LncRNA MIR205HG accelerates cell proliferation, migration and invasion in hepatoblastoma through the activation of MAPK signaling pathway and PI3K/AKT signaling pathway

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Abstract

Background: Hepatoblastoma (HB) is identified to be the most common liver malignancy which occurs in children. Long non-coding RNAs (lncRNAs) have been implicated in numerous biological processes and diseases, including HB. LncRNA MIR205 host gene (MIR205HG) has been investigated in multiple cancers, however, its role in HB remains to be elucidated.

Methods: MIR205HG expression was analyzed by RT-qPCR. EdU, colony formation and transwell assays were implemented to measure the biological function of MIR205HG on the progression of HB. Mechanism assays were carried out to probe into the underlying mechanism of MIR205HG in HB cells.

Results: MIR205HG was significantly overexpressed in HB. Moreover, MIR205HG inhibition suppressed the proliferative, migratory and invasive capacities of HB cells. Furthermore, MIR205HG competitively bound to microRNA-514a-5p (miR-514a-5p) and targeted mitogen-activated protein kinase 9 (MAPK9) to stimulate mitogen activated protein kinase (MAPK) signaling pathway. Besides, MIR205HG also served as a sponge for microRNA-205-5p (miR-205-5p) to activate the PI3K/AKT signaling pathway.

Conclusion: MIR205HG drives the progression of HB which might provide an efficient marker and new therapeutic target for HB.

Keywords: Hepatoblastoma, MIR205HG, miR-514a-5p, miR-205-5p, MAPK9

Background

HB is the most common primary liver tumor which frequently occurs in infants and in children younger than 5 years [1]. It accounts for more than 25% pediatric hepatic tumors and almost half of those are malignant [2]. It has been reported that the occurrence of HB is correlated with Beckwith-Weidemann syndrome, familial adenomatosis polyp as well as low birth weight [3]. For the treatment of HB, complete surgical removal is of great significance in curing HB. However, the tumor is unresectable due to its extensive hepatic involvement [4], leading to the unsatisfactory overall survival rate and poor prognosis of HB patients [5, 6]. Thence, exploring therapeutic strategies of HB from a novel insight may be helpful for the treatment of HB.

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Long non-coding RNAs (lncRNAs) have been identified as valuable therapeutic targets for cancers due to their distinctive roles in cancers [7]. For instance, Li et al. have demonstrated that TUG1 exacerbates the initiation of epithelial ovarian cancer via enhancing AURKA expression (8). Luo et al. have discovered that DANCR plays a promoting role in pancreatic cancer through serving as a sponge for miR-186a-5p/ZEB1 axis [11]. Chen et al. have elucidated that IncRNA CRNDE influences the angiogenesis of HB cells through functioning as a competing endogenous RNA (ceRNA) [12]. Cui et al. have substantiated that IncRNA ZFAS1 accelerates tumor growth in HB by sequestering miR-193a-3p [13].

As a common lncRNA, MIR205HG has been also investigated in multiple malignancies, including esophageal cell carcinoma, lung squamous cell carcinoma, cervical cancer and so on [14–16]. In this study, we probed into the effects of MIR205HG on the progression of HB and investigated into the latent regulatory mechanism.

Results

LncRNA MIR205HG is overexpressed in HB and mainly located in cytoplasm of HB cells

According to GEO database (https://medworm.com/journal/geo-gene-expression-omnibus/), we discovered that lncRNA MIR205HG was up-regulated in HB tissues. Therefore, MIR205HG was chosen for our investigation. Firstly, RT-qPCR was used to examine MIR205HG expression in HepG2, HuH-7, HuH-1, HuH-6 and THLE-3 cell lines, and the results suggested that MIR205HG expression was distinctly high in HB cell lines (HepG2, HuH-7, HuH-1, HuH-6) compared to normal cell line (THLE-3) (Fig. 1A). Meanwhile, the subcellular location of MIR205HG in HB cells was explored through subcellular fractionation and FISH assays. The experimental results manifested that MIR205HG was prominently distributed in the cytoplasm of HepG2 and HuH-6 cells (Fig. 1B–C). To be summarized, MIR205HG is overexpressed in HB and mainly located in cytoplasm of HB cells.

