Available online at www.sciencedirect.com
SCIENCE DIRECT
ELSEVIER
Steroids 68 (2003) 1–9
Steroids
www.elsevier.com/locate/steroids

Review

Estrogen receptor phosphorylation

Deborah A. Lannigan*

Center for Cell Signaling, Health Sciences Center, University of Virginia, Hospital West, Room 7041, Box 800577, Charlottesville, VA 22908-0577, USA

Received 30 April 2002; accepted 13 June 2002

Abstract

Estrogen receptor α (ERα) is phosphorylated on multiple amino acid residues. For example, in response to estradiol binding, human ERα is predominately phosphorylated on Ser-118 and to a lesser extent on Ser-104 and Ser-106. In response to activation of the mitogen-activated protein kinase pathway, phosphorylation occurs on Ser-118 and Ser-167. These serine residues are all located within the activation function 1 region of the N-terminal domain of ERα. In contrast, activation of protein kinase A increases the phosphorylation of Ser-236, which is located in the DNA-binding domain. The in vivo phosphorylation status of Tyr-537, located in the ligand-binding domain, remains controversial. In this review, I present evidence that these phosphorylations occur, and identify the kinases thought to be responsible. Additionally, the functional importance of ERα phosphorylation is discussed.
© 2002 Elsevier Science Inc. All rights reserved.

Keywords: Estrogen receptor; Phosphorylation; Transcription

1. Overview

This review will focus on the major phosphorylation sites in estrogen receptor α (ERα) that occur in response to either estradiol or through the activation of second messenger signaling pathways. The following questions will be addressed: (1) What are the sites of ER phosphorylation and which kinases are responsible for these phosphorylations? (2) How does phosphorylation influence ER function? (3) What is known about ER phosphatases? (4) How does estradiol directly influence signal transduction pathways? (5) What lessons on the function of phosphorylation can be learned from other steroid receptors?

1.1. Introduction

The ER belongs to a superfamily of ligand-activated transcription factors [1]. However, it is now well established that ER-mediated transcription can also be stimulated by ligand-independent mechanisms involving second messenger signaling pathways [2–15]. Furthermore, there are cell-type specific differences in the ability of second messenger signaling pathways to enhance ER-mediated transcription, which may account for the differences in ER action in various cells [16].

There are two known ER isoforms, α and β, which differ in their ligand specificities and physiological functions [17–19]. There are also a number of splice variants for each of the isoforms, some of which influence the activity of the wild type receptor [20–23]. Like other members of the superfamily, ERα and ERβ are made up of several functional domains (Fig. 1) [24]. The N-terminal domains of ERα and ERβ are highly divergent whereas the DNA binding domain (DBD) and the ligand-binding domain (LBD) are approximately 95 and 55% homologous, respectively.

The N-terminal domain contains a ligand-independent activation function (AF1) and was originally identified by its ability to stimulate transcription in an ERα deletion mutant that contained only the N-terminus fused to a heterologous DBD [25]. It seems reasonable to suggest that in the context of the holoreceptor, AF1 activity is silenced because of steric hindrance by the LBD. This inhibition appears to be relieved by addition of ligand. This model is supported by the ability of the LBD to control the function, in a ligand-dependent manner, of a wide variety of proteins to which it has been fused [26–30]. AF1 activity is also enhanced by the action of second messenger signaling pathways, which presumably must relieve the inhibition by the LBD. In response to ligand, AF1 synergizes with the ligand-dependent activation function (AF2) in the LBD [31,32]. AF1 plays a role in both ligand-dependent and ligand-independent transcription. However, in some cell types and on some promoters, AF1 does not significantly contribute to the transcriptional

* Tel.:+1-434-924-1144; fax: +1-434-924-1236.
E-mail address: dal5f@virginia.edu (D.A. Lannigan).

0039-128X/02/$ – see front matter © 2002 Elsevier Science Inc. All rights reserved.
PII: S0039-128X(02)00110-1

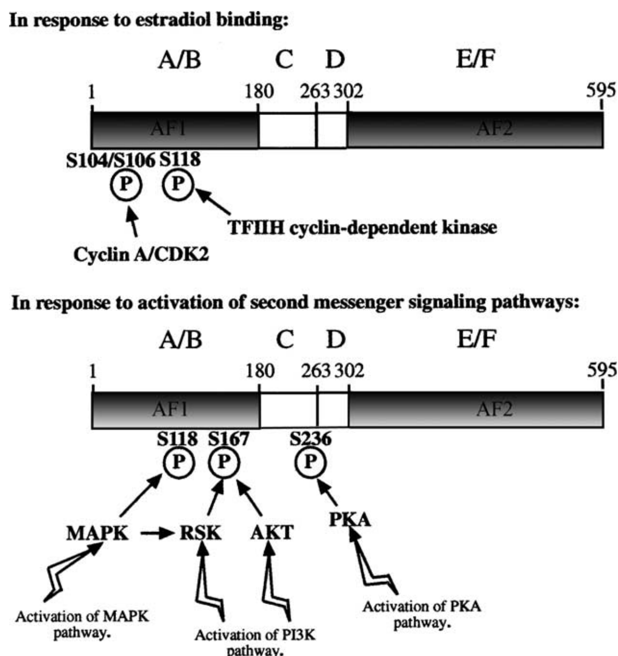

Fig. 1. Schematic illustrating the residues whose phosphorylations are enhanced in response to estradiol binding or activation of second messenger signaling pathways. The kinases thought to be responsible for these phosphorylations are also shown.

activation induced by ligand [33,34]. AF2 in the LBD was identified by its ability to stimulate transcription, only in response to ligand, of a mutant that contained just the LBD fused to a heterologous DBD [25,35]. In response to agonist, the receptor undergoes a conformational change in which helices 3, 5 and 12 form a surface with which co-activators interact [36–39]. The position of helix 12, relative to the body of the LBD, determines whether or not a ligand behaves as an agonist or an antagonist [38,40,41].

1.1.1. What are the sites of ER phosphorylation and which kinases are responsible for these phosphorylations?

Phosphorylation of ERα is enhanced in response to estradiol binding and through the action of second messenger signaling pathways [9,42–44]. Phosphorylation of ERβ in response to estradiol binding has not been examined in detail, although phosphorylation of ERβ has been shown to increase in response to activation of the MAPK pathway [45]. Several investigators have demonstrated that in a number of different cell types, in response to estradiol binding, ERα is phosphorylated only on serine residues [4,9,42,43,46–48]. Additionally, Le Goff et al. [9] demonstrated that stimulation of either the mitogen activated-protein kinase (MAPK) or cAMP-dependent kinase pathways resulted only in serine phosphorylation in ERα. However, others have reported that ERα may also be phosphorylated on tyrosine residues [49–53]. This phosphorylation does not change in response to estradiol binding. In Fig. 1, the residues whose phosphorylations are enhanced in response to ligand binding or activation of signaling cascades are shown. Additionally, the kinases thought to be responsible for these phosphorylations are indicated.

