

REVIEW

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Mechanisms for estrogen receptor expression in human cancer

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Abstract

Estrogen is a steroid hormone that has critical roles in reproductive development, bone homeostasis, cardiovascular remodeling and brain functions. However, estrogen also promotes mammary, ovarian and endometrial tumorigenesis. Estrogen antagonists and drugs that reduce estrogen biosynthesis have become highly successful therapeutic agents for breast cancer patients. The effects of estrogen are largely mediated by estrogen receptor (ER) α and ER β , which are members of the nuclear receptor superfamily of transcription factors. The mechanisms underlying the aberrant expression of ER in breast cancer and other types of human tumors are complex, involving considerable alternative splicing of ER α and ER β , transcription factors, epigenetic and post-transcriptional regulation of ER expression. Elucidation of mechanisms for ER expression may not only help understand cancer progression and evolution, but also shed light on overcoming endocrine therapy resistance. Herein, we review the complex mechanisms for regulating ER expression in human cancer.

Keywords: Cancer, Estrogen receptor, Transcription, Epigenetic modification

Background

Estrogens are steroidal hormones that function as the primary female sex hormone. There are three major forms of estrogen, namely estrone (E1), estradiol (E2) and estriol (E3). Estradiol (E2) is the predominant estrogen in non-pregnant females, while estrone and estriol are primarily produced during pregnancy and following the onset of menopause [1], respectively. 17- β -estradiol is the primary estrogen from menarche to menopause [2]. All estrogens are produced from androgens through actions of enzymes such as aromatase [3]. Follicle-stimulating hormone and luteinizing hormone stimulate the synthesis of estrogen in the ovaries [4]. However, some estrogens are also produced in smaller amounts by other tissues such as the liver, adrenal glands, and mammary gland [5]. Previous studies suggest that estrogen is associated with mammary tumorigenesis, ovarian and endometrial carcinogenesis [6]. Also, mounting evidence demonstrate that estrogen and its target progesterone receptor

(PR) play critical roles in regulating breast cancer progression and cancer stem cell fate [7, 8]. However, estrogen may have anti-cancer effects in some organs such as the liver and colon, whilst more studies are needed to clarify this argument and better understand the mechanisms [9–12].

The biological effects of estrogen are mostly mediated by its binding and activation of ER α and ER β , which are members of the nuclear receptor superfamily of transcription factors that are characterized by highly conserved DNA- and ligand-binding domains [3, 13]. The DNA binding domain, which is extremely well conserved between ER α and ER β (97% homology), contains two functionally distinct zinc finger motifs that are responsible for specific DNA binding, as well as mediating receptor dimerization [3]. The unliganded ER has been shown to be present in a cytosolic complex with hsp90 and associated proteins, with ligand binding allowing dissociation from the hsp90 complex, receptor dimerisation, nuclear localisation and binding to estrogen response elements (ERE, 5'-AGGTCAnnnTGACCT-3') in promoters of estrogen-regulated genes [14, 15]. Genome-wide chromatin immunoprecipitation studies have confirmed that the majority of ER-binding sites in estrogen responsive

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genes conform well to this consensus sequence [16]. While ER α and ER β can bind to most ERE identically, the differences in ER α and ER β may lead to tethering differential transcription factors and then modulating different target genes [17, 18]. Thus, the activation of ER α or ER β can produce both unique and overlapping effects.

ER α has also been shown to modulate gene transcription through heterodimerizing with other transcription factors such as activating protein 1 (AP1) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) [19, 20]. There is a large profile of estrogen-responsive genes, including pS2, cathepsin D, c-fos, c-jun, c-myc, TGF- α , retinoic acid receptor α 1, efp, progesterone receptor (PR), insulin-like growth factor 1 (IGF1) [21]. Many of these ER-regulated genes, including IGF1, cyclin D1, c-myc, and efp, are important for cell proliferation and survival. C-myc is a bona-fide oncogene that is amplified or overexpressed in a variety of human tumors [22]. Efp is an ubiquitin ligase that promotes proteasomal degradation of 14-3-3 sigma thereby stimulating cellular proliferation [23]. While PR is an estrogen-responsive gene, it may antagonize ER α action to inhibit tumor growth, particularly through interacting with RNA polymerase III and inhibiting tRNA transcription [24].

