Am J Cancer Res 2021;11(3):760-772
www.ajcr.us /ISSN:2156-6976/ajcr0108234

Original Article

SOX13 regulates cancer stem-like properties and tumorigenicity in hepatocellular carcinoma cells

Hui Jiao*, Fei Fang*, Ting Fang*, Yuting You, Min Feng, Xiaomin Wang, Zhenyu Yin, Wenxiu Zhao

*Fujian Provincial Key Laboratory of Chronic Liver Disease and Hepatocellular Carcinoma, Xiamen Translational Medical Key Laboratory of Digestive Tumor, Zhongshan Hospital, Xiamen University, Xiamen 361004, People's Republic of China. *Equal contributors.*

Received January 21, 2020; Accepted December 16, 2020; Epub March 1, 2021; Published March 15, 2021

Abstract: Sex-determining region Y (SRY)-related high mobility group (HMG) box (SOX) proteins are pivotal transcriptional factors that play essential roles in embryonic development, cell fate decisions and cancer development. The molecular mechanism of SOX13, a member of the SOX family, in hepatocellular carcinoma (HCC) remains largely unknown. In the current study, we found that HCC cells were able to form spheroids in serum-free suspension culture and that SOX13 expression was upregulated in spheroids enriched for cancer stem cells (CSCs). Inhibition of SOX13 in HCC-LM3 and MHCC-97H cells decreased the expression of stemness-related genes; attenuated spheroid formation, anchor-dependent and anchor-independent cell proliferation and tumorigenicity; and enhanced sensitivity to drug treatment. Furthermore, based on analysis of TCGA dataset, the results indicated that SOX13 expression was obviously upregulated and closely associated with poor prognosis in HCC patients. Moreover, SOX13 was correlated with TAZ and CD24 expression. These data strongly demonstrated that SOX13 is involved in maintaining cancer stem-like properties in HCC cells and plays a critical role in HCC development.

Keywords: SOX13, hepatocellular carcinoma, tumorigenicity, TAZ

Introduction

Cancer stem cells (CSCs) are rare, highly malignant cells that have been found in diverse tumor types and are responsible for cancer initiation, malignant progression, recurrence and resistance to chemotherapy [1]. Hepatocellular carcinoma (HCC) is a highly aggressive cancer that possesses stem-like characteristics and is resistant to radiotherapies and chemotherapies, which has been shown to be driven by CSCs or tumor-initiating stem-like cells (TICs) [2, 3]. However, the molecular mechanisms and maintenance of liver CSCs are still poorly understood.

To date, more than 20 members of the SOX family have been identified in all vertebrates [4]. Increasing evidence has shown that SOX proteins play pivotal roles in stemness phenotype maintenance, tumor initiation and metastasis [5, 6]. SOX2 is noteworthy because is widely regarded as a key CSC marker. It has been reported that SOX2 regulates tumor initiation and CSC functions in various tumors, including squamous cell carcinoma [7], medulloblastoma [8], breast cancer [9], osteosarcoma [10], and HCC [11]. SOX9 is a stem cell factor in HCC [12] and has been demonstrated to control self-renewal and tumorigenicity by promoting symmetrical cell division and inhibiting differentiation [13, 14]. SOX4 is expressed in stem cells [15], regulates the activation of stem cells [16] and confers stem cell-like properties to bladder and gastric cancer cells [17, 18].

SOX13 is involved in multiple aspects of embryonic development [19] and is a key regulator of T lymphocyte differentiation [20]. SOX13 is highly expressed in a number of human cancers, including oligodendroglioma [21], glioma [22], and gastric cancer [23]. Recently, we reported that SOX13 exhibits upregulated expression in HCC and activates Twist1 transcription to induce HCC metastasis [24]. However, whether SOX13 is involved in the regulation of the cancer stem-like properties of HCC has not yet been investigated.

Table 1. Primers for qPCR

Gene	Sense	Anti-sense
GAPDH	CTTTGGTATCGTGGAAGGACTC	AGTAGAGGCAGGG ATGATGT
SOX13	GACCTCATCAGCCTGGACTCAT	ATCTTCC TCCGCTCATCCTTGG
CD24	TGCTCCTACCCACGCAGATT	GGCCAACCCAGAGTTGGAA
c-myc	CCTCAACGTTAGCTTCACCA	CTCCTCGTCGCAGTAGAAATAC
Oct4	CTTGCTGCAGAAGTGGGTGGAGGAA	CTGCAGTGTGGGTTTCGGGCA
CTGF	GCCCAGACCCAACTATGATTAG	GGAGGCGTTGTCATTGGTAA
TAZ	CTCGAAGCCCTCTTCAACTC	CCCGAATCAGGCTCCTTAAA
CYR61	GGCAAGAAATGCAGCAAGAC	CAGTACTTGGGCCGGTATTT
CCND1	CCTCGGTGTCCTACTTCAAATG	CACTT CTGTTCCTCGCAGAC
EDN1	GCTCGTCCCT GA TGGATAAAG	TCCAAGTCCATACGGAACAAC

In this study, we assessed the role of SOX13 in the maintenance of stem-like properties in HCC cells. Our results demonstrated for the first time that SOX13 was involved in mediating the cancer stem-like characteristics of HCC cells, including self-renewal, chemoresistance, and tumorigenicity, revealing a novel role of SOX13 in the regulation of the malignant behavior of HCC.

Materials and methods

Cell lines and animals

Human Huh7 and PLC/PRF/5 cells were obtained from the Shanghai Cell Bank of the Chinese Academy of Sciences. MHCC-97H and HCC-LM3 cells were kind gifts from Zhongshan Hospital of Fudan University. Stable knockdown of SOX13 in MHCC-97H and HCC-LM3 cells was established using lentivirus expressing short hairpin SOX13 (shSOX13). Eight-week-old male nonobese diabetic/severe combined immunodeficient (NOD-SCID) or nude mice were purchased from the National Rodent Laboratory Animal Resources, Shanghai, China, and maintained under specific pathogen-free conditions in the Xiamen University Animal Center.

qPCR analysis and western blot

qPCR and western blot assays were performed as previously described [25]. The primers used are listed in **Table 1**.

