MicroRNA-155 Regulates Cell Survival, Growth, and Chemosensitivity by Targeting FOXO3a in Breast Cancer*

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This article has been withdrawn by all the authors except for William Kong. The same data were used to represent different experimental conditions. Specifically, the U6 panel from Fig. 1B was reused in Figs. 2B and 5B. The U6 panel from Fig. 1C was reused in Fig. 5B. The miR-155 band in lane 2 from BT-474 cells in Fig. 2B was reused as the miR-155 band from Hs578T cells in Fig. 5A. The actin panel in Fig. 3A was reused as the actin panel in Fig. 3C. The authors state that they stand by the findings and overall conclusions.
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|   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|
| 1) MCF-10A | 7) MDA-MB-453 |
| 2) MCF-7 | 8) MDA-MB-468 |
| 3) MDA-MB-157 | 9) BT474 |
| 4) MDA-MB-231 | 10) H578T |
| 5) MDA-MB-361 | 11) SKBR3 |
| 6) MDA-MB-435 | 12) T47D |

**B** miR-155:
- Vector: - +

**C** miR-155 ASO:
- Scramble ASO: + -

**D** BT-474

**E** BT-474

**F** HS578T

**G**

**H**

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unknown PR and Her2 status. Each cancer specimen contained at least 80% tumor cells, as confirmed by microscopic examination and/or protein extraction. Tissues were either preserved by snap-freeze and stored at −80 °C or embedded in paraffin blocks for subsequent RNA isolation.

Plasmids—Lenti-miR-155 was purchased from System Biosciences and miR-155 and control mimics (20). miR-155 and control mimics were purchased from Ambion. miR-155 antisense oligonucleotides (ASOs) were synthesized from IDT-DNA with sequence as previously described (20). FOXO3a expression vector was kindly provided by Dr. B. M. T. Burgering.

Northern Blot, Locked Nucleic Acid in Situ Hybridization (LNA-ISH), and Immunohistochemical Staining—Total RNA was extracted from cell lines and breast cancer and normal tissue was isolated using TRIZol® reagent (Invitrogen) according to the manufacturer’s protocol. Norther analysis on breast cancer cell lines and tissue RNA were performed using the Starfire™ oligonucleotide-labeling kit (IDT-DNA). The expression of miR-155 was determined by comparing the miR155/U6 ratio between samples. The resulting value was then transformed by applying 2⁻ΔΔCt, where the Ct value of miR-155 was divided by the U6 Ct from the same sample. The resulting value was then transformed by applying 2⁻ΔΔCt. B and C, Northern blot. BT-474, expressing low endogenous miR-155, was stably infected with lentivirus expressing miR-155 and vector (B). HS578T cells, presenting high endogenous miR-155, were transfected with anti-miR-155 (ASO) and control oligonucleotide (C). After incubation of 24 h, total RNAs were isolated and subjected to Northern blot analysis with the indicated probes. D–F, expression of miR-155 induces cell growth, survival, and chemoresistance. miR-155- and vector-infected or oligonucleotide mimic-transfected BT-474 cells were treated with and without doxorubicin for the indicated times (D) or with the indicated chemotherapeutic agents for 24 h (E and F). The growth curve was determined by counting cell number at different time points (D). Apoptosis was assayed by a terminal deoxynucleotidyltransferase-mediated dUTP nick-end labeling assay (E) as well as caspase 3/7 activity (F). G–I, knockdown of miR-155 inhibits cell growth/survival and sensitizes cells to chemotherapeutic drug-induced cell growth arrest and apoptosis. Anti-miR-155 and scrambled oligonucleotide-treated HS578T cells were treated with the same agents and assayed with the same methods as described in D–F. Data represent three independent experiments with four replicates each. * p < 0.05. Error bars, S.E.
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tems). Briefly, 200 ng of total RNA from each cell line and tumor RNA were used for primer-specific reverse transcription (RT) in both Hsa-miR-155 and U6, and then 2 μl of the RT product was used for subsequent quantitative PCR. The quantitative PCR was performed on an Applied Biosystems 7900HT fast real-time PCR system, and data were collected and analyzed using ABI SDS version 2.3. To calculate relative concentration, miR-155 and U6 C_T values for all samples were obtained. A normalized expression for each sample was obtained by dividing the C_T value of miR-155 by the same sample’s U6 C_T and designated as ΔC_T. This value was then transformed by performing 2^-ΔΔC_T. Furthermore, the (ΔΔC_T) method was used in comparing miR-155 expression in immortalized cells with cancer cells or comparing normal breast with cancer tissues according to the manufacturer’s protocol.

