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MINIREVIEWS

Polyubiquitination inhibition of estrogen receptor alpha and its implications in breast cancer

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Abstract

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

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 (ERα) 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 17beta-estradiol hormone (E2), and a hinge region that connects the DBD and the LBD[1-3] (Figure 1). Many nuclear functions of ERα are triggered by the binding of E2 to the receptor[4,5], inducing ERα 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 ERα 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 ERα and other signaling pathways: ERα acts as a coregulator by interacting with other transcription factors, such as activator protein 1 (AP-1), specificity protein 1 (Sp1), and nuclear factor-κB (NF-κB)[3,5,13-17]. Additionally, ERα 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 ERα interacting protein that modulates and re–directs the binding of ERα to the chromatin and the expression of specific genes in breast cancer cells [21] (Figure 2).

ERα 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, ERα 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 ERα are connected and are critical in about 70% of breast cancer cases (ERα+ breast cancer)[13,24,25]. Consequently, ERα 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 ERα to inhibit its transcriptional activity, as well as, *via* the use of selective estrogen receptor degraders (SERDs) such as fulvestrant that decreases the ERα stability[8,14,26,27]. The acquisition of resistance to these treatments commonly occurs in ERα+ breast cancer, and although the mechanisms are unclear, the extranuclear signaling of ERα is strongly activated under this condition[19,20,26,28-31].

The activation or inhibition of ERα 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 ERα+ breast cancers to inhibit ERα 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 ERα IN BREAST CANCER CELLS

ERα is a monoubiquitination and polyubiquitination-target. However, fewer reports are available to demonstrate monoubiquitination of ERα, in comparison to those that exhibit polyubiquitination of this receptor. Nevertheless, these studies clearly show that ERα 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 ERα 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 ERα lysine residues is mediated by several E3 ubiquitin ligases for ERα, that include CHIP[34], E6AP[35], BRCA1[36], BARD1[37], SKP2[38], MDM2[39], and Hbo1[40]. Importantly, E2 treatment induces ERα polyubiquitination, followed by its degradation by the UPS[14,17,33,41-43].

Although polyubiquitination leads to ERα 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 ERα. Likewise, it has been evidenced that ERα 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 ERα, 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 ERα[17,44,45].

ERα 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 ERα stability in untreated breast cancer cells[46]. Against this background, it maybe envisaged that, several factors delicately modulate the stability and degradation of ERα, which may be altered

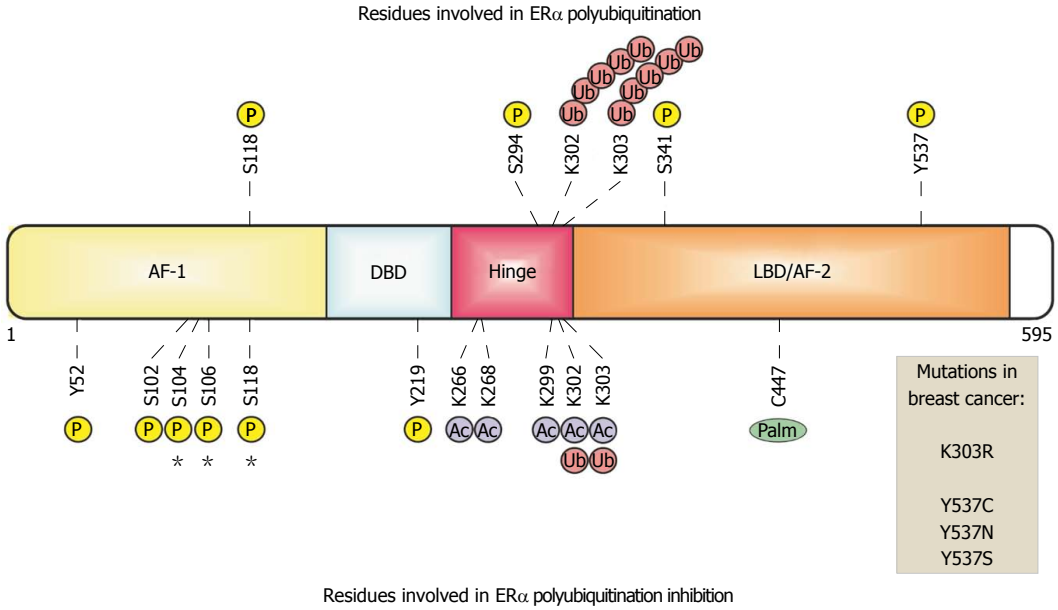

Figure 1 Estrogen receptor α in breast cancer cells. ERα is organized in functional domains. The transactivation domains AF-1 and AF-2 recruit both coactivators and corepressors. The DNA-binding domain (DBD) recognizes and binds to estrogen response elements in enhancers or promoters. The ligand-binding 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 ERα polyubiquitination. Sites of phosphorylation or mutations in ERα that have been identified in breast–cancer biopsy samples are indicated.

in breast cancer.

