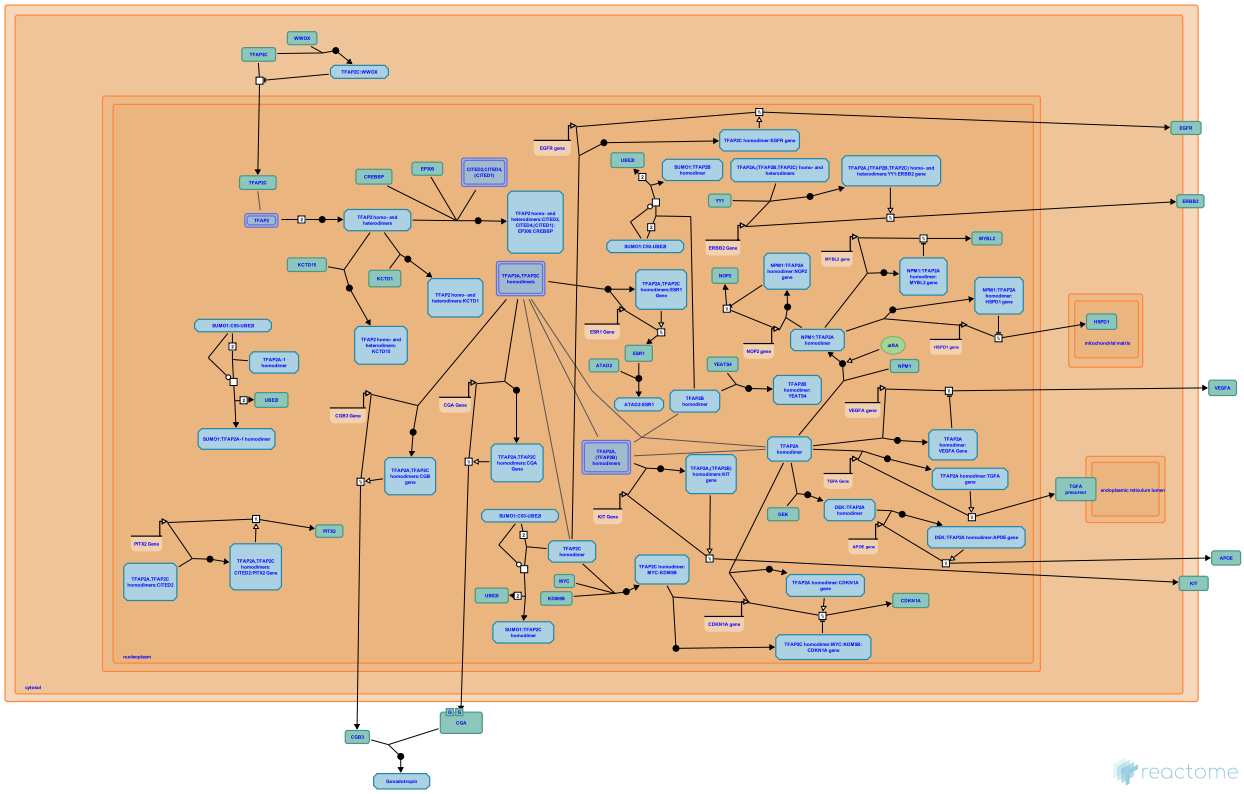
Transcriptional regulation by the AP-2 (TFAP2) family of transcription factors



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04/08/2021

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

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

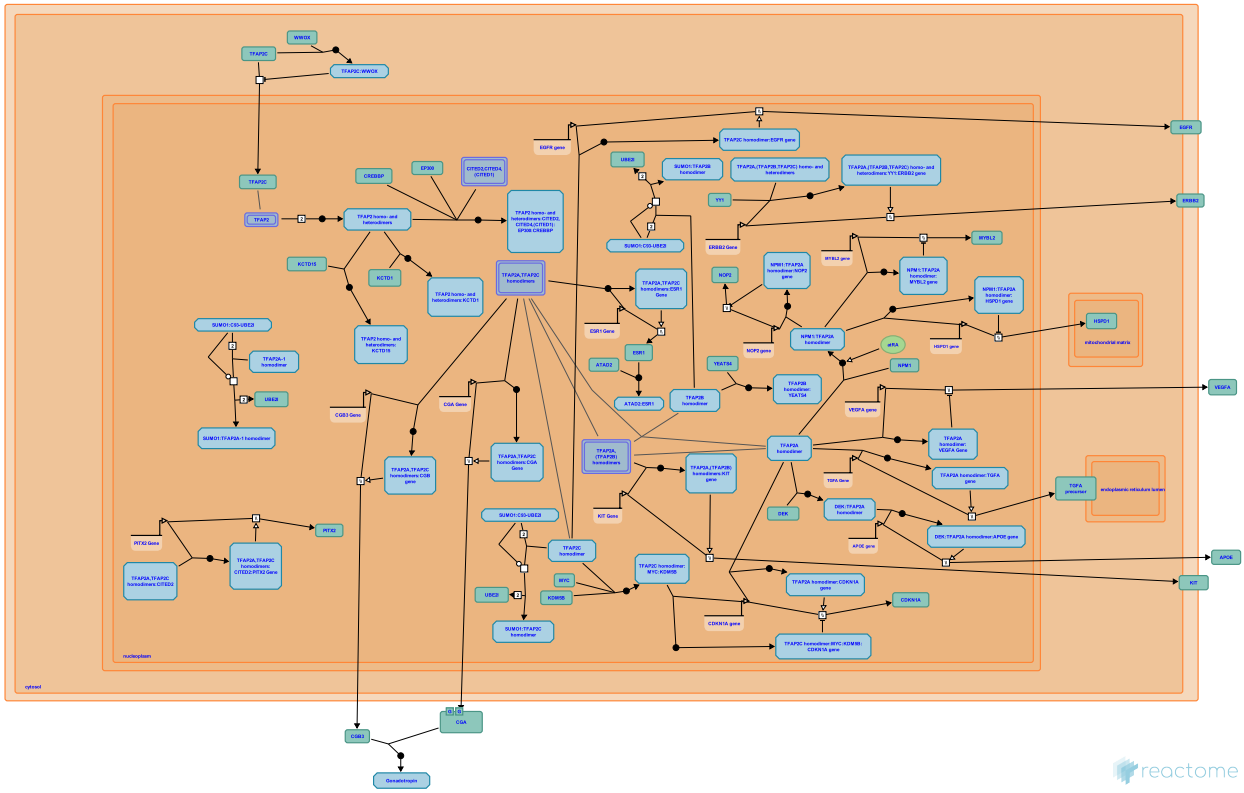
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Transcriptional regulation by the AP-2 (TFAP2) family of transcription factors ↗

Stable identifier: R-HSA-8864260



The AP-2 (TFAP2) family of transcription factors includes five proteins in mammals: TFAP2A (AP-2 alpha), TFAP2B (AP-2 beta), TFAP2C (AP-2 gamma), TFAP2D (AP-2 delta) and TFAP2E (AP-2 epsilon). The AP-2 family transcription factors are evolutionarily conserved in metazoans and are characterized by a helix-span-helix motif at the C-terminus, a central basic region, and the transactivation domain at the N-terminus. The helix-span-helix motif and the basic region enable dimerization and DNA binding (Eckert et al. 2005).

