Epigenetic Information and Estrogen Receptor Alpha Expression in Breast Cancer

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Learning Objectives
After completing this course, the reader will be able to:
1. Describe the role of epigenetic information in the regulation of gene expression and in the development of cancer.
2. Explain the important role of estrogen receptor expression in breast cancer as a prognostic marker and predictive factor of response to endocrine therapy.
3. Evaluate the current and potential role that the comprehension of the molecular biology of a tumor may have in finding a new therapeutic approach in cancer treatment.

Abstract
In industrialized countries, breast cancer is the most common tumor in women. The tumor expression of estrogen receptors (ERs) is a very important marker for prognosis and a marker that is predictive of response to endocrine therapy. The loss of ER expression portends a poor prognosis and, in a significant fraction of breast cancers, this repression is a result of the hypermethylation of CpG islands within the ER-α promoter. Hypermethylation is one of the best known epigenetic events in mammalian cells. Over the last few years, many studies have found that other epigenetic events, such as deacetylation and methylation of histones, are involved in the complex mechanism that regulates promoter transcription. The exact interplay of these factors in transcriptional repression activity is not yet well understood. Inhibitors of some of these are currently being studied as new drugs able to restore ER-α protein expression in ER-α-negative breast cancer cells and to promote apoptosis and differentiation. Demethylating agents and histone deacetylase (HDAC) inhibitors are candidates for becoming potent new drugs in cancer therapy. This paper reviews the current understanding of the role of epigenetic information in the development of cancer and its significance in breast cancer as predictive markers of ER status and as new targets of anticancer therapy. The Oncologist 2006;11:1–8
INTRODUCTION

In industrialized countries, breast cancer is the most common tumor in women, and it is the most important cause of cancer-associated morbidity and mortality. Thanks to early diagnosis and the discovery of new drugs, cancer-associated mortality has decreased. Over the last few years, new molecular markers have been discovered as important targets for diagnosis and therapy. One goal is to identify a specific molecular assay for each breast tumor and then to obtain an individualized therapeutic approach.

Today, a variety of molecular factors is being used in clinical practice to predict the prognosis and response to therapy of breast cancer patients, and the tumor expression of estrogen receptors (ERs) is one of the most important. ERs are members of the nuclear receptor (NR) superfamily that mediates the effects of the steroid hormone estrogen in a diverse range of physiological processes. Estrogens regulate growth, differentiation, and homeostasis in eukaryotic cells but have been associated pathologically with a higher risk for breast and endometrial cancer [1]. In fact, breast cancer hormone dependence is correlated with tumor progression and patient prognosis [2]. As such, tumor ER expression plays an important role in the clinical care of breast cancer patients as a prognostic factor and therapeutic target. ER absence is correlated with a more malignant disease and poor prognosis.

Binding of 17-β-estradiol (E2) to the active form of ERs (Fig. 1) induces tumor growth in ER-positive breast cancers. Therefore, reducing estrogen levels or altering the activity of the receptor can induce these cancers to regress. E2 action involves ligand-mediated activation of nuclear ER-α and ER-β, which interact directly with estrogen response elements (EREs) in the promoter and/or enhancer regions of target genes and recruit various coactivators to mediate transcriptional regulation [3]. ER regulation is not limited to direct ligand binding. It can also be modulated by several other pathways that include the epidermal growth factor (EGF) and insulin-like growth factor 1 (IGF-1) mitogenic pathways and the second messengers cyclic AMP and dopamine [1, 4, 5].

To date, two isoforms of ER (ER-α and ER-β) have been identified, encoded by independent genes. Both ER isoforms show modular structure characteristics of the NR superfamily and, although both ER-α and ER-β display similar binding affinities for E2, they have different roles in the regulation of gene expression [1]. ER-α was believed for many years to be the only ER. ER-β was identified more recently, and it is still subject to ongoing research as to whether mutations and splice variance of this receptor play any role in breast cancer development and/or prognosis and in response to endocrine therapy [6–8]. The role of ER-β in breast cancer remains elusive, but the presence of ER-α at the time of diagnosis is an indication for endocrine therapy.