Additionally, the ubiquitination of ERα 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 ERα in breast cancer. The main residues of ERα 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 ERα, where, first, the ERα Y537 residue is phosphorylated by Src kinase in E2-treated cells, followed by E6AP, an E3-ubiquitin ligase, which induces ERα polyubiquitination and its degradation[35]. Thus, phosphorylation and ubiquitination of ERα are interconnected in order to control both, the abundance and the functions of this receptor.

IS ERα IN BREAST CANCER CELLS POLYUBIQUITINATED AND DEGRADED?

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

ERα polyubiquitination inhibitor proteins in breast cancer cells

ERα polyubiquitination inhibitor proteins (EPIP). There has been a progressive increase in the number of ERα 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 ERα, 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 ERα 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 ERα phosphorylated at S118, inducing its cis/trans isomerization. Moreover, PIN1 blocks the polyubiquitination and degradation of ERα by preventing its interaction with the E6AP E3 ligase, hence enhancing its stability, binding to EREs, and the subsequent transcriptional activity of ERα[10,49,55-57]. High levels of PIN1 and ERα, and low levels of E6AP are observed in endocrine resistance[49].

Other examples are GSK3, LMTK3, and ABL1 kinases that phosphorylate ERα to inhibit its polyubiquitination[58,59]. First, the glycogen synthase kinase-3 (GSK3) isoforms interact with and phosphorylate ERα 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 ERα to protect it from