AP-2 dimers bind palindromic GC-rich DNA response elements that match the consensus sequence 5'-GCCNNNGGC-3' (Williams and Tjian 1991a, Williams and Tjian 1991b). Transcriptional co-factors from the CITED family interact with the helix-span-helix (HSH) domain of TFAP2 (AP-2) family of transcription factors and recruit transcription co-activators EP300 (p300) and CREBBP (CBP) to TFAP2-bound DNA elements. CITED2 shows the highest affinity for TFAP2 proteins, followed by CITED4, while CITED1 interacts with TFAP2s with a very low affinity. Mouse embryos defective for CITED2 exhibit neural crest defects, cardiac malformations and adrenal agenesis, which can at least in part be attributed to a defective Tfap2 transactivation (Bamforth et al. 2001, Braganca et al. 2002, Braganca et al. 2003). Transcriptional activity of AP-2 dimers in inhibited by binding of KCTD1 or KCTD15 to the AP-2 transactivation domain (Ding et al. 2009, Zarelli and Dawid 2013). Transcriptional activity of TFAP2A, TFAP2B and TFAP2C is negatively regulated by SUMOylation mediated by UBE2I (UBC9) (Eloranta and Hurst 2002, Berlato et al. 2011, Impens et al. 2014, Bogachek et al. 2014).

During embryonic development, AP-2 transcription factors stimulate proliferation and suppress terminal differentiation in a cell-type specific manner (Eckert et al. 2005).

TFAP2A and TFAP2C directly stimulate transcription of the estrogen receptor ESR1 gene (McPherson and Weigel 1999). TFAP2A expression correlates with ESR1 expression in breast cancer, and TFAP2C is frequently overexpressed in estrogen-positive breast cancer and endometrial cancer (deConinck et al. 1995,

Turner et al. 1998). TFAP2A, TFAP2C, as well as TFAP2B can directly stimulate the expression of ERBB2, another important breast cancer gene (Bosher et al. 1996). Association of TFAP2A with the YY1 transcription factor significantly increases the ERBB2 transcription rate (Begon et al. 2005). In addition to ERBB2, the expression of another receptor tyrosine kinase, KIT, is also stimulated by TFAP2A and TFAP2B (Huang et al. 1998), while the expression of the VEGF receptor tyrosine kinase ligand VEGFA is repressed by TFAP2A (Ruiz et al. 2004, Li et al. 2012). TFAP2A stimulates transcription of the transforming growth factor alpha (TGFA) gene (Wang et al. 1997). TFAP2C regulates EGFR in luminal breast cancer (De Andrade et al. 2016).

TFAP2C plays a critical role in maintaining the luminal phenotype in human breast cancer and in influencing the luminal cell phenotype during normal mammary development (Cyr et al. 2015).

In placenta, TFAP2A and TFAP2C directly stimulate transcription of both subunits of the human chorionic gonadotropin, CGA and CGB (Johnson et al. 1997, LiCalsi et al. 2000).

TFAP2A and/or TFAP2C, in complex with CITED2, stimulate transcription of the PITX2 gene, involved in left-right patterning and heart development (Bamforth et al. 2004, Li et al. 2012).

TFAP2A and TFAP2C play opposing roles in transcriptional regulation of the CDKN1A (p21) gene locus. While TFAP2A stimulates transcription of the CDKN1A cyclin-dependent kinase inhibitor (Zeng et al. 1997, Williams et al. 2009, Scibetta et al. 2010), TFAP2C represses CDKN1A transcription (Williams et al. 2009, Scibetta et al. 2010, Wong et al. 2012). Transcription of the TFAP2A gene may be inhibited by CREB and E2F1 (Melnikova et al. 2010).

For review of the AP-2 family of transcription factors, please refer to Eckert et al. 2005.

Literature references

Begon, DY., Delacroix, L., Vernimmen, D., Jackers, P., Winkler, R. (2005). Yin Yang 1 cooperates with activator protein 2 to stimulate ERBB2 gene expression in mammary cancer cells. *J. Biol. Chem., 280*, 24428-34. ↗

Eloranta, JJ., Hurst, HC. (2002). Transcription factor AP-2 interacts with the SUMO-conjugating enzyme UBC9 and is sumolated in vivo. *J. Biol. Chem., 277*, 30798-804. ↗

Bragança, J., Swingler, T., Marques, FI., Jones, T., Eloranta, JJ., Hurst, HC. et al. (2002). Human CREB-binding protein/p300-interacting transactivator with ED-rich tail (CITED) 4, a new member of the CITED family, functions as a co-activator for transcription factor AP-2. *J. Biol. Chem., 277*, 8559-65. ↗

McPherson, LA., Weigel, RJ. (1999). AP2alpha and AP2gamma: a comparison of binding site specificity and trans-activation of the estrogen receptor promoter and single site promoter constructs. *Nucleic Acids Res., 27*, 4040-9. ↗

Melnikova, VO., Dobroff, AS., Zigler, M., Villares, GJ., Braeuer, RR., Wang, H. et al. (2010). CREB inhibits AP-2alpha expression to regulate the malignant phenotype of melanoma. *PLoS ONE, 5*, e12452. ↗

