MicroRNA-221/222 Negatively Regulates Estrogen Receptor α and Is Associated with Tamoxifen Resistance in Breast Cancer*

Received for publication, August 5, 2008, and in revised form, September 10, 2008 Published, JBC Papers in Press, September 12, 2008, DOI 10.1074/jbc.M806041200

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A search for regulators of estrogen receptor α (ERα) expression has yielded a set of microRNAs (miRNAs) for which expression is specifically elevated in ERα-negative breast cancer. Here we show distinct expression patterns of miRNAs between ERα-positive and ERα-negative breast tumors. Of the 37 miRNAs with known targets that are overexpressed in ERα-negative breast cancers, miR-221 and miR-222 are particularly enriched in miRNA expression patterns that ERα-positive breast tumors do not recapitulate. Transfection of miR-221 and/or miR-222 sensitized MDA-MB-468 cells to tamoxifen-resistant T47D cells. Furthermore, knockdown of miR-221 and/or miR-222 restored ERα expression in a subset of breast cancers.

This article has been withdrawn by the authors. The same data were used to represent different experimental conditions. Specifically, the ERα mRNA band from MCF7 cells in Fig. 4A was duplicated in the BT474 lane of the same panel. The authors stand by the overall conclusions of the study.

Estrogen receptor α (ERα) is an important marker for prognosis and is predictive of response to endocrine therapy in patients with breast cancer. Although the majority of primary breast cancers are ERα-positive and respond to antiestrogen therapy, up to one-third of patients with breast cancer lack ERα at the time of diagnosis, and a fraction of breast cancers that are initially ERα-positive lose ERα expression during tumor progression (1). These patients fail to respond to antiestrogen therapy and have a poor prognosis. Previous studies have shown that ERα absence is a result of hypermethylation of CpG islands in the 5'-regulatory regions of ERα in a fraction of breast cancers (1). However, the molecular mechanism of the role of ERα expression in breast cancer progression remains largely unknown (1).

MicroRNAs (miRNAs) are a new class of small (20-25 nucleotide) noncoding RNAs and negatively regulate protein-coding gene expression by targeting mRNA degradation or translation (2). The role of miRNAs in breast oncogenesis and cancer progression has been well documented in several laboratories (3–5). However, the molecular mechanism of the role of miRNAs in breast cancer, and some are associated with breast cancer cell lines and primary tumors and identified the deregulation of a panel of miRNAs in ERα-negative cases and the molecule(s) involving ERα hypermethylation remain largely unknown (1). Here we show distinct expression of a panel of miRNAs between ERα-positive and ERα-negative human breast cancer cell lines and primary tumors. Of the elevated miRNAs in ERα-negative breast cancer, miR-221 and miR-222 play a significant role in the regulation of ERα expression at the protein level and could be potential targets to antiestrogen resistance.

EXPERIMENTAL PROCEDURES

Cell Lines, Transfection, and Human Tumor Tissues—Human breast cancer cell lines (T47D, BT474, MDA-MB-361, MCF-7, MDA-MB-453, MDA-MB-157, SKBr3, MDA-MB-468, Hs578T, MDA-MB-231, and MDA-MB-435s) and spontaneously immortalized human breast epithelial cells (MCF-10A) were obtained from American Type Culture Collection. Breast cancer cell lines were grown in either RPMI 1640 medium (Sigma) or Dulbecco’s modified Eagle’s medium (Sigma) supplemented with 10% fetal bovine serum. MCF-10A cells were cultured in mammary epithelium basal medium plus mammary epithelial growth medium (Clonetics). Transfection of 2′-O-Me-antamiR oligonucleotides or pcDNA6.2-GW/EmGFP-miR (BLOCK-iT) plasmids was performed using Lipofectamine 2000 (Invitrogen) following the manufacturer’s instructions. Stable cell lines were obtained by blasticidin selection. The sequences of 2′-O-Me-antamiR-221 and 2′-O-Me-antamiR-222 are 5′-GAAACCCAGCAGACAAUGUAGCU-3′ and 5′-ACCCAGUAGCCAGAUGUAGCU-3′. Scrambled 2′-O-Me-antamiR oligonucleotides were used as controls.

