

FOXM1 Drives Subtype-Specific Dysregulation of Prognostic miRNAs in Breast Cancer Cells

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ABSTRACT

Objective: Breast cancer is a heterogeneous disease comprising distinct molecular subtypes, including estrogen receptor-positive (ER+) breast cancer and triple-negative breast cancer (TNBC). MicroRNAs (miRNAs) regulate post-transcriptional gene expression and play important roles in cancer progression by functioning as oncogenic or tumor-suppressive molecules. Forkhead box M1 (FOXM1) is an oncogenic transcription factor that is frequently upregulated in aggressive breast cancers, particularly TNBC, and is associated with proliferation, invasion, metastasis, therapy resistance, and poor prognosis.

Materials and Methods: Clinically relevant miRNAs associated with survival in patients with ER+ and ER– breast cancer were identified using publicly available datasets. The expression levels of miR-34a-5p, miR-873-5p, miR-193b-5p, miR-330-5p, miR-10b-5p, miR-155-5p, and miR-484 were evaluated in MDA-MB-231 TNBC cells and MCF-7 ER+ breast cancer cells following FOXM1 knockdown.

Results: FOXM1 knockdown was associated with increased expression of several tumor-suppressive miRNAs, including miR-34a-5p, miR-873-5p, miR-193b-5p, miR-330-5p, miR-10b-5p, and miR-484, in MDA-MB-231 cells. In contrast, most of these miRNAs were not markedly altered in MCF-7 cells, except for miR-10b-5p, whose expression decreased following FOXM1 knockdown. miR-155-5p expression remained largely unchanged in both cell lines.

Conclusion: Our findings demonstrate that FOXM1 knockdown was associated with differential expression of clinically relevant miRNAs in the two breast cancer cell models examined. These findings suggest that FOXM1-associated alterations in miRNA expression may contribute to the aggressive phenotype of TNBC and warrant further mechanistic investigation.

Keywords: Breast cancer, estrogen receptor-positive breast cancer, FOXM1, microRNA, miR-10b-5p, miR-193b-5p, miR-34a-5p, triple-negative breast cancer



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INTRODUCTION

Breast cancer (BC) is the most frequently diagnosed malignancy among women worldwide and remains one of the leading causes of cancer-related mortality, accounting for approximately 670,000 deaths annually, according to the World Health Organization (WHO).^{1,2} Despite considerable advances in early diagnosis and systemic therapies, BC remains a highly heterogeneous disease comprising distinct molecular subtypes that differ substantially in their biological behavior, prognosis, and therapeutic response. Based on the expression status of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), BC is classified into ER-positive (ER+), HER2-positive, and triple-negative breast cancer (TNBC) subtypes.³

ER+ breast cancer accounts for approximately 70% of all breast cancer cases and generally has a more favorable clinical outcome because of its responsiveness to endocrine therapies such as tamoxifen and fulvestrant.³ In contrast, TNBC lacks ER, PR, and HER2 expression and accounts for approximately 15% of invasive breast cancers. TNBC is characterized by aggressive tumor behavior, high metastatic potential, frequent recurrence, and poor overall survival. Owing to the absence of well-defined therapeutic targets, chemotherapy remains the primary systemic treatment; however, nearly half of patients with TNBC fail to achieve a pathological complete response following neoadjuvant chemotherapy.⁴ These clinical challenges highlight the urgent need to better understand the molecular mechanisms underlying TNBC progression and identify novel therapeutic targets.

Forkhead box M1 (FOXM1), a member of the Forkhead box family of transcription factors, plays a central role in regulating genes involved in cell-cycle progression, proliferation, migration, invasion, metastasis, and therapeutic resistance.^{5,6} FOXM1 is frequently overexpressed in TNBC and numerous aggressive solid tumors, in which elevated FOXM1 expression has consistently been associated with unfavorable clinical outcomes and reduced patient survival.⁵ Previous studies have demonstrated that FOXM1 contributes to multiple oncogenic processes, including tumor growth, epithelial–mesenchymal transition, stemness, and chemotherapy resistance. Nevertheless, the downstream molecular networks through which FOXM1 exerts these oncogenic effects have not yet been fully characterized.^{7,8}

MicroRNAs (miRNAs) are small noncoding RNA molecules that regulate post-transcriptional gene expression through sequence-specific binding to complementary regions within target messenger RNAs, thereby modulating mRNA stability and translation.^{9,10} Aberrant miRNA expression contributes to tumor initiation and progression by regulating diverse biological

