

# Circ\_0072995 Promotes Proliferation and Invasion via Regulating miR-1253/EIF4A3 Signaling in HCC

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**Background:** Hepatocellular carcinoma (HCC) is a major threat for human health. This work aimed to determine the potential function of circ\_0072995 in HCC progression and its molecular mechanism.

**Methods:** qRT-PCR was conducted to analyze circ\_0072995 expression. CCK8 and colony formation assays were utilized to detect cell proliferation. Transwell assay was performed to determine migration and invasion. Interactions among circ\_0072995, miR-1253 and EIF4A3 (Eukaryotic Translation Initiation Factor 4A3) were predicted through bioinformatics methods and confirmed via luciferase reporter assay and RNA pulldown assay.

**Results:** circ\_0072995 expression was upregulated in HCC tissues. Circ\_0072995 high level was associated with poor prognosis. Circ\_0072995 knockdown impaired proliferation, migration, invasion and survival. MiR-1253 was sponged by circ\_0072995 and targeted EIF4A3 directly. Circ\_0072995 inhibited miR-1253 to upregulate EIF4A3 level.

**Conclusion:** Circ\_0072995 exerted tumorigenic roles to enhance HCC progression through activating EIF4A3 by sponging miR-1253.

**Keywords:** circ\_0072995, miR-1253, EIF4A3, HCC

## Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers around the world and is a leading cause for cancer-related deaths.<sup>1</sup> Surgery combined with chemotherapy or radiotherapy is the main therapeutic strategy for HCC treatment.<sup>2,3</sup> However, the prognosis of HCC patients remains unfavorable due to recurrence and distant metastasis.<sup>4</sup> Thus, determining the underlying molecular mechanism of HCC progression seems to be critical and urgent.

Circular RNAs (circRNAs), one type of noncoding RNAs, are characterized by a closed-loop structure.<sup>5</sup> circRNAs also lack the ability to code protein.<sup>5,6</sup> As the development of sequencing technology, more and more numbers of circRNAs have been identified. And the close association between circRNA and cancer is gradually uncovered. Emerging evidence indicates that circRNAs play important roles in regulating the biological processes of cancer cells, such as proliferation, migration and survival.<sup>7,8</sup> For example, hsa\_circ\_0001944 enhances bladder cancer proliferation and invasion through sponging miR-548.<sup>9</sup> Hsa\_circ\_0020123 upregulation promotes lung cancer growth and migration via facilitating HOXC9 expression by inhibiting miR-495.<sup>10</sup> circCCDC66 is overexpressed in lung cancer cells and contributes to tumor progression through regulating miR-211/SRCIN1 axis.<sup>11</sup> Therefore, dissecting circRNA function will be benefit for the understanding of tumor pathogenesis.

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Circ\_0072995 has been reported to promote breast cancer progression and ovarian cancer development.<sup>12,13</sup> Nevertheless, circ\_0072995 role in HCC remains undetermined. In this research, we found that circ\_0072995 was highly expressed in HCC tissues and predicted poor prognosis. Circ\_0072995 knockdown suppressed HCC growth and invasion while inducing apoptosis. Circ\_0072995 was identified to sponge miR-1253 and enhance EIF4A3 expression. Thus, our work discovered that circ\_0072995/miR-1253/EIF4A3 axis plays an essential oncogenic role in HCC progression.

## Materials and Methods

### Clinical Sample

HCC tissues and normal tissues were collected from The First Affiliated Hospital of Wenzhou Medical University. Tissues were not treated by radiotherapy or chemotherapy before collection. Tissues were stored in liquid nitrogen. All patients provided written informed consents. Correlation between circ\_0072995 expression and clinicopathologic parameters in HCC samples is analyzed in Table 1. This study was approved by the Ethics Committee of The First Affiliated Hospital of Wenzhou Medical University. The experiments were conducted in accordance with the Declaration of Helsinki.

### Cell Lines and Transfection

Cell lines were obtained from Shanghai Institute of Cell Biology (Shanghai, China) and cultured using RPMI-1640 medium (Gibco, Carlsbad, CA, USA) containing 10% FBS. siRNAs, miR-1253 mimics, miR-1253 inhibitors and corresponding negative controls were purchased from Ribobio Co. Ltd (Guangzhou, China) and transfected into cells using Lipofectamine 3000 (Invitrogen, Carlsbad, CA, USA) following the manufacturer's instructions.

