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Original Article

Downregulation of miR-19a promotes the HBV replication via suppressing type I IFN responses in pregnant women

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Abstract: HBV infection is one of the most harmful infectious diseases worldwide, especially for pregnant women. The present study was aimed to investigate the molecular mechanism of miRNA regulating the virus replication in hepatitis B virus (HBV)-infected pregnant women. Firstly, microRNA array was used to select PBMC miRNA expression in 10 healthy controls, 10 pregnant women infected with HBV. MiR-19a was found significantly downregulated in pregnant women with HBV infection ($P<0.01$). Furthermore, we found that treatment of miR-19a inhibitors promotes the replication of HBV in HepG2 cells. In order to further investigate the mechanism of miR-19a regulating HBV, we identified that miR-19a directly targets in the SOCS1 mRNA, the protein encoded by which is a negative regulator of type I IFN response. And moreover, we demonstrated that downregulation of miR-19a suppressed type I IFN response in HepG2 cells infected with HBV, while miR-19a mimics enhanced type I IFN response in HBV infection HepG2 cells. Based on the above findings, it is, therefore, concluded that HBV-decreased miR-19a may promote the replication of HBV through a negative regulatory mechanism of type I IFN response in pregnant women.

Keywords: HBV, pregnant women, SOCS1, miR-19a

Introduction

Hepatitis B virus (HBV) is a very common human pathogen. Infection of HBV leads to a major cause of fibrosis [1], cirrhosis and the development of hepatocellular carcinoma (HCC) [2, 3]. More seriously, for pregnant women, once infected the virus during pregnancy, HBV positive mothers can vertically transmit the infection to their infants, and thereby causing a high risk of maternal death [4-6]. HBV infection, therefore, has become one of the most harmful infectious diseases worldwide.

MicroRNAs (miRNA) are endogenous non-coding RNA transcripts of approximately 18-22 nucleotides in length, which bind to the 3'-untranslated region of mRNAs and induce degradation of targeted mRNA [7]. It has been acknowledged that miRNA plays important regulatory roles in cell differentiation, development and disease progression [8, 9]. Many microRNAs related to virus infection disease, such as HBV, HCV infection, have been reported [10, 11]. Recent reports have demonstrated that several miRNAs are deregulated by HBV infection and contribute to viral replication and pathogenesis [10, 12]. However, the molecular mechanism of miRNA on HBV replication in pregnant women is not fully understood.

The present study aims to investigate the basic principles of miRNAs regulating HBV infection in pregnant women. In this study, firstly, we report here that miR-19a was significantly down in HBV infection pregnant women. Next, we demonstrated that down-regulation of miR-19a enhances the HBV replication. In order to further investigate the mechanism of miR-19a regulating HBV, we identified that miR-19a directly targets SOCS1 mRNA. And furthermore, we demonstrated that downregulation of miR-19a inhibited type I IFN response. We concluded that in pregnant women infected with HBV, downregulation of miR-19a upregulates its target gene SOCS1, which inhibits type I IFN

