miR-182-5p affects human bladder cancer cell proliferation, migration and invasion through regulating Cofilin 1

Fei Wang1†, Dinglan Wu2†, Zhanping Xu3†, Jianxiang Chen4, Jiye Zhang5, Xiaojuan Li5, Shiliang Chen6, Fengrong He1, Jianbing Xu1, Liangju Su1, Defan Luo1, Shufang Zhang7* and Weifu Wang1*

Abstract
Background: Human bladder cancer is one of the common malignant tumors, and it mainly occurs in men. miR-182-5p, a member of miR-183 family, acts as tumor suppressor or oncogene in various kinds of tumors. In this study, we first investigate that the absence of miR-182-5p in human bladder cancer promotes tumor growth by regulating the expression of Cofilin 1, an actin modulating-protein.

Methods: Human bladder tumor tissue specimens were collected to detect the expression of miR-182-5p and Cofilin 1 by qRT-PCR. Luciferase activity assay was performed to demonstrate the regulation of Cofilin 1 mRNA 3′UTR by miR-182-5p. Then, cell experiments were performed to analysis the effect of miR-182-5p/Cofilin 1 pathway on tumor cell proliferation, migration, invasion and colony forming efficiency. Finally, xenograft tumor models were established to evaluate the role of miR-182-5p in tumorigenesis abilities in vivo.

Results: qRT-PCR and Western blotting analysis showed that Cofilin 1 expression was up-regulated in both bladder cancer tissues and cell lines compared with normal. Luciferase activity assay showed that miR-182-5p specifically targets Cofilin 1 mRNA 3′UTR and represses the expression of Cofilin 1. Also, miR-182-5p inhibited bladder tumor cell proliferation, migration, invasion and colony forming efficiency. Furthermore, xenograft tumor model assay showed that miR-182-5p plays a negative role in bladder cancer tumorigenesis abilities in vivo.

Conclusion: Present results suggest that miR-182-5p could inhibit human bladder tumor growth by repressing Cofilin 1 expression. Our findings may provide a new horizon for exploring therapeutic target of bladder cancer.

Keywords: miR-182-5p, Bladder cancer, Cofilin 1, Proliferation, Migration, Invasion

Background
According to the global cancer statistics from 2018, bladder cancer caused estimated 549,393 new cases and 199,922 death in the year 2018. As the tenth most common cancer in the world, bladder cancer has an over 75% occurring in men. Smoking is the most determined risk factor for bladder cancer [1, 2].

MicroRNAs (miRNAs) are endogenous approximate 22 nt in length RNAs that can suppress target gene mRNA translation by sufficient or partial complementarity to 3′UTR of the mRNA [3]. miRNAs play crucial roles in multiple bio-progress, including cell proliferation, cell differentiation and cell death [4–6]. Furthermore, increasing studies showed that miRNAs have an intertwined pathway regulation in various human cancers by acting as tumor suppressors or oncogenes [7, 8]. miR-182-5p is a member of miR-183/96/182 cluster, and locates in the chromosome 7q31-34. In diverse kinds of tumors, miR-182-5p plays an implicated role through acting as a tumor suppressor or oncogene. Specifically, miR-182-5p act as tumor suppressor in renal cell cancer.

*Correspondence: haikuoyiyuan@163.com; 13698987211@163.com
†Fei Wang, Dinglan Wu and Zhanping Xu equally contributed to this work
1 Department of Urology, Hainan General Hospital, Haikou, China
2 Central Laboratory, Affiliated Haikou Hospital Xiangya School of Medicine Central South University (Haikou Municipal People Hospital), Haikou, Hainan, China
Full list of author information is available at the end of the article

© The Author(s) 2019. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
stored in liquid nitrogen until use. All patients signed a written consent, and this study approved by the institutional ethics committee of the first people’s Hospital of Hainan.

