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Jin-Lei Wang, Director
World Journal of Clinical Oncology
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242

Fax: +1-925-2238243
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Polyubiquitination inhibition of estrogen receptor alpha and its implications in breast cancer

Angeles C Tecalco-Cruz, Josué O Ramírez-Jarquín

Angeles C Tecalco-Cruz, Programa de Investigación de Cáncer de Mama (PICM), Departamento de Biología Molecular y Biotecnología, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, México 04510, México

Josué O Ramírez-Jarquín, Instituto de Fisiología Celular, Universidad Nacional Autónoma de México, México 04510, México

ORCID number: Angeles C Tecalco-Cruz (0000-0001-9199-3834); Josué O Ramírez-Jarquín (0000-0001-7574-8724).

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Correspondence to: Angeles C Tecalco-Cruz, PhD, Full Professor, Programa de Investigación de Cáncer de Mama (PICM), Departamento de Biología Molecular y Biotecnología, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, Ciudad Universitaria, México 04510, México. 12anget@gmail.com
Telephone: +52-55-56229208

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Abstract

Estrogen receptor alpha (ER α) is detected in more than 70% of the cases of breast cancer. Nuclear activity of ER α , a transcriptional regulator, is linked to the development of mammary tumors, whereas the extranuclear activity of ER α is related to endocrine therapy resistance. ER α polyubiquitination is induced by the estradiol hormone, and also by selective estrogen receptor degraders, resulting in ER α degradation *via* the ubiquitin proteasome system. Moreover, polyubiquitination is related to the ER α transcription cycle, and some E3-ubiquitin ligases also function as coactivators for ER α . Several studies have demonstrated that ER α polyubiquitination is inhibited by multiple mechanisms that include posttranslational modifications, interactions with coregulators, and formation of specific protein complexes with ER α . These events are responsible for an increase in ER α protein levels and deregulation of its signaling in breast cancers. Thus, ER α polyubiquitination inhibition may be a key factor in the progression of breast cancer and resistance to endocrine therapy.

Key words: Estrogen receptor alpha polyubiquitination; Breast cancer; Estrogen receptor alpha

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Core tip: The inhibition of the estrogen receptor alpha polyubiquitination and degradation by several molecular mechanisms is related to the progression of breast cancer and resistance to endocrine therapy.

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INTRODUCTION

Estrogen receptor alpha (ER α) protein, also known as nuclear receptor subfamily3 group A member 1 (NR3A1), comprises of 595 amino acids, organized in two activation function domains (AF-1 and AF-2), a DNA-binding domain (DBD), a ligand-binding domain (LBD) that recognize the 17 β -estradiol hormone (E2), and a hinge region that connects the DBD and the LBD^[1-3] (Figure 1). Many nuclear functions of ER α are triggered by the binding of E2 to the receptor^[4,5], inducing ER α homodimers to bind to estrogen responsive elements (ERE) within the enhancer and promoter regions of E2-target genes^[6,7]. In these events, pioneer factors expose chromatin sections, facilitating the association of ER α with EREs^[8]. Moreover, transcriptional coregulators are recruited by the AF-1 and AF-2 domains of the receptor for the remodeling of the chromatin structure^[9,10] and promotion of chromatin loops that modulate E2-responsive gene expression^[11,12]. In addition, there is crosstalk between ER α and other signaling pathways: ER α acts as a coregulator by interacting with other transcription factors, such as activator protein 1 (AP-1), specificity protein 1 (Sp1), and nuclear factor- κ B (NF- κ B)^[3,5,13-17]. Additionally, ER α is phosphorylated and transcriptionally activated in response to growth factors such as the epidermal growth factor (EGF) and insulin-like growth factor (IGF)^[13,14,18-20]. Recently, progesterone receptor (PR) was shown as an ER α interacting protein that modulates and re-directs the binding of ER α to the chromatin and the expression of specific genes in breast cancer cells^[21] (Figure 2).

ER α also exhibits extranuclear activity by associating with the cell membrane *via* palmitoylation, and with the help of protein complexes, linked to the cell membrane or cytoplasm^[22] (Figure 2). Thereafter, ER α transduces rapid extranuclear signaling that can trigger second messengers such as calcium and cAMP, and activate kinases such as ERK/MAPK, PI3K/AKT, PKC and Src kinase^[13,23,24]. Both nuclear and extranuclear signaling of ER α are connected and are critical in about 70% of breast cancer cases (ER α + breast cancer)^[13,24,25]. Consequently, ER α is a target for endocrine therapy *via* the use of selective estrogen receptor modulators (SERMs), such as tamoxifen (Tam), which competes with E2 by binding to ER α to inhibit its transcriptional activity, as well as, *via* the use of selective estrogen receptor degraders (SERDs) such as fulvestrant that decreases the ER α stability^[8,14,26,27]. The acquisition of resistance to these treatments commonly occurs in ER α + breast cancer, and although the mechanisms are unclear, the

extranuclear signaling of ER α is strongly activated under this condition^[19,20,26,28-31].

