Predicting resistance to endocrine therapy in breast cancer: It's time for epigenetic biomarkers (Review)

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Abstract. Notwithstanding the marked progress in breast cancer (BC) management, it still constitutes the most common malignancy in women and a major cause of morbidity and mortality, thus remaining a major health issue worldwide. Most BC cases are hormone receptor (HR) positive (luminal A or B molecular subtypes) and endocrine treatment (ET) is an important therapeutic modality at all disease stages. Nevertheless, despite substantial improvements in BC patient outcome, effectiveness of ET is limited, as up to 40% of patients eventually relapse or progress and endocrine resistant BC has a less favorable prognosis and constitutes a therapeutic challenge. The biological mechanisms underlying endocrine resistance are, however, still poorly understood. In this review, we focused on data regarding the main epigenetic mechanisms associated with the development of endocrine treated-resistant BC described so far, including alterations in DNA methylation, non-coding RNAs, chromatin remodeling, post-translational histone modifications and histone variants. Notably, specific epigenetic alterations have been characterized in this subset of breast tumors and may be of clinical value for individualized patient management in the future.

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Contents

1. Introduction

Most breast cancers (BC), over 2/3 of cases, express estrogen (ER) and progesterone (PR) receptors (1). This is extremely important since these are used as biomarkers for subtype classification, with implications in choice of treatment and prognosis in BC patients (2). Notably, endocrine therapies (ET) have been successfully used for treating ER positive BC patients with significant impact in patient outcome. Several endocrine drugs are approved for BC treatment, most notably tamoxifen, toremifene, anastrozole, letrozole, exemestane and fulvestrant, which may be used in different clinical contexts, such as chemoprophylaxis, neoadjuvant, adjuvant and palliative treatments. However, the effectiveness of ET is limited as up to 40% of patients may experience disease recurrence while on ET adjuvant treatment (1,3). Moreover, in the metastatic setting, acquired resistance to ET is virtually an universal feature, and is clinically defined in accordance to the 3rd ESO-ESMO International Consensus Guidelines (4) and many efforts have been made to understand the mechanisms involved in acquisition of acquired resistance to ET. These, however, remain mostly elusive and no biomarkers have been validated in this setting despite intense drug development and approval.

Epigenetics may be defined as mechanisms that regulate cell fate specifications, while the DNA remains unchanged (5). Some of these mechanisms include DNA methylation, non-coding RNAs, chromatin remodeling and histone post-translational modifications or variants. Collectively, these components constitute the epigenome machinery whose role is to define

which information is available for transcription and for translation (5). DNA methylation is performed by specific enzymes, the DNA methyltransferases (DNMTs) that introduce a methyl group at the 5' position of a cytosine ring inside CpG dinucleotides (6). Globally, promoter methylation of genes is associated with transcription inhibition (6). Furthermore, the N-terminal tails of histones may undergo post-translation modifications that subsequently impact the chromatin structure (7). The most well-studied histone post-translation modifications are histone acetylation and histone methylation. Histone acetylation is associated with gene expression and is carried out by histone acetyltransferases (HATs), while histone deacetylation is accomplished by histone deacetylases (HDACs) (7). Histone methylation, which depending on the residue and the number of methyl groups may lead either to transcription repression or activation (8), is catalyzed by histone methyltransferases (HMTs), while histone demethylation is performed by histone demethylases (HDMs) (7). In addition to post-translational histone modifications, histone variants that can replace canonical histones are an additional level of epigenetic complexity, and contribute to the shaping of the chromatin structure.

Non-coding RNAs (ncRNAs) comprise a hidden layer of internal signals that control various levels of gene expression (9). Among these, microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) are the most frequently reported in BC. lncRNAs are ncRNA molecules usually longer than 200 nucleotides that do not fit into known classes of small or structural RNAs (9) and may act as protein-DNA or protein-protein scaffolds, miRNA sponges, protein decoys, or regulators of translation (10). miRNAs are endogenous, small non-coding single-stranded RNAs with ~22 nucleotides in length, that exert a finely tuned regulation of gene expression at the post-transcriptional level (11) by binding to mRNA targets, inducing its cleavage or repressing its translation (11).

