European Review for Medical and Pharmacological Sciences 2021; 25: 1845-1852

Circular RNA circSOX4 promotes the proliferation, migration and apoptosis of hepatocellular carcinoma cells by down regulating microRNA-432 expression

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Abstract. – OBJECTIVE: As the research of circular RNAs (circRNAs) in human malignant tumors has been increasing, multiple circRNAs have been discovered to be engaged in the modulation of the liver cancer cell functions. This study aims at exploring how circSOX4 affects the progression of hepatocellular carcinoma (HCC).

PATIENTS AND METHODS: CircSOX4 levels in HCC tissue samples were detected by quantitative real-time polymerase chain reaction (qRT-PCR) analysis, and the relationship between circSOX4 expression and HCC patients' prognosis was analyzed. CircSOX4 expression was knocked down by transfection of small interfering RNA. The effects of circSOX4 on cell functions including proliferation, invasiveness and migration ability were examined by cell counting kit-8 (CCK-8), transwell, cell wound healing test and flow cytometry experiments, respectively. The target RNA of circSOX4 was predicted through searching bioinformatics website, and the binding between the two was verified through Luciferase assay.

RESULTS: CircSOX4 was abnormally highly expressed either in HCC tissues or in cell lines, which was positively correlated with the poor prognosis of HCC patients. Transfection of small interfering RNA against circSOX4 in HCC cells resulted in inhibited migration and proliferation of HCC cells, while an increase in cell apoptosis. Bioinformatics analysis revealed that microRNA-432 contained the binding site pairing to circSOX4 3'UTR, and their binding relationship was confirmed by Luciferase assay. Their expression levels were negatively correlated. In addition, downregulation of microRNA-432 can partially reverse the effect of silenced circSOX4 on regulating apoptosis, proliferation and migration of HCC cells.

CONCLUSIONS: CircSOX4, highly expressed in HCC, indicates a poor prognosis. CircSOX4 may mediate the progression of HCC by binding to microRNA-432.

Key Words:
Hepatocellular carcinoma, CircSOX4, MicroRNA-432, Cell proliferation, Cell migration.

Introduction

Liver cancer, with its high incidence and mortality, is the fifth most common human malignant tumor worldwide[1,2]. The development of hepatocellular carcinoma (HCC) is a complex process that is associated with many risk factors, including environmental factors, hepatitis, smoking and drinking[3]. At present, treatment methods for HCC include surgery, radiotherapy, chemotherapy, immunotherapy, interventional therapy, etc., but the efficiency is often unsatisfactory, resulting in high recurrence and metastasis rate and poor prognosis[4,5]. Therefore, it is particularly important to explore the molecular mechanism of HCC occurrence and development, so as to provide new targets for the diagnosis and treatment.

Circular RNAs (circRNAs) are a class of non-coding RNAs that are widely expressed in mammals. They are highly conservative and stable covalently closed circular RNA transcripts that can regulate gene expressions at the post-transcription level[6]. CircRNAs are engaged in various physiological and pathophysiological processes[7] and recently they have been increasingly studied in human malignant tumors. Of note, has_circ_0005075 is able to accelerate the proliferation and invasion of colorectal cancer cells[8]. hsa_circ_0052112 promotes the migration of breast cancer cells by binding to microRNA-125a-5p[9]. circMAN2B2 promotes lung cancer cell invasion and proliferation through the mi-

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croRNA-1275/FOXK1 axis[10]. Although circRNAs have been increasingly studied in human tumors, further research is needed to explore their roles in HCC.

MicroRNAs (miRNAs) are small non-coding RNAs of approximately 22 nt in length that usually bind to the 3'-untranslated region (3'-UTR) of mRNA and suppress gene expressions by degrading mRNA or inhibiting the translation process[11,12]. They are transcribed by RNA polymerases II and III, and the resulting precursors are cleaved to form mature miRNAs[13]. MiRNAs play a vital role in a host of physiological and pathological processes such as apoptosis, metabolism and differentiation[14]. They can regulate about 30% of human genes at post-transcriptional level. MiRNAs may play a key role in human carcinogenesis[15]. MicroRNA-486-3p inhibits cervical cancer cell metastasis and proliferation by targeting ECM1[16]. MicroRNA-375 attenuates gastric cancer cell proliferation by binding to JAK2[17]. MicroRNA-15a reduces the proliferation of osteosarcoma cells by targeting TNFAIP1[18]. Although the research of miRNAs in human malignant tumors has become popular, the research on HCC is still very limited.