The activation or inhibition of ER α activity is modulated by its transcriptional coregulators, by phosphorylation induced by E2 hormones and growth factors, and by other posttranslational modifications such as ubiquitination. Remarkably, several studies have emerged to demonstrate that multiple mechanisms are activated in ER α + breast cancers to inhibit ER α polyubiquitination, increasing its signaling pathways (Figure 2), which have crucial implications in the progression of this cancer type, as we will describe in the following sections.

GENERALITIES OF THE POSTTRANSLATIONAL MODIFICATION “UBIQUITINATION” FOR ER α IN BREAST CANCER CELLS

ER α is a monoubiquitination and polyubiquitination-target. However, fewer reports are available to demonstrate monoubiquitination of ER α , in comparison to those that exhibit polyubiquitination of this receptor. Nevertheless, these studies clearly show that ER α monoubiquitination is decreased by E2, and that, this modification is important, both for stability and for the transcriptional activity of this receptor in breast cancer. In contrast, polyubiquitination is induced by E2, resulting in a signal to direct ER α degradation *via* the UPS^[14,32,33], facilitated by the concerted action of the enzymes E1 (ubiquitin activating enzyme), E2 (ubiquitin conjugating enzyme), and E3 (ubiquitin ligase)^[32,33]. The specific covalent binding of ubiquitin to ER α lysine residues is mediated by several E3 ubiquitin ligases for ER α , that include CHIP^[34], E6AP^[35], BRCA1^[36], BARD1^[37], SKP2^[38], MDM2^[39], and Hbo1^[40]. Importantly, E2 treatment induces ER α polyubiquitination, followed by its degradation by the UPS^[14,17,33,41-43].

Although polyubiquitination leads to ER α downregulation through its degradation by the 26S proteasome, it is important to note that, this modification and the proteasome activity, have also been reported as elements required for the transcriptional cycle of ER α . Likewise, it has been evidenced that ER α bound to ERE can recruit coactivators, some of which possess E3-ubiquitin ligase activity, such as SKP2^[17], E6AP, and RNF8. As coactivators enhance the activity of ER α , and the activity of E3-ubiquitin ligases mediate the downregulation of this receptor, the recruitment of these proteins with dual function may maintain a balance in the level and activity of ER α ^[17,44,45].

ER α residues, K302 and K303, have been suggested as the lysine targets for ubiquitination and degradation, in response to E2 and fulvestrant, but the same residues are also important for ER α stability in untreated breast cancer cells^[46]. Against this background, it maybe envisaged that, several factors delicately modulate the stability and degradation of ER α , which may be altered

