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Original Article

Circ_0007429 promotes hepatocellular carcinoma resistance to sorafenib through the miR-377-3p/THBS1 axis

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Abstract: Objective: To elucidate the function of circ_0007429 in hepatocellular carcinoma (HCC) chemoresistance, with a focus on its regulatory mechanisms via the miR-377-3p/THBS1 (Thrombospondin 1) axis. Methods: The expression levels of circ_0007429, miR-377-3p, and THBS1 mRNA were quantified using quantitative Reverse Transcription Polymerase Chain Reaction (qRT-PCR). Cell viability was assessed with the CCK-8 assay, and THBS1 protein expression was evaluated by western blotting. The interactions between miR-377-3p and circ_0007429 or THBS1 were confirmed using luciferase reporter assays. Results: Circ_0007429 expression was substantially upregulated in sorafenib-resistant (SR) HCC cells. Knockdown of circ_0007429 accelerated sorafenib sensitivity by suppressing cell survival. Mechanistically, circ_0007429 acted as a molecular sponge for miR-377-3p, whose activity was increased upon circ_0007429 silencing. THBS1 was recognized as a downstream target of miR-377-3p, and its expression was suppressed by miR-377-3p. Circ_0007429 is a ceRNA for miR-377-3p, thus controlling THBS1 translation and contributing to sorafenib resistance. Conclusion: Circ_0007429 silencing enhances sorafenib sensitivity in HCC through the miR-377-3p/THBS1 axis. circ_0007429 may be a biomarker and therapeutic target for overcoming chemoresistance in HCC.

Keywords: Circ_0007429, sorafenib resistance, hepatocellular carcinoma, miR-377-3p, THBS1

Introduction

Hepatocellular carcinoma (HCC) is an aggressive malignancy with high mortality rates [1]. While surgical resection remains the primary treatment for early-stage HCC, chemotherapy is widely employed to prolong survival in patients with intermediate to advanced disease [2, 3]. Sorafenib, the first FDA-approved targeted agent for systemic treatment of HCC, has become the standard first-line therapy [4, 5]. However, the emergence of sorafenib resistance (SR) poses a major challenge to effective clinical management [4]. Therefore, a deeper understanding of the mechanisms underlying SR in HCC is crucial for improving therapeutic outcomes.

Circular RNAs (circRNAs), a class of covalently closed RNA molecules, play essential roles in physiologic processes and disease development, including cancers [6]. Several circRNAs have been associated with chemoresistance in HCC, largely by acting as molecular sponges for microRNAs (miRNAs) [7, 8]. For instance, exosomal circ_0032704 promotes SR in HCC and facilitate tumor progression through the miR-514a-3p/PD-L1 axis [9], while circ_0001944 promotes SR in HCC by inhibiting ferroptosis by modulating the miR-1292-5p/FBLN2 (Fibulin-2) axis [10]. Moreover, circ_HMGCS1 has been found to mediate HCC chemoresistance through themiR-338-5p/IL-7 pathway [11]. In addition, circRNA-SORE has been shown to sustain sorafenib resistance by stabilizing YBX1 (Y-box binding protein 1) [11], and exosome-derived circUPF2 enhances resistance by modulating ferroptosis sensitivity in HCC [12]. Notably, circ_0007429 was reported to promote proliferation, invasion, migration, apoptosis resis-

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Table 1. Primer sequences

Name	Primer (5'-3') F: forward; R: reverse
circ_0007429 F	GGAACAUGCACAGUGUCAATT
circ_0007429 R	UUGACACUGUGCAUGUUCCTT
miR-377-3p F	GGGCCATCACACAAAGGCAACTT
miR-377-3p R	ATCCAGTGCAGGGTCCGAGG
THBS1 F	GGGGAGATAACGGTGTGTTTG
THBS1 R	CGGGGATCAGGTTGGCATT
U6 F	CGCTTCGGCAGCACATATAC
U6 R	TTCACGAATTTGCGTGTCAT
GAPDH F	GGAGCGAGATCCCTCCAAAAT
GAPDH R	GGCTGTTGTCATACTTCTCATGG

tance, and aerobic glycolysis in HCC cells [13]. However, its role in HCC chemoresistance remains poorly defined.

This study aimed to elucidate the function of circ_0007429 in HCC chemoresistance. Two SR HCC cell lines were established to explore the molecular mechanisms driven by circ_0007429, with a focus on its regulation of the miR-377-3p/THBS1 axis. The findings support that circ_0007429 contributes to sorafenib resistance and may serve as a therapeutic target for chemoresistant HCC.

Materials and methods

Establishment of SR HCC cell lines

HCC cell lines, Huh7 and SK-HEP-1, were obtained from the China Center for Type Culture Collection (Wuhan, China). Cells were cultured in DMEM (R&D Systems, USA) supplemented with 10% fetal bovine serum (FBS; R&D Systems) under standard conditions (37°C, 5% CO_2). Both cell lines were exposed to sorafenib (4 μM) for 14 days to establish SR cell lines. The surviving cells were treated with increasing concentrations (5, 6, 7, or 8 μM) of sorafenib for over 30 days. The resistant Huh7/SR and SK-HEP-1/SR cells were maintained in media containing 5 μM sorafenib.

qRT-PCR

Total RNA was extracted using TRIzol regent (Invitrogen, USA), while cytosolic and nuclear RNA fractions were isolated using the Nuclear/Cytosol Fractionation Kit (Biovision, USA). The extracted RNA served as a template for cDNA synthesis *via* the 1st Strand cDNA Synthesis SuperMix (Yeasen, Shanghai, China). Expression levels of circ_0007429, miR-377-3p, *GAPDH,* THBS1, and *U6* were quantified using SYBR Green Master Mix (Yeasen) on a real-time PCR system. RNA levels were determined by Ct values and quantified by the $2^{-\Delta\Delta Ct}$ method, with normalization to GAPDH for mRNA and circRNA and to U6 for miRNA. Primer sequences are shown in **Table 1**.

