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Review
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Molecular mechanisms affecting estrogen receptor levels in breast cancer

Meme kanserinde östrojen reseptör seviyelerini etkileyen moleküler mekanizmalar

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Abstract

The initiation of breast cancer, estrogen and its receptor (ER) perform significant functions. ER has two dissimilar forms, and they are commonly called as ER-alpha (-α) and ER-beta (-β). ERs are transcription factors. Expressions of ER-alpha (-α) protein are mainly arranged by the pathway of ubiquitin-proteasome. The hormone-responsive gene expression modulated by ER-α in addition to other nuclear receptors is a complicated process, which involves various cellular responses. And also, ER-α levels are related with the pathology and etiology of breast cancer. In this review which is about the transcription and expression of the ER-α gene may provide the find out biochemical mechanisms behind the breast carcinogenesis. The regulation of ER expression, histone-modifying enzymes, Progesterone receptor (PR), peroxisome proliferator-activated receptors (PPAR), hydrocarbon receptor (AhR), Glucocorticoid receptor (GR), hypoxia and lysine residuals in ER region described in detail in this work. Increasing the number of these studies, are very significant for developing new methods of estrogen-dependent cancers.

Keywords: Breast cancer, Estrogen receptors, Progesterone receptor, Peroxisome proliferator-activated receptor, Aryl hydrocarbon receptor, Glucocorticoid receptor

Öz

Meme kanserinin tetiklenmesinde, östrojen ve reseptörünün (ER) önemli işlevleri bulunmaktadır. ER'nin iki farklı şekli yer almakta ve bunlar ER-alfa (-α) ve ER-beta (-β) olarak adlandırılmaktadır. ER'ler birer transkripsiyon faktörüdür. ER-alfa (-α) proteininin ifadeleri esas olarak ubikuitin-proteazom yolağı ile düzenlenmektedir. Diğer nükleer reseptörlere ek olarak ER-alfa tarafından modüle edilen hormona duyarlı gen ekspresyonu, çeşitli hücresel tepkimeleri içeren karmaşık bir moleküler süreçtir. Ayrıca ER-α düzeyleri, meme kanseri patolojisi ve etyolojisi ile de ilişkilendirilmektedir. ER-α geninin transkripsiyonu ve ekspresyonu ile ilgili olan bu derleme yoluyla meme karsinojenezinin alt yapısında yer alan biyokimyasal mekanizmaların daha net anlaşılabileceği düşünülmektedir. ER ekspresyonu, histon değiştirici enzimler, Progesteron reseptörü (PR), peroksizom proliferatörü ile aktive edilmiş reseptörler (PPAR), aril-hidrokarbon reseptörü (AhR), Glukokortikoid reseptörü (GR), hipoksi ve ER bölgesinde yer alan lizinin kalıntılarının regülasyonu bu derlemede detaylı bir biçimde anlatılmaktadır. Buna benzer çalışmaların sayısının artırılması, östrojen bağımlı kanserler için yeni yöntemlerin geliştirilmesi açısından oldukça önemlidir.

Anahtar kelimeler: Meme kanseri, Östrojen reseptörleri, Progesteron reseptörü, Peroksizom proliferatör aktive reseptör, Aril hidrokarbon reseptörü, Glukokortikoid reseptörü

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Introduction

In current works show that, estrogen associated with the function and differentiation of the gland of mammary. Estrogen hormone performs its molecular affect by binding to its receptors, ER-α and ER-β [1]. Besides these knowledge, the expression of ER-α is related with breast cancer etiology, especially the growth of tumor. Beside of these explanations, it was shown that the expression levels of ER-α is more suitable as a marker for the treatment of breast cancer [2]. For this reasons; in this present study, we have been investigating the regulation of ER expression, histone-modifying enzymes, Glucocorticoid receptor (GR), peroxisome proliferator-activated receptors (PPAR), hydrocarbon receptor (AhR), Progesterone receptor (PR), hypoxia and lysine residuals in ER region [1,2].

Histone deacetylase inhibitors and ER alpha

Histone acetylation remains among the widely studied topics and plays different roles especially in the formation of nucleosome. For instance, lysine acetylation causes changes in the structure of chromatin and by reducing histone-DNA interaction; it induces DNA to provide transcriptional activation [3].

