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REVIEW

ERα, A Key Target for Cancer Therapy: A Review

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

Keywords: ERα, 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 (ERα) and estrogen receptor β (ERβ), are located in the nucleus and are encoded by ESR1 and ERS2, respectively.[2] Once activated, nuclear ERs transcriptionally regulate the expression of targeted genes.[3] Extra-nuclear ERs include cytosolic ERα and ERβ, 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 ERα and ERβ.[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 ERα. We hope this will help doctors to find more effective ways to treat ERα-related cancers.

The Structure of ERα

ERα was the first ER to be discovered and cloned.[9] The gene ESR1 that encodes ERα is located on chromosome 6.[18] As shown in Figure 1, the ERα protein consists of 595 amino acids with a molecular weight of approximately 66.2kD.[18] The ERα 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 ERα's endocrine-sensitivity.[20] AF-1 is critical to the transactivation function and shows the

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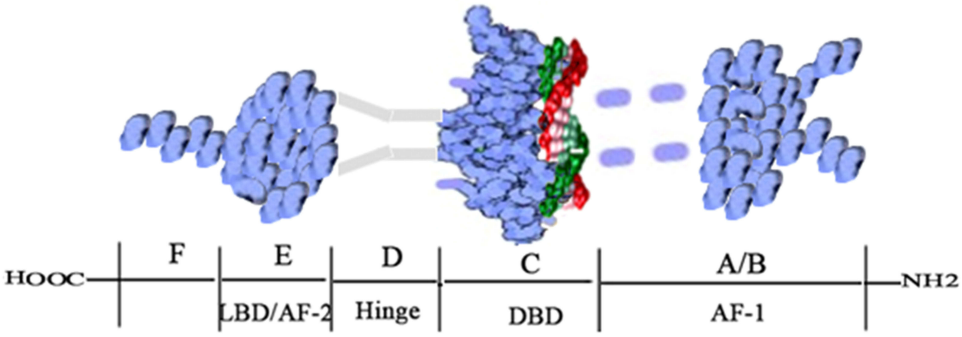

Figure 1 Structure of the ERα protein.
Note: Adapted from *Bioorg Chem*, 71, Jameera Begam A, Jubie S, Nanjan MJ. Estrogen receptor agonists/antagonists in breast cancer therapy: a critical review, 257–274, Copyright (2017), with permission from Elsevier.[18]

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 ERα has been studied extensively, the function of the F domain has not been clarified. Understanding the structure of ERα is essential for the treatment of ERα-overexpressing cancers.

Localization and Activation of ERα

ERα is widely expressed in human tissues, including breast, prostate, uterus, liver, and bone.[25] As stated above, there are two types of ERα, 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 ERα, the LBD region contains nuclear localization signals that guide the estrogen-ERα homodimer transfer from the cytoplasm to the nucleus.[24,27] Once ERα has been relocated to the nucleus, its DBD then links with an ERE on the DNA.[4,9,28] Through this process, nuclear ERα is activated.[4,9,28]

Activated nuclear ERα regulates the expression of target genes by activating transcription factors downstream.[29] The E domain is fundamental to membrane translocation of ERα.[30] Studies have shown that membrane ERα 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 ERα 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 ERα exert distinct functions in multiple ways.

Post-Translational Modification and Function of ERα

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 For ERα include phosphorylation, palmitoylation, and ubiquitination.[43–47] Studies have revealed that frequent phosphorylation sites of ERα 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 ERα is Cys-447, and studies have demonstrated that the palmitoylation of ERα is essential for locating ERα in the plasma membrane.[4,49] By binding to E2, the palmitoylation of ERα activates downstream signaling pathways.[45] The ubiquitination of ERα is the primary way of degrading ERα. However, emerging evidence shows that the function of the ubiquitination of ERα is complicated.[46,47,50] ERα 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 ERα is dependent on post-translational modifications.

Mutation of ERα

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 ERα plays a significant part in endocrine resistance.[56] Modification of ERα frequently results in changes in the activity of ERα and variations in protein expression and function, which lead to the proliferation of cancer cells.[56,57]

ERα 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 ERα is critical for cancer development and drug resistance.

Co-Activators of ERα

ERα regulates the expression of its target genes through the participation of its co-activators.[62] In the presence of E2, co-activators combine with ERα 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 ERα.[63–65]

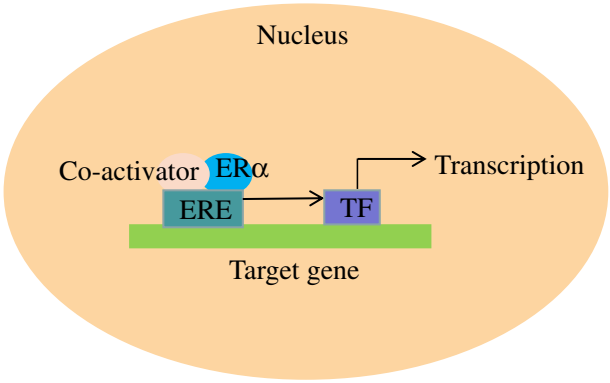

Figure 2 ERα's contribution to the transcription of target genes with the help of co-activators.

