

STEROID-INDEPENDENT ACTIVATION OF STEROID RECEPTORS

Factor ^a	ER ^b	PR ^c	AR
ATP	1		
CXCL12 / SDF-1	2		3
Dopamine	4	4	
Epidermal growth factor (EGF)	5,6	7	8
EGFR (activated by AR)	9		
erbB2 = HER-2	10		11
Fibroblast growth factor 2 (FGF-2 = bFGF)	12		
Gas-6			13
Gonadotropin release hormone (GnRH)	14	15	
GRP			13
Heregulin	10	16	13
Insulin and insulin-like growth factors (IGF)	17-19		8
Interleukin-1 β	20		
Interleukin-4			21
Interleukin-6	22		23,24
Interleukin-8			25
Keratinocyte growth factor			8
Leptin	26		
Prolactin	27		
Sex hormone binding globulin			28
TGF α	6		
TNF α	20,29		
Amino acids (through mTOR and S6K)	30		
β -catenin + FKBP52			31
Cdk2		32	
Cyclin A-Cdk2	33		
Cyclin D1	34,35		
Ets-1	36		
G α	37		
Hif-1 α (hypoxia)	38		

IKK ϵ	39		
MAPKK (constitutive mutant)	40		
MEKK1 (constitutive mutant)			41
Pak1	42		
PI3K	43		
PKC δ	44		
Progesterone receptor (PR)	45	NA	
Protein kinase B (= Akt)	43,46-48		
Ras (constitutive mutant)	49		
v-Src	50		
TBK1	51		
Vav3 (a Rho GEF)	52		53
XBP1s	54		
Activators of protein kinase A	17,55,56	57	58
Activator of protein kinase C	44,49,59		60
Caffeine	1		
Ca ²⁺	1		
Inhibitors of protein phosphatases 1 and 2A	4	4,57	
Inhibitor of phosphotyrosine phosphatases		7	
SIRT1 inhibitors	61		
Metals, arsenite, selenite	62-65		

- ^a This list may be incomplete as the extent of steroid-independent activation varies widely; moreover, several reports have indicated that some of the effects may be cell- and/or promoter-specific (see for example ref. ^{11,66}).
- ^b Almost all publications have examined ER α . ER β has only been shown to be activated by EGF (^{67,68}) and SDF-1 (2), and indirectly by 3,3'-diindolylmethane (⁶⁹).
- ^c The response of PR displays marked species differences: chicken and rodent PRs can be activated in the absence of cognate hormone by a whole series of activators that will only affect human PR in the presence of a ligand, for example the partial antagonist RU486 (refs. ⁷⁰⁻⁷²; exceptions to the rule are the activation of human PR by heregulin [16] and Cdk2 [32]).

Notes:

- other steroid receptors, notably GR and MR, are more restricted in their ability to be activated in the absence of ligands. A noteworthy "exception" is the activation of GR by GnRH and TNF α signaling (^{73,74}).
- We have published a reformatted version of this table in 2015 (ref. ⁷⁵).

