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MicroRNA-152 Inhibits Cell Proliferation, Migration, and Invasion in Breast Cancer

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The aim of the present study was to investigate the roles of microRNA-152 (miR-152) in the initiation and progression of breast cancer. The expression level of miR-152 was detected in human breast cancer tissue and a panel of human breast cancer cell lines using qRT-PCR. Results found that miR-152 expression was significantly downregulated in breast cancer tissue samples compared to adjacent noncancerous tissues as well as in breast cancer cell lines. Overexpression of miR-152 significantly suppressed breast cancer cell proliferation, migration, and invasion. Luciferase reporter assay results found that ROCK1 is a direct and functional target gene of miR-152 in breast cancer. In addition, downexpression of ROCK1 could inhibit breast cancer cell proliferation, migration, and invasion. These findings indicate that miR-152 inhibited breast cancer growth and metastasis through negative regulation of ROCK1 expression. These data suggest that miR-152/ROCK1 pathway may be a useful therapeutic target for breast cancer treatment.

Key words: Breast cancer; MicroRNA-152; Growth; Metastasis; Therapy; Rho-associated protein kinase 1 (ROCK1)

INTRODUCTION

Breast cancer is the most commonly occurring cancer in women and one of the leading causes of cancer-related deaths worldwide[1]. Every year, there are approximately 1.3 million women diagnosed with breast cancer and approximately 40,000 deaths as a result[2]. Since 2008, breast cancer incidence has increased by more than 20%, and mortality has increased by 14%[3]. Currently, the primary treatments for breast cancer include surgery, hormonal therapy, cytotoxic chemotherapy, immunotherapy, and targeted therapy[4]. Although these therapies have significantly improved patient survival, they often do not result in complete eradication due to acquiring resistance, significant toxicities, or relapse following an initial response. This results in recurrence or metastasis at later stages leading to patient death[5]. A better understanding of the mechanisms involved in breast cancer progression will aid in the development of new and effective therapeutic strategies for breast cancer treatment.

MicroRNAs (miRNAs) are a class of small noncoding RNAs, typically 17–22 nucleotides in length that are known to play a critical role in gene regulation[6]. They bind to the 3 -untranslated regions (3 -UTRs) of target mRNAs with a nearly perfect complementarity, resulting in gene suppression through translational inhibition and/or mRNA destabilization[7]. A single miRNA can modulate the expression levels of hundreds of target genes and therefore play a fundamental role in a variety of biological processes, including cell growth, apoptosis, differentiation, invasion, migration, and metastasis[8–10]. Abnormal expression of miRNAs contributes to various pathologies[11–13], including breast cancer[14], bladder cancer[15], hepatocellular carcinoma[16], glioma[17], and colorectal cancer[18]. Studies have shown that miRNAs can act as oncogenes in the initiation and progression of human cancers[19] and have also been found to act as tumor suppressors[20]. Given this, miRNAs are evolving as potential therapeutic targets for cancer treatment.

In the present study, we found that the expression level of miR-152 was significantly lower in breast cancer tissue and cell lines compared to controls. Results also found that miR-152 overexpression significantly inhibited breast cancer cell proliferation, migration, and invasion in vitro. Finally, Rho-associated protein kinase 1

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(ROCK1) was identified as a direct and functional target of miR-152 in breast cancer.

MATERIALS AND METHODS

Tissue Collection

Primary breast cancer tissue and paired adjacent noncancerous tissue were collected from 32 patients undergoing surgical resection of breast cancer at the People's Hospital of Xinjiang Uygur Autonomous Region. None of the patients had been treated with hormonal therapy, cytotoxic chemotherapy, immunotherapy, or targeted therapy. All fresh tissues were washed with PBS (Gibco, Grand Island, NY, USA) before being snap frozen in liquid nitrogen and stored at −80°C before RNA extraction. This study was approved by the ethics committee of People's Hospital of Xinjiang Uygur Autonomous Region. All procedures were in accordance with the institutional guidelines, and written informed consent was obtained from all patients.

Cell Lines, Culture Conditions, and Cell Transfection

Breast cancer cell lines (MDA-MB-231, MCF-7, SKBR3, T47D, BT-549) and human breast epithelial cell lines (HBL-100) were purchased from the Institute of Biochemistry and Cell Biology of the Chinese Academy of Sciences (Shanghai, P.R. China). All the cells were cultured in DMEM (Gibco) supplemented with 10% fetal bovine serum (FBS; Gibco), and 1% penicillin–streptomycin solution (Gibco) in humidified air at 37°C with 5% CO_2.

