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 ERs 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) remodeling2,13 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
highest variability among ERs. 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. The D domain shows 30% homology among ERs and links the C and E domains. LBD (also called AF-2) or the E domain, showing 55% homology with other ERs, is mainly involved in protein and estradiol (E2) binding. LBD combines with estrogen to form a homodimer that regulates gene suppression and activation and contributes to transcriptional activation. Studies have also shown that LBD is responsible for nuclear localization. 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. 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. In the nuclear ERα, the LBD region contains nuclear localization signals that guide the estrogen-ERα homodimer transfer from the cytoplasm to the nucleus. Once ERα has been relocated to the nucleus, its DBD then links with an ERE on the DNA. Through this process, nuclear ERα is activated.

Activated nuclear ERα regulates the expression of target genes by activating transcription factors downstream. The E domain is fundamental to membrane translocation of ERα. 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. Therefore, the interaction between E2 and membrane ERα activates various signaling pathways and signaling molecules, subsequently triggering downstream gene transcription and affecting cancer progression. 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. Common post-translational modifications of ERα include phosphorylation, palmitoylation, and ubiquitination. Studies have revealed that frequent phosphorylation sites of ERα are Ser118, Ser167, and Ser305. The phosphorylation of these three sites leads to cancer progression, tumor metastasis, and endocrine therapy resistance. Interestingly, the phosphorylation of Ser305 activates the phosphorylation of Ser118, which subsequently promotes cancer development.

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. By binding to E2, the palmitoylation of ERα activates downstream signaling pathways. 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. ERα ubiquitination promotes tumorigenesis in hepatocellular carcinoma, resulting in the slow growth of cancer cells in breast cancer.

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.
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

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 ERα 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 Ca signaling pathway, resulting in cell apoptosis.73 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 Ca2+ 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
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. In breast cancer, ERα activation contributes to cancer progression by binding to IGF-IR, which subsequently activates the IGF pathway (Figure 3). 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, which accounts for approximately 70% of all breast cancers. Overexpression of ERα frequently sensitizes tumors to endocrine therapy. When exposed to E2, ERα activation stimulates downstream signaling pathways and leads to EMT and ECM remodeling (Figure 3). In ER+ breast cancer, estrogen contributes to cancer progression by activating the PI3K/AKT signaling pathway. In the ER+ breast cancer cell line MCF-7, calcium mediates the activation of estrogen signaling. 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. Emerging evidence shows that ERα is also crucial to the progression of prostate cancer. Overexpression of ERα in prostate cancer is strongly associated with adverse survival outcomes. ERα acts as an oncogene and contributes to the development of prostate cancer by inducing EMT and the activation of matrix metalloproteinases. 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. In hormone-independent cancers, such as colorectal cancer, ERα expression was shown to inhibit tumors in women. In non-small-cell lung cancer, ERα expression contributed to sensitivity to pemetrexed and carboplatin. However, high ERα expression is also significantly related to poor survival outcomes in colorectal cancer patients. 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. 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. ERβ also contributes to beneficial gut microbiota diversity, which suppresses colorectal cancer development. However, in prostate cancer cell line PC-3, ERβ exerts its oncogenic effect by activating β-catenin and regulating the PI3K/AKT signaling pathway. 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. In TAM-resistant breast cancer cells, GPER-1/EGFR receptor signaling contributes to the development of TAM resistance, 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. In endometrial cancer, GPER-1 promotes cell growth by binding to autocrine motility factor. GPER also contributes to insulin-driven endometrial cancer cell proliferation by regulating the PI3K/AKT signaling pathway. 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. However, another study reported that GPER –1 inhibits the activation of NFKB by the canonical IKKα/IκBα pathway. In vivo experiments confirmed that GPER-1 suppresses progression of colorectal cancer. 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. In vivo experiments showed that ERβ and GPER-1 co-regulate the effects of E2 on arginine-vasopressin immunoreactivity. In human renal tubular epithelial cells, E2 leads to cell proliferation via ERα and GPER-1. In vitro experiments showed that ERβ suppressed the transcriptional and oncogenic effects of ERα. 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. 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. Currently, ERα antagonists such as TAM are widely used in clinical settings with great success. Nevertheless, endocrine resistance remains partially responsible for patient relapse. 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. 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. 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

