

MicroRNA Regulates Estrogen Receptor Alpha in Breast Cancer Metastasis

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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 ER α under the influence of estradiol (E2) such as miR-101, miR-21 whereas miR145, miR-29a, miR-206, let-7 potentiates ER α 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 ER α mediated tumor progression is a challenging area of research that will open new clinical values as novel biomarkers in diagnosis and therapy.

Keywords: Estradiol; ER α ; 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 (ER α), which are major candidates for hormone refractory treatment. The effect of E2 change 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 ER α / 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 ER α , 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 over all 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].

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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 ER α 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 ER α , and anti proliferating ER β [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 ER α signaling, genomic and non-genomic. Growth factors are involved in alteration of cytoplasmic kinase/phosphatase activity as ligand-independent ER α 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

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	TGF β -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	ER α	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	ER α	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

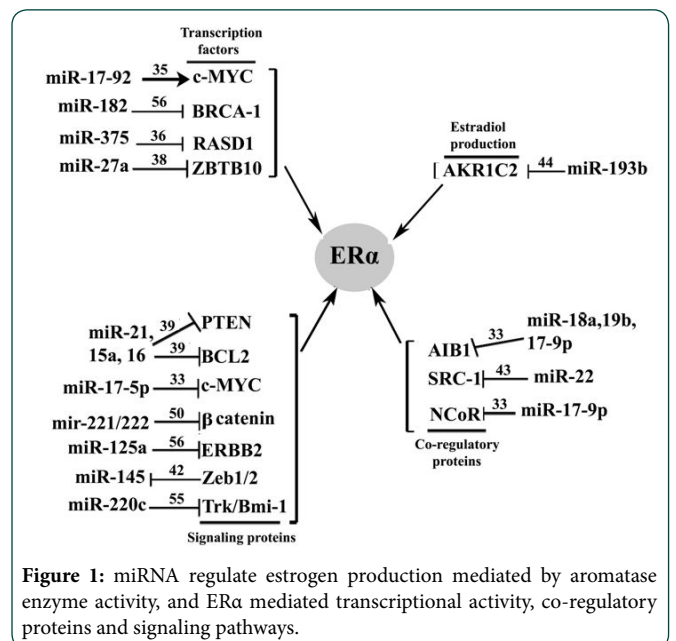


Figure 1: miRNA regulate estrogen production mediated by aromatase enzyme activity, and ER α mediated transcriptional activity, co-regulatory proteins and signaling pathways.

stimulates inactive ER-positive cells to make growth promoting environment by stimulating benign cell to malignant[22]. E2 binding to ER α recruit various corepressor 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-

ing and receptor dimerization. The genetic alteration in a AIB1 gene activate ER α expression in absence of ligand and it is major factor for hormone refractory environment[24,25].

Estrogen receptor beta

ER β belongs to the nuclear receptor superfamily, with similar expression pattern, as of ER α and their balanced cross-talk requires mammary gland development. Experimental evidence suggests ER β have suppressive role over ER α during breast cancer proliferation and morphogenesis. Usually, mammary tissue express two third anti-proliferative receptor ER β whereas low expression have seen in invasive breast tumor tissues[26,27]. Leung YK et al 2006 has shown ER β isoforms, especially ER β 1 a statutory partner of ER β dimer, whereas ER β -2/4/5 works as enhancer[28]. Epigenetic modification of ER β 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 ER β and activate expression, but chemically synthesized SERMs inhibit expression of ER α . ER β -E2 complex activated gene expression pattern are different than ER α -E2 and hetero dimerization influence inhibitory action of ER β over ER α has been studied as cell based in vitro experiment[30].

Effect of miRNA on estrogen receptor

Estrogen regulates biological events in endocrine carcinogenesis mediated by ER α and ER β nuclear receptor. E2- ER α 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 ER α mediated cell proliferation and tumor growth[13,32]. E2 inhibit miR-101, miR-21 action on cell proliferation, which has proven by using fulvestrant and TAM metabolite (4-OHT) mediated PTEN regulation a well known function by regulating ER α / 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 ER α activity in cell proliferation and metastasis. ER α 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 ER α responsive breast cancer and opposite expression in hormone refractory cancer cell[36]. MiR-206 down regulate ER α 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 ER α 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 ER α in BCa cell line[39]. Additionally, miR345 and elevates ER α 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 ER α regulatory gene/coregulatory expression for example CyclinD1, cdc2, SMART and NCoR[41]. MiR-145 suppress directly the ER α protein expression by binding at 3'UTR at coding sequence[42]. The interaction of miR-22 of 3'UTR sequence of ER α 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 ER α 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 ER α mediated regulation of cell proliferation and restoration of AIB1 enhance growth in ER independent cells[41].

The ER β function as gate keeper gene has been recognized in BCa, and it antagonize role of ER α in estrogen mediated genomic mechanism[29,46]; inhibit miR30a biogenesis, promotes miR-23b, -27b and 24-1 accumulation in cells for reverse action of ER α on Drosha microprocessor complex[47]. ER β 1 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 ER β 1 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-7s including miR-221/222 are associated with TAM and fulvestrant resistance cell lines[49], and miR-221/222 mediate via disappearance of ER α expression and cell promoting gene level. ER α 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- β 1 in aromatase resistant (aromatase independent-AI) cell line, suggest their role in failure of endocrine therapy[54]. Classical chemotherapy 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 ER α 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/b/i expression among 13 benign, 16 ductal carcinoma in situ (DCIS) and 15 invasive carcinoma found suppressive role on ER α [58]. High of miR-92 was seen in 29 FFPE breast tumor tissue samples and low intensity of ER β 1 in IHC specimens in comparison to normal[48]. MiR-17-92 positively regulate ER α 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.

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