Generic Transcription Pathway

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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.

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Reactome database release: 88

This document contains 15 pathways and 4 reactions (see Table of Contents)

Generic Transcription Pathway ↗

Stable identifier: R-HSA-212436

OVERVIEW OF TRANSCRIPTION REGULATION:

Detailed studies of gene transcription regulation in a wide variety of eukaryotic systems has revealed the general principles and mechanisms by which cell- or tissue-specific regulation of differential gene transcription is mediated (reviewed in Naar, 2001. Kadonaga, 2004, Maston, 2006, Barolo, 2002; Roeder, 2005, Rosenfeld, 2006). Of the three major classes of DNA polymerase involved in eukaryotic gene transcription, Polymerase II generally regulates protein-encoding genes. Figure 1 shows a diagram of the various components involved in cell-specific regulation of Pol-II gene transcription.

Core Promoter: Pol II-regulated genes typically have a Core Promoter where Pol II and a variety of general factors bind to specific DNA motifs:
i: the TATA box (TATA DNA sequence), which is bound by the "TATA-binding protein" (TBP).
ii: the Initiator motif (INR), where Pol II and certain other core factors bind, is present in many Pol II-regulated genes.
iii: the Downstream Promoter Element (DPE), which is present in a subset of Pol II genes, and where additional core factors bind.
The core promoter binding factors are generally ubiquitously expressed, although there are exceptions to this.

Proximal Promoter: immediately upstream (5') of the core promoter, Pol II target genes often have a Proximal Promoter region that spans up to 500 base pairs (b.p.), or even to 1000 b.p.. This region contains a number of functional DNA binding sites for a specific set of transcription activator (TA) and transcription repressor (TR) proteins. These TA and TR factors are generally cell- or tissue-specific in expression, rather than ubiquitous, so that the presence of their cognate binding sites in the proximal promoter region programs cell- or tissue-specific expression of the target gene, perhaps in conjunction with TA and TR complexes bound in distal enhancer regions.

Distal Enhancer(s): many or most Pol II regulated genes in higher eukaryotes have one or more distal Enhancer regions which are essential for proper regulation of the gene, often in a cell or tissue-specific pattern. Like the proximal promoter region, each of the distal enhancer regions typically contain a cluster of binding sites for specific TA and/or TR DNA-binding factors, rather than just a single site.

Enhancers generally have three defining characteristics:
i: They can be located very long distances from the promoter of the target gene they regulate, sometimes as far as 100 Kb, or more.
ii: They can be either upstream (5') or downstream (3') of the target gene, including within introns of that gene.
iii: They can function in either orientation in the DNA.

Combinatorial mechanisms of transcription regulation: The specific combination of TA and TR binding sites within the proximal promoter and/or distal enhancer(s) provides a "combinatorial transcription code" that mediates cell- or tissue-specific expression of the associated target gene. Each promoter or enhancer region mediates expression in a specific subset of the overall expression pattern. In at least some cases, each enhancer region functions completely independently of the others, so that the overall expression pattern is a linear combination of the expression patterns of each of the enhancer modules.

Co-Activator and Co-Repressor Complexes: DNA-bound TA and TR proteins typically recruit the assembly of specific Co-Activator (Co-A) and Co-Repressor (Co-R) Complexes, respectively, which are essential for regulating target gene transcription. Both Co-A's and Co-R's are multi-protein complexes that contain several specific protein components.

Co-Activator complexes generally contain at lease one component protein that has Histone Acetyl Transferase (HAT) enzymatic activity. This functions to acetylate Histones and/or other chromatin-associated factors, which typically increases that transcription activation of the target gene. By contrast, Co-Repressor complexes generally contain at lease one component protein that has Histone De-Acetylase (HDAC) enzymatic activity. This functions to de-acetylate Histones and/or other chromatin-associated factors. This typically increases the transcription repression of the target gene.

Adaptor (Mediator) complexes: In addition to the co-activator complexes that assemble on particular cell-specific TA factors, - there are at least two additional transcriptional co-activator complexes common to most cells. One of these is the Mediator complex, which functions as an "adaptor" complex that bridges between the tissue-specific co-activator complexes assembled in the proximal promoter (or distal enhancers). The human Mediator complex has been shown to contain at least 19 protein distinct components. Different combinations of these co-activator proteins are also found to be components of specific transcription Co-Activator complexes, such as the DRIP, TRAP and ARC complexes described below.

TBP/TAF complex: Another large Co-A complex is the "TBP-associated factors" (TAFs) that assemble on TBP (TATA-Binding Protein), which is bound to the TATA box present in many promoters. There are at least 23 human TAF proteins that have been identified. Many of these are ubiquitously expressed, but TAFs can also be expressed in a cell or tissue-specific pattern.

Specific Coactivator Complexes for DNA-binding Transcription Factors.

A number of specific co-activator complexes for DNA-binding transcription factors have been identified, including DRIP, TRAP, and ARC (reviewed in Bourbon, 2004, Blazek, 2005, Conaway, 2005, and Malik, 2005). The DRIP co-activator complex was originally identified and named as a specific complex associated with the Vitamin D Receptor member of the nuclear receptor family of transcription factors (Rachez, 1998). Similarly, the TRAP co-activator complex was originally identified as a complex that associates with the thyroid receptor (Yuan, 1998). It was later determined that all of the components of the DRIP complex are also present in the TRAP complex, and the ARC complex (discussed further below). For example, the DRIP205 and TRAP220 proteins were show to be identical, as were specific pairs of the other components of these complexes (Rachez, 1999).

In addition, these various transcription co-activator proteins identified in mammalian cells were found to be the orthologues or homologues of the Mediator ("adaptor") complex proteins (reviewed in Bourbon, 2004). The Mediator proteins were originally identified in yeast by Kornberg and colleagues, as complexes associated with DNA polymerase (Kelleher, 1990). In higher organisms, Adapter complexes bridge between the basal transcription factors (including Pol II) and tissue-specific transcription factors (TFs) bound to sites within upstream Proximal Promoter regions or distal Enhancer regions (Figure 1). However, many of the Mediator homologues can also be found in complexes associated with specific transcription factors in higher organisms. A unified nomenclature system for these adapter / co-activator proteins now labels them Mediator 1 through Mediator 31 (Bourbon, 2004). For example, the DRIP205 / TRAP220 proteins are now identified as Mediator 1 (Rachez, 1999), based on homology with yeast Mediator 1.

Example Pathway: Specific Regulation of Target Genes During Notch Signaling:

One well-studied example of cell-specific regulation of gene transcription is selective regulation of target genes during Notch signaling. Notch signaling was first identified in Drosophila, where it has been studied in detail at the genetic, molecular, biochemical and cellular levels (reviewed in Justice, 2002; Bray, 2006; Schweisguth, 2004; Louvri, 2006). In Drosophila, Notch signaling to the nucleus is thought always to be mediated by one specific DNA binding transcription factor, Suppressor of Hairless. In mammals, the homologous genes are called CBF1 (or RBPJkappa), while in worms they are called Lag-1, so that the acronym "CSL" has been given to this conserved transcription factor family. There are at least two human CSL homologues, which are now named RBPJ and RBPJL.

In Drosophila, Su(H) is known to be bifunctional, in that it represses target gene transcription in the absence of Notch signaling, but activates target genes during Notch signaling. At least some of the mammalian CSL homologues are believed also to be bifunctional, and to mediate target gene repression in the absence of Notch signaling, and activation in the presence of Notch signaling.

Notch Co-Activator and Co-Repressor complexes: This repression is mediated by at least one specific co-repressor complexes (Co-R) bound to CSL in the absence of Notch signaling. In Drosophila, this co-repressor complex consists of at least three distinct co-repressor proteins: Hairless, Groucho, and dCtBP (Drosophila C-terminal Binding Protein). Hairless has been show to bind directly to Su(H), and Groucho and dCtBP have been shown to bind directly to Hairless (Barolo, 2002). All three of the co-repressor proteins have been shown to be necessary for proper gene regulation during Notch signaling in vivo (Nagel, 2005).

In mammals, the same general pathway and mechanisms are observed, where CSL proteins are bifunctional DNA binding transcription factors (TFs), that bind to Co-Repressor complexes to mediate repression in the absence of Notch signaling, and bind to Co-Activator complexes to mediate activation in the presence of Notch signaling. However, in mammals, there may be multiple co-repressor complexes, rather than the single Hairless co-repressor complex that has been observed in Drosophila.

During Notch signaling in all systems, the Notch transmembrane receptor is cleaved and the Notch intracellular domain (NICD) translocates to the nucleus, where it there functions as a specific transcription co-activator for CSL proteins. In the nucleus, NICD replaces the Co-R complex bound to CSL, thus resulting in de-repression of Notch target genes in the nucleus (Figure 2). Once bound to CSL, NICD and CSL proteins recruit an additional co-activator protein, Mastermind, to form a CSL-NICD-Mam ternary co-activator (Co-A) complex. This Co-R complex was initially thought to be sufficient to mediate activation of at least some Notch target genes. However, there now is evidence that still other co-activators and additional DNA-binding transcription factors are required in at least some contexts (reviewed in Barolo, 2002).

Thus, CSL is a good example of a bifunctional DNA-binding transcription factor that mediates repression of specific targets genes in one context, but activation of the same targets in another context. This bifunctionality is mediated by the association of specific Co-Repressor complexes vs. specific Co-Activator complexes in different contexts, namely in the absence or presence of Notch signaling.

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Editions

2008-02-26	Reviewed	Freedman, LP.

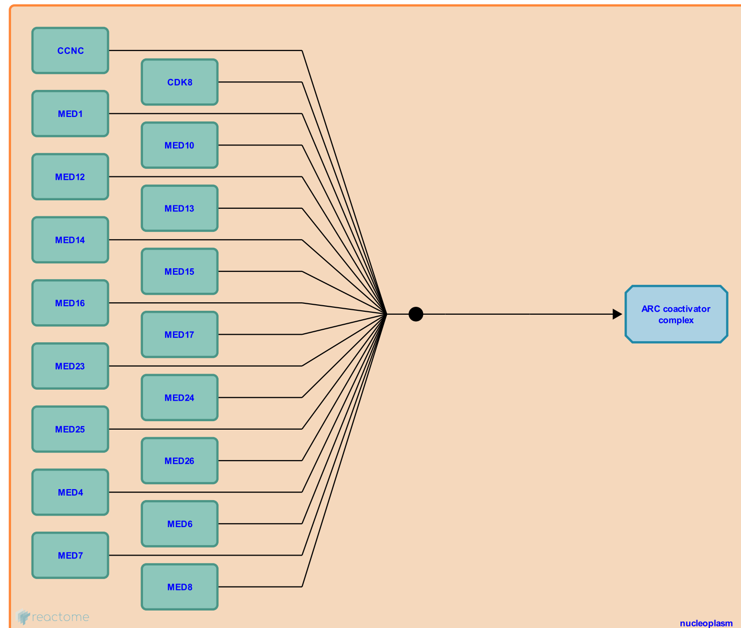
Formation of ARC coactivator complex ↗

Location: Generic Transcription Pathway

Stable identifier: R-HSA-212352

Type: binding

Compartments: nucleoplasm



ARC co-activator complex and assembly

The ARC co-activator complex is a subset of 18 proteins from the set of at least 31 Mediator proteins that, in different combinations, form "Adapter" complexes in human cells. Adapter complexes bridge between the basal transcription factors (including Pol II) and tissue-specific transcription factors (TFs) bound to sites within upstream Proximal Promoter regions or distal Enhancer regions (reviewed in Maston, 2006 and Naar, 2001).

The ARC complex was originally identified and named as a co-activator complex associated with transcription activator proteins (reviewed in Malik, 2005 and references therein). It was subsequently determined that many of the components of the ARC complex are also in the DRIP complex, and in the TRAP complex..

The ARC complex contains the following 14 proteins, which also are common to the DRIP and TRAP complexes: MED1, MED4, MED6, MED7, MED10, MED12, MED13, MED14, MED16, MED17, MED23, MED24, CDK8, CycC.

The ARC complex also contains 4 additional, ARC-specific components, which are now called: MED8, MED15, MED25, and MED 26 in the unified nomenclature scheme (Bourbon, 2004).

In addition, these various transcription co-activator proteins identified in mammalian cells were found to be the orthologues or homologues of the Mediator complex proteins in yeast, first identified by Kornberg and colleagues (Kelleher, 1990). The unified nomenclature system for these adapter / co-activator proteins now labels them Mediator 1 through Mediator 31 (Bourbon, 2004).

The order of addition of the ARC proteins during complex assembly is not fully determined, and may vary in different cell contexts. Therefore, ARC complex assembly is represented as a single reaction event, in which all 19 components assemble simultaneously into the ARC co-activator complex.

