Introduction
Hepatocellular carcinoma (HCC) is a severe malignancy with a high mortality and morbidity worldwide [1]. In China, HCC is the fourth most common cancer, which is identified as a leading cause of cancer-related death [2]. Currently, there are various available strategies for HCC treatment, such as surgery, liver transplantation, locoregional treatment, transcatheter arterial chemoembolization (TACE) and systemic treatment [3]. However, the clinical outcomes of HCC patients are still dismal, due to metastasis and relapse [4,5]. Unfortunately, the molecular mechanisms of HCC still remain unclear. Therefore, it is crucial to identify the genes and proteins that take part in the aetiology of HCC, which may be employed as therapeutic targets.

Long non-coding RNAs (lncRNAs) refer to a group of RNAs without protein-coding ability and their lengths are more than 200 nucleotides [6]. LncRNAs are associated with diverse biological processes, especially gene expression [7]. LncRNA could regulate gene expression at chromatin modification, transcription and post-transcriptional levels, thus play an important role in both physiological and pathological conditions [8,9]. In human cancer, the abnormally expressed lncRNAs may serve as oncogenes or tumour suppressors [10]. Growing evidence have demonstrated that lncRNAs play critical regulatory roles in the pathogenesis of HCC [11,12].

CASC15 (cancer susceptibility candidate 15) belongs to lncRNA family and locates in human chromosome 6p22.3 [13]. CASC15 is identified as a cancer-related lncRNA and its alterations have been observed in several cancers, including neuroblastoma, melanoma and gastric cancer [13–15]. In HCC, it has been reported that the up-regulation of CASC15 showed positive association with cancer progression and aggressive cell behaviours [16]. However, the molecular mechanisms underlying the functional roles of CASC15 in aetiology of HCC still remained poorly known.

In this study, we investigated the expression patterns of CASC15 in HCC tissues and cell lines, as well as its association with disease progression of the patients. In addition, the cell experiments were carried out to investigate the molecular mechanisms of CASC15 in HCC.

Materials and methods
Study subjects and tissue samples
A total of 118 patients who were pathologically diagnosed with HCC were recruited from 302 Hospital, Beijing during October 2016 and March 2018. The HCC tissues and adjacent normal tissues were collected from each patient. None of the
patients had received any pre-operative treatments, such as chemotherapy, radiotherapy. The clinical characteristics of the patients were collected from the medical records. The present study was approved by the Ethics Committee of the hospital. All the patients signed the written informed contents.

**Cell culture**

The human HCC cell line HepG2 (code: TCHu 72) and normal hepatocyte line THLE3 (code: GNHu40) were purchased from Shanghai Cell Bank of Chinese Academy of Sciences (Shanghai, China). The cells were cultured in Roswell Park Memorial Institute-1640 (RPMI-1640), with the addition of 10% FBS, 100 U/mL penicillin and 100 µg/mL streptomycin. Then the cultures were maintained in a humidified incubator with 5% CO2 at 37°C.

**RNA extraction and quantitative real-time polymerase chain reaction (qRT-PCR)**

Total RNA was isolated from the cells and tissues using TRIzol reagent (Invitrogen, Carlsbad, CA, USA) according to the instructions. The reverse transcription was performed using PrimerScript RT reagent kit (Takara, Chiga, Japan). Then, qRT-PCR was used to investigate the relative expression of the genes. GAPDH was employed as an internal control. The primer sequences were as follows: GAPDH forward: 5'-TGGA CTCCACGAGCTAAG-3'; reverse: 5'-CCGGAACTGTATCAATGGAA-3'; CASC15 forward: 5'-CACACGCATGAAAACCCAG-3'; reverse: 5'-GAGGACGTGAGCTGAAAGC-3'; SOX4 forward: 5'-GGCTTCGAGCTGGAATGCC-3'; reverse: 5'-GCCCAGTGGGTTCTGCA-3'. The relative expression of the target genes was calculated using $2^{-\Delta\Delta C_T}$ method. Each test was repeated three times.

