

# CircRNA\_102272 Promotes Cisplatin-Resistance in Hepatocellular Carcinoma by Decreasing MiR-326 Targeting of RUNX2

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**Background:** Hepatocellular carcinoma (HCC) is the leading cause of tumor-associated death in males and females worldwide. HCC is mostly diagnosed at advanced stages and the chemotherapeutic cisplatin is one of the major therapeutic options in the treatment of patients with treating advanced HCC. Despite several reports on HCC multidrug resistance, the underlying regulatory mechanisms are still unclear.

**Methods:** RT-PCR was performed to detect circRNA\_102272, miR-326 and RUNX2 expression. The CCK8 assay was used to examine cell proliferation and cisplatin IC<sub>50</sub> values. The luciferase reporter assay was performed to verify complementary combinations between circRNA\_102272 and miR-326 and between miR-326 and RUNX2.

**Results:** CircRNA\_102272 expression was upregulated in HCC tissues and cells. CircRNA\_102272 knockdown suppressed HCC cell proliferation and decreased cisplatin-resistance. In addition, circRNA\_102272 facilitated HCC cisplatin-resistance by regulating the miR-326/RUNX2 axis.

**Conclusion:** CircRNA\_102272 is significantly increased in HCC tissues and cells and promotes HCC cell proliferation and cisplatin-resistance. More importantly, circRNA acts as a ceRNA to suppress the expression and activity of miR-326, leading to the increase in RUNX2 expression. By elucidating circRNA\_102272 role and mechanism of action in HCC, our study provides insights and an opportunity to overcome cisplatin-resistance in HCC.

**Keywords:** circRNA\_102272, cisplatin-resistance, miR-326, RUNX2, HCC

## Introduction

Hepatocellular carcinoma (HCC) is the leading cause of tumor-associated death in males and females worldwide.<sup>1</sup> HCC is mostly diagnosed at advanced stages of disease, and the chemotherapeutic drug cisplatin is one of the major therapeutic options for the treatment of patients with advanced HCC. Although several studies reported on HCC multidrug resistance, the regulatory mechanisms are still unclear. Thus, it is necessary to further study these mechanisms of resistance.

Circular RNAs (circRNAs) are a new type of non-coding RNAs, characterized by covalently closed-loop structures of endogenous RNAs. Their specificity and stability have been shown to be cell-type dependent.<sup>2-4</sup> Recently, several studies pointed out to circRNA association with tumorigenesis and metastasis. For example, circNT5E acts as a sponge of microRNA-422a to promote glioblastoma tumorigenesis.<sup>5</sup> CircRNA hsa\_circ\_0001564 facilitates osteosarcoma tumorigenesis via sponging miR-29c-3p.<sup>6</sup> CircRNA circC3P1 suppresses hepatocellular carcinoma growth and metastasis

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through the miR-4641/PCK1 pathway<sup>7</sup> and CircRNA hsa\_circ\_0000064 promotes lung cancer cell proliferation and metastasis.<sup>8</sup> Although some studies indicated that circRNAs play a significant role in multidrug resistance, the regulatory mechanisms are still unclear.

Mechanistically, circRNA functions mainly include miRNA binding, proteins interactions and splicing machine regulation.<sup>9</sup> Notably, circRNAs affect tumors by sponging miRNA. For example, circRNA\_0025202 regulates tamoxifen sensitivity and tumor progression via regulating the miR-182-5p/FOXO3a axis in breast cancer.<sup>10</sup> CircRNA\_100269 is downregulated in gastric cancer and suppresses tumor cell growth by targeting miR-630.<sup>11</sup> Circular RNA circMAN2B2 facilitates lung cancer cell proliferation and invasion via the miR-1275/FOXK1 axis.<sup>12</sup> In addition, miRNA is playing significant regulatory roles in cell growth, proliferation, differentiation and cell death. For example, anti-miR-203 suppresses breast cancer growth and stemness by targeting SOCS3.<sup>13</sup> MiR-331-3p inhibits the Hepatocellular Carcinoma (HCC) bel-7402 cell line by downregulation of E2F1.<sup>14</sup> Thus, circRNAs regulate the expression of target genes via a circRNA-miRNA-mRNA function network.

Chemotherapy drugs have always been one of the strategies for cancer treatment. For example, bitter melon extract inhibits breast cancer growth in preclinical model by inducing autophagic cell death.<sup>15</sup> Bitter melon enhances natural killer-mediated toxicity against head and neck cancer cells.<sup>16</sup> Methyl- $\beta$ -cyclodextrin enhance the efficacy of doxorubicin in solid tumor cells.<sup>17</sup> Thus, it is very meaningful to study the multidrug resistance of chemotherapy.