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References

1. Butler MJ, Hildebrandt RP, Eckel LA. Selective activation of estrogen receptors, ERalpha and GPER-1, rapidly decreases food intake in female rats. Horm Behav. 2018;103:54–61. doi:10.1016/j.yhbeh.2018.05.018

2. Piperigkou Z, Karamanos NK. Estrogen receptor-mediated targeting of the extracellular matrix network in cancer. Semin Cancer Biol. 2019. doi:10.1016/j.semcancer.2019.07.006

3. Nilsson S, Makela S, Treuter E, et al. Mechanisms of estrogen action. Physiol Rev. 2001;81(4):1535–1565. doi:10.1152/physrev.2001.81.4.1535

4. Pedram A, Razandi M, Sainson RC, Kim JK, Hughes CC, Levin ER. A conserved mechanism for steroid receptor translocation to the plasma membrane. J Biol Chem. 2007;282 (31):22278–22288. doi:10.1074/jbc.M611877200

5. Tominna R, Chokr S, Feri M, Chuo T, Sinchak K. Plasma membrane G protein-coupled estrogen receptor 1 (GPER) mediates rapid estradiol facilitation of sexual receptivity through the orphanin-FQ-ORL-1 system in estradiol primed female rats. Horm Behav. 2019;112:89–99. doi:10.1016/j.yhbeh.2019.04.004

6. Carmeci C, Thompson DA, Ring HZ, Francke U, Weigel RJ. Identification of a gene (GPR30) with homology to the G-protein-coupled receptor superfamily associated with estrogen receptor expression in breast cancer. Genomics. 1997;45(3):607–617. doi:10.1006/geno.1997.4972

7. Leone S, Busonero C, Acconia F. A high throughput method to study the physiology of E2: eRalphasignaling in breast cancer cells. J Cell Physiol. 2018;233(5):3713–3722. doi:10.1002/jcp.26251

8. He WH, Jin MM, Liu AP, et al. Estradiol promotes trophoblast viability and invasion by activating SGK1. Biomed Pharmacother. 2019;117:109092. doi:10.1016/j.biopha.2019.109092

9. Duhman-Wright K, Cavailles V, Fuqua SA, et al. International union of pharmacology. LXIV. Estrogen receptors. Pharmacol Rev. 2006;58(4):773–781. doi:10.1124/pr.58.4.8

10. Li Q, Gao H, Yang H, Wei W, Jiang Y. Estradiol promotes the progression of ER+ breast cancer through methylation-mediated RSK4 inactivation. Onco Targets Ther. 2019;12:5907–5916. doi:10.2147/OTT.S209888

11. Jallow F, O’Leary KA, Rugowski DE, Guerrero JF, Ponik SM, Schuler LA. Dynamic interactions between the extracellular matrix and estrogen activity in progression of ER+ breast cancer. Oncogene. 2019;38(43):6913–6925.

12. Che Q, Xiao X, Jun X, et al. 17beta-estradiol promotes endometrial cancer proliferation and invasion through IL-6 pathway. Endocr Connect. 2019.

13. Menendez-Menendez J, Hermida-Prado F, Granda-Diaz R, et al. Deciphering the molecular basis of melatonin protective effects on breast cells treated with doxorubicin: TWIST1 transcription factor involved in EMT and metastasis, a novel target of melatonin. Cancers (Basel). 2019;11:7. doi:10.3390/cancers11071011

14. Wu Y, Zhang Z, Cenciarini ME, et al. Tamoxifen resistance in breast cancer is regulated by the EZH2-ERalpha-GREB1 transcriptional axis. Cancer Res. 2018;78(3):671–684. doi:10.1158/0008-5472.CAN-17-1327

15. Selmin OI, Donovan MG, Skovan B, Paine-Murieta GD, Romagnolo DF. Arsenicinduced B RCA1 CpG promoter methylation is associated with the downregulation of ERalpha and resistance to tamoxifen in MCF7 breast cancer cells and mouse mammary tumor xenografts. Int J Oncol. 2019;54(3):869–878. doi:10.3892/ijo.2019.4687

16. Button B, Crossmann S, Chu D, et al. The estrogen receptor-alpha S118P variant does not affect breast cancer incidence or response to endocrine therapies. Breast Cancer Res Treat. 2019;174(2):401–412. doi:10.1007/s10549-018-5087-7

17. Arpino G, Wiechmann L, Osborne CK, Schiff R. Crossover between the estrogen receptor and the HER tyrosine kinase receptor family: molecular mechanism and clinical implications for endocrine therapy resistance. Endocrin Rev. 2008;29(2):217–233. doi:10.1210/er.2006-0045