**Cell transfection**

CASC15-siRNA, SOX4-siRNA and SOX4 over-expression fragments were purchased from (Ribo Bio Co., Ltd, China). The fragments were respectively ligated to pcDNA 3.1 vector to construct recombinant plasmid. The empty pcDNA 3.1 vector served as a negative control (NC). Then the plasmids were transfected to HepG2 cells in log phase using Lipofectamine™ 2000. Forty-eight hours later, the transfection effects were estimated using qRT-PCR method.

**Cell proliferation assay**

Cell proliferation assay was performed by 3-[4,5-dimethylthiazo-l-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assay. The cells were seeded into 96-well plate, with the density of $5 \times 10^4$ cells/well. Then, the plates were cultured at 37°C in a humidified incubator with 5% CO2. Twenty microlitres MTT (5 mg/ml; Sigma, St. Louis, MO, USA) was added to the culture at 0 h, 24 h, 48 h and 72 h, respectively. The plate was incubated in the dark for 4 h, and 150 µL dimethyl sulfoxide (Sigma) was added. 15 min later, the absorbance of the culture was measured at 490 nm using a microplate reader (Biotek, USA), to estimate cell density. Each sample was tested in triplicate.

**Transwell assay**

Transwell assays were performed to investigate cell migration and invasion. In cell migration assay, the upper chamber of Transwell contained 200 µL serum-free medium while the medium with 10% fetal bovine serum was added at the bottom chamber. Forty-eight hours after transfection, $4 \times 10^4$ cells were seeded to the upper chamber and incubated for 48 h. Then, the membranes were isolated and stained using DiffQuick (Polyscience, Warrington, PA, USA) according to the manufacturer’s protocols. The cells were counted using an inverted microscope (Leica, Malvern, PA, USA) in 10 random fields. For cell invasion assay, 40 µL diluted Matrigel (1:8) was added to the upper chamber of the Transwell and incubated at 37°C for 15 min. The subsequent procedures were performed according to migration assay.

**Cell apoptosis assay**

The effects of CASC15 expression on cell apoptosis was evaluated using flow cytometry which was stained using FITC-Annexin V and propidium iodid (PI) method. The procedures were performed using a FITC-Annexin V/PI Apoptosis Detection Kit (BD Biosciences, San Jose, CA), and the results were analyzed using flow cytometry.

** Luciferase reporter assay**

The 3'-UTR fragment of SOX4 gene contained the putative binding site of CASC15. The 3'-UTR of SOX4 gene was amplified using the PCR method and cloned to p-GL3 vector (Promega, Madison, WI, USA) with firefly luciferase reporter gene. The p-GL3 vector which contained 3'UTR of SOX4 with a mutant sequence of the CASC15 binding site was also constructed. Then, the vectors were transfected into HepG2 cells with or without CASC15-siRNA vector. The cells were cultured for 48 h. Then luciferase activity was detected using a dual-luciferase reporter assay system (Promega) and normalized to Renilla activity.

**Western blot**

Western blot assay was performed according to the standard procedures. The cells were harvested at 48 h after transfection, and total protein was isolated. Then, the protein samples were quantified using the bichinchoninic acid protein assay system (Google Biotechnology Ltd. Co.). Equal amounts of protein were separated by 10% SDS-PAGE and transferred to a polyvinylidene fluoride membrane (Millipore, Billerica, MA, USA). Then the membranes were blocked with 5% bovine serum albumin and probed with the specific antibodies. After washing, the membranes were incubated with the secondary antibody which was marked by horseradish peroxidase (Cat. no. A24537; polyclonal, goat, targeted against rabbit; Life Technologies, Carlsbad, CA, USA) and visualized.
under UV transilluminator (Uvitec Ltd., Avebury House, Cambridge, UK). GAPDH protein was considered as a control.