1.1.1.1. Serine 104, Serine 106 and Serine 118 phosphorylation. Serine 106 (Ser-106) and Ser-118 are highly conserved residues, whereas Ser-104 appears to be conserved only in mammals. These sites were initially determined to be phosphorylated by comparison of phosphopeptide patterns generated by wild type and mutant ERαs [9]. Joel et al. then demonstrated by peptide sequencing and manual Edman degradation that Ser-118 was the major site phosphorylated in response to estradiol [44]. In response to estradiol binding, the change in Ser-118 phosphorylation is dramatically larger than the change in Ser-104 and Ser-106 phosphorylation (unpublished observations). Upon activation of the MAPK pathway by EGF, phosphorylation of Ser-118 is enhanced whereas phosphorylation of Ser-104 and Ser-106 does not appear to change significantly [54]. Thus, although Ser-104, Ser-106 and Ser-118 are each followed by Pro residues, the phosphorylation of Ser-118 appears to be regulated differently from that of Ser-104 and Ser-106. These results may be due to the action of a single kinase with Ser-118 being the preferred substrate, or the preferential action of a phosphatase for phosphoSer-104 and phosphoSer-106 compared to phosphoSer-118. On the other hand, the results may reflect that Ser-104 and Ser-106 are phosphorylated by different kinases than Ser-118. In fact there is evidence for the latter possibility because cyclin-A-cyclin dependent kinase 2 (Cdk2) complex phosphorylates Ser-104 and Ser-106 but not Ser-118 [55].

Phosphorylation of Ser-118 results in reduced ERα mobility on SDS-PAGE [14]. Using this upshift assay the stoichiometry of Ser-118 phosphorylation in MCF-7 cells, a human breast cancer cell line, in response to estradiol binding is ∼0.67 mol of phosphate/mol of ERα, whereas in response to activation of the MAPK pathway, the stoichiometry is ∼0.25. Thus ERα is significantly phosphorylated on Ser-118 in response to either estradiol binding or activation of the MAPK pathway, which suggests that this phosphorylation plays an important role in ERα function. Ser-118 is the only site in ERα in which the stoichiometry of phosphorylation is known.

There is overwhelming in vitro and in vivo evidence that activated MAPK phosphorylates Ser-118 [12,14,44,56]. However, the identity of the kinase responsible for Ser-118 phosphorylation in response to estradiol binding is controversial [14]. Migliaccio et al. have reported that in cell lines of breast, prostate or kidney origin estradiol enhances the activity of c-src resulting in activation of the MAPK pathway and the subsequent enhancement of Ser-118 phosphorylation [57–59]. However, a number of other laboratories have not observed activation of the MAPK pathway in response to estradiol in cell lines of breast or kidney origin [14,60–63]. Other groups have observed that estradiol activates MAPK in cell lines of vascular or neural origin but

there appears to be disagreement as to whether the effect is through ER [64–67]. Furthermore, inhibition of MAPK did not prevent the estradiol-induced increase in Ser-118 phosphorylation and basal MAPK activity could not account for the increase. Joel et al. have proposed that a kinase in addition to MAPK regulates Ser-118 phosphorylation [14]. One possible candidate for the estradiol-induced Ser-118 phosphorylation is TFIIH cyclin-dependent kinase [60].

1.1.1.2. Serine 167 phosphorylation. It has been reported that Ser-167 is a major site of phosphorylation in response to estradiol binding [68]. However, Le Goff et al. [9] did not observe Ser-167 phosphorylation in response to estradiol and these results are in agreement with observations made using a phosphospecific Ser-167 antibody [69]. However, Ser-167 does get phosphorylated in response to activation of the MAPK pathway [54]. In vivo and in vitro evidence demonstrated that the kinase downstream from MAPK, p90 ribosomal S6 kinase (Rsk) [70], can phosphorylate Ser-167 [54]. Thus ERα is phosphorylated by two different kinases in the MAPK pathway. The significance of this dual phosphorylation by kinases in the same signal transduction pathway is not understood. Ser-167 can also be phosphorylated in vitro by casein kinase II and by AKT, which is also called protein kinase B [71–74]. There is as yet no evidence that casein kinase II phosphorylates Ser-167 in vivo. In general, kinases have a broader substrate specificity in vitro than they have in vivo. Thus it is difficult to determine the physiological relevance of a kinase based solely on in vitro assays. Additionally, the extensive cross talk that exists between different signal transduction pathways in vivo makes it difficult to determine the in vivo contributions of a kinase to a particular phosphorylation event. For example, Rsk and AKT have identical consensus phosphorylation sequences that they recognize and therefore in vitro they will phosphorylate the same substrates. Furthermore, in vivo, signal transduction pathways that activate AKT also stimulate PDK1 activity. PDK1 influences the activity of both Rsk and AKT (Fig. 2). Currently, there are no known specific inhibitors of either Rsk or AKT activity that do not also inhibit the activity of upstream kinases [75]. However, a constitutively active mutant of Rsk in combination with estradiol synergistically enhances ERα-mediated transcription under conditions in which AKT activity should be extremely low [69]. These results suggest that Rsk plays an important role in ERα-mediated transcription. However, it is likely that both Rsk and AKT regulate ERα activity but their importance in this regulation may vary depending on the cell type and extracellular signal.

1.1.1.3. Serine 236 phosphorylation. In vitro, protein kinase A (PKA) can phosphorylate Ser-236, which is located in the DNA binding domain [76]. Additionally, 8-bromo cAMP treatment increases the phosphorylation of wild type ERα to a greater extent than a mutant in which Ser-236 is changed to Ala in vivo. These results are in agreement with

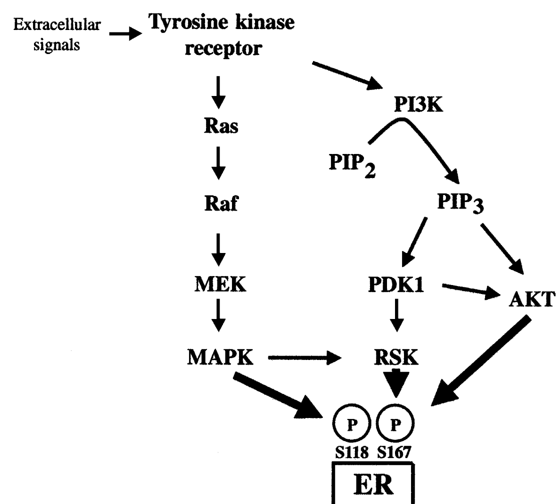

Fig. 2. Schematic demonstrating the crosstalk that occurs between the pathways that activate Rsk and AKT.

Le Goff et al. who demonstrated that in response to activation of the cAMP-dependent kinase pathway ERα is phosphorylated on serine residues not located in the N-terminal domain [9].

1.1.1.4. Tyrosine 537 phosphorylation. Arnold et al. [49,50] have reported that Tyr-537 of human ERα is phosphorylated in MCF7 and in insect cells and that this phosphorylation does not change in response to ligand. However, the phosphoTyrosine antibody used in these studies has also been shown to interact with a mutant ERα in which Tyr-537 has been altered to Ala [77]. Tyrosine phosphorylation has also been reported in ERα isolated from calf uterus, and from breast cancer cells that overexpress the HER-2 receptor [52,78–80] but tyrosine phosphorylation has not been observed by a number of other groups [9,42,43,46–48]. These conflicting reports may be due to the fact that tyrosine phosphorylation occurs on a small minority of the receptor molecules, is cell-specific or occurs only under conditions in which the tyrosine kinase is present in great abundance. In vitro tyrosine phosphorylation has been observed using src tyrosine kinases and a kinase purified from calf uterus [50,81].

