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MicroRNA-139 suppresses proliferation in luminal type breast cancer cells by targeting Topoisomerase II alpha

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ABSTRACT

The classification of molecular subtypes of breast cancer improves the prognostic accuracy and therapeutic benefits in clinic. However, because of the complexity of breast cancer, more biomarkers and functional molecules need to be explored. Here, analyzing the data in a huge cohort of breast cancer patients, we found that Topoisomerase II alpha (TOP2a), an important target of chemotherapy is a biomarker for prognosis in luminal type breast cancer patients, but not in basal like or HER2 positive breast cancer patients. We identified that miR-139, a previous reported anti-metastatic microRNA targets 3'-untranslated region (3′UTR) of TOP2a mRNA. Further more, we revealed that the forced expression of miR-139 reduces the TOP2a expression at both mRNA and protein levels. And our functional experiments showed that the ectopic expression of miR-139 remarkably inhibits proliferation in luminal type breast cancer cells, while exogenous TOP2a expression could rescue inhibition of cell proliferation mediated by miR-139. Collectively, our present study demonstrates the miR-139-TOP2a regulatory axis is important for proliferation in luminal type breast cancer cells. This functional link may help us to further understand the specificity of subtypes of breast cancer and optimize the strategy of cancer treatment.

1. Introduction

Topoisomerase II (TOPO II) plays an essential role in cell division. The catalytic activity of Top II in mammalian cells is mediated by two isoforms, TOPO IIα (TOP2a) and TOPO IIβ (TOP2b). TOP2a plays a more functional role compared with TOP2b. It provides a torsional strain to induce transient breaks on double-stranded DNA and then subsequently reseals them. In this process, it controls the topological states of DNA during replication and thus regulates chromosome condensation and chromatid separation [1]. It has been demonstrated that the aberrantly high activity of TOP2a results in a high level of proliferation rate in many human malignancies and correlates with shortened patient survival [2,3]. According to its biological effect on mammalian cell division and aberrantly high activity in tumor cells, TOP2a-targeted anthracycline has emerged as an attractive strategy in many malignant diseases, including breast cancer [4]. However, the relative benefit of anthracycline has not been achieved in each specific molecular subtype of breast cancer. This indicates that TOP2a addiction may not be a general trait for all breast cancers [5–7]. The contribution of TOP2a activity in intrinsic molecular subtypes of human breast cancer is still elusive.

MicroRNAs (miRNAs) are composed of 22 nucleotides and predominantly perform negative regulation of gene expression through a partial complementarity with the 3′ untranslated regions (3′UTRs) of mRNAs [8]. Recently, a number of miRNAs have been reported to be abnormally regulated in breast cancer. Strikingly, distinct intrinsic subtypes of breast cancer have different miRNA expression patterns [9–11]. This indicates that specific miRNAs functionally regulate malignant behaviors of breast cancer cells in a

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cellular context dependent manner. More mechanistic studies may help us to deeply understand this complex disease and improve our current breast cancer treatment.

In the present study, we found that a high level of TOP2a expression is only associated with poor prognosis in luminal type breast cancer patients but not in basal like or HER2 positive breast cancer patients. Mechanistically, miR-139 was identified as a directly upstream regulator for TOP2a. Moreover, overexpression of miR-139 inhibits proliferation in luminal type breast cancer cells by targeting TOP2a. These results suggest that the miR-139-TOP2a axis is a novel explanation for progression of specific subtype of breast cancer.

2. Materials and methods

2.1. Kaplan–Meier plotter analysis

The prognostic value of the TOP2a gene in breast cancer was analyzed using Kaplan–Meier Plotter (http://kmplot.com/analysis/), a database that integrates gene expression data and clinical data. To date, Kaplan–Meier Plotter contains information on 22,277 genes and their effect on survival in 4142 breast cancer patients [12]. Our analysis was focused on disease free survival (DFS) and overall survival (OS) patient information. The patient samples have been split into two groups. The two patient groups (higher and lower expression levels) were compared using a Kaplan–Meier survival plot. The hazard ratio with 95% confidence intervals and log rank p value was calculated. In order to reduce our false discovery rate, we selected $p < 0.01$ as a threshold.

