MicroRNA Regulates Estrogen Receptor Alpha in Breast Cancer Metastasis

Rajeev Kumar1,*, Xiu Jin1, Yuanhuan Zhen2 and Pingsheng Hu1

1Cancer Immunotherapy Center, Guiyang Medical College Hospital, Guiyi Jie 28, Guizhou, People's Republic of China- 500004
2Department of Surgery, Guiyang Medical College Hospital, Guiyi Jie 28, Guizhou, People's Republic of China- 500004

*Corresponding author: Rajeev Kumar, Cancer Immunotherapy Center, Guiyang Medical College Hospital, Guiyi Jie 28, Guizhou, People's Republic of China- 500004; E-mail: rajeev.bioraj@gmail.com

Abstract
Breast cancer (BCa) is a common endocrine disorder among postmenopausal women and estradiol (E2) known causative agent for metastasis. During previous decade, tiny microRNAs (miRNAs) become a potential mediator of tumor suppressor or tumorigenic factor. Numerous miRNA regulates nuclear receptor ERα under the influence of estradiol (E2) such as miR-101, miR-21 whereas miR145, miR-29a, miR-206, let-7 potentiates ERα proliferating activity. MiR-221/222 have established in hormone refractory condition after long exposure of Selective Estrogen Receptor Modulators (SERMs) or Selective Estrogen Receptor Down Regulator (SERDs). The target genes and the role of miRNAs in ERα mediated tumor progression is a challenging area of research that will open new clinical values as novel biomarkers in diagnosis and therapy.

Keywords: Estradiol; ERα; MicroRNA; Metastasis; Breast cancer

Introduction
Breast cancer (BCa) is most leading causes of cancer among women in western world that resulting in more than 200,000 new cases and about 40,000 deaths occurring annually in United State of America, but recent obtained clinical data show assumed decline in mortality rates during previous decades[1]. Estradiol (E2) regulates mammary gland differentiation and development in women during early menarche and late menopause. BCa cell arise from luminal epithelial cells of mammary gland and approximately, third fourth of tumors found expression of estrogen receptor alpha (ERα), which are major candidates for hormone refractory treatment. The effect of E2change the miRNA expression pattern as it lead to cause histological modification in rat mammary tissue architecture and some study expresses clear evidence about the miRNA expression profile (38 miR alterations) after E2 exposure in a tropical fresh water fish i.e. zebrafish male [Daniorerio][2,3].

A several decades ago, discovery of Estrogen Receptor (ER) isoforms such as ERα/β implicate possible use of Selective Estrogen Receptor Modulators (SERMs) such as Tamoxifen (TAM) are well recognized chemotherapeutic agent for the treatment of breast cancer, which kill cancer cell by down regulation of ERα, but one fourth become hormone refractory. TAM induces endometrial cancer after long exposure and sometime pure antiestrogen fulvestrant recommend as estrogen receptor down regulator (SERD) for estrogen sensitive BCa in postmenopausal women[4-7]. TAM treatment is a common known therapeutic drug for hormone responsive metastatic cancer but tumor regrowth often seen among long term treatment and discontinuation[6,8]. Aromatase inhibitor (AI) has also used as alternate of estrogen modulators but it has better efficacy seems as in adjuvant therapy with TAM[9]. Strong association of HER2 level with disease pathogenesis and prognosis become a important therapeutic target in BCa[10]. Clifford A et al 2007 has specified the overall improved survival of metastatic breast cancer patient with HER2 monoclonal antibody Trastuzumab (Herceptin; Genentech, South San Francisco, CA) treatment, and the combination with chemotherapy has been revealed to increase both survival and response rate, in comparison to Trastuzumab alone[11].
MicroRNA biogenesis and their regulatory role during tumor growth