ROCK1 siRNA, a scrambled negative control (scrambled-siRNA), miR-152 mimics, and NC were obtained from RiBoBio (Guangzhou, P.R. China). Breast cancer cells were transfected with the above oligonucleotides using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instruction.

Quantitative Real-Time PCR (qRT-PCR)

Total RNA was isolated from the tissue and cell lines using TRIzol reagent (Invitrogen) following the manufacturer's instruction. Total RNA was reversed transcribed to cDNA using M-MLV Reverse Transcription system (Promega, Madison, WI, USA). Real-time PCR for miR-152 expression was performed using SYBR green I mix (Takara, Dalian, P.R. China). To quantify ROCK1 mRNA expression, reverse transcription reaction and cDNA synthesis were performed according to the manufacturer's instructions (Promega). Real-time PCR analysis was performed using SYBR Green Real-Time Master Mix (Toyobo, Osaka, Japan). Relative quantification of miR-152 and ROCK1 mRNA was achieved by normalizing U6 and -actin, respectively.

MTT Assay

Twenty-four hours after transfection, 3,000 cells per well were seeded in 96-well plates with five replicate wells. Proliferation rates were measured at 24, 48, 72, and 96 h after incubation. Following this, 20 µl of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT; 5 mg/ml; Sigma-Aldrich, St. Louis, MO, USA) solution was added into each well and incubated at 37°C for another 4 h. Finally, 150 µl of DMSO was added following removal of the supernatant. Absorbance was detected at 490 nm using an Elx800 Reader (Bio-Tek Instruments Inc., Winooski, VT, USA). Each assay was repeated three times.

Migration and Invasion Assay

Forty-eight hours after transfection, cells were harvested for migration and invasion assays using Transwell chambers (Corning, Corning, NY, USA). For migration assays, 2×10^4 cells suspended into FBS-free culture medium were seeded into the upper chamber, while 500 µl of DMEM supplemented with 20% FBS was added into the lower chambers. After incubation at 37°C for 24 h, the cells remaining on the upper membranes were removed carefully, and the cells on the bottom of the membranes were fixed with 4% paraformaldehyde for 20 min, stained with 0.5% crystal violet for 30 min, washed with PBS, and then counted using a microscope. The invasion assays were performed the same as the migration assays except that Transwell chambers were coated with Matrigel (BD Biosciences, San Jose, CA, USA).

Western Blot

Seventy-two hours after transfection, cells were washed with PBS and lysed in RIPA buffer containing protease inhibitor. Protein concentration was determined by BCA (Pierce, Rockford, IL, USA) assay. Total proteins (20 µg) were resolved by 10% SDS polyacrylamide gels and immobilized on PVDF membranes (Millipore, Billerica, MA, USA). Membranes were then blocked with 5% nonfat dried milk in Tris-buffered saline/0.1% Tween (TBST) and incubated overnight at 4°C with the following primary antibodies: mouse anti-human monoclonal ROCK1 antibody (sc-365628; Santa Cruz Biotechnology, Santa Cruz, CA, USA) and mouse anti-human monoclonal GADPH antibody (sc-365062; Santa Cruz Biotechnology). Membranes were then washed with TBST and incubated for 1 h with goat anti-mouse IgG conjugated to horseradish peroxidase (1:5,000; Santa Cruz Biotechnology). The bands were visualized using ECL Western Blot Detection kit (Amersham Life Sciences, Piscataway, NJ, USA). GADPH was used to ensure equivalent protein loading.

Luciferase Reporter Assay

Luciferase wild-type (psiCHECK2-ROCK1-Wt 1, psiCHECK2-ROCK1-Wt 2) or mutant reporter vectors (psiCHECK2-ROCK1-Mut 1, psiCHECK2-ROCK1-Mut 2) were synthesized by GenePharma (Shanghai, China). For luciferase reporter assays, HEK293T cells of

60%–70% confluence in 24-well plates were transfected with luciferase reporter vectors along with miR-152 mimics or NC using Lipofectamine 2000, according to manufacturer's instruction. After incubation for 48 h at 37°C, luciferase activity was determined using Dual-Luciferase Reporter Assay system (Promega). Firefly luciferase activity was normalized to *Renilla* luciferase activity. All experiments were performed a minimum of three times.