Cell transfection

Cells were transfected with si-NC, si-circ_0007429, pcDNA-NC, or pcDNA-THBS1 using Lipofectamine 3000 (Invitrogen), or with miR-377-3p mimic, inhibitor, or miRNA control (GenePharma, Shanghai, China) using Lipofectamine RNAiMAX (Invitrogen) following the instructions of the manufacturers. After 48 h transfection, the cells were harvested for subsequent functional experiments. The sequence of si-NC were 5' GGAACATGCACAGTGTCAA 3'. The sequence of si-circ_0007429 were 5' ATGGGAACATGCACAGTGTCA 3'.

Cell viability assays

SR cells were transfected and seeded into 96-well plates at a density of 5000 cells/well. After overnight incubation, cells were treated with increasing concentrations of sorafenib for an additional 48 h. Ten microliters of CCK-8 reagent (Beyotime, China) were added to each well and incubated for approximately 1 h. Absorbance was measured at 450 nm using a microplate reader.

Dual-luciferase reporter assays

Wild-type (WT) and mutant (MUT) sequences of circ_0007429, along with the 3' UTR of THBS1 containing predicted miR-377-3p binding sites, were inserted into the pmirGLO luciferase reporter vector (Promega, USA). Cells were seeded in 24-well plates and co-transfected with WT or MUT reporter constructs, along with either miR-377-3p mimics or a negative control miRNA (miR-NC), using Lipofectamine 2000 (Invitrogen). Luciferase activity was measured after 48 h using a dual-luciferase reporter assay system.

Western blotting

Following SR cell lysis in RIPA buffer (Beyotime), protein concentrations were determined using

