Transcriptional regulation by RUNX1

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27/09/2019
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.

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Literature references


Reactome database release: 70

This document contains 13 pathways (see Table of Contents)

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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.

**Literature references**


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Regulation of RUNX1 Expression and Activity

**Location:** Transcriptional regulation by RUNX1

**Stable identifier:** R-HSA-8934593

At the level of transcription, expression of the RUNX1 transcription factor is regulated by two alternative promoters: a distal promoter, P1, and a proximal promoter, P2. P1 is more than 7 kb upstream of P2 (Ghozi et al. 1996). In mice, the Runx1 gene is preferentially transcribed from the proximal P2 promoter during generation of hematopoietic cells from hemogenic endothelium. In fully committed hematopoietic progenitors, the Runx1 gene is preferentially transcribed from the distal P1 promoter (Sroczynska et al. 2009, Bee et al. 2010). In human T cells, RUNX1 is preferentially transcribed from P1 throughout development, while developing natural killer cells transcribe RUNX1 predominantly from P2. Developing B cells transcribe low levels of RUNX1 from both promoters (Telfer and Rothenberg 2001).

RUNX1 mRNAs transcribed from alternative promoters differ in their 5'UTRs and splicing isoforms of RUNX1 have also been described. The function of alternative splice isoforms and alternative 5'UTRs has not been fully elucidated (Challen and Goodell 2010, Komeno et al. 2014).

During zebrafish hematopoiesis, RUNX1 expression increases in response to NOTCH signaling, but direct transcriptional regulation of RUNX1 by NOTCH has not been demonstrated (Burns et al. 2005). RUNX1 transcription also increases in response to WNT signaling. Both TCF7 and TCF4 bind the RUNX1 promoter (Wu et al. 2012, Hoverter et al. 2012), and RUNX1 transcription driven by the TCF binding element (TBE) in response to WNT3A treatment is inhibited by the dominant-negative mutant of TCF4 (Medina et al. 2016). In developing mouse ovary, Runx1 expression is positively regulated by Wnt4 signaling (Naillat et al. 2015).

Studies in mouse hematopoietic stem and progenitor cells imply that RUNX1 may be a direct transcriptional target of HOXB4 (Oshima et al. 2011).

Conserved cis-regulatory elements were recently identified in intron 5 of RUNX1. The RUNX1 breakpoints observed in acute myeloid leukemia (AML) with translocation (8;21), which result in expression of
a fusion RUNX1-ETO protein, cluster in intron 5, in proximity to these not yet fully characterized cis regulatory elements (Rebolledo-Jaramillo et al. 2014).

At the level of translation, RUNX1 expression is regulated by various microRNAs which bind to the 3'UTR of RUNX1 mRNA and inhibit its translation through endonucleolytic and/or nonendonucleolytic mechanisms. MicroRNAs that target RUNX1 include miR-378 (Browne et al. 2016), miR-302b (Ge et al. 2014), miR-18a (Miao et al. 2015), miR-675 (Zhuang et al. 2014), miR-27a (Ben-Ami et al. 2009), miR-17, miR-20a, miR106 (Fontana et al. 2007) and miR-215 (Li et al. 2016).

At the posttranslational level, RUNX1 activity is regulated by postranslational modifications and binding to co-factors. SRC family kinases phosphorylate RUNX1 on multiple tyrosine residues in the negative regulatory domain, involved in autoinhibition of RUNX1. RUNX1 tyrosine phosphorylation correlates with reduced binding of RUNX1 to GATA1 and increased binding of RUNX1 to the SWI/SNF complex, leading to inhibition of RUNX1-mediated differentiation of T-cells and megakaryocytes. SHP2 (PTPN11) tyrosine phosphatase binds to RUNX1 and dephosphorylates it (Huang et al. 2012).

Formation of the complex with CBFB is necessary for the transcriptional activity of RUNX1 (Wang et al. 1996). Binding of CCND3 and probably other two cyclin D family members, CCND1 and CCND2, to RUNX1 inhibits its association with CBFB (Peterson et al. 2005), while binding to CDK6 interferes with binding of RUNX1 to DNA without affecting formation of the RUNX1:CBFB complex. Binding of RUNX1 to PML plays a role in subnuclear targeting of RUNX1 (Nguyen et al. 2005).