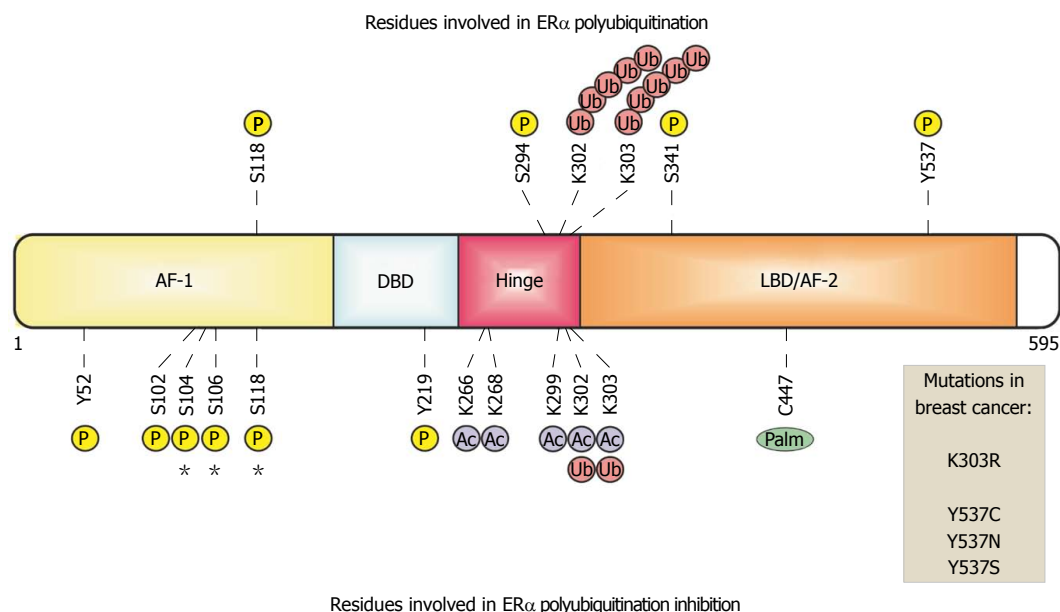


Figure 1 Estrogen receptor α in breast cancer cells. ER α is organized in functional domains. The transactivation domains AF-1 and AF-2 recruit both coactivators and corepressors. The DNA-binding domain (DBD) recognizes and binds to estrogen response elements in enhancers or promoters. The ligand-binding domain (LBD) is recognized and activated by the 17 beta estradiol hormone. The hinge domain links LBD and DBD allowing the conformational changes of this receptor. Some residues are modified by phosphorylation, acetylation, ubiquitination and palmitoylation, which are related with ER α polyubiquitination. Sites of phosphorylation or mutations in ER α that have been identified in breast-cancer biopsy samples are indicated.

in breast cancer.

Additionally, the ubiquitination of ER α is also related to its phosphorylation state. Several kinases, such as CDK11p58^[47], cyclin E-CDK2^[17], Src^[35], PKC^[42], p38MAPK^[38], and ERK7^[48] have been reported as modifiers of ER α in breast cancer. The main residues of ER α that are phosphorylated in E2-response, and have been associated with its polyubiquitination and degradation, are S118^[49], S294^[38], S341^[17], and Y537^[35]. A key example is the sequential modification of ER α , where, first, the ER α Y537 residue is phosphorylated by Src kinase in E2-treated cells, followed by E6AP, an E3-ubiquitin ligase, which induces ER α polyubiquitination and its degradation^[35]. Thus, phosphorylation and ubiquitination of ER α are interconnected in order to control both, the abundance and the functions of this receptor.

IS ER α IN BREAST CANCER CELLS POLYUBIQUITINATED AND DEGRADED?

In recent years, several studies have emerged to demonstrate the inhibition of polyubiquitination of ER α and consequently, a decrease in its degradation *via* the UPS, increasing its protein stability in breast cancer cells, through several mechanisms and ER α -associated proteins. Here, we describe these evidences.

ER α polyubiquitination inhibitor proteins in breast cancer cells

ER α polyubiquitination inhibitor proteins (EPIP). There has been a progressive increase in the number of ER α polyubiquitination inhibitor proteins that have been

discovered in breast cancer cells, which we have grouped and identified as EPIP. So far, it has been reported that proteins such as Mucin 1 (MUC1), PIN1, GSK3, LMTK3, RNF8, RNF31, RB, ABL, SHARPIN, and SMURF1 have the ability to interact with ER α , conferring it protection against polyubiquitination and degradation. Interestingly, not all of these proteins have related sequences and structures, but some of them are functionally similar.

MUC1 and Protein interacting with Never in mitosis A (PIN1), for example, induce the formation of stable transcription complexes on the DNA^[49,50]. MUC1 interacts with ER α to inhibit its polyubiquitination and degradation, and recruits coactivators such as SRC1 and GRIP on E2-regulated promoters to enhance gene transcription linked to cellular proliferation, migration, tumorigenicity, and endocrine resistance^[50-54]. Likewise, PIN1 interacts with ER α phosphorylated at S118, inducing its cis/trans isomerization. Moreover, PIN1 blocks the polyubiquitination and degradation of ER α by preventing its interaction with the E6AP E3 ligase, hence enhancing its stability, binding to EREs, and the subsequent transcriptional activity of ER α ^[10,49,55-57]. High levels of PIN1 and ER α , and low levels of E6AP are observed in endocrine resistance^[49].

Other examples are GSK3, LMTK3, and ABL1 kinases that phosphorylate ER α to inhibit its polyubiquitination^[58,59]. First, the glycogen synthase kinase-3 (GSK3) isoforms interact with and phosphorylate ER α at S102, S104, S106, and S118. GSK3 depletion decreases phosphorylation and E2-induced transcriptional activity by increasing polyubiquitination and degradation of this receptor^[59-61]. Thereafter, LMTK3 (lemur tyrosine kinase 3) interacts with and phosphorylates ER α to protect it from