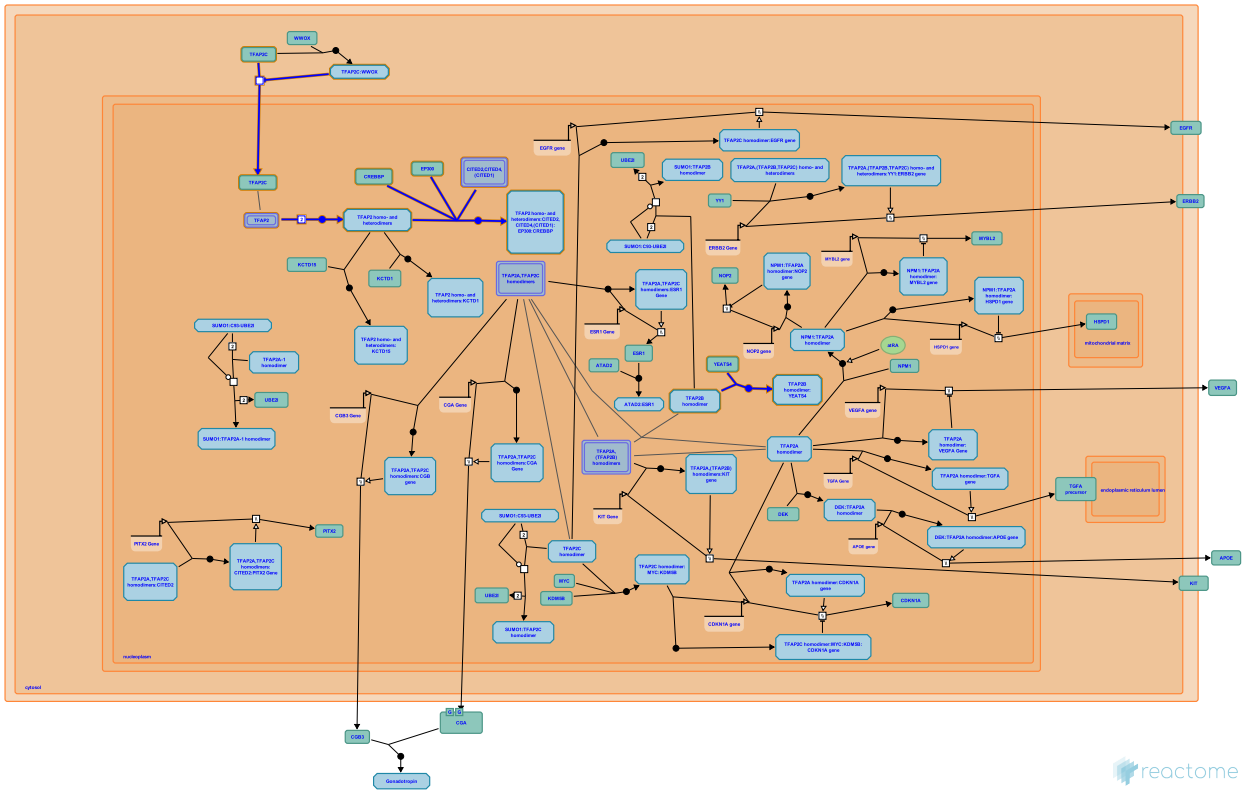
Editions

2016-03-14	Authored, Edited	Orlic-Milacic, M.
2016-05-04	Reviewed	Dawid, IB., Zarelli, VE.
2016-05-17	Reviewed	Weigel, RJ., Bogachek, MV.

Activation of the TFAP2 (AP-2) family of transcription factors ↗

Location: Transcriptional regulation by the AP-2 (TFAP2) family of transcription factors

Stable identifier: R-HSA-8866907



The helix-span-helix motif and the basic region of TFAP2 (AP-2) transcription factor family members TFAP2A, TFAP2B, TFAP2C, TFAP2D and TFAP2E enable dimerization and DNA binding. AP-2 dimers bind palindromic GC-rich DNA response elements that match the consensus sequence 5'-GCCNNNGGC-3' (Williams and Tjian 1991a, Williams and Tjian 1991b). Most of the AP-2 binding sites slightly differ from the consensus, and individual AP-2 family members may differ in their binding site preferences (McPherson and Weigel 1999, Orso et al. 2010). Transcriptional co-factors from the CITED family interact with the helix-span-helix (HSH) domain of TFAP2 (AP-2) family of transcription factors and recruit transcription co-activators EP300 (p300) and CREBBP (CBP) to TFAP2-bound DNA elements. CITED2 shows the highest affinity for TFAP2 proteins, followed by CITED4, while CITED1 interacts with TFAP2s with a very low affinity. Mouse embryos defective for CITED2 exhibit neural crest defects, cardiac malformations and adrenal agenesis, which can at least in part be attributed to a defective Tfap2 transactivation (Bamforth et al. 2001, Braganca et al. 2002, Braganca et al. 2003). DNA binding and transcriptional activity of TFAP2B homodimers is increased by binding to YEATS4 (GAS41) (Ding et al. 2006).

Literature references

Williams, T., Tjian, R. (1991). Analysis of the DNA-binding and activation properties of the human transcription factor AP-2. *Genes Dev., 5*, 670-82. ↗

Williams, T., Tjian, R. (1991). Characterization of a dimerization motif in AP-2 and its function in heterologous DNA-binding proteins. *Science, 251*, 1067-71. ↗

Bragança, J., Eloranta, JJ., Bamforth, SD., Ibbitt, JC., Hurst, HC., Bhattacharya, S. (2003). Physical and functional interactions among AP-2 transcription factors, p300/CREB-binding protein, and CITED2. *J. Biol. Chem., 278*, 16021-9 . ↗

Bragança, J., Swingler, T., Marques, FI., Jones, T., Eloranta, JJ., Hurst, HC. et al. (2002). Human CREB-binding protein/p300-interacting transactivator with ED-rich tail (CITED) 4, a new member of the CITED family, functions as a co-activator for transcription factor AP-2. *J. Biol. Chem., 277*, 8559-65. ↗

Bamforth, SD., Bragança, J., Eloranta, JJ., Murdoch, JN., Marques, FI., Kranc, KR. et al. (2001). Cardiac malformations, adrenal agenesis, neural crest defects and exencephaly in mice lacking Cited2, a new Tfap2 co-activator. *Nat. Genet., 29*, 469-74. ↗