MicroRNAs (miRNAs) are short, non-coding RNAs, which regulate their corresponding target genes through post-transcriptional repression[12], located at un-translated region and evolutionary conserved RNA molecules that usually prevent protein synthesis by two different possible mechanisms such as cleavage of target mRNA or translational inhibition. Small mature RNA molecule produces over two steps such as formation of long hairpin pre-miRNA and RNA-induced silencing complex (RISC) contains dsRNA binding proteins including protein kinase RNA activator (PACT), transactivation response RNA binding protein (TRBP) process into mature miRNA[13]. Microprocessor complex composed of Drosha and DGCR8 protein molecule and exportin-5 transport pre-miRNA (~70nt) duplex with the help of Ran-ATP from nucleus to cytoplasm. Dicer cleaves intermediate 60-70nt long miRNA into precursor 18-25nt duplex for the binding with RISC complex. RISC complex form mature single stranded miRNA for the inhibitory function over transcript of target gene[14,15]. More than 50% miRNA resides in cancer associated gene, which functions as tumor suppressor/oncogene[16]. The regulatory power of miRNA is a unique feature as expression pattern, stability and potential to adjust nuclear receptor (NR) transcript regulation, and indicate their important use in clinic as prominent biomarkers[15]. The use of miRNA therapy could have beneficial use in breast cancer therapy and prevention. Table 1 shows the list of miRNAs that regulate ERα and mechanism involve in hormone response, drug resistance and proliferation during BCa metastasis.

Breast cancer and estrogen receptor

The role of estrogen, mediated through ER in breast carcinogenesis and tumor progression has been well established. BCa classes subdivide in; luminal A (ER+, PR+ and HER2+), luminal B (ER+, PR+ and HER2-), Basal (triple negative), and HER2 (ER-, PR- and HER2+)[17]. Patients with basal subtypes are known to have the worst overall survival, reflected by the abundance of triple negative tumors followed by patients with cancer subtypes of HER2[18]. ER is categorized as a type I nuclear receptor that undergoes nuclear translocation after ligand binding, regulate mammary development. Kuiper G et al. (1996), reclassified ER into a growth promoting ERα, and anti proliferating ERβ[19] that exposed new concept in endocrine related oncology area. We have categorized that how miRNA regulates transcription factors, oncogene and estrogen metabolism during BCa metastasis (Figure 1).

Estrogen receptor alpha

Estrogen (E2) influence their action mediated by different mechanisms such as ligand-independent ERα signaling, genomic and non-genomic. Growth factors are involved in alteration of cytoplasmic kinase/phosphatase activity as ligand-independent ERα signaling[20] whereas genomic and non genomic mechanism involve in participation of ER with interaction of transcription factor such as c-Fos/c-Jun (AP-1), which regulate downstream cellular mechanism[21]. E2 stimulates inactive ER-positive cells to make growth promoting environment by stimulating benign cell to malignant[22]. E2 binding to ERα recruit various coressor and coactivator in cancer cell proliferation that stimulate to occupy promoter of their targeted gene[23]. The p160 coactivator such as SRC-1/2, AIB1 influence transcription activation after ligand bind-

| miRNA       | Target       | Function                  | Ref. |
|-------------|--------------|---------------------------|-----|
| miR-27a     | ZBTB10       | Hormone response          | 38  |
| miR-18a, -19b, -20b | p160 and AIB1 | E2 response              | 33  |
| miR-193b    | AKR1C2       | E2 production             | 44  |
| miR-21, -5a, -16, -342 | Bcl-2 and PTEN | TAM response             | 39, 40 |
| miR-221/222, -206 | β-catenin      | Fulvestrant resistance    | 50  |
| miR-128a    | TGFβ-R1      | Aromatase inhibitors resistance | 54  |
| miR-23b, -24-1, -27b, -29a | ESR1         | Dicer activity           | 47  |
| miR-375     | RASD1        | Tumor progression         | 36  |
| miR-145     | TP53         | Growth inhibition         | 42  |
| miR-22, -191/425 cluster | ERα        | Tumorigenesis             | 43, 31 |
| miR-17-9p   | AIB1 and c-Myc | Metastasis               | 41  |
| miR-125a    | ERBB2        | HER2 expression           | 59  |
| miR-101     | Akt          | Cell survival             | 29  |
| miR-17-92   | c-Myc        | Promote transcription     | 35  |
| miR-206, -34a | ERα          | Proliferation             | 37, 32 |
| miR-200c    | ZEB1/2, Trk/Bmi1 | BRCA-1                   | 55  |
| miR-182     | BRCA-1       | DNA repair                | 56  |

Table 1: Lists of miRNA, whose expression regulates drug resistance, transcriptional factors, and other co-regulatory proteins involve in breast cancer metastasis
ing and receptor dimerization. The genetic alteration in a AIB1 gene activate ERα expression in absence of ligand and it is major factor for hormone refractory environment[24,25].