CircSOX4 is abnormally expressed in lung cancer[19,20]. However, the biological function of cicrSOX4 in HCC and its underlying mechanism have not been studied yet. In this study, through a series of *in vitro* experiments, we preliminarily discussed the potential functions of circSOX4 in regulating the progression of HCC and the molecular mechanism.

Patients and Methods

Patients and Specimens

A total of 23 pairs of HCC tissue samples and matched adjacent cancer tissue samples were collected in this study. All patients did not receive adjuvant radiotherapy or chemotherapy before surgery. Tumor pathological classification and staging were implemented in accordance with the Union of International Cancer Control (UICC). The specimens were quickly frozen immediately after being isolated and stored at -80°C. The investigation was approved by the Ethics Committee of the Liaocheng People's Hospital. Signed written informed consents were obtained from all participants before the study.

Quantitative Real-Time Polymerase Chain Reaction (qRT-PCR)

Total RNA was extracted from HCC tissues or cells using TRIzol reagent (Invitrogen, Carlsbad, CA, USA), and the concentration was measured using a spectrophotometer. According to the product specification, PrimeScript-RT reagent kit was used to reverse transcribe RNA into complementary deoxyribose nucleic acid (cDNA). SYBR Premix ExTaq™ II (TaKaRa Co., Ltd., Otsu, Shiga, Japan) was applied to perform qPCR on the ABI 7500 system to detect gene expression levels, with U6 and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) as internal controls. Primers used in qRT-PCR detection were as follows: CircSOX4-F: 5′-ATGCACAACGCCGAGATC-3′, CircSOX4-R: 5′-GTCAGCCATGTGCTTGAG-3′. GAPDH-F: 5′-ATGGGGAAGGTGAAGGTCG-3′, GAPDH-R: 5′-GGGGTCATTGATGGCAACAATA-3′. U6-F: 5′-CTCGCTTCGGCAGCACA-3′, U6-R: 5′-ACGCTTCACGAATTTGCGT-3′. microRNA-432-F: 5′-AACGAGACGACGACAGACT-3′, microRNA-432-R: 5′-CTTGGAGTAGGTCATTGGGT-3′.

Cell Culture

The normal liver cells (LO2) and HCC cell lines (HCCLM3, Huh6, SMMC-7721, QGY-7703) used in this study (Shanghai, China) were cultured with Roswell Park Memorial Institute-1640 (RPMI-1640) (Hyclone, South Logan, UT, USA) containing 10% fetal bovine serum (FBS) (Gibco, Rockville, MD, USA) and 1% penicillin/streptomycin in a cell incubator at 37°C with 5% CO_2.

Transfection

The primers for circSOX4 and microRNA-432 were provided by Guangzhou Ribobio (RIBOBIO, Guangzhou, China). After the cells adhered to more than 60%, transfection was carried out with si-circSOX4 and microRNA-432 mimics or inhibitor.

Sequences of transfection plasmids were as follows: hsa-microRNA-423 mimics, 5′-CAGUGCAAUGAUGAAAGGGCAU-3′; microRNA-423 inhibitor, 5′-CCCAUGCUUCACUGCCAAUUGU-3′; NC, 5′-GUACUUUCACGAAGUGGGAA-3′;

Cell Counting Kit-8 (CCK-8) Test

CCK-8 assay (Dojindo Molecular Technologies, Kumamoto, Japan) was conducted to evaluate cell proliferation based on manufacturer's instructions.

Cell Wound Healing Test

The cell monolayer membrane was scratched with a 200 μL pipette tip after cells were fully adhered. The 6-well plate was observed under the microscope and captured, and Image-Pro Plus 6.0 software was used for quantitative analysis (Media Cybernetics, Inc., Silver Springs, MD, USA).

Cell Migration Assay

Transwell chamber (8-μm pore membrane filter) was purchased from Corning Corporation and used to determine the cell migration ability. Cells were prepared into cell suspensions and seeded in upper chamber supplemented with serum-free medium, and then 10% FBS medium was added to the bottom compartment. Penetrating cells to the bottom were captured at 48 h and counted.

Flow Cytometry

FITC and PI were used to stain HCC cells, and then FACScan (BD Biosciences, San Jose, CA, USA) was used to perform fluorescence-activated cell sorting analysis.

Luciferase Assay

Lipofectamine 2000 was applied to complete the co-transfection of circSOX4-wt or circSOX4-mut and microRNA-432 mimics or NC into HCC cells. 24 hours after transfection, the luciferase activity of each group was measured using the Dual-Luciferase reporter kit.

