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Original Article

miR-145 suppresses breast cancer cell migration by targeting FSCN-1 and inhibiting epithelial-mesenchymal transition

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Abstract: MicroRNAs (miRNAs), small non-coding RNAs, regulate fundamental cellular and developmental processes such as cell growth, apoptosis, migration, and invasion. In our present study, we investigated the inhibitory role of miR-145 on breast cancer cell migration as well as its underlying mechanism. Wound healing assay and transwell migration assay showed that ectopic expression of miR-145 significantly inhibited breast cancer cell migration. Bioinformatics analysis revealed that FSCN-1 was a putative target of miR-145. The expression of FSCN-1 varied among four different breast cancer cells, and inversely correlated with miR-145 levels. Moreover, miR-145 mimic transfection enhanced the expression of FSCN-1 in Bcap-37 and HCC-1937 cells. We also found that siRNA- mediated down-regulation of FSCN-1 inhibited cell motility in breast cancer cells. In addition, we found that up-regulation of miR-145 blocked EMT and decreased the expression of MMP-2/9 in breast cancer cells. These results reveal a new link between miR-145, FSCN-1 and EMT in the regulation of breast cancer migration.

Keywords: Breast cancer, migration, miR-145, FSCN-1, epithelial-mesenchymal transition

Introduction

Breast cancer has been remained as a highly malignant tumor among women, posing a serious threat to women health worldwide. It has become the leading cause of cancer death among females, accounting for 23% of the total cancer cases and 14% of the cancer deaths [1]. In recent years, significant progress has been achieved in surgical techniques and chemotherapy regimens. However, relapse remains almost inevitable in patients with advanced breast cancer [2]. Thus, it is critical to explore the underlying molecular mechanism of cancer pathogenesis.

Recent discoveries of microRNAs (miRNAs) have greatly advanced our knowledge of disease pathogenesis. MiRNAs are a novel class of regulatory non-coding RNAs that target specific mRNAs for modulation of translation and expression of a targeted protein [3-5]. Several studies have demonstrated that the expression level of miR-145 is reduced in various human cancers such as ovarian carcinoma, prostate cancer, and colorectal cancer [6-8]. Documented effects of miR-145 include inhibition of tumor growth, stimulation of tumor apoptosis, and regulation of cancer stemness [9, 10]. In breast cancer, miR-145 was reported to suppress tumor cells migration through down-regulation of junctional adherin molecule A (JAMA), fascin and mucin1 [11, 12]. However, to date, the precise role of miR-145 in breast cancer tumorigenesis is incompletely understood.

Metastasis, which is the cause of most mortality in cancer patients, is a multi-step process, including tumor cells detachment from the primary sites, migration along the circulation, extravasation to the secondary sites, and proliferation the disease [13]. Furthermore, epithelial-mesenchymal transition (EMT) has been shown to play a critical role during the initiation

stage of metastasis [14]. In the current study, we aimed to investigate the relationship between miR-145 and EMT-mediated cell migration in breast cancer.

Materials and methods

Cell culture and siRNA transfection

Human breast cancer cell lines including Bcap-37, HCC-1937, MDA-MB-231 and MDA-MB-486 were purchased from the ATCC (Manassas, VA, USA) and cultured in DMEM (Gibco, Carlsbad, CA, USA) supplemented with 10% FBS and 1% penicillin/streptomycin. All cells were maintained at 37°C in 5% CO_2 incubator. The miR-145 mimics, small interfering RNA for FSCN-1 (FSCN-1 siRNA), and their respective controls were purchased from GenePharma (Shanghai, China). Cells were transfected with indicated miRNAs using Lipofactamine 2000 reagent (Invitrogen, USA) according to the manufacture's protocol. 48 h after transfection, cells were harvested for further assays.

Wound healing assay

Breast cancer cells were seeded into six-well plates and cultured until almost totally confluent. Then, monolayer cells were scraped to generate artificial wounds with a sterile pipette tip, and the wound distances were measured at 0 and 48 h under the microscope.

Migration assay

Cells at the density of 1.0×10^5 were harvested and added into the upper chamber of Transwell chambers with polycarbonate membranes (8-μm-pore-size, Corning) for migration assay after transfection. 48 h later, the migrated cells were fixed, stained, and counted under an inverted microscope.

