

## *Retraction*

# **Retracted: circSOX4 Enhances Hepatocellular Carcinoma Progression via miR-218-5p/YY1 Signaling**

### **BioMed Research International**

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This article has been retracted by Hindawi, as publisher, following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of systematic manipulation of the publication and peer-review process. We cannot, therefore, vouch for the reliability or integrity of this article.

Please note that this notice is intended solely to alert readers that the peer-review process of this article has been compromised.

Wiley and Hindawi regret that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

### **References**

- [1] T. Jia, L. Wang, W. Zhang, Y. Hu, and K. Tuerxun, “circSOX4 Enhances Hepatocellular Carcinoma Progression via miR-218-5p/YY1 Signaling,” *BioMed Research International*, vol. 2023, Article ID 3370440, 10 pages, 2023.

## Research Article

# circSOX4 Enhances Hepatocellular Carcinoma Progression via miR-218-5p/YY1 Signaling

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Liver cancer ranks fifth leading malignancy in incidence and third in mortality worldwide. Recently, its comprehensive treatment has greatly progressed; however, the prognosis is still poor due to difficulties in early diagnosis, high recurrence and metastasis rates, and lack of specific treatment. The search for new molecular biological factors that target the early diagnosis of cancer, predict recurrence, evaluate treatment efficacy, and identify high-risk individuals and specific therapeutic targets during follow-up becomes a great urgent task. circSOX4 is upregulated in lung cancer and plays the role of oncogene. This study attempted to assess circSOX4's role in hepatocellular carcinoma (HCC). HCC tissues and cells were collected to measure circSOX4 level by qRT-PCR, cell behaviors by CCK-8 assay and Transwell assay, and relationship between circSOX4 and downstream targets by dual-luciferase gene assay and RIP. circSOX4 was upregulated in HCC tissue and cell lines, and its level was correlated with reduced patient survival. Interestingly, circSOX4 knockdown reduced HCC behaviors, glucose consumption, and lactate production. Furthermore, circSOX4 knockdown resulted in decreased *in vivo* tumor growth. circSOX4 was confirmed to target miR-218-5p, and the effect of circSOX4 downregulation on inhibiting tumor growth was diminished after miR-218-5p inhibition or YY1 overexpression in HCC cells. circSOX4 expression is closely associated with HCC through miR-218-5p and YY1-dependent pathways and may be a target and marker for HCC.

## 1. Introduction

Recent data has indicated HCC as a major cause of deaths throughout the world [1] and may account for over 80% of primary liver tumors [2, 3]. Regardless of cause, liver cirrhosis has been known to precede HCC [4]. In recent years, HCC incidence and mortality have been constantly increasing in North America and several countries across Europe, which indicates the lack of proper surveillance and early detection even in countries with advanced public health facilities [3]. Nonetheless, almost 85% of the cases of HCC are attributed to low- and middle-income countries [5, 6]. Despite the availability of multiple therapies, only liver transplants or surgical removal of the tumor have proven to be curative. Hence, early detection of HCC may drastically improve the prognostic outcomes.

Circular RNAs (circRNAs) regulate cellular physiology through multiple ways, such as sponging of miRNAs to

modulate gene level [7]. Numerous researches are available that confirm the regulatory role of circRNAs in cancers through mechanisms that involve miRNAs. For instance, circ-0000670 promotes gastric cancer development through miR-384 [8]. circ-0014359 has been shown to stimulate glioma progression by inhibiting miRNA-153 [9]. Similarly, circ-0072309 inhibits renal carcinoma cell lines by sponging miR-100 [10]. In contrast, circ-0046600 promoted HCC by competitively inhibiting miR-640 [11]. Recently, circRNAs have also been suggested as the biomarkers of multiple cancers [12]. Pan et al. showed circ-0004771 to be a marker of colorectal cancer [13]. Another study has suggested circRNA 1656 as a potential marker in ovarian cancer with high grade [14]. circ-000696 has also been revealed to be a marker of breast cancer [15].

The role of a novel circRNA circSOX4 has been recently reported in the tumorigenesis of lung adenocarcinoma. It was observed that circSOX4 promotes tumors through