KEY MESSAGES

- FOXM1 regulates subtype-specific expression of prognostic miRNAs in breast cancer cells.
- FOXM1 silencing differentially alters oncogenic and tumor-suppressive miRNAs across luminal and triple-negative breast cancer models.
- These findings identify FOXM1-associated miRNA networks as potential biomarkers and therapeutic targets in breast cancer.

processes, including proliferation, apoptosis, angiogenesis, metastasis, and therapeutic resistance. Depending on their target genes, miRNAs may function as either oncogenes or tumor suppressors.^{9,10}

Previous studies, including our own, have demonstrated that dysregulated miRNA expression is closely associated with breast cancer progression, therapeutic response, and patient survival.¹⁰ In particular, we previously identified FOXM1-associated alterations in miR-186 and miR-200b expression in TNBC cells.¹¹ Building on these findings, further characterization of additional clinically relevant miRNAs associated with FOXM1 signaling may provide a more comprehensive understanding of FOXM1-related regulatory networks in breast cancer.

Therefore, in the present study, we investigated the association between FOXM1 knockdown and the expression profiles of clinically relevant prognostic miRNAs in MDA-MB-231 and MCF-7 breast cancer cells. We further evaluated the prognostic significance of these miRNAs using publicly available patient datasets and examined whether FOXM1 knockdown was associated with differential miRNA expression patterns in these two breast cancer cell models. Our findings suggest that FOXM1 is associated with subtype-specific alterations in the expression of clinically relevant miRNAs and may contribute to the dysregulation of tumor-suppressive miRNAs linked to breast cancer prognosis. These observations provide further insight into the molecular mechanisms underlying TNBC progression and warrant additional mechanistic investigation.

MATERIALS AND METHODS

Cell Lines and Culture Conditions

Human triple-negative breast cancer (MDA-MB-231) and estrogen receptor-positive (ER+) breast cancer (MCF-7) cells were obtained from the American Type Culture Collection (Manassas, VA, USA). MDA-MB-231 and MCF-7 cells were cultured in Dulbecco's modified Eagle's medium (DMEM)/F12 supplemented with 10% fetal bovine serum (Sigma-Aldrich, St. Louis, MO, USA). Nontumorigenic human breast epithelial

cells (MCF10A) were grown in DMEM/F12 supplemented with 5% horse serum, epidermal growth factor, hydrocortisone, insulin, and cholera toxin (Calbiochem). Cells were cultured at 37°C in a humidified incubator with 5% CO₂.^{11–15}

Transfection With siRNAs

FOXM1 expression was silenced using two independent small interfering RNAs (siRNAs) targeting different regions of the FOXM1 transcript (FOXM1 siRNA#1, SASI_Hs01_00052108; FOXM1 siRNA#2, SASI_Hs01_00243977; Sigma-Aldrich, St. Louis, MO, USA), which were previously validated by our group for efficient FOXM1 knockdown.^{11–15} A nontargeting siRNA (MISSION® siRNA Universal Negative Control, Sigma-Aldrich) was used as a negative control.

Exponentially growing MDA-MB-231 and MCF-7 cells were seeded 24 h before transfection and transfected with either FOXM1 siRNAs or control siRNA at a final concentration of 50 nM using HiPerFect Transfection Reagent (Qiagen, Valencia, CA, USA), according to the manufacturer's instructions. Cells were harvested 72 h after transfection for subsequent RNA isolation and gene expression analyses. All experiments were independently repeated at least three times.^{11–15}

RNA Isolation and Real-Time Quantitative Polymerase Chain Reaction (RT-qPCR) for miRNA Profiling in BC Cells

Total RNA, including small RNAs, was isolated from untreated MCF10A cells and from MDA-MB-231 and MCF-7 cells transfected with FOXM1 siRNAs or control siRNA using the High Pure RNA Isolation Kit (Roche Diagnostics, Mannheim, Germany), according to the manufacturer's protocol. RNA concentration and purity were determined spectrophotometrically.

For miRNA expression analysis, 1 µg of total RNA was reverse transcribed using the Mir-X™ miRNA First-Strand Synthesis Kit (Takara Bio USA, Mountain View, CA, USA). Quantitative real-time PCR (RT-qPCR) was performed using TB Green® Premix Ex Taq™ II (Takara Bio USA) on a LightCycler® 480 Real-Time PCR System (Roche Applied Science). U6 small nuclear RNA (U6 snRNA) served as the endogenous control for miRNA normalization to maintain methodological consistency with our previous study using the same experimental approach.¹¹ The expression levels of miR-34a-5p, miR-873-5p, miR-193b-5p, miR-330-5p, miR-10b-5p, miR-484, and miR-155-5p were analyzed in triplicate.