18. Jameera Begam A, Jubie S, Nanjan MJ. Estrogen receptor agonists/antagonists in breast cancer therapy: a critical review. Bioorg Chem. 2017;71:257–274. doi:10.1016/j.bioorg.2017.02.011

19. Ogawa S, Inoue S, Watanabe T, et al. The complete primary structure of human estrogen receptor beta (hER beta) and its heterodimerization with ER alpha in vivo and in vitro. Biochem Biophys Res Commun. 1998;245(1):122–126. doi:10.1006/bbrc.1997.7893

20. Kaiper GG, Enmark E, Pelto-Huikko M, Nilsson S, Gustafsson JA. Cloning of a novel receptor expressed in rat prostate and ovary. Proc Natl Acad Sci U S A. 1996;93(12):5925–5930. doi:10.1073/pnas.93.12.5925

21. Kumar V, Chambon P. The estrogen receptor binds tightly to its responsive element as a ligand-induced homodimer. Cell. 1988;55(1):145–156. doi:10.1016/0092-8674(88)90017-7

22. Ruff M, Gangloff M, Wurtz JM, Moras D. Estrogen receptor transcription and transactivation: structure-function relationship in DNA- and ligand-binding domains of estrogen receptors. Breast Cancer Res. 2000;2(5):353–359. doi:10.1186/ber80

23. Huang W, Peng Y, Kiselar J, et al. Multidomain architecture of estrogen receptor reveals interfacial cross-talk between its DNA-binding and ligand-binding domains. Nat Commun. 2018;9(1):3520. doi:10.1038/s41467-018-06034-2

24. Beato M, Sanchez-Pacheco A. Interaction of steroid hormone receptors with the transcription initiation complex. Endocr Rev. 1996;17(6):587–609. doi:10.1210/edrv-17-6-587

25. Mokarram P, Alizadeh J, Razban V, Barazeh M, Solomon C, Kavoussipour S. Interconnection of estrogen/testosterone metabolism and mevalonate pathway in breast and prostate cancers. Curr Mol Pharmacol. 2017;10(2):86–114. doi:10.2174/18744672096616011215631

26. Frydman J. Folding of newly translated proteins in vivo: the role of molecular chaperones. Annu Rev Biochem. 2001;70:603–647. doi:10.1146/annurev.biochem.70.1.603

27. Evans RM. The steroid and thyroid hormone receptor superfamily. Science. 1988;240(4854):889–895. doi:10.1126/science.3283939

28. Vanacker JM, Pettersson K, Gustafsson JA, Lauder V. Transcriptional targets shared by estrogen receptor-related receptors (ERs) and estrogen receptor (ER) alpha, but not by ERbeta. EMBO J. 1999;18(15):4270–4279. doi:10.1093/emborbo/18.15.4270

29. Kos M, Reid G, Denger S, Gannon F. Minireview: genomic organization of the human ERalpha gene promoter region. Mol Endocrinol. 2001;15(12):2057–2063. doi:10.1210/mend.15.12.0731

30. Razandi M, Alton G, Pedram A, Ghoshani S, Webb P, Levin ER. Identification of a structural determinant necessary for the localization and function of estrogen receptor alpha at the plasma membrane. Mol Cell Biol. 2003;23(5):1613–1646. doi:10.1128/ MCB.23.5.1633-1646.2003

31. Razandi M, Pedram A, Greene GL, Levin ER. Cell membrane and nuclear estrogen receptors (ERs) originate from a single transcript: studies of ERalpha and ERbeta expressed in Chinese hamster ovary cells. Mol Endocrinol. 1999;13(2):307–319. doi:10.1210/mend.13.2.0239

32. Wyckoff MH, Chambliss KL, Mineo C, et al. Plasma membrane estrogen receptors are coupled to endothelial nitric-oxide synthase through Galphai(1). J Biol Chem. 2001;276(29):27071–27076. doi:10.1074/jbc.M100312200

33. Aronica SM, Kraus WL, Katzenellenbogen BS. Estrogen action via the eAMP signaling pathway: stimulation of adenylate cyclase and cAMP-regulated gene transcription. Proc Natl Acad Sci U S A. 1994;91(18):8517–8521. doi:10.1073/pnas.91.18.8517
Castoria G, Barone MV, Di Domenico M, et al. Non-transcriptional action of oestradiol and progesterin triggers DNA synthesis. *EMBO J.* 1999;18(9):2500–2510. doi:10.1093/emboj/18.9.2500

