Transcriptional Regulation by VENTX

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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.

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: 78

This document contains 1 pathway and 13 reactions (see Table of Contents)
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 stem 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 (Skerbo 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).

**Literature references**


\textbf{Editions}

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VENTX binds the IL6 gene promoter

**Location:** Transcriptional Regulation by VENTX

**Stable identifier:** R-HSA-8853890

**Type:** binding

**Compartments:** nucleoplasm

VENTX binds to the NFkB (NF-kappa B) site in the promoter of the Interleukin-6 (IL6) gene, competing with binding of the NFkB complex to the IL6 promoter (Wu et al. 2014).

**Followed by:** Regulation of IL6 transcription

**Literature references**


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Activated CEBPB and NFKB complex bind IL6 promoter

**Location:** Transcriptional Regulation by VENTX

**Stable identifier:** R-HSA-3857305

**Type:** binding

**Compartments:** nucleoplasm

RSK6A1/2/3-mediated phosphorylation of CEBPB downstream of activated RAS stimulates CEBPB homodimerization and DNA binding (Lee, Shuman et al. 2010) and, specifically, RAS-induced CEBPB activation stimulates CEBPB binding to the IL6 promoter (Kuilman et al. 2008; Lee, Shuman et al. 2010). RAS-activated CEBPB is able to recruit additional transcription activators, such as EP300, to the IL6 promoter (Lee, Miller et al. 2010). NFKB transcription complex, activated by interleukin-1-alpha (IL1A) signaling (Jimi et al. 1996, Hartupee et al. 2008, Orjalo et al. 2009), also binds the promoter of the IL6 gene (Shimizu et al. 1990, Libermann and Baltimore 1990) and cooperates with CEBPB in the activation of IL6 transcription (Matsusaka et al. 1993).

**Followed by:** Regulation of IL6 transcription

**Literature references**


## Editions

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Regulation of IL6 transcription

Location: Transcriptional Regulation by VENTX

Stable identifier: R-HSA-3790130

Type: omitted

Compartments: nucleoplasm, extracellular region

Methylation of the IL6 promoter by EHMT1:EHMT2 (GLP:G9a) histone methyltransferases inhibits IL6 transcription, while Cdh1:APC/C-mediated degradation of EHTM1:EHTM2 downstream of the ATM-TP53-CDKN1A axis stimulates IL6 transcription (Takahashi et al. 2012). Oncogenic RAS signaling stimulates activation of the CEBPB transcription factor (C/EBP-beta) which binds IL6 promoter and stimulates IL6 transcription (Kuilman et al. 2008, Lee et al. 2010). NF kappa B transcription factor is also activated in senescent cells (Chien et al. 2011) through interleukin-1-alpha (IL1A) signaling (Jimi et al. 1996, Hartupee et al. 2008, Orjalo et al. 2009), and it cooperates with CEBPB in the activation of IL6 transcription (Shimizu et al. 1990, Libermann and Baltimore 1990, Matsusaka et al. 1993, Acosta et al. 2008). Autocrine IL6 signaling stimulates CEBPB expression (Kuilman et al. 2008), creating a positive feedback loop. STAT3, activated by IL6 signaling cascade is necessary for CEBPB transcription, but the direct binding of STAT3 to the CEBPB promoter has not been demonstrated (Niehof et al. 2001).

VENTX inhibits transcription of the Interleukin-6 (IL6) gene, thus promoting differentiation of primary monocytes into dendritic cells (Wu et al. 2014). The NFKB complex which competes with VENTX for binding to the IL6 gene promoter (Wu et al. 2014). It is not known whether histone H3K9 dimethylation at the VENTX promoter (Takahashi et al. 2012) is involved in VENTX-mediated transcriptional repression of IL6.

Preceded by: VENTX binds the IL6 gene promoter, Activated CEBPB and NFKB complex bind IL6 promoter

Literature references


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VENTX binds the CSF1R (M-CSF-R) gene promoter

**Location:** Transcriptional Regulation by VENTX

**Stable identifier:** R-HSA-8853898

**Type:** binding

**Compartments:** nucleoplasm

VENTX binds to the homeodomain binding site (HDB) in the promoter of the macrophage colony stimulating factor receptor (M-CSFR, CSF1R) gene (Wu et al. 2011).

**Literature references**


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VENTX stimulates CSF1R (M-CSF-R) expression

**Location:** Transcriptional Regulation by VENTX

**Stable identifier:** R-HSA-8853908

**Type:** omitted

**Compartments:** plasma membrane, nucleoplasm

Binding of VENTX to the homeobox domain binding (HDB) site in the promoter of the macrophage colony stimulating factor receptor (M-CSFR, CSF1R) gene results in up-regulation of CSF1R transcription. Expression of CSF1R is necessary for differentiation of monocytes into macrophages (Wu et al. 2011).

**Literature references**


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VENTX binds the TP53 gene promoter

**Location:** Transcriptional Regulation by VENTX

**Stable identifier:** R-HSA-8853915

**Type:** binding

**Compartments:** nucleoplasm

VENTX binds to the promoter of the TP53 (p53) gene (Wu et al. 2011).