**Statistical analysis**

All the statistical analyses were performed using SPSS 18.0 software (SPSS Inc., Chicago, IL, USA), and the figures were plotted by GraphPad Prism version 5.0 (GraphPad, San Diego, CA, USA). The continuous variables were shown as mean ± SD, and their comparison between two groups was analyzed using student’s t-test. Chi-square test was used to investigate the association of CASC15 expression with clinical parameters of HCC patients. All the analyses were two-tailed, and p values less than 0.05 were considered significant.

**Results**

**Baseline characteristics of the study population**

A total of 118 HCC patients including 64 males and 54 females were enrolled in our study, and their average age was 57.25 ± 15.21 years. Eighty-one patients were infected by HBV while 78 patients presented liver cirrhosis. According to TNM stage, 74 patients were at stage I–II, and the rest 44 patients were confirmed as stage III–IV. Tumour metastasis was observed in 42 patients. The baseline characteristics of the included patients were summarized in Table 1.

**The expression profile of CASC15 in HCC patients**

QRT-PCR was performed to investigate the relative expression of CASC15 in HCC tissues and cell lines. Compared to adjacent normal tissues, the levels of CASC15 were obviously up-regulated in HCC tissues (**p < .01**) (Figure 1(a)). Furthermore, the expression of CASC15 was significantly higher in HCC cell line HepG2 than that in normal liver cell line THLE3 (**p < .01**) (Figure 1(b)).

**Relationship between CASC15 expression and clinical characteristics of HCC patients**

The included patients were divided into high expression group (n = 48) and low expression group (n = 70) according to their mean expression value of CASC15 in cancer tissues. Chi-square was used to analyze the association of CASC15 with clinical parameters of HCC patients. Analysis results demonstrated that the expression level of CASC15 showed positive association with large tumour size (p = .016), advanced TNM stage (p = .018) and positive lymph node metastasis (p = .021). Meanwhile, CASC15 expression had no association with age, gender, HBV or liver cirrhosis (p > .05 for all) (Table 1).

**Effects of CASC15 expression on biological behaviours of HCC cells**

In order to investigate the functional roles of CASC15 in HCC development, CASC15-siRNA vector was constructed to inhibit the expression of CASC15 in HCC cell line HepG2. QRT-PCR analysis suggested that the expression of CASC15 was significantly down-regulated after the transfection of CASC15-siRNA (***p < .001**) (Figure 2).

We investigated the biological behaviours of the transfected cells. MTT assay indicated that the knockdown of

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**Table 1.** The association of CASC15 expression with clinical characteristics of HCC patients.

| Characteristics | n = 118 | High expression (n = 48) | Low expression (n = 70) | p    |
|-----------------|--------|-------------------------|------------------------|------|
| Age (years)     |        |                         |                        | .749 |
| <50             | 52     | 22                      | 30                     |      |
| ≥50             | 66     | 26                      | 40                     |      |
| Gender          |        |                         |                        | .460 |
| Male            | 64     | 28                      | 36                     |      |
| Female          | 54     | 20                      | 34                     |      |
| HBV             |        |                         |                        | .701 |
| Yes             | 81     | 32                      | 49                     |      |
| No              | 37     | 16                      | 21                     |      |
| Liver cirrhosis |        |                         |                        | .369 |
| Yes             | 78     | 34                      | 44                     |      |
| No              | 40     | 14                      | 26                     |      |
| Tumour size (cm)|        |                         |                        | .016 |
| ≤5              | 60     | 18                      | 42                     |      |
| >5              | 58     | 30                      | 28                     |      |
| TNM stage       |        |                         |                        | .018 |
| I–II            | 74     | 24                      | 50                     |      |
| III–IV          | 44     | 24                      | 20                     |      |
| Lymph node metastasis | |                  |                        | .021 |
| Yes             | 42     | 23                      | 19                     |      |
| No              | 76     | 25                      | 51                     |      |

