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# MiRNA-1179 suppresses the metastasis of hepatocellular carcinoma by interacting with ZEB2

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**Abstract. – OBJECTIVE: To investigate the biological function of microRNA-1179 (miRNA-1179) in regulating the proliferative and migratory abilities of the hepatocellular carcinoma (HCC) by targeting zinc-finger E-box-binding homeobox 2 (ZEB2).**

**PATIENTS AND METHODS: The miRNA-1179 level in 40 HCC tissues and matched normal tissues was detected by quantitative Real Time-Polymerase Chain Reaction (qRT-PCR). The association between the miRNA-1179 level and the clinical parameters of HCC patients was analyzed. The regulatory effects of miRNA-1179 on influencing proliferative and migratory abilities of HepG2 and Bel-7402 cells were assessed. The dual-luciferase reporter gene assay was conducted to verify the binding relationship between miRNA-1179 and ZEB2. Subsequently, the expression pattern and the biological function of ZEB2 in HCC were explored. The rescue experiments were finally carried out to uncover the role of the miRNA-1179/ZEB2 axis in regulating the progression of HCC.**

**RESULTS: MiRNA-1179 was downregulated in HCC tissues and cell lines. HCC patients with low expression of miRNA-1179 had higher metastatic rates (lymphatic metastasis and distant metastasis) and worse prognosis relative to those with low expression. The overexpression of miRNA-1179 attenuated the proliferative and migratory abilities of HCC cells. ZEB2 was confirmed to be the direct target of miRNA-1179 and its level was negatively regulated by miRNA-1179. ZEB2 was upregulated in HCC tissues and cell lines. The high expression of ZEB2 predicted a worse prognosis of HCC. The overexpression of ZEB2 reversed the inhibitory effects of miRNA-1179 on the proliferative and migratory abilities in HCC cells.**

**CONCLUSIONS: MiRNA-1179 is closely related to lymphatic metastasis, distant metastasis, and overall survival of HCC. It alleviates the malignant progression of HCC by downregulating ZEB2.**

*Key Words:*
MiRNA-1179, ZEB2, Hepatocellular carcinoma (HCC).

## Introduction

Primary liver cancer is highly malignant. Hepatocellular carcinoma (HCC) is the most common subtype of primary liver cancer, which is regarded as the second cancer with highest incidence in the Chinese population[1,2]. HCC mostly occurs in the setting of chronic liver diseases, accounting for 70-90% of all HCC cases[3]. Globally, HBV infection is the most important risk factor for HCC. Over 50% of HCC patients are infected with HBV[4,5]. Since the infection rates of HBV and HCV are extremely high in China, HCC seriously threatens human health in the Chinese population[3-5]. Currently, surgical resection, liver transplantation, radiotherapy, chemotherapy, interventional therapy, and molecular targeted therapy are preferred for HCC treatment according to the individual situation[2]. Nevertheless, the long-term survival of HCC is unsatisfactory due to the recurrence and metastasis of cancer cells[6,7]. It is generally believed that the abnormal expressions of the oncogenes, tumor-suppressor genes, and cancer-related pathway dysregulation lead to phenotype changes of the cancer cells, thus leading to the postoperative recurrence and metastasis of HCC[8]. It is of great significance to uncover the mechanism of the HCC pathogenesis, thus guiding the clinical treatment of HCC.

MicroRNAs (miRNAs) are small non-coding RNAs of about 19 to 25 nucleotides in length, which are produced by a series of endonucleases and transporters in the nucleus and

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cytoplasm[9,10]. MiRNAs are highly conserved, and are characterized by sequence homologous, timing-, and tissue-specificity. They regulate the target gene expressions by binding to mRNA 3'UTR, thus influencing various biological processes[11]. About 20-30% of human genes could be regulated by miRNAs[12,13]. In addition, miRNAs are differentially expressed in cancer tissues and normal ones. They are capable of mediating tumor biology by targeting various factors and affecting the therapeutic efficacy and disease prognosis[14,15].

With the in-depth researches on miRNAs, several miRNAs related to HCC have been identified[16,17]. MiRNA-1179 has been extensively explored in many types of cancers[18,19]. In this paper, we mainly uncover the biological function of miRNA-1179 in regulating the cellular behaviors of the HCC cells and the underlying mechanism.

## Patients and Methods

### Patients and Samples

40 paired HCC tissues and matched normal tissues were surgically resected. None of the enrolled HCC patients received preoperative anti-tumor therapies. Their clinical indexes were collected for further analyses. The patients and their families in this study have been fully informed. This study was approved by the Ethics Committee of Binzhou People's Hospital.