1.1.2. How does phosphorylation influence ER function?

In general, phosphorylation of Ser residues in the AF1 domain appears to influence the recruitment of coactivators, resulting in enhanced ER-mediated transcription [82–84]. The importance of Ser-118 phosphorylation has been studied by a number of different investigators and there is significant discrepancy in the literature concerning the transcriptional activity of the mutant ERα, in which Ser-118 is mutated to Ala(S118-ERα), compared to the wild type ERα. A number of groups have reported, in cell lines of either fibroblast or epithelial origin, that S118A-ERα has a diminished ability to activate transcription in response to estradiol compared

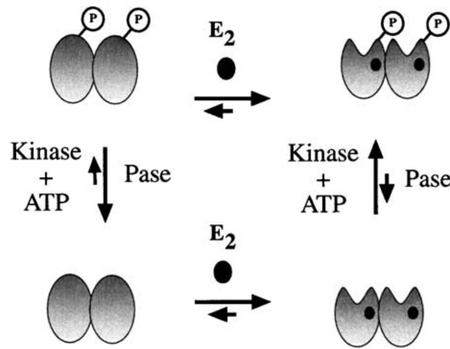

Fig. 3. Schematic showing the effect of estradiol binding on the equilibrium of the unphosphorylated and phosphorylated ERα.

to wild type ERα [12,54,56,85]. Additionally, mutation of Ser-118 to an acidic residue could enhance the transcriptional response [85]. In contrast, Le Goff et al. found that S118A-ERα had approximately the same estrogen-induced transcriptional activity compared to the wild type ERα [9]. These studies were also performed in cell lines of either fibroblast or epithelial origin. However, an ERα mutant in which Ser-104, Ser-106 and Ser-118 were all mutated to Ala did have a decreased ability to activate estrogen-induced transcription as compared to wild type ERα.

It is important to account for the possible sources of these discrepancies in order to determine the physiological significance of ERα phosphorylation. One problem is that no two groups have used reporter constructs that have identical promoters in the same cell line, which may explain the discrepancies. To account for the discrepancies that could occur we will consider a simple model (Fig. 3). In the absence of estradiol, the ER exists predominantly in a dephosphorylated form presumably because the phosphatase is more effective at dephosphorylating the ER than the kinase is at phosphorylating the ER. However, in the presence of estradiol, the receptor undergoes a conformational change, which either enhances the ability of the kinase to phosphorylate ER or decreases the ability of the phosphatase to dephosphorylate ER. Regardless, in the presence of estradiol ER phosphorylation is increased. It is possible that part of the disparity in the literature arises from the use of different transient transfection systems to study the effects of ER mutants. Overexpression of the wild type or mutant ERs from an expression plasmid may result in a mass-action-driven shift in equilibrium toward the formation of a receptor co-activator complex. Thus, differences in affinity of the phosphorylated and the unphosphorylated ER for the co-activator could be masked, resulting in similar transcriptional responses for both the wild type and mutant ERs. It is also very likely that the activity of the phosphatase and kinase and thus the extent of ER phosphorylation in response to estradiol may vary considerably between different cell types. Thus, in cells in which ER is not significantly phosphorylated because the kinase activity is low, the difference between wild type ER and phosphorylation-defective ER mutants to stimulate transcription will be similar. Some of the disparity in the literature may therefore, be accounted for by variations in the stoichiometry of ER phosphorylation between cell types. Furthermore, if the function of ER phosphorylation is to enhance the ability of ER to interact with a co-activator it is possible that the ER and co-activator complex is more important for some promoters than for others.

There are also differences in the literature on the ability of the S118A-ERα mutant to transactivate in response to activation of the MAPK pathway. Some groups have reported that mutation of Ser-118 to Ala resulted in a receptor that is completely unable to transactivate in response to EGF or overexpression of ras [12,56]. However, Joel et al. [54] found that, in response to overexpression of constitutively active MAPK kinase (MEK), the S118A-ERα mutant transactivated but at a diminished level compared to wild type ERα. The discrepancy between these results might also be explained by cell type and promoter specificity. Activation of the MAPK pathway brings additional complications to the model shown in Fig. 3 because the ability of co-activators to influence transcription can be effected by their phosphorylation. For example, MAPK phosphorylation of ERβ and steroid receptor coactivator-1 enhances their ability to interact and it is thought that this increased complex formation stimulates ERβ-mediated transcription [82,86]. MAPK phosphorylation of AIB1, a member of the p160 coactivator family that stimulates ER-mediated transcription, enhances the amount of histone acetylase transferase activity associated with AIB and thus facilitates chromatin reorganization [87]. However, mutation of Ser-118 to Ala did not reduce the ability of GRIP1, another member of the p160 coactivator family, to enhance ERα-mediated transcription and so in some cases the phosphorylation of the co-activator may be more important in regulating ERα activity than phosphorylation of ERα [88,89].

It is of interest to note that the kinetics of Ser-118 phosphorylation induced by estradiol binding and activation of the MAPK pathway are quite different [44]. In MCF-7 cells, estradiol induces a steady state phosphorylation of Ser-118 within 20 min, whereas in response to epidermal growth factor (EGF) or phorbol 12-myristate 13-acetate (PMA), Ser-118 is rapidly but only transiently phosphorylated. It is possible that phosphorylation of Ser-118 performs the same function either in response to estradiol binding or activation of the MAPK pathway. However, it is also possible that the transient phosphorylation of Ser-118 in response to EGF is not as important in MCF-7 cells as the EGF-induced phosphorylation of Ser-167 in ERα and of coactivators. In support of this latter hypothesis are observations that in MCF-7 cells, the EGF-induced transient MAPK activation leads to sustained activation of Rsk and Ser-167 phosphorylation in ERα (unpublished observations). The importance of Ser-167 phosphorylation has been shown by the diminished transcriptional ability in response to activation of the MAPK pathway of an ERα mutant, which has Ser-167 replaced by Ala, compared to the activity of the wild type ERα [54,69].

Clark et al. have suggested that Rsk2 plays a more important role than MAPK in the stimulation of ERα-mediated transcription in response to EGF. They have also shown that Rsk2 does not stimulate ERβ-mediated transcription and have hypothesized that MAPK plays different roles in regulating ERα and ERβ transcriptional activity. They have suggested that direct MAPK phosphorylation of ERβ is important in ERβ-mediated transcriptional activation whereas MAPK activation of Rsk and the subsequent Rsk phosphorylation of ERα is important in ERα transcriptional activation.

The AF-2 region plays an important role in mediating transcriptional activation by cAMP [90]. However, mutagenesis of putative PKA phosphorylation sites did not prevent activation of ERα-mediated transcription by cAMP [91]. It may be that PKA regulation of co-activator function rather than the phosphorylation of ERα plays a more important role in cAMP activation of ERα-mediated transcription. This hypothesis is supported by the observations that the association of cyclin D1 with ER is regulated by cAMP-dependent pathways [92]. Cyclin D1 has been shown to stimulate ERα-mediated transcription by a mechanism that does not depend on its ability to associate with cyclin-dependent kinase 4 [93,94].

Although there have been conflicting reports on the phosphorylation of Tyr-537, a number of investigators have shown that this Tyr residue does play an important role in AF2 function. Some mutations at Tyr-537 produce constitutively active receptors that are able to recruit co-activators in a ligand-independent manner [95,96]. Tyr-537 is also thought to be involved in the association of ERα with the c-src tyrosine kinase [59]. The importance of this interaction in regulating signal transduction by the MAPK pathway will be discussed later.

