Anti-microRNA-222 (Anti-miR-222) and -181B Suppress Growth of Tamoxifen-resistant Xenografts in Mouse by Targeting TIMP3 Protein and Modulating Mitogenic Signal

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This article has been withdrawn by the authors. The Journal raised questions regarding Figs. 5C, 5D, 6A, 6B, 6C, 6D, 7A, 7C, 7D, 8E, and S3. The authors were able to locate some, but not all, of the original data and were able to locate some repeat experiments performed at the time of the original work, which the authors state support the conclusions of the paper. The authors state that the results of this paper are confirmed by the results of complementary experiments presented in the manuscript and that the principal observation of this paper was further confirmed in a 2014 paper (PMID Medline), in which tamoxifen resistance in breast cancer was connected to miR-221/222, by suppression of TIMP3. The authors stand by the reproducibility of the experimental data and the conclusions of the paper.

The on-line version of this article (available at http://www.jbc.org) contains supplemental text and Figs. S1–S3.

The abbreviation used are: ER, estrogen receptor; miR, microRNA; OHT®, 4-hydroxytamoxifen-resistant; ADAM, a disintegrin and metalloprotease; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; vec, vector.
confer resistance to this drug when ectopically expressed in tamoxifen-sensitive cells (9, 10). This is achieved, at least in part, by targeting cell cycle inhibitory protein p27/Kip1, which is significantly reduced in tamoxifen-resistant cells. Besides miR-221/222, the expression of miR-181b was also significantly augmented in the resistant cells. Here, we demonstrate that treatment with anti-miR-222 or anti-miR-181b can render tamoxifen-resistant xenografts in mice sensitive to the drug and cause suppression of tumor growth and that the tissue metalloprotease inhibitor TIMP3, a direct target of miR-221/222 and miR-181b, plays a key role in this process. Our study also demonstrates that these miRs confer tamoxifen resistance in breast cancer cells by facilitating growth factor signaling, which is ameliorated by high levels of TIMP3 or depletion of the metalloprotease ADAM17, a target of TIMP3, in tamoxifen-sensitive cells.

EXPERIMENTAL PROCEDURES

Cell Culture and Tissue Procurement—Tamoxifen-sensitive MCF-7 cells and resistant OHT® cells were obtained from Dr. Kenneth P. Nephew (Indiana University) and maintained as described (11). T47D cells were obtained from the ATCC (American Type Culture Collection) and maintained as instructed. Primary human breast samples were obtained from the Stephanie Spielman Tissue Bank (Protocol 2003C0036). T47D cells were obtained from the ATCC (American Type Culture Collection) and maintained as instructed. These analyses were done as described (15).

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Cell Proliferation Assay—Cell proliferation was monitored using the cell proliferation reagent kit I (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT); Roche Applied Science). Cells (4000/well) seeded in 96-well plates were serum-starved overnight and treated with 5 μM tamoxifen. To measure cell proliferation, 10 μl of MTT labeling reagent I was added to each well at the indicated time and incubated at 37 °C for 4 h followed by the addition of 100 μl of solubilization reagent in each well. Absorbance was measured at 570 nm in the ELISA reader (TriStar; Berthold Technologies) after overnight incubation.

Cell Migration Assay—For cell migration, OHT® cells stably expressing pCMV3/FLAG or TIMP3 (1 × 104) were placed in a serum-free medium in 24-well Transwell inserts of 8-μm pore size (Corning Costar Corp.) for 24 h. The bottom chambers contained serum-supplemented medium that acted as a chemoattractant. The migration of cells was allowed to proceed for 48 h at 37 °C. Cells that migrated to the bottom of the insert were fixed, stained, and counted, and the percentage of migration was determined. Each experiment was performed at least three times.

Matrix Metalloproteinase (MMP) Assay—MMP activity was analyzed as described (16).

Wound Healing Assay—Cells were grown in 6-well chambers to 80% confluency. A scratch wound was inflicted diagonally in the monolayer with a pipette tip. The image of the wound was captured at the beginning and every 24 h under the microscope (15).