Sixty percent of primary breast cancers are ER-positive and two thirds of advanced ER-positive breast cancers respond to therapy with antiestrogens (Fig. 2), such as tamoxifen (Nolvadex®, AstraZeneca Pharmaceuticals, Wilmington, DE, http://www.astrazeneca-us.com) [6]. However, up to one third of breast cancers lack ER-α at the time of diagnosis, and a fraction of breast cancers that are initially ER-α-positive lose ER expression during tumor progression [9]. This deprives us of an important possibility of tumor patient care by endocrine therapy and increases poor clinical outcome. In a significant fraction of breast cancers, ER absence is a result of aberrant methylation of CpG islands, cytosine–guanine-rich areas that are located in the 5’ regulatory regions of the ER-α gene [9–11].

Methylation of a specific site on a gene is an epigenetic event that causes transcriptional repression of that site. The genome contains two types of information: genetic and epigenetic; the epigenetic information provides instructions on how, where, and when the genetic information should be used. The most important form of epigenetic information in mammalian cells is DNA methylation, the covalent addition of a methyl group to the 5’ position of cytosine, predominantly within the CpG dinucleotide [9, 12, 13]. CpG islands are CpG- and CpG-rich regions of 1 kilobase (kb) that are usually associated with the promoter

![Figure 1. Estrogen receptors trigger gene activation.](http://theoncologist.alphamedpress.org/)

Figure 1. Estrogen receptors trigger gene activation. Estrogen receptors normally reside in the cell’s nucleus. When an estrogen molecule enters a cell and binds to its receptor, this estrogen-receptor complex then binds to specific DNA sites, called estrogen response elements, near genes that are controlled by estrogens. This mechanism activates gene transcription and then synthesis of specific proteins that can influence cell behavior in different ways, depending on the cell type involved.
or 5′ end of genes. If a promoter of a tumor suppressor gene is hypermethylated, the expression of the associated gene is silenced and this event provides the cell with a growth advantage, as well as deletions or mutations [13].

Hypermethylation events can occur early in tumorigenesis, involving the disruption of pathways that may predispose cells to malignant transformation. Preneoplastic lesions often show aberrant methylation, and the frequency of aberrations increases with the progression of disease [13–15]. CpG island methylation is not random. The genes that are more susceptible to hypermethylation within their CpG islands are likely to be those that are involved in the regulation of cell growth, and so the cells that lack them could have a growth advantage [16]. ER-α promoter methylation is an example of cell growth advantage.

Breast cancer is usually a hormone-dependent tumor. Estrogens can regulate the growth of breast cells by binding with ERs. This means that exposure to estrogens could increase breast cancer incidence and proliferation, but also that tumor progression could be controlled by antiestrogenic drugs. Loss of ER expression means that breast cancer cells are no longer regulated by estrogen in their growth and that they cannot be stopped by endocrine therapy. This results in higher tumor aggressiveness and poor prognosis. Therefore, ER-α is a critical growth regulatory gene in breast cancer, and its expression in breast cancer cells is critical for tumor progression.

ER transcriptional regulation is a result of a very complex mechanism, which is still poorly defined. Our comprehension of the mechanism that regulates transcriptional repression could allow us to interfere with it and to restore gene expression. This would permit us to re-establish cancer cell growth control by endocrine therapy. It could also be interesting to find new markers that may be predictive of lacking ER expression in primary breast cancers with an ER-positive phenotype. This finding could guide physicians in their choice between chemotherapy and endocrine therapy as a better treatment for patients with ER-positive breast cancer, in addition to the other prognostic factors and factors predicting therapy response used in clinical practice.

**Epigenetic Information and Repression of Transcription**

DNA methylation in mammalian cells is established and maintained by a complex interplay among three DNA methyltransferases, DNMT1, DNMT3a, and DNMT3b. DNMT1 is the most abundant and catalytically active DNA methyltransferase; it is thought to function as a maintenance methyltransferase by copying DNA methylation patterns from the parental to the daughter strand following DNA replication. DNMT3a and DNMT3b are referred to as de novo DNA methyltransferases. The function of a fourth DNMT family member, DNMT2, remains unknown [17].