Cell proliferation, viability and cytotoxicity assays

Cell proliferation, viability, and cytotoxicity were measured using the Cell Counting Kit-8 (CCK8, Dojindo) assay according to the manufacturer's instructions. The absorbance was detected with a spectrophotometer at 450 nm. For cell proliferation, 2×10^3 cells were seeded into 96-well plates and observed every day for 5 consecutive days. For cell viability, 2×10^3 cells were seeded; 24 h later, cells were treated with cisplatin (cis) and then observed every day for 5 consecutive days. For the cytotoxicity assay, 1×10^4 cells were seeded into 96-well plates and then treated with various concentrations of 5-fluorouracil (5-Fu) and cis. Twenty-four hours later, CCK8 was added, and the plates were measured by spectrophotometry.

Colony formation assay

A total of 3×10^3 cells were seeded in 6-well plates and cultured in complete medium for 10-14 days. Colonies were fixed with 4% paraformaldehyde and then stained with crystal violet.

Three-dimensional (3D) Matrigel culture

3D Matrigel culture was performed in a 24-well plate. The wells were coated with 150 μl of Matrigel, which polymerized at 37°C for 30 min. Cells were then disassociated, suspended at 4×10^4 cells/ml in a 1:2 mixture of culture medium/Matrigel. Then, 100 μl of the suspension was added per well. Twelve days later, the colonies were photographed and counted.

Sphere formation assay

HCC cells (3×10^3 per well) were seeded into 6-well ultra-low attachment culture plates and maintained in DMEM/F12 (Gibco) supplemented with 15 ng/ml IGF (Peprotech), 20 ng/ml bFGF (Peprotech), 20 ng/ml EGF (Peprotech), 4 mU/ml insulin, 1 × B27 (Gibco) and 4 μg/ml heparin (Invitrogen). After 7 days, the spheroids (1st generation spheroids) were photographed, dissociated and seeded in plates (equal cell numbers per well), followed by a second round of spheroid formation (2nd generation spheroids). The number of 2nd generation spheroids was photographed under a microscope and counted.

Chromatin immunoprecipitation assay (ChIP)

ChIP assays were carried out using the Magna ChIP™ HiSens kit (Millipore) according to the manufacturer's protocol. For qPCR, the primer sequences were as follows: sense, 5'-TTCTG-TTCTCTTTCTTTCTGGA-3' and antisense, 5'-GA-CAAAGAAAAGGACAATA GG-3'.

In vitro limiting dilution assay

Control and shSOX13-transduced MHCC-97H or HCC-LM3 cells were seeded into 96-well ultra-low attachment culture plates at 2, 4, 6, 8, 16, and 32 cells per well and then incubated for 7 days. Sphere frequency and statistical significance were evaluated using Poisson distribution statistics.

Animal experiments

All animal experimental protocols were performed in compliance with the guidelines set by the Institutional Animal Care and Use Committee of Xiamen University. To establish a xenograft model, 3×10^6 HCC-LM3 cells transduced with empty vector or SOX13 shRNA were subcutaneously inoculated into the left or right flanks of nude mice. The length and width of the tumor were measured with a caliper, and tumor volume was calculated by the formula $0.5 \times \text{length} \times \text{width}^2$. For the in vivo limiting dilution assay, various cell numbers of shSOX13 and control MHCC-97H cells were subcutaneously inoculated into the left and right flanks of NOD-SCID mice as indicated. All mice were euthanized at the end of the experiments, and the tumors were resected and photographed. Tumorigenicity was determined by the tumor incidence.

Statistical analysis

Data are expressed as the means ± SD and were analyzed using GraphPad Prism. Student's *t* test was used for statistical analysis, and $P < 0.05$ was considered statistically significant.

Results

SOX13 expression was upregulated in tumorspheres

Isolation and enrichment of CSCs could be achieved successfully via a sphere culture system [26]. Thus, to investigate the potential association between SOX13 and liver CSCs, HCC cell lines (PLC/PRF/5, Huh7, HCC-LM3 and MHCC-97H) were dissociated and seeded into an ultra-low attachment culture plate to form tumorspheres. As shown in **Figure 1A**, all four HCC cell lines were able to form spheres of varying sizes, and the tumorspheres derived from HCC-LM3 and MHCC-97H cells presented a tighter appearance (**Figure 1A**). Then, the spheres were collected to detect SOX13 mRNA levels in these cells, and the results showed that these spheres expressed much higher levels of SOX13 mRNA than did primary adherent cells (**Figure 1B**), which demonstrated that SOX13 may participate in the regulation of cell stemness in HCC cell lines.

Knockdown of SOX13 attenuated spheroid formation

To explore the role of SOX13 in regulating the stem-like properties of HCC cells, we stably knocked down SOX13 in MHCC-97H and HCC-LM3 cells. Both the protein and mRNA levels of SOX13 in shSOX13-transduced cells were diminished compared with those in Ctrl cells (**Figure 2A** and **2B**). The mRNA levels of stem cell-related genes, including CD24, Oct4, and c-myc, were downregulated after SOX13 inhibition in both MHCC-97H and HCC-LM3 cell lines (**Figure 2C**). Moreover, silencing SOX13 expression in MHCC-97H and HCC-LM3 cells resulted in fewer and smaller spheroids than those produced by the corresponding control cells (**Figure 2D**, left). Quantitative analysis of the tumorsphere number and volume further confirmed these results (**Figure 2D**, right). These data demonstrated that knockdown of SOX13 dramatically hampered tumorsphere formation capacity.