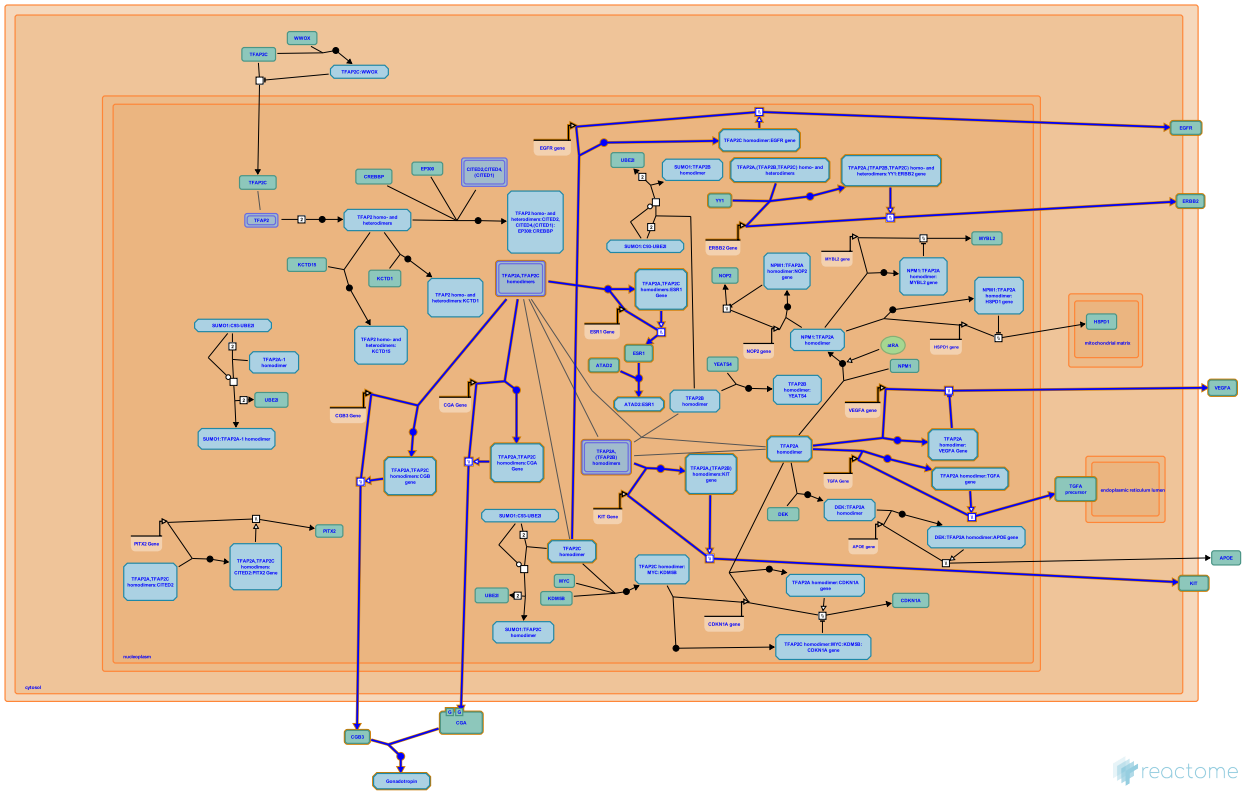
Editions

2016-03-14	Authored, Edited	Orlic-Milacic, M.
2016-05-04	Reviewed	Dawid, IB., Zarelli, VE.
2016-05-17	Reviewed	Weigel, RJ., Bogachek, MV.

TFAP2 (AP-2) family regulates transcription of growth factors and their receptors ↗

Location: Transcriptional regulation by the AP-2 (TFAP2) family of transcription factors

Stable identifier: R-HSA-8866910



TFAP2A and TFAP2C directly stimulate transcription of the estrogen receptor ESR1 gene (McPherson and Weigel 1999). TFAP2A expression correlates with ESR1 expression in breast cancer, and TFAP2C is frequently overexpressed in estrogen-positive breast cancer and endometrial cancer (deConinck et al. 1995, Turner et al. 1998). TFAP2A, TFAP2C, as well as TFAP2B can directly stimulate the expression of ERBB2, another important breast cancer gene (Bosher et al. 1996). Association of TFAP2A with the YY1 transcription factor significantly increases the ERBB2 transcription rate (Begon et al. 2005). In addition to ERBB2, the expression of another receptor tyrosine kinase, KIT, is also stimulated by TFAP2A and TFAP2B (Huang et al. 1998), while the expression of the VEGF receptor tyrosine kinase ligand VEGFA is repressed by TFAP2A (Ruiz et al. 2004, Li et al. 2012). TFAP2A stimulates transcription of the transforming growth factor alpha (TGFA) gene (Wang et al. 1997). TFAP2C regulates EGFR expression in luminal breast cancer (De Andrade et al. 2016). In placenta, TFAP2A and TFAP2C directly stimulate transcription of both subunits of the human chorionic gonadotropin, CGA and CGB (Johnson et al. 1997, LiCalsi et al. 2000).

Literature references

McPherson, LA., Weigel, RJ. (1999). AP2alpha and AP2gamma: a comparison of binding site specificity and trans-activation of the estrogen receptor promoter and single site promoter constructs. *Nucleic Acids Res., 27*, 4040-9. ↗

deConinck, EC., McPherson, LA., Weigel, RJ. (1995). Transcriptional regulation of estrogen receptor in breast carcinomas. *Mol. Cell. Biol., 15*, 2191-6. ↗

Turner, BC., Zhang, J., Gumbs, AA., Maher, MG., Kaplan, L., Carter, D. et al. (1998). Expression of AP-2 transcription factors in human breast cancer correlates with the regulation of multiple growth factor signalling pathways. *Cancer Res., 58*, 5466-72. ↗

Johnson, W., Albanese, C., Handwerger, S., Williams, T., Pestell, RG., Jameson, JL. (1997). Regulation of the human chorionic gonadotropin alpha- and beta-subunit promoters by AP-2. *J. Biol. Chem., 272*, 15405-12. ↗

LiCalsi, C., Christophe, S., Steger, DJ., Buescher, M., Fischer, W., Mellon, PL. (2000). AP-2 family members regulate basal and cAMP-induced expression of human chorionic gonadotropin. *Nucleic Acids Res., 28*, 1036-43. ↗