2.2. Cell culture

293T cells and luminal type breast cancer cell lines MCF-7 and T47D were from the Type Culture Collection of the Chinese Academy of Sciences. All cells were maintained in DMEM supplemented with 10% fetal bovine serum (Gibco, New York, USA), 100 U/mL penicillin and 100 mg/mL streptomycin in humidified air with 5% CO_2 at 37 °C.

2.3. Luciferase reporter assay

For luciferase reporter assay, 293T cells (1×10^5) were plated in a 48-well plate and then cotransfected with 200 ng of either pCDNA3-miR-139 or pcDNA3-EGFP control vector, 200 ng of either wild-type or mutant luciferase construct, and 5 ng of PRL-TK (Promega, Madison, WI, USA), using Lipofectamine2000 (Invitrogen) according

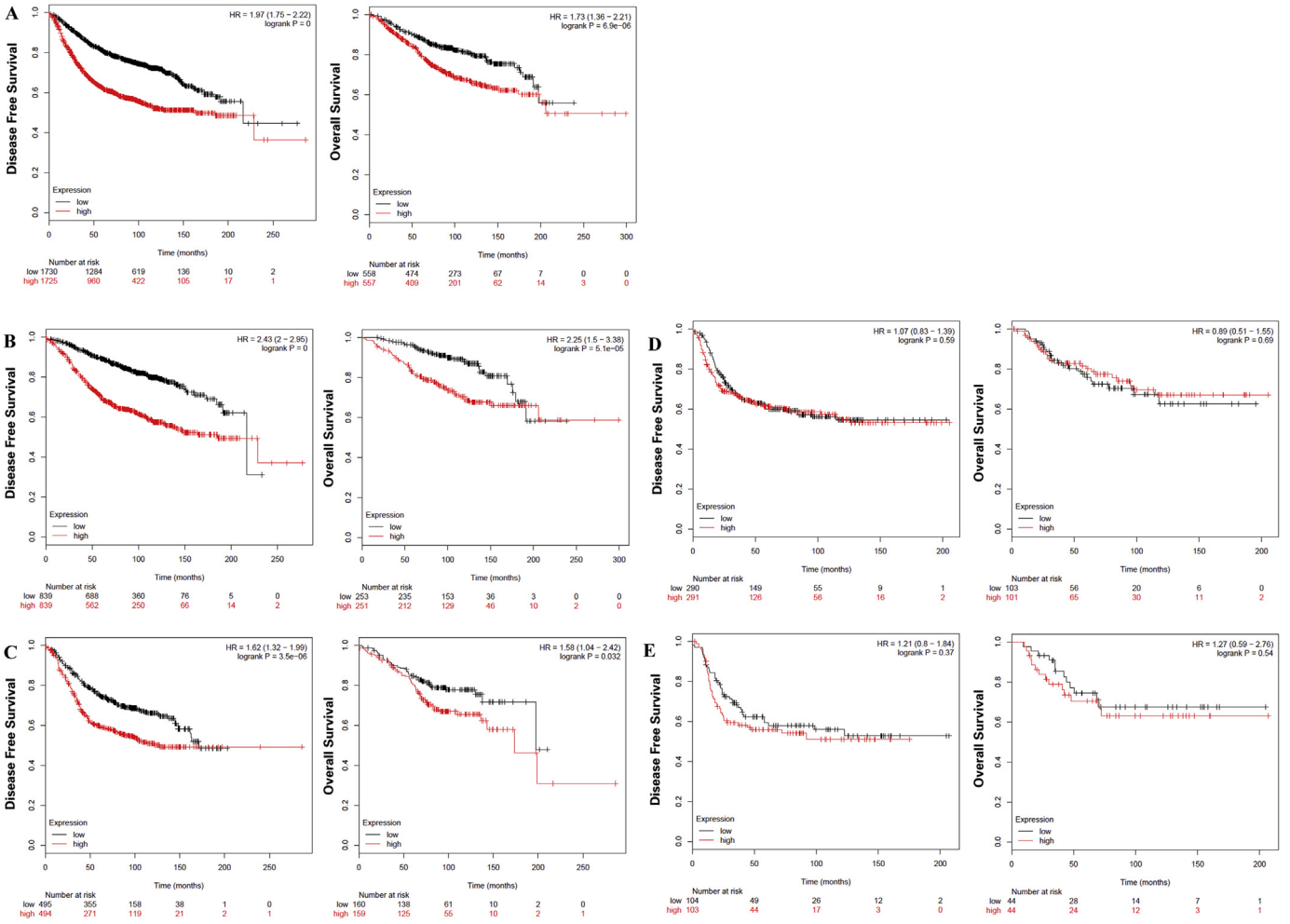

Fig. 1. Correlation of TOP2a levels in patient tumors with disease-free survival and overall survival. (A) Correlation of TOP2a levels in all analyzed patient tumors with DFS and OS. (B) Correlation of TOP2a levels in luminal A type breast cancer patient tumors with DFS and OS. (C) Correlation of TOP2a levels in luminal B type breast cancer patient tumors with DFS and OS. (D) Correlation of TOP2a levels in basal type breast cancer patient tumors with DFS and OS. (E) Correlation of TOP2a levels in HER2 positive type breast cancer patient tumors with DFS and OS.

to manufacturer's instruction. Cells were collected 48 h after transfection and analyzed using the Dual-Luciferase reporter assay kit (Promega, Madison, WI, USA). The pRL-TK vector provided the constitutive expression of Renilla luciferase, and was used as an internal control to correct the differences in transfection and harvest efficiencies. Each experiment was done in triplicates and repeated in three independent experiments.