**Materials and methods**

**Tissue specimens**

Eight pairs of bladder tumor and homologous para-tumor tissue samples were collected from the first people’s Hospital of Hainan. All samples were frozen and stored in liquid nitrogen until use. All patients signed a
pCDNA 3.1 expression vector in our lab. The primers for Cofilin 1 amplification were as follows, forward: 5′-CCC AAG CTT GCC ACC ATG GCC TCC GTG GTG GCT GTC TCT G-3′, reverse: 5′-CCG GAA TTC TCA CAA AGG TTT GCC CTC CAG G-3′. Hsa-miR-182-5p mimics (Catalogue No. miR10000259-1-5) and has-miR-182-5p inhibitor (Catalogue No. miR20000259-1-5) were purchased from Ribo Bio Co., Ltd (Guangzhou, China).

Western blotting
Prepared cells or tissues were added with pre-cooling RIPA (Beyotime Bio, Shanghai, China) lystate buffer applied with proteases inhibitor cocktail (Sigma, USA). Protein concentration were measured using BCA Protein Assay kit (Keygen Biotech, Nanjing, China). Total proteins were mixed with 5× SDS-PAGE loading buffer and heat to 100 °C for 10 min, then, were separated with 4–15% SDS-PAGE and transferred to PVDF membranes (Millipore, USA). After blocked with 5% non-fat milk for 1 h, the PVDF membranes were incubated with specific primary and secondary (horseradish peroxidase, HRP-conjugated) antibodies. Finally, the protein bands were visualized using chemiluminescence HRP substrate (Millipore) in a dark room. The primary antibodies used are anti-GAPDH (1:10000, Kangchen, Shanghai, China) and anti-Cofilin 1 (1:1000, Abcam, USA). The secondary antibody used is HRP-conjugated goat anti-rabbit IgG (1:20000, Southern biotech, China).

Luciferase reporter assay
Wild type (wt) 3′UTR fragment of Cofilin 1 containing miR-182-5p binding site was amplified and cloned into psi-CHECK-2 luciferase reporter vector (Promega). A mutant type (mut) of 3′UTR fragment of Cofilin 1, mutation within the miR-182-5p binding site, also was cloned into psi-CHECK-2 vector as control. Reporter-vectors, Cofilin 1 ectopic expression vectors and RNAs were respectively transfected into HEK 293T cells. 48 h after transfection, cells were lysed with passive lysis buffer. Then, luciferase activity was measured by GloMax 20/20 (Promega) detector using the Dual-Luciferase Reporter Assay System (Promega) according to the instructions.

Cell viability assay
Cell viability was measured using cell count kit-8 (CCK8, Beyotime, China). 2 × 10^3 cells were seeded into 96-well plates, and incubated for 24 h. After proper plasmids or RNAs transfection, cell viability was measured every day in the following 4 days. 10 µl CCK8 solutions was supplied into each of the 96-well plates. After 1.5 h 37 °C 5% CO2 incubation, cells were subjected to measure absorbance at 450 nm using an automatic absorbance microplate reader (Bioteke, Beijing, China). Each experiment was independently performed 3 times.

Cell cycle assay
Cells were collected at least 1 × 10^6 in number, washed with pre-cooling PBS twice, fixed with 70% ethanol at 4 °C overnight. Then, cells were washed with pre-cooling PBS, incubated with 0.5 ml PBS, 50 µg/ml PI, 0.5% RNase A and 0.02% Triton X-100 at 4 °C without light for 10 min. Finally, cell cycle was analyzed by flow cytometry (BD Biosciences, San Jose, USA).

Cell migration and invasion assays
Tumor cell migration and invasion were determined using an 8 µm pore size membrane in trans-well chamber (BD Biosciences). In cell migration assay, 1 × 10^5 cells were seeded in upper chamber, 0.6 ml medium containing 10% FBS was applied to the lower chamber as a chemoattractant. After 24 h 37 °C 5% CO2 incubation, the cells on the upper chamber were removed with a cotton swab. Migration cells were fixed with 4% paraformaldehyde and stained with crystal violet. Cell images were captured using an Olympus (Japan) microscope at 100× magnification, and analyzed using ImageJ 1.44 software (Java). In cell invasion assay, the trans-well membrane was coated with matrigel (BD Biosciences). The follow procedures were same as cell migration assay. Each experiment was independently performed 3 times.