### qRT-PCR

Total RNA was isolated through Trizol reagent (Invitrogen). cDNA was synthesized using First-Strand cDNA Synthesis SuperMix (Transgen Biotech). qPCR was performed using SYBR Green (Solarbio, Beijing, China) and calculated according to the  $2^{-\Delta\Delta C_t}$  method. Relative expression was normalized to GAPDH or U6.

### CCK8 Assay

Cells were seeded into 96-well plates and cultured for indicated times. Then CCK8 solution (Beyotime,

**Table 1** Correlation Between Circ\_0072995 Expression and Clinicopathologic Parameters in HCC Samples

| Parameters      | Low (n=30) | High (n=30) | P value |
|-----------------|------------|-------------|---------|
| Age             |            |             | 0.604   |
| <55 years       | 18         | 15          |         |
| ≥55 years       | 12         | 15          |         |
| Gender          |            |             | 0.360   |
| Male            | 25         | 21          |         |
| Female          | 5          | 9           |         |
| TNM stage       |            |             | 0.009   |
| I + II          | 19         | 8           |         |
| III             | 11         | 22          |         |
| Metastases      |            |             | 0.033   |
| Absent          | 23         | 14          |         |
| Present         | 7          | 16          |         |
| HBV-DNA         |            |             | 0.707   |
| Negative        | 25         | 27          |         |
| Positive        | 5          | 3           |         |
| HCV             |            |             | 1.000   |
| Negative        | 29         | 28          |         |
| Positive        | 1          | 2           |         |
| AFP (ng/mL)     |            |             | 0.422   |
| ≤20             | 17         | 21          |         |
| >20             | 13         | 9           |         |
| Liver cirrhosis |            |             | 0.795   |
| No              | 14         | 12          |         |
| Yes             | 16         | 18          |         |
| GGT (U/L)       |            |             | 0.360   |
| ≤60             | 21         | 25          |         |
| >60             | 9          | 5           |         |

Shanghai, China) was added into each plate and incubated for 4 h. The absorbance at 450 nm was determined using a microplate reader.

### Colony Formation Assay

Cells were seeded into 6-well plates and cultured for 14 days. Then colonies were fixed and stained using crystal violet. Colony number was determined finally.

### Tumor Xenograft Assay

6-week old female Nude mice were inoculated subcutaneously on the right flank with  $2 \times 10^6$  Hep3B cells. Tumor volumes were measured every one week according to the formula: Tumor volume =  $(\text{length} \times \text{width}^2)/2$ . All mouse experiments were conducted in accordance with the Guide for the Care and

Use of Laboratory Animals (People's Republic of China National Standard GB/T 35892 2018) and were approved by the Institutional Animal Care and Use Committee of the First Affiliated Hospital of Wenzhou Medical University.

## Transwell Assay

Cell migration and invasion were analyzed by Transwell chambers (Corning Inc., Corning, NY, USA). The cells were seeded into the upper chamber filled with serum-free medium. The lower chamber was filled with serum-containing medium. After cultured for 48 h, the migrated or invaded cells in the lower member was fixed and stained with crystal violet. Then, the number of cells was counted using a microscope.

## Dual-Luciferase Reporter Assay

The circ\_0072995 or EIF4A3 sequence containing the binding element for miR-1253 was constructed into pmirGLO expression vector (Promega, Madison, WI, USA). For luciferase reporter assay, the luciferase vector and miR-1253 mimics were transfected into cells. After cultured for 48 h, the luciferase activity was measured using the Dual-Luciferase Assay System (Promega).