FOXM1 mRNA expression was quantified using Platinum™ Taq DNA Polymerase (Life Technologies, Carlsbad, CA, USA) with gene-specific primers, while β-actin was used as the internal reference gene. Relative expression levels were calculated using the comparative 2^{-ΔΔCt} method. All reactions were performed

in triplicate, and the mean values from three independent biological experiments were used for statistical analysis.¹¹

Bioinformatic Analysis of miRNA Expression and Patient Survival

The expression profiles of the selected miRNAs in breast cancer were explored using the Database of Differentially Expressed miRNAs in Human Cancers (<https://www.biosino.org/dbDEMC/index>). To evaluate the prognostic significance of these miRNAs, Kaplan–Meier survival analyses were performed using publicly available breast cancer datasets from The Cancer Genome Atlas (TCGA) through the KM Plotter platform (<https://kmplot.com/analysis/>).

Statistical Analysis

Data are presented as the mean±SD from three independent biological experiments. Statistical analyses were performed using GraphPad Prism software (version 8.00; GraphPad Software Inc., San Diego, California, USA). Comparisons between two groups were performed using an unpaired two-tailed Student's t-test, whereas comparisons involving more than two groups were analyzed using one-way analysis of variance (ANOVA), followed by an appropriate post hoc multiple-comparison test. Each miRNA was analyzed individually, and no false discovery rate (FDR) correction was applied. Statistical significance was defined as p<0.05.

RESULTS

Expression of miR-10b-5p, miR-34a-5p, miR-330-5p, miR-873-5p, and miR-155-5p Is Associated With Favorable Prognosis and Longer Survival in Patients With BC

To determine the clinical relevance of the selected miRNAs, Kaplan–Meier survival analyses were performed using the TCGA breast cancer dataset (KM Plotter), separately for ER– and ER+ patient cohorts. High expression of miR-10b-5p (HR=0.39, p=0.013), miR-34a-5p (HR=0.31, p=0.0079), miR-330-5p (HR=0.37, p=0.014), miR-155-5p (HR=0.37, p=0.025), and miR-873-5p (HR=0.27, p=0.0031) was significantly associated with improved overall survival in patients with ER– breast cancer (Fig. 1). In contrast, the expression of miR-193b-5p (HR=0.57, p=0.16) and miR-484 (HR=0.68, p=0.32) was not significantly associated with survival.

In the ER+ cohort, elevated miR-10b-5p expression was also associated with favorable overall survival (HR=0.51, p=0.011). Conversely, increased expression of miR-34a-5p (HR=0.31, p=0.0079), miR-193b-5p (HR=1.94, p=0.04), miR-873-5p (HR=3.63, p=2.4×10⁻⁶), and miR-484 (HR=3.63, p=4×10⁻⁴) was associated with poorer overall survival, whereas miR-330-5p (HR=0.76, p=0.32) and miR-155-5p (HR=0.62, p=0.11) were not significantly associated with patient outcomes.