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§ The abbreviations used are: ERα, estrogen receptor α; miRNA, microRNA; 3′-UTR, 3′-untranslated region; RT, reverse transcription; GFP, green fluorescent protein.

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modified RNA (5′-AAGGCAACGUGACCCUGAAGU-3′) was used as a negative control. Frozen and formalin-fixed paraffin-embedded human primary breast cancer and normal breast tissues were obtained from the Tissue Procurement Facility at the H. Lee Moffitt Cancer Center.

Plasmids—Expression plasmids of hsa-miR-221 and has-miR-222 were created by annealing self-complementary oligonucleotides encompassing the sequences of miR-221 and miR-222 and cloning into the pcDNA6.2-GW/EmGFP-miR vector (BLOCK-iT Pol II miR RNAi expression vector, Invitrogen). The oligonucleotides used were as follows: hsa-miR-221, 5′-TGCTGACTACAGTCGTTTGGTGGCTGACCTGAGCAAAACCAGCAATGAGTC-3′ (sense) and 5′-TGCTGACTACAGTCGTTTGGTGGCTGACCTGAGCAAAACCAGCAATGAGTC-3′ (antisense); has-miR-222, 5′-TGCTGACCTACATCGTCGTTTGGCTGACCTGAGCAAAACCAGCAATGAGTC-3′ (sense) and 5′-TGCTGACCTACATCGTCGTTTGGCTGACCTGAGCAAAACCAGCAATGAGTC-3′ (antisense); and has-miR-221, 5′-TGCTGACCTACATCGTCGTTTGGCTGACCTGAGCAAAACCAGCAATGAGTC-3′ (antisense). Expression of miR-221 and miR-222 were confirmed following our routine procedures (14, 16).

Cell Viability and Apoptosis Assays—Cell viability was examined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay as described previously (10). Cells were seeded in a 96-well plate. After a 24-h incubation, the cells were treated with tamoxifen (5, 10, and 20 μM) or a dimethyl sulfoxide control for 48 h and then subjected to 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide and apoptotic detection assay using a Cell Death Detection ELISAPLUS kit (Roche Applied Science) according the manufacturer’s protocol. Each experiment was repeated three times in triplicate. The results are expressed as the enrichment factor relative to the untreated controls.

Target in Vivo Luciferase Reporter Assay—Two pmiR-Report plasmids for the miR-221 and miR-222 target ERα 3′-UTRs were constructed. ERα 1 contains a conserved target site of miR-221 3′-UTR, and pmiR-ERα2 contains a scrambled sequence. The sequences used to construct the luciferase reporter vector (Ambion), 5′-CGCGTCCGCGTTGACATGAAAGGCAAGCUGACCCUGAAGU-3′ (forward) and 5′-AGGTGGGTCGCTGCTGATGCA-3′ (reverse); and LNA-scrambled oligonucleotides, 5′-CAATTTTAGTATATGTGCTGCCGAAGCGA-3′ (forward) and 5′-CAATTTTAGTATATGTGCTGCCGAAGCGA-3′ (reverse). The oligonucleotides were annealed and premixed prior to the pmiR-Report vector (Ambion). The vector (200 ng) alone was used as a negative control. MCF-7 and MDA-MB-468 cells were transfected with 0.1 μg of the reporter plasmids and 0.3 μg of pCMV-β-gal. Following a 36-h incubation, cells were subjected to luciferase reporter assay using the luciferase assay system (Promega). Luciferase activities were normalized to β-galactosidase activities. Each experiment was repeated three times in triplicate.

Statistical Analysis—Statistical significance was analyzed by unpaired Student’s t test, and p ≤ 0.05 was considered to be statistically significant.