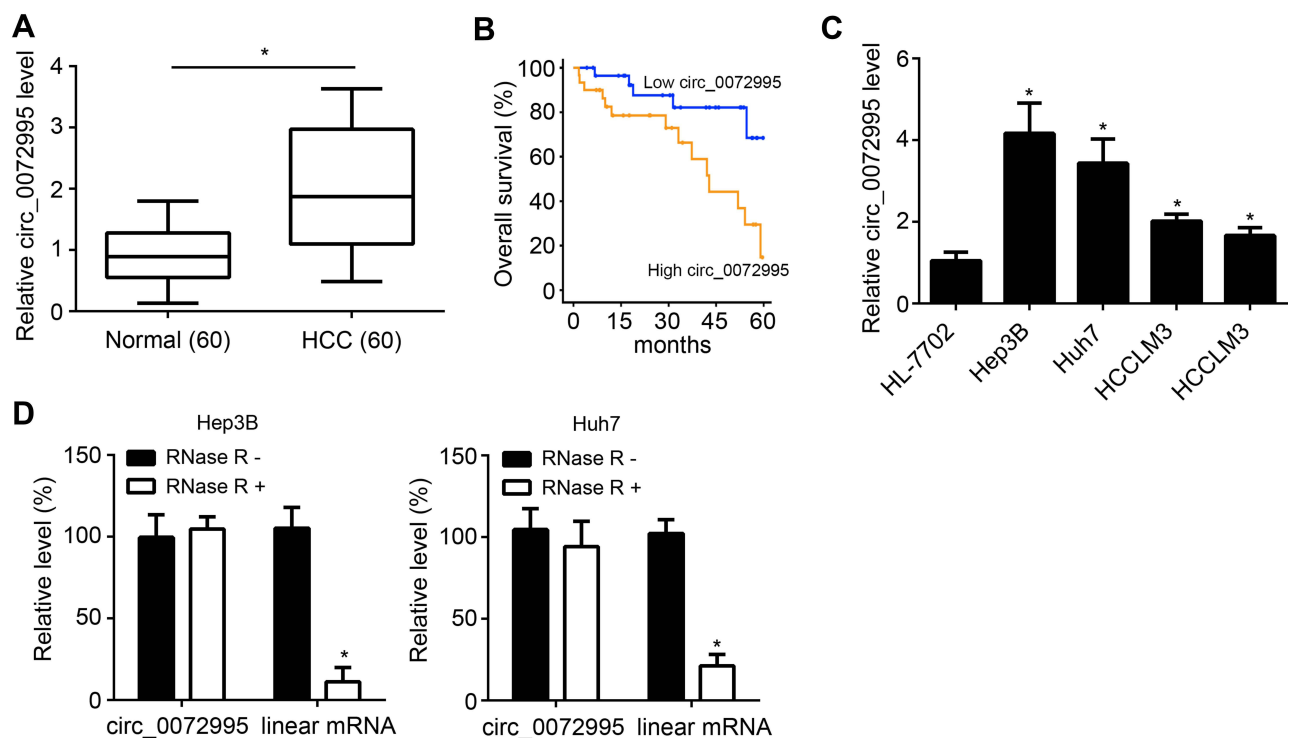
## Statistical Analysis

Results from three independent experiments were analyzed by GraphPad Prism 6 software (San Diego, CA, USA) and expressed as the mean  $\pm$  standard deviation. Student's *t* test or one-way analyses of variance followed by Tukey's test was used for statistical analyses.  $P < 0.05$  was defined as statistically significant.

## Results

### Circ\_0072995 Was Upregulated in HCC

Firstly, the expression of circ\_0072995 was examined by qRT-PCR in HCC tissues. Results indicated that circ\_0072995 level was raised in HCC tissues compared to normal tissues (Figure 1A). Then HCC tissues were divided into circ\_0072995 high and circ\_0072995 low groups based on the median value. Overall survival rate was plotted. As shown, circ\_0072995 high expression was associated with low survival rate (Figure 1B). Afterwards, HCC cell lines were obtained and qRT-PCR was performed. Circ\_0072995 expression was also increased in HCC cell lines compared to HL-7702 cells (Figure 1C). To prove circ\_0072995 is a circular RNA, we treated RNA with RNase R, followed by qRT-PCR analysis. Circ\_0072995 was resistant to RNase R digestion (Figure 1D).