Knockdown of SOX13 inhibited cell proliferation and tumor growth

First, SOX13 inhibition obviously mitigated cell proliferation in both MHCC-97H and HCC-LM3 cells (**Figure 3A**). Next, we performed colony formation and 3D Matrigel culture assays to detect the effects of SOX13 on cell growth. The data showed that knocking down SOX13 reduced the frequency of foci formation of cells grown both on solid plates and in Matrigel (**Figure 3B** and **3C**), suggesting that SOX13 induced anchorage-dependent and anchorage-independent growth of HCC cells. Next, we established an in vivo animal model via subcutaneous injection of HCC-LM3 cells stably expressing control shRNA (left flank) or SOX13 shRNA (right flank). As expected, control shR-

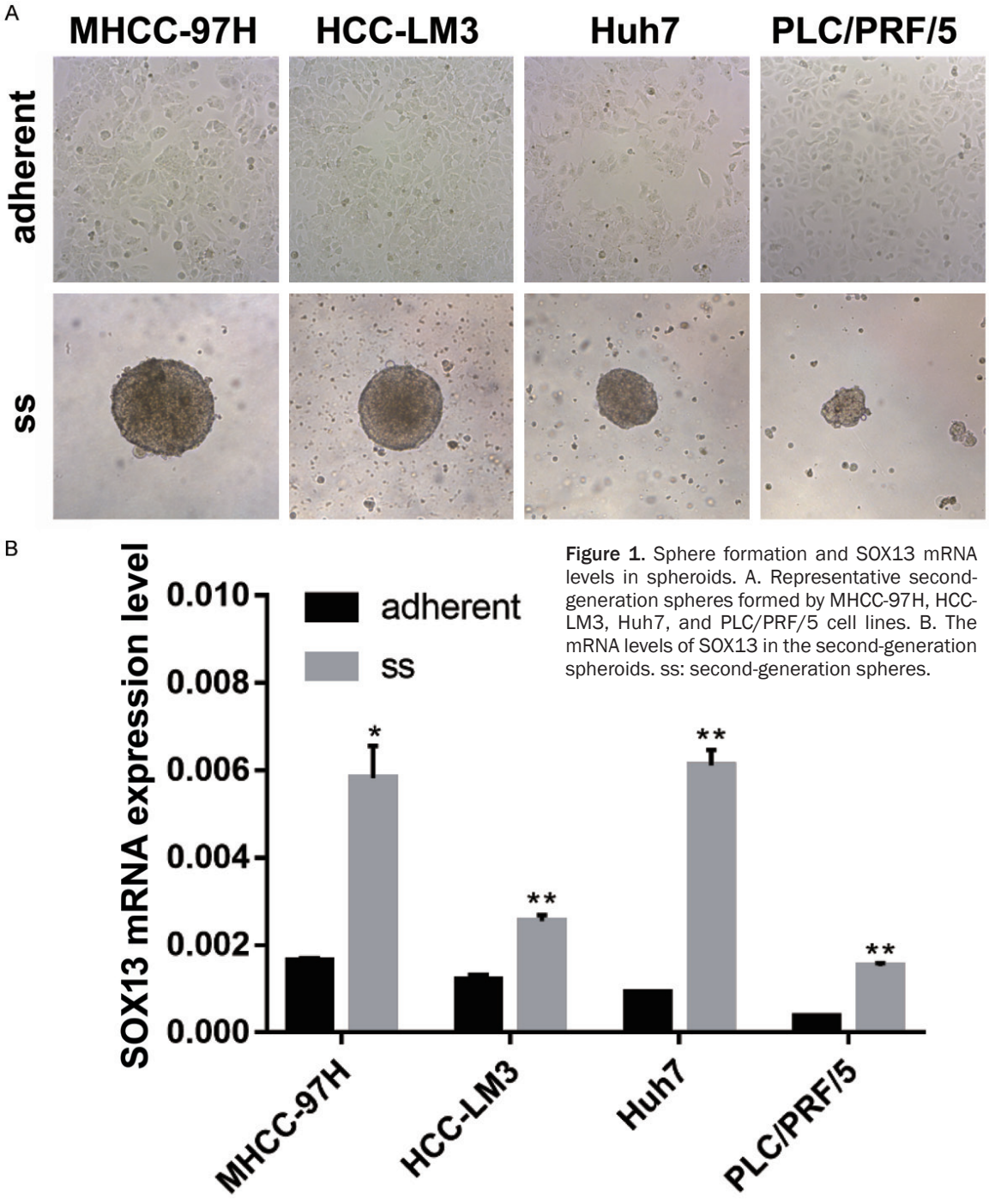
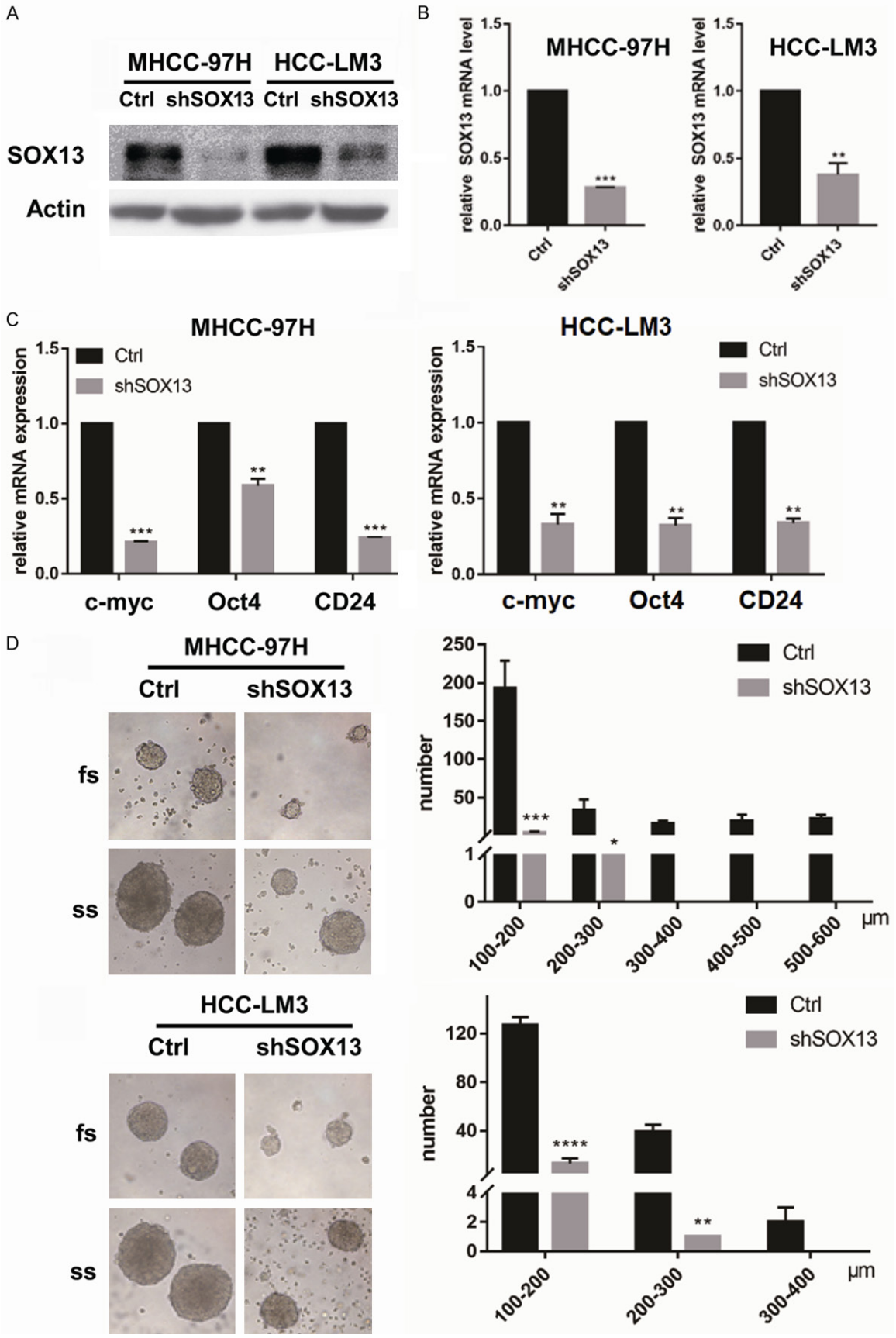


