RUNX1 regulates genes involved in mega-karyocyte differentiation and platelet function

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12/09/2020
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: 73

This document contains 1 pathway and 33 reactions (see Table of Contents)
RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

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-Stohlwetz 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 alpha 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).

**Literature references**


**Editions**

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RUNX1 binds PRMT1

Location: RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

Stable identifier: R-HSA-8934742

Type: binding

Compartments: nucleoplasm

RUNX1 forms a complex with protein arginine methyltransferase 1 (PRMT1) in a RNA- and DNA-independent manner. The interaction with PRMT1 involves the C-terminus of RUNX1. Since PRMT1 colocalizes with RUNX1 at RUNX1 target promoters, RUNX1 is shown as part of the RUNX1:CBFB complex (Zhao et al. 2008).

Followed by: PRMT1 arginine-methylates RUNX1

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PRMT1 arginine-methylates RUNX1

Location: RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

Stable identifier: R-HSA-8934735

Type: transition

Compartments: nucleoplasm

Protein arginine methyltransferase 1 (PRMT1) methylates arginine residues R206 and R210 of RUNX1. Methylation of R206 and R210 inhibits binding of co-repressors to RUNX1, thus enhancing RUNX1 transcriptional activity (Zhao et al. 2008). In mice, arginine methylation seems to be dispensable for the function of RUNX1 in definitive hematopoiesis and steady-state platelet production, but is needed for the maintenance of the peripheral population of CD4+ T cells (Mizutani et al. 2015).

Preceded by: RUNX1 binds PRMT1

Followed by: RUNX1 and GATA1 bind the promoter of the ITGA2B gene, RUNX1 and GATA1 bind the promoter of the GP1BA gene, RUNX1 and GATA1 bind the promoter of the THBS1 gene, RUNX1 and GATA1 bind the promoter of the MIR27A gene

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RUNX1 and GATA1 bind the promoter of the ITGA2B gene ➼

Location: RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

Stable identifier: R-HSA-8935740

Type: binding

Compartments: nucleoplasm

The RUNX1:CBFB complex can bind to the promoter of the ITGA2B (CD41) gene, encoding Integrin alpha-IIb, both in the absence and in the presence of PRMT1. PRMT1-mediated arginine-methylation significantly increases transcriptional activity of the RUNX1:CBFB complex at the ITGA2B promoter (Zhao et al. 2008). In addition to the RUNX1:CBFB complex, the complex of GATA1 and ZFPM1 (FOG1) (Freson et al. 2003) is also recruited to the ITGA2B promoter (Herglotz et al. 2013), likely through the interaction between GATA1 and RUNX1 (Elagib et al. 2003). The zinc finger domain of GATA1 is involved in binding to RUNX1 (Xu et al. 2006). Along with RUNX1 and GATA1, histone acetyltransferases p300 (EP300) and PCAF (KAT2B), as well as the WDR5-containing histone methyltransferase MLL complexes are also recruited to the ITGA2B promoter (Herglotz et al. 2013). Dimethylation of histone H3 on lysine residue K4 (K5 when taking into account the initiator methionine), known as the H3K4me2 mark, is characteristic of nucleosomes associated with megakaryocyte specific promoters, including the ITGA2B gene, prior to the onset of differentiation (Herglotz et al. 2013).

Preceded by: PRMT1 arginine-methylates RUNX1

Followed by: ITGA2B gene transcription is stimulated by the complex of RUNX1, GATA1 and PRMT1 and inhibited by the complex of RUNX1, SIN3A and PRMT6, Core MLL complex methylates H3K4Me2-Nucleosome at the ITGA2B gene promoter

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Core MLL complex methylates H3K4Me2-Nucleosome at the ITGA2B gene promoter

**Location:** RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

**Stable identifier:** R-HSA-8936481

**Type:** transition

**Compartments:** nucleoplasm

The WDR5-containing histone methyltransferase MLL complex, recruited to the ITGA2B promoter via RUNX1 (and possibly GATA1), methylates histone H3 on dimethylated lysine residue K4 (K5 when taking into account the initiator methionine), producing the H3K4me3 mark. The H3K4me3 mark is characteristic of nucleosomes associated with transcriptionally active promoters of megakaryocyte-specific genes (Herglotz et al. 2013).

**Preceded by:** RUNX1 and GATA1 bind the promoter of the ITGA2B gene

**Literature references**

RUNX1 binds SIN3A,(SIN3B) co-repressor

Location: RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

Stable identifier: R-HSA-8935732

Type: binding

Compartments: nucleoplasm

The RUNX1:CBFB complex can bind to transcriptional co-repressors SIN3A and SIN3B. The interaction with SIN3A has been studied in more detail. Binding to SIN3A leads to transcriptional repression of RUNX1 target genes, which may involve SIN3A-mediated recruitment of histone deacetylases (HDACs) to target promoters (Lutterbach et al. 2000). Arginine methylation of RUNX1 by PRMT1 inhibits association of RUNX1 with SIN3A (Zhao et al. 2008). RUNX1 transcriptional repressor complex with SIN3A also includes histone arginine methyltransferase PRMT6 and HDAC1 (Herglotz et al. 2013).

Followed by: RUNX1:CBFB, SIN3A(SIN3B), PRMT6 and HDAC1 bind the ITGA2B promoter

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RUNX1:CBFB, SIN3A(SