Regulation of RUNX1 Expression and Activity

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30/06/2019
Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 69

This document contains 1 pathway and 19 reactions (see Table of Contents)
Regulation of RUNX1 Expression and Activity

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).

**Literature references**


miR-17 binds RUNX1 mRNA

**Location:** Regulation of RUNX1 Expression and Activity

**Stable identifier:** R-HSA-8938440

**Type:** binding

**Compartments:** cytosol

MicroRNA miR-17 binds the 3' UTR of the RUNX1 mRNA. As miR-17 does not affect RUNX1 mRNA levels, it presumably function as part of the nonendonucleolytic RISC (Fontana et al. 2007).

Followed by: RUNX1 mRNA translation is inhibited by miR-17, miR-18a, miR-20a, miR-27a, miR-106a, miR-215, miR-302b, miR-378 and miR-675

**Literature references**


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miR-18a binds RUNX1 mRNA

Location: Regulation of RUNX1 Expression and Activity

Stable identifier: R-HSA-8935930

Type: binding

Compartments: cytosol

Mature single stranded microRNA miR-18a-5p, one of the two products of miR-18a, encoded by the MIR18A gene, binds to the 3'UTR of RUNX1 mRNA, resulting in decreased RUNX1 mRNA and protein levels. As it affects RUNX1 mRNA levels, miR-18a is assumed to function as a component of the endonucleolytic RISC, but it is possible that it additionally functions as a component of the nonendonuclease RISC (Miao et al. 2015).

Followed by: RUNX1 mRNA translation is inhibited by miR-17, miR-18a, miR-20a, miR-27a, miR-106a, miR-215, miR-302b, miR-378 and miR-675

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miR-20a binds RUNX1 mRNA

**Location:** Regulation of RUNX1 Expression and Activity

**Stable identifier:** R-HSA-8938487

**Type:** binding

**Compartments:** cytosol

MicroRNA miR-20a binds the 3' UTR of the RUNX1 mRNA. As miR-20a does not affect RUNX1 mRNA levels, it presumably function as part of the nonendonucleolytic RISC (Fontana et al. 2007).

**Followed by:** RUNX1 mRNA translation is inhibited by miR-17, miR-18a, miR-20a, miR-27a, miR-106a, miR-215, miR-302b, miR-378 and miR-675

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miR-27a binds RUNX1 mRNA

Location: Regulation of RUNX1 Expression and Activity

Stable identifier: R-HSA-8937134

Type: binding

Compartments: cytosol

MicroRNA miR-27a binds the 3'UTR of the RUNX1 mRNA. As miR-27a inhibits translation of the RUNX1 mRNA without affecting the RUNX1 mRNA stability, miR-27a is assumed to function within the nonendonucleolytic RISC (Ben-Ami et al. 2009).

Followed by: RUNX1 mRNA translation is inhibited by miR-17, miR-18a, miR-20a, miR-27a, miR-106a, miR-215, miR-302b, miR-378 and miR-675

Literature references

miR-106a binds RUNX1 mRNA

Location: Regulation of RUNX1 Expression and Activity

Stable identifier: R-HSA-8938507

Type: binding

Compartments: cytosol

MicroRNA miR-106a binds the 3' UTR of the RUNX1 mRNA. As miR-106a does not affect RUNX1 mRNA levels, it presumably function as part of the nonendonucleolytic RISC (Fontana et al. 2007).

Followed by: RUNX1 mRNA translation is inhibited by miR-17, miR-18a, miR-20a, miR-27a, miR-106a, miR-215, miR-302b, miR-378 and miR-675

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miR-215 binds RUNX1 mRNA

**Location:** Regulation of RUNX1 Expression and Activity

**Stable identifier:** R-HSA-8939129

**Type:** binding

**Compartments:** cytosol

MicroRNA miR-215 binds to the 3’UTR of RUNX1 (Li et al. 2016).

**Followed by:** RUNX1 mRNA translation is inhibited by miR-17, miR-18a, miR-20a, miR-27a, miR-106a, miR-215, miR-302b, miR-378 and miR-675

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miR-302b binds RUNX1 mRNA

**Location:** Regulation of RUNX1 Expression and Activity

**Stable identifier:** R-HSA-8935864

**Type:** binding

**Compartments:** cytosol

Mature single stranded microRNA miR-302b-3p, one of the two products of miR-302b encoded by the MIR302B gene, binds to the 3'UTR of RUNX1 mRNA, which results in decreased RUNX1 mRNA and protein levels. As it affects RUNX1 mRNA levels, miR-302b is assumed to function as a component of the endonucleolytic RISC, but it is possible that it additionally functions as a component of the nonendonucleolytic RISC. Levels of miR-302b are decreased in epithelial ovarian carcinoma (Ge et al. 2014).

**Followed by:** RUNX1 mRNA translation is inhibited by miR-17, miR-18a, miR-20a, miR-27a, miR-106a, miR-215, miR-302b, miR-378 and miR-675

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miR-378 binds RUNX1 mRNA

Location: Regulation of RUNX1 Expression and Activity

Stable identifier: R-HSA-8935766

Type: binding

Compartments: cytosol

The mature microRNA miR-378a-3p, one of the two single strand products derived from microRNA miR-378 encoded by the MIR378 gene locus, binds the 3'UTR of the RUNX1 mRNA. Since miR-378 does not induce RUNX1 mRNA degradation, it is assumed that miR-378 functions as a component of the nonendonucleolytic RISC. Levels of miR-378 are decreased in triple negative breast cancer (Browne et al. 2016).

Followed by: RUNX1 mRNA translation is inhibited by miR-17, miR-18a, miR-20a, miR-27a, miR-106a, miR-215, miR-302b, miR-378 and miR-675

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H19 is cleaved to produce miR-675

Location: Regulation of RUNX1 Expression and Activity

Stable identifier: R-HSA-8936068

Type: omitted

Compartments: nucleoplasm, cytosol

A long non-coding RNA (lncRNA) H19, frequently overexpressed in gastric cancer, functions as a precursor (pri-microRNA) in the production of microRNA miR-675 (Cai and Cullen 2007), which targets and downregulates RUNX1 mRNA, thus interfering with RUNX1 transcription (Zhuang et al. 2014).

Followed by: miR-675 binds RUNX1 mRNA

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miR-675 binds RUNX1 mRNA

Location: Regulation of RUNX1 Expression and Activity

Stable identifier: R-HSA-8936058

Type: binding

Compartments: cytosol

Mature single stranded microRNA miR-675-5p is one of the two products of miR-675, which is produced from a precursor long non-coding RNA H19 (Cai and Cullen 2007). miR-675-5p binds to the 3'UTR of RUNX1 mRNA, resulting in decreased RUNX1 mRNA and protein levels. As it decreases RUNX1 mRNA levels, miR-675 is assumed to function as a component of the endonucleolytic RISC, but it is possible that it additionally functions as a component of the nonendonucleolytic RISC. Levels of miR-675 are increased in gastric cancer (Zhuang et al. 2014).

Preceded by: H19 is cleaved to produce miR-675

Followed by: RUNX1 mRNA translation is inhibited by miR-17, miR-18a, miR-20a, miR-27a, miR-106a, miR-215, miR-302b, miR-378 and miR-675

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RUNX1 mRNA translation is inhibited by miR-17, miR-18a, miR-20a, miR-27a, miR-106a, miR-215, miR-302b, miR-378 and miR-675

Location: Regulation of RUNX1 Expression and Activity

Stable identifier: R-HSA-8935785

Type: omitted

Compartments: cytosol, nucleoplasm

Several microRNAs inhibit RUNX1 mRNA translation without affecting RUNX1 mRNA levels and are thus assumed to function as components of the nonendonucleolytic RISC. These microRNAs include miR 17, miR 20a and miR 106a (Fontana et al. 2007), miR 27a (Ben-Ami et al. 2009), miR 378a (Browne et al. 2016). As RUNX1 directly regulates transcription of the MIR27A gene, RUNX1 and MIR27A constitute a negative feedback loop involved in megakaryocyte differentiation and may regulate the switch between megakaryocytic and erythroid lineages (Ben Ami et al. 2009).