2.4. RNA isolation, reverse transcription and real-time polymerase chain reaction

Total RNA was extracted using TRIzol (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions. Reverse transcription (RT) for mRNA or microRNA was carried out using the PrimeScript™ RT Master Mix (TaKaRa, Japan) or the miScript Reverse Transcription Kit (Qiagen, Germany), respectively. The quantitative real-time PCR (qPCR) was conducted using the SYBR Green dye (TaKaRa, Japan). The following primers were as the following: TOP2a, forward primer, 5′-ACAATTGGCCGCTAAACTTG-3′, reverse primer, 5′-GCGAGTGTGCTGGTCACTAA-3′; GAPDH (as an endogenous control), forward primer, 5′-TCACCAGGGCTGCTTT-TAAC-3′, reverse primer, 5′-GACAAGCTTCCCGTTCTCAG-3′; mature miR-139, forward primer, 5′-TCTACAGTGCACGTGTCTCCAGT-3′, reverse primer, Universal Primer (QIAGEN, Germany); U6-snRNA, forward primer, RNU6B_2 miScript Primer (QIAGEN, Germany), reverse primer, Universal Primer (QIAGEN, Germany). Real-time PCR was performed in triplicate on CFX96 Real Time PCR Detection System (Bio-Rad, USA), the 2ˆ-ΔΔCT method was used to determine the relative gene expression, and mature miRNA were normalized to U6-snRNA.

2.5. Antibodies for western blot

The TOP2a antibody (ab52934) is from Abcom, β-actin antibody (A5441) from Sigma–Aldrich.

2.6. MTT and colony formation assays

The standard protocol was described in our previous study [13].