RUNX1 activity and protein levels vary during the cell cycle. RUNX1 protein levels increase from G1 to S and from S to G2 phases, with no increase in RUNX1 mRNA levels. CDK1-mediated phosphorylation of RUNX1 at the G2/M transition is implicated in reduction of RUNX1 transactivation potency and may promote RUNX1 protein degradation by the anaphase promoting complex (reviewed by Friedman 2009).

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RUNX1 regulates transcription of genes involved in differentiation of HSCs

Location: Transcriptional regulation by RUNX1

Stable identifier: R-HSA-8939236

The RUNX1:CBFB complex regulates transcription of the SPI1 (PU.1) gene, involved in differentiation of hematopoietic stem cells (HSCs). RUNX1 recruits histone methyltransferase KMT2A (MLL) to the SPI1 gene locus, leading to generation of the activating H3K4Me3 mark on nucleosomes associated with the SPI1 promoter and the upstream regulatory element (Huang et al. 2011). SPI1 transactivation represses self-renewal and proliferation of HSCs (Fukuchi et al. 2008) and is needed for commitment of HSCs to specific hematopoietic lineages (Imperato et al. 2015).

As a component of the TAL1 transcription factor complex, involved in acute T cell lymphoblastic leukemia (T-ALL), RUNX1 can promote growth and inhibit apoptosis of hematopoietic stem cells by stimulating transcription of the MYB gene and possibly the TRIB2 gene (Sanda et al. 2012, Mansour et al. 2014).

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RUNX1 regulates transcription of genes involved in differentiation of myeloid cells

Location: Transcriptional regulation by RUNX1

Stable identifier: R-HSA-8939246

The RUNX1:CBFB complex regulates expression of genes involved in differentiation of myeloid progenitors which can commit to hematopoietic lineages that lead to generation of platelets, erythrocytes, leukocytes or monocytes.

The RUNX1:CBFB complex recruits histone acetyltransferase CREBBP (CBP) to the promoter of the CSF2 gene, encoding Granulocyte-macrophage colony stimulating factor (GM-CSF), thus inducing GM-CSF expression (Oakford et al. 2010). GM-CSF induces growth, differentiation and survival of macrophages, granulocytes, erythrocytes and megakaryocytes from myeloid progenitors (Barreda et al. 2004).

The RUNX1:CBFB complex directly stimulates transcription of the LGALS3 gene, encoding galectin-3 (Zhang et al. 2009). Galectin-3 is expressed in myeloid progenitors and its levels increase during the maturation process (Le Marer 2000).

The PRKCB gene, encoding protein kinase C-beta, which regulates apoptosis of myeloid cells, is directly transactivated by the RUNX1:CBFB complex (Hu et al. 2004).

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RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

**Location:** Transcriptional regulation by RUNX1

**Stable identifier:** R-HSA-8936459

In human hematopoietic progenitors, RUNX1 and its partner CBFB are up-regulated at the onset of megakaryocytic differentiation and down-regulated at the onset of erythroid differentiation. The complex of RUNX1 and CBFB cooperates with the transcription factor GATA1 in the transactivation of megakaryocyte-specific genes. In addition, RUNX1 and GATA1 physically interact (Elagib et al. 2003), and this interaction involves the zinc finger domain of GATA1 (Xu et al. 2006). Other components of the RUNX1:CBFB activating complex at megakaryocytic promoters are GATA1 heterodimerization partner, ZFPM1 (FOG1), histone acetyltransferases EP300 (p300) and KAT2B (PCAF), the WDR5-containing histone methyltransferase MLL complex and the arginine methyltransferase PRMT1 (Herglotz et al. 2013). In the absence of PRMT1, the transcriptional repressor complex can form at megakaryocytic promoters, as RUNX1 that is not arginine methylated can bind to SIN3A/SIN3B co-repressors (Zhao et al. 2008). Besides SIN3A/SIN3B, the RUNX1:CBFB repressor complex at megakaryocytic promoters also includes histone deacetylase HDAC1 and histone arginine methyltransferase PRMT6 (Herglotz et al. 2013).