Cell colony formation assay
Transfected cells were digested and counted. 300 cells were seeded in each well of 6-well plates containing 2 ml 10% FBS medium. After 7 days 37 °C 5% CO2 incubation, colonies were fixed with 4% paraformaldehyde and stained with crystal violet. Then, colony images were captured, and the number of colony was counted. The ratio of colony counts and inoculated cell number regarded as the colony-forming efficiency.

Xenograft tumor model assay
Four to five week-old BCLB/C nude mice were obtained from Vital River Laboratory Animal Technology Co., Ltd (Beijing, China). Mice were randomly divided into 4 groups (n = 6). miR-182-5p mimics, miR-182-5p inhibitor and Cofilin 1 expression plasmids were respectively transfected into RT4 cells for 48 h, and 1 × 10^7 cells were respectively collected and subcutaneously injected into mouse left dorsal flank. Then, tumor width (W) and length (L) were measured every few days. Tumor volume was represented as L × W^2/2. On day 44, mice were executed by cervical dislocation, and the tumors were excised to weigh.
Statistical analysis
Data in this study were analyzed and exhibited using Origin 8.5 (OriginLab, USA) software and shown as mean ± SD. Difference level between groups were evaluated by Student’s t-test. p < 0.05 was regarded as statistically significant.

Results
Cofilin 1 is up-regulated in human bladder cancer tissues and cell lines
We firstly measured the expression of Cofilin 1 in human bladder cancer tissues and cell lines. In eight human bladder cancer tissue samples, Cofilin 1 mRNA expression remarkably increased compared with homologous para-cancer tissues (Fig. 1a). Similarly, Western blotting analysis revealed a higher Cofilin 1 protein level in bladder cancer tissues than in adjacent normal tissues (Fig. 1b). Furthermore, we determined Cofilin 1 expression in two human bladder cancer cell lines, RT4 and T24. Compared with bladder epithelial cells, Cofilin 1 expressed much higher in RT4 and T24 cells both in mRNA and protein level (Fig. 1c, d). These data suggest that the high expression of Cofilin 1 in human bladder cancer correlates to bladder tumorigenesis.

miR-182-5p direct targets Cofilin 1 mRNA 3′ UTR and regulates gene expression
miR-182-5p plays an important role in various kinds of tumors by participating in multiple cell signal pathways [10, 12, 28]. First, professional share databases (TargetscanHuman and PicTar) were used to predict target genes of miR-182-5p. CFL1 was one of miR-182-5p predicted target genes, and had a relative good efficiency score of prediction (Fig. 2a). To further confirm miR-182-5p targeting gene CFL1, wild and mutant Cofilin 1 mRNA 3’TUR were respectively constructed into psi-CHECK2 vector (Fig. 2b), then luciferase activity assay was performed. In wt-Cofilin 1–3’UTR group, luciferase activity was markedly repressed by miR-182-5p mimics transfection, and promoted by miR-182-5p inhibitor transfection. However, the luciferase activity have no significant difference compared with control group when either promoting or interference miR-182-5p expression in mut-Cofilin 1–3’UTR groups (p > 0.05) (Fig. 2c). In RT4 cells, Cofilin 1 mRNA expression was down-regulated with miR-182-5p mimics transfection, and up-regulated with miR-182-5p inhibitor transfection (Fig. 2d). All these results indicate that miR-182-5p can negatively regulate Cofilin 1 expression by binding to gene 3’UTR at position 135–142.

miR-182-5p is down-regulated in human bladder cancer tissues and cell lines
miR-182-5p level was measured in 8 human bladder cancer tissue samples by qRT-PCR. The results showed that expression of miR-182-5p was decreased in bladder cancer tissues compared with homologous para-tumor tissues (Fig. 2f). Similarly, miR-182-5p expression reduced in both RT4 and T24 cells compared with normal bladder epithelial cells (Fig. 2e). These results indicate that low level of miR-182-5p contributes to an up-regulation expression of Cofilin 1 in bladder cancer cells.