1. Divekar, S. D. *et al.* The role of calcium in the activation of estrogen receptor- α . *Cancer Res.* **71**, 1658-1668 (2011).
2. Sauve, K., Lepage, J., Sanchez, M., Heveker, N. & Tremblay, A. Positive feedback activation of estrogen receptors by the CXCL12-CXCR4 pathway. *Cancer Res.* **69**, 5793-5800 (2009).
3. Kasina, S. & Macoska, J. A. The CXCL12/CXCR4 axis promotes ligand-independent activation of the androgen receptor. *Mol. Cell. Endocrinol.* **351**, 249-263 (2012).
4. Power, R. F., Mani, S. K., Codina, J., Conneely, O. M. & O'Malley, B. W. Dopaminergic and ligand-independent activation of steroid hormone receptors. *Science* **254**, 1636-1639 (1991).
5. Ignar-Trowbridge, D. M. *et al.* Coupling of dual signaling pathways: epidermal growth factor action involves the estrogen receptor. *Proc. Natl. Acad. Sci. USA* **89**, 4658-4662 (1992).
6. Ignar-Trowbridge, D. M. *et al.* Peptide growth factors elicit estrogen receptor-dependent transcriptional activation of an estrogen-responsive element. *Mol. Endocrinol.* **7**, 992-998 (1993).
7. Zhang, Y., Bai, W., Allgood, V. E. & Weigel, N. L. Multiple signaling pathways activate the chicken progesterone receptor. *Mol. Endocrinol.* **8**, 577-584 (1994).
8. Culig, Z. *et al.* Androgen receptor activation in prostatic tumor cell lines by insulin-like growth factor-I, keratinocyte growth factor, and epidermal growth factor. *Cancer Res.* **54**, 5474-5478 (1994).
9. Ciupek, A. *et al.* Androgen receptor promotes tamoxifen agonist activity by activation of EGFR in ER α -positive breast cancer. *Breast Cancer Res. Treat.* **154**, 225-237 (2015).
10. Pietras, R. J. *et al.* HER-2 tyrosine kinase pathway targets estrogen receptor and promotes hormone-independent growth in human breast cancer cells. *Oncogene* **10**, 2435-2446 (1995).
11. Craft, N., Shostak, Y., Carey, M. & Sawyers, C. L. A mechanism for hormone-independent prostate cancer through modulation of androgen receptor signaling by the HER-2/neu tyrosine kinase. *Nat. Med.* **5**, 280-285 (1999).
12. Piotrowicz, R. S., Ding, L., Maher, P. & Levin, E. G. Inhibition of cell migration by 24-kDa fibroblast growth factor-2 is dependent upon the estrogen receptor. *J. Biol. Chem.* **16**, 16 (2000).
13. Liu, Y. *et al.* Dasatinib inhibits site-specific tyrosine phosphorylation of androgen receptor by Ack1 and Src kinases. *Oncogene* **29**, 3208-3216 (2010).

14. Demay, F., De Monti, M., Tiffoche, C., Vaillant, C. & Thieulant, M. L. Steroid-independent activation of ER by GnRH in gonadotrope pituitary cells. *Endocrinology* **142**, 3340-3347. (2001).
15. Turgeon, J. L. & Waring, D. W. Activation of the progesterone receptor by the gonadotropin-releasing hormone self-priming signaling pathway. *Mol. Endocrinol.* **8**, 860-869 (1994).
16. Labriola, L. *et al.* Heregulin induces transcriptional activation of the progesterone receptor by a mechanism that requires functional ErbB-2 and mitogen-activated protein kinase activation in breast cancer cells. *Mol. Cell. Biol.* **23**, 1095-1111 (2003).
17. Aronica, S. M. & Katzenellenbogen, B. S. Stimulation of estrogen receptor-mediated transcription and alteration in the phosphorylation state of the rat uterine estrogen receptor by estrogen, cyclic adenosine monophosphate, and insulin-like growth factor-I. *Mol. Endocrinol.* **7**, 743-752 (1993).
18. Ma, Z. Q. *et al.* Insulin-like growth factors activate estrogen receptor to control the growth and differentiation of the human neuroblastoma cell line SK- Er3. *Mol. Endocrinol.* **8**, 910-918 (1994).
19. Newton, C. J. *et al.* The unliganded estrogen receptor (ER) transduces growth factor signals. *J. Steroid Biochem. Mol. Biol.* **48**, 481-486 (1994).
20. Stender, J. D. *et al.* Structural and molecular mechanisms of cytokine-mediated endocrine resistance in human breast cancer cells. *Mol. Cell* **65**, 1122-1135 (2017).
21. Lee, S. O., Lou, W., Hou, M., Onate, S. A. & Gao, A. C. Interleukin-4 enhances prostate-specific antigen expression by activation of the androgen receptor and Akt pathway. *Oncogene* **22**, 7981-7988 (2003).
22. Speirs, V. *et al.* Direct activation of oestrogen receptor- α by interleukin-6 in primary cultures of breast cancer epithelial cells. *Br. J. Cancer* **82**, 1312-1316. (2000).
23. Hobisch, A. *et al.* Interleukin-6 regulates prostate-specific protein expression in prostate carcinoma cells by activation of the androgen receptor. *Cancer Res.* **58**, 4640-4645. (1998).
24. Chen, T., Wang, L. H. & Farrar, W. L. Interleukin 6 activates androgen receptor-mediated gene expression through a signal transducer and activator of transcription 3-dependent pathway in LNCaP prostate cancer cells. *Cancer Res.* **60**, 2132-2135 (2000).
25. Seaton, A. *et al.* Interleukin-8 signaling promotes androgen-independent proliferation of prostate cancer cells via induction of androgen receptor expression and activation. *Carcinogenesis* **29**, 1148-1156 (2008).
26. Catalano, S. *et al.* Leptin induces, via ERK1/ERK2 signal, functional activation of estrogen receptor α in MCF-7 cells. *J. Biol. Chem.* **279**, 19908-19915 (2004).
27. González, L. *et al.* Activation of the unliganded estrogen receptor by prolactin in breast cancer cells. *Oncogene* **28**, 1298-1308 (2009).
28. Nakhla, A. M., Romas, N. A. & Rosner, W. Estradiol activates the prostate androgen receptor and prostate-specific antigen secretion through the intermediacy of sex hormone-binding globulin. *J. Biol. Chem.* **272**, 6838-6841 (1997).