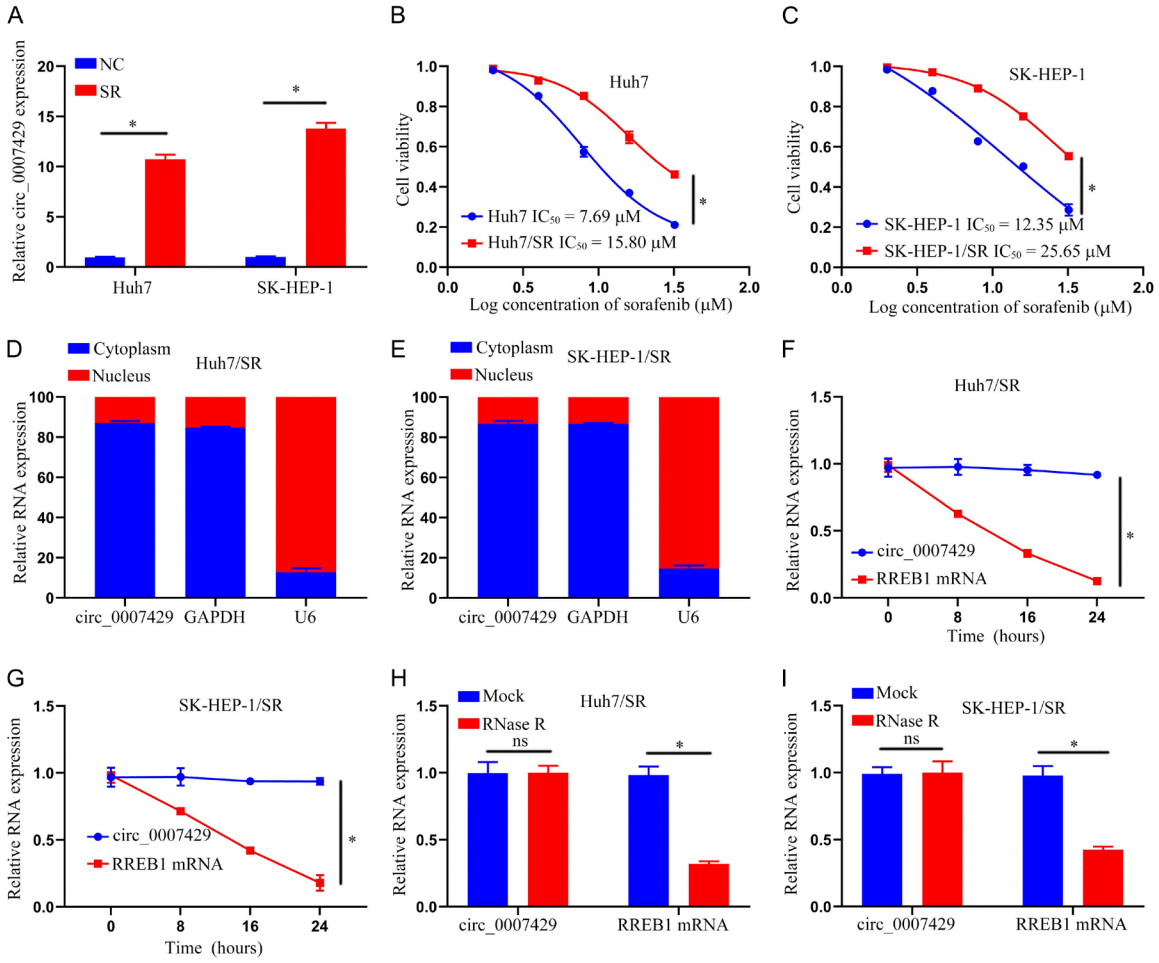

Figure 1. Elevated expression of circ_0007429 in sorafenib-resistant hepatocellular carcinoma (HCC) cell lines. A: qRT-PCR analysis of circ_0007429 expression in Huh7 vs. Huh7/SR and SK-HEP-1 vs. SK-HEP-1/SR cells. B, C: Cell survival and IC_{50} values following 24 h of sorafenib treatment were assessed using CCK-8 assays. D, E: Subcellular localization of circ_0007429, GAPDH, and U6 in SR cells was determined by qRT-PCR. F, G: RNA stability of circ_0007429 and RREB1 mRNA after actinomycin D treatment (0, 8, 16, and 24 h), assessed by RT-qPCR. H, I: Resistance of circ_0007429 and *RREB1* mRNA to RNase R digestion was evaluated by RT-qPCR. $^{*}P < 0.05$, $^{ns}P > 0.05$.

a BCA kit (Takara). Equal amounts of protein (30 μg) were electrophoresed on SDS-PAGE and transferred to PVDF membranes. Membranes were incubated with an anti-THBS1 antibody (Abcam, UK), followed by a horseradish peroxidase (HRP)-conjugated anti-rabbit IgG secondary antibody (Sangon, China) at a 1:1000 dilution. GAPDH (ab8245, Abcam) was used as a loading control at a 1:10000 dilution. Protein bands were visualized using enhanced chemiluminescence (ECL).

Statistical analysis

GraphPad Prism 8 were used for data processing. Results were presented as means ± standard deviation (SD) from at least three independent experiments. Depending on the experimental design, comparisons between or among groups were performed using t-tests, one-way ANOVA, or two-way ANOVA followed by Tukey's post-hoc test. Associations were assessed using Pearson's correlation coefficients. A *p*-value < 0.05 was considered significant.

Results

Overexpression of circ_0007429 in SR HCC cell

SR HCC cell lines were successfully established, demonstrating substantially elevated circ_0007429 expression compared to their corresponding parental cells (**Figure 1A**). Furthermore, the IC_{50} of sorafenib was mark-

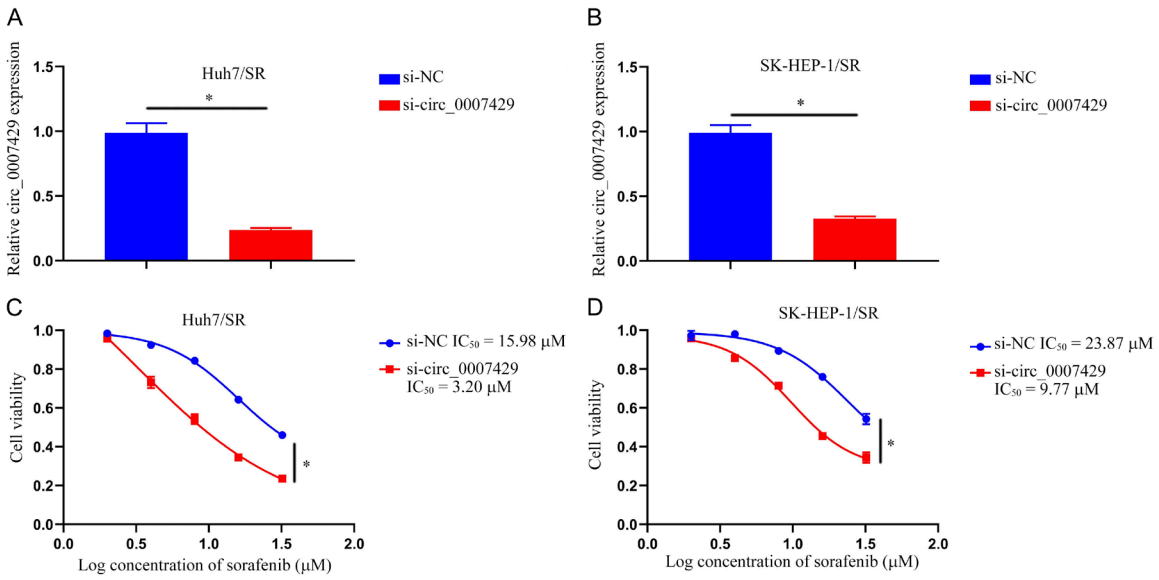

Figure 2. Silencing circ_0007429 enhanced the susceptibility of SR cells to sorafenib. A, B: RT-qPCR analysis of circ_0007429 expressions in SR cells after transfection with si-NC or si-circ_0007429. C, D: CCK-8 assay evaluated cell survival and IC_{50} values following 24 h of sorafenib treatment in si-NC- and si-circ_0007429-transfected SR cells. *$P < 0.05$.

edly elevated in both Huh7/SR and SK-HEP-1/SR cells, versus with Huh7 cells and SK-HEP-1 cells (**Figure 1B** and **1C**). Subcellular fractionation revealed that circ_0007429 was distributed in both the cytoplasm and nucleus, with predominant localization in the cytoplasm (**Figure 1D** and **1E**). After treatment with actinomycin D, circ_0007429 levels remained stable over 24 h, whereas *RREB1* mRNA levels significantly decreased (**Figure 1F** and **1G**). RNase R digestion further demonstrated that RNase R markedly degraded the linear transcript, while circ_0007429 revealed resistances to RNase R-mediated degradation (**Figure 1H** and **1I**), confirming the circular nature of circ_0007429. These findings collectively demonstrate that circ_0007429 was upregulated and showed stable expression in SR HCC cells.