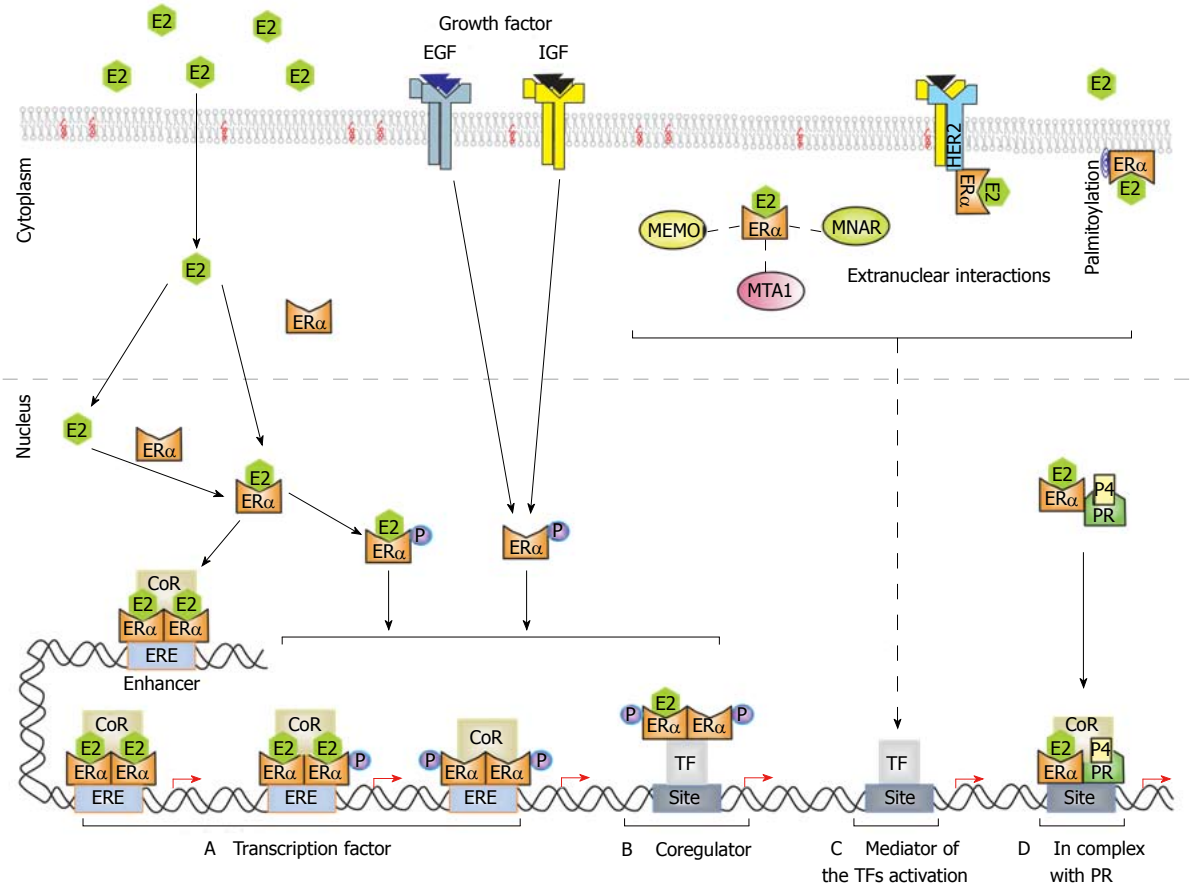

Figure 2 Nuclear and extranuclear signaling of estrogen receptor α. E2 binds to ERα in the cytoplasm and/or nucleus. Then ERα forms homodimers that recognize the ERE sequence (AGGTCAnnnTGACCT) in target enhancers and promoters, recruiting coregulator (CoR) complexes such as coactivators to induce gene expression. ERα 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 ERα phosphorylation in an E2-independent manner to promote ERα activity as a transcription factor or CoR for some transcription factors (*i.e.*, AP-1, Sp1, and NF-κB); C: Cell membrane-associated ERα (*via* palmitoylation) associated with transmembranal receptors (*i.e.*, HER2) or with cytoplasmatic 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 ERα to coordinate the binding of ERα 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 ERα at Y52 and Y219, increasing the ERα 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 ERα with chaperone proteins[64]. Hence, retinoblastoma (RB) interacts with ERα, HSP90, and p23 in the cytoplasm to protect ERα from polyubiquitination and degradation by the UPS. ERα 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 ERα to block its polyubiquitination and to promote the proliferation of breast cancer cells. RNF8, RNF31, and SHARPIN inhibit ERα polyubiquitination by catalyzing monoubiquitination of this receptor, and as a result, ERα protein levels and E2-dependent transcriptional activity are enhanced in breast cancer cells[65]. SHARPIN could monoubiquitinate the ERα K302/303, but whether these residues are also modified by RNF8 and/or RNF31 is unclear. Moreover, RNF8 also acts as a coactivator for ERα in breast cancer cells. Instead, SMURF1 apparently inhibits polyubiquitination of ERα, but the implicated mechanisms need to be studied[65-68].

Other proteins and modifications that inhibit ERα polyubiquitination

ERα polyubiquitination indirect inhibitors (EPII), intriguingly, the inhibition of ERα polyubiquitination also occurs with the help of other proteins that lack the ability to directly interact with ERα. For instance, it has been suggested that Src-dependent phosphorylation of ERα 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 ERα induced by Src[69].

Furthermore, although the mechanisms are unclear,

it has been reported that ERα protein levels decrease in cells with low levels of REGγ (PA28γ, a nuclear proteasome coactivator), but when the proteasome is inhibited by MG132 treatment, ERα protein levels are recovered, suggesting that downregulation of REGγ promotes ERα polyubiquitination and degradation. High levels of REGγ and ERα in breast tumors correlated with poor prognosis in patients with breast cancer[69].

Additionally, some posttranslational modifications are also associated with ERα polyubiquitination inhibition. Hence, ERα 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 ERα polyubiquitination since it has been shown that the ERα mutants that cannot be palmitoylated are polyubiquitinated and degraded *via* UPS[72].

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

ERα polyubiquitination has a clinical relevance, since mutations and/or posttranslational modifications such as phosphorylation in residues of ERα 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 ERα 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, ERα 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 ERα 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 ERα stability, have been found to be phosphorylated in breast tumor samples[15,73].

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

ERα 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 ERα polyubiquitination for its degradation decreases the abundance and pro-tumor activity of ERα, consequently novel drugs including AZD9496[76], GDC-0810[77], bazedoxifene[78], and RAD1901[79] have been synthetized 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 ERα polyubiquitination are enhanced in ERα+ 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 ERα+ 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 ERα protein levels, expression of ERα 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 ERα stability in ERα negative (ERα−) 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 ERα+ breast cancer.