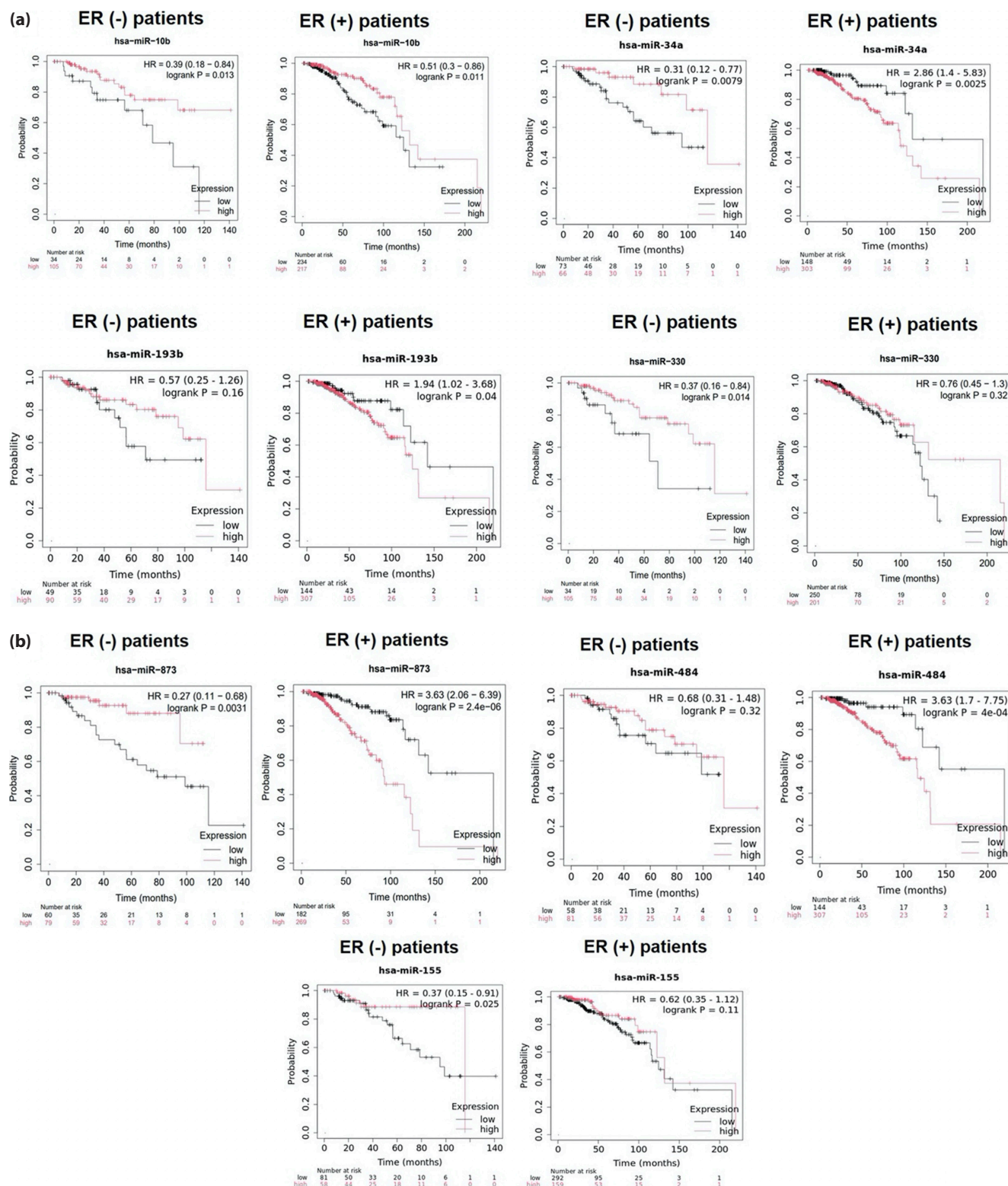


Figure 1. Kaplan–Meier survival analysis of miRNAs and their association with breast cancer survival. The clinical significance of the selected miRNAs was evaluated using the NCI-TCGA breast cancer database based on Kaplan–Meier survival analysis. Kaplan–Meier survival curves illustrate the associations between miRNA expression and patient survival in ER+ **(a)** and ER– **(b)** patients.