Statistical Analysis

All data were expressed as mean ± SD. Statistical analysis was performed using SPSS 17.0 software (SPSS, Inc, Chicago, IL, USA). A value of $p < 0.05$ was considered statistically significant.

RESULTS

miR-152 Was Downregulated in Breast Cancer

Results found that the expression of miR-152 was significantly reduced in breast cancer tissue compared with adjacent noncancerous tissues ($p < 0.05$) (Fig. 1A). Results also found that miR-152 was significantly downregulated in breast cancer cell lines (MDA-MB-231, MCF-7, SKBR3, T47D, BT-549) compared with that in HBL-100 ($p < 0.05$) (Fig. 1B). The expression of miR-152 in SKBR3 and T47D was significantly lower than in the other three cell lines. Given this, SKBR3 and T47D were selected for further study.

miR-152 Inhibited Breast Cancer Cell Proliferation, Migration, and Invasion

As a result of downregulation of miR-152 in breast cancer, it was hypothesized that miR-152 acts as a tumor suppressor in breast cancer initiation and progression. To examine this possibility, miR-152 mimics or NC were transfected into SKBR3 and T47D cells. Relative miR-152 expression after transfection was verified using qRT-PCR ($p < 0.05$) (Fig. 2A). Effects of miR-152 on breast cancer cells were assessed using MTT assay. MTT assay results found that miR-152 overexpression inhibited cell proliferation relative to NC transfection in SKBR3 and T47D cells ($p < 0.05$) (Fig. 2B). Results also showed that miR-152 overexpression decreased SKBR3 and T47D cell migration and invasion compared with NC groups ($p < 0.05$) (Fig. 2C). These results suggest that miR-152 is involved in breast cancer cell proliferation, migration, and invasion.

miR-152 Repressed Breast Cancer Cell Proliferation, Migration, and Invasion via Directly Targeting ROCK1

To uncover the molecular mechanisms by which miR-152 inhibits breast cancer cell growth and metastasis, miRanda (www.microrna.org) and TargetScan (www.targetscan.org) were used to predicate potential miR-152 target genes. Bioinformatic analysis found that ROCK1 is a target gene of miR-152 (Fig. 3A). To explore whether miR-152 modulated endogenous ROCK1 expression, qRT-PCR and Western blot were used to examine expression levels of ROCK1 in SKBR3 and T47D cells, which were transfected with miR-152 mimics or NC. Results found that miR-152 overexpression significantly decreased ROCK1 mRNA ($p < 0.05$) (Fig. 3B) and protein ($p < 0.05$) (Fig. 3C) levels in SKBR3 and T47D cells. Luciferase assay results found that miR-152 mimics significantly suppressed luciferase activity (Fig. 3D), whereas the luciferase mutant reporter vectors were not affected. This suggests that miR-152 bound directly to the predicted binding sites on the 3 -UTR of ROCK1, which the authors believe is a novel finding.

ROCK1 May Be Involved in miR-152-Induced Suppression Functions in Breast Cancer Cells

To investigate whether the suppressive roles of miR-152 in breast cancer cells were induced by ROCK1,

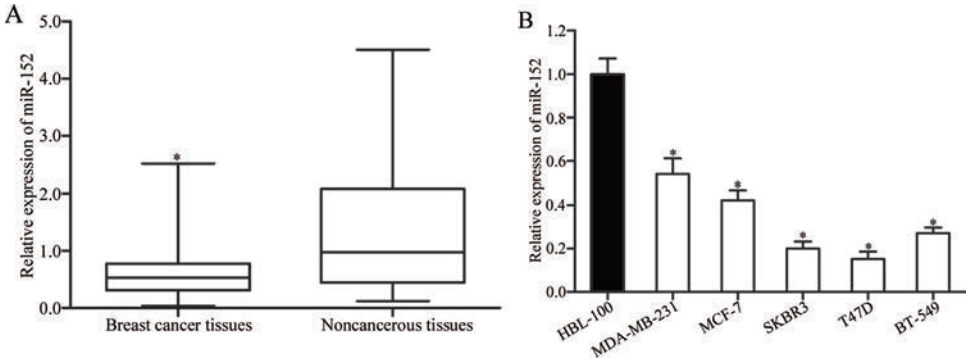

Figure 1. Quantitative real-time PCR (qRT-PCR) analysis of microRNA-152 (miR-152) in breast cancer tissues and cell lines. (A) miR-152 was significantly downregulated in breast cancer tissue compared with paired adjacent noncancerous tissue. *$p < 0.05$ compared with respective controls. (B) Expression of miR-152 in breast cancer cell lines (MDA-MB-231, MCF-7, SKBR3, T47D, BT-549) and human breast epithelial cell line (HBL-100). *$p < 0.05$ compared with respective controls.

