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AEBP1 inhibition reduces cell growth and PI3K/AKT pathway while less regulates cell mobility in hepatocellular carcinoma

Liyou Liu[1], Qingshan Cai[1], Dongyang Wu[1], Shudong Li[1], Dong Liu[1] and Jianxing Zheng[1*]

Abstract

Background Adipocyte enhancer-binding protein 1 (AEBP1) regulates collagen fibrosis, extracellular matrix, and important oncogene pathways, but its regulation on hepatocellular carcinoma (HCC) is not known. This study aimed to investigate the effect of AEBP1 knockdown on HCC cell proliferation, apoptosis, migration, invasion and PI3K/AKT pathway.

Methods MHCC-97 H and Huh7 cell lines were applied. Negative control or AEBP1 siRNA (siAEBP1) were transfected into cells, and cells without transfection were set as blank control. Quantitative polymerase chain reaction (qPCR), western blot, Cell Counting Kit-8 (CCK-8), 5-Ethynyl-2′-deoxyuridine (EdU) staining, Terminal-deoxynucleotidyl Transferase Mediated Nick End Labeling (TUNEL) staining, Transwell invasion, and cell scratch assays were performed.

Results AEBP1 mRNA and protein expressions were lower after siAEBP1 transfection in MHCC-97 H and Huh7 cells. OD value of CCK-8 and EdU positive cell percentage were decreased, while TUNEL reflected cell apoptosis rate was increased, after siAEBP1 transfection in MHCC-97 H and Huh7 cells. However, invasive cell number and cell migration rate were only reduced after siAEBP1 transfection in Huh7 cells but not in MHCC-97 H cells. Expressions of p-PI3K/PI3K and p-AKT/AKT were downregulated after siAEBP1 transfection in MHCC-97 H and Huh7 cells. Subsequent rescue experiment revealed that th activation of PI3K/AKT pathway by 740Y-P attenuated the effect of siAEBP1 transfection in MHCC-97 H and Huh7 cells.

Conclusion AEBP1 exhibits the potency to be a target for HCC treatment, reflected by its regulation on HCC proliferation, apoptosis and PI3K/AKT pathway, but its effect on HCC invasion and migration seems limited.

Keywords AEBP1, Hepatocellular carcinoma, Proliferation and apoptosis, Invasion and migration, PI3K/AKT pathway

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Introduction

Liver cancer ranks as one of the most common and fatal cancers, presenting with 865,269 new cases and 757,948 new deaths annually over the world, and predominantly 367,700 new cases and 316,500 new deaths annually in China [1–3]. As the majority type of liver cancer, hepatocellular carcinoma (HCC) is usually diagnosed at a late stage that losing the chance for radical treatment [4, 5]. Besides, systemic chemotherapy lacks enough efficiency therefore not commonly applied in the late-stage HCC patients, highlight the role of target agents such as sorafenib, lenvatinib, and apatinib [6–9]. Consequently, seeking for novel targets to improve the treatment of HCC is essential.

Adipocyte enhancer-binding protein 1 (AEBP1), as a controller of collagen fibrosis process, is implicated in the production of the extracellular matrix, and modifies MAP-kinase activity, phosphorylation of I-kappa-B-alpha, and PI3K/AKT pathway to participate in a vary of disease pathogenesis [10–13]. Apart from that, AEBP1 is found to promote cancer progression: it promotes breast cancer proliferation, migration, invasion, and activates ERK, Smad2/3, and AKT signaling [14], its knockdown represses papillary thyroid cancer growth, invasiveness and epithelial-mesenchymal transition (EMT) [15]; besides, its inhibition by a parthenolide-derived ACT001 restrains glioblastoma stem cell proliferation and sphere-formation ability via inactivating PI3K/AKT pathway [16]. Recently, a systemic review collected the published evidences and reported AEBP1 serving as a novel oncogene [17]. Regarding HCC, only a clinical study revealed that AEBP1 was upregulated in HCC tissues compared to normal liver tissues [18]. However, the regulation of AEBP1 on HCC cellular functions is not discovered.

This study investigated the effect of AEBP1 knockdown on HCC cell proliferation, apoptosis, migration, invasion and PI3K/AKT pathway, aiming to provide some evidence for the potency of AEBP1 as a target for HCC.

Methods

Cell culture

The HCC cells, including MHCC-97 H (iCell-h143) and Huh7 (iCell-h080), were bought from iCell (Shanghai, China). Dulbecco's Modified Eagle Medium (G4511, Servicebio, China) comprising 10% fetal bovine serum (G8802, Servicebio, China) was adopted for culture. Cells were cultivated at 37 °C under 5% CO_2 and appropriate humidity.