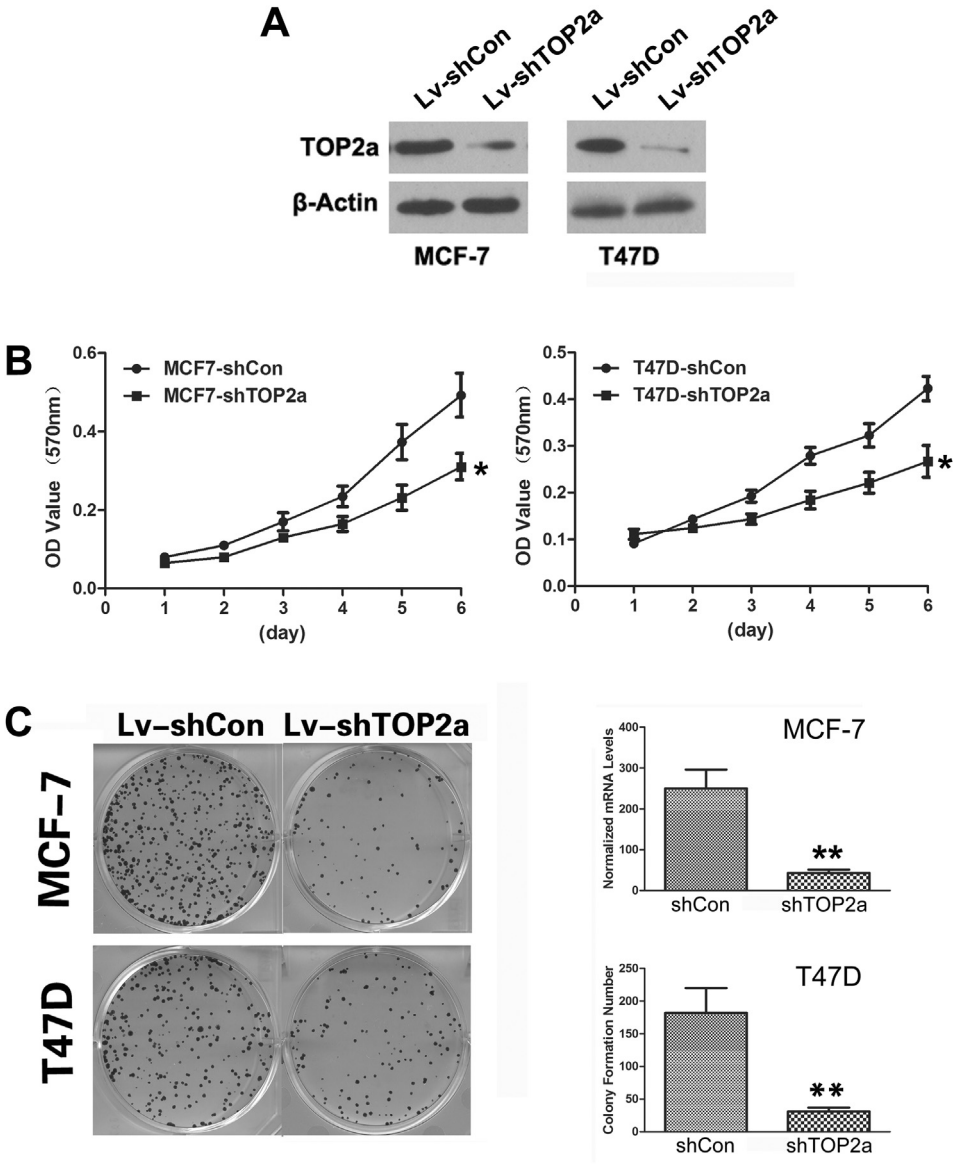

Fig. 2. Suppressive effects of loss of TOP2a on growth of luminal type breast cancer cells. (A) Western blot analysis of TOP2a expression levels in TOP2a-silenced breast cancer cells. (B) Analysis of MTT assays in breast cancer cells (*P < 0.05, independent t test). (C) Analysis of colony formation assays in tumor cells. (**P < 0.01, independent t test).

2.7. Statistical analysis

A Student's test was performed to analyze the significance of differences between the samples means obtained from three independent experiments. Differences were considered statistically significant at $p < 0.05$. Survival estimates were calculated using the Kaplan–Meier method and compared using the log-rank test.

