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Gene Section
Review

ESRRA (estrogen-related receptor alpha)

Rebecca Stein Kunder, Donald P McDonnell

Department of Pharmacology and Cancer Biology, Duke University Medical Center, Box 3813, Durham, NC 27710, USA (RSK, DPMD)

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Identity

Other names: ERR-alpha; ERR1; ERRa; ERRalpha; ESRL1; NR3B1

HGNC (Hugo): ESRRA

Location: 11q13.1

Note: Size: 11,172 bases; Orientation: plus strand.

DNA/RNA

Description

-Sequence length 11,172 bases;
-CDS: 2221;
-Exons: 7.

Transcription

Alternative splicing results in transcript variants, but these have not yet been well-characterized.

Pseudogene

A pseudogene has been reported, ESRRAP, located at 13q12.1. However, it is possible that this pseudogene is not transcribed (Sladek et al., 1997).

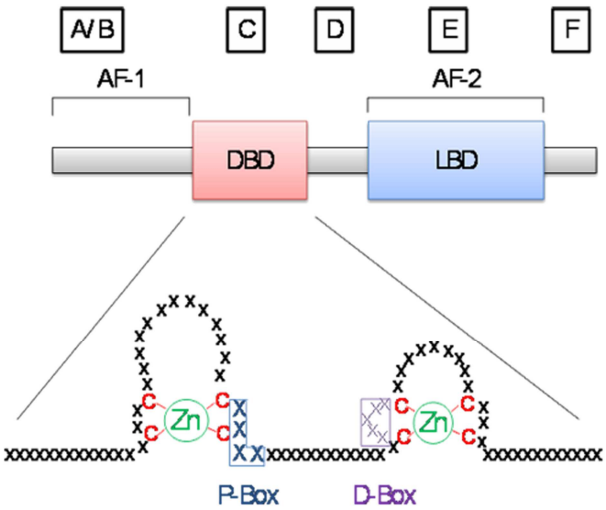
Protein

Description

ERRa is a 45.5 kDa, 423 amino acid orphan nuclear receptor. Although closely related to the estrogen receptors, its transcriptional activity is regulated to any significant degree by estrogens. ERRa binds to specific DNA sequences within target gene promoters as a monomer or homodimer and recruits coactivating proteins, the best known of which is PGC-1a.

Expression

ERRa is ubiquitously expressed throughout development with the highest levels of expression in tissues that oxidize fatty acids such as kidney, heart, cerebellum, intestine and skeletal muscle (nursa).



Schematic of nuclear receptor structure and function.
ERRa is a member of the nuclear receptor (NR) superfamily of transcription factors and is most closely related to estrogen receptor alpha (ERa). The modular structure of NRs consists of seven (A-F) domains. The A/B region, which harbors activation function 1 (AF-1), is not well-conserved across NRs, but regions C and E are highly conserved and harbor, respectively, the DNA-binding domain (DBD) and ligand-binding domain (LBD). ERRa shares with ERa 68% sequence identity within the DBD and 33% within the LBD. The functional regions of the DBD have been finely mapped. In addition to two zinc finger motifs, this domain contains a Proximal-box (P-box) which determines DNA sequence specificity, and a Dimerization-box (D-box), which part of the dimerization interface.

Localisation

ERRa is thought to be predominately nuclear, although recently it has been reported to be perinuclear and cytoplasmic in breast cancer tissue (Jarzabek et al., 2009).

Function

The function of ERRa as a metabolic regulator is supported by the observation that erra-null mice demonstrate impaired fat metabolism and absorption (Luo et al., 2003). It has recently been demonstrated that erra-null mice also have a reduced capacity for adaptation to hemodynamic stressors. Due to this functional deficit, these mice often develop cardiac contractile dysfunction. The cardiac remodeling under stress in ERR-null mice is due to defects in ATP synthesis and reduced phosphocreatine stores, which are both characteristic of pathologic cardiac hypertrophy (Huss et al., 2007). That the expression of ERRa is elevated in exercising muscle and in fasting liver specifically implicates this receptor in beta-oxidation of fatty acids, a metabolic pathway that is highly active under these conditions. On a mechanistic level, several studies have revealed that ERRa is involved in the transcriptional regulation of genes required for mitochondrial biogenesis, oxidative phosphorylation and fatty acid oxidation (Huss et al., 2004; Mootha et al., 2004; Dufour et al., 2007).

