Estrogen-dependent gene expression

Chuang, LS., Earp HS, 3rd., Harris, RC., Ito, Y., Magnani, L., Matthews, L., Misior, AM., Orlic-Milacic, M., Rothfels, K., Shamovsky, V., Stern, DF., Zeng, F.

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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.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 75

This document contains 1 pathway and 66 reactions (see Table of Contents)

https://reactome.org
Estrogens mediate their transcriptional effects through interaction with the estrogen receptors, ESR1 (also known as ER alpha) and ESR2 (ER beta). ESR1 and ESR2 share overlapping but distinct functions, with ESR1 playing the primary role in transcriptional activation in most cell types (Hah and Krauss, 2014; Haldosén et al, 2014. The receptors function as ligand-dependent dimers and can activate target genes either through direct binding to an estrogen responsive element (ERE) in the target gene promoter, or indirectly through interaction with another DNA-binding protein such as RUNX1, SP1, AP1 or NF-kappa beta (reviewed in Bai and Gust, 2009; Hah and Krause, 2014). Binding of estrogen receptors to the DNA promotes the assembly of higher order transcriptional complexes containing methyltransferases, histone acetyltransferases and other transcriptional activators, which promote transcription by establishing active chromatin marks and by recruiting general transcription factors and RNA polymerase II. ESR1- and estrogen-dependent recruitment of up to hundreds of coregulators has been demonstrated by varied co-immunoprecipitation and proteomic approaches (Kittler et al, 2013; Mohammed et al, 2013; Foulds et al, 2013; Mohammed et al, 2015; Liu et al, 2014; reviewed in Magnani and Lupien, 2014; Arnal, 2017). In some circumstances, ligand-bound receptors can also promote the assembly of a repression complex at a target gene, and in some cases, heterodimers of ESR1 and ESR2 serve as repressors of ESR1-mediated target gene activation (reviewed in Hah and Kraus, 2014; Arnal et al, 2017). Phosphorylation of the estrogen receptor also modulates its activity, and provides cross-talk between nuclear estrogen-dependent signaling and non-genomic estrogen signaling from the plasma membrane (reviewed in Anbalagan and Rowan, 2015; Haldosén et al, 2014; Schwartz et al, 2016)

A number of recent genome wide studies highlight the breadth of the transcriptional response to estrogen. The number of predicted estrogen-dependent target genes ranges from a couple of hundred (based on microarray studies) to upwards of 10000, based on ChIP-chip or ChIP-seq (Cheung and Kraus, 2010; Kinnis and Kraus, 2008; Lin et al, 2004; Welboren et al, 2009; Ikeda et al, 2015; Lin et al, 2007; Carroll et al,
2006). Many of these predicted sites may not represent transcriptionally productive binding events, however. A study examining ESR1 binding by ChIP-seq in 20 primary breast cancers identified a core of 484 ESR-binding events that were conserved in at least 75% of ER+ tumors, which may represent a more realistic estimate (Ross-Innes et al, 2012). These studies also highlight the long-range effect of estrogen receptor-binding, with distal enhancer or promoter elements regulating the expression of many target genes, often through looping or other higher order chromatin structures (Kittler et al, 2013; reviewed in Dietz and Carroll, 2008; Liu and Cheung, 2014; Magnani and Lupien, 2014). Transcription from a number of estrogen-responsive target genes also appears to be primed by the binding of pioneering transcription factors such as FOXA1, GATA3, PBX1 among others. These factors bind to heterochromatin by virtue of their winged helix domains and promote chromatin opening, allowing subsequent recruitment of other transcription factors (reviewed in Zaret and Carroll, 2011; Fiorito et al, 2013; Arnal et al, 2017; Magnani et al, 2011)

**Literature references**


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Although there is not a classical estrogen response element (ERE) in the proximal CCND1 promoter, estrogen-responsive transcription is mediated through recruitment of hormone-bound ESR1 by other DNA-binding proteins (reviewed in Guo et al, 2011; Klein and Assoian, 2008). A heterodimer of JUN:FOS binds to an estrogen-responsive G1 element (ERGE) between nucleotides -948 and -925 and is responsible for recruitment of ESR1 and estrogen to this site. OCT1 may facilitate this binding by displacing a YY1:HDAC1 repressive complex that occupies an adjacent site in unstimulated cells (Albanese et al, 1995; Cicatiello et al, 2004; Shen et al, 2007). Binding of ATF2:JUN heterodimers to a cyclic AMP response element (CRE) located 52 nucleotides upstream of the transcriptional start site may also contribute to estrogen-responsive signaling (Sabbah et al, 1999; Castro-Rivera at al, 2001). An ERE has been identified in an enhancer element downstream of the CCND1 gene (enh2). This enhancer binds to FOXA1, and also mediates recruitment of the histone acetyltransferase p300 to the CCND1 promoter (Eeckhoute et al, 2006).

Although FOXA1 and GATA3 were initially characterized as 'pioneer' transcription factors that bind to closed chromatin conformations and prime recruitment of sequence-specific DNA binding factors, more recent studies have questioned the order of recruitment of the estrogen receptors, FOXA1 and GATA3 to estrogen-responsive targets (Swinstead et al, 2016).

**Preceded by:** FOXA1 and GATA3 bind to CCND1 promoter  
**Followed by:** Estrogen-responsive CCND1 gene expression

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FOXA1 and GATA3 bind to CCND1 promoter

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-9009065

Type: transition

Compartments: nucleoplasm

Estrogen induces cellular proliferation by upregulating expression of critical cell cycle regulators that govern progression through G1, such as Myc and Cyclin D1 (reviewed in Butt et al, 2005). In the absence of estrogen, Cyclin D1 expression is inhibited, at least in part, by the binding of a transcriptional repressor complex YY1:HDAC1 to the promoter (Cicatiello et al, 2004). Estrogen-stimulated induction of target gene expression appears in many cases to be primed by the binding of ‘pioneer’ transcription factors, such as FOXA and GATA family proteins (Carroll et al, 2005; Laganière et al, 2005; Eeckhoute et al, 2006; Hurtado et al, 2011; Kong et al, 2011; Theodorou et al, 2013; Swinstead et al, 2016; reviewed in Zaret and Carroll, 2011; Augello et al, 2011; Fiorito et al, 2013; Wilson and Giguere, 2008). FOXA factors have a winged helix structure that is thought to bind to closed chromatin structures in a manner analogous to linker histones, displacing linker histones and rendering the DNA more accessible to other transcription factors (reviewed in Zaret and Carroll, 2011). FOXA binding sites tend to be enriched at enhancer elements, characterized by H3K4 mono- and dimethylation, and expression of the histone demethylase KDM1A abrogates FOXA recruitment (Lupien et al, 2008). An enhancer element has been defined downstream of the CCND1 gene that mediates the binding of both the pioneer factor FOXA1 and estrogen-responsive ESR1 (Eeckhoute et al, 2006).

Followed by: Binding of API transcriptional activator complexes to CCND1 promoter

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**Estrogen-responsive CCND1 gene expression**

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-9009378

**Type:** omitted

**Compartments:** nucleoplasm

The proliferative effects of estrogen stimulation arise in part through the estrogen-dependent activation of key cell cycle regulators such as Cyclin D1, encoded by the CCND1 gene. Although there is not a classical estrogen response element (ERE) in the proximal CCND1 promoter, estrogen-responsive transcription is mediated through recruitment of hormone-bound ESR1 by other DNA-binding proteins (reviewed in Guo et al, 2011; Klein and Assoian, 2008). A heterodimer of JUN:FOS binds to an estrogen-responsive G1 element (ERGE) between nucleotides -948 and -925 and is responsible for recruitment of ESR1 and estrogen to this site. OCT1 may facilitate this binding by displacing a YY1:HDAC1 repressive complex that occupies an adjacent site in unstimulated cells (Albanese et al, 1995; Cicatiello et al, 2004; Shen et al, 2007). Binding of ATF2:JUN heterodimers to a cyclic AMP response element (CRE) located 52 nucleotides upstream of the transcriptional start site may also contribute to estrogen-responsive signaling (Sabbah et al, 1999; Castro-Rivera et al, 2001).