Quantitative real-time PCR (qRT-PCR)

RNA was extracted from breast cancer cells with Trizol reagents (Invitrogen, USA) according to the manufacturer's protocol. Total RNA was used to perform reverse transcription by One Step PrimeScript miRNA cDNA Synthesis Kit (Takara). Real-time PCR was performed with the SYBR green Premix Ex Taq II (Takara) with StepOne Plus Real-Time PCR System (Applied Biosystems) with U6 or GAPDH used as the endogenous control.

Western blot analysis

Cells were lysed and protein concentration was quantified with Pierce BCA Protein Assay Kit (Thermo). Protein samples were separated by 10% SDS-PAGE and transferred to polyvinylidene difluoride (PVDF) membranes (Millipore, Billerica, MA, USA). Membranes were blocked with 5% fat-free milk, and incubated with primary antibodies (anti-FSCN-1, anti-MMP-2/9, anti-E-cadherin, anti-Vimentin and anti-N-cadherin antibodies, Cell Signaling Technology, USA) followed by secondary antibody (Sigma). The signals were determined using an enhanced chemiluminescence, and the anti-GAPDH or anti-β-actin antibodies were used as a loading control.

Immunofluorescence

HCC-1937 and Bcap-37 cells were seeded into 48-well plates at 6.0×10^3 cells/well. Cells were fixed with 4% formaldehyde for 15 min, washed with PBS, treated with 5% BSA for 30 min at room temperature. Then cells were incubated with mouse anti-human Vimentin or anti-human E-cadherin primary antibodies (Cell Signaling Technology, USA) at 4°C overnight followed by goat anti-mouse FITC-conjugated secondary antibody (Abcam). Finally, cells were incubated with DAPI (Sigma-Aldrich) and observed under an inverted fluorescence microscope (Olympus, Tokyo, Japan).

Statistical analysis

Each experiment was performed in triplicate, and repeated at least three times. All the data were presented as means ± SD and treated for statistics analysis by SPSS program. Comparison between groups was made using ANOVA and statistically significant difference was defined as $P<0.05$.

Results

Overexpression of miR-145 suppresses breast cancer cell migration

Firstly we explored the inhibitory effects of miR-145 on the migratory ability of breast cancer cells by wound healing assay and transwell migration assay. Two breast cancer cells including Bcap-37 and HCC-1937 were transfected with miR-145 mimic or mock. Wound-healing assay showed that miR-145 mimic obviously suppressed the migratory ability of Bcap-37