Over the last few years, convincing data has suggested that altered epigenetic regulation may be involved in tumor initiation, progression and cancer resistance to therapy, including endocrine resistance, particularly in BC. For instance, ER expression is currently one of the foremost predictive biomarkers of response to ET, and altered expression of ER may be due to hypermethylation of CpG islands within its promoter, increased histone deacetylase activity in the ESR1 promoter or translational repression by miRNAs (12). Since ER was found to be deleted in only 15-20% of endocrine-resistant BC, several epigenetic mechanisms may be involved in the development of endocrine treatment-resistance (3), and some of these are depicted in Fig. 1.

Our objective was to review the published evidence regarding epigenetic mechanisms associated to ET resistance in BC, as it may be considered an emerging subject and worth special focus.

2. Evidence acquisition

For the selection of the most relevant bibliography, we conducted a PubMed® search using the terms 'endocrine resistance', 'breast cancer' and 'epigenetic mechanisms'. Reference lists from key articles were also searched for additional relevant data. The criteria for article selection were: written in English, central theme based on ET resistance on BC and epigenetic mechanisms. Original studies were selected based on the detail of analysis, mechanistic support of data, novelty, and potential clinical usefulness of the findings. Chemotherapy/radiotherapy-resistance, HER2-enriched subtype or 'triple negative' BC citations were excluded for being outside the scope of this review.

DNA methylation. DNA methylation is one of the most common epigenetic changes and has been reported in multiple tumors, including BC (9,13). This epigenetic alteration is inherently stable and has been proposed as a promising cancer biomarker in multiple cancers since it can be sampled from less invasive sources such as liquid biopsies (plasma or urine) (13-15). Thus, the role of DNA methylation as a predictor of ET resistance is a field of growing interest and has become the focus of several research teams (16-18) since it may improve BC patients' risk stratification.

Notably, Stone *et al* reported that in endocrine treated-resistant cell lines, DNA hypermethylation occurs predominantly at estrogen-responsive enhancers, leading to reduced ER binding and subsequently to expression downregulation. Furthermore, luminal subtype BC patients with relapsed disease exhibited significantly higher methylation levels at all enhancer loci studied (19). By comparing anti-estrogen-resistant cell lines with the parental sensitive cell line, DNA methylation of the promoter region of genes was also suggested to play a role in the emergence of endocrine resistance (17,20) (Table I). Multicenter studies, including several cohorts of BC patients were able to confirm these findings. Specifically, PITX2 methylation levels were consistently identified as a valuable biomarker to predict outcome in low-risk BC patients (ER-positive, node-negative) treated with surgery followed by adjuvant tamoxifen (21,22). Nevertheless, multiple validations are still required before the implementation of these markers in the clinical setting (Table I). Thus, to date, no clinical trials have assessed the clinical relevance of these candidate biomarkers.

Non-coding RNAs. As previously mentioned, decreased ER expression may be due to post-transcription regulation of miRNAs, including that of miR-221/222, whose overexpression has been associated with resistance to tamoxifen (23,24) and fulvestrant (25). Conversely, miR-342-3p levels were revealed to be positively correlated with ER mRNA expression in human BC and associated with tamoxifen sensitivity (26,27). miRNAs that regulate growth, survival, apoptosis, epithelial-mesenchymal transition (EMT) and metastasis of BC cells may be implicated in loss of responsiveness to ET. In particular, PTEN downregulation due to specific miRNAs, permitting abnormal Pi3K/Akt pathway activation, promote estrogen-independent growth and survival of BC cells leading to endocrine treatment resistance (28,29).

Several clinical trials are currently ongoing to evaluate the role of miRNAs as predictive biomarkers in BC. Specifically, trials such as NCT01231386 and NCT01722851, aim to identify circulating miRNAs aiding at the identification of biomarkers of early response to neoadjuvant therapy, including ET, which may be used as potential targets for personalized therapies. Conversely, the NCT01612871 trial was set to explore a panel of circulating miRNAs that could aid to monitor the disease status of the patient while on adjuvant ET (30-32).

