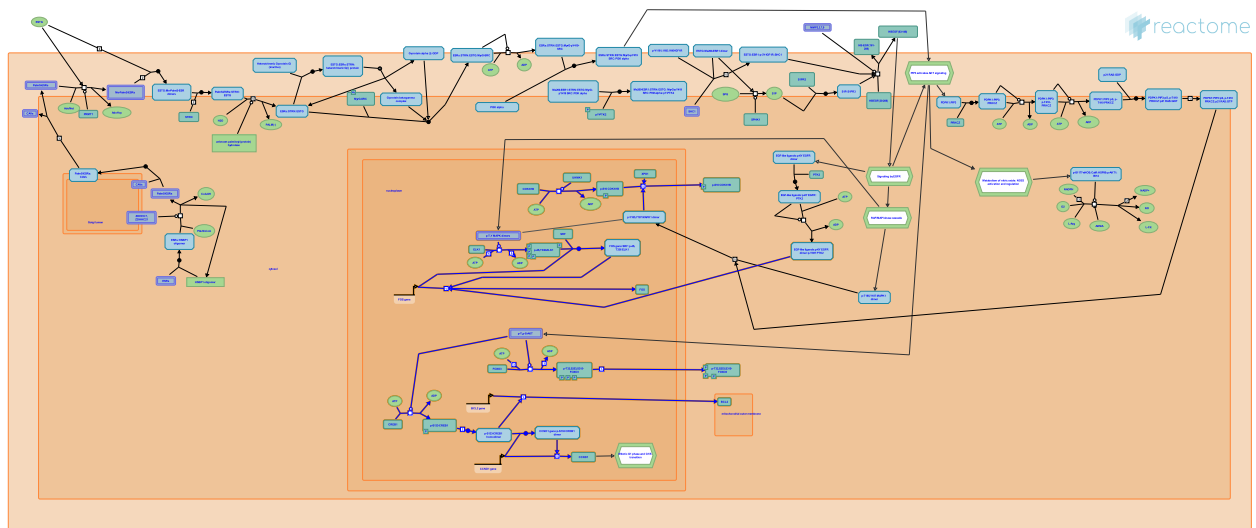


# Estrogen-dependent nuclear events downstream of ESR-membrane signaling



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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the [Reactome Textbook](https://reactome.org/textbook/).

29/04/2024

## Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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## Literature references

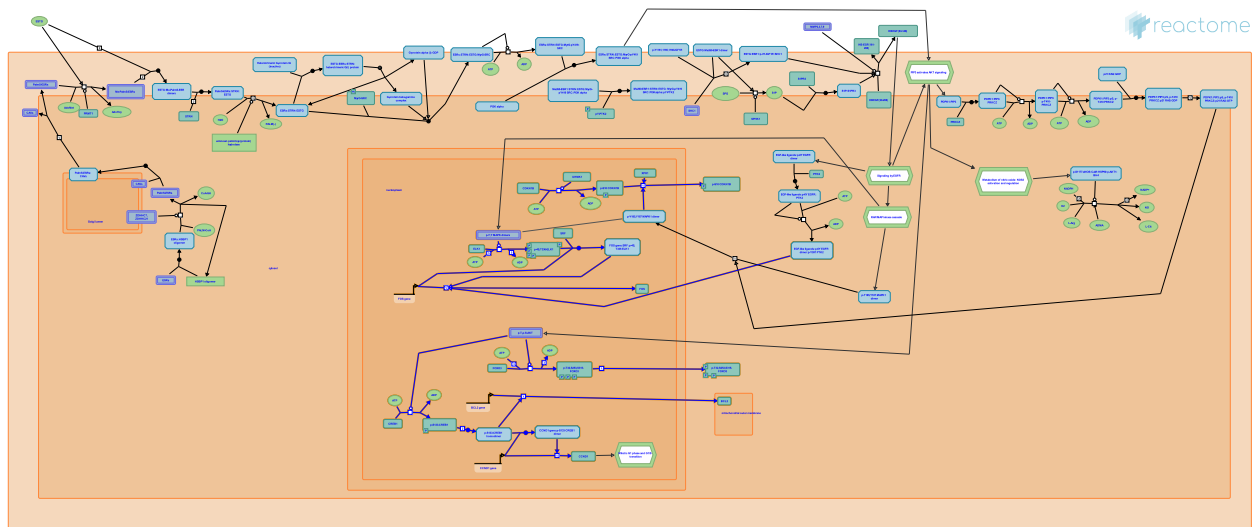
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Reactome database release: 88

This document contains 1 pathway and 12 reactions ([see Table of Contents](#))

## Estrogen-dependent nuclear events downstream of ESR-membrane signaling ↗

Stable identifier: R-HSA-9634638



Although membrane-localized estrogen receptors stimulate rapid, transcription-independent responses such as calcium mobilization and alterations to the fibronectin matrix to affect cell migration, among others, the pathways activated by rapid signaling may also ultimately affect nuclear events. Activation of MAPK and PI3K/AKT pathways downstream of membrane-localized ESR1 contributes to estrogen-responsive changes in cellular proliferation and survival in part through changes in gene expression (reviewed in Levin et al, 2005; Lange et al, 2007; Le Romancer et al, 2011).

### Literature references

Marker, PC., Hammes, SR., Gioeli, D., Lange, CA. (2007). Integration of rapid signaling events with steroid hormone receptor action in breast and prostate cancer. *Annu. Rev. Physiol.*, 69, 171-99. ↗

Levin, ER. (2005). Integration of the extranuclear and nuclear actions of estrogen. *Mol. Endocrinol.*, 19, 1951-9. ↗

Poulard, C., Corbo, L., Renoir, JM., Sentis, S., Cohen, P., Le Romancer, M. (2011). Cracking the estrogen receptor's posttranslational code in breast tumors. *Endocr. Rev.*, 32, 597-622. ↗

### Editions

2018-12-15	Authored	Rothfels, K.
2019-02-20	Reviewed	Levin, ER.

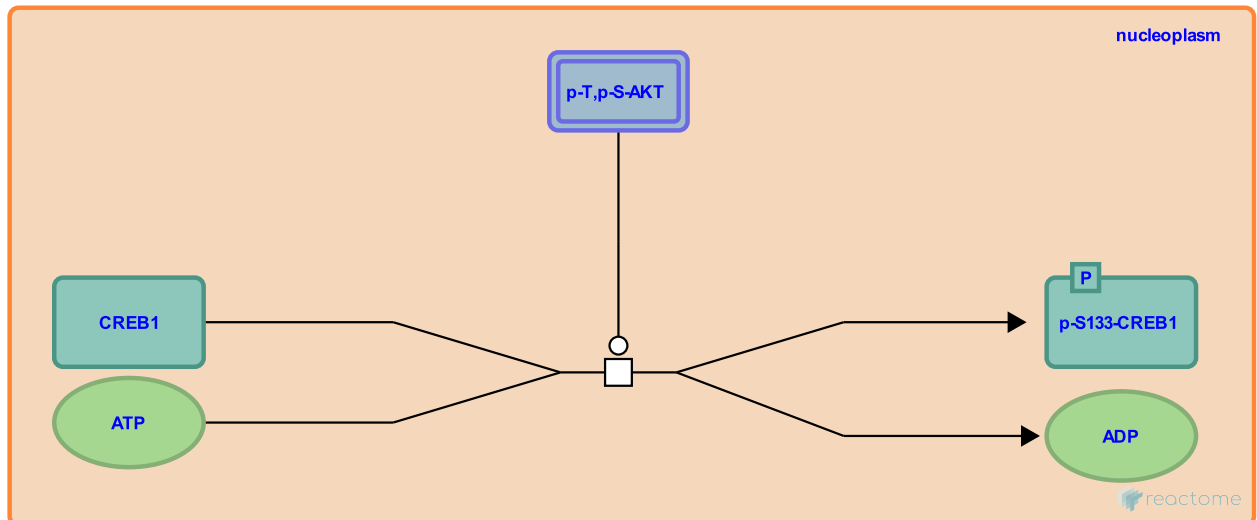
## AKT phosphorylates CREB1 ↗

**Location:** [Estrogen-dependent nuclear events downstream of ESR-membrane signaling](#)

**Stable identifier:** R-HSA-199298

**Type:** transition

**Compartments:** nucleoplasm



AKT phosphorylates CREB (cAMP response element-binding protein) at serine 133 and activates gene expression via a CREB-dependent mechanism, thus promoting cell survival.

**Followed by:** [Dimerization of p-S133-CREB1](#)

### Literature references

Du, K., Montminy, M. (1998). CREB is a regulatory target for the protein kinase Akt/PKB. *J Biol Chem*, 273, 32377-9. ↗

### Editions

2006-10-10	Authored	Annibali, D., Nasi, S.
2007-11-08	Reviewed	Greene, LA.

## Dimerization of p-S133-CREB1 ↗

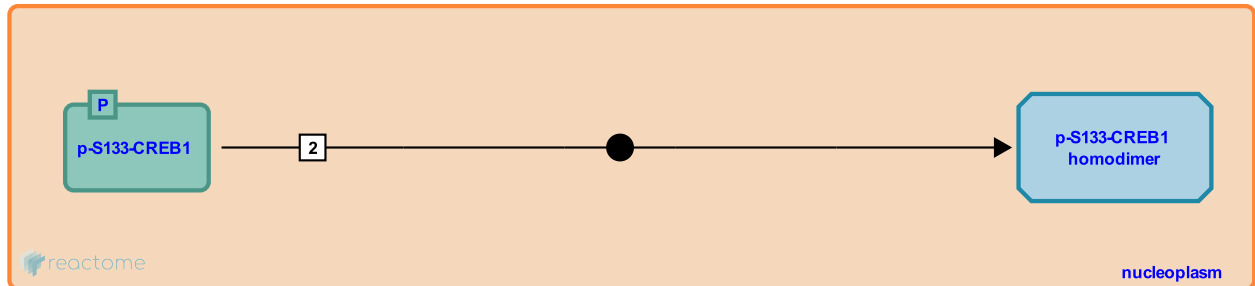
**Location:** Estrogen-dependent nuclear events downstream of ESR-membrane signaling

**Stable identifier:** R-HSA-111916

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Dimerization of p-S133-Creb1 (Rattus norvegicus)



Based on studies in rat cells, activation of CREB1 by phosphorylation at serine residue S133 induces formation of CREB1 homodimers which are able to bind DNA (Yamamoto et al. 1988). The DNA binding and dimerization domains reside in the C-terminal region of CREB1 (Yun et al. 1990).

**Preceded by:** AKT phosphorylates CREB1

**Followed by:** p-S133 CREB1 dimer binds the CCND1 promoter

### Editions

2004-03-31	Authored	Jassal, B., Le Novere, N.
2008-11-06	Reviewed	Castagnoli, L.
2008-11-06	Edited	Jassal, B.

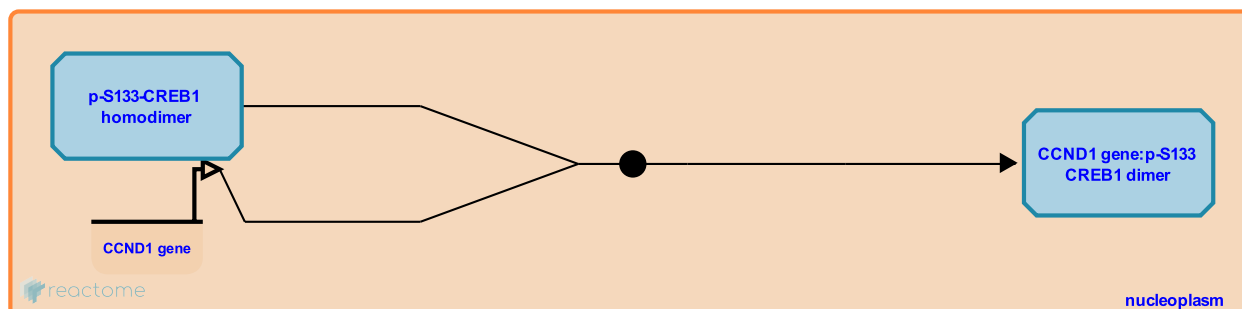
## p-S133 CREB1 dimer binds the CCND1 promoter ↗