Literature references

Suldan, Z., Freedman, LP., Chang, CP., Ward, J., Tempst, P., Rachez, C. et al. (1998). A novel protein complex that interacts with the vitamin D3 receptor in a ligand-dependent manner and enhances VDR transactivation in a cell-free system. *Genes Dev, 12*, 1787-800. ↗

Bromleigh, V., Gamble, M., Suldan, Z., Lemon, BD., Freedman, LP., Tempst, P. et al. (1999). Ligand-dependent transcription activation by nuclear receptors requires the DRIP complex. *Nature, 398,* 824-8. ↗

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Editions

2008-02-26	Reviewed	Freedman, LP.

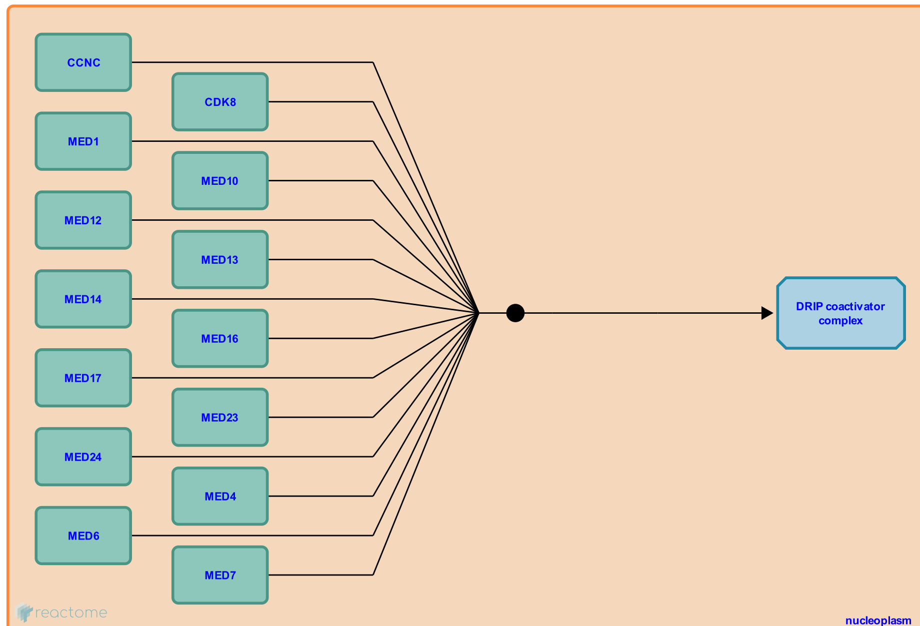
Formation of DRIP coactivator complex ↗

Location: Generic Transcription Pathway

Stable identifier: R-HSA-212432

Type: binding

Compartments: nucleoplasm



DRIP co-activator complex and assembly

The DRIP co-activator complex is a subset of 14 proteins from the set of at least 31 Mediator proteins that, in different combinations, form "Adapter" complexes. Adapter complexes bridge between the basal transcription factors (including Pol II) and tissue-specific transcription factors (TFs) bound to sites within upstream Proximal Promoter regions or distal Enhancer regions (reviewed in Maston, 2006 and Naar, 2001).

The DRIP complex was originally identified and named as a co-activator complex associated with the Vitamin D Receptor member of the nuclear receptor family of transcription factors (Rachez, 1998). It was later determined that all of the components of the DRIP complex were also in the TRAP complex, and the ARC complex.

The DRIP complex contains the following 14 proteins, which also are common to the ARC and TRAP complexes: MED1, MED4, MED6, MED7, MED10, MED12, MED13, MED14, MED16, MED17, MED23, MED24, CDK8, CycC.

All of the DRIP adapter complex components are present in the ARC adapter complex, but the ARC complex also has 4 additional components (Rachez, 1999). These ARC-specific components are now called: MED8, MED15, MED25, and MED 26 in the unified nomenclature scheme (Bourbon, 2004).

Similarly, all 14 of the DRIP adapter complex components are present in the TRAP adapter complex, but the TRAP complex also has 4 additional components (Bourbon, 2004), These TRAP-specific components are now called: MED20, MED27, MED30, and MED 31 in the unified nomenclature scheme.

In addition, these various transcription co-activator proteins identified in mammalian cells were found to be the orthologues or homologues of the Mediator complex identified in yeast, first identified by Kornberg and colleagues (Kelleher, 1990).

Literature references

Suldan, Z., Freedman, LP., Chang, CP., Ward, J., Tempst, P., Rachez, C. et al. (1998). A novel protein complex that interacts with the vitamin D3 receptor in a ligand-dependent manner and enhances VDR transactivation in a cell-free system. *Genes Dev, 12*, 1787-800. ↗

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Kornberg, RD., Kelleher RJ, 3rd., Flanagan, PM. (1990). A novel mediator between activator proteins and the RNA polymerase II transcription apparatus. *Cell, 61,* 1209-15. ↗

Editions

2008-02-26	Reviewed	Freedman, LP.

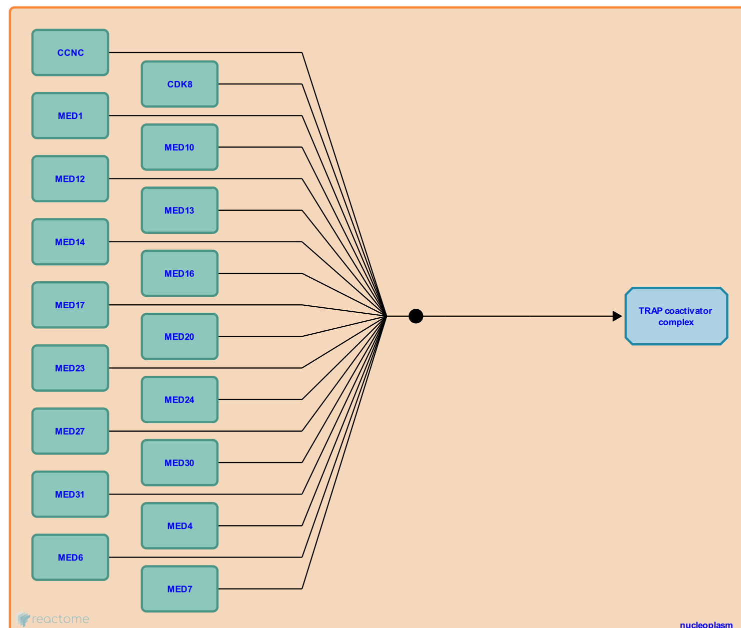
Formation of TRAP coactivator complex ↗

Location: Generic Transcription Pathway

Stable identifier: R-HSA-212380

Type: binding

Compartments: nucleoplasm



TRAP co-activator complex and assembly

The TRAP co-activator complex is a subset of 18 proteins from the set of at least 31 Mediator proteins that, in different combinations and in different contexts, form specific co-activator or "Adapter" complexes in human cells. These complexes bridge between the basal transcription factors (including Pol II) and tissue-specific transcription factors (TFs) bound to sites within upstream Proximal Promoter regions or distal Enhancer regions (reviewed in Maston, 2006 and Naar, 2001).

The TRAP complex was originally identified and named as a co-activator complex associated with the Thyroid Hormone Receptor member of the nuclear receptor family of transcription factors (Yuan, 1998). It was later determined that many of the components of the TRAP complex are also in the DRIP complex, and in the ARC complex.

The TRAP complex contains the following 14 proteins, which also are common to the DRIP and ARC complexes: MED1, MED4, MED6, MED7, MED10, MED12, MED13, MED14, MED16, MED17, MED23, MED24, CDK8, CycC.

The TRAP complex also contains 4 additional components, which are now called: MED20, MED27, MED30, and MED 31 in the unified nomenclature scheme (Bourbon, 2004).

In addition, these various transcription co-activator proteins identified in mammalian cells were found to be the orthologues or homologues of the Mediator complex proteins in yeast, first identified by Kornberg and colleagues (Kelleher, 1990). The unified nomenclature system for these adapter / co-activator proteins now labels them Mediator 1 through Mediator 31 (Bourbon, 2004).

The order of addition of the TRAP proteins during complex assembly is not fully determined, and may vary in different cell contexts. Therefore, TRAP co-activator complex assembly is represented as a single reaction event, in which all 18 components assemble simultaneously into the TRAP co-activator complex.

Literature references

Suldan, Z., Freedman, LP., Chang, CP., Ward, J., Tempst, P., Rachez, C. et al. (1998). A novel protein complex that interacts with the vitamin D3 receptor in a ligand-dependent manner and enhances VDR transactivation in a cell-free system. *Genes Dev, 12*, 1787-800. ↗

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Naar, AM., Roeder, RG., Sadowski, I., Sipiczki, M., Carey, M., He, X. et al. (2004). A unified nomenclature for protein subunits of mediator complexes linking transcriptional regulators to RNA polymerase II. *Mol Cell, 14*, 553-7. ↗

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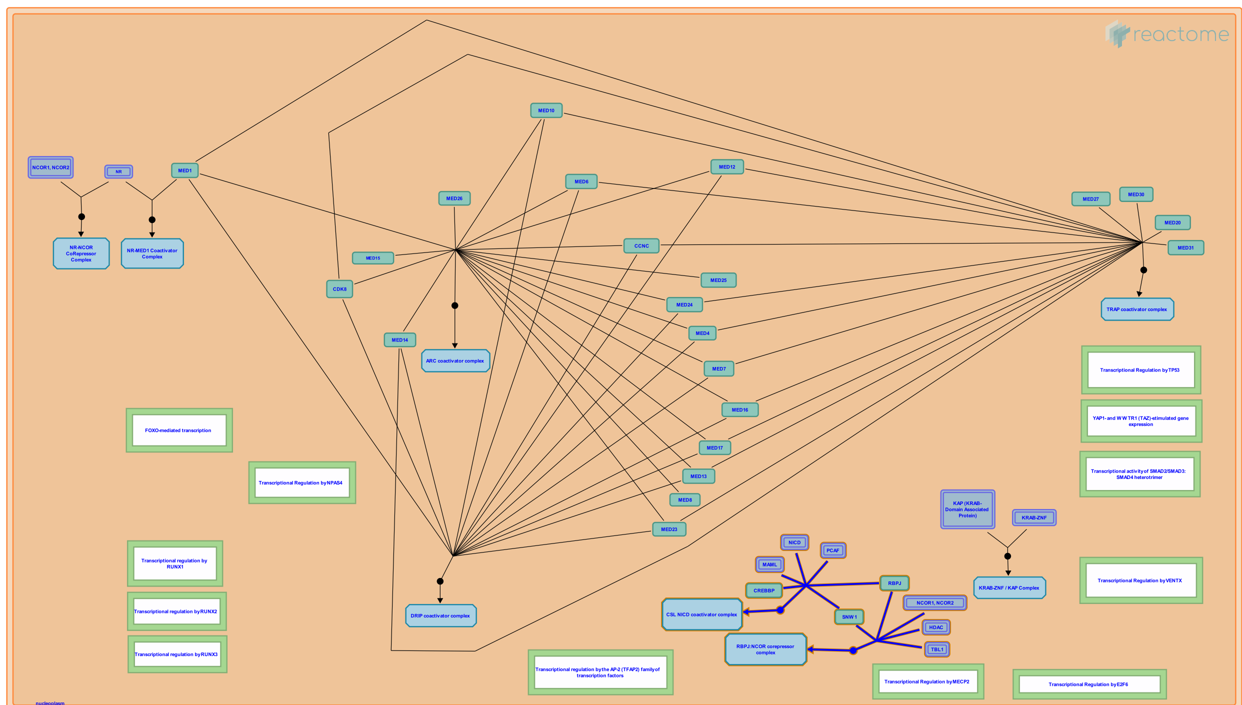
Editions

2008-02-26	Reviewed	Freedman, LP.

Notch-HLH transcription pathway ↗

Location: Generic Transcription Pathway

Stable identifier: R-HSA-350054



THE NOTCH-HLH TRANSCRIPTION PATHWAY:

Notch signaling was first identified in Drosophila, where it has been studied in detail at the genetic, molecular, biochemical and cellular levels (reviewed in Justice, 2002; Bray, 2006; Schweisguth, 2004; Louvri, 2006). In Drosophila, Notch signaling to the nucleus is thought always to be mediated by one specific DNA binding transcription factor, Suppressor of Hairless. In mammals, the homologous genes are called CBF1 (or RBPJkappa), while in worms they are called Lag-1, so that the acronym "CSL" has been given to this conserved transcription factor family. There are at least two human CSL homologues, which are now named RBPJ and RBPJL.

CSL is an example of a bifunctional DNA-binding transcription factor that mediates repression of specific target genes in one context, but activation of the same targets in another context. This bifunctionality is mediated by the association of specific Co-Repressor complexes vs. specific Co-Activator complexes in different contexts, namely in the absence or presence of Notch signaling.