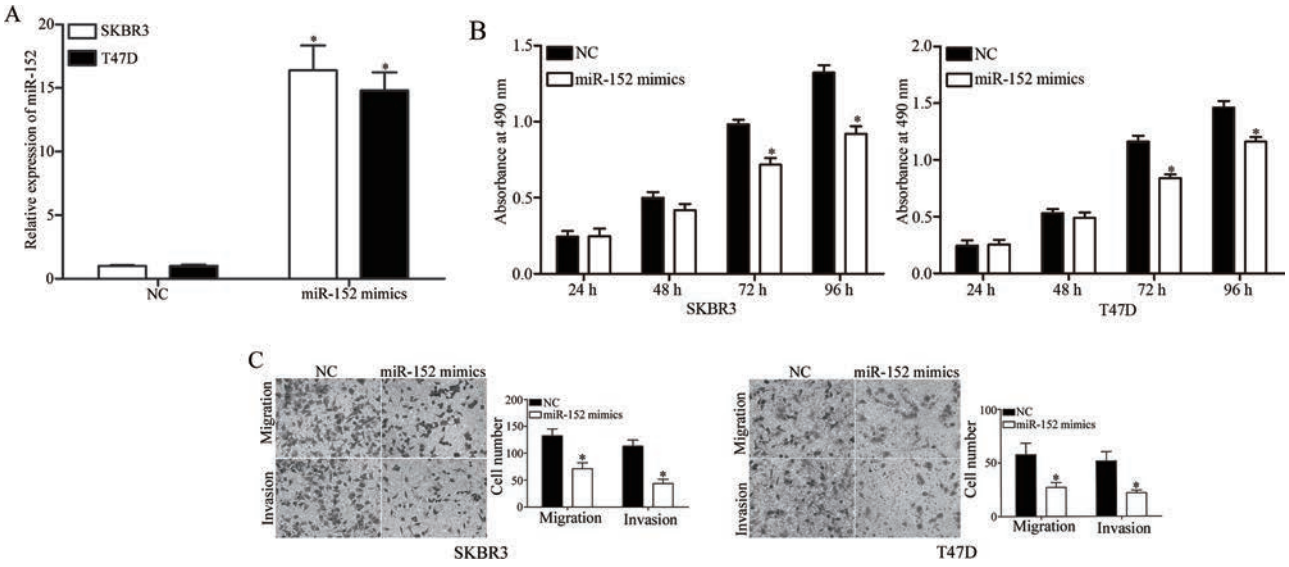

Figure 2. Restoration of miR-152 expression repressed breast cancer cell proliferation, migration, and invasion. (A) miR-152 was markedly upregulated in SKBR3 and T47D cells transfected with miR-152 mimics. (B) 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay showed that upregulation of miR-152 suppressed proliferation of SKBR3 and T47D. (C) Representative pictures of migration and invasion assays. $*p < 0.05$ compared with respective controls.

ROCK1 siRNA or scrambled-SiRNA was introduced into SKBR3 cells. Expression levels of ROCK1 mRNA were determined using qRT-PCR (Fig. 4A). Cell proliferation, migration, and invasion assay showed that ROCK1 underexpression significantly inhibited the proliferation ($p < 0.05$) (Fig. 4B), migration, and invasion ($p < 0.05$) (Fig. 4C) of SKBR3 cells, similar to those induced by miR-152 overexpression. These results indicated that ROCK1 was a functional target of miR-152 in breast cancer.

DISCUSSION

This study explored miR-152 expression in breast cancer tissue and paired adjacent noncancerous tissues. Results found that the expression of miR-152 was significantly reduced in breast cancer tissues compared with that in paired adjacent noncancerous tissues. Levels of miR-152 were also measured in five breast cancer cell lines. Results found that the breast cancer cell lines had lower miR-152 levels compared with human breast epithelial cell line. To better understand the role of miR-152 in breast cancer, miR-152 mimics were transfected into breast cancer cells. MTT assay results found that miR-152 overexpression significantly inhibited proliferation, migration, and invasion of breast cancer cells. These results indicate that miR-152 may act as a tumor suppressor in breast cancer.