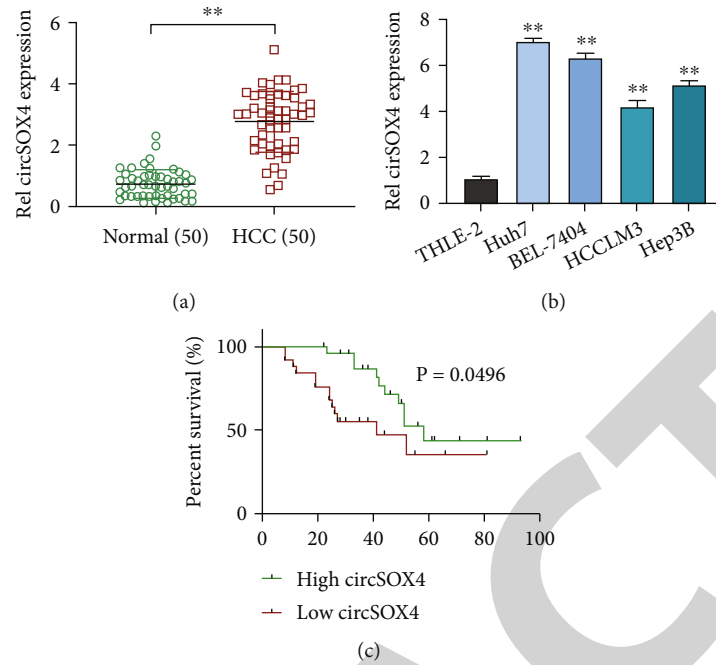


FIGURE 1: Increased circSOX4 in HCC tissues. (a) circSOX4 level in HCC and adjacent tissues. (b) circSOX4 level in HCC cell lines and normal liver cell (THLE-2). (c) Patients in (a) were assigned into the high- ( $n = 25$ ) and low-expression ( $n = 25$ ) groups to assess survival rate. \*\* $P < 0.01$ , HCC group vs. normal group; \*\* $P < 0.01$ , Huh7, BEL-7404, HCCLM3, and Hep3B vs. THLE-2.

TABLE 1: circSOX4 is increased in hepatocellular carcinoma.

Clinicopathological characteristics	Total	circSOX4 high level ( $n = 25$ )	circSOX4 low level ( $n = 25$ )	$\chi^2$	$P$ value
Gender					
Male	21	11	10	0.082	0.774
Female	29	14	15		
Age					
$\leq 50$	30	16	14	0.333	0.564
$> 50$	20	9	11		
Tumor size					
T1 + T2	27	12	15	0.725	0.395
T3 + T4	23	13	10		
Differentiation					
High	22	15	7	6.253	0.044
Moderate	13	6	7		
Poor	15	4	11		
Lymph node metastasis					
Positive	28	18	10	5.195	0.023
Negative	22	7	15		
TMN stages					
I + II	24	8	16	5.128	0.024
III + IV	26	17	9		
HBV infection					
Positive	24	11	13	0.321	0.571
Negative	26	14	12		
Distant metastasis					
M0	22	7	15	5.195	0.023
M1	28	18	10		