**Cell Viability and Apoptosis Assays**—Optimal drug concentration for induction of apoptosis in BT-474 and Hs578T cell lines was titrated by measuring cleaved caspase activity with Caspase-Glo® 3/7 assays (Promega). The following concentrations were used for all subsequent experiments: doxorubicin (2.5 μM), paclitaxel (5 nM), and VP-16 (400 μM). After infection of miR-155-lentivirus (BT-474) or transfection of 2′-O-Me anti-miR-155 (Hs578T) and treatment with individual drugs, cell viability was examined with a 3-(4,5-di methylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay, as described previously (42). Apoptosis was detected using the Cell Death Detection ELISAPLUS kit according to the manufacturer’s protocol (Roche Applied Science). Cleaved PARP was quantified as described for caspase activity, and survival was calculated relative to chemotherapeutic agents. Initially, we compared miR-155 expression in 12 breast cancer cell lines by Northern blot. Three cell lines, MDA-MB-157, MDA-MB-435, and MDA-MB-453, had significantly elevated levels of miR-155, whereas the remaining cell lines had lower expression of miR-155 (Fig. 1A and Table 1). To examine the effect of miR-155 on chemosensitivity, we ectopically expressed miR-155 in BT-474 (e.g. low miR-155) and knocked down miR-155 in Hs578T (e.g. high miR-155) cells. Briefly, BT-474 and Hs578T cells were infected with lentivirus expressing miR-155 and 2′-O-methyl antisense-miR-155 oligonucleotides, respectively. The cells infected with lentiviral vector and transfected with scrambled oligonucleotides were used as controls. After 48 h of incubation, expression of miR-155 was confirmed by Northern blot analysis (Fig. 1A, B and C). Notably, modulation of miR-155 alone is sufficient to significantly affect cell growth and the programmed cell death (i.e. ectopic expression of miR-155 in BT-474 promotes cell proliferation and cell survival (Fig. 1, D–F; p < 0.05), whereas depletion of miR-155 in HS578T induces cell growth arrest and apoptosis (Fig. 1, G–I; p < 0.01). Moreover, expression of miR-155 renders BT-474 cells resistant to doxorubicin, VP16, and paclitaxel (Fig. 1, E and F). On the other hand, knockdown of miR-155 sensitizes HS578T cells to apoptosis induced by these chemotherapeutic agents (Fig. 1, H and I). These data indicate that miR-155 is a determinant of chemosensitivity in breast cancer cells.

FOXO3a Is Negatively Regulated by miR-155—Because miR-155 plays a significant role in cell growth and the programmed cell death, we performed an *in silico* search for reporter plasmids, 0.1 μg of pCMV-β-gal, and, where applicable, 5 nm miR-155 precursor or control or 50 nm miR-155 ASO or control per well on 96-well plates. Following 24 h of incubation, cells were subjected to a luciferase reporter assay using the Luciferase Assay System (Promega). Luciferase activities were normalized by β-galactosidase activities. Each experiment was repeated at least three times in triplicate.

### Statistical Analysis

The significance was analyzed by unpaired Student’s test. A p value of 0.05 was considered to be statistically significant.