miR-182-5p reduces bladder cancer cell proliferation through promoting Cofilin 1
Since miR-182-5p could direct targets Cofilin 1 mRNA 3’UTR, we next observed the Cofilin 1 level after miR-182-5p mimics, miR-182-5p inhibitor, Cofilin 1 and miR-182-5p mimics + Cofilin 1 transfection in RT4

---

Fig. 1 Cofilin 1 upregulates in bladder tumor tissues and cell lines. a Cofilin 1 mRNA expression in bladder tumor and homologous para-tumor tissues were measured by qRT-PCR. b Cofilin 1 protein expression in bladder tumor (T) and homologous para-tumor (N) tissues were measured by Western blotting. c, d Cofilin 1 mRNA and protein expression in bladder cancer cell lines (RT4 and T24) and normal bladder epithelial cell line (SV-Huc-1) measured by qRT-PCR and Western blotting. ** Indicates p < 0.01, ***indicates p < 0.001
cells by Western blotting. The results showed that miR-182-5p plays a negative role in regulating Cofilin 1, and the overexpression of Cofilin 1 could be partly reverted by miR-182-5p co-transfection (Fig. 3a). In CCK8 assay, cell proliferation was inhibited by miR-182-5p mimics transfection, and promoted by miR-182-5p inhibitor transfection. Cofilin 1 transfection could remarkably promote RT4 and T24 cell proliferation, however, this promotion effect was counteracted by miR-182-5p co-expression (p < 0.0001) (Fig. 3b). In cell cycle assay, miR-182-5p expression blocked cells at G1 phase of cell cycle, in contrast, miR-182-5p inhibitor transfection increased the cell percentage of S and G2 phase. Cofilin 1 expression could significantly promote cells to transfer from G1 to S and G2 phase. Also, this promotion effect was counteracted by miR-182-5p co-expression (Fig. 3c–f). These data suggest that the loss of miR-182-5p in bladder cancer cell can promote cell proliferation viability by accelerating Cofilin 1 expression.

miR-182-5p represses bladder cancer cell migration, invasion and colony formation ability through promoting Cofilin 1

Next, the influence of miR-182-5p and Cofilin 1 on RT4 and T24 cell migration and invasion were evaluated using trans-well membrane. Compared with control and blank (RT4 and T24) groups, miR-182-5p mimics transfection suppressed cell migration and invasion, Cofilin 1 expression and miR-182-5p inhibition enhanced the ability of cell migration and invasion. While miR-182-5p and Cofilin 1 was co-expressed, the number of migration and invasion cells had no significant difference compared with control and blank groups (Fig. 4a, b). In colony formation assay, miR-182-5p inhibition and Cofilin 1 expression had a higher colony forming efficiency than control and blank groups. miR-182-5p mimics and Cofilin 1 co-transfection converted the colony forming ability to normal level (p > 0.01) (Fig. 4c). Thus, the low level of miR-182-5p in bladder cancer also facilitate
Effects of miR-182-5p on xenograft tumor growth in nude mice

For further investigating the functions of miR-182-5p in bladder cancer, xenograft tumor assay was performed. miR-182-5p mimics, miR-182-5p inhibitor and Cofilin 1 expression vectors transfected RT4 cells were injected into nude mice, then, tumor volume was determined every few days. The results showed that xenograft tumor volume and growth of miR-182-5p inhibitor and Cofilin 1 groups were obviously increased compared with control (RT4, \( p < 0.05 \)) (Fig. 5c). On day 44, xenograft tumors were excised to weigh (Fig. 5a). Also, xenograft tumor weight of miR-182-5p inhibitor and Cofilin 1 groups are more than control (\( p < 0.01 \)) (Fig. 5b). No significant difference of xenograft tumor weight was observed between miR-182-5p mimics and control groups (\( p > 0.05 \)). But, paired-samples \( t \)-test statistical analysis in samples that tumor volume on day 4 to day 44 showed that there is a significant statistical difference (\( p = 0.0009 \)) between miR-182 mimics and control groups. So we considered that miR-182 mimics transfection can suppress tumor growth in xenografts (Fig. 5c).