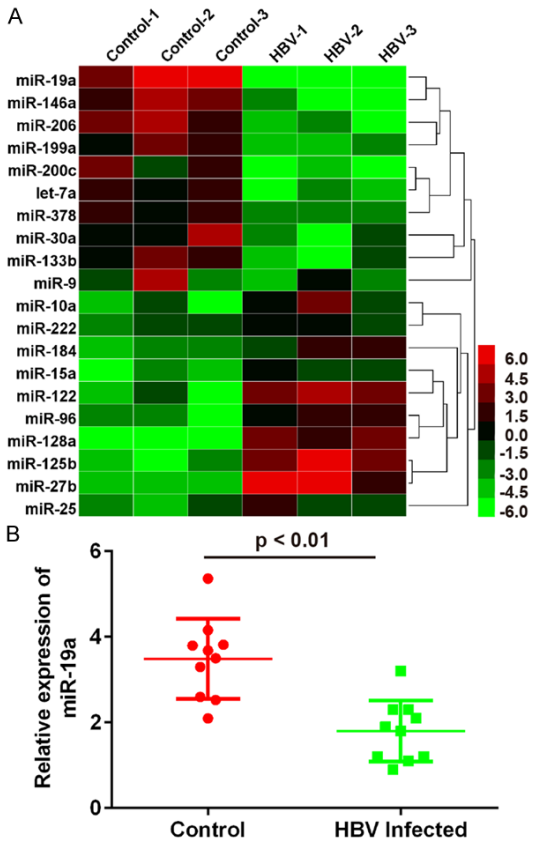

Figure 1. miRNA expression in PBMC of pregnant women infected with HBV. A. Microarray analysis for miRNA was performed with RNA extracts from PBMC of pregnant women infected with HBV. Heat map analysis represented the significantly up/down expressed miRNAs. Notably, miR-19a was the most significant down expression miRNA in PBMC of HBV infected pregnant women compared to healthy controls. B. MiR-19a expression was validated by qRT-PCR in PBMC of pregnant women infected with HBV.

response and therefore enhance HBV replication.

Materials and methods

Participants

Ten pregnant women diagnosed with HBV infection and ten healthy volunteers were included in the control group of our research. Written and verbal informed consent was obtained from patients and healthy volunteers. All of the procedures of the study were approved by Research Ethics Committee of Capital Medical University. A total of 5 ml peripheral blood was collected from each patient and healthy controls and was transferred into EDTA anticoagulation tubes. The PBMC obtained from the first cohort was immediately lysed by adding 0.5 mL Lysis Buffer (Ambion, Austin, TX, USA).

Microarray for detecting miRNA expression and data analysis

The RNA from the PBMC was purified using a mirVana RNA Isolation Kit (Ambion) according to the manufacturer's instructions. All of the RNA samples were quality controlled by measuring the optical density at 260 and 280 nm and by analyzing an aliquot of the RNA preparation on an Agilent 2100 Bioanalyzer using RNA 6000 Nano chips (Agilent Technologies, Santa Clara, CA, USA). Human miRNA V3 microarray and miRNA Complete Labeling and Hyb Kit (Agilent Technologies) were used for the RNA labeling and hybridization. The processing steps and fluorescence scanning were performed by a commercial service provider (Agilent Technologies).

Data were analyzed using ANOVA and t tests. Two databases, TargetScan (http://www.targetscan.org) and PicTar (http://pictar.mdc-berlin.de/), were used for miRNA target prediction.

Cell culture

The cells of HepG2 (American Type Culture Collection, USA), which constitutively replicated HBV, were cultured in Dulbecco's modified Eagle medium (DMEM) with 10% fetal bovine serum (Life Technologies Inc, Gaithersburg, MD, USA). Cells were incubated at 37°C in a humidified atmosphere with 5% CO_2.

Quantitative real-time PCR

For qPCR, RNA was reverse transcribed to cDNA from 100 ng of total RNA by using a Reverse Transcription Kit (Takara). Real-time PCR (RT-PCR) were performed with SYBR Green (Takara, Dalian, China). All protocols were carried out according to the manufacturer's instructions. Fold variations between RNA samples were calculated after normalizing to the U6 RNA or the GAPDH mRNA. The primer sequences in terms of GAPDH, miR-19a were listed as follows: GAPDH: Forward (F): 5'-CCA TGT TCG TCGTGG GTG TG-3', Reverse (R): 5'-CCT GCC TTC CTC ACC TGA TG-3'; U6: F: 5'-GCTTCGGCAGCACATATACTAAAAT-3', R: 5'-CGCTTCACGAATTTGCGTGTCAT-3'; miR-19a-RT: GTCGTATCCAGTGCAGGGTCCGAGGTATTCG-