**Preceded by:** Binding of AP1 transcriptional activator complexes to CCND1 promoter

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Estrogen-responsive MYC gene expression

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-9011975

Type: omitted

Compartments: nucleoplasm

MYC gene expression is estrogen-responsive and expression of MYC and CCND1 contribute to the proliferative response stimulated by estrogen treatment (Dubnik et al, 1987; Dubnik et al, 1988; Dubnik and Shu, 1992; Prall et al, 1998). Estrogen-responsive MYC expression appears to depend at least in part on a distal enhancer element 67 kb from the transcriptional start site that contains a half ERE and an AP-1 site (Denardo et al, 2005; Carroll et al, 2006; Wang et al, 2011). Upon estrogen stimulation, these sites are occupied by ESR1 and a JUND:FOSB heterodimer, respectively (Wang et al, 2011). Estrogen-responsive MYC expression also depends on the cohesin complex, as depletion of the RAD21 cohesin subunit abrogates expression (Stedman et al, 2008; Schmidt et al, 2010; McEwan et al, 2011; Antony et al, 2015). Genome-wide studies have shown that RAD21 and ESR1 binding sites overlap in a fraction of estrogen-responsive genes, including MYC (Schmidt et al, 2010). Cohesin may contribute to target gene expression by promoting chromatin looping structures between distal enhancers and the target gene promoters or through other mechanisms that remain to be elucidated (Li et al, 2012; Antony et al, 2015; reviewed Rhodes et al, 2011; Losada, 2014). Overexpression of histone isoform HIST1H2AC in breast cancer has been shown to contribute to MYC gene expression by promoting the formation of activating chromatin loops and facilitating the recruitment of ESR1, EP300 and RNA polymerase II (Su et al, 2014).

Preceded by: ESR1:ESTG, JUND:FOSB and Cohesin Complex bind distal enhancer elements in MYC gene promoter, EP300 is recruited to MYC and BCL2 genes

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ESR1:ESTG, JUND:FOSB and Cohesin Complex bind distal enhancer elements in MYC gene promoter

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-9011997

Type: binding

Compartments: nucleoplasm

MYC gene expression is estrogen-responsive and expression of MYC and CCND1 contribute to the proliferative response stimulated by estrogen treatment (Dubnik et al, 1987; Dubnik et al, 1988; Dubnik and Shu, 1992; Prall et al, 1998). Estrogen-responsive MYC expression appears to depend at least in part on a distal enhancer element 67 kb from the transcriptional start site that contains a half ERE and an AP-1 site (Denardo et al, 2005; Carroll et al, 2006; Wang et al, 2011). Upon estrogen stimulation, these sites are occupied by ESR1 and a JUND:FOSB heterodimer, respectively (Wang et al, 2011). Estrogen-responsive MYC expression also depends on the cohesin complex, as depletion of the RAD21 cohesin subunit abrogates expression (Stedman et al, 2008; Schmidt et al, 2010; McEwan et al, 2011; Antony et al, 2015). Genome-wide studies have shown that RAD21 and ESR1 binding sites overlap in a fraction of estrogen-responsive genes, including MYC (Schmidt et al, 2010). Cohesin may contribute to target gene expression by promoting chromatin looping structures between distal enhancers and the target gene promoters or through other mechanisms that remain to be elucidated (Li et al, 2012; Antony et al, 2015; reviewed Rhodes et al, 2011; Losada, 2014). Overexpression of histone isoform HIST1H2AC in breast cancer has been shown to contribute to MYC gene expression by promoting the formation of activating chromatin loops and facilitating the recruitment of ESR1, EP300 and RNA polymerase II (Su et al, 2014).

Followed by: Estrogen-responsive MYC gene expression

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ESR1:ESTG and KDM4B bind H3K9me3 target gene enhancers

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-9011952

Type: binding

Compartments: nucleoplasm

Transcriptional induction of a number of estrogen-responsive genes, including MYC, MYB, GREB1 and KDM4B itself, is dependent on KDM4B-dependent H3K9 promoter/enhancer demethylation. KDM4B interacts with ESR1 and is recruited to estrogen-responsive target gene promoters or enhancers in an estrogen-dependent manner (Kawazu et al, 2011; Gaughan et al, 2013). Depletion of KDM4B in T47D and MCF7 breast cancer cell lines abrogates the proliferative response to estrogen, consistent with its role in driving expression of estrogen-dependent cell cycle regulators like MYC and CCND1 (Kawazu et al, 2011; Yang et al, 2010). KDM4B additionally interacts with the transcriptional activator SMARCA4, and depletion of KDM4B compromises the recruitment of RNA polymerase II to the MYB promoter in T47D cells (Kawazu et al, 2011). KDM4B is highly expressed in ER alpha-positive breast cancer and prostate cancer (Gaughan et al, 2013; Coffey et al, 2013). KDM4B may also promote estrogen-responsive signaling by interacting with GATA3 and binding to the enhancers of ESR1 and FOXA1 genes (Gaughan et al, 2013).

Followed by: KDM4B demethylates H3K9me3 on estrogen-responsive target enhancers

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KDM4B demethylates H3K9me3 on estrogen-responsive target enhancers

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-9011949

**Type:** transition

**Compartments:** nucleoplasm

KDM4B (also known as JMJD2B) is an H3 K9 demethylase that is recruited to estrogen-responsive enhancers through interaction with ESR1 (Kawazu et al, 2011; Gaughan et al, 2013). KDM4B promotes target gene activation in the presence of estrogen by removing the repressive H3K9 methylation mark, and KDM4B has been shown to interact with the SWI/SNF-B complex component SMARCA4 and to promote recruitment of RNA polymerase II (Kawazu et al, 2011; Gaughan et al, 2013).

**Preceded by:** ESR1:ESTG and KDM4B bind H3K9me3 target gene enhancers

**Followed by:** Estrogen-responsive KDM4B gene expression, NR5A2, ZNF217 and NCOA3 bind GREB1 promoter

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**Estrogen-responsive KDM4B gene expression**

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-9011966

**Type:** omitted

**Compartments:** nucleoplasm

KDM4B regulates its own expression by interacting with the estrogen receptor to promote estrogen-dependent demethylation of its promoter. KDM4B also interacts with the transcriptional activator SMARCA4 to promote recruitment of RNA polymerase II (Kawazu et al, 2011; Gaughan et al, 2013).