Megakaryocytic promoters regulated by the described RUNX1:CBFB activating and repressing complexes include ITGA2B, GP1BA, THBS1 and MIR27A (Herglotz et al. 2013). ITGA2B is only expressed in maturing megakaryocytes and platelets and is involved in platelet aggregation (Block and Poncz 1995). GP1BA is expressed at the cell surface membrane of maturing megakaryocytes and platelets and participates in formation of platelet plugs (Cauwenberghs et al. 2000, Jilma-Stohlawetz et al. 2003, Debili et al. 1990). THBS1 homotrimers contribute to stabilization of the platelet aggregate (Bonnefoy and Hoylaerts 2008). MIR27A is a negative regulator of RUNX1 mRNA translation and may be involved in erythroid/megakaryocytic lineage determination (Ben-Ami et al. 2009).

The RUNX1:CBFB complex stimulates transcription of the PF4 gene, encoding a component of platelet al-
pha granules (Aneja et al. 2011), the NR4A3 gene, associated with the familial platelet disorder (FPD) (Bluteau et al. 2011), the PRKCQ gene, associated with inherited thrombocytopenia (Jalagadugula et al. 2011), the MYL9 gene, involved in thrombopoiesis (Jalagadugula et al. 2010), and the NFE2 gene, a regulator of erythroid and megakaryocytic maturation and differentiation (Wang et al. 2010).

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RUNX1 and FOXP3 control the development of regulatory T lymphocytes (Tregs)

Location: Transcriptional regulation by RUNX1

Stable identifier: R-HSA-8877330

The complex of CBFB and RUNX1 (AML1) controls transcription of the FOXP3 gene. FOXP3 is a transcription factor that acts as a key regulator of development and function of regulatory T lymphocytes (Tregs). Tregs are CD25+CD4+ T lymphocytes involved in suppression of aberrant immune responses seen in autoimmune diseases and allergies. FOXP3 can bind to RUNX1 and control transcriptional activity of the RUNX1:CBFB complex. RUNX1 stimulates transcription of IL2 and IFNG1 (IFN-gamma), and the expression of these two genes is repressed upon binding of FOXP3 to RUNX1. The complex of FOXP3 and RUNX1, on the other hand, stimulates transcription of cell surface markers of Tregs, such as CD25, CTLA-4 and GITR. In the absence of FOXP3, RUNX1 represses transcription of these genes (Shevach 2000, Maloy and Powrie 2001, Sakaguchi 2004, Ono et al. 2007, Kitoh et al. 2009).

The RUNX1:CBFB complex directly stimulates transcription of the CR1 gene, encoding Complement receptor type 1 (CD35) (Kim et al. 1999, Rho et al. 2002). Expression of CR1 on the surface of activated T cells contributes to generation of Tregs (Torok et al. 2015).

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RUNX1 regulates transcription of genes involved in BCR signaling

Location: Transcriptional regulation by RUNX1

Stable identifier: R-HSA-8939245

The RUNX1:CBFB complex, in association with transcription co-factors ELF1 (MEF), ELF2 (NERF2) or PAX5 (BSAP) stimulates transcription of the BLK gene, encoding a B-cell specific tyrosine kinase involved in B cell receptor (BCR) signaling, B cell development and differentiation (Libermann et al. 1999, Cho et al. 2004).

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RUNX1 regulates transcription of genes involved in interleukin signaling

Location: Transcriptional regulation by RUNX1

Stable identifier: R-HSA-8939247

The RUNX1:CBFB complex regulates transcription of at least a couple of genes involved in interleukin signaling. The LIFR gene, a direct transcriptional target of the RUNX1:CBFB complex (Qadi et al. 2016), encodes the receptor for the leukemia inhibitory factor (LIF), a member of the interleukin-6 family. LIFR is implicated in hematopoiesis, embryo implantation, placental formation and nervous system development (Nicola et al. 2015). In association with its co-activator ELF1, the RUNX1:CBFB complex stimulates transcription of the IL3 gene, encoding interleukin-3 (Mao et al. 1999).