MIR205HG contributes to cell proliferation, migration and invasion in HB cells

To evaluate the function of MIR205HG on HB progression via loss-of-function assays, MIR205HG expression was firstly cut down in HepG2 and HuH-6 cells (Fig. 2A). Due to the relative higher efficiency, sh-MIR205HG#1 and sh-MIR205HG#2 were chosen for the follow-up assays. We conducted colony formation and EdU assays to detect the effect of MIR205HG on HB cell proliferation. It’s unmasked by the results that the proliferation of HepG2 and HuH-6 cells was impeded when MIR205HG was down-regulated (Fig. 2B–C). In addition, the experimental results of wound healing and transwell assays disclosed that the migratory ability of HB cells was accordingly attenuated after MIR205HG was silenced (Fig. 2D–E). Subsequently, transwell assay using Matrigel was conducted to examine cell invasion in HepG2 and HuH-6 cells. It’s shown by the results that the number of invaded cells was also decreased when MIR205HG was interfered (Fig. 2F).

Results

MIR205HG binds to miR-514a-5p in HB cells

Based on the previous findings of subcellular fractionation and FISH assays, we made a hypothesis that MIR205HG might act as a ceRNA at post-transcriptional level. For validation, RIP assay attested that MIR205HG was enriched in precipitates by Ago2 antibodies (Fig. 3A), which indicated the existence of MIR205HG in RNA-induced silencing complex (RISC). This indicated that MIR205HG may be a ceRNA as RISC is the major workplace for miRNAs [17]. With the application of starBase (http://starbase.sysu.edu.cn/index.php), it’s discovered that only miR-514a-5p was overtly down-regulated in HB cells among the predicted 12 miRNAs (Supplementary Table 1). RT-qPCR analysis was performed to detect miR-514a-5p expression in HB cells and normal cells, uncovering that miR-514a-5p was notably down-regulated in HB cells (Fig. 3B). Subsequently, we performed RNA pull down assay to detect the binding of MIR205HG with miR-514a-5p. The results showed that MIR205HG was enriched in Bio-miR-514a-5p-Wt instead of Bio-miR-514a-5p-Mut, indicating the interaction between them (Fig. 3C). As exhibited in
Fig. 3D, the binding regions between MIR205HG and miR-514a-5p were acquired based on the data from starBase. To elevate the expression of miR-514a-5p, miR-514a-5p mimics were transfected into HepG2 and HuH-6 cells (Fig. 3E). Afterwards, we performed luciferase reporter assay to further prove the interaction between MIR205HG and miR-514a-5p. It’s unmasked that when miR-514a-5p was overexpressed, the luciferase activity of MIR205HG-Wt was reduced (Fig. 3F). In conclusion, miR-514a-5p binds to MIR205HG.

MIR205HG modulates MAPK9 expression and activates MAPK signaling pathway by competitively binding to miR-514a-5p

We conducted luciferase reporter assay for detecting the luciferase activities of common signaling pathways when MIR205HG was depleted. It was discovered that MIR205HG was associated with MAPK signaling pathway for that MIR205HG knockdown led to the decrease in the luciferase activity of MAPK signaling pathway (Fig. 4A). As MAPK9 is a key member of the MAPK
Fig. 2 MIR205HG contributes to cell proliferation, migration and invasion in HB cells. 

A. MIR205HG expression was cut down in HepG2 and HuH-6 cells.

B–C Colony formation and EdU assays evaluated the proliferative capacity of HB cells after MIR205HG was silenced.

