

ER α , A Key Target for Cancer Therapy: A Review

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Yanfeng Liu*

Hong Ma*

Jing Yao

Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, People's Republic of China

*These authors contributed equally to this work

Abstract: Estrogen receptor α (ER α) is closely associated with both hormone-dependent and hormone-independent tumors, and it is also essential for the development of these cancers. The functions of ER α are bi-faceted; it can contribute to cancer progression as well as cancer inhibition. Therefore, understanding ER α is vital for the treatment of those cancers that are closely associated with its expression. Here, we will elaborate on ER α based on its structure, localization, activation, modification, and mutation. Also, we will look at co-activators of ER α , elucidate the signaling pathway activated by ER α , and identify cancers related to its activation. A comprehensive understanding of ER α could help us to find new ways to treat cancers.

Keywords: ER α , estrogen receptors, estradiol, signaling pathway, cancer

Introduction

Estrogen receptors (ERs) consist of nuclear ERs, extra-nuclear ERs, and G protein-coupled ERs (GPERs).¹ Nuclear ERs, including estrogen receptor α (ER α) and estrogen receptor β (ER β), are located in the nucleus and are encoded by ESR1 and ESR2, respectively.² Once activated, nuclear ERs transcriptionally regulate the expression of targeted genes.³ Extra-nuclear ERs include cytosolic ER α and ER β , both of which are located in the plasma membrane.⁴ GPERs are expressed both in the plasma membrane and cytoplasm,⁵ and are structurally different from ER α and ER β .⁶ ERs show similar main structures; however, their sequential homology is as low as 47%.² The different functions of ERs depend on structural differences. ERs can be activated when cells are exposed to estrogen.^{7–9} Emerging evidence shows that the activation of ERs is highly associated with cancer formation and metastasis,^{10–12} extracellular matrix (ECM) remodeling^{2,13} and drug resistance.^{14–17}

Here, we focus on providing a comprehensive understanding of ER α . We hope this will help doctors to find more effective ways to treat ER α -related cancers.

The Structure of ER α

ER α was the first ER to be discovered and cloned.⁹ The gene ESR1 that encodes ER α is located on chromosome 6.¹⁸ As shown in Figure 1, the ER α protein consists of 595 amino acids with a molecular weight of approximately 66.2kD.¹⁸ The ER α protein contains six domains (A-F), three of which are functionally significant.¹⁹ The three functional domains are the N-terminal A/B domain (NTD), the C domain (which includes the DNA-binding domain, DBD), and the E domain (the ligand-binding domain, LBD).¹⁹ NTD has a low degree of conservation and contains AF-1, which has the function of transcriptional activation and is also the main reason for ER α 's endocrine-sensitivity.²⁰ AF-1 is critical to the transactivation function and shows the

Correspondence: Jing Yao
Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Jiefang Road 1277, Wuhan, Hubei Province 430022, People's Republic of China
Tel +86-189 8627 1157
Email 2007XH0839@hust.edu.cn

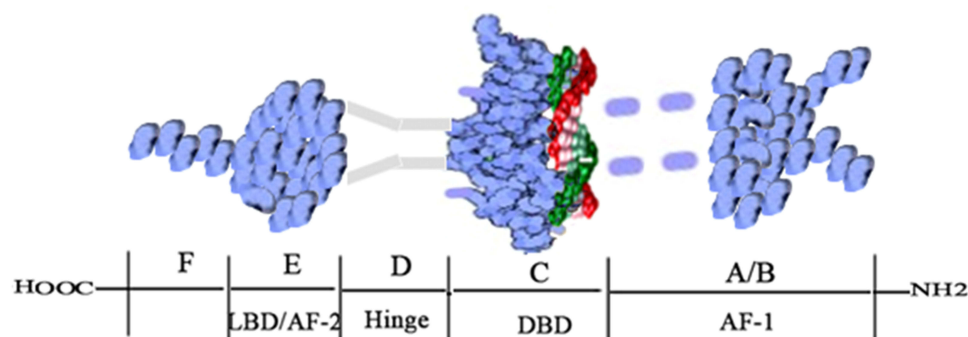


Figure 1 Structure of the ER α protein.