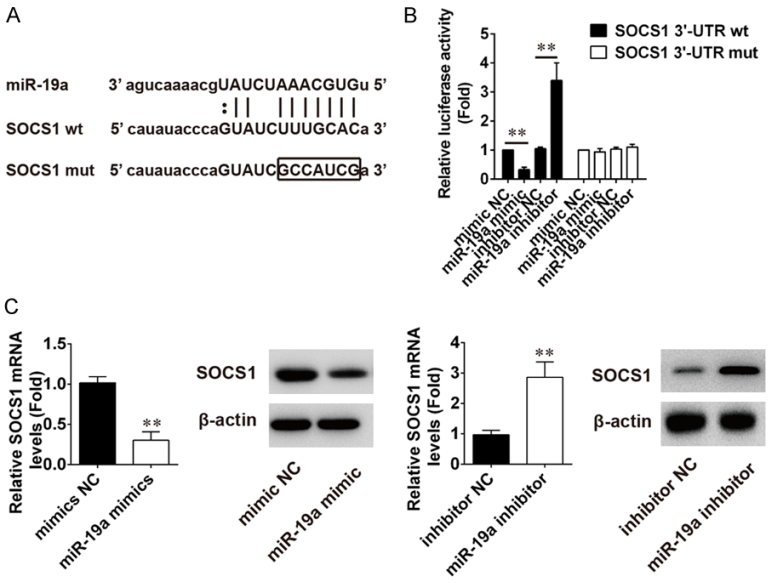

Figure 2. SOCS1 is the direct target of miR-19a. A. A putative miR-19a-binding site exists in the 3'-UTR of SOCS1 mRNA and point mutations were generated in the binding site. B. The luciferase reporter plasmid containing wild-type or mutant SOCS1 3'-UTR was cotransfected into HEK-293T cells with miR-19a mimic/inhibitor or miR-NC. Luciferase activity was determined by the dual luciferase assay and shown as the relative firefly activity normalized to Renilla activity. Each bar represents the mean and s.d. of three independent experiments. *P<0.05, **P<0.01. C. The expression of SOCS1 was detected by Real-time PCR and Western blotting after treatment with miR-19a mimics. U6 and β-actin was used as control. *P<0.05; **P<0.01. D. The expression of SOCS1 was detected by Real-time PCR and Western blotting after treatment with miR-19a inhibitor. U6 and β-actin was used as control. *P<0.05; **P<0.01.

CACTGGATACGACTCAGTTT, miR-19a F: 5'-CTGGAGTGTGCAAATCTATGC-3', R: 5'-GTGCAGGGTCCGAGGT-3'. The SOCS1 primer sequences were designed as: F: 5'-GATAATGTAGTTTTTATAGTAGTAGAGTTT-3', R: 5'-TAATACTCCAACAACTCTAAAAAACAATC-3'.

Real-time PCR assay was performed on a StepOne Plus Real-Time PCR System (Applied Biosystems, USA), and each RT reaction was performed in triplicate, including no-template controls. The reaction was performed in the following conditions: 5 min at 95°C, followed by 40 cycles with denaturing for 15 s at 95°C and annealing for 50 s at 60°C. The relative quantification of miR-34a was normalized to the expression of U6 and GAPDH using the $2^{-\Delta\Delta CT}$ method, respectively.

Luciferase reporter assay

MiR-19a mimics, miR-19a inhibitors, and miRNA normal control (miR-nc) were purchased from GenePharma (Shanghai, China). After placed into 48-well plates, cells were cotransfected with miR-19a, luciferase reporter plasmids (200 ng) containing wild-type (WT) or mutant type (Mut) of SOCS1 3'-UTR. Fourty-eight hours after transfection, luciferase activities were measured using the dual-luciferase reporter assay system (Promega). Each transfection was performed in triplicate.

Western blot

Total cell protein was abstracted from cells with different treatments. The concentration of the protein was measured by BCA protein assay kit (Beyotime, Shanghai, China), following manufacturer's instruction. Samples were electrophoresed by using 10% SDS-PAGE. The protein was then transferred onto a PVDF (polyvinylidene fluoride) membrane (Bio-Rad, USA). After blocking in skim milk, the membranes were incubated with specific antibodies. Autoradiograms were quantified by densitometry (Quantity One software; Bio-Rad). β-actin was used as internal reference; goat anti-SOCS1 (1:1000) was purchased from Sigma. Densitometric levels of miR-19a signals were quantified and shown as their ratio to actin.