Figure 1. Sphere formation and SOX13 mRNA levels in spheroids. A. Representative second-generation spheres formed by MHCC-97H, HCC-LM3, Huh7, and PLC/PRF/5 cell lines. B. The mRNA levels of SOX13 in the second-generation spheroids. ss: second-generation spheres.

NA-expressing cells grew more rapidly and formed larger tumors than did shSOX13-expressing cells (**Figure 3D** and **3E**). Thus, these findings clearly indicated that SOX13 could promote HCC tumor growth in vitro and in vivo.

Knockdown of SOX13 enhanced chemosensitivity in HCC cells

The acquisition of chemoresistance is another intrinsic property of CSCs. To determine whether there exists a difference in chemosensitivity in HCC cells after SOX13 knockdown, cells from each group were exposed to cis or 5-Fu, two chemotherapy drugs commonly used for treating HCC. The cytotoxicity assay revealed an increase in sensitivity of MHCC-97H and HCC-LM3 cells with SOX13 inhibition to both drugs (**Figure 4A** and **4B**). Consistent results were achieved in the cell viability assay by exposing MHCC-97H cells to 3 μg/mL cis and HCC-LM3 cells to 5 μg/mL cis (**Figure 4C**).


A
MHCC-97H
HCC-LM3
Ctrl
shSOX13
Ctrl
shSOX13
SOX13
Actin
B
MHCC-97H
HCC-LM3
relative SOX13 mRNA level
1.5
1.0
0.5
0.0
***
**
Ctrl
shSOX13
C
MHCC-97H
HCC-LM3
Ctrl
shSOX13
relative mRNA expression
c-myc
Oct4
CD24
D
MHCC-97H
HCC-LM3
Ctrl
shSOX13
fs
ss
number
250
200
150
100
50
1
0
100-200
200-300
300-400
400-500
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μm
120
80
40
4
2
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μm

Figure 2. Knockdown of SOX13 expression inhibited the expression of cancer stemness genes and sphere formation capacity. A and B. The protein (A) and mRNA (B) levels of SOX13 in MHCC-97H or HCC-LM3 cells expressing control (Ctrl) or SOX13 shRNA (shSOX13). C. The expression of stem cell marker genes was analyzed by qPCR. GAPDH was used as an internal control. D. The capacity of spheroid formation of MHCC-97H and HCC-LM3 cells with stable knockdown of SOX13. Representative images of first- and second-generation spheres are shown in the left panel, and quantitative data representing the means ± SD are shown in the right panel. fs: first-generation spheres; ss: second-generation spheres.