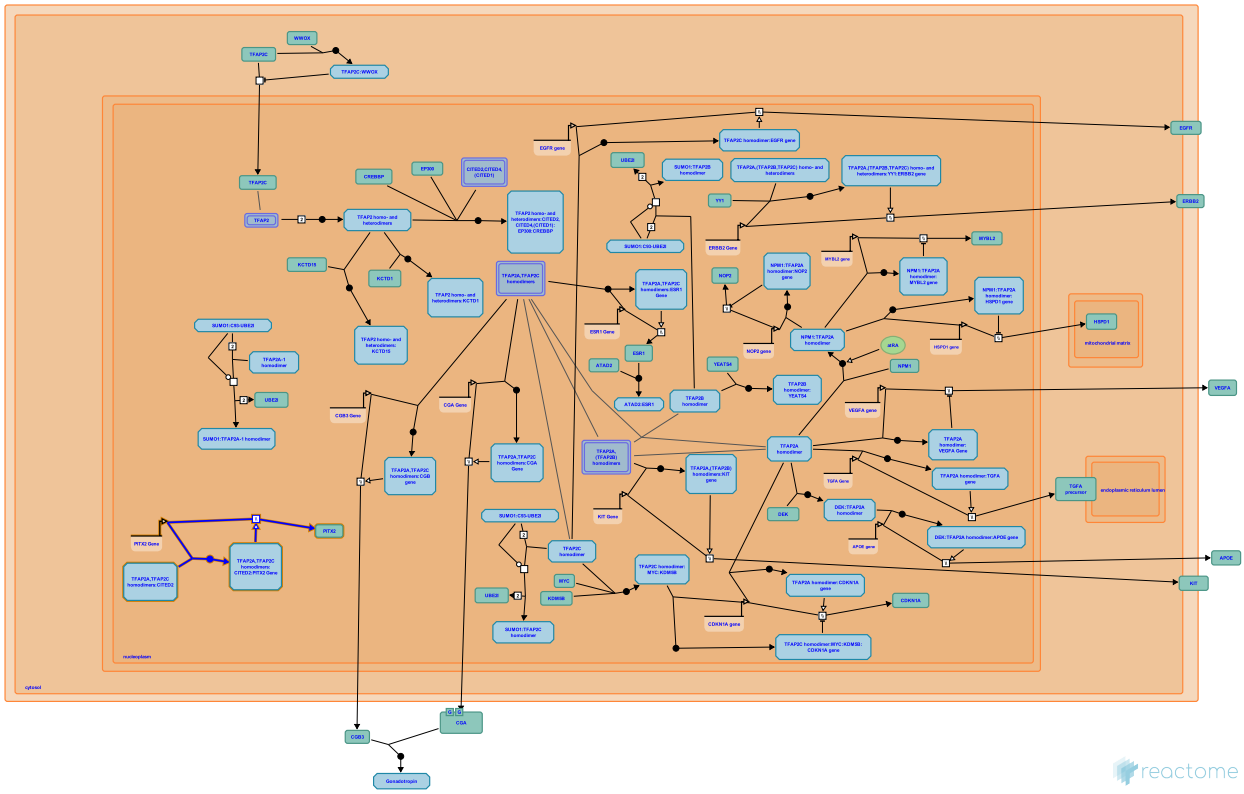
Editions

2016-03-14	Authored, Edited	Orlic-Milacic, M.
2016-05-04	Reviewed	Dawid, IB., Zarelli, VE.
2016-05-17	Reviewed	Weigel, RJ., Bogachek, MV.

TFAP2 (AP-2) family regulates transcription of other transcription factors ↗

Location: Transcriptional regulation by the AP-2 (TFAP2) family of transcription factors

Stable identifier: R-HSA-8866906



Homodimers and possibly heterodimers of TFAP2A and TFAP2C, in complex with CITED2, stimulate transcription of the PITX2 gene, involved in left-right patterning and heart development (Bamforth et al. 2004, Li et al. 2012).

Literature references

Li, Q., Pan, H., Guan, L., Su, D., Ma, X. (2012). CITED2 mutation links congenital heart defects to dysregulation of the cardiac gene VEGF and PITX2C expression. *Biochem. Biophys. Res. Commun., 423*, 895-9. ↗

Bamforth, SD., Bragança, J., Farthing, CR., Schneider, JE., Broadbent, C., Michell, AC. et al. (2004). Cited2 controls left-right patterning and heart development through a Nodal-Pitx2c pathway. *Nat. Genet., 36*, 1189-96. ↗

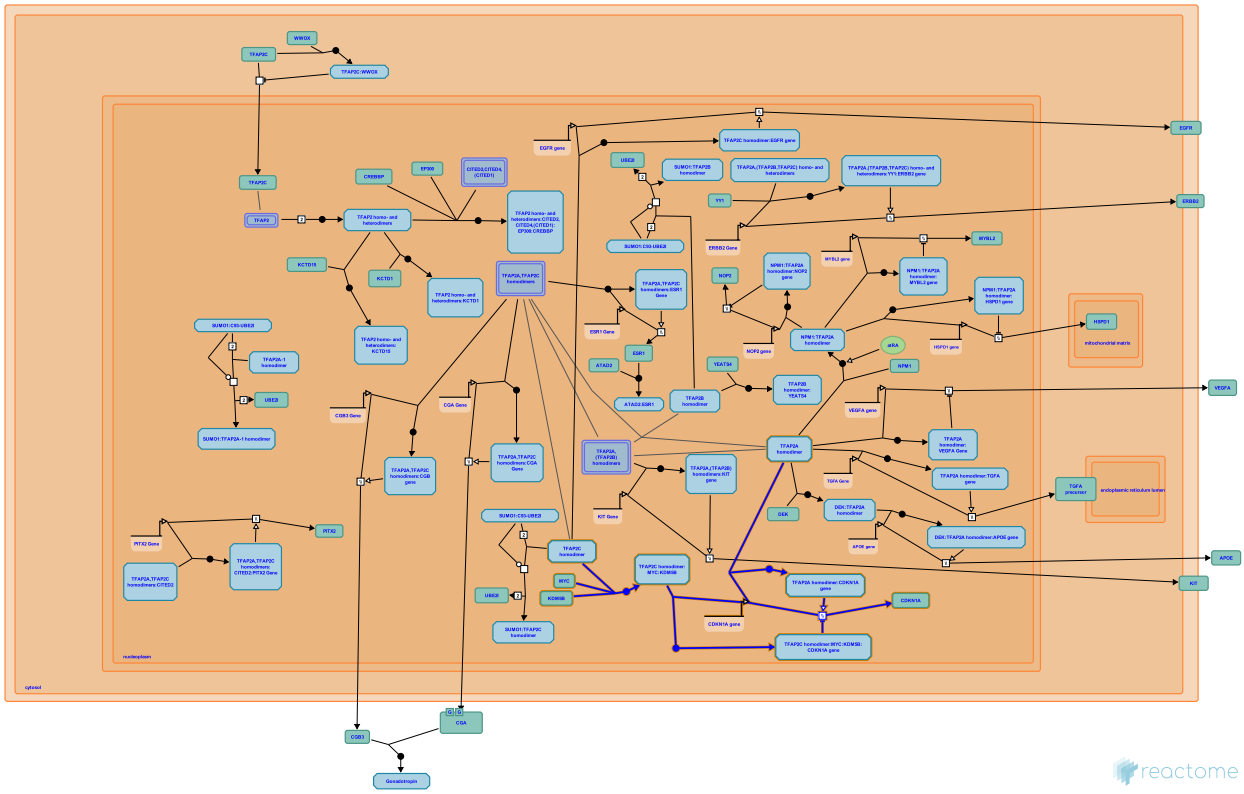
Editions

2016-03-14	Authored, Edited	Orlic-Milacic, M.
2016-05-04	Reviewed	Dawid, IB., Zarelli, VE.
2016-05-17	Reviewed	Weigel, RJ., Bogachek, MV.

TFAP2 (AP-2) family regulates transcription of cell cycle factors ↗

Location: Transcriptional regulation by the AP-2 (TFAP2) family of transcription factors

Stable identifier: R-HSA-8866911



TFAP2A and TFAP2C play opposing roles in transcriptional regulation of the CDKN1A (p21) gene locus. While TFAP2A stimulates transcription of the CDKN1A cyclin-dependent kinase inhibitor (Zeng et al. 1997, Williams et al. 2009, Scibetta et al. 2010), TFAP2C, in cooperation with MYC and histone demethylase KDM5B, represses CDKN1A transcription (Williams et al. 2009, Scibetta et al. 2010, Wong et al. 2012).