In Drosophila, Su(H) represses target gene transcription in the absence of Notch signaling, but activates target genes during Notch signaling. At least some of the mammalian CSL homologues are believed also to be bifunctional, and to mediate target gene repression in the absence of Notch signaling, and activation in the presence of Notch signaling.

Notch Co-Activator and Co-Repressor complexes: This repression is mediated by at least one specific co-repressor complexes (Co-R) bound to CSL in the absence of Notch signaling. In Drosophila, this co-repressor complex consists of at least three distinct co-repressor proteins: Hairless, Groucho, and dCtBP (Drosophila C-terminal Binding Protein). Hairless has been show to bind directly to Su(H), and Groucho and dCtBP have been shown to bind directly to Hairless (Barolo, 2002). All three of the co-repressor proteins have been shown to be necessary for proper gene regulation during Notch signaling in vivo (Nagel, 2005).

In mammals, the same general pathway and mechanisms are observed, where CSL proteins are bifunctional DNA binding transcription factors (TFs), that bind to Co-Repressor complexes to mediate repression in the absence of Notch signaling, and bind to Co-Activator complexes to mediate activation in the presence of Notch signaling. However, in mammals, there may be multiple co-repressor complexes, rather than the single Hairless co-repressor complex that has been observed in Drosophila.

During Notch signaling in all systems, the Notch transmembrane receptor is cleaved and the Notch intracellular domain (NICD) translocates to the nucleus, where it there functions as a specific transcription co-activator for CSL

proteins. In the nucleus, NICD replaces the Co-R complex bound to CSL, thus resulting in de-repression of Notch target genes in the nucleus. Once bound to CSL, NICD and CSL proteins recruit an additional co-activator protein, Mastermind, to form a CSL-NICD-Mam ternary co-activator (Co-A) complex. This Co-A complex was initially thought to be sufficient to mediate activation of at least some Notch target genes. However, there now is evidence that still other co-activators and additional DNA-binding transcription factors are required in at least some contexts (reviewed in Barolo, 2002).

Mammalian CSL Corepressor Complexes: In the absence of activated Notch signaling, DNA-bound CSL proteins recruit a corepressor complex to maintain target genes in the repressed state until Notch is specifically activated. The mammalian corepressor complexes include NCOR complexes, but may also include additional corepressor proteins, such as SHARP (reviewed in Mumm, 2000 and Kovall, 2007). The exact composition of the CSL NCOR complex is not known, but in other pathways the "core" NCOR corepressor complex includes at least one NCOR protein (NCOR1, NCOR2, CIR), one Histone Deacetylase protein (HDAC1, HDAC2, HDAC3, etc), and one TBL1 protein (TBL1X, TBL1XR1) (reviewed in Rosenfeld, 2006). In some contexts, the core NCOR corepressor complex may also recruit additional corepressor proteins or complexes, such as the SIN3 complex, which consists of SIN3 (SIN3A, SIN3B), and SAP30, or other SIN3-associated proteins. An additional CSL - NCOR binding corepressor, SHARP, may also contribute to the CSL corepressor complex in some contexts (Oswald, 2002). The CSL corepressor complex also includes a bifunctional cofactor, SKIP, that is present in both CSL corepressor complexes and CSL coactivator complexes, and may function in the binding of NICD and displacement of the corepressor complex during activated Notch signaling (Zhou, 2000).

Mammalian CSL Coactivator Complexes: Upon activation of Notch signaling, cleavage of the transmembrane Notch receptor releases the Notch Intracellular Domain (NICD), which translocates to the nucleus, where it binds to CSL and displaces the corepressor complex from CSL (reviewed in Mumm, 2000 and Kovall, 2007). The resulting CSL-NICD "binary complex" then recruits an additional coactivator, Mastermind (Mam), to form a ternary complex. The ternary complex then recruits additional, more general coactivators, such as CREB Binding Protein (CBP), or the related p300 coactivator, and a number of Histone Acetytransferase (HAT) proteins, including GCN5 and PCAF (Fryer, 2002). There is evidence that Mam also can subsequently recruit specific kinases that phosphorylate NICD, to downregulate its function and turn off Notch signaling (Fryer, 2004).

Combinatorial Complexity in Transcription Cofactor Complexes: HDAC9 has at least 7 splice isoforms, with some having distinct interaction and functional properties. Isoforms 6 and 7 interact with NCOR1. Isoforms 1 and 4 interact with MEF2 (Sparrow, 1999), which is a specific DNA-binding cofactor for a subset of HLH proteins. Isoform 3 interacts with both NCOR1 and MEF2. Although many HDACs only have one or two isoforms, this complexity for HDAC9 illustrates the level of transcript complexity and functional specificity that such "general" transcriptional cofactors can have.

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Editions

2008-02-09	Authored, Edited	Caudy, M.

Nuclear Receptor transcription pathway ↗

Location: Generic Transcription Pathway

Stable identifier: R-HSA-383280

A classic example of bifunctional transcription factors is the family of Nuclear Receptor (NR) proteins. These are DNA-binding transcription factors that bind certain hormones, vitamins, and other small, diffusible signaling molecules. The non-liganded NRs recruit specific corepressor complexes of the NCOR/SMRT type, to mediate transcriptional repression of the target genes to which they are bound. During signaling, ligand binding to a specific domain the NR proteins induces a conformational change that results in the exchange of the associated CoR complex, and its replacement by a specific coactivator complex of the TRAP / DRIP / Mediator type. These coactivator complexes typically nucleate around a MED1 coactivator protein that is directly bound to the NR transcription factor.

A general feature of the 49 human NR proteins is that in the unliganded state, they each bind directly to an NCOR corepressor protein, either NCOR1 or NCOR2 (NCOR2 was previously named "SMRT"). This NCOR protein nucleates the assembly of additional, specific corepressor proteins, depending on the cell and DNA context. The NR-NCOR interaction is mediated by a specific protein interaction domain (PID) present in the NRs that binds to specific cognate PID(s) present in the NCOR proteins. Thus, the human NRs each take part in an NR-NCOR binding reaction in the absence of binding by their ligand.

A second general feature of the NR proteins is that they each contain an additional, but different PID that mediates specific binding interactions with MED1 proteins. In the ligand-bound state, NRs each take part in an NR-MED1 binding reaction to form an NR-MED1 complex. The bound MED1 then functions to nucleate the assembly of additional specific coactivator proteins, depending on the cell and DNA context, such as what specific target gene promoter they are bound to, and in what cell type.

The formation of specific MED1-containing coactivator complexes on specific NR proteins has been well-characterized for a number of the human NR proteins (see Table 1 in (Bourbon, 2004)). For example, binding of thyroid hormone (TH) to the human TH Receptor (THRA or THRB) was found to result in the recruitment of a specific complex of Thyroid Receptor Associated Proteins - the TRAP coactivator complex - of which the TRAP220 subunit was later identified to be the Mediator 1 (MED1) homologue.

Similarly, binding of Vitamin D to the human Vitamin D3 Receptor was found to result in the recruitment of a specific complex of D Receptor Interacting Proteins - the DRIP coactivator complex, of which the DRIP205 subunit was later identified to be human MED1.

Editions

2008-11-20	Authored	Caudy, M.
2009-05-27	Edited	Caudy, M.
2009-08-29	Reviewed	Freedman, LP.

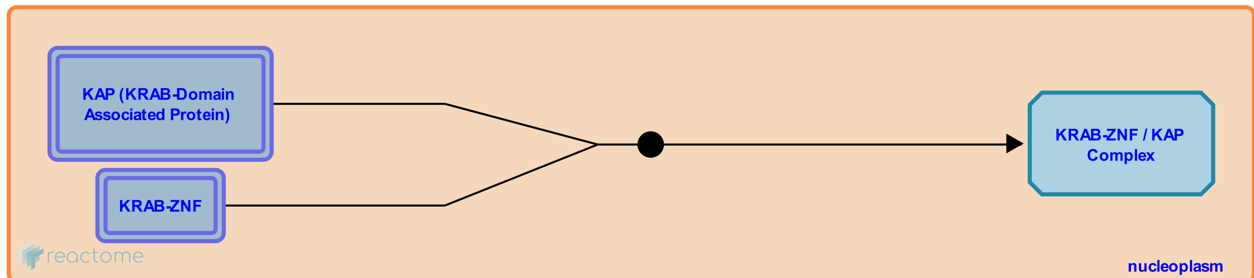
KRAB-ZNF / KAP Interaction ↗

Location: Generic Transcription Pathway

Stable identifier: R-HSA-975040

Type: binding

Compartments: nucleoplasm



Formation of the KRAB ZNF / KAP1 Corepressor Complex:

Transcription factors which contain tandem copies of the C2H2 zinc finger DNA binding motif (ZNFs) are the most abundant class of TFs in the human proteome, comprising more than 1000 members. The KRAB ZNF proteins are the largest subset of these (with 423 members) and are defined by having an additional conserved domain, the KRAB domain (Bellefroid,1991, Margolin, 1994, Urrutia, 2003, Huntley, 2006). The Kruppel Associated Box (KRAB) domain is a transcription repression domain (Margolin, 1994) which mediates the recruitment of a specific and dedicated co repressor protein for the KRAB-ZNF family - KAP1 - which is required for transcriptional repression and gene silencing (Friedman, 1996).

The larger family of ZNF transcription factors are present in almost all metazoans and generally their DNA binding specificities and transcription regulation functions are conserved from Drosophila to humans. Although the biological functions of most ZNF TFs is not known, they often function biochemically as sequence specific DNA binding proteins and can be activators, or more oftenly observed, repressors of transcription, depending on cellular context. Transcriptional repression is mediated via specific protein protein interaction surfaces in the ZNF that function as repression domains, by recruiting specific co repressors, such as KAP1 in humans (Friedman, 1996), and dCTBP in Drosophila (Nibu, 1998).

In contrast to the larger ZNF family, the KRAB-ZNFs only appear much later in vertebrate evolution: genes encoding the primordial KRAB ZNF subfamily first arose in tetrapods and the family has been greatly expanded in numbers and complexity in mammals. Interestingly,a large fraction of KRAB-ZNFs are found only in primates. In addition to their rapid and dynamic evolutionary history, comparative genomics and expression studies of primate KRAB-ZNFs suggest that these genes have played a significant role in shaping primate specific traits (Huntley, 2006, Nowick, 2009).

The biochemical pathway utilized by KRAB-ZNFs is well defined and probably nearly identical for each member: All KRAB-ZNF proteins which have been studied in detail are repressors and utilize the KRAB domain to bind the KAP1 co-repressor. This interaction is direct, of high affinity, and is obligate for the KRAB-ZNF to function as a repressor when bound to DNA in vivo (Peng, 2000a,b).. The KAP1co-repressor appears to function as a scaffold protein to assemble and coordinate multiple enzymes (histone de-acetylases, histone methyltransferases and heterochromatin proteins) which target and modify chromatin structure thus leading to a compacted, silent state (Lechner, 2000; Schultz, 2001 Schultz, 2002 , Ayyanathan, 2003). The post-translational modification of KAP1 by SUMO controls its ability to assemble the enzymatic apparatus in chromatin (Ivanov, 2007; Zeng, 2008). It is formally possible that some KRAB ZNF proteins may have additional functional domains that recruit coactivators in specific contexts, given that such bifunctionality is common for many classes of DNA binding transcription factors,. However, there is no experimental evidence for this yet.

There also is good evidence that the KRAB ZNF-KAP1 complex proteins can have long range gene silencing functions, by nucleating chromatin complexes that inactivate transcription of large numbers of genes over large distances by assembling silent heterochromatin (Ayyanathan, 2003). Although KAP1 was originally identified as a mediator of specific gene transcription repression, subsequent studies have shown that KAP1 also is involved in the recruitment of homologues of the HP1 protein family (Ryan, 1999, Ayyanathan, 2003; Lechner, 2000). These nonhistone heterochromatin associated proteins were first shown to have an epigenetic gene silencing function in

Drosophila and more recently in mammalian cells . These studies suggest that KRAB ZNF proteins and KAP1 may also be involved in large scale chromatin regulation and gene silencing, not just in gene specific transcriptional repression. Whether this is a general property of most or all KRAB ZNF proteins will require additional studies.

Finally, several KRAB containing ZNFs in mammals also contain a conserved SCAN domain which, like the KRAB domain also functions as a protein protein interaction domain. (Edelstein, 2005, Peng, 2000a,b). The SCAN domain does not participate in KAP1 binding but rather functions to mediate homodimerization, or selective heterodimerization with other SCAN containing proteins. However, the biochemical and biological functions of the SCAN domain in KRAB-ZNF mediated repression are not known.