D. The migratory capacity of HB cells was evaluated by wound healing assay.

E–F Transwell assays were implemented to observe the migration and invasion of HB cells. Each experiment was performed in triplicate. One-way ANOVA was used for statistics. **P < 0.01.
signaling pathway, we speculated that MIR205HG might activate MAPK signaling pathway via targeting MAPK9. Western blot showed that after MIR205HG was silenced, the protein levels of MAPK9 and its downstream proteins, p-ERK, p-JNK and p-P38 were all decreased, indicating the positive correlation (Fig. 4B). As depicted in
Fig. 4C, the binding regions between miR-514a-5p and MAPK9 were obtained. The results of RIP assay indicated the coexistence of MIR205HG, miR-514a-5p and MAPK9 in RISC, suggesting the ceRNA mode (Fig. 4D). Meanwhile, we performed luciferase reporter assay for the detection of the interaction between miR-514a-5p and MAPK9. The results unearthed that when miR-514a-5p was enhanced, the luciferase activity of MAPK9 3’UTR-Wt was attenuated (Fig. 4E). Then, miR-514a-5p inhibitor was transfected into HB cells to lessen miR-514a-5p expression (Fig. 4F). Subsequently, rescue experiments were performed. RT-qPCR and western blot were applied to detect MAPK9 expression after the transfection of sh-NC, sh-MIR205HG#1 or sh-MIR205HG#1 + miR-514a-5p inhibitor. The data manifested that MIR205HG deficiency led to a decrease on MAPK9 mRNA and protein levels and this effect was completely restored by miR-514a-5p inhibitor (Fig. 4G-H). Taken together, MIR205HG mediates MAPK9 expression by competitively binding to miR-514a-5p.

**MIR205HG sponges miR-205-5p to activate PI3K/AKT signaling pathway**

According to the previous findings, we made a conjecture that miR-205-5p was also regulated by MIR205HG as MIR205HG is a host gene for miR-205. Firstly, we performed RT-qPCR analysis to detect miR-205-5p after the knockdown of MIR205HG. The results suggested that silencing of MIR205HG exerted no influence on miR-205-5p expression (Fig. 6A). We then performed RNA pull down assay to detect the interaction between MIR205HG and miR-205-5p. The results showed that MIR205HG was enriched in biotin-labeled miR-205-5p-Wt probe instead of biotin-labeled miR-205-5p-Mut probe, suggesting the interaction (Fig. 6B). Besides, after the overexpression of miR-205-5p by miR-205-5p mimics, luciferase reporter assay further confirmed the interaction between miR-205-5p and MIR205HG (Fig. 6C–D). It has been reported that MiR-205-5p is involved in PI3K/AKT signaling pathway [18]. We performed western blot analysis to detect the activation level of p-PI3K and p-AKT in HepG2 and HuH-6 cells. The transfection of miR-205-5p mimics inactivated the PI3K/AKT signaling pathway as evidenced by the reduction of p-PI3K and p-AKT (Fig. 6E). To affirm that whether MIR205HG contributed to HB progression by sponging miR-514a-5p and miR-205-5p, rescue assays were implemented. MiR-205-5p expression was firstly reduced after transfection of miR-205-5p inhibitor (Additional file 3: Fig. S2A). Next, we performed functional experiments to detect HB cell progression after the transfection of sh-NC, sh-MIR205HG#1, sh-MIR205HG#1 + miR-205-5p inhibitor or sh-MIR205HG#1 + pcDNA3.1/MAPK9. As attested by colony formation and EdU assays, MIR205HG depletion suppressed the proliferation of HepG2 cells while this effect was partially counterbalanced by miR-514a-5p inhibitor or MAPK9 overexpression (Fig. 5B–C). Similarly, wound healing and transwell assays proved that the weakened migratory and invasive capacities of HB cells due to MIR205HG interference were also partially rescued by miR-514a-5p down-regulation or MAPK9 over-regulation (Fig. 5D–F). Overall, MIR205HG contributes to HB development via modulating miR-514a-5p/MAPK9 axis.
Fig. 4 (See legend on previous page.)
Discussion
It is implicated that MIR205HG widely participates in diverse types of cancers. For example, Li et al. have certified that MIR205HG aggravates the process of esophageal cell carcinoma through sponging miR-214 and regulating SOX4 expression [14]. Liu et al. have identified that MIR205HG acts as an oncogene in lung squamous cell carcinoma [15]. Dong et al. have proved that MIR205HG influences the biological activities of cervical cancer cells by targeting SRSF1/KRT17 axis [16]. In accordance with these findings, MIR205HG was discovered to be prominently up-regulated in HB cells. Functionally, silencing of MIR205HG impeded cell proliferation, migration and invasion in HB.