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 ERα.[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 ERα 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 ERα regulates its target genes.

ERα and Signaling Pathways

Studies have shown that the activation of ERα leads to the activation of downstream signaling pathways.[69,70] In endometrial carcinoma, estrogen contributes to carcinogenesis by activating ERα, 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 ERα, which results in drug resistance and epithelial-to-mesenchymal transition (EMT) (Figure 3).[70,72] Targeting ERα reportedly causes changes in the expression of components of the PI3K/AKT-protein kinase Cα signaling pathway, resulting in cell apoptosis.[73] Also, the activation of ERα results in increased expression of the PI3K/AKT/NF-κB signaling pathway, leading to tumor invasion and metastasis in breast cancer.[74]

As discussed above, membrane ERα 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 Ca^{2+} is rapidly enhanced in the presence of estrogen; this contributes to the activation of estrogen signaling by activating the C-terminal of ERα (Figure 3).[78,79] Emerging evidence shows that the membrane ERα 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 ERα leads to

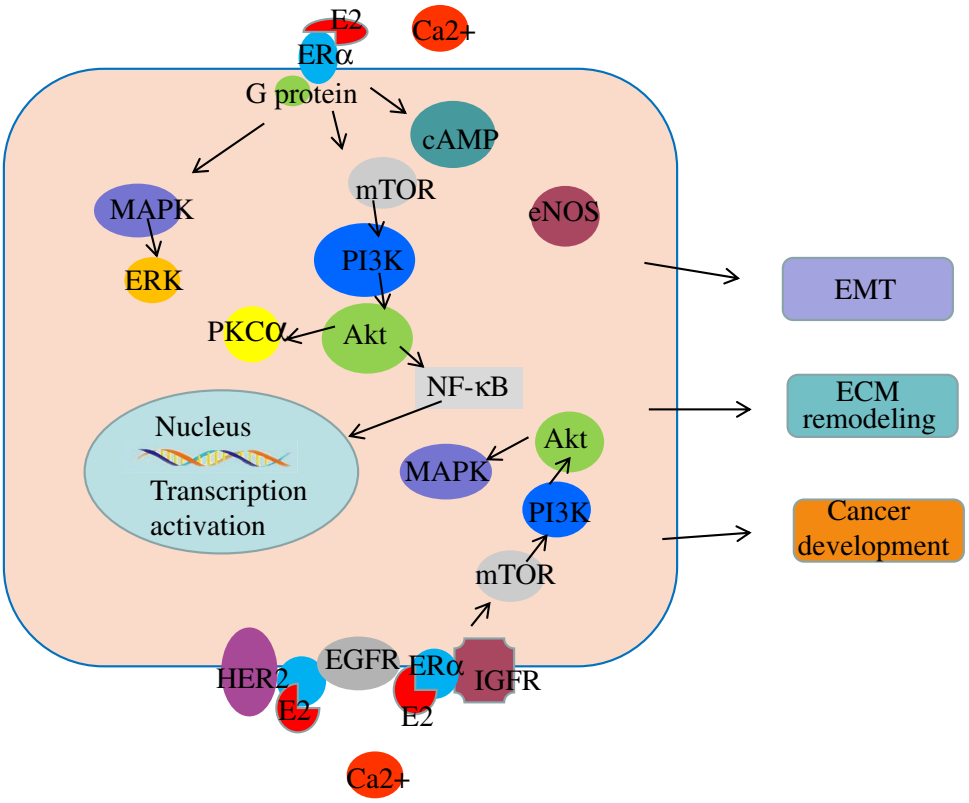

Figure 3 The signaling pathways in which ERα is involved.

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-in dependent 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 ERα, ERβ, and GPERs greatly affect cell proliferation and cancer development.[98] As discussed above, the functions of ERs are bi-faceted. ERβ also exerts its functions through various mechanisms. In triple-negative breast cancer cells, ERβ suppresses tumor progression by interacting with androgen receptors.[99] ERβ also contributes to beneficial gut microbiota diversity, which suppresses colorectal cancer development.[100] However, in prostate cancer cell line PC-3, ERβ exerts its oncogenic effect by activating β-catenin and regulating the PI3K/AKT signaling pathway.[101] Therefore, the effects of ERβ 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 ERβ-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-κB by the canonical IKKα/IκBα pathway. In vivo experiments confirmed that GPER-1 suppresses progression of colorectal cancer.[108] Overall, GPER has complicated functions in cancers.

As important ERs, ERα, ERβ, 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, ERα is a core factor, interacting with ERβ and GPER to regulate vitellogenesis.[109] In vivo experiments showed that ERβ 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 ERα and GPER-1.[111] In vitro experiments showed that ERβ suppressed the transcriptional and oncogenic effects of ERα.[112,113] The functions of ERα and ERβ are antagonistic; therefore, their ratio is important in the development of diseases. An ERβ/ERα 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.

ERα 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 ERα expression is closely linked to cancer development.[33] The activation of ERα by estrogen leads to tumor progression and metastasis, which subsequently promotes the transduction of downstream signaling pathways.[82,83] Currently, ERα 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 ERα, which we hope will help in the search for new ways to treat ERα-related cancers.

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Disclosure

The authors report no conflicts of interest in this work.

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