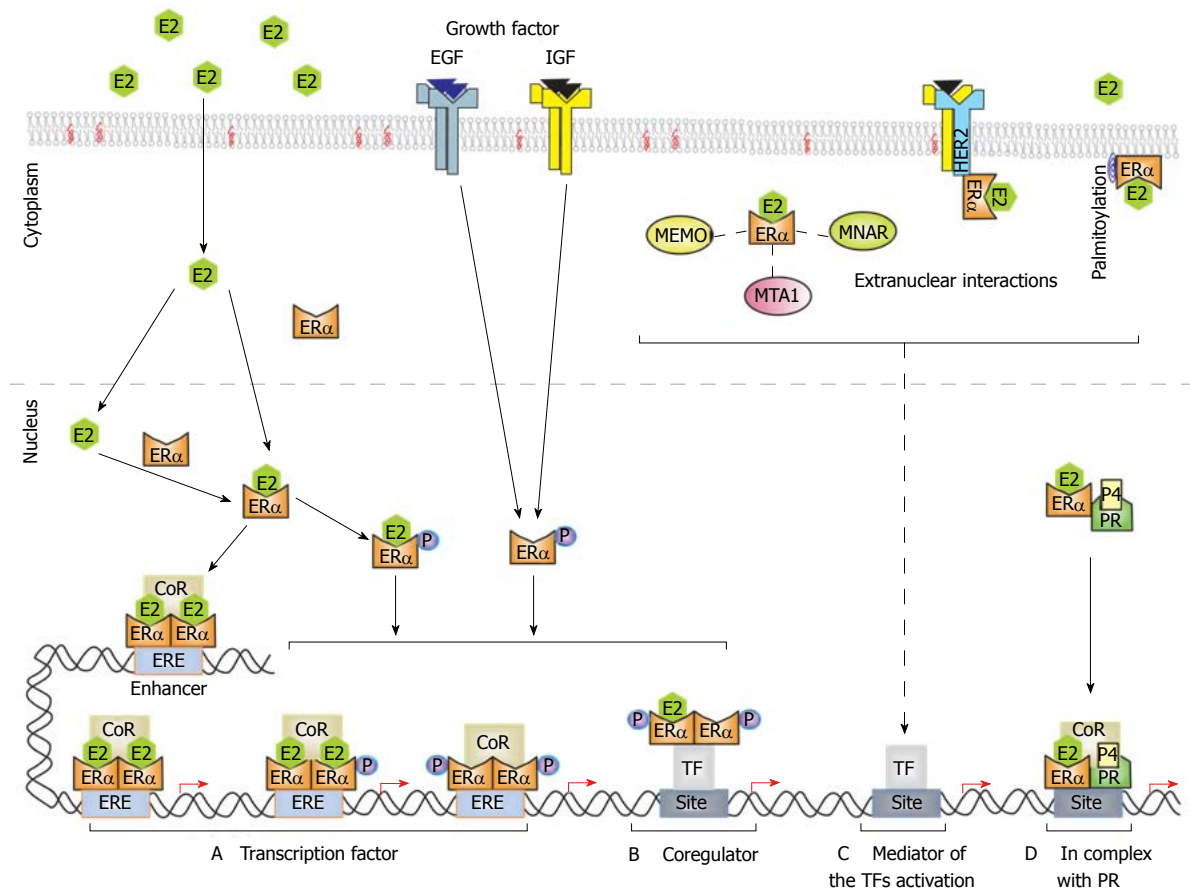


Figure 2 Nuclear and extranuclear signaling of estrogen receptor α . E2 binds to ER α in the cytoplasm and/or nucleus. Then ER α forms homodimers that recognize the ERE sequence (AGGTCAAnnnTGACCT) in target enhancers and promoters, recruiting coregulator (CoR) complexes such as coactivators to induce gene expression. ER α phosphorylation can be induced by E2 to modulate its activity as a transcription regulator. A and B: Growth factors (epidermal growth factor and insulin-like growth factor) also induce ER α phosphorylation in an E2-independent manner to promote ER α activity as a transcription factor or CoR for some transcription factors (*i.e.*, AP-1, Sp1, and NF- κ B); C: Cell membrane-associated ER α (via palmitoylation) associated with transmembrane receptors (*i.e.*, HER2) or with cytoplasmic proteins as (*i.e.*, MEMO, MTA1 and MNAR). These extranuclear interactions can induce kinase-dependent signaling that could finalize in the activation of some transcription factors; D: PR can associate with ER α to coordinate the binding of ER α to the chromatin modulating the expression of specific genes.

polyubiquitination and degradation *via* the UPS in breast cancer cells^[58]. Similarly, ABL (ABL proto-oncogene 1, non-receptor tyrosine kinase) interacts with and phosphorylates ER α at Y52 and Y219, increasing the ER α stability and resistance to Tam; both proteins are increased in breast tumor tissue samples^[62,63].