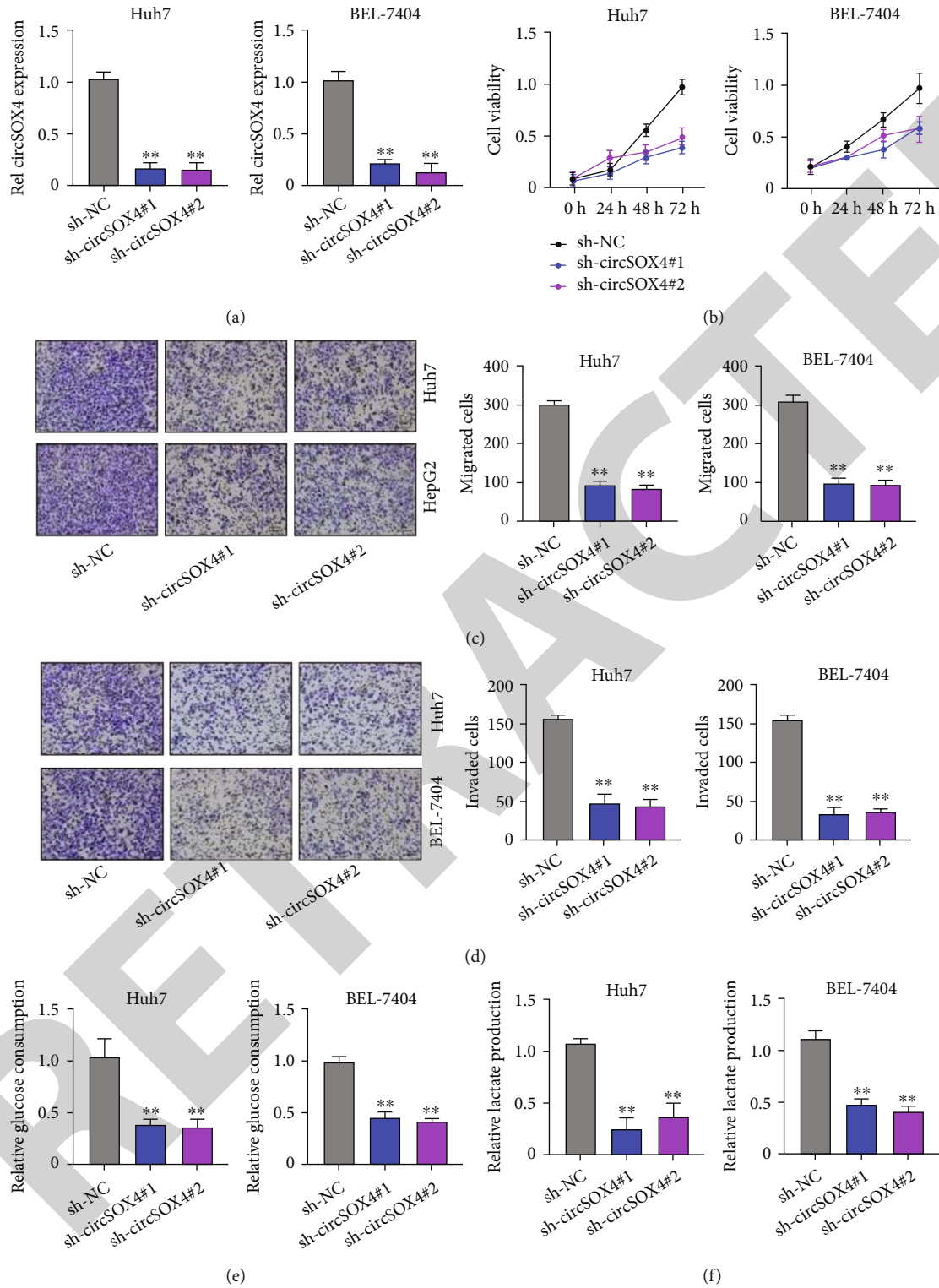


FIGURE 2: Continued.

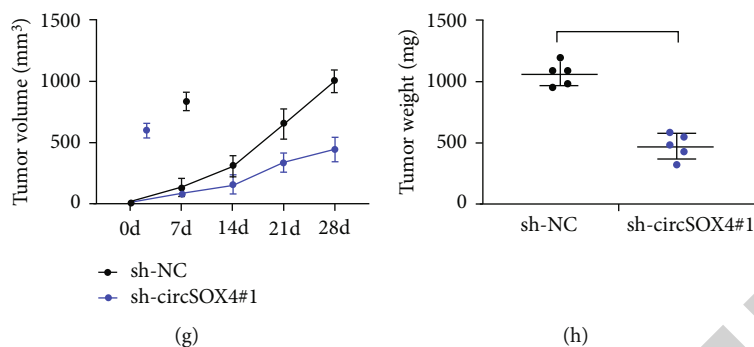


FIGURE 2: Effect of circSOX4 knockdown on hepatoma cells. (a) Knockdown efficiency of sh-circSOX4#1 and sh-circSOX4#2 in HCC cells. (b) Effect of circSOX4 knockdown on cell viability. (c, d) Cell migration and invasion capacity. (e, f) Glucose consumption and lactate production in Huh7 and BEL-7404 cells after different interventions. (g, h) Tumor growth in nude mice.  $**P < 0.01$ , sh-circSOX4#1 vs. sh-NC;  $**P < 0.01$ , sh-circSOX4#2 vs. sh-NC.

modulation of miR-1270 and PLAGL2 [16]. However, circSOX4's role in HCC is unclear. Hence, we intend to assess circSOX4's role and mechanism in HCC.

## 2. Materials and Methods

**2.1. Tissues.** 100 tissues including 50 normal and 50 HCC were obtained. Informed consents were acquired before surgery. All protocols were explained to the patients and were approved by the Ethics Committee of our hospital. Samples were placed at  $-80^{\circ}\text{C}$  after collection.

**2.2. Cell Culture and Transfection.** THE-2 and Huh7 cells were cultured in RPMI-1640, and BEL-7404, HCCLM3, and Hep3B were cultured in DMEM (Invitrogen, USA). For the knockdown experiments, shRNAs (sh-circSOX4#1, sh-circSOX4#2, and sh-NC), miR-NC, and miR-218-5p mimic and inhibitor, pcDNA3.1.YY1, and controls were utilized for transfection by Lipofectamine 2000 (Invitrogen, USA).

**2.3. Tumor Mouse Model.** Nude mice weighing around 20 g and aging 4-5 weeks from Vital River Laboratory Animal Technology were fed under standard laboratory conditions ( $22 \pm 3^{\circ}\text{C}$ , relative humidity  $48 \pm 10\%$ ) and received subcutaneously inoculation of approximately  $3 \times 10^6$  Huh7 cells (sh-NC, sh-circSOX4#1), and tumor size was assessed each week for 4 weeks. All protocols were approved by the Ethics Committee of our hospital (protocol approval number KY-E-2019-12-20).

**2.4. Nucleocytoplasmic Fractionation Experiments.** This assay was performed to separate cell nuclear and cytoplasmic fractions according to previously described procedures [16] using PARIS™ Kit (Ambion, Austin, TX, USA) followed by measuring circSOX4 level by qRT-PCR. U6 and GAPDH served as control of the nucleus and cytoplasm, respectively.

**2.5. qRT-PCR Assay.** RNA was extracted for qRT-PCR. Gene level was determined using the  $2^{-\Delta\Delta\text{Ct}}$  method.