### Cell Lines and Reagents

HCC cell lines (Hep3B, Huh7, SMMC-7221, MHCC88H, HepG2, and Bel-7402) and normal hepatocytes LO2 were provided by the American Type Culture Collection (ATCC; Manassas, VA, USA). The cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM; Gibco, Rockville, MD, USA) containing 10% fetal bovine serum (FBS; Life Technologies, Gaithersburg, MD, USA) and maintained at 37°C, 5% in a $CO_2$ incubator. The medium was replaced every 2-3 days. The cell passage was conducted at 80-90% of confluence.

### Transfection

The transfection plasmids were provided by GenePharma (Shanghai, China). The cells pre-seeded in the 6-well plates were transfected using Lipofectamine 2000 at 70% of confluence. At 48 h, the transfected cells were harvested for subsequent experiments.

### Cell Counting Kit-8 (CCK-8)

The cells were seeded in the 96-well plate with $2\times10^3$ cells per well. At the appointed time points, the absorbance value at 450 nm of each sample was recorded using the CCK-8 kit (Dojindo Laboratories, Kumamoto, Japan) for depicting the viability curve.

### Colony Formation Assay

The cells were seeded in a 6-well plate with 200 cells per well and incubated for 2-3 weeks. Subsequently, the colonies were fixed in 100% methanol and dyed with 0.5% crystal violet for 20 min. The colonies were finally captured and calculated (magnification 10×).

### Transwell Migration Assay

The cells were adjusted to a dose of $2.0\times10^5$/mL. 200 μL/well suspension and 700 μL of medium containing 10% FBS were applied in the upper and bottom side of the transwell chamber (Millipore, Billerica, MA, USA), respectively. After 48 h of incubation, the cells penetrated to the bottom side, were fixed in methanol for 15 min, were stained in crystal violet for 20 min, and were counted using a microscope. The number of migratory cells was counted in 5 randomly selected fields per sample (magnification 10×).

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

The total RNA was extracted from cells using the TRIzol reagent (Invitrogen, Carlsbad, CA, USA), purified by DNase I treatment, and reversely transcribed into cDNA using the PrimeScript RT Reagent (TaKaRa, Otsu, Shiga, Japan). The obtained cDNA has been subjected to qRT-PCR using SYBR® Premix Ex Taq™ (TaKaRa, Otsu, Shiga, Japan). The glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and U6 were used as internal references. Each sample was performed in triplicate, and the relative level was calculated by the $2^{-\Delta\Delta Ct}$ method. QRT-PCR reaction conditions were as follows: 94°C for 30 s, 55°C for 30 s, and 72°C for 90 s, for a total of 40 cycles. The primer sequences used in this study were as follows: miRNA-1179, F: 5'-GCGAGGAAAATGCTCCTCCGCTC-3', R: 5'-GCTAGTTATGTAACCATGGA-3'; ZEB2, F: 5'-CATGCACCGCATTAAGACAA-3', R: 5'-CGGTGAATATAGTTACAGTCCT-3'; U6: F: 5'-GCTTCGGCAGCACATATACTAAAAT-3', R: 5'-CGCTTCAGAATTTGCGTGTCAT-3'; GAPDH: F: 5'-CGCTCTCTGCTCCTCCTGTTC-3', R: 5'-ATCCGTTGACTCCGACCTTCAC-3'.

### Western Blot

The cells were lysed for the extraction of the total proteins using radioimmunoprecipitation assay (RIPA; Beyotime, Shanghai, China), quantified by bicinchoninic acid (BCA) method (Beyotime, Shanghai, China) and loaded for electrophoresis. The protein samples were electrophoresed on polyacrylamide gels and then transferred to polyvinylidene difluoride (PVDF) membranes (Merck Millipore, Billerica, MA, USA). After non-specific site blockage in 5% skimmed milk, the membranes were incubated with primary antibody (Cell Signaling Technology, Danvers, MA, USA) at 4°C overnight. The membrane was incubated with the secondary antibody after rinsing with the buffer solution (TBST). The bands were exposed by enhanced chemiluminescence (ECL) and analyzed by the Image Software (NIH, Bethesda, MD, USA).

### Dual-Luciferase Reporter Gene Assay

The cells were co-transfected with miRNA-1179 mimics/NC and pmirGLO-zinc-finger E-box-binding homeobox 2 (ZEB2)-WT/pmirGLO-ZEB2-MUT using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA), respectively. 24 hours later, the co-transfected cells were harvested to determine the luciferase activity using a dual-luciferase reporter assay system (Promega, Madison, WI, USA).