Although there are several studies on multidrug resistance,<sup>18,19</sup> the relationship between circRNA and HCC multidrug resistance is still unclear. Thus, in this study, we investigated the relationship between circRNA\_102,272 and cisplatin-resistance. Moreover, we report for the first time that circRNA\_102272 is upregulated in HCC tissues and cells. In addition, we also found that circRNA\_102272 promotes cisplatin-resistance in HCC through the miR-326/RUNX2 axis.

## Materials and Methods

### HCC Tissues Collection

Human HCC and adjacent normal tissues were obtained from the Second Hospital of Dalian Medical University. This study was approved by the Human Research Ethics Committee of the Second Hospital of Dalian Medical

University. Signed written informed consents were obtained from all patients.

### Cell Culture

The human normal liver cell line 7701 and the HCC cell lines HepG2 and Huh7 were obtained from the Cell Bank of Type Culture Collection (Shanghai City, China). All cell lines were cultured in DMEM with 10% fetal calf serum in a 37°C incubator with 5% CO<sub>2</sub> and 100% humidity. STR profiling of cells was identified by the Cell Bank of Type Culture Collection (Shanghai City, China), and the mycoplasmas were tested in culture once a month.

Cells (2 x 10<sup>5</sup> cells/well) were seeded onto 6-well dishes at 24 h and then transfected with control or experimental siRNA for circRNA\_102272 or si-RUNX2 per dish at 80% confluence using the Lipofectamine 3000 (Life Technologies, Shanghai, China) according to the manufacturer's instructions. The primers of si-circRNA\_102272 were 5'-CCGTCGAGCATCATTGGTT-3'; the primers of si-RUNX2 were 5'-GGACTGTGGTTACTGTGCAT-3'.

### CCK8 Assay

Cell proliferation and cisplatin IC<sub>50</sub> were determined using the Cell Counting Kit-8 (CCK-8, Roche, Basel, Switzerland) and following the manufacturer's instructions. The absorbance was detected spectrophotometrically at 450 nm.

### RT-PCR Analysis

Total RNA was collected using the mirVana™ kit (Ambion, TX), according to the manufacturer's recommendations. After purification, the RNA was transcribed into cDNA using a Reverse Transcription Kit (Takara, Tokyo, Japan). RT-PCR analysis was performed using the SYBR Green (Takara). The primers used for RT-PCR were: circRNA\_102272 primers were 5'-GAGTGAG GAGAGATCCCCCTAAC-3' (sense) and 5'-GGCATCAT GACGTCATCCGAATC-3' (anti-sense); RUNX2 primers were: 5'-CCGCCTCAGTGATTTAGGGC-3' (sense) and 5'-GGGTCTGTAATCTGACTCTGTCC-3' (anti-sense); GAPDH primers were 5'-ACAACCTTGGTATCGTGGA AGG-3' (sense) and 5'-GCCATCACGCCACAGTTTC-3' (anti-sense).

### Mice Xenografts

The in vivo experiments were approved by the Human Research Ethics Committee of the Second Hospital of Dalian Medical University and followed the guidelines on the welfare and use of animals (Laboratory animal—Guideline for ethical

review of animal welfare, GB/T 35,892–2018, China) that was issued by China National Standardization Management Committee. BALB/c nude mice were purchased from the Animal Experimental Center, Shanghai University of Traditional Chinese Medicine, and randomly divided into two groups ( $n=5$ ). The Huh cells ( $5 \times 10^6$ ) with sh-circRNA\_102272 or sh-NC were injected into the right flanks of nude mice and tumors' volume was measured every 5 days.

### Luciferase Reporter Assay

For the luciferase assay, cells (50,000 cells/well) were co-transfected with luciferase reporter plasmids containing wild-type or mutated 3'UTR and miR-326 mimics using Lipofectamine 2000 (Invitrogen) and according to manufacturer's recommendations. The luciferase activity was

detected by the Dual-Luciferase Assay kit (Promega, UK) and according to the manufacturer's protocol.