Discussion

With the increasing and aging of population, cancer has growing incidence and mortality worldwide, and has become a heavy burden on society especially in cell migration, invasion and colony forming efficiency through promoting Cofilin 1.
developing countries. Human bladder cancer is one of the most common cancer with an incident of 549,393 in the year 2018 [2]. Not smoking, schistosomiasis controlling, more fruit, vegetables taking in and proper treatment are the major prevention measures for bladder cancer [29].

Cofilin 1, belongs to the actin depolymerizing factor (ADF), is a ubiquitous protein that binds to actin, participates in directed cell movement in response to chemoattractant or stimulation by involving in actin dynamics at plasma membrane during cell protrusion [18, 30, 31]. Also, Kanellos et al. [32] indicated that Cofilin 1 involves in maintaining tissue homeostasis and promoting cell survival by preventing the cell nucleus from being damaged by actin contractility. In our study, we found that expression of Cofilin 1 accelerates tumor cell proliferation and decreases cells of G1-arrested. So we consider that Cofilin 1 accelerate cell proliferation mainly through enhancing stress tolerance of cells and promoting movement into the beneficial environment. In cancer cells, Cofilin 1 activity, which is affected by factors of phosphorylation level, pH, subcellular localization and binding of phosphoinositides, is necessary for tumor cell motility and invasion. Notably, LIM kinase 1 (LMK1), which can phosphorylates and inactivates Cofilin 1, and Cofilin 1 were simultaneously increased in invasive cells [33]. Interfering the expression of Cofilin 1 in cancer cell inhibit cell invasion by weaken the maturation and stability of invadopodia [34]. Wang et al. [35] reported that Cofilin 1 overexpressed in invasive subpopulation of cancer cells from the primary tumor. In bladder cancer, Patrick et al. [36] proved that with the increasing of tumor grade, Cofilin 1 expression was significant elevated, and localization of Cofilin 1 to nucleus also increased. However, the mechanism of Cofilin 1 up-regulated in cancer cells was not presented in these studies. In our earlier study, we reported that transcription factor TCF7L2

![Image](image-url)
can binds to Cofilin 1 promoter and increases the gene expression in bladder cancer, which promotes the tumor progress [25, 27]. Here, we found another regulated pathway by miR-182-5p that can elevate levels of Cofilin 1 in tumor cells.

It is well known that miRNAs have close correlation with tumorigenesis through participating in multiple bioprocess, including cell proliferation, migration, invasion and apoptosis [7, 37, 38]. As a member of miR-183 family, miR-182-5p plays a key and complex role in diverse kinds of tumors by acting as oncogene and tumor suppressor. For instance, miR-182-5p inhibits renal cell cancer (RCC) cell proliferation, invasion and apoptosis by regulating PI3K/AKT/mTOR pathway [9]; miR-182-5p suppresses non-small cell lung cancer (NSCLC) cell proliferation, invasion and invadopodia formation by targeting cortical, an actin-associated protein [10, 39]; miR-182 reduces proliferation of human osteosarcoma cell (OS) by targeting HOXA9 [12]; miR-182 acts as an oncogene and promote hepatocellular cancer (HCC) progression by targeting FOXO3a [40]; In gastric adenocarcinoma, miR-182 inhibit tumor growth by targeting cAMP responsive element binding protein 1 (CREB1) [41]. Due to the numerous miR-182 target genes, the mechanisms of miR-182 involving in tumorigenesis is quite complex, even be inconsistent. At present, the research about miR-182-5p functions in human bladder cancer is rare, and the mechanism involved in is unclear.
In this study, we demonstrated that Cofilin 1 is over-expressed in human bladder cancer tissues and cell lines compared with normal tissues or epithelial cells, which is consistent with our earlier research [25, 27]. miR-214-5p direct targets Cofilin 1 mRNA 3’UTR and regulates the gene expression. Therefore, decline expression of miR-182-5p contributes to the high level of Cofilin 1 in bladder cancer, for which enhanced the tumor cell proliferation, migration and invasion and tumorgenesis abilities. In xenograft mice model assay, miR-182-5p inhibition observably increased the xenograft tumor growth compared with control. Also, miR-182-5p mimics transfection is able to suppress the xenograft tumor growth.