SiRNA transfection

The siRNA (GenePharma, China) was used to inhibit the expression of AEBP1 in the MHCC-97 H and Huh7 cells. The sequence of negative control siRNA (siNC) and AEBP1 siRNA (siAEBP1) was listed (5'-3'): siNC (sense, UUCUCCGAACGUGUCACGUTT; antisense, ACGUGACACGUUCGGAGAATT) and siAEBP1 (sense, CCACACUGGACUACAAUGATT; antisense, UCAUUGUAGUCCAGUGUGGTT). The cells were seeded into 6-well plates and cultivated to 50% confluence. Then, the transfection working solution containing siRNA (75 pmol), transfection buffer (42.5 μL), siRNA-mate plus (7.5 μL) (G04026, GenePharma, China), and medium (2 mL) was added to cells. The cells were divided into three groups: Control, siNC, and siAEBP1 groups. Briefly, the siNC group and siAEBP1 group were transfected with negative control or AEBP1 siRNA. The cells without transfection were set as the Control group. After 48 h of culture, the cells were used for quantitative polymerase chain reaction (qPCR), western blot, Cell Counting Kit-8 (CCK-8), 5-Ethynyl-2'-deoxyuridine (EdU) staining, Terminal-deoxynucleotidyl Transferase Mediated Nick End Labeling (TUNEL) staining, Transwell invasion, and cell scratch assays.

qPCR

RNA extraction solution (G3013, Servicebio, China) was added to lyze cells. Total RNA was isolated according to the kit's protocol. For the qPCR assay, reverse transcription and qPCR program was accomplished via RT-qPCR kit (G3352, Servicebio, China). The following primers were used (5'-3'): AEBP1 (forward: GAGGAGTTGGAGGAGGAGTGGAC, reverse: AGGAGGCTCGGATCTGGTTGTC) and GAPDH (forward: GAAAGCCTGCCGGTGACTAA, reverse: GCCCAATACGACCAAATCAGAGA).

Western blot

MHCC-97 H and Huh7 cells were harvested and lysed in the protein isolation solution (G2002, Servicebio, China) for 30 min. The protein quantitative kit (G2026, Servicebio, China) was adopted to assess the concentration of protein. Following that, electrophoresis and membrane transfer experiments were performed. Membranes were blocked with non-fat milk (GC310001, Servicebio, China), and incubated with antibodies against AEBP1 (DF2427), p-PI3K (AF3242), PI3K (AF6241), p-AKT (AF0016), AKT (AF6261), or GAPDH (AF7021) (Affinity, China) for 1.5 h and secondary antibody (GB23303, Servicebio, China) for 0.5 h at room temperature (RT). Signals were visualized via a Super ECL Kit (G2020, Servicebio, China).

CCK-8

MHCC-97 H and Huh7 cells were replated into 96-well plates. After being cultivated for 0 h, 24 h, 48 h, and