Knockdown of circ_0007429 sensitized SR cells to sorafenib

SR cells transfected with si-circ_0007429 showed a significant reduction in circ_0007429 expression compared to si-NC transfection (**Figure 2A** and **2B**). This reduction in circ_0007429 level significantly reduced IC_{50} of sorafenib in both Huh7/SR and SK-HEP-1/SR cells (**Figure 2C** and **2D**). These results indicate that silencing circ_0007429 effectively enhances sorafenib sensitivity and attenuates drug resistance in SR HCC cells *in vitro*.

Circ_0007429 sponges miR-377-3p

The mechanistic role of circ_0007429 in SR was further investigated. Bioinformatic analysis using the Starbase program predicted potential binding sites between circ_0007429 and miR-377-3p (**Figure 3A**). This interaction was verified through luciferase reporter assays, which demonstrated a substantial reduction in luciferase activity in both SR cell lines following co-transfection with WT-circ_0007429 and miR-377-3p (**Figure 3B** and **3C**). Moreover, miR-377-3p expression was considerably lower in both resistant cells compared to their parental counterparts (**Figure 3D** and **3E**), indicating a possible regulatory role in SR in HCC. Circ_0007429 knockdown significantly upregulated miR-377-3p expression in SR cells (**Figure 3F** and **3G**), whereas circ_0007429 overexpression suppressed miR-377-3p expression (**Figure 3H** and **3I**). Collectively, these results indicate that circ_0007429 sponges miR-377-3p, negatively regulating its expression in SR HCC cells.

Circ_0007429 silencing enhanced sorafenib sensitivity through miR-377-3p

To evaluate whether miR-377-3p mediated the effects of circ_0007429 on SR, both SR cell lines were transfected with si-circ_0007429, si-NC, si-circ_0007429 + miR-NC inhibitor, or