Notably, a pool of ER α are located in the plasma membrane and cytoplasm [25], where it binds to diverse membrane or cytoplasmic signaling molecules such as the p85 regulatory subunit of class I phosphoinositide 3-kinase, mitogen-activated protein kinase (MAPK) and Src [26, 27]. Activation of these signal transduction pathways by estrogen initiates cell survival and proliferation signals. Additionally, these signaling molecules are able to phosphorylate the ER α and its co-regulators to augment nuclear ER α signaling [28]. The genomic and non-genomic actions of ER α play a crucial role in breast epithelial cell proliferation and survival, as well as mammary tumorigenesis [28]. The purpose of this review is to decipher the complex mechanisms underlying the aberrant expression of ER α and ER β in human cancer.

Expression of ER in normal tissues

The human ER α and ER β cDNA were cloned in 1985 and 1986, respectively [29, 30]. In human mammary gland, ER α positive cells are present in ducts and lobules, but not in stromal cells. ER α expression is largely heterogeneous within different areas of breast tissue. Only a small fraction of epithelial cells in ducts and lobules are ER α -positive [31]. The ER α levels in mammary gland are affected by menstrual cycle, with more ER α -positive cells in the follicle stage of the cycle [32]. ER α -positive epithelial cells may promote proliferation of surrounding ER α -negative cells, probably through secretion of paracrine factors [33]. While ER α is expressed in luminal epithelial

cells but not in the stroma, ER β is present in luminal, myoepithelial and stromal cells [7]. Depletion of ER α leads to failure to initiate the pre- and postpubertal stages of mammary gland growth, as well as pregnancy-induced maturation [34]. ER β knockout, however, has little effects on mammary gland development [35]. In addition, ER α expression is also detectable in endometrium and ovary. ER α knockout severely disrupts sexual maturation of the whole reproductive tract [36]. ER β knockout, however, predominantly disrupts the maturation of ovarian function [37].

ER α and ER β are both expressed in other cell types, though at lower levels than those found in reproductive tissues. Myeloid and lymphoid progenitor cells, mature lymphocytes, and neutrophils express ER α , ER β , or both receptors [38]. Although 17- β -estradiol inhibits T and B cell development, it enhances B cell function in ER α -dependent manner, involving both genomic and non-genomic ER signaling in B lymphocytes [39, 40]. Moreover, the brain of both sexes is a major target of estradiol and a site of estrogen synthesis [41, 42]. ER β is a dominant ER subtype in the adult cerebellum. ER β expression was detected in Golgi type neurons, Purkinje cells, and basket cells in the adult cerebellum [43]. High levels of ER α expression are also found in the hypothalamus, with particularly elevated expression within the medial preoptic area, as well as the amygdala and ventral medial hypothalamus [44]. Estrogen and its receptors may improve memory and social behaviors, regulate brain lipid metabolism and prevent cortical damage following an ischemic episode [45–47]. In addition, estrogen and ER are important for bone homeostasis, hepatic lipid metabolism and reverse cholesterol transport [48, 49]. While the liver predominantly expresses ER α , the gastrointestinal tract and the lung exclusively harbour ER β [50]. Moreover, both ER α and ER β are expressed in platelets [51]. An estrogen analogue is able to induce platelets apoptosis and autophagy [52]. Therefore, ER is a vital hormone receptor for human health.

Expression of ER in human tumors

Based on the ER status, breast tumors can be classified as ER-positive and ER-negative. About 75% of breast cancer cases are ER α positive at diagnosis [53]. Luminal A and basal subtypes are two major subtypes of human breast cancer. ER α is more frequently expressed in luminal A tumors than in basal tumors [54]. ER α -positive cases are not only responsive to endocrine therapies, but also sensitive to CDK4/6 inhibitors [55, 56]. Thus, ER positivity may be associated with a better prognosis [57]. ER α -negative tumors, on the other hand, are more aggressive and metastatic [58]. Importantly, ER α expression in breast cancer is dynamic and reversible. About 50% of

patients with ER α -positive primary breast tumors that relapse after adjuvant endocrine therapy have recurrent tumors in which ER α expression is lost [59]. The ER α -negative and human epidermal growth factor receptor 2 (HER2)-positive breast cancer can be treated by HER2-targeting agents [60]. Some ER α -negative breast tumors that are treated with growth factor receptor inhibitors may reexpress ER α and respond to endocrine therapy [61]. Except for ER α , various ER β isoforms are expressed in breast cancer. Both ER β 1 and ER β 2/cx repress the transcriptional activity of ER α [62].

