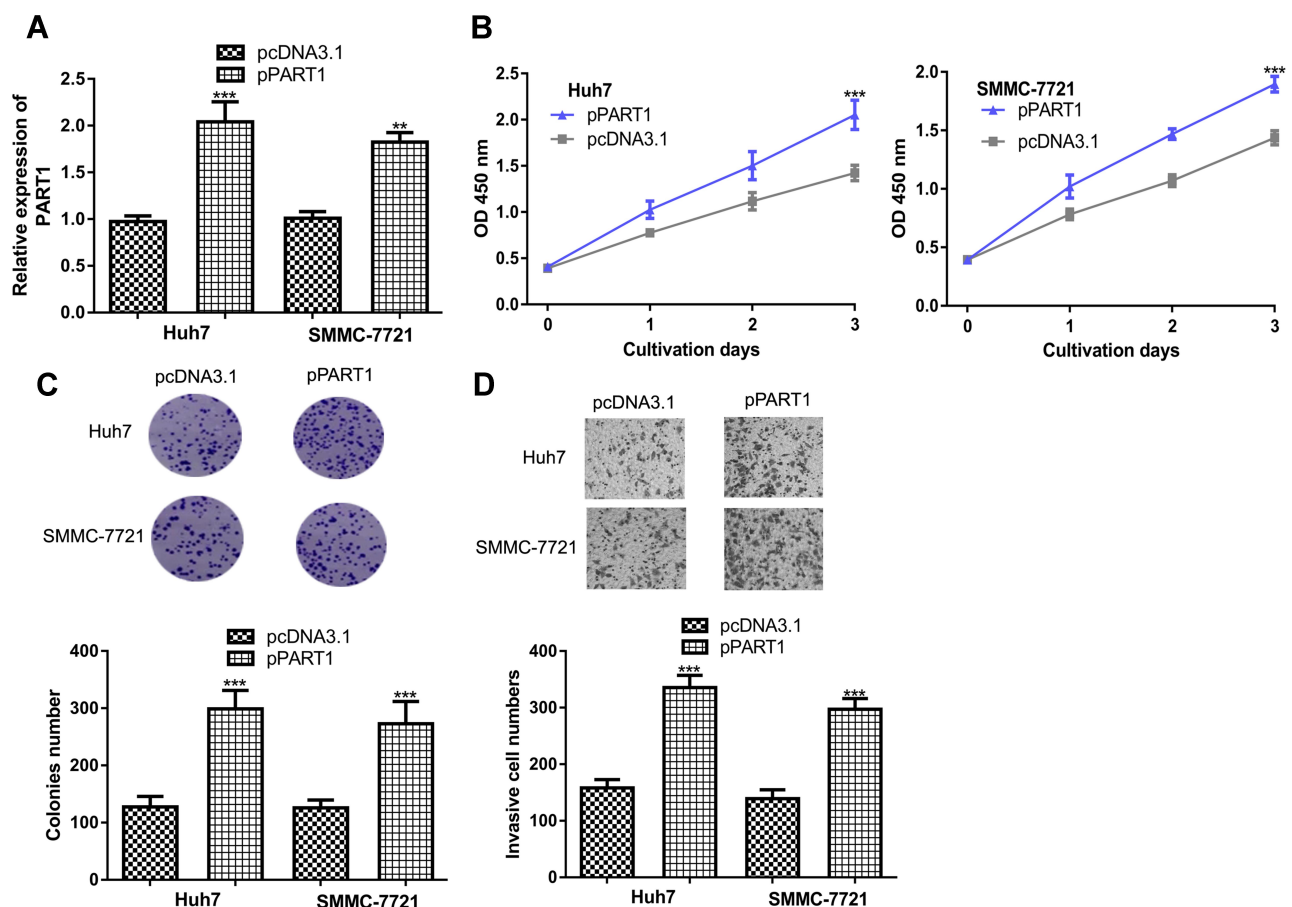


Figure 3 *PART1* overexpression promotes HCC cell proliferation, colony formation and invasion. (A) Transfection efficacy of p*PART1* and pcDNA3.1 in HCC cells. (B) CCK-8 assay revealed HCC cell proliferation was stimulated by *PART1* overexpression. (C) Colony numbers were increased by *PART1* overexpression in HCC cells. (D) Transwell invasion assay found that *PART1* overexpression promoted invasion of HCC cells. **P*<0.001, ***P*<0.01.

Abbreviations: *PART1*, prostate androgen-regulated transcript 1; HCC, hepatocellular carcinoma; CCK-8, cell counting kit-8.