**Estrogen receptor beta**

ERβ belongs to the nuclear receptor superfamily, with similar expression pattern, as of ERα and their balanced cross-talk requires mammary gland development. Experimental evidence suggests ERβ have suppressive role over ERα during breast cancer proliferation and morphogenesis. Usually, mammary tissue express two third anti-proliferative receptor ERβ whereas low expression have seen in invasive breast tumor tissues[26,27]. Leung YK et al 2006 has shown ERβ isoforms, especially ERβ1 a statutory partner of ERβ dimer, whereas ERβ-2/4/5 works as enhancer[28]. Epigenetic modification of ERβ influence lower expression pattern in breast tumor carcinoma and complete loss has observed in one fourth of invasive carcinomas[29]. Phyto-estrogens are known natural SERMs that bind to ERβ and activate expression, but chemically synthesized SERMs inhibit expression of ERα. ERβ –E2 complex activated gene expression pattern are different than ERα-E2 and hetero dimerization influence inhibitory action of ERβ over ERα has been studied as cell based in vitro experiment[30].

**Effect of miRNA on estrogen receptor**

Estrogen regulates biological events in endocrine carcinoma mediated by ERα and ERβ nuclear receptor. E2- ERα mediated miR-191/425 cluster expression controls high level of early growth response-1 (EGR-1), which converse a proliferative lead to metastatic BCa cells[31].

The set of 54 miRNA regulated by estrogen including miR34 that targets lemur tyrosine kinase 3 (LMTK3) regulates ERα mediated cell proliferation and tumor growth[13,32]. E2 inhibit miR-101, miR-21 action on cell proliferation, which proven by using fulvestrant and TAM metabolite (4-OHT) mediated PTEN regulation a well known function by regulating ER/β ratio[33,34]. The ER-α mRNA has a long 3' UTR of about 4.3kb, which has evolutionarily conserved miRNA target sites. E2 induce various miRNA belong to let-7 family that down regulate ERα activity in cell proliferation and metastasis. ERα is a key regulatory nuclear protein in BCa, which regulate several growth transcription factor such as c-MYC, and miR-17-92 regulate these transcription factor on estrogenic stimulation[35].

The high expression of miR-375 and RASD1 is validated target in ERα responsive breast cancer and opposite expression in hormone refractory cancer cell[36]. MiR-206 down regulate ERα expression by targeting existing two 3' UTR sequences, which were proved by the use of ER antagonist[37]. Recent findings suggest miR-27a regulate transcription factor by inhibition of ZBTB10 and their inhibition recruit ERα with their transactivation for protein-protein interaction[38]. MiR-15a and miR-16 are well established as the target of Bcl-2, which sensitize TAM effect mediated by ERα in BCa cell line[39]. Additionally, miR345 and elevates ERα expression and promotes TAM mediated apoptosis in MCF-7 cell[40]. MiR-17-9p located on chromosome 13q31 that target AIB1 gene expression and modulate ERα regulatory gene/coregulatory expression for example CyclinD1, cdc2, SMART and NCoR[41]. MiR-145 suppress directly the ERα protein expression by binding at 3' UTR at coding sequence[42]. The interaction of miR-22 of 3'UTR sequence of ERα shows a suppressive role in tumor progression. The tumor suppressor function of miR-22 was clearly found in various cell line, and significantly less expression was detected in ERα positive cells comparison of ER negative[43]. The proteomic analysis of functional role of miR-193b by high-throughput strategy utilizing quantitative iTRAQ was demonstrated in transfected E2 responsive MCF-7 cell, and results found as 39 up regulation and 44 down regulation among 390 analyzed protein in post transfected cell[44]. MiR-193b target 5'UTR of AKR1C2 which is important aldo-keto enzyme coding gene and it catalyzes local estradiol production[45]. Depletion of AIB1 data clearly support role of miR-17-92 in regulation of ERα mediated regulation of cell proliferation and restoration of AIB1 enhance growth in ER independent cells[41].

The ERβ function as gate keeper gene has been recognized in BCa, and it antagonize role of ERα in estrogen mediated genomic mechanism[29,46]; inhibit miR30a biogenesis, promotes miR-23b, -27b and 24-1 accumulation in cells for reverse action of ERα on Drosha microprocessor complex[47]. ERβ1 is the important isoform and it has been recognized as disappearance or down-regulation in late stage of endocrine related cancer compared with normal cells[28]. The restrictive role of miR-92 has been recognized in various breast cancer cell line and their in vitro manipulation induce ERβ1 disappearance[48], which indicate use of specific agonist could help in management of aggressive tumor phenotype mediated by nuclear receptor.