Conclusions
We first proved that Cofilin 1 is a direct target of miR-182-5p in human bladder cancer. Following with the demonstrating of TCF7L2/Cofilin 1 regulating pathway in bladder cancer, we uncovered another regulating mechanism of which Cofilin 1 promoting tumor progression through miR-182-5p/Cofilin 1 regulating axis. Loss of miR-182-5p in bladder cancer can promotes Cofilin 1 expression, which may have a potential diagnostic and targeted therapy value for bladder cancer.

Abbreviations
miRNAs: microRNAs; CFL1: Cofilin 1; TCF7L2: transcription factor 7-like 2; ADF: actin depolymerizing factor.

Authors’ contributions
FW, DW, SZ and WW drafted and revised the paper. All authors read and approved the final manuscript.

Author details
1 Department of Urology, Hainan General Hospital, Haikou, China. 2 Shenzhen Key Laboratory of Viral Oncology, The Clinical Innovation & Research Centre, Shenzhen Hospital, Southern Medical University, Shenzhen, Guangdong Province, China. 3 Department of Urology, Foshan Hospital of TCM, Foshan, Guangdong Province, China. 4 Department of Urology, Affiliated Hospital of Xiangnan College, Chenzhou, China. 5 Central Laboratory, Hainan General Hospital, Haikou, China. 6 Department of Pathology, Hainan General Hospital, Haikou, China. 7 Central Laboratory, Affiliated Haikou Hospital Xiangya School of Medicine Central South University (Haikou Municipal People Hospital), Haikou, Hainan, China.

Acknowledgements
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Availability of data and materials
The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Consent for publication
Consent for publications is all agreed on by all the patients included in this study (consent form available).

Ethics approval and consent to participate
This study approved by the institutional ethics committee of the first people’s Hospital of Hainan.

Funding
This work was supported by National Nature Science Foundation of China (Grant Nos. 81760461, 81640540, 81760465), Hainan province scientific and technological cooperation special foundation (Grant No. KJHZ2015-25, Science and Technology Project of Shenzhen (Grant No. JCYJ20170307144115825), Shenzhen Key Laboratory of Viral Oncology (Grant No. ZDSYS201707311140430) and Sanming Project of Medicine in Shenzhen (Grant No. SZSM201612023).