3. Results

3.1. A high level of TOP2a expression is significantly associated with poor prognosis in luminal type breast cancer patients but not in basal like or HER2 positive breast cancer patients

Since TOP2a plays a critical role in initiation of DNA replication, theoretically, the aberrantly high activity of TOP2a should be associated with poor prognosis in breast cancer patients. Here, our Kaplan–Meier analysis revealed that in all analyzed breast cancer patients, high levels of TOP2a expression positively correlate with low survival rates in both disease free survival (DFS) and overall survival (OS) (Fig. 1A). Unexpectedly, further analysis showed that high levels of TOP2a expression are only significantly associated with poor prognosis in luminal type breast cancer patients (Fig. 1B and C). In the cohorts of basal like and HER2 positive breast cancer patients, high levels of TOP2 expression are not associated with the survival rate (Fig. 1C and D). The results indicate that TOP2a may not be a general biomarker for prognosis in all molecular subtypes of breast cancer patients.

3.2. Knockdown of TOP2a suppresses growth of luminal type breast cancer cells

Considering that high levels of TOP2a expression is positively associated with poor prognosis in luminal type breast cancer patients, we asked that if TOP2a is a functional molecule controlling proliferation in this subtype breast cancer cells. As shown in Fig. 2A, we used a lentiviral delivery system to stably knock down TOP2a expression in MCF-7 and T47D, two luminal type breast cancer cells [14]. The MTT assay showed that knockdown of TOP2a significantly inhibits proliferation in both breast cancer cell lines (Fig. 2B). Furthermore, to evaluate a longer-time impact, we performed the colony formation assay. Knockdown of TOP2a significantly decreased the clonogenic ability in tumor cells (Fig. 2C). These results indicate that TOP2a is a potential regulator for proliferation in luminal type breast cancer cells. However, the mechanism of abnormal high levels of TOP2a in luminal type breast cancer is still an open question.

3.3. TOP2a is a direct target of miR-139

Our previous studies focused on miRNA-mediated post-transcriptional regulation of gene expression [13,15,16]. Here, we hypothesized that some specific miRNAs may also involve in regulating TOP2a expression in luminal type breast cancer cells. To identify miRNAs that can efficiently target TOP2a, we combined the database (miRBase, DIANA and Targetscan) and the manual check for the matched sequences [17,18]. We noticed that miR-139, one of our previous reported anti-metastatic miRNA is one of the candidates containing the matched sequences to the 3′UTR of TOP2a mRNA (Fig. 3A). To determine whether TOP2a is a direct target of miR-139, we cloned the full length 3′UTR of TOP2a mRNA containing a wild type or mutant miR-139 binding sequence downstream of the firefly luciferase reporter gene (Fig. 3A). We examined the effects of miR-139 on the luciferase activity in 293T cells. The results showed that the luciferase activity was significantly suppressed in the reporter containing the wild type 3′UTR of TOP2a but was not affected in the reporter containing a mismatched binding site (Fig. 3B). This indicates that miR-139 may suppress the expression of TOP2a through the binding sequence on its 3′UTR region.

To further confirm that TOP2a is negatively regulated by miR-139, we used a lentiviral delivery system to overexpress miR-139 in tumor cells. The result of quantitative RT-PCR showed an obviously increasing expression of miR-139 in tumor cells (Fig. 4A). Subsequently, analysis of Western blot showed the TOP2a protein level dramatically decreases compared with it in the counterparts (Fig. 3C). In addition, analysis of quantitative RT-PCR also showed that exogenous expression of miR-139 significantly decreases mRNA levels of TOP2 (Fig. 3D). These results suggest for the first time that TOP2a is a directly novel target of miR-139 in luminal type breast cancer cells.