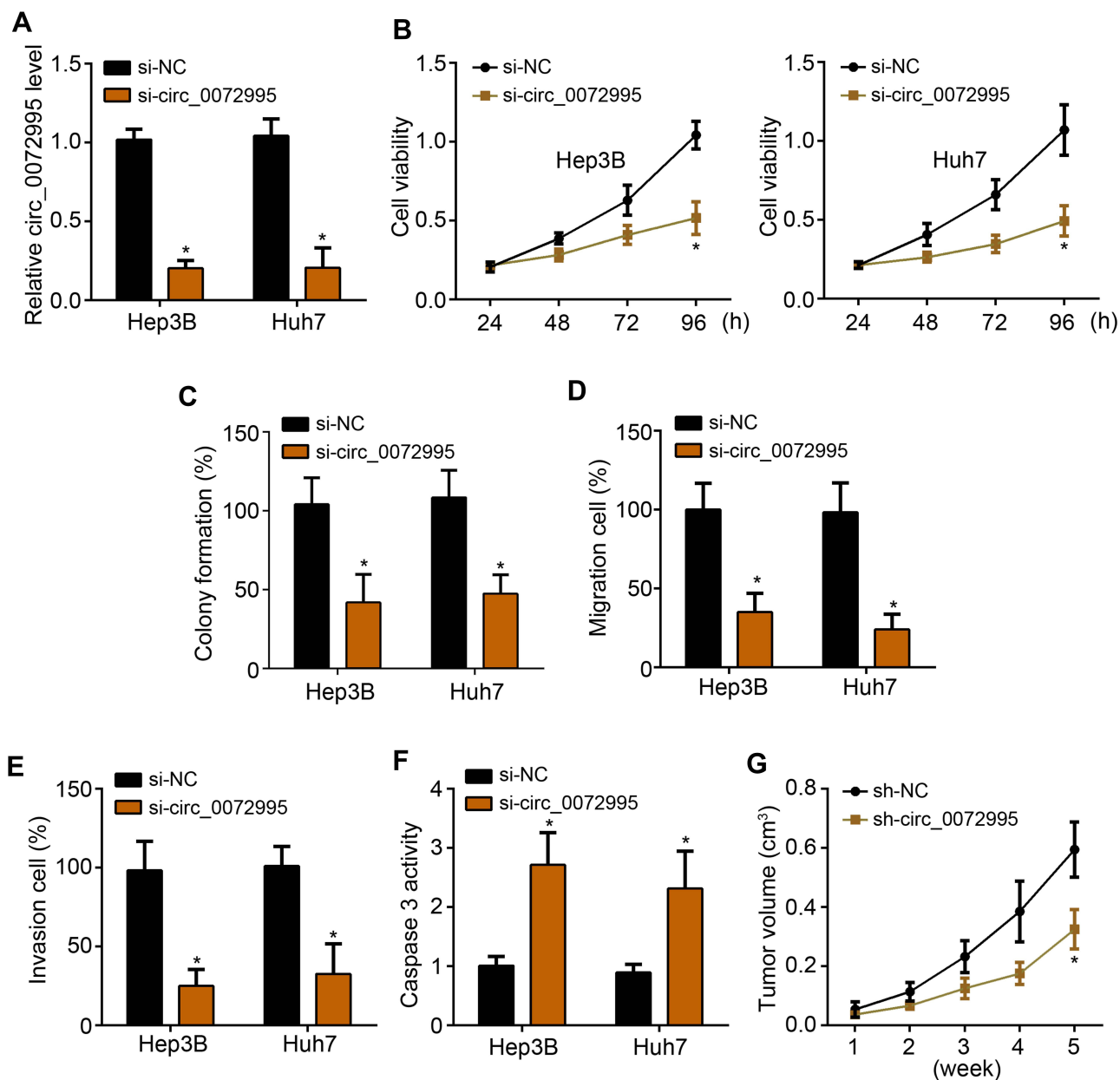


**Figure 1** Circ\_0072995 was upregulated in HCC. (A) qRT-PCR analysis for circ\_0072995 expression in HCC tissues. (B) Overall survival rate was plotted based on circ\_0072995 level in HCC tissues. (C) Circ\_0072995 expression in HCC cell lines was assessed through qRT-PCR. (D) qRT-PCR analysis indicated that circ\_0072995 was resistant to RNase R digestion. \* $P < 0.05$ .