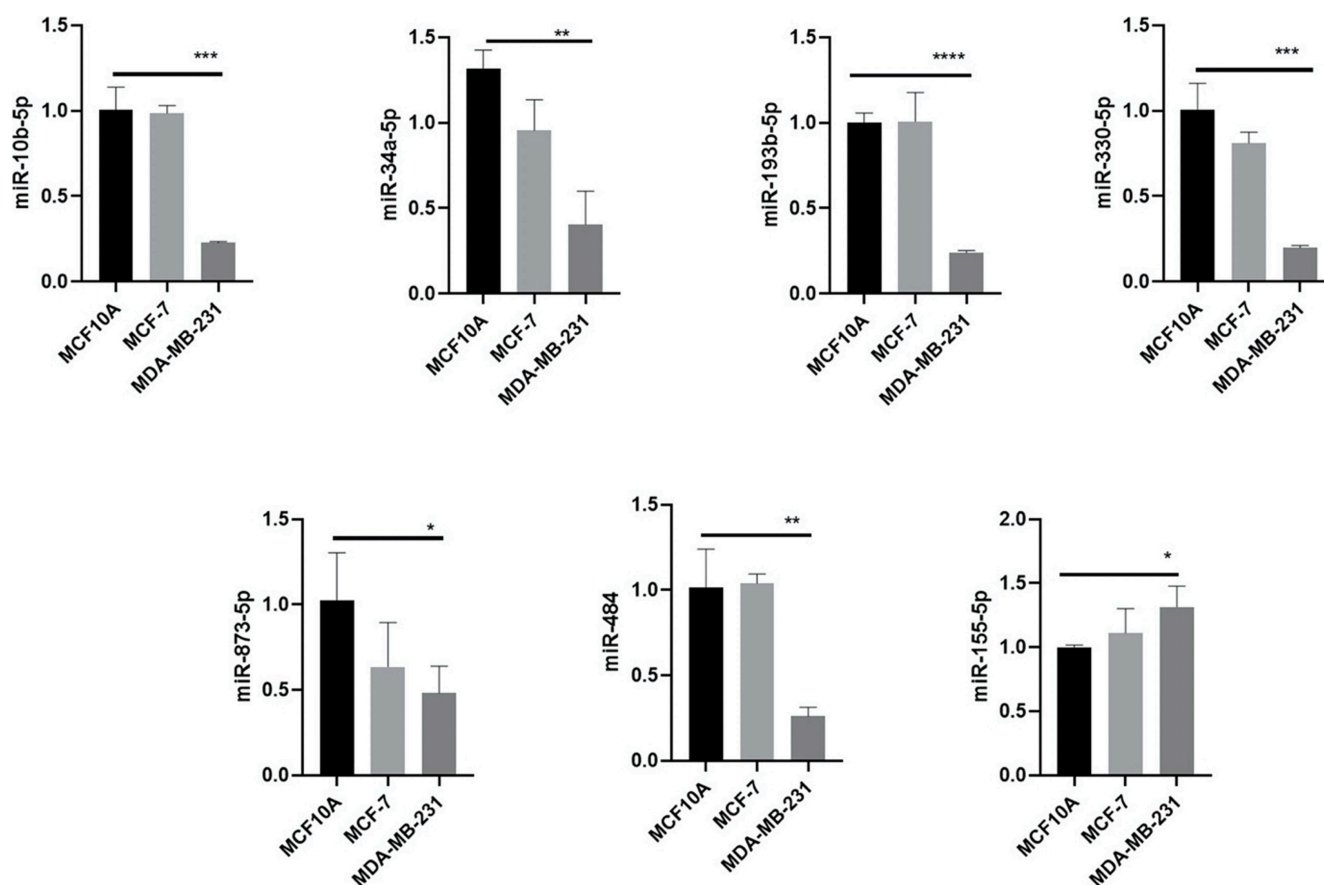


Figure 2. Endogenous expression levels of the selected miRNAs in breast cancer and normal cells. The expression levels of miRNAs were analyzed by RT-qPCR in normal breast epithelial cells (MCF10A), ER– MDA-MB-231 cells, and ER+ MCF-7 cells.

P<0.05; *P<0.01; **P<0.001; ***P<0.0001.

Collectively, these findings demonstrate that the prognostic value of several FOXM1-associated miRNAs differs according to breast cancer subtype, suggesting subtype-specific biological functions.

Endogenous miRNA Expression Profiles Differ Between TNBC and ER-Positive Breast Cancer Cells

To investigate whether the selected prognostic miRNAs exhibit subtype-specific expression patterns, their endogenous expression levels were analyzed by RT-qPCR in TNBC (MDA-MB-231), ER+ (MCF-7), and nontumorigenic breast epithelial (MCF10A) cells.

Compared with MCF-7 and MCF10A cells, MDA-MB-231 cells exhibited significantly lower expression of miR-10b-5p, miR-34a-5p, miR-193b-5p, miR-330-5p, miR-873-5p, and miR-484. In contrast, miR-155-5p expression was markedly elevated in MDA-MB-231 cells. No significant differences were observed between MCF-7 and MCF10A cells for the remaining miRNAs (Fig. 2).

These findings indicate that TNBC cells exhibit a distinct miRNA expression profile characterized by the suppression of multiple tumor-suppressive miRNAs and increased expression of the oncogenic miR-155-5p.

Expression Patterns of miRNAs in Breast Cancer Tissues Compared With Normal Tissues

To validate the clinical relevance of our experimental observations, the expression profiles of the selected miRNAs were further examined using the dbDEMC database. The analysis revealed that miR-34a-5p, miR-484, and miR-10b-5p were significantly downregulated in breast cancer tissues compared with normal breast tissues (logFC=–2.52, –1.83, and –2.10, respectively). Conversely, miR-330-5p (logFC=0.98) and miR-155-5p (logFC=0.76) were upregulated in tumor tissues. Comparison of high-grade and low-grade breast tumors demonstrated increased expression of miR-873-5p (logFC=0.49) and miR-10b-5p (logFC=0.24) in high-grade tumors. In addition, miR-193b-5p expression was relatively