On the other hand, RB induces the assembly of ER α with chaperone proteins^[64]. Hence, retinoblastoma (RB) interacts with ER α , HSP90, and p23 in the cytoplasm to protect ER α from polyubiquitination and degradation by the UPS. ER α is highly ubiquitinated and degraded in RB-knockdown cells; however, its levels are restored with MG132 (a proteasome inhibitor) treatment in breast cancer^[64].

Interestingly, E3 ubiquitin ligases such as RNF8, RNF31, SHARPIN, and SMURF1 interact with ER α to block its polyubiquitination and to promote the proliferation of breast cancer cells. RNF8, RNF31, and SHARPIN inhibit ER α polyubiquitination by catalyzing monoubiquitination of this receptor, and as a result, ER α protein levels and E2-dependent transcriptional activity are enhanced in

breast cancer cells^[65]. SHARPIN could monoubiquitinate the ER α K302/303, but whether these residues are also modified by RNF8 and/or RNF31 is unclear. Moreover, RNF8 also acts as a coactivator for ER α in breast cancer cells. Instead, SMURF1 apparently inhibits polyubiquitination of ER α , but the implicated mechanisms need to be studied^[65-68].

Other proteins and modifications that inhibit ER α polyubiquitination

ER α polyubiquitination indirect inhibitors (EPII), intriguingly, the inhibition of ER α polyubiquitination also occurs with the help of other proteins that lack the ability to directly interact with ER α . For instance, it has been suggested that Src-dependent phosphorylation of ER α allows E6AP to polyubiquitinate and induce the degradation of this receptor. However, PEBP4 (phosphatidyl ethanolamine-binding protein 4) protein^[69,70] interacts with Src, blocking the phosphorylation and degradation of ER α induced by Src^[69].

Furthermore, although the mechanisms are unclear,

it has been reported that ER α protein levels decrease in cells with low levels of REG γ (PA28 γ , a nuclear proteasome coactivator), but when the proteasome is inhibited by MG132 treatment, ER α protein levels are recovered, suggesting that downregulation of REG γ promotes ER α polyubiquitination and degradation. High levels of REG γ and ER α in breast tumors correlated with poor prognosis in patients with breast cancer^[69].

Additionally, some posttranslational modifications are also associated with ER α polyubiquitination inhibition. Hence, ER α acetylation induced by trichostatin (a deacetylase inhibitor) increases the p300 levels and the stability of the receptor in breast cancer cells, but the mechanisms implicated need to be investigated (Figure 1)^[71]. Palmitoylation has also been linked to ER α polyubiquitination since it has been shown that the ER α mutants that cannot be palmitoylated are polyubiquitinated and degraded *via* UPS^[72].

Mutations and modifications that affect ER α polyubiquitination detected in mammary tumors from patients

ER α polyubiquitination has a clinical relevance, since mutations and/or posttranslational modifications such as phosphorylation in residues of ER α have been identified in tumor tissues from samples of patients with breast cancer, and these residues have been linked to the polyubiquitination and downregulation by degradation of this receptor. Thus, the Y537 residue is required for the ER α phosphorylation, and this modification subsequently promotes polyubiquitination and degradation of the receptor^[35]. However, mutations in the residues Y537N, Y537C, and Y537S are detected in mammary tumors of patients with metastasis and endocrine resistance. Accordingly, ER α polyubiquitination and degradation is prevented by experimentally induced mutations at the Y537 residue, and similarly, these mutations have been associated with the development of endocrine therapy resistance in breast cancer^[15,73,74]. In the same way, the K303 residue is needed for ER α polyubiquitination and degradation, but this residue has been identified to be mutated as K303R in tumors of patients who have poor survival outcome and prognosis^[46,74]. Other residues, such as S104, S106, S118, and S294, that seem to be related with ER α stability, have been found to be phosphorylated in breast tumor samples^[15,73].

ER α POLYUBIQUITINATION INHIBITION IN BREAST CANCER AS A KEY FACTOR FOR THERAPEUTIC STRATEGY

ER α polyubiquitination for its downregulation *via* the UPS, is a central mechanism of some endocrine therapies with SERDs, such as fulvestrant^[46,75]. Clearly, the induction of ER α polyubiquitination for its degradation decreases the abundance and pro-tumor activity of ER α , consequently

novel drugs including AZD9496^[76], GDC-0810^[77], bazedoxifene^[78], and RAD1901^[79] have been synthesized as SERDs, but more studies are required. Despite the importance of SERDs in the therapy of breast cancer, EPIP are promising targets for the management of this disease. Remarkably, the proteins that inhibit the ER α polyubiquitination are enhanced in ER α + breast cancers, contributing to disease progression. For this reason, EPIP may be useful as a biomarker for breast cancer and as a therapeutic target.