The expression patterns of miR-152 have been widely reported in a number of human cancers. In gastrointestinal cancers, low expression of miR-152 was correlated with increased tumor size and advanced pT stage[21]. Li et al. reported that downregulation of miR-152 in colorectal cancer correlated with advanced tumor-node-metastasis stage and lymph node metastasis[22]. Zhu et al. showed that patients with prostate cancer with Gleason scores >7 exhibited lower miR-152 levels than those with <7[23]. Furthermore, low miR-152 expression was correlated with advanced pathological T-stages in patients with prostate cancer. In hepatocellular carcinoma, miR-152 levels were correlated with advanced clinical stage, larger tumor size, and positive HBV infection[24]. These studies indicate that miR-152 may be a promising prognostic marker for these human cancers.

Recent studies also have investigated the function of miR-152 in various human cancers. Su et al. reported that miR-152 overexpression suppressed non-small cell lung cancer cell proliferation, colony formation, migration, and invasion[25]. Cheng et al.[26] and Zhang et al.[27] found similar roles of miR-152 in non-small cell lung cancer. Li et al. found that increased miR-152 expression reduced colorectal cancer cell proliferation, migration, invasion, and enhanced apoptosis and caspase 3 activity in vitro, as well as suppressed tumor growth in vivo[22]. Tsuruta et al. demonstrated that miR-152 inhibited glioma cell invasion and angiogenesis. In endometrial cancer, miR-152 decreased cell growth in vitro and in vivo[28]. In hepatocellular carcinoma, abnormal miR-152 expression suppressed cell growth and motility, and enhanced caspase activity and apoptosis[24]. All these studies suggest that miR-152 may be a promising prognostic marker and therapeutic target in multiple human cancers.

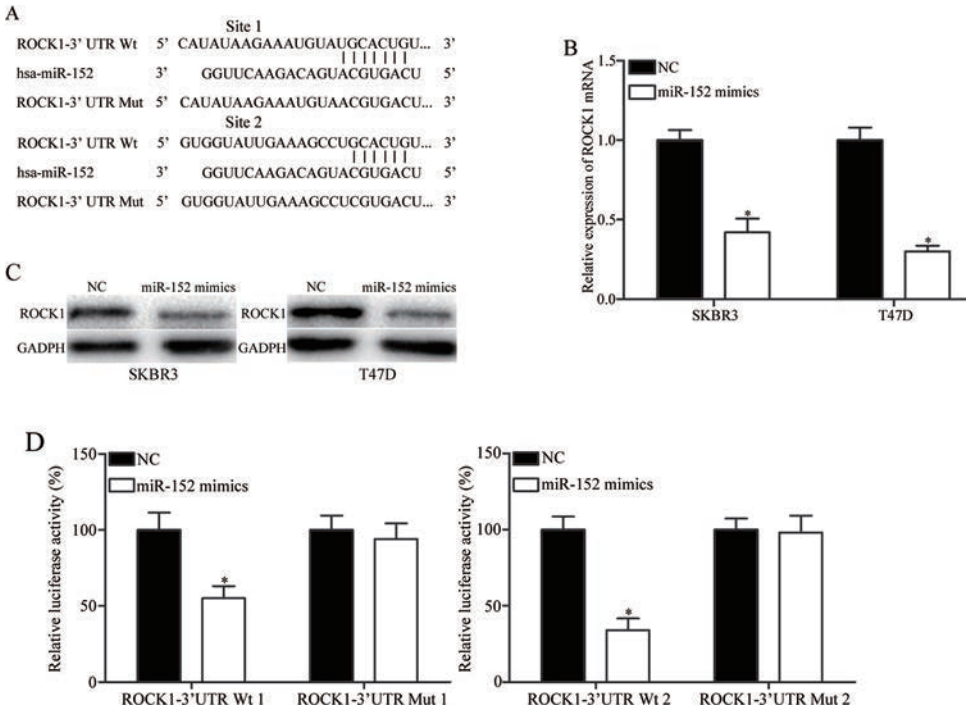

Figure 3. Rho-associated protein kinase 1 (ROCK1) was a direct target gene of miR-152 in breast cancer. (A) Predicted miR-152 target sequence in the 3 -untranslated region (3 -UTR) of ROCK1 and positions of mutated nucleotides in the 3 -UTR of ROCK1. ROCK1 expression at mRNA (B) and protein (C) levels in SKBR3 and T47D cells transfected with miR-152 mimics or NC were examined by qRT-PCR and Western blot. (D) Luciferase reporter assays of HEK293T cells transfected with luciferase reporter vectors along with miR-152 mimics or NC. *$p < 0.05$ compared with respective controls.