#### Table 1

*Quantification of miR-155 expression in breast cancer cell lines*

| Cell line | C_T | S.D. | ΔC_T | 2^-ΔΔC_T |
|-----------|-----|------|------|----------|
| MCF-10A   | 28.56 | 2.99  | 3.34  | 0.10     |
| MCF-7     | 26.89 | 2.09  | 2.72  | 0.15     |
| MDA-MB-157| 18.54 | 1.68  | 5.77  | 54.47    |
| MDA-MB-231| 28.16 | 3.45  | 4.47  | 0.05     |
| MDA-MB-361| 28.46 | 2.40  | 4.40  | 0.05     |
| MDA-MB-435| 20.81 | 2.80  | 1.38  | 2.60     |
| MDA-MB-453| 28.64 | 2.56  | 4.97  | 0.03     |
| MDA-MB-468| 28.56 | 2.19  | 3.95  | 0.06     |
| BT-474    | 27.79 | 1.81  | 4.85  | 0.03     |
| HS578T    | 18.71 | 1.57  | 5.68  | 51.35    |
| SKBR3     | 27.78 | 3.20  | 4.33  | 0.05     |
| T47D      | 28.71 | 2.27  | 5.04  | 0.03     |

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miR-155 targets using miRanda (available on the World Wide Web), TargetScan, MicroCosm, and RNA22. Both miRanda and RNA22 data base analyses revealed that 3’-UTR of FOXO3a, an important transcriptional factor in regulation of cell growth and apoptosis (32, 43, 44), contains a conserved motif (3370–3392 bp, NM_001455) that

A

5’ - GGGG-GTCAGAAAAGAAGCATTAA - 3’ Xenopus L. FOXO3a
5’ - ACAACCATGTA-TAT-AGAGTTAA - 3’ Danio R. FOXO3a
5’ - CGAGGCTTAA-CAGGG-GAGGTTAA - 3’ Homo S. FOXO3a
3’ - UGG--GAUAGUCAAUCGUAAU - 5’ miR-155

5’ - ATGAACCTTA-CAGGG-GAGGTTAA - 3’ FOXO3a Mutant
3’ - UGG--GAUAGUCAAUCGUAAU - 5’ miR-155

B

C

D

E

F

G

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matches with the “seed” sequence (e.g. nucleotides 2–8) of miR-155 (Fig. 2A).

Because BT-474 and MDA-MB-468 cells normally express low levels of miR-155 and high FOXO3a (Figs. 2B and 4A), we transfected the cells with pre-miR-155. This resulted in an about 50–60% reduction of FOXO3a proteins (Fig. 2B) (data not shown). In contrast, HS578T and MDA-MB-157 normally express low FOXO3a proteins and high miR-155 (Figs. 2C and 4A), so we proceeded to suppress miR-155 expression with miR-155 ASO. This resulted in an increase of FOXO3a protein expression (Fig. 2C) (data not shown). However, RT-PCR analysis revealed that FOXO3a mRNA levels remained unchanged (Fig. 2, B and C), indicating that miR-155 targets FOXO3a by translational inhibition, not mRNA degradation.

3′-UTR of FOXO3a Interacts with miR-155—To investigate whether miR-155 repression of FOXO3a is mediated by direct interaction of miR-155 with FOXO3a 3′-UTR, we cloned two tandem repeats of WT miR-155–FOXO3a response element or MUT into pMIR-REPORT plasmid downstream of luciferase (Fig. 2, A and D). Basal levels of pMIR-FOXO3a reporter activ-
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Downstream Targets of FOXO3a Were Inhibited by miR-155—Because FOXO3a is an important transcriptional factor that regulates proapoptotic and growth inhibition genes, we next examined if expression of Bim and p27, two major downstream targets of FOXO3a, is affected by modulation of miR-155 in breast cancer. Immunoblotting analysis with anti-Bim and -p27 antibodies revealed that basal levels of Bim and p27 were reduced by stable expression of miR-155 in breast cancer cell lines. Further, expression of miR-155 represses WT-pMiR-FOXO3a but not MUT-pMiR-FOXO3a reporter activity in BT-474 (Fig. 2F). In contrast, cotransfection of miR-155 ASO and WT-pMiR-FOXO3a in HS578T resulted in an increase of luciferase activity, but the same experiment carried out with the MUT-pMiR-FOXO3a construct resulted in little change (Fig. 2G). As a control, miR-199a-5p, a FOXO3a-unrelated microRNA, and miR-199a-ASO were transfected into the cells and were shown no effects on miR-FOXO3a activity (Figs. 2, F and G). These data indicate that miR-155 directly targets FOXO3a 3′-UTR at the miR-155-FOXO3a response element (Fig. 2, A and D) to repress FOXO3a protein expression.