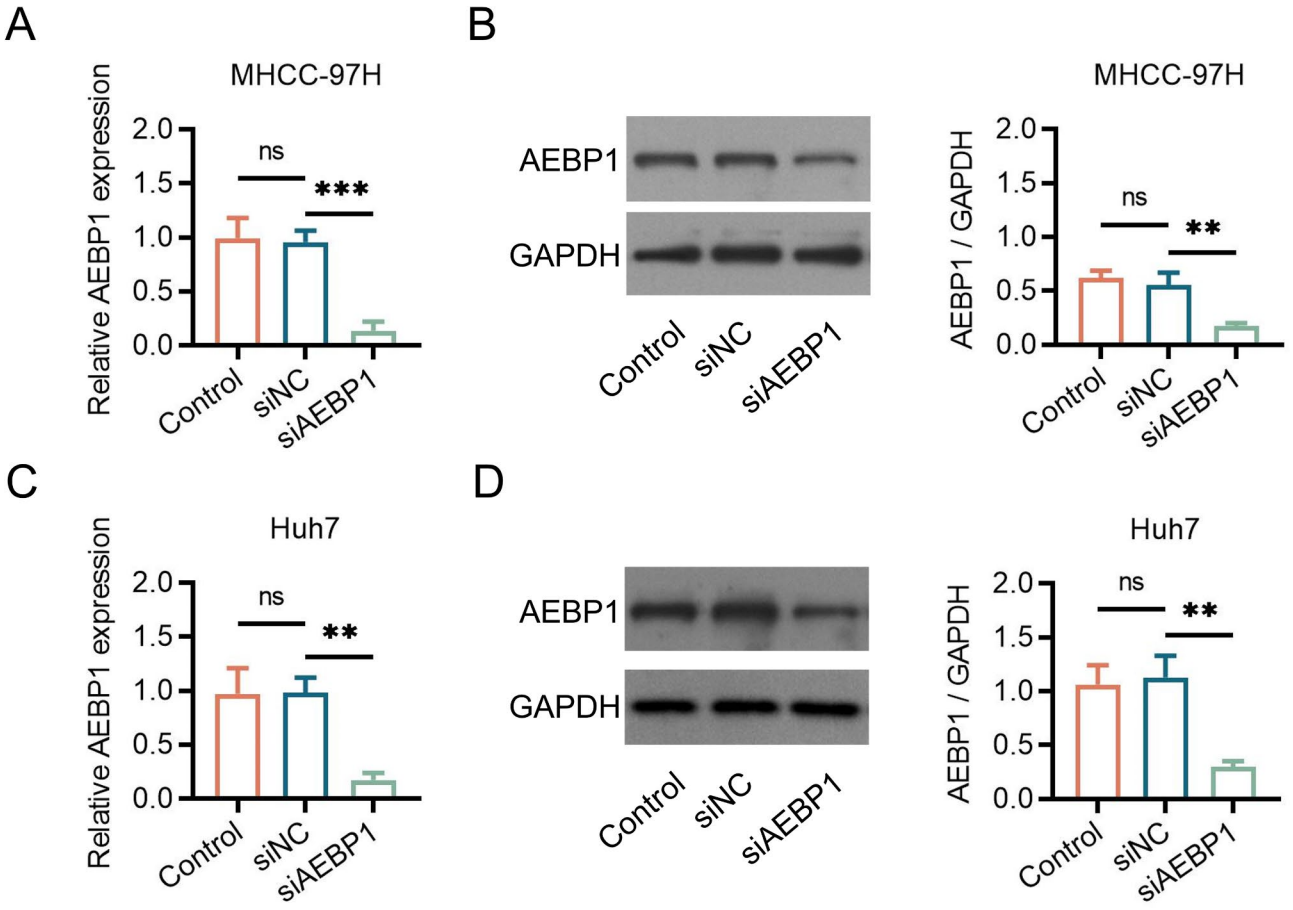

Fig. 1 Transfection efficiency. The expression of AEBP1 mRNA expression (**A**), western blot images and AEBP1 protein expression (**B**) after transfection in MHCC-97 H cells. The expression of AEBP1 mRNA expression (**C**), western blot images and AEBP1 protein expression (**D**) after transfection in Huh7 cells

72 h, cells were added with 10 μL of CCK-8 reagent (G4103, Seivicebio, China) and incubated for 2 h. Then, the microplate reader (DG5035A, Huadong Electronics, China) was adopted to assess optical density value at 450 nm (OD_{450}).

EdU staining

MHCC-97 H and Huh7 cells were treated with 10 μM of EdU staining buffer (G1601, Servicebio, China) for 2 h at RT. Next, cells were washed and blocked with 4% paraformaldehyde (P0099, Beyotime, China). The Click additive solution (G1601, Servicebio, China) was added for 15 min at RT. The 4'6-diamidino-2-phenylindole (DAPI) (HY-D0814, MCE, China) was applied for nuclei staining. The rate of EdU positive cells was evaluated under a fluorescence microscope (PX43 FS6, Motic, China).

TUNEL staining

MHCC-97 H and Huh7 cells were incubated with Triton X-100 (G1204, Servicebio, China) and fixed with 4% paraformaldehyde. The TUNEL working buffer (G1502, Servicebio, China) was prepared using the TdT enzyme, 5-dUTP labeling mix, and equilibration buffer. Subsequently, cells were treated with TUNEL working buffer for 1 h at RT. After staining with DAPI, the apoptosis rate was evaluated under the microscope.

Transwell

MHCC-97 H and Huh7 cells were cultivated in serum-free medium for 12 h, and replated to a Matrigel matrix-coated Transwell insert (No. 356234, Corning, USA) in 24-well plates. Next, 600 μL of complete medium was dispensed to the lower chamber. After incubating for 24 h, invasive cells were stained with crystal violet (G1014, Servicebio, China) and counted under the microscope.

Cell scratch

MHCC-97 H and Huh7 cells were cultivated until they reached 100% confluence. Pipette tips were applied to produce scratches. Then, cells were cultivated without serum for 24 h. Images of scratches were taken at 0 h and 24 h. The cell migration rate was determined as