Note: Adapted from *Bioorg Chem*, 71, Jameera Begam A, Jubie S, Nanjan MJ. Estrogen receptor agonists/antagonists in breast cancer therapy: a critical review, 257–274, Copyright (2017), with permission from Elsevier.¹⁸

highest variability among ERs.² DBD in the C domain is highly conserved and exerts its function by binding to the estrogen-responsive element (ERE), which subsequently regulates the expression of target genes.²¹ The D domain shows 30% homology among ERs and links the C and E domains.^{22,23} LBD (also called AF-2) or the E domain, showing 55% homology with other ERs, is mainly involved in protein and estradiol (E2) binding.²² LBD combines with estrogen to form a homodimer that regulates gene suppression and activation and contributes to transcriptional activation.^{22,23} Studies have also shown that LBD is responsible for nuclear localization.^{22,24} The F domain, which is not conserved and shows only 18% homology, is regarded as an extension of the E domain.²² Although the structure of ER α has been studied extensively, the function of the F domain has not been clarified. Understanding the structure of ER α is essential for the treatment of ER α -over-expressing cancers.

Localization and Activation of ER α

ER α is widely expressed in human tissues, including breast, prostate, uterus, liver, and bone.²⁵ As stated above, there are two types of ER α , nuclear and extra-nuclear. Proteins are generally synthesized in the ribosome and then relocated under the guidance of a signal peptide.²⁶ In the nuclear ER α , the LBD region contains nuclear localization signals that guide the estrogen-ER α homodimer transfer from the cytoplasm to the nucleus.^{24,27} Once ER α has been relocated to the nucleus, its DBD then links with an ERE on the DNA.^{4,9,28} Through this process, nuclear ER α is activated.^{4,9,28}

Activated nuclear ER α regulates the expression of target genes by activating transcription factors downstream.²⁹ The E domain is fundamental to membrane translocation

of ER α .³⁰ Studies have shown that membrane ER α acts as a kind of G protein-coupled receptor, activates G proteins, and stimulates G protein-induced signal transduction.^{31,32} Therefore, the interaction between E2 and membrane ER α activates various signaling pathways and signaling molecules, subsequently triggering downstream gene transcription and affecting cancer progression.^{33–39} It is, for that reason, understandable that different locations of ER α exert distinct functions in multiple ways.

Post-Translational Modification and Function of ER α

Proteins exert their functions, including phosphorylation and dephosphorylation, lipidation or palmitoylation, methylation, acetylation, and SUMOylation, after post-translational modifications.^{40–42} Common post-translational modifications of ER α include phosphorylation, palmitoylation, and ubiquitination.^{43–47} Studies have revealed that frequent phosphorylation sites of ER α are Ser118, Ser167, and Ser305.^{43,44} The phosphorylation of these three sites leads to cancer progression, tumor metastasis, and endocrine therapy resistance.^{43,44} Interestingly, the phosphorylation of Ser305 activates the phosphorylation of Ser118, which subsequently promotes cancer development.⁴⁸

The palmitoylation site of ER α is Cys-447, and studies have demonstrated that the palmitoylation of ER α is essential for locating ER α in the plasma membrane.^{4,49} By binding to E2, the palmitoylation of ER α activates downstream signaling pathways.⁴⁵ The ubiquitination of ER α is the primary way of degrading ER α . However, emerging evidence shows that the function of the ubiquitination of ER α is complicated.^{46,47,50} ER α ubiquitination promotes tumorigenesis in hepatocellular carcinoma,⁴⁶ resulting in the slow growth of cancer cells in breast cancer.^{47,50} In

conclusion, the function of ER α is dependent on post-translational modifications.

Mutation of ER α

ER-positive (ER+) breast cancer has a good prognosis, mainly owing to endocrine therapy,^{51,52} which has shown great success.⁵² However, endocrine resistance is partially responsible for patient relapse,^{53–55} and the mutation of ER α plays a significant part in endocrine resistance.⁵⁶ Modification of ER α frequently results in changes in the activity of ER α and variations in protein expression and function, which lead to the proliferation of cancer cells.^{56,57}

ER α mutations are commonly observed in ER+ breast cancer. Two ESR1 mutations, Y537S and D538G, are most easily identified.^{56,58} Investigations have demonstrated that ESR1 mutations result in cancer cell resistance to tamoxifen (TAM) in breast cancer patients.^{56,58} Y537S mutants reportedly are not dependent on estrogen, but D538G mutants are.⁵⁶ Both mutants have been shown to be associated with endocrine resistance,⁵⁶ and neither change the ability of ERs to bind to transcription factors.^{59–61} We may, therefore, conclude that the mutation of ER α is critical for cancer development and drug resistance.