In general, ER α and ER β differentially contribute to carcinogenesis and tumor progression with ER α as an oncogene and ER β as a tumor suppressor. However, some ER β isoforms, such as ER β 5, may act as oncogene [63]. Studies on the distribution of estrogen receptor (ER) subtypes in ovarian tumors demonstrated that 40–60% of ovarian cancers express ER α , especially in serous tumors and in metastasis [64, 65]. However, less than 20% of patients (ranging from 7 to 18%) respond clinically to anti-estrogen treatment [66]. ER β expression, however, is significantly higher in normal ovary tissues compared with ovarian carcinoma [67]. Advanced colon cancer is associated with a loss of ER β , the predominant ER in colon tissue [11]. ER β specific agonists have anti-cancer effects on colon cancer [12]. In addition, estrogen increases the risk of endometrial carcinoma [64]. It appears that ER α is more frequently expressed in lower grade of endometrial carcinoma [68]. ER α expression in endometrial carcinoma is inversely associated with lymph node metastasis [69].

Previous study demonstrated that both ER α and ER β were overexpressed in a proportion of hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC) [70]. However, another study shows that the expression of ER α and ER β were lower in HCC tissues than in normal liver tissues [71]. The expression of ER α was lower in HCC with portal vein tumor thrombus (PVTT) than those without PVTT, suggesting that ER α -positive HCC is less aggressive [72]. In addition, a specific isoform of ER α , ER α -36, is overexpressed in HCC [73]. Estrogen stimulates HCC cells growth through ER α -36 [74]. Therefore, variance in ER α subtypes and isoforms may dictate the response of HCC to estrogen.

Alternative splicing of ER

Alternatively spliced ER α mRNA has been detected in both normal and cancerous tissues [71, 75]. Variances in ER α transcripts may lead to loss of ligand-dependent transactivation activity, gain of ligand-independent transactivation activity, and differential response to tamoxifen [76]. The most characterized isoform of ER α is a 66-kDa protein encoded by a 6.6-kb mRNA with eight exons [76].

There are six human ER α mRNA isoforms that encode the same 66-kDa protein but differ in their 5' untranslated region. Moreover, other variant isoforms of ER α mRNA that encode different proteins from the 66-kDa protein can occur in the presence or absence of wild-type ER α transcript (Fig. 1a). The variance in ER α mRNA may be attributed to frame-shift mutations or alternative splicing [77]. A genomic rearrangement in which ER α exons 6 and 7, which encode part of the ligand-binding domain of ER α , are duplicated in an in-frame fashion results in an ER α mRNA that can be translated into a 80 kDa ER α [78]. In addition, a 46-kDa amino-terminal truncated form of ER α , ER α -46, has been identified in endothelial cells and breast cancer cells [75]. ER α -46 is encoded by an ER α transcript that lacks the first exon of the ER α gene [79]. The high mobility group A protein 1a (HMGA1a) induces alternative splicing of ER α thereby increasing ER α -46 expression and reducing tamoxifen sensitivity in breast cancer cells [80]. Mechanistically, HMGA1 traps U1 snRNP at the 5' splice site of exon 1 in ER α gene thereby inducing alternative splicing [81]. Moreover, some normal or cancer tissues may express the ER α variant that is lack of exon 7 [82]. While the splicing factor HTRA2- β 1 is responsible for ER α exon 7 inclusion, heterogeneous nuclear ribonucleoprotein (hnRNP) G induces exon 7 skipping and then promotes the generation of the exon 7-skipping isoform of ER α [83]. In addition, a 36-kDa spliced variant of ER α , ER α -36, has been cloned. ER α -36 is defective of exons 1, 7 and 8, which encode transcriptional activation domains AF1 and AF2 [73]. Both ER α -46 and ER α -36 are located in the plasma membrane, cytosol, and nucleus. ER α -46 and ER α -36 can mediate, at least in part, the membrane-initiated estrogen-dependent activation of mitogenic signaling pathways [27]. ER α -36 also negatively regulates the transactivation activity of ER α -66 and ER β [84]. Finally, overexpression of the nuclear protein E3-3 (NPE3-3) promotes the generation of another alternatively spliced variant of ER α , ER α V, which contains only exons 1, 2, 7 and 8, and encodes a 37-kDa ER α [85]. Notably, NPE3-3 interacts with multiple splicing factors, including serine/arginine-rich protein (SRp)-30c, SRp40, and splicing factor SC-35 [85].