**Location:** [Estrogen-dependent nuclear events downstream of ESR-membrane signaling](#)

**Stable identifier:** R-HSA-9623341

**Type:** binding

**Compartments:** nucleoplasm



Estrogen stimulation promotes cell cycle progression in a number of cell lines by upregulating the expression of the G1 cyclin CCND1 (Cyclin D1) (Castoria et al,1999; Castoria et al, 2001; reviewed in Castoria et al, 2010). Estrogen-responsive CCND1 expression is promoted through both the canonical ESR1 receptor and through the alternate receptor GPER1 (Castoria et al, 2001; Castoria et al, 2012; Kanda and Watanabe, 2003; Kanda and Watanabe, 2004). By electrophoretic mobility shift assay, phosphorylated CREB1 binds to a CRE element in the CCND1 promoter, and expression of a CRE-driven CCND1 reporter gene increases upon stimulation of cells with E2 (Kanda and Watanabe, 2003; Kanda and Watanabe, 2004). Expression of CCND1 downstream of E2 and ESR1 or GPER1 stimulates cellular proliferation, consistent with studies in other cell lines (Vivacqua et al, 2006a; Vivacqua et al, 2006b; Albanito et al, 2007; Albanito et al, 2008; Lin et al, 2009; Ariazi et al, 2010; reviewed in Filardo, 2018).

**Preceded by:** [Dimerization of p-S133-CREB1](#)

**Followed by:** [ESR1-dependent CCND1 expression](#)

### Literature references

- Kanda, N., Watanabe, S. (2003). 17beta-estradiol inhibits oxidative stress-induced apoptosis in keratinocytes by promoting Bcl-2 expression. *J. Invest. Dermatol.*, 121, 1500-9. ↗
- Ariazi, EA., Slifker, MJ., Yerrum, S., Cunliffe, HE., Prossnitz, ER., Brailoiu, E. et al. (2010). The G protein-coupled receptor GPR30 inhibits proliferation of estrogen receptor-positive breast cancer cells. *Cancer Res.*, 70, 1184-94. ↗
- Kanda, N., Watanabe, S. (2004). 17beta-estradiol stimulates the growth of human keratinocytes by inducing cyclin D2 expression. *J. Invest. Dermatol.*, 123, 319-28. ↗
- Auricchio, F., Giovannelli, P., Castoria, G., Migliaccio, A. (2010). Cell proliferation regulated by estradiol receptor: Therapeutic implications. *Steroids*, 75, 524-7. ↗
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### Editions

2018-12-15	Authored	Rothfels, K.
2019-02-20	Reviewed	Levin, ER.

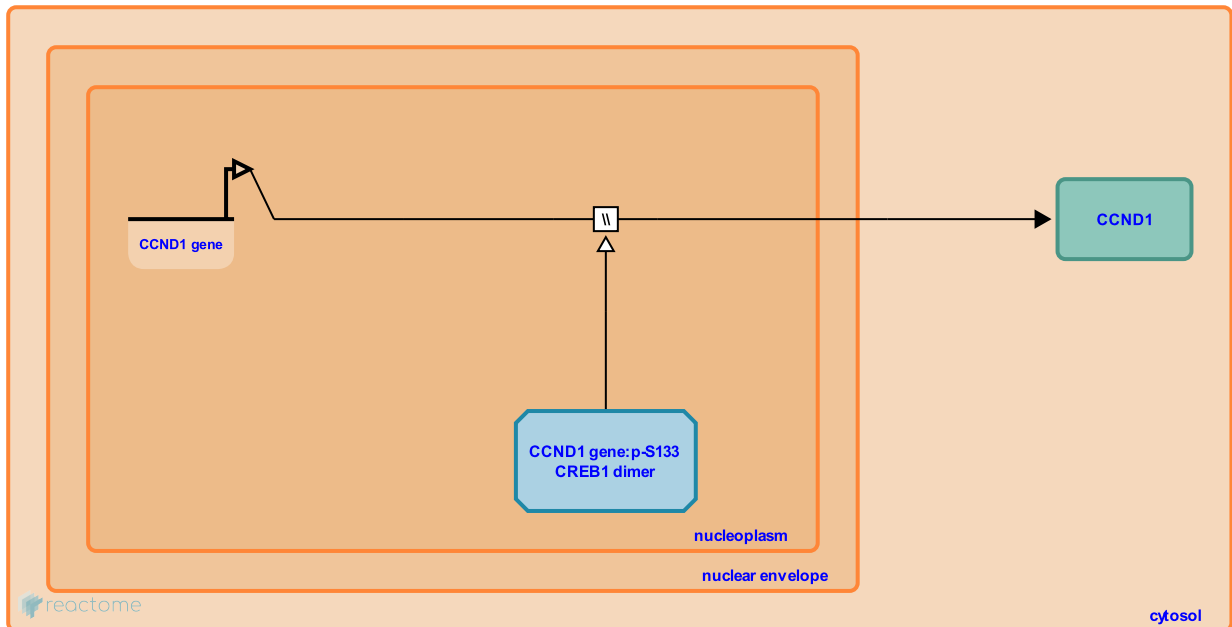
## ESR1-dependent CCND1 expression ↗

**Location:** [Estrogen-dependent nuclear events downstream of ESR-membrane signaling](#)

**Stable identifier:** R-HSA-9623355

**Type:** omitted

**Compartments:** nucleoplasm, cytosol



Expression of CCND1, the gene encoding cyclin D1, is stimulated by treatment of cells with E2. Expression is dependent on ESR1-mediated signaling through the PKA and AKT pathways, and consistent with this, levels of phosphorylated CREB1 increase upon treatment with E2. The CCND1 promoter has a CRE element that is bound by phosphorylated CREB1 upon E2 treatment as assessed by electrophoretic mobility shift assay (Park et al, 2001; Felty et al, 2005).