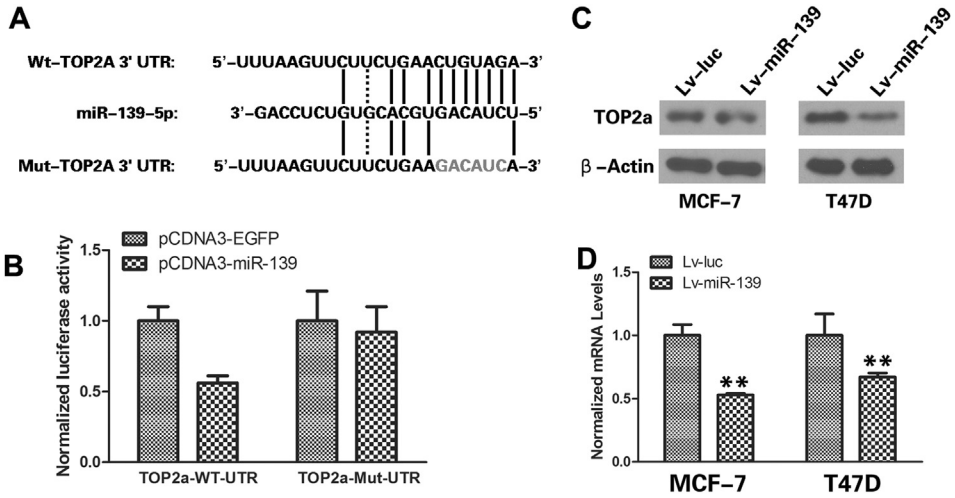

Fig. 3. : TOP2a is a direct target of miR-139. (A) Schematic of in silico analysis of predicted binding sites on miR-139 binding to the 3′UTR region of TOP2a mRNA. The seed sequence of miR-139 and mutant mismatched TOP2a 3′UTR are all as shown. (B) 293T cells were cotransfected with Renilla luciferase control (pRL-TK), firefly luciferase reporter containing either wild-type or seed region mutated TOP2a 3′UTR (indicated as WT or MUT), and either the pCDNA3-miR-139 vector or a control pCDNA3-EGFP vector. (C) Western blot analysis of TOP2a expression levels in miR-139-overexpressing luminal type breast cancer cells. β-actin was used as an internal loading control. (D) qRT-PCR analysis of TOP2a expression levels in miR-139-overexpressing luminal type breast cancer cells.