Thus far, metabolic studies of ERRa function have mainly focused on its role as the downstream effector of PGC-1a. PGC-1a is a promiscuous nuclear receptor coactivator expressed at low basal levels but induced by fasting and other metabolic stresses (Puigserver and Spiegelman, 2003). PGC-1beta, a related cofactor, may have similar functions, although its expression level is not as acutely regulated by variations in energy demand (Yoon et al., 2001). Rather than being regulated by ligand, the magnitude of ERRa activity is thought to be largely dependent on the presence of transcriptional coactivators such as PGC-1a and beta. Interest in the ERR-PGC-1 regulatory axis was heightened by the observation that there is a decrease in both PGC-1a and PGC-1beta in the skeletal muscle of patients with diabetes and obesity (Mootha et al., 2003).

Homology

Sequence analysis reveals that the ERRs and the classical estrogen receptors share a high degree of homology within their DNA and ligand binding domains. In particular, ERRa shares with ERa approximately 68% sequence identity within the DNA binding domain and 33% within the ligand binding domains. This relationship provides a structural basis both for the conserved nature of DNA binding and the divergence in hormone binding between these two receptors.

Mutations

Note

Although over 80 SNPs have been reported, only one variant has been shown to carry clinical associations.

Laflamme et al. reported a polymoprohic hormone response element within the ESRRA promoter (Laflamme et al., 2005). The variant sequence, present in 11% of the population tested (white, premenopausal women), included an ERRa responsive element within the additional 23-nucelotides. This longer variant was associated with higher bone mineral density measured in the lumbar spine.

Kamei et al. reported that the longer variant is associated with a significantly higher body mass index in their study population of 729 Japanese men and women (Kamie et al., 2005).

Implicated in

Breast cancer

Prognosis

Two independent clinical studies have implicated ERRa in breast cancer progression (Ariazi et al., 2002; Suzuki et al., 2004). In the first study to link ERRa to clinical and pathological characteristics of breast cancer, Ariazi et al. found that ERRa expression is significantly associated with ERa-negative and progesterone receptor-negative tumor status as well as Her2 status. Further exploring the relationship between ERRa and Her2, Barry et al. demonstrated that ERRa transcriptional activity can be enhanced by phosphorylation events downstream of Her2 (Barry and Giguere, 2005). Building on the association between ERRa and negative prognostic biomarkers, Suzuki et al. demonstrated a direct correlation between ERRa expression and unfavorable breast cancer patient outcomes including increased tumor recurrence and decreased survival (Suzuki et al., 2004). Importantly, the predictive value of ERRa expression was shown to be independent of ERa status, confirming that targeting the ERRa pathway may be of therapeutic benefit in patients with either ERa-positive or ERa-negative breast cancer.

Recently, the function of ERRa has been evaluated in xenograft models of breast cancer. Stein et al. demonstrated that ERRa is critical for the growth of ERa-negative breast cancer through use of RNAi (Stein et al., 2008). Furthermore, Chisamore and coworkers found that an ERRa antagonist inhibited the growth of ERa-positive and ERa-negative breast cancer cell lines in a xenograft model (Chisamore et al., 2009).

Ovarian cancer

Prognosis

Sun et al. demonstrated that the ovarian tumors had significantly higher ERRa mRNA levels than normal ovaries and that high ERRa expression correlated with clinically advanced and histologically aggressive disease. Furthermore, ERRa expression was shown to be an independent prognostic factor for poor overall patient survival (Sun et al., 2005).

Colorectal cancer

Prognosis

Analysis of 80 colorectal tumor samples demonstrated that higher levels of ERRa mRNA are expressed in

tumor tissue versus in the surrounding normal mucosa. Furthermore, tumor tissue ERRa mRNA levels are positively correlated with increased tumor stage and histological grade (Cavallini et al., 2005).

