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ORIGINAL RESEARCH

LncRNA *HCG18* Promotes Clear Cell Renal Cell Carcinoma Progression by Targeting *miR-152-3p* to Upregulate *RAB14*

This article was published in the following Dove Press journal:
Cancer Management and Research

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Background: Long noncoding RNAs (lncRNAs) have been regarded as crucial regulators in many cancers, including clear cell renal cell carcinoma (ccRCC). This research aimed to explore the biological role and molecular mechanism of lncRNA *HCG18* in ccRCC.

Materials and Methods: The expression levels of *HCG18, miR-152-3p* and *RAB14* were examined by RT-qPCR. Cell viability, migration and invasion were examined by CCK-8 and transwell assays. Luciferase reporter and RIP assays were adopted to verify the interaction between *miR-152-3p* and *HCG18* or *RAB14*.

Results: It was found that *HCG18* expression was highly expressed in ccRCC tissues and cells, and patients with high expression of *HCG18* had a short overall survival time. Moreover, *HCG18* depletion attenuated ccRCC cell viability, migration and invasion. In addition, *miR-152-3p* was confirmed as a downstream target of *HCG18* and was inversely regulated by *HCG18*, and *RAB14* was a target of *miR-152-3p*. Functional assays demonstrated that *miR-152-3p* silencing or *RAB14* addition abolished the inhibitory effects of *HCG18* knockdown on ccRCC progression.

Conclusion: The results of the present study indicated that *HCG18* accelerated the development and progression of ccRCC by upregulating *RAB14* via sponging *miR-152-3p*, suggesting a potential therapeutic target for patients with ccRCC.

Keywords: *HCG18*, *miR-152-3p*, *RAB14*, clear cell renal cell carcinoma

Introduction

Renal cell carcinoma (RCC) is one of the most common urological malignancies with high mortality worldwide. Clear cell renal cell carcinoma (ccRCC) is one of the main subtypes of RCC and occupies about 80% of RCC cases.[1,2] Although early ccRCC can be cured, patients with metastatic ccRCC still have a poor prognosis.[3] Nowadays, increasing molecular biomarkers have been identified as diagnostic, prognostic, and therapeutic biomarkers in human cancers, which can improve the early detection of cancers and decreased the mortality rate.[4–6] Therefore, it is essential to discover novel biomarkers for diagnosis, treatment, and prognosis of ccRCC.

Long non-coding RNAs (lncRNAs) are a type of non-coding RNAs with >200 nts in length.[7] LncRNAs have been found to exert essential functions in many types of cancers, including ccRCC. For example, lncRNA *TUG1* facilitated the proliferation of ccRCC cells by targeting *miR-31-5p* and regulating *FLOT1* expression.[8] LncRNA *DARS-AS1* promoted the tumorigenesis of ccRCC through the *miR-194-5p*/*DARS* axis.[9] Recently, a cancer-related lncRNA *HCG18* was identified to participate in

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http://doi.org/10.2147/CMAR.S298649

several malignant cancers, such as bladder cancer, gastric cancer, and nasopharyngeal carcinoma.[10–12] However, the regulatory role of *HCG18* in ccRCC remains undetermined.

MicroRNAs (miRNAs) are non-coding RNAs with 17–25 nucleotides in length.[13] Emerging evidence implied that dysregulation of miRNAs was implicated in the progression of multiple tumors. For instance, *miR-448* restrained the growth of pituitary adenoma cells by regulating BLC2.[14] *miR-335-5p* overexpression suppressed the metastasis of lung adenocarcinoma cells via downregulating *CCNB2*.[15] *miR-152-3p* was identified to act as a tumor suppressor in several cancers, such as prostate cancer and glioma.[16,17] Nevertheless, the biological significance of *miR-152-3p* in ccRCC is still obscure.

The current study explored the regulatory mechanism of *HCG18* in ccRCC and found that *HCG18* contributed to ccRCC tumorigenesis by regulating *miR-152-3p*/*RAB14* axis. The novel regulatory pathway might provide a potential diagnosis and treatment strategy for ccRCC.