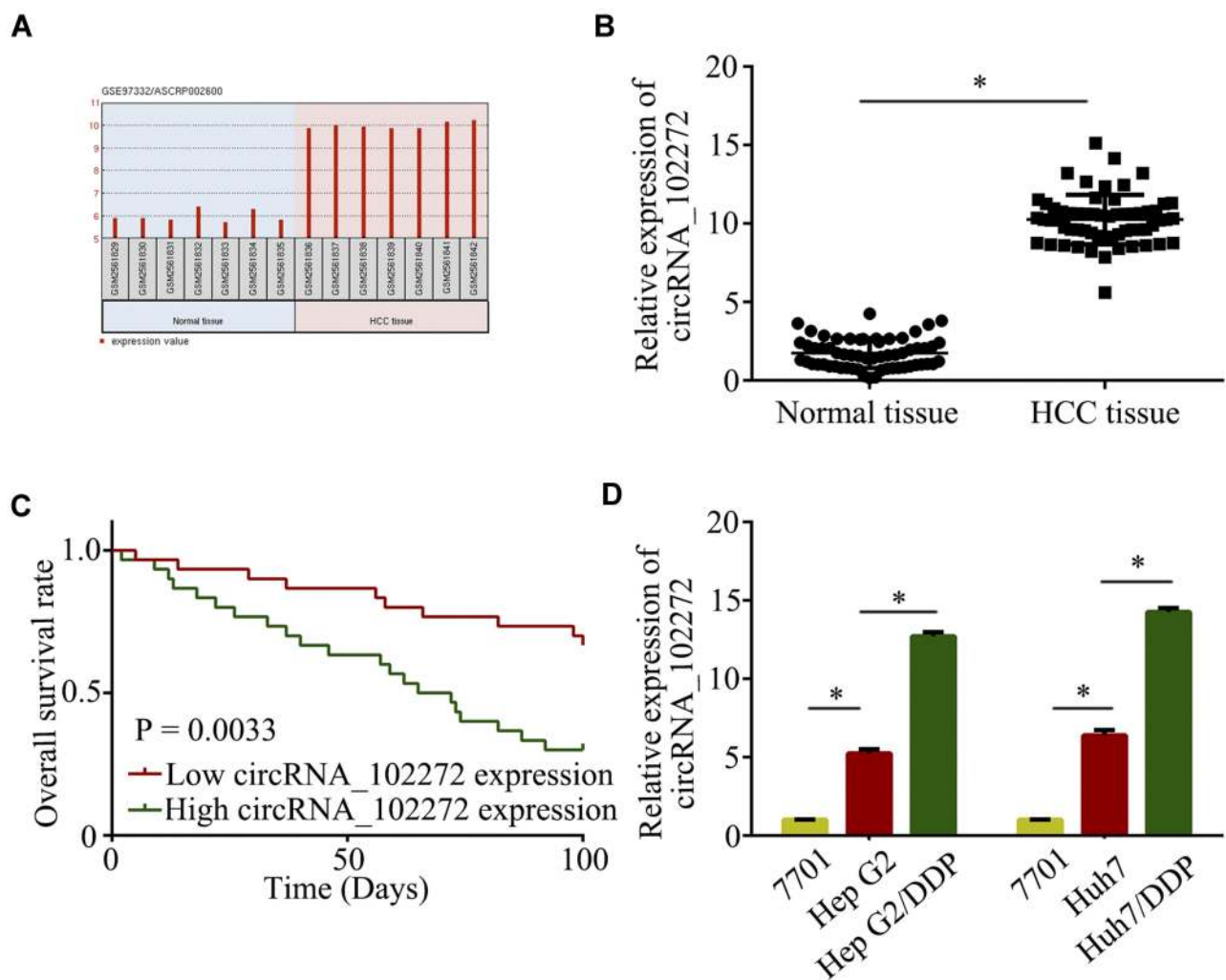
### Statistical Analysis

Each experiment was performed at least 3 times. All values were presented as mean  $\pm$  SD. Student's *t*-test and one-way analysis of variance (ANOVA) were performed to compare differences between the two groups.  $P < 0.05$  was considered statistically significant.

## Results

### CircRNA\_102272 is Upregulated in HCC Tissues and Cells

The microarray data in the GEO dataset (GSE97332) were used to initially detect circRNAs expression, and