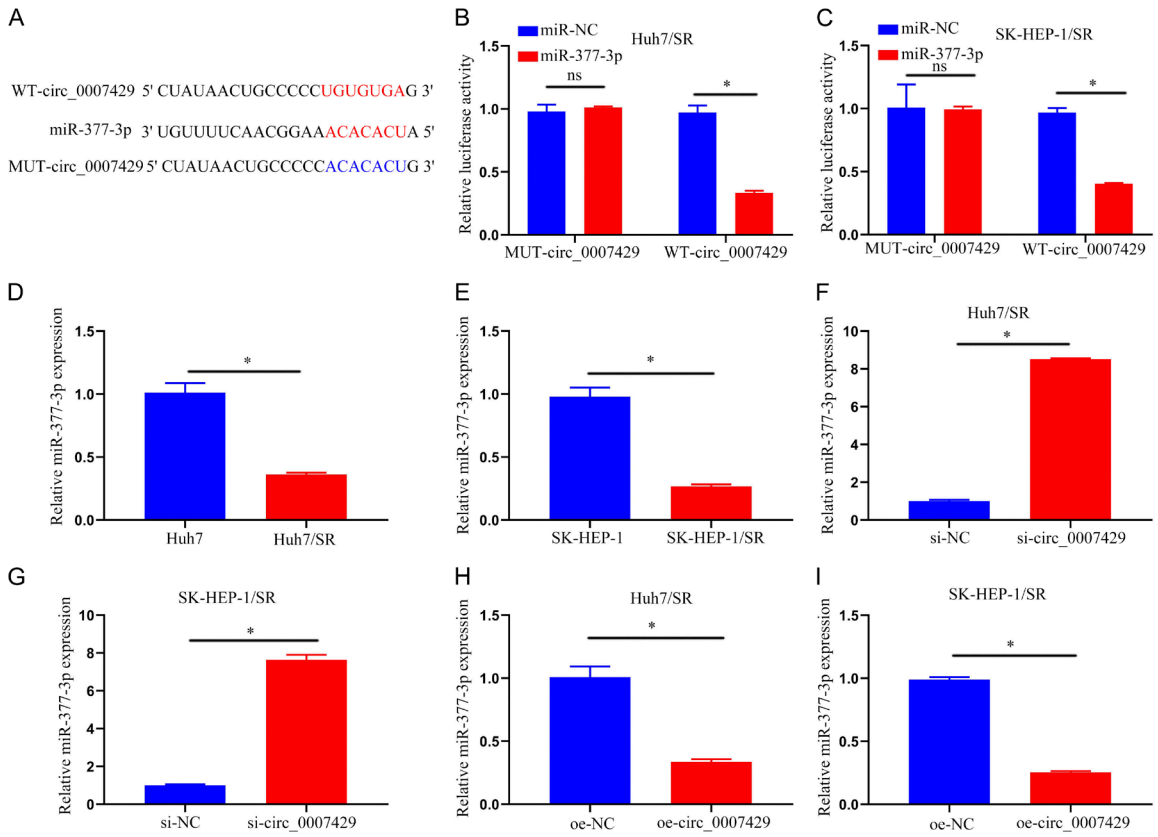

Figure 3. Circ_0007429 functions as a molecular sponge for miR-377-3p. A: Predicted binding sites between circ_0007429 and miR-377-3p. B, C: Luciferase reporter assay result in sorafenib-resistant cell lines co-transfected with WT or MUT circ_0007429 reporter plasmids and miR-377-3p mimics. D, E: qRT-PCR analysis of miR-377-3p expression in SR and parental cells. F, G: qRT-PCR quantification of miR-377-3p in resistant cell lines transfected with si-NC or si-circ_0007429. H, I: qRT-PCR analysis of miR-377-3p expression following transfection with control or circ_0007429 overexpression vectors. *$P < 0.05$, $^{ns}P > 0.05$.

si-circ_0007429 + miR-377-3p inhibitor. qRT-PCR revealed that transfection with si-circ_0007429 substantially increased miR-377-3p levels. However, this upregulation was suppressed by the miR-377-3p inhibition (**Figure 4A** and **4B**). Next, CCK-8 assays further demonstrated that circ_0007429 knockdown markedly reduced SR, as evidenced by decreased cell viability. However, this sensitizing effect was reversed by miR-377-3p inhibition (**Figure 4C** and **4D**). These data suggest that miR-377-3p mediates the regulatory role of circ_0007429 in SR in HCC cells.

THBS1 is a direct target of miR-377-3p

Bioinformatic analysis using the StarBase platform predicted putative binding sites for miR-377-3p in the 3' untranslated region (UTR) of THBS1 mRNA (**Figure 5A**). This interaction was further verified using dual-luciferase reporter (DLR) assays, which showed that miR-377-3p overexpression substantially reduced THBS1 3' UTR WT reporter activity, whereas no marked change was observed in the MUT construct (**Figure 5B** and **5C**). Furthermore, both THBS1 mRNA and protein levels were upregulated in both resistant cell lines (**Figure 5D-G**). However, overexpression of miR-377-3p markedly downregulated *THBS1* (**Figure 5H-K**). These findings confirm that miR-377-3p directly targets and downregulates *THBS1*.

miR-377-3p alleviated sorafenib resistance in HCC cells by regulating THBS1 expression

To assess the functional relevance of the miR-377-3p/THBS1 axis in modulating SR in HCC cells, both SR cell lines were transfected with miR-377-3p mimics, miR-NC, miR-377-3p + pcDNA-NC, or miR-377-3p + pcDNA-THBS1. *THBS1* overexpression reversed the miR-377-

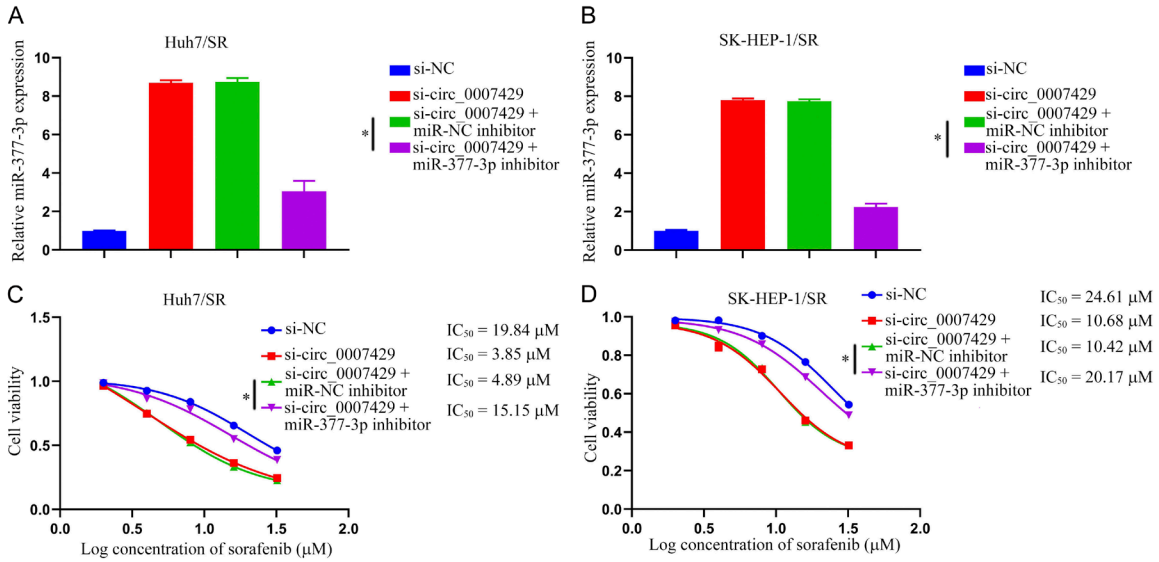

Figure 4. Circ_0007429 silencing enhanced sorafenib sensitivity in HCC cells by miR-377-3p sponging. A, B: qRT-PCR analysis of miR-377-3p expression following circ_0007429 knockdowns. C, D: CCK-8 assay assessing cell viability of resistant HCC cells after combined treatment with sorafenib and circ_0007429 silencing, with or without miR-377-3p inhibitor. *$P < 0.05$.