Analysis of HBV DNA

Viral loads in the supernatants were quantified by real-time PCR using Diagnostic Kit for Quantification of HBV DNA (Da-An, Guangzhou, China).

Statistical analysis

Data were shown as mean ± standard deviation (SD) from at least three separate experiments. The Student's t test and one-way ANOVA were used to conduct the comparison of the different protein, mRNA, luciferase reporter and miRNA expression levels. Statistical analy-

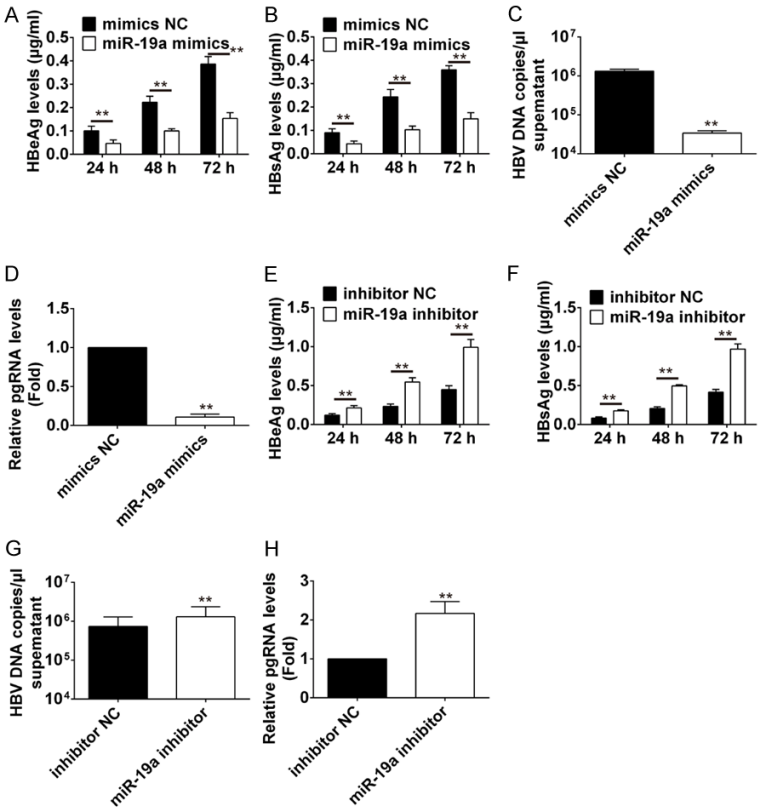

Figure 3. MiR-19a inhibits HBV replication in HepG2 cells. HepG2 cells were cotransfected with 50 nM of miR-19a mimic or a randomized oligonucleotide as mock and pHBV. (A) The secretion of HBeAg was measured by ELISA at 24, 48, and 72 hours after transfection, respectively. (B) The secretion of HBsAg was measured by ELISA at 24, 48, and 72 hours after transfection, respectively. (C) HBV DNA levels in the supernatant were analyzed by real-time PCR. (D) HBV pgRNA levels were measured by real-time PCR. GAPDH was used as an internal control. (E-H) HepG-2 cells were co-transfected with 50 nM of miR-19a inhibitor or mock and pHBV. The levels of HBeAg and HBsAg in the supernatant were detected by ELISA (E, F). HBV-DNA (G) and RNA (H) levels were detected by real-time PCR. Data are presented as the mean ± SD from three independent experiments. **P<0.01 compared with mock.

ses were performed by SPSS 16.0 software. A *P*-value less than 0.05 was considered statistically significant difference.