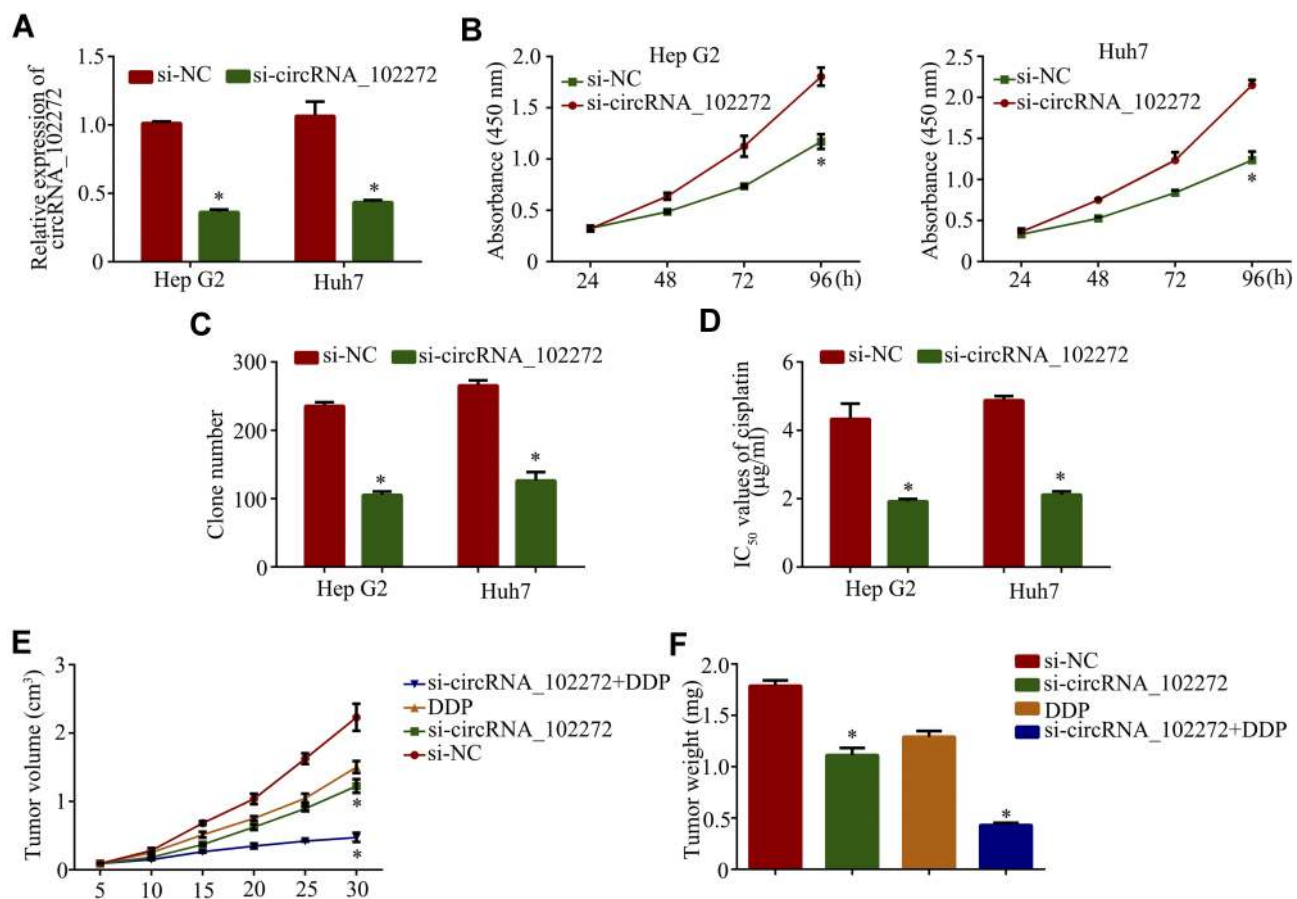


**Figure 1** CircRNA\_102272 is upregulated in HCC tissues and cells. **(A)** GEO dataset (GSE97332) showed that circRNA\_102272 is significantly increased in HCC tissues compared to normal tissues. **(B)** CircRNA\_102272 expression was significantly increased in HCC tissues compared to normal tissues. **(C)** Survival rates were examined by Kaplan–Meier analysis in HCC patients. **(D)** CircRNA\_102272 expression was significantly increased in HCC cells compared to normal cells. The data shown represent the mean  $\pm$  SD. \* $p < 0.05$ .

normalized microarray data were measured using GEO2R after applying log<sub>2</sub> transformation. The results showed that circRNA\_10227 expression was increased in HCC samples compared to normal samples (Figure 1A). Subsequently, circRNA\_10227 expression in 60 pairs of HCC tissues was investigated. The result showed that circRNA\_10227 expression was significantly upregulated in HCC tissues compared to normal tissues (Figure 1B), and Kaplan–Meier analysis showed that HCC patients with high circRNA\_10227 expression had lower survival rates (Figure 1C). In addition, RT-PCR indicated that circRNA\_10227 expression was significantly increased in Hep G2/DDP and Huh 7/DDP cells compared with Hep G2 and Huh 7 cells (Figure 1D). Thus, these results revealed that circRNA\_10227 overexpression may be involved in HCC tumorigenesis and multidrug resistance.