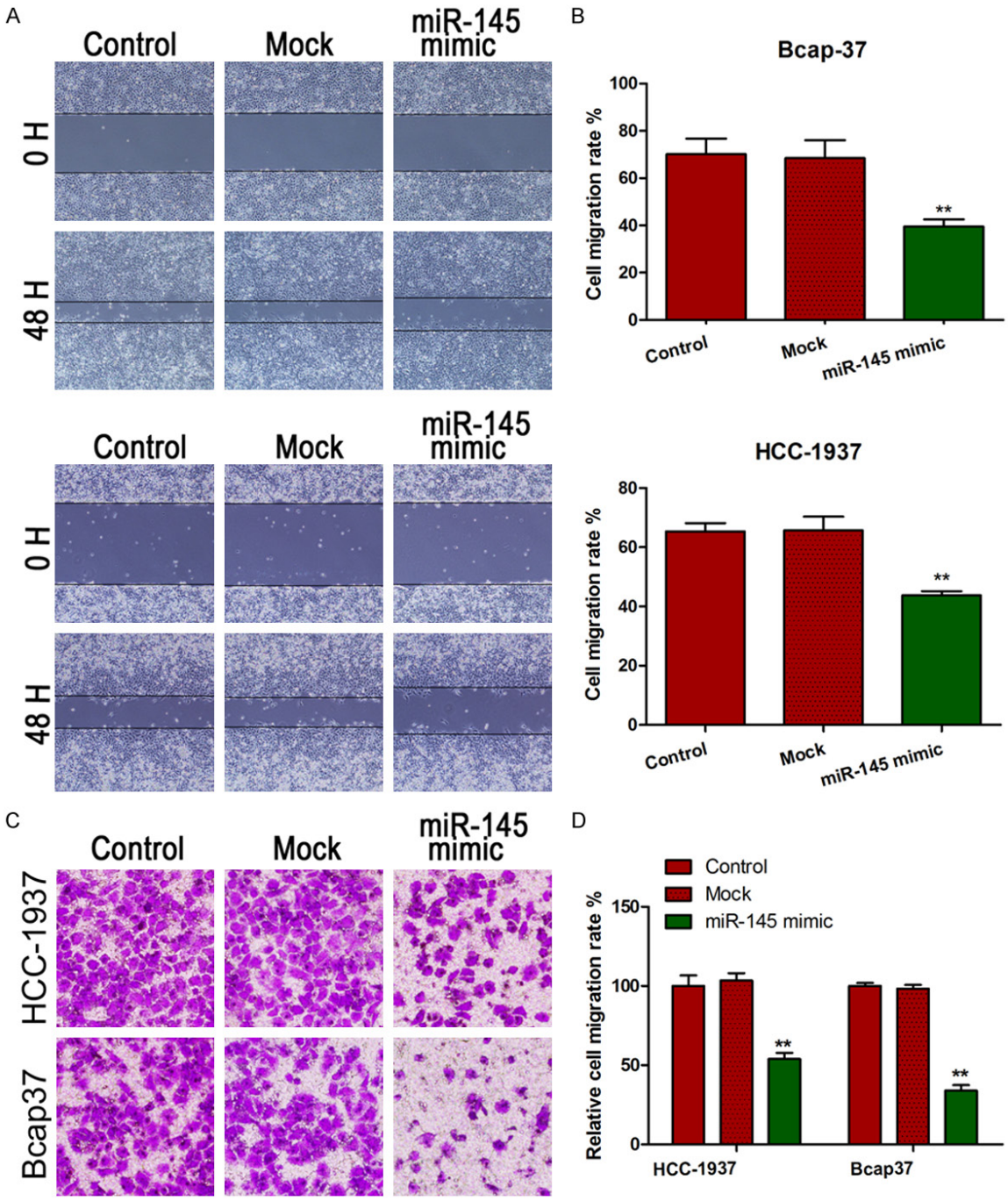

Figure 1. Overexpression of miR-145 inhibits breast cancer cell migration. Representative photographs (A) and quantification (B) of the wound healing assay with Bcap-37 and HCC-1937 cells transfected with miR-145 mimic or miRNA control. Representative photographs (C) and quantification (D) of the Transwell migration assay with cap-37 and HCC-1937 cells transfected with miR-145 mimic or miRNA control. ** $P < 0.01$ compared with control.

and HCC-1937 cells (**Figure 1A** and **1B**). The transwell migration assay further validated that overexpression of miR-145 dramatically inhibited breast cancer cells migration (**Figure 1C** and **1D**). These results suggested that up-regulation of miR-145 could reduce the migration ability of breast cancer cells.

miR-145 targets FSCN-1 in breast cancer cells

To investigate the mechanism by which miR-145 suppresses metastasis, bioinformatics analysis was used to identify the functional target of miR-145. There were four putative miR-145 binding sites in the 3' UTR of FSCN-1 mRNA

A

	predicted consequential pairing of target region (top) and miRNA (bottom)	seed match
Position 116-123 of FSCN1 3' UTR hsa-miR-145	5' ...CCCCCUUGCCUUUCA-AACUGGAA... 3' UCCCUAAGGACCCUUUUGACCUG	8mer
Position 377-384 of FSCN1 3' UTR hsa-miR-145	5' ...CUGGGCGUGUAGUGUAACUGGAA... 3' UCCCUAAGGACCCUUUUGACCUG	8mer
Position 729-735 of FSCN1 3' UTR hsa-miR-145	5' ...UUUCACCCUAGCCUGACUGGAAG... 3' UCCCUAAGGACCCUUUUGACCUG	7mer-1A
Position 1140-1147 of FSCN1 3' UTR hsa-miR-145	5' ...AUGAUAGUAGCUUCAAACUGGAA... 3' UCCCUAAGGACCCUUUUGACCUG	8mer