Co-Activators of ER α

ER α regulates the expression of its target genes through the participation of its co-activators.⁶² In the presence of E2, co-activators combine with ER α and subsequently activate transcription factors, which contribute to the transcription of target genes (Figure 2).⁶² Many co-regulators have been found; however, their mechanism of action is not always clear. Co-activators act as co-regulators, exerting their effect through various mechanisms. Specifically, SRC-1 and SRC-2 are functionally similar and contribute to the activation of ER α .^{63–65}

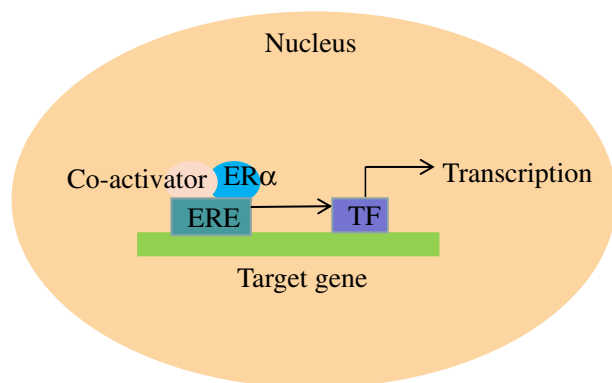


Figure 2 ER α 's contribution to the transcription of target genes with the help of co-activators.

Previous research revealed that SRC-1 and SRC-2 could lead to resistance to TAM in ER+ breast cancer patients,⁶⁶ while another investigation demonstrated that SRC-3 is overexpressed in breast cancer and acts as a selective activator of ER α .⁶⁶ In vivo experiments showed that SWI2/SNF2 protein enhanced gene transcription by interacting with the AF-2 domain,⁶⁷ and PBP contributed to mammary epithelial differentiation in breast cancer.⁶⁸ AIB1 interacts with ERs and resulting enhancement of estrogen-related gene transcription, which leads to development of breast and ovarian cancer.⁶⁴ There are other co-activators whose functions are unclear.⁶⁵ In all, many co-activators have been discovered that work together with ER α to co-regulate the expression of target genes. More co-activators will undoubtedly be studied in the future, which should be very helpful in understanding the mechanisms by which ER α regulates its target genes.

ER α and Signaling Pathways

Studies have shown that the activation of ER α leads to the activation of downstream signaling pathways.^{69,70} In endometrial carcinoma, estrogen contributes to carcinogenesis by activating ER α , which subsequently activates the downstream signaling pathways of phosphatidylinositol 3-kinase (PI3K)/AKT and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) (Figure 3).^{69,71} In ER+ breast cancer, estrogen activates the PI3K/AKT/mTOR signaling pathway by associating with extra-nuclear ER α , which results in drug resistance and epithelial-to-mesenchymal transition (EMT) (Figure 3).^{70,72} Targeting ER α reportedly causes changes in the expression of components of the PI3K/AKT-protein kinase C signaling pathway, resulting in cell apoptosis.⁷³ Also, the activation of ER α results in increased expression of the PI3K/AKT/NF- κ B signaling pathway, leading to tumor invasion and metastasis in breast cancer.⁷⁴

As discussed above, membrane ER α is linked to G proteins, transmitting signals from the outside to the inside of the cell.⁷⁵ Downstream signaling pathways, including adenosine monophosphate (cAMP) signaling,³³ PI3K/AKT, and endothelial nitric oxide synthase, are activated after receiving signals.^{76,77} As a result, cAMP levels increase, and the mobilization of Ca²⁺ is rapidly enhanced in the presence of estrogen; this contributes to the activation of estrogen signaling by activating the C-terminal of ER α (Figure 3).^{78,79} Emerging evidence shows that the membrane ER α activated by E2 interacts with signaling molecules, including PI3K, MAPK, AKT, p21ras, and PKC, contributing to the cascade amplification reaction of signaling molecules.^{2,80} Reportedly, the activation of ER α leads to