Remaining Questions: The single most important unanswered question for KRAB-ZNFDs is to determine their biological functions. While the mechanism utilized by the KRAB ZNF / KAP1 protein complex to mediate gene specific transcription repression is well understood , much less known about the specific biological pathways they control. Preliminary evidence from recent whole genome analysis of the target genes for the KRAB- ZNF263 protein suggest that it can have both positive and negative effects on transcriptional regulation of its target genes (Frietze, 2010). Presumably, each KRAB-ZNF, via its array of zinc fingers can bind to specific DNA recognition sequences in target promoters. This, combined with highly tissue specific expression of each gene, makes the potential transcriptome controlled by the 423 KRAB-ZNFs extremely large.

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Singh, PB., Fredericks, WJ., Rauscher FJ, 3rd., Ayyanathan, K., Friedman, JR., Schultz, DC. et al. (1999). KAP-1 corepressor protein interacts and colocalizes with heterochromatic and euchromatic HP1 proteins: a potential role for Krüppel-associated box-zinc finger proteins in heterochromatin-mediated gene silencing. *Mol Cell Biol, 19*, 4366-78. ↗

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Editions

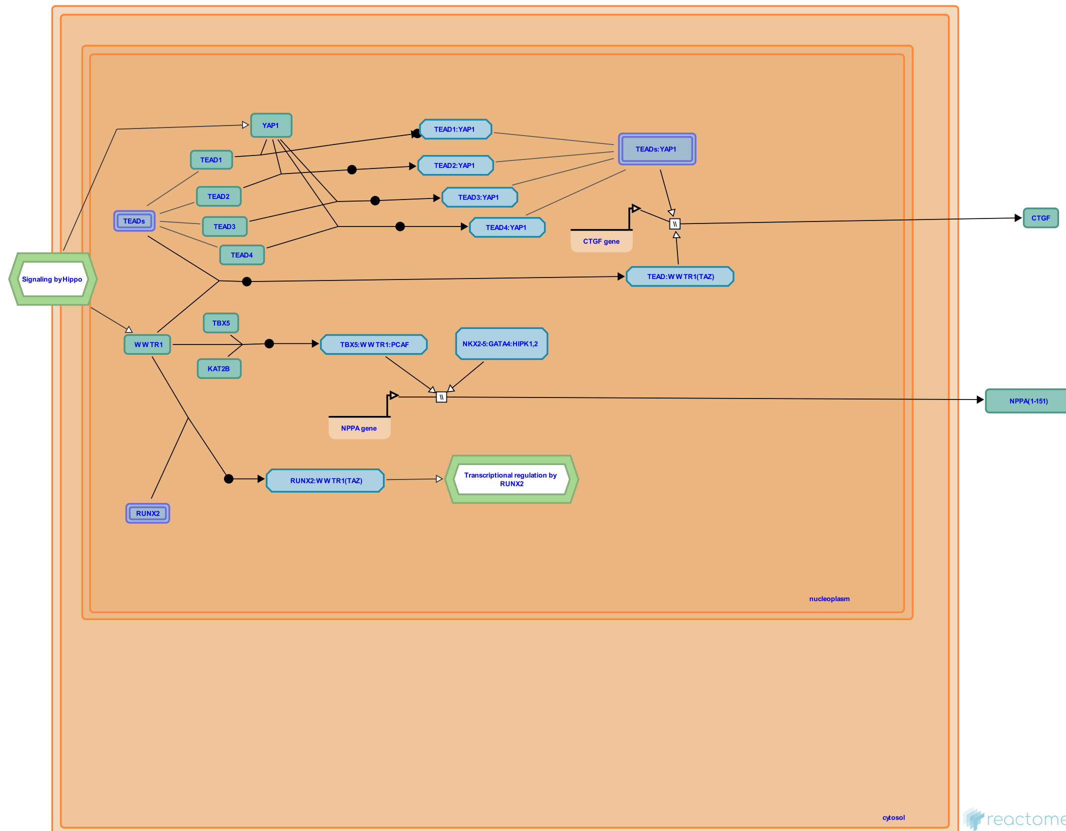
2010-09-22	Authored	Caudy, M.
2010-11-28	Edited	D'Eustachio, P.
2011-02-16	Reviewed	Rauscher, F.
2013-05-13	Revised	Caudy, M.

YAP1- and WWTR1 (TAZ)-stimulated gene expression ↗

Location: Generic Transcription Pathway

Stable identifier: R-HSA-2032785

Compartments: nucleoplasm, cytosol



YAP1 and WWTR1 (TAZ) are transcriptional co-activators, both homologues of the Drosophila Yorkie protein. They both interact with members of the TEAD family of transcription factors, and WWTR1 interacts as well with TBX5 and RUNX2, to promote gene expression. Their transcriptional targets include genes critical to regulation of cell proliferation and apoptosis. Their subcellular location is regulated by the Hippo signaling cascade: phosphorylation mediated by this cascade leads to the cytosolic sequestration of both proteins (Murakami et al. 2005; Oh and Irvine 2010).

Literature references

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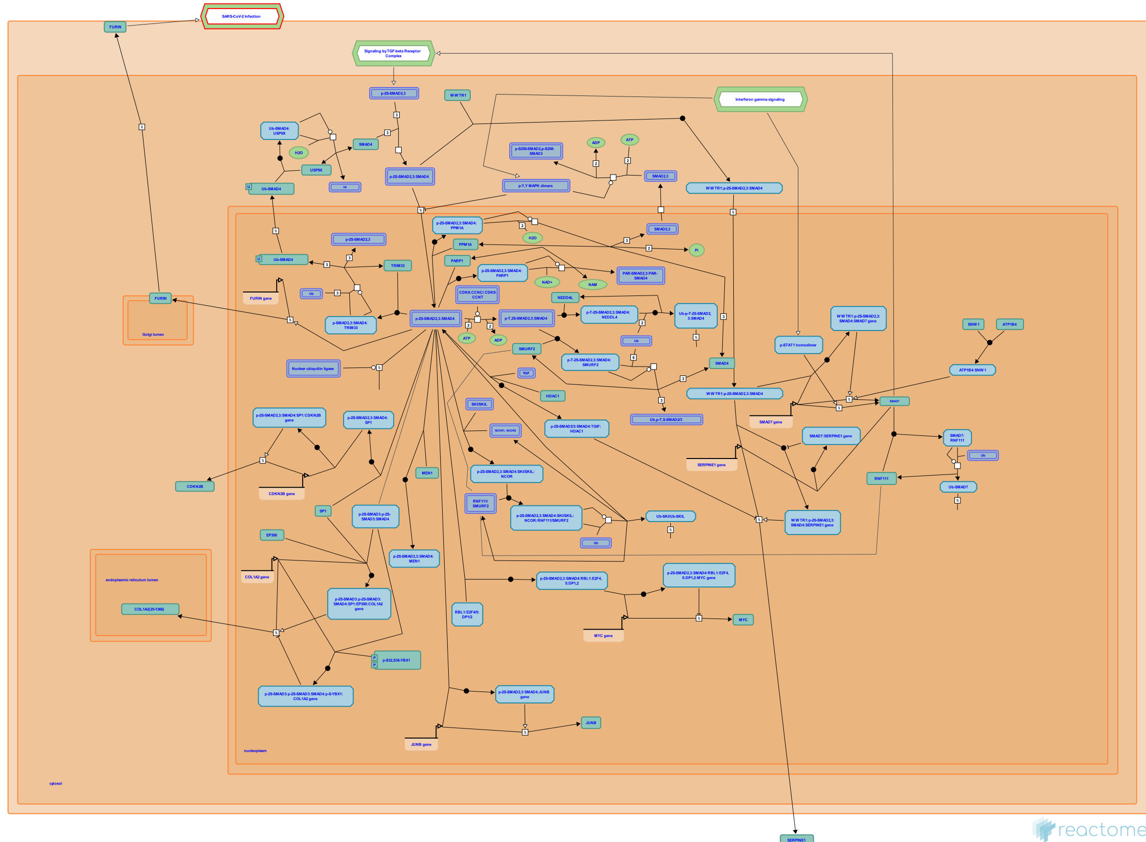
Editions

2012-01-07	Edited	D'Eustachio, P.
2012-02-03	Authored	D'Eustachio, P.
2012-02-03	Reviewed	Sudol, M.

Transcriptional activity of SMAD2/SMAD3:SMAD4 heterotrimer ↗

Location: Generic Transcription Pathway

Stable identifier: R-HSA-2173793



In the nucleus, SMAD2/3:SMAD4 heterotrimer complex acts as a transcriptional regulator. The activity of SMAD2/3 complex is regulated both positively and negatively by association with other transcription factors (Chen et al. 2002, Varelas et al. 2008, Stroschein et al. 1999, Wotton et al. 1999). In addition, the activity of SMAD2/3:SMAD4 complex can be inhibited by nuclear protein phosphatases and ubiquitin ligases (Lin et al. 2006, Dupont et al. 2009).

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Stinchfield, MJ., Montagner, M., Morsut, L., Piccolo, S., Inui, M., Moro, S. et al. (2009). FAM/USP9x, a deubiquitinating enzyme essential for TGFbeta signaling, controls Smad4 monoubiquitination. *Cell, 136*, 123-35. ↗

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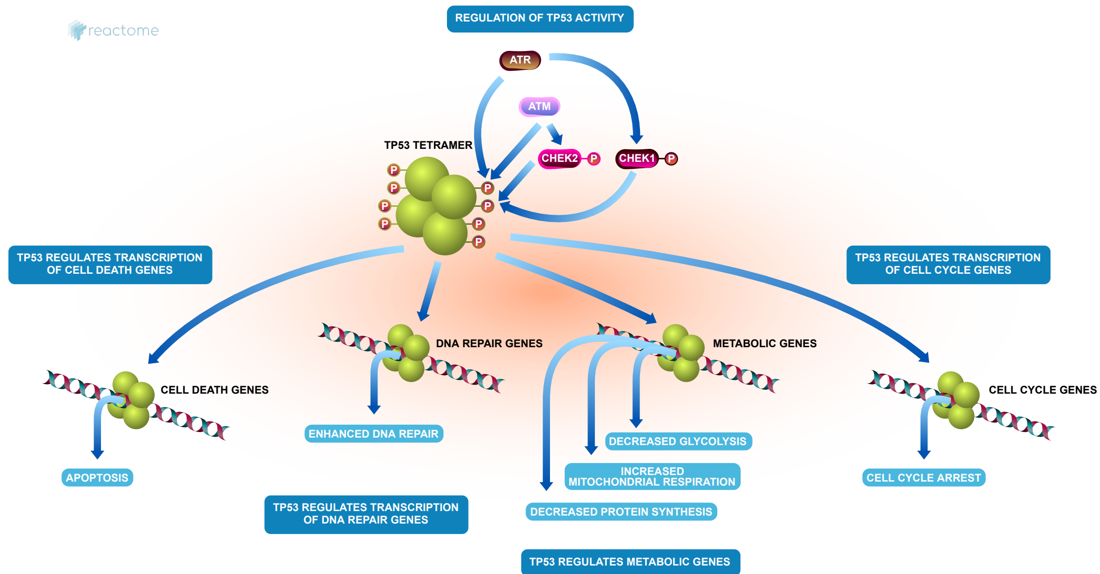
Editions

2012-04-05	Authored	Orlic-Milacic, M.
2012-04-10	Edited	Jassal, B.
2012-05-14	Reviewed	Huang, T.
2012-11-14	Reviewed	Chen, YG.
2022-05-02	Reviewed	Contreras, O.
2022-05-09	Edited	Orlic-Milacic, M.

Transcriptional Regulation by TP53 ↗

Location: Generic Transcription Pathway

Stable identifier: R-HSA-3700989



The tumor suppressor TP53 (encoded by the gene p53) is a transcription factor. Under stress conditions, it recognizes specific responsive DNA elements and thus regulates the transcription of many genes involved in a variety of cellular processes, such as cellular metabolism, survival, senescence, apoptosis and DNA damage response. Because of its critical function, p53 is frequently mutated in around 50% of all malignant tumors. For a recent review, please refer to Vousden and Prives 2009 and Kruiswijk et al. 2015.