PIN1 is overexpressed in breast cancer and is related to mammary tumor growth, and epithelial-mesenchymal transition, and natural and synthetic inhibitors are being probed to control its activity^[55,57,80-87]. Similarly, LMTK3 overexpression stimulates cellular proliferation and tumor formation, and correlates with shorter survival times in ER α + breast cancer, and resistance to Tam treatment, but these events are reduced when LMTK3 expression is decreased^[58,88-90]. Moreover, CG0009, is a GSK3 inhibitor that decreases proliferation of breast cancer cells^[61,73,91-94].

Another molecule is RNF31, whose overexpression increases ER α protein levels, expression of ER α target genes and the growth of breast cancer cells, and these events are decreased when RNF31 is abated^[65]. Lastly, the loss of RB expression seems to be related to the loss of ER α stability in ER α negative (ER α -) breast cancers and with poor responses to hormonal therapies in patients^[64,95-98]. Thus, these proteins can be potential biomarkers and target for the treatment of ER α + breast cancer.

Among EPIIs, PEBP4 inhibits ER α polyubiquitination and enhances its transcriptional activity in breast cancer cells. Because PEBP4 is overexpressed in breast cancer and competes with ER α for components of the UPS, this protein may be an important target for breast cancer. Additionally, specific posttranslational modifications, such as palmitoylation, acetylation and phosphorylation, as well as, mutations of sites linked to ER α polyubiquitination and degradation, demands more research to find new strategies for detection and treatment of breast cancer.

Muc1 is an EPIP in breast cancer

Mucin 1 (MUC1) is a heterodimeric glycoprotein conformed by MUC1 N-terminal (MUC1-N) and MUC1 C-terminal (MUC1-C) subunits^[52]. MUC1-N is an extracellular glycosylated subunit and MUC1-C is a transmembrane subunit with a cytoplasmic domain that interacts with diverse proteins^[54]. MUC1 is localized on the apical borders in normal mammary epithelium, but under breast cancer conditions, it also localizes to the nucleus. An aberrant expression of MUC1-C is detected in breast cancer cells through a regulation loop that implicates Rab31 protein inhibits the lysosomal degradation of MUC1-C, and *Rab31* gene expression is induced by MUC1-C^[52-54,99]. Furthermore, *MUC1* is upregulated in 90% of breast cancers, where the expression of *Rab31* gene and other genes associated with endocrine resistance are modu-

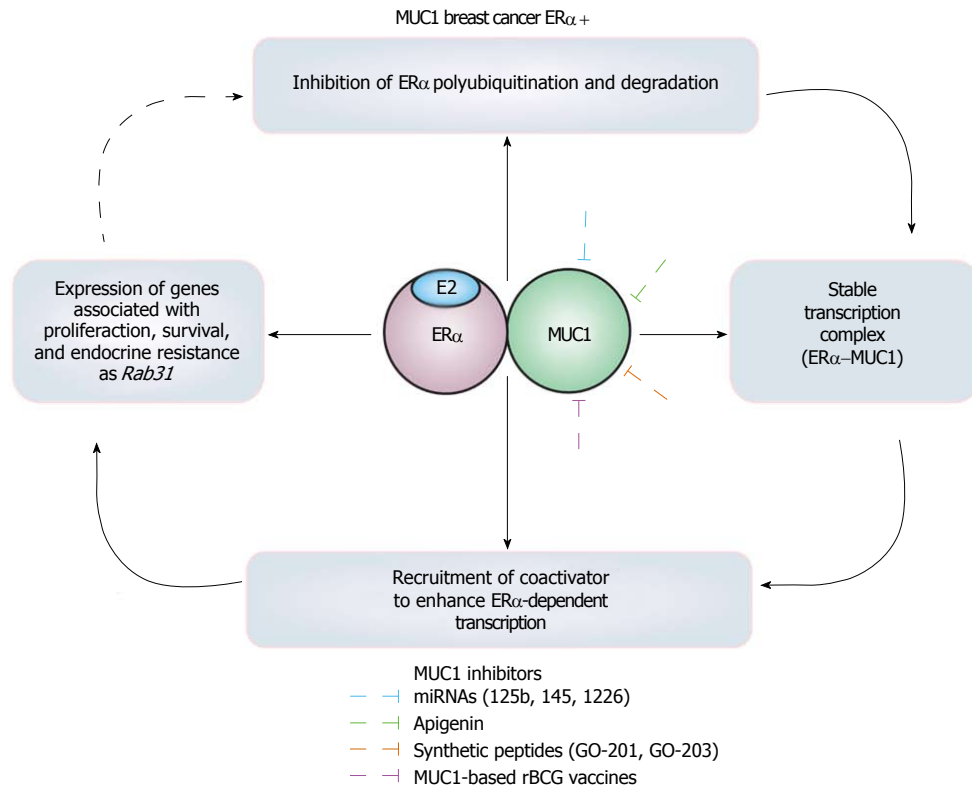


Figure 3 Mucin 1 is an estrogen receptor α polyubiquitination inhibitor protein in breast cancer cells.