Cooper LF, Tiffée JC, Griffin JP, Hamano H, Guo Z. Estrogen-induced resistance to osteoblast apoptosis is associated with increased hsp27 expression. *J Cell Physiol.* 2000;183(3):401–407. doi:10.1002/(ISSN)1097-4652

Le Mellay V, Grosse B, Lieberherr M. Phospholipase C beta and membrane action of calcitriol and estradiol. *J Biol Chem.* 1997;272(18):11902–11907. doi:10.1074/jbc.272.18.11902

Liu et al. *Mol Endocrinol.* 2017

Levin ER. Cellular functions of the plasma membrane estrogen receptor. *Trends Endocrinol Metab.* 1999;10(9):374–377. doi:10.1016/S1043-2760(99)01927-7

Razandi M, Pedram A, Levin ER. Plasma membrane estrogen receptors signal to antiapoptosis in breast cancer. *Mol Endocrinol.* 2000;14(9):1434–1447. doi:10.1210/mend.14.9.0526

Wise PM, Dubal DB, Wilson ME, Rau SW, Bottner M. Minireview: neuroprotective effects of estrogen-new insights into mechanisms of action. *Endocrinology.* 2001;142(3):969–973. doi:10.1210/endo.142.3.8033

Xu FQ, Xue HW. The ubiquitin-proteasome system in plant responses to environments. *Plant Cell Environ.* 2019.

Ficarro SB, McCleland ML, Stukenberg PT, et al. Phosphoproteome analysis by mass spectrometry and its application to Saccharomyces cerevisiae. *Nat Biotechnol.* 2002;20(3):301–305. doi:10.1038/s00345-002-0301-1

Davis BG. *Biochemistry.* Mimicking posttranslational modifications of proteins. *Science.* 2004;303(5657):480–482. doi:10.1126/science.1093449

Anbalagan M, Rowan BG. Estrogen receptor alpha phosphorylation and its functional impact in human breast cancer. *Mol Cell Endocrinol.* 2015;418(Pt 3):264–272. doi:10.1016/j.mce.2015.01.016

Park J, Lee Y. Hypoxia induced phosphorylation of estrogen receptor at serine 118 in the absence of ligand. *J Steroid Biochem Mol Biol.* 2017;174:146–152. doi:10.1016/j.jsbmb.2017.08.013

Anadlamerini M, Solinhasc R, Abot A, et al. Mutation of the palmitoylation site of estrogen receptor alpha in vivo reveals tissue-specific roles for membrane versus nuclear actions. *Proc Natl Acad Sci U S A.* 2014;111(2):E283–E290. doi:10.1073/pnas.1320571111

Wu H, Yao S, Zhang S, et al. Elevated expression of Erbin destabilizes ERalpha protein and promotes tumorigenesis in hepatocellular carcinoma. *J Hepatol.* 2017;66(6):1193–1204. doi:10.1016/j.jhep.2017.01.030

Yang H, Yu N, Xu J, et al. SMURF1 facilitates estrogen receptor α signaling in breast cancer cells. *J Exp Clin Cancer Res.* 2018;37(1):24. doi:10.1186/s13046-018-0672-z

Oladimeji P, Skerf R, Rusch C, Diakonova M. Synergistic activation of ERalpha by estrogen and prolactin in breast cancer cells requires tyrosyl phosphorylation of PAK1. *Cancer Res.* 2016;76(9):2600–2611. doi:10.1158/0008-5472.CAN-15-1758

Acconcia F, Ascenzi P, Bocedi A, et al. Palmitoylation-dependent estrogen receptor alpha membrane localization: regulation by 17beta-estradiol. *Mol Biol Cell.* 2005;16(1):231–237. doi:10.1091/mbc.e04-07-0547

Xue M, Zhang K, Mu K, et al. Regulation of estrogen signaling and breast cancer proliferation by an ubiquitin ligase TRIM56. *Oncogene.* 2019;8(5):30. doi:10.1038/s41389-019-0139-x

Turner NC, Neven P, Lohli S, Andre F. Advances in the treatment of advanced oestrogen-receptor-positive breast cancer. *Lancet.* 2017;389(10087):2403–2414. doi:10.1016/S0140-6736(16)32419-9