Growth Factor Treatment—Cells at 60% confluency were starved in phenol red-free medium containing 1% serum for 1 day for EGFR (3 μg/ml) and 1 ng/ml) and 4 days for 17-β-estradiol (50 pM) or OHT-tamoxifen (50 nm) (Sigma) treatment. MCF-7 cells and resistant OHTR cells were analyzed by Western blot analysis.

Results

Anti-miR-222/181 Inhibits Tamoxifen-resistant Tumor Growth

Anti-miR-222 and -181b Treatment Sensitizes Mouse Mammary Tumors to Tamoxifen—Based on the observation that miR-221/222 and -181b are markedly up-regulated in tamoxifen-resistant xenografts in mice sensitive to the drug and cause suppression of tumor growth and that the tissue metalloprotease inhibitor TIMP3, a direct target of miR-221/222 and miR-181b, plays a key role in this process. Our study also demonstrates that these miRs confer tamoxifen resistance in breast cancer cells by facilitating growth factor signaling, which is ameliorated by high levels of TIMP3 or depletion of the metalloprotease ADAM17, a target of TIMP3, in tamoxifen-sensitive cells.
resistant breast cancer cell lines and tumors, we hypothesized that the corresponding anti-miRs could sensitize the resistant tumors to tamoxifen. To test this hypothesis, OHTR cell xenografts induced in mouse mammary fat pads (~100 mm³) were treated with tamoxifen citrate along with negative control anti-miR or anti-miR-222 or -181b once a week for four consecutive weeks. A significant decrease (40–45%, p < 0.001) in the tumor size was observed in mice treated with either anti-miR-181b or anti-miR-222 when compared with the control group (Fig. 1A). It is noteworthy that in both anti-miR-222-treated and anti-miR-181b-treated groups, tumor growth was significantly reduced beginning with the 2nd week of treatment when compared with the control group and that some tumor growth regressed completely after four treatments. A marked decrease in the levels of miR-222 and -181b was observed in the recovered tumors treated with the corresponding anti-miR (Fig. 1B).
TIMP3 Is a Common Target of miR-221, -222, and -181 In HER2/neu-positive Primary Human Breast Cancer Tissues—To determine whether these three miRs target TIMP3, we selected TIMP3 as a candidate target and performed a search for miR seed sequences in the 3′-UTR of human TIMP3 mRNA (Fig. 1C). To verify that TIMP3 is a direct target of these miRs in breast cancer cell lines, MCF-7 cells were transfected with pSilencer 3′-UTR of TIMP3-Luc plasmid harboring 3′-UTR of TIMP3 (Fig. 1D). Luciferase expression was reduced significantly (~50%, Fig. 1E) when transfected with miR-221, -222, or -181b when compared with the negative control miRs (Fig. 1E). Conversely, deletion or mutation of the miR seed sequences blocked the inhibitory effects of all three miRs, and luciferase activity was completely recovered. Further analysis demonstrated ~50% reduction of endogenous TIMP3 mRNA level in OHTR cells as well as miR-221/222-overexpressing cells when compared with MCF-7 cells and when miR-181b was transiently overexpressed (Fig. 1E). In addition, a marked reduction (75%) in TIMP3 protein was observed in OHTR cells when compared with an ~50% reduction when individual miRs were overexpressed (Fig. 1F). These data suggest a cumulative inhibitory effect of miR-221/222 and -181 on TIMP3 expression in the OHTR cells. Analysis of the tumor tissues recovered from the mice also revealed an increase in the TIMP3 level in the anti-miR-222 (n = 2) and -181b (n = 2)-treated group when compared with the control group (n = 4) (Fig. 1G), confirming that TIMP3 is a direct target of these miRs in breast tumor.

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Ectopic Expression of TIMP3 Sensitizes Breast Cancer Cells to Tamoxifen—Next, we determined the role of TIMP3 in altering sensitivity of breast cancer cells to tamoxifen in vitro and in vivo. The proliferation of stable FLAG-tagged TIMP3-overexpressing OHTR cells (~3-fold overexpression, Fig. 3A) was significantly reduced in response to 5 μM tamoxifen when compared with the control cells (Fig. 3B). In Transwell migration assays where cells were allowed to migrate in response to serum, TIMP3 markedly impeded cell migration in the presence or absence of tamoxifen (Fig. 3C). In wound healing assays, where a scratch-inflicted wound was allowed to heal over time (Fig. 3D), the rate of wound healing after 72 h was comparable between the vector-transfected and OHTR/TIMP3 cells, but...
the healing process was delayed markedly in the latter cells upon 1.0 μM tamoxifen treatment.