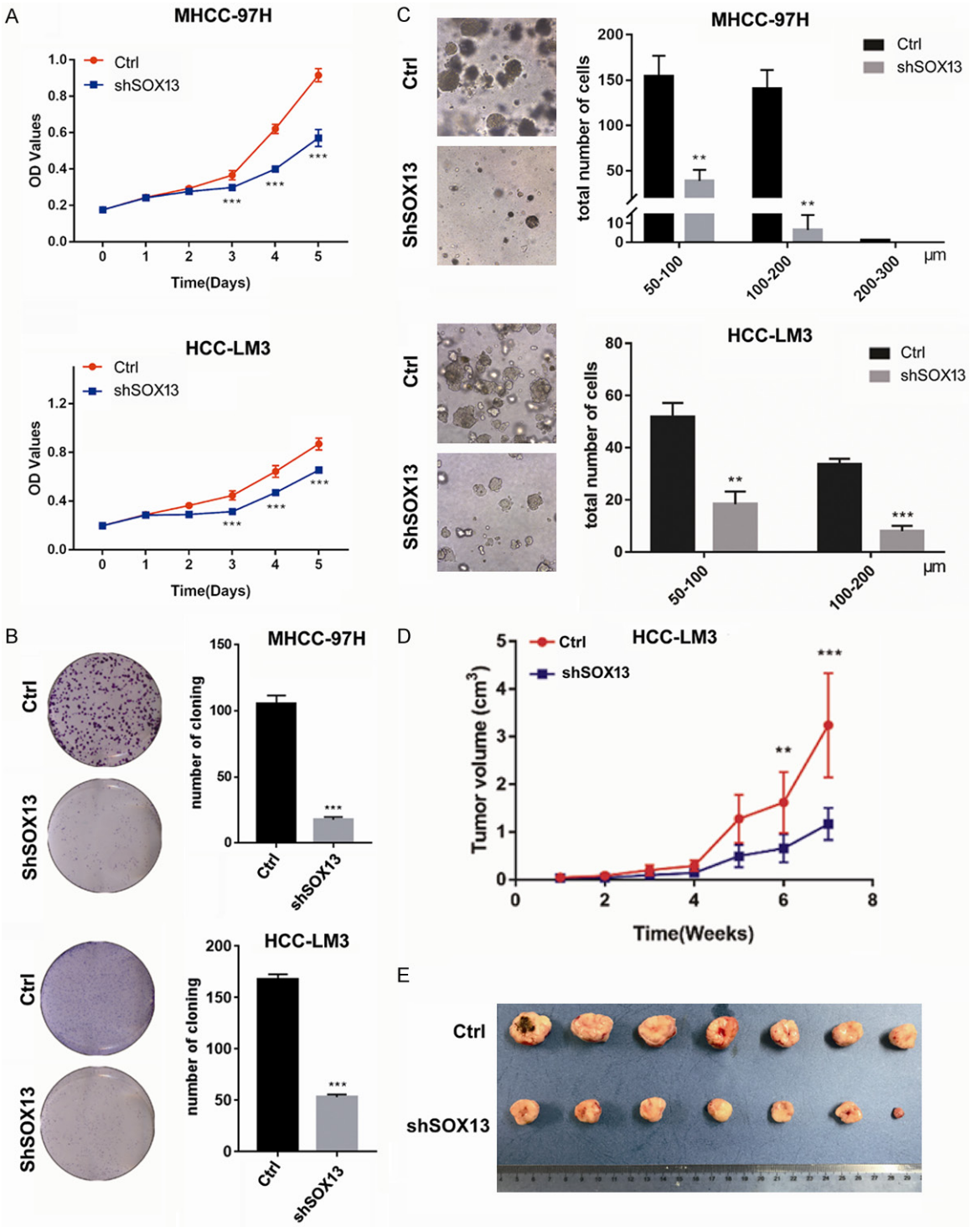

Figure 3. Knockdown of SOX13 expression attenuated cell proliferation in vitro and in vivo. A. Cell proliferation was detected by CCK8. B. The clonogenic potential was assessed by the colony formation assay. C. Knockdown of SOX13 reduced the anchorage-independent growth of HCC cells. D and E. HCC-LM3 cells expressing control (Ctrl) or SOX13 shRNA (shSOX13) were used for in vivo tumorigenesis. Tumor volume at indicated times (weeks) (D) and tumors at day 49 after tumor inoculation (E).

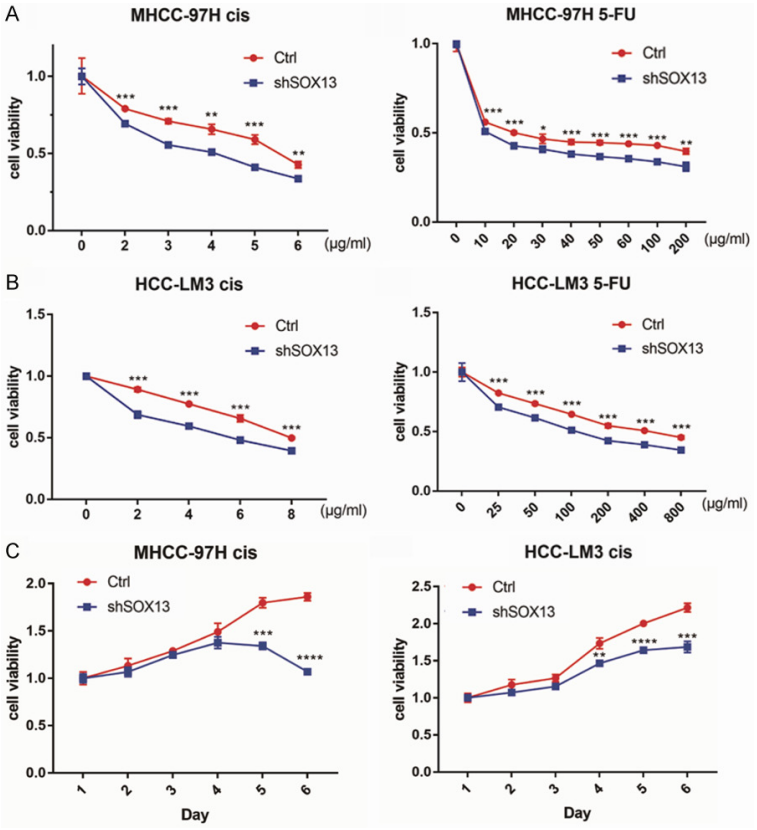

Figure 4. Knockdown of SOX13 expression enhanced the chemosensitivity of HCC cells. A and B. MHCC-97H (A) or HCC-LM3 (B) cells expressing control (Ctrl) or SOX13 shRNA (shSOX13) were cultured with various concentrations of 5-FU or cis, and then cell viability was evaluated by the CCK8 assay. C. Ctrl and shSOX13 MHCC-97H and HCC-LM3 cells were treated with 3 μg/mL and 5 μg/ml cis, respectively, and cell viability was detected at the indicated time with CCK8.