Statistical Analysis

Statistical analysis was performed using Statistical Product and Service Solutions (SPSS) 22.0 software (IBM, Armonk, NY, USA). Data were represented as mean ± Standard Deviation (SD). The *t*-test was used for comparison between groups, Pearson's method was used for correlation analysis. Log-rank test was applied for analyzing Kaplan-Meier survival curves. *p* less than 0.05 was statistically significant.

Results

CircSOX4 Has an Increased Expression in HCC

First, we detected circSOX4 expression in HCC tissues by qRT-PCR. We selected tumor tissues and para-cancerous control tissues of 23 HCC patients. CircSOX4 expression was remarkably higher in HCC tissues than in normal control ones (Figure 1A). A consistent result was observed in HCC cell lines and normal hepatocytes (Figure1B). Survival analysis showed high expression of SOX4 was more likely to lead to poor prognosis of HCC patients as compared with patients expressing low expression of circSOX4 (Figure1C).

Knockdown of CircSOX4 Inhibits HCC Cells Proliferation and Migration Ability While Promotes Their Apoptosis

To study the impact of circSOX4 on HCC cells, we transfected small interfering RNA against circSOX4 (si-circSOX4) or its negative control (si-NC). Transfection of si-circSOX4 markedly inhibited the expression of circSOX4 in HCC cell lines (Figure 2A). As shown in Figure 2B and 2C, cell viability in HCC cells transfected with si-circSOX4 was remarkably reduced in compar-

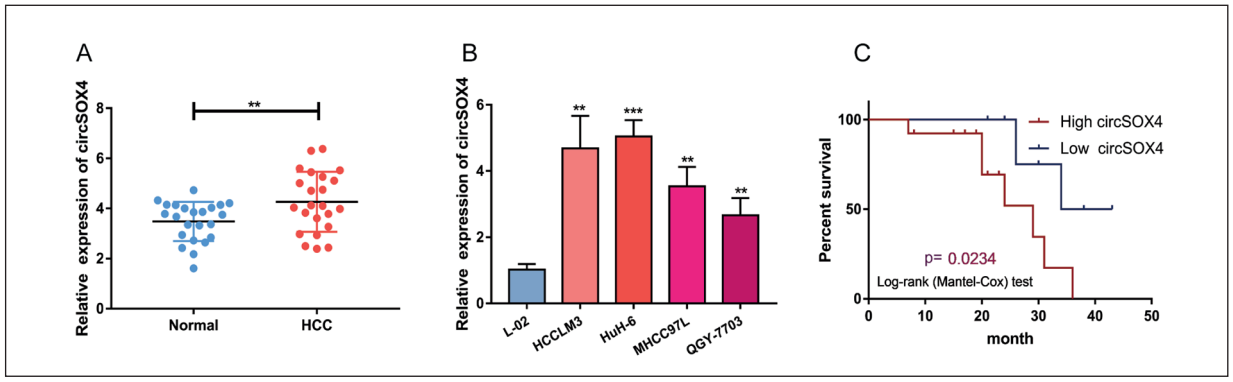

Figure 1. A, qRT-PCR results show that the expression level of circSOX4 in liver cancer tissue is significantly higher than that in normal liver tissue; **B,** qRT-PCR results show that the expression level of circSOX4 in liver cancer cell lines is significantly higher than that in normal liver cell lines; **C,** Survival analysis results show that the survival prognosis of patients in high expression of circSOX4 group is worse than that of those in lower expression. ** $p<0.01$, *** $p<0.001$.