RESULTS

miR-221 and miR-222 Are Highly Expressed in ERα-negative Breast Cancer Cell Lines and Primary Tumors—In an attempt to identify the miRNAs that contribute to regulation of ERα expression in breast cancer, we performed miRNA profiling in ERα-positive versus ERα-negative breast cancer cell lines as well as primary tumors. RNAs isolated from a total of five cell lines and 10 primary tumors were hybridized to a custom miRNA microarray platform containing 515 miRNAs. After three times of hybridization, quantification, and normalization, a dozen miRNAs, especially miR-221 and miR-222, were elevated in the ERα-negative cell lines and primary tumors compared with ERα-positive breast cancers (Fig. 1A). Consistent with the miRNA microarray data, Northern blot analysis revealed the expression of miR-221 and miR-222 in five of eight ERα-negative cell lines examined, with higher levels in MDA-
FIGURE 1. Frequently increased expression of miR-221 and miR-222 in ERα-negative breast cancer. A, partial heat map of miRNA microarray analysis of ERα-positive versus ERα-negative breast cancer cell lines and primary tumors. Several miRNAs were significantly elevated in ERα-negative cells. B and C, elevated levels of miR-221 and miR-222 in ERα-negative breast cancer cell lines and primary tumors. Total RNAs from the cell lines and primary tumors were subjected to Northern blot (B) and quantitative RT-PCR (C) analyses. U6 small nuclear RNA (snRNA) and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) were used as loading controls. The blots were quantified by dividing miR-221 and miR-222 signals by U6 and by dividing ERα by glyceraldehyde-3-phosphate dehydrogenase. ERα-negative tumors overexpressing both miR-221 and miR-222 are labeled by asterisks, and the tumors also expressing ERα mRNA are indicated by triangles (C). M stands for marker. D, representation of the inverse correlation of expression of ERα and miR-221/miR-222. Breast tumor specimens were immunohistochemically stained with anti-ERα antibody (first and third panels). The second and fourth panels are the same specimens that were hybridized with the LNA-miR-221 and LNA-miR-222 probes using miRNA locked nucleic acid in situ hybridization as described under “Experimental Procedures.”
MB-468, Hs578T, and MDA-MB-231 cells (Fig. 1B). Notably, all four ERα-positive breast cancer lines had very low levels of miR-221 and miR-222 (Fig. 1B). Furthermore, RT-PCR, immunostaining, and miRNA in situ hybridization analyses revealed overexpression of miR-221 and miR-222 in 13 of 25 (52%) ERα-negative primary tumors, 11 of which had ERα mRNA expression (Fig. 1C). In contrast, of 16 ERα-positive tumors examined, only four expressed moderate levels of miR-221 and miR-222.
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MCF-7 and T47D cells became resistant to tamoxifen-induced cell death (Fig. 2E).

To further demonstrate the direct regulation of ERα by miR-221 and miR-222, we constructed luciferase reporters with two targeting sequences of wild-type (pmiR-ERα1-3'-UTR and pmiR-ERα2-3'-UTR) and mutated (Fig. 2A) ERα1-3'UTRs. Both the wild-type and mutant reporters were introduced into MCF-7 (miR-221/222-negative) and MDA-MB-468 (miR-221/222-positive) cells. The luciferase activities of pmiR-ERα1-3'UTR but not pmiR-ERα2-3'UTR were significantly suppressed in miR-221/222-positive MDA-MB-468 cells but not in miR-221/222-negative MCF-7 cells (Fig. 3A). Furthermore, ectopic expression of miR-221 in MCF-7 cells decreased the wild-type and mutant luciferase reporter activity (Figs. 2A and 3B). Moreover, the reporter activities of pmiR-ERα1 and pmiR-ERα1-3 but not pmiR-ERα1-5 were reduced in MDA-MB-468 cells (Fig. 3C). In addition, pmiR-ERα1 and miR-221/222 reporter activities were increased by knockdown of miR-221 and/or miR-222 in MDA-MB-468 cells (Fig. 3D).

Taken collectively, these data indicate that ERα is inhibited by miR-221 and miR-222 at the translational level.