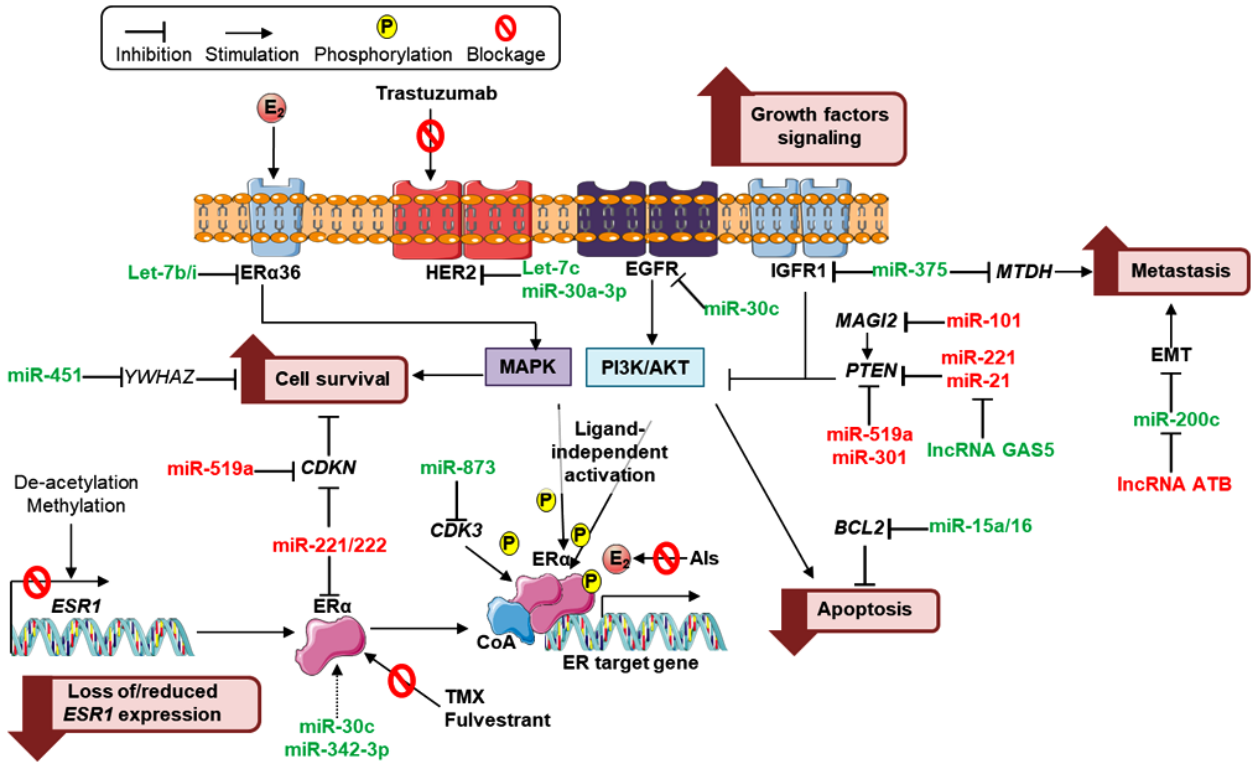

Figure 1. NcRNAs and their established targets involved in endocrine resistance. The ncRNAs and their targets involved in several mechanisms associated with endocrine resistance, along with their functional implication (in pink boxes), including loss of/reduced ESR1 expression, alternative growth-factor signaling inducing downstream signaling, including PI3K/Akt and MAPK signaling pathways, dysregulation of cell survival and apoptosis pathways, and increased metastasis. NcRNAs that confer sensitivity and resistance to endocrine therapies are depicted in green and red, respectively. ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; EGFR, epidermal growth factor receptor; IGFR1, insulin-like growth factor 1 receptor; YWHAZ, tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein ζ; MTDH, metadherin; MAGI2, membrane-associated guanylate kinase inverted 2; PTEN, phosphatase and tensin homolog; EMT, epithelial-mesenchymal transition; CDKN, cyclin-dependent kinase inhibitor; CDK3, cyclin dependent kinase 3; BRCAL2, B-cell CLL/lymphoma 2; PI3K/AKT, phosphoinositide 3-kinase/protein kinase B; ESR1, estrogen receptor 1; TMX, tamoxifen; AIs-aromatase inhibitors; E2, estradiol; miR, microRNA.