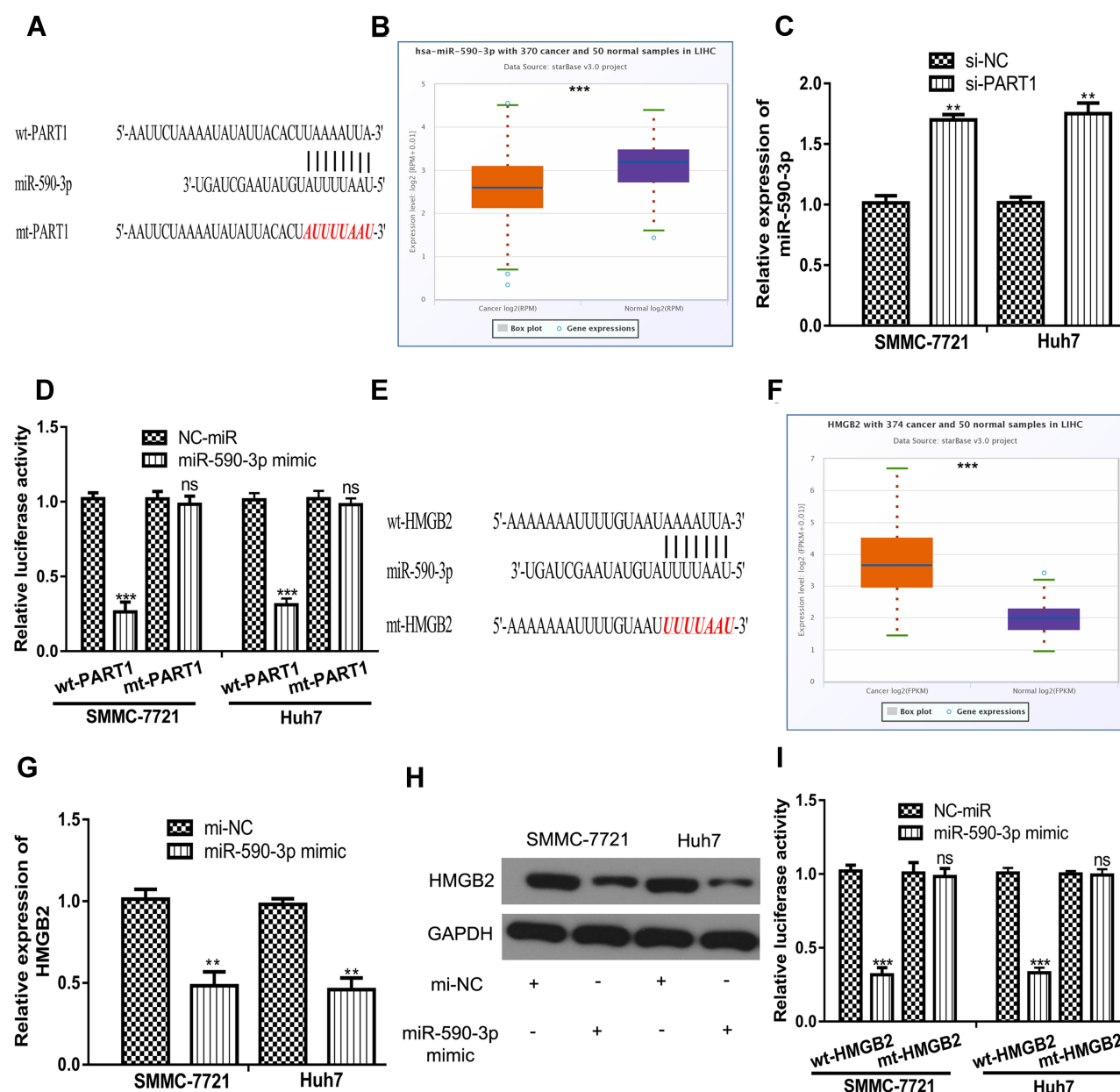


Figure 4 *PART1* regulates the levels of miR-590-3p and *HMGB2* in HCC cells. (A) Interaction between *PART1* and miR-590-3p. (B) Expression of miR-590-3p in HCC tissues and normal tissues. (C) Knockdown of *PART1* increased the levels of miR-590-3p in HCC cells. (D) miR-590-3p overexpression inhibits the relative luciferase activity of cells transfected with wt-*PART1*. (E) Interaction between *HMGB2* and miR-590-3p. (F) Expression of *HMGB2* in HCC tissues and normal tissues. (G) miR-590-3p overexpression decreased the mRNA levels of *HMGB2* in HCC cells. (H) miR-590-3p overexpression decreased the protein levels of *HMGB2* in HCC cells. (I) miR-590-3p overexpression inhibits the relative luciferase activity of cells transfected with wt-*HMGB2*. * $P < 0.001$, ** $P < 0.01$.

Abbreviations: ns, not significant; *PART1*, prostate androgen-regulated transcript 1; HCC, hepatocellular carcinoma; miR-590-3p, microRNA-590-3p; mi-NC, negative control miRNA; *HMGB2*, high mobility group box 2; wt, wild-type; mt, mutant.

Roles of *PART1* on HCC Tumor Growth in vivo

To analyze the roles of *PART1* in vivo, cells with *PART1* knockdown or overexpression were used to establish xenograft model. The results in Figure 6A and B showed that both tumor volume and tumor weight were decreased by sh-*PART1* compared with sh-NC. On the contrary, tumor

volume and weight were increased after *HMGB2* overexpression (Figure 6A and B). Furthermore, we showed the expression of *PART1* and *HMGB2* was significantly decreased by *PART1* knockdown, while increased by *PART1* overexpression (Figure 6C). Moreover, the expression of miR-590-3p was dramatically increased by *PART1* knockdown and decreased by *PART1* overexpression (Figure 6C).

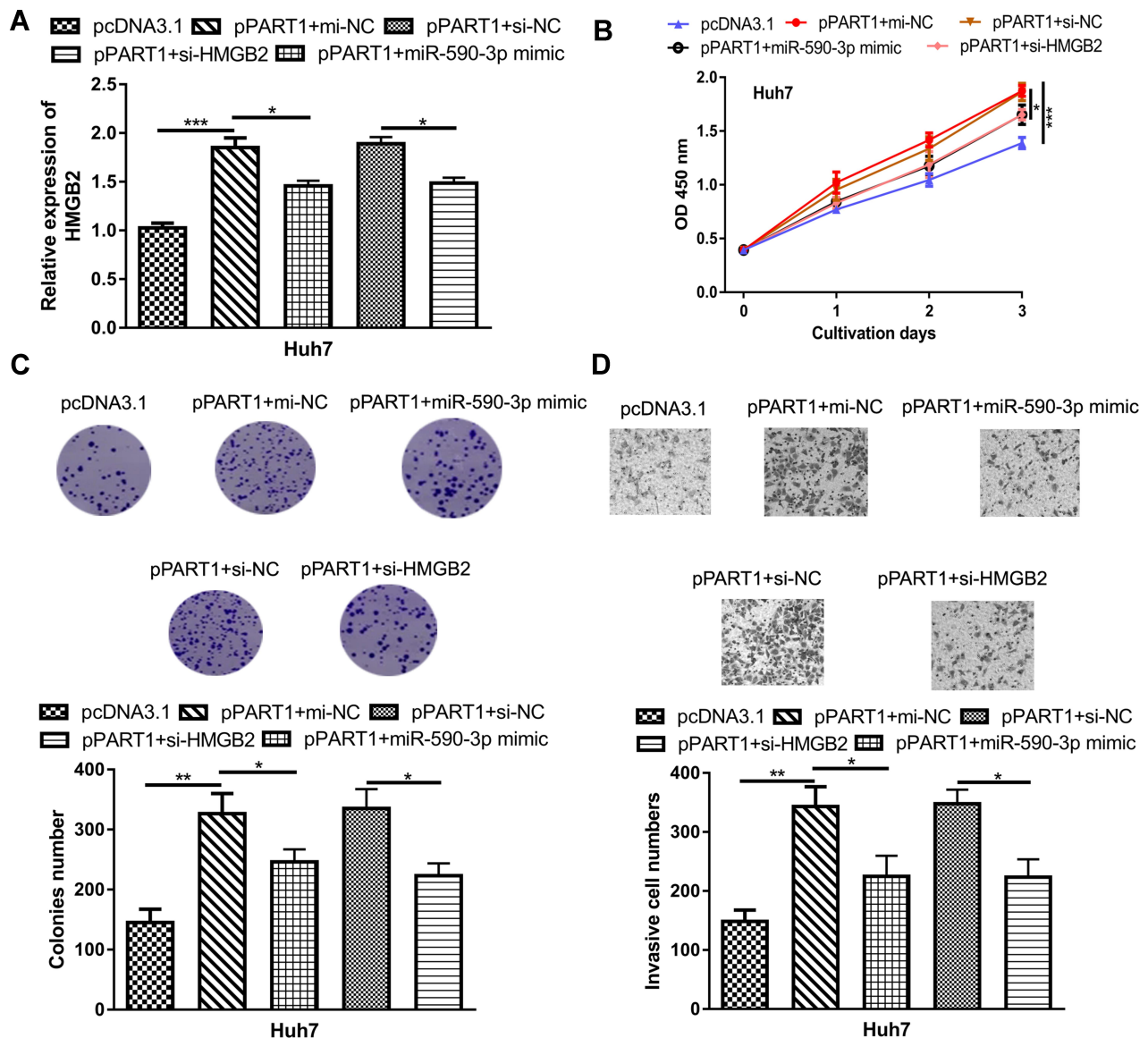


Figure 5 miR-590-3p overexpression and HMGB2 overexpression partially reverses *PART1* overexpression-induced effects on HCC cells. **(A)** HMGB2 expression in HCC cell transfected with *pPART1*, *pPART1*+miR-590-3p mimic, or *pPART1*+si-HMGB2. **(B)** CCK-8 assay, **(C)** colony formation assay, and **(D)** transwell invasion assay were performed to detect the proliferation, and invasion of HCC cells in each group. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Abbreviations: *PART1*, prostate androgen-regulated transcript 1; HCC, hepatocellular carcinoma; miR-590-3p, microRNA-590-3p; HMGB2, high mobility group box 2; si-HMGB2, small interfering RNA targeting HMGB2; CCK-8, cell counting kit-8.

Discussion

Growing evidence indicated lncRNAs played crucial roles in regulating HCC progression.^{16,17} lncRNA activated by transforming growth factor beta was revealed as a predictor for poorer overall survival of HCC patients, and regulated HCC cell autophagy via activating Yes-associated protein and autophagy-related protein five expression.¹⁶ Moreover, a recent study showed small nucleolar RNA host gene 7 (*SNHG7*) increased expression in HCC tissues compared with those in normal tissues.¹⁷ Mechanism studies showed *SNHG7* could promote HCC

tumorigenesis via sponging miR-122-5p to upregulate ribosomal protein L4 expression.¹⁶

In this study, our RT-qPCR data and ENCORI analysis data showed *PART1* was highly expressed in HCC cells and tissues. Moreover, silencing of *PART1* could inhibit HCC cell growth and invasion. Importantly, forcing of *PART1* could promote HCC cell growth and invasion. In vivo analyses indicated that silencing of *PART1* could suppress tumor growth, while forcing of *PART1* exerts opposite effects on tumor growth. These results collectively may suggest the oncogenic role of *PART1* in HCC,