### Statistical Analysis

The Statistical Product and Service Solutions (SPSS) 22.0 (IBM Corp., Armonk, NY, USA) was used for data analyses. The data were expressed as mean ± standard deviation. The intergroup differences were analyzed by the t-test. The Kaplan-Meier curves were introduced to assess the overall survival in HCC patients, based on their levels of miRNA-1179. The Spearman regression test was performed to evaluate the relationship between the expression levels of the two genes. $p<0.05$ was considered as statistically significant.

## Results

### Downregulated MiRNA-1179 Was Related to Metastasis and Prognosis of HCC

Compared with matched normal tissues, miRNA-1179 was downregulated in HCC tissues (Figures 1A, 1B). Similarly, the *in vitro* expression of miRNA-1179 was lower in the HCC cell lines

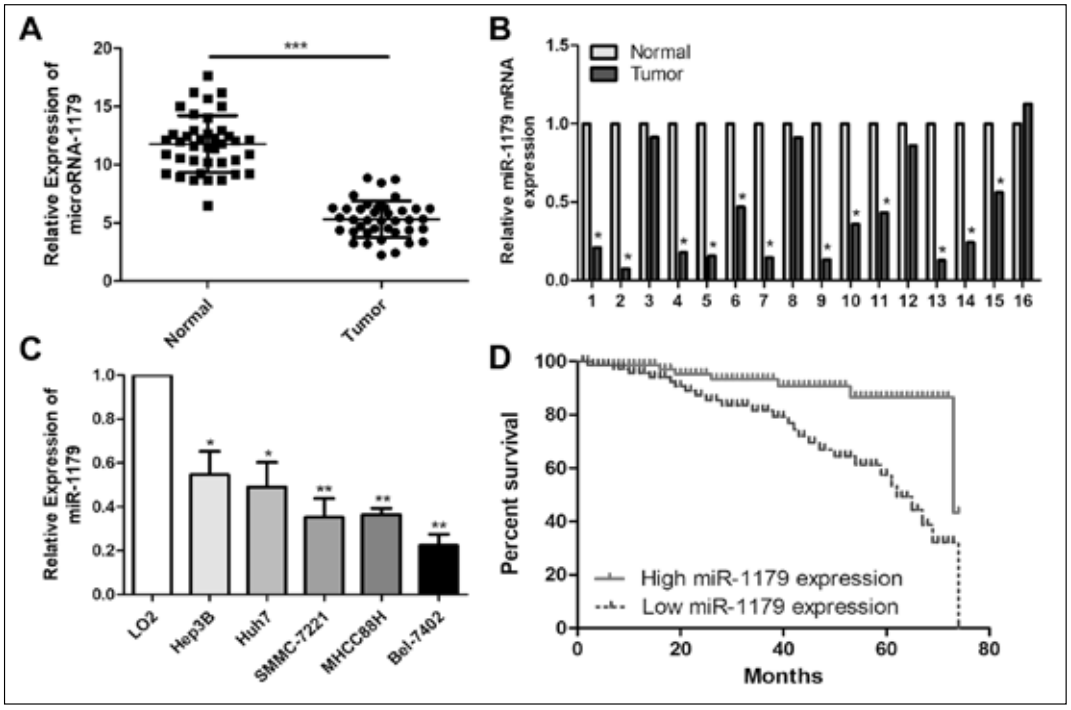


**Figure 1.** Downregulated miR-1179 was related to metastasis and prognosis of HCC. ***A,*** The relative level of miR-1179 in HCC tissues and matched normal tissues (n=40). ***B,*** The relative level of miR-1179 in 16 paired HCC tissues and adjacent normal tissues. ***C***, The relative level of miR-1179 in HCC cell lines (Hep3B, Huh7, SMMC-7221, MHCC88H, HepG2 and Bel-7402) and normal hepatocytes LO2. ***D,*** The Kaplan-Meier curves revealed the overall survival in HCC patients with high and low expression of miR-1179.

than that of normal hepatocytes LO2 (Figure 1C). Based on the median level of miRNA-1179, the enrolled HCC patients were divided into high expression and low expression group. The Kaplan-Meier curves revealed worse prognosis in the HCC patients with a low expression of miRNA-1179, compared to those in high expression group (Figure 1D).

Subsequently, the correlation abetween the miRNA-1179 level and clinical indexes of HCC patients was assessed. It is indicated that miRNA-1179 level was negatively correlated to lymphatic metastasis and distant metastasis rates, rather than age, gender, and TNM staging of HCC patients (Table I). It is suggested that miRNA-1179 could serve as a hallmark predicting the malignant progression of HCC.