3p-induced suppression of *THBS1* expression, indicating successful transfection (**Figure 6A-D**). CCK-8 assays depicted that miR-377-3p overexpression substantially reduced cell viability in the presence of sorafenib, whereas this effect was partially reversed by THBS1 overexpression (**Figure 6E** and **6F**). These results suggest that miR-377-3p mitigates sorafenib resistance in HCC cells by downregulating THBS1.

Circ_0007429 functions as a ceRNA for miR-377-3p in regulating THBS1 expression

To explore whether circ_0007429 modulates THBS1 expression via miR-377-3p, SR cells were transfected with si-circ_0007429 alone or in combination with miR-377-3p inhibitors. WB analysis revealed that circ_0007429 knockdowns significantly reduced THBS1 expression in both resistant cell lines. However, this reduction in THBS1 levels was partially reversed upon inhibition of miR-377-3p (**Figure 7A-D**). The data indicate that circ_0007429 positively regulates THBS1 level by sponging miR-377-3p, thereby contributing to SR in HCC cells.

Discussion

Hepatocellular carcinoma (HCC) is an aggressive malignancy with a high recurrence rate. The limited effectiveness of conventional therapy is largely attributed to the development of chemoresistance [14, 15]. Recent studies have implicated dysregulated circRNAs in both HCC tumorigenesis and the acquisition of chemoresistance [16-19]. For instance, circ_0044539 promotes lymph node metastasis in HCC through exosomal miR-29a-3p signaling [20], while hsa_circ_0000098 has been recognized as a possible therapeutic target that drives both HCC progression and doxorubicin resistance [21]. This study demonstrated that circ_0007429 expression was related to sorafenib resistance (SR) in HCC. Silencing circ_0007429 considerably sensitized resistant cells to sorafenib *in vitro*. Furthermore, the underlying molecular mechanisms of circ_0007429-mediated SR were partially elucidated.

The ceRNA hypothesis posits that circRNAs modulate gene expression by sponging miRNAs, thereby preventing miRNAs-mediated repression of target mRNAs [22, 23]. miRNAs play critical roles in HCC progression and chemoresistance. For example, miRNA-223 suppresses hepatocarcinogenesis by inhibiting hypoxia-induced angiogenesis and immune suppression [24]. miR-21-5p enhances SR and promotes HCC progression by modulating Sirtuin 7 (SIRT7) ubiquitination through Ubi-