Literature references

Kruiswijk, F., Labuschagne, CF., Vousden, KH. (2015). p53 in survival, death and metabolic health: a lifeguard with a licence to kill. *Nat. Rev. Mol. Cell Biol., 16*, 393-405. ↗

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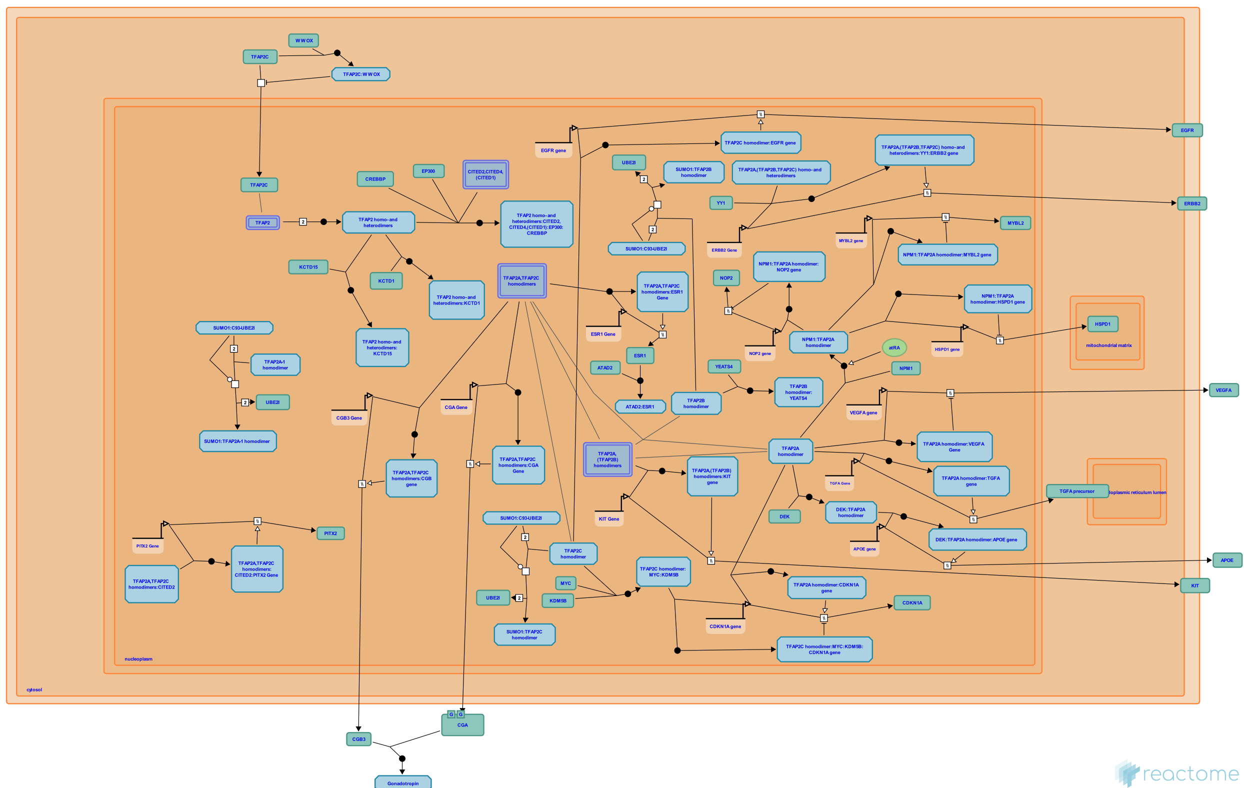
Editions

2015-10-14	Authored, Edited	Orlic-Milacic, M.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

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

Location: Generic Transcription Pathway

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.

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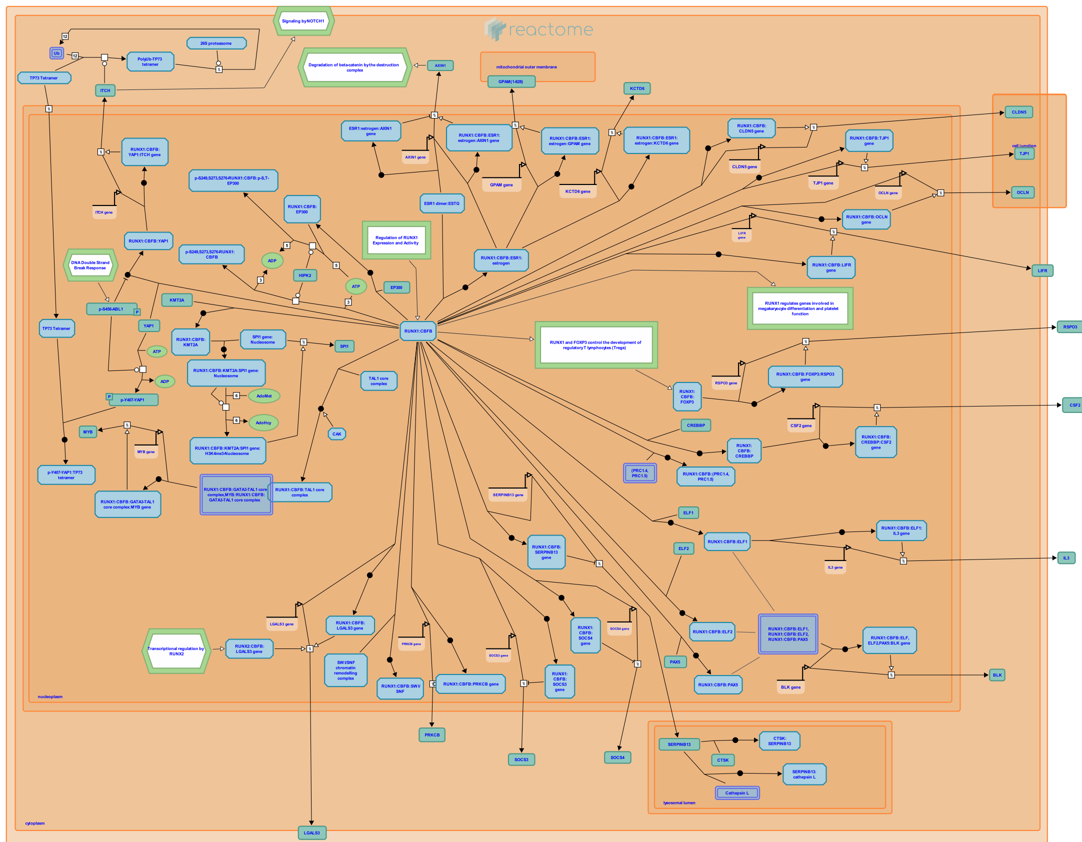
Editions

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

Transcriptional regulation by RUNX1 ↗

Location: Generic Transcription Pathway

Stable identifier: R-HSA-8878171



The RUNX1 (AML1) transcription factor is a master regulator of hematopoiesis (Ichikawa et al. 2004) that is frequently translocated in acute myeloid leukemia (AML), resulting in formation of fusion proteins with altered transactivation profiles (Lam and Zhang 2012, Ichikawa et al. 2013). In addition to RUNX1, its heterodimerization partner CBFB is also frequently mutated in AML (Shigesada et al. 2004, Mangan and Speck 2011).
The core domain of CBFB binds to the Runt domain of RUNX1, resulting in formation of the RUNX1:CBFB heterodimer. CBFB does not interact with DNA directly. The Runt domain of RUNX1 mediated both DNA binding and heterodimerization with CBFB (Tahirov et al. 2001), while RUNX1 regions that flank the Runt domain are involved in transactivation (reviewed in Zhang et al. 2003) and negative regulation (autoinhibition). CBFB facilitates RUNX1 binding to DNA by stabilizing Runt domain regions that interact with the major and minor grooves of the DNA (Tahirov et al. 2001, Backstrom et al. 2002, Bartfeld et al. 2002). The transactivation domain of RUNX1 is located C-terminally to the Runt domain and is followed by the negative regulatory domain. Autoinhibiton of RUNX1 is relieved by interaction with CBFB (Kanno et al. 1998).
Transcriptional targets of the RUNX1:CBFB complex involve genes that regulate self-renewal of hematopoietic stem cells (HSCs) (Zhao et al. 2014), as well as commitment and differentiation of many hematopoietic progenitors, including myeloid (Friedman 2009) and megakaryocytic progenitors (Goldfarb 2009), regulatory T lymphocytes (Wong et al. 2011) and B lymphocytes (Boller and Grosschedl 2014).
RUNX1 binds to promoters of many genes involved in ribosomal biogenesis (Ribi) and is thought to stimulate their transcription. RUNX1 loss-of-function decreases ribosome biogenesis and translation in hematopoietic stem and progenitor cells (HSPCs). RUNX1 loss-of-function is therefore associated with a slow growth, but at the same time it results in reduced apoptosis and increases resistance of cells to genotoxic and endoplasmic reticulum stress, conferring an overall selective advantage to RUNX1 deficient HSPCs (Cai et al. 2015).
RUNX1 is implicated as a tumor suppressor in breast cancer. RUNX1 forms a complex with the activated estrogen receptor alpha (ESR1) and regulates expression of estrogen-responsive genes (Chimge and Frenkel 2013).
RUNX1 is overexpressed in epithelial ovarian carcinoma where it may contribute to cell proliferation, migration and invasion (Keita et al. 2013).
RUNX1 may cooperate with TP53 in transcriptional activation of TP53 target genes upon DNA damage (Wu et al. 2013).
RUNX1 is needed for the maintenance of skeletal musculature (Wang et al. 2005).
During mouse embryonic development, Runx1 is expressed in most nociceptive sensory neurons, which are involved in the perception of pain. In adult mice, Runx1 is expressed only in nociceptive sensory neurons that express the Ret

receptor and is involved in regulation of expression of genes encoding ion channels (sodium-gated, ATP-gated and hydrogen ion-gated) and receptors (thermal receptors, opioid receptor MOR and the Mrgpr class of G protein coupled receptors). Mice lacking Runx1 show defective perception of thermal and neuropathic pain (Chen CL et al. 2006). Runx1 is thought to activate the neuronal differentiation of nociceptive dorsal root ganglion cells during embryonal development possibly through repression of Hes1 expression (Kobayashi et al. 2012). In chick and mouse embryos, Runx1 expression is restricted to the dorso-medial domain of the dorsal root ganglion, to TrkA-positive cutaneous sensory neurons. Runx3 expression in chick and mouse embryos is restricted to ventro-lateral domain of the dorsal root ganglion, to TrkC-positive proprioceptive neurons (Chen AI et al. 2006, Kramer et al. 2006). RUNX1 mediated regulation of neuronally expressed genes will be annotated when mechanistic details become available.

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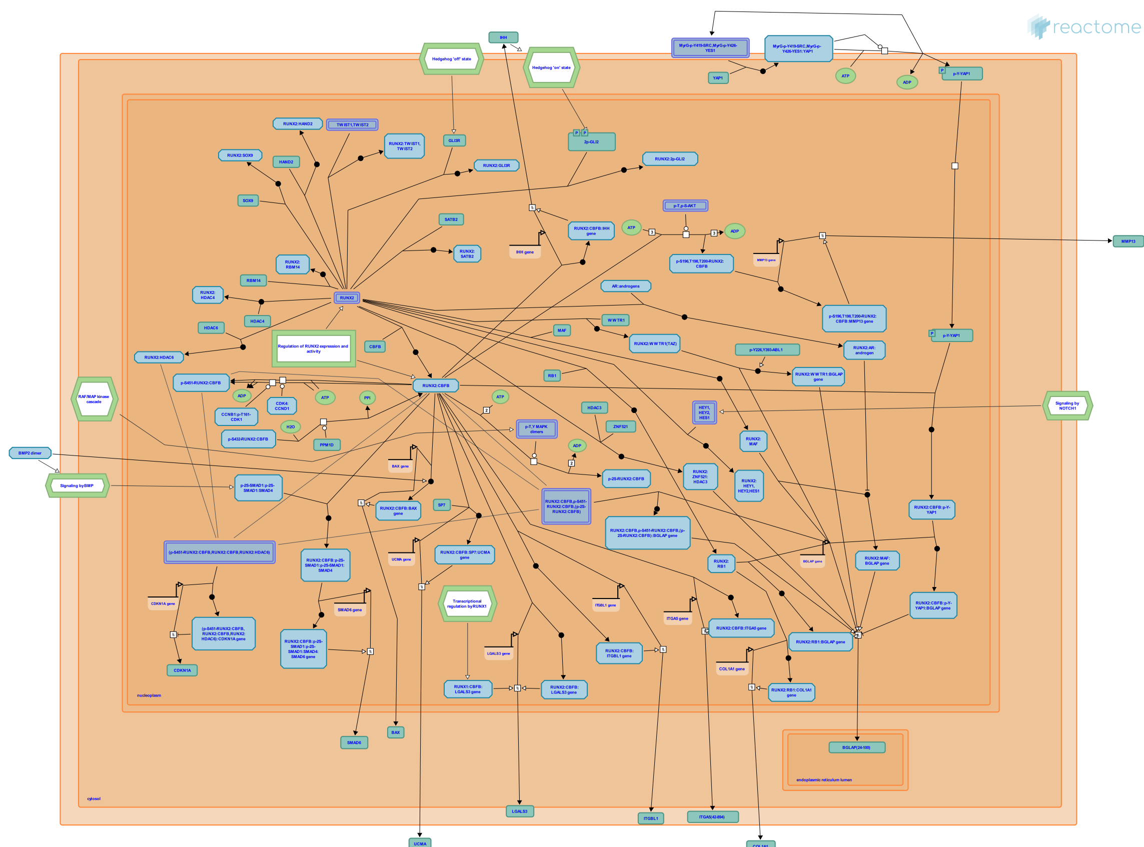
Editions

2016-09-14	Authored	Orlic-Milacic, M.
2016-12-20	Reviewed	Ito, Y., Chuang, LS.
2017-05-09	Edited	Orlic-Milacic, M.