**MicroRNA and hormone/chemo resistance**

Endocrine therapy is a highly effective form of adjuvant therapy for hormone sensitive breast cancer. The up regulations of miR-146a, -27a, -145, -21, -155, -15a, -125b, and let-7 including miR-221/222 are associated with TAM and fulvestrant resistance cell lines[49], and miR-221/222 mediate via disappearance of ERα expression and cell promoting gene level. ERα re-expression have suppressive play on miR-221/222 pairs, which have significant role in hormone therapy resistance by regulating various signaling pathways including β-catenin and TGF-β[50-52]. Some in vivo experiment demonstrated prolonged exposure of rats to TAM has association between alterations in miRNA-target proteins such as Bcl2, E2F1[53]. The high expression of miR-128a regulates cell growth by targeting TGF-β1 in aromatase resistant (aromatase independent-AI) cell line, suggest their role in failure of endocrine therapy[54]. Classical chemotheraphy is commonly used in patient treatments over hormone and targeted therapy, which results in epithelial-mesenchymal transition (EMT), and promote stemness property of exposed cells. EMT modulated by miR-200c by targeting Zeb1/ Zeb2 and Trk/Bmi1, mediate doxorubicin exposed resistance in breast cancer cell lines[55]. Radiotherapy is another practice of cancer treatment that applies the ability of ionizing radiation to induce cell in-
activation and cell death in sporadic BCa, miR-182 promote sensitivity of IR radiation by causing adaptation in DNA repair mechanism of BRCA-1 gene[56].

Medical usefulness of miRNA

Breast tissue clinical specimens were evaluated for the ERs as direct target of miR-22 and a potential prognostic biomarker in estrogen responsive cancer patients[43]. Among various miR expressions, miR-21 frequently found high expression in pregnancy associated breast cancer patients that are potential target of Bcl-2 and some study showed their over-expression results as prognostic biomarker ER response. Loss of expression of Bcl-2 suggest ER negative status of breast cancer stages[57]. LMA technology was applied for the study of functional role of various miRNA in breast cancer progression and correlation with stages of cancer. Inverse coalition of miR-18a and miR-18b has been setup by IHC staining in both estrogen responsive and negative tumor tissue[44]. The comparative analysis of let-7a/bi expression among 13 benign, 16 ductal carcinoma in situ (DCIS) and 15 invasive carcinoma found suppressive role on ERα[58]. High of miR-92 was seen in 29 FFPE breast tumor tissue samples and low intensity of ERβ1 in IHC specimens in comparison to normal[48]. MiR-17-92 positively regulate ERα expression by recruitment of c-MYC transcription factor in primary stage of breast tumor and highest staining of altered AIB1 in tumor tissue than normal[25,35]. Polymorphic variant of pre-miR125a is correlated with ERBB2 expression, which may use as genetic markers in the prognosis of BCa[59]. MRX-34 (Mirna Therapeutics Inc., Austin USA), a liposome-based miR-34 is the first series of miRNA therapeutic agents that regulate p53-mediated cancer cell proliferation and growth, entered under phase I clinical trials in metastatic cancer with liver involvement.

Conclusion

The role of miRNA has been established as tiny regulatory molecule in initiation and progression of BCa. Various study indicating interaction of ER, small RNA molecule in tumor microenvironment lead to progressive cancer stage. E2, their receptor protein imbalance and regulatory miRNA have been found differently in different stages, which clearly suggest a tumor suppressor function. Numerous studies are indicating anti proliferative key nuclear receptor can be a target of micro agent for the chemotherapy, and specific agonist could be used as anti proliferative drug molecule. Identification and validation of nuclear receptor-targeted miRNA can be a possible biomarker in prognosis, diagnostic and therapeutic targets in endocrine cancer.