Prostate cancer

Prognosis

Cheung et al. investigated the expression patterns of the three ERR family members in normal and malignant human prostate epithelial cells and cell lines (Cheung et al., 2005). The authors also characterized ERR protein expression and localization in normal, dysplastic, and malignant prostate tissue (Cheung et al., 2005). They concluded that ERRbeta and ERRgamma protein expression is reduced in neoplastic prostatic cells versus their non-malignant counterparts and suggested that each is down-regulated in the progression of prostate cancer. The authors went on to measure the effect of overexpressing the ERRs on proliferation of an immortalized prostate cell line and a prostate cancer cell line in vitro and on prostate cancer xenograft growth in vivo (Yu et al., 2007; Yu et al., 2008). They found that ERRbeta and ERRgamma can inhibit proliferation in cells derived from normal and malignant prostate epithelium by inducing a G1-S cell cycle arrest. Furthermore, activation of either ERRbeta or ERRgamma using the agonist DY131 resulted in a decreased rate of prostate tumor growth in a xenograft model.

Endometrial cancer

Prognosis

Gao et al. explored the extent to which the ERRs are involved in ERa-positive endometrial adenocarcinoma (Gao et al., 2006). They measured the expression of each ERR family member in malignant versus normal endometrium and compared the expression levels to clinical and pathologic features. They concluded that the expression of ERRa mRNA was lower in ERa-positive endometrial adenocarcinoma versus normal endometrium. However, they also found that ERRa mRNA expression was positively correlated with tumor stage and myometrial invasion. Additionally Gao et al. found that the expression of ERRgamma mRNA was increased in endometrial adenocarcinoma compared to normal endometrium.

Breakpoints

None.

To be noted

Note

In the absence of known endogenous ligand, considerable effort has been made toward identifying small molecules to modulate ERRa activity. Several ERRa antagonists have been developed and recently a novel antagonist was described that inhibited the growth of breast cancer xenografts (Chisamore et al., 2009).

References

Giguère V, Yang N, Segui P, Evans RM. Identification of a new class of steroid hormone receptors. Nature. 1988 Jan 7;331(6151):91-4

Johnston SD, Liu X, Zuo F, Eisenbraun TL, Wiley SR, Kraus RJ, Mertz JE. Estrogen-related receptor alpha 1 functionally binds as a monomer to extended half-site sequences including ones contained within estrogen-response elements. Mol Endocrinol. 1997 Mar;11(3):342-52

Shi H, Shigeta H, Yang N, Fu K, O'Brian G, Teng CT. Human estrogen receptor-like 1 (ESRL1) gene: genomic organization, chromosomal localization, and promoter characterization. Genomics. 1997 Aug 15;44(1):52-60

Sladek R, Beatty B, Squire J, Copeland NG, Gilbert DJ, Jenkins NA, Giguère V. Chromosomal mapping of the human and murine orphan receptors ERRalpha (ESRRA) and ERRbeta (ESRRB) and identification of a novel human ERRalpha-related pseudogene. Genomics. 1997 Oct 15;45(2):320-6

Vega RB, Kelly DP. A role for estrogen-related receptor alpha in the control of mitochondrial fatty acid beta-oxidation during brown adipocyte differentiation. J Biol Chem. 1997 Dec 12;272(50):31693-9

Vanacker JM, Delmarre C, Guo X, Laudet V. Activation of the osteopontin promoter by the orphan nuclear receptor estrogen receptor related alpha. Cell Growth Differ. 1998 Dec;9(12):1007-14

Yang C, Zhou D, Chen S. Modulation of aromatase expression in the breast tissue by ERR alpha-1 orphan receptor. Cancer Res. 1998 Dec 15;58(24):5695-700

Vanacker JM, Bonnelye E, Chopin-Delannoy S, Delmarre C, Cavaillès V, Laudet V. Transcriptional activities of the orphan nuclear receptor ERR alpha (estrogen receptor-related receptor-alpha). Mol Endocrinol. 1999 May;13(5):764-73