**2.6. CCK-8 Assay.**  $1 \times 10^3$  cells/well were cultured for 24, 48, and 72 h followed by adding  $10 \mu\text{L}$  CCK-8 for 4 h incubation. After incubation, the absorbance was assessed at 450 nm.

**2.7. Transwell Assay.**  $1 \times 10^3$  cells were introduced into the upper membrane of the chamber (Corning, USA) precoated with Matrigel and 10% serum in the lower chamber for 24 h. After removing cells in the upper membrane, cells in the lower membrane were fixed and stained to be observed under an inverted laboratory microscope (Olympus, Japan). Migration assay was done without Matrigel.

**2.8. Luciferase Reporter Assay.** After transfection, luciferase reported activity was done using a kit (Promega, USA). Subsequently, relative luciferase activities were detected by a microplate reader (Olympus, Japan).

**2.9. RNA Pull-Down and RNA Immunoprecipitation (RIP) Assays.** This was done as described previously [17]. Biotinylated miR-218-5p probe and NC probe were from Sangon Biotech. Huh7 and BEL-7404 cells were lysed, and magnetic Dynabeads M-280 Streptavidin beads were added for incubation overnight at  $4^{\circ}\text{C}$ , and relative enrichment of circSOX4 and YY1 was estimated by qRT-PCR. RNA immunoprecipitation was carried out using a kit (Millipore, Bedford, MA). Briefly, cell lysate was incubated with Sepharose beads coupled to an AgO<sub>2</sub>-specific antibody (Cell Signaling Technology, USA) at  $4^{\circ}\text{C}$ . Finally, RNA was isolated from beads to estimate relative enrichment [18].

**2.10. Western Blot.** Briefly, cell protein was isolated and quantified by BCA method followed by separation on SDS-PAGE for western blot. Protein band was visualized with Bioimaging System.

**2.11. Statistical Method.** GraphPad Prism processed data which were displayed as mean  $\pm$  SD and assessed by Student's *t*-test or one-way ANOVA.  $P < 0.05$  refers to a difference.

## 3. Results

**3.1. circSOX4 Is Increased in Hepatocellular Carcinoma.** HCC tissues had significantly upregulated circSOX4 ( $P < 0.01$ ) than controls (Figure 1(a)). Meanwhile, HCC cell lines also exhibited increased circSOX4 expression ( $P < 0.01$ ) (Figure 1(b)). Henceforth, based on the median circSOX4

