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The Significant Suppression of miR-4521 and Up Regulation of FOXM1 Isoforms in Breast Cancer

Sahar Kargar[1], **Shirin Shahbazi**[1*], **Loabat Geranpayeh**[2]

[1]Department of Medical Genetics, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran
[2]Department of Surgery, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran

*Corresponding Author: Shirin Shahbazi, Email: sh.shahbazi@modares.ac.ir

Abstract

Introduction: As a transcription factor, FOXM1 is elaborate in diverse aspects of cancer, such as proliferation, invasion as well as metastasis. *Alternative* splicing creates several FOXM1 isoforms, among which FOXM1b and FOXM1c are the key transcripts evaluated. Recently, FOXM1 was reported to be direct target of miR-4521, a microRNA with a possible tumor suppressor role. In this study alterations in miR-4521 expression and its association with FOXM1b and FOXM1c were investigated in ductal carcinoma of breast.

Methods: Gene expression was examined in 44 matched tumor and adjacent normal tissue samples, along with the MCF-7 cell line. By designing specific primers, the expression of two FOXM1 transcript variants and the miR-4521 gene, along with internal controls were calculated by quantitative Real-time PCR. The amplified fragments were checked via Sanger sequencing.

Results: The expression of FOXM1b and FOXM1c significantly increased in tumor tissues, emphasizing the oncogenic role of both transcript variants in breast cancer. The fold change in FOXM1b and FOXM1c were 4.62 and 3.12, respectively. miR-4521 was significantly down-regulated in tumors (fold change: 0.218), which validate the tumor suppressor effect. A decrease in miR-4521 expression had a statistically significant association with the increased expression of FOXM1b and FOXM1c ($P=0.000$).

Conclusion: Targeting the FOXM1 transcription factor represents a promising approach to halt breast cancer progression. Our findings indicate that FOXM1b and FOXM1c might have a role in the progress of breast cancer, and miR-4521 could be a potential candidate for their suppression.

Keywords: Alternative splicing, MicroRNAs, Forkhead box protein M1, Carcinoma, Ductal

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Introduction

Forkhead box M1 (FOXM1) is a key member of the FOX transcription factor family that has a vital role in late cell cycle progression. It targets a wide spectrum of genes, mainly present in DNA replication, genomic stability, and cell division. FOXM1 knockout mice are not viable due to the multiple impaired organs (1). A significant relationship between the increase of FOXM1 and the decrease in microRNA-4521 (miR-4521) has been verified in a childhood brain tumor, medulloblastoma (2). The miR-4521 gene is located on chromosome 17p13.1 and is known as a tumor suppressor microRNA. A recent publication on breast cancer has highlighted that miR-4521 downregulates FOXM1using luciferase reporter assay (3).

Breast cancer is the most prevalent and lethal female cancer. Since 2020, it has surpassed lung cancer and gained the highest cancer incidence in both sexes (https://gco.iarc.fr/today/en). With the advances that have been made on the characteristics of breast tumors, the prospects of patient`s treatment and survival have increased. However, chemotherapy resistance and a lack of response to targeted therapy remain serious concerns in breast cancer treatment (4, 5).

FOXM1 overexpression is one of the crucial factors in treatment failure in breast cancer. To overcome chemoresistance and insensitive to targeted therapy insensitivity, inhibition of FOXM1 was considered. Recently it has been described that when the FOXM1 inhibitors used in conjunction with CDK4/6 inhibitors as well as proteasome inhibitors synergistically promoted G2/M arrest in breast cancer (6).

The *FOXM1* gene spans ~25 kb on the chromosome 12p, encompasses 10 exons. Alternating splicing of exons Va and VIIa generate four mRNA isoforms, namely, FOXM1a, FOXM1b, FOXM1c, and FOXM1d. Exons Va and VIIa are present in FOXM1a and are absent in FOXM1b, whereas FOXM1c and FOXM1d have exons Va and exon VIIa, respectively. The main isoforms studied in cancer research are FOXM1b and FOXM1c (7, 8). It

has been shown that the inactivation of FOXM1b and FOXM1c in triple negative breast cancer (TNBC) confers growth as well as colony formation (9). Using various cell line and tissue RNA-seq datasets, Barger et al. identified FOXM1c as the main expressed isoforms in breast cancer. They performed further analyses on paired TCGA normal and tumor samples and reported that both FOXM1 isoforms are almost equally elevated in breast cancer (10).

This study aimed to determine the FOXM1 transcripts that are responsible for oncogenic action in breast cancer and are related to miR-4521 expression. To achieve these goals, we investigated the association between miR-4521 levels and the mRNA expression of FOXM1b and FOXM1c in tumor samples from women with breast ductal carcinoma.