Knockdown of SOX13 impaired the tumor initiation capacity of HCC cells

Tumor initiation capacity was used to assess the stemness of tumor cells. An in vitro limiting dilution assay illustrated that SOX13 inhibition obviously reduced the CSC population among MHCC-97H (**Figure 5A**) and HCC-LM3 (**Figure 5B**) cells. Next, we investigated the tumor initiation capacity of these cells in vivo. The xenograft tumors in NOD/SCID mice were derived from MHCC-97H Ctrl and shSOX13 cells that were inoculated at varying cell numbers. Mice injected with MHCC-97H Ctrl cells developed tumors at a faster rate than did mice injected with an equivalent number of shSOX13 cells (**Figure 5C**). As shown in **Table 2**, when 1000 cells were injected, four out of five mice injected with Ctrl cells developed xenograft tumors, whereas none of the mice injected with shSOX13 cells formed tumors, which revealed that inhibiting SOX13 significantly attenuated the tumorigenicity of HCC cells.

SOX13 transactivates TAZ and affects its downstream targets

TAZ is a key effector of the Hippo pathway and exerts regulatory functions in the maintenance of CSC properties [27, 28]. SOX13 is a transcription factor; subsequently, we investigated whether SOX13 could modulate TAZ expression at the transcriptional level. First, we observed that downregulating SOX13 expression obviously inhibited TAZ mRNA levels (**Figure 6A**). Meanwhile, the mRNA levels of TAZ target genes, including CTGF, CCND1, END1, and CYR61, were dramatically inhibited when SOX13 expression was knocked down (**Figure 6A**). Sequence analysis showed that there was a SOX13 binding site at the TAZ promoter (-1871 to -1876) (**Figure 6B**). ChIP assays demonstrated that SOX13 could directly bind to the TAZ promoter (**Figure 6C**). Thus, the suppression of the stem cell-like features in HCC induced by SOX13 knockdown may be partially mediated by TAZ downregulation.

SOX13 is highly expressed in HCC and is positively correlated with TAZ and CD24 expression

We recently reported that Sox13 expression is abnormally upregulated in HCC and associated

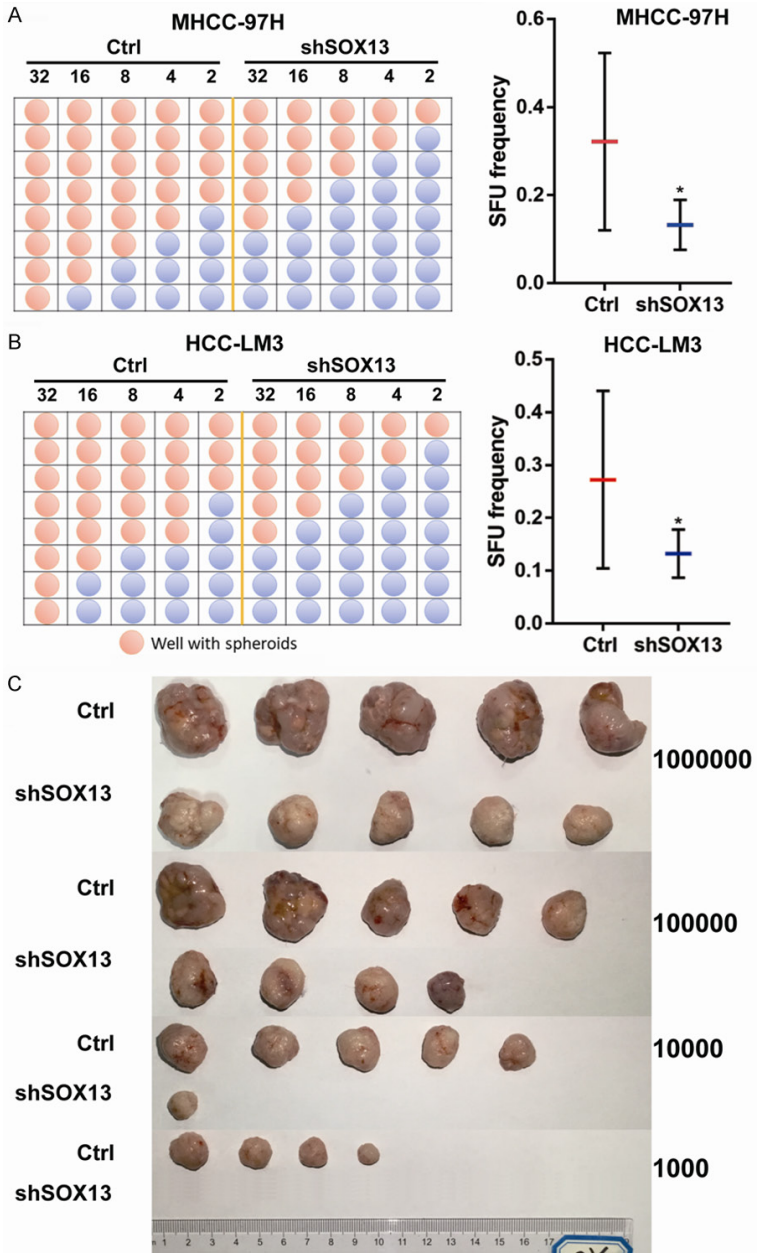

Figure 5. Downregulation of SOX13 expression impaired the tumorigenic ability of HCC cells. A and B. The frequency of sphere formation in MHCC-97H (A) or HCC-LM3 (B) cells expressing control (Ctrl) or SOX13 shRNA (shSOX13) was assessed by an in vitro limiting dilution assay. C. In vivo limiting dilution assay with varying numbers of MHCC-97H Ctrl and shSOX13 cells subcutaneously injected into the left and right flanks of NOD-SCID mice (n = 5/group), respectively. Tumor formation was evaluated at day 30 post-inoculation.