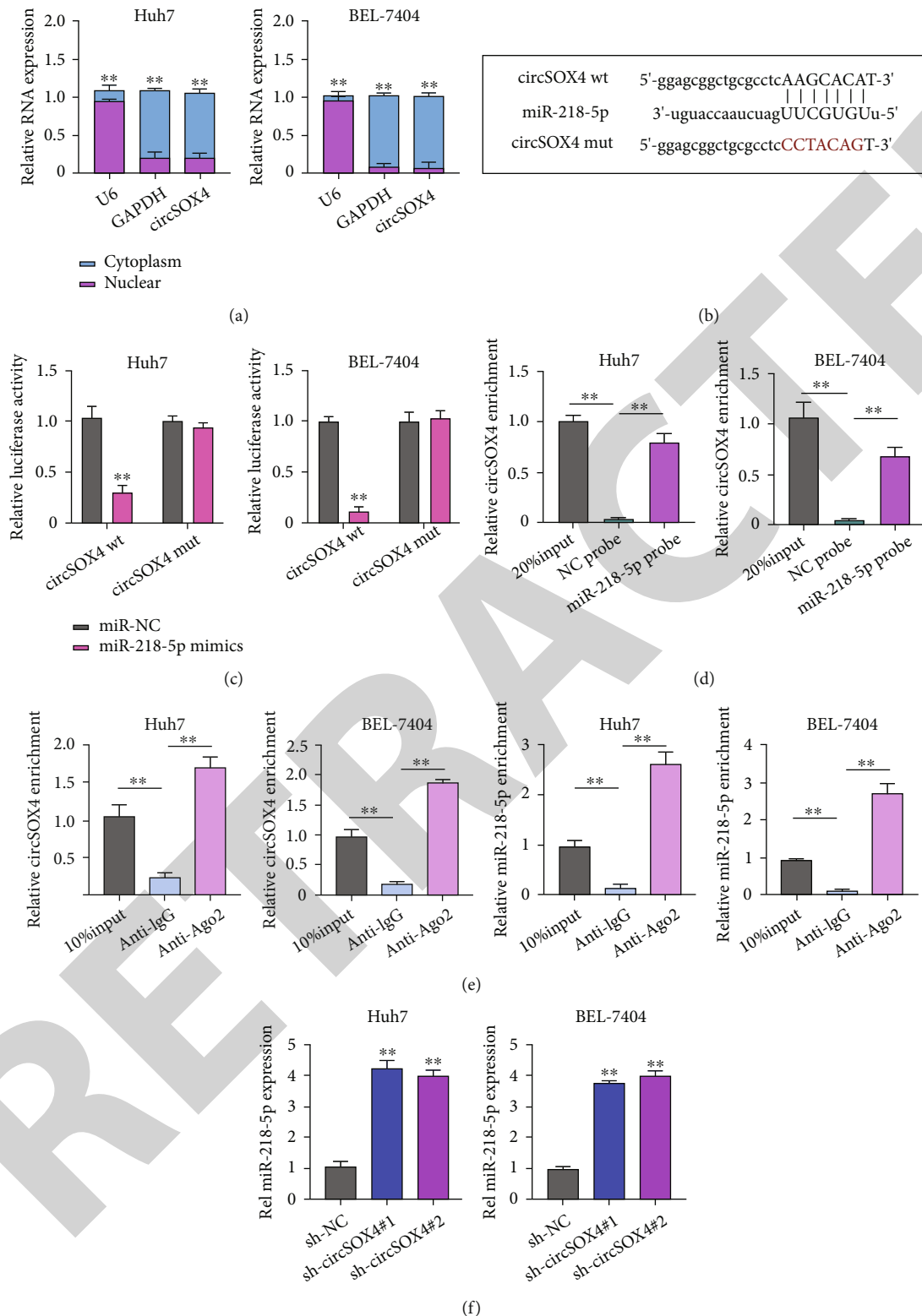


FIGURE 3: circSOX4 shares the binding site and targets miR-218-5p. (a) Nucleoplasm separation experiment detects the subcellular localization of circSOX4. (b) circBank prediction on the circSOX4 and miR-218-5p binding sites. (c, d) WT: wild-type sequence, MUT: mutated sequence. (e) RIP experiment. (f) miR-218-5p expression after sh-mediated knockdown of circSOX4. \*\* $P < 0.01$ , miR-218-5p-mimic vs. miR-NC; \*\* $P < 0.01$ , NC probe vs. 20% input; \*\* $P < 0.01$ , miRNA-218-5p probe vs. NC probe; \*\* $P < 0.01$ , anti-IgG vs. 10% input; \*\* $P < 0.01$ , anti-Ago2 vs. anti-IgG. \*\* $P < 0.01$  and \*\* $P < 0.01$ , sh-circSOX4#1 vs. sh-NC; \*\* $P < 0.01$ , sh-circSOX4#2 vs. sh-NC.