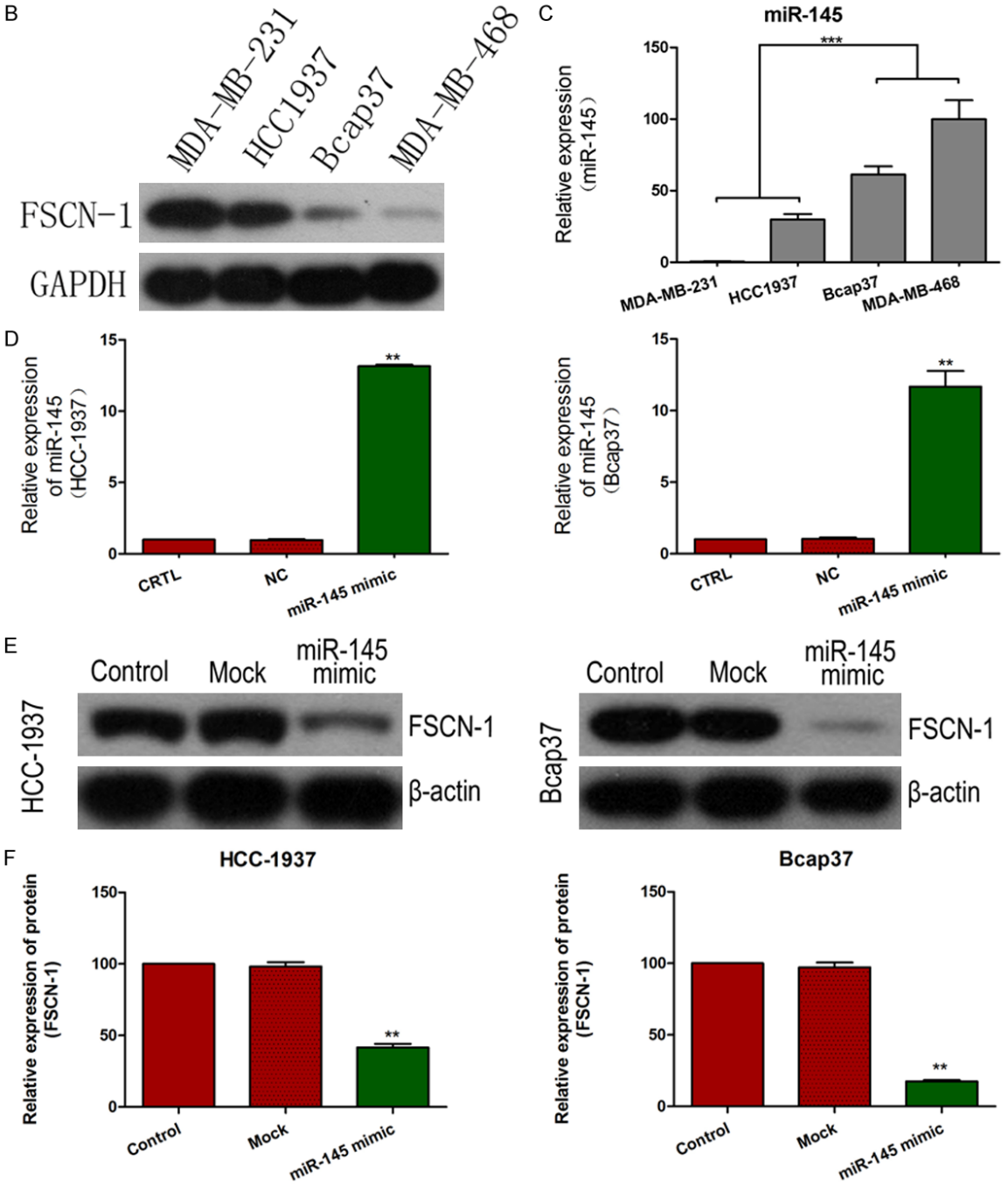

Figure 2. FSCN-1 is a direct target of miR-145 in breast cancer cells. (A) Putative binding sites of miR-145 in the 3' UTR of FSCN-1 mRNA. (B) Protein expression of FSCN-1 in MDA-MB-231, HCC1937, Bcap37 and MDA-MB-486 cells. (C) Negative correlation between miR-145 and FSCN-1. (D) Ectopic expression of miR-145 in Bcap-37 and HCC-1937 cells. Representative photographs (E) and quantification (F) of FSCN-1 protein expression in HCC-1937 and Bcap-37 cells transfected with miR-145 mimic or miRNA control. ** P < 0.01, *** P < 0.001 compared with control.

