15

The Role of MicroRNAs in Estrogen Receptor α-Positive Human Breast Cancer

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1. Introduction

MicroRNAs (miRNAs) are a class naturally occurring small non-coding RNAs that control gene expression by targeting mRNAs for translational repression or cleavage (Krol et al., 2010). Recent evidence has shown that miRNA mutations or mis-expression correlate with various human cancers, and that loss- or gain-of function of specific miRNAs contributes to breast epithelial cellular transformation and tumorigenesis (Esquela-Kerscher et al., 2006). miRNA expression profiling also revealed that miRNAs are differently expressed among molecular subtypes in breast cancer (Blenkiron et al., 2007; Iorio et al., 2005).

There are large-scale molecular differences between estrogen receptor (ER) α-positive and ERα-negative breast cancers (Perou et al., 2000; Sorlie et al., 2003). Endocrine therapy has become the most important treatment option for women with ERα-positive breast cancer, and approximately 70% of primary breast cancers express ERα. ERα is essential for estrogen-dependent growth, and its level of expression is a crucial determinant of response to endocrine therapy and prognosis in ERα-positive breast cancer (Dowsett et al., 2008; Harvey et al., 1999; Yamashita et al., 2006). Multiple mechanisms involved in altering ERα gene expression in breast cancer have been proposed, including ERα gene amplification (Holst et al., 2007) as well as transcriptional silencing by DNA methylation of CpG islands within the ERα promoter (Giacinti et al., 2006) and mutations within the open reading frame of ERα (Herynk et al., 2004). However, expression levels of ERα in breast cancer tissues differ widely among patients (Yamashita et al., 2011), and frequently change during disease progression and in response to systemic therapies (Yamashita et al., 2009). It was reported that the microRNA miR-206 decreases endogenous ERα mRNA and protein levels in human MCF-7 breast cancer cells via two specific target sites within the 3′-untranslated region (UTR) of the human ERα transcript (Adams et al., 2007). We found that the expression levels of miR-206 were gradually decreased as ERα protein expression increased in breast cancer tissues, suggesting that miR-206 is a key factor for the regulation of ERα expression in human breast cancer (Kondo et al., 2008). Moreover, recent studies have shown that ERα-regulating miRNAs, miR-18a, miR-18b, miR-22, miR-193b, miR-302c, and miR-221/222, as well as miR-206, directly targeted ERα in 3′UTR reporter assays, and suggested that several miRNAs regulate ERα expression.

2. Estrogen receptor (ER) α expression in human breast cancer

2.1 Expression of ERα in human breast cancer tissues

2.1.1 ERα expression in normal and malignant breast epithelial cells

ERα expression in normal and premalignant breast epithelial cells has been assessed by immunohistochemistry. It was reported that on average, normal premenopausal terminal duct lobular units contain about 30% ERα-positive cells (Allred et al., 2004). In contrast, nearly all cells express very high levels of ERα in the majority of premalignant breast lesions, including atypical ductal hyperplasia, atypical lobular hyperplasia and lobular carcinoma in situ. DCIS (Ductal carcinoma in situ) shows various levels of ERα expression ranging from high levels of lower-grade lesions to low levels of higher-grade lesions, including entirely ERα-negative. Furthermore, the wide range of ERα expression is observed in invasive ductal carcinoma. There is a substantial (~25%) subset of invasive breast cancers that does not contain any ERα-expressing cells. The majority (~75%) of invasive breast cancers, however, does contain ERα-expressing cells, but the proportion varies ranging from very low, to intermediate, to very high. We examined ERα expression in breast cancer tissues by immunohistochemistry using Allred score (Allred et al., 1998), and demonstrated that breast tumors show a wide range of ERα expression levels (Yamashita et al., 2011). Moreover, intensity of ERα expression is not equal among breast cancer cells in an individual tumor. Eastern cooperative oncology group compared the distribution of ERα protein expression by immunohistochemistry and ERα mRNA expression by quantitative reverse transcription (RT)-PCR in ECOG 2197 study (Badve et al., 2008). They reported that ERα mRNA expression in breast cancer tissues also showed continuous and the wide range.