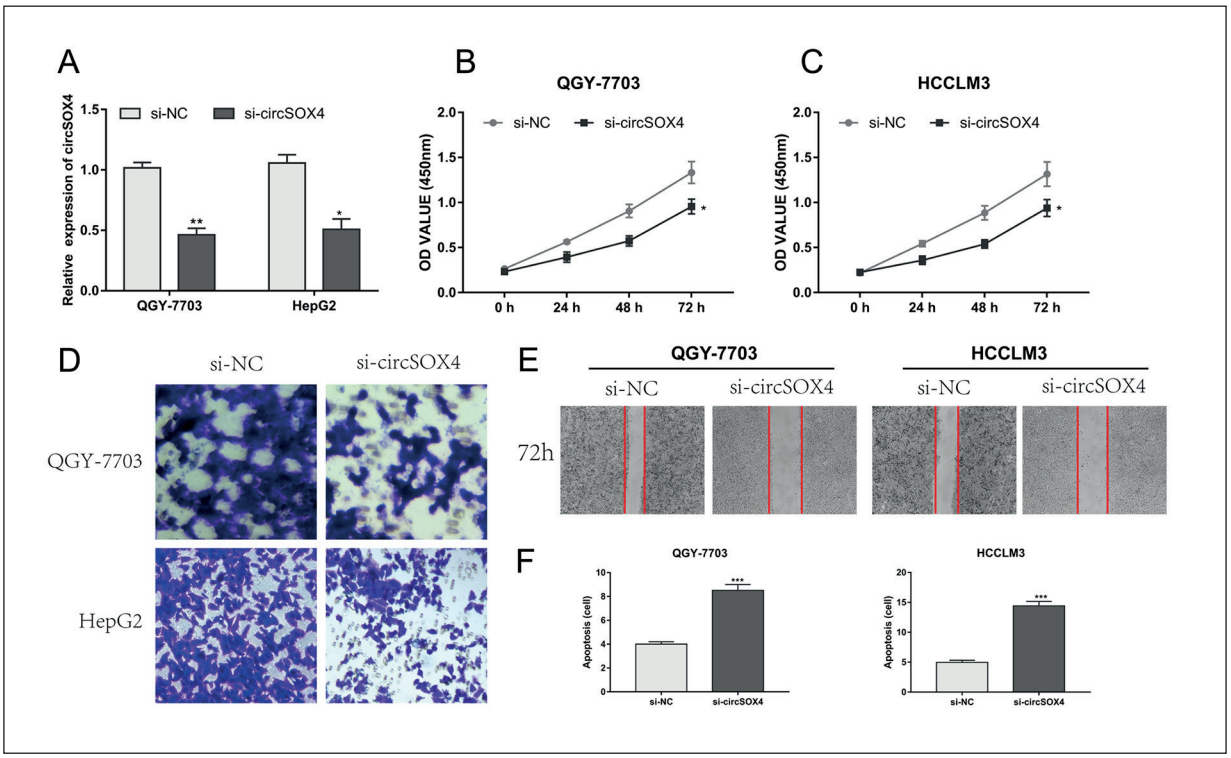

Figure 2. A, Transfection with si-circSOX4 can significantly down-regulate the expression of circSOX4 gene in QGY-7703 and HCCLM3 cell lines. **B-C,** The results of CCK-8 experiment show that after knocking down circSOX4 significantly inhibits the proliferation ability of QGY-7703 and HCCLM3 cell lines. **D,** Transwell experimental results indicate that knocking down circSOX4 significantly inhibits the invasive and migration ability of QGY-7703 and HCCLM3 cell lines (magnification: 200×). **E,** The results of cell wound healing experiment show that knocking down circSOX4 significantly inhibits the migration ability of QGY-7703 and HCCLM3 cell lines (magnification: 20×). **F,** Flow cytometry results show that after knocking down circSOX4 increases the apoptosis level of QGY-7703 and HCCLM3 cell lines. * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

ison to si-NC group, indicating an inhibited cell proliferation ability. Meanwhile, transwell and cell wound healing assay showed that knockdown of circSOX4 also attenuated invasive (Figure 2D) and migratory capacities (Figure 2E) of HCC cells. Conversely, the results of flow cytometry indicated an enhanced cell apoptosis induced by knockdown of circSOX4 (Figure 2F).

MicroRNA-432 Is a Downstream Regulator of CircSOX4

We found through the bioinformatics analysis that microRNA-432 contained a binding sequence pairing to circSOX4 3'UTR (Figure 3A). Then we verified the binding between the two through the luciferase assay (Figure 3B, 3C). Additionally, in HCC cell lines, we found that knockdown of circSOX4 upregulated the expression level of microRNA-432 (Figure 3D). Pearson analysis also revealed a consistent negative correlation between that two in HCC tissue specimens (Figure 3E).

MicroRNA-432 Mediates the Effect of CircSOX4 on the Malignant Phenotype of HCC Cells

To further verify the regulation between microRNA-432 and circSOX4, we co-transfected microRNA-432 inhibitor and si-circSOX4 in HCC cells. Transfection of microRNA-432 inhibitor partially restored the suppressing effect of si-circSOX4 on proliferation activity (Figure 4A, 4B). Meanwhile, knockdown of microRNA-432 also enhanced the reduced migration and invasive capacities of HCC cells induced by knockdown of circSOX4 (Figure 4C-4F). In addition, the enhanced cell apoptotic activity of HCC cells caused by si-circSOX4 was inhibited by microRNA-432 inhibitor (Figure 4G, 4H).