Competing endogenous RNA (ceRNA) network is determined as an important regulatory mechanism in cancers [19]. In our study, we observed that MIR205HG was mainly accumulated in the cytoplasm of HB cells. As a result, we speculated that MIR205HG might modulate mRNAs to exert its functions by modulating miRNAs. As expected, miR-514a-5p was selected due to the fact that it was most down-regulated in HB cells among the predicted miRNAs from starBase. The strong affinity of MIR205HG with miR-514a-5p was also confirmed by mechanism assays.

It has been found that MAPK signaling pathway is involved in cell malignant phenotypes, including cell proliferation, cell differentiation and cell migration [20]. As a key member in the MAPK signaling pathway, MAPK9 is also correlated with several diseases, including non-small-cell lung carcinoma [21], haemophilia A [22], and type 1 diabetes [23]. Through our investigation, MAPK9 was discovered to be a downstream target of miR-514a-5p. Thence, MIR205HG activates MAPK signaling pathway via targeting miR-514a-5p and regulating MAPK9 expression. Besides, down-regulation of miR-514a-5p or up-regulation of MAPK9 partially restored the suppressed cell proliferation, migration and invasion on account of MIR205HG depletion.

It is acknowledged that MIR205HG acts as the host gene of miR-205. Meanwhile, miR-205-5p has been reported to play suppressive roles in many cancers. For instance, miR-205-5p suppresses the development of prostatic carcinoma cells via being regulated by p63 or targeting ZEB1 [24] [25]; moreover, the cell progression of osteosarcoma [26] and pancreatic cancer [27] have been reported to be inhibited by miR-205-5p. Similarly, we demonstrated that miR-205-5p also interacted with MIR205HG and participated in the activation of PI3K/AKT signaling pathway. Eventually, rescue assays attested that ablation of miR-514a-5p and miR-205-5p completely counteracted the suppressive role of MIR205HG insufficiency in HB progression.

Conclusion
All in all, MIR205HG was highly expressed in HB cells. Functionally, MIR205HG interference hampered the proliferative, migratory and invasive capacities of HB cells. From the perspective of mechanism, MIR205HG competitively bound to miR-514a-5p to modulate MAPK9 expression and stimulate MAPK signaling pathway. Besides, MIR205HG had a binding with miR-205-5p and activated PI3K/AKT signaling pathway.

Methods
Cell lines and culture
HB cell lines including HepG2, HuH-7, HuH-1, HuH-6 and normal epithelial cell line (THLE-3) were selected for this investigation. HepG2 and THLE-3 cell lines were both obtained from ATCC (Manassas, VA, USA) while HuH-7, HuH-1, HuH-6 cell lines were purchased from Huatuo Biological Technology Co., Ltd. (Shenzhen, China). Among them, HepG2 and THLE-3 cell lines were cultured in Eagle’s Minimum Essential Medium (EMEM) and BEGM respectively. HuH-7 and HuH-6 cells were incubated in Dulbecco’s Modified Eagle’s medium (DMEM) while HuH-1 cell line was cultured in RPMI-1640 Medium. All mediums contained 10% fetal bovine serum (FBS) and incubated at 37 °C with 5% CO₂.