2.1.2 Role of expression levels of ERα in human breast cancer

It is well established that expression levels of ERα govern response to endocrine therapy and prognosis in ERα-positive human breast cancer. Allred and colleagues first reported that expression levels of ERα assessed by immunohistochemistry affected prognosis (Harvey et al., 1999). ERα status using Allred score was a highly significant predictor of disease-free survival for patients who received adjuvant endocrine therapy. Recently, relationship between expression levels of ERα and prognosis was analyzed in adjuvant endocrine therapy trials for postmenopausal breast cancer, and demonstrated that disease-free survival or time to recurrence were significantly different according to expression levels of ERα (Dowsett et al., 2008; Viale et al., 2007). It was reported that the use of a cutoff of 1% staining cells for ERα indicated a better prognosis and at least some degree of endocrine responsiveness (Hammond et al., 2010). In the neoadjuvant endocrine therapy trial for postmenopausal women, correlation between expression levels of ERα assessed by Allred score and response to neoadjuvant endocrine therapy was analyzed (Ellis et al., 2001). It showed that letrozole response rates were superior to tamoxifen response rates in every ERα Allred score from 3 to 8, indicating that letrozole is more effective than tamoxifen regardless of the level of ERα expression. We also studied expression levels of ERα on pretreatment biopsies and post-treatment surgical specimens in postmenopausal patients with ERα-positive primary breast cancer who were treated with aromatase inhibitors for 6 months (Yamashita et al., 2009). We showed that ERα expression was decreased in post-treatment tumors compared to pretreatment specimens. On the other hand, we analyzed expression levels of ERα in primary breast cancer specimens from 75 metastatic breast cancer patients who received endocrine therapy on relapse, and analyzed the correlation between

expression levels of ERα and response to endocrine therapy and post-relapse survival (Yamashita et al., 2006). Our results indicated that patients with higher ERα expression responded significantly to endocrine therapy, and that patients with higher ERα expression had better survival after relapse. Moreover, we recently reported that patients whose breast tumors contained high ERα expression effectively responded to aromatase inhibitors and displayed longer time to progression during first-line endocrine therapy with aromatase inhibitors and time to endocrine therapy failure (Endo et al., 2011).

2.2 Regulation of expression levels of ERα

Multiple mechanisms involved in the regulation of ERα expression in breast cancer have been identified, including mutations of ERα gene (Herynk et al., 2004) and transcriptional silencing by DNA methylation within the ERα promoter (Gaudet et al., 2009; Giacinti et al., 2006; Iwase et al., 1999). It was recently reported ERα gene amplification in breast cancer (Holst et al., 2007; Tomita et al., 2009). Holst and colleagues demonstrated that ERα gene amplification was frequent and more than 20% of breast cancers harbored genomic amplification by FISH analysis. They reported that ESR1 amplification was tightly linked to ERα protein expression, and that ESR1 amplification was also found in benign and precancerous breast diseases, such as atypical ductal hyperplasia, ductal carcinoma in situ and lobular carcinoma in situ. However, breast cancer patients show a wide range of ERα expression levels (Yamashita et al., 2011), and the levels of expression in individual patients change during disease progression and in response to systemic therapies (Yamashita et al., 2009). Therefore, other mechanisms may also regulate ERα expression in breast cancer.

2.2.1 miRNA biogenesis and function

MicroRNAs (miRNAs) comprise a large family of ~21-nucleotide-long RNAs that have emerged as key post-transcriptional regulators of gene expression (Krol et al., 2010). In mammals, miRNAs are predicted to control the activity of ~50% of all protein-coding genes. Functional studies indicate that miRNAs participate in the regulation of almost every cellular process investigated so far and that changes in their expression are associated with many human pathologies. Primary miRNA transcripts are cleaved into 70- to 80-nucleotide precursor miRNA (pre-miRNA) hairpins by RNase III Drosha in the cell nucleus and transported to the cytoplasm, where pre-miRNAs are processed by RNA Dicer into 19- to 25-nucleotide miRNA duplexes. One strand of each duplex is degraded, and the other strands become mature miRNAs, which, incorporated into the RNA-induced silencing complex, recognize sites in the 3'-UTR of the target mRNAs and cause translational repression or mRNA cleavage. miRNAs are a new player among gene regulation mechanisms, and their functions have not been fully explored but are known to include the regulation of cellular differentiation, proliferation and apoptosis. Recent evidence has shown that miRNA mutations or mis-expression are associated with various human cancers (Esquela-Kerscher et al., 2006).