## Circ\_0072995 Downregulation Inhibited HCC Progression

Because Circ\_0072995 was the most highly expressed in Hep3B and Huh7 cells among all detected HCC cell lines (new Figure 1C), we chose hep3B and Huh7 for following experiments. siRNAs were synthesized to knock down circ\_0072995 in Hep3B and Huh7 cells (Figure 2A). CCK8 and colony formation assays were carried out and results showed that circ\_0072995 knockdown impaired the growth

of Hep3B and Huh7 cells (Figure 2B and C). Moreover, transwell assay was performed and we found that circ\_0072995 silencing suppressed HCC cell migration and invasion (Figure 2D and E). We also noticed that the caspase3 activity in the cells of si-circ\_0072995 group was higher than that in control group (Figure 2F), suggesting that circ\_0072995 knockdown promoted apoptosis. Importantly, circ\_0072995 silencing also inhibited tumor growth in vivo (Figure 2G).



**Figure 2** Circ\_0072995 downregulation inhibited HCC progression. (A) Circ\_0072995 level was decreased by siRNA transfection. (B and C) CCK8 assay and colony formation assay were performed to analyze proliferation. (D and E) Transwell assay was performed to analyze migration and invasion. (F) Apoptosis was analyzed by detecting Caspase3 activity. (G) Tumor volumes were measured every week. \* $P < 0.05$ .

## Circ\_0072995 Promoted EIF4A3 Expression via Sponging miR-1253

To explore the downstream molecular mechanism, bioinformatics analysis was performed using circinteractome and TargetScan7 tools. Circ\_0072995 was found to sponge miR-1253 while EIF4A3 was the most potential target of miR-1253. To prove it, luciferase reporter assays were carried out. MiR-1253 suppressed the luciferase activity of either WT-circ\_0072995 or WT-EIF4A3 (Figure 3A and B). miRNAs are often associated with the AGO2 complex. Thus, we used anti-AGO2 to perform RIP assay. Results showed that Ago2 antibody can enrich both circ\_0072995 and miR-1253 (Figure 3C). Additionally, Ago2 antibody also enriched miR-1253 and EIF4A3 (Figure 3D). We found that miR-1253 level was increased after circ\_0072995 knockdown (Figure 3E). However, miR-1253 suppressed the expression of EIF4A3 (Figure 3F). Interestingly, circ\_0072995 knockdown inhibited EIF4A3 expression while miR-1253 inhibition reversed it (Figure 3G). Therefore, circ\_0072995 promoted EIF4A3 expression by sponging miR-1253.

## Circ\_0072995 Promoted HCC Progression Through Regulating miR-1253/EIF4A3 Axis

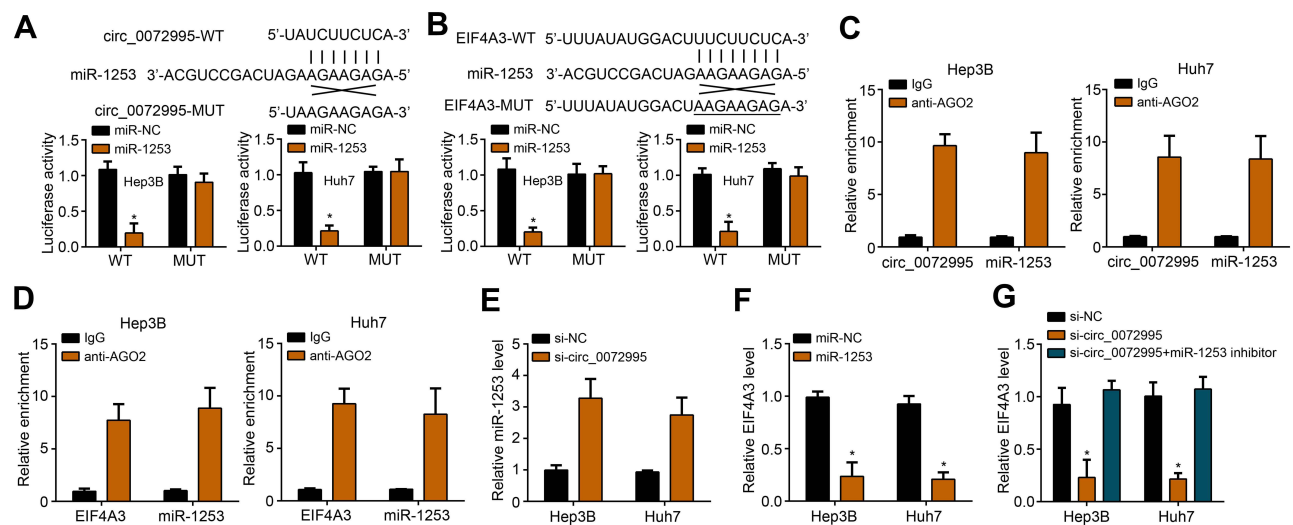
In HCC tissues, circ\_0072995 or EIF4A3 was negatively correlated with miR-1253 (Figure 4A and B) while circ\_0072995 was positively correlated with EIF4A3 (Figure 4C). Through TCGA data using ualcan tool, we