1.1.3. What is known about ER phosphatases?

Okadaic acid, an inhibitor of protein Ser/Thr phosphatases 1 and 2, has been shown to stimulate ERα-mediated transcription; however, the identities of the ER phosphatases are unknown [2]. The phosphatase Cdc25B, which activate Cdks by removal of inhibitory phosphates, acts as an ERα co-activator but its phosphatase activity is not required for its ability to enhance ERα-mediated transcription [97]. Inhibition of protein phosphatase 5 (PP5) expression stimulates glucocorticoid receptor-mediated transcription but no studies of other steroid receptors have been described [98]. However, vanadate, a Tyr phosphatase inhibitor, has been shown to stimulate proliferation of MCF7 cells presumably through activation of ER, since antiestrogens inhibited the proliferative response [99]. Vanadate is also known to stimulate the activity of the epidermal growth factor receptor (EGFR), resulting in enhanced MAPK activity [100]. The situation is confusing because antiestrogens can also prevent the stimulation of EGFR phosphorylation in response to vanadate, but the mechanism of this inhibition is unknown [99].

1.1.4. How does estradiol influence signal transduction pathways?

The classical model for estrogen action is through alterations in gene expression. However, evidence is accumulating for novel paradigms of estrogen action that occur rapidly and do not involve changes in gene expression. One of the most striking examples of the new paradigms is the activation of signal transduction cascades that are the result of estradiol-induced associations of ERα with the tyrosine kinase, c-src, and with the regulatory subunit of phosphatidylinositol-3-OH (PI(3)) kinase. It is also of interest to note that addition of estradiol increases cAMP levels by enhancing adenylate cyclase activity. However, the mechanism for this activation is unknown [10]. Additionally, ERα interacts with and stimulates autophosphorylation of the insulin-like growth factor-1 receptor in an estradiol-dependent manner by a mechanism that has not yet been determined [101].

Migliaccio et al. have shown that addition of estradiol to MCF7 cells increases MAPK activity and they have proposed that phosphoTyr-537 of ERα is involved in the recruitment of c-src in a ligand-dependent manner [57,59]. However, a mutant in which Tyr-537 has been altered to Phe was used to demonstrate the importance of the Tyr-537 in c-src binding. It is not clear that the inability of the mutant to bind c-src was only due to the elimination of Tyr because the Phe mutation destabilizes ERα, most likely by altering ERα conformation [77]. There also appears to be disagreement as to whether the estradiol-induced activation of MAPK depends on src [102]. Filardo et al. have proposed that estradiol activates MAPK through the release of heparin-bound EGF, which results in activation of the EGF receptor [103,104]. This group has also proposed that estradiol-dependent activation of MAPK depends on a G protein-coupled receptor rather than on the presence of the ER.

Migliaccio et al. [58,59] have shown that hormonal stimulation of the progesterone (PR) or the androgen receptor only in the presence of co-expressed ERα stimulates c-src activity. However, Boonyaratanakornkit et al. [105] have shown that purified PR interacts and stimulates the activity of c-src whereas purified ERα interacts with but is not able to stimulate the activity of c-src. They have suggested that the binding of PR to the SH3 domain in c-src relieves c-src autoinhibition, which results in an increase in kinase activity. Interestingly, they observed that in vivo co-expression of ERα was necessary to observe the hormonal stimulation of c-src activity by the PR. It appears that ERα lowers the basal activity of c-src in vivo, but the mechanism of this inhibition is not clear. Nonetheless, enhancement of c-src activity increases the extent of Shc phosphorylation, which stimulates the formation of the complex consisting of Shc, the adapter protein, GRB2 and the GTP exchange factor, Sos. This complex increases the amount of GTP bound p21ras, which leads to activation of Raf and the subsequent activation of MAPK.

There are now a number of conflicting reports on the ability of estradiol to activate MAPK in MCF7 cells and thus there must be unexplained differences between the MCF7 sublines [14,61–63,106–108]. It is important to note that the activation of MAPK by estradiol is substantially smaller than the activation that is observed with EGF or other growth factors. This observation is important because the physiological action of MAPK has been shown to depend on the extent of MAPK activation [109–112].

Estradiol has been shown to increase endothelial nitric oxide synthase activity in vascular endothelial cells [65,113,114]. This increase is apparently mediated by an estradiol-induced increase in phosphatidylinositol-3,4,5-P_3 (PI(3)) levels. ERα is able to form a ternary complex with the regulatory subunit of PI(3) kinase (p85) and src in a ligand-dependent manner [115]. It is possible that ERα interacts with the SH2 domain in p85 and that this interaction relieves the inhibition of the catalytic subunit of PI(3) kinase [116]. The thyroid receptor and glucocorticoid receptors were also able to interact with the p85 regulatory subunit in a ligand-dependent manner. Estradiol also activates AKT activity in an ER-dependent manner in vascular cells but in an ER-independent manner in breast cells [65,117].

In addition to the ability of ERα enhancing the activity of associated kinases, Clark et al. [69] have reported that the physical interaction of Rsk with ERα enhances the transcriptional activity of ERα. ERβ has also been shown to interact with the Rsk related kinase, Mnk2 but the functional consequences of this association are unknown [118].

1.1.5. What lessons on the function of phosphorylation can be learned from other steroid receptors?

GR phosphorylation has been shown to be regulated in a cell cycle dependent manner, which influences GR transcriptional activity through the cell cycle [119]. I am not aware of any studies demonstrating cell cycle involvement in regulating ERα phosphorylation. In addition to enhancing transcriptional activation there is evidence that phosphorylation of PR and glucocorticoid receptor (GR) enhances their rate of degradation by the ubiquitin/proteasome pathway [120,121]. In response to hormone binding, the rate of ERα destruction is also enhanced by the ubiquitin/proteasome pathway but as yet there is no evidence that phosphorylation is involved in regulating ERα destruction [122–124].

1.2. Conclusion

In summary, in response to estradiol, ERα becomes predominantly phosphorylated on Ser-118 and to a lesser extent on Ser-104 and Ser-106. Activation of the MAPK pathway enhances phosphorylation of Ser-118 and Ser-167. Phosphorylation of Ser-118 leads to an increased association with known ERα co-activators. The mechanism by which Ser-104, Ser-106 and Ser-167 phosphorylation enhances ERα-mediated transcription is not known. Phosphorylation of Ser-236 by PKA does not appear to be involved in the activation of ERα-mediated transcription in response to activation of the PKA pathway. However, stimulation of the PKA pathway enhances the association of ERα with cyclin D1, a known enhancer of ERα-mediated transcription. Tyr-537 is thought to play a critical role in the ability of ERα to interact with kinases containing SH2 domains; however, the phosphorylation status of this residue in vivo remains controversial. The association of ERα with various kinases appears to influence both the activity of the kinase and ERα. The functional consequences of this crosstalk have only begun to be explored.

Acknowledgments

I thank Margaret Shupnik for helpful discussions and critical reading of the manuscript. This work was supported by Research Project Grant #TBE-97523 from the American Cancer Society.