Transcriptional regulation by RUNX2 ↗

Location: Generic Transcription Pathway

Stable identifier: R-HSA-8878166



RUNX2 (CBFA1 or AML3) transcription factor, similar to other RUNX family members, RUNX1 and RUNX3, can function in complex with CBFB (CBF-beta) (Kundu et al. 2002, Yoshida et al. 2002, Otto et al. 2002). RUNX2 mainly regulates transcription of genes involved in skeletal development (reviewed in Karsenty 2008). RUNX2 is involved in development of both intramembraneous and endochondral bones through regulation of osteoblast differentiation and chondrocyte maturation, respectively. RUNX2 stimulates transcription of the BGLAP gene (Ducy and Karsenty 1995, Ducy et al. 1997), which encodes Osteocalcin, a bone-derived hormone which is one of the most abundant non-collagenous proteins of the bone extracellular matrix (reviewed in Karsenty and Olson 2016). RUNX2 directly controls the expression of most genes associated with osteoblast differentiation and function (Sato et al. 1998, Ducy et al. 1999, Roce et al. 2005). RUNX2-mediated transcriptional regulation of several genes involved in GPCR (G protein coupled receptor) signaling is implicated in the control of growth of osteoblast progenitors (Teplyuk et al. 2009). RUNX2 promotes chondrocyte maturation by stimulating transcription of the IHH gene, encoding Indian hedgehog (Takeda et al. 2001, Yoshida et al. 2004). Germline loss-of-function mutations of the RUNX2 gene are associated with cleidocranial dysplasia syndrome (CCD), an autosomal skeletal disorder (reviewed in Jaruga et al. 2016). The function of RUNX2 is frequently disrupted in osteosarcoma (reviewed in Mortus et al. 2014). Vitamin D3 is implicated in regulation of transcriptional activity of the RUNX2:CBFB complex (Underwood et al. 2012).

RUNX2 expression is regulated by estrogen signaling, and RUNX2 is implicated in breast cancer development and metastasis (reviewed in Wysokinski et al. 2014). Besides estrogen receptor alpha (ESR1) and estrogen-related receptor alpha (ERRA) (Kammerer et al. 2013), RUNX2 transcription is also regulated by TWIST1 (Yang, Yang et al. 2011), glucocorticoid receptor (NR3C1) (Zhang et al. 2012), NKX3-2 (BAPX1) (Tribioli and Lufkin 1999, Lengner et al. 2005), DLX5 (Robledo et al. 2002, Lee et al. 2005) and MSX2 (Lee et al. 2005). RUNX2 can autoregulate, by directly inhibiting its own transcription (Drissi et al. 2000). Several E3 ubiquitin ligases target RUNX2 for proteasome-mediated degradation: STUB1 (CHIP) (Li et al. 2008), SMURF1 (Zhao et al. 2003, Yang et al. 2014), WWP1 (Jones et al. 2006), and SKP2 (Thacker et al. 2016). Besides formation of RUNX2:CBFB heterodimers, transcriptional activity of RUNX2 is regulated by binding to a number of other transcription factors, for example SOX9 (Zhou et al. 2006, TWIST1 (Bialek et al. 2004) and RB1 (Thomas et al. 2001).

RUNX2 regulates expression of several genes implicated in cell migration during normal development and bone

metastasis of breast cancer cells. RUNX2 stimulates transcription of the ITGA5 gene, encoding Integrin alpha 5 (Li et al. 2016) and the ITGBL1 gene, encoding Integrin beta like protein 1 (Li et al. 2015). RUNX2 mediated transcription of the MMP13 gene, encoding Colagenase 3 (Matrix metalloproteinase 13), is stimulated by AKT mediated phosphorylation of RUNX2 (Pande et al. 2013). RUNX2 is implicated in positive regulation of AKT signaling by stimulating expression of AKT-activating TORC2 complex components MTOR and RICTOR, which may contribute to survival of breast cancer cells (Tandon et al. 2014).

RUNX2 inhibits CDKN1A transcription, thus preventing CDKN1A-induced cell cycle arrest. Phosphorylation of RUNX2 by CDK4 in response to high glucose enhances RUNX2-mediated repression of the CDKN1A gene in endothelial cells (Pierce et al. 2012). In mice, Runx2-mediated repression of Cdkn1a may contribute to the development of acute myeloid leukemia (AML) (Kuo et al. 2009). RUNX2 can stimulate transcription of the LGALS3 gene, encoding Galectin-3 (Vladimirova et al. 2008, Zhang et al. 2009). Galectin 3 is expressed in myeloid progenitors and its levels increase during the maturation process (Le Marer 2000).

For a review of RUNX2 function, please refer to Long 2012 and Ito et al. 2015.

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Editions

2016-06-30	Authored	Orlic-Milacic, M.
2017-08-04	Reviewed	Ducy, P.
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Transcriptional regulation by RUNX3 ↗

Location: Generic Transcription Pathway

Stable identifier: R-HSA-8878159

The transcription factor RUNX3 is a RUNX family member. All RUNX family members, RUNX1, RUNX2 and RUNX3, possess a highly conserved Runt domain, involved in DNA binding. For a more detailed description of the structure of RUNX proteins, please refer to the pathway 'Transcriptional regulation by RUNX1'. Similar to RUNX1 and RUNX2, RUNX3 forms a transcriptionally active heterodimer with CBFB (CBF-beta). Studies in mice have shown that RUNX3 plays a role in neurogenesis and development of T lymphocytes. RUNX3 is implicated as a tumor suppressor gene in various human malignancies.

During nervous system formation, the Cbfb:Runx3 complex is involved in development of mouse proprioceptive dorsal root ganglion neurons by regulating expression of Ntrk3 (Neurotrophic tyrosine kinase receptor type 3) and possibly other genes (Inoue et al. 2002, Kramer et al. 2006, Nakamura et al. 2008, Dykes et al. 2011, Ogihara et al. 2016). It is not yet known whether RUNX3 is involved in human neuronal development and neuronal disorders.

RUNX3 plays a major role in immune response. RUNX3 regulates development of T lymphocytes. In mouse hematopoietic stem cells, expression of Runx3 is regulated by the transcription factor TAL1 (Landry et al. 2008). RUNX3 promotes the CD8+ lineage fate in developing thymocytes. In the CD4+ thymocyte lineage in mice, the transcription factor ThPOK induces transcription of SOCS family members, which repress Runx3 expression (Luckey et al. 2014). RUNX3, along with RUNX1 and ETS1, is implicated in regulation of transcription of the CD6 gene, encoding a lymphocyte surface receptor expressed on developing and mature T cells (Arman et al. 2009). RUNX3 and ThPOK regulate intestinal CD4+ T cell immunity in a TGF-beta and retinoic acid-dependent manner, which is important for cellular defense against intestinal pathogens (Reis et al. 2013). Besides T lymphocytes, RUNX3 is a key transcription factor in the commitment of innate lymphoid cells ILC1 and ILC3 (Ebihara et al. 2015). RUNX3 regulates expression of CD11A and CD49D integrin genes, involved in immune and inflammatory responses (Dominguez-Soto et al. 2005). RUNX3 is involved in mouse TGF-beta-mediated dendritic cell function and its deficiency is linked to airway inflammation (Fainaru et al. 2004).

In addition to its developmental role, RUNX3 is implicated as a tumor suppressor. The loss of RUNX3 expression and function was first causally linked to the genesis and progression of human gastric cancer (Li et al. 2002). Expression of RUNX3 increases in human pancreatic islet of Langerhans cells but not in pancreatic adenocarcinoma cells in response to differentiation stimulus (serum withdrawal) (Levkovitz et al. 2010). Hypermethylation of the RUNX3 gene is associated with an increased risk for progression of Barrett's esophagus to esophageal adenocarcinoma (Schulmann et al. 2005). Hypermethylation-mediated silencing of the RUNX3 gene expression is also frequent in granulosa cell tumors (Dhillon et al. 2004) and has also been reported in colon cancer (Weisenberger et al. 2006), breast cancer (Lau et al. 2006, Huang et al. 2012), bladder cancer (Wolff et al. 2008) and gastric cancer (Li et al. 2002). In colorectal cancer, RUNX3 is one of the five markers in a gene panel used to classify CpG island methylator phenotype (CIMP+) (Weisenberger et al. 2006).

RUNX3 and CBFB are frequently downregulated in gastric cancer. RUNX3 cooperates with TGF-beta to maintain

homeostasis in the stomach and is involved in TGF-beta-induced cell cycle arrest of stomach epithelial cells. Runx3 knockout mice exhibit decreased sensitivity to TGF-beta and develop gastric epithelial hyperplasia (Li et al. 2002, Chi et al. 2005). RUNX3-mediated inhibition of binding of TEADs:YAP1 complexes to target promoters is also implicated in gastric cancer suppression (Qiao et al. 2016).
RUNX3 is a negative regulator of NOTCH signaling and RUNX3-mediated inhibition of NOTCH activity may play a tumor suppressor role in hepatocellular carcinoma (Gao et al. 2010, Nishina et al. 2011).
In addition to RUNX3 silencing through promoter hypermethylation in breast cancer (Lau et al. 2006), Runx3+/- mice are predisposed to breast cancer development. RUNX3 downregulates estrogen receptor alpha (ESR1) protein levels in a proteasome-dependent manner (Huang et al. 2012).
Besides its tumor suppressor role, mainly manifested through its negative effect on cell proliferation, RUNX3 can promote cancer cell invasion by stimulating expression of genes involved in metastasis, such as osteopontin (SPP1) (Whittle et al. 2015).

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Editions

2016-12-13	Authored	Orlic-Milacic, M.
2017-01-31	Reviewed	Ito, Y., Chuang, LS.
2017-01-31	Edited	Orlic-Milacic, M.

Transcriptional Regulation by VENTX ↗

Location: Generic Transcription Pathway

Stable identifier: R-HSA-8853884

The VENTX (also known as VENT homeobox or VENTX2) gene is a member of the homeobox family of transcription factors. The ortholog of VENTX was first described in Xenopus where it participates in BMP and Nanog signaling pathways and controls dorsoventral mesoderm patterning (Onichtchouk et al. 1996, Scerbo et al. 2012). The zebrafish ortholog of VENTX is also involved in dorsoventral patterning in the early embryo (Imai et al. 2001). Rodents lack the VENTX ortholog (Zhong and Holland 2011). VENTX is expressed in human blood cells (Moretti et al. 2001) and appears to play an important role in hematopoiesis. The role of VENTX in hematopoiesis was first suggested based on its role in mesoderm patterning in Xenopus and zebrafish (Davidson and Zon 2000). VENTX promotes cell cycle arrest and differentiation of hematopoietic stem cells and/or progenitor cells (Wu, Gao, Ke, Giese and Zhu 2011, Wu et al. 2014). Ventx suppression leads to expansion of hematopoietic stem cells and multi-progenitor cells (Gao et, J. Biol.Chem, 2012). VENTX induces transcription of cell cycle inhibitors TP53 (p53) and p16INK4A and activates tumor suppressor pathways regulated by TP53 and p16INK4A (Wu, Gao, Ke, Hager et al. 2011), as well as macrophage colony stimulating factor receptor (CSF1R) (Wu, Gao, Ke, Giese and Zhu 2011) and inhibits transcription of cyclin D1 (CCND1) (Gao et al. 2010) and Interleukin-6 (IL6) (Wu et al. 2014). Chromatin immunoprecipitation showed that EGR3 transcription factor directly binds to the promoter of IL6 and IL8 genes (Baron VT et al, BJC 2015). While VENTX expression may suppress lymphocytic leukemia (Gao et al. 2010), high levels of VENTX have been reported in acute myeloid leukemia cells, with a positive effect on their proliferation (Rawat et al. 2010). Another homeobox transcription factor that regulates differentiation of hematopoietic stemm cells is DLX4 (Bon et al. 2015). Studies on colon cancer showed that VentX regulates tumor associated macrophages and reverts immune suppression in tumor microenvironment (Le et al. 2018). MEK1 is required for Xenopus Ventx2 asymmetric distribution during blastula cell division. Ventx2 inhibition by MEK1 is required for embryonic cell commitment (Scerbo et al, eLife, 2017). VENTX induces TP53-independent apoptosis in cancer cells (Gao H, Oncotarget, 2016). During Xenopus embryonic development, VENTX ortholog regulates transcription of the sox3 gene (Rogers et al. 2007) as well as the early neuronal gene zic3 (Umair et al. 2018).