Materials and Methods

Clinical Samples

A total of 32 paired ccRCC tissues and adjacent normal tissues were collected from patients who underwent nephrectomy at the Third Affiliated Hospital of Soochow University, and serum was also sampled from each patient before the operation. Besides, serum samples were also collected from 32 healthy individuals during the same period as a healthy control group. All the samples were rapidly frozen in liquid nitrogen and stored at -80°C until use. Our study was approved by the Ethics Committee of the Third Affiliated Hospital of Soochow University and conducted in accordance with the Declaration of Helsinki. Written informed consent forms were signed by all participants.

Cell Culture

Human ccRCC cell lines (Caki-1, 786-O, 769-P and ACHN) and normal human kidney cells HK-2 were obtained from the American Type Culture Collection (ATCC) and incubated in Dulbecco's Modified Eagle Medium (DMEM; Gibco, USA) containing 10% fetal bovine serum (FBS) at 37°C with 5% CO_2.

Cell Transfection

Short hairpin (sh) RNA targeting *HCG18* (sh*HCG18*; 5′-UGAGCGGCUGUGCUAUACAUGUG-3′), *RAB14* (sh*RAB14*; 5′-GCAGUUCACAAGUAGUACUGG-3′) with their negative control (shNC), *miR-152-3p* mimics/inhibitor with their negative controls (NC mimics/inhibitor), and pcDNA3.1/*RAB14* with its negative control (pcDNA3.1) were synthesized by GenePharma (Shanghai, China). Cell transfection was performed using Lipofectamine 2000 (Invitrogen).

RT-qPCR

Total RNA was extracted using Trizol reagent (Invitrogen, CA, USA). Then, 1 μg of total RNA was reverse transcribed to cDNA using the PrimeScript RT reagent kits (Takara). RT-qPCR was performed by SYBR Premix Ex Taq II (TaKaRa) on ABI 7500 real-time PCR system (Applied Biosystems). The data were analyzed using the $2^{-\Delta\Delta Cq}$ method. GAPDH or U6 were used as the internal controls for *HCG18* and *RAB14* or *miR-152-3p*, respectively.

CCK-8 Assay

Transfected cells were seeded into 96-well plates. After cultured for 0, 24, 48, 72 h, 10 μL CCK-8 solution was added into each well, and the cells were incubated for 2 h. The absorbance at 450 nm was examined using a microplate reader (Bio-Rad, USA).

Transwell Assay

Cell migration and invasion were detected using transwell chambers (Corning, NY, USA). For cell invasion, the transwell chambers were coated with Matrigel (BD Biosciences). The transfected cells ($1x10^5$ cells) were suspended in DMEM without serum and added to the upper chambers. Then, the lower chamber was filled with 600μL DMEM plus 10% FBS. After 24 incubation, the invaded cells were stained with 0.5% crystal violet. Cell migration was measured by the method same as that for cell invasion, except that the transwell chambers were not coated with Matrigel.

Luciferase Reporter Assay

HCG18-(wild type) Wt, *RAB14*-Wt and their mutants (*HCG18*-Mut and *RAB14*-Mut) were constructed by GenePharma (Shanghai, China). Then, the above reporters were co-transfected *miR-152-3p* mimics or NC mimics into HEK-293T cells for 48 h. Luciferase activities were estimated by the dual-luciferase reporter assay system (Promega, USA).

RNA Immunoprecipitation (RIP)

RIP assay was conducted using Magna RIP-Kit (Millipore, Bedford, USA). Briefly, the treated Caki-1 and 786-O cells

were lysed by RIP buffer that contained magnetic beads coupled with anti-Ago2 or anti-IgG antibody. Then, the enrichment of *HCG18* and *miR-152-3p* was detected by RT-qPCR.

In vivo Experiments

The animal study was approved by the Animal Ethics Committee of the Third Affiliated Hospital of Soochow University and conducted following the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. Briefly, cells transfected with shNC or sh*HCG18* were injected into BALB/C nude mice. The volume and weight of tumors were measured every 7 days. Four weeks later, mice were sacrificed by cervical dislocation after deep anesthesia with 2% isoflurane. Then, the tumors were dissected and detected.

Statistical Analysis

Data were presented as mean ± SD. Statistical analysis was conducted using SPSS 22.0 (IBM, Chicago, IL, USA). Group difference was analyzed by Student's *t*-test or one-way ANOVA. Overall survival rate was assessed by Kaplan–Meier method. The correlation between *miR-152-3p* and *HCG18* or *RAB14* was estimated by Pearson's correlation analysis. $p<0.05$ was thought as statistically significant.