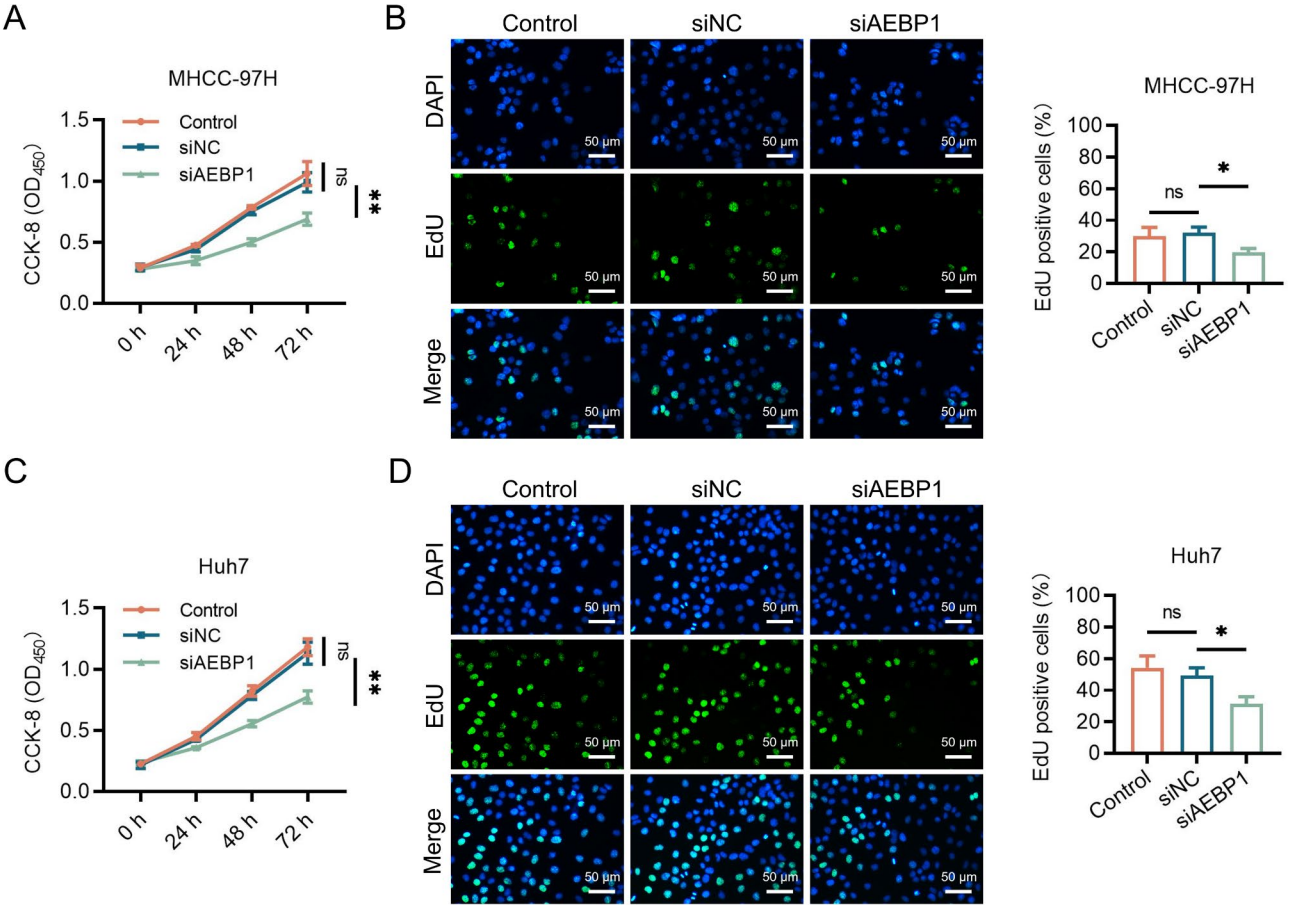

Fig. 2 Cell proliferative detection after transfection. OD value by CCK-8 at 0 h, 24 h, 48 h, and 72 h (**A**), EdU staining images and positive cell percentage (**B**) after transfection in MHCC-97 H cells. OD value by CCK-8 at 0 h, 24 h, 48 h, and 72 h (**C**), EdU staining images and positive cell percentage (**D**) after transfection in Huh7 cells

follows: (scratch area at 0 h - scratch area at 24 h) / scratch area at 0 h.

740Y-P treatment

MHCC-97 H and Huh7 cells were transfected for 48 h, then cells were replated into 96-well plates and divided into four groups: the siNC group and the siAEBP1 group were set as indicated above. The 740Y-P group was transfected with siNC and treated with 10 μM of 740Y-P (an activator of the PI3K/AKT pathway) (HY-P0175, MCE, China). The siAEBP1 + 740Y-P group was transfected with siAEBP1 and treated with 10 μM of 740Y-P. After 0 h, 24 h, 48 h, and 72 h of 740Y-P treatment, the CCK-8 assay was carried out, respectively.

Public database

Gene Expression Profiling Interactive Analysis (http://gepia.cancer-pku.cn/) was used to analyze the expression of AEBP1 in HCC tissues, its correlation with stages and prognosis in HCC patients. In addition, the Human Protein Atlas (www.proteinatlas.org) was used to show the expression location of AEBP1 in HCC tissue, and its expression level in HCC cell lines.

Statistical analysis

The experiments were performed in triplicates. To analyze differences across multiple groups, we employed one-way Analysis of Variance (ANOVA) and Tukey's test via GraphPad 9.0 software (GraphPad, USA). Statistical significance was set at P value < 0.05.

Results

AEBP1 expression after transfection

The relative expressions of AEBP1 mRNA ($P < 0.001$) and protein ($P < 0.01$) were both lower in siAEBP1 group compared to siNC group in MHCC-97 H cells (Fig. 1A-B). Similarly, both AEBP1 mRNA ($P < 0.01$) and protein ($P < 0.01$) expression were reduced in siAEBP1 group compared to siNC group in Huh7 cells (Fig. 1C-D).