Abnormal activation or deactivation of the transcription depends on the condition of histone acetylation and correlates with tumorigenesis [4]. Via different analyses, histone deacetylases (HDAC) are widely characterized, and they cause the development of most of the specific malignancy forms associated with cellular oncogenes and tumor suppressor genes [5]. Histone deacetylases (HDAC) regulate the expressions of the tumor suppressor genes and affect the triggering or progression of cancer by manipulating the activities of transcriptional factors over the changes in DNA and the structure of chromatin components [6]. Recently, with the acetylations detected in cancer patients via clinical applications using HDAC inhibitors, gene suppressions have been realized by certain regulation mechanisms. Since HDAC inhibitors involve anti-cancer functions, they are among the new therapeutic drug classes in different types of cancer [7].

Estrogen shows the proliferative response in breast epithelium cells by activating ER mediative CCND1 (codes Cyclin D1) gene transcription [8]. CCND1 promoter does not include estrogen response element (ERE). CCND1 realizes the ER alpha up regulation via cyclic-AMP response element (CRE) in the promotor [9]. Decreasing of cyclin D1 mRNA and protein expression is the most important indicator of early antiestrogenic effect [10]. The induction of the increase in the cyclin D1 expression causes resistance against antiestrogens [11]. Cyclin D1 induces the ER-α transcription over ERE sequences in genes regulated with estrogen by binding to ER-α with and without ligand bonds. As a result, Cyclin D shows the increase in ER-α by boosting the transcriptions of the genes with ERE with or without estrogen presence [12].

Cyclin D1 bypasses the estrogen requirements of ER-α positive breast cancer cells, realizes the advanced expression increase free of estrogen, and is not inhibited via antiestrogens [12]. Trichostatin A (TSA) which includes in HDAC inhibitors class, prevents the proliferation of tumor cells in breast cancer cell lines. In studies which is performed by in vivo, this effect is realized by increasing the shift to the resting period in cell cycle, the differentiation or apoptosis [13].

Cellular control of the D type-cyclins is realized via cell cycle and CDK4 and CDK6 activations of cyclin dependent kinase partners mediates this control. Retinoblastoma proteins are phosphorylated with CDK4 and CDK6 activations and E2F oscillation from the transcription factor family is realized [14].

Normally, cyclin D1 accumulation is strictly regulated. However, in almost 50% of the certain type of breast cancer, several expressions of cyclins have been reported. Cyclin D1 expression in overs can be observed in all breast cancers histopathologic types and it is especially correlated with metastasis [12].

In the studies demonstrated that the deficiency of the protein cyclin D1 which localized in breast tissues of transgenic mice with neu and ras oncogenes induced breast cancer causes resistance against breast cancer [15]. Cyclin D1 can be severely expressed via CCND1 gene amplification, chromosomal translocation and Cyclin D1-mRNA stabilization. Cyclin E, p21, p27, E2F-1 of D type cyclins are induced with ubiquitin and degraded in 26 S proteasomes. Cyclin D1 is made a target for ubiquitination by being phosphorylated from 286th threonine residual via glycogen synthesis kinase 3B [16]. In the current analyses, tamoxifen is also detected to inhibit cyclin D1 transcription via ER alpha.

PPAR and ER alpha

PPAR is a transcription factor and activation of PPAR is a multi-phased process and it includes ligand binding, heterodimerization with Retionic X Receptors (RXR) showing DR1 or DR2 motif structure repeating with one or two nucleotide gaps, its interaction with line specific gene promotor elements, enabling of various co-activators and inclusion into the structure of other nuclear co-regulator proteins, and thus activation of various target genes in this way [8,9].

There are three sub-types with the high incidence of sequence protection. Firstly, PPAR alpha 3 has been reported in 1990, and PPARδ (or PPARβ), and PPARγ isomers have been revealed in various laboratory trials. These isomers are formed as a result of using alternative splicing and different promotors [17].