Table I. DNA methylation of the promoter region of genes as predictive biomarkers to different modalities of endocrine therapies along with their role and the biological samples used in each study.

Biomarker	Role	Agent	Samples	Ref.
PTEN	Hypermethylation is associated with resistance	TMX	Cell lines	(47)
PTGER4	Hypomethylation is associated with resistance	EDT		(48)
CDK10	Hypermethylation is associated with shorter PFS and OS	TMX	Cell lines and	(49)
HOXC10	Hypermethylation is associated with resistance	EDT, AIs and TMX	tumor tissues	(50)
ESR1 CYP1B1	High methylation levels are associated with a better outcome	TMX	Tumor tissues	(16)
ID4	Hypomethylation is associated with resistance			(51)
NAT1	Hypermethylation is associated with resistance			(52)
PITX2	Hypermethylation is associated with worse outcome and shorter MFS			(21,22,53)
PR	Hypermethylation is associated with resistance			(54)
PSAT1	Hypermethylation is associated with good clinical benefit			(55)

PFS, progression-free survival; OS, overall survival; MFS, metastasis-free survival; TMX, tamoxifen; AIs, aromatase inhibitors; EDT, estrogen deprivation therapy; PTEN, phosphatase and tensin homolog; PTGER4, prostaglandin E receptor 4; CDK10, cyclin dependent kinase 10; HOXC10, homeobox C10; BRCA1, BRCA1 DNA repair associated; ESR1, estrogen receptor 1; CYP1B1, cytochrome P450 family 1 subfamily B member 1; ID4, inhibitor of DNA binding 4 HLH protein; NAT1, N-acetyltransferase 1; PITX2, paired like homeodomain 2; PR, progesterone receptor; PSAT1, phosphoserine aminotransferase 1.

Table II. Non-coding RNAs involved in response (sensitivity/resistance) to different modalities of endocrine therapies along with their putative targets/mechanism and the biological samples used in each study.

ET	Role	miRNA	Putative target	Agent	Samples	Refs.
AntiE	Sensitivity	miR-375	*MTDH*	TMX	Cell lines	(56)
		miR-873	*CDK3*			(57)
		miR-320a	*ARPP19, ESRRG*			(58)
		Let-7b/i	*ESR1* (ER-α36 variant)			(59)
		miR-451	*YWHAZ*			(60)
		miR-17/20	*CCND1*			(61)
		miR-148a	*ALCAM*			(62)
		miR-152				(63)
		miR-200c/b	*ZEB1/2*	TMX and FULV		(64)
		miR-15a/16	*BRCAL2*	TMX	Cell lines and xenografts	(26)
		miR-342-3p	*BMP7, GEMIN4*		Cell lines and tumor tissues	(65)
		miR-26a	*EZH2*		Tumor tissues	(66)
		miR-30c	*EGFR*			(67)
		miR-10a	-			
		miR-126				(68)
	Resistance	miR-10b	*HDAC4*	TMX	Cell lines	(35)
		lncRNA DSCAM-AS1	Binding to the hnRNPL protein	Tumor tissue and cell lines		(29)
		miR-519a	*CDKN1A, PTEN, RB1*			(34)
		lncRNA BRCAAR4	-			(23,25,69)
		miR-221/222	*ESR1, CDKN1B, CTNNB1*	TMX and FULV		(28)
		miR-301	*FOXF2, PTEN, BBRCA3iso2, COL2A1*	TMX	Tumor tissue, cell lines and xenografts	(70)
		miR-155	*SOCS6*			(71)
		miR-210	*EFNA3, E2F3, RAD52, FGFRL1, MET*		Tumor tissue	(72)
AIs	Sensitivity	Let-7f	*CYP19A1*	LET	Cell lines	(73)
		miR-125b let-7c	*ERBB2*	LET and ANA	Tumor tissues and cell lines	(74)
	Resistance	miR-128a	*TGFBR1*	LET	Cell lines	(75)
		miR-181a	*BRCAL2L11*		Cell lines, xenografts and tumor tissue	

