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

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19/12/2019
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: 71

This document contains 7 pathways and 3 reactions (see Table of Contents)
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’-GC-CNNGGC-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 is 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 (UBE9) (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).


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

**Literature references**


**Editions**

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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).

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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 (Rui 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).

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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).

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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


Literature references


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.


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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).

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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