Musgrove EA, Sutherland RL. Biological determinants of endocrine resistance in breast cancer. *Nat Rev Cancer.* 2009;9(9):631–643. doi:10.1038/nrc2713

Early Breast Cancer Trials’ Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet.* 2005;365(9472):1687–1717. doi:10.1016/S0140-6736(05)66544-0

Bosch A, Li Z, Bergamaschi A, et al. PI3K inhibition results in enhanced estrogen receptor function and dependence in hormone receptor-positive breast cancer. *Sci Transl Med.* 2015;7(303):283ra251. doi:10.1126/scitranslmed.aaa4442

Toska E, Osmanbeyoglu HU, Castel P, et al. PI3K pathway regulates ER-dependent transcription in breast cancer through the epigenetic regulator KMT2D. *Science.* 2017;355(6331):1324–1330. doi:10.1126/science.aah6893

Fiorillo M, Sanchez-Alvarez R, Sotgia F, Lisanti MP. The ER-alpha mutation Y537S confers Tamoxifen-resistance via enhanced mitochondrial metabolism, glycolysis and Rho-GDI/PTEN signaling: implicating TIGAR in somatic resistance to endocrine therapy. *Aging (Albany NY).* 2018;10(12):4000–4023. doi:10.18632/aging.v10i12

Jia S, Miedel MT, Ngo M, et al. Clinically observed estrogen receptor alpha mutations within the ligand-binding domain confer distinguishable phenotypes. *Onco. Biology.* 2018;94(3):176–189. doi:10.1159/000485510

Bahreini A, Li Z, Wang P, et al. Mutation site and context dependent effects of ESRI mutation in genome-edited breast cancer cell models. *Breast Cancer Res.* 2017;19(1):60. doi:10.1186/s13058-017-0851-4

Weis KE, Ekena K, Thomas JA, Lazennec G, Katzenellenbogen BS. Constitutively active human estrogen receptors containing amino acid substitutions for tyrosine 537 in the receptor protein. *Mol Endocrinol.* 1996;10(11):1388–1398. doi:10.1210/mend.111.10.8923465

Zhang QX, Borg A, Wolf DM, Oesterreich S, Fuqua SA. An estrogen receptor mutant with strong hormone-independent activity from a metastatic breast cancer. *Cancer Res.* 1997;57(7):12 44–1249.

Fanning SW, Mayne CG, Dharmarajan V, et al. Estrogen receptor alpha somatic mutations Y537S and D538G confer breast cancer endocrine resistance by stabilizing the activating function-2 binding conformation. *Elife.* 2016;5.

McKenna NJ, Lanz RB, O’Malley BW. Nuclear receptor coregulators: cellular and molecular biology. *Endocr Rev.* 1999;20(3):321–344. doi:10.1210/edrv.20.3.0366

Smith CL, Nawaz Z, O’Malley BW. Coactivator and corepressor regulation of the agonist/antagonist activity of the mixed anties- trogen, 4-hydroxytamoxifen. *Mol Endocrinol.* 1997;11(6):657–666. doi:10.1210/mend.11.6.0009

Anzick SL, Kononen J, Walker RL, et al. AIB1, a steroid receptor coactivator amplified in breast and ovarian cancer. *Science.* 1997;277(5328):965–968. doi:10.1126/science.277.5328.2896

Heery DM, Kalkhoven E, Hoare S, Parker MG. A signature motif in transcriptional co-activators mediates binding to nuclear receptors. *Nature.* 1997;387(6634):733–736. doi:10.1038/42750

Spencer TE, Jenster G, Burcin MM, et al. Steroid receptor coactivator-1 is a histone acetyltransferase. *Nature.* 1997;389(6647):194–198. doi:10.1038/38304

Ichinose H, Garnier JM, Chambon P, Losson R. Ligand-dependent interaction between the estrogen receptor and the human homologues of SWI2/SNF2. *Gene.* 1997;188(1):95–100. doi:10.1016/S0378-1119(96)00785-8

Zhu Y, Qi C, Jain S, et al. Amplification and overexpression of peroxisome proliferator-activated receptor binding protein (PPBP/PPARBP) gene in breast cancer. *Proc Natl Acad Sci U S A.* 1999;96(19):10848–10853. doi:10.1073/pnas.96.19.10848
69. Tian W, Teng F, Gao J, et al. Estrogen and insulin synergistically promote endometrial cancer progression via crosstalk between their receptor signaling pathways. *Cancer Biol Med*. 2019;16(1):55–70. doi:10.20892/j.issn.2095-3941.2018.0157