**Preceded by:** [p-S133 CREB1 dimer binds the CCND1 promoter](#)

### Literature references

Cho-Chung, YS., Lim, SO., Lee, MS., Ryu, CK., Kim, I., Park, YG. et al. (2001). Reduction in cyclin D1/Cdk4/retinoblastoma protein signaling by CRE-decoy oligonucleotide. *Biochem. Biophys. Res. Commun.*, 281, 1213-9. ↗

Singh, KP., Felty, Q., Roy, D. (2005). Estrogen-induced G1/S transition of G0-arrested estrogen-dependent breast cancer cells is regulated by mitochondrial oxidant signaling. *Oncogene*, 24, 4883-93. ↗

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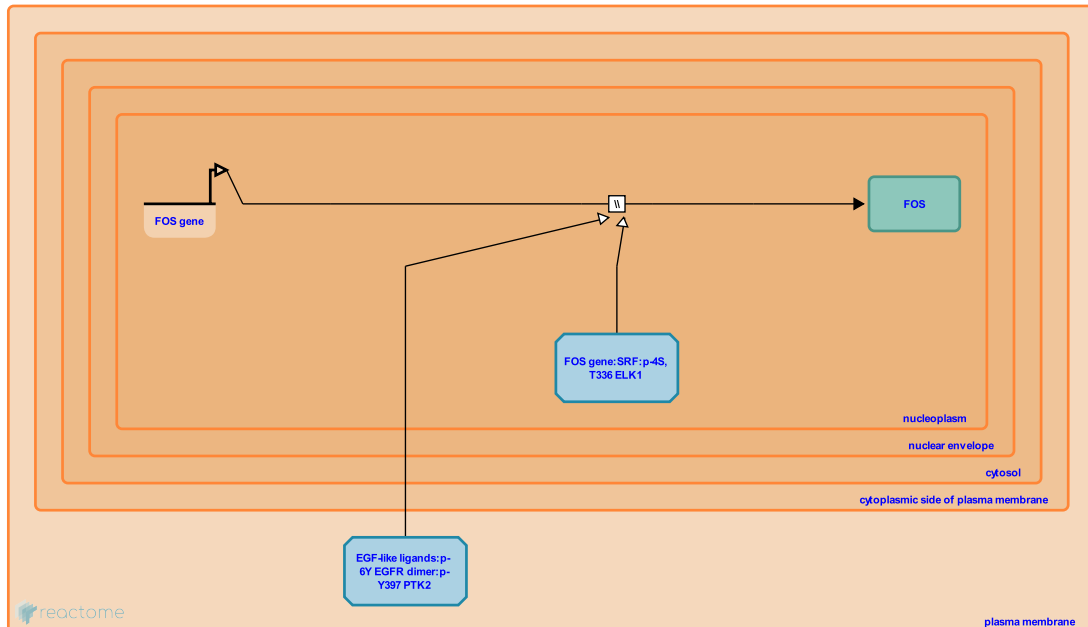
## E2-mediated FOS gene expression ↗

**Location:** [Estrogen-dependent nuclear events downstream of ESR-membrane signaling](#)

**Stable identifier:** R-HSA-9625465

**Type:** omitted

**Compartments:** nucleoplasm



The FOS gene encodes FOS, a leucine zipper protein that dimerizes with other FOS, JUN or ATF family members to form the ubiquitous transcription factor complex AP-1 (reviewed in Milde-Langosch, 2005; Hess et al, 2004). AP-1 transcription factors regulate gene expression in response to numerous upstream stimuli, including growth factors, hormones and cytokines and influence proliferation, differentiation and apoptosis, among other processes (reviewed in Shaulina et al, 2002; Thiel and Rossler, 2017).

Transcription of the FOS gene is regulated in part by binding of TCF (a complex of SRF and phosphorylated ELK1) to the serum response element (SRE) in the promoter (Marais et al, 1993; Gille et al, 1995; Duan et al, 2001; reviewed in Treisman, 1995)

### Literature references

- Milde-Langosch, K. (2005). The Fos family of transcription factors and their role in tumourigenesis. *Eur. J. Cancer*, 41, 2449-61. ↗
- Angel, P., Schorpp-Kistner, M., Hess, J. (2004). AP-1 subunits: quarrel and harmony among siblings. *J Cell Sci*, 117, 5965-73. ↗
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2018-12-15	Authored	Rothfels, K.
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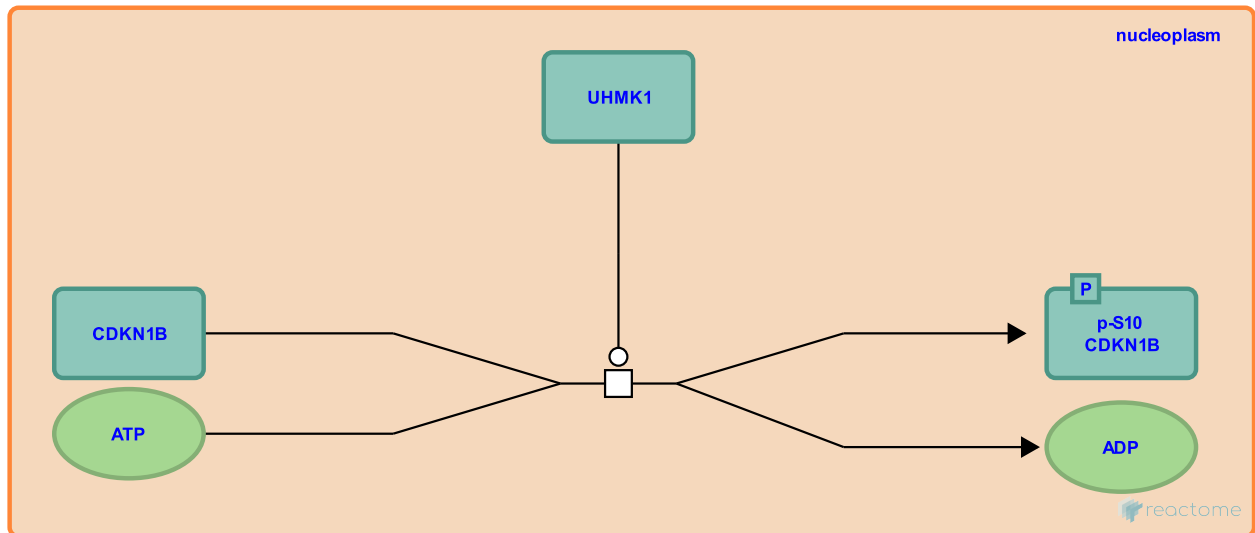
## CDKN1B is phosphorylated in response to estrogen ↗