Variant isoforms of ER β have also been identified in both normal and cancerous tissues (Fig. 1b). Alternative splicing of exon 8 in the ER β gene results in five ER β isoforms (ER β 1, ER β 2, ER β 3, ER β 4 and ER β 5) [86]. The originally cloned ER β transcript is termed as ER β 1, which is the only isoform that is fully functional. The levels of ER β 1 are low in many tissues, while ER β 2 (also known as ER β cx) is expressed in many tissues and aggressive cancer [87–91]. ER β 4 and ER β 5, however, are predominantly expressed in the testis and placenta, respectively

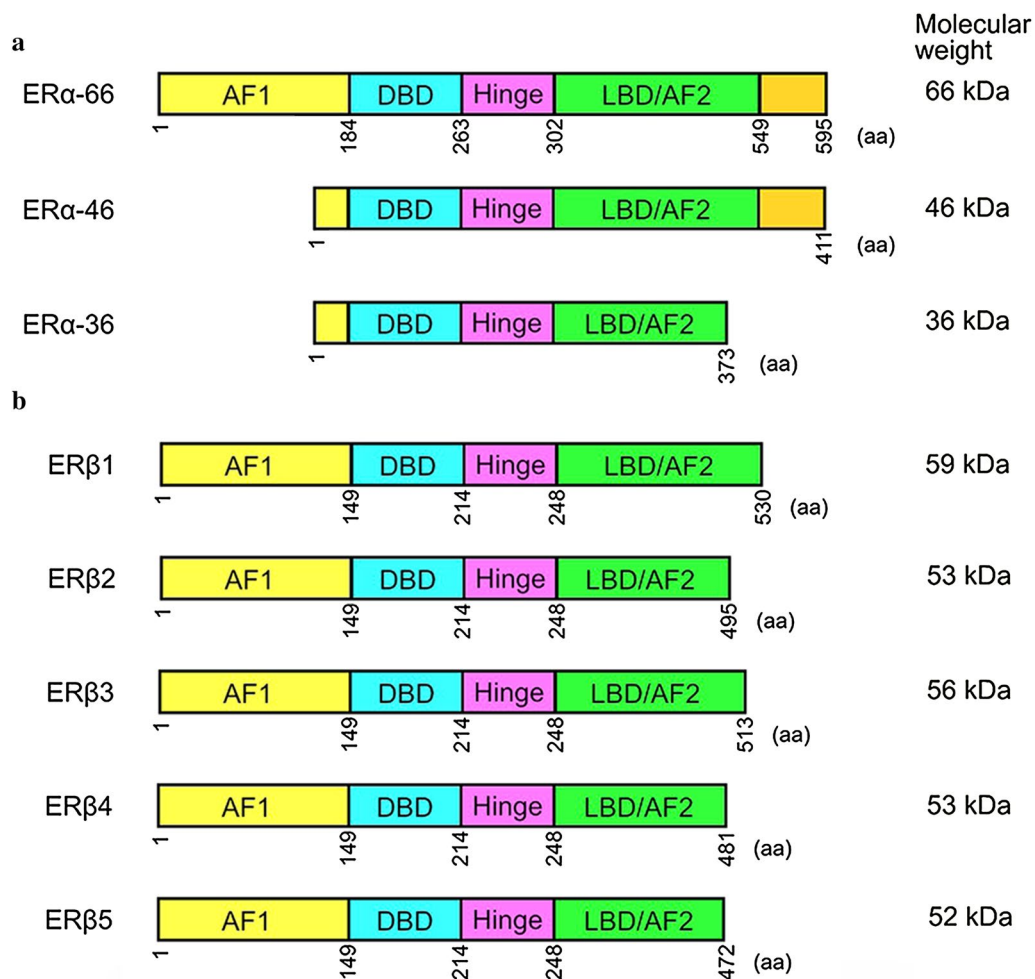


Fig. 1 The major ERα and ERβ isoforms. **a** There are three major isoforms of ERα, including ERα-66, ERα-46 and ERα36. ERα-36 differs with ERα-46 in the C-termini. **b** ERβ has five major isoforms, namely ERβ1, ERβ2, ERβ3, ERβ4 and ERβ5. AF1 activation function 1, AF2 activation function 2, DBD DNA-binding domain, LBD ligand-binding domain