70. Cuesta R, Gritsenko MA, Petyuk VA, et al. Phosphoproteome analysis reveals estrogen-ER pathway as a modulator of mTOR activity via DEPTOR. *Mol Cell Proteomics*. 2019;18(8):1607–1618. doi:10.1074/mcp.RA119.015056

71. Chen R, Zhang M, Liu W, et al. Estrogen affects the negative feedback loop of PTENp1-miR200c to inhibit PTEN expression in the development of endometrioid endometrial carcinoma. *Cell Death Dis*. 2018;10(1):4. doi:10.1038/s41419-018-1204-7

72. Salmeron-Hernandez A, Noriega-Reyes MY, Jordan A, Baranda-Avilá N, Langley E. BCAS2 enhances carcinogenic effects of estrogen receptor alpha in breast cancer cells. *Int J Mol Sci*. 2019;20:204. doi:10.3390/ijms20040966

73. Arun A, Ansari MI, Popli P, et al. New piperverine derivative DTPEP acts as dual-acting anti-breast cancer agent by targeting ERalpha and downregulating PI3K/Akt- PKCalpha leading to caspase-dependent apoptosis. *Cell Probl*. 2018;51(6):e12501. doi:10.1111/cpr.12501

74. Han R, Gu S, Zhang Y, et al. Estrogen promotes progression of hormone-dependent breast cancer through CCL2-CCR2 axis by upregulation of Twist via PI3K/AKT/NF-kappaB signaling. *Sci Rep*. 2018;8(1):9575. doi:10.1038/s41598-018-27810-6

75. Dohlman HG. Thematic minireview series: cell biology of G protein signaling. *J Biol Chem*. 2015;290(11):6679–6680. doi:10.1074/jbc.R114.613093

76. Chambliis KL, Wu Q, Olmann S, et al. Non-nuclear estrogen receptor alpha signaling promotes cardiovascular protection but not uterine or breast cancer growth in mice. *J Clin Invest*. 2010;120(7):2319–2330. doi:10.1172/JCI38291

77. Banerjee S, Chambliis KL, Mineo C, Shaul PW. Recent insights into non-nuclear actions of estrogen receptor alpha. *Steroids*. 2014;81:64–69. doi:10.1016/j.steroids.2013.11.002

78. Divekar SD, Storchen GB, Sperle K, et al. The role of calcium in estrogen receptors alpha and beta in the normal, hyperplastic and carcinomatous human prostate. *J Endocrinol*. 2001;168(3):447–454. doi:10.1677/0joe.0.1680447

79. Mishra S, Tai Q, Gu X, et al. Estrogen and estrogen receptor alpha promotes malignancy and osteoblastic tumorigenesis in prostate cancer. *Oncotarget*. 2015;6(42):44388–44402. doi:10.18632/oncotarget.6462

80. Slavin S, Yeh CR, Da J, et al. Estrogen receptor alpha in cancer-associated fibroblasts suppresses prostate cancer invasion via modulation of thrombospondin 2 and matrix metalloprotease 3. *Carcinogenesis*. 2014;35(6):1301–1309. doi:10.1093/carcin/bgt488

81. Hou XW, Liang YK, Lin HY, et al. Nov3 maintains luminal phenotype and suppresses tumorigenesis and metastasis of breast cancer via trans-activating estrogen receptor-alpha. *Theranostics*. 2017;7(16):4041–4056. doi:10.7150/thno.19989

82. Hasson RM, Briggs A, Carothers AM, et al. Estrogen receptor alpha or beta loss in the colon of Min/+ mice promotes crypt expansion and impairs TGFbeta and HNF3beta signaling. *Carcinogenesis*. 2014;35(1):96–102. doi:10.1093/carcin/bgt323

83. Lund-Iversen M, Scott H, Strom EH, Theiss N, Brustugun OT, Porto CS. Estrogen receptor beta (ERbeta) mediates expression of beta-catenin and proliferation in prostate cancer cell line PC-3. *Clin Exp Pharmacol Physiol*. 2015;42(12):3098–3109. doi:10.1111/cepp.12715