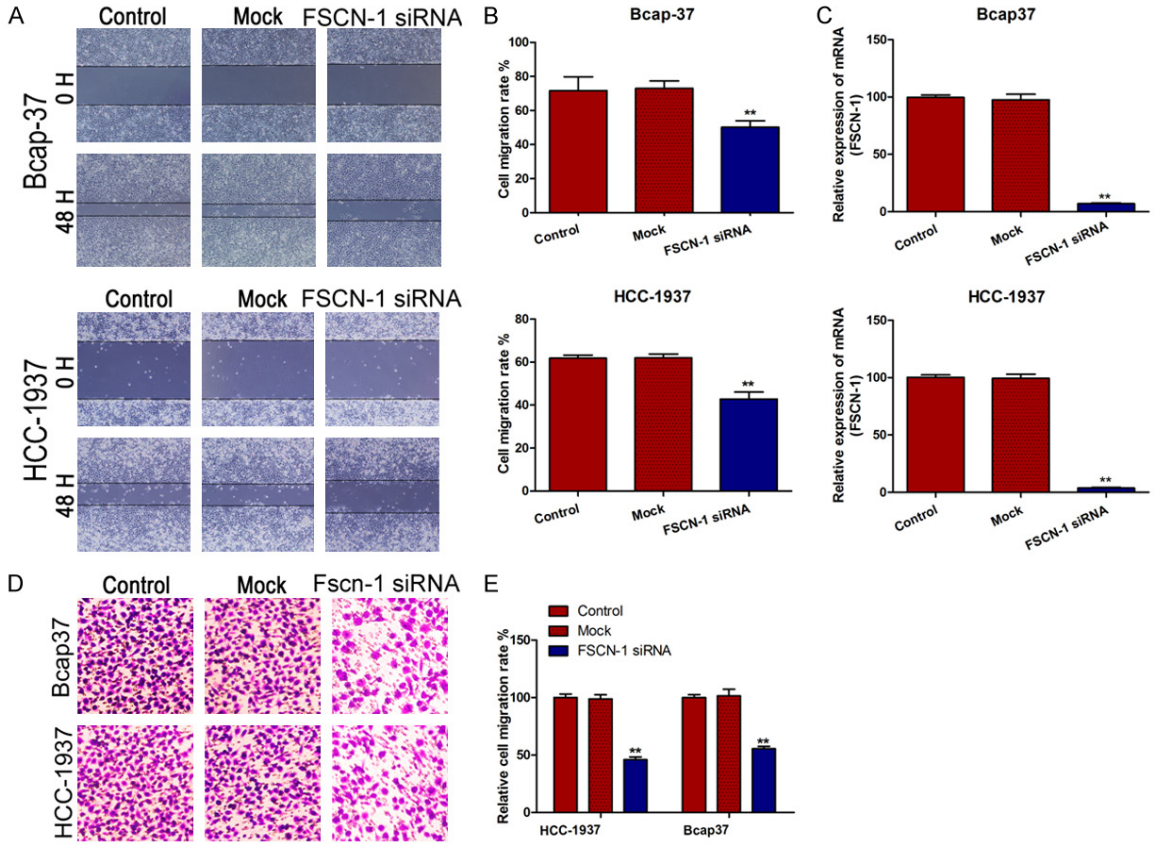

Figure 3. FSCN-1 is involved in the breast cancer migration. Representative photographs (A) and quantification (B) of the wound healing assay with Bcap-37 and HCC-1937 cells transfected with FSCN-1 siRNA. (C) Relative mRNA expression of FSCN-1. (D) Representative photographs and quantification (E) of the Transwell migration assay with Bcap-37 and HCC-1937 cells transfected with FSCN-1 siRNA. ** P < 0.01 compared with control.

(**Figure 2A**). We next measured the protein expression of FSCN-1 in four different breast cancer cell lines by western blot. Results showed that the FSCN-1 was differently expressed in MDA-MB-231, HCC1937, Bcap37 and MDA-MB-486 cells (**Figure 2B**). In addition, there was a negative correlation between miR-145 and FSCN-1 in breast cancer cells (**Figure 2C**). Next, miR-145 was up-regulated in Bcap-37 and HCC-1937 cells after transfection with miR-145 mimic (**Figure 2D**). As a result, the protein expression of FSCN1 was significantly reduced in Bcap-37 and HCC-1937 cells (**Figure 2E** and **2F**), suggesting that FSCN-1 was a functional target of miR-145 in breast cancer cells.