Discussion

Each year, about 700,000 people are newly diagnosed with HCC and about 750,000 die from

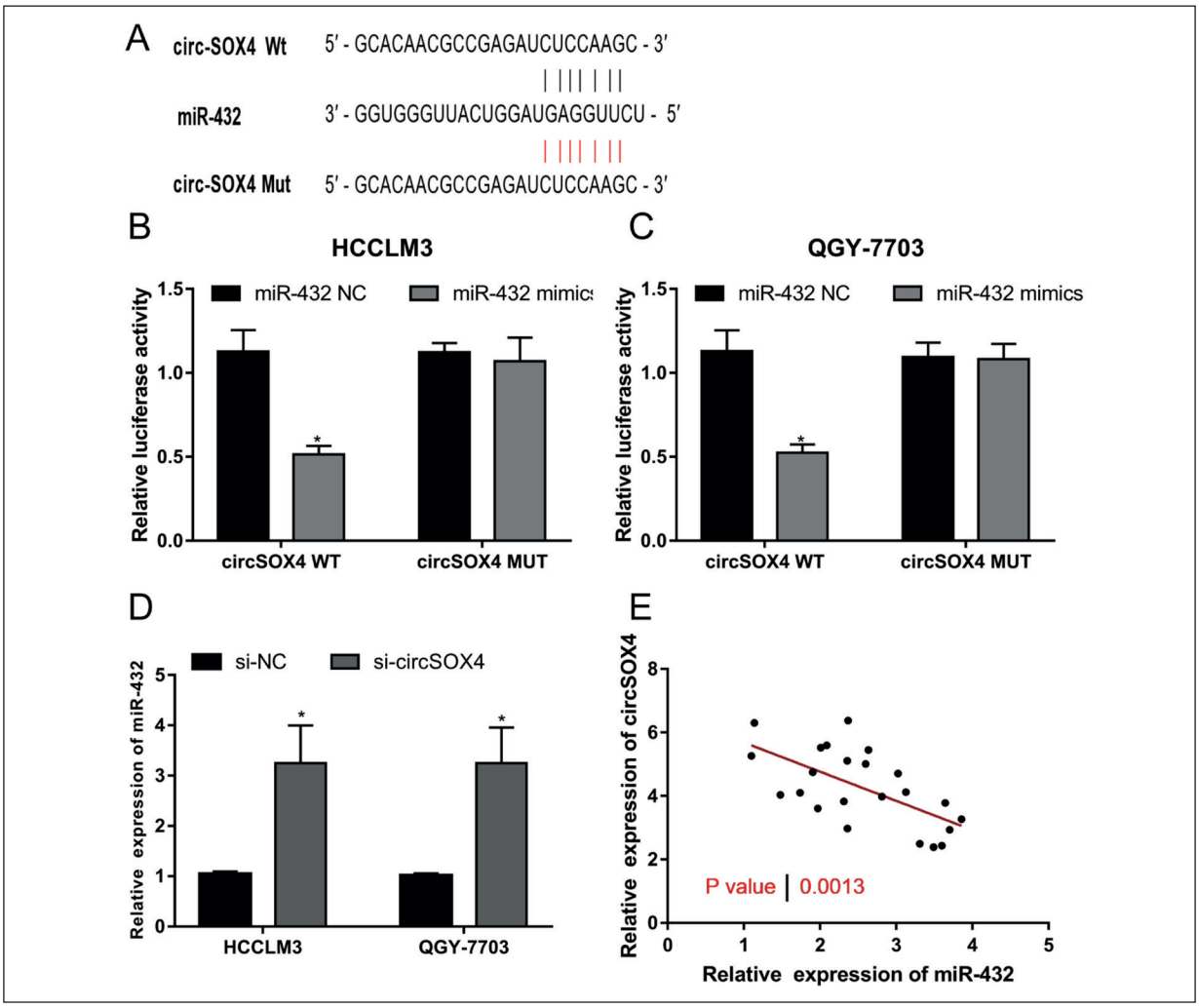

Figure 3. A, Bioinformatics technology predicts that the 3'UTR region of circSOX4 has a binding site with miR-432. **B-C,** Dual-Luciferase reporter gene experiments confirm that circSOX4 and miR-432 have a binding relationship in liver cancer cells. **D,** After knocking down circSOX4 in QGY-7703 and HCCLM3 cell lines, miR-432 expression level is increased. **E,** circSOX4 and miR-432 are negatively correlated. * $p<0.05$.

it[21]. Chronic hepatitis b (HBV) and hepatitis c virus (HCV) infections are the most common causes of HCC[22]. Although surgical resection and chemotherapy can prolong the survival time of HCC patients, most of them are diagnosed in the advanced tumor stage, leading to poor treatment effect, and poor prognosis[23]. In this study, we preliminarily found that circSOX4 was abnormally highly expressed in HCC tissues. Taking this as an entry point, we discussed the specific molecular mechanism of circSOX4 in HCC.