Methods

Culture of the Cells

The MCF-7 cell line which represents Luminal A breast pathology was employed to validate the expression analysis. The cells were cultured in Dulbecco's Modified Eagle Medium (DMEM), 10% fetal bovine serum (FBS) and 1% penicillin/streptomycin. The cultures were incubated in a humidified atmosphere of 5% CO_2 at 37°C.

Patients and samples

Informed consent was attained from all patients. The histologically confirmed primary invasive ductal carcinoma (IDC) of the breast and the corresponding normal adjacent tissues (NATs) were collected from Sina and Farmaniyeh hospitals in Tehran (n = 44). The clinicopathological status of each tumor tissue including size, grade, as well as the levels of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2/neu) were recorded.

RNA extraction and cDNA synthesis

Total RNA from cells and tissues was extracted using TRIzol reagent (Yektatajhiz, Iran). After total RNA extraction, the quality and quantity of the extracted RNAs were evaluated by electrophoresis and nano-spectrophotometer (11). The RNA samples with a ratio of $1.8 \leq A260/A280 \leq 2.2$ were reverse-transcribed using cDNA synthesis kit (Yektatajhiz, Iran). To analyze miR-4521 expression, total RNA was converted to cDNA through the stem loop method (Table 1). The stable stem loop primers were designed for miR-4521 and SNORD47 (U47), according to the miRBase database (https://www.mirbase.org/). The noncoding-RNA U47 was used as the internal control in miR-4521 expression assays.

Quantitative Real-time PCR assay (qRT-PCR)

To accurately distinguish FOXM1b (Ensembl transcript: ENST00000361953.7) and FOXM1c (Ensembl transcript: ENST00000359843.7), the primers were specifically designed based on the Ensembl GRCh38 (Table 1). The forward primer for FOXM1c was considered on exons Va/VI junction and the reverse primer on VII/VIII junction. The FOXM1b forward and reverse primers were located at the junction of exons V/VI and inside exon VI, respectively (Figure 1). To quantify FOXM1b and FOXM1c expression levels, the *PUM1* gene was selected as the internal control gene.

The qRT-PCRs were performed on an ABI StepOne Plus using high ROX SYBR green master mix (Ampliqon). The reaction mixtures contained 5 pmol/µl of each forward and reverse primer, 5 µl of master mix including SYBR green, and 1 µl of cDNA. Each cDNA sample was applied in duplicate. The thermal cycling program was initiated with 15 min at 95°C as a pre-denaturation step and followed by 40 cycles of 95°C for 15 sec, 60°C for 45 sec, and finally, 15 sec at 95°C, 60 sec at 60°C.

Electrophoresis and Sanger sequencing

Amplified PCR fragments were analyzed on a 1.5% agarose gel using a 100 bp DNA ladder as reference. To validate the fidelity of the PCR amplification, bi-directional Sanger sequencing was carried out. The sequencing data

Table 1. The sequence of designed primers

Genes	Primer sequences (5´- 3´)
FOXM1b	F: GACCAGGTGTTTAAGCAGCAGA
	R: CGTGGTAGCAGTGGCTTCAT
FOXM1c	F: CACTTGGAATCACAGCAGAAACGA
	R: TCCTCAACTAGCAGCACCTTG
PUM1*	F: TCGGAAGTAGCAGTTCTCTCG
	R: CTGTGTCCAATGGGGGTCAA
U47*	F: CCACTGCTGTAATGATTCTGC
miR-4521	F: ATCGTGGGCTAAGGAAGTCC
Universal reverse (miR-4521& U47)	R: CCAGTGCAGGGTCCGAGGTA
miR-4521- Stem Loop	GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACCTGAGC
U47- Stem Loop**	GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACAACCTCAG

* PUM1 and U47 were applied as the internal control in mRNA expression and microRNA expression assays, respectively.
**The stable stem loops were designed for miR-4521 and U47 cDNA synthesis.