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The RUNX1:CBFB complex can associate with the activated estrogen receptor alpha (ESR1) through direct interaction between RUNX1 and ESR1. The RUNX1:CBFB complex is thus involved in transcriptional regulation of estrogen responsive genes, including GPAM, KCTD6 and AXIN1 (Stender et al. 2010). High GPAM expression correlates with better overall survival in breast cancer (Brockmoller et al. 2012).

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Brockmoller, SF., Bucher, E., Müller, BM., Budczies, J., Hilvo, M., Griffin, JL. et al. (2012). Integration of metabolomics and expression of glycerol-3-phosphate acyltransferase (GPAM) in breast cancer-link to patient survival, hormone receptor status, and metabolic profiling. *J. Proteome Res.*, 11, 850-60.

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RUNX1 regulates transcription of genes involved in WNT signaling

Location: Transcriptional regulation by RUNX1

Stable identifier: R-HSA-8939256

Compartments: nucleoplasm

The RUNX1:CBFB complex directly regulates transcription of at least two components of WNT signaling. In association with its co-factor FOXP3, the RUNX1:CBFB complex stimulates transcription of the RSPO3 gene, encoding a WNT ligand that is implicated as a breast cancer oncogene (Recouvreux et al. 2016). In association with the activated estrogen receptor alpha (ESR1), the RUNX1:CBFB complex stimulates the expression of AXIN1, which functions as a regulator of WNT signaling (Stender et al. 2010).

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RUNX1 regulates expression of components of tight junctions

Location: Transcriptional regulation by RUNX1

Stable identifier: R-HSA-8935964

Compartments: nucleoplasm

The RUNX1 transcription factor, which functions as part of the RUNX1:CBFB complex, was shown to directly transcriptionally regulate expression of several genes that encode components of tight junctions. Namely, RUNX1 binds to promoters of TJP1 (encoding ZO-1), OCLDN (encoding Occludin) and CLDN5 (encoding Claudin-5) and stimulates their transcription. Downregulation of RUNX1 by microRNA miR-18a negatively regulates expression of these three tight junction genes, which may affect the permeability of blood-tumor barrier in glioma (Miao et al. 2015).

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RUNX1 regulates transcription of genes involved in differentiation of keratinocytes

**Location:** Transcriptional regulation by RUNX1

**Stable identifier:** R-HSA-8939242

The RUNX1:CBFB complex directly inhibits transcription of the SERPINB13 gene (Nomura et al. 2005), a gene involved in keratinocyte differentiation that is frequently down-regulated in head and neck cancers (Boyapati et al. 2011). RUNX1 also inhibits transcription of STAT3 inhibitors SOCS3 and SOCS4, resulting in elevated STAT3 activity. RUNX1-mediated increase in STAT3 activity, first discovered in keratinocytes, is thought to be involved in the maintenance of epithelial stem cells and contributes to development of epithelial cancers, including squamous cell carcinoma (SCC) of the skin (Scheitz et al. 2012).

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RUNX1 interacts with co-factors whose precise effect on RUNX1 targets is not known

**Location:** Transcriptional regulation by RUNX1

**Stable identifier:** R-HSA-8939243

The transcriptional activity of the RUNX1:CBFB complex is regulated by interaction with co-factors and posttranslational modifications of RUNX1. Protein serine/threonine kinase HIPK2 can phosphorylate RUNX1 and affect transcriptional activity of the RUNX1:CBFB complex during hematopoiesis. Some CBFB mutations found in leukemia interfere with HIPK2-mediated phosphorylation of RUNX1. HIPK2 can simultaneously phosphorylate RUNX1 and EP300 (p300) bound to the RUNX1:CBFB1 complex (Aikawa et al. 2006, Wee et al. 2008).

The RUNX1:CBFB complex can associate with the polycomb repressor complex 1 (PRC1). PRC1 complexes are found at many RUNX1 target promoters and can act either as co-activators or co-repressors in the transactivation of RUNX1 targets (Yu et al. 2011).

RUNX1 recruits the SWI/SNF chromatin remodeling complex to many RUNX1 target promoters by directly interacting with several SWI/SNF subunits (Bakshi et al. 2010).

Other co-factors of the RUNX1:CBFB complex are annotated in the context of transcriptional regulation of specific genes.

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