Table 1. Expression profiles of miR-34a-5p, miR-873-5p, miR-193b, miR-330-5p, miR-10b-5p, miR-484, and miR-155-5p in breast cancer tissues compared with normal tissues based on the dbDEMC database

miRNA ID	Cancer type	Cell line	Design	logFC	Expression status
hsa-miR-34a	Breast cancer	N/A	Cancer vs. normal	-2.52	Downregulated
hsa-miR-873-5p	Breast cancer	N/A	High grade vs. low grade	0.49	Upregulated
hsa-miR-193b	Breast cancer	N/A	ER-positive breast tumor vs. ER-negative breast tumor	0.28	Upregulated
hsa-miR-330-5p	Breast cancer	N/A	Cancer vs. normal	0.98	Upregulated
hsa-miR-10b-5p	Breast cancer	N/A	Cancer vs. normal	-2.10	Downregulated
hsa-miR-10b-5p	Breast cancer	N/A	Breast invasive carcinoma stage 3 vs. breast invasive carcinoma stage 2	0.24	Upregulated
hsa-miR-484	Breast cancer	N/A	Cancer vs. normal	-1.83	Downregulated
miR-155-5p	Breast cancer	N/A	Cancer vs. normal	0.76	Upregulated

logFC: Logarithm of fold change; ER: Estrogen receptor; N/A: Not applicable.

higher in ER-positive breast tumors than in ER-negative tumors (logFC=0.28) (Table 1).

Overall, these database findings support the subtype-specific dysregulation of FOXM1-associated miRNAs observed in our experimental analyses.

FOXM1 Knockdown Is Associated With Altered miRNA Expression Profiles in Breast Cancer Cells

To determine whether FOXM1 regulates the expression of clinically relevant miRNAs, MDA-MB-231 and MCF-7 cells were transfected with two independent FOXM1-targeting siRNAs, followed by RT-qPCR analysis. FOXM1 knockdown efficiency was confirmed only at the mRNA level in the present study. Protein-level validation was not repeated because the same FOXM1 siRNAs had previously been validated by our group to efficiently suppress FOXM1 protein expression by Western blot analysis.^{11–15}

Consistent with their endogenous expression profiles, MDA-MB-231 cells exhibited substantially lower basal levels of miR-10b-5p, miR-34a-5p, miR-193b-5p, miR-330-5p, miR-873-5p, and miR-484 than MCF-7 cells (Fig. 3a). FOXM1 knockdown significantly increased the expression of all six tumor-suppressive miRNAs in MDA-MB-231 cells, whereas miR-155-5p expression remained unchanged following FOXM1 inhibition (Fig. 3b, c).