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**Figure 1.** The expression patterns of CASC15 in HCC tissues and cells. (a) The expression of CASC15 was significantly higher in HCC tissues than that in adjacent normal tissues (**p < .01**). (b) Compared to normal liver cell line THLE3, the levels of CASC15 were significantly increased in HCC cell line HepG2 (**p < .01**).
CASC15 could obviously inhibit cell proliferation (*: p < .05, **: p < .01, Figure 3(a)). Transwell assay demonstrated the reduced migration and invasion abilities after the transfection of CASC15-siRNA (**: p < .01, Figure 3(a,b)). In addition, we found that the apoptosis rate of the cells transfected by CASC15-siRNA vector exhibited increased trend (*: p < .05, Figure 3(d)).

The influences of CASC15 on SOX4 and Wnt/β-catenin signalling pathway

In addition, we also investigated the levels of SOX4 and Wnt/β-catenin signalling pathway-related proteins in HCC cells transfected by CASC15-siRNA vector. Compared to NC group, the protein levels of SOX4, β-catenin, Cyclin D1 and c-Myc was obviously decreased in the cells transfected by CASC15-siRNA vector (Figure 4).

SOX4 was the target gene of CASC15 in HCC

To investigate the relationship between SOX4 and CASC15, luciferase reporter assay was performed. HepG2 cells were co-transfected by SOX4-wt (wild type) or SOX4-mt (mutant type) and CASC15-siRNA or NC. Analysis results demonstrated that the knockdown of CASC15 could reduce the luciferase activity of cell transfected by SOX4-wt (**: p < .01), but it had no effects on the cells transfected by SOX4-mt (p > .05) (Figure 5). The data revealed the target regulation between SOX4 and CASC15.

In order to verify the target regulatory relationship between SOX4 and CASC15, the SOX4-siRNA vector was constructed and transfected to HepG2 cells. QRT-PCR was performed to investigate the expression patterns of SOX4 and
CASC15 in the transfected cells. We found that the expression of SOX4 was significantly down-regulated (**: \( p < .01 \)), but the expression of CASC15 had no obvious changes (\( p > .05 \)) (Figure 6). All the evidence confirmed that SOX4 was located at the downstream of CASC15 gene, which might be a target gene of CASC15 in HCC.

**CASC15 enhanced Wnt/β-catenin signalling pathway and malignant behaviours of HCC cells through targeting SOX4**

In order to investigate the molecular mechanisms of CASC15 in aetiology of HCC, HepG2 cells were co-transfected by CASC15-siRNA and SOX4-overexpression vectors. Western blot was performed to investigate the related protein levels in the transfected cells. The results displayed in Figure 7 suggested that the enhanced expression of SOX4 could promote β-catenin, Cyclin D1 and c-Myc expression in HCC cells transfected by CASC15-siRNA vector. CASC15 might regulate Wnt/β-catenin signalling pathway through mediating the expression of SOX4 in HCC.

In addition, we also investigated the biological behaviours of the HepG2 cells co-transfected by CASC15-siRNA and SOX4-overexpression vectors. The results shown in Figure 8 suggested that compared to the cells transfected by CASC15-siRNA vector only, the co-transfection of CASC15-siRNA and SOX4-overexpression vectors could significantly enhance cell proliferation, migration and invasion and suppress cell apoptosis (*: \( p < .05 \), **: \( p < .01 \), Figure 8). The evidence demonstrated that the enforced expression of SOX4 could reverse the ant-tumour action induced by the knockdown of CASC15 in HCC.

**Discussion**

HCC is a malignant tumour, and its morbidity exhibits increasing trend in recent years [17]. The identified risk factors for HCC include hepatitis B and C infection, liver cirrhosis and exposure to dietary aflatoxin, etc. [18]. However, the molecular pathogenesis still remains unclear. Accumulating evidence have suggested that lncRNAs play an important role in aetiology of HCC [11,12]. To investigate the cancer-related IncRNAs may provide new insight into the aetiology of HCC, thus contributing to targeted therapy. In the current study, we investigated the function of lncRNA CASC15 in pathogenesis of HCC, as well as the related molecular mechanisms.