## CircRNA\_10227 Knockdown Suppresses HCC Cell Proliferation and Cisplatin-Resistance

Since circRNA-10227 is upregulated in HCC, RNA interference was used to downregulate circRNA\_10227 expression and to assess its biological functions in HCC. RT-PCR analysis showed that circRNA\_10227 expression in si-circRNA\_10227-transfected HCC cells was decreased (Figure 2A). CCK8 and colony formation assays showed that circRNA\_10227 knockdown significantly suppressed cell proliferation of Hep G2 and Huh7 cells (Figure 2B and C). In addition, we further studied the relationship between circRNA\_10227 expression and cisplatin-resistance. The result showed that circRNA\_10227 knockdown decreases cisplatin IC<sub>50</sub> values in Hep G2 and Huh7 cells (Figure 2D). Meanwhile, in vivo experiments indicated that tumors' volume and weight in the circRNA\_10227 knockdown group were



**Figure 2** Knockdown of circRNA\_10227 suppresses cell proliferation and cisplatin-resistance in HCC. (A) CircRNA\_10227 expression was significantly decreased in HCC cells, transfected with si-circRNA\_10227. (B) Cell proliferation was detected by CCK8 assay. (C) Cell proliferation was examined by colony formation assay. (D) IC<sub>50</sub> values of cisplatin were determined by the CCK8 assay. (E) The tumor volumes were measured every 5 days. (F) Tumors' weight was measured after surgical removal. The data shown represent the mean ± SD. \*p < 0.05.

significantly suppressed and that circRNA\_102272 knock-down, combined with an intraperitoneal injection of cisplatin into the mice, further inhibited tumors' volume and weight (Figure 2E and F). Thus, these data demonstrate that circRNA\_102272 acts as an oncogene in HCC.

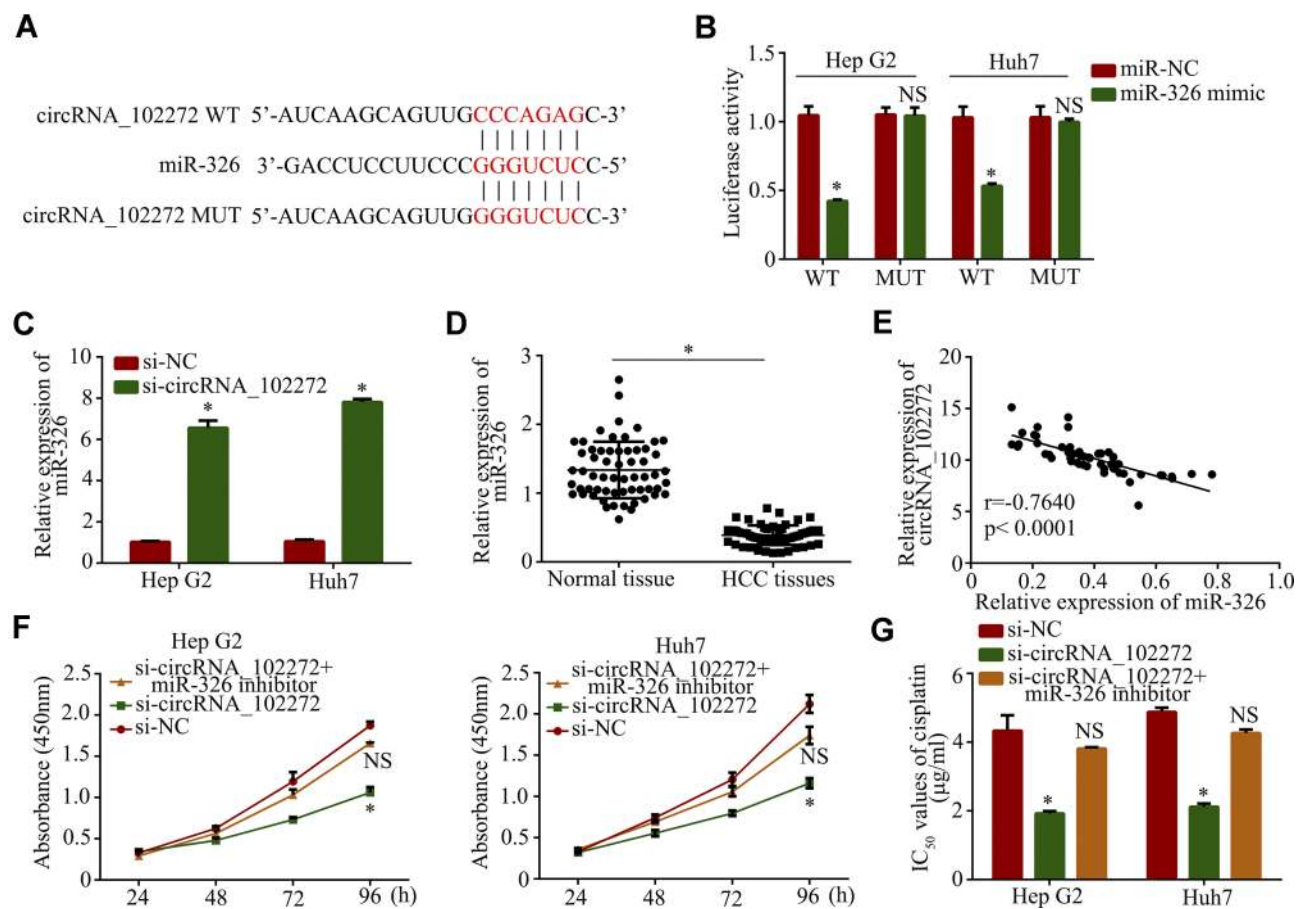
## CircRNA\_102272 Promotes Cisplatin-Resistance Through MiR-326 Sponging