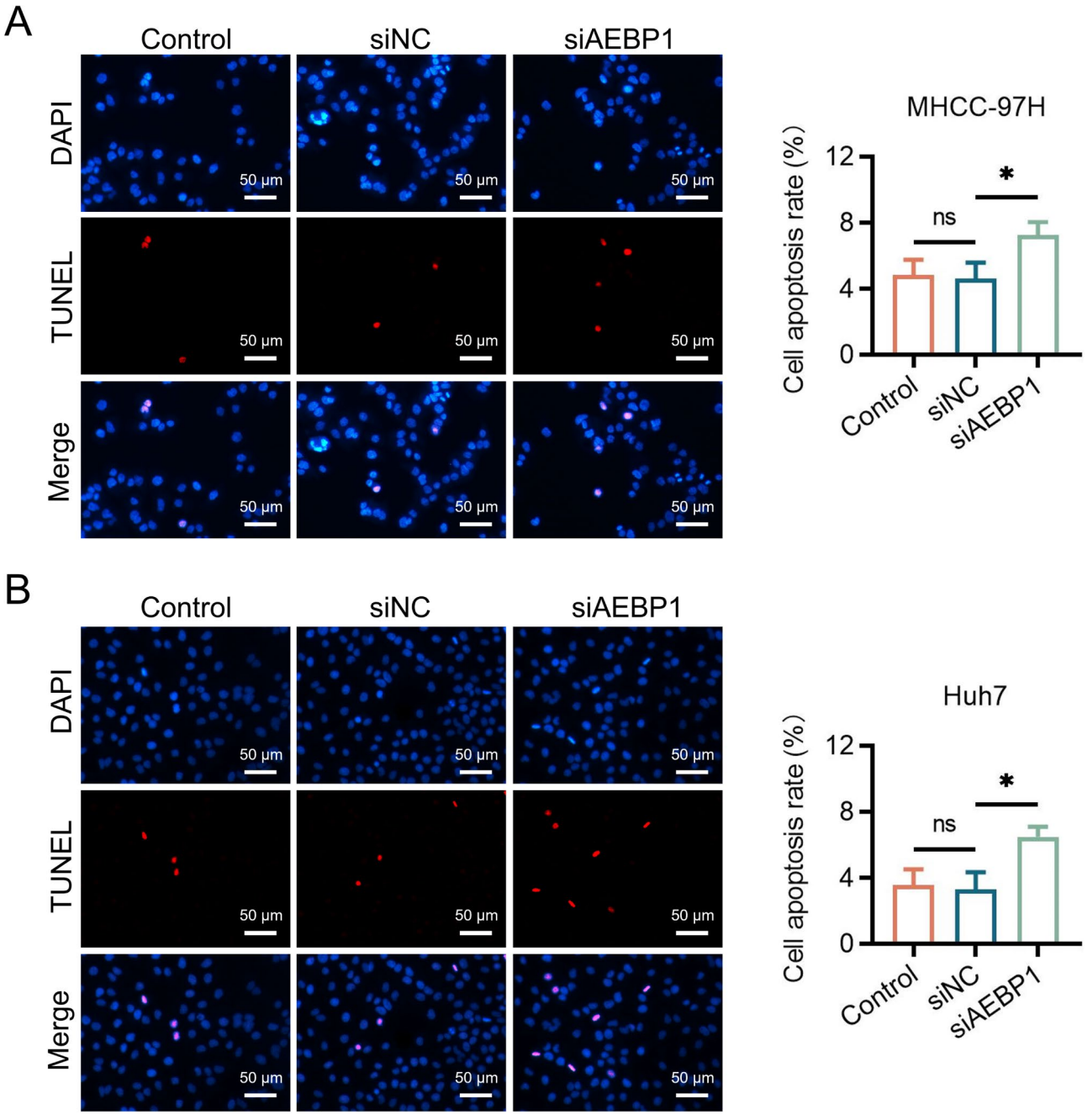

Fig. 3 Cell apoptotic detection after transfection. TUNEL images and cell apoptosis rate by TUNEL after transfection in MHCC-97 H cells (**A**) and Huh7 cells (**B**)

HCC cell proliferation and apoptosis after transfection

OD value of CCK-8 was decreased in siAEBP1 group compared to siNC group ($P < 0.01$), so did EdU positive cell percentage ($P < 0.05$) in MHCC-97 H cells (Fig. 2A-B). Regarding Huh7 cells, OD value of CCK-8 ($P < 0.01$) and EdU positive cell percentage ($P < 0.05$) were both lower in siAEBP1 group compared to siNC group (Fig. 2C-D). TUNEL assay revealed that cell apoptosis rate was higher in siAEBP1 group compared to siNC group in both MHCC-97 H cells and Huh7 cells (both $P < 0.05$, Fig. 3A-B).

HCC cell invasion and migration after transfection

Invasive cell number ($P > 0.05$) and cell migration rate ($P > 0.05$) were not statistically changed between siAEBP1 group and siNC group in MHCC-97 H cells (Fig. 4A-B). In the terms of Huh7 cells, invasive cell number ($P < 0.01$) and cell migration rate ($P < 0.01$)