References

[1] Mangelsdorf DJ, Thummel C, Beato M, Herrlich P, Schütz G, Umesono K, et al. The nuclear receptor superfamily: the second decade. Cell 1995;83:835–9.
[2] Power RF, Mani SK, Codina J, Conneely OM, O'Malley BW. Dopaminergic and ligand-independent activation of steroid hormone receptors. Science 1991;254:1636–9.
[3] Ignar-Trowbridge DM, Nelson KG, Bidwell MC, Curtis SW, Washburn TF, McLachlan JA, et al. Coupling of dual signaling pathways: epidermal growth factor action involves the estrogen receptor. Proc Natl Acad Sci USA 1992;89:4658–62.
[4] Aronica SM, Katzenellenbogen BS. Stimulation of estrogen receptor-mediated transcription and alteration in the phosphorylation state of the rat uterine estrogen receptor by estrogen, cyclic adenosine monophosphate, and insulin-like growth factor-1. Mol Endocrinol 1993;7:743–52.
[5] Cho H, Katzenellenbogen BS. Synergistic activation of estrogen receptor-mediated transcription by estradiol and protein kinase activators. Mol Endocrinol 1993;7:441–52.
[6] Smith CL, Conneely OM, O'Malley BW. Modulation of the ligand-independent activation of the human estrogen receptor by hormone and antihormone. Proc Natl Acad Sci USA 1993;90:6120–4.
[7] Ignar-Trowbridge DM, Teng CT, Ross KA, Parker MG, Korach KS, McLachlan JA. Peptide growth factors elicit estrogen receptor-dependent transcriptional activation of an estrogen-responsive element. Mol Endocrinol 1993;7:992–8.
[8] Ince BA, Montano MM, Katzenellenbogen BS. Activation of transcriptionally inactive human estrogen receptors by cyclic adenosine 3′,5′-monophosphate and ligands including antiestrogens. Mol Endocrinol 1994;8:1397–406.
[9] Le Goff P, Montano MM, Schodin DJ, Katzenellenbogen BS. Phosphorylation of the human estrogen receptor. Identification of hormone-regulated sites and examination of their influence on transcriptional activity. J Biol Chem 1994;269:4458–66.
[10] Aronica SM, Kraus WL, Katzenellenbogen BS. Estrogen action via the cAMP signaling pathway: stimulation of adenylate cyclase and cAMP-regulated gene transcription. Proc Natl Acad Sci USA 1994;91:8517–21.
[11] Ignar-Trowbridge DM, Pimentel M, Parker MG, McLachlan JA, Korach KS. Peptide growth factor cross-talk with the estrogen receptor requires the A/B domain and occurs independently of protein kinase C or estradiol. Endocrinology 1996;137:1735–44.

[12] Bunone G, Briand PA, Miksicek RJ, Picard D. Activation of the unliganded estrogen receptor by EGF involves the MAP kinase pathway and direct phosphorylation. EMBO J 1996;15:2174–83.

[13] Curtis SW, Washburn T, Sewall C, DiAugustine R, Lindzey J, Couse JF, et al. Physiological coupling of growth factor and steroid receptor signaling pathways: estrogen receptor knockout mice lack estrogen-like response to epidermal growth factor. Proc Natl Acad Sci USA 1996;93:12626–30.

[14] Joel PB, Traish AM, Lannigan DA. Estradiol-induced phosphorylation of Serine 118 in the estrogen receptor is independent of p42/p44 mitogen-activated protein kinase. J Biol Chem 1998;273: 13317–23.

[15] Klotz DM, Hewitt SC, Ciana P, Raviscioni M, Lindzey JK, Foley J, et al. Requirement of estrogen receptor-alpha in insulin-like growth factor-1 (IGF-1)-induced uterine responses and in vivo evidence for IGF-1/estrogen receptor cross-talk. J Biol Chem 2002;277:8531–7.

[16] Schreihofer DA, Resnick EM, Lin VY, Shupnik MA. Ligand-independent activation of pituitary ER: dependence on PKA-stimulated pathways. Endocrinology 2001;142:3361–8.

[17] Gustafsson JA. An update on estrogen receptors. Semin Perinatol 2000;24:66–9.

[18] Kuiper GG, Lemmen JG, Carlsson B, Corton JC, Safe SH, van der Saag PT, et al. Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta. Endocrinology 1998;139: 4252–63.

[19] Katzenellenbogen BS, Montano MM, Ediger TR, Sun J, Ekena K, Lazennec G, et al. Estrogen receptors: selective ligands, partners, and distinctive pharmacology. Recent Prog Horm Res 2000;55:163–93.

[20] Hopp TA, Fuqua SA. Estrogen receptor variants. J Mammary Gland Biol Neoplasia 1998;3:73–83.

[21] Shupnik MA, Pitt LK, Soh AY, Anderson A, Lopes MB, Laws ER. Selective expression of estrogen receptor alpha and beta isoforms in human pituitary tumors. J Clin Endocrinol Metab 1998;83:3965–72.

[22] Jazaeri O, Shupnik MA, Jazaeri AA, Rice LW. Expression of estrogen receptor alpha mRNA and protein variants in human endometrial carcinoma. Gynecol Oncol 1999;74:38–47.

[23] Schreihofer DA, Stoler MH, Shupnik MA. Differential expression and regulation of estrogen receptors (ERs) in rat pituitary and cell lines: estrogen decreases ERalpha protein and estrogen responsiveness. Endocrinology 2000;141:2174–84.

[24] Kumar R, Thompson EB. The structure of the nuclear hormone receptors. Steroids 1999;64:310–9.

[25] Lees JA, Fawell SE, Parker MG. Identification of two transactivation domains in the mouse oestrogen receptor. Nucleic Acids Res 1989;17:5477–88.

[26] Crowe DL, Brown TN, Kim R, Smith SM, Lee MK. A c-fos/ estrogen receptor fusion protein promotes cell cycle progression and proliferation of human cancer cell lines. Mol Cell Biol Res Commun 2000;3:243–8.

[27] Kametaka M, Kume A, Mizukami H, Hanazono Y, Ozawa K. A suicide gene encoding fas-estrogen receptor chimeric molecule for inducible apoptosis of cytotoxic T lymphocytes. Exp Hematol 2000;28:1495.

[28] Fialka I, Schwarz H, Reichmann E, Oft M, Busslinger M, Beug H. The estrogen-dependent c-JunER protein causes a reversible loss of mammary epithelial cell polarity involving a destabilization of adherens junctions. J Cell Biol 1996;132:1115–32.

[29] Littlewood TD, Hancock DC, Danielian PS, Parker MG, Evan GI. A modified oestrogen receptor ligand-binding domain as an improved switch for the regulation of heterologous proteins. Nucleic Acids Res 1995;23:1686–90.

[30] Boehmelt G, Madruga J, Dorfler P, Briegel K, Schwarz H, Enrietto PJ, et al. Dendritic cell progenitor is transformed by a conditional v-Rel estrogen receptor fusion protein v-RelER. Cell 1995;80:341–52.

[31] Kraus WL, McInerney EM, Katzenellenbogen BS. Ligand-dependent, transcriptionally productive association of the amino-and carboxyl-terminal regions of a steroid hormone nuclear receptor. Proc Natl Acad Sci USA 1995;92:12314–8.

[32] Gandini O, Kohno H, Curtis S, Korach KS. Two transcription activation functions in the amino terminus of the mouse estrogen receptor that are affected by the carboxy terminus. Steroids 1997;62:508–15.