Results

MiR-19a is significantly down-regulated in HBV infected pregnant women

To identify miRNA participating in the pathogenesis of HBV-induced liver disease in pregnant women, we used microarray to investigate the miRNA expression profiles in PBMC from ten HBV patients and ten healthy controls. MiRNAs were considered as differentially expressed when differences in expression levels were significant both in Student's t test (P<0.01) and analysis of microarray test (q value <5%). Among the individual miRNAs displayed on the microarray, twenty miRNAs were significantly up-/down-regulated in PBMC of HBV infected pregnant women compared to controls. The most significantly down-regulated miRNA was miR-19a (**Figure 1A**). Next, we carried out real-time PCR to detect the expression of miR-19a in PBMC of HBV infected pregnant women, and compared with controls. Results showed that miR-19a was significantly down-regulated in pregnant women infected with HBV (P<0.01) than that of controls (**Figure 1B**). Summarizing, these data demonstrated that miR-19a was down-regulated in pregnant women infected with HBV.

Prediction of miR-19a targets in the SOCS1 mRNA

We used bioinformatic tools (Targetscan and miRBase) to identify the target gene of miR-19a. As shown in **Figure 2A**, SOCS1 is the theoretical target gene of miR-19a. To further validate whether SOCS1 is a direct target gene, we fused the 3'-UTR region of SOCS1 to a luciferase system. As shown in **Figure 2B**, miR-19a obviously suppressed the luciferase activities of the 3'-UTR segment of SOCS1, whereas miR-19a inhibitor significantly increased the luciferase activities of the 3'-UTR segment of SOCS1, but not those of the construct containing a mutant binding site (SOCS1 3'-UTR-MUT), compared to the NC group.

Real-time PCR and western blot analysis showed that the expression of SOCS1 was significantly decreased after miR-19a mimic treatment both at mRNA and protein levels (**Figure 2C**). While expression of SOCS1 both at mRNA and protein levels were significantly increased after miR-19a inhibitor treatment, compared to the NC group (**Figure 2D**).

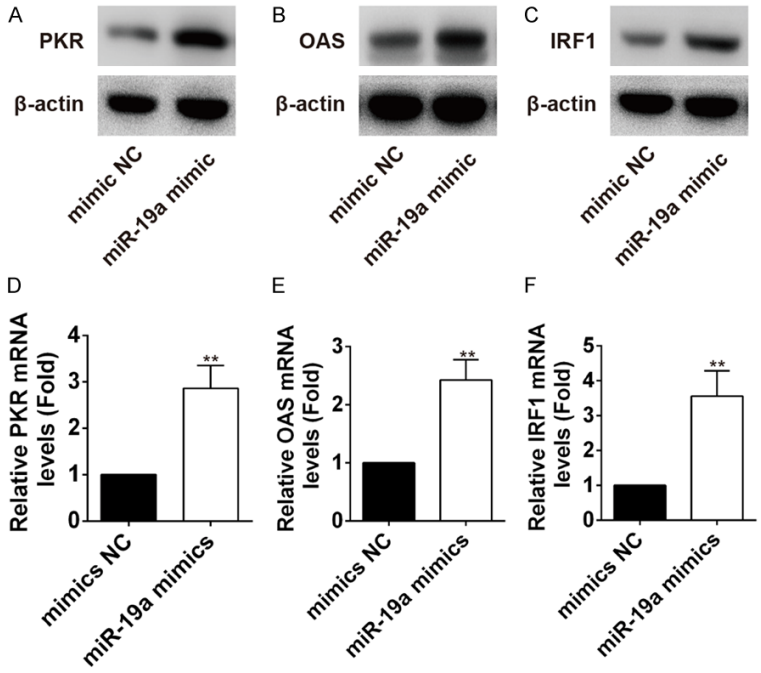

Figure 4. miR-19a mimics upregulated the expression of PKR, OAS and IRF1. A-C. HepG2 cells were treated with miR-19a mimics. Total cell lysates were harvested at 48 hours post-transfection and immunoblots probed with antibodies for PKR, OAS, IRF1 and GAPDH. D-F. HepG2 cells were treated with miR-19a mimics. Total RNA was harvested at 48 hours post-transfection for RT-qPCR of PKR, OAS and IRF1 mRNA levels. MiR-19a upregulated the expression of PKR, OAS and IRF1 both at protein and mRNA levels (data are represented as mean ± SD, *P<0.05; **P<0.01).