**Preceded by:** KDM4B demethylates H3K9me3 on estrogen-responsive target enhancers

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NR5A2, ZNF217 and NCOA3 bind GREB1 promoter

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-9012000

**Type:** omitted

**Compartments:** nucleoplasm

GREB1 (growth regulation by estrogen in breast cancer 1) is an estrogen-responsive gene that contains three EREs located 1.6, 9.5 and 21.2 kb upstream of the transcriptional start site (Ghosh et al 2000; Lin et al, 2004; Rae et al, 2005; Deschenes et al, 2007; Sun et al, 2007). By ChIP, all three EREs are bound by ESR1 and the transcriptional co-activator NCOA3 (also known as SRC3). Although this binding occurs even in the absence of estradiol treatment, binding is enhanced after estrogen stimulation (Sun et al, 2007). Estrogen-dependent GREB1 expression also depends on removal of the repressive H3K9 methylation mark by KDM4B (Kawazu et al, 2011; Gaughan et al, 2013). Estrogen stimulation increases the occupancy of RNA polymerase II at the GREB1 gene and may promote transcription through the formation of chromat-in loops. Estrogen stimulation also increases the level of H4 acetylation at the promoter (Sun et al, 2007; Deschenes et al, 2007). In addition to ESR1 and NCOA3, Kruppel-like finger (KLF) protein ZNF217 has also been shown to bind to ESR1 and enhance recruitment to GREB1 EREs. ZNF217 overexpression is associated with anchorage independent growth in MCF7 cell lines (Nguyen et al, 2014). Although both NCOA3 and ZNF217 have been shown to interact with the GREB1 EREs, no study has examined co-occupancy of the GREB1 enhancer by these two regulators.

**Preceded by:** KDM4B demethylates H3K9me3 on estrogen-responsive target enhancers

**Followed by:** Estrogen-responsive GREB1 gene transcription

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Estrogen-responsive GREB1 gene transcription

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-9011950

Type: omitted

Compartments: nucleoplasm

GREB1 is transcribed in response to estrogen stimulation in a manner that depends on NCOA3, ZNF217 and KDM4B (Ghosh et al, 2000; Rae et al, 2005; Sun et al, 2007; Kawazu et al, 2011; Nguyen et al, 2014). Estrogen-responsive transcription is directed by three EREs at -21.2, -9.5 and -1.6kb relative to the transcription start site and may be facilitated by the formation of chromatin loops (Lin et al, 2004; Sun et al, 2007; Deschenes et al, 2007; Lin et al, 2007).

Preceded by: NR5A2, ZNF217 and NCOA3 bind GREB1 promoter

Followed by: GREB1 binds ESR1:ESTG and co-activators, miR-26A and B bind to the 3'UTR of the GREB1 mRNA, GREB1 translation is negatively regulated by miR-26A and B, KPNA2 translation is negatively regulated by miR-26A and B, CHD1 translation is negatively regulated by miR-26A and B

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miR-26A and B bind to the 3'UTR of the GREB1 mRNA

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-9011958

**Type:** binding

**Compartments:** cytosol

Translation of GREB1 mRNA is negatively regulated by miR-26A and B, which bind directly to the 3'UTR. miR-26A and B are both downregulated in the presence of estrogen in a manner that depends on estrogen-stimulated MYC gene expression. Of the nine identified estrogen-responsive, miR-26 regulated genes, GREB1, CHD1 and KPNA2 are the only three that contribute to the proliferative response to estrogen (Tan et al, 2014).

**Preceded by:** Estrogen-responsive GREB1 gene transcription

**Followed by:** GREB1 translation is negatively regulated by miR-26A and B, KPNA2 translation is negatively regulated by miR-26A and B, CHD1 translation is negatively regulated by miR-26A and B

**Literature references**

Tan, S., Ding, K., Li, R., Zhang, W., Li, G., Kong, X. et al. (2014). Identification of miR-26 as a key mediator of estrogen stimulated cell proliferation by targeting CHD1, GREB1 and KPNA2. *Breast Cancer Res.*, 16, R40.

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GREB1 translation is negatively regulated by miR-26A and B

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-9011961

**Type:** omitted

**Compartments:** cytosol

Translation of GREB1 mRNA is negatively regulated by direct binding of miR-26A and miR-26B to the 3' UTR. miR-26 expression is itself negatively regulated in response to estrogen in a manner that depends on estrogen-stimulated MYC gene expression (Tan et al, 2014).

**Preceded by:** miR-26A and B bind to the 3'UTR of the GREB1 mRNA, Estrogen-responsive GREB1 gene transcription

**Literature references**

Tan, S., Ding, K., Li, R., Zhang, W., Li, G., Kong, X. et al. (2014). Identification of miR-26 as a key mediator of estrogen stimulated cell proliferation by targeting CHD1, GREB1 and KPNA2. *Breast Cancer Res.*, 16, R40.

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GREB1 binds ESR1:ESTG and co-activators

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-9038052

**Type:** binding

**Compartments:** nucleoplasm

In addition to being an estrogen-responsive target, GREB1 also interacts directly with ESR1 and functions as an coactivator at numerous estrogen-responsive promoters, as assessed in MCF7 cell lines, xenograft models and primary tumors (Mohammed et al, 2013). ESR1-binding coincides with ~95% of GREB1 binding events sites as assessed by ChIP-seq, and expression of up to half of ESR1- and estrogen-dependent genes is compromised when GREB1 expression is silenced, without affecting ESR1 binding. GREB1 may function to stabilize interactions with other coactivators such as EP300 and CREBBP (also known as p300 and CBP, respectively), as co-occupancy with these proteins is lost upon GREB1 silencing (Mohammed et al, 2013). GREB1 expression is high in ER+ cancers and is associated with positive prognosis (Mohammed et al, 2013; reviewed in Hodgkinson and Vanderhyden, 2014).

**Preceded by:** Estrogen-responsive GREB1 gene transcription

**Literature references**


**Editions**

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**Estrogen-responsive CHD1 gene transcription**

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-9012205

**Type:** omitted

**Compartments:** nucleoplasm

CHD1 is an ATP-dependent chromatin remodelling factor that is a component of the SAGA complex (Sims et al, 2007; reviewed in Marfella and Imbalzano, 2007). CHD1 expression has been shown to be responsive to estrogen stimulation, and negatively regulated by direct binding of mIR-26A and mIR-26B to the 3' UTR. MYC- and estrogen-dependent down-regulation of mIR-26 expression abrogates the repressive effect on CHD1 expression and promotes the estrogen-responsive proliferative effect (Tan et al, 2014).

**Followed by:** miR-26A and B bind to the 3'UTR of the CHD1 mRNA

**Literature references**


Tan, S., Ding, K., Li, R., Zhang, W., Li, G., Kong, X. et al. (2014). Identification of miR-26 as a key mediator of estrogen stimulated cell proliferation by targeting CHD1, GREB1 and KPNA2. *Breast Cancer Res.*, 16, R40.


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</table>
miR-26A and B bind to the 3'UTR of the CHD11 mRNA

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-9012203

Type: binding

Compartments: cytosol

Translation of CHD1 mRNA is negatively regulated by miR-26A and B, which bind directly to the 3'UTR. miR-26A and B are both downregulated in the presence of estrogen in a manner that depends on estrogen-stimulated MYC gene expression. Of the nine identified estrogen-responsive, miR-26 regulated genes, GREB1, CHD1 and KPNA2 are the only three that contribute to the proliferative response to estrogen (Tan et al, 2014).

Preceded by: Estrogen-responsive CHD1 gene transcription

Literature references
Tan, S., Ding, K., Li, R., Zhang, W., Li, G., Kong, X. et al. (2014). Identification of miR-26 as a key mediator of estrogen stimulated cell proliferation by targeting CHD1, GREB1 and KPNA2. *Breast Cancer Res.*, 16, R40.

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CHD1 translation is negatively regulated by miR-26A and B

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-9012186

**Type:** omitted

**Compartments:** cytosol

Translation of CHD1 is negatively regulated by binding of mIR-26A and mIR-26B to the 3'UTR. Estrogen- and MYC-dependent CHD1 expression contributes to the proliferative response to estrogen stimulation (Tan et al, 2014).