FSCN-1 is involved in the breast cancer migration

Next we investigated whether FSCN-1 was involved in breast cancer cells migration. Bcap-37 and HCC-1937 cells were transfected with FSCN-1 siRNA or control siRNA. Data from qRT-PCR showed that mRNA expression of FSCN-1 was significantly reduced in Bcap-37 and HCC-1937 after transfection with FSCN-1 siRNA (**Figure 3C**). Wound healing assay showed that Bcap-37 and HCC-1937 cells transfected with FSCN-1 siRNA migrated slower than cells transfected with control siRNA (**Figure 3A** and **3B**). In addition, down-regulation of FSCN-1 dramati-

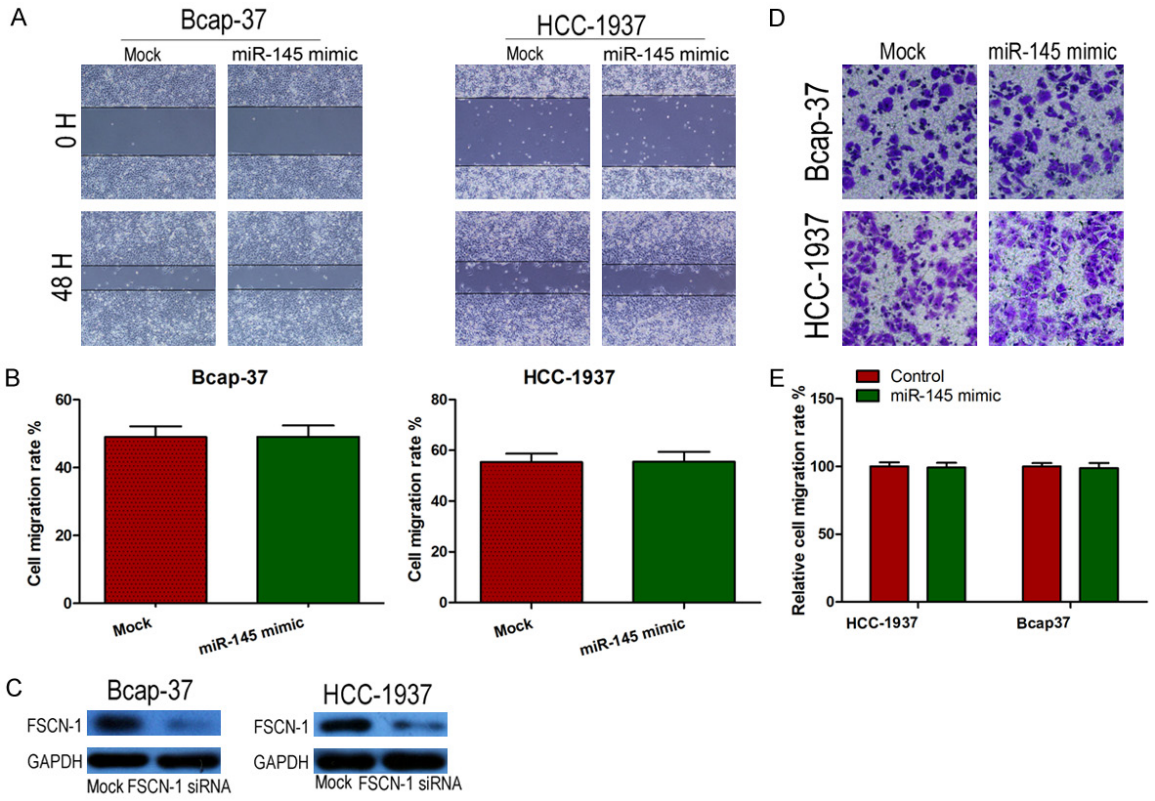

Figure 4. miR-145 inhibits breast cancer cell motility via FSCN-1. Representative photographs (A) and quantification (B) of the wound healing assay with Bcap-37 and HCC-1937 cells co-transfected with miR-145 mimic and FSCN-1 siRNA. (C) Down-regulation of FSCN-1 in breast cancer cells. (D) Representative photographs and quantification (E) of the Transwell migration assay with Bcap-37 and HCC-1937 cells co-transfected with miR-145 mimic and FSCN-1 siRNA.

cally inhibited the migratory ability of HCC-1937 and Bcap-37 cells (**Figure 3D** and **3E**). Taken together, these data demonstrated that FSCN-1 was involved in breast cancer cell migration.

miR-145 inhibits breast cancer cell motility via FSCN-1

In order to confirm the inhibitory effect of miR-145 on migration was mediated by FSCN-1, a siRNA targeting FSCN-1 was transfected into Bcap-37 and HCC-1937 cells. Western blot analysis showed that FSCN-1 siRNA efficiently decreased the expression of FSCN-1 in breast cancer cells (**Figure 4C**). Consequently, we found that siRNA-mediated knockdown of FSCN-1 diminished the suppressive migratory function of miR-145 in breast cancer cells (**Figure 4A** and **4B**). Furthermore, transwell migration assay showed that up-regulation of miR-145 failed to inhibit the migratory activity in Bcap-37 and HCC-1937 cells transfected with FSCN-1 siRNA (**Figure 4D** and **4E**). Taken together, these data demonstrated that miR-145 suppressed breast cancer cell migration via FSCN-1.