Among EPIIs, PEBP4 inhibits ERα polyubiquitination and enhances its transcriptional activity in breast cancer cells. Because PEBP4 is overexpressed in breast cancer and competes with ERα 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 ERα 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-

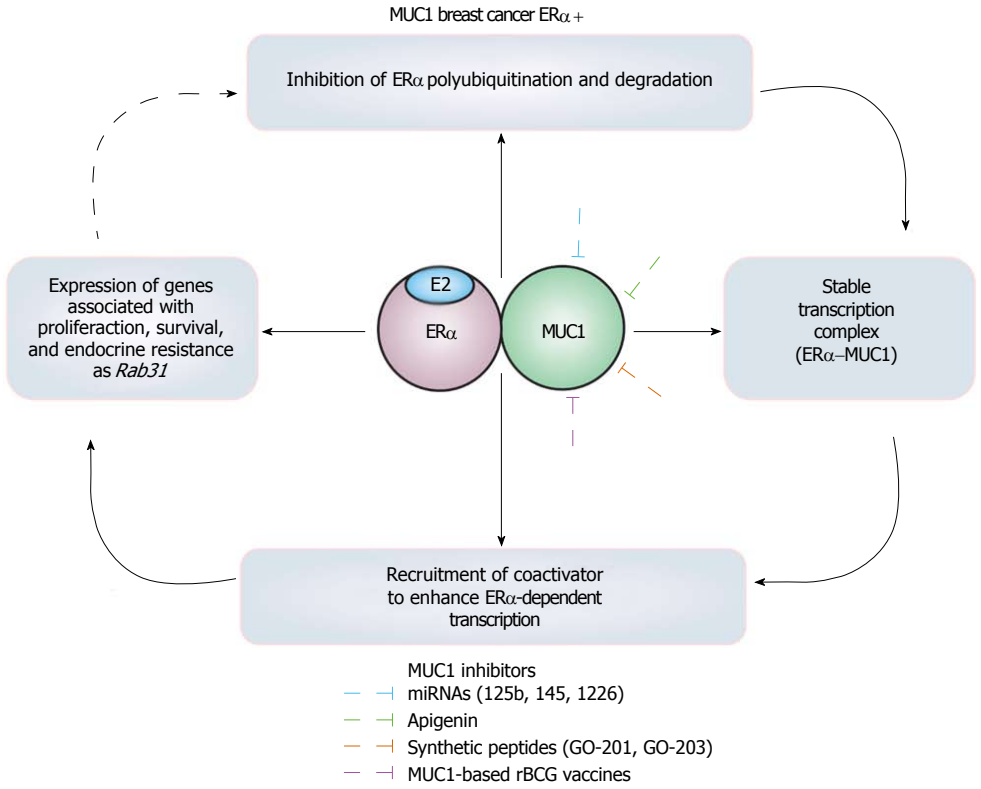

Figure 3 Mucin 1 is an estrogen receptor α polyubiquitination inhibitor protein in breast cancer cells.

lated by the MUC1-C/ERα 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 ERα promoting (1) Inhibition of ERα polyubiquitination maintaining high levels of this receptor; (2) a stable complex between MUC1-C and ERα; and (3) an enhancement in the pro-tumor transcriptional activity of ERα 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 ERα+ breast cancer. Consequently, the Rab31 antigen levels in mammary tumors have been suggested as a biomarker for ERα+ breast cancers that may also to be useful in the selection of patients for MUC1-targeted therapeutic strategies[110].

CONCLUSION

Several mechanisms seem to cooperate to inhibit ERα polyubiquitination, decreasing its degradation in ERα+ breast cancer cells. These cells become resistant to ERα 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 ERα polyubiquitination. Some of the reported EPIPs are MUC1, GSK3, LMTK3, RNF8, RNF31, SHARPIN, SMURF1, RB, and PIN1. All of them inhibit ERα polyubiquitination and its degradation in a dissimilar manner, *via* subcellular compartments or mechanisms. Some of them can be grouped as coactivators for ERα (MUC1, PIN1, and RNF8), kinases for ERα (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 ERα monoubiquitination, suggesting a possible competition between monoubiquitination and polyubiquitination of this receptor.