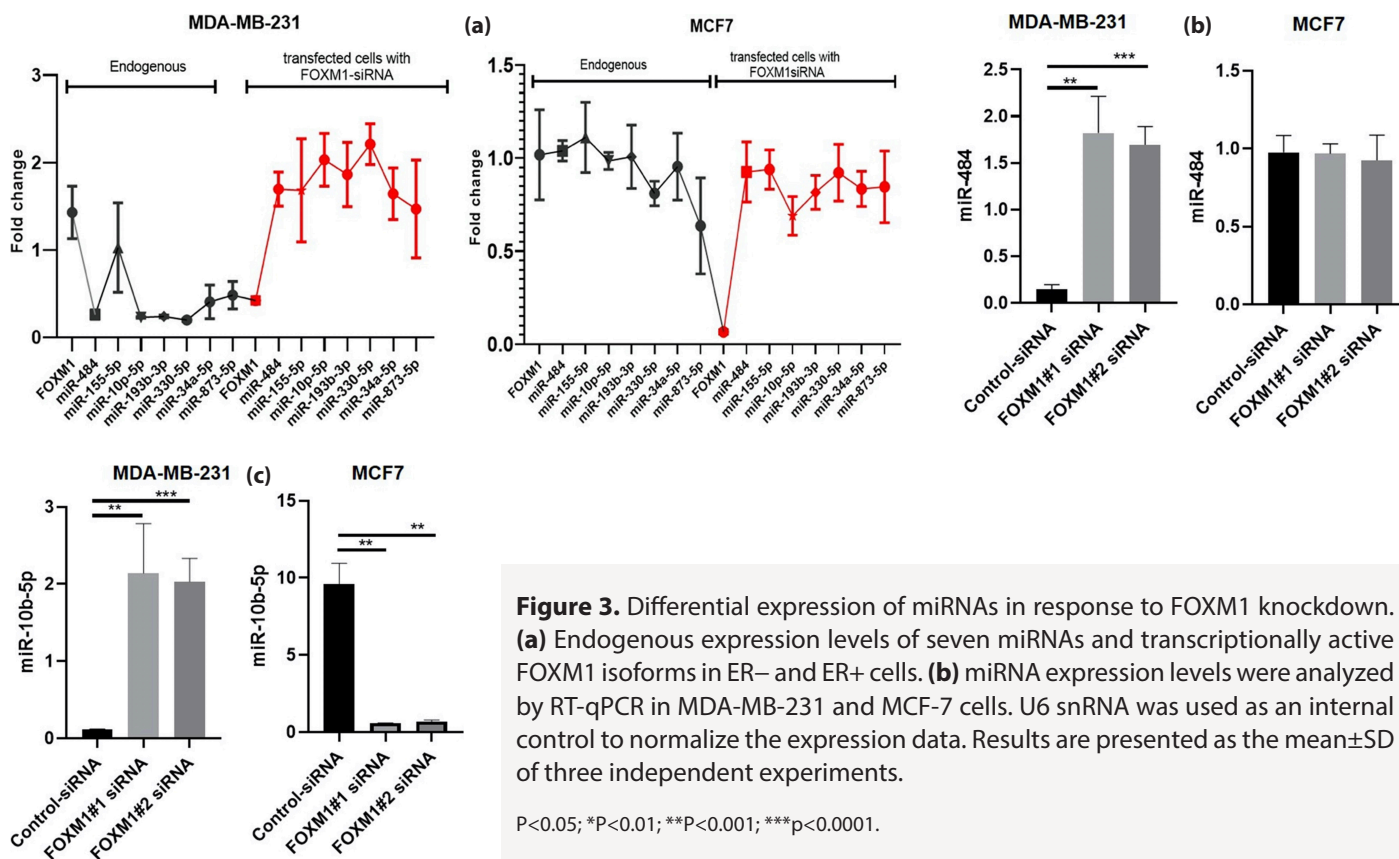
In contrast, FOXM1 silencing had minimal effects on miRNA expression in MCF-7 cells. Among the analyzed miRNAs, only miR-10b-5p showed a significant decrease following FOXM1 knockdown, whereas the expression levels of the remaining miRNAs were not significantly altered.

These findings indicate that FOXM1 inhibition is associated with subtype-specific alterations in the expression of clinically relevant miRNAs. The observed changes were considerably more pronounced in TNBC cells than in ER-positive breast cancer cells, suggesting that FOXM1 may contribute to the regulation of tumor-suppressive miRNAs in a subtype-dependent manner.

DISCUSSION

Breast cancer is a biologically heterogeneous disease in which distinct molecular subtypes exhibit substantial differences in clinical behavior, therapeutic response, and patient prognosis. Among these subtypes, triple-negative breast cancer (TNBC) remains the most aggressive because of its high metastatic potential, frequent chemoresistance, and lack of effective molecularly targeted therapies.^{12,13,16} Although aberrant miRNA expression has long been recognized as a hallmark of breast cancer progression, the upstream regulatory mechanisms responsible for subtype-specific miRNA dysregulation remain incompletely understood. In the present study, FOXM1 inhibition was associated with significant alterations in the expression of several clinically relevant miRNAs in TNBC cells, whereas only limited changes were observed in ER-positive breast cancer cells. These findings suggest that FOXM1 may contribute to subtype-specific miRNA regulation and support an association between FOXM1 signaling and the expression of tumor-suppressive miRNAs involved in TNBC biology.

FOXM1 is one of the most frequently overexpressed transcription factors in TNBC and has been implicated in cell-cycle progression, proliferation, epithelial–mesenchymal transition, metastasis, stemness, and therapeutic



resistance.^{5–8,11–15} The high prevalence of TP53 mutations in TNBC contributes to persistent FOXM1 activation through disruption of p53-mediated transcriptional repression, whereas ER-positive tumors generally exhibit lower FOXM1 expression because TP53 mutations occur less frequently. Although FOXM1 has previously been shown to regulate numerous oncogenic signaling pathways, its role in coordinating subtype-specific miRNA expression has remained largely unexplored. Our findings suggest that FOXM1 may contribute to the reduced expression of several prognostically significant tumor-suppressive miRNAs in TNBC cells. Although the present study demonstrates a clear association between FOXM1 inhibition and altered miRNA expression, the precise molecular mechanisms underlying this relationship remain to be determined. Future studies investigating direct transcriptional regulation, including promoter binding and chromatin occupancy analyses, will be required to establish whether FOXM1 regulates these miRNAs directly or indirectly.