[33] Tora L, White J, Brou C, Tasset D, Webster N, Scheer E, et al. The human estrogen receptor has two independent nonacidic transcriptional activation functions. Cell 1989;59:477–87.

[34] Tzukerman MT, Esty A, Santiso-Mere D, Danielian P, Parker MG, Stein RB, et al. Human estrogen receptor transactivational capacity is determined by both cellular and promoter context and mediated by two functionally distinct intramolecular regions. Mol Endocrinol 1994;8:21–30.

[35] Webster NJ, Green S, Jin JR, Chambon P. The hormone-binding domains of the estrogen and glucocorticoid receptors contain an inducible transcription activation function. Cell 1988;54:199–207.

[36] Feng W, Ribeiro RC, Wagner RL, Nguyen H, Apriletti JW, Fletterick RJ, et al. Hormone-dependent coactivator binding to a hydrophobic cleft on nuclear receptors. Science 1998;280:1747–9.

[37] Darimont BD, Wagner RL, Apriletti JW, Stallcup MR, Kushner PJ, Baxter JD, et al. Structure and specificity of nuclear receptor-coactivator interactions. Genes Dev 1998;12:3343–56.

[38] Shiau AK, Barstad D, Loria PM, Cheng L, Kushner PJ, Agard DA, et al. The structural basis of estrogen receptor/coactivator recognition and the antagonism of this interaction by tamoxifen. Cell 1998;95:927–37.

[39] Mak HY, Hoare S, Henttu PM, Parker MG. Molecular determinants of the estrogen receptor-coactivator interface. Mol Cell Biol 1999;19:3895–903.

[40] Nichols M, Rientjes JM, Stewart AF. Different positioning of the ligand-binding domain helix 12 and the F domain of the estrogen receptor accounts for functional differences between agonists and antagonists. EMBO J 1998;17:765–73.

[41] Brzozowski AM, Pike AC, Dauter Z, Hubbard RE, Bonn T, Engstrom O, et al. Molecular basis of agonism and antagonism in the oestrogen receptor. Nature 1997;389:753–8.

[42] Denton RR, Koszewski NJ, Notides AC. Estrogen receptor phosphorylation: hormonal dependence and consequence on specific DNA binding. J Biol Chem 1992;267:7263–8.

[43] Washburn T, Hocutt A, Brautigan DL, Korach KS. Uterine estrogen receptor in vivo: phosphorylation of nuclear specific forms on serine residues. Mol Endocrinol 1991;5:235–42.

[44] Joel PB, Traish AM, Lannigan DA. Estradiol and phorbol ester cause phosphorylation of serine 118 in the human estrogen receptor. Mol Endocrinol 1995;9:1041–52.

[45] Tremblay GB, Tremblay A, Copeland NG, Gilbert DJ, Jenkins NA, Labrie F, et al. Cloning, chromosomal localization, and functional analysis of the murine estrogen receptor beta. Mol Endocrinol 1997;11:353–65.

[46] Ali S, Metzger D, Bornert JM, Chambon P. Modulation of transcriptional activation by ligand-dependent phosphorylation of the human oestrogen receptor A/B region. EMBO J 1993;12:1153–60.

[47] Lahooti H, White R, Danielian PS, Parker MG. Characterization of ligand-dependent phosphorylation of the estrogen receptor. Mol Endocrinol 1994;8:182–8.

[48] Lahooti H, White R, Hoare SA, Rahman D, Pappin DJ, Parker MG. Identification of phosphorylation sites in the mouse oestrogen receptor. J Steroid Biochem Mol Biol 1995;55:305–13.

[49] Arnold SF, Melamed M, Vorojeikina DP, Notides AC, Sasson S. Estradiol-binding mechanism and binding capacity of the human estrogen receptor is regulated by tyrosine phosphorylation. Mol Endocrinol 1997;11:48–53.

[50] Arnold SF, Obourn JD, Jaffe H, Notides AC. Phosphorylation of the human estrogen receptor on tyrosine 537 in vivo and by Src family tyrosine kinases in vitro. Mol Endocrinol 1995;9:24–33.

[51] Arnold SF, Vorojeikina DP, Notides AC. Phosphorylation of tyrosine 537 on the human estrogen receptor is required for binding to an estrogen response element. J Biol Chem 1995;270:30205–12.

[52] Auricchio F, Migliaccio A, Castoria G, Di Domenico M, Pagano M. Phosphorylation of uterus estradiol receptor on tyrosine. Prog Clin Biol Res 1990;322:133–55.

[53] Auricchio F, Migliaccio A, Castoria G, Rotondi A, Di Domenico M, Pagano M, et al. Phosphorylation of estradiol receptor on tyrosine and interaction of estradiol and glucocorticoid receptors with antiphosphotyrosine antibodies. Adv Exp Med Biol 1988;231:519–40.

[54] Joel PB, Smith J, Sturgill TW, Fisher TL, Blenis J, Lannigan DA. pp90rsk1 regulates estrogen receptor-mediated transcription through phosphorylation of Ser-167. Mol Cell Biol 1998;18:1978–84.

[55] Rogatsky I, Trowbridge JM, Garabedian MJ. Potentiation of human estrogen receptor alpha transcriptional activation through phosphorylation of serines 104 and 106 by the cyclin A-CDK2 complex. J Biol Chem 1999;274:22296–302.

[56] Kato S, Endoh H, Masuhiro Y, Kitamoto T, Uchiyama S, Sasaki H, et al. Activation of the estrogen receptor through phosphorylation by mitogen-activated protein kinase. Science 1995;270:1491–4.

[57] Migliaccio A, Di Domenico M, Castoria G, de Falco A, Bontempo P, Nola E, et al. Tyrosine kinase/p21ras/MAP-kinase pathway activation by estradiol-receptor complex in MCF-7 cells. EMBO J 1996;15:1292–300.

[58] Migliaccio A, Piccolo D, Castoria G, Didomenico M, Bilancio A, Lombardi M, et al. Activation of the src/p21(Ras)/Erk pathway by progesterone receptor via cross-talk with estrogen receptor. EMBO J 1998;17:2008–18.

[59] Migliaccio A, Castoria G, Di Domenico M, de Falco A, Bilancio A, Lombardi M, et al. Steroid-induced androgen receptor-oestradiol receptor beta-Src complex triggers prostate cancer cell proliferation. EMBO J 2000;19:5406–17.

[60] Chen D, Riedl T, Washbrook E, Pace PE, Coombes RC, Egly JM, et al. Activation of estrogen receptor alpha by S118 phosphorylation involves a ligand-dependent interaction with TFIIH and participation of CDK7. Mol Cell 2000;6:127–37.

[61] Lobenhofer EK, Marks JR. Estrogen-induced mitogenesis of MCF-7 cells does not require the induction of mitogen-activated protein kinase activity. J Steroid Biochem Mol Biol 2000;75:11–20.

[62] Lobenhofer EK, Huper G, Iglehart JD, Marks JR. Inhibition of mitogen-activated protein kinase and phosphatidylinositol 3-kinase activity in MCF-7 cells prevents estrogen-induced mitogenesis. Cell Growth Differ 2000;11:99–110.

[63] Caristi S, Galera JL, Matarese F, Imai M, Caporali S, Cancemi M, et al. Estrogens do not modify MAP kinase-dependent nuclear signaling during stimulation of early G(1) progression in human breast cancer cells. Cancer Res 2001;61:6360–6.