Inhibition of RUNX1 mRNA translation by other microRNAs results in decreased RUNX1 mRNA levels and these microRNAs are therefore assumed to function as components of the endonucleolytic RISC but it is possible that they additionally function as components of nonendonucleolytic RISC. MicroRNAs in this group include miR-18a (Miao et al. 2015), miR-215 (Li et al. 2016), miR-302b (Ge et al. 2014) and miR 675 (Zhuang et al. 2014).

MicroRNA miR 215 binding to the 3'UTR of RUNX1 mRNA inhibits RUNX1 mRNA translation and reduces RUNX1 mRNA levels (Li et al. 2016).

Preceded by: miR-378 binds RUNX1 mRNA, miR-302b binds RUNX1 mRNA, miR-18a binds RUNX1 mRNA, miR-675 binds RUNX1 mRNA, miR-215 binds RUNX1 mRNA, miR-17 binds RUNX1 mRNA, miR-20a binds RUNX1 mRNA, miR-27a binds RUNX1 mRNA, miR-106a binds RUNX1 mRNA

Followed by: RUNX1 binds SRC, CBFB binds RUNX1, CDK6 binds RUNX1, CCND3,(CCND1,CCND2) binds RUNX1, PML binds RUNX1

Literature references


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RUNX1 binds SRC

**Location:** Regulation of RUNX1 Expression and Activity

**Stable identifier:** R-HSA-8937682

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Runx1 binds Src (Mus musculus)

Based on studies in mouse megakaryocytes and T cells, RUNX1 forms a complex with SRC in the nucleus (Huang et al. 2012).

**Preceded by:** RUNX1 mRNA translation is inhibited by miR-17, miR-18a, miR-20a, miR-27a, miR-106a, miR-215, miR-302b, miR-378 and miR-675

**Followed by:** SRC phosphorylates RUNX1

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Based on studies in developing mouse megakaryocytes and T cells, SRC phosphorylates RUNX1 at seven tyrosine residues in the negative regulatory domain (Y254, Y258, Y260, Y376, Y379, Y380 and Y387). Endogenous human RUNX1 is tyrosine phosphorylated, and tyrosine residues in murine Runx1 that are phosphorylated by Src are conserved in human RUNX1. SRC-mediated phosphorylation interferes with binding of RUNX1 to GATA1, thus negatively regulating differentiation of hematopoietic progenitors. SRC-mediated phosphorylation promotes association of RUNX1 with the SWI/SNF complex (Huang et al. 2012).

**Preceded by:** RUNX1 binds SRC

**Followed by:** PTPN11 binds p-7Y-RUNX1

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PTPN11 binds p-7Y-RUNX1

**Location:** Regulation of RUNX1 Expression and Activity

**Stable identifier:** R-HSA-8937744

**Type:** binding

**Compartments:** nucleoplasm

Based on mouse studies, tyrosine phosphorylated RUNX1 forms a complex with PTPN11 (SHP2) protein tyrosine phosphatase in the nucleus (Huang et al. 2012).

**Preceded by:** SRC phosphorylates RUNX1

**Followed by:** PTPN11 dephosphorylates RUNX1

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PTPN11 dephosphorylates RUNX1

Location: Regulation of RUNX1 Expression and Activity

Stable identifier: R-HSA-8937767

Type: transition

Compartments: nucleoplasm

Based on mouse studies, PTPN11 (SHP2) protein tyrosine phosphatase dephosphorylates SRC-phosphorylated RUNX1 (Huang et al. 2012).

Preceded by: PTPN11 binds p-7Y-RUNX1

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CDK6 binds RUNX1

Location: Regulation of RUNX1 Expression and Activity

Stable identifier: R-HSA-8938853

Type: binding

Compartments: nucleoplasm

CDK6 binds to the Runt domain of RUNX1 and interferes with RUNX1 binding to DNA and transcription co-factors. Formation of the RUNX1:CBFB complex does not affect the ability of CDK6 to interact with RUNX1. Neither the catalytic activity nor the cyclin-binding activity of CDK6 are required for its association with RUNX1 (Fujimoto et al. 2007).