Up-regulation of miR-145 inhibits EMT in breast cancer cells

Finally, we tested the hypothesis that miR-145 inhibited cancer cell migration by blocking EMT. Western blot analysis showed that overexpression of miR-145 inhibited the expression of MMP-2 and MMP-9 in HCC-1937 and Bcap-37 cells. In addition, transfection of miR-145 into breast cancer cells blocked EMT progression by up-regulation of E-cadherin and β-catenin and down-regulation of Vimentin and N-cadherin (**Figure 5A** and **5B**). Consistently, immunostaining assay indicated that miR-145 overexpression inhibited Vimentin and promoted E-cadherin in HCC-1937 and Bcap-37 cells (**Figure 5C**). These results demonstrated that overexpression of miR-145 could reverse EMT in breast cancer cells.

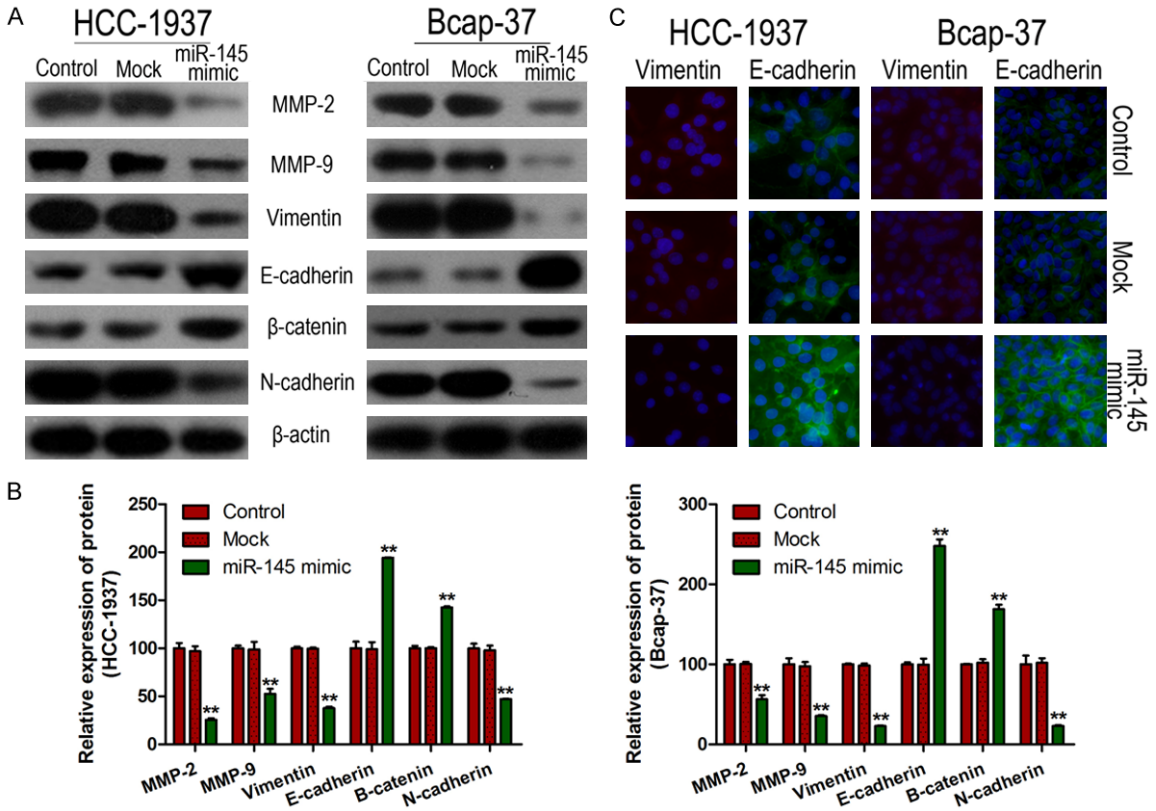

Figure 5. Up-regulation of miR-145 inhibits EMT in breast cancer cells. Representative photographs (A) and quantification (B) of protein expression including MMP-2, MMP-9, Vimentin, E-cadherin, β-catenin and N-cadherin with Bcap-37 and HCC-1937 cells transfected with miR-145 mimic. (C) Immunostaining with Vimentin and E-cadherin in HCC-1937 and Bcap-37 cells transfected with miR-145 mimic. ** $P < 0.01$ compared with control.