Results

HCG18 is Overexpressed in ccRCC and Knockdown of *HCG18* Represses the Tumorigenesis of ccRCC

Firstly, the expression of HCG18 in ccRCC was evaluated by RT-qPCR and the results indicated that *HCG18* was overexpressed in ccRCC tissues and cells (Figure 1A and B). In addition, we found that the AUC of *HCG18* for diagnosing

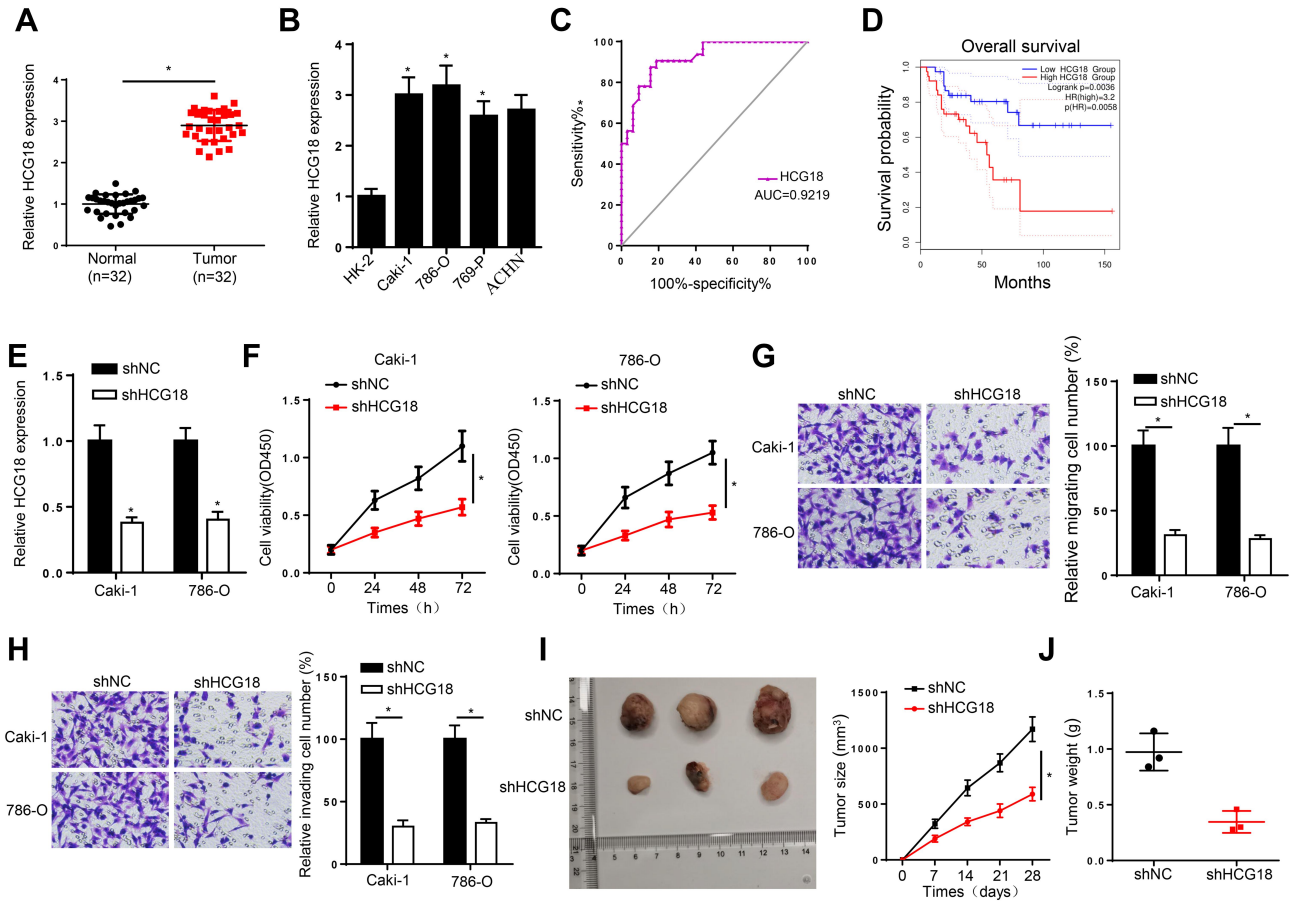

Figure 1 *HCG18* is overexpressed in ccRCC and knockdown of *HCG18* represses the tumorigenesis of ccRCC. (**A** and **B**) RT-qPCR assay was applied to detect the expression of *HCG18* in ccRCC tissues (n=32) and cell lines. (**C**) The ROC curve of serum *HCG18* for diagnosing ccRCC. (**D**) Kaplan–Meier method was used to assess the association between *HCG18* expression and overall survival rate in ccRCC patients. (**E**) RT-qPCR assay was applied to detect the transfection efficiency of shNC and sh*HCG18* in Caki-1 and 786-O cells. (**F**) CCK-8 assay was used to measure cell proliferation in Caki-1 and 786-O cells after knocking down *HCG18*. (**G** and **H**) Transwell assay was performed to assess cell migration and invasion in Caki-1 and 786-O cells transfected with sh*HCG18*. (**I** and **J**) In vivo experiments the tumor growth rate in mice of ccRCC cells transfected with sh*HCG18*. *$p < 0.05$.

ccRCC was 0.922, indicating that it might be used as an indicator for ccRCC screening (Figure 1C). Moreover, ccRCC patients with a high level of *HCG18* were associated with a low survival rate (Figure 1D). To investigate the biological function of *HCG18* in ccRCC, sh*HCG18* was transfected into Caki-1 and 786-O cells, and the transfection efficiency was performed by RT-qPCR (Figure 1E). Moreover, CCK-8 assay showed