To confirm the role of TIMP3 in altering tamoxifen resistance in vivo, the control and OHTβ/TIMP3 cells were used to induce tumors in mammary fat pads of mice. Because TIMP3 overexpression impeded tumor growth (supplemental Fig. S1), we generated TIMP3-depleted stable MCF-7 cells (MCF-7-shTIMP3) and the respective control (MCF-7-Vec) cells (Fig. 3E). Although tamoxifen inhibited growth of both cell lines, MCF-7-shTIMP3 cells were relatively less sensitive to the drug when compared with the controls (Fig. 3F). In addition, tamoxifen treatment resulted in significant reduction of MCF-7-Vec tumors in mice. On the contrary, tumors induced with MCF-7-shTIMP3 cells continued to grow with time, and significant increase in tumor growth was observed when compared with the controls in the presence of the drug at all time points beginning day 60 after injection (Fig. 3G). TIMP3 level at harvest was higher in the control group when compared with the tumors induced with TIMP3-depleted cells (Fig. 3H).

To test further the hypothesis that TIMP3 overexpression can alter response to tamoxifen, TIMP3 was overexpressed in T47D cells (T47D/TIMP3) that are relatively more resist-
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Figure 4. Ectopic expression of TIMP3 sensitizes T47D cells to tamoxifen in vitro and in vivo. A and B, Western blot analysis of TIMP3 expression in ER-positive cell lines (A) and endogenous TIMP3 and ectopic TIMP3-FLAG expression in T47D and MCF-7 cells (B). C, fold change in proliferation was compared between T47D-Vect and T47D-TIMP3 cells grown without (70) or with (75) 5 μM tamoxifen S. D, growth curve of xenografts in mouse mammary fat pads induced with T47D-vec and T47D-TIMP3 cells upon treatment with tamoxifen. Average tumor volume ± S.E. is plotted against time (in days).

Ant to endocrine therapy and exhibit significantly reduced basal TIMP3 expression when compared with MCF-7 cells (Fig. 4, A and B). In vitro proliferation assay revealed increased (30%) sensitivity of the T47D/TIMP3 cells to tamoxifen-induced growth inhibition when compared with the control cells (Fig. 4C). In vivo treatment with tamoxifen caused significant regression of the T47D/TIMP3-induced tumors, but not in control cells (Fig. 4D). These data support the hypothesis that TIMP3 could play a key role in mediating response of breast cancer cells to tamoxifen.

TIMP3 Overexpression Curtails Tamoxifen-resistant Growth Factor Signaling in OHTR Cells. Our data demonstrated that TIMP3 could mimic the effect of TIMP3 knockdown in MCF-7 cells in response to EGF. Indeed, phosphoMAPK level was markedly elevated in MCF-7 cells overexpressing miR-221/222 when treated with 0.1 and 1.0 ng/ml EGF (1.7- and 2.5-fold, respectively) but not in control cells (Fig. 5E). Our effort to study the effect of miR-181b on growth factor stimulation failed due to lethality of transient or stable miR-181b overexpression in MCF-7 cells. A sharp decline in ERα level within 36 h of miR-181b transfection (supplementary Fig. S2) could be attributed to miR-181 seed sequence on 3’-UTR of ERα mRNA (TargetScan4.0). Indeed, miR-181b has been shown to suppress estrogen-dependent proliferation of MCF-7 cells earlier (24). We, therefore, knocked down miR-181b in OHTR cells using anti-miR-181b. The MAPK phosphorylation at 0.1 and 1.0 ng/ml EGF was reduced by ~50 and 25%, respectively, in anti-miR-181b-transfected cells when compared with the respective controls (Fig. 5F). miR-181b expression was reduced by 60% in cells transfected with the corresponding anti-miR (Fig. 5F, bottom panel).