Discussion

In recent years, great achievements in our understanding of breast cancer pathogenesis have contributed to improved diagnostic techniques and therapeutic approach. However, the limited efficacy of novel therapeutics has become a major obstacle due to our inadequate comprehension of tumor cell signaling pathways [15]. In the present study, we demonstrated that miR-145 suppressed breast cancer cell migration via direct targeting FSCN-1 and EMT-related key regulators.

Metastasis is one of the most common features of malignant tumors, which is responsible for the majority of cancer-related deaths [16]. During the past years, investigations on genes and gene products which result in the occurrence of metastasis have been conducted [17]. Nevertheless, the molecular mechanisms underlying tumorigenesis are still not elucidated. In addition to genetic alteration, miRNAs also take part in the regulation of cancer pathological processes, especially tumor metastasis [18]. Previous studies indicated that miR-145 was decreased in various human cancers and may serve as a prognostic marker in cancer patients [19, 20]. In breast cancer, functional investigation showed that miR-143/145 synergistically inhibited cell proliferation and invasion by targeting ERBB3 [21]. Dong et al demonstrated that miR-145 suppressed tumor growth and metastasis by down-regulation of metadherin in ovarian carcinoma [22]. It was also reported that miR-145 could modulate cell cycle distribution, promote apoptosis, and inhibit migration and invasion in colon cancer cells [23].

In our study, we demonstrated that overexpression of miR-145 significantly reduced the migratory activity in breast cancer cells. Moreover, FSCN-1 was identified as a functional target of miR-145. Many studies report that FSCN-1

plays diverse roles in the pathogenesis, progression, invasion, and metastasis in diverse human cancers [24, 25]. The expression of FSCN-1 is frequently up-regulated in malignancies, and is associated with tumors aggressive behavior [26]. In addition, increased FSCN-1 expression in nasopharyngeal carcinoma was correlated with poor prognosis [27]. In vitro assay demonstrated that miR-145 inhibited tumor cell motility by inhibition of FSCN-1 expression in nasopharyngeal carcinoma cells [28]. Our study showed that down-regulation of FSCN-1 inhibited cell migration in breast cancer cells. Furthermore, ectopic expression of miR-145 had no effects on the migratory ability in breast cancer cells transfected with FSCN-1 siRNA. These findings implied that FSCN-1 was involved in tumor metastasis and miR-145 suppressed breast cancer cell migration in a FSCN-1 dependent manner.

The etiology of breast cancer involves a complex interplay of various factors, of which the accumulation of oncogenes and loss of tumor repressors are crucial events in the initiation and progression of breast cancer [29]. EMT has been recognized as a critical procedure regulating the pathogenesis of breast cancer [30]. Many signaling pathways are involved in the EMT program, and a theme that has emerged is that signals from soluble extracellular factors are integrated with contextual molecules for cellular phenotype regulation [14]. Among these extracellular signals, MMPs serve as critical regulators of EMT through modulation of cell-cell and cell-ECM interactions [31, 32]. In order to test the hypothesis that miR-145's migration inhibitory effects depended on EMT, miR-145 was ectopically expressed in breast cancer cells. We found that up-regulation of miR-145 reversed EMT and inhibited the expression of MMP-2 and MMP-9 in HCC-1937 and Bcap-37 cells. Immunofluorescence assay further indicated that miR-145 mimic transfection induced expression of E-cadherin and impaired expression of Vimentin, suggesting that miR-145 may serve as one of the key blockers of EMT in breast cancer.

In conclusion, our study demonstrates that miR-145 functions as a tumor suppressor and has a suppressive role in the processes of breast cancer cell migration. Mechanically, it exerts its function by specifically inhibits the expression of FSCN-1 and EMT progression. These findings imply that miR-145 could serve as a novel therapeutic target for breast cancer therapy.

Acknowledgements

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Disclosure of conflict of interest

None.

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