2.2.2 Regulation of expression levels of ERα by miRNAs

Adams and colleagues first identified two potential miRNA miR-206 target sites within the 3'-UTR of ERα mRNA via in Silico analysis (Adams et al., 2007). The validation assay revealed that both miR-206 target sites specifically interacted with miR-206, which in turn repressed the corresponding ERα mRNA and protein expression. They also demonstrated

that expression levels of endogenous miR-206 were significantly higher in ERα-negative MDA-MB-231 cells than in ERα-positive MCF-7 cells. Moreover, they showed that miR-206 repressed ERα mRNA and protein expression in MCF-7 and T47D cells. We showed that miR-206 expression assayed by quantitative RT-PCR analysis was inversely correlated with ERα but not ERβ mRNA expression in human breast cancer tissues (Kondo et al., 2008). Moreover, miR-206 expression levels were gradually decreased as ERα protein expression increased in human breast cancer. Transfection experiments revealed that introduction of miR-206 in estrogen dependent MCF-7 cells inhibited cell growth. Transfection of miR-206 into MCF-7 cells suppressed ERα expression and inhibited cell growth in a dose-dependent manner. Furthermore, introduction of miR-206 produced a dose-dependent decrease of mRNA expression of ERα-target genes, such as progesterone receptor, cyclin D1 and pS2. Adams and colleagues recently reported that miR-206 coordinately targeted mRNAs encoding the coactivator proteins SRC-1 and SRC-3, and the transcription factor GATA-3, all of which contribute to estrogenic signaling and a luminal A phenotype (Adams et al., 2009). Furthermore, they identified that miR-206 contributed to the epidermal growth factor (EGF) induced repression of ERα signaling in MCF-7 cells.

2.2.3 MiRNAs that directly target ERα in human breast cancer

Zhao and colleagues demonstrated that miR-221 and miR-222 were highly expressed in ERα-negative breast cancer cells, and that miRNA in situ hybridization analyses also showed overexpression of miR-221 and miR-222 in ERα-negative breast tumors (Zhao et al., 2008). Recently, two groups reported several miRNAs that down-regulated ERα in breast cancer cells. They identified the target sites of miRNAs, such as miR-18a and b, miR-302, miR-193b, miR-22, and miR221/222 as well as miR-206, in the ERα 3'-UTR, and showed that these miRNAs inhibited estrogen signaling by directly targeting ERα mRNA (Leivonen et al., 2009; Pandey et al., 2009) (Fig.1).

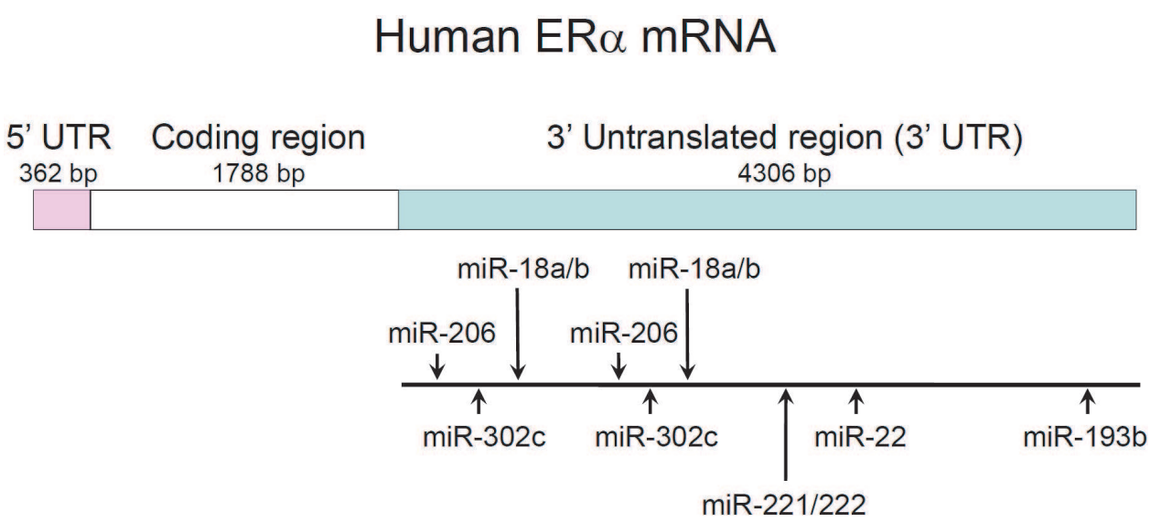

Fig. 1. Schematic representation of the human ERα mRNA and the predicted miRNA target sites.