Knockdown of miR-221 and miR-222 in MDA-MB-468 Cells Partially Restores ERα Expression and Tamoxifen Sensitivity—Having demonstrated the miR-221 and miR-222 repression of ERα expression at the protein but not mRNA level, we reasoned that up-regulation of miR-221 and miR-222 is responsible for a subset of ERα protein-negative/mRNA-positive breast cancers. To test this hypothesis, we examined expression of ERα protein and mRNA in 12 breast cancer cell lines. Western blot and RT-PCR analyses revealed that six ERα protein-negative cell lines expressed ERα mRNA with more abundance in MDA-MB-468 and MCF-10A cells. Both cell lines also had high levels of miR-221 and miR-222 (Fig. 1B). Thus, we transfected MDA-MB-468 cells with 2′-O-Me-anta-miR-221 and/or 2′-O-Me-anta-miR-222 and control 2′-O-Me oligonucleotides. After a 72-h incubation, the expression levels of miR-221 and miR-222 were reduced essentially in the cells treated with 2′-O-Me-anta-miR-221 and/or 2′-O-Me-anta-miR-222 (Fig. 4B). Immunoblot analysis showed that ERα protein was partially restored in miR-221 and/or miR-222 knockdown cells but not in control 2′-O-Me-treated cells (Fig. 4C). However, there was no significant difference between individual knockdown of miR-221 and miR-222 and their combination (Fig. 4C). Similar results were obtained in the MCF-10A cell line (Fig. 4C). Res-
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We next examined whether the miR-221- and/or miR-222-knocked down MDA-MB-468 cells became sensitive to tamoxifen. As shown in Fig. 4 (D and E), knockdown of miR-221 or miR-222 reduced MDA-MB-468 cells resistant to tamoxifen-induced cell growth arrest and apoptosis. Cells with knock-
down of both miR-221 and miR-222 became more vulnerable to tamoxifen-inhibited cell growth (Fig. 4D) and tamoxifen-induced apoptosis (Fig. 4E) compared with cells with knockdown of either one alone.

**DISCUSSION**

Because expression of ERα is a main predictor of response to endocrine therapy, lack of expression of ERα is a major mechanism of tamoxifen resistance in breast cancer. In this respect, the loss of ERα gene expression has been associated with the aberrant methylation of its CpG islands and histone deacetylation in a fraction of breast cancers (17–19). A recent report showed that miR-206 represses ERα mRNA and protein expression (20). In this study, we have demonstrated frequent up-regulation of miR-221 and miR-222 in ERα-negative breast cancer cell lines and primary tumors. miR-221 and miR-222 inhibit ERα expression at the protein but not mRNA level, indicating the suppression of ERα by these two miRNAs at the translational level. Taken collectively, these studies indicate that miRNAs are important regulators of ERα and could be major determinants of ERα status in human breast cancer.

Previous studies have focused primarily on ERα protein expression in breast cancer. Several reports have shown that a subset of ERα protein-negative breast cancer cell lines and primary tumors express ERα mRNA (21–25). However, the mechanisms by which the mRNA of ERα does not translate to protein are unclear. It was speculated that lack of ERα due to loss of mRNA expression or methylation of the promoter, but might be due to post-translational mechanisms (23–25). Our results show that miR-221 and miR-222 inhibit ERα expression with the 3′-UTR of ERα mRNA and do not target the promoter region of the ERα gene, indicating the suppression of ERα translation by these two miRNAs at the translational level. Taken collectively, these studies indicate that miRNAs are important regulators of ERα and could be major determinants of ERα status in human breast cancer.

It has been well documented that each miRNA negatively regulates hundreds of protein-coding genes by binding to the 3′-untranslated region (3′-UTR) of their target mRNAs. It has been suggested that miR-221 and miR-222 have shown to target the inhibitory proteins p27Kip1 and p57 as well as the receptor, leading to cell proliferation and survival and inhibition of differentiation (26–31). In this study, we identified ERα as a direct target of miR-221 and miR-222. Knockdown of miR-221 and miR-222 restores ERα protein expression and sensitizes MDA-MB-468 cells to tamoxifen-induced cell growth arrest and apoptosis (Fig. 4), whereas ectopic expression of miR-221 and miR-222 in MCF-7 and T47D cells reduces the ERα protein level and renders the cells resistant to tamoxifen (Fig. 2E). Although miR-221 and miR-222 have an identical eight-nucleotide seed sequence and redundantly regulate p27, p57, and c-Kit (26–31) as well as ERα, the effect of the combined knockdown of miR-221 and miR-222 on tamoxifen-induced cell death is more significant than that of knockdown of either one alone (Fig. 4, D and E). This suggests that miR-221 and miR-222 might target different genes because the rest of nucleotide sequences of miR-221 and miR-222 are quite different (Fig. 2A).