In this study, we found that circSOX4 expression was abnormally upregulated in HCC cells. Knockdown of circSOX4 markedly suppressed the proliferation and migration of HCC cells while enhanced cell apoptosis, indicating that circSOX4 may serve as an oncogene in the progression of HCC. CircRNAs, miRNAs and long non-coding RNAs (lncRNAs) are the most widely studied non-coding RNAs (ncRNAs), Although circRNAs have been discovered for decades, their association with various biological processes has been gradually explored in recent years[24]. CircRNA exerts critical functions in the progression of HCC. Notably, circRHOT1 stimulates progression of liver cancer by modulating the expression of NR2F6[25]. CircRNA104718, as an endogenous competitive RNA, accelerates the progression of HCC through the microRNA-218-5p/TXNDC5 signaling pathway[26]. Previously, in lung adenocarcinoma, circSOX4 has been found to regulate PLAGL2 activation of Wnt signaling pathway by

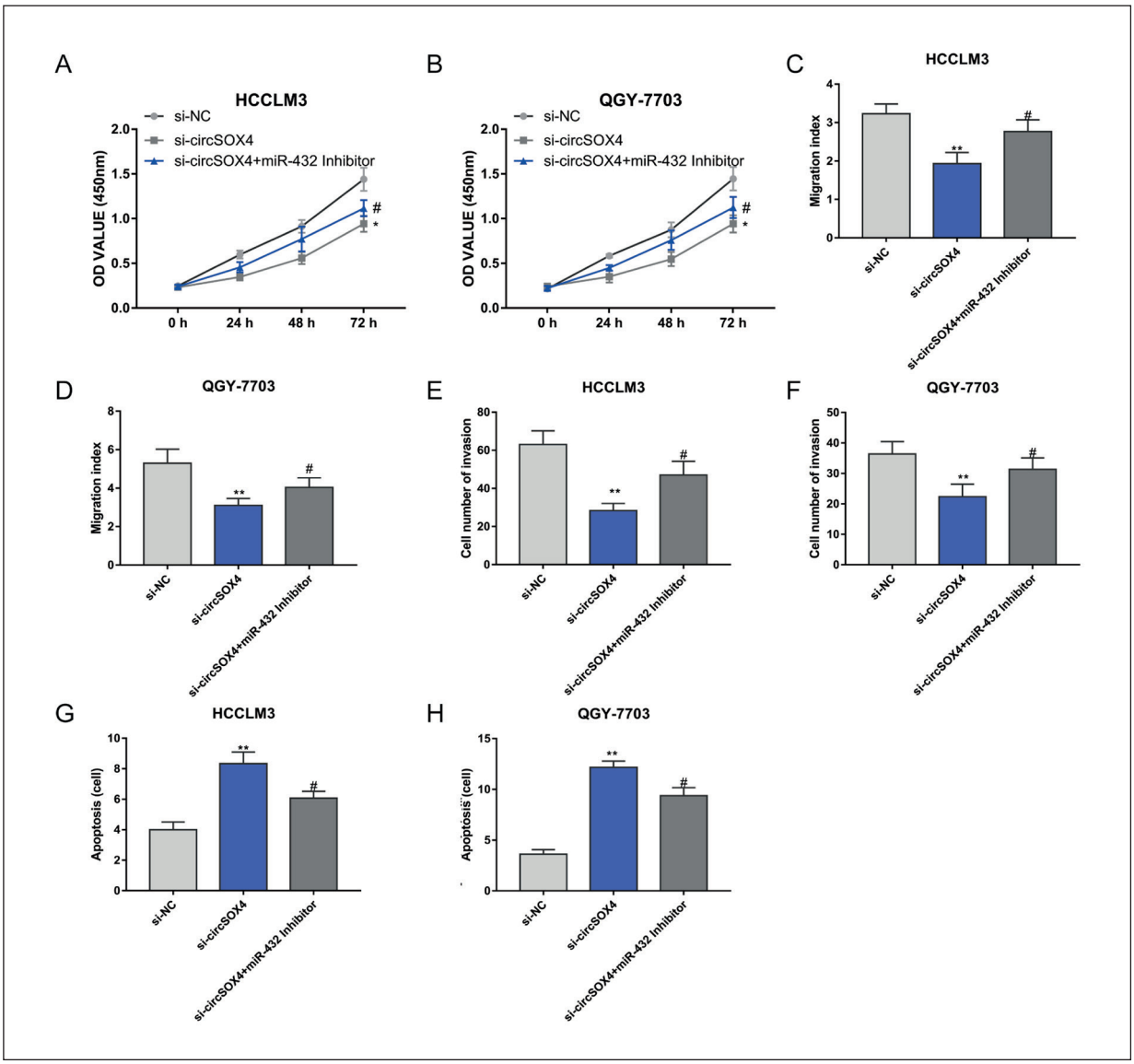

Figure 4. A-B, The results of CCK-8 experiment show that transfection of miR-432 inhibitor can restore the inhibited proliferation activity of QGY-7703 and HCCLM3 cells caused by si-circSOX4. **C-D,** Cell wound healing experiment results show that transfection of miR-432 inhibitor can restore the inhibited invasion and migration activity of QGY-7703 and HCCLM3 cells caused by si-circSOX4 (magnification: 20×). **E-F,** Transwell experimental results show that transfection of miR-432 inhibitor can restore the inhibited migration activity of QGY-7703 and HCCLM3 cells caused by si-circSOX4 (magnification: 200×). **G-H,** Flow cytometry apoptosis results showed that transfection of miR-432 inhibitor can reduce the elevated apoptosis level of QGY-7703 and HCCLM3 cells caused by si-circSOX4. * $p<0.05$, ** $p<0.01$, $^{\#}$ $p<0.05$.