**Location:** [Estrogen-dependent nuclear events downstream of ESR-membrane signaling](#)

**Stable identifier:** R-HSA-9632868

**Type:** transition

**Compartments:** nucleoplasm



CDKN1B (also known as p27 KIP) is an inhibitor of G1 cyclin dependent kinase complexes. CDKN1B interacts with CCND1:CDK4/6 complexes to prevent progression into S phase (reviewed in Vermeulen et al, 2003; Hnit et al, 2015). Relief of CDKN1B-mediated inhibition in response to mitogenic signals is accomplished by multiple mechanisms including localization, transcriptional, translational and proteolytic regulation of CDKN1B.

CDKN1B is phosphorylated at serine 10 during G1 in response to serum and estrogen stimulation, resulting in its XPO1-dependent nuclear export (Ishida et al, 2000; Rodier et al, 2001; Ishida et al, 2003). RAS signaling and PRKCZ-dependent MAPK1 nuclear translocation is required for nuclear export of CDKN1B in response to estrogen stimulation in MCF cells (Aktas et al, 1997; Cheng et al, 1998; Foster et al, 2003; Castoria et al, 2004; Kawada et al, 1997; Migliaccio et al, 1996). Although MAP kinases have been shown to phosphorylate CDKN1B in vitro, it has not been demonstrated in vivo. In another study, UHMK1 was identified as the kinase responsible for S10 phosphorylation in response to serum stimulation (Boehm et al, 2001).

**Followed by:** [p-S10 CDKN1B translocates to the cytosol](#)

### Literature references

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- Foster, JS., Fernando, RI., Wimalasena, J., Nakayama, KI., Ishida, N. (2003). Estrogens down-regulate p27Kip1 in breast cancer cells through Skp2 and through nuclear export mediated by the ERK pathway. *J. Biol. Chem.*, 278, 41355-66. ↗

### Editions

2018-12-15	Authored	Rothfels, K.
2019-02-20	Reviewed	Levin, ER.

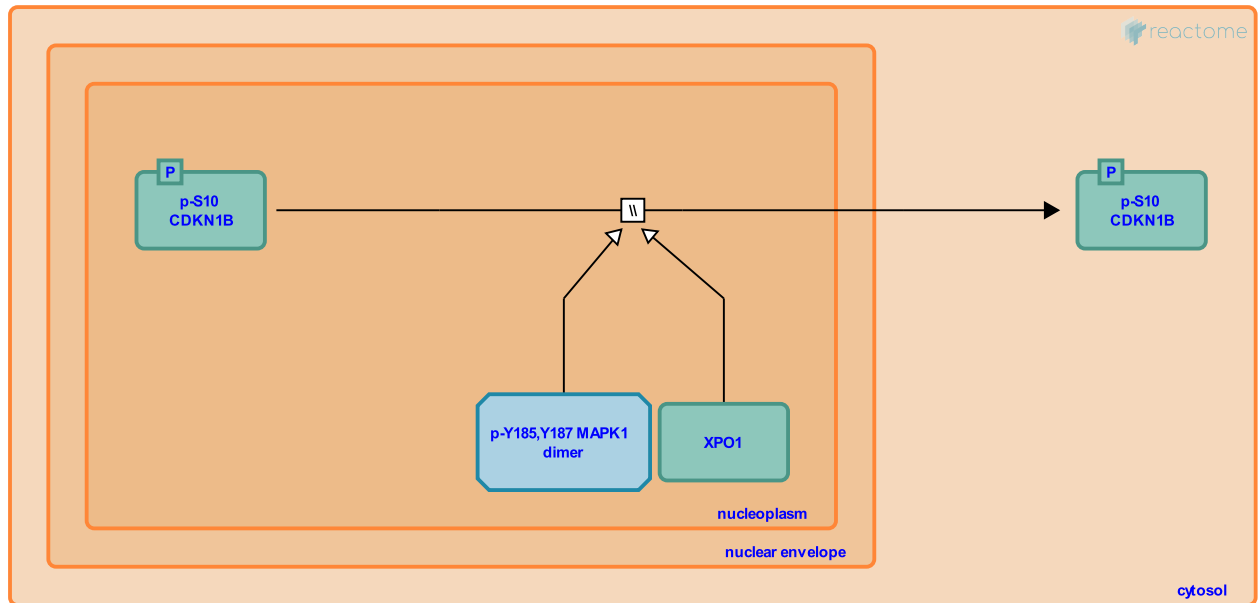
## p-S10 CDKN1B translocates to the cytosol ↗

**Location:** Estrogen-dependent nuclear events downstream of ESR-membrane signaling

**Stable identifier:** R-HSA-9632873

**Type:** omitted

**Compartments:** nucleoplasm, cytoplasm



Estrogen stimulation causes a partial redistribution of CDKN1B into the cytosol in a manner that depends on Ras and PI3K signaling and the atypical PKC zeta (Rodier et al, 2002; Castoria et al, 2004). Nuclear localization of CDKN1B inhibits cell cycle progression (Reynisdottir et al, 1997).

**Preceded by:** CDKN1B is phosphorylated in response to estrogen

### Literature references

- Auricchio, F., Di Domenico, M., Barone, MV., Bilancio, A., de Falco, A., Lombardi, M. et al. (2004). Role of atypical protein kinase C in estradiol-triggered G1/S progression of MCF-7 cells. *Mol. Cell. Biol.*, 24, 7643-53. ↗
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2018-12-15	Authored	Rothfels, K.
2019-02-20	Reviewed	Levin, ER.