### Overexpression of MiRNA-1179 Attenuated Proliferative and Migratory Abilities of HCC

We constructed miRNA-1179 mimics and tested its transfection efficacy. The transfection of miRNA-1179 mimics greatly upregulated miRNA-1179 level in HepG2 and Bel-7402 cells (Figure 2A). In HCC cells overexpressing miRNA-1179, their viability markedly decreased (Figure 2B). The number of colonies was reduced after the transfection of miRNA-1179 mimics in HepG2 and Bel-7402 cells (Figure 2C). Moreover, the transwell assay showed the reduced migratory cell number in HCC cells overexpressing miRNA-1179 (Figure 2D). Collectively, miRNA-1179 overexpression inhibited HCC cells to proliferate and migrate.

### MiRNA-1179 Bound to ZEB2

Based on the binding sequences between miRNA-1179 and ZEB2, pmirGLO-ZEB2-WT and pmirGLO-ZEB2-MUT were constructed to perform the dual-luciferase reporter gene assay (Figure 3A). The co-transfection of miRNA-1179 mimics and pmirGLO-ZEB2-WT remarkably decreased the luciferase activity, suggesting a binding relationship between miRNA-1179 and ZEB2 (Figure 3B). The transfection of miRNA-1179 mimics downregulated mRNA and the protein levels of ZEB2 in HCC cells (Figures 3C, 3D).

### ZEB2 Was Upregulated in HCC

Subsequently, the expression pattern and biological function of ZEB2 in HCC were investigated. ZEB2 level remained higher in the HCC tissues and cell lines (Figures 4A, 4B). We next assessed the relationship between miRNA-1179 and ZEB2 in 40 HCC tissues. The Spearman regression test showed a negative relationship between the expression levels of miRNA-1179 and ZEB2 in the HCC tissues (Figure 4C). By analyzing the collected follow-up data, HCC patients expressing a high level of ZEB2 presented a worse survival (Figure 4D).

**Table I.** Association of miR-1179 expression with clinicopathologic characteristics of hepatocellular carcinoma.

| Parameters | Number of cases | miR-1179 expression | | *p*-value |
|---|---|---|---|---|
| | | High (%) | Low (%) | |
| Age (years) | | | | 0.896 |
| <60 | 17 | 10 | 7 | |
| ≥60 | 23 | 14 | 9 | |
| Gender | | | | 0.301 |
| Male | 19 | 13 | 6 | |
| Female | 21 | 11 | 10 | |
| T stage | | | | 0.121 |
| T1-T2 | 28 | 19 | 9 | |
| T3-T4 | 12 | 5 | 7 | |
| Lymph node metastasis | | | | 0.008 |
| No | 25 | 19 | 6 | |
| Yes | 15 | 5 | 10 | |
| Distance metastasis | | | | 0.037 |
| No | 23 | 17 | 6 | |
| Yes | 17 | 7 | 10 | |