In current studies demonstrate that PPARα acts a pivotal function in the metabolism of lipoproteins and fatty acids. Studies which is conducted on rodents about peroxisome proliferators, although carcinogenic results are obtained in the rodent livers, this affective mechanism has been reported to be different from the epidemiological studies on humans [18].

In terms of the studies on the relation between PPARδ and oncogenes, there are controversial roles especially on the molecular bases of colon cancer ethiology. Current studies dedicated that PPARδ induces tumorigenesis and cell proliferation [19]. Beside these, Prostaglandin J2 (PGJ2) is the most important activator of PPAR gamma [20].

Another study has been shown that Cyclin D1 and ER alpha down regulation by PPAR gamma agonists is banned via cell proteasome inhibitors MG 132 and PS II applications, but the treatments of calpain II and calpeptin of the protease inhibitors do not cause the same inhibition condition [21]. New anticancer drugs have been tried to be developed dependent on PPAR gamma because of its wide expression in various tumor

types and cell lines and its antiproliferative effect. For instance, in one of the new studies, PPAR gamma expression has been determined in 339 clinic tumor samples (in the studies with patient profiles of colon, breast, lung, prostate, glioblastoma and leukemia cancers) [22].

Aryl hydrocarbon receptors (AhR) and ER alpha

Aryl hydrocarbon receptors (AhR) are transcription factors activated with ligand [23]. AhR proteins play an adaptor and sensor role in the environmental xenobiotic exposure [24]. In cytosol, they contribute to the toxicity induced via xenobiotics and carcinogenesis especially in the absence of ligands [25]. In the recent studies, it has been shown that signal inhibition of ERs is associated with AhR activated via ligand. In the studies on rodent models, selective AhR modulators are observed to highly inhibit the estrogen induced gene expression and estrogen dependent breast tumor growth [26]. TCDD is an environmental toxin and causes damage on various endocrine signal systems by activating AhRs. When human breast cancer cell lines (MCF-7, ZR-75, T47D) are treated with TCDD, it is observed that ER alpha induces proteasomal degradation [27]. T47D, expresses both ER alpha and beta. When the cells belonging to this cancer line are treated with 17-beta estradiol and TCDD, a rapid decrease is observed in the ER levels depending on the proteasomal degradation. E2 application does not affect AhR, but TCDD degrades both ER and AhR in T47D and MCF-7 cell lines depending on the proteasome [28]. Studies showed that this response is blocked with proteasome inhibitors [27]. In the previous studies, it has been observed that TCDD down regulates ER alpha in rat uterus and breast cancer cells, and there is a mutual relation between AhR-ER alpha inhibitor links [29]. In another study, TCDD applied with 17-beta estradiol (E_2) is observed to cause ER alpha and AhR degradation in a proteasomal way and especially TCDD down regulates AhR in in vivo and in vitro media [30].

Glucocorticoid receptors (GR) - ER crosstalk

Glucocorticoid receptors (GR) are included in nuclear hormone family and they provide the repression of gene expression [31]. In a ligand bound position, GR gene expression is triggered or repressed depending on the cell type [32]. For example, while GR activation induces apoptosis in lymphocytes, it causes inhibition of apoptosis in breast epithelial cells [33]. Both GR and ER are nuclear receptors included in the steroid hormone receptor family [20]. Both GR and ER have significant functions in various different tissues. Both receptors are expressed in tissues and have opposite roles in estrogen activities of glucocorticoids. For instance, while glucocorticoids show antiproliferative effect in mammary gland, estrogens demonstrate an increasing effect in cell growth and proliferation. Glucocorticoids induce bone resorption in bones but estrogens impede this function. Even if estrogens and glucocorticoids are included in different biological processes in the same cell content, mutual interaction mechanisms have not been clarified between GR and ER signal pathways [34].

In a model developed in a study, MCF-7's potential mechanism in the regulation of ligand dependent ER's glucocorticoid receptor mediative transcription has been analyzed. This study has reported that GR down regulated via ER and realizes this over the pathway of proteasome degradation. The decrease in the GR levels is related with the augment of Mdm2 protein expression (E3 ubiquitin ligase) and thus GR is targeted for proteasome [34].