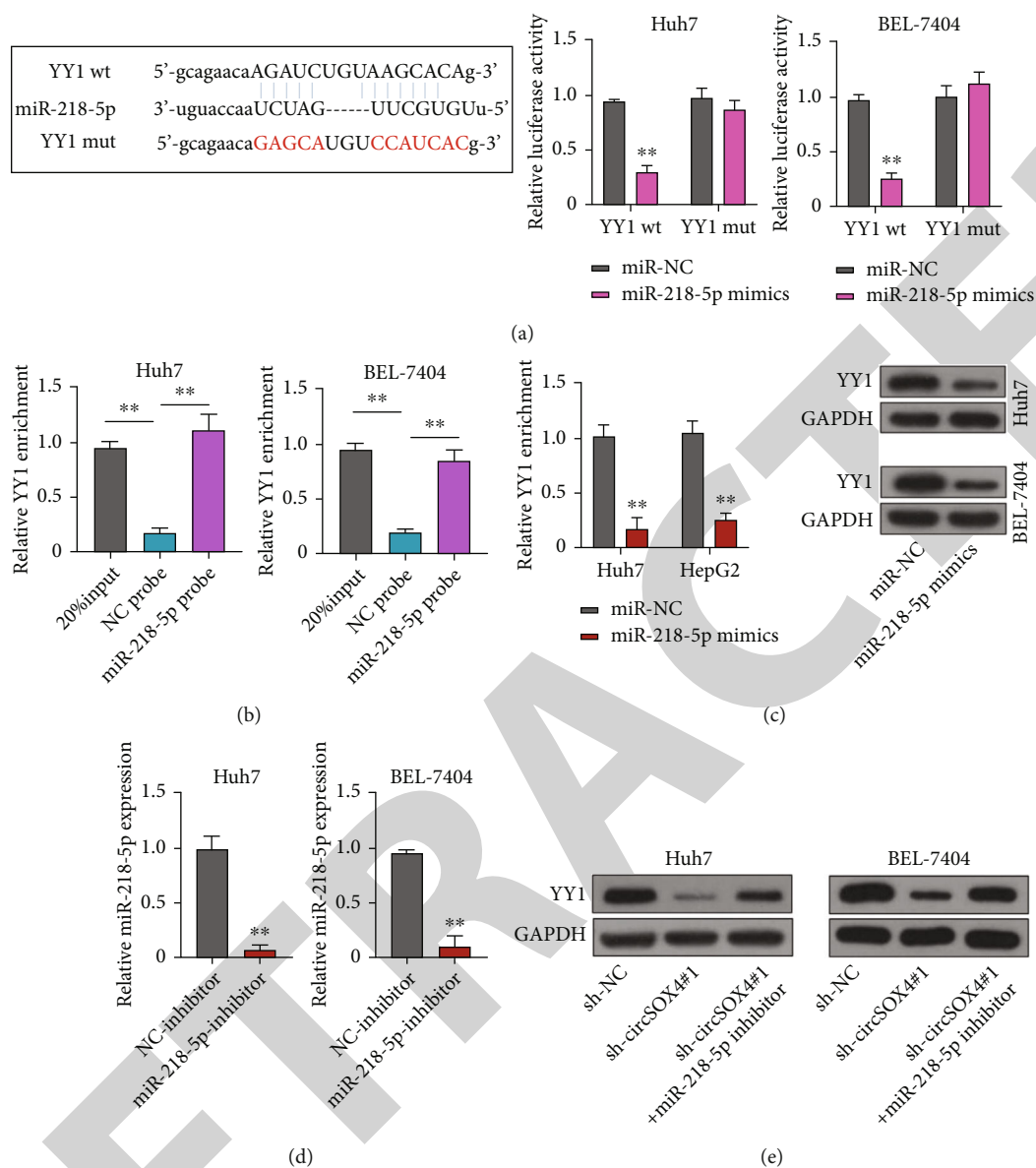


FIGURE 4: YY1 is the target of miR-218-5p. (a) miR-218-5p binding site in the 3' noncoding region of YY1 predicted by the online bioinformatics tool starBase. Luciferase reporter gene experiments following different interventions. (b) WT: wild-type sequence; MUT: mutant sequence. RNA pull-down experiment in Huh7 and BEL-7404. (c) YY1 mRNA and protein level. (d) miR-218-5p level. (e) YY1 expression after different treatments. \*\* $P < 0.01$ , miR-218-5p-mimic vs. miR-NC; \*\* $P < 0.01$ , NC probe vs. 20% input; \*\* $P < 0.01$ , miRNA-218-5p probe vs. NC probe; \*\* $P < 0.01$ , miR-218-5p inhibitor vs. NC inhibitor.

expression (Figure 1(a)), 50 HCC patients were assigned into a low- ( $n = 25$ ) and a high-level ( $n = 25$ ) group. Patients with high circSOX4 level had significantly reduced survival ( $P < 0.05$ ) compared to the low-expression group (Figure 1(c)). No differences in gender, age, tumor size, or history of HBV infection were found between the two groups (Table 1). However, the high expression group exhibited significantly ( $P < 0.05$ ) higher differentiation, greater incidences of lymph node and distant metastasis, and a higher TMN stage, as shown in Table 1.

**3.2. Knockdown of circSOX4 Inhibits HCC Cell Behaviors and Glycolysis.** We selected two cell lines from Figure 1(b) that exhibited the highest expression of circSOX4, i.e., Huh7 and

BEL-7404 cells. Thereafter, two shRNA targeting circSOX4 were designed which were termed sh-circSOX4#1 and sh-circSOX4#2, respectively (Figure 2(a)). Compared with sh-NC, sh-circSOX4#1 and sh-circSOX4#2 effectively knocked down more than 50% of circSOX4 ( $P < 0.01$ ). Knocking down circSOX4 significantly reduced light absorption by Huh7 and BEL-7404 cells at 450 nm after 72 h of treatment than control, as shown in Figure 2(b). Furthermore, circSOX4 knockdown was also associated with reduced cell migration and invasion ability (Figures 2(c) and 2(d)). Accordingly, circSOX4 knockdown also inhibited glucose consumption and lactate production ( $P < 0.01$ ) (Figures 2(e) and 2(f)). In all such experiments, no differences were found between sh-circSOX4#1 and sh-circSOX4#2 which followed similar trends, as shown in