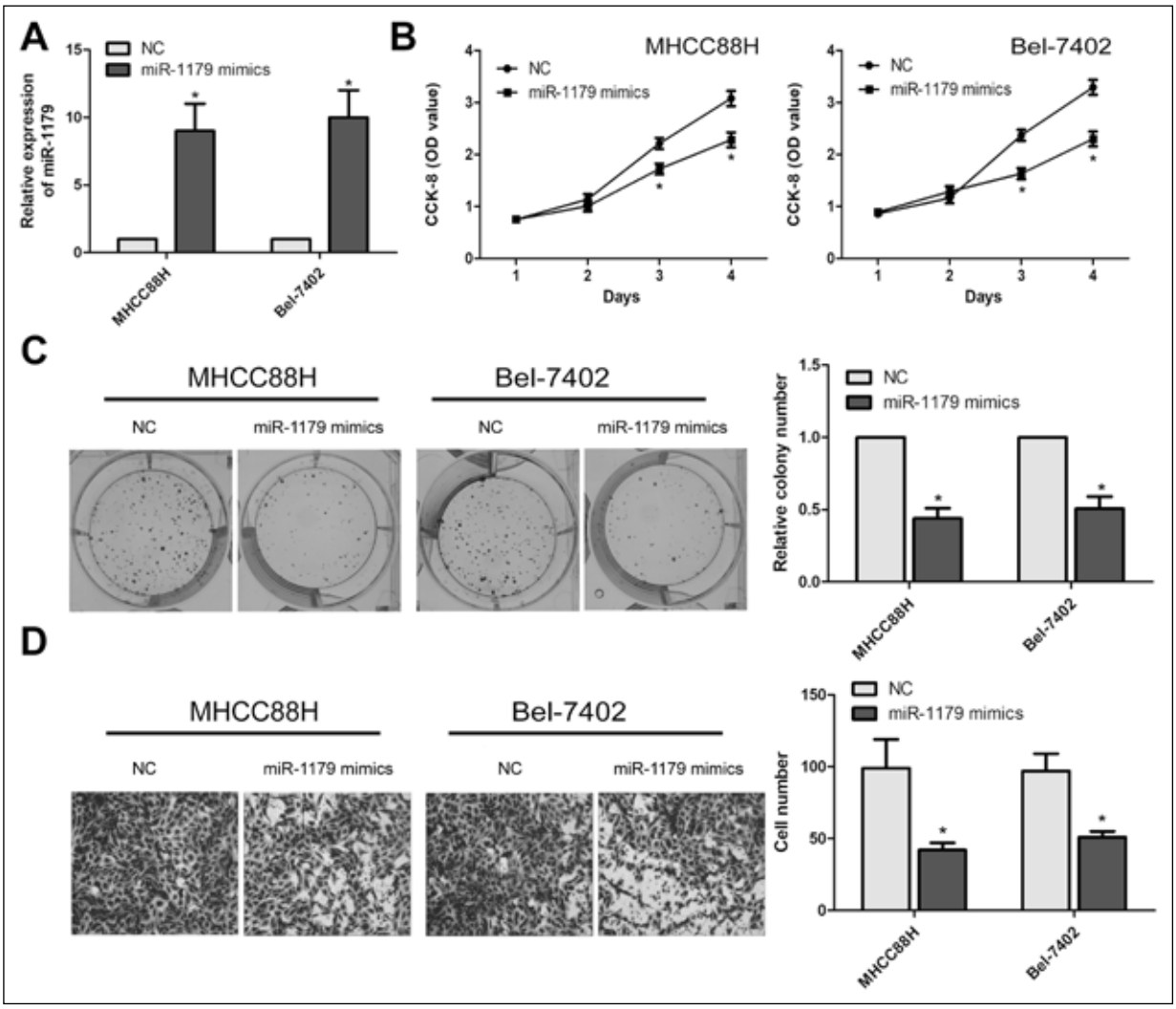


**Figure 2.** The overexpression of miR-1179 attenuated the proliferative and migratory abilities of HCC. ***A,*** The transfection efficacy of miR-1179 mimics in HepG2 and Bel-7402 cells. ***B,*** CCK-8 assay showed viability in HepG2 and Bel-7402 cells transfected with NC or miR-1179 mimics. ***C,*** The colony formation assay showed a relative colony number in HepG2 and Bel-7402 cells transfected with NC or miR-1179 mimics (magnification 10×). ***D,*** The transwell assay showed a migratory cell number in HepG2 and Bel-7402 cells transfected with NC or miR-1179 mimics (magnification 10×).

### *MiRNA-1179 Regulated Cellular Behaviors of HCC Cells by Targeting ZEB2*

Based on the above findings, we speculated that ZEB2 was involved in the HCC progression influenced by miRNA-1179. Firstly, pcDNA-ZEB2 was constructed, and significantly upregulated ZEB2 level in the HCC cells (Figure 5A). It is shown that the transfection of miRNA-1179 mimics could downregulate ZEB2 level, and in addition it was further elevated by the overexpression of ZEB2 (Figure 5A). The overexpression of ZEB2 remarkably enhanced viability, colony number, and the migratory cell number of the HCC cells. Notably, the inhibited viability, proliferation, and migration in HCC cells overexpressing miRNA-1179 were partially reversed by the co-transfection of pcDNA-ZEB2 (Figures 5B-5D). Hence, it is concluded that miRNA-1179 inhibited the proliferative and migratory abilities of HCC cells by negatively regulating ZEB2 level.

## Discussion

HCC is a highly malignant cancer[1-3]. It seriously threatens human lives and poses a great