miR, microRNA; lncRNA, long non-coding RNA; ET, endocrine therapies; AntiE, anti estrogen; AIs, aromatase inhibitors; ANA, anastrozole; FULV, fulvestrant; DSCAM-AS1, DSCAM antisense RNA 1; BRCAAR4, breast cancer anti-estrogen resistance 4; MTDH, metadherin; CDK, cyclin-dependent kinase; ARPP19, cAMP-regulated phosphoprotein 19; ESRRG, estrogen related receptor gamma; YWHAZ, tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein ζ; CCND1, cyclin D1; ALCAM, activated leukocyte cell adhesion molecule; ZEB, zinc finger E-box-binding homeobox; BRCAL-2, B-cell lymphoma 2; BMP7, bone morphogenetic protein 7; GEMIN4, gem (nuclear organelle)-associated protein 4; EZH2, enhancer of zeste homolog 2; EGFR, epidermal growth factor receptor; HDAC4, histone deacetylase 4; HnRNPL, heterogeneous nuclear ribonucleoprotein L; CDKN, cyclin-dependent kinase inhibitor ; PTEN, phosphatase and tensin homolog; RB1, retinoblastoma 1; ESR1, estrogen receptor 1; CTNNB1, catenin β 1; FOXF2, forkhead box F2; BBRCA3iso-2, BRCAL2 binding component 3 isoform 2; COL2A1, collagen type II alpha 1; SOCS, suppressor of cytokine signaling; EFNA3, ephrin A3; E2F3, E2F transcription factor 3; RAD52, RAD52 homolog DNA repair protein; FGFRL1, fibroblast growth factor receptor-like 1; MET, hepatocyte growth factor receptor; CYP19A1, cytochrome P450 family 19 subfamily A member 1; ERBB2, erb-b2 receptor tyrosine kinase 2; TGFBR1, transforming growth factor β-receptor 1; BRCAL2L11, BRCAL2 like 11; ZNF217, zinc finger protein 217.

Table III. Chromatin remodeling, post-translational histone modifications and histone variants involved in response (sensitivity/resistance) to endocrine therapies along with their putative epigenetic mechanism and role in response.

Biomarker	Epigenetic mechanism	Role	Samples	Refs.
H3K27me3 profiles	Post-translational histone modification	H3K27me3 profile predicts the treatment outcomes for first-line AIs	Tumor tissues	(38)
PBX1	Chromatin remodeling	Resistance to ET	Cell lines and tumor tissues	(46)
HDAC6	Post-translational histone modification	Sensitivity to TMX by deacetylation of alpha-tubulin		(76,77)
HIST1H2BE	Histone variant	Overexpressed in AI-resistant tumors/cell lines compared to AI-sensitive tumors/cell lines		(45)
NSD2	Post-translational histone modification	Histone H3K36 methyltransferase that confers resistance to TAM by upregulating key glucose metabolic enzyme genes		(37)
H3K27me3 demethylation	Post-translational histone modification	Resistance to ET due to BrCal-2 expression	Cell lines	(78)
H2A.Z	Histone variant	Increased H2A.Z expression promotes cellular proliferation, namely when E2 levels are low and during TMX treatment		(44)

PBX1, PBX homeobox 1; HDAC6, histone deacetylase 6; HIST1H2BE, histone cluster 1 H2B family member E; NSD2, nuclear receptor binding SET domain protein 2; H2A.Z, H2A histone family member Z; ET, endrocrine therapies; TMX, tamoxifen; AIs, aromatase inhibitors.

lncRNAs have also been associated with endocrine treatment resistance. Particularly, lncRNAs, breast cancer anti-estrogen resistance 4 (BRCAAR4) overexpression (33,34) and DSCAM antisense RNA 1 (DSCAM-AS1) (35), which contains an ER promoter binding motif, have been revealed to predict tamoxifen resistance in primary BC (Table II and Fig. 1).