Down-regulation of miR-19a enhances the HBV replication

Transfection of miR-19a mimic in the miR-19a low-expressed HepG2 cells resulted in a 2 to 3-fold decrease of HBeAg (**Figure 3A**) and HBsAg expressions (**Figure 3B**), and about a 20-fold decrease of HBV-DNA levels (**Figure 3C**) in the cell supernatant. Consistently, the treatment with miR-19a mimic significantly reduced HBV pgRNA mRNA transcripts, as shown by real-time PCR (**Figure 3D**), indicating that miR-19a mimics inhibits HBV replication.

Inversely, when HepG2 cells were transfected with 50 nM of chemically synthesized miR-19a inhibitor for antisense inhibition of endogenous miR-19a, significant increases of HBeAg and HBsAg expressions were observed compared with mock-treated cells (**Figure 3E**, **3F**) (both P<0.01 at all time points). Inhibition of miR-19a caused a clear increase (P<0.01) of HBV-DNA copies in the cell supernatant (**Figure 3G**). Real-time PCR analysis showed that the HBV pgRNA levels were also significantly increased (P<0.01) (**Figure 3H**).

Downregulation of miR-19a suppressed type I IFN response

As previous study shows that SOCS1 is a negative regulator of type I IFN response, we wondered whether miR-19a, downregulated by HBV, would affect type I IFN response. HepG2 cells were treated with miR-19a mimics or inhibitors, respectively. The effects of miR-19a on the expression of ISGs, including PKR, OAS and IRF1 were investigated. Western blot analysis showed that the protein expression levels of PKR, OAS and IRF1 were all increased by treated with miR-19a mimics (**Figure 4A-C**). Then, real-time PCR assay also confirmed that miR-19a mimics would upregulated the mRNA levels of PKR, OAS and IRF1 (**Figure 4D-F**). Whereas, when cells treated with miR-19a inhibitors, protein expression levels of PKR, OAS and IRF1 were all downregulated (**Figure 5A-C**). Real-time PCR analysis also indicated that when transfected with miR-19a inhibitors, the mRNA expression levels of PKR, OAS and IRF1, which were all ISGs, were all downregulated (**Figure 5D-F**).

Discussion

MicroRNAs are a large class of non-coding RNA molecules of approximately 22 nucleotides, that play important roles in diverse cellular processes including immune function, apoptosis and tumorigenesis [13]. MicroRNAs are messengers during interferon-virus interplay and are involved in antiviral immunity. Serum microRNA has been used as potential biomarkers for early diagnosis of hepatitis B/C virus infection in patients [14-16]. MiR-19a, the most abundant liver-specific miRNA, plays a central role in the progression of liver diseases, owing to its ability to control gene networks and signaling pathways [17]. It has been found that