adsorption of microRNA-1270, promoting the occurrence of lung adenocarcinoma[20]. However, the specific molecular mechanism of circSOX4 in liver cancer has not yet been fully understood and needs to be further studied.

With the development of high-throughput sequencing, molecular biology techniques and bioinformatics, the molecular mechanisms of circRNAs have been partially elucidated, and they can be involved in a host of physiological and pathological processes through sponging miRNAs[27]. In this study, we found binding sites between microRNA-432 and the 3 'UTR region of circSOX4 through the bioinformatics website. We thus speculate that circSOX4 may play an important biological role in liver cancer by binding to microRNA-432. Later, we confirmed the binding between the two through the luciferase gene re-

porting experiment and found that the expression levels of these two were negatively correlated. In addition, microRNA-432 partially reversed the effects of downregulation of circSOX4 on proliferation, migration and apoptosis of HCC cells. Jiang et al[28] have found that down-regulation of microRNA-432 might be capable of promoting the proliferation of liver cancer cells through the Wnt/ β-catenin axis. This study for the first time uncovered the abnormally expressed circSOX4 in HCC and its oncogenic role. The regulatory effects of circSOX4 on proliferation, migration and apoptosis of HCC have been declared. CircSOX4/ microRNA-432 axis is responsible for regulating HCC development, which provides new ideas for the diagnosis and treatment of HCC, but the specific regulation still needs to be further investigated.