Both estrogen and tamoxifen elicit rapid increase in MAPK phosphorylation in the tamoxifen-resistant cells when compared with the sensitive cells (19). We explored the possibility that overexpression of miR-221/222 in MCF-7 cells mimics these characteristics of the resistant cells, which could be blocked by overexpressing TIMP3 in OHTR cells.
Indeed, phosphoMAPK was markedly augmented (6–7-fold, when compared with untreated cells) in MCF-7 cells/miR-221/222-overexpressing cells in response to 17-β-estradiol within 3–5 min as opposed to 3–4-fold increase in control cells (Fig. 6A). Similarly, treatment with 50 nM tamoxifen elicited robust MAPK phosphorylation (5–7-fold, when compared with untreated cells) in MCF-7 cells/miR-221/222-overexpressing cells (Fig. 6B), supporting the role of these miRs in agonistic activity of tamoxifen in the resistant cells. Treatment of OHTR/TIMP3 cells with 17-β-estradiol or 50 nM tamoxifen resulted in 50% reduction in MAPK activation when compared with OHTR/vector cells (Fig. 6, C and D, compare lane 2 with lane 5 and lane 3 with lane 6). In summary, growth factor signaling is facilitated in OHTRK cells due to reduced TIMP3 level that, in turn, is regulated by miR-221/222 and -181b in these cells.

**EGF-induced AKT Phosphorylation Is Inversely Modulated by miR-221/222 and TIMP3 in Breast Cancer Cells**

Constitutive activation of PKB/AKT is a hallmark of tamoxifen-resistant cells that leads to aggressive cell proliferation. Growth factors such as EGF can significantly increase Ser-473 phosphorylation of AKT in the resistant cells (25). We observed increase in basal (1.9-fold) and EGF-induced (0.1 and 1 ng/ml) AKT phosphorylation (Ser-473) in the OHTRK cells (1.9- and 3.5-fold, respectively) when compared with the MCF-7 cells (Fig. 7A). The basal phosphoAKT level was also higher (1.8-fold) in MCF-7
cells overexpressing miR-221/222 when compared with the controls that peaked at 0.1 ng/ml EGF (2.6-fold) (Fig. 7B). AKT phosphorylation was reduced by ~65% in OHT<sup>R</sup>/TIMP3 cells treated with 0.1 ng/ml EGF when compared with the controls (Fig. 7C). Similarly, treatment of OHT<sup>R</sup> cells with anti-miR-181b curtailed EGF-induced AKT phosphorylation (~50% at 0.1 ng/ml EGF) (Fig. 7D). These data suggest the role of miR-221/222/181b and TIMP3 in facilitating AKT-mediated proliferation of tamoxifen-resistant cells.

ADAM17 and ADAM10 Are Essential for Growth and Migration of Tamoxifen-resistant Cells—To test our hypothesis that ADAM17 and ADAM10 are required for growth factor signaling and proliferation of tamoxifen-resistant cells, ADAM17 and ADAM10 were depleted from OHTR cells using siRNA. A 35 and 50% reduction in ADAM10 and ADAM17, respectively, at the protein level was achieved upon siRNA transfection in OHTR cells (Fig. 8A). A 30% decrease in cell proliferation was observed in both cells when compared with the scramble siRNA-transfected controls (Fig. 8B). Further growth inhibition was not observed in the presence of externally added tamoxifen, demonstrating that these metalloproteases are important for maintenance of the resistant cells. The Transwell migration of ADAM17-depleted OHT<sup>R</sup> cells was inhibited by 64% (p < 0.0001), and migration of ADAM10-depleted cells was inhibited by 38% (p < 0.001) (Fig. 8C). Migration of ADAM17-depleted cells was further reduced by 21 and 38% compared with untreated control. Similar inhibition was also observed with ADAM10-depleted cells (22% at 1.0 μM tamoxifen and 46% at 2.0 μM tamoxifen). The control siRNA-treated cells demonstrated a 15 and 31% decrease in migration when treated with 1.0 and 2.0 μM tamoxifen, respectively. Wound healing assay demonstrated ~20% inhibition in healing of ADAM17- and ADAM10-depleted cells in the absence of tamoxifen, whereas an ~50% inhibition was observed in the presence of 2.0 μM tamoxifen when compared with control siRNA-transfected cells (Fig. 8D).