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References
1. Antoni S, Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray F. Bladder cancer incidence and mortality: a global overview and recent trends. Eur Urol. 2017;71(1):96–108.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
3. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell. 2004;116(2):281–97.
4. Brennecke J, Hipfner DR, Stark A, Russell RB, Cohen SM. bantam encodes a developmentally regulated microRNA that controls cell proliferation and regulates the proapoptotic gene hid in Drosophila Cell. 2003;113(1):25–36.
5. Hatfield SD, Shcherbata HR, Fischer KA, Nakahara K, Carthew RW, Ruhola-Baker H. Stem cell division is regulated by the microRNA pathway. Nature. 2005;435(7044):974–8.
6. Su Z, Yang Z, Xu Y, Chen Y, Yu Q. MicroRNAs in apoptosis, autophagy and necroptosis. Oncotarget. 2015;6(11):8474–90.
7. Calin GA, Croce CM. MicroRNA signatures in human cancers. Nat Rev Cancer. 2006;6(11):857–66.
8. Kent OA, Mendell JT. A small piece in the cancer puzzle: microRNAs as tumor suppressors and oncogenes. Oncogene. 2006;25(46):6188–96.
9. Fu JH, Yang S, Nan CJ, Zhou CC, Lu DQ, Li S, et al. MiR-182-5p regulates cell proliferation, apoptosis, and invasion by regulating PI3 K/AKT/mTOR signaling pathway. Eur Rev Med Pharmacol Sci. 2018;22(2):351–7.
10. Li Y, Zhang H, Gong H, Jiang Y, Li Y, Wang C, et al. miR-182 suppresses invadopodia formation and metastasis in non-small cell lung cancer by targeting cortactin gene. J Exp Clin Cancer Res. 2018;37(1):141.
11. Li Y, Zhang H, Li Y, Zhao C, Fan Y, Liu J, et al. MiR-182 inhibits the epithelial to mesenchymal transition and metastasis of lung cancer cells by targeting the Met gene. Mol Carcinog. 2018;57(1):125–36.
12. Zhang ZF, Wang YJ, Fan SH, Du SX, Li XD, Wu DM, et al. MicroRNA-182 downregulates Wnt/beta-catenin signaling, inhibits proliferation, and promotes apoptosis in human osteosarcoma cells by targeting HOXA9. Oncotarget. 2017;8(60):101345–61.
13. Kouri FM, Ritter C, Stegh AH. miRNA-182 and the regulation of the glioblastoma phenotype—toward miRNA-based precision therapeutics. Cell Cycle. 2015;14(24):3794–800.
14. Li F, Sheng C, Huang L, Zhang H, Huang L, Cheng Z, et al. MiR-183/96-182 cluster is up-regulated in most breast cancers and increases cell proliferation and migration. Breast Cancer Res. 2014;16(6):473.
15. Xu X, Ayub B, Liu Z, Serna VA, Qiang W, Liu Y, et al. Anti-miR182 reduces ovarian cancer burden, invasion, and metastasis: an in vivo study in orthotopic xenografts of nude mice. Mol Cancer Ther. 2014;13(7):1729–39.
16. Wallis CJ, Gordanpour A, Bendavid JS, Sugar L, Nam RK, Seth A. MiR-182 is associated with growth, migration and invasion in prostate cancer via suppression of FOXO1. J Cancer. 2015;6(12):1295–305.

17. Vartiainen MK, Mustonen T, Mattila PK, Ojala PJ, Partanen J, et al. The three mouse actin-depolymerizing factor/cofilins evolved to fulfill cell-type-specific requirements for actin dynamics. Mol Biol Cell. 2002;13(1):183–94.

18. DesMarais V, Ghosh M, Eddy R, Condeelis J. Cofilin takes the lead. J Cell Sci. 2005;118(Pt 1):19–26.

19. Aizawa H, Sutoh K, Yahara I. Overexpression of cofilin stimulates bundling of actin filaments, membrane ruffling, and cell movement in Dictyostelium. J Cell Biol. 1996;132(3):335–44.

20. Wang W, Mouneime J, Sidani M, Wyckoff J, Chen X, Makris A, et al. The activity status of cofilin is directly related to invasion, intravasation, and metastasis of mammary tumors. J Cell Biol. 2006;173(3):395–404.

21. Tahtamouni LH, Shaw AE, Hasan MH, Yasin SR, Bamburg JR. Non-overlapping activities of ADF and cofilin-1 during the migration of metastatic breast tumor cells. BMC Cell Biol. 2013;14:45.

22. Lu LI, Fu NI, Luo XU, Li XY, Li XP. Overexpression of cofilin 1 in prostate cancer and the corresponding clinical implications. Oncol Lett. 2015;9(6):2757–61.

23. Liu Y, Wang Z, Huang D, Wu C, Li H, Zhang X, et al. LMO2 promotes tumor cell invasion and metastasis in basal-type breast cancer by altering actin cytoskeleton remodeling. Oncotarget. 2017;8(6):9513–24.