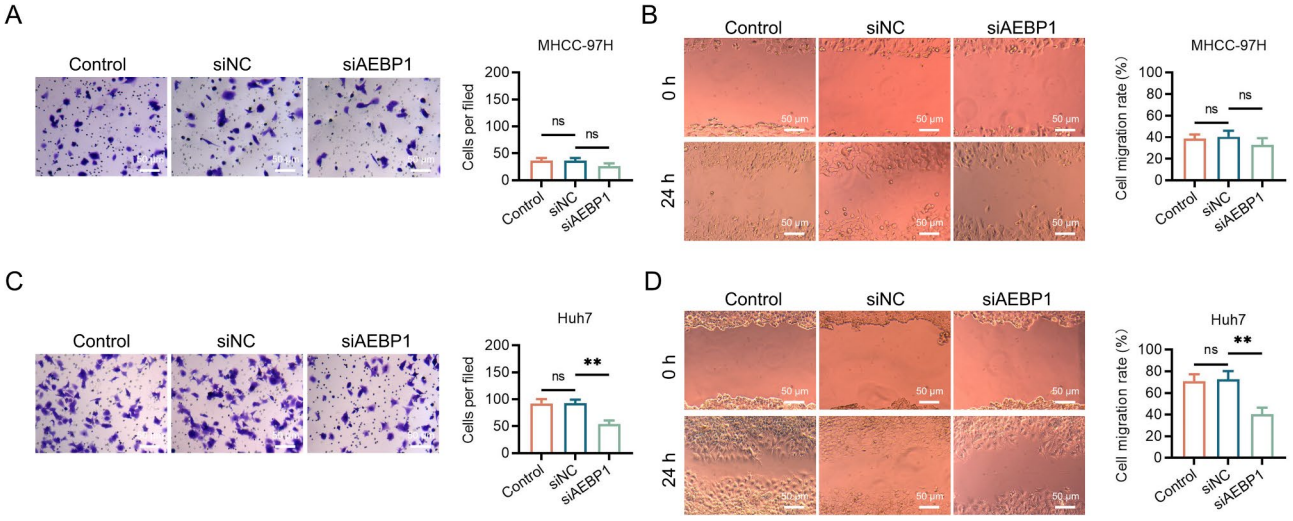

Fig. 4 Cell mobility after transfection. Transwell staining images and invasive cell count (**A**), cell scratch images and cell migration rate (**B**) after transfection in MHCC-97 H cells. Transwell staining images and invasive cell count (**C**), cell scratch images and cell migration rate (**D**) after transfection in Huh7 cells

were both lower in siAEBP1 group compared to siNC group (Fig. 4C-D).

PI3K/AKT pathway after transfection

Expressions of p-PI3K/PI3K ($P < 0.05$) and p-AKT/AKT ($P < 0.01$) were both lower in siAEBP1 group compared to siNC group in MHCC-97 H cells (Fig. 5A). Similar trends of p-PI3K/PI3K ($P < 0.05$) and p-AKT/AKT ($P < 0.05$) were observed in Huh7 cells (Fig. 5B).

Rescue experiments

The rescue experiments were performed via using 740Y-P (an activator of the PI3K/AKT pathway) treatment along with siAEBP1, to detect whether siAEBP1 functions via inactivating PI3K/AKT. OD value of CCK-8 was increased in 740Y-P group compared with siNC group ($P < 0.01$), and elevated in siAEBP1 + 740Y-P group compared to siAEBP1 group ($P < 0.001$) in MHCC-97 H cells (Fig. 6A). In addition, OD value of CCK-8 was also raised in 740Y-P group compared with siNC group ($P < 0.01$), and enhanced in siAEBP1 + 740Y-P group compared to siAEBP1 group ($P < 0.01$) in Huh7 cells (Fig. 6B).

Analysis derived from public database

According to the Gene Expression Profiling Interactive Analysis, AEBP1 expression tended to be increased in HCC tumor tissues compared to non-tumor tissues (Supplementary Fig. 1A); however, AEBP1 was not correlated with tumor stages or overall survival in HCC patients (Supplementary Fig. 1B-C). In addition, according to the Human Protein Atlas, AEBP1 was mainly expressed in cytoplasm and membrane of HCC tissues (Supplementary Fig. 1D), and its expression was highest in Huh-7 cell line among all liver cancer cell lines (Supplementary Fig. 1E).

Discussion

AEBP1 has been reported to promote cancer progression via multiple ways. For instance, AEBP1 facilitates cell viability, mobility and EMT by NF-κB signaling, and its high expression is correlated with poor differentiation, larger tumor size and lymph node metastasis in colon cancer [19]. AEBP1 can also induce glioblastoma progression both in vitro and in vivo, and its high expression predicts poor outcomes in glioblastoma patients [20]. Furthermore, AEBP1 enhances cervical cancer proliferation, migration, and invasion, and it upregulated in human cervical cancer tissues [21]. Due to the above-mentioned pro-oncogene function of AEBP1, it's recently considered to be a potential target for cancer treatment [17, 18]. Targeting AEBP1 by shRNA reduces gastric cancer growth, metastasis and EMT [22], and targeting AEBP1 by shRNA represses oral cancer growth in vitro and in vivo [23]. In addition, targeting AEBP1 by a parthenolide-derived ACT001 treatment decreases glioma stemness and viability [16]. But until the study completion, no study reports the function of targeting AEBP1 in HCC. Correspondingly, this study targeted AEBP1 by siRNA, and explored its effect on attenuating the malignant behaviors of two HCC cell lines (MHCC-97 H and Huh7). The rationale for selecting MHCC-97 H and Huh7 cells was as follows: (1) MHCC-97 H was a cell line derived from Chinese patients with HCC [24]; since the investigators of this study were in China, this cell line from Chinese patients was meaningful. (2) Via The Human Protein Atlas database (http://www.prote