Histone deacetylase (HDAC) family members remove acetyl groups from lysine residues of core histones, particularly H3 and H4, increasing ionic interactions between positively charged lysines of histones and negatively charged DNA, which results in a more compact nucleosome structure that limits transcription [9]. DNMT1 has been found to interact physically with either HDAC1 or HDAC2 through its N-terminus, thereby forming a transcriptionally inactive chromatin structure that represses transcription. Thus, DNA methylation and histone deacetylation function through a common mechanistic pathway to repress transcription [9, 18–21].

A direct interaction between the plant homeodomain (PHD) domain of DNMT3a and HDAC1 has been demonstrated, which is consistent with the finding that the majority of the repressive activity mediated by DNMT3a can be relieved by treatment with the HDAC inhibitor trichostatin A (TSA). The role of the interaction of DNMT3a and HDAC1 remains unclear, but it may involve targeting DNMT3a to transcriptionally silenced regions to carry out de novo DNA methylation. Thus, the association of these two activities is likely to be critical for the establishment and maintenance of heterochromatic regions.

DNA methylation represses genes partly by recruitment of methyl-CpG-binding domain (MBD) proteins, which selectively recognize methylated CpG dinucleotides and tend to cluster at certain chromosomal loci [15, 23, 24]. An abundant chromosomal MBD protein, MeCP2, was

![Figure 2. Antiestrogen. Antiestrogens work by binding to estrogen receptors and blocking estrogen from binding to these receptors. This also blocks estrogen from activating specific genes and blocks the expression of the relative specific proteins.](http://theoncologist.alphamedpress.org/)
the first protein identified as linking methylated DNA with HDAC-containing transcriptionally repressive complexes for gene silencing [25–27]. Subsequently, several MBD proteins have been identified that, similar to MeCP2, couple methylated DNA to HDAC [28, 29]. The recruitment of MeCP2 to methylated CpG dinucleotides represents a major mechanism by which DNA methylation can repress transcription [30, 31]. However, the inhibition of histone deacetylase activity using drugs such as TSA only partially relieves MeCP2-mediated transcriptional repression. This partial relief indicates that additional mechanisms of repression by MeCP2 likely exist in addition to the recruitment of histone deacetylase [25, 27, 32].

Recent findings show that MeCP2 acts as a bridge between DNA methylation and histone methylation, reinforcing the repressive chromatin state [32]. Histone methylation is an important epigenetic mechanism for the organization of chromatin structure and the regulation of gene expression. In particular, methylation at lysine 9 of histone H3 resulting from the activity of SUV39H1, a human homologue of the *Drasophila* position effect variegation modifier Su(rar)3-9, is associated with gene silencing [33]. MeCP2-mediated repression might also include a second stage involving histone methylation, in addition to histone deacetylation [32, 34, 35]. MeCP2 could be considered as a protein that can connect a repressive modification on DNA to a repressive modification on histones. Recent evidence from *Neurospora crassa* and *Arabidopsis thaliana* indicates that the reverse is also possible: methylation of histone H3 at lysine 9 leads to methylation of DNA [36, 37]. MeCP2 may set up a self-reinforcing cycle of repression by promoting further rounds of DNA methylation following histone methylation, and thus, these two global epigenetic events act together to perpetuate and maintain a repressed chromatin state [32]. In DNMT1 knockout human cancer cells (KO1), the loss of DNMT1 results in an overall change in the histone H3 modification pattern. The effect of the loss of DNMT1 is an increase in the acetylation of histone H3 and a decrease in the dimethylation and trimethylation of lysine 9 (TriMetK9H3). TriMetK9H3 is a marker for constitutive heterochromatin. This means that the loss of DNMT1 in human cells may be associated with the disorganization of heterochromatin. In addition, in these cells, we can observe that HDACs and HP1 (methyl-lysine binding proteins) no longer interact with histone H3 and pericentrometric repetitive sequences (satellite 2). Interaction of HP1 and MetK9H3 is involved in the silencing of specific promoters and in the formation of heterochromatin. In KO1 cells, this complex is totally abrogated. The hyperacetylation of H3 in KO1 is not the result of a loss of HDAC activity, but it may likely be the result of a loss of targeted HDAC activity at specific DNA sequences. It is possible that a change in DNA methylation also causes histone modification changes and that DNMT1 activity is important to preserve the correct organization of chromatin domains inside the cell nucleus [38].