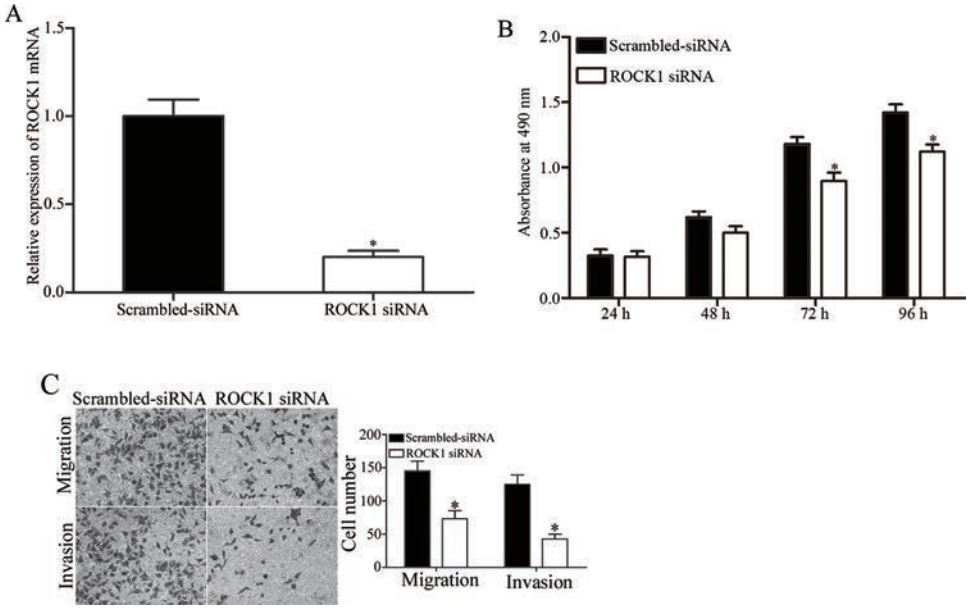

Figure 4. The relative ROCK1 mRNA expression. (A) Expression was significantly downregulated in SKBR3 cells transfected with ROCK1 siRNA. Knockdown of ROCK1 inhibited proliferation (B), migration, and invasion (C) of SKBR3 cells. *$p < 0.05$ compared with respective controls.

To further explore the molecular mechanism by which miR-152 acts as a tumor suppressor in breast cancer, target genes were investigated. Previous studies have identified several miR-152 target genes including neuropilin-1[27], FGF2[26], and ADAM17[25] in non-small cell lung cancer, PIK3R3[22] in colorectal cancer, DKK1[29] in multiple myeloma, KLF4[30] in glioblastoma, CD151[31] in gastric cancer, TNFRSF6B[24] in hepatocellular carcinoma, TGF- [23] in prostate cancer, and NRP-2 and MMP-3[32] in glioma. In the present study, ROCK1 was validated as a novel direct target gene of miR-152 using predictive bioinformatics. ROCK1, located at chromosome 18 (18q11.1)[33], is upregulated in breast cancer and plays a role in cancer progression and metastasis and is a marker for poor prognosis[34–37]. Furthermore, qRT-PCR and Western blot analysis revealed that restoration of miR-152 expression in breast cancer cells decreased ROCK1 at both the mRNA and protein level. Finally, luciferase reporter assay showed that miR-152 was able to directly target the 3 -UTR of ROCK1. Knockdown of ROCK1 had similar tumor-suppressive effects induced by miR-152 overexpression in breast cancer cells. These results indicate that miR-152 has as tumor-suppressive role in breast cancer carcinogenesis and progression through negative regulation of ROCK1 expression. This suggests that miR-152/ROCK1-based targeted therapy could be a new therapeutic strategy for patients with breast cancer.

In conclusion, findings show that miR-152 was downregulated in breast cancer cells, and restoration of miR-152 expression decreased proliferation, migration, and invasion of breast cancer cells through targeting ROCK1. This study provides new insights into the mechanisms underlying the growth and metastasis of breast cancer; however, the details of the underlying mechanism should be explored further.