[90]. Both ERβ4 and ERβ5 bind to promoter sequences of DNA but do not bind estrogen. ERβ2, ERβ4 and ERβ5 can heterodimerize with ERα and negatively regulate its transactivation activity [91]. ERβ1 overexpression is associated with better survival in women with breast cancer [92, 93]. Cytoplasmic expression of ERβ2 is associated with poor overall survival in patients with breast cancer and serous ovarian carcinoma [94, 95]. While ERβ1 has tumor suppressive effects on glioblastoma, ERβ5 exhibits oncogenic effects on this type of cancer [62]. Moreover, ERβ5 is associated with poor outcome in HER2-positive and triple-negative breast cancer patients [96]. Taken together, it appears that the ERβ isoforms have different roles in tumorigenesis. Identification of the relative levels of ERβ isoforms may help predict the prognosis in cancer patients. The mechanisms underlying the alternative splicing of ERβ remains largely unknown. The

RNA-binding protein Nova1 can bind to the consensus sequences in the ERβ pre-mRNA transcript and then promote exon exclusion of the ERβ2-specific nucleotide sequence, which in turn abolishes ERβ2 mRNA expression but increases ERβ1 mRNA expression [97].

Transcriptional regulation of ER expression

Transcription factors that regulate ER expression

The human ERα gene spans approximately 300 kb of chromosome 6, including the 140 kb containing the eight protein-coding exons. Since 1988, intensive efforts have been taken to identify human ERα promoters. The regulation of ERα transcription is controlled by multiple promoters. So far, at least nine promoters have been discovered upstream of the translation start site of human ERα. A unified nomenclature for human ERα promoters was suggested by Gannon et al. [98]. The promoters of

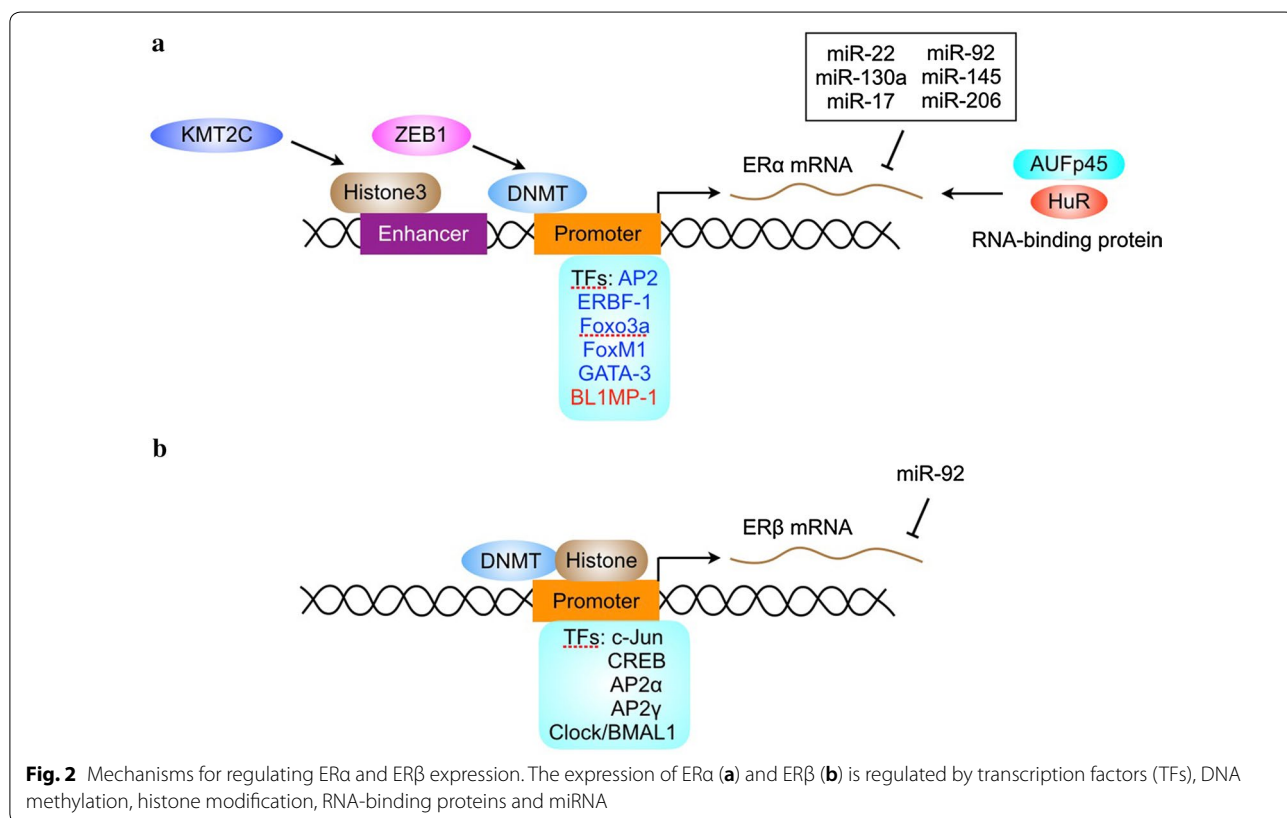
ER α contain multiple transcription factors-binding sites. The availability of these transcription factors may dictate the tissue-specific or context-dependent expression of ER α (Fig. 2a).