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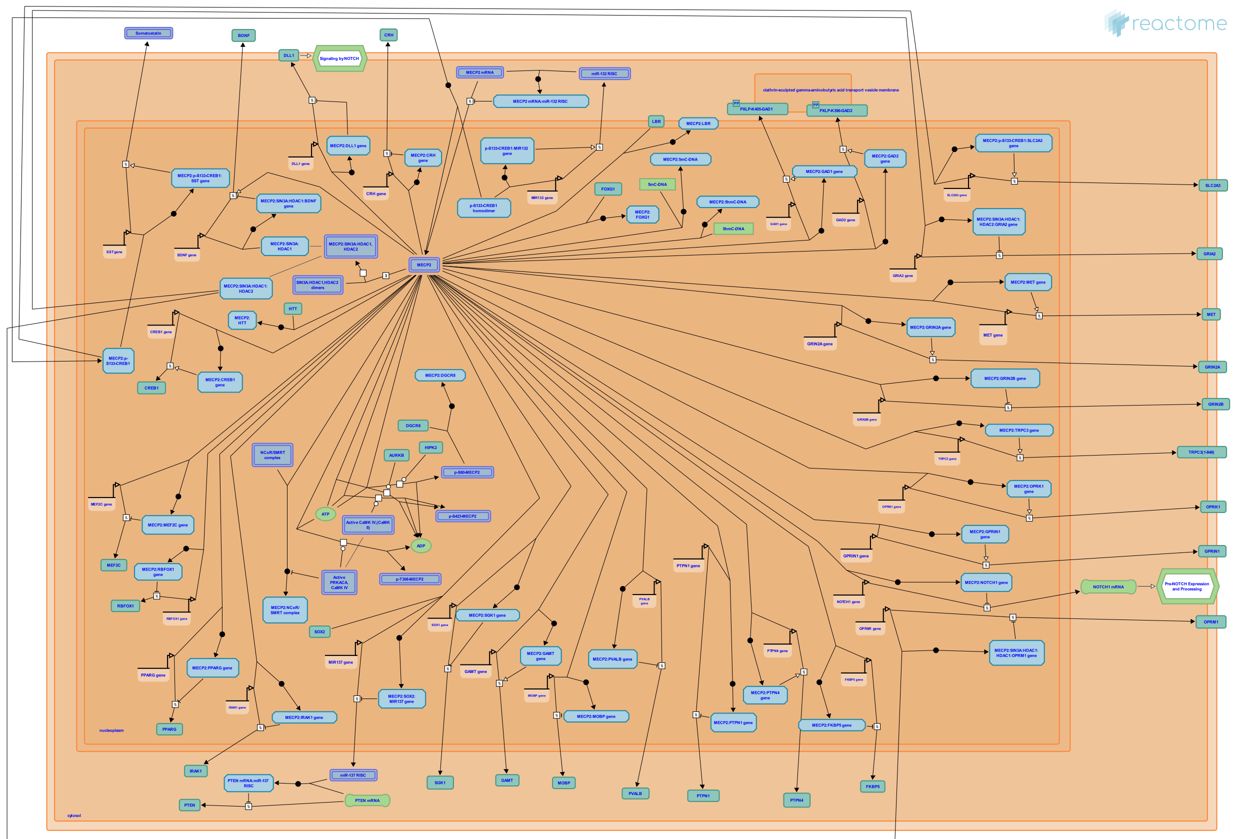
Editions

2019-06-28	Authored	Orlic-Milacic, M.
2019-10-18	Reviewed	Vegi, NM.
2019-11-01	Edited	Orlic-Milacic, M.

Transcriptional Regulation by MECP2 ↗

Location: Generic Transcription Pathway

Stable identifier: R-HSA-8986944



MECP2 is an X chromosome gene whose loss-of-function mutations are an underlying cause of the majority of Rett syndrome cases. The MECP2 gene locus consists of four exons. Both exon 1 and exon 2 contain translation start sites. Alternative splicing of the second exon results in expression of two MECP2 transcript isoforms, MECP2_e1 (MECP2B or MECP2alpha) and MECP2_e2 (MECP2A or MECP2beta). The N-terminus of the MECP2_e1 isoform, in which exon 2 is spliced out, is encoded by exon 1. The N-terminus of the MECP2_e2 isoforms, which includes both exon 1 and exon 2, is encoded by exon 2, as the exon 2 translation start site is used. Exons 3 and 4 are present in both isoforms. The MECP2_e2 isoform was cloned first and is therefore more extensively studied. The MECP2_e1 isoform is more abundant in the brain (Mnatzakanian et al. 2004, Kriaucionis and Bird 2004, Kaddoum et al. 2013). Mecp2 isoforms show different expression patterns during mouse brain development and in adult brain regions (Dragich et al. 2007, Olson et al. 2014). While Rett syndrome mutations mainly occur in exons 3 and 4 of MECP2, thereby affecting both MECP2 isoforms (Mnatzakanian et al. 2004), some mutations occur in exon 1, affecting MECP2_e1 only. No mutations have been described in exon 2 (Gianakopoulos et al. 2012). Knockout of Mecp2_e1 isoform in mice, through a naturally occurring Rett syndrome point mutation which affects the first translation codon of MECP2_e1, recapitulates Rett-like phenotype. Knockout of Mecp2_e2 isoform in mice does not result in impairment of neurologic functions (Yasui et al. 2014). In Mecp2 null mice, transgenic expression of either Mecp2_e1 or Mecp2_e2 prevents development of Rett-like phenotype, with Mecp2_e1 rescuing more Rett-like symptoms than Mecp2_e2. This indicates that both splice variants can fulfill basic Mecp2 functions in the mouse brain (Kerr et al. 2012). Changes in gene expression upon over-expression of either MECP2_e1 or MECP2_e2 imply overlapping as well as distinct target genes (Orlic-Milacic et al. 2014).

Methyl-CpG-binding protein 2 encoded by the MECP2 gene binds to methylated CpG sequences in the DNA. The binding is not generic, however, but is affected by the underlying DNA sequence (Yoon et al. 2003). MECP2 binds to DNA containing 5 methylcytosine (5mC DNA), a DNA modification associated with transcriptional repression (Mellen et al. 2012), both in the context of CpG islands and outside of CpG islands (Chen et al. 2015). In addition, MECP2 binds to DNA containing 5 hydroxymethylcytosine (5hmC DNA), a DNA modification associated with transcriptional activation (Mellen et al. 2012). MECP2 binds to DNA as a monomer, occupying about 11 bp of the DNA. Binding of one MECP2 molecule facilitates binding of the second MECP2 molecule, and therefore clustering can occur at target sites. MECP2 binding to chromatin may be facilitated by nucleosome methylation (Ghosh et al. 2010).

MECP2 was initially proposed to act as a generic repressor of gene transcription. However, high throughput studies of MECP2-induced changes in gene expression in mouse hippocampus (Chahrour et al. 2008), and mouse and human cell lines (Orlic-Milacic et al. 2014) indicate that more genes are up-regulated than down-regulated when MECP2 is overexpressed. At least for some genes directly upregulated by MECP2, it was shown that a complex of MECP2 and CREB1 was involved in transcriptional stimulation (Chahrour et al. 2008, Chen et al. 2013).

MECP2 expression is the highest in postmitotic neurons compared to other cell types, with MECP2 being almost as abundant as core histones. Phosphorylation of MECP2 in response to neuronal activity regulates binding of MECP2 to DNA, suggesting that MECP2 may remodel chromatin in a neuronal activity-dependent manner. The resulting changes in gene expression would then modulate synaptic plasticity and behavior (reviewed by Ebert and Greenberg 2013). In human embryonic stem cell derived Rett syndrome neurons, loss of MECP2 is associated with a significant reduction in transcription of neuronally active genes, as well as the reduction in nascent protein synthesis. The reduction in nascent protein synthesis can at least in part be attributed to the decreased activity of the PI3K/AKT/mTOR signaling pathway. Neuronal morphology (reduced soma size) and the level of protein synthesis in Rett neurons can be ameliorated by treating the cells with growth factors which activate the PI3K/AKT/mTOR cascade or by inhibition of PTEN, the negative regulator of AKT activation. Mitochondrial gene expression is also downregulated in Rett neurons, which is associated with a reduced capacity of the mitochondrial electron transport chain (Ricciardi et al. 2011, Li et al. 2013). Treatment of Mecp2 null mice with IGF1 (insulin-like growth factor 1) reverses or ameliorates some Rett-like features such as locomotion, respiratory difficulties and irregular heart rate (Tropea et al. 2009).

MECP2 regulates expression of a number of ligands and receptors involved in neuronal development and function. Ligands regulated by MECP2 include BDNF (reviewed by Li and Pozzo-Miller 2014, and KhorshidAhmad et al. 2016), CRH (McGill et al. 2006, Samaco et al. 2012), SST (Somatostatin) (Chahrour et al. 2008), and DLL1 (Li et al. 2014). MECP2 also regulates transcription of genes involved in the synthesis of the neurotransmitter GABA – GAD1 (Chao et al. 2010) and GAD2 (Chao et al. 2010, He et al. 2014). MECP2 may be involved in direct stimulation of transcription from the GLUD1 gene promoter, encoding mitochondrial glutamate dehydrogenase 1, which may be involved in the turnover of the neurotransmitter glutamate (Livide et al. 2015). Receptors regulated by MECP2 include glutamate receptor GRIA2 (Qiu et al. 2012), NMDA receptor subunits GRIN2A (Durand et al. 2012) and GRIN2B (Lee et al. 2008), opioid receptors OPRK1 (Chahrour et al. 2008) and OPRM1 (Hwang et al. 2009, Hwang et al. 2010, Samaco et al. 2012), GPRIN1 (Chahrour et al. 2008), MET (Plummer et al. 2013), NOTCH1 (Li et al. 2014). Channels/transporters regulated by MECP2 include TRPC3 (Li et al. 2012) and SLC2A3 (Chen et al. 2013). MECP2 regulates transcription of FKBP5, involved in trafficking of glucocorticoid receptors (Nuber et al. 2005, Urdinguio et al. 2008). MECP2 is implicated in regulation of expression of SEMA3F (semaphorin 3F) in mouse olfactory neurons (Degano et al. 2009). In zebrafish, Mecp2 is implicated in sensory axon guidance by direct stimulation of transcription of Sema5b and Robo2 (Leong et al. 2015). MECP2 may indirectly regulate signaling by neuronal receptor tyrosine kinases by regulating transcription of protein tyrosine phosphatases, PTPN1 (Krishnan et al. 2015) and PTPN4 (Williamson et al. 2015).

MECP2 regulates transcription of several transcription factors involved in functioning of the nervous system, such as CREB1, MEF2C, RBFOX1 (Chahrour et al. 2008) and PPARG (Mann et al. 2010, Joss-Moore et al. 2011).

MECP2 associates with transcription and chromatin remodeling factors, such as CREB1 (Chahrour et al. 2008, Chen et al. 2013), the HDAC1/2-containing SIN3A co-repressor complex (Nan et al. 1998), and the NCoR/SMRT complex (Lyst et al. 2013, Ebert et al. 2013). There are contradictory reports on the interaction of MECP2 with the SWI/SNF chromatin-remodeling complex (Harikrishnan et al. 2005, Hu et al. 2006). Interaction of MECP2 with the DNA methyltransferase DNMT1 has been reported, with a concomitant increase in enzymatic activity of DNMT1 (Kimura and Shiota 2003).

In addition to DNA binding-dependent regulation of gene expression by MECP2, MECP2 may influence gene expression by interaction with components of the DROSHA microprocessor complex and the consequent change in the levels of mature microRNAs (Cheng et al. 2014, Tsujimura et al. 2015).

Increased MECP2 promoter methylation is observed in both male and female autism patients (Nagarajan et al. 2008). Regulatory elements that undergo methylation are found in the promoter and the first intron of MECP2 and their methylation was shown to regulate Mecp2 expression in mice (Liyanage et al. 2013). Mouse Mecp2 promoter methylation was shown to be affected by stress (Franklin et al. 2010).

The Rett-like phenotype of Mecp2 null mice is reversible (Guy et al. 2007), but appropriate levels of Mecp2 expression need to be achieved (Alvarez-Saavedra et al. 2007). When Mecp2 expression is restored in astrocytes of Mecp2 null mice, amelioration of Rett symptoms occurs, involving non-cell-autonomous positive effect on mutant neurons and increasing level of the excitatory glutamate transporter VGLUT1 (Lioy et al. 2011). Microglia derived from Mecp2 null mice releases higher than normal levels of glutamate, which has toxic effect on neurons. Increased

glutamate secretion may be due to increased levels of glutaminase (Gls), involved in glutamate synthesis, and increased levels of connexin-32 (Gjb1), involved in glutamate release, in Mecp2 null microglia (Maezawa and Jin 2010). Targeted deletion of Mecp2 from Sim1-expressing neurons of the mouse hypothalamus recapitulates some Rett syndrome-like features and highlights the role of Mecp2 in feeding behavior and response to stress (Fyffe et al. 2008).