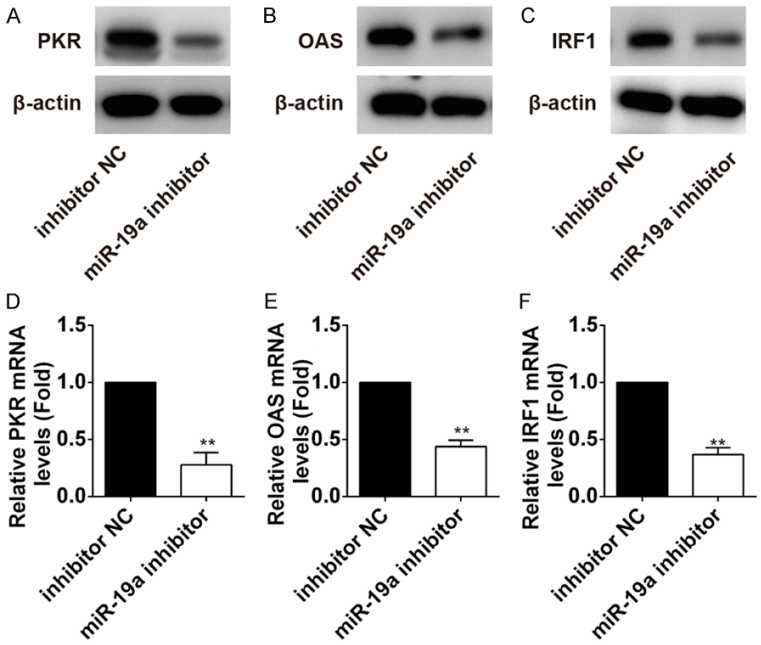

Figure 5. miR-19a inhibitors downregulated the expression of PKR, OAS and IRF1. A-C. HepG2 cells were treated with miR-19a inhibitor. Total cell lysates were harvested at 48 hours post-transfection and immunoblots probed with antibodies for PKR, OAS, IRF1 and GAPDH. D-F. HepG2 cells were treated with miR-19a inhibitor. Total RNA was harvested at 48 hours post-transfection for RT-qPCR of PKR, OAS and IRF1 mRNA levels. MiR-19a inhibitor downregulated the expression levels of PKR, OAS and IRF1. (Data are represented as mean ± SD, *P<0.05; **P<0.01).

miR-19a was differentially regulated by hepatitis B virus X protein and involve in cell proliferation in hepatoma cells [18]. In this study, we found that expression of serum miR-19a was significantly decreased in HBV pregnant women. Furthermore, we found that downregulation of miR-19a enhance HBV replication. These findings suggested that miR-19a plays an important role in hepatitis virus infection in pregnant women. However, the mechanisms of these effects remain unclear. In order to investigate the molecular mechanism of HBV infected pregnant women with lower miR-19a abundance in the serum, we carried out the following experiments.

Previous studies have showed that miR-19a can also target several other genes in hepatocytes. For example, miR-19a regulates PTEN expression to mediate glycogen synthesis in hepatocytes [19]. MiR-19a directly targets Cyclin D1 expression in hepatocellular carcinoma (HCC) cells [20]. It has been demonstrated that miR-19a significantly decreased SOCS3 mRNA and protein in hepatocyte cell line [21]. In the present study, we found that downregulation of miR-19a leads to increased expression of its target, SOCS1, by targeting a sequence in the 3'-UTR of the SOCS1 mRNA. This was partially consistent with the previous study carried out by Wang et al., who reported that SOCS1 was a direct target of miR-19a in neuropathic pain models [22].

Suppressors of cytokine signaling (SOCS) proteins are classic inhibitors of the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway. Many cytokines and pathogenic mediators, such as IL-6 and IFN-α, induce expression of SOCS, which act as a negative feedback to inhibit further signal transduction. For example, SOCS1 suppressed IFN-lambda pathways thus resulted in the activation of NF-κB [23]. MiR-122 modulates type I interferon expression through blocking SOCS1 [24]. These findings suggested that SOCS1 is the negative regulator of type I IFN immune response.

The type I IFN is recognized as key component of the innate immune response and thus plays a critical role for hepatocytes to defense against virus infection [3]. Wang et al. demonstrated that suppression of IFN signaling by SOCS-1 results in the excessive production during influenza virus infection [23]. In the present study, we found that pregnant women with HBV infection have lower abundance of miR-19a, and *in vitro* study confirmed that downregulation of miR-19a enhance HBV replication. Based on the present findings that miR-19a directly target SOCS1, and SOCS1 is the negative regulator of IFN-α, we hypothesized miR-19a, would affect type I IFN response by targeting SOCS1. We found that downregulation of miR-19a inhibited type I IFN response, as can be evidenced from the lower expression of PKR, OAS and ORF1 both at mRNA and protein levels. It is therefore, or at least, partially sug-

gested that downregulation of miR-19a upregulates SOCS1, and inhibited type I IFN responses, which therefore enhance HBV replication.

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Disclosure of conflict of interest

None.

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