with poor prognosis [24]. To further confirm the changes in SOX13 expression in HCC, we downloaded TCGA datasets and found that SOX13 levels were upregulated in tumors compared with paired normal liver tissues (**Figure 7A**, P < 0.001). Further analysis of the RNA-seq data of all patients from the TCGA dataset also revealed higher SOX13 mRNA levels in HCC tissues than in normal tissues (**Figure 7B**, P < 0.001). Then, we performed Kaplan-Meier analysis to assess the prognostic value of SOX13 mRNA expression in HCC, which indicated that patients with high SOX13 expression had worse overall survival (OS) than those with low SOX13 expression (HR = 2.11, P = 0.015) (**Figure 7C**). We analyzed the correlation of SOX13 and either TAZ or CD24 expression in the TCGA dataset. The results showed that both SOX13 and TAZ expression (**Figure 7D**, r = 0.41, P < 0.0001) and SOX13 and CD24 expression (**Figure 7E**, r = 0.23, P < 0.0001) were positively correlated in HCC samples.

Discussion

To date, over 20 SOX proteins and their corresponding genes have been identified, and they are classified into Groups A-G [29]. In the current work, based on HCC datasets from the TCGA, we determined that SOX13 expression is amplified and upregulated in HCC patients and is inversely correlated with patient survival. Silencing SOX13 results in decreased cell proliferation in vitro and in vivo, reduced anchorage-dependent and anchorage-independent cell growth, and mitigated sphere formation of MHCC-97H and HCC-LM3 cells, suggesting that SOX13 is essential for the proliferation and self-renewal of HCC. Knockdown of SOX13 enhanced the sensitivity of HCC cells to the chemotherapeutic agents 5-FU and cis, which demonstrated that SOX13 is involved in the chemoresistance

Table 2. Tumor-initiating capacity of MHCC-97H control and shSOX13 cells in NOD-SCID mice

No.of cells injected	MHCC-97H Ctrl	MHCC-97H shSOX13
1000000	5/5	5/5
100000	5/5	4/5
10000	5/5	1/5
1000	4/5	0/5

of HCC cells. Moreover, SOX13 depletion inhibited the tumorigenic ability of HCC cells.

SOX13, a member of the sex-determining gene family, is located in human chromosome 1 band q32 [30] and encodes an 84 kD protein. SOX13 [31], together with SOX5 and SOX6, belongs to the SOXD family. Emerging studies have identified that the SOXD family plays a key role in tumorigenesis and metastasis [31]. The SOX5 and SOX6 genes act as oncogenes or tumor suppressor genes to regulate different target genes during the development of different types of cancer. However, SOX13 has not been studied as extensively as SOX5 and SOX6 [31]. SOX13 has been implicated in the regulation of glioma and gastric cancer [22, 23]. Gain and loss of SOX13 function in human GECs suggested that SOX13 promoted cell viability, migration, and tube formation [22]. SOX13 expression is upregulated in primary gastric cancer and modulates gastric cancer cell proliferation by mediating PAX8 expression [23]. However, little is known about the role of SOX13 in HCC tumorigenesis and progression, especially its function in the maintenance of stemness of HCC cells.

There has been accumulating evidence based primarily on experimental and clinical observations supporting the existence of CSCs with the capacity to self-renew, limitlessly divide and produce heterogeneous progeny as well as increase resistance to chemo- and radiotherapy [32]. CSCs were initially discovered in acute myeloid leukemia [33] and then were found to be more abundant in solid tumors, including breast [34], prostate [35], pancreatic [36], colon [37] and liver cancer [38], among many others. Liver CSCs are thought to drive HCC initiation, metastasis, and progression [39, 40].

The ability to form tumorspheres in serum-free conditions at low density in non-adherent cultures was used for the identification, enrichment, and expansion of CSCs [41, 42]. Sphere formation is a feature of self-renewal that can be used to identify CSCs. Therefore, we first detected the sphere-forming ability of HCC cells and found that SOX13 expression was upregulated in hepatoma spheroids. In addition, cells with SOX13 knockdown formed fewer and smaller hepatospheres in their first and second passages. Meanwhile, the expression levels of CSC markers, including CD24, Oct4, and c-myc, were downregulated. It has been proven that CD24 not only is a physical marker for CSCs but also exerts a unique function in HCC CSCs, which is critical for driving tumor initiation and self-renewal [43]. Interestingly, we found that SOX13 expression was positively associated with CD24 expression in clinical HCC samples. Our results suggest that SOX13 is involved in HCC cell stemness regulation.

HCC has a poor prognosis and is notoriously resistant to standard radiation treatments and chemotherapy [44]. The chemotherapeutic agents 5-FU and cis are frequently used in the treatment of HCC, although they elicit a low response. Given the contribution of CSCs in the regulation of chemotherapy resistance, depletion of SOX13 leads to sensitization of HCC cells to 5-FU and cis, indicating that SOX13 plays a role in the drug resistance of HCC cells.

A key property of CSCs is their unique tumor-initiating potential and self-renewal ability in immunodeficient mice [26]. One method of evaluating the tumor-initiating capacity is in vivo and in vitro limiting dilution assays [45]. An in vivo limiting assay, which is used to detect tumorigenesis in a serial xenotransplantation assay, is the gold standard for evaluating the presence of CSCs [41, 46]. A significant difference in tumor incidence was observed between Ctrl and SOX13-knockdown cells, which indicated that SOX13 could enhance tumorigenic capacity.