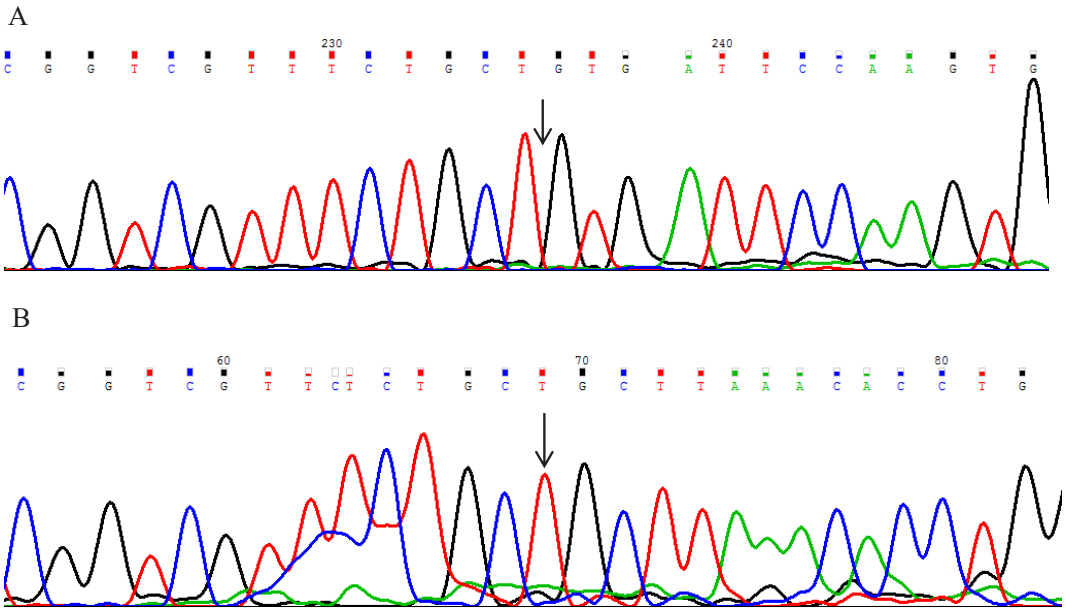

Figure 1. A: Electropherogram of FOXM1c, the arrow shows the junction of exons Va/VI and the presence of exon Va. B: Electropherogram of FOXM1b the arrow shows the junction of exons V/VI and the absence of exon Va

were subsequently examined using Chromas software (version 2.01).

Statistical analysis

Gene expression was evaluated using REST software, which applies a mathematical model accounting for precise PCR efficiencies and mean cross-point variations between the experimental and control groups. The statistical significance of the expression ratios was determined through the Pair Wise Fixed Reallocation Randomisation Test. The associations between gene expression and pathological parameters (Table 2) were examined using SPSS software. For group comparisons, non-parametric Wilcoxon, Mann–Whitney, and Kruskal–Wallis were employed. Statistically significant level was considered at $P < 0.05$.

Results

Verification of FOXM1b and FOXM1c mRNA expression

The designed primers effectively amplified the desired fragments of 113 bp and 275 bp for FOXM1b and FOXM1c, respectively, and yielded *a single sharp band following RT-PCR*. Melting curve analysis of Real-time PCR showed a single specific peak for each amplicon. The amplification products were sequenced to check the specificity of the transcripts. As shown in Figure 1, the presence and absence of exon Va were confirmed in the FOXM1b and FOXM1c amplicons, respectively.

MCF-7 cells displayed FOXM1b as well as FOXM1c expression. The analysis of the three successive repetitions of cell culture did not show significant differences in the delta CT values of FOXM1b and FOXM1c in MCF-7 cell line compared to tumor tissues (Figure 2).

Up-regulation of FOXM1b and FOXM1c transcripts in tumor tissues

The raw amplification data were transferred to LinReg software and used to calculate primer efficiency. The relative expression levels of FOXM1b and FOXM1c mRNAs in tumors compared with NATs indicated significant upregulation of both transcripts. FOXM1b was expressed with a fold change of 4.62 (*P-value*; 0.000). The upregulation of FOXM1c was also statistically significant ($P = 0.001$) with a fold change of 3.12 comparing tumors to NATs (Figure 3A).

Down-regulation of miR-4521 correlated to FOXM1b and FOXM1c transcripts

The results show a significant decrease in miR-4521 levels compared to NATs (Figure 3B). Analysis by REST software calculated the fold change of 0.218 with a significant *P-value* of 0.000. According to the results obtained by non-parametric Wilcoxon test (SPSS software), increases in the expression of FOXM1b and FOXM1c transcripts have a significant association with miR-4521 $P = 0.01$).

Patient's data and clinicopathological status links to gene expression

The mean age of the participated breast cancer female patients was 54.31 ± 2.9 years with a minimum age of 34 years and a maximum age of 84 years. The pathological assessments of ER, PR, and HER2 expression revealed that 50% of the tumors were luminal, 36.3% were HER2 positive, and 13.6% were basal-like subtypes. Grade I was reported in 18.3%, Grade II in 54.5%, and Grade III in 27.2% of the tumors (Table 2).