Considering the findings described above, inhibition

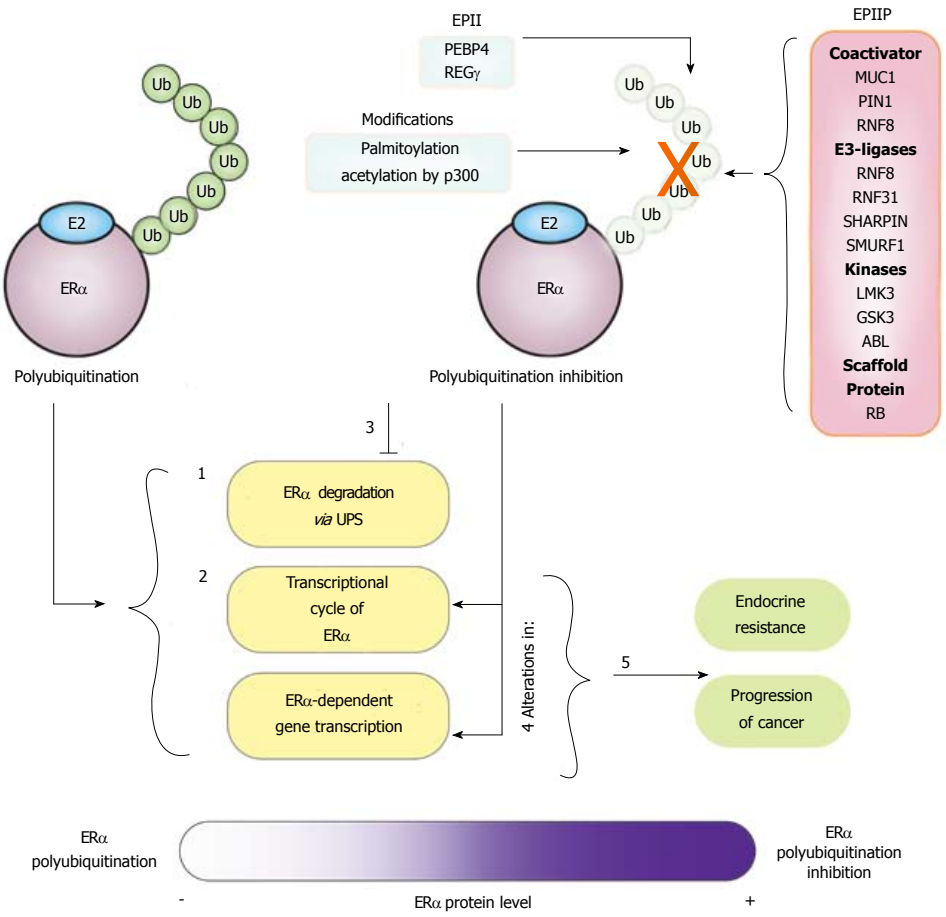

Figure 4 Mechanisms implicated in the estrogen receptor α polyubiquitination inhibition. Half-life of estrogen receptor α protein oscillates between 3-5 h under basal condition. E2 treatment induces ERα polyubiquitination, and as result: (1) Degradation of this receptor is promoted, decreasing its protein levels starting from 1h after treatment; (2) the ERα transcriptional cycle is activated. ERα polyubiquitination inhibitor proteins (EPIP) and ERα polyubiquitination indirect inhibitors (EPII) and other modifications increased in breast cancer cells can inhibit the basal and E2-induced polyubiquitination of ERα; resulting in (3) the inhibition of its degradation and an enhancement in the ERα 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 ERα polyubiquitination, increases its abundance, and the expression of E2-dependent genes linked to proliferation and tumor development. In addition, inhibition of ERα 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 ERα protein levels are related to ERα binding to other DNA regulatory regions of genes that are atypically activated under this condition[111]. Thus, inhibition of ERα polyubiquitination and its degradation increases the stability of this receptor, but also affects ERα/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 ERα polyubiquitination and endocrine therapy resistance in ERα+ breast cancer, promoted by EPIP and EPII [49,50,58,65]. In contrast, in luminal B breast cancers or ERα− breast cancers, RB is commonly lost or dysfunctional, leading to high levels of polyubiquitination and degradation of ERα, with a poor prognosis for patients. Therefore, EPIP, EPII, and mutations and modifications that inhibit ERα 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 ERα 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 ERα 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 ERα inhibition and its correlation with the progression of breast tumors remains to be elicited.

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