**Preceded by:** miR-26A and B bind to the 3'UTR of the GREB1 mRNA, Estrogen-responsive GREB1 gene transcription

**Literature references**

Tan, S., Ding, K., Li, R., Zhang, W., Li, G., Kong, X. et al. (2014). Identification of miR-26 as a key mediator of estrogen stimulated cell proliferation by targeting CHD1, GREB1 and KPNA2. *Breast Cancer Res.*, 16, R40.

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</table>
KPNA2 is a member of the karyopherin alpha family that recognized cargo proteins at the nuclear pore to facilitate their nucleocytoplasmic transport (reviewed in Christiansen and Dyrskjot, 2013). KPNA2 is highly expressed in many cancers and has been shown to be stimulated by estrogen (Tan et al, 2014). KPNA2 expression is negatively regulated by direct binding of mIR-26A and mIR-26B to the 3'UTR (Tan et al, 2014).

Followed by: miR-26A and B bind to the 3'UTR of the KPNA2 mRNA

Literature references


Tan, S., Ding, K., Li, R., Zhang, W., Li, G., Kong, X. et al. (2014). Identification of miR-26 as a key mediator of estrogen stimulated cell proliferation by targeting CHD1, GREB1 and KPNA2. Breast Cancer Res., 16, R40.
miR-26A and B bind to the 3'UTR of the KPNA2 mRNA

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-9012208

**Type:** binding

**Compartments:** cytosol

Translation of KPNA2 mRNA is negatively regulated by miR-26A and B, which bind directly to the 3'UTR. miR-26A and B are both downregulated in the presence of estrogen in a manner that depends on estrogen-stimulated MYC gene expression. Of the nine identified estrogen-responsive, miR-26 regulated genes, GREB1, CHD1 and KPNA2 are the only three that contribute to the proliferative response to estrogen (Tan et al, 2014). KPNA2 expression has also been demonstrated to be regulated by miR-26 binding in ovarian cancer (Lin et al 2015).

**Preceded by:** Estrogen-responsive KPNA2 gene transcription

**Literature references**

Tan, S., Ding, K., Li, R., Zhang, W., Li, G., Kong, X. et al. (2014). Identification of miR-26 as a key mediator of estrogen stimulated cell proliferation by targeting CHD1, GREB1 and KPNA2. *Breast Cancer Res.*, 16, R40.

KPNA2 translation is negatively regulated by miR-26A and B

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-9012196

Type: omitted

Compartments: cytosol

Translation of KPNA2 is negatively regulated by binding of miR-26A and miR-26B to the 3' UTR.

**Preceded by:** miR-26A and B bind to the 3' UTR of the GREB1 mRNA, Estrogen-responsive GREB1 gene transcription

**Literature references**

Tan, S., Ding, K., Li, R., Zhang, W., Li, G., Kong, X. et al. (2014). Identification of miR-26 as a key mediator of estrogen stimulated cell proliferation by targeting CHD1, GREB1 and KPNA2. Breast Cancer Res., 16, R40.

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ESR1:ESTG:P-TEFb recruited to paused RNA polymerase II on MYB gene

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-9012315

**Type:** binding

**Compartments:** nucleoplasm

MYB is frequently expressed in breast cancer and its expression is correlated with ER positive tumors (Guerin et al, 1990; Kauraniemi et al, 2000). MYB expression is estrogen-responsive, but hormone-dependent control is exerted at the level of transcriptional elongation rather than initiation (Frasor et al, 2003; Carroll et al, 2006; Bender et al, 1987; Watson et al, 1988; Drabsch et al, 2007). In the absence of estrogen, RNA polymerase II stalls at a stem-loop poly-T (SL-dT) tract between within intron 1 (Drabsch et al, 2007). Upon estrogen stimulation, a complex containing estrogen, the estrogen receptor and P-TEFb (an elongation factor consisting of Cyclin T and CDK9) is recruited to an ERE near the SL-dT. P-TEFb phosphorylates serine 2 in the RNA polymerase II CTD, allowing the polymerase to continue elongating (Drabsch et al, 2007; Mitra et al, 2012; reviewed in Gonda et al, 2008; Garriga and Grana, 2004). Although EREs have been identified around the SL-dT and have been shown by ChIP to be bound by ESR1, mutation of the EREs does not abrogate estrogen-responsive MYB expression, suggesting that the estrogen receptor either binds to a non-canonical site or it interacts through another transcription factor in this reaction (Drabsch et al, 2007; Mitra et al, 2012)

**Followed by:** p-TEFb phosphorylates serine 2 in RNA polymerase II CTD

**Literature references**


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Estrogen-responsive MYB gene expression

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-9011971

Type: omitted

Compartments: nucleoplasm

MYB is frequently expressed in breast cancer and its expression is correlated with ER positive tumors (Guerin et al, 1990; Kauraniemi et al, 2000). MYB expression is estrogen-responsive, but hormone-dependent control is exerted at the level of transcriptional elongation rather than initiation (Frasor et al, 2003; Carroll et al, 2006; Bender et al, 1987; Watson et al, 1988; Drabsch et al, 2007). In the absence of estrogen, RNA polymerase II stalls at a stem-loop poly-T (SL-dT) tract between within intron 1 (Drabsch et al, 2007). Upon estrogen stimulation, a complex containing estrogen, the estrogen receptor and P-TEFb (an elongation factor consisting of Cyclin T and CDK9) is recruited to an ERE near the SL-dT. P-TEFb phosphorylates serine 2 in the RNA polymerase II CTD, allowing the polymerase to continue elongating (Drabsch et al, 2007; Mitra et al, 2012; reviewed in Gonda et al, 2008; Garriga and Grana, 2004). Although EREs have been identified around the SL-dT and have been shown by ChIP to be bound by ESR1, mutation of the EREs does not abrogate estrogen-responsive MYB expression, suggesting that the estrogen receptor either binds to a non-canonical site or it interacts through another transcription factor in this reaction (Drabsch et al, 2007; Mitra et al, 2012).

Transcriptional induction of MYB is also dependent on KDM4B-dependent H3K9 promoter/enhancer demethylation. KDM4B interacts with ESR1 and is recruited to estrogen-responsive target gene promoters or enhancers in an estrogen-dependent manner (Kawazu et al, 2011; Gaughan et al, 2013). Depletion of KDM4B in T47D and MCF7 breast cancer cell lines abrogates the proliferative response to estrogen, consistent with its role in driving expression of estrogen-dependent cell cycle regulators like MYC and CCND1 (Kawazu et al, 2011; Yang et al, 2010). KDM4B additionally interacts with the transcriptional activator SMARCA4, and depletion of KDM4B compromises the recruitment of RNA polymerase II to the MYB promoter in T47D cells (Kawazu et al, 2011). KDM4B is highly expressed in ER alpha-positive breast cancer and prostate cancer (Gaughan et al, 2013; Coffey et al, 2013). KDM4B may also promote estrogen-responsive signaling by interacting with GATA3 and binding to the enhancers of ESR1 and FOXA1 genes (Gaughan et al, 2013). How and when (or whether) KDM4B interacts with P-TEFb has not been examined.
Preceded by: p-TEFb phosphorylates serine 2 in RNA polymerase II CTD

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p-TEFb phosphorylates serine 2 in RNA polymerase II CTD

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-9012319

Type: transition

Compartments: nucleoplasm

Transcriptional pausing at the SL-dT site in the MYB gene is overcome in response to estrogen by the P-TEFb-mediated phosphorylation of serine 2 in the C-terminal domain of RNA polymerase II (Drabsch et al, 2007; Mitra et al, 2012).