By applying non-parametric Wilcoxon signed rank test (SPSS software), a significant inverse relationship between miR-4521 and tumor size was disclosed ($P = 0.000$). A weakly significant association was also identified between FOXM1b and family history of any type of cancer, using Mann-Whitney test ($P = 0.045$).

We could not detect significant expression differences of FOXM1b, FOXM1c, and miR-4521 related to ER, PR,

Table 2. The histopathological data of the tumor samples

Estrogen receptor		Progesterone receptor		Her-2		Histology grade		Lympho-vascular invasion	
Positive	81.8%	Positive	68.2%	Positive (1-2)	18.2%	Grade I	18.3%	Positive	59.1%
Negative	13.6%	Negative	27.3%	Positive (3+)	13.6%	Grade II	54.5%	Negative	36.4%
Not specified	4.6%	Not specified	4.5%	Negative	68.2%	Grade III	27.2%	Not specified	4.5%

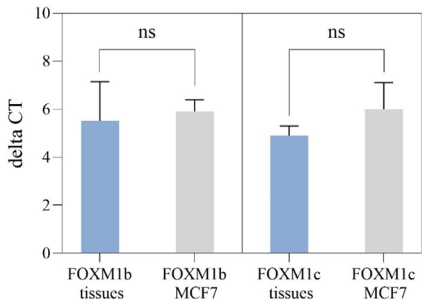

Figure 2. A: FOXM1b and FOXM1c gene expression in tumor tissues compared to MCF-7 cell line. Since the gene expression results in MCF-7 were not normalized, the values of FOXM1b and FOXM1c are displayed as delta CT to allow for proper comparison

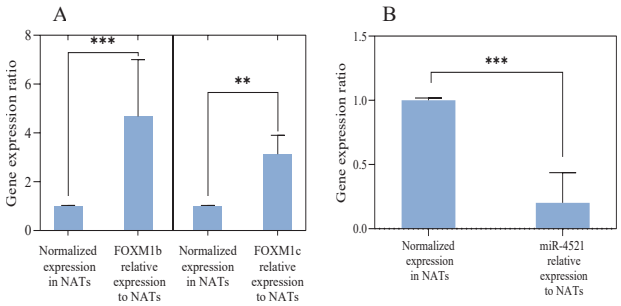

Figure 3. A: FOXM1b and FOXM1c relative gene expression. B: miR-4521 relative gene expression. The bar plots signify expression in the tumor compared to NATS

HER2, lymphatic invasion and/or histological grade of tumors. Adjustment for menopausal status did not alter the overall gene expression profile.

Discussion

Since, all cancer hallmarks such as proliferation, mitosis, invasion, and metastasis are under regulation of FOXM1; the impact of its transcript variants on cancer, worth taking into consideration. Among FOXM1 isoforms, FOXM1b and FOXM1c are RNA-synthesizing and explored in cancer studies from different molecular aspects (12, 13). A comprehensive bioinformatics study identified increased expression of FOXM1 in tumors with an inactivated retinoblastoma 1 (*RB1*) gene. This increased expression was observed at both the mRNA and protein levels and was found to be associated with genomic instability (10). They also found that among the FOXM1 transcripts, FOXM1c has the strongest activity in non-tumors and tumors tissues. Using the CRISPR-based silencing technique, it was further displayed that FOXM1b and FOXM1c promoted transcription, while FOXM1a lacked such activity (10). RB1 is known as a negative regulator of FOXM1c, which exerts its effect by binding to internal inhibitory domains including amino acids encoded by exon Va (13). However, recently a pro-metastatic role of RB1 in complex with FOXM1 has been determined. Since some targeted therapy drugs induce RB1 activity, these researchers suggested that FOXM1 expression levels must be examined before starting treatment in patients (14). But it is still not clear which FOXM1 variants play a major role in drug resistance.

Investigations have shown that the activation of the RAF/MEK/MAPK signaling pathway increases FOXM1c expression and activation. Using transient reporter assays, it was found that MEK1 enhances the activation effect of FOXM1c, but it has no specific effect on FOXM1b (15). Due to the regulatory differences between the two isoforms and the inhibitory effects on the regulation of FOXM1c, it is partly believed that FOXM1b is the dominant isoform in most cancers (12).