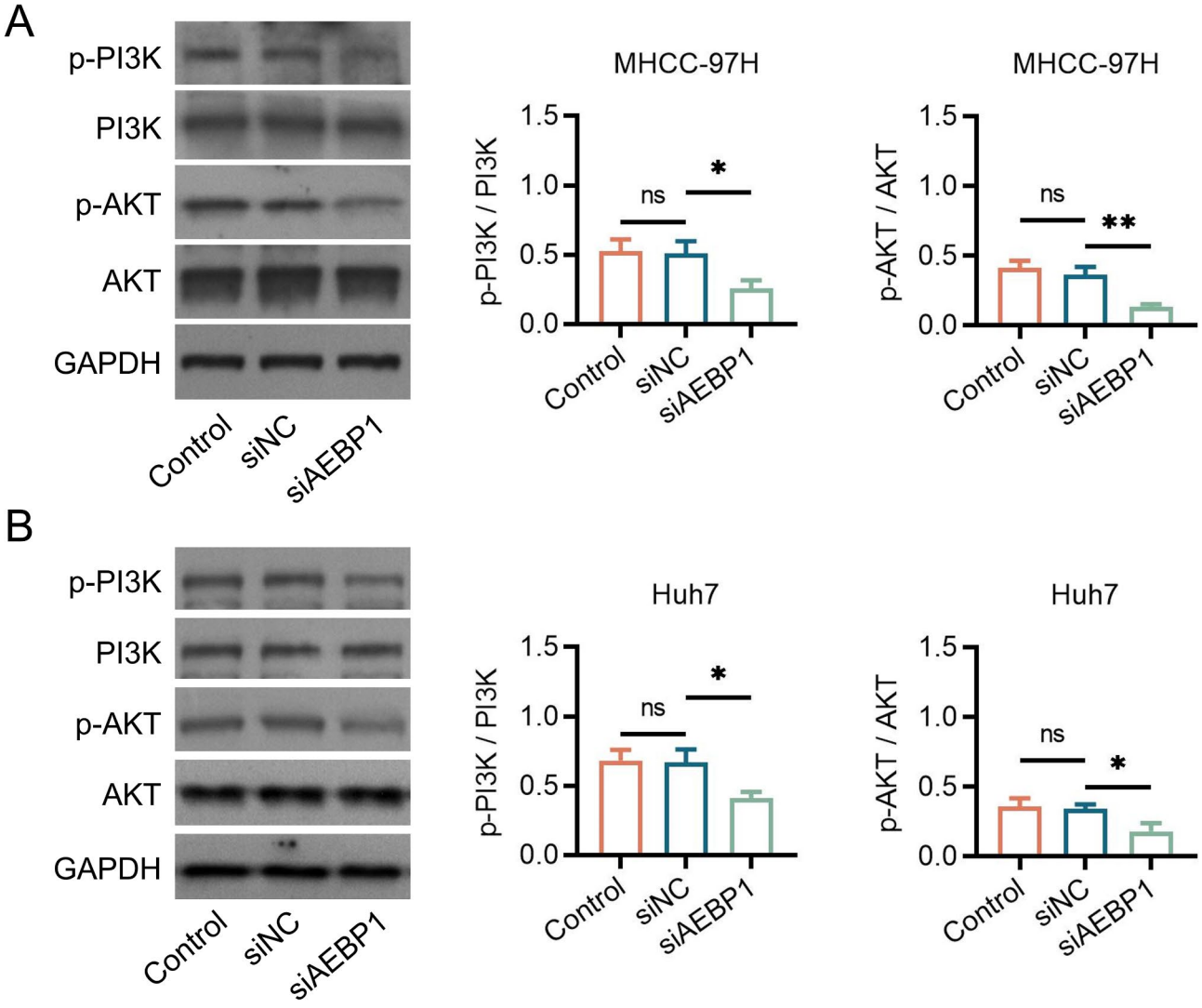

Fig. 5 PI3K/AKT pathway after transfection. Expressions of p-PI3K, PI3K, p-AKT, AKT after transfection in MHCC-97 H cells (**A**) and Huh7 cells (**B**)

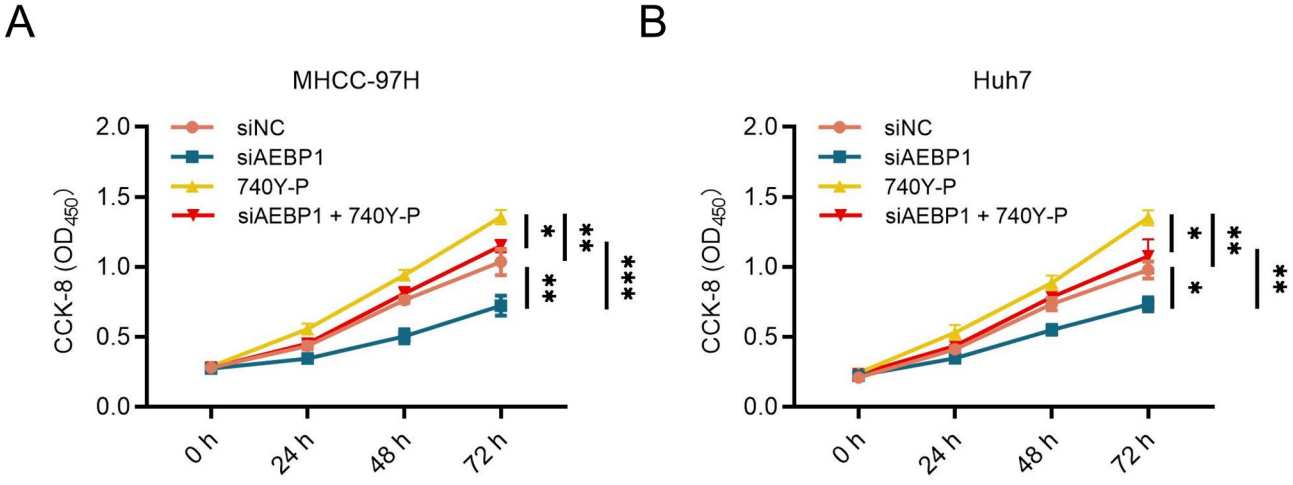

Fig. 6 740Y-P treatment. OD value by CCK-8 at 0 h, 24 h, 48 h, and 72 h after 740Y-P treatment along with or without siAEBP1 transfection in MHCC-97 H cells (**A**) and Huh7 cells (**B**)

inatlas.org/), the expression of AEBP1 was highest in Huh7 cell line among liver cancer cell lines.