**Followed by:** VENTX stimulates TP53 gene expression

**Literature references**


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VENTX stimulates TP53 gene expression

**Location:** Transcriptional Regulation by VENTX

**Stable identifier:** R-HSA-8853911

**Type:** omitted

**Compartments:** nucleoplasm

Binding of VENTX to the promoter of the TP53 (p53) gene stimulates TP53 transcription, resulting in cell cycle arrest that depends on the expression of the downstream TP53 target CDKN1A (Wu et al. 2011). VENTX-mediated cell cycle arrest is implicated as an important step in differentiation of human hematopoietic cells (Gao et al. 2012).

**Preceded by:** VENTX binds the TP53 gene promoter

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VENTX binds the CDKN2A gene

**Location:** Transcriptional Regulation by VENTX

**Stable identifier:** R-HSA-8853920

**Type:** binding

**Compartments:** nucleoplasm

VENTX binds to the CDKN2A promoter that regulates the expression of the p16-INK4A cyclin-dependent kinase inhibitor. Binding of VENTX to an alternative CDKN2A promoter, which regulates the expression of p14-ARF, has not been examined (Wu et al. 2011). CDKN2A locus encodes tumor suppressor genes p16INK4A and p14ARF (p19ARF in mouse). p16INK4A and p14ARF are expressed from different promoters and translated in different reading frames. They use different exon 1 (exon 1-alpha in p16INK4A and exon 1-beta in p14ARF) but share exons 2 and 3. Therefore, while their mRNAs are homologous, they share no similarity at the amino acid sequence level and perform distinct functions in the cell (Quelle et al. 1995).

**Followed by:** VENTX stimulates p16-INK4A transcription

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VENTX stimulates p16-INK4A transcription

**Location:** Transcriptional Regulation by VENTX

**Stable identifier:** R-HSA-8853921

**Type:** omitted

**Compartments:** nucleoplasm


**Preceded by:** VENTX binds the CDKN2A gene

**Followed by:** Translation of p16INK4A mRNA is inhibited by miR-24

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miR-24 binds p16INK4A and p14ARF mRNAs

Location: Transcriptional Regulation by VENTX

Stable identifier: R-HSA-3209151

Type: binding

Compartments: cytosol

MicroRNA miR-24 is able to bind both p16INK4A mRNA (Lal et al. 2008) and p14ARF mRNA (To et al. 2012) through their shared 3'UTR. miR-24 inhibits translation of p16INK4A and p14ARF mRNAs, but does not induce mRNA degradation, resulting in expression of high levels of p16INK4A and p14ARF transcripts, while protein levels of p16INK4A and p14ARF are low (Lal et al. 2008, To et al. 2012).

Followed by: Translation of p16INK4A mRNA is inhibited by miR-24

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Translation of p16INK4A mRNA is inhibited by miR-24

Location: Transcriptional Regulation by VENTX

Stable identifier: R-HSA-3209114

Type: omitted

Compartment: cytosol

MicroRNA miR-24 inhibits translation of p16INK4A mRNA without causing mRNA degradation. This results in high p16INK4A transcript level accompanied by low p16INK4A protein level (Lal et al. 2008). p16INK4A acts as the inhibitor of cyclin-dependent kinases CDK4 and CDK6 which phosphorylate and inhibit RB1 protein thereby promoting G1 to S transition and cell cycle progression (Serrano et al. 1993).

Preceded by: miR-24 binds p16INK4A and p14ARF mRNAs, VENTX stimulates p16-INK4A transcription

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VENTX disrupts binding of CTNNB1 (beta-catenin) to TCF4 or LEF1

**Location:** Transcriptional Regulation by VENTX

**Stable identifier:** R-HSA-8853965

**Type:** transition

**Compartments:** nucleoplasm

VENTX binds to TCF4/LEF1 transcription factors at the cyclin D1 (CCND1) promoter and disrupts the interaction of beta-catenin (CTNNB1) with TCF4 and/or LEF1 (Gao et al. 2010).

**Followed by:** Expression of CCND1 is stimulated by CTNNB1:TCF4,LEF1 and inhibited by VENTX:TCF4,LEF1

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Expression of CCND1 is stimulated by CTNNB1:TCF4,LEF1 and inhibited by VENTX:TCF4,LEF1

**Location:** Transcriptional Regulation by VENTX

**Stable identifier:** R-HSA-8853956

**Type:** omitted

**Compartments:** nucleoplasm

While the complex of beta-catenin (CTNNB1) and TCF4/LEF1 transcription factors stimulates cyclin D1 (CCND1) transcription, binding of VENTX to TCF4 and/or LEF1 results in the inhibition of CCND1 transcription. VENTX is predominantly expressed in hematopoietic cells and its interaction with TCF4/LEF1 is implicated in the inhibition of cellular proliferation induced by WNT signaling (Gao et al. 2010).

**Preceded by:** VENTX disrupts binding of CTNNB1 (beta-catenin) to TCF4 or LEF1

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