We recently analyzed expression levels of miRNAs that directly target ERα, including miR-18a, miR-18b, miR-22, miR-193b, miR-221/222 and miR-302c in human breast cancer

samples by quantitative RT-PCR analysis (Yoshimoto et al., 2011). Our results showed that miR-18a expression was much higher in ERα-negative than ERα-positive tumors, with the expression levels of miR-18a not differing in ERα-positive breast cancer as a function of ERα protein level. Surprisingly, expression levels of miR-193b and miR-221 were significantly lower in ERα-negative than ERα-positive tumors, and the levels of these miRNAs gradually increased as ERα protein expression increased. There was no statistically significant association between miR-22 and ERα expression, and miR-302c expression was minimal in human breast cancer samples. Prognostic analysis showed that low miR-18b expression was significantly associated with improved survival in HER2-negative breast cancer. Our results suggest that miRNAs that directly target ERα have distinct roles in not only regulating ERα but also regulating other target genes in human breast cancer, and that some miRNAs might be associated with characteristics of ERα-positive breast cancer.

2.3 Role of miRNAs in breast cancer

miRNAs can function as tumor suppressors and oncogenes (Esquela-Kerscher et al., 2006). The reduction or deletion of a miRNA that functions as a tumor suppressor leads to tumor formation. On the other hand, the amplification or overexpression of a miRNA that function as an oncogene results in tumor formation. Lu and colleagues first analyzed miRNA expression profiling in normal and tumor samples, and revealed global changes in miRNA expression (Lu et al., 2005). It was found that miRNA expression seems globally higher in normal tissues compared with tumors. Moreover, miRNAs are differentially expressed in various cancers. miRNA expression profiling also revealed that miRNAs are differently expressed among molecular subtypes in breast cancer (Blenkiron et al., 2007; Iorio et al., 2005). Iorio and colleagues first reported the miRNA gene expression profile in human breast cancer (Iorio et al., 2005). Compared with normal breast tissue, miRNAs are aberrantly expressed in human breast cancer. They also reported differentially expressed miRNAs associated with ERα expression, including miR-206. Blenkiron and colleagues analyzed miRNA expression in human breast cancer, and found that many miRNAs were differently expressed between breast cancer subtypes, such as luminal A, luminal B, HER2-positive, basal-like and normal-like (Blenkiron et al., 2007). They also found significant association between miRNA expression profiling and clinicopathological factors such as ERα status and tumor grade. Furthermore, recent studies have demonstrated that loss- or gain-of function of specific miRNAs contributes to breast epithelial cellular transformation and tumorigenesis. The interconnections between miRNAs and tumor suppressor genes and oncogenes in breast cancer were summarized by Zoon and colleagues (Zoon et al., 2009).

3. Conclusion

It is well recognized that individual miRNA sequences can suppress the production of hundreds of proteins (Krol et al., 2010). Reduction of protein levels in this way is often modest, however, and many such RNAs probably collectively fine-tune gene expression. Accumulating evidence supports the hypothesis that the ability of miRNAs to simultaneously regulate many target genes makes them attractive candidates for regulating normal and cancer cells. miRNAs are potential therapeutic targets for more tailored treatment strategies for breast cancer.

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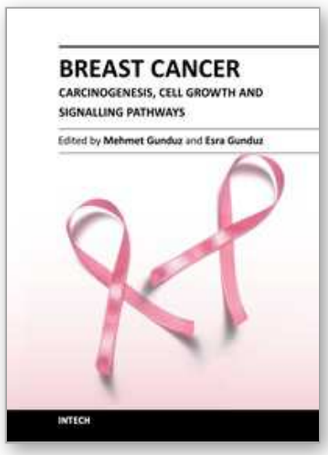

Breast Cancer - Carcinogenesis, Cell Growth and Signalling Pathways

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Cancer is the leading cause of death in most countries and its consequences result in huge economic, social and psychological burden. Breast cancer is the most frequently diagnosed cancer type and the leading cause of cancer death among females. In this book, we discussed various aspects of breast cancer carcinogenesis from clinics to its hormone-based as well as genetic-based etiologies for this deadly cancer. We hope that this book will contribute to the development of novel diagnostic as well as therapeutic approaches.

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