Transfection of cells
The knockdown of MIR205HG in HB cells was implemented by transfection with sh-MIR205HG#1/2/3 plasmids acquired from Ribobio (Guangzhou, China). MiR-514a-5p mimics/inhibitor, miR-205-5p mimics/inhibitor and their respective negative controls were commercially obtained from GenePharma (Shanghai, China). Furthermore, pcDNA3.1 vectors were obtained from Invitrogen to overexpress MAPK9. Lipofectamine 2000 was used to transfect HB cells as per the instruction of manufacturer.
Fig. 5 (See legend on previous page.)
RNA extraction and quantitative real-time PCR (RT-qPCR)

The total RNA was subjected to extraction from cells using Trizol reagent. PrimeScript™ RT Master Mix (TaKaRa, Shiga, Japan) was used to obtain cDNA through reverse transcribing two micrograms of total RNA. SYBR Premix Ex TaqTM II (Takara Bio, Tokyo, Japan) was applied to perform RT-qPCR. GAPDH and U6 were utilized as internal references for RT-qPCR. Each experiment was performed in triplicate. Student’s t test, one-way ANOVA and two-way ANOVA were adopted for statistics. **P < 0.01
references. The $2^{-\Delta\Delta Ct}$ method was used to evaluate gene expression. The experiment was implemented in triplicate.

**Colony formation assay**
In brief, cultured cells were inoculated into 6-well plates. After 14 days of incubation, cells were subjected to fixation using ethanol, followed by the staining with crystal violet. Finally, the stained cell colonies were observed and counted. The experiment was independently conducted in triplicate.

**5-ethynyl-20-deoxyuridine (EdU) staining assay**
Cells at logarithmic growth stage were taken and seeded in 96-well plates with $4 \times 10^3 \sim 1 \times 10^5$ cells per well. Subsequently, the cells were cultured to the normal growth stage. A total of 50 μM EdU culture medium was prepared via the dilution of EdU solution (reagent A) by 1:1000. The cells were subjected to fixation, followed by the staining using Apollo. The assay was independently conducted in triplicate.

**Wound healing assay**
A total of $3 \times 10^4$ cells were seeded into 6-well plates and cultured in serum-free medium for 24 h at 37 °C. When cells reached 80% confluence, a straight scratch wound was made. Then cells were cultured for another 24 h, and scratches were monitored and photographed at 0 and 24 h. An inverted microscope (DMi1, Leica, Wetzlar, Germany) at 100× magnification was used to monitor the wound healing. The assay was independently conducted in triplicate.

**Transwell assay**
The transfected HB cells were harvested and put into the upper chamber of Transwell inserts. Afterwards, 10% FBS was added to the lower chamber. The chambers coated with Matrigel (BD Biosciences, San Diego, CA, USA) were used for invasion assay, while without Matrigel for migration assay. After 24 h, migrated or invaded cells were finally visualized using optical microscope (Olympus) after being stained by crystal violet. The assay was independently conducted in triplicate.

**Subcellular fractionation**
Cytoplasmic and nuclear RNA were isolated with the employment of PARIS™ Kit (Ambion, Austin, TX, USA) in line with the manufacturer’s protocols. Cells were washed in PBS. Afterwards, cell samples were treated with cell fractionation buffer and disruption buffer. GAPDH and U6 were seen as the cytoplasmic control and the nuclear control respectively. The isolated RNA in the nucleus and the cytoplasm was measured by PCR analysis. The assay was independently conducted in triplicate.

**Fluorescent in situ hybridization (FISH)**
RNA FISH probe (Ribobio) targeting MIR205HG was designed and utilized as per the guide of provider. After hybridization using FISH probe, cells were counterstained by DAPI solution, followed by the detection using fluorescence microscope (Olympus). The experiment was independently performed in triplicate.

**RNA pull down assay**
RNA pull down assay was implemented by use of Pierce Magnetic RNA–Protein Pull-Down Kit (Thermo Fisher Scientific, Waltham, MA, USA). The cell extracts from HepG2 and HuH-6 cells were used for incubation with biotinylated probes of miR-514a-5p-WT/Mut or miR-205-5p-WT/Mut. After adding magnetic beads, relative RNA enrichment was assessed by RT-qPCR. The experiment was independently performed in triplicate.

**RNA-binding protein immunoprecipitation (RIP)**
Z-Magna RIP™ RNA-binding Protein Immunoprecipitation kit (Millipore Corporation, USA) was adopted to perform RIP assay. Anti-Ago2 (Abcam) antibody as well as anti-IgG (Abcam) antibody were used for immunoprecipitation with cell lysates. Finally, the RNA complexes were subjected to extraction for RT-qPCR analysis. The experimental procedure was independently carried out in triplicate.