that *HCG18* depletion impaired the viability of ccRCC cells (Figure 1F). Furthermore, transwell assays revealed that *HCG18* depletion repressed the migration and invasion of ccRCC cells (Figure 1G and H). In addition, an in vivo xenograft experiment showed that depletion of *HCG18* reduced the tumor growth rate in mice (Figure 1I and J). Thus, these results implied that *HCG18* accelerated the development of ccRCC.

HCG18 is a Molecular Sponge for *miR-152-3p* in ccRCC

Through using StarBase website (http://starbase.sysu.edu.cn/), *miR-152-3p* was predicted as a potential target of *HCG18* (Figure 2A). Luciferase reporter assay determined that *miR-152-3p* mimics remarkably decreased the luciferase activity of *HCG18*-Wt, but had no effect on *HCG18*-Mut in 293T cells (Figure 2B). Meanwhile, RIP assay manifested that *miR-152-3p* and *HCG18* were enriched in the AGO2 group (Figure 2C and D). Then, RT-qPCR analysis revealed that *miR-152-3p* level was reduced in ccRCC tissues (Figure 2E). Moreover, an inverse correlation between *HCG18* and *miR-152-3p* expression was observed in ccRCC tissues (Figure 2F). Besides, RT-qPCR results indicated that *HCG18* depletion enhanced *miR-152-3p* expression in ccRCC cells (Figure 2G). The above data determined that *miR-152-3p* was a target of *HCG18*, and was inversely modulated by *HCG18*.

HCG18 Sponges *miR-152-3p* and Positively Modulates *RAB14* Expression in ccRCC

Subsequently, starBase website predicted that *RAB14* was a potential target of *miR-152-3p* (Figure 3A). RT-qPCR analysis exhibited that *RAB14* level was increased in ccRCC tissues (Figure 3B), and *RAB14* expression was decreased by silencing of *HCG18* (Figure 3C). Then, we