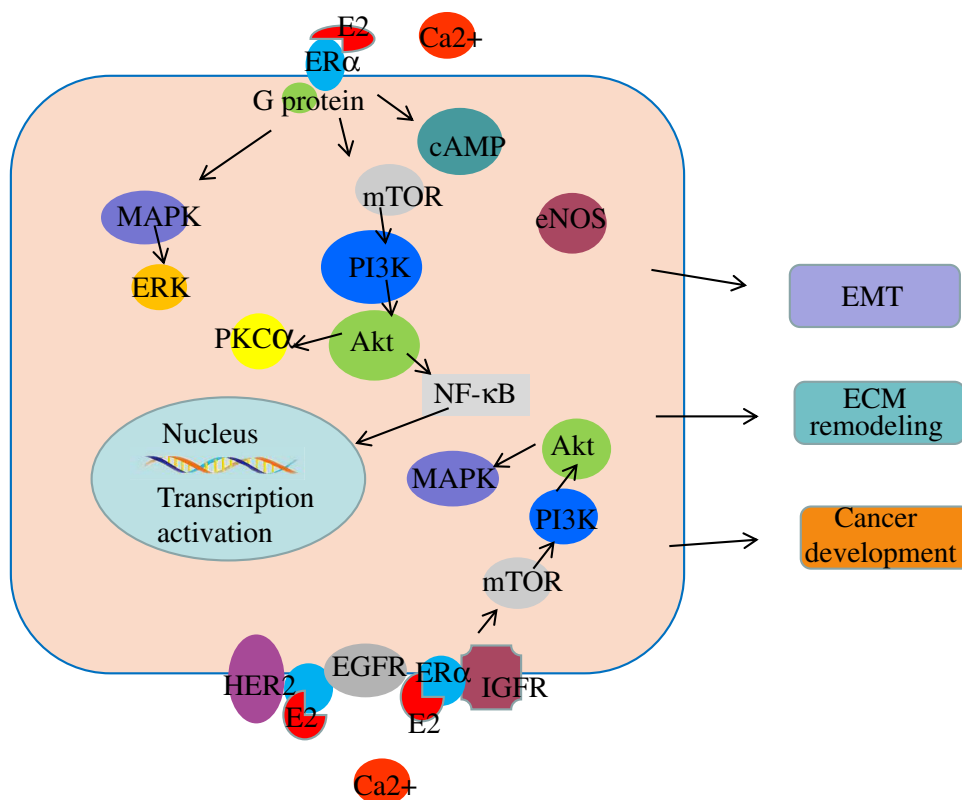


Figure 3 The signaling pathways in which ERα is involved.

the activation of human epidermal growth factor receptor 2 and epidermal growth factor receptor (EGFR), resulting in the upregulation of the mTOR/PI3K/AKT/MAPK signaling pathway.⁸¹ In breast cancer, ERα activation contributes to cancer progression by binding to IGF-IR, which subsequently activates the IGF pathway (Figure 3).^{82,83}

Overall, ERα is extremely important in cancer progression. Understanding the mechanisms involving ERα is key to treating cancers.

ERα and Cancer

ERα is critical to the development of ER+ breast cancer,⁸⁴ which accounts for approximately 70% of all breast cancers.^{7,85} Overexpression of ERα frequently sensitizes tumors to endocrine therapy.⁸⁴ When exposed to E2, ERα activation stimulates downstream signaling pathways,⁸⁶ and leads to EMT and ECM remodeling (Figure 3).^{87,88} In ER+ breast cancer, estrogen contributes to cancer progression by activating the PI3K/AKT signaling pathway.^{89,90} In the ER+ breast cancer cell line MCF-7, calcium mediates the activation of estrogen signaling.⁷⁸ Overall in all, ERα plays a significant part in the progression of ER+ breast cancer.

ERα is widely expressed in cells and has a critical role in both hormone-dependent and hormone-independent cancers. In hormone-related cancers, such as breast, endometrial and ovarian cancers, ERα expression contributes to disease progression mostly by regulating the PI3K/AKT signaling pathway.^{69,73} Emerging evidence shows that ERα is also crucial to the progression of prostate cancer.⁹¹ Overexpression of ERα in prostate cancer is strongly associated with adverse survival outcomes.⁹¹ ERα acts as an oncogene and contributes to the development of prostate cancer by inducing EMT and the activation of matrix metalloproteinases.^{92,93} However, ERα also has a key role in inhibiting tumor development, maintaining the luminal phenotype, and restoring the sensitivity of breast cancer to hormone therapy.⁹⁴ In hormone-independent cancers, such as colorectal cancer, ERα expression was shown to inhibit tumors in women.⁹⁵ In non-small-cell lung cancer, ERα expression contributed to sensitivity to pemetrexed and carboplatin.⁹⁶ However, high ERα expression is also significantly related to poor survival outcomes in colorectal cancer patients.⁹⁷ Therefore, we can conclude that the regulation of ERα is complicated, and its role is bi-faceted.