29. Gori, I. *et al.* Tumor necrosis factor- α activates estrogen signaling pathways in endometrial epithelial cells via estrogen receptor α . *Mol. Cell. Endocrinol.* **345**, 27-37 (2011).
30. Della Torre, S. *et al.* Amino acid-dependent activation of liver estrogen receptor α integrates metabolic and reproductive functions via IGF-1. *Cell Metab.* **13**, 205-214 (2011).
31. Storer Samaniego, C. *et al.* The FKBP52 cochaperone acts in synergy with β -catenin to potentiate androgen receptor signaling. *PLoS ONE* **10**, e0134015 (2015).
32. Pierson-Mullany, L. K. & Lange, C. A. Phosphorylation of progesterone receptor serine 400 mediates ligand-independent transcriptional activity in response to activation of cyclin-dependent protein kinase 2. *Mol. Cell. Biol.* **24**, 10542-10557 (2004).
33. Trowbridge, J. M., Rogatsky, I. & Garabedian, M. J. Regulation of estrogen receptor transcriptional enhancement by the cyclin A/Cdk2 complex. *Proc. Natl. Acad. Sci. USA* **94**, 10132-10137 (1997).
34. Zwijsen, R. M. *et al.* CDK-independent activation of estrogen receptor by cyclin D1. *Cell* **88**, 405-415 (1997).
35. Neuman, E. *et al.* Cyclin D1 stimulation of estrogen receptor transcriptional activity independent of cdk4. *Mol. Cell. Biol.* **17**, 5338-5347 (1997).
36. Tolón, R. M., Castillo, A. I., Jimenez-Lara, A. M. & Aranda, A. Association with Ets-1 causes ligand- and AF2-independent activation of nuclear receptors. *Mol. Cell. Biol.* **20**, 8793-8802 (2000).
37. Bratton, M. R. *et al.* G α potentiates estrogen receptor α activity via the ERK signaling pathway. *J. Endocrinol.* **214**, 45-54 (2012).
38. Cho, J., Bahn, J. J., Park, M., Ahn, W. & Lee, Y. J. Hypoxic activation of unoccupied estrogen-receptor- α is mediated by hypoxia-inducible factor-1 α . *J. Steroid Biochem. Mol. Biol.* **100**, 18-23 (2006).
39. Guo, J. P. *et al.* IKK ϵ phosphorylation of estrogen receptor α Ser-167 and contribution to tamoxifen resistance in breast cancer. *J. Biol. Chem.* **285**, 3676-3684 (2010).
40. Bunone, G., Briand, P.-A., Miksicek, R. J. & Picard, D. Activation of the unliganded estrogen receptor by EGF involves the MAP kinase pathway and direct phosphorylation. *EMBO J.* **15**, 2174-2183 (1996).
41. Abreu-Martin, M. T., Chari, A., Palladino, A. A., Craft, N. A. & Sawyers, C. L. Mitogen-activated protein kinase kinase kinase 1 activates androgen receptor-dependent transcription and apoptosis in prostate cancer. *Mol. Cell. Biol.* **19**, 5143-5154 (1999).
42. Wang, R. A., Mazumdar, A., Vadlamudi, R. K. & Kumar, R. P21-activated kinase-1 phosphorylates and transactivates estrogen receptor- α and promotes hyperplasia in mammary epithelium. *EMBO J.* **21**, 5437-5447 (2002).
43. Campbell, R. A. *et al.* Phosphatidylinositol 3-kinase/AKT-mediated activation of estrogen receptor α : a new model for anti-estrogen resistance. *J. Biol. Chem.* **276**, 9817-9824. (2001).
44. De Servi, B., Hermani, A., Medunjanin, S. & Mayer, D. Impact of PKC δ on estrogen receptor localization and activity in breast cancer cells. *Oncogene* **24**, 4946-4955 (2005).