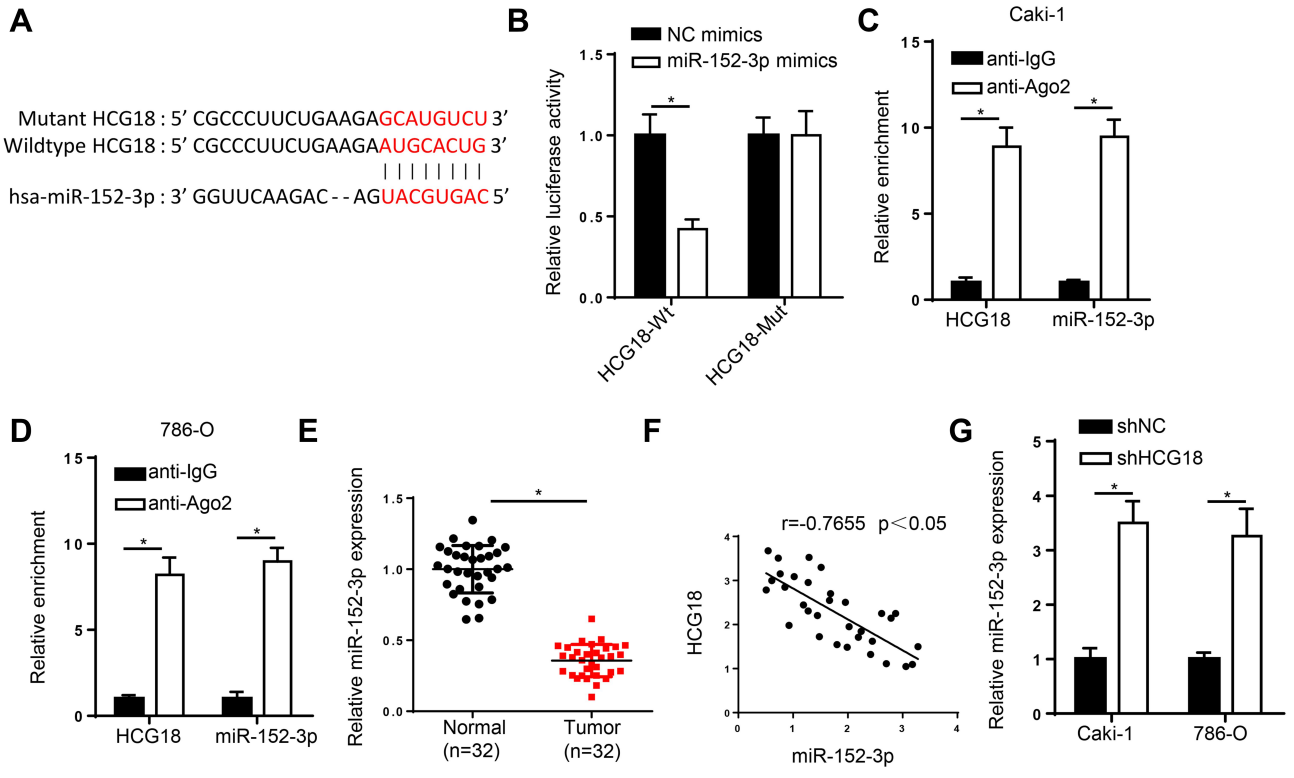

Figure 2 *HCG18* is a molecular sponge for *miR-152-3p* in ccRCC. (**A**) Binding sequences between *HCG18* and *miR-152-3p* were predicted by starBase website. (**B**) Luciferase reporter assay was adopted to verify the binding ability between *HCG18* and *miR-152-3p* in 293T cells. (**C** and **D**) RIP assay was used to analyze enrichment of *HCG18* and *miR-152-3p* in Caki-1 and 786-O cells of anti-Ago2 group compared with anti-IgG group. (**E**) RT-qPCR assay was performed to measure the expression of *miR-152-3p* in ccRCC tissues. (**F**) Pearson's correlation analysis showed the correlation between *HCG18* and *miR-152-3p* in ccRCC tissues. (**G**) RT-qPCR analysis was applied to detect *miR-152-3p* expression in Caki-1 and 786-O cells transfected with sh*HCG18*. *$p < 0.05$.