We further tested growth factor signaling in these metalloprotease-depleted cells by assessing AKT and MAPK phosphorylation levels. A marked decrease in AKT phosphorylation...
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A.

B.

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DISCUSSION

Although endocrine therapy that blocks the ER pathway is a very effective treatment for ER-positive breast cancers, the response has not been uniform due to de novo or acquired resistance to this therapy. Extensive studies led to identification of several alternative growth factor signaling pathways that are aberrantly activated in the resistant tumors (for review, see Ref. 5) as well as the role of macroautophagy in protection against tamoxifen-induced cell death and developing anti-estrogen resistance (26). Recently, we observed deregulation of several miRs in tamoxifen-resistant breast cancer, significantly specifically elevation in the expression of miR-221, -222, and -181b (9). Here, we have demonstrated increased sensitivity of the tamoxifen-resistant xenografts in mice to the tumor upon combined treatment with the corresponding anti-miRs. In breast cancer cells and in primary breast tumors, these three miRs were found to target TIMP3. In addition, alteration in TIMP3 expression could modulate mec-to-estrogenic signaling, thereby contributing to resistance both in vitro and in vivo. Although ADAM17 and ADAM10 in OHTR cells that were depleted of these proteins demonstrated the dependence of these cells on the metalloproteases for survival. These data also suggest that these proteins, particularly ADAM17, play a predominant role in growth factor signaling in OHTR cells, and increased expression combined with miR-mediated TIMP3 suppression facilitates growth of the resistant cells. Based on these observations, we conclude that the suppression of miR expression by anti-miRs could sensitize resistant tumors to tamoxifen. A recent study demonstrated that unconjugated tiny locked nucleic acid oligonucleotides could be taken up by mouse mammary tumors following systemic delivery that led to long term miR silencing (27). A similar approach could further establish the beneficial role of knocking down miR-221/222/181 in sensitizing resistant tumors to tamoxifen.

miR-221 and -222 are closely located on human chromosome X and appear to be transcribed as a single primary transcript. A recent in vitro study demonstrated that ERs suppress miR-221/222 levels through the recruitment of nuclear receptor corepressor (NCoR) and silencing mediator of retinoic acid and thyroid hormone receptor (SMRT) (28). It can be speculated that inhibition of ERs by anti-estrogenic compounds could release the suppression and increase miR-221/222 expression upon prolonged exposure to the drugs. Similarly, the increase in miR-181b expression in MCF10A cells over-expressing Src was attributed to STAT3 activation (29). However, in hepatocellular carcinoma, the TGFβ pathway was found to up-regulate miR-181b expression (12).

We were the first to demonstrate the role of miR-221/222 in conferring resistance to tamoxifen in breast cancer (9). Subsequently, up-regulation of miR-221 and -222 has been implicated in resistance to drugs such as fulvestrant (30) and cisplatin (31) in breast cancer, castration-resistant prostate cancer (32), TNF-related apoptosis-inducing ligand (TRAIL)-resistant non-small cell lung cancer cells (33), and radiation-resistant gastric carcinoma cells (34). Here, we have shown that miR-221 and -222 can confer resistance to tamoxifen by regulating TIMP3 levels. Furthermore, up-regulation of miR-181 family has frequently correlated with drug resistance. Interestingly, miR-181b expression is significantly elevated in hepatocellular carcinoma (12), breast cancer (35), and pancreatic cancer (36). This study has also opened the possibility that increased levels of miR-181 in different cancer types could contribute to resistance against other potent anticancer drugs by targeting TIMP3.

Although a close correlation exists among high levels of TIMP3 mRNAs, success of adjuvant endocrine therapy (37, 38), and distant metastasis-free survival (39), the mechanism underlying this observation has not been studied in detail. In this study, we provided strong evidence for miR-mediated regulation of TIMP3 level and offered mechanism of its action through inhibition of metalloproteases in facilitating growth of the resistant cells. In summary, we have identified miRs and their targets that contribute to tamoxifen resistance in cell culture models, mouse xenograft models, as well as in primary breast tumors. Identification of the molecular signature of a select panel of deregulated microRNAs that can potentially target multiple genes and modulate several biological pathways could lead to a novel regulatory mechanism of drug resistance.
and open up alternate strategies for treatment of patients resistant to this important class of drugs.

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