**Luciferase reporter assay**
MIR205HG or MAPK9 sequence with the wild-type (Wt) and mutant type (Mut) miR-514a-5p binding sites was inserted into pmirGLO dual-luciferase vector to form pmirGLO-MIR205HG Wt/Mut and pmirGLO-MAPK9 3’-UTR-Wt/Mut respectively. Later, miR-514a-5p mimics or control mimics were co-transfected with the reporter construct into HB cells. Similarly, MIR205HG sequence of Wt and Mut of miR-205-5p was also utilized to pmirGLO-MIR205HG Wt/Mut and then was co-transfected with NC mimics and miR-205-5p mimics into HB cells. After 48 h, luciferase activity was measured via the employment of the Dual Luciferase Reporter Assay Kit (Promega, Madison, WI, USA). The assay was independently conducted in triplicate.

**Western blot analysis**
Separated protein samples were subjected to transference to PVDF membranes (Millipore, Bedford, MA, USA). After being blocked with skimmed milk, the membranes were subjected to incubation with the following primary antibodies against MAPK9, ERK, p-ERK, JNK, p-JNK,
P38, p-P38, p-P13K, P13K, p-AKT, AKT and GAPDH. Subsequently, the blots were subjected to incubation with secondary antibody. At last, Chemiluminescence system (GE Healthcare, Chicago, USA) was applied for the quantification of proteins. The assay was independently conducted in triplicate.

**In vivo study**
Ten male BALB/c nude mice (4–5 weeks old) were purchased from the Beijing Chilres River Experimental Animal Technology Co., LTD. A total of $1 \times 10^7$ HepG2 cells stably transfected with sh-NC or sh-MIR205HG#1 were independently injected subcutaneously into the back of each nude mouse. Seven days after the injection, tumor volume was recorded every 3 days. Twenty-eight days after the injection, all the mice were sacrificed for tumor weighing.

**Statistical analysis**
Experimental data were subjected to analysis by use of SPSS 22.0 statistical software package. All data were presented as mean ± standard deviation (SD). For differences comparison between two groups or more, Student’s t-test or ANOVA was adopted. All the experiments were independently implemented in triplicate. Differences were considered to be statistically significant when $P < 0.05$.

**Abbreviations**
HB: Hepatoblastoma; lncRNAs: Long non-coding RNAs; MIR205HG: MIR205 host gene; miR-514a-5p: MicroRNA-514a-5p; MAPK9: Mitogen-activated protein kinase 9; miR-205-5p: MicroRNA-205-5p; ceRNA: Competing endogenous RNA; ATCC: American Type Culture Collection; EMEM: Eagle’s Minimum Essential Medium; DMEM: Dulbecco’s Modified Eagle’s medium; FBS: Fetal Bovine Serum; RT-qPCR: Quantitative real-time PCR; EdU: 5-Ethynyl-2’-deoxyuridine; FISH: Fluorescence in situ hybridization; RIP: RNA immunoprecipitation; WT: Wild-type; Mut: Mutant type; SD: Standard deviation.

**Supplementary Information**
The online version contains supplementary material available at [https://doi.org/10.1186/s13062-021-00309-3](https://doi.org/10.1186/s13062-021-00309-3).

**Acknowledgements**
We sincerely thank for the help provided by all lab personnel in this research.

**Authors’ contributions**
We Zhang designed the study. Feng Liang and Qiongfeng Li took charge of the material collecting and performed experiment. Hong Sun and Fei Li prepared all the figures. Wei Zhang and Zhibo Jiao analyzed all data. Jie Lei wrote the study. All authors read and approved the final manuscript.

**Funding**
No funding.

**Availability of data and materials**
Not applicable.

**Declarations**

**Ethics approval and consent to participate**
The mice experiments were approved by the First Affiliated Hospital of Hebei North University.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare that they have no competing interests.

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**Received:** 17 June 2021  **Accepted:** 12 October 2021  **Published online:** 07 January 2022

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