Preceded by: ESR1:ESTG:P-TEFb recruited to paused RNA polymerase II on MYB gene

Followed by: Estrogen-responsive MYB gene expression

Literature references


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ESR1:ESTG binds CXXC5 gene

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-9018325

Type: binding

Compartments: nucleoplasm

ESR1 binds to an ERE at -242 in the promoter of the CXXC5 gene and promotes transcription in an estrogen-dependent fashion. CXXC5 is a member of the zinc finger CXXC family of transcription factors and plays roles in cellular proliferation and differentiation (Nott et al, 2009; Yaşar et al, 2016).

Followed by: Estrogen-responsive CXXC5 gene expresion

Literature references


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Estrogen-responsive CXXC5 gene expression

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-9018334

Type: omitted

Compartments: nucleoplasm


Preceded by: ESR1:ESTG binds CXXC5 gene

Literature references


Kim, MY., Kim, HY., Hong, J., Kim, D., Lee, H., Cheong, E. et al. (2016). CXXC5 plays a role as a transcription activator for myelin genes on oligodendrocyte differentiation. Glia, 64, 350-62.

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FOXA1 and GATA3 bind TFF genes

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-9018494

Type: transition

Compartments: nucleoplasm

Trefoil factor family (TFF) 1 and 3 are secreted in mucous epithelia and the nervous system and have been implicated in oncogenesis and metastasis (reviewed in Busch and Dünker, 2015). TFF1 and 3 are estrogen-responsive genes with ESR1-bound promoters/enhancers that are primed for ligand-dependent expression by the binding of 'pioneer' transcription factors, such as FOXA1 and GATA3 (Berry et al, 1989; Shang et al, 2000; Carroll et al, 2005; Laganière et al, 2005; Eeckhoute et al, 2006; Hurtado et al, 2011; Kong et al, 2011; Theodorou et al, 2013; reviewed in Zaret and Carroll, 2011; Augello et al, 2011; Fiorito et al, 2013; Wilson and Giguere, 2008). FOXA factors have a winged helix structure that is thought to bind to closed chromatin structures in a manner analogous to linker histones, displacing linker histones and rendering the DNA more accessible to other transcription factors (reviewed in Zaret and Carroll, 2011). FOXA binding sites tend to be enriched at enhancer elements, characterized by H3K4 mono- and di-methylation and H3K27 acetylation, active histone markers (Heintzman et al, 2009; Creyghton et al, 2010; Theodorou et al, 2013).

Followed by: ESR1 binds to TFF1 gene promoter, ESR1:ESTG and EP300 are recruited to TFF3 promoter

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ESR1:ESTG and EP300 are recruited to TFF3 promoter

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-9018499

**Type:** binding

**Compartments:** nucleoplasm

TFF3 is an estrogen-responsive gene whose expression is primed prior to estrogen receptor binding by the formation of FOXA1- and GATA3-dependent chromatin loops. Interaction of ligand-bound ESR1 with the enhancer promotes recruitment of EP300 and other chromatin modifying enzymes, and stimulates the deposition of active chromatin marks like H3K4 methylation and H3K27 acetylation (Laganière et al, 2005; Theodorou et al, 2013; reviewed in Zaret and Carroll, 2011)

**Preceded by:** FOXA1 and GATA3 bind TFF genes

**Followed by:** Estrogen-responsive TFF3 gene expression

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Estrogen-responsive TFF3 gene expression

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-9018497

Type: omitted

Compartments: nucleoplasm

Estrogen-dependent TFF3 expression is promoted by the formation of FOXA1- and GATA3-dependent chromatin loops. Interaction of ligand-bound ESR1 with the enhancer promotes recruitment of EP300 and other chromatin modifying enzymes, and stimulates the deposition of active chromatin marks like H3K4 methylation and H3K27 acetylation (Laganière et al, 2005; Theodorou et al, 2013; reviewed in Zaret and Carroll, 2011)

Preceded by: ESR1:ESTG and EP300 are recruited to TFF3 promoter

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ESR1 binds to TFF1 gene promoter

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-9009541

Type: binding

Compartments: nucleoplasm

TFF1 is an estrogen-responsive gene with an ESR1-bound promoter/enhancer that is primed for ligand-dependent expression by the binding of 'pioneer' transcription factors, such as FOXA1 and GATA3 (Berry et al, 1989; Shang et al, 2000; Carroll et al, 2005; Laganière et al, 2005; Eeckhoute et al, 2006; Hurtado et al, 2011; Theodorou et al, 2013; reviewed in Klinge, 2001; Zaret and Carroll, 2011; Fiorito et al, 2013). Ligand-bound estrogen receptor binds to a functional ERE between -405 and -393 and to a region 10.5 kb upstream of the TFF1 transcription start site (Berry et al, 1989; Sewack and Hansen, 1997; Métivier et al, 2003; Carroll et al, 2005).

Detailed ChIP studies of the TFF1 promoter in synchronized cells after estrogen stimulation reveal an ordered and cyclical recruitment of co-activators, chromatin remodelers and general transcriptional machinery that modify the epigenetic and chromatin environment to regulate transcriptional activity (Métivier et al, 2003; Métivier et al, 2008; Kangaspeska et al, 2008). Three phases are observed after estrogen stimulation of blocked cells, including an initial unproductive cycle followed by two transcriptionally productive cycles. These are marked by the combinatorial recruitment of different subsets of proteins and cyclical alterations to the methylation and acetylation status of the promoter (Métivier et al, 2003; Métivier et al, 2008; Kangaspeska et al, 2008; reviewed in Reid et al, 2009).

Preceded by: FOXA1 and GATA3 bind TFF genes

Followed by: DDX5 binds ESR1:estrogen:TFF1 gene promoter

Literature references


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DDX5 binds ESR1:estrogen:TFF1 gene promoter

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-9009536

**Type:** binding

**Compartments:** nucleoplasm

DDX5, also known as p68, is a putative RNA helicase that is implicated in estrogen-responsive signaling (Métivier et al, 2003; Métivier et al, 2004; Wortham et al, 2009; reviewed in Caretti et al, 2007; Arnal et al, 2017). DDX5 is recruited to the TFF1 promoter early during transcriptional activation and modulates the activity of the AF1 activator region of the estrogen receptor (Métivier et al, 2001; Métivier et al, 2003, Métivier et al, 2004).

**Preceded by:** ESR1 binds to TFF1 gene promoter

**Followed by:** PRMT1 binds TBP:TFIIA:DDX5:ESR1:estrogen:TFF1 gene, TBP and TFIIA bind TATA box on ESR1:estrogen bound TFF1 gene promoter

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TBP and TFIIA bind TATA box on ESR1:estrogen bound TFF1 gene promoter

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-9009533

**Type:** binding

**Compartments:** nucleoplasm

TFIIA and TBP are recruited to the TFF1 promoter early during transcriptional activation and are often found at the promoter with DDX5 (Métivier et al, 2003; reviewed in Caretti et al, 2007).

**Preceded by:** DDX5 binds ESR1:estrogen:TFF1 gene promoter

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</table>
CARM1 binds TBP:TFIIA:DDX5:ESR1:estrogen:TFF1 gene

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-9009526

**Type:** binding

**Compartments:** nucleoplasm

CARM1 is an H3 R17 methyltransferase that is recruited to the TFF promoter where, in conjunction with acetyltransferases, it establishes transcriptionally active chromatin (Métivier et al, 2003; Chen et al, 2000; Daujat et al, 2002). PRMT1 is an alternate arginine methyltransferase with activity toward H4 R3 that acts at the TFF enhancer, however CARM1 and PRMT1 are never found simultaneously at the TFF1 gene (Métivier et al, 2003; reviewed in Xu et al, 2003; Arnal et al, 2017). Note that in this diagram, methylation of H3 R17 is not depicted.