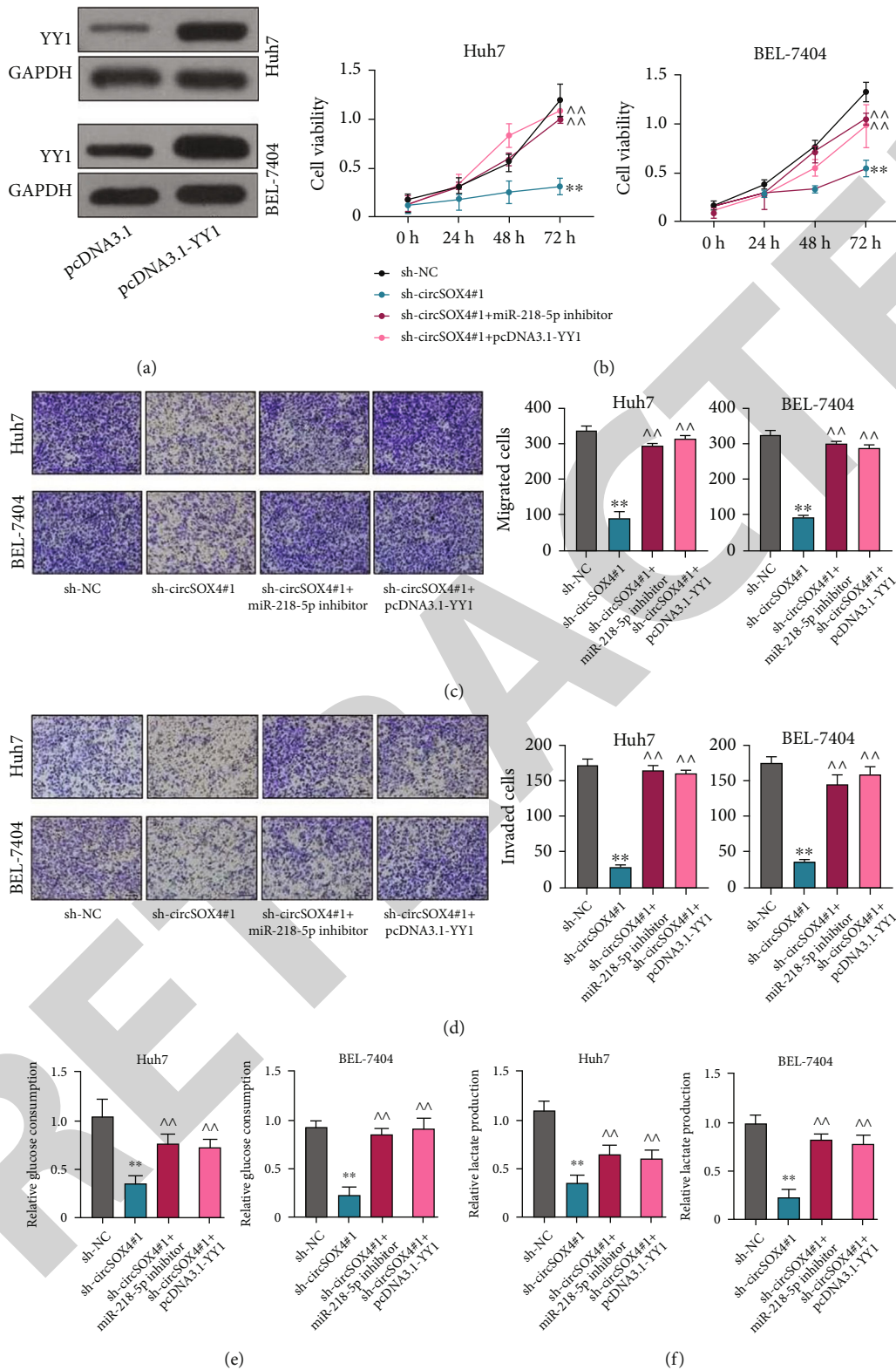


FIGURE 5: circSOX4 modulates HCC progression via the miR-218-5p/YY1 axis. (a) Protein expression of YY1 after transfection. (b) Cell viability in different groups of Huh7 and BEL-7404 cells (sh-NC, sh-circSOX4 # 1, sh-circsox4 # 1+mir-218-5p suppressor, and sh-circsox4 # 1+pcDNA3.1-YY1). (c, d) Cell migration and invasion capacity following different treatments. (e, f) Glucose consumption and lactate production in different groups. \*\* $P < 0.01$ , sh-circSOX4#1 vs. sh-NC; ^^ $P < 0.01$ , sh-circsox4#1+mir-218-5p inhibitor vs. sh-circsox4#1; ^^ $P < 0.01$ , sh-circsox4#1+pcDNA3.1-YY1 vs. sh-circsox4#1.



Figures 2(b)–2(f). Interestingly, circSOX4 knockdown inhibited tumor formation ( $P < 0.05$ ), both in terms of volume and weight in tumor-inoculated nude mice, as shown in Figures 2(g) and 2(h).

**3.3. circSOX4 Targets miR-218-5p.** The nucleoplasm separation experiment was carried out to detect the subcellular localization of circSOX4. circSOX4 was mainly located in the cytoplasm (Figure 3(a)). Online bioinformatics tool circBank predicted miR-218-5p as a potential target of circSOX4 with binding sites (Figure 3(b)). miR-218-5p mimics inhibited cell luciferase activity, and this inhibition was abolished after the binding site of circSOX4 was mutated (Figure 3(c)). Furthermore, the biotinylated miR-218-5p probe enriched significantly more ( $P < 0.01$ ) circSOX4 than the NC probe during RNA pull-down experiments (Figure 3(d)). In addition, compared with IgG-probe, Ago2-probe enriched more circSOX4 and miR-218-5p, respectively, during RNA immunoprecipitation, as shown in Figure 3(e). Knocking down circSOX4 significantly downregulated miR-218-5p ( $P < 0.01$ ) which further strengthens our findings, as shown in Figure 3(f).