Previous studies demonstrated that estrogen receptor promoter B associated factor 1 (ERBF-1) is critical for the transcription activity of a distal promoter (promoter B) in ER α -positive breast cancer cells [99]. ERBF-1 is exclusively expressed in cells expressing ER α mRNA transcribed from promoter B and plays an important role in the expression of the ER α gene in breast cancer [100]. In addition, the transcription factor AP2 interacts with cis-regulatory elements via formation of dimers to regulate target gene expression. ER α expression is associated with AP2 activity in human breast and endometrial cancer [101]. The AP2 family proteins are recognized as key regulators in the development and progression of breast and endometrial cancer [102]. Both AP2 α and AP2 γ can trans-activate the human ER α promoter [100]. AP2 γ recognizes a region in ER α promoter containing the sequence CCCTGCGGGG thereby inducing changes in the chromatin structure of ER α promoter and stimulating ER α transcription [103, 104].

The Forkhead box protein FOXO3a, which can be inactivated by Akt, is a positive regulator of ER α gene transcription [105]. However, FOXO3a interacts with ER α

and ER β proteins and inhibits ligand-dependent ER signaling and tumorigenesis [106]. FOXM1, another forkhead transcription factor, also regulates ER α transcription. FOXM1 activates the transcriptional activity of human ER α promoter primarily through two closely located forkhead response elements located at the proximal region of the ER promoter [107]. Reciprocally, FOXM1 protein and mRNA expression is regulated by estrogen, tamoxifen and fulvestrant in breast carcinoma. Depletion of ER α in MCF-7 cells down-regulates FOXM1 expression [108]. Moreover, FOXM1 and ER α can simultaneously bind to the same genomic sites and stimulate ER α transcriptional activity [109]. These finding suggest that ER α and FOXM1 may be two key components within a positive cross-regulatory loop.

The GATA proteins are a family of zinc finger DNA binding proteins that recognize the consensus motif T/A GATA A/G [110]. GATA-3 is highly expressed in T lymphoid cells and is a master regulator of immune cell function [111]. In the mammary gland, GATA-3 is expressed only by the epithelium and its expression increases during early pregnancy [111]. GATA-3 is an essential regulator of mammary gland morphogenesis and luminal cell differentiation [112]. The expression of GATA-3 is tightly correlated with ER α in human breast carcinoma [113]. GATA-3 binds to two *cis*-regulatory elements located



within the *ERα* gene and stimulates *ERα* transcription [114].

While there are many transcription factors that positively regulate *ERα* expression, little is known about the negative regulators of *ERα* transcription. The zinc finger repressor B-lymphocyte-induced maturation protein (BLIMP1) is able to bind to *ERα* promoter and inhibit *ER* transcription [115]. In addition, the transcription factor NF- κ B can indirectly repress *ERα* transcription through inducing the expression of BLIMP1 and the Enhancer of Zeste Homolog2 (EZH2), which negatively regulates *ERα* transcription by inducing the di- and tri-methylation of histone 3 residue 27 [20, 115]. However, NF- κ B enhances the recruitment of *ERα* to target DNA and increases the transcriptional activity of *ERα* [116]. Thus, the levels of *ERα* may be not always proportional to its activity.