TAZ is an essential regulator of CSC properties in a wide range of human cancers [28], including breast [47], lung [48], esophageal [49], and liver cancers [50]. HIF-1 binds directly to the TAZ promoter and activates TAZ transcription, resulting in increases in the mRNA and protein expression of TAZ; this has been shown to enrich for breast CSCs [51]. Our data demonstrated that knockdown of SOX13 decreased TAZ expression and the expression of its direct

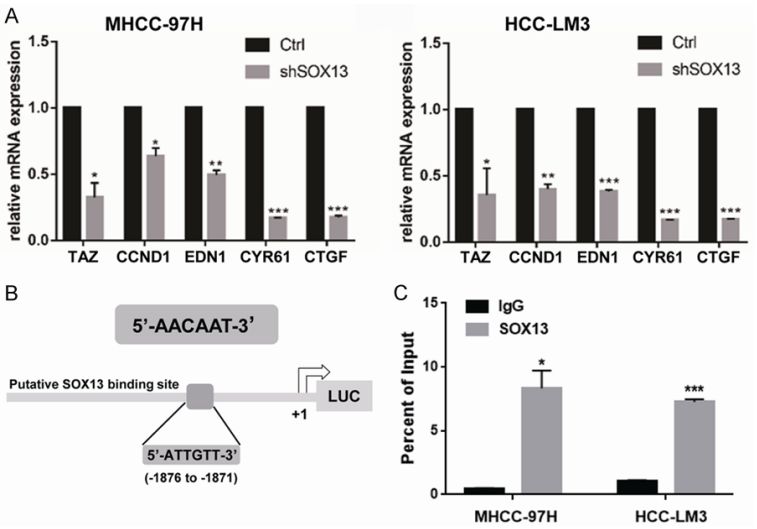

Figure 6. SOX13 transactivated TAZ expression. A. The mRNA levels of TAZ and its target genes after SOX13 depletion. B. The putative SOX13 binding site in the TAZ promoter. C. SOX13 bound to the TAZ promoter directly as indicated by the ChIP assay.

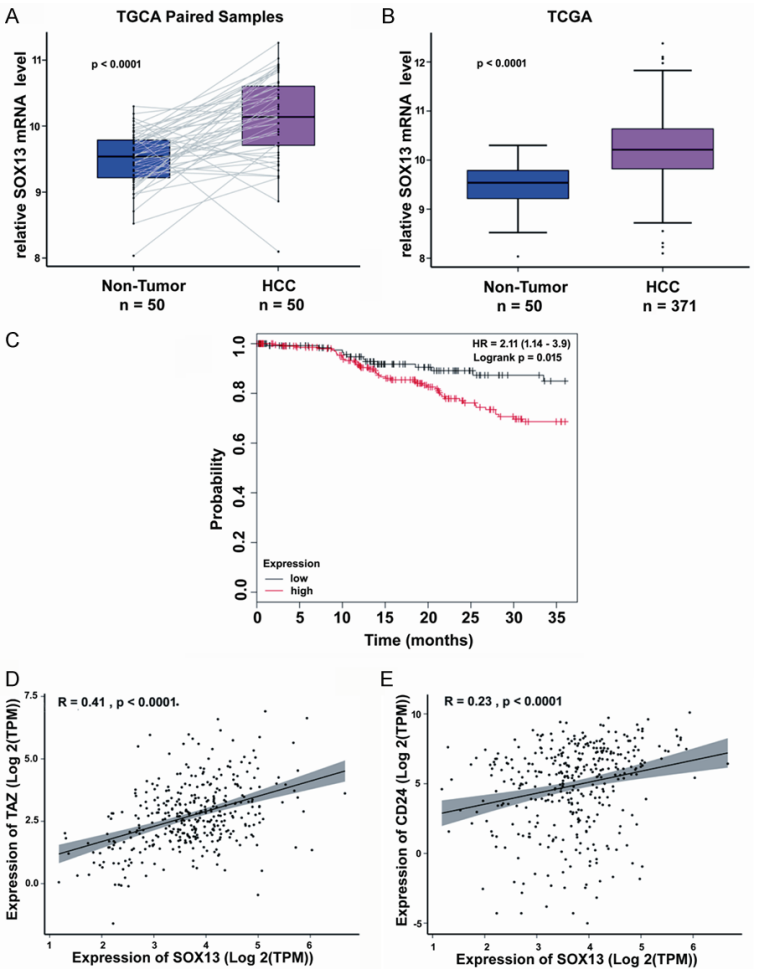

Figure 7. SOX13 was overexpressed and associated with poor survival in human HCC. A and B. SOX13 mRNA expression in paired tissues from HCC patients (n = 50) (A) and all patients from the TCGA dataset (n = 371) (B). C. Overall survival (OS) curve according to SOX13 expression based on the TCGA dataset. D and E. Correlation between SOX13 and TAZ expression (D) and SOX13 and CD24 expression (E) based on the TCGA data.

downstream genes (CCND1, END1, CYR61, CTGF). More importantly, sequence analysis showed that the TAZ promoter contains a consensus SOX13 binding site. We further identified that SOX13 directly binds the TAZ promoter and regulates TAZ expression at the transcriptional level. Based on TCGA data analysis, we observed that SOX13 expression was positively associated with TAZ expression in HCC samples. Our data demonstrated that SOX13 may regulate CSC properties in HCC cells through transcriptional activating TAZ. However, the detail mechanisms that how TAZ pathway mediated the function of SOX13 need to be explored in more detail in future studies.

In conclusion, we provide evidence and mechanistic insights of the oncogenic functions of SOX13 in the regulation of the stem-like properties of HCC cells, including promoting tumor cell proliferation, maintaining self-renewal, impairing chemosensitivity, increasing tumor tumorigenicity, and transcriptionally activating TAZ expression. All the results suggest that SOX13 is as a promising therapeutic target in HCC.

Acknowledgements

This work was supported by grants from the National Nature Science Foundation of

China (81871963 and 81772630); the National Nature Science Foundation of Fujian (2020J0-11204); Medical and Health Key Project of Xiamen (3502Z20191106).

Disclosure of conflict of interest

None.

Address correspondence to: Wenxiu Zhao, Fujian Provincial Key Laboratory of Chronic Liver Disease and Hepatocellular Carcinoma, Zhongshan Hospital, Xiamen University, Xiamen 361004, People's Republic of China. Tel: +86-592-2292576; Fax: +86-592-2212328; E-mail: wxzhao@xmu.edu.cn

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