An important observation of the present study is that the prognostic significance of several miRNAs differed markedly between ER-negative and ER-positive breast cancers. High expression of miR-10b-5p consistently predicted improved survival regardless of ER status, whereas miR-34a-5p, miR-330-

5p, and miR-873-5p exhibited opposite prognostic associations between patients with ER-negative and ER-positive breast cancer.^{17–26} These findings emphasize that the biological functions of individual miRNAs are highly dependent on the molecular context of the tumor rather than representing universal biomarkers. Such subtype-dependent behavior has been reported previously and is likely attributable to differences in transcriptional programs, receptor signaling, chromatin organization, and target gene availability across breast cancer subtypes.

Consistent with the clinical analyses, endogenous expression profiling demonstrated that multiple tumor-suppressive miRNAs were markedly downregulated in MDA-MB-231 cells compared with ER-positive MCF-7 and nontumorigenic MCF10A cells, whereas the oncogenic miR-155-5p was significantly upregulated. These findings support previous reports linking miR-155 to epithelial–mesenchymal transition, inflammatory signaling, immune modulation, and resistance to anticancer therapy.^{21–23} Interestingly, FOXM1 inhibition did not significantly alter miR-155-5p expression, suggesting that miR-155 may be regulated predominantly through alternative signaling pathways independent of FOXM1. This observation further highlights the selective nature of FOXM1-mediated miRNA regulation.

Collectively, these observations support a subtype-dependent association between FOXM1 signaling and clinically relevant miRNA expression. The differential response observed between TNBC and ER-positive cells further suggests that the influence of FOXM1 on miRNA expression may depend on the molecular context of individual breast cancer subtypes.

However, this study has several limitations. First, our findings are based on two representative breast cancer cell lines and therefore require validation in additional breast cancer models. Second, FOXM1 knockdown efficiency was confirmed only at the mRNA level, and protein-level validation was not performed in the present study. Third, miRNA expression was normalized using U6 snRNA as the endogenous reference gene. Although U6 is widely used for miRNA normalization, the inclusion of an additional validated reference gene would further strengthen the robustness of the analysis.¹¹ Fourth, because the seven selected miRNAs were analyzed using a hypothesis-driven targeted approach, no correction for multiple comparisons using the false discovery rate (FDR) was applied, which should be considered when interpreting the statistical findings. Finally, although FOXM1 knockdown was associated with significant alterations in miRNA expression, direct transcriptional regulation was not investigated using promoter-binding or chromatin occupancy assays, and the biological functions of the identified miRNAs were not evaluated in rescue experiments. These limitations should be addressed in future mechanistic and in vivo studies.

CONCLUSION

In conclusion, our findings demonstrate that FOXM1 inhibition is associated with subtype-specific alterations in the expression of clinically relevant miRNAs, particularly in TNBC cells. These observations suggest that FOXM1 may contribute to the dysregulation of tumor-suppressive miRNAs associated with the aggressive phenotype of TNBC. Although the present study establishes a strong regulatory association between FOXM1 signaling and miRNA expression, additional mechanistic studies are required to determine whether this regulation occurs through direct or indirect molecular mechanisms. Nevertheless, our findings provide further evidence supporting the FOXM1/miRNA axis as a potential therapeutic target for aggressive breast cancer.

Ethics Committee Approval: This study was conducted using established cell lines; therefore, ethical approval was not required as it did not involve human participants or animal subjects.

Informed Consent: Written informed consent was not required for this study.

Conflict of Interest: The authors have no conflicts of interest to declare.

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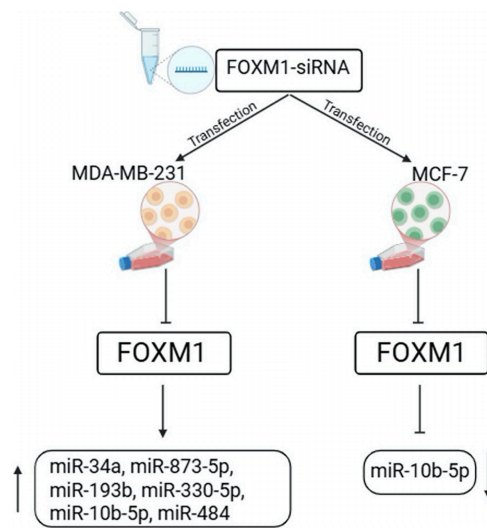
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Graphical abstract. Proposed association between FOXM1 signaling and the expression of clinically relevant miRNAs in breast cancer subtypes. Drawn using Biologic rendering software.