To explore the regulatory mechanisms of circRNA\_102272 in cisplatin-resistance, the online software miRBase and circinteractome were used to predict potential miRNAs involvements in these mechanisms. The result showed that circRNA\_102272 may bind to miR-326 (Figure 3A), and the luciferase reporter assay confirmed their complementary combinations (Figure 3B). The result also suggested that miR-326 binds and suppresses circRNA\_102272 activity. The downregulation of circRNA\_102272 in Hep G2 and

Huh7 cells also increased miR-326 expression (Figure 3C). In addition, the expression of miR-326 in HCC tissues was decreased compared to normal tissues (Figure 3D), and the Pearson correlation analysis revealed that circRNA\_102272 expression inversely correlates with miR-326 expression (Figure 3E). Subsequently, cell proliferation and cisplatin IC<sub>50</sub> values in the Hep G2/si-circRNA\_102272 and Huh7/si-circRNA\_102272 cells, transfected with miR-326 inhibitor, were significantly rescued (Figure 3F and G). Thus, circRNA\_102272 promotes cisplatin-resistance through miR-326 sponging.

## CircRNA\_102272 Facilitates HCC Cisplatin-Resistance by Regulating the MiR-326/RUNX2 Axis

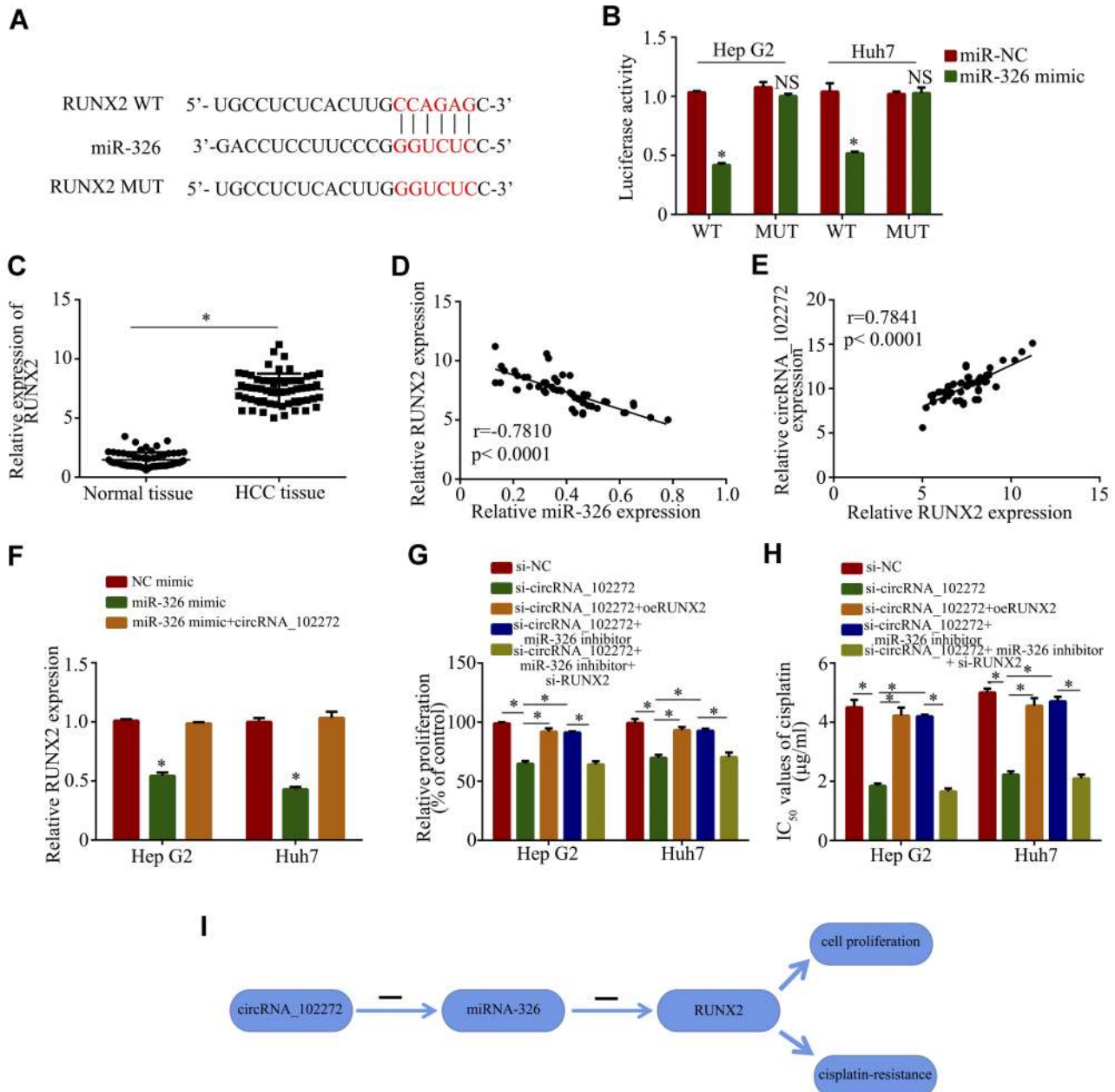
To explore the potential existence of a circRNA-miRNA-mRNA axis in cisplatin-resistance, the online software TargetScan, miRanda and PicTar were used to predict



**Figure 3** CircRNA\_102272 promotes cisplatin-resistance by sponging miR-326. (A) The estimated binding sites of circRNA\_102272 and miR-326. (B) Luciferase reporter assay confirmed their complementary combinations. (C) MiR-326 expression was detected by RT-PCR. (D) MiR-326 expression was significantly decreased in HCC tissues compared to normal tissues. (E) CircRNA\_102272 expression inversely correlates with miR-326 expression. (F) Cell proliferation were detected by the CCK8 assay. (G) IC<sub>50</sub> values of cisplatin were detected by the CCK8 assay. The data shown represent the mean  $\pm$  SD. \* $p < 0.05$ ; <sup>ns</sup> $p > 0.05$ .