Introduction of FOXO3a cDNA Lacking 3′-UTR Largely Abrogates miR-155 Cellular Function—Because miR-155 directly targets FOXO3a through interaction between FOXO3a 3′-UTR and miR-155, we reasoned that ectopic expression of FOXO3a by transfection of the cDNA that only contains the open reading frame of FOXO3a (FOXO3a-ORF) should escape the regulation by miR-155 and thus attenuate or decrease miR-155 function. To this end, we transfected pcDNA-FOXO3a-ORF and/or miR-155 into BT-474 cells and treated them with and without doxorubicin for 24 h. Immunoblotting analysis revealed that expression of FOXO3a alone moderately induced expression of Bim and p27 as well as PARP cleavage (Fig. 4A, lane 3), but combination of FOXO3a and doxorubicin considerably enhanced these effects (Fig. 4A, lane 7). In agreement with Fig. 3, expression of miR-155 alone reduced expression of FOXO3a, Bim, and p27 as well as PARP cleavage (Fig. 4A, lanes 2 and 6) compared with the cells transfected with pcDNA3 vector (Fig. 4A, lanes 1 and 5) in the absence and the presence of doxorubicin. However, co-expression of FOXO3a with miR-155 largely reduced the miR-155-inhibitory effect on Bim and p27 expression and PARP cleavage (Fig. 4A, lanes 4 and 8 versus lanes 2 and 6). Further, miR-155-inhibited apoptosis and caspase 3/7 activity induced by doxorubicin were also significantly reduced by ectopic expression of FOXO3a (Fig. 4, B and C). Based on these results, we conclude
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that the FOXO3a is a major target of miR-155 and largely mediates miR-155 antiapoptotic function.

**Inverse Correlation of Expression of miR-155 and FOXO3a in Breast Cancer**—Having demonstrated FOXO3a as a major target of miR-155, we next investigated the correlation between miR-155 and FOXO3a expression in breast cancer cell lines and breast tumors. Of 12 cell lines examined, three expressing high levels of miR-155 exhibited undetectable or low level FOXO3a. Of nine cell lines with low levels of miR-155, eight expressed high levels of FOXO3a (Fig. 5A). Moreover, we examined 77 human breast cancer specimens and 11 normal breast tissues with Western blots, Northern blots, immunohistochemical staining, and LNA-microRNA in situ hybridization. Up-regulation of miR-155 was detected in 55 breast cancers and one normal breast tissue (Fig. 5, B–D). Of the 55 tumors with elevated miR-155, 41 (75%) had low levels of FOXO3a (p < 0.001), whereas 16 of 22 (73%) specimens with down-regulated miR-155 presented high levels of FOXO3a (Fig. 5E). However, we did not observe a significant relationship of miR-155 levels with tumor stage, grade, and status of ERa, PR, and Her2, which could be due to the limited number of tumor samples examined. In addition, we examined miR-155 and FOXO3a levels in 38 recurrent breast cancers due to chemo- and/or radioresistance after surgical removal. The qRT-PCR and/or immunoblotting analyses show that 31 recurrent tumors expressed elevated miR-155 and low FOXO3a (p < 0.001; Fig. 5D, E). These findings suggest that miR-155 regulates FOXO3a in vivo and that elevated levels of miR-155 are associated with chemo- and/or radio-resistance.

**DISCUSSION**

miR-155 has emerged as an important regulator of immune cell physiology, particularly of the adaptive system (23, 36, 37). For instance, miR-155 regulates immune response in activated T lymphocytes (46), germinal centers B cells (23), and monocytes (21). BIC/miR-155 knock-out mice resulted in impaired immune response and cytokine production (23), further supporting the vital role of miR-155 in immunology. In addition, Down syndrome or trisomy 21 was recently linked with high levels of miR-155 and thus provides further insights into the resulting cognitive impairment and congenital heart defects seen in patients (47). In cancer, deregulation of miR-155 is implicated in a wide range of malignancies, including various forms of lymphoma and carcinomas of breast, lung, pancreas, head and neck, and kidney (9, 11, 13–15). In immunology and lymphoma, miR-155 has been extensively investigated; however, it is only evident that miR-155 expression is elevated in breast cancer (13, 15), and detailed function remains elusive. We demonstrate in this study that miR-155 is a determinant of chemosensitivity by targeting FOXO3a in breast cancer. We show that miR-155 directly interacts with 3’-UTR of FOXO3a and blocks FOXO3a translation. As a result, Bim and p27, major downstream targets of FOXO3a, are inhibited by miR-155. Ectopic expression of FOXO3a-ORF largely abrogated miR-155-induced chemoresistance. In addition, inverse correlation between miR-155 and FOXO3a expression was detected in breast cancer cell lines and tumors. These findings demonstrate for the first time that deregulation of miR-155 in breast cancer is associated with chemosensitivity and that FOXO3a is a bona fide target of miR-155.