Despite the lack of protein-coding capacity, IncRNAs take part in various biological processes, including gene expression, cellular differentiation and development [19]. Dysregulation of IncRNAs may contribute to human diseases, like cancer [20]. In HCC, a variety of IncRNAs have been
identified. For example, Yu et al. reported that SPRY4-IT1 expression was increased in HCC patients and showed negative correlation with 5-year survival of the patients. SPRY4-IT1 might promote aggressive biological behaviours of HCC cells by enhancing the expression of estrogen-related receptor α (ERRα) [21]. The study carried out by Liu et al. suggested that lncRNA HOXA11-AS could facilitate HCC cell proliferation via suppressing the expression of DUSP5 [22]. All the researches confirmed the pivotal role of lncRNAs in the development and progression of HCC, which could be employed as biomarkers and therapeutic targets in HCC management.

LncRNA CASC15 is located in human chromosome 6p22, where was identified as the neuroblastoma susceptibility locus [13]. In the current study, we found that the expression of CASC15 was significantly up-regulated in HCC tissues and cell line. Moreover, the elevated expression of CASC15 was significantly correlated with large tumour size, advanced TNM stage and positive lymph node metastasis. The up-regulation of CASC15 might contribute to malignant progression of HCC. Cell experiments suggested that the knockdown of CASC15 might impair cell proliferation, migration and invasion and promote apoptosis in HCC cells in vitro. The data might reveal that CASC15 might be an oncogene in HCC. The conclusions were consistent with the previous studies [16]. However, CASC15 might serve as a tumour suppressor in neuroblastoma [13]. The function of CASC15 was distinct in different types of cancer.

In the present study, we also investigated the molecular mechanisms underlying the functional roles of CASC15 in HCC. Luciferase reporter assay demonstrated that SOX4 might be a potential target gene of CASC15 in HCC. The enhanced expression of SOX4 could reverse the anti-tumour action induced by suppression of CASC15. CASC15 might regulate HCC progression via Wnt/β-catenin signalling pathway which was mediated by SOX4. The regulatory relationship between CASC15 and SOX4 was also confirmed in RUNX1-rearranged acute leukaemia [23]. CASC15 could enhance the promoter activity of SOX4, thus promoting its gene expression. The elevated expression of SOX4 holds the capacity to activate Wnt/β-catenin signalling pathway in diverse cancer cancers, such as osteosarcoma, melanoma and chondrosarcoma [24–26]. The activation of Wnt/β-catenin signalling pathway might contribute to enhanced cell growth, migration and invasion, as well as decreased apoptosis rate in HCC, thereby leading to aggressive tumour progression [27,28].

Despite the encouraging results, there were several limitations in the current study. First, the sample size was relatively small that might reduce the statistical power of our analysis. Second, we found that SOX4 was a potential target gene of CASC15 in HCC. However, SOX4 might be not the only target gene of CASC15 in tumorigenesis. Zuo et al. reported that CASC15 promoted progression of tongue squamous carcinoma through regulating miR-33a-5p expression [29]. Wu et al. suggested that CASC15 regulated progression of gastric cancer via targeting CDKN1A and ZEB1 [30]. All the articles revealed that CASC15 might take part in tumorigensis through multiple signalling pathways. Further researches will be required to investigate the regulatory network of CASC15 in HCC.

In conclusion, the expression of lncRNA CASC15 is significantly up-regulated in HCC tissues and cell lines. Moreover, its elevated expression is closely correlated with large sample size, advanced tumour stage, and positive lymph node metastasis. CASC15 may promote malignant biological behaviours of HCC cells through enhancing SOX4/Wnt/β-catenin signalling pathway.
Disclosure statement

No potential conflict of interest was reported by the authors.

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