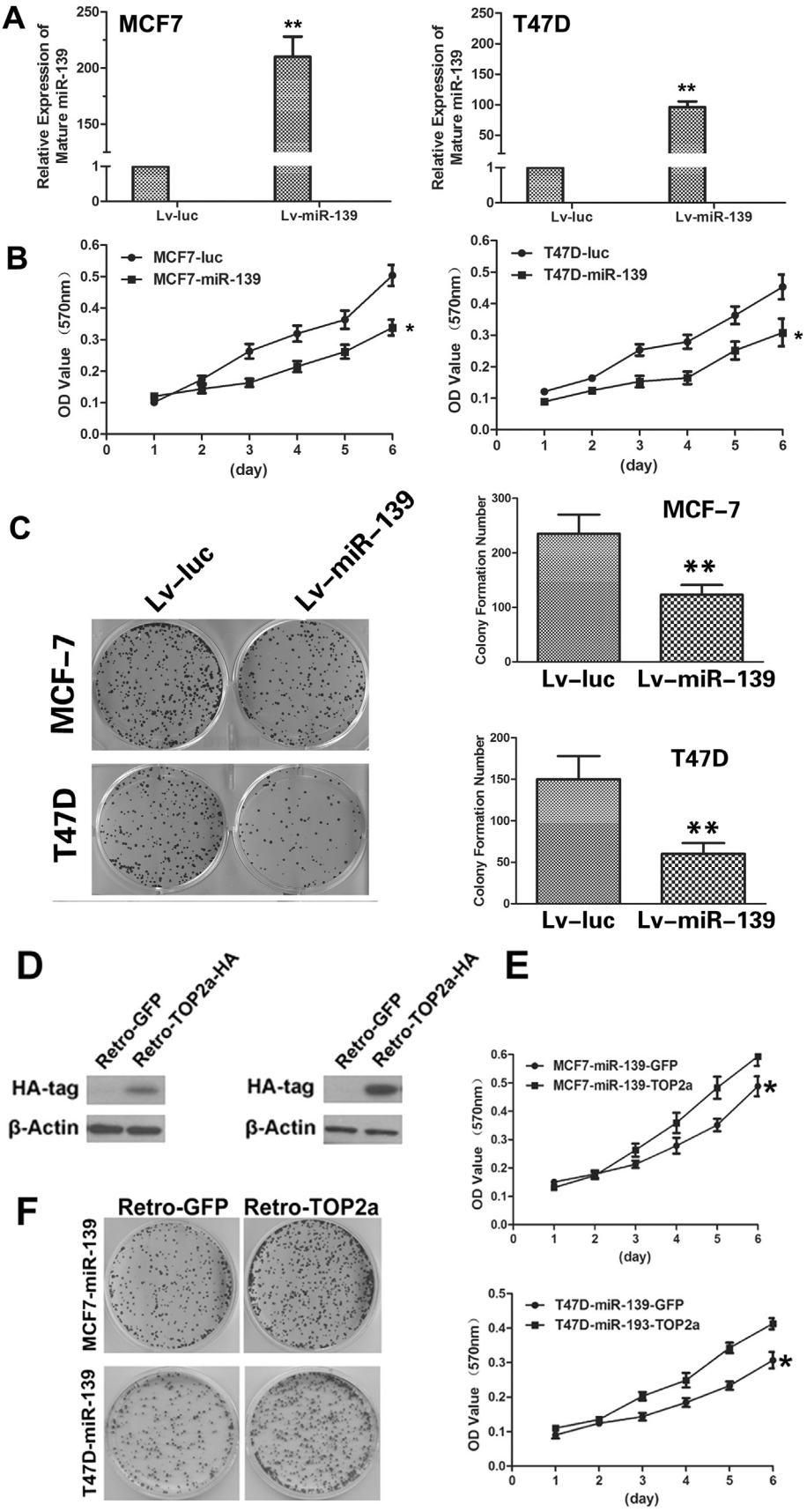

Fig. 4. Inhibitory effects of miR-139 on proliferation of luminal type breast cancer cells. (A) QRT-PCR analysis of miR-139 levels in cancer cells (**P < 0.01, independent t test). (B) Analysis of MTT assays in tumor cells. (*P < 0.05, independent t test). (C) Analysis of colony formation assays in tumor cells. (**P < 0.01, independent t test). (D)Western blot analysis of exogenous TOP2a expression levels in miR-139-overexpressing breast cancer cells. The HA peptides were fused in the 3′ terminal of TOP2a as a tag for the detection. (E) Analysis of MTT assays showing the effect of reconstitution of TOP2a in miR-139-overexpressing breast cancer cells (*P < 0.05, independent t test). (F) Analysis of colony formation assays showing the effect of reconstitution of TOP2a in miR-139-overexpressing breast cancer cells.

3.4. TOP2a is essential for miR-139 induced cell proliferation arrest in luminal type breast cancer cells

A recent study reported that overexpression of miR-139 has a slight effect on cell proliferation in basal like breast cancer cells [19]. However, according to our finding in the regulatory mechanism between miR-139 and TOP2a and the prognostic value of TOP2a in luminal type breast cancer, we hypothesized that miR-139's functions in breast cancer cells may be in a cellular context dependent manner. Using MTT assay and colony formation assay, we demonstrated that overexpression of miR-139 significantly suppresses proliferation in luminal type breast cancer cells (Fig. 4B and C). If TOP2a acts as a functional target of miR-139 in cancer cell proliferation, reconstitution of TOP2a in miR-139-overexpressing cells should be able to antagonize the effects of miR-139. To test the hypothesis, we reintroduced TOP2a using a retroviral expression system in miR-139-overexpressing cells (Fig. 4D). Analysis of both MTT assay and colony formation assay showed that reconstitution of TOP2a increases proliferation in miR-139-overexpressing cells (Fig. 4E and F). These findings demonstrate that TOP2A is a functional mediator for miR-139 on proliferation in luminal type breast cancer cells.