Xie W, Hong H, Yang NN, Lin RJ, Simon CM, Stallcup MR, Evans RM. Constitutive activation of transcription and binding of coactivator by estrogen-related receptors 1 and 2. Mol Endocrinol. 1999 Dec;13(12):2151-62

Yang C, Chen S. Two organochlorine pesticides, toxaphene and chlordane, are antagonists for estrogen-related receptor alpha-1 orphan receptor. Cancer Res. 1999 Sep 15;59(18):4519-24

Zhang Z, Teng CT. Estrogen receptor-related receptor alpha 1 interacts with coactivator and constitutively activates the estrogen response elements of the human lactoferrin gene. J Biol Chem. 2000 Jul 7;275(27):20837-46

Lu D, Kiriyama Y, Lee KY, Giguère V. Transcriptional regulation of the estrogen-inducible pS2 breast cancer marker gene by the ERR family of orphan nuclear receptors. Cancer Res. 2001 Sep 15;61(18):6755-61

Yoon JC, Puigserver P, Chen G, Donovan J, Wu Z, Rhee J, Adelmant G, Stafford J, Kahn CR, Granner DK, Newgard CB, Spiegelman BM. Control of hepatic gluconeogenesis through the transcriptional coactivator PGC-1. Nature. 2001 Sep 13;413(6852):131-8

Zhang Z, Teng CT. Estrogen receptor alpha and estrogen receptor-related receptor alpha1 compete for binding and coactivator. Mol Cell Endocrinol. 2001 Feb 14;172(1-2):223-33

Ariazi EA, Clark GM, Mertz JE. Estrogen-related receptor alpha and estrogen-related receptor gamma associate with unfavorable and favorable biomarkers, respectively, in human breast cancer. Cancer Res. 2002 Nov 15;62(22):6510-8

Giguère V. To ERR in the estrogen pathway. Trends Endocrinol Metab. 2002 Jul;13(5):220-5

Horard B, Vanacker JM. Estrogen receptor-related receptors: orphan receptors desperately seeking a ligand. J Mol Endocrinol. 2003 Dec;31(3):349-57

Kamei Y, Ohizumi H, Fujitani Y, Nemoto T, Tanaka T, Takahashi N, Kawada T, Miyoshi M, Ezaki O, Kakizuka A. PPARgamma coactivator 1beta/ERR ligand 1 is an ERR protein ligand, whose expression induces a high-energy expenditure and antagonizes obesity. Proc Natl Acad Sci U S A. 2003 Oct 14;100(21):12378-83

Liu D, Zhang Z, Gladwell W, Teng CT. Estrogen stimulates estrogen-related receptor alpha gene expression through conserved hormone response elements. Endocrinology. 2003 Nov;144(11):4894-904

Luo J, Sladek R, Carrier J, Bader JA, Richard D, Giguère V. Reduced fat mass in mice lacking orphan nuclear receptor estrogen-related receptor alpha. Mol Cell Biol. 2003 Nov;23(22):7947-56

Mootha VK, Lindgren CM, Eriksson KF, Subramanian A, Sihag S, Lehar J, Puigserver P, Carlsson E, Ridderstråle M, Laurila E, Houstis N, Daly MJ, Patterson N, Mesirov JP, Golub TR, Tamayo P, Spiegelman B, Lander ES, Hirschhorn JN, Altshuler D, Groop LC. PGC-1alpha-responsive genes involved in oxidative phosphorylation are coordinately downregulated in human diabetes. Nat Genet. 2003 Jul;34(3):267-73

Schreiber SN, Knutti D, Brogli K, Uhlmann T, Kralli A. The transcriptional coactivator PGC-1 regulates the expression and activity of the orphan nuclear receptor estrogen-related receptor alpha (ERRalpha). J Biol Chem. 2003 Mar 14;278(11):9013-8

Busch BB, Stevens WC Jr, Martin R, Ordentlich P, Zhou S, Sapp DW, Horlick RA, Mohan R. Identification of a selective inverse agonist for the orphan nuclear receptor estrogen-related receptor alpha. J Med Chem. 2004 Nov 4;47(23):5593-6