In summary, we have demonstrated that miR-221 and miR-222 are frequently up-regulated in ERα-negative breast cancer cell lines and primary tumors. The elevated level of miR-221 and miR-222 is responsible for a subset of ERα-negative breast tumors that express ERα mRNA. Furthermore, overexpression of miR-221 and miR-222 contributes to tamoxifen resistance through negative regulation of ERα, whereas knockdown of miR-221 and/or miR-222 restores ERα expression and tamoxifen sensitivity. Therefore, miR-221 and miR-222 could serve as potential therapeutic targets for a subset of ERα-negative breast cancers.

Acknowledgments—We are grateful to the Tissue Procurement, DNA Sequence, and Flow Cytometry Core Facilities at the H. Lee Moffitt Cancer Center for providing cancer specimens, sequencing, and cell cycle analysis.

**REFERENCES**

1. Giacinti, L., Claudio, P. P., Lopez, M., and Giordano, A. (2006) Oncologist 11, 1–8
2. Lee, R. C., Feinbaum, R. L., and Ambros, V. (1993) Cell 75, 843–854
3. Pasquinelli, A. E., Reinhart, B. J., Slack, F., Martindale, M. Q., Kuroda, M. I., Maller, B., Hayward, D. P., Guo, L., Egan, E., Degnan, B., Muller, P., Spring, J., Srivisan, A., Fishel, R., Jay, J., Corbo, J., Levine, M., Leahey, P., Davidson, E., and Ambros, V. (2000) Nature 408, 86–89
4. Reinhart, B. J., Pasquinelli, A. E., Bettinger, J. C., Ruvkun, G. (2000) Nature 403, 86–92
5. Ambros, V. (2001) Cell 107, 181–195
6. Iorio, M. V., Ferracin, M., Liu, C. G., Veronese, A., Spizzo, R., Sabbioni, S.,能满足, M., Menard, S., Palazzo, J. P., Barbaresi, V., Bertoni, F., Nenci, I., Calin, G. A., Querzoli, P., Picardi, E., and Croce, C. M. (2005) Cancer Res. 65, 7065–7070
7. Jarzabek, K., Koda, M., Kozlowski, L., Mittre, H., Sulkowski, S., Kottler, M. L., and Wolczynski, S. (2005) Childs Nerv. Syst. 21, 552–556
8. Zhao, J.-J., Sun, D. G., Liu, C. G., Yang, H., Kong, W., He, L., Zhao, J.-J., O’Donnell, J. D., Kong, W., Wenham, R. M., Coppola, D., Kruk, P. A., Nicason, S. V., and Cheng, J. Q. (2008) Cancer Res. 68, 425–433
9. Wang, J. W., and Cheng, J. Q. (2008) Methods Mol. Biol. 414, 183–190
10. Zhao, J.-J., Sun, D. G., Kong, W., He, L., Zhao, J.-J., O’Donnell, J. D., Wang, J., Wenham, R. M., Coppola, D., Kruk, P. A., Nicosia, S. V., and Cheng, J. Q. (2008) Cancer Res. 68, 425–433
11. Issa, J. P., Ottaviano, Y. L., Celano, P., Hamilton, S. R., Davidson, N. E., and Baylin, S. B. (1994) Nature Genet. 7, 536–540
12. Zhao, J.-J., Sun, D. G., Wang, J., Liu, C. G., Yang, H., Kong, W., He, L., Zhao, J.-J., O’Donnell, J. D., Wang, J., Wenham, R. M., Coppola, D., Kruk, P. A., Nicason, S. V., and Cheng, J. Q. (2008) Cancer Res. 68, 2924–2934
13. Issa, J. P., Ottaviano, Y. L., Celano, P., Hamilton, S. R., Davidson, N. E., and Baylin, S. B. (1994) Nature Genet. 7, 536–540