References

1) Jemal A, Siegel R, Xu J, Ward E (2010) Cancer statistics. CA Cancer J Clin 60: 277-300.
2) Kovalchuk O, Tryndyak VP, Montgomery B, Boyko A, Kutanzi K, et al. (2007) Estrogen-induced rat breast carcinogenesis is characterized by alterations in DNA methylation, histone modifications and aberrant microRNA expression. Cell Cycle 6: 2010-2018.
3) Cohen A, Shmoish M, Levi L, Cherutti U, Levavi-Sivan B, et al. (2008) Alterations in micro-ribonucleic acid expression profiles reveal a novel pathway for estrogen regulation. Endocrinology 149: 1687-96.
4) Johnston SJ, Cheung KL (2010) Fulvestrant - a novel endocrine therapy for breast cancer. Curr Med Chem 17: 902-914.
5) Saxena R, Dwivedi A (2010) ErbB family receptor inhibitors as therapeutic agents in breast cancer: Current status and future clinical perspective. Med Res Rev 32:166-215.
6) Rutqvist LE, Cedermark B, Glas U, Mattsson A, Skoog L, et al. (1991) Contralateral primary tumors in breast cancer patients in a randomized trial of adjuvant tamoxifen therapy. J Natl Cancer Inst 83: 1299-1306.
7) Weihsa Z, Andersson S, Cheng G, Simpson ER, Warner M, et al. (2003) Update on estrogen signaling. FEBS Lett 546, 17-24.
8) Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) (2005) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 365: 1687-1717.
9) Kaklamani VG, Gradishar WJ (2005) Adjuvant therapy of breast cancer. Cancer Invest 23: 548-560.
10) Nahta R, Esteva FJ (2003) HER-2-targeted therapy: lessons learned and future directions. Clin Cancer Res 9: 5078-5084.
11) Hudis CA (2007) Trastuzumab—mechanism of action and use in clinical practice. N Engl J Med 357: 39-51.
12) Carthew RW, Sontheimer EJ (2009) Origins and Mechanisms of miRNAs and siRNAs. Cell 136: 642-655.
13) Lee HY, Zhou K, Smith AM, Noland CL, Doudna JA (2013) Differential roles of human Dicer-binding proteins TRBP and PACT in small RNA processing. Nucleic Acids Res 41: 6568-6576.
14) Perron MP, Provost P (2008) Protein interactions and complexes in human microRNA biogenesis and function. Front Biosci 13: 2537-47.
15) Redfern AD, Colley SM, Beveridge DJ, Ikeda N, Epis MR, et al. (2013) RNA-induced silencing complex (RISC) Proteins PACT, TRBP, and PACT are SRA binding nuclear receptor coregulators. Proc Natl Acad Sci U S A 110: 6536-6541.
16) Calin GA, Sevignani C, Dumitru CD, Hyslop T, Noch E, et al. (2004) Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. Proc Natl Acad Sci U S A 101: 2999-3004.
17) Sotiriou C, Neo SY, McShane LM, Korn EL, Long PM, et al. (2003) Breast cancer classification and prognosis based on gene expression profiles from a population-based study. Proc Natl Acad Sci U S A 100: 10393-10398.
18) Hu Z, Fan C, Oh DS, Marron JS, He X, et al. (2006) The molecular portraits of breast tumors are conserved across microarray platforms. BMC Genomics 7: 96.
19) Kuiper GG, Enmark E, Pelto-Huikko M, Nilsson S, Gustafsson JA (1996) Cloning of a novel receptor expressed in rat prostate and ovary. Proc Natl Acad Sci U S A 93: 5925-5930.
20) Weigel NL, Zhang Y (1998) Ligand-independent activation of steroid hormone receptors. J Mol Med 76: 469-479.
21) Webb P, Lopez GN, Uht RM, Kusner P (1995) Tamoxifen activation of the estrogen receptor/AR-1 pathway: potential origin for the cell-specific estrogen-like effects of antiestrogens. Mol Endocrinol 9: 443-456.
22) Cunha GR, Cooke PS, Kurita T (2004) Role of stromal-epithelial
interactions in hormonal responses. Arch Histol Cytol 67: 417-434.

23) Ali S, Coombes RC (2002) Endocrine-responsive breast cancer and strategies for combating resistance. Nat Rev Cancer 2: 101-12.

24) Xu J, Li Q (2003) Review of the in vivo functions of the p160 steroid receptor coactivator family. Mol Endocrinol 17: 1681-1692.

25) Torres-Arzayus MI, Font de Mora J, Yuan J, Vazquez F, Bronson R, et al. (2004) High tumor incidence and activation of the PI3K/AKT pathway in transgenic mice define AIB1 as an oncogene. Cancer Cell 6: 263-274.