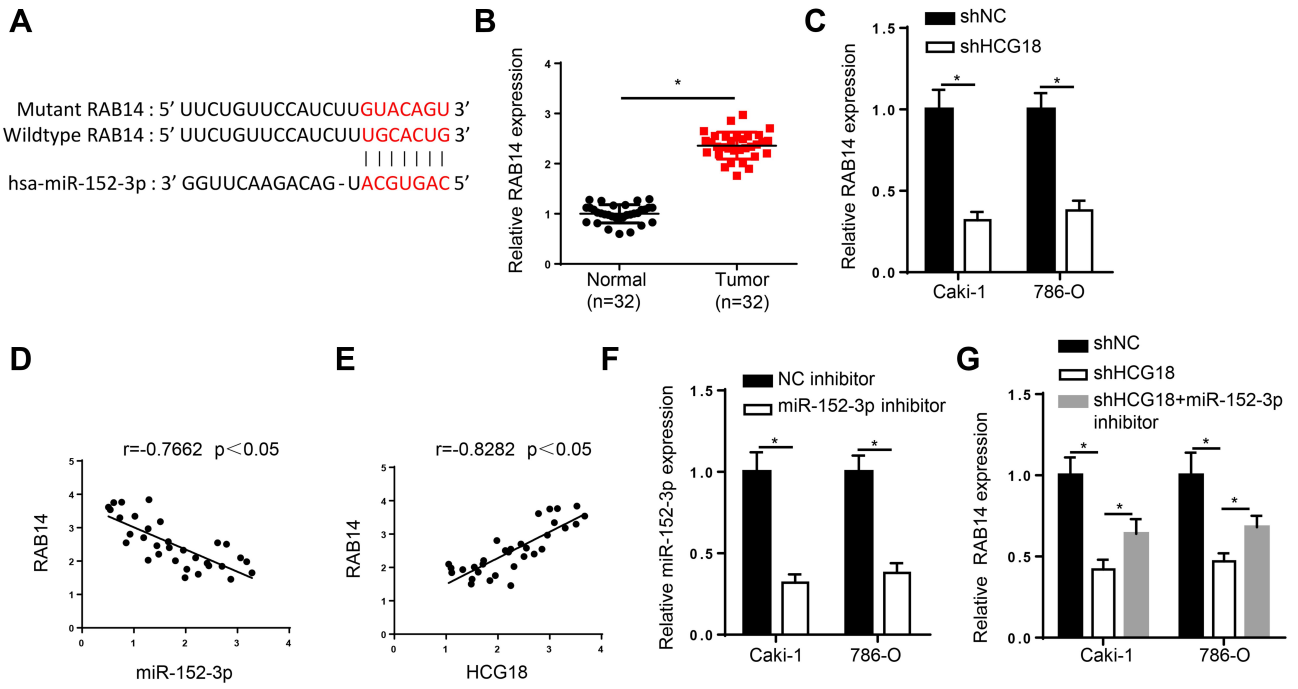

Figure 3 *HCG18* sponges *miR-152-3p* and positively modulates *RAB14* expression in ccRCC. (**A**) Binding sequences between *miR-152-3p* and *RAB14* were predicted by starBase website. (**B**) RT-qPCR assay showed the expression of *RAB14* in ccRCC tissues. (**C**) RT-qPCR assay was applied to assess the expression of *RAB14* in Caki-1 and 786-O cells transfected with sh*HCG18*. (**D** and **E**) Pearson's correlation analysis showed the correlation between *RAB14* and *miR-152-3p* or *HCG18* in ccRCC tissues. (**F**) RT-qPCR assay was applied to assess the expression of *miR-152-3p* in Caki-1 and 786-O cells transfected with *miR-152-3p* inhibitor. (**G**) RT-qPCR assay showed *RAB14* expression in Caki-1 and 786-O cells transfected with shNC, sh*HCG18*, and sh*HCG18*+*miR-152-3p* inhibitor. *$p < 0.05$.

found that *RAB14* expression was inversely correlated with *miR-152-3p* expression, and *RAB14* expression was positively correlated with *HCG18* expression in ccRCC tissues (Figure 3D and E). To elucidate whether *HCG18* modulated *RAB14* expression by targeting *miR-152-3p*, Caki-1 and 786-O cells were transfected with shNC, sh*HCG18*, and sh*HCG18*+*miR-152-3p* inhibitor. RT-qPCR analysis demonstrated that *miR-152-3p* was lowly expressed in ccRCC cells transfected with *miR-152-3p* inhibitor (Figure 3F). Additionally, depletion of *HCG18* reduced *RAB14* expression, while this effect was reversed by *miR-152-3p* inhibition (Figure 3G). In sum, the results elucidated that *HCG18* sponged *miR-152-3p* and positively modulated *RAB14* expression in ccRCC.

HCG18 Contributes to ccRCC Progression by Modulating the *miR-152-3p/RAB14* Axis

To investigate whether *HCG18* participated in ccRCC progression via modulating the *miR-152-3p*/*RAB14* axis, a string of functional experiments was conducted. Firstly, CCK-8 and transwell assays disclosed that the inhibition of *miR-152-3p* reversed the repressive effect of *HCG18* interference on the viability, migration and invasion of Caki-1 and 786-O cells (Figure 4A–C). Next, pcDNA3.1/*RAB14* and sh*HCG18* were co-transfected into Caki-1 and 786-O cells. RT-qPCR results confirmed that addition of *RAB14* significantly upregulated *RAB14* expression in ccRCC cells (Figure 4D). Functional assays elaborated that the impacts of *HCG18* knockdown on cell viability, and metastasis were eliminated by *RAB14* overexpression (Figure 4E–G). Taken together, *HCG18* contributed to ccRCC progression via sponging *miR-152-3p* and upregulating *RAB14*.