Recent data also show that DNMT3a associates primarily with histone H3 Lys9 methyltransferase but also, to a lesser extent, with histone H3 Lys4 activity [39]. The mechanism by which histone H3 Lys4 methylation is linked to transcriptional silencing is currently unknown. The effect of histone H3 Lys4 methylation on transcription may well depend on its combination with other histone modifications, whereby methylation at Lys4 of histone H3 might function in concert with DNA methylation to repress transcription [32].

SUV39H1 is also involved in transcriptional repression by the retinoblastoma protein Rb [34, 40, 41]. SUV39H1 creates a high-affinity binding site for proteins of the HP1 family, and its activity is required for the proper localization of HP1 at heterochromatic sites [34, 42, 43]. Both HP1 localization and repression by Rb also require, at least in part, histone deacetylases. SUV39H1 can physically interact with HDAC1, HDAC2, and HDAC3, suggesting that transcriptional repression by SUV39H1 could be the consequence of histone deacetylase recruitment [34]. The N-terminal transcriptional repression domain of SUV39H1 binds the so-called “core histone deacetylase complex,” composed of HDAC1, HDAC2, and the Rb-associated proteins [34]. SUV39H1 interacts physically with Rb and functions as a corepressor of activity. E2F is a family of transcription factors indicated in cell cycle control. E2F-containing promoters are repressed by the members of the Rb family, which are recruited by a physical interaction with the E2F protein. It is possible that transcriptional repression by Rb and its cousins involves the recruitment of HDACs to E2F-containing promoters [20, 44, 45]. Inhibition of histone deacetylase activity by TSA inhibits Rb-mediated repression, and this finding involves only a determined subset of genes, demonstrating that the requirement of HDACs for Rb-mediated transcriptional repression is promoter specific [45, 46].

The order and the timing of these modifications and their impact on transcription inactivation are less well understood. In a transgenic model, it was recently shown that histone H3 and histone H4 hypoacetylation and loss of methylation at histone H3 lysine 4 all occurred during the same window of time and that these histone modifications were the primary events in gene silencing [47]. New investigations are required to better understand the correct action of each regulating factor, its interplay, and the temporal sequence of its binding to DNA.

Epigenetic lesions may affect all the molecular pathways involved in malignant transformation, and they are often an early event in tumorigenesis. Aberrant methylation of certain genes reflects their very selected involvement in spe-
cific tumor types; therefore, it is possible to propose a specific “methyloype” for each kind of tumor. In breast cancer, we can observe promoter hypermethylation and silencing in different kinds of genes. Some of the most important are cell cycle inhibitor genes (p16ink4a); DNA repair genes (BRCA1); genes that encode BRCA1-binding protein (SRBC), tyrosine kinase (SYK), metabolic enzymes (GSTP1), and estrogen and progesterone receptors (ER, PR); genes involved in cell adherence and the metastatic process (CDH1-E cadherin, CDH13-H cadherin) and in histone/protein methyltransferase (RIZ1); and proapoptotic genes (TMS1). The specific “methyloype” of a tumor could be a marker for prognosis and response to therapy in clinical practice. The profile of genes that have been hypermethylated and then inactivated may provide information about the biological behavior of a particular disease and may enable clinicians to predict the response to chemotherapy or hormonal therapy in a patient with that specific malignancy [48, 49].

Regulation of ER-Promoter Transcription and Breast Cancer Therapy

ER-α promoter transcription is also involved in the complex interplay of transcriptional regulating factors. Up to one third of breast cancers lack ER-α at the time of diagnosis, and a fraction of breast cancers that are initially ER-α positive lose ER during tumor progression [50]. In a significant fraction of breast cancers, the loss of ER protein expression is a result of the hypermethylation of the CpG islands within the ER-α promoter [50, 51]. The loss of ER expression causes tumor growth that is no longer under estrogen control, which leads to greater cancer aggressiveness and the failure of endocrine therapy.