84. Yang T, Trenk C, Kalinski T, Ornmann O, Ignatov A. GPER-1 expression is associated with a decreased response rate to primary estrogen receptor-positive triple-negative breast cancer. *Breast Cancer Res Treat*. 2020;309(8):1233. doi:10.1007/s10549-020-06323-9

85. Ibrahim A, Hugerth LW, Hases L, et al. Colitis-induced colorectal cancer via trans-activating estrogen receptor-alpha. *Theranostics*. 2018;8(4):2261–2269. doi:10.2217/ten.17.571

86. Stojiljkovic VM, Ilic-Djilovic J, Zarkovic N, et al. Estrogen receptor alpha mediates epithelial to mesenchymal transition, expression of specific matrix effectors and functional properties of breast cancer cells. *Matrix Biol*. 2015;43:42–60. doi:10.1016/j.matbio.2015.02.008

87. Misra SK, Talukder AH, Gururaj AE, et al. Upstream determinants of estrogen receptor-alpha regulation of metastatic tumor antigen 3 pathway. *J Biol Chem*. 2004;279(31):32709–32715. doi:10.1074/jbc.M402942200

88. Boursi P, Skandalis SS, Piperigkou Z, et al. Estrogen receptor alpha mediates epithelial to mesenchymal transition, expression of specific matrix effectors and functional properties of breast cancer cells. *Matrix Biol*. 2015;43:42–60. doi:10.1016/j.matbio.2015.02.008

89. Zhu C, Wang S, Wang B, et al. 17beta-Estradiol up-regulates Nr2f2 via PI3K/AKT and estrogen receptor signaling pathways to suppress light-induced degeneration in rat retina. *Neuroscience*. 2015;304:328–339. doi:10.1016/j.neuroscience.2015.07.057

90. Leung HW, Wang Z, Yue GG, et al. Cyclopeptide RA-V inhibits cell adhesion and invasion in both estrogen receptor positive and negative breast cancer cells via PI3K/AKT and NF-kappaB signaling pathways. *Biochim Biophys Acta*. 2015;1853(8):18 27–1840. doi:10.1016/j.bbamcr.2015.04.020

91. Royuela M, de Miguel MP, Bethencourt FR, et al. Estrogen receptors alpha and beta in the normal, hyperplastic and carcinomatous human prostate. *J Endocrinol*. 2001;168(3):447–454. doi:10.1677/0joe.0.1680447
102. Ignatov A, Ignatov T, Weissborn C, et al. G-protein-coupled estrogen receptor GPR30 and tamoxifen resistance in breast cancer. Breast Cancer Res Treat. 2011;128(2):457–466. doi:10.1007/s10549-011-1584-1

103. Ignatov A, Ignatov T, Roessner A, Costa SD, Kalinski T. Role of GPR30 in the mechanisms of tamoxifen resistance in breast cancer MCF-7 cells. Breast Cancer Res Treat. 2010;123(1):87–96. doi:10.1007/s10549-009-0624-6

104. Yang K, Yao Y. Mechanism of GPER promoting proliferation, migration and invasion of triple-negative breast cancer cells through RAF. Am J Transl Res. 2019;11(9):5858–5868.

105. Li Y, Jia Y, Bian Y, et al. Autocrine motility factor promotes endometrial cancer progression by targeting GPER-1. Cell Commun Signal. 2019;17(1):22. doi:10.1186/s12961-019-0336-4

106. Xie BY, Lv QY, Ning CC, et al. TET1-GPER-Pi3K/AKT pathway is involved in insulin-driven endometrial cancer cell proliferation. Biochim Biophys Res Commun. 2017;482(4):857–862. doi:10.1016/j.jbrc.2016.11.124

107. Bustos V, Nolan AM, Nijhuis A, et al. GPER mediates differential effects of estrogen on colon cancer cell proliferation and migration under normoxic and hypoxic conditions. Oncotarget. 2017;8(48):84258–84275. doi:10.18632/oncotarget.20653

108. Liu Q, Chen Z, Jiang G, et al. Epigenetic down regulation of G protein-coupled estrogen receptor (GPER) functions as a tumor suppressor in colorectal cancer. Mol Cancer. 2017;16(1):87. doi:10.1186/s12943-017-0654-3

109. Chen Y, Tang H, He J, et al. Interaction of nuclear ERs and GPER in vitellogenesis in zebrafish. J Steroid Biochem Mol Biol. 2019;189:10–18. doi:10.1016/j.jsbmb.2019.01.013