potentially involved mRNAs. The result showed that miR-326 may bind to the 3'-UTR region of RUNX2 (Figure 4A), and the luciferase reporter assay confirmed their complementary combinations (Figure 4B) and revealed that miR-326 binds and suppresses RUNX2 activity. In addition, the expression of RUNX2 in HCC tissues was increased compared to normal tissues (Figure 4C). Notably, Pearson

correlation analysis showed that miR-326 expression inversely correlates with RUNX2 expression (Figure 4D), and that circRNA\_102272 expression positively correlates with RUNX2 expression (Figure 4E). It also revealed that circRNA\_102272 may regulate RUNX2 expression via miR-326. Moreover, miR-326 upregulation in Hep G2 and Huh7 cells significantly suppressed RUNX2 expression



**Figure 4** CircRNA\_102272 facilitates HCC cisplatin-resistance by regulating the miR-326/RUNX2 axis. (A) The estimated binding sites of miR-326 and RUNX2. (B) Luciferase reporter assay confirmed their complementary combinations. (C) RUNX2 expression was significantly increased in HCC tissues compared to normal tissues. (D) MiR-326 expression inversely correlates with RUNX2. (E) CircRNA\_102272 expression positively correlates with RUNX2. (F) RUNX2 expression were detected by RT-PCR. (G) Cell proliferation was assessed by the CCK8 assay. (H) IC<sub>50</sub> values of cisplatin were evaluated by the CCK8 assay. (I) CircRNA\_102272 facilitated HCC cisplatin-resistance by regulating the miR-326/RUNX2 axis. The data shown represent the mean ± SD. \* $p < 0.05$ , <sup>ns</sup> $p > 0.05$ . oeRUNX2: overexpression of RUNX2.