Hypoxia and ER alpha

Hypoxia and low oxygen ranks take place for the period of neovascularization in various tissues. When tumors subjected to these conditions, it has been shown that the tumor's growth, proliferations, metastases processes change in the metabolism [35]. Cellular adaptation to hypoxic medium affects glucose transportation and metabolism, angiogenesis, gene activations responsible in erythropoiesis and down regulates the beta oxidation pathway of the fatty acids [36]. Regulation ways of the genes induced with hypoxia are realized via the expressions of several transcriptional factors at different levels. For example, factor 1 alpha (HIF1-alpha) induced with hypoxia, several hypoxia tissues and tumors increase and promotors of the genes regulated via low oxygen levels especially include hypoxic response elements - (HREs) specific to this factor [37]. HIF1-alpha with protein levels too low to determine in normal tissues can be identified because of the increase in the expression in many tumor types [37]. Another study has determined a linear correlation between HIF1-alpha expression and neovascularization in brain tumors. In many histopathologically classified breast cancer types, depending on the increase in the pathologic level of tumor, an increase has also been identified in HIF1-alpha level and these kinds of tumors are associated with more aggressive and lower lifespans. The increase of HIF-1 alpha levels in breast tumors is in a linear relationship with VEGF and ER alpha increases. ER alpha positive tumors better responds to endocrine treatment than ER alpha negative aggressive tumors, and an increase can be detected in these kinds of patients [38]. Paradoxically, ER alpha levels are caused by its being a negative prognostic factor just like VEGF and HIF1-alpha [39]. A study has researched E_2's induction of VEGF gene expression in ER positive ZR75 cell line, the change in the HIF1-alpha and ER alpha protein levels in two cell lines under 1% low oxygen conditions, and its effect on transactivation depending on the hormone [40]. When ZR-75 cell line cells are released into growth media at normal oxygen levels (21% O_2) or under hypoxic conditions (1% O_2 or cobalt chloride), it is determined that factor 1 alpha (HIF-1 alpha) protein induced with hypoxia under hypoxic condition is induced after a 3-hour application, and ER alpha protein levels show an important decrease within 6-12 hours [41]. This response is determined to be blocked via proteasome inhibitor MG-132. In addition, under hypoxic condition, while a minimal decrease occurs in cellular Sp1 protein, ER alpha mRNA level is preserved. On the other hand, hypoxic conditions have been determined to decrease the Sp2 gene expressions (mRNA) levels induced with 17-beta estradiol in ZR-75 cells [41].

The connection of Progesterone receptors (PR) to ER

Advanced breast cancer often occurs through lack of steroid hormone receptor or because of resistance to endocrine therapies. More than 95% of the breast cancers are degraded within 6 hours after progestin application. However, the root causes under this down regulation is still unknown [42]. PR are prognostic determiners of breast cancer. In the lack of PR

receptors, sensitivity to growth factors increases concerning the formation of aggressive tumor phenotype [43].

PR are also included in this receptor class. After an 6-8 hour treatment with progestins, one of the ligands, PR are largely down regulated, but the root causes of this regulation is not completely clear yet [44].

The expression of PR regulated and modulated by means of ligands happens both at protein and mRNA levels. The decrease in the PR mRNA level occurs after a 4-20 hours progestin application, and PR mRNA level returns to the previous level within 24-48 hours. On the other hand, the relationship between two PR isoform levels in the PR mRNA fluctuation has not been clarified yet [44]. One or two receptor isoforms can be coded in order to the variation of PR transcripts. Alongside the diversity in the PR mRNA and protein levels are intensely down regulated by binding the specific ligand. After the biosynthetic application of endogenous PRs with H^2, N^{15} and C^{13}, densely found control cells of amino acids have been reported to incur turnover within 21 hours compared to control cells. Besides, half-life is 6 hours in progestin applied cells.

In a current study, the effects of mitogen activated kinases (MAPKs) on PR phosphorylation have been investigated [44,45]. In this research, changing S294A mutation of PR serine residual with alanine is shown and it is determined that this mutation completely hinders the ligand dependent down regulation. These results show that PR breakdown is realized in two alternative ways via 26S proteasome. Especially mature PR down regulation is realized with the activation by ligand binding of PR phosphorylation of serine residuals by MAPKs, and followed by the degradation of the targets in receptor [44,45].