Huss JM, Kelly DP. Nuclear receptor signaling and cardiac energetics. Circ Res. 2004 Sep 17;95(6):568-78

Huss JM, Torra IP, Staels B, Giguère V, Kelly DP. Estrogen-related receptor alpha directs peroxisome proliferator-activated receptor alpha signaling in the transcriptional control of energy metabolism in cardiac and skeletal muscle. Mol Cell Biol. 2004 Oct;24(20):9079-91

Laganière J, Tremblay GB, Dufour CR, Giroux S, Rousseau F, Giguère V. A polymorphic autoregulatory hormone response

element in the human estrogen-related receptor alpha (ERRalpha) promoter dictates peroxisome proliferator-activated receptor gamma coactivator-1alpha control of ERRalpha expression. J Biol Chem. 2004 Apr 30;279(18):18504-10

Mootha VK, Handschin C, Arlow D, Xie X, St Pierre J, Sihag S, Yang W, Altshuler D, Puigserver P, Patterson N, Willy PJ, Schulman IG, Heyman RA, Lander ES, Spiegelman BM. Erralpha and Gabpa/b specify PGC-1alpha-dependent oxidative phosphorylation gene expression that is altered in diabetic muscle. Proc Natl Acad Sci U S A. 2004 Apr 27;101(17):6570-5

Schreiber SN, Emter R, Hock MB, Knutti D, Cardenas J, Podvinec M, Oakeley EJ, Kralli A. The estrogen-related receptor alpha (ERRalpha) functions in PPARgamma coactivator 1alpha (PGC-1alpha)-induced mitochondrial biogenesis. Proc Natl Acad Sci U S A. 2004 Apr 27;101(17):6472-7

Suzuki T, Miki Y, Moriya T, Shimada N, Ishida T, Hirakawa H, Ohuchi N, Sasano H. Estrogen-related receptor alpha in human breast carcinoma as a potent prognostic factor. Cancer Res. 2004 Jul 1;64(13):4670-6

Barry JB, Giguère V. Epidermal growth factor-induced signaling in breast cancer cells results in selective target gene activation by orphan nuclear receptor estrogen-related receptor alpha. Cancer Res. 2005 Jul 15;65(14):6120-9

Cavallini A, Notarnicola M, Giannini R, Montemurro S, Lorusso D, Visconti A, Minervini F, Caruso MG. Oestrogen receptor-related receptor alpha (ERRalpha) and oestrogen receptors (ERalpha and ERbeta) exhibit different gene expression in human colorectal tumour progression. Eur J Cancer. 2005 Jul;41(10):1487-94

Cheung CP, Yu S, Wong KB, Chan LW, Lai FM, Wang X, Suetsugi M, Chen S, Chan FL. Expression and functional study of estrogen receptor-related receptors in human prostatic cells and tissues. J Clin Endocrinol Metab. 2005 Mar;90(3):1830-44

Kamei Y, Lwin H, Saito K, Yokoyama T, Yoshiike N, Ezaki O, Tanaka H. The 2.3 genotype of ESRRA23 of the ERR alpha gene is associated with a higher BMI than the 2.2 genotype. Obes Res. 2005 Oct;13(10):1843-4

Laflamme N, Giroux S, Loredo-Osti JC, Elfassihi L, Dodin S, Blanchet C, Morgan K, Giguère V, Rousseau F. A frequent regulatory variant of the estrogen-related receptor alpha gene associated with BMD in French-Canadian premenopausal women. J Bone Miner Res. 2005 Jun;20(6):938-44

Sun P, Sehouli J, Denkert C, Mustea A, Könsgen D, Koch I, Wei L, Lichtenegger W. Expression of estrogen receptor-related receptors, a subfamily of orphan nuclear receptors, as new tumor biomarkers in ovarian cancer cells. J Mol Med. 2005 Jun;83(6):457-67