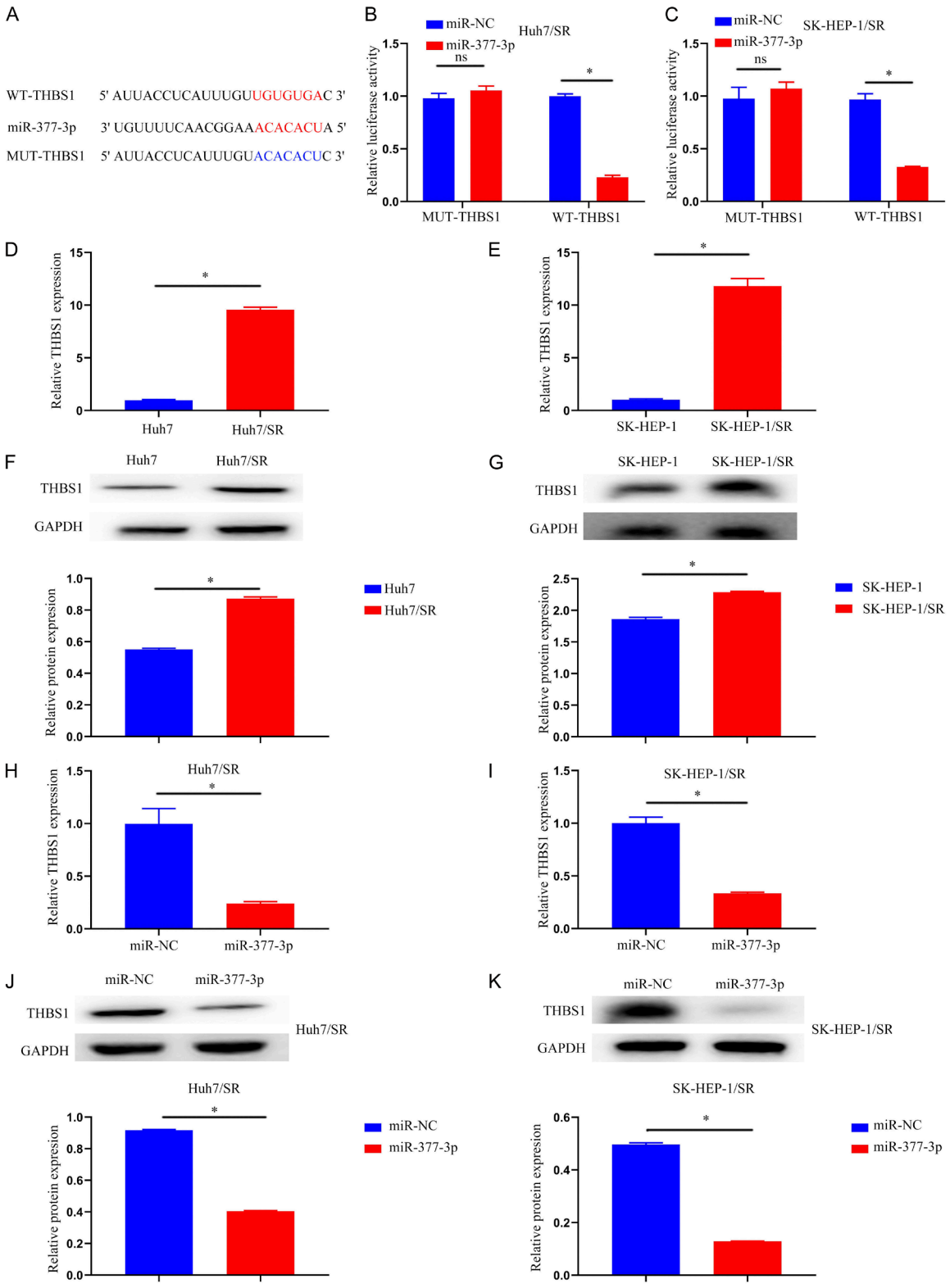

Figure 5. THBS1 is a direct target of miR-377-3p. A: Predicted binding sites of miR-377-3p within the THBS1 3' UTR region. B, C: Dual-luciferase reporter (DLR) assays in both resistant cell lines co-transfected with MUT and WT THBS1 reporter constructs and miR-377-3p mimics. D-G: THBS1 mRNA and protein levels in resistant and parental HCC cells examined using qRT-PCR and western blot. H-K: THBS1 mRNA and protein levels in resistant cells following miR-377-3p overexpression examined using qRT-PCR and western blot. *$P < 0.05$, $^{ns}P > 0.05$.

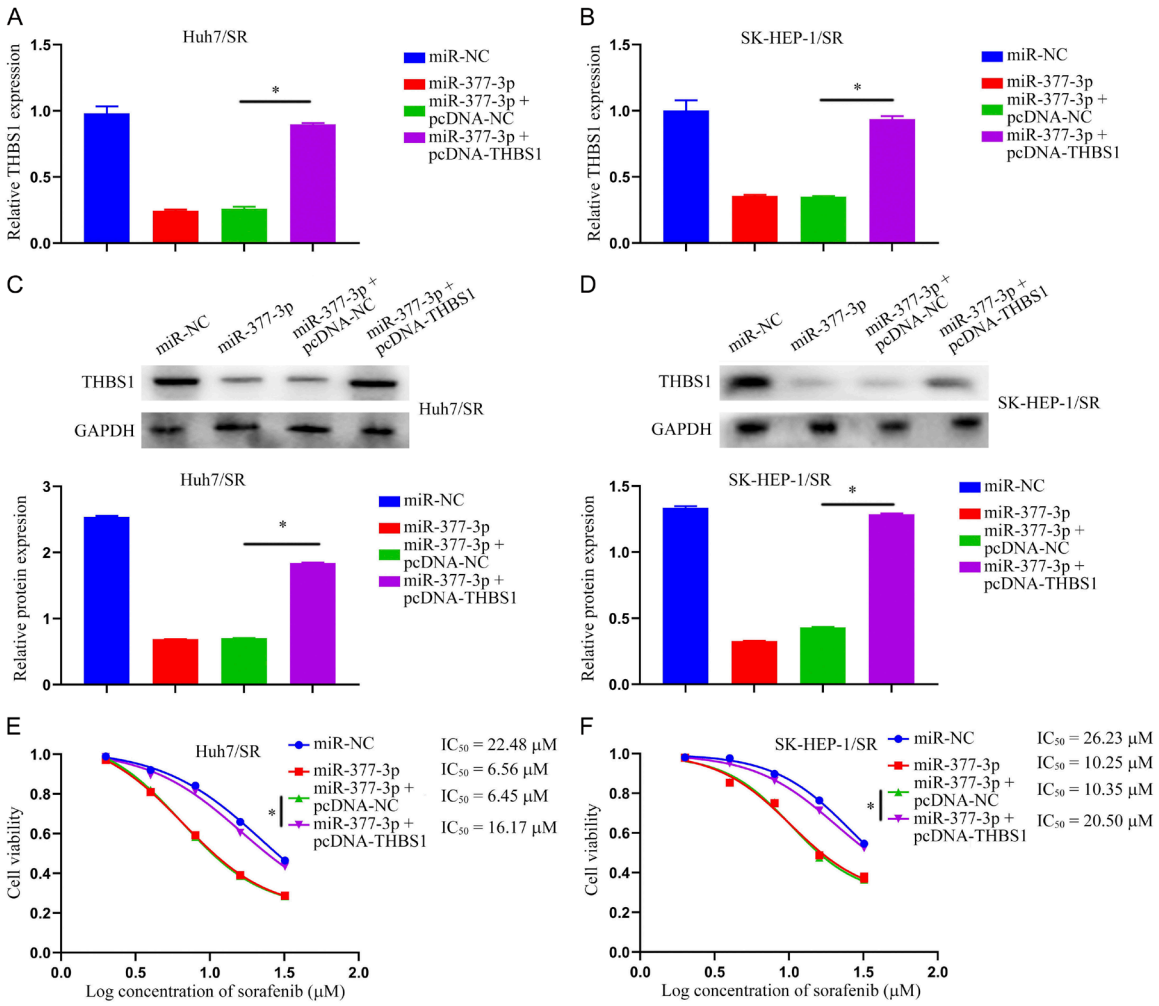

Figure 6. miR-377-3p reduced HCC cell resistance by downregulating THBS1. A-D: qRT-PCR and western blot analyses of THBS1 expression in resistance HCC cells after miR-377-3p transfection. E, F: CCK-8 assays measuring cell viability of resistant HCC cells treated with varying doses of sorafenib and miR-377-3p modulation. *$P < 0.05$.