lated by the MUC1-C/ER α complex. For these reasons, MUC1 has been suggested as a potential biomarker of breast cancer and predictor of resistance to Tam treatment^[51,100,101] (Figure 3).

Interestingly, MUC1-C subunit interacts with DBD of ER α promoting (1) Inhibition of ER α polyubiquitination maintaining high levels of this receptor; (2) a stable complex between MUC1-C and ER α ; and (3) an enhancement in the pro-tumor transcriptional activity of ER α since SRC1 and GRIP coactivators with histone acetyltransferase activity are recruited by MUC1^[50]. Thus, MUC1-C increases the growth and survival induced by E2 in breast cancer cells, but also transformation, loss of cellular polarity, cellular proliferation and migration, anchorage-independent growth, and tumorigenicity in transgenic mouse models^[51,99,102-104].

Remarkably, MUC1 is an EPIP involved in proliferation and endocrine resistance^[50,53,54,100,105], inhibited by miR-125b^[106], miR-145^[104], miR-1226^[103], and by specific siRNAs, inducing apoptosis, reducing cell proliferation, and increasing sensitivity to Tam^[100]. Similarly, apigenin^[107], and the synthetic peptides GO-201^[54] and GO-203^[100], affect localization and dimerization of MUC1, and as a result, tumor development is decreased, and sensitivity to Tam is increased^[54,100,107]. Moreover, MUC1-based rBCG (Bacillus Calmette-Guerin) vaccines induce anti-MUC immune responses inhibiting the growth of tumors in mice^[108,109]. Interestingly, high levels of Rab31 antigen have been associated with a proliferative status, a high tumor grade, and with poor 5-year disease-free survival

in patients with ER α + breast cancer. Consequently, the Rab31 antigen levels in mammary tumors have been suggested as a biomarker for ER α + breast cancers that may also be useful in the selection of patients for MUC1-targeted therapeutic strategies^[110].

CONCLUSION

Several mechanisms seem to cooperate to inhibit ER α polyubiquitination, decreasing its degradation in ER α + breast cancer cells. These cells become resistant to ER α polyubiquitination due to the evident upregulation of proteins, modifications, and mutations that protect it from ubiquitination. There is no pattern of the characteristics of the inhibitor or protector proteins for ER α polyubiquitination. Some of the reported EPIPs are MUC1, GSK3, LMTK3, RNF8, RNF31, SHARPIN, SMURF1, RB, and PIN1. All of them inhibit ER α polyubiquitination and its degradation in a dissimilar manner, *via* subcellular compartments or mechanisms. Some of them can be grouped as coactivators for ER α (MUC1, PIN1, and RNF8), kinases for ER α (GSK3, LMTK3, and ABL1), E3 ubiquitin ligase (RNF8, RNF31, SHARPIN, and SMURF1), and scaffold protein (RB). Amongst these different mechanisms, the participation of E3-ubiquitin ligases, such as RNF8, RNF31, and SHARPIN, are interesting, since they catalyze ER α monoubiquitination, suggesting a possible competition between monoubiquitination and polyubiquitination of this receptor.