Ariazi EA, Jordan VC. Estrogen-related receptors as emerging targets in cancer and metabolic disorders. Curr Top Med Chem. 2006;6(3):203-15

Gaillard S, Grasfeder LL, Haeffele CL, Lobenhofer EK, Chu TM, Wolfinger R, Kazmin D, Koves TR, Muoio DM, Chang CY, McDonnell DP. Receptor-selective coactivators as tools to define the biology of specific receptor-coactivator pairs. Mol Cell. 2006 Dec 8;24(5):797-803

Gao M, Sun P, Wang J, Zhao D, Wei L. Expression of estrogen receptor-related receptor isoforms and clinical significance in endometrial adenocarcinoma. Int J Gynecol Cancer. 2006 Mar-Apr;16(2):827-33

Stein RA, McDonnell DP. Estrogen-related receptor alpha as a therapeutic target in cancer. Endocr Relat Cancer. 2006 Dec;13 Suppl 1:S25-32

Sun PM, Gao M, Wei LH, Mustea A, Wang JL, Könsgen D, Lichtenegger W, Sehouli J. An estrogen receptor alpha-dependent regulation of estrogen receptor-related receptor alpha in the proliferation of endometrial carcinoma cells. Int J Gynecol Cancer. 2006;16 Suppl 2:564-8

Watanabe A, Kinoshita Y, Hosokawa K, Mori T, Yamaguchi T, Honjo H. Function of estrogen-related receptor alpha in human endometrial cancer. J Clin Endocrinol Metab. 2006 Apr;91(4):1573-7

Ariazi EA, Kraus RJ, Farrell ML, Jordan VC, Mertz JE. Estrogen-related receptor alpha1 transcriptional activities are regulated in part via the ErbB2/HER2 signaling pathway. Mol Cancer Res. 2007 Jan;5(1):71-85

Dufour CR, Wilson BJ, Huss JM, Kelly DP, Alaynick WA, Downes M, Evans RM, Blanchette M, Giguère V. Genome-wide orchestration of cardiac functions by the orphan nuclear receptors ERRalpha and gamma. Cell Metab. 2007 May;5(5):345-56

Fujimoto J, Alam SM, Jahan I, Sato E, Sakaguchi H, Tamaya T. Clinical implication of estrogen-related receptor (ERR) expression in ovarian cancers. J Steroid Biochem Mol Biol. 2007 May;104(3-5):301-4

Fujimura T, Takahashi S, Urano T, Kumagai J, Ogushi T, Horie-Inoue K, Ouchi Y, Kitamura T, Muramatsu M, Inoue S. Increased expression of estrogen-related receptor alpha (ERRalpha) is a negative prognostic predictor in human prostate cancer. Int J Cancer. 2007 Jun 1;120(11):2325-30

Gaillard S, Dwyer MA, McDonnell DP. Definition of the molecular basis for estrogen receptor-related receptor-alpha-cofactor interactions. Mol Endocrinol. 2007 Jan;21(1):62-76

Huss JM, Imahashi K, Dufour CR, Weinheimer CJ, Courtois M, Kovacs A, Giguère V, Murphy E, Kelly DP. The nuclear receptor ERRalpha is required for the bioenergetic and functional adaptation to cardiac pressure overload. Cell Metab. 2007 Jul;6(1):25-37

Hyatt SM, Lockamy EL, Stein RA, McDonnell DP, Miller AB, Orband-Miller LA, Willson TM, Zuercher WJ. On the intractability of estrogen-related receptor alpha as a target for activation by small molecules. J Med Chem. 2007 Dec 27;50(26):6722-4

Lanvin O, Bianco S, Kersual N, Chalbos D, Vanacker JM. Potentiation of ICI182,780 (Fulvestrant)-induced estrogen receptor-alpha degradation by the estrogen receptor-related receptor-alpha inverse agonist XCT790. J Biol Chem. 2007 Sep 28;282(39):28328-34