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REFERENCES

1. Wang RJ, Lu LJ, Jin LB, Li HY, Ren GS, Wu KN, Liu SC, Kong LQ. Clinicopathologic features of breast cancer patients with type 2 diabetes mellitus in southwest of China. Med Oncol. 2014;31(1):788–95.
2. Mangolini A, Ferracin M, Zanzi MV, Saccenti E, Ebnaof SO, Poma VV, Sanz JM, Passaro A, Pedriali M, Frassoldati A. Diagnostic and prognostic microRNAs in the serum of breast cancer patients measured by droplet digital PCR. Biomark Res. 2015;3:12.
3. Shi W, Bruce J, Lee M, Yue S, Rowe M, Pintilie M, Kogo R, Bissey PA, Fyles A, Yip KW. MiR-449a promotes breast cancer progression by targeting CRIP2. Oncotarget 2016;44(32):2222–34.
4. Rakha EA. Pitfalls in outcome prediction of breast cancer. J Clin Pathol 2013;66(6):458–64.
5. Szymanski M, Barciszewska MZ, Erdmann VA, Barciszewski J. A new frontier for molecular medicine: Noncoding RNAs. Biochim Biophys Acta 2005;1756(1):65–75.
6. Di Leva G, Garofalo M, Croce CM. MicroRNAs in cancer. Annu Rev Pathol 2014;9:287–314.
7. Bartel DP. MicroRNAs: Genomics, biogenesis, mechanism, and function. Cell 2004;116(2):281–97.
8. Chen CZ, Li L, Lodish HF, Bartel DP. MicroRNAs modulate hematopoietic lineage differentiation. Science 2004;303(5654):83–6.
9. Cimmino A, Calin GA, Fabbri M, Iorio MV, Ferracin M, Shimizu M, Wojcik SE, Aqeilan RI, Zupo S, Dono M. miR-15 and miR-16 induce apoptosis by targeting BCL2. Proc Natl Acad Sci USA 2005;102(39):13944–9.
10. Wu D, Zhou Y, Pan H, Zhou J, Fan Y, Qu P. microRNA-99a inhibiting cell proliferation, migration and invasion by targeting fibroblast growth factor receptor 3 in bladder cancer. Oncol Lett. 2014;7(4):1219–24.
11. Lewis BP, Shih IH, Jones-Rhoades MW, Bartel DP, Burge CB. Prediction of mammalian microRNA targets. Cell 2003; 115(7):787–98.
12. Chang TC, Mendell JT. microRNAs in vertebrate physiology and human disease. Annu Rev Genomics Hum Genet. 2007;8:215–39.
13. Ling H, Fabbri M, Calin GA. MicroRNAs and other noncoding RNAs as targets for anticancer drug development. Nat Rev Drug Discov. 2013;12(11):847–65.
14. Jiang Q, He M, Ma MT, Wu HZ, Yu ZJ, Guan S, Jiang LY, Wang Y, Zheng DD, Jin F. MicroRNA-148a inhibits breast cancer migration and invasion by directly targeting WNT-1. Oncol Rep. 2016;35(3):1425–32.
15. Zhang J, Wang S, Han F, Li J, Yu L, Zhou P, Chen Z, Xue S, Dai C, Li Q. MicroRNA-542-3p suppresses cellular proliferation of bladder cancer cells through post-transcriptionally regulating survivin. Gene 2016;579(2):146–52.
16. Zou CD, Zhao WM, Wang XN, Li Q, Huang H, Cheng WP, Jin JF, Zhang H, Wu MJ, Tai S. MicroRNA-107: A novel promoter of tumor progression that targets the CPEB3/EGFR axis in human hepatocellular carcinoma. Oncotarget 2016;7(1):266–78.
17. Wei X, Chen D, Lv T, Li G, Qu S. Serum microRNA-125b as a potential biomarker for glioma diagnosis. Mol Neurobiol. 2016;53(1):163–70.
18. Mokutani Y, Uemura M, Munakata K, Okuzaki D, Haraguchi N, Takahashi H, Nishimura J, Hata T, Murata K, Takemasa I. Down-regulation of microRNA-132 is associated with poor prognosis of colorectal cancer. Ann Surg Oncol. 2016;45(6):111–22.
19. Slack FJ. MicroRNAs regulate expression of oncogenes. Clin Chem. 2013;59(1):325–6.
20. Thorsen SB, Obad S, Jensen NF, Stenvang J, Kauppinen S. The therapeutic potential of microRNAs in cancer. Cancer J. 2012;18(3):275–84.
21. Chen Y, Song Y, Wang Z, Yue Z, Xu H, Xing C, Liu Z. Altered expression of MiR-148a and MiR-152 in gastrointestinal cancers and its clinical significance. J Gastrointest Surg. 2010;14(7):1170–9.
22. Li B, Xie Z, Li B. miR-152 functions as a tumor suppressor in colorectal cancer by targeting PIK3R3. Tumour Biol. 2016;56(4):33–9.
23. Zhu C, Li J, Ding Q, Cheng G, Zhou H, Tao L, Cai H, Li P, Cao Q, Ju X. miR-152 controls migration and invasive potential by targeting TGFalpha in prostate cancer cell lines. Prostate 2013;73(10):1082–9.