There are several transcription factors that regulate *ERβ* transcription (Fig. 2b). The transcription factors c-jun and CREB can bind to *ERβ* promoter and promote *ERβ* transcription [117]. In addition, AP2 α and AP2 γ , two transcription factors that regulate *ERα* transcription, bind to *ERβ* promoter and stimulate *ERβ* transcription [118]. An evolutionally conserved E-box motif (CAC GTG) has been identified in the *ERβ* promoter. Transcription factors containing the basic-helix-loop-helix (bHLH) protein structural motif typically bind to E-boxes or related variant sequences and enhance transcription of the downstream gene [119]. CLOCK and BMAL1 are members of the bHLH-PAS family of transcription factors that bind to E-box motifs and induce the transcription of target genes [120]. Both CLOCK and BMAL1 are positive set of components in an evolutionarily conserved feedback loop that controls the oscillation of circadian clock [120]. CLOCK-BMAL1 induces *ERβ* transcription via the E-box motif, whereas it does not regulate *ERβ* mRNA levels [121].

Epigenetic regulation of ER expression

ER promoter methylation

Gene expression may be silenced by methylation of a cytosine- and guanine-rich area, termed CpG island, in the promoter of the gene [122]. Methylation of CpG islands has been shown to inhibit transcription by preventing the binding of transcription factors to the promoter or by stabilizing structural changes in chromatin that prevent transcription [123]. The absence of *ERα* gene expression in *ERα*-negative breast cancer cells is associated with abnormal methylation in the CpG islands of multiple promoters of the *ERα* gene [124, 125]. Mechanistically, methylation of *ERα* promoter may prevent the recruitment of transcription factor such as AP2. In addition, ZEB1 can induce *ERα* promoter methylation, down-regulate *ERα* expression and promote anti-estrogen

resistance in breast cancer [126]. Treatment of *ERα* negative human breast cancer cells with demethylating agents can induce partial demethylation of the *ERα* CpG islands and reactivate *ERα* gene expression [127]. Inhibition of DNMT1 by antisense oligonucleotides also caused *ERα* gene re-expression and the restoration of estrogen responsiveness in *ERα* negative breast cancer cells [128]. Demethylation of promoter C region in the *ERα* gene is in part responsible for the enhanced expression of *ERα* gene in long-term estrogen deprived MCF7 cells [129].

The expression of *ERβ* is also regulated by promoter methylation. Two promoters, promoter 0K and 0N, control the transcription of *ER-β* [130]. The lack of *ERβ*1, *ERβ*2 and *ERβ*4 transcription in some breast, ovarian and prostate cancer tissues and cell lines may be attributed to methylation of CpG sites in the promoter 0N [131]. In contrast, the 0K promoter is demethylated in malignant breast and ovarian cancer cells, as well as in normal breast and ovarian epithelial cells [132, 133]. Hence, *ERβ* promoter 0N methylation may be a target for manipulating *ERβ* expression.

Histone modification and ER transcription

Gene transcription is also regulated by chromatin remodeling. The so-called histone code is important for dynamic regulation of chromatin assembly and gene transcription [122]. Chromatin structure is modulated by histone phosphorylation, acetylation, and methylation. Histone acetyltransferases (HAT) transfer an acetyl moiety to lysine residue on histones, leading to neutralization of the positive charge, reduced affinity of histone for DNA, and the transformation of a tight-coiled inactive chromatin structure into a loose, transcriptionally active one [134]. Histone acetylation also plays a role in *ER* expression. Treatment of *ERα* negative breast cancer cells with histone deacetylase (HDAC) inhibitors can restore *ERα* transcription [135]. Moreover, combination of DNA demethylating agents and HDAC inhibitors can induce *ERα* expression to more extent than treatment of *ERα* negative breast cancer cells with these agents alone [136]. Moreover, *ERα* expression is regulated by histone methylation in *ERα* enhancers. The H3K4 methyltransferase KMT2C up-regulates *ERα* through regulating H3K4me1 and H3K27ac at *ERα* enhancers [137]. Regulation of both enhancers and promoters may synergistically affect *ERα* transcription.

Posttranscriptional regulation of ER expression

Transcription of the *ERα* gene gives rise to an mRNA that is 4.3 kb long and contains an extensive 3' untranslated region (UTR) that is three-fold longer than its open reading frame [76]. The *ERα* 3'-UTR is known to contain several regulatory elements, including long tracts of

AU-rich sequence and 13 copies of AUUUA [138]. AU-rich elements may direct mRNA destabilization through mechanisms involving polyadenylase tail digestion and distributive deadenylation [139, 140]. Similar to AU rich elements in the 3'-UTR of other transcripts, the AU-rich elements in the 3'-UTR of ER α mRNA play critical roles in ER α mRNA destabilization [137]. AUFp45 binds ER α mRNA and increase its stability by protecting it from RNAases [141]. In addition, the RNA-binding protein HuR plays a critical role in stabilizing ER α mRNA [142]. It remains to know if there are other RNA-binding proteins that regulate the stability of ER α mRNA.