noticed that EIF4A3 was upregulated in HCC tissues and correlated with poor prognosis (Figure 4C and D), suggesting that EIF4A3 may be an oncogene. To confirm whether circ\_0072995 promotes HCC progression through regulating miR-1253/EIF4A3 axis, rescue assays were performed. CCK8 and Transwell assays showed that miR-1253 inhibitors or EIF4A3 overexpression reversed the inhibitory effects of circ\_0072995 siRNA on malignant behaviors in HCC cells (Figure 4E–G).

## Discussion

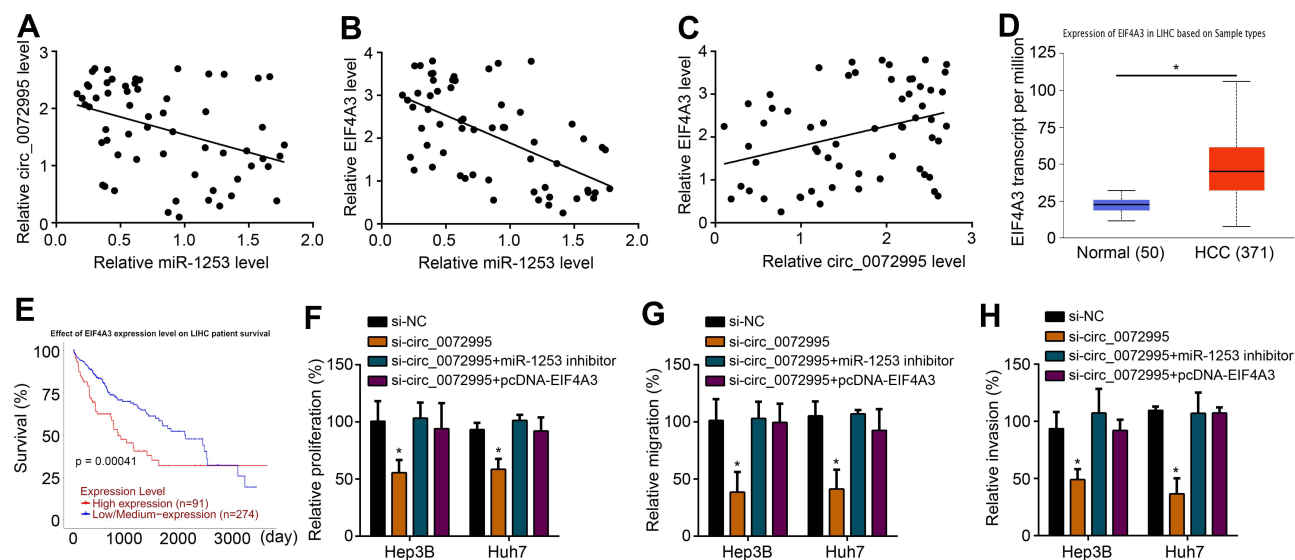
HCC is a major public problem for human health.<sup>14</sup> However, how HCC development and progression still remains unclear. In this study, we found that circ\_0072995 was upregulated in HCC tissues and predicted poor prognosis. Circ\_0072995 knockdown resulted in decreased proliferation, migration and invasion. Moreover, circ\_0072995 was proven to sponge miR-1253, leading to upregulation of EIF4A3 expression. Thus, our findings supported circ\_0072995 is an important oncogene in HCC.