**Followed by:** Histone acetyltransferases are recruited to the TFF1 gene

**Literature references**


**Editions**

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https://reactome.org
PRMT1 binds TBP:TFIIA:DDX5:ESR1:estrogen:TFF1 gene

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-9023861

Type: binding

Compartments: nucleoplasm

PRMT1 is an H4 R3 methyltransferase that is recruited to the TFF promoter where, in conjunction with acetyltransferases, it establishes transcriptionally active chromatin (Métivier et al, 2003). CARM1 is an alternate arginine methyltransferase with activity toward H3 R17 that acts at the TFF enhancer, however CARM1 and PRMT1 are never found simultaneously at the TFF1 gene (Métivier et al, 2003; reviewed in Xu et al, 2003; Arnal et al, 2017). Note that in this diagram, methylation of H4 R3 is not depicted.

Preceded by: DDX5 binds ESR1:estrogen:TFF1 gene promoter

Followed by: Histone acetyltransferases are recruited to the TFF1 gene

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</table>
Histone acetyltransferases are recruited to the TFF1 gene

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-9023860

Type: binding

Compartments: nucleoplasm

Estrogen-dependent expression of TFF1 depends on the recruitment of histone acetyltransferases such as KAT5, EP300, CITED1 and KAT2B, as well as coactivators such as NCOA1 and NCOA3 (Métivier et al, 2003; reviewed in Arnal et al, 2017). ChIP analysis suggests that NCOA1 and NCOA3 do not co-occupy the TFF1 promoter, but may be differentially recruited under different conditions (Métivier et al, 2003). Note that the acetyltransferase activity of these HATs is not depicted in this diagram.


Followed by: Estrogen-responsive TFF1 gene expression

Literature references


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</table>
Estrogen-responsive TFF1 gene expression

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-9023859

Type: omitted

Compartments: nucleoplasm

Estrogen-dependent TFF1 expression is promoted by the formation of FOXA1- and GATA3-dependent chromatin loops. (Laganière et al, 2005; Theodorou et al, 2013; reviewed in Zaret and Carroll, 2011). Interaction of ligand-bound ESR1 with the enhancer promotes recruitment of histone acetyltransferases and methyltransferases, which establish transcriptionally active chromatin structures and facilitate recruitment of RNA polymerase II (Métivier et al, 2003; reviewed in Xu et al, 2003, Arnal et al, 2017).

Preceded by: Histone acetyltransferases are recruited to the TFF1 gene

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</table>
ESR1 binds to TGFA gene promoter

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-9008267

Type: binding

Compartments: nucleoplasm

Hormone-activated estrogen receptor (ER) binds with high affinity to specific DNA sequences, estrogen response elements (EREs), found in the regulatory regions of estrogen-responsive genes (Klinge CM 2001). The majority of known estrogen responsive genes contain imperfect EREs that differ from the consensus ERE sequence, 5′-GGTCAnnnTGACC-3′, by one or more base pairs. The individual ERE sequences were found to differentially induce changes in ER conformation that may influence the recruitment of specific coactivator proteins (Wood JR et al. 2001). The promoter of the TGFA gene has two imperfect EREs between -252 to -200 and an additional upstream sequence between -623 and -549. These elements confer estrogen-responsiveness to the promoter and are bound by ESR1 as assessed by electrophoretic mobility shift assay (Vyhidal et al, 2000).


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</table>
CITED1 and EP300 bind ESR1:estrogen:TGFA gene promoter

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-9008271

Type: binding

Compartments: nucleoplasm

CITED1 and EP300 contribute to the estrogen-dependent expression of the TGFA gene. CITED1 (also known as CBP) interacts directly with ESR1 through the transcriptional activation AF2 domain and enhances its activity. The interaction between ESR1 and exogenous CITED1 also stabilizes the interaction with EP300 (Yahate et al, 2001).

Preceded by: ESR1 binds to TGFA gene promoter

Followed by: TGFA gene expression is stimulated by the CITED1:EP300:ESR1:estrogen

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TGFA gene expression is stimulated by the CITED1:EP300:ESR1:estrogen

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-9008315

Type: omitted

Compartments: nucleoplasm

The TGFA gene encodes the precursor of the transforming growth factor alpha (TGF alpha). Binding of the CITED1 to the promoter of the TGFA gene in the estrogen:ESR1-dependent manner stimulates TGFA transcription in MCF-7 breast cancer cell line (Yahata T et al. 2001).

Preceded by: CITED1 and EP300 bind ESR1:estrogen:TGFA gene promoter

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NCOA1 binds ESR1:estrogen:TGFA gene

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-9008270

Type: binding

Compartments: nucleoplasm

NCOA1 is a nuclear receptor coactivator that is recruited to the TGFA promoter through direct interaction with ESR1 (Halachmi et al, 1994; Cavaillès et al, 1994; Harnstein et al, 2001). Although NCOA1 has intrinsic histone acetyltransferase activity, it plays a more predominant role in activating gene transcription through its ability to recruit EP300 to the promoter (Harnstein et al, 2001; reviewed in Arnal el al, 2017).

Preceded by: ESR1 binds to TGFA gene promoter

Followed by: NCOA1 recruits EP300 to TGFA promoter

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NCOA1 recruits EP300 to TGFA promoter

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-9023884

Type: binding

Compartments: nucleoplasm


Preceded by: NCOA1 binds ESR1:estrogen:TGFA gene

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</table>
**NCOA3 binds ESR1:estrogen:TFGA gene**

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-9008258

**Type:** binding

**Compartments:** nucleoplasm

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X-ray crystallography studies illustrated that the ligand-bound ESR1 interacts with LXXLL motif-containing NCOA3 (SRC3) through the ligand-binding domain (LBD) at the C-terminus of ESR1, which also has a ligand-dependent transactivation function (known as AF-2) (Brzozowski et al. 1997). Cryoelectron microscopy (cryo-EM) determined the quaternary structure of an active complex of DNA-bound ESR1, steroid receptor coactivator 3 (SRC3 or NCOA3), and a secondary coactivator (p300/EP300). Structural models suggests the following assembly mechanism for the complex: each of the two ligand-bound ESR1 monomers independently recruits one NCOA3 protein via the transactivation domain of ESR1; the two NCOA3s in turn bind to different regions of one p300 protein through multiple contacts (Yi P et al. 2015).

**Preceded by:** ESR1 binds to TGFA gene promoter

**Followed by:** NCOA3 recruits EP300 to ESR1:estrogen:TFGA gene:NCOA3

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**Literature references**


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**Preceded by:** NCOA3 binds ESR1:estrogen:TFGA gene

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</table>
EBAG9 is an estrogen-responsive gene with an ill-characterized role in tumorigenesis and is overexpressed in a number of cancers (Jóźwicki et al, 2015; Xu et al, 2014; Giagnis et al, 2013). EBAG9 has been implicated in glycan maturation at the Golgi, and may also play roles in immune response and apoptosis during tumor growth (Wolf et al, 2010; Miyazaki et al, 2014; Tanaka et al, 2014; Mayeama et al, 2011). Estrogen-dependent transcription is mediated by an ERE in the 5'-flanking region which has been shown to bind ESR1 by electrophoretic mobility shift assay (Ikeda et al, 2000).