[64] Watters JJ, Campbell JS, Cunningham MJ, Krebs EG, Dorsa DM. Rapid membrane effects of steroids in neuroblastoma cells: effects of estrogen on mitogen activated protein kinase signalling cascade and c-fos immediate early gene transcription. Endocrinology 1997;138:4030–3.

[65] Hisamoto K, Ohmichi M, Kurachi H, Hayakawa J, Kanda Y, Nishio Y, et al. Estrogen induces the Akt-dependent activation of endothelial nitric oxide synthase in vascular endothelial cells. J Biol Chem 2000;23:23.

[66] Manthey D, Heck S, Engert S, Behl C. Estrogen induces a rapid secretion of amyloid beta precursor protein via the mitogen-activated protein kinase pathway. Eur J Biochem 2001;268:4285–91.

[67] Singh M, Setalo Jr G, Guan X, Frail DE, Toran-Allerand CD. Estrogen-induced activation of the mitogen-activated protein kinase cascade in the cerebral cortex of estrogen receptor-alpha knock-out mice. J Neurosci 2000;20:1694–700.

[68] Arnold SF, Obourn JD, Jaffe H, Notides AC. Serine 167 is the major estradiol-induced phosphorylation site on the human estrogen receptor. Mol Endocrinol 1994;8:1208–14.

[69] Clark DE, Poteet-Smith CE, Smith JA, Lannigan DA. Rsk2 allosterically activates estrogen receptor alpha by docking to the hormone-binding domain. EMBO J 2001;20:3484–94.

[70] Frodin M, Gammeltoft S. Role and regulation of 90 kDa ribosomal S6 kinase (RSK) in signal transduction. Mol Cell Endocrinol 1999;151:65–77.

[71] Arnold SF, Obourn JD, Jaffe H, Notides AC. Phosphorylation of the human estrogen receptor by mitogen-activated protein kinase and casein kinase. II. Consequence on DNA binding. J Steroid Biochem Mol Biol 1995;55:163–72.

[72] Martin MB, Franke TF, Stoica GE, Chambon P, Katzenellenbogen BS, Stoica BA, et al. A role for Akt in mediating the estrogenic functions of epidermal growth factor and insulin-like growth factor I. Endocrinology 2000;141:4503–11.

[73] Campbell RA, Bhat-Nakshatri P, Patel NM, Constantinidou D, Ali S, Nakshatri H. PI3 kinase/AKT-mediated activation of estrogen receptor alpha: a new model for anti-estrogen resistance. J Biol Chem 2001;3:3.

[74] Sun M, Paciga JE, Feldman RI, Yuan Z, Coppola D, Lu YY, et al. Phosphatidylinositol-3-OH kinase (PI3K)/AKT2, activated in breast cancer, regulates and is induced by estrogen receptor alpha (ERalpha) via interaction between ERalpha and PI3K. Cancer Res 2001;61:5985–91.

[75] Davies SP, Reddy H, Caivano M, Cohen P. Specificity and mechanism of action of some commonly used protein kinase inhibitors. Biochem J 2000;351:95–105.

[76] Chen D, Pace PE, Coombes RC, Ali S. Phosphorylation of human estrogen receptor alpha by protein kinase A regulates dimerization. Mol Cell Biol 1999;19:1002–15.

[77] Yudt MR, Vorojeikina D, Zhong L, Skafar DF, Sasson S, Gasiewicz TA, et al. Function of estrogen receptor tyrosine 537 in hormone binding, DNA binding, and transactivation. Biochemistry 1999;38:14146–56.

[78] Migliaccio A, Rotondi A, Auricchio F. Estradiol receptor: phosphorylation on tyrosine in uterus and interaction with anti-phosphotyrosine antibody. EMBO J 1986;5:2867–72.

[79] Migliaccio A, Pagano M, Auricchio F. Immediate and transient stimulation of protein tyrosine phosphorylation by estradiol in MCF-7 cells. Oncogene 1993;8:2183–91.

[80] Pietras RJ, Arboleda J, Reese DM, Wongvipat N, Pegram MD, Ramos L, et al. HER-2 tyrosine kinase pathway targets estrogen receptor and promotes hormone-independent growth in human breast cancer cells. Oncogene 1995;10:2435–46.

[81] Castoria G, Migliaccio A, Green S, Di Domenico M, Chambon P, Auricchio F. Properties of a purified estradiol-dependent calf uterus tyrosine kinase. Biochemistry 1993;32:1740–50.

[82] Tremblay A, Tremblay GB, Labrie F, Giguere V. Ligand-independent recruitment of SRC-1 to estrogen receptor beta through phosphorylation of activation function AF-1. Mol Cell 1999;3:513–9.

[83] Endoh H, Maruyama K, Masuhiro Y, Kobayashi Y, Goto M, Tai H, et al. Purification and identification of p68 RNA helicase acting as a transcriptional coactivator specific for the activation function 1 of human estrogen receptor alpha. Mol Cell Biol 1999;19:5363–72.

[84] Lavinsky RM, Jepsen K, Heinzel T, Torchia J, Mullen TM, Schiff R, et al. Diverse signaling pathways modulate nuclear receptor recruitment of N-CoR and SMRT complexes. Proc Natl Acad Sci USA 1998;95:2920–5.

[85] Ali S, Metzger D, Bornert J-M, Chambon P. Modulation of transcriptional activation by ligand-dependent phosphorylation of the human oestrogen receptor A/B region. EMBO J 1993;12:1153–60.

[86] Rowan BG, Weigel NL, O'Malley BW. Phosphorylation of steroid receptor coactivator-1. Identification of the phosphorylation sites and phosphorylation through the mitogen-activated protein kinase pathway. J Biol Chem 2000;275:4475–83.