The relationship between circRNA and HCC has been discovered gradually.<sup>15</sup> Several circRNAs are demonstrated to regulate several biological processes of HCC cells, such as metastasis and survival.<sup>15</sup> For example, circ\_0015756 is upregulated in HCC and promotes cell proliferation, migration and invasion.<sup>16</sup> CircRNA cIARS affects HCC ferroptosis by binding to ALKBH5.<sup>17</sup> Circ\_0046599 initiates HCC development and promotes metastasis via miR-1258/RPN2 signaling.<sup>18</sup> circ\_0072995 was found to promote breast cancer



**Figure 3** Circ\_0072995 promoted EIF4A3 expression via sponging miR-1253. (A and B) Luciferase reporter assay was performed to confirm the interaction between circ\_0072995 and miR-1253 or between miR-1253 and EIF4A3. Circinteractome and TargetScan7 were used to predict their interactions. (C and D) RIP assays were performed to demonstrate the interaction between circ\_0072995 and miR-1253 or between miR-1253 and EIF4A3. (E) Circ\_0072995 knockdown promoted miR-1253 expression. (F) miR-1253 inhibited EIF4A3 expression. (G) Relative expression of EIF4A3 after transfection with indicated plasmids by qRT-PCR. \*P<0.05.





**Figure 4** Circ\_0072995 promoted HCC progression through regulating miR-1253/EIF4A3 axis. (A–C) Expression correlations among circ\_0072995, miR-1253 and EIF4A3 in HCC tissues were performed by qRT-PCR. (D) EIF4A3 was upregulated in HCC tissues according to TCGA data. (E) EIF4A3 overexpression predicted poor prognosis in HCC according to TCGA data. (F) CCK8 assay for proliferation analysis. (G and H) Transwell assay for evaluating migration and invasion. \* $P < 0.05$ .

metastasis.<sup>12</sup> Another work found that circ\_0072995 initiates ovarian cancer development.<sup>13</sup> However, whether circ\_0072995 affects HCC development is unknown. Our data uncovered that circ\_0072995 was upregulated in HCC tissues. And circ\_0072995 knockdown repressed proliferation, migration and invasion of HCC tissues. Thus, this study for the first time proved circ\_0072995 exerts oncogenic functions in HCC.

CircRNA is a classical type of competing endogenous RNAs (ceRNAs) for microRNAs.<sup>10</sup> circRNA-miRNA axis plays crucial roles in the regulation of tumorigenesis.<sup>12</sup> For instance, circ-SEC31A is the ceRNA for miR-520a-5p to promote lung cancer progression.<sup>19</sup> Hsa\_circ\_103809 plays an oncogenic function in gastric cancer through interacting with miR-101-3p.<sup>20</sup> In addition, circ-CSPP1 contributes to HCC growth and invasion through sponging miR-577.<sup>21</sup> circ\_0072995 was found to be the ceRNA for miR-147a and miR-30c.<sup>12,13</sup> In HCC, we did not observe it. However, we found that circ\_0072995 targeted miR-1253. Through luciferase reporter assay and RIP assay, their direct interaction was validated. MiR-1253 expression was also inhibited by circ\_0072995. Previously, miR-1253 was found to be a tumor suppressor in lung cancer, osteosarcoma, prostate cancer and pancreatic ductal adenocarcinoma.<sup>22–25</sup> Its role in HCC is unclear. Our study showed that miR-1253 inhibitors promoted the proliferation, migration and invasion of HCC cells. Thus, miR-1253 promotes HCC progression.

Next, bioinformatics analysis was conducted to search the downstream target of miR-1253. EIF4A3 was identified.

Luciferase report assay and RIP assay confirmed the interaction between miR-1253 and EIF4A3. EIF4A3 is an important oncogene and promotes tumorigenesis in various types of cancer.<sup>26</sup> For example, EIF4A3 promotes breast cancer growth and metastasis.<sup>27</sup> EIF4A3 promotes circMMP9 expression and induces glioblastoma multiforme tumorigenesis.<sup>28</sup> However, there is still no study about EIF4A3 function in HCC. We showed that EIF4A3 was upregulated in HCC and linked with poor prognosis. Moreover, EIF4A3 overexpression enhanced HCC progression. Therefore, EIF4A3 was the downstream signaling of circ\_0072995/miR-1253 axis and promoted HCC development.

In sum, this work demonstrates that circ\_0072995 was upregulated in HCC and promotes tumor growth and invasion through regulating miR-1253/EIF4A3 axis, which suggests that circ\_0072995 may be a new therapeutic target in HCC.

## Disclosure

The authors declare that they have no conflicts of interest.

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