Sonoda J, Laganière J, Mehl IR, Barish GD, Chong LW, Li X, Scheffler IE, Mock DC, Bataille AR, Robert F, Lee CH, Giguère V, Evans RM. Nuclear receptor ERR alpha and coactivator PGC-1 beta are effectors of IFN-gamma-induced host defense. Genes Dev. 2007 Aug 1;21(15):1909-20

Villena JA, Hock MB, Chang WY, Barcas JE, Giguère V, Kralli A. Orphan nuclear receptor estrogen-related receptor alpha is essential for adaptive thermogenesis. Proc Natl Acad Sci U S A. 2007 Jan 23;104(4):1418-23

Vu EH, Kraus RJ, Mertz JE. Phosphorylation-dependent sumoylation of estrogen-related receptor alpha1.

Biochemistry. 2007 Aug 28;46(34):9795-804

Zhang Z, Teng CT. Interplay between estrogen-related receptor alpha (ERRalpha) and gamma (ERRgamma) on the regulation of ERRalpha gene expression. Mol Cell Endocrinol. 2007 Jan 29;264(1-2):128-41

Ao A, Wang H, Kamarajugadda S, Lu J. Involvement of estrogen-related receptors in transcriptional response to hypoxia and growth of solid tumors. Proc Natl Acad Sci U S A. 2008 Jun 3;105(22):7821-6

Arany Z, Foo SY, Ma Y, Ruas JL, Bommi-Reddy A, Girnun G, Cooper M, Laznik D, Chinsomboon J, Rangwala SM, Baek KH, Rosenzweig A, Spiegelman BM. HIF-independent regulation of VEGF and angiogenesis by the transcriptional coactivator PGC-1alpha. Nature. 2008 Feb 21;451(7181):1008-12

Hu P, Kinyamu HK, Wang L, Martin J, Archer TK, Teng C. Estrogen induces estrogen-related receptor alpha gene expression and chromatin structural changes in estrogen receptor (ER)-positive and ER-negative breast cancer cells. J Biol Chem. 2008 Mar 14;283(11):6752-63

Stein RA, Chang CY, Kazmin DA, Way J, Schroeder T, Wergin M, Dewhirst MW, McDonnell DP. Estrogen-related receptor alpha is critical for the growth of estrogen receptor-negative breast cancer. Cancer Res. 2008 Nov 1;68(21):8805-12

Tremblay AM, Wilson BJ, Yang XJ, Giguère V. Phosphorylation-dependent sumoylation regulates estrogen-related receptor-alpha and -gamma transcriptional activity through a synergy control motif. Mol Endocrinol. 2008 Mar;22(3):570-84

Villena JA, Kralli A. ERRalpha: a metabolic function for the oldest orphan. Trends Endocrinol Metab. 2008 Oct;19(8):269-76

Yu S, Wong YC, Wang XH, Ling MT, Ng CF, Chen S, Chan FL. Orphan nuclear receptor estrogen-related receptor-beta suppresses in vitro and in vivo growth of prostate cancer cells via p21(WAF1/CIP1) induction and as a potential therapeutic target in prostate cancer. Oncogene. 2008 May 22;27(23):3313-28

Zirngibl RA, Chan JS, Aubin JE. Estrogen receptor-related receptor alpha (ERRalpha) regulates osteopontin expression through a non-canonical ERRalpha response element in a cell context-dependent manner. J Mol Endocrinol. 2008 Feb;40(2):61-73

Chisamore MJ, Wilkinson HA, Flores O, Chen JD. Estrogen-related receptor-alpha antagonist inhibits both estrogen receptor-positive and estrogen receptor-negative breast tumor growth in mouse xenografts. Mol Cancer Ther. 2009 Mar;8(3):672-81

Jarzabek K, Koda M, Kozlowski L, Sulkowski S, Kottler ML, Wolczynski S. The significance of the expression of ERRalpha as a potential biomarker in breast cancer. J Steroid Biochem Mol Biol. 2009 Jan;113(1-2):127-33

Wang J, Fang F, Huang Z, Wang Y, Wong C. Kaempferol is an estrogen-related receptor alpha and gamma inverse agonist. FEBS Lett. 2009 Feb 18;583(4):643-7

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