Lysine residuals in ER region

Cellular levels of ER alpha are regulated with ubiquitin dependent proteasome pathway. Thanks to the dynamic relation between ER alpha and protein degradation machine, polyubiquitination of the receptor's lysine residuals easily via down regulation process. Today, lysines controlling the receptor degradation have not been fully clarified. In different studies, two lysines of receptor, K302 and K303, are localized in the hinge region of ER alpha and accompany several regulator functions [34]. While the influence of monoubiquitination of K302 on the ER alpha stability is not clear, the special effects of lysines in the hinge region on post-translational modification have been revealed and these regions have been determined to be suitable places for polyubiquitination [46].

Maturation of ER alpha involves a transactivation process realized via the interaction of receptor with co-chaperones after the binding of ligates to the receptor [47]. In the analyses, several chaperones have been identified. Hsp 70 and Hsp 90 are among them. Chaperones mediate ER alpha progression, and realize this by easing the interaction of ER alpha with co-chaperones via some folding models. CHIP (an E3 ubiquitin ligase), Bag 1 and p23 are among these co-chaperones [48]. At the same time, geldanamycin (GA) increases ER alpha's CHIP relation with Hsp 90 and also increases receptor degradation in the lack of ligand [49]. Co-chaperone Bag 1 and p23 are reported to be included in the Hsp 90-ER alpha complex. However, the roles of co-chaperone Bag 1 and p23 in the receptor turnover have not been clarified yet. Bag 1 is mostly included in the receptor-chaperone complex, and enables the interaction of Hsp related proteins with proteasome via N terminal ubiquitin domain of Bag 1 [50]. By this way, Bag 1 increases the receptor degradation. By being included in the mature receptor-Hsp complex, p23 increases both ligand and basal prompted receptor transactivation [51]. Besides, p23 contend for the link between CHIP and receptor, but p23 has no stabilizing effect on ER alpha. The results of the previous studies show that Bag 1 and P23 may have functional roles in receptor turnovers [52]. In another analysis, ER alpha negative breast cancer cell line C4-1 is used. This line expresses the ER alpha types including the lysine-alanine change in both wild type and K302-303 regions. The polyubiquitination of ER alpha, turnover and receptor co-chaperone interactions of these lysines have been analyzed over C4-12 line. Under the condition without ligand binding, it has been revealed that ER alpha AA rapidly incurs polyubiquitination compared to wild-type (wt) ER alpha cells. The reason for this is the increasing relation of ER alpha-AA with Hsc70 interacting protein (CHIP) Ubiquitin ligase carboxyl terminal and its link with proteasome related co-chaperone Bag 1 [46].

Under the condition with ligand binding, it has been determined that a rapid degradation occurs in wt ER alpha with ubiquitin proteasome pathway after the application of C4-12 cells with both 17-beta estradiol and pure antiestrogen ICI 182,780. On the other hand, in the existance of these ligands, ER alpha AA degrades at a lower level. Moreover, ER alpha AA has been reported to be more resistant to ICI induced polyubiquitination. These two lysine mechanism have a different role in the polyubiquitinated and ICI induced receptor down regulation as a response to antiestrogens. Under the conditions without ligand binding, ER alpha AA's stability decreases and degrades, and under the condition without ligand binding, its stability increases [46].

As a result, K302-303 lysines protects ER alpha without ligand binding from basal turnover by inhibiting CHIP-Bag 1 interaction and inducing the receptors' p23 relation. Therefore, new roles have been revealed for these lysines in the receptor turnover regulation [46].

Conclusion

Increasing the number of related revisions of the function, levels and degradation of ERs, particularly from the side of cancer-specific occurrences, are actually significant for enlightening new approaches of avoidance, diagnosis, and therapy of estrogen-dependent cancers. In conclusion, revelation of the molecular mechanism of the arrangement of ERα protein expression level may assist a new plan to impede the progression of breast cancer, and ER alpha expression position may provide in the correctness of therapeutic processes.

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