Discussion

LncRNAs have been reported to serve as oncogenes or tumor suppressors in the tumorigenesis of ccRCC. For example, lncRNA-*LET* restrained the growth of ccRCC cells by modulating *miR-373-3p*.[18] LncRNA *LUCAT1* facilitated ccRCC cell viability and invasion by the *AKT*/*GSK-3β* pathway.[19] LncRNA *DLEU1* accelerated ccRCC cell viability and migration by sponging *miRNA-194-5p*.[20] This research focused on the role and regulatory mechanism of *HCG18* in ccRCC, and the results elucidated that *HCG18* accelerated ccRCC progression through sponging *miR-152-3p* and upregulating *RAB14*.

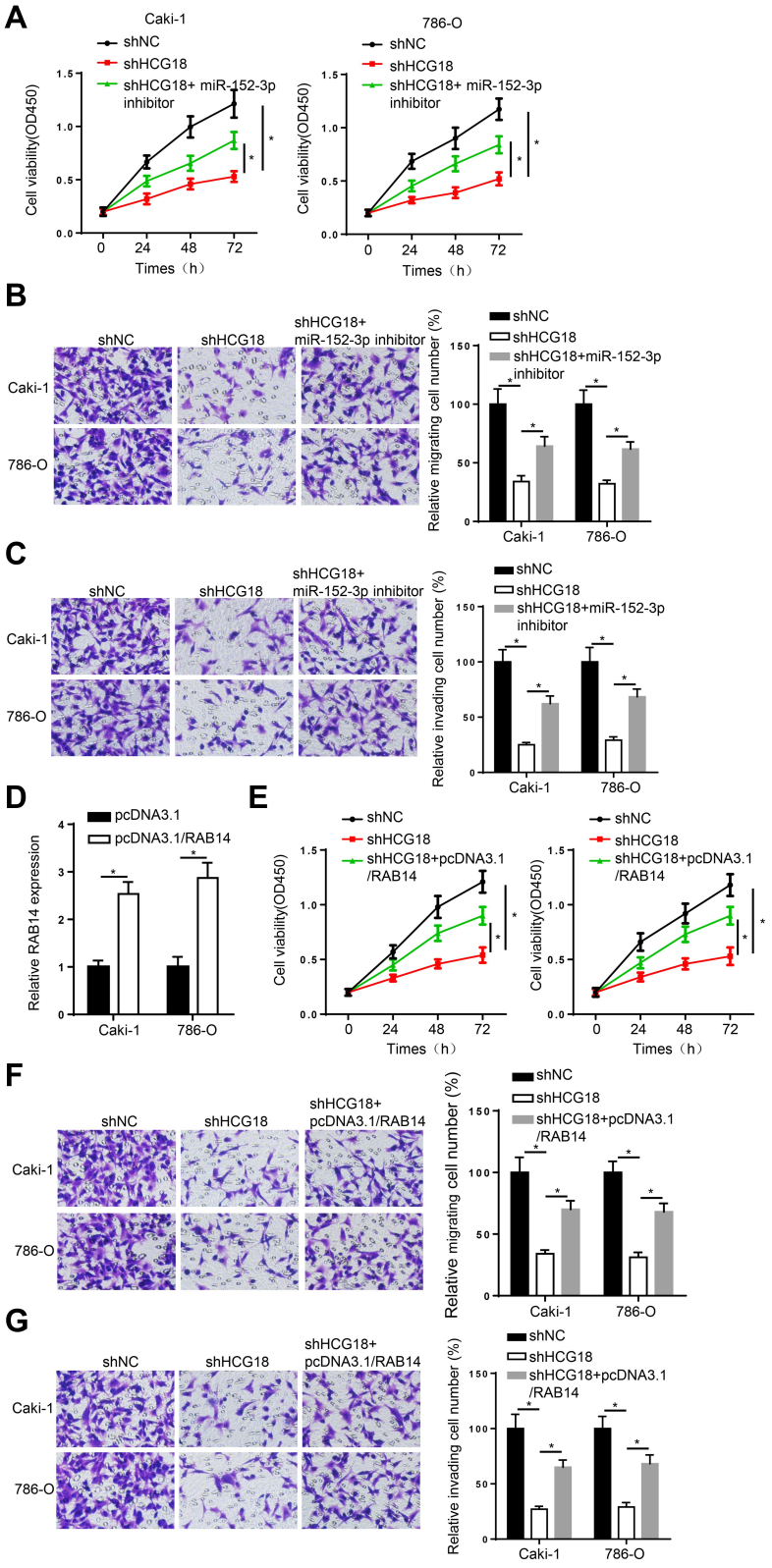

Figure 4 *HCG18* plays an oncogenic role in ccRCC by regulating the *miR-152-3p*/*RAB14* axis. (**A**–**C**) CCK-8 and transwell assays were used to test the proliferation, migration and invasion abilities in Caki-1 and 786-O cells transfected with shNC, sh*HCG18*, and sh*HCG18*+*miR-152-3p* inhibitor. (**D**) RT-qPCR assay showed the expression of *RAB14* in Caki-1 and 786-O cells transfected with pcDNA3.1/*RAB14*. (**E**–**G**) CCK-8 and transwell assays were used to measure the proliferation, migration and invasion abilities in Caki-1 and 786-O cells transfected with shNC, sh*HCG18*, and sh*HCG18*+pcDNA3.1/*RAB14*. *$p < 0.05$.

Numerous studies have revealed that *HCG18* acted as an oncogene in several tumors. For example, *HCG18* expedited the progression of colorectal cancer via targeting *miR-1271* and regulating *MTDH*/*Wnt*/*β-catenin* axis.[21] *HCG18* facilitated lung adenocarcinoma cells growth in vitro and promoted tumor growth in vivo via the *miR-34a-5p*/*HMMR* axis.[22] Herein, we manifested that *HCG18* expression was elevated in ccRCC tissues and cells. ccRCC patients with high *HCG18* expression had short overall survival time. Moreover, interference of *HCG18* markedly attenuated ccRCC cell viability and metastasis and suppressed tumor growth in vivo.