Chromatin remodeling, post-translational histone modifications and histone variants. Histone post-translation modifications induce chromatin landscape changes that subsequently favor ER repression, thus promoting other signaling pathways that could lead to endocrine resistance, as exemplified by Magnani *et al* that revealed how the genome's accessibility is altered in drug-resistant vs. drug-responsive BC cells (36). Recently, expression of the H3K36 methyltransferase NSD2 was found to be higher in tamoxifen-resistant BC cell lines, associated with disease recurrence and worse survival (37). Furthermore, H3K37me3 profiles enabled the identification of patients with poor outcome after aromatase inhibitor (AI) treatment (38).

Furthermore, it was recently demonstrated that transcription repression performed by ER co-repressors confer tamoxifen sensitivity through recruitment of HDACs to DNA (39). This evidence suggests that loss of ER co-repressors may sensitize BC cells to the cytotoxic effects of HDACs inhibitors (HDACi). Notably, some clinical trials have demonstrated that HDACi appears to re-establish sensitivity to anti-estrogens in a subset of endocrine treated-resistant tumors (40,41). In addition, the ENCORE-301, a randomized phase II trial (41) tested entinostat, an oral HDACi, in the endocrine-resistance, more specifically AI in post-menopausal women. The results revealed modest improvement in PFS but much greater improvement in overall survival (OS)-median OS improved to 28.1 months in the experimental arm vs. 19.8 months (HR, 0.59; 95% CI, 0.36 to 0.97; P=0.036). Ongoing clinical trials are further testing entinostat in monotherapy or in combination. Moreover, in custom-generated tamoxifen resistant cell lines, treatment with HDACi re-established sensitivity to tamoxifen through significant Bcl-2 downregulation, growth arrest and apoptosis (42).

Histone variants, such as H2A.Z, an H2A variant, have been shown to be intimately linked to estrogen signaling (43). Notably, a study has already provided a link (yet uncharacterized) between H2A.Z and endocrine resistance by revealing that H2A.Z overexpression led to increased estrogen-independent proliferation (44). Furthermore, another study demonstrated that the histone HIST1H2BE, an H2B variant, was overexpressed not only in endocrine-resistant cell lines, but also in AI-treated tumors from patients which relapsed compared to those that did not (45).

Furthermore, an emerging class of transcription factors named 'pioneer factors', appear to be key players in shaping chromatin structure through binding to chromatin prior to transcription factors, making it accessible for transcription factors, together with histone post-translation modifications and histone variants [68-70]. PBX1 is an example of this class-its expression levels have been associated with reduced metastasis-free survival in ER-positive BC patients (46). Furthermore, a gene expression signature based on NOTCH-PBX1 activity was found to discriminate BC patients that are responsive to ET from those which are not. Notably, PBX1 knockdown was sufficient to arrest ER-resistant BC cell growth (36).

These and other chromatin remodeling complexes associated with endocrine resistance are summarized in Table III along with their putative role and the biological samples in which they were characterized.

3. Conclusion

Notwithstanding the prevalence of endocrine treatment resistance in BC, predictive and diagnostic biomarkers in this setting are markedly lacking in clinical practice. In this review, we summarized emerging evidence that epigenetic mechanisms may prove useful for this purpose. These would perform as non-invasive predictive biomarkers of treatment-resistance, providing affordable and sequential monitoring during the course of treatment. The concept of early detection (preclinical) of therapy resistance is compelling, as it could assist clinicians in choosing the most appropriate individualized therapeutic strategy.

Furthermore, some epigenetic modifications in addition to conveying information concerning prediction of response, are also appealingly targetable, in particular due to their reversible nature. The clinical usefulness of these findings, however, is still elusive, mostly due to lack of standardization in methodology, limiting reproducibility.

Promising results have been arising in clinically meaningful trials, such as ENCORE-301. A useful approach would be the integration of the candidate biomarkers into a panel, enabling its validation in a clinical trial setting. Hopefully, this will be accomplished in the near future.

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Availability of data and materials

The datasets used during the present study are available from the corresponding author upon reasonable request.

Authors' contributions

MFS, SPDS, RH and CJ conceived and designed the review. MFS, MA, SS performed the literature search and wrote the manuscript. SPDS, RH and CJ reviewed and edited the manuscript. All authors read and approved the manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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