FOXO3a is a well studied transcriptional factor that contains a forkhead DNA binding domain and plays a crucial role in apoptosis and cell growth by transcriptional regulation of a number of apoptosis/cell growth-associated genes (24, 32, 43). Overexpression of FOXO3a inhibits tumor cell growth in vitro and tumor size in vivo in breast cancer cells (28, 48). In addition, genetic deletion of three FOXO (FOXO1, FOXO3, and FOXO4) alleles generates progressive carcinogenetic phenotypes, such as thymic lymphoma and hemangiomata (49). These data elucidated FOXOs as potential tumor suppressor genes. Recent studies also revealed FOXOs in the self-renewal of hematopoietic stem cells (50, 51). Moreover, FOXO3a is predicted to be deregulated in breast cancer, which is often linked to a decline in chemoresistance in cancer. The translational regulation of FOXO3a by miR-155 nega- 

tively regulates expression of FOXO3a in breast cancer cells (28, 48). In addition, FOXO3a is a major but not necessarily the only target for the expression of miR-155; other genes may also contribute to the expression of miR-155 in breast cancer.

**FIGURE 5.** miR-155 inversely correlates with FOXO3a expression in breast cancer tissue and cell lines. A, Western (top two panels) and Northern (panels 3 and 4) analyses of 12 breast cell lines for expression of FOXO3a and miR-155. The bottom panel shows the quantification of FOXO3a and miR-155. B and C, expression of FOXO3a and miR-155 was analyzed in representative of breast tumors with Western/Northern blot (B), miR-155 LNA-ISH, and immunohistochemical staining (C, D, representatives of recurrent tumors (RT1–RT10) were analyzed with qRT-PCR (top; miR-155) and immunoblotting analysis (bottom). Expression levels of miR-155 and FOXO3a were quantified as described under “Experimental Procedures.” E, x^2 test analysis of miR-155 and FOXO3a expression in 77 breast cancer specimens was examined. The inverse correlation is significant (p < 0.001). Error bars, S.E.
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that mediates miR-155 function in the control of cell growth, survival, and chemosensitivity.

Finally, we noticed that miR-155 is more frequently up-regulated in breast tumors than cancer cell lines. A possible reason is that miR-155 in tumor cells could be induced by cytokines that are released from the tumor microenvironment. In agreement with this notion, miR-155 has been shown to be transcriptionally regulated by NFκB, AP1, and Foxp3 in response to cytokines during immune cell maturation and development (36, 63–65). We also demonstrated transcriptional regulation of miR-155 via transforming growth factor-β/Smad pathway (20). In addition, accumulated studies show that gene expression, biology, and clinical outcome of cancer are significantly influenced by the microenvironment (66, 67). A three-dimensional culture model has been established to recapitulate the in vivo functions, interactions, and architecture of the mammary gland and breast tumor (66, 67), which more closely resembles the tumor microenvironment than traditional tissue culture. In order to address if miR-155 expression is influenced by microenvironment, further investigation is required using a three-dimensional culture system and animal models.

In summary, we demonstrated that miR-155 contributes to chemoresistance in breast cancer. FOXO3a is negatively regulated by miR-155 and mediates miR-155 function in the control of breast cancer cell survival and growth. In combination with our previous findings of miR-155 induction of epithelial-mesenchymal transition, cell migration, and invasion of epithelial cells, miR-155, therefore, is a critical target for breast cancer intervention.

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