26) Järvinen TA, Pelto-Huikkio M, Holli K, Isola J (2000) Estrogen receptor beta is coexpressed with ERL alpha and PR and associated with nodal status, grade, and proliferation rate in breast cancer. Am J Pathol 156: 29-35.

27) Rody A, Holtrich U, Solbach C, Kourtis K, von Minckwitz G, et al. (2005) Methylation of estrogen receptor beta promoter correlates with loss of ER-beta expression in mammary carcinoma and is an early indication marker in premalignant lesions. Endocr Relat Cancer 12: 903-916.

28) Leung YK, Mak P, Hassan S, Ho SM (2006) Estrogen receptor (ER)-beta isoforms: a key to understanding ER-beta signaling. Proc Natl Acad Sci U S A 103: 13162-13167.

29) Skliris GP, Munot K, Bell SM, Carder PJ, Lane S, et al. (2003) Reduced expression of oestrogen receptor beta in invasive breast cancer and its re-expression using DNA methyl transferase inhibitors in a cell line model. J Pathol 201: 213-220.

30) Lin CY, Ström A, Li Kong S, Kietz S, Thomsen JS, et al. (2007) Inhibitory effects of estrogen receptor beta on specific hormone-responsive gene expression and association with disease outcome in primary breast cancer. Breast Cancer Res 9: R25.

31) Di Leva G, Piowan C, Gasparini P, Ngenkeu A, Taccioli C, et al. (2013) Estrogen mediated-activation of miR-191/425 cluster modulates tumorigenicity of breast cancer cells depending on estrogen receptor status. PLoS Genet 9: e1003311.

32) Zhao G, Guo J, Li D, Jia C, Yin W, et al. (2013) MicroRNA-34a suppresses cell proliferation by targeting LMTK3 in human breast cancer mcf-7 cell line. DNA Cell Biol 32: 699-707.

33) Sachdeva M, Wu H, Ru P, Hwang L, Tieue U, et al. (2011) MicroRNA-101-mediated Akt activation and estrogen-independent growth. Oncogene 30: 822-831.

34) Jordan VC, O’Malley BW (2007) Selective estrogen-receptor modulators and antihormonal resistance in breast cancer. J Clin Oncol 25: 5815-5824.

35) Castellano L, Giamas G, Jacob J, Coombes RC, Lucchesi W, et al. (2009) The estrogen receptor-alpha-induced microRNA signature regulates itself and its transcriptional response. Proc Natl Acad Sci U S A 106: 15732-15737.

36) de Souza Rocha Simonini P, Breiling A, Gupta N, Malekpour M, Youns M, et al. (2010) Epigenetically deregulated microRNA-375 is involved in a positive feedback loop with estrogen receptor alpha in breast cancer cells. Cancer Res 70: 9175-9184.

37) Adams BD, Furneaux H, White BA (2007) The micro-ribonucleic acid (miRNA) miR-206 targets the human estrogen receptor-alpha (ERalpha) and represses ERalpha messenger RNA and protein expression in breast cancer cell lines. Mol Endocrinol 21: 1132-1147.

38) Li X, Mertens-Talcott SU, Zhang S, Kim K, Ball J, et al. (2010) MicroRNA-27a Indirectly Regulates Estrogen Receptor [alpha] Expression and Hormone Responsiveness in MCF-7 Breast Cancer Cells. Endocrinology 151: 2462-2473.

39) Cittelly DM, Das PM, Salvo VA, Fonseca JP, Burow ME, et al. (2010) Oncogenic HER2[Delta]16 suppresses miR-15a/16 and deregulates BCL-2 to promote endocrine resistance of breast tumors. Carcinogenesis 31: 2049-2057.

40) He YJ, Wu JZ, Ji MH, Ma T, Qiao EQ, et al. (2013) miR-342 is associated with estrogen receptor-alpha expression and response to tamoxifen in breast cancer. Exp Ther Med 5: 813-818.

41) Hossain A, Kuo MT, Saunders GF (2006) Mir-17-5p regulates breast cancer cell proliferation by inhibiting translation of AIB1 mRNA. Mol Cell Biol 26: 8191-8201.

42) Spizzo R, Nicoloso MS, Lupini L, Lu Y, Fogarty J, et al. (2010) miR-145 participates with TP53 in a death-promoting regulatory loop and targets estrogen receptor-alpha in human breast cancer cells. Cell Death Differ 17: 246-254.