**3.4. miR-218-5p Targets YY1.** miR-218-5p binding region was predicted by the bioinformatics tool starBase database (Figure 4(a)). miR-218-5p overexpression inhibited luciferase activity, and its inhibition was abolished after mutation of YY1 3'-UTR (Figure 4(a)). In addition, the biotinylated miR-218-5p probe enriched significantly more ( $P < 0.01$ ) YY1 than the control in these cells (Figure 4(b)). In accordance, miR-218-5p overexpression significantly downregulated YY1 level (Figure 4(c)). The inhibitory activity of the miR-218-5p suppressor was assessed by qRT-PCR (Figure 4(d)). Knocking down circSOX4 downregulated YY1 protein, and this effect disappeared by miR-218-5p inhibitor (Figure 4(e)).

**3.5. circSOX4 Regulates HCC Progression through miR-218-5p/YY1 Axis.** pcDNA3.1-YY1 transfection significantly increased YY1 level ( $P < 0.01$ ) (Figure 5(a)). Henceforth, Huh7 and BEL-7404 cells were divided into different treatment groups. Knocking down sh-circSOX4 decreased cell viability ( $P < 0.01$ ) (Figure 5(b)). In contrast, cell viability after sh-circSOX4 knockdown with miR-218-5p inhibition or YY1 overexpression resulted in a nonsignificant difference in cell viability than control, as shown in Figure 5(b). In addition, circSOX4 knockdown resulted in decreased cell behaviors than control and the effects disappeared after miR-218-5p inhibition or YY1 overexpression in these cells, as shown in Figures 5(c) and 5(d). Furthermore, circSOX4 knockdown significantly reduced ( $P < 0.01$ ) glucose consumption and lactate production than in control while miR-218-5p inhibition or YY1 overexpression resulted in partially increased values of these parameters, as shown in Figures 5(e) and 5(f).

## 4. Discussion

Our results indicate that circSOX4 knockdown was associated with decreased HCC viability and metastasis *in vivo*

and *in vitro*. miR-218-5p involves in cancers. Zhu et al. have shown that it could inhibit lung cancer proliferation via regulating epidermal growth factor receptors [19]. Another study suggested that its inhibition resulted in decreased metastatic properties of triple-negative breast cancer cells [20]. Decreased miR-218-5p might be a marker of bone metastasis in prostate cancer [21]. Li et al. showed association of miR-218-5p downregulation with enhanced oral squamous cell carcinoma cell invasion [22]. Liu et al. have shown that the lncRNA SNHG16 sponge targeted miR-218-5p thereby promoting pancreatic cancer development [23]. Another lncRNA CCAT1 enhances human retinoblastoma cell growth through negative regulation of miR-218-5p [24]. Indeed, circRNA-104718 has been shown to promote HCC in a miR-218-5p-dependent pathway [25]. In addition, lncRNA MNX1-AS1 promotes HCC behaviors via targeting miR-218-5p [26].

In our study, circSOX4 knockdown or miR-218-5p overexpression downregulated YY1, along with reduced HCC cell behaviors. YY1 participates in a variety of cancers as a transcription factor [27]. For instance, Chinnappan et al. have shown YY1 overexpression in human colon cancer cells [28]. In addition, YY1 expression is increased in differentiated thyroid cancer [29]. Another study indicated that miR-381 inhibited epithelial ovarian cancer cell behaviors by suppressing YY1 which corroborates our findings [30]. A study involving lung cancer indicated large tumor size and greater lymph node metastasis in patients with high YY1 expression, consistent with our findings [31]. Interestingly, circSOX4 knockdown was also associated with reduced glucose consumption and lactate production by HCC. It is known that cancer progression is closely linked with metabolic reprogramming and tumor cells tend to shift towards glycolysis even under normal oxygen conditions (Warburg effect) [32]. The subsequent accumulation of lactate may serve to acidify the tumor microenvironment that may facilitate the degradation of the extracellular matrix directly as well as through the activation of various proteases including MMPs and uPA [33]. Additionally, abnormal level of glycolytic enzymes and transporters is associated with tumor progression [34]. It was observed that decreased glucose consumption and lactate production observed after circSOX4 knockdown were partially restored after miR-218-5p suppression or YY1 overexpression. This observation further confirms the regulatory role of circSOX4 on tumor progression through the miR-218-5p/YY1-dependent pathway.

## 5. Conclusion

circSOX4 is a prognostic indicator of HCC. We propose that future large-scale studies confirm these findings before circSOX4/miR-218-5p/YY1 axis may be a target for HCC.

## Data Availability

The data underlying this article are available in the article. If needed, please contact the corresponding author.

## Ethical Approval

The study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University, according to declaration of Helsinki. It was also done in compliance with the ARRIVE guidelines.

## Consent

Written informed consent of patients was obtained.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Authors' Contributions

Tengfei Jia designed the study and obtained data. Li Wang analyzed data. Wenbin Zhang wrote the manuscript. Yuting Hu did experiments, and Kamili Tuerxun collected and analyzed data. All the authors read and approved the manuscript. Tengfei Jia and Li Wang are co-first authors.

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