Literature references

Zeng, YX., Somasundaram, K., el-Deiry, WS. (1997). AP2 inhibits cancer cell growth and activates p21WAF1/CIP1 expression. *Nat. Genet., 15*, 78-82. ↗

Scibetta, AG., Wong, PP., Chan, KV., Canosa, M., Hurst, HC. (2010). Dual association by TFAP2A during activation of the p21cip/CDKN1A promoter. *Cell Cycle, 9*, 4525-32. ↗

Williams, CM., Scibetta, AG., Friedrich, JK., Canosa, M., Berlato, C., Moss, CH. et al. (2009). AP-2gamma promotes proliferation in breast tumour cells by direct repression of the CDKN1A gene. *EMBO J., 28*, 3591-601. ↗

Wong, PP., Miranda, F., Chan, KV., Berlato, C., Hurst, HC., Scibetta, AG. (2012). Histone demethylase KDM5B collaborates with TFAP2C and Myc to repress the cell cycle inhibitor p21(cip) (CDKN1A). *Mol. Cell. Biol., 32*, 1633-44. ↗

Editions

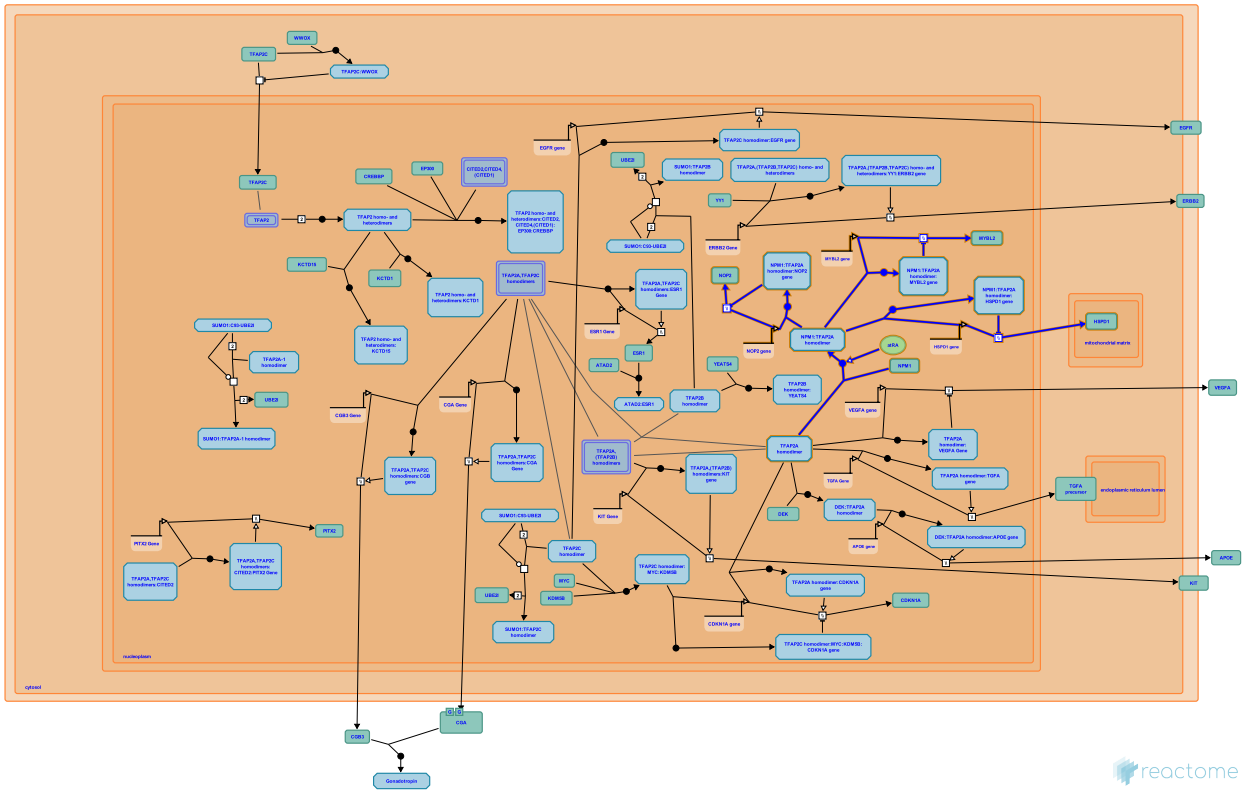
2016-03-14	Authored, Edited	Orlic-Milacic, M.
2016-05-04	Reviewed	Dawid, IB., Zarelli, VE.
2016-05-17	Reviewed	Weigel, RJ., Bogachek, MV.

TFAP2A acts as a transcriptional repressor during retinoic acid induced cell differentiation ↗

Location: Transcriptional regulation by the AP-2 (TFAP2) family of transcription factors

Stable identifier: R-HSA-8869496

Compartments: nucleoplasm



During retinoic acid-induced cell differentiation, TFAP2A, in complex with NPM1 (nucleophosmin), represses transcription of HSPD1 (Hsp60), NOP2 (p120) and MYBL2 (b-Myb). The repression of gene expression probably involves the recruitment of histone deacetylases HDAC1 and HDCA2 to target promoters by NPM1. The complex of TFAP2A and NPM1 can also be detected at the NPM1 promoter, which is in agreement with decreased NPM1 expression after retinoic acid treatment. The level of TFAP2A increases in response to the retinoic acid treatment (Liu et al. 2007). NOP2 and MYBL2 are both proliferation markers (Valdez et al. 1992, Saville and Watson 1998).

Literature references

Liu, H., Tan, BC., Tseng, KH., Chuang, CP., Yeh, CW., Chen, KD. et al. (2007). Nucleophosmin acts as a novel AP2alpha-binding transcriptional corepressor during cell differentiation. *EMBO Rep., 8*, 394-400. ↗

Valdez, BC., Perlaky, L., Saijo, Y., Henning, D., Zhu, C., Busch, RK. et al. (1992). A region of antisense RNA from human p120 cDNA with high homology to mouse p120 cDNA inhibits NIH 3T3 proliferation. *Cancer Res., 52*, 5681-6. ↗

Saville, MK., Watson, RJ. (1998). The cell-cycle regulated transcription factor B-Myb is phosphorylated by cyclin A/Cdk2 at sites that enhance its transactivation properties. *Oncogene, 17*, 2679-89. ↗

Editions

2016-03-14	Authored, Edited	Orlic-Milacic, M.
2016-05-04	Reviewed	Dawid, IB., Zarelli, VE.