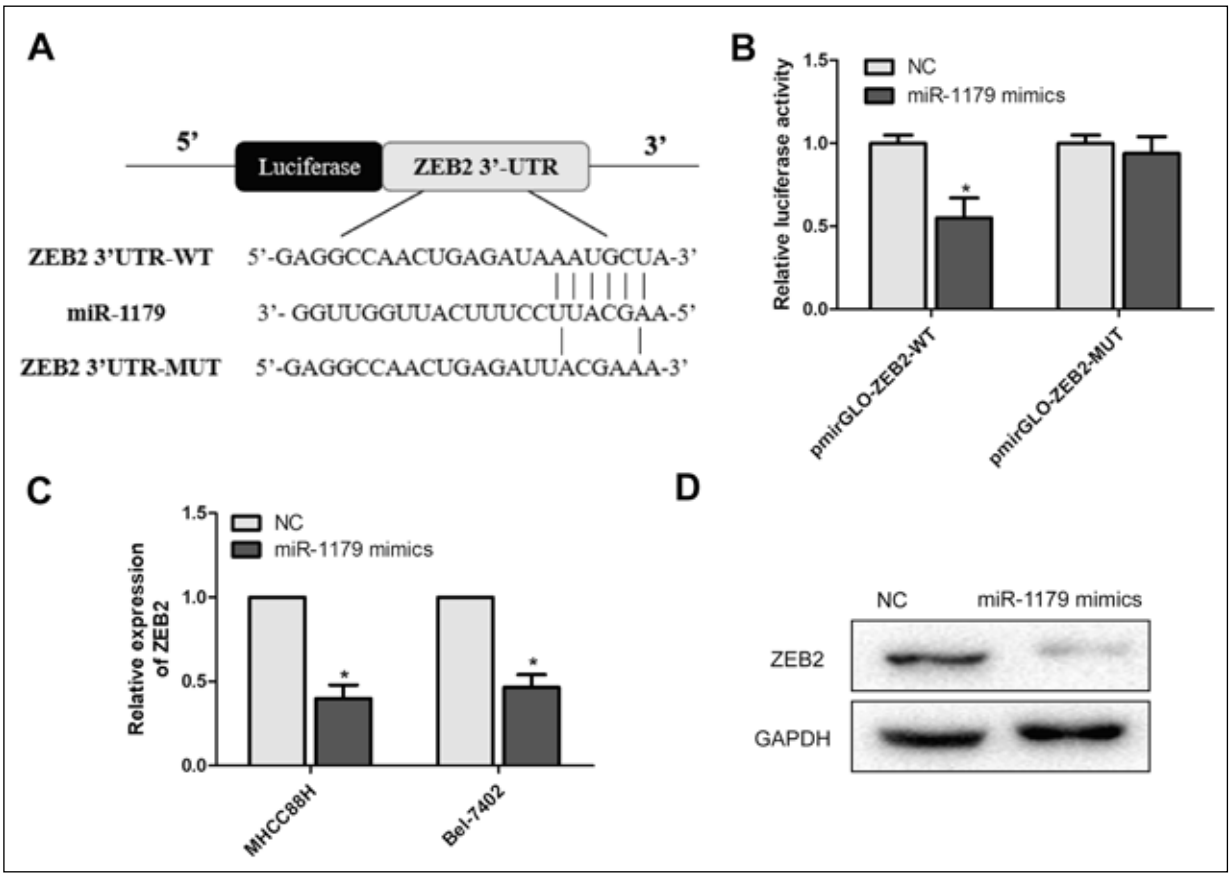


**Figure 3.** MiR-1179 bound to ZEB2. *A,* The potential binding sequences between miR-1179 and ZEB2. ***B,*** The dual-luciferase reporter gene assay showed the relative luciferase activity in HepG2 cells co-transfected with miR-1179 mimics/NC and pmirGLO-ZEB2-WT/pmirGLO-ZEB2-MUT. ***C,*** The relative level of ZEB2 in HepG2 and Bel-7402 cells transfected with NC or miR-1179 mimics. ***D,*** The protein level of ZEB2 in HepG2 and Bel-7402 cells transfected with NC or miR-1179 mimics.

burden on medical expense[3,4]. The overall survival of HCC is not very satisfying, with the 5-year survival of only 30-40% or even less in some regions[5-7]. The therapeutic strategies on the advanced, recurrent, and metastatic HCC are ineffective, leading to the poor prognosis of these patients[7,8]. There are about 70-85% HCC patients diagnosed in the advanced stage, and thus, they lose the optimal opportunity to undergo radical resection[8]. More seriously, the high rate of postoperative recurrence restricts the efficacy of surgical treatment in HCC[5,8]. Hence, postoperative recurrence and metastasis are the leading factors influencing the prognosis of HCC[6,7]. It is urgent to clarify the mechanism underlying the recurrence and metastasis of HCC, so as to develop sensitive and effective therapeutic strategies.

A mature miRNA is derived from short hairpin by Dicer enzyme[9-11]. MiRNAs are differentially expressed in different tissues and developmental stages[12-15]. Plenty of miRNAs are involved in hepatitis, liver fibrosis, and liver cancer[16,17]. MiRNA-1179 is a miRNA that participates in the progression of many cancer diseases[18,19]. The vast majority of HCC originates from the uncontrolled and aggravated chronic liver diseases, and the incidence of the latter is rising nowadays[20]. This study explored the biological function of miRNA-1179 in HCC and may provide a theoretical basis for improving the prognosis of HCC. In this paper, miRNA-1179 was downregulated in HCC tissues and cell lines. Its level was markedly correlated to lymphatic metastasis and distant metastasis of HCC patients. *In vitro* experiments demonstrated the inhibitory effects of miRNA-1179 on proliferative and migratory abilities of HCC cells, verifying miRNA-1179 as a tumor suppressor in HCC.