(Figure 4F), suggesting that miR-326 suppresses RUNX2 expression. Furthermore, miR-326 overexpression rescued RUNX2 expression in transfected miR-326 mimics Hep G2 and Huh7 cells. Subsequently, the CCK8 assay revealed that RUNX2 knockdown rescues the inhibitory effects on cell proliferation and cisplatin IC<sub>50</sub> values in Hep G2 and Huh 7 cells (Figure 4G and H), suggesting that circRNA\_102272 facilitates HCC cisplatin-resistance by regulating the miR-326/RUNX2 axis (Figure 4I).

## Discussion

Circular RNAs (circRNAs) are a new type of non-coding RNAs, characterized by covalently closed-loop structures of endogenous RNAs. CircRNAs specificity and stability are cell-type dependent.<sup>2-4</sup> Several studies indicated that circRNAs play significant roles in tumor progression, metastasis and multidrug resistance. For example, the circRNA circ\_0067934 promotes tumor growth and metastasis in hepatocellular carcinoma through regulating the miR-1324/FZD5/Wnt/β-catenin axis.<sup>20</sup> Circ-ZEB1.33 promotes the proliferation of human HCC by sponging miR-200a-3p and upregulating CDK6.<sup>21</sup> CircFADS2 regulates lung cancer cells proliferation and invasion via miR-498 sponging.<sup>22</sup> Thus, circRNAs are biomarkers for multiple types of tumors.<sup>23-25</sup> In addition, several miRNAs and lncRNAs have been reported to regulate HCC development.<sup>26,27</sup> However, there are currently few studies that reported on the function of circRNAs in HCC, especially in terms of multidrug resistance.

In this study, we first found that circRNA\_102272 was significantly upregulated in HCC tissues and cells, especially in Hep G2/DDP and Huh7/DDP cells. We also found by Kaplan–Meier analysis that HCC patients with high circRNA\_102272 expression have lower survival rates. Furthermore, we studied the function of circRNA\_102272 in HCC progression and the in vitro results indicated that circRNA\_102272 promotes HCC cell proliferation and reduces HCC's cisplatin-resistance. Notably, circRNA\_102272 knockdown inhibited HCC cell proliferation and enhanced HCC cells' sensitivity to cisplatin in vivo. These data revealed that circRNA\_102272 acts as an oncogene in HCC.

Accumulating evidence indicated that circRNA affects tumorigenesis by sponging miRNAs. The online software miRBase and circinteractome were used to predict the potential target miRNAs. The results showed that circRNA\_102272 may bind to miR-326, which was confirmed using the luciferase reporter assay. Previous studies revealed that miR-326 acts as a tumor suppressor in human tumors. For example, miR-

326 reverses chemoresistance in human lung adenocarcinoma cells by specifically targeting protein 1.<sup>28</sup> MiR-326 regulates endometrial cancer EMT and metastasis through TWIST1 targeting.<sup>29</sup> In this study, the miR-326 expression in HCC tissues was decreased compared to normal tissues, and Pearson correlation analysis revealed that circRNA\_102272 expression inversely correlates with miR-326. Thus, CircRNA\_102272 modulates HCC cisplatin-resistance by sponging miR-326.

RUNX2, a member of runt-related transcription factors (RUNX), has been reported to be involved in tumor occurrence, development, and metastasis in several types of cancers, such as breast,<sup>30</sup> lung,<sup>31</sup> prostate<sup>32</sup> and thyroid cancer.<sup>33</sup> However, the roles of RUNX2 in HCC cisplatin-resistance remain unclear. In this study, RUNX2 was identified as a direct target of miR-326 and its expression was increased in HCC. Moreover, rescue experiments further indicated the antagonistic roles of si-circRNA\_102272 and si-RUNX2 in the modulation of HCC cells' cisplatin-resistance. Therefore, circRNA\_102272 facilitates HCC cisplatin-resistance by regulating the miR-326/RUNX2 axis.

Taken together, our results demonstrated that circRNA\_102272 is significantly increased in HCC tissues and cells, and that it promotes HCC cell proliferation and cisplatin-resistance. More importantly, circRNA\_102272 acted as a ceRNA that suppresses miR-326 expression and activity, leading to RUNX2 increased expression. By elucidating circRNA\_102272 role and mechanism of action in HCC, our study provides insights and an opportunity to overcome multidrug resistance in HCC.

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## Disclosure

The authors declare no conflicts of interest.

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