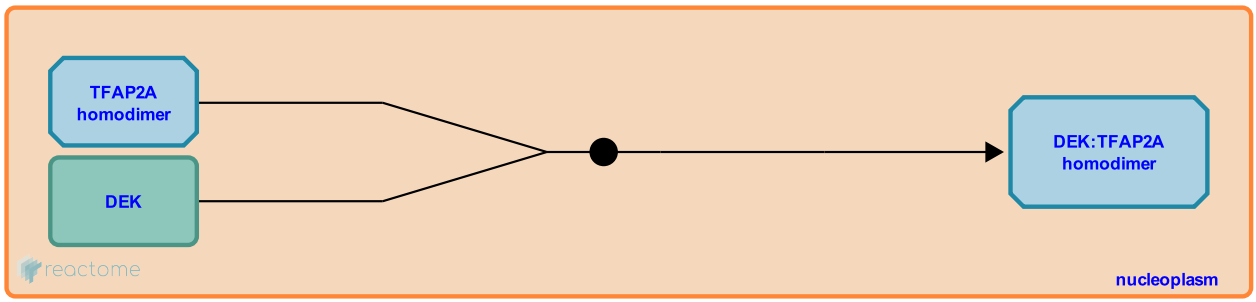
DEK binds TFAP2A homodimers ↗

Location: Transcriptional regulation by the AP-2 (TFAP2) family of transcription factors

Stable identifier: R-HSA-8869580

Type: binding

Compartments: nucleoplasm



DEK forms a complex with TFAP2A homodimers (Campillos et al. 2003).

Followed by: TFAP2A in complex with DEK binds the APOE gene promoter

Literature references

Campillos, M., García, MA., Valdivieso, F., Vázquez, J. (2003). Transcriptional activation by AP-2alpha is modulated by the oncogene DEK. *Nucleic Acids Res., 31*, 1571-5. ↗

Editions

2016-03-14	Authored, Edited	Orlic-Milacic, M.
2016-05-04	Reviewed	Dawid, IB., Zarelli, VE.

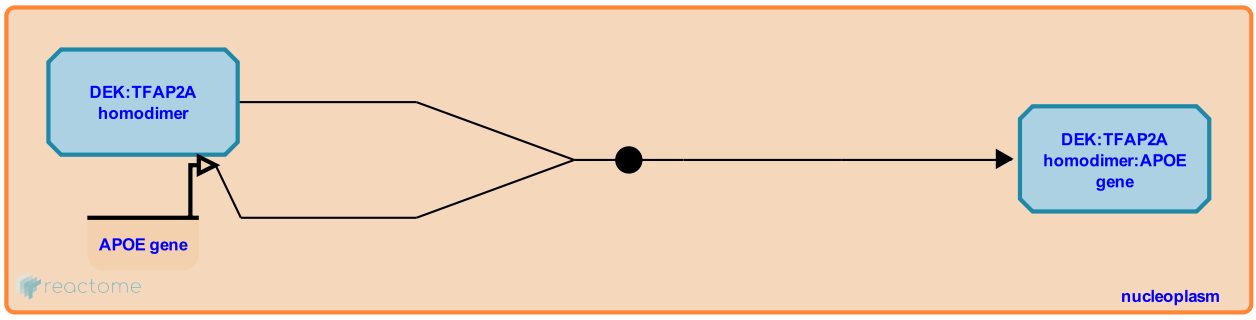
TFAP2A in complex with DEK binds the APOE gene promoter ↗

Location: Transcriptional regulation by the AP-2 (TFAP2) family of transcription factors

Stable identifier: R-HSA-8869575

Type: binding

Compartments: nucleoplasm



DEK is recruited to the APOE gene promoter via its interaction with the TFAP2A (AP-2 alpha) homodimer. In the presence of DEK, TFAP2A associates with the APOE promoter more tightly (Campillos et al. 2003). Binding of TFAP2A to the APOE gene promoter may be stimulated by PKA-mediated phosphorylation of TFAP2A (Garcia et al. 1999).

Preceded by: DEK binds TFAP2A homodimers

Followed by: The APOE gene transcription is stimulated by the complex of TFAP2A homodimer and DEK

Literature references

Campillos, M., García, MA., Valdivieso, F., Vázquez, J. (2003). Transcriptional activation by AP-2alpha is modulated by the oncogene DEK. *Nucleic Acids Res., 31*, 1571-5. ↗

Editions

2016-03-14	Authored, Edited	Orlic-Milacic, M.
2016-05-04	Reviewed	Dawid, IB., Zarelli, VE.

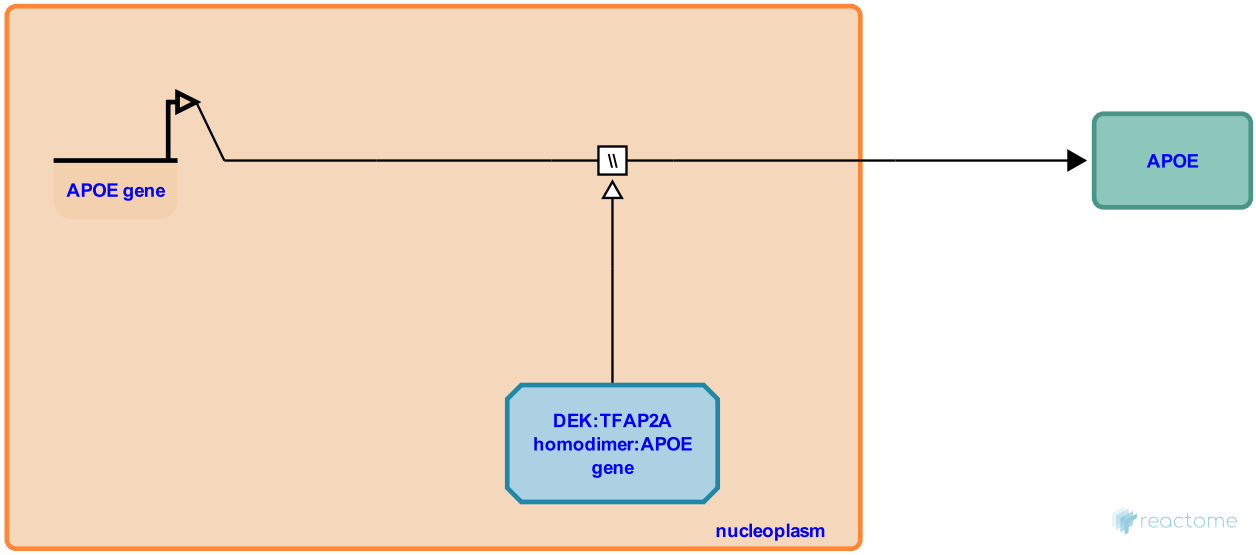
The APOE gene transcription is stimulated by the complex of TFAP2A homodimer and DEK ↗

Location: Transcriptional regulation by the AP-2 (TFAP2) family of transcription factors

Stable identifier: R-HSA-8869590

Type: omitted

Compartments: nucleoplasm



The complex of TFAP2A homodimer and DEK stimulates transcription of the APOE gene (Campillos et al. 2003).