Preceded by: RUNX1 mRNA translation is inhibited by miR-17, miR-18a, miR-20a, miR-27a, miR-106a, miR-215, miR-302b, miR-378 and miR-675, CBFB binds RUNX1

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CCND3, (CCND1, CCND2) binds RUNX1

**Location:** Regulation of RUNX1 Expression and Activity

**Stable identifier:** R-HSA-8938867

**Type:** binding

**Compartments:** nucleoplasm

Cyclin D3 (CCND3) binds to the runt domain and the activation domain (AD) of RUNX1, thus inhibiting RUNX1 association with CBFB and RUNX1 binding to DNA. Based on in vitro studies, cyclins D1 (CCND1) and D2 (CCND2) can also bind to RUNX1 (Peterson et al. 2005).

**Preceded by:** RUNX1 mRNA translation is inhibited by miR-17, miR-18a, miR-20a, miR-27a, miR-106a, miR-215, miR-302b, miR-378 and miR-675

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**PML binds RUNX1**

**Location:** Regulation of RUNX1 Expression and Activity

**Stable identifier:** R-HSA-8938887

**Type:** binding

**Compartments:** nucleoplasm

RUNX1 interacts with PML, and the interaction involves the C-terminus of PML and the C-terminus of RUNX1. PML targets RUNX1 to nuclear bodies, which may be important for activation of some RUNX1 target genes, such as CSF2 (GM-CSF) (Nguyen et al. 2005).

**Preceded by:** RUNX1 mRNA translation is inhibited by miR-17, miR-18a, miR-20a, miR-27a, miR-106a, miR-215, miR-302b, miR-378 and miR-675

**Literature references**


**Editions**

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The heterodimerization domain of CBFB binds to the Runt domain of RUNX1 (AML1) to form a RUNX1:CBFB heterodimer (Warren et al. 2000, Lukasik et al. 2002). Formation of the RUNX1:CBFB heterodimer was first demonstrated in Drosophila (Ogawa et al. 1993). While RUNX1 is the DNA binding subunit, the presence of CBFB is necessary for the transcriptional activity of the RUNX1:CBFB complex, based on knockout mouse studies (Wang et al. 1996).

The RUNX1:CBFB transcription complex is essential for hematopoiesis (Warren et al. 2000).

Both CBFB and RUNX1 are subject to frequent mutations in leukemia (Ustun and Marcucci 2015).

**Preceded by:** RUNX1 mRNA translation is inhibited by miR-17, miR-18a, miR-20a, miR-27a, miR-106a, miR-215, miR-302b, miR-378 and miR-675

**Followed by:** CDK6 binds RUNX1

### Literature references


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</tr>
</tbody>
</table>
# Table of Contents

- **Introduction** 1
- **Regulation of RUNX1 Expression and Activity** 2
  - miR-17 binds RUNX1 mRNA 4
  - miR-18a binds RUNX1 mRNA 5
  - miR-20a binds RUNX1 mRNA 6
  - miR-27a binds RUNX1 mRNA 7
  - miR-106a binds RUNX1 mRNA 8
  - miR-215 binds RUNX1 mRNA 9
  - miR-302b binds RUNX1 mRNA 10
  - miR-378 binds RUNX1 mRNA 11
  - H19 is cleaved to produce miR-675 12
  - miR-675 binds RUNX1 mRNA 13
  - RUNX1 mRNA translation is inhibited by miR-17, miR-18a, miR-20a, miR-27a, miR-106a, miR-215, miR-302b, miR-378 and miR-675 14
- RUNX1 binds SRC 16
- SRC phosphorylates RUNX1 17
- PTPN11 binds p-7Y-RUNX1 18
- PTPN11 dephosphorylates RUNX1 19
- CDK6 binds RUNX1 20
- CCND3,(CCND1,CCND2) binds RUNX1 21
- PML binds RUNX1 22
- CBFB binds RUNX1 23

Table of Contents 24