110. Lagunas N, Marraudino M, de Amorim M, et al. Estrogen receptor beta and G protein-coupled estrogen receptor 1 are involved in the acute estrogenic regulation of arginine-vasopressin immunoreactive nuclei in the supraoptic and paraventricular hypothalamic nuclei of female rats. Brain Res. 2019;1712:93–100. doi:10.1016/j.brainres.2019.02.002

111. Sanchez DS, Fischer Sigel LK, Azurmendi PJ, et al. Estradiol stimulates cell proliferation via classic estrogen receptor-alpha and G protein-coupled estrogen receptor-1 in human renal tubular epithelial cell primary cultures. Biochem Biophys Res Commun. 2019;512(2):170–175. doi:10.1016/j.bbrc.2019.03.056

112. Jonsson P, Katchy A, Williams C. Support of a bi-faceted role of estrogen receptor beta (ERbeta) in ERalpha-positive breast cancer cells. Endocr Relat Cancer. 2014;21(2):143–160. doi:10.1530/ERC-13-0444

113. Lu W, Katzenellenbogen BS. Estrogen Receptor-β modulation of the ERα-p53 loop regulating gene expression, proliferation, and apoptosis in breast cancer. Horm Cancer. 2017;8(4):230–242. doi:10.1007/s12672-017-0298-1

114. Linares PM, Algabe A, Urzainqui A, et al. Ratio of circulating estrogen receptors beta and alpha (ERβ/ERα) indicates endoscopic activity in patients with Crohn’s disease. Dig Dis Sci. 2017;62(10):2744–2754. doi:10.1007/s10620-017-4717-5

115. Sosa L, Gutierrez S, Petiti JP, et al. 17beta-Estradiol modulates the prolactin secretion induced by TRH through membrane estrogen receptors via Pi3K/Akt in female rat anterior pituitary cell culture. Am J Physiol Endocrinol Metab. 2012;302(10):E1189–E1197. doi:10.1152/ajpendo.00408.2011

116. Acconcia F, Totta P, Ogawa S, et al. Survival versus apoptotic 17beta-estradiol effect: role of ER alpha and ER beta activated non-genomic signaling. J Cell Physiol. 2005;203(1):193–201. doi:10.1002/jcp.20219

117. Reinbold RE, Mangini N, Hill JL, et al. Endocrine therapy in breast cancer: the needadvantaj, adjuvant, and metastatic approach. Semin Oncol Nurs. 2015;31(2):146–155. doi:10.1016/j.soncn.2015.02.002

118. Liu X, Miao W, Huang M, Li L, Dai X, Wang Y. Elevated Hexokinase II expression confers acquired resistance to 4-hydroxytamoxifen in breast cancer cells. Mol Cell Proteomics. 2019;18(11):2273–2284. doi:10.1074/mcp.RA119.001576

119. Khan SA, Rogers MA, Khurana KK, Meguid MM, Numann PJ. Estrogen receptor expression in benign breast epithelium and breast cancer risk. J Natl Cancer Inst. 1998;90(1):37–42. doi:10.1093/jnci/90.1.37

120. Widschwendter M, Siegmund KD, Muller HM, et al. Association of breast cancer DNA methylation profiles with hormone receptor status and response to tamoxifen. Cancer Res. 2004;64(11):3807–3813. doi:10.1158/0008-5472.CAN-03-3852

121. Haque MM, Desai KV. Pathways to endocrine therapy resistance in breast cancer. Front Endocrinol (Lausanne). 2019;10:573. doi:10.3389/fendo.2019.00573

122. Weiner M, Skoog L, Forander T, Nordenskjold B, Sgroi DC, Stal O. Oestrogen receptor co-activator AIB1 is a marker of breast cancer. Biochem Biophys Res Commun. 2019;512(2):170–175. doi:10.1016/j.bbrc.2019.03.056

123. Nicholson RL, Hutcheson IR, Jones HE, et al. Growth factor signalling in endocrine and anti-growth factor resistant breast cancer. Rev Endocr Metab Disord. 2007;8(3):241–253. doi:10.1007/s11540-007-9033-5

124. Hasson SP, Rubinek T, Ryvo L, Wolf J. Endocrine resistance in breast cancer: focus on the phosphatidylinositol 3-kinase/akt/mammalian target of rapamycin signaling pathway. Breast Care (Basel). 2013;8(4):248–255. doi:10.1159/000354757

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