Preceded by: TFAP2A in complex with DEK binds the APOE gene promoter

Literature references

Campillos, M., García, MA., Valdivieso, F., Vázquez, J. (2003). Transcriptional activation by AP-2alpha is modulated by the oncogene DEK. *Nucleic Acids Res., 31*, 1571-5. ↗

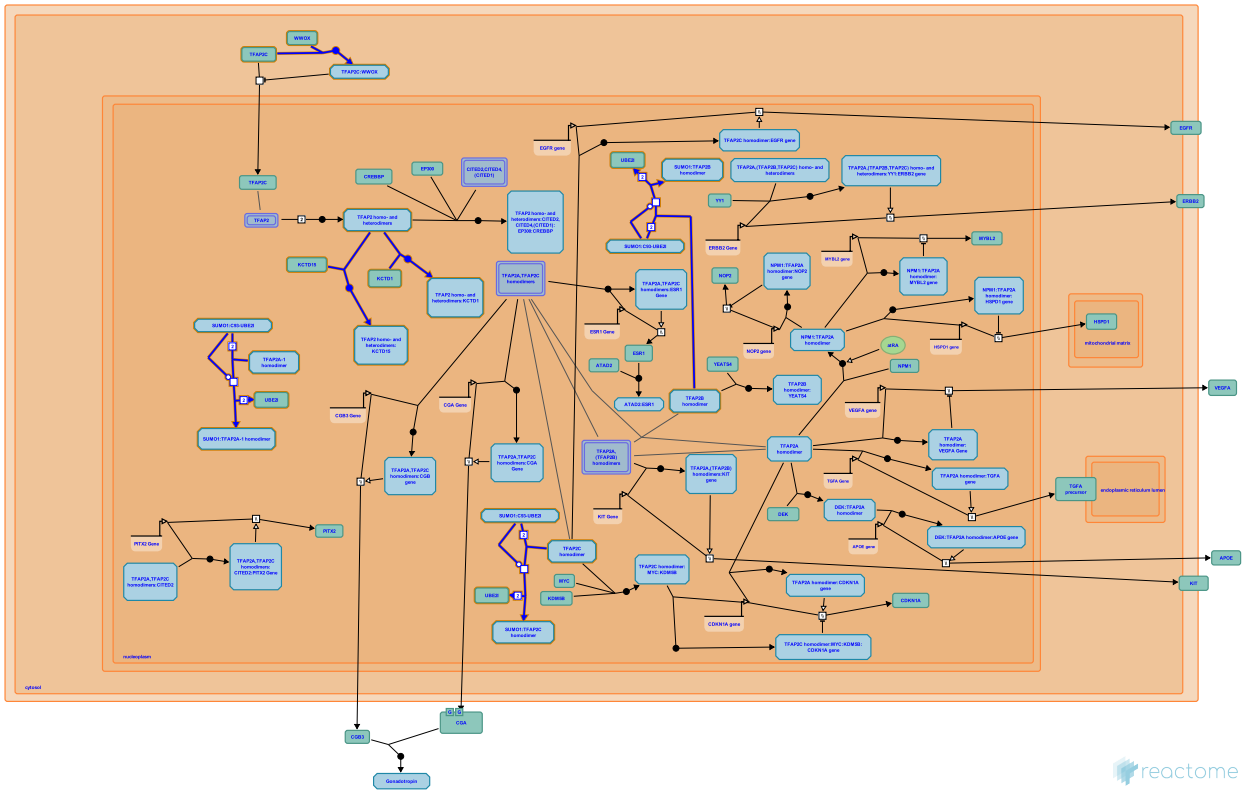
Editions

2016-03-14	Authored, Edited	Orlic-Milacic, M.
2016-05-04	Reviewed	Dawid, IB., Zarelli, VE.

Negative regulation of activity of TFAP2 (AP-2) family transcription factors ↗

Location: Transcriptional regulation by the AP-2 (TFAP2) family of transcription factors

Stable identifier: R-HSA-8866904



Transcriptional activity of TFAP2 (AP-2) transcription factor family homo- and heterodimers in inhibited by binding of KCTD1 or KCTD15 to the AP-2 transactivation domain (Ding et al. 2009, Zarelli and Dawid 2013). Transcriptional activity of TFAP2A, TFAP2B and TFAP2C is also negatively regulated by SUMOylation mediated by UBE2I (UBC9) (Eloranta and Hurst 2002, Berlato et al. 2011, Impens et al. 2014, Bogachek et al. 2014). Binding of the tumor suppressor WWOX to TFAP2C inhibits TFAP2C translocation to the nucleus (Aqeilan et al. 2004). Transcription of the TFAP2A gene may be inhibited by CREB and E2F1 (Melnikova et al. 2010).

Literature references

Aqeilan, RI., Palamarchuk, A., Weigel, RJ., Herrero, JJ., Pekarsky, Y., Croce, CM. (2004). Physical and functional interactions between the Wwox tumor suppressor protein and the AP-2gamma transcription factor. *Cancer Res., 64*, 8256-61. ↗

Ding, X., Luo, C., Zhou, J., Zhong, Y., Hu, X., Zhou, F. et al. (2009). The interaction of KCTD1 with transcription factor AP-2alpha inhibits its transactivation. *J. Cell. Biochem., 106*, 285-95. ↗

Zarelli, VE., Dawid, IB. (2013). Inhibition of neural crest formation by Kctd15 involves regulation of transcription factor AP-2. *Proc. Natl. Acad. Sci. U.S.A., 110*, 2870-5. ↗

Eloranta, JJ., Hurst, HC. (2002). Transcription factor AP-2 interacts with the SUMO-conjugating enzyme UBC9 and is sumolated in vivo. *J. Biol. Chem., 277*, 30798-804. ↗

Berlato, C., Chan, KV., Price, AM., Canosa, M., Scibetta, AG., Hurst, HC. (2011). Alternative TFAP2A isoforms have distinct activities in breast cancer. *Breast Cancer Res., 13*, R23. ↗

Editions

2016-03-14	Authored, Edited	Orlic-Milacic, M.
2016-05-04	Reviewed	Dawid, IB., Zarelli, VE.
2016-05-17	Reviewed	Weigel, RJ., Bogachek, MV.

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