24. Dang YW, Zeng J, He RQ, Rong MH, Luo DZ, Chen G. Effects of miR-152 on cell growth inhibition, motility suppression and apoptosis induction in hepatocellular carcinoma cells. Asian Pac J Cancer Prev. 2014;15(12):4969–76.
25. Su Y, Wang Y, Zhou H, Lei L, Xu L. MicroRNA-152 targets ADAM17 to suppress NSCLC progression. FEBS Lett. 2014;588(10):1983–8.
26. Cheng Z, Ma R, Tan W, Zhang L. MiR-152 suppresses the proliferation and invasion of NSCLC cells by inhibiting FGF2. Exp Mol Med. 2014;46(5):122–8.
27. Zhang YJ, Liu XC, Du J, Zhang YJ. MiR-152 regulates metastases of non-small cell lung cancer cells by targeting neuropilin-1. Int J Clin Exp Pathol. 2015;8(11):14235–40.
28. Tsuruta T, Kozaki K, Uesugi A, Furuta M, Hirasawa A, Imoto I, Susumu N, Aoki D, Inazawa J. miR-152 is a tumor suppressor microRNA that is silenced by DNA hypermethylation in endometrial cancer. Cancer Res. 2011;71(20): 6450–62.
29. Xu Y, Chen B, George SK, Liu B. Downregulation of microRNA-152 contributes to high expression of DKK1 in multiple myeloma. RNA Biol. 2015;12(12):1314–22.
30. Ma J, Yao Y, Wang P, Liu Y, Zhao L, Li Z, Li Z, Xue Y. MiR-152 functions as a tumor suppressor in glioblastoma stem cells by targeting Kruppel-like factor 4. Cancer Lett. 2014;355(1):85–95.
31. Zhai R, Kan X, Wang B, Du H, Long Y, Wu H, Tao K, Wang G, Bao L, Li F. miR-152 suppresses gastric cancer cell proliferation and motility by targeting CD151. Tumour Biol. 2014;35(11):11367–73.
32. Zheng X, Chopp M, Lu Y, Buller B, Jiang F. MiR-15b and miR-152 reduce glioma cell invasion and angiogenesis via NRP-2 and MMP-3. Cancer Lett. 2013;329(2):146–54.
33. Lock FE, Ryan KR, Poulter NS, Parsons M, Hotchin NA. Differential regulation of adhesion complex turnover by ROCK1 and ROCK2. PLoS One 2012;7(2):122–30.
34. Zhou X, Wei M, Wang W. MicroRNA-340 suppresses osteosarcoma tumor growth and metastasis by directly targeting ROCK1. Biochem Biophys Res Commun. 2013; 437(4):653–8.
35. Oellers P, Schroer U, Senner V, Paulus W, Thanos S. ROCKs are expressed in brain tumors and are required for glioma-cell migration on myelinated axons. Glia 2009; 57(5):499–509.
36. Lochhead PA, Wickman G, Mezna M, Olson MF. Activating ROCK1 somatic mutations in human cancer. Oncogene 2010;29(17):2591–8.
37. Gilkes DM, Xiang L, Lee SJ, Chaturvedi P, Hubbi ME, Wirtz D, Semenza GL. Hypoxia-inducible factors mediate coordinated RhoA-ROCK1 expression and signaling in breast cancer cells. Proc Natl Acad Sci USA 2014;111(3):E384–93.