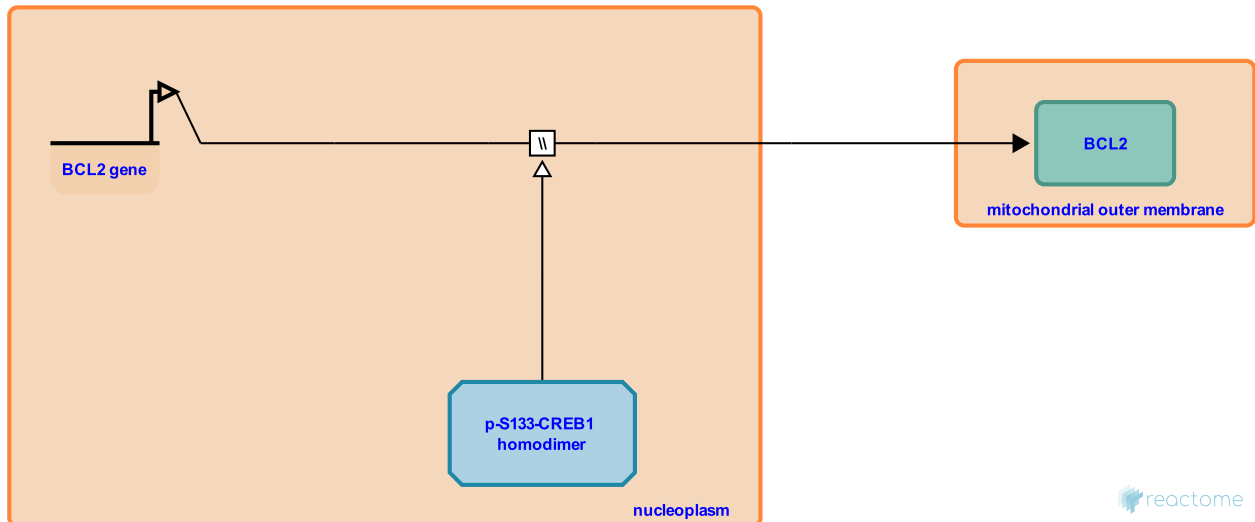
## BCL gene expression downstream of ESR1 [↗](#)

**Location:** [Estrogen-dependent nuclear events downstream of ESR-membrane signaling](#)

**Stable identifier:** R-HSA-9623999

**Type:** omitted

**Compartments:** nucleoplasm, mitochondrial outer membrane



BCL2 mRNA and protein levels increase in response to E2 stimulation in a PKA-dependent manner (Grimaldi et al, 2002; Yune et al, 2008). Levels of phosphorylated CREB1 also increase with estrogen stimulation, however direct binding of phosphorylated CREB to the BCL2 promoter has not been demonstrated. Estrogen-dependent BCL2 expression is also dependent on Sp1 (Dong et al, 1999; Yune et al, 2008; reviewed in Ladikou and Kassi, 2017).

### Literature references

- Yune, TY., Park, HG., Oh, TH., Lee, JY. (2008). Estrogen-induced Bcl-2 expression after spinal cord injury is mediated through phosphoinositide-3-kinase/Akt-dependent CREB activation. *J. Neurotrauma*, 25, 1121-31. [↗](#)
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### Editions

2018-12-15	Authored	Rothfels, K.
2019-02-20	Reviewed	Levin, ER.

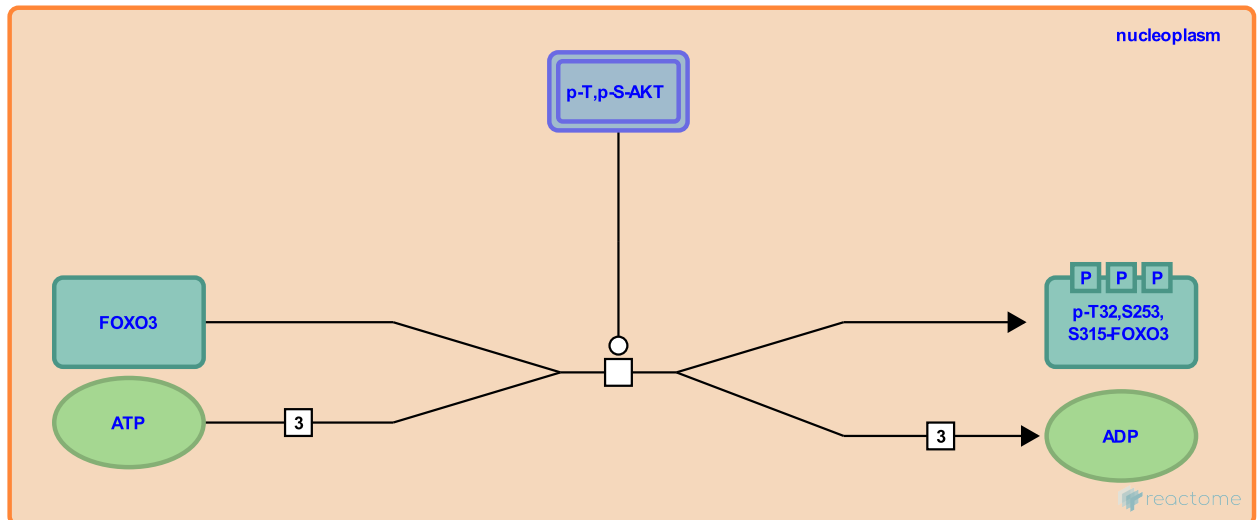
## AKT phosphorylates FOXO3 downstream of ESR1 and EGFR ↗

**Location:** [Estrogen-dependent nuclear events downstream of ESR-membrane signaling](#)

**Stable identifier:** R-HSA-9624526

**Type:** transition

**Compartments:** nucleoplasm



AKT phosphorylation of the pro-apoptotic Forkhead transcription factor FOXO3 and other Foxo family members occurs downstream of E2 stimulation (Richards et al, 2002; reviewed in Levin, 2005). AKT-mediated phosphorylation promotes nuclear export, resulting in a decrease in expression of apoptosis-promoting FOXO3-target genes (Brunet et al, 1999; reviewed in Burgering, 2008).