Studies have identified the miRNAs that affect FOXM1 expression (3). In a research conducted on medulloblastoma tumor samples and related cell lines, a significant correlation between increased FOXM1 and decreased miRNA-4521 expression was observed. To prove this correlation, miRNA-4521 was overexpressed in the DAOY and UW228.2 cell lines, which led to a decrease in FOXM1 levels and subsequent cell-cycle arrest (2). In non-small cell lung cancer (NSCLC), reduced miR-4521 levels are linked to enhanced tumor cell proliferation, migration, and invasion, contributing to poor patient outcomes. Complementary bioinformatics analyses using TargetScan identified FOXM1 as a principal downstream target of miR-4521 in NSCLC (16). Using a luciferase reporter assay, Kuthethur et al. also investigated breast cancer and proved that miRNA-4521 directly targets FOXM1. It was also shown that up-regulation of miRNA-4521 meaningfully down-regulate the expression of FOXM1 (3).

In our project, we observed a significant increase in FOXM1b and FOXM1c in tumors compared with NATs. We also discovered significant down-regulation in miR-4521 that favors a tumor suppressor role.

The tumor-suppressive role of miR-4521 has been demonstrated across multiple cancer types. In clear cell renal cell carcinoma (ccRCC), the loss of this microRNA was observed align with disease progression. Conversely, enforced miR-4521 expression in ccRCC cell lines (786-O and ACHN) diminished invasive capacity and enhanced apoptotic activity (17). Investigation on hepatocellular carcinoma cell lines HCCLM3 and HepG2 disclosed that upregulation of miR-4521 declined cell proliferation and repressed comportment of migration and invasion. It was also found that elevated expression of miR-4521 increases apoptosis via the focal adhesion kinase (FAK) and AKT phosphorylation pathways (18). Analyses of breast cancer

specimens demonstrated that miR-4521 expression is downregulated and is correlated with tumor grade, lymph node involvement, and clinical stage. Conversely, enforced expression of miR-4521 inhibited breast cancer cell proliferation, invasion, and progression through the cell cycle (19). However, in our study, we could not find a significant relationship between the pathological characteristics of the breast tumors and gene expression, which can be caused by the limited number of samples in each category.

By specifically evaluating the gene expression data of breast cancer patients, Park et al. indicated that among the transcription factors, FOXM1 has the highest correlation with overall survival (OS) in TNBC subtype. Silencing FOXM1 increases the susceptibility of breast cancer cells to doxorubicin treatment (20). Another study found that overexpression of FOXM1 causes resistance to the process of apoptosis by upregulating X-linked inhibitor of apoptosis protein (XIAP) and Survivin. Their obtained results showed that the simultaneous increase in the expression of FOXM1, Survivin, and XIAP is significantly related to chemotherapy resistance and reduced OS in breast cancer patients (21). The significant association of FOXM1 with poor OS in breast cancer patients has been confirmed by another research showing that a reduction in FOXM1 sensitizes breast cancer cells to paclitaxel-induced senescence (22). Using different techniques, it was confirmed that an anticancer drug that inhibits FOXM1 resulted in pronounced suppression of proliferation and migration, together with elevated apoptosis in TNBC cells. It was also found that the combination of this FOXM1 inhibitor and Doxorubicin significantly improves the effectiveness of chemotherapy and reduces side effects (23).

Conclusion

Our findings revealed a significant difference in FOXM1b and FOXM1c mRNA expression between breast tumor tissues and their non-tumor counterparts. Additionally, raised levels of FOXM1b and FOXM1c were significantly associated with reduced expression of miR-4521. Considering the growing importance of FOXM1 in cancer therapeutics—especially in breast cancer—further characterization of its diverse functions may lead to the development of more effective treatment strategies.

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Authors' Contribution

Conceptualization: Shirin Shahbazi
Data curation: Shirin Shahbazi, Loabat Geranpayeh, Sahar Kargar
Formal analysis: Shirin Shahbazi, Sahar Kargar
Investigation: Shirin Shahbazi, Loabat Geranpayeh, Sahar Kargar
Methodology: Shirin Shahbazi, Loabat Geranpayeh
Project administration: Shirin Shahbazi, Sahar Kargar
Resources: Shirin Shahbazi, Loabat Geranpayeh, Sahar Kargar
Software: Shirin Shahbazi, Sahar Kargar
Supervision: Shirin Shahbazi
Validation: Shirin Shahbazi
Visualization: Shirin Shahbazi, Sahar Kargar
Writing–original draft: Shirin Shahbazi, Loabat Geranpayeh, Sahar Kargar

Competing Interests

The authors declare that they have no conflict of interest.

Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article

Ethical Approval

This study was approved by the Ethics Committee of Tarbiat Modares University, Tehran, Iran (Ethical code: IR.MODARES.REC.1399.132). Informed consent was obtained from all participants included in the study.

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