Mecp2 overexpression, similar to MECP2 duplication syndrome, causes neurologic phenotype similar to Rett (Collins et al. 2004, Luikenhuis et al. 2004, Van Esch et al. 2005, Alvarez-Saavedra 2007, Van Esch et al. 2012). The phenotype of the mouse model of the MECP2 duplication syndrome in adult mice is reversible when Mecp2 expression levels are corrected (Sztainberg et al. 2015).

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Editions

2017-10-02	Authored	Orlic-Milacic, M.
2018-08-07	Reviewed	Christodoulou, J., Krishnaraj, R.
2018-08-08	Edited	Orlic-Milacic, M.

Transcriptional Regulation by E2F6 ↗

Location: Generic Transcription Pathway

Stable identifier: R-HSA-8953750

E2F6, similar to other E2F proteins, possesses the DNA binding domain, the dimerization domain and the marked box. E2F6, however, does not have a pocket protein binding domain and thus does not interact with the retinoblastoma family members RB1, RBL1 (p107) and RBL2 (p130) (Gaubatz et al. 1998, Trimarchi et al. 1998, Cartwright et al. 1998). E2F6 lacks the transactivation domain and acts as a transcriptional repressor (Gaubatz et al. 1998, Trimarchi et al. 1998, Cartwright et al. 1998). E2F6 forms a heterodimer with TFDP1 (DP-1) (Trimarchi et al. 1998, Ogawa et al. 2002, Cartwright et al. 1998) or TFDP2 (DP-2) (Gaubatz et al. 1998, Trimarchi et al. 1998, Cartwright et al. 1998).

E2f6 knockout mice are viable and embryonic fibroblasts derived from these mice proliferate normally. Although E2f6 knockout mice appear healthy, they are affected by homeotic transformations of the axial skeleton, involving vertebrae and ribs. Similar skeletal defects have been reported in mice harboring mutations in polycomb genes, suggesting that E2F6 may function in recruitment of polycomb repressor complex(es) to target promoters (Storre et al. 2002).

E2F6 mediates repression of E2F responsive genes. While E2F6 was suggested to maintain G0 state in quiescent cells (Gaubatz et al. 1998, Ogawa et al. 2002), this finding has been challenged (Giangrande et al. 2004, Bertoli et al. 2013, Bertoli et al. 2016). Instead, E2F6-mediated gene repression in proliferating (non-quiescent) cells is thought to repress E2F targets involved in G1/S transition during S phase of the cell cycle. E2F6 does not affect E2F targets involved in G2/M transition (Oberley et al. 2003, Giangrande et al. 2004, Attwooll et al. 2005, Trojer et al. 2011, Bertoli et al. 2013). In the context of the E2F6.com-1 complex, E2F6 was shown to bind to promoters of E2F1, MYC, CDC25A and TK1 genes (Ogawa et al. 2002). E2F6 also binds the promoters of CDC6, RRM1 (RR1), PCNA and TYMS (TS) genes (Giangrande et al. 2004), as well as the promoter of the DHFR gene (Gaubatz et al. 1998). While transcriptional repression by the E2F6.com 1 complex may be associated with histone methyltransferase activity (Ogawa et al. 2002), E2F6 can also repress transcription independently of H3K9 methylation (Oberley et al. 2003).

During S phase, E2F6 is involved in the DNA replication stress checkpoint (Bertoli et al. 2013, Bertoli et al. 2016). Under replication stress, CHEK1-mediated phosphorylation prevents association of E2F6 with its target promoters, allowing transcription of E2F target genes whose expression is needed for resolution of stalled replication forks and restart of DNA synthesis. Inability to induce transcription of E2F target genes (due to CHEK1 inhibition or E2F6 overexpression) leads to replication stress induced DNA damage (Bertoli et al. 2013, Bertoli et al. 2016). E2F6 represses transcription of a number of E2F targets involved in DNA synthesis and repair, such as RRM2, RAD51, BRCA1, and RBBP8 (Oberley et al. 2003, Bertoli et al. 2013).

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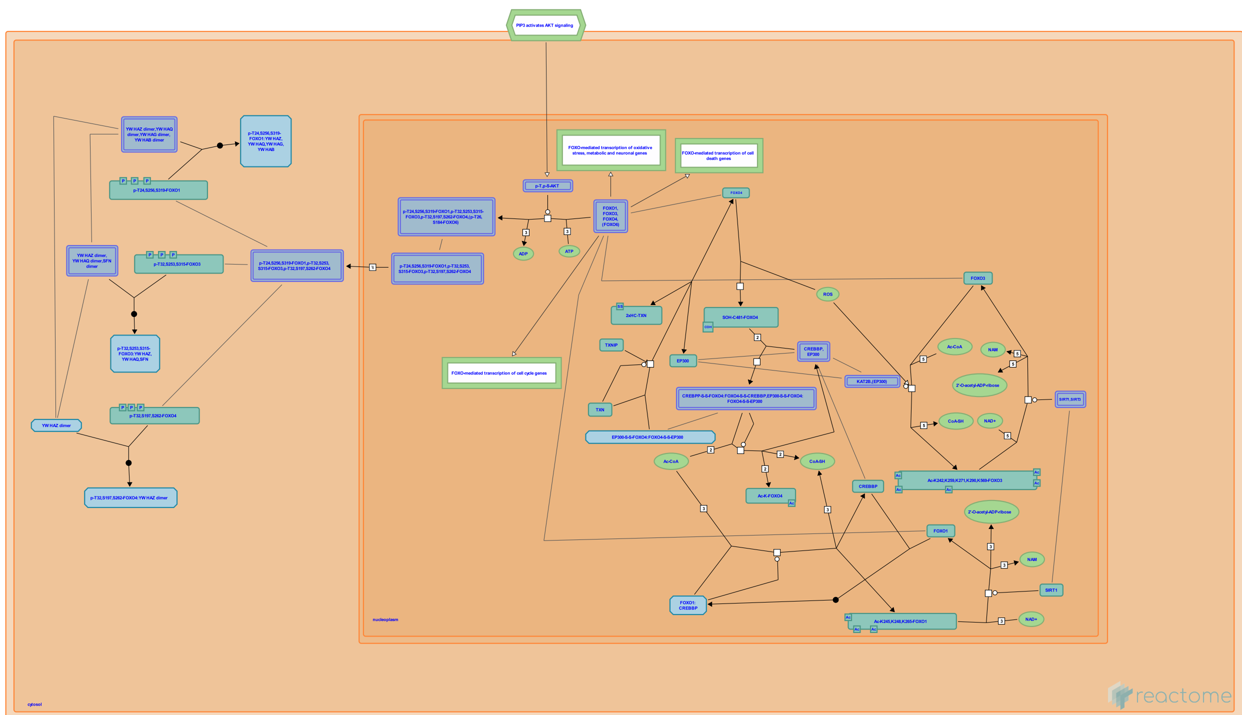
Editions

2017-01-05	Authored	Orlic-Milacic, M.
2017-05-12	Reviewed	Herlihy, A.
2017-06-01	Edited	Orlic-Milacic, M.

FOXO-mediated transcription ↗

Location: Generic Transcription Pathway

Stable identifier: R-HSA-9614085



The family of FOXO transcription factors includes FOXO1, FOXO3, FOXO4 and FOXO6. FOXO transcription factors integrate pathways that regulate cell survival, growth, differentiation and metabolism in response to environmental changes, such as growth factor deprivation, starvation and oxidative stress (reviewed by Accili and Arden 2004, Calnan and Brunet 2008, Eijkelenboom and Burgering 2013).

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Editions

2018-10-11	Authored	Orlic-Milacic, M.
2018-10-17	Reviewed	Donlon, T.
2018-10-26	Reviewed	Bertaggia, E.
2018-10-31	Edited	Orlic-Milacic, M.

Transcriptional Regulation by NPAS4 ↗

Location: Generic Transcription Pathway

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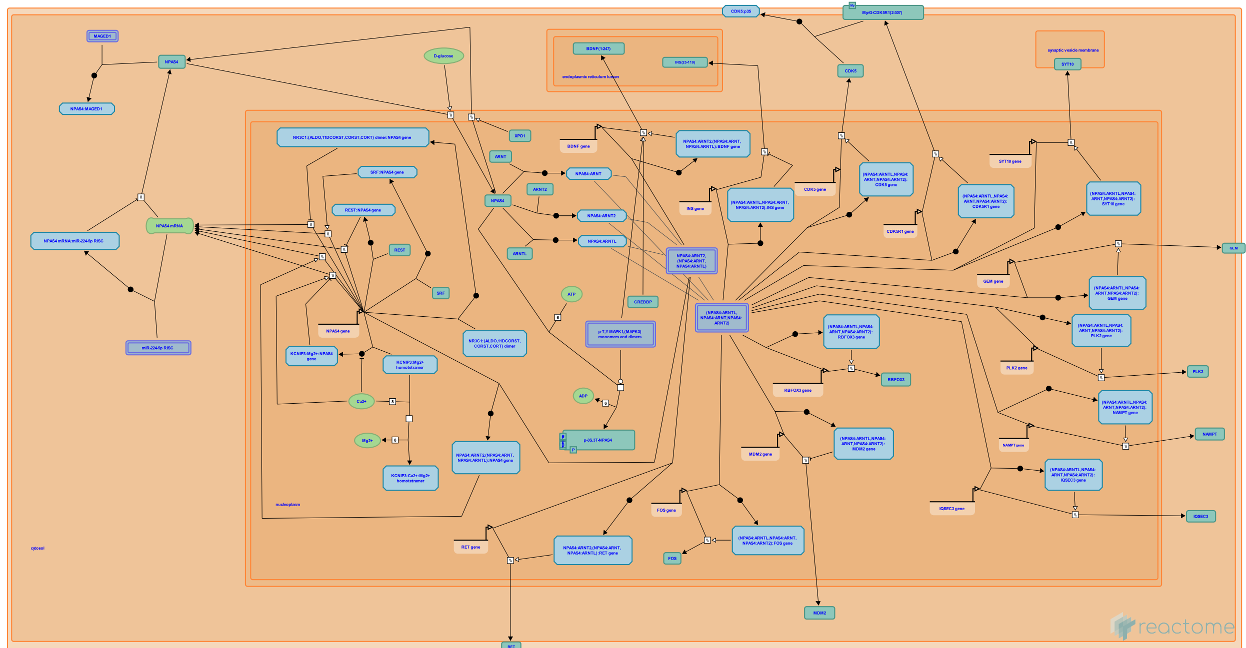

NPAS4 (Neuronal PAS domain containing protein 4) is a calcium dependent transcription factor predominantly expressed in neurons that regulates activation of genes involved in neuronal circuit formation, function, and plasticity (Ooe et al. 2004; Lin et al. 2008; Ramamoorthi et al. 2011; Maya-Vetencourt 2013; Sun and Lin 2016; Weng et al. 2018). NPAS4 possesses a conserved basic helix loop helix (bHLH) motif and a PAS domain (Fahim et al. 2018). NPAS4 is among the most rapidly induced immediate early genes (IEGs), which are activated after sensory and behavioral experience and thought to be crucial for formation of long term memory (Ramamoorthi et al. 2011; Sun et al. 2016; Heslin and Coutellier 2018; Weng et al. 2018). NPAS4 is activated within minutes of neuronal stimulation to regulate the formation of inhibitory synapses (Lin et al. 2008). NPAS4 enables gene regulation to be tailored to the type of depolarizing activity along the somato dendritic axis of a neuron (Brigidi et al. 2019). Transcriptional targets of NPAS4 include transcription factors and proteins involved in signal transduction and protein trafficking (Lin et al. 2008, Brigidi et al. 2019). NPAS4 regulates development of glutamatergic and GABAergic synapses essential for information processing and memory formation (Lin et al. 2008, Weng et al. 2018). NPAS4 induced gene expression programs differ between excitatory and inhibitory neurons (Spiegel et al. 2014), leading to a circuit wide homeostatic response. Besides directly regulating function of neurons, NPAS4 may be involved in the regulation of neuroinflammation and neuronal apoptosis (Zhang et al. 2009; Choy et al. 2015; Fan et al. 2016; Zhang et al. 2021). NPAS4 is expressed in the pancreatic beta cells and regulates their function under stress conditions (Sabatini et al. 2018). For review, please refer to Sun and Lin 2016, and Fu et al. 2020.

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