**Followed by:** [AKT-phosphorylated FOXO3 translocates to cytosol](#)

### Literature references

Hu, LS., Bonni, A., Brunet, A., Blenis, J., Zigmond, MJ., Anderson, MJ. et al. (1999). Akt promotes cell survival by phosphorylating and inhibiting a Forkhead transcription factor. *Cell*, 96, 857-68. ↗

Burgering, BM. (2008). A brief introduction to FOXology. *Oncogene*, 27, 2258-62. ↗

Lo, YH., Falender, AE., Richards, JS., Sharma, SC. (2002). Expression of FKHR, FKHL1, and AFX genes in the rodent ovary: evidence for regulation by IGF-I, estrogen, and the gonadotropins. *Mol. Endocrinol.*, 16, 580-99. ↗

Levin, ER. (2005). Integration of the extranuclear and nuclear actions of estrogen. *Mol. Endocrinol.*, 19, 1951-9. ↗

### Editions

2018-12-15	Authored	Rothfels, K.
2019-02-20	Reviewed	Levin, ER.

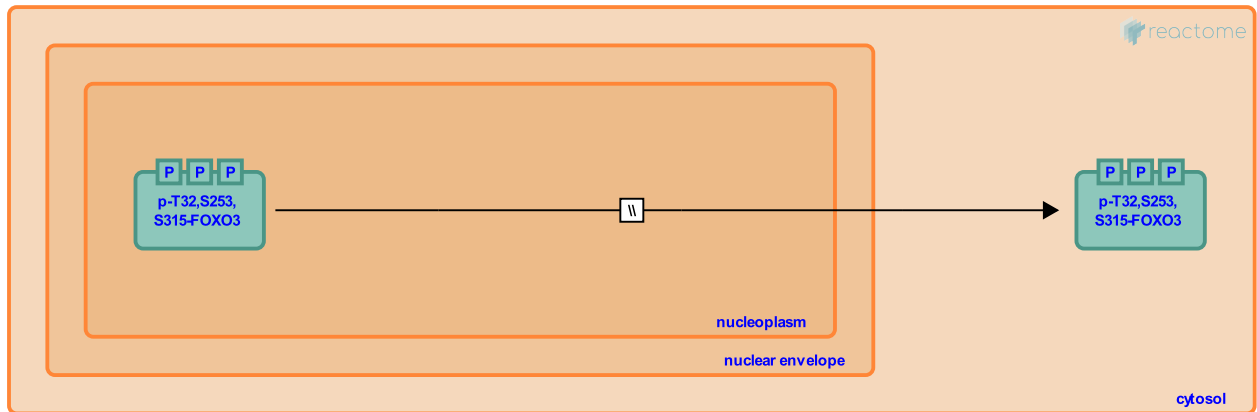
## AKT-phosphorylated FOXO3 translocates to cytosol ↗

**Location:** [Estrogen-dependent nuclear events downstream of ESR-membrane signaling](#)

**Stable identifier:** R-HSA-9624527

**Type:** omitted

**Compartments:** nucleoplasm, cytosol



AKT-mediated phosphorylation of FOXO3 downstream of estrogen stimulation promotes its inactivation and translocation to the cytosol, interfering with its pro-apoptotic transcription factor activity (Richards et al, 2002; Brunet et al, 1999; reviewed in Levin, 2005; Burgering, 2008).

**Preceded by:** [AKT phosphorylates FOXO3 downstream of ESR1 and EGFR](#)

### Literature references

Hu, LS., Bonni, A., Brunet, A., Blenis, J., Zigmond, MJ., Anderson, MJ. et al. (1999). Akt promotes cell survival by phosphorylating and inhibiting a Forkhead transcription factor. *Cell*, 96, 857-68. ↗

Burgering, BM. (2008). A brief introduction to FOXology. *Oncogene*, 27, 2258-62. ↗

Lo, YH., Falender, AE., Richards, JS., Sharma, SC. (2002). Expression of FKHR, FKHL1, and AFX genes in the rodent ovary: evidence for regulation by IGF-I, estrogen, and the gonadotropins. *Mol. Endocrinol.*, 16, 580-99. ↗

Levin, ER. (2005). Integration of the extranuclear and nuclear actions of estrogen. *Mol. Endocrinol.*, 19, 1951-9. ↗

### Editions

2018-12-15	Authored	Rothfels, K.
2019-02-20	Reviewed	Levin, ER.

## ERK1/2 activates ELK1 ↗

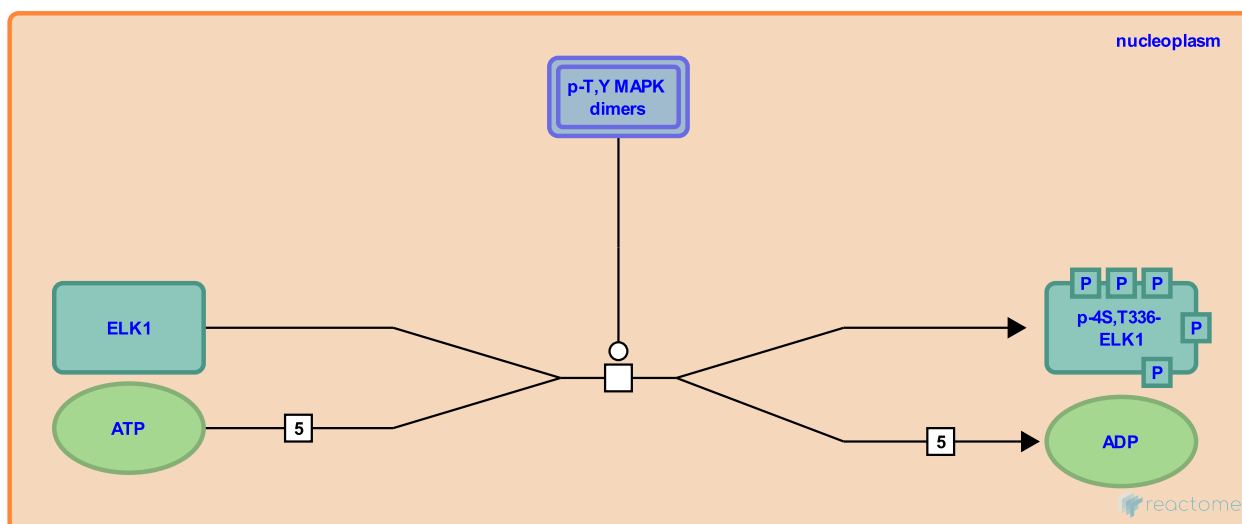
**Location:** [Estrogen-dependent nuclear events downstream of ESR-membrane signaling](#)