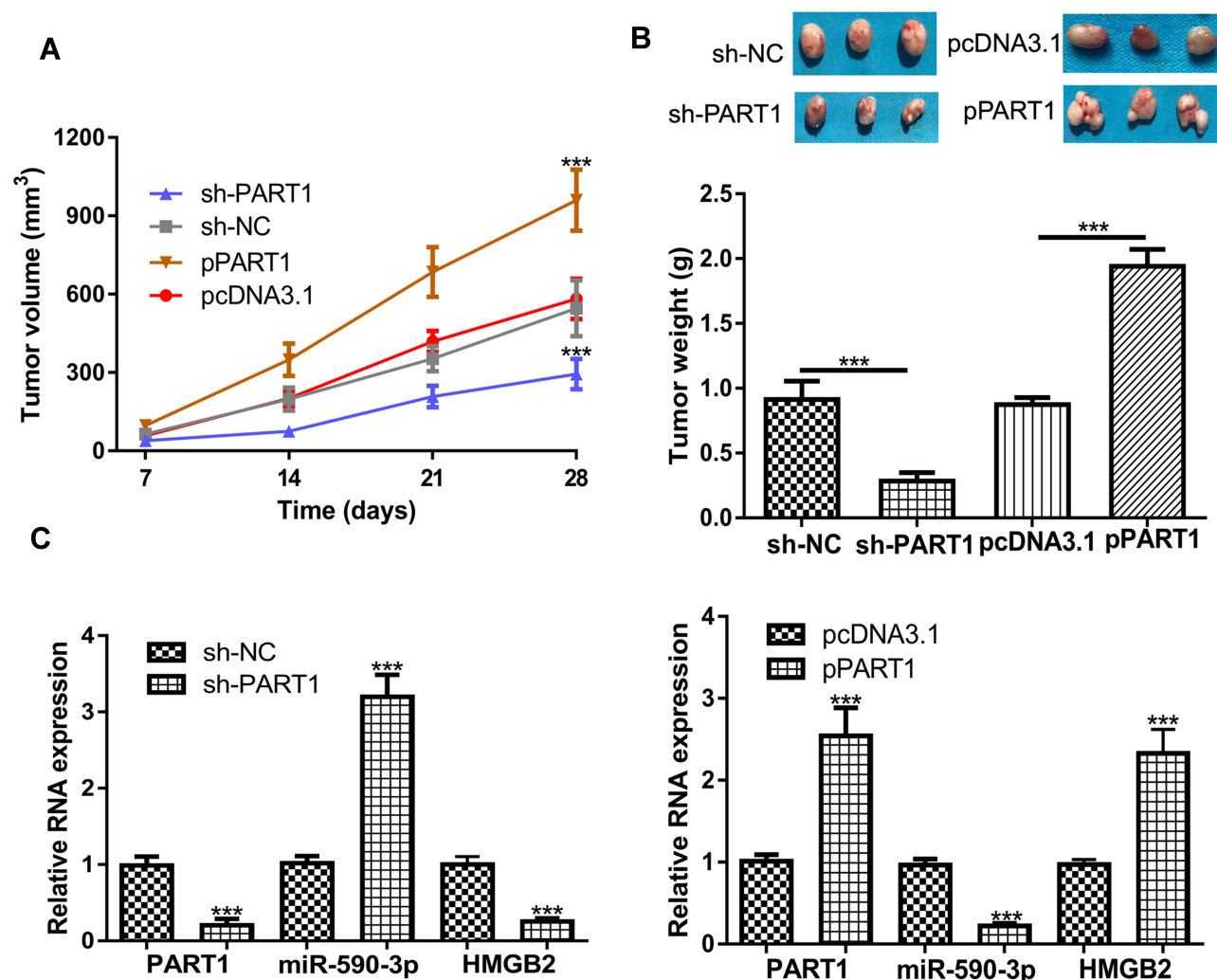


Figure 6 Effects of *PART1* on HCC tumor growth in vivo. (A) Tumor volume after *PART1* knockdown or overexpression was calculated every week. (B) Mice were killed and tumor weight was examined after *PART1* knockdown or overexpression. (C) The expressions of *PART1*, miR-590-3p and *HMGB2* were detected after *PART1* knockdown or overexpression. * $P < 0.001$.

Abbreviations: *PART1*, prostate androgen-regulated transcript 1; HCC, hepatocellular carcinoma; miR-590-3p, microRNA-590-3p; *HMGB2*, high mobility group box 2; sh-*HMGB2*, short hairpin RNA targeting *HMGB2*; sh-NC, negative control shRNA.

a role that was reported in previous studies.^{10,11} A very recent study conducted by Zhou et al indicated *PART1* could boost HCC progression via the miR-149-5p/ MAP2K1 pair in vitro.¹⁸ Our work can be regarded as another proof for the oncogenic role of *PART1* in HCC. However, there is a difference between our current work and this work, which is that we provided in vivo analysis results to support the oncogenic role of *PART1*.

It has been widely recognized lncRNA exerts biological roles via regulating miRNA and target gene. We found miR-590-3p, downregulated expression in HCC, was a putative target for *PART1*. We confirmed the direct interaction of *PART1* and miR-590-3p through luciferase activity reporter assay. miR-590-3p was reported to

function as either tumor promoter or suppressor gene in cancers.^{19,20} Considering the distinct role of miR-590-3p in cancers, hence the roles of miR-590-3p in HCC was explored. We validated the interaction of miR-590-3p and *HMGB2*. *HMGB2* was reported to function as an oncogene in cancers.¹²⁻¹⁴ In our work, we also found *HMGB2* expression was elevated in HCC tissues and cells. Importantly, miR-590-3p overexpression or *HMGB2* knockdown partially reversed *PART1* overexpression on HCC cell proliferation, colony formation and invasion. The limitation of this work is that we did not explore the expression levels of this newly identified ceRNA triplet in HCC clinical samples. In addition, the clinical significance of these genes in HCC was not investigated. Hence,

further experiments are still needed to validate the importance of this *PART1*/miR-590-3p/*HMGB2* axis in HCC.

Conclusion

To conclude, our work provided evidence that *PART1* was elevated expression in HCC. In vitro and in vivo assays revealed *PART1* could promote HCC tumor progression by regulating miR-590-3p/*HMGB2*. Our work provided novel evidence regarding mechanisms underlying HCC pathogenesis.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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