MicroRNAs (miRNAs) are small non-coding RNA that regulates gene expression at posttranscripton or translational level [143]. Both ER α and ER β expression are regulated by miRNAs [144]. The expression of miRNA-206 is increased in ER α -negative tumors and it directly targets ER α by base pairing to the 3'-untranslated region of the ER α mRNA [145, 146]. miR-22, miR-130a, miR-17/92, miR-145 and miR-206 also directly target ER α mRNA and inhibits its expression [147, 148]. In addition, miR-27a indirectly regulates ER α expression by targeting ZBTB10, a repressor of specificity protein that regulates ER α expression [149]. Interestingly, some of the ER α -targeting miRNAs are also regulated by ER α . For example, ER α agonists downregulate miR-22, miR-206, miR-221, and miR-222 expression [150]. Moreover, miR-92 inhibits ER β 1 expression by direct targeting the 3'-untranslated region of the ER β mRNA [151]. Certainly, there will be more ER β -targeting miRNAs that may be uncovered in future studies. Furthermore, both ER α and ER β regulate the expression of multiple miRNAs [152–156]. Because one miRNA is able to regulate many genes, ER α and ER β may link multiple miRNAs to regulate the expression of a large pool of genes.

Concluding remarks

In light of the critical roles of estrogen receptors signaling in diverse cellular processes and development, it is reasonable that the expression of ER and the activity of ER must be tightly regulated. Deregulation of ER is involved in tumorigenesis in multiple organ sites, including breast, ovary, endometrium and colon. ER expression can be regulated at multiple levels. Dynamic expression of ER is also a feature of human breast cancer. Even in ER-positive breast tumors, the expression of ER is not always permanent. Progression from an ER-positive phenotype to an ER-negative phenotype typically involves the constitutive activation of growth-promoting signals, thereby leading to a loss of estrogen dependence and resistance to anti-estrogens. This increased activation of growth factor receptors correlates with increased MAPK activity [156, 157]. Abrogation of MAPK activity can reverse the

downregulation of ER α by growth factor signaling and restore its activity [158].

The detection of ER α expression in breast cancer is a routine practice in clinical setting. Given that there are multiple isoforms of ER α with different localization and functions, it may be necessary to discriminate which isoform is expressed in human breast cancer specimens. Moreover, the expression of ER β isoforms should be detected. Detection of these isoforms may not only guide endocrine therapy and/or other emerging therapeutics for breast cancer [159], but also help better judge the prognosis of cancer patients. Except for the levels of ER, the activity of ER may be more critical for the sensitivity to endocrine therapy. The levels of estrogen responsive genes may reflect, at least in part, the activity of ER in human breast cancer. Currently, immunohistochemical analysis of PR positivity in human breast cancer is routine procedure in the clinic. Other estrogen responsive genes may also be detected to strengthen this facet.

Since ER α -negative breast tumors are less likely to be responsive to endocrine therapy, restoration of ER α expression could allow endocrine therapy to be effective in a subset of ER α -negative breast cancer. After reviewing the mechanisms underlying the regulation of ER expression, it is obvious that ER expression can be restored by multiple agents, including signal transduction inhibitors, monoclonal antibodies, DNA-demethylating agents or HDAC inhibitors. In addition, inhibition of Src can enhance ER α expression and anti-estrogen response by preventing ER α proteolysis [160]. Conversion of ER α -negative tumors to ER α -positive phenotype may allow an endocrine therapy that would prevent tumor progression. Whether or not these approaches can achieve clinical success remains to be determined.

Abbreviations

AP: activating protein; E2: estradiol; ER: estrogen receptor; ERBF-1: estrogen receptor promoter B associated factor 1; ERE: estrogen response element; HDAC: histone deacetylase; IGF1: insulin-like growth factor 1; MAPK: mitogen-activated protein kinase; NF- κ B: nuclear factor kappa-light-chain-enhancer of activated B cells; PR: progesterone receptor.

Authors' contributions

HH and YJ conceived the review and wrote the manuscript. HZ edited the references. QK prepared the figures. All authors read and approved the final manuscript.

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