It is widely reported that lncRNA can serve as a ceRNA to sponge target miRNAs.[23,24] *MiR-152-3p* was discovered to be downregulated in various cancers. For instance, *miR-152* attenuated cell viability and induced apoptosis in breast cancer through regulating *PIK3CA*.[25] *miR-152-3p* inhibited hepatocellular carcinoma progression by targeting *CDK8*.[26] *LINC00174* expedited carcinogenesis of glioma via modulating *miR-152-3p*/*SLC2A1* axis.[27] At present study, we confirmed that *miR-152-3p* expression was declined and inversely correlated with *HCG18* in ccRCC tissues. Moreover, functional assays demonstrated that *miR-152-3p* inhibition rescued the suppressive effect of *HCG18* interference on ccRCC cell viability, migration and invasion. Therefore, our data confirmed that *HCG18* accelerated ccRCC progression via sponging *miR-152-3p*.

Additionally, miRNAs have been reported to modulate gene expressions by binding to the 3′-UTR of mRNAs.[28] Previous studies have implied that *RAB14* participated in the progression of human cancers, such as cervical cancer, gastric cancer and colorectal cancer.[29–31] In this study, we identified that *RAB14* was a downstream target of *miR-152-3p*, and *RAB14* expression was enhanced in ccRCC tissues. Moreover, *RAB14* was inversely correlated with *miR-31-5p* and positively correlated with *HCG18* expression. Besides, *RAB14* addition partially abolished the suppressive effect of *HCG18* knockdown on cell viability and metastasis. Thus, above results determined that *HCG18* promoted ccRCC progression through sponging *miR-152-3p*/*RAB14* axis.

Conclusion

The present investigated the ceRNA regulatory network of *HCG18*/*miR-152-3p*/*RAB14* in ccRCC for the first time, which might provide a new treatment target for ccRCC patients.

Funding

This work was supported by Young Talent Development Plan of Changzhou Health Commission (CZQM2020049).

Disclosure

The authors report no conflicts of interest in this work.

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