45. Diep, C. H., Ahrendt, H. & Lange, C. A. Progesterone induces progesterone receptor gene (PGR) expression via rapid activation of protein kinase pathways required for cooperative estrogen receptor alpha (ER) and progesterone receptor (PR) genomic action at ER/PR target genes. *Steroids* **114**, 48-58 (2016).
46. Martin, M. B. *et al.* A role for Akt in mediating the estrogenic functions of epidermal growth factor and insulin-like growth factor I. *Endocrinology* **141**, 4503-4511 (2000).
47. Sun, M. *et al.* Phosphatidylinositol-3-OH Kinase (PI3K)/AKT2, activated in breast cancer, regulates and is induced by estrogen receptor α (ER α) via interaction between ER α and PI3K. *Cancer Res.* **61**, 5985-5991. (2001).
48. Ma, Y., Hu, C., Riegel, A. T., Fan, S. & Rosen, E. M. Growth factor signaling pathways modulate BRCA1 repression of estrogen receptor- α activity. *Mol. Endocrinol.* **21**, 1905-1923 (2007).
49. Patrone, C. *et al.* Cross-coupling between insulin and estrogen receptor in human neuroblastoma cells. *Mol. Endocrinol.* **10**, 499-507 (1996).
50. Feng, W. *et al.* Potentiation of estrogen receptor activation function 1 (AF-1) by Src/JNK through a serine 118-independent pathway. *Mol. Endocrinol.* **15**, 32-45. (2001).
51. Wei, C. *et al.* Elevated expression of TANK-binding kinase 1 enhances tamoxifen resistance in breast cancer. *Proc. Natl. Acad. Sci. USA* **111**, E601-610 (2014).
52. Lee, K. *et al.* Vav3 oncogene activates estrogen receptor and its overexpression may be involved in human breast cancer. *BMC Cancer* **8**, 158 (2008).
53. Lyons, L. S. *et al.* Ligand-independent activation of androgen receptors by Rho GTPase signaling in prostate cancer. *Mol. Endocrinol.* **22**, 597-608 (2008).
54. Ding, L. *et al.* Ligand-independent activation of estrogen receptor α by XBP-1. *Nucleic Acids Res.* **31**, 5266-5274 (2003).
55. Carascossa, S., Dudek, P., Cenni, B., Briand, P.-A. & Picard, D. CARM1 mediates the ligand-independent and tamoxifen-resistant activation of the estrogen receptor α by cAMP. *Genes Dev.* **24**, 708-719 (2010).
56. Etique, N., Flament, S., Lecomte, J. & Grillier-Vuissoz, I. Ethanol-induced ligand-independent activation of ER α mediated by cyclic AMP/PKA signaling pathway: an in vitro study on MCF-7 breast cancer cells. *Int. J. Oncol.* **31**, 1509-1518 (2007).
57. Denner, L. A., Weigel, N. L., Maxwell, B. L., Schrader, W. T. & O'Malley, B. W. Regulation of progesterone receptor-mediated transcription by phosphorylation. *Science* **250**, 1740-1743 (1990).
58. Nazareth, L. V. & Weigel, N. L. Activation of the human androgen receptor through a protein kinase A signaling pathway. *J. Biol. Chem.* **271**, 19900-19907 (1996).
59. Ignar-Trowbridge, D. M., Pimentel, M., Teng, C. T., Korach, K. S. & McLachlan, J. A. Cross talk between peptide growth factor and estrogen receptor signaling systems. *Environ. Health Perspect.* **103**, 35-38 (1995).
60. Darne, C., Veyssiere, G. & Jean, C. Phorbol ester causes ligand-independent activation of the androgen receptor. *Eur. J. Biochem.* **256**, 541-549. (1998).