CCK-8 and EdU are commonly used to detect cell proliferation, but there are some differences in their principle of action. In detail, CCK-8 is a cell proliferation reagent based on WST-8. In the presence of electron-coupled reagents, WST-8 can be reduced by dehydrogenases within mitochondria to yield an orange-yellow formazan product. The number of viable cells can be indirectly reflected by the OD value measured at 450 nm using a microplate reader. EdU is a thymidine analogue that can be incorporated into replicating DNA molecules in place of thymidine during cellular proliferation. Proliferating cells are visually detected by click chemistry with fluorescently labeled azide. This study applied these two methods (CCK-8 AND EdU) to double check the effect of siAEBP1 on HCC cell proliferation, and found that siAEBP1 could reduce the HCC cell proliferation; besides, via TUNEL assay reflection, siAEBP1 was able to elevate the HCC cell apoptosis rate. The following aspects might explain this phenomenon: (1) AEBP1 was an important factor regulating collagen fibrosis process, the latter was closely engaged in HCC development and progression [25]. (2) AEBP1 modified DNA damage to participate the regulation of cell proliferation and apoptosis [26]. (3) AEBP1 was able to regulate several well-known oncogene-related pathways, such as PI3K/AKT, NF-κB, MAP-kinase [10–14, 16, 17].

However, via Transwell and cell scratch assays, this study found that siAEBP1 lacked an enough impact on repressing cell invasion and migration in MHCC-97 H cells, who only reduced cell invasion and migration statistically in Huh7 cells. This condition indicated the effect of siAEBP1 on HCC invasion and migration was restricted to the specific HCC cell heterogeneity, therefore a solid conclusion could not be made in this study. The possible explanation was that AEBP1 mainly modified cancer cell growth via its regulation on collage fibrosis process and DNA damage [25, 26], while cell mobility was less affected.

Since previous studies have revealed the implication of PI3K/AKT pathway in the regulatory function of AEBP1 on cancer progression [14, 16, 17], this study further detected the activation of PI3K/AKT pathway after siAEBP1 transfection in HCC, which observed that siAEBP1 inactivated PI3K/AKT pathway in HCC cells. PI3K/AKT pathway is a well-known oncogene signaling in various cancers including HCC [27, 28]. For instance, the activation of PI3K/AKT pathway by 740Y-P accelerates HCC growth and metastasis both in vitro and in vivo [29]. This finding provided further explanation for the effect of siAEBP1 in HCC progression.

This study further performed rescue experiments, and observed that the activation of PI3K/AKT pathway by 740Y-P treatment enhanced both MHCC-97 H and Huh7 cell proliferation, and attenuates the effect of siAEBP1 on the cell proliferation. These implied siAEBP1 functioned via inactivating PI3K/AKT in HCC. In addition, regarding the in-depth interaction between AEBP1 and PI3K/AKT pathway, a recent review reported that [17]: (1) AEBP1 augmented PI3K/AKT pathway via TNF-α; (2) AEBP1 interacted with PI3KCB (a specific PI3K enzyme) to activate PI3K/AKT pathway; (3) AEBP1 might mediate a crosstalk between PI3K-Akt pathway and the canonical NF-κB pathway.

Conclusions

Collectively, AEBP1 exhibits the potency to be a target for HCC treatment, via its regulation on HCC proliferation, apoptosis and PI3K/AKT pathway, but its effect on HCC invasion and migration seems limited. In addition, a future study that investigate targeting AEBP1 in HCC animal models is needed for verification.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12957-025-03750-0.

Supplementary figure 1: Publica database analyses. The AEBP1 TPM between HCC tumor tissues and non-tumor tissues (**A**), the AEBP1 TPM among HCC patients with different stages (**B**), the correlation of AEBP1 expression with overall survival in HCC patients (**C**). The data in A-C were derived from the Gene Expression Profiling Interactive Analysis (http://gepia.cancer-pku.cn/). The expression location of AEBP1 in HCC tissue (**D**), and AEBP1 nTPM among liver cancer cell lines (**E**). The data in D-E were derived from the Human Protein Atlas (www.proteinatlas.org)

Supplementary Material 2

Acknowledgements

Not applicable.

Author contributions

Liyou Liu and Jianxing Zheng contributed to study design and data analysis. Qingshan Cai, Dongyang Wu, Shudong Li, Dong Liu collected the data. Liyou Liu, Qingshan Cai, Dongyang Wu, Shudong Li, Dong Liu and Jianxing Zheng wrote and revised the the manuscript. All authors read and approved the final manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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