**Stable identifier:** R-HSA-198731

**Type:** transition

**Compartments:** nucleoplasm

**Inferred from:** [ERK1/2 activates ELK1 \(Mus musculus\)](#)



Following translocation to the nucleus, ERK1/2 directly phosphorylates key effectors, including the ubiquitous transcription factors ELK1 (Ets like protein 1). At least five residues in the C terminal domain of ELK1 are phosphorylated upon stimulation with growth factor stimulation. ELK1 can form a ternary complex with the serum response factor (SRF) and consensus sequences, such as serum response elements (SRE), on DNA, thus stimulating transcription of a set of immediate early genes like FOS (c-fos) (Marais et al, 1993; Gille et al, 1995; Duan et al, 1998; reviewed in Treisman, 1995).

**Followed by:** [SRF and ELK1 bind the FOS gene](#)

### Literature references

Treisman, R., Wynne, J., Marais, R. (1993). The SRF accessory protein Elk-1 contains a growth factor-regulated transcriptional activation domain. *Cell*, 73, 381-93. ↗

Treisman, R. (1995). Journey to the surface of the cell: Fos regulation and the SRE. *EMBO J.*, 14, 4905-13. ↗

Xie, W., Safe, S., Duan, R., Burghardt, RC. (2001). Estrogen receptor-mediated activation of the serum response element in MCF-7 cells through MAPK-dependent phosphorylation of Elk-1. *J. Biol. Chem.*, 276, 11590-8. ↗

Moomaw, C., Gille, H., Shaw, PE., Cobb, MH., Thomae, O., Slaughter, C. et al. (1995). ERK phosphorylation potentiates Elk-1-mediated ternary complex formation and transactivation. *EMBO J*, 14, 951-62. ↗

### Editions

2006-10-10	Authored	Annibaldi, D., Nasi, S.
2007-11-08	Reviewed	Greene, LA.

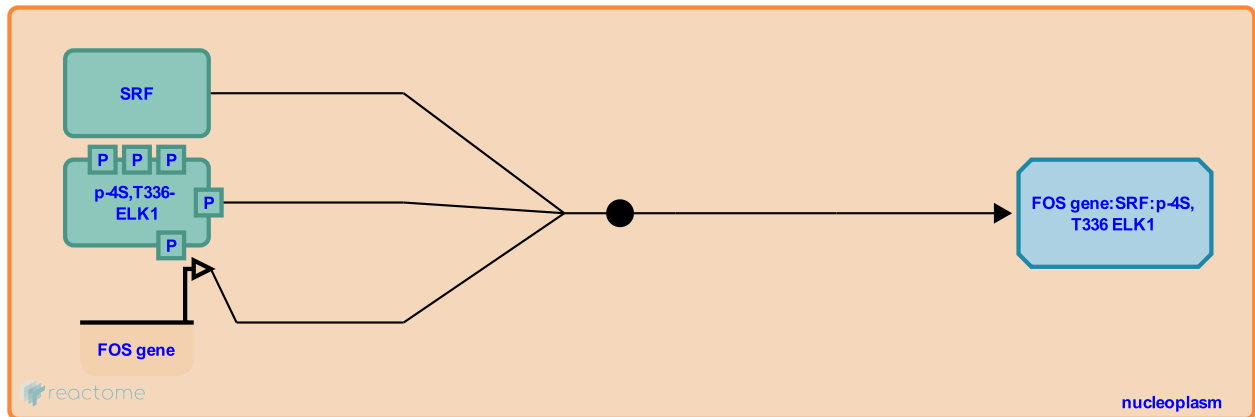
## SRF and ELK1 bind the FOS gene ↗

**Location:** [Estrogen-dependent nuclear events downstream of ESR-membrane signaling](#)

**Stable identifier:** R-HSA-9625479

**Type:** binding

**Compartments:** nucleoplasm



SRF and phosphorylated ELK1 bind to sterol response elements (SRE) in the FOS promoter downstream of E2- and growth factor stimulation (Marais et al, 1993; Gille et al, 1995; Duan et al, 2001; reviewed in Treisman, 1995). FOS gene expression downstream of estrogen stimulation occurs in both an ER alpha (ESR1)- and GPER1-dependent fashion (Maggiolini et al, 2004; Vivacqua et al, 2006; Tsai et al, 2013).

**Preceded by:** [ERK1/2 activates ELK1](#)

### Literature references

Lin, CY., Hsueh, S., Chao, A., Lin, YJ., Wang, HS., Tsai, CL. et al. (2013). Estradiol and tamoxifen induce cell migration through GPR30 and activation of focal adhesion kinase (FAK) in endometrial cancers with low or without nuclear estrogen receptor  $\alpha$  (ER $\alpha$ ). *PLoS ONE*, 8, e72999. ↗

Maggiolini, M., Musti, AM., Montanaro, D., Sisci, D., Picard, D., Recchia, AG. et al. (2004). The G protein-coupled receptor GPR30 mediates c-fos up-regulation by 17 $\beta$ -estradiol and phytoestrogens in breast cancer cells. *J. Biol. Chem.*, 279, 27008-16. ↗

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Xie, W., Safe, S., Duan, R., Burghardt, RC. (2001). Estrogen receptor-mediated activation of the serum response element in MCF-7 cells through MAPK-dependent phosphorylation of Elk-1. *J. Biol. Chem.*, 276, 11590-8. ↗

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2018-12-15

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