43) Xiong J, Yu D, Wei N, Fu H, Cai T, et al. (2010) An estrogen receptor alpha suppressor, microRNA-22, is downregulated in estrogen receptor alpha-positive human breast cancer cell lines and clinical samples. FEBS J 277: 1684-1694.

44) Leivonen SK, Mäkelä R, Ostling P, Kohonen P, Haapa-Paananen S (2009) Protein lysate microarray analysis to identify microRNAs regulating estrogen receptor signaling in breast cancer cell lines. Oncogene 28: 3926-3936.

45) Leivonen SK, Rokka A, Ostling P, Kohonen P, Corthals GL, et al. (2011) Identification of miR-193b targets in breast cancer cells and systems biological analysis of their functional impact. Mol Cell Proteomics 10: M110.005322.

46) Wang M, Yu B, Westerlind K, Strange R, Khan G, et al. (2009) Prepubertal physical activity up-regulates estrogen receptor beta, BRCA1 and p53 mRNA expression in the rat mammary gland. Breast Cancer Res Treat 115: 213-220.

47) Paris O, Ferraro L, Grober OM, Ravo M, De Filippo MR, et al. (2012) Direct regulation of microRNA biogenesis and expression by estrogen receptor beta in hormone-responsive breast cancer. Oncogene 31: 4196-4206.

48) Al-Nakhlle H, Burns PA, Cummings M, Hanby AM, Hughes TA, et al. (2010) Estrogen receptor {beta} expression is regulated by miR-92 in breast cancer. Cancer Res 70: 4778-4784.

49) Nam S, Long X, Kwon C, Kim S, Nephew KP (2012) An integrative analysis of cellular contexts, miRNAs and mRNAs reveals network clusters associated with androgen-resistant breast cancer cells. BMC Genomics 13: 732.

50) Di Leva G, Gasparini P, Piowan C, Ngenkeu A, Garofalo M, et al. (2010) MicroRNA cluster 221-222 and estrogen receptor alpha interactions in breast cancer. J Natl Cancer Inst 102: 706-721.

51) Zhao JJ, Lin J, Yang H, Kong W, He L, et al. (2008) MicroRNA-NA-221/222 negatively regulates estrogen receptor alpha and is associated with tamoxifen resistance in breast cancer. J Biol Chem 283: 31079-31086.

52) Rao X, Di Leva G, Li M, Fang F, Devlin C, et al. (2011) MicroRNA-221/222 confers breast cancer fulvestrant resistance by regulating multiple signaling pathways. Oncogene 30: 1082-1097.

53) Pogribny IP, Tryndyak VP, Boyko A, Rodriguez-Juarez R, Beland FA, et al. (2007) Induction of microRNAoome deregulation in rat liver by long-term tamoxifen exposure. Mutat Res 619: 30-37.

54) Masri S, Liu Z, Phung S, Wang E, Yuan YC, et al. (2010) The role of microRNA-128a in regulating TGFbeta signaling in letrozole-resistant breast cancer cells. Breast Cancer Res Treat 124: 89-99.

55) Alters SE, McLaughlin B, Spink B, Lachiniya T, Wang CW, et al. (2013) GLP2-2G-XTEN: a pharmaceutical protein with improved serum half-life and efficacy in a rat Crohn’s. PLoS One 7:e50630.
56) Moskwa P, Buffa FM, Pan Y, Panchakshari R, Gottipati P, et al. (2011) miR-182-mediated downregulation of BRCA1 impacts DNA repair and sensitivity to PARP inhibitors. Mol Cell 41: 210-220.

57) Walter BA, Gómez-Macias G, Valera VA, Sobel M, Merino MJ (2011) miR-21 Expression in Pregnancy-Associated Breast Cancer: A Possible Marker of Poor Prognosis. J Cancer 2: 67-75.

58) Zhao Y, Deng C, Wang J, Xiao J, Gatalica Z, et al. (2011) Let-7 family miRNAs regulate estrogen receptor alpha signaling in estrogen receptor positive breast cancer. Breast Cancer Res Treat 127: 69-80.

59) Lehmann TP1, Korski K, Ibbs M, Zawierucha P, Grodecka-Gazdecka S, et al. (2013) rs12976445 variant in the pri-miR-125a correlates with a lower level of hsa-miR-125a and ERBB2 overexpression in breast cancer patients. Oncol Lett 5: 569-573.