quitin-Specific Protease 24 (USP24) [25]. In this study, circ_0007429 directly modulated miR-377-3p. Earlier research has demonstrated that miR-377-3p suppresses epithelial-mesenchymal transition (EMT) and metastasis in cervical carcinoma by targeting Serum/Glucocorticoid Regulated Kinase 3 (SGK3) [26], and inhibits HCC progression by downregulating carnitine palmitoyl transferase 1C (CPT1C)-mediated fatty acid oxidation [27]. Our findings indicate that circ_0007429 contributes to SR in HCC by modulating miR-377-3p activity.

THBS1 has been associated with calcium signaling, a pathway implicated in the acquisition of resistance to various pharmacologic agents and genotoxic stress [28]. Furthermore, recent studies have demonstrated that the *THBS1* upregulation facilitates cellular proliferation and suppresses apoptosis in HCC [29]. In this study, miR-377-3p was identified for the first time as a direct regulator of *THBS1* in HCC. Elevated miR-377-3p levels were shown to reduce THBS1 expression, thereby attenuating sorafenib resistance in HCC cells. Importantly, these findings elucidate that circ_0007429 acts as a molecular sponge for miR-377-3p, regulating *THBS1* expression and contributing to SR in HCC.

This study presents certain limitations. First, the interactions among circ_0007429, miR-377-3p, and THBS1 were not validated in clinical HCC tissue samples. Second, the functional role of the circ_0007429/miR-377-3p/

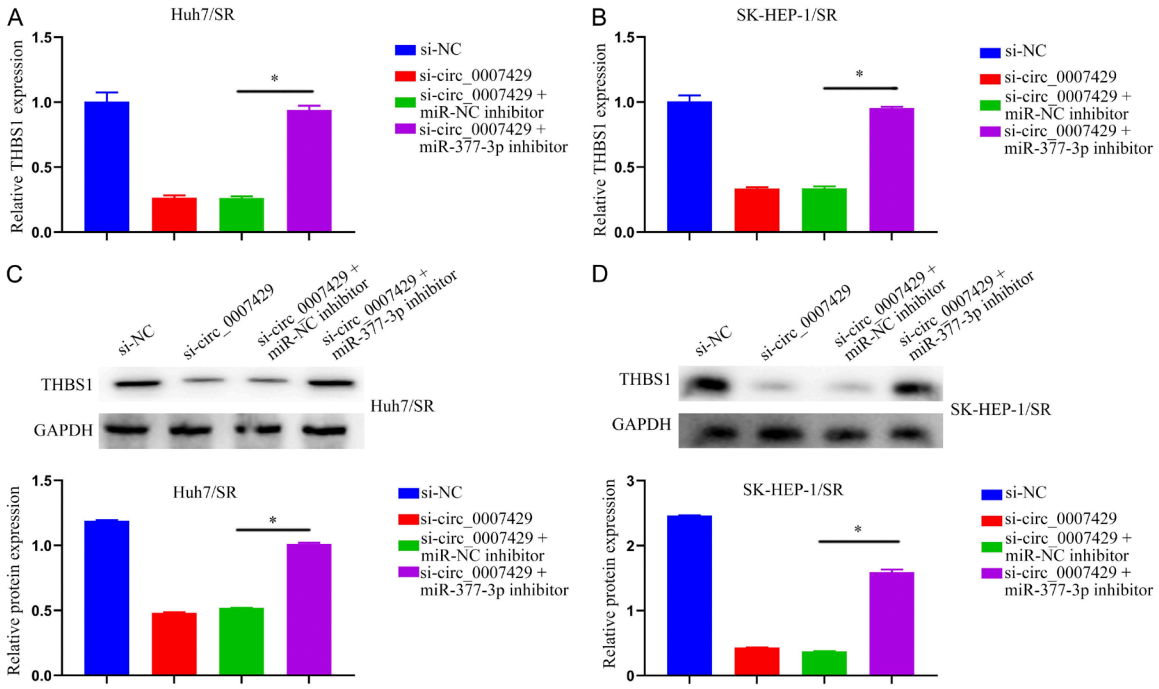

Figure 7. Circ_0007429 acts as a ceRNA for miR-377-3p to regulate THBS1 expression. A-D: qRT-PCR and western blot analysis of THBS1 expression in both resistant cell lines following transfection with si-circ_0007429 alone or in combination with miR-377-3p inhibitor. *$P < 0.05$.

THBS1 axis in modulating SR was not explored by animal models. Despite these limitations, the molecular mechanism by which circ_0007429 affects SR in HCC was successfully elucidated using comprehensive *in vitro* experiments.

Conclusion

This study showed a specific role of circ_0007429 in contributing to chemoresistance in HCC. Mechanistically, circ_0007429 promotes sorafenib resistance in HCC cells by sponging miR-377-3p and upregulating THBS1. These findings identify circ_0007429 as a promising therapeutic option for overcoming chemoresistance in HCC.

Acknowledgements

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Disclosure of conflict of interest

None.

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