[87] Font de Mora J, Brown M. AIB1 is a conduit for kinase-mediated growth factor signaling to the estrogen receptor. Mol Cell Biol 2000;20:5041–7.
[88] Webb P, Nguyen P, Shinsako J, Anderson C, Feng W, Nguyen MP, et al. Estrogen receptor activation function 1 works by binding p160 coactivator proteins. Mol Endocrinol 1998;12:1605–18.
[89] Lopez GN, Turck CW, Schaufele F, Stallcup MR, Kushner PJ. Growth factors signal to steroid receptors through mitogen-activated protein kinase regulation of p160 coactivator activity. J Biol Chem 2001;276:22177–82.
[90] El-Tanani MK, Green CD. Two separate mechanisms for ligand-independent activation of the estrogen receptor. Mol Endocrinol 1997;11:928–37.
[91] Lazennec G, Thomas JA, Katzenellenbogen BS. Involvement of cyclic AMP response element binding protein (CREB) and estrogen receptor phosphorylation in the synergistic activation of the estrogen receptor by estradiol and protein kinase activators. J Steroid Biochem Mol Biol 2001;77:193–203.
[92] Lamb J, Ladha MH, McMahon C, Sutherland RL, Ewen ME. Regulation of the functional interaction between cyclin D1 and the estrogen receptor. Mol Cell Biol 2000;20:8667–75.
[93] Zwijsen RM, Wientjens E, Klompmaker R, van der Sman J, Bernards R, Michalides RJ. CDK-independent activation of estrogen receptor by cyclin D1. Cell 1997;88:405–15.
[94] Neuman E, Ladha MH, Lin N, Upton TM, Miller SJ, DiRenzo J, et al. Cyclin D1 stimulation of estrogen receptor transcriptional activity independent of cdk4. Mol Cell Biol 1997;17:5338–47.
[95] 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;10:1388–98.
[96] White R, Sjoberg M, Kalkhoven E, Parker MG. Ligand-independent activation of the oestrogen receptor by mutation of a conserved tyrosine. EMBO J 1997;16:1427–35.
[97] Ma ZQ, Liu Z, Ngan ES, Tsai SY. Cdc25B functions as a novel coactivator for the steroid receptors. Mol Cell Biol 2001;21:8056–67.
[98] Dean DA, Urban G, Aragon IV, Swingle M, Miller B, Rusconi S, et al. Serine/threonine protein phosphatase 5 (PP5) participates in the regulation of glucocorticoid receptor nucleocytoplasmic shuttling. BMC Cell Biol 2001;2:6.
[99] Auricchio F, Di Domenico M, Migliaccio A, Castoria G, Bilancio A. The role of estradiol receptor in the proliferative activity of vanadate on MCF-7 cells. Cell Growth Differ 1995;6:105–13.
[100] Griswold-Prenner I, Carlin CR, Rosner MR. Mitogen-activated protein kinase regulates the epidermal growth factor receptor through activation of a tyrosine phosphatase. J Biol Chem 1993;268:13050–4.
[101] Kahlert S, Nuedling S, van Eickels M, Vetter H, Meyer R, Grohe C. Estrogen receptor alpha rapidly activates the IGF-1 receptor pathway. J Biol Chem 2000;275:18447–53.
[102] Watters JJ, Chun TY, Kim YN, Bertics PJ, Gorski J. Estrogen modulation of prolactin gene expression requires an intact mitogen-activated protein kinase signal transduction pathway in cultured rat pituitary cells. Mol Endocrinol 2000;14:1872–81.
[103] Filardo EJ, Quinn JA, Bland KI, Frackelton Jr AR. Estrogen-induced activation of Erk-1 and Erk-2 requires the G protein-coupled receptor homolog, GPR30, and occurs via trans-activation of the epidermal growth factor receptor through release of HB-EGF [In Process Citation]. Mol Endocrinol 2000;14:1649–60.
[104] Filardo EJ, Quinn JA, Frackelton Jr AR, Bland KI. Estrogen action via the G protein-coupled receptor, GPR30: stimulation of adenylyl cyclase and cAMP-mediated attenuation of the epidermal growth factor receptor-to-MAPK signaling axis. Mol Endocrinol 2002;16:70–84.
[105] Boonyaratanakornkit V, Scott MP, Ribon V, Sherman L, Anderson SM, Maller JL, et al. Progesterone receptor contains a proline-rich motif that directly interacts with SH3 domains and activates c-Src family tyrosine kinases. Mol Cell 2001;8:269–80.
[106] Improta-Brears T, Whorton AR, Codazzi F, York JD, Meyer T, McDonnell DP. Estrogen-induced activation of mitogen-activated protein kinase requires mobilization of intracellular calcium. Proc Natl Acad Sci USA 1999;96:4686–91.
[107] Song RX, McPherson RA, Adam L, Bao Y, Shupnik M, Kumar R, et al. Linkage of rapid estrogen action to MAPK activation by ERalpha-Shc association and Shc pathway activation. Mol Endocrinol 2002;16:116–27.
[108] Duan R, Xie W, Safe S. Estrogen receptor-mediated activation of the serum response element in MCF-7 cells through MAPK-dependent phosphorylation of Elk-1. J Biol Chem 2001;5:5.
[109] Marshall CJ. Specificity of receptor tyrosine kinase signaling: transient versus sustained extracellular signal-regulated kinase activation. Cell 1995;80:179–85.
[110] Cowley S, Paterson H, Kemp P, Marshall CJ. Activation of MAP kinase is necessary and sufficient for PC12 differentiation and for transformation of NIH 3T3 cells. Cell 1994;77:841–52.
[111] York RD, Yao H, Dillon T, Ellig CL, Eckert SP, McCleskey EW, et al. Rap1 mediates sustained MAP kinase activation induced by nerve growth factor. Nature 1998;392:622–6.
[112] Sabbagh Jr W, Flatauer LJ, Bardwell AJ, Bardwell L. Specificity of MAP kinase signaling in yeast differentiation involves transient versus sustained MAPK activation. Mol Cell 2001;8:683–91.
[113] Simoncini T, Hafezi-Moghadam A, Brazil DP, Ley K, Chin WW, Liao JK. Interaction of oestrogen receptor with the regulatory subunit of phosphatidylinositol-3-OH kinase. Nature 2000;407:538–41.
[114] Haynes MP, Sinha D, Russell KS, Collinge M, Fulton D, Morales-Ruiz M, et al. Membrane estrogen receptor engagement activates endothelial nitric oxide synthase via the PI3-kinase-Akt pathway in human endothelial cells. Circ Res 2000;87:677–82.
[115] Castoria G, Migliaccio A, Bilancio A, Di Domenico M, de Falco A, Lombardi M, et al. PI3-kinase in concert with Src promotes the S-phase entry of oestradiol-stimulated MCF-7 cells. EMBO J 2001;20:6050–9.
[116] Katso R, Okkenhaug K, Ahmadi K, White S, Timms J, Waterfield MD. Cellular function of phosphoinositide 3-kinases: implications for development, homeostasis, and cancer. Annu Rev Cell Dev Biol 2001;17:615–75.
[117] Tsai EM, Wang SC, Lee JN, Hung MC. Akt activation by estrogen in estrogen receptor-negative breast cancer cells. Cancer Res 2001;61:8390–2.
[118] Slentz-Kesler K, Moore JT, Lombard M, Zhang J, Hollingsworth R, Weiner MP. Identification of the human mnk2 gene (MKNK2) through protein interaction with estrogen receptor beta. Genomics 2000;69:63–71.
[119] Bodwell JE, Webster JC, Jewell CM, Cidlowski JA, Hu JM, Munck A. Glucocorticoid receptor phosphorylation: overview, function and cell cycle-dependence. J Steroid Biochem Mol Biol 1998;65:91–9.
[120] Lange CA, Shen T, Horwitz KB. Phosphorylation of human progesterone receptors at serine-294 by mitogen-activated protein kinase signals their degradation by the 26S proteasome. Proc Natl Acad Sci USA 2000;97:1032–7.
[121] Webster JC, Jewell CM, Bodwell JE, Munck A, Sar M, Cidlowski JA. Mouse glucocorticoid receptor phosphorylation status influences multiple functions of the receptor protein. J Biol Chem 1997;272:9287–93.
[122] Nawaz Z, Lonard DM, Dennis AP, Smith CL, O'Malley BW. Proteasome-dependent degradation of the human estrogen receptor. Proc Natl Acad Sci USA 1999;96:1858–62.
[123] Alarid ET, Bakopoulos N, Solodin N. Proteasome-mediated proteolysis of estrogen receptor: a novel component in autologous down-regulation. Mol Endocrinol 1999;13:1522–34.
[124] Lonard DM, Nawaz Z, Smith CL, O'Malley BW. The 26S proteasome is required for estrogen receptor-alpha and coactivator turnover and for efficient estrogen receptor-alpha transactivation. Mol Cell 2000;5:939–48.