Followed by: Estrogen-responsive EBAG9 gene expression

Literature references


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Estrogen-responsive EBAG9 gene expression

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-9018505

**Type:** omitted

**Compartments:** nucleoplasm

EBAG9, also known as RCAS1, is an estrogen-responsive gene with an ERE in the 5' flanking region (Ikeda et al, 2000). EBAG9 may play a role in immune response during tumorigenesis, and expression of EBAG9 is often upregulated in malignant tumors (Jóźwicki et al, 2015; Miyazaki et al, 2014; Xu et al, 2014; Tanaka et al, 2014; Wolf et al, 2010; Maeyama et al, 2011)

**Preceded by:** ESR1:ESTG bind the EBAG9 5' region

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</table>
Overexpressed HIST1H2AC and ESR1:ESTG bind MYC and BCL2 genes

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-9011983

**Type:** binding

**Compartments:** nucleoplasm

HIST1H2AC (also known as H2ac) is a replicative histone H2A isoform that is overexpressed in breast cancer (Shann et al, 2008). HIST1H2AC and HIST1H2AA, unique among HIST1H2 family members, contains a HAR domain that in yeast has been shown mediate interaction with histone H3 and to regulate gene expression (Zheng et al, 2010). Estrogen-dependent recruitment of HIST1H2AC to target genes contributes to the proliferative response to estrogen, and siRNA depletion of HIST1H2AC abrogates expression of genes including MYC, CCND1 and BCL2, among others, and results in cell cycle arrest at G0/G1. By ChIP, both the estrogen receptor and HIST1H2AC are present at distal enhancer elements and in the 3' UTR of target genes upon estrogen stimulation, and the proteins physically interact both in vitro and in vivo. HIST1H2AC and ESR1 contribute to target gene activation by promoting the formation of long distance chromatin loops between disparate regulatory regions (Su et al, 2013). Overexpression of HIST1H2AC additionally decreases the levels of the repressive epigenetic modification H3K9me2 that is associated with estrogen-responsive signaling, and HIST1H2AC contributes to the recruitment of the histone demethylase KDM1A (Perillo et al, 2008; Su et al, 2014).

Followed by: KDM1A is recruited to MYC and BCL2 genes

**Literature references**


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</table>
Histone demethylase KDM1A (also known as LSD1) is recruited to estrogen-responsive promoters and enhancers in a manner that depends on the HAR domain of HIST1H2AC. KDM1A removes the repressive H3K9me2 epigenetic mark, and consistent with this, KDM1A knockdown leads to abrogated expression of BCL2 and MYC genes in response to estrogen stimulation (Perillo et al, 2008; Su et al, 2014; Wang et al, 2009; Wissmann et al, 2007)

Preceded by: Overexpressed HIST1H2AC and ESR1:ESTG bind MYC and BCL2 genes

Followed by: KDM1A demethylates H3 on MYC and BCL genes in response to estrogen

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</table>
KDM1A demethylates H3 on MYC and BCL genes in response to estrogen

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-9011985

**Type:** transition

**Compartments:** nucleoplasm

KDM1A removes the H3K9me2 repressive epigenetic mark at estrogen-responsive enhancers, allowing transcriptional activation (Wang et al, 2009; Su et al, 2014).

**Preceded by:** KDM1A is recruited to MYC and BCL2 genes

**Followed by:** EP300 is recruited to MYC and BCL2 genes

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**EP300 is recruited to MYC and BCL2 genes**

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-9011981

**Type:** binding

**Compartments:** nucleoplasm

ESR1 and HIST1H2AC contribute to estrogen-responsive transcriptional activation at the BCL and MYC genes by promoting long-range chromatin loops between enhancer elements. This is accompanied by the recruitment of EP300 and RNA polymerase II (Su et al, 2014).

**Preceded by:** KDM1A demethylates H3 on MYC and BCL genes in response to estrogen

**Followed by:** Estrogen-responsive BCL2 gene expression, Estrogen-responsive MYC gene expression

**Literature references**

ESR1 and HIST1H2AC contribute to estrogen-responsive transcriptional activation at the BCL and MYC genes by promoting long-range chromatin loops between enhancer elements. This is accompanied by the recruitment of EP300 and RNA polymerase II (Su et al, 2014).

**Preceded by:** EP300 is recruited to MYC and BCL2 genes

**Literature references**

RUNX1 binds ESR1

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-8931981

**Type:** binding

**Compartments:** nucleoplasm

The RUNX1:CBFB complex binds the estrogen receptor alpha (ESR1). The interaction between RUNX1 and ESR1 is significantly enhanced upon ESR1 activation by estrogens (Stender et al. 2010).

**Followed by:** RUNX1 and ESR1 bind the GPAM gene enhancer, RUNX1 and ESR1 bind the KCTD6 gene enhancer, RUNX1 and ESR1 bind the AXIN1 gene

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</table>
RUNX1 and ESR1 bind the GPAM gene enhancer

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-8932021

Type: binding

Compartments: nucleoplasm

RUNX1 and ESR1 cooperatively bind to the enhancer of the GPAM gene, which contains both estrogen response elements and RUNX1 binding sites (Stender et al. 2010).

Preceded by: RUNX1 binds ESR1

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</table>
GPAM gene expression is stimulated by RUNX1 and ESR1

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-8932020

Type: omitted

Compartments: nucleoplasm, mitochondrial outer membrane

GPAM gene expression is cooperatively stimulated by RUNX1 and ESR1, which form a complex and bind the GPAM gene enhancer (Stender et al. 2010). GPAM encodes a glycerol-3-phosphate acyltransferase whose high expression correlates with better overall survival in breast cancer (Brockmoller et al. 2012).

Literature references


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RUNX1 and ESR1 bind the KCTD6 gene enhancer

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-8932037

**Type:** binding

**Compartments:** nucleoplasm

RUNX1 and ESR1 cooperatively bind the KCTD6 gene enhancer, which contains both estrogen response elements and RUNX1 response elements (Stender et al. 2010).

**Preceded by:** RUNX1 binds ESR1

**Followed by:** KCTD6 gene expression is stimulated by RUNX1 and ESR1

**Literature references**


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KCTD6 gene expression is stimulated by RUNX1 and ESR1

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-8932033

**Type:** omitted

**Compartments:** nucleoplasm, cytosol

RUNX1 and ESR1, which form a complex that binds to the KCTD6 gene enhancer, cooperatively stimulate the expression of the KCTD6 gene (Stender et al. 2010).

**Preceded by:** RUNX1 and ESR1 bind the KCTD6 gene enhancer

**Literature references**


**Editions**

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</table>
ESR1 binds the AXIN1 gene

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-8932070

Type: binding

Compartments: nucleoplasm

Estrogen receptor alpha (ESR1) binds to estrogen response elements in the second intron of the AXIN1 gene (Chimge et al. 2016).

Followed by: AXIN1 gene expression is inhibited by ESR1 and stimulated by RUNX1

Literature references


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**AXIN1 gene expression is inhibited by ESR1 and stimulated by RUNX1**

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-8932076

**Type:** omitted

**Compartments:** nucleoplasm, cytosol

Transcription of the AXIN1 gene, which encodes a component of the beta-catenin (CTNNB1) destruction complex, is inhibited by binding of the activated estrogen receptor alpha (ESR1) to estrogen response elements in the second intron of AXIN1 (Chimge et al. 2016).

The AXIN1 gene expression is stimulated by cooperative binding of RUNX1 and estrogen receptor alpha (ESR1) to adjacent RUNX1 binding sites and estrogen response elements in the second intron of AXIN1 (Chimge et al. 2016).

**Preceded by:** ESR1 binds the AXIN1 gene

**Literature references**


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</table>
RUNX1 and ESR1 bind the AXIN1 gene

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-8932084

**Type:** binding

**Compartments:** nucleoplasm

RUNX1 and ESR1, which are known to form a complex (Stender et al. 2010), cooperatively bind to adjacent Runx binding sites and estrogen response elements, respectively, in the second intron of the AXIN1 gene (Chimge et al. 2016).