14. Sun, M., Paciga, J. E., Feldman, R. I., Yuan, Z., Coppola, D., Lu, Y. Y., Shelley, S. A., Nicason, S. V., and Cheng, J. Q. (2006) Cancer Res. 66, 5985–5991
15. Shi, X. B., Xu, L., Yang, L., Yang, J., Ma, A. H., Zhao, J., Xu, M., Tepper, C. G., Evans, C. P., Kung, H. J., and de Vere White, R. W. (2007) Proc. Natl. Acad. Sci. U. S. A. 104, 19983–19988
16. Zhao, J.-J., Sun, D. G., Wang, J., Liu, S. R., Zhang, C. Y., Zhu, M. X., and Ma, X. (2008) Childs Nerv. Sys. 24, 485–492
17. Yuan, L., Nass, S. J., Smith, D., Nelson, W. G., Herman, J. G., and Davidson, N. E. (2003) Cancer Biol. Ther. 2, 552–556
18. Adams, P. D., and Cairns, P. (2003) Cancer Biol. Ther. 2, 557–558
19. Yang, X., Phillips, D. L., Ferguson, A. T., Nelson, W. G., Herman, J. G., and Davidson, N. E. (2001) Cancer Res. 61, 7025–7029
20. Adams, B. D., Furrinail, H., and White, B. A. (2007) Mol. Endocrinol. 21, 1132–1147
21. Roll, J. D., Rivenbark, A. G., Jones, W. D., and Coleman, W. B. (2008) Mol. Cancer 7, 1–14
22. Cullen, R., Maguire, T. M., McDermott, E. W., Hill, A. D., O’Higgins, N. J., and Duffy, M. J. (2001) Eur. J. Cancer 37, 1118–1122
23. Jarzabek, K., Koda, M., Kozlowski, L., Mittre, H., Sulkowski, S., Kottler, M. L., and Wolczynski, S. (2005) Eur. J. Cancer 41, 2924–2934
24. Alkarain, A., McMahon, C., and Seth, A. (2004) Eur. J. Cancer 2, 46
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25. Poola, I., and Yue, Q. (2007) BMC Cancer 7, 56
26. Galardi, S., Mercatelli, N., Giorda, E., Massalini, S., Frajese, G. V., Ciafre, S. A., and Farace, M. G. (2007) J. Biol. Chem. 282, 23716–23724
27. le Sage, C., Nagel, R., Egan, D. A., Schrier, M., Mesman, E., Mangiola, A., Anile, C., Maira, G., Mercatelli, N., Ciafre, S. A., Farace, M. G., and Agami, R. (2007) EMBO J. 26, 3699–3708
28. Visone, R., Russo, L., Pallante, P., De Martino, L., Ferraro, A., Leone, V., Borbone, E., Petrocca, F., Alder, H., Croce, C. M., and Fusco, A. (2007) Endocr.-Relat. Cancer 14, 791–798
29. Felli, N., Fontana, L., Pelosi, E., Botta, R., Bonci, D., Facchiano, F., Liuzzi, F., Lulli, V., Morsilli, O., Santoro, S., Valtieri, M., Calin, G. A., Liu, C. G., Sorrentino, A., Croce, C. M., and Peschle, C. (2005) Proc. Natl. Acad. Sci. U. S. A. 102, 18081–18086
30. Medina, R., Zaidi, S. K., Liu, C. G., Stein, J. L., van Wijnen, A. J., Croce, C. M., and Stein, G. S. (2008) Cancer Res. 68, 2773–2780
31. Felicetti, F., Errico, M. C., Bottero, L., Segnalini, P., Stoppacciaro, A., Biffoni, M., Felli, N., Mattia, G., Petrini, M., Colombo, M. P., Peschle, C., and Carè, A. (2008) Cancer Res. 68, 2745–2754
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J. Biol. Chem. 2008, 283:31079-31086. 
doi: 10.1074/jbc.M806041200 originally published online September 12, 2008

Access the most updated version of this article at doi: 10.1074/jbc.M806041200

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