4. Discussion

Breast cancer is the most common malignant disease and one of the major causes of cancer-related death in women, especially in developed countries [5]. Accumulation of genetic and epigenetic alterations controls initiation and progression of breast cancer. Distinct entities, including clinical, morphological and molecular events are in this complex disease. Even with the classification of distinct histological types of breast cancer, there was still little impact on the therapeutic decision making [20]. With a breakthrough of high-throughput genome sequencing technology, the altered gene expression has been observed in breast cancer. It leads to the determination that breast cancer comprises at least four molecularly distinct diseases. The intrinsic molecular subtypes are identified as: basal-like, HER2 positive, luminal A and luminal B subtypes. They have different features, clinical behaviors, treatment response profiles and even prognostic significance [21,22].

Unlimited proliferation is one of the most common characteristics of transformed cells. As a key catalytic enzyme in initiation of DNA replication, TOP2a has been widely recognized as a potential target in cancer treatment. In the present study, using the online survival analysis tool to assess the effect of genes on breast cancer prognosis of thousands of patients [12], we found that high levels of TOP2a expression are closely associated with poor prognosis in all detected breast cancer patients. However, when we further analyzed the relationship between the TOP2a expression and prognosis in distinct molecular subtypes of breast cancer, we found that high levels of TOP2a are only significantly associated with poor prognosis of patients in luminal type breast cancer but not in basal like or HER2 positive breast cancer.

The anti-metastatic effect of miR-139 in different types of cancer has been well documented. In human hepatocellular carcinoma cells, downregulation of miR-139 leads to intrahepatic invasion of tumor cell by upregulating Rho-kinase 2 (ROCK2) [23]. Our previous study also showed that overexpression of miR-139 inhibits the CXCR4 expression and consequently blocks metastasis of gastric cancer cells [16]. And recently, studies in colorectal cancer (CRC) showed that miR-139 inhibits migration and invasion of tumor cells by targeting insulin growth factor receptor 1 (IGF1R) and Notch1 [24,25]. All the evidence confirms an important role of miR-139 on suppression of cancer metastasis. However, its biological function and molecular mechanism on cell proliferation are still elusive. With deeply understanding of tumor suppressor miRNAs in multiple types of cancer cells, we hypothesized that the specific effect of one miRNA in cancer cells may be functionally associated with the cellular context. In gastric tumor cells, miR-218 inhibits cancer metastasis by targeting Robo-Slit signal pathway, but has no obvious effect on cell proliferation [26]. However, in cervical and nasopharyngeal cancer cells exogenous expression of miR-218 could suppress growth and metastasis of cancer cells by targeting both survivin and Robo-Slit pathway [27,28]. One recent report showed that overexpression of miR-139 inhibits migration and invasion but has no impact on cell proliferation in MDA-MB-231, a basal like breast cancer cell line [19]. In the mechanistic study, authors performed an RNA pull-down approach to obtain the target genes of miR-139, and further explored its functions on cancer metastasis. However, when we read this paper carefully, we noticed a logical problem in it. The RNA pull-down experiment was carries out in MCF7, a luminal type breast cancer cell line. But all the functional experiments were done in MDA-MB-231, a basal like breast cancer cell line. Definitely, the biological functions of miR-139 in luminal type breast cancer cells were ignored. In this study, we found that overexpression of miR-139 significantly suppresses growth of MCF7 cells. To rule out a possibility that this is only a specific effect in MCF7 cells, we performed the similar experiment in T47D, another luminal type breast cancer cell line. Although our finding is not consistent with the previous report in basal like breast cancer cells, it may because of distinct functions of one miRNA in cellular context dependent manner. Our results imply that miR-139 might be a potential tumor suppressor miRNA that plays important roles in the regulation of both tumor growth and metastasis.

In summary, we for the first time establish a functional link between miR-139 and TOP2a in tumor cells. This mechanistic study would partially explain the inhibitory effect of miR-139 on cancer cell proliferation. This would provide more information to understand specificity of breast cancer, a heterogeneous disease, and improve the therapeutic efficiency and prognostic accuracy.

Conflict of interest

All the authors, including Wei Hua, Ke-Di Sa, Xiang Zhang, Shi-Jie Hu, Lin-Tao Jia, Jing Zhao, An-Gang Yang, Rui Zhang, Jing Fan, Ka Bian have no conflict of interest.

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