The role of DNMT and HDAC activity in the repression of ER-α transcription has been investigated in a variety of studies in which the re-expression of ER was a result of the use of DNMT and HDAC inhibitors. Treatment of ER-negative human breast cancer cells with the methyltransferase inhibitor 5-aza-2’-deoxycytidine (5-aza-dC) led to partial demethylation of the ER CpG island, re-expression of ER mRNA, and synthesis of functional ER protein [52, 53]. Inhibition of DNMT1 by antisense oligonucleotides also caused ER gene re-expression and the restoration of estrogen responsiveness in ER-negative breast cancer cells [54]. These results have been confirmed by recent findings showing that selective depletion of DNMT1 by either antisense oligonucleotides or siRNA induces global and gene-specific demethylation and re-expression of tumor suppressor genes in human cancer cells and also enhances 5-aza-dC activity in the re-expression of silenced genes [55]. However, some other evidence shows that inhibiting the activity of DNMT1 alone is not sufficient to obtain demethylation and re-expression of a hypermethylated gene. Recent findings in colorectal cancer cell lines demonstrate that DNMT1 cooperates with DNMT3b to silence genes and maintain DNA methylation. The lack of single DNMT1 and DNMT3b genes (single DNMT knockout) in colorectal cancer cell lines has only a small effect in reducing global DNA methylation, while the disruption of both DNMT1 and DNMT3b induces a decrease in DNA methylation by greater than 95% and the reactivation of the genes that were transcriptionally silenced by CpG island hypermethylation [56, 57].

HDAC1 interacts with ER-α in vitro and in vivo and suppresses ER-α transcriptional activity. The interaction of HDAC1 with ER-α is mediated by the activation function-2 (AF-2) domain and DNA-binding domain of ER-α. An endogenous interaction of HDAC1 with ER-α in breast cancer cells has been observed, and this interaction is decreased in the presence of estrogen. Furthermore, treatment of ER-negative breast cancer cells with the HDAC-specific inhibitor TSA induced re-expression of ER-α mRNA and protein. These findings strongly suggest that HDAC1 affects breast cancer progression by promoting cellular proliferation in association with a reduction in both ER-α protein expression and transcriptional activity. Thus, HDAC1 may be a potential target for therapeutic intervention in the treatment of a subset of ER-negative breast cancers [53, 58].

Cotreatment with DNMT and HDAC inhibitors, such as TSA, can synergistically induce ER gene expression in ER-negative breast cancer cells. Induced expression of ER mRNA and protein is associated with expected ER function on estrogen-responsive targets. Synergistic induction of ER occurs in conjunction with reduced soluble DNMT1 expression and DNMT activity, partial demethylation of the ER CpG island, and increased acetylation of histones H3 and H4. These data suggested that pharmacological intervention against both DNMT and HDAC can synergistically reactivate the methylated ER gene expression and restore ER function [9].

A novel HDAC inhibitor, scriptaid, has been shown to inhibit tumor growth in vivo and to cause re-expression of functional ER in vivo in conjunction with 5-aza-dC. Scriptaid treatment of three ER-negative cell lines (MDA-MB-231, MDA-MB 435, Hs578t) resulted in significant growth inhibition and increased acetylation of H3 and H4 histone tails. As seen with TSA and 5-aza-dC, scriptaid and 5-aza-dC cotreatment was more effective in inducing ER expression than either scriptaid or 5-aza-dC alone [59].

Several studies in the last year have shown that ER transcription is regulated by a complex mechanism of interplay among a variety of factors that are not yet well understood. Recent results show that p53 is involved in this regulation pathway. p53 upregulates ER-α gene expression by increasing
transcription of the gene through elements located upstream of ER-α promoter. The p53-induced increase in ER-α gene transcription is not dependent on the ability of p53 to bind to DNA but on its ability to interact with other proteins.