24. Wang WS, Zhong HJ, Xiao DW, Huang X, Liao LD, Xie ZF, et al. The expression of CFL1 and N-WASP in esophageal squamous cell carcinoma and its correlation with clinicopathological features. Dis Esophagus. 2010;23(6):512–21.

25. Wang F, Wu D, He F, Fu H, Xu J, Chen J, et al. Study on the significance of cofilin 1 overexpression in human bladder cancer. Tumori. 2017;103(6):537–42.

26. Wang L, Xiong L, Wu Z, Xiao X, Liu Z, Li D, et al. Expression of UGP2 and CFL1 expression levels in benign and malignant pancreatic lesions and their clinicopathological significance. World J Surg Oncol. 2018;16(1):11.

27. Wang F, Wu D, He F, Fu H, Xu C, Zhou J, et al. Cofilin 1 promotes bladder cancer and is regulated by TCF7L2. Oncotarget. 2017;8(54):92043–54.

28. Cao MQ, You AB, Zhu XD, Zhang W, Zhang YY, Zhang SZ, et al. miR-182-5p promotes hepatocellular carcinoma progression by repressing FOXO3a. J Hematol Oncol. 2018;11(1):12.

29. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87–108.

30. Ghosh M, Song X, Mouneime G, Sidani M, Lawrence DS, Condeelis JS. Cofilin promotes actin polymerization and defines the direction of cell motility. Science. 2004;304(5671):743–6.

31. Mouneime G, Soon L, DesMarais V, Sidani M, Song X, Yip SC, et al. Phospholipase C and cofilin are required for carcinoma cell directionality in response to EGF stimulation. J Cell Biol. 2004;166(5):697–708.

32. Kanellos G, Zhou J, Patel H, Ridgway RA, Huels D, Guniai CB, et al. ADF and Cofilin1 control actin stress fibers, nuclear integrity, and cell survival. Cell Rep. 2015;13(9):1949–64.

33. Zebda N, Bernard O, Bailly M, Welti S, Lawrence DS, Condeelis JS. Phosphorylation of ADF/cofilin abolishes EGF-induced actin nucleation at the leading edge and subsequent lamellipod extension. J Cell Biol. 2000;151(5):1119–28.

34. Yamaguchi H, Lorenz M, Kempf S, Sarmiento C, Coniglio S, Symons M, et al. Molecular mechanisms of invadopodium formation: the role of the N-WASP-Abp2/3 complex pathway and cofilin. J Cell Biol. 2005;168(6):441–52.

35. Wang W, Goswami S, Lapidus K, Wells AL, Wyckoff JB, Sahai E, et al. Identification and testing of a gene expression signature of invasive carcinoma cells within primary mammary tumors. Can Res. 2004;64(23):8585–94.

36. Hansley PJ, Zetter D, Horbinski CM, Strup SE, Kyprianou N. Association of epithelial–mesenchymal transition and nuclear cofilin with advanced urethelial cancer. Hum Pathol. 2016;57:68–77.

37. Calin GA, Croce CM. MicroRNA-cancer connection: the beginning of a new tale. Can Res. 2006;66(15):7390–4.

38. Hwang HW, Mendell JT. MicroRNAs in cell proliferation, cell death, and tumorigenesis. Br J Cancer. 2007;96(Suppl):R40–4.

39. Wang M, Wang Y, Zang W, Wang H, Chu H, Li P, et al. Downregulation of miRNA-182 inhibits cell growth and invasion by targeting programmed cell death 4 in human lung adenocarcinoma cells. Tumour Biol. 2014;35(1):39–46.

40. Cao MQ, You AB, Zhu XD, Zhang W, Zhang YY, Zhang SZ, et al. Correction to: miR-182-5p promotes hepatocellular carcinoma progression by repressing FOXO3a. J Hematol Oncol. 2018;11(1):56.

41. Kong WQ, Bai R, Liu T, Cai CL, Liu M, Li X, et al. MicroRNA-182 targets cAMP-responsive element-binding protein 1 and suppresses cell growth in human gastric adenocarcinoma. FEBS J. 2012;279(7):1252–60.