Considering the findings described above, inhibition

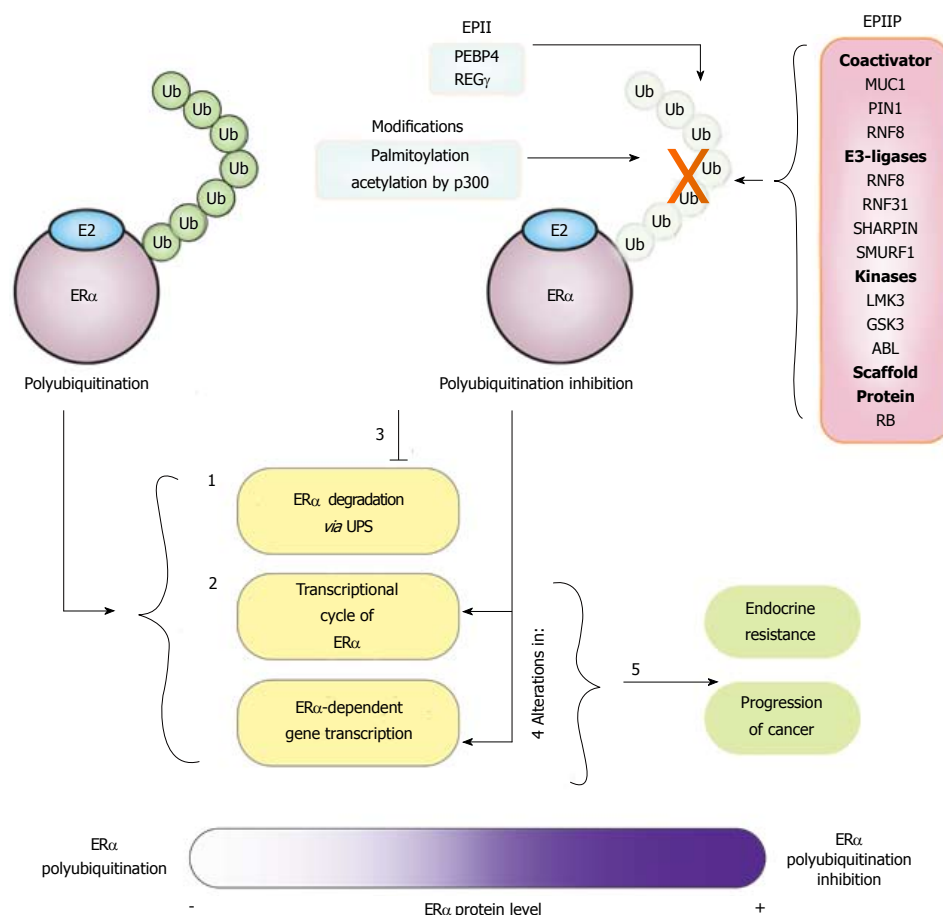


Figure 4 Mechanisms implicated in the estrogen receptor α polyubiquitination inhibition. Half-life of estrogen receptor α protein oscillates between 3-5 h under basal condition. E2 treatment induces ER α polyubiquitination, and as result: (1) Degradation of this receptor is promoted, decreasing its protein levels starting from 1h after treatment; (2) the ER α transcriptional cycle is activated. ER α polyubiquitination inhibitor proteins (EPIP) and ER α polyubiquitination indirect inhibitors (EPII) and other modifications increased in breast cancer cells can inhibit the basal and E2-induced polyubiquitination of ER α ; resulting in (3) the inhibition of its degradation and an enhancement in the ER α protein levels; (4) alterations in the transcription cycle of this receptor and the expression of its targets genes; and (5) these events seem to be associated with endocrine resistance and progression of breast cancer.

of ER α polyubiquitination, increases its abundance, and the expression of E2-dependent genes linked to proliferation and tumor development. In addition, inhibition of ER α polyubiquitination may have other serious implications, since it has been reported that this modification and proteasome activity are coupled to the transcriptional cycle of this receptor^[45]. Moreover, it has been proposed that high ER α protein levels are related to ER α binding to other DNA regulatory regions of genes that are atypically activated under this condition^[111]. Thus, inhibition of ER α polyubiquitination and its degradation increases the stability of this receptor, but also affects ER α /E2 signaling and its transcriptional activity, involved with the development of tumor and endocrine resistance^[111,112] (Figure 4).

Importantly, there is an interplay between inhibition of ER α polyubiquitination and endocrine therapy resistance in ER α + breast cancer, promoted by EPIP and EPII^[49,50,58,65]. In contrast, in luminal B breast cancers or ER α - breast cancers, RB is commonly lost or dysfunctional, leading to high levels of polyubiquitination and degradation of ER α , with a poor prognosis

for patients. Therefore, EPIP, EPII, and mutations and modifications that inhibit ER α polyubiquitination and degradation may act in a cooperative manner to enhance the stability of the receptor in the progression of breast cancer. Consequently, the mechanisms involved in the inhibition of ER α polyubiquitination represent useful biomarkers, therapeutic targets, and prognostic indicators of endocrine therapy in breast cancer.

In conclusion, EPIP, EPII, and mutations and modifications associated to ER α polyubiquitination inhibition, enhance the signaling pathways of this receptor. These findings represent a new field in breast cancer, for the establishment of potential biomarkers, as well as, in the design of effective therapeutic targets to control the progression of this disease. Integration between the molecular basis of ER α inhibition and its correlation with the progression of breast tumors remains to be elicited.

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