Conclusions

In summary, high expression of circSOX4 in HCC tissues leads to poor prognosis in HCC patients. CircSOX4 may regulate the proliferation, migration and apoptosis of HCC cells through negatively regulating microRNA-432.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424.
2) Waller LP, Deshpande V, Pyrsopoulos N. Hepatocellular carcinoma: a comprehensive review. World J Hepatol 2015; 7: 2648-2663.
3) Sherman M. Hepatocellular carcinoma: New and emerging risks. Dig Liver Dis 2010; 42 Suppl 3: S215-S222.
4) Chan EW, Cheng SC, Sin FW, Xie Y. Triptolide induced cytotoxic effects on human promyelocytic leukemia, T cell lymphoma and human hepatocellular carcinoma cell lines. Toxicol Lett 2001; 122: 81-87.
5) Huang W, He T, Chai C, Yang Y, Zheng Y, Zhou P, Qiao X, Zhang B, Liu Z, Wang J, Shi C, Lei L, Gao K, Li H, Zhong S, Yao L, Huang ME, Lei M. Triptolide inhibits the proliferation of prostate cancer cells and down-regulates SUMO-specific protease 1 expression. PLoS One 2012; 7: e37693.
6) Jeck WR, Sharpless NE. Detecting and characterizing circular RNAs. Nat Biotechnol 2014; 32: 453-461.
7) Yao Y, Chen X, Yang H, Chen W, Qian Y, Yan Z, Liao T, Yao W, Wu W, Yu T, Chen Y, Zhang Y. Hsa_circ_0058124 promotes papillary thyroid cancer tumorigenesis and invasiveness through the NOTCH3/GATAD2A axis. J Exp Clin Cancer Res 2019; 38: 318.
8) Zhong D, Li P, Gong PY. Hsa_circ_0005075 promotes the proliferation and invasion of colorectal cancer cells. Int J Biol Markers 2019; 34: 284-291.
9) Zhang HD, Jiang LH, Hou JC, Zhong SL, Zhou SY, Zhu LP, Li J, Wang DD, Sun DW, Ji ZL, Tang JH. Circular RNA hsa_circ_0052112 promotes cell migration and invasion by acting as sponge for miR-125a-5p in breast cancer. Biomed Pharmacother 2018; 107: 1342-1353.
10) Ma X, Yang X, Bao W, Li S, Liang S, Sun Y, Zhao Y, Wang J, Zhao C. Circular RNA circMAN2B2 facilitates lung cancer cell proliferation and invasion via miR-1275/FOXK1 axis. Biochem Biophys Res Commun 2018; 498: 1009-1015.
11) Esteller M. Non-coding RNAs in human disease. Nat Rev Genet 2011; 12: 861-874.
12) He L, Hannon GJ. MicroRNAs: small RNAs with a big role in gene regulation. Nat Rev Genet 2004; 5: 522-531.
13) Macfarlane LA, Murphy PR. MicroRNA: biogenesis, function and role in cancer. Curr Genomics 2010; 11: 537-561.
14) Xiao G, Wang Q, Li B, Wu X, Liao H, Ren Y, Ai N. MicroRNA-338-3p suppresses proliferation of human liver cancer cells by targeting SphK2. Oncol Res 2018; 26: 1183-1189.
15) Lewis BP, Burge CB, Bartel DP. Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. Cell 2005; 120: 15-20.
16) Ye H, Yu X, Xia J, Tang X, Tang L, Chen F. MiR-486-3p targeting ECM1 represses cell proliferation and metastasis in cervical cancer. Biomed Pharmacother 2016; 80: 109-114.
17) Tanaka M, Earnhardt RC, Murry CE, Richard VJ, Jennings RB, Reimer KA. Hypoxic reperfusion to remove ischaemic catabolites prior to arterial reperfusion does not limit the size of myocardial infarcts in dogs. Cardiovasc Res 1991; 25: 7-16.
18) Tian X, Zhang J, Yan L, Dong JM, Guo Q. MiRNA-15a inhibits proliferation, migration and invasion by targeting TNFAIP1 in human osteosarcoma cells. Int J Clin Exp Pathol 2015; 8: 6442-6449.
19) Wang L, Zheng C, Wu X, Zhang Y, Yan S, Ruan L, Dai H. Circ-SOX4 promotes non-small cell lung cancer progression by activating the Wnt/beta-catenin pathway. Mol Oncol 2020 Feb 28. doi: 10.1002/1878-0261.12656. Epub ahead of print.

20) Gao N, Ye B. Circ-SOX4 drives the tumorigenesis and development of lung adenocarcinoma via sponging miR-1270 and modulating PLAGL2 to activate WNT signaling pathway. Cancer Cell Int 2020; 20: 2.

21) Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87-108.

22) Tanaka M, Katayama F, Kato H, Tanaka H, Wang J, Qiao YL, Inoue M. Hepatitis B and C virus infection and hepatocellular carcinoma in China: a review of epidemiology and control measures. J Epidemiol 2011; 21: 401-416.

23) Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, Pracht M, Yokosuka O, Rosmorduc O, Breder V, Gerolami R, Masi G, Ross PJ, Song T, Bronowicki JP, Ollivier-Hourmand I, Kudo M, Cheng AL, Llovet JM, Finn RS, LeBerre MA, Baumhauer A, Meinhardt G, Han G. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017; 389: 56-66.

24) Memczak S, Jens M, Elefsinioti A, Torti F, Krueger J, Rybak A, Maier L, Mackowiak SD, Gregersen LH, Munschauer M, Loewer A, Ziebold U, Landthaler M, Kocks C, le Noble F, Rajewsky N. Circular RNAs are a large class of animal RNAs with regulatory potency. Nature 2013; 495: 333-338.

25) Wang L, Long H, Zheng Q, Bo X, Xiao X, Li B. Circular RNA circRHOT1 promotes hepatocellular carcinoma progression by initiation of NR2F6 expression. Mol Cancer 2019; 18: 119.

26) Yu J, Yang M, Zhou B, Luo J, Zhang Z, Zhang W, Yan Z. CircRNA-104718 acts as competing endogenous RNA and promotes hepatocellular carcinoma progression through microRNA-218-5p/TXNDC5 signaling pathway. Clin Sci (Lond) 2019; 133: 1487-1503.

27) Hansen TB, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK, Kjems J. Natural RNA circles function as efficient microRNA sponges. Nature 2013; 495: 384-388.

28) Jiang N, Chen WJ, Zhang JW, Xu C, Zeng XC, Zhang T, Li Y, Wang GY. Downregulation of miR-432 activates Wnt/beta-catenin signaling and promotes human hepatocellular carcinoma proliferation. Oncotarget 2015; 6: 7866-7879.