Conclusions and Perspectives

Study have shown that changes in expression of ER α , ER β , and GPERs greatly affect cell proliferation and cancer development.⁹⁸ As discussed above, the functions of ERs are bi-faceted. ER β also exerts its functions through various mechanisms. In triple-negative breast cancer cells, ER β suppresses tumor progression by interacting with androgen receptors.⁹⁹ ER β also contributes to beneficial gut microbiota diversity, which suppresses colorectal cancer development.¹⁰⁰ However, in prostate cancer cell line PC-3, ER β exerts its oncogenic effect by activating β -catenin and regulating the PI3K/AKT signaling pathway.¹⁰¹ Therefore, the effects of ER β in cancer cells are complicated.

The functions of GPERs are also multi-faceted. In hormone-dependent cancers, such as breast cancer and endometrial cancer, GPER expression leads to tumor progression. Specifically, analysis of data from a subset of breast cancer patients showed that GPER-1 expression was positively correlated with overexpression of EGFR.¹⁰² In TAM-resistant breast cancer cells, GPER-1/EGFR receptor signaling contributes to the development of TAM resistance,¹⁰³ indicating that either GPER-1 exerts its function by regulating EGFR or there is a mutual regulation between the two. In breast cancer MDA-MB-231 cells, down-regulation of GPER induces inhibition of cell proliferation and tumor metastasis.¹⁰⁴ In endometrial cancer, GPER-1 promotes cell growth by binding to autocrine motility factor.¹⁰⁵ GPER also contributes to insulin-driven endometrial cancer cell proliferation by regulating the PI3K/AKT signaling pathway.¹⁰⁶ Overall, GPER expression contributes to the development of hormone-dependent cancers. However, in hormone-independent cancers, such as colorectal cancer, the relationship between GPER expression and tumor progression is more complicated. In ER β -negative colorectal cancer cells, GPER-induced hypoxic condition leads to tumor development.¹⁰⁷ However, another study reported that GPER-1 inhibits the activation of NF- κ B by the canonical IKK α /I κ B α pathway. In vivo experiments confirmed that GPER-1 suppresses progression of colorectal cancer.¹⁰⁸ Overall, GPER has complicated functions in cancers.

As important ERs, ER α , ER β , and GPER do not function independently from each other. Cross-regulation among ERs has an important role in physiological activities and biological behaviors. In zebrafish, ER α is a core factor, interacting with ER β and GPER to regulate vitellogenesis.¹⁰⁹ In vivo experiments showed that ER β

and GPER-1 co-regulate the effects of E2 on arginine-vasopressin immunoreactivity.¹¹⁰ In human renal tubular epithelial cells, E2 leads to cell proliferation via ER α and GPER-1.¹¹¹ In vitro experiments showed that ER β suppressed the transcriptional and oncogenic effects of ER α .^{112,113} The functions of ER α and ER β are antagonistic; therefore, their ratio is important in the development of diseases. An ER β /ER α ratio lower than 0.85 was associated with and could potentially be used to predict endoscopic activity in Crohn's disease.¹¹⁴ In conclusion, the expression changes of different ERs are associated with abnormal regulation and disorders.

ER α is localized in the nucleus and the plasma membrane; however, the membrane-localized receptors mediate faster signal transduction via the MAPK/ERK, PI3K/AKT, and p38/MAPK signaling pathways.^{115,116} In this review, we emphasize that ER α expression is closely linked to cancer development.³³ The activation of ER α by estrogen leads to tumor progression and metastasis, which subsequently promotes the transduction of downstream signaling pathways.^{82,83} Currently, ER α antagonists such as TAM are widely used in clinical settings with great success.¹¹⁷ Nevertheless, endocrine resistance remains partially responsible for patient relapse.^{53–55} TAM is structurally similar to estrogen and competitively combines with ERs, subsequently blocking the entry of estrogen into tumor cells and inhibiting the development of cancers.¹¹⁸ However, resistance to TAM has multiple mechanisms, including ER mutation, loss of ER expression, overexpression of ER co-activators, activation of the EGFR or PI3K/AKT signaling pathway, epigenomic and post-translational modifications in ER, and enhanced mitochondrial metabolism of TAM.^{56,119–124} Endocrine therapy resistance is a challenge, and successfully solving this problem would greatly benefit cancer patients. This review provides a comprehensive understanding of ER α , which we hope will help in the search for new ways to treat ER α -related cancers.

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Disclosure

The authors report no conflicts of interest in this work.

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