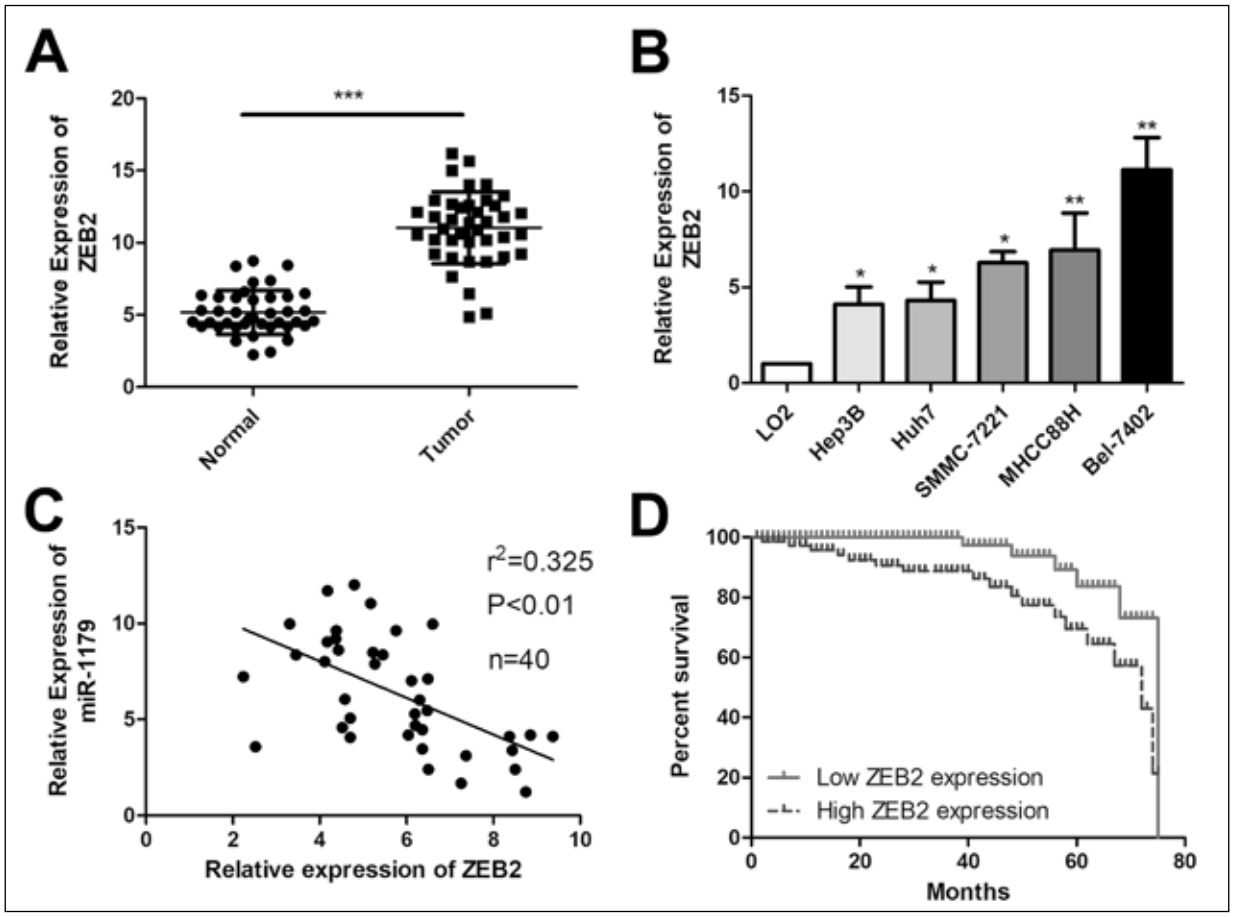


**Figure 4.** ZEB2 was upregulated in HCC. ***A,*** The relative level of ZEB2 in HCC tissues and matched normal tissues (n=40). ***B,*** The relative level of ZEB2 in HCC cell lines (Hep3B, Huh7, SMMC-7221, MHCC88H, HepG2, and Bel-7402) and normal hepatocytes LO2. ***C,*** A negative correlation between the expression levels of miR-1179 and ZEB2 in HCC tissues. ***D,*** The Kaplan-Meier curves revealed the overall survival in HCC patients with high and low expression of ZEB2.