**Preceded by:** RUNX1 binds ESR1

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ERBB4s80 forms a complex with estrogen receptor ESR1

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-1254386

**Type:** binding

**Compartments:** nucleoplasm

ERBB4s80 forms a complex with activated estrogen receptor ESR1 in the nucleus and acts as a transcriptional co-factor for ESR1 (Zhu et al. 2006).

**Followed by:** ERBB4s80:ESR1 binds PGR gene promoter, ERBB4s80:ESR1 binds CXCL12 gene promoter

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</table>
ERBB4s80:ESR1 binds PGR gene promoter

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-8954208

Type: binding

Compartments: nucleoplasm

The complex of ERBB4s80 and activated estrogen receptor ESR1 binds estrogen response elements (EREs) in the promoter of the PGR (NR3C3) gene, encoding Progesterone receptor (Zhu et al. 2006).

Preceded by: ERBB4s80 forms a complex with estrogen receptor ESR1

Followed by: PGR gene expression is stimulated by ERBB4s80:ESR1:estrogen

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</table>
ERBB4s80:ESR1 binds CXCL12 gene promoter

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-8954207

**Type:** binding

**Compartments:** nucleoplasm

The complex of ERBB4s80 and activated estrogen receptor ESR1 binds estrogen response elements (EREs) in the promoter of the CXCL12 gene, encoding Stromal cell-derived factor 1 (Zhu et al. 2006).

**Preceded by:** ERBB4s80 forms a complex with estrogen receptor ESR1

**Followed by:** CXCL12 gene expression is stimulated by ERBB4s80:ESR1:estrogen

**Literature references**


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</table>
PGR gene expression is stimulated by ERBB4s80:ESR1:estrogen

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-1254392

Type: omitted

Compartments: nucleoplasm

The complex of ERBB4s80 and activated estrogen receptor ESR1 promotes transcription of the PGR gene, encoding progesterone receptor (Zhu et al. 2006).

Preceded by: ERBB4s80:ESR1 binds PGR gene promoter

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Progesterone stimulation promotes PGR:P4 binding to ESR1:ESTG

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-9038161

Type: omitted

Compartments: nucleoplasm

In addition to being a target of estrogen-dependent transcription, the progesterone receptor (PGR) interacts directly with ER alpha after stimulation with progesterone and modulates ESR1:ESTG binding (Ballare et al, 2003; Mohammed et al, 2015). Progesterone stimulation under estrogen-rich conditions promotes the release of PGR from the chaperone complex to facilitate interaction with ESR1 (Mohammed et al, 2015; reviewed in ).

Followed by: ESR1:ESTG:PGR:P4 bind pioneer factors and coactivators

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ESR1:ESTG:PGR:P4 bind pioneer factors and coactivators

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-9038163

**Type:** omitted

**Compartments:** nucleoplasm

Rapid immunoprecipitation by mass spectrometry of endogenous proteins (RIME) analysis shows that in addition to interacting with PGR after progesterone stimulation, ESR1 also interacts with known co-activators NRIP, GATA3 and TLE3 (Mohammed et al, 2013; Mohammed et al, 2015). Progesterone treatment of breast cancer cell lines under estrogen-rich conditions promotes a redistribution of ER alpha binding to PGR binding sites. This redistribution coincides with co-occupancy of FOXA1 and EP300 at the novel binding sites as well as with the H3K27Ac mark, suggesting that the binding events are functional (Clarke et al, 2012; Mohammed et al, 2015).

**Preceded by:** Progesterone stimulation promotes PGR:P4 binding to ESR1:ESTG

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CXCL12 gene expression is stimulated by ERBB4s80:ESR1:estrogen

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-8954199

**Type:** omitted

**Compartments:** nucleoplasm

The complex of ERBB4s80 and activated estrogen receptor ESR1 promotes transcription of the CXCL12 gene, encoding Stromal cell-derived factor 1 (SDF1) (Zhu et al. 2006).

**Preceded by:** ERBB4s80:ESR1 binds CXCL12 gene promoter

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ESR1:ESTG binds to proximal and distal regions of the CTSD promoter

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-9023845

**Type:** binding

**Compartments:** nucleoplasm

Cathepsin D (CTSD) is an estrogen-responsive gene encoding a lysosomal protease with roles in cellular proliferation, apoptosis, cell migration and differentiation, among others (reviewed in Zaidi et al, 2008; Khalkhal-Ellis and Hendrix, 2015). Estrogen-dependence is conferred by the presence of non-canonical EREs in the proximal and distal promoter regions which are bound by ESR1 in a ligand-dependent manner (Augereau et al, 1994; Cavaillès et al, 1993; Wang et al, 1997; Wang et al, 1998; Xing and Archer, 1998; Shang et al, 2000; Wang et al, 2001; Bourdeau et al, 2004). Estrogen-stimulated transcriptional activation is facilitated by the formation of ESR1-dependent loops and by the cyclic recruitment of activators, co-activators, HATs and other components of the general transcriptional machinery (Shang et al, 2000; Bretschneider et al, 2008).

**Followed by:** HATs and coactivators are recruited to the CTSD gene

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HATs and coactivators are recruited to the CTSD gene

Location: Estrogen-dependent gene expression

Stable identifier: R-HSA-9023840

Type: binding

Compartments: nucleoplasm

Estrogen-stimulated expression of CTSD depends on the cyclic recruitment of DNA-binding and other transcriptional activators. Binding sites for the DNA-binding transcriptional activators SP1, USF1 and 2 have been identified in the proximal CTSD promoter (Xing and Archer, 1998; Wang et al, 1998; Krishnan et al, 1994; Wang et al, 2001; reviewed in Safe, 2000). Other early factors that contribute to estrogen-dependent CTSD expression include the co-activator NCOA3, EP300 and MED1, a component of the mediator complex. These factors contribute to the formation of transcriptionally active chromatin and to the recruitment of RNA polymerase II (Shang et al, 2000; Bretschneider et al, 2008). Note that although these factors are shown at the CTSD promoter simultaneously, they have not all been demonstrated to form part of a single complex on an individual CTSD promoter.

Preceded by: ESR1:ESTG binds to proximal and distal regions of the CTSD promoter

Followed by: Estrogen-responsive CTSD expression

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Estrogen-responsive CTSD expression

**Location:** Estrogen-dependent gene expression

**Stable identifier:** R-HSA-9023846

**Type:** omitted

**Compartments:** nucleoplasm

Cathepsin D (CTSD) is a lysosomal aspartyl protease that plays a role in the protein processing and degradation. In addition to its 'housekeeping' roles, CTSD controls the processing of proteins involved in cell cycle progression, differentiation, migration, immunology, neurogenesis, apoptosis and angiogenesis (reviewed in Zaidi et al, 2008; Khalkhali-Ellis and Hendrix, 2015). CTSD is overexpressed in many breast cancers and is implicated in tumor progression and metastasis (Fusek and Vetvicka, 2005). CTSD expression is constitutive in ESR1-negative cells, but estrogen-dependent in ESR1-positive cells (Liaudet-Coopman et al, 2006). Estrogen-responsiveness is conferred by imperfect EREs in both the proximal and the distal promoter and is facilitated by ESR1-dependent looping of the enhancer (Cavaillès et al, 1993; Augereau et al, 1994; Shang et al, 2004; Bourdeau et al, 2004; Bretschneider et al, 2008)

**Preceded by:** HATs and coactivators are recruited to the CTSD gene

**Literature references**


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ESR1:ESTG:P4 bind pioneer factors and coactivators

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ESR1:ESTG binds to proximal and distal regions of the CTSD promoter

HATs and coactivators are recruited to the CTSD gene

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