61. Moore, R. L. & Faller, D. V. SIRT1 represses estrogen-signaling, ligand-independent ER α -mediated transcription, and cell proliferation in estrogen-responsive breast cells. *J. Endocrinol.* **216**, 273-285 (2013).
62. Martin, M. B. *et al.* Estrogen-like activity of metals in MCF-7 breast cancer cells. *Endocrinology* **144**, 2425-2436 (2003).
63. Stoica, A., Katzenellenbogen, B. S. & Martin, M. B. Activation of estrogen receptor- α by the heavy metal cadmium. *Mol. Endocrinol.* **14**, 545-553 (2000).
64. Stoica, A., Pentecost, E. & Martin, M. B. Effects of arsenite on estrogen receptor- α expression and activity in MCF-7 breast cancer cells. *Endocrinology* **141**, 3595-3602 (2000).
65. Stoica, A., Pentecost, E. & Martin, M. B. Effects of selenite on estrogen receptor- α expression and activity in MCF-7 breast cancer cells. *J. Cell. Biochem.* **79**, 282-292 (2000).
66. Gehm, B. D., McAndrews, J. M., Jordan, V. C. & Jameson, J. L. EGF activates highly selective estrogen-responsive reporter plasmids by an ER-independent pathway. *Mol. Cell. Endocrinol.* **159**, 53-62 (2000).
67. Tremblay, A., Tremblay, G. B., Labrie, F. & Giguère, V. Ligand-independent recruitment of SRC-1 to estrogen receptor β through phosphorylation of activation function AF-1. *Mol. Cell* **3**, 513-519 (1999).
68. Tremblay, A. & Giguère, V. Contribution of steroid receptor coactivator-1 and CREB binding protein in ligand-independent activity of estrogen receptor β . *J. Steroid Biochem. Mol. Biol.* **77**, 19-27. (2001).
69. Vivar, O. I., Saunier, E. F., Leitman, D. C., Firestone, G. L. & Bjeldanes, L. F. Selective activation of estrogen receptor- β target genes by 3,3'-diindolylmethane. *Endocrinology* **151**, 1662-1667 (2010).
70. Beck, C. A., Weigel, N. L., Moyer, M. L., Nordeen, S. K. & Edwards, D. P. The progesterone antagonist RU486 acquires agonist activity upon stimulation of cAMP signaling pathways. *Proc. Natl. Acad. Sci. USA* **90**, 4441-4445 (1993).
71. Sartorius, C. A., Tung, L., Takimoto, G. S. & Horwitz, K. B. Antagonist-occupied human progesterone receptors bound to DNA are functionally switched to transcriptional agonists by cAMP. *J. Biol. Chem.* **268**, 9262-9266 (1993).
72. Sartorius, C. A. *et al.* New T47D breast cancer cell lines for the independent study of progesterone B- and A-receptors: only antiprogestin-occupied B-receptors are switched to transcriptional agonists by cAMP. *Cancer Res.* **54**, 3868-3877 (1994).
73. Kotitschke, A., Sadie-Van Gijsen, H., Avenant, C., Fernandes, S. & Hapgood, J. P. Genomic and nongenomic cross talk between the gonadotropin-releasing hormone receptor and glucocorticoid receptor signaling pathways. *Mol. Endocrinol.* **23**, 1726-1745 (2009).
74. Verhoog, N. J., Du Toit, A., Avenant, C. & Hapgood, J. P. Glucocorticoid-independent repression of tumor necrosis factor (TNF) α -stimulated interleukin (IL)-6 expression by the glucocorticoid receptor: a potential mechanism for protection against an excessive inflammatory response. *J. Biol. Chem.* **286**, 19297-19310 (2011).
75. Bennesch, M. A. & Picard, D. Tipping the balance: ligand-independent activation of steroid receptors. *Mol. Endocrinol.* **29**, 349-363 (2015).