A miRNA could negatively regulate the downstream mRNA expression by binding to it[21]. The targeted therapy based on miRNAs has been well studied in recent years[21,22]. The incidence and progression of cancers are accompanied by the changes in miRNA expression profiles[22]. Our study confirmed that ZEB2 was the target gene of miRNA-1179. ZEB2 was upregulated in HCC tissues and cell lines. High expression of ZEB2 predicted a worse prognosis of HCC. Of note, the overexpression of ZEB2 reversed the attenuated proliferative and migratory abilities in HCC cells overexpressing miRNA-1179. To sum up, miRNA-1179 alleviated the progression of HCC by binding to and negatively regulating ZEB2.

## Conclusions

We demonstrated that miRNA-1179 is closely related to lymphatic metastasis, distant metastasis, and overall survival of HCC. It alleviates the malignant progression of HCC by negatively regulating ZEB2.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

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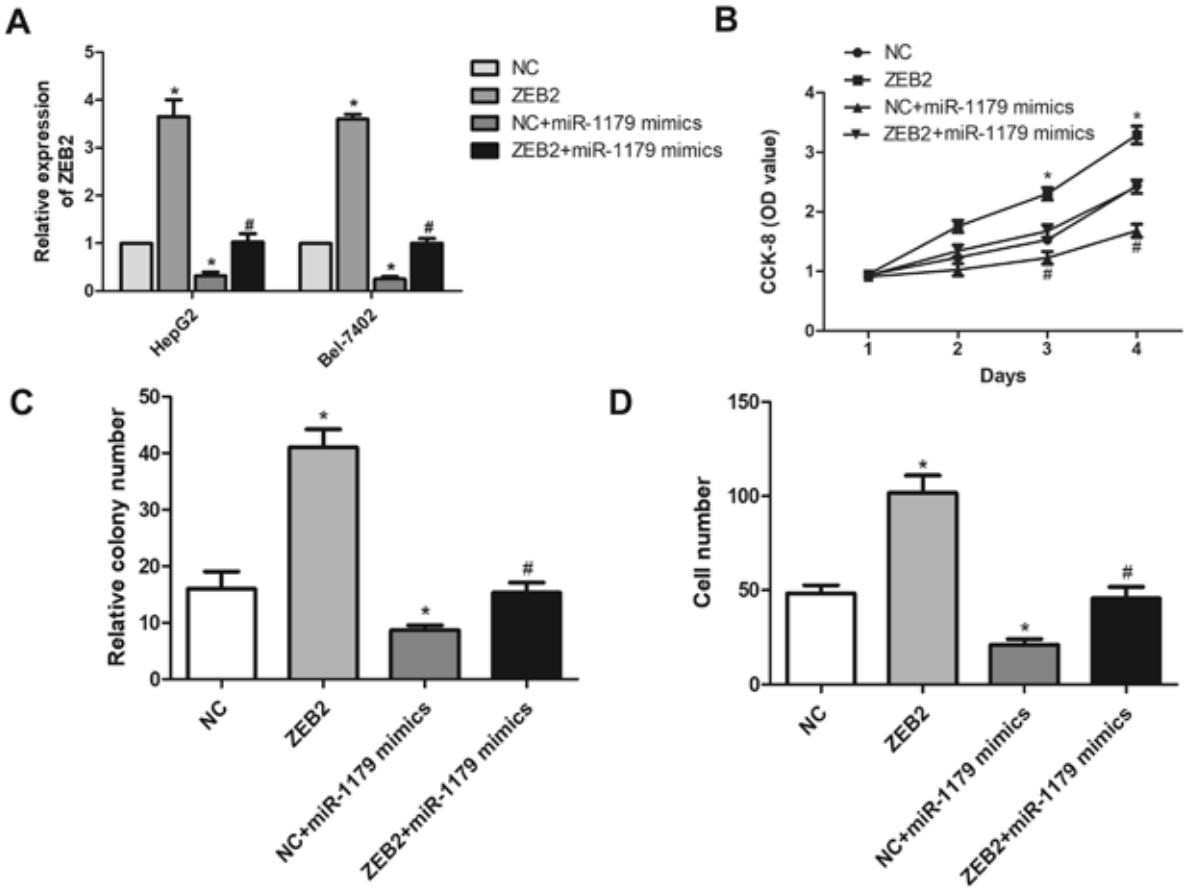


**Figure 5.** MiR-1179 regulated the cellular behaviors of HCC cells by targeting ZEB2. The cells were transfected with NC, pcDNA-ZEB2, NC+miR-1179 mimics, or pcDNA-ZEB2+miR-1179 mimics. ***A,*** The relative level of ZEB2. ***B,*** CCK-8 assay showed the viability. ***C,*** The colony formation assay showed a relative colony number. D, The transwell assay showed a migratory cell number.

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