The ability of p53 to control ER-α expression suggests that specific p53 mutations in breast tumors may contribute not only to oncogenesis and drug resistance but also to the more aggressive phenotype associated with the loss of ER expression. Interestingly, a high percentage of breast tumors with p53 mutations are ER-negative. These studies suggest that p53 not only regulates the ER-α promoter but may play a role in determining ER status. It may be postulated that p53 plays a role in the progression of breast cancer from a hormone-dependent phenotype to a more aggressive phenotype that is unresponsive to hormones [60]. Furthermore, it has been found that the treatment of MCF-7 cells with paclitaxel (Taxol®; Bristol-Myers Squibb, Princeton, NJ, http://www.bms.com) results in the induction of ER-α gene transcription, which may be mediated through the induction of p53 [61].

pRb2/p130 has been shown to have an important role in the transcriptional regulation of the ER-α promoter as well. We recently showed a new molecular mechanism of ER-α gene inactivation mediated by pRb/p130 in ER-negative breast cancer cells. We investigated, in vivo, the occupancy of the ER-α promoter by pRb2/p130-E2F4/5-HDAC1-SUV39H1-DNMT1 complexes and provided a link between pRb2/p130 and chromatin-modifying enzymes in the regulation of ER-α transcription in a physiological setting. These findings suggest that pRb2/p130 can be key elements in the regulation of ER-α gene expression and may be viewed as promising targets for the development of novel therapeutic strategies in the treatment of breast cancer, especially for those tumors that are ER-negative [62]. The possibility of re-establishing ER expression in ER-negative breast cancers opens new therapeutic perspectives.

In a recent study, it was found that TSA sensitizes ER-α-negative, anti-hormone-unresponsive breast cancer cells to tamoxifen treatment, possibly by upregulating ER-β activity. We can, therefore, explore a new strategy for inducing apoptosis, differentiation, and/or cell growth arrest in human breast and other cancer cell lines [19].

Inhibition of HDAC activities in cancer cells leads to cell cycle arrest and the induction of apoptosis. To date, only a few inhibitors of HDAC are known. TSA, a natural product, and other synthetic compounds, such as suberoylanilide hydroxamic acid (SAHA) and analogues, have been reported as antitumor agents that inhibit proliferation of tumor cells by inducing terminal differentiation of tumor cells [63–66]. TSA and SAHA also cause cytoplasmic α-tubulin acetylation, and this finding could indicate new roles for HDAC inhibitors in other cellular processes, in addition to transcriptional repression [67].

SAHA induces differentiation in the ER-negative cell line SKBr-3 and in the Rb-negative cell line MDA-468. SAHA exhibits a profound antiproliferative activity by causing these cells to undergo cell cycle arrest and differentiation that is dependent on the presence of SAHA [68]. The mechanism of SAHA also leads to induction of pRb-2/p130 interaction and nuclear translocation with E2F-4, causing a significant repression of E2F-1 and PCNA (Proliferating cell nuclear antigen) nuclear levels, which leads to inhibition of DNA synthesis in mammary epithelial cell lines [69]. HDAC inhibitors such as SAHA may provide an alternative therapeutic approach for the treatment of breast cancer.

TSA and SAHA also promote apoptosis in different drug-resistant cells. Both HDAC inhibitors promote endogenous downregulation of P-glycoprotein, which is overexpressed in drug-resistant cells. This result suggests a therapeutic potential for these drugs in the treatment of cancer with acquired resistance [70].

SAHA also significantly enhances the DNA damage induced by topoisomerase-II inhibitors; however, synergy is dependent on the sequence of drug administration and the expression of the target. This finding may have an impact on the clinical development of combining HDAC inhibitors with DNA-damaging agents. [71].

**CONCLUSION**

A better understanding of the epigenetic mechanisms that cause transcriptional repression has allowed researchers to find new agents that are very effective in inducing apoptosis, differentiation, and/or cell growth arrest in human lung cancer, breast cancer, thoracic cancer, leukemia, and colon cancer cell lines [19]. The combination of demethylating agents and HDAC inhibitors has been demonstrated to be synergic in the re-expression of ER-α in ER-α-negative breast cancer cells, and their combination with commonly used hormonal drugs or other chemotherapeutic agents opens new possibilities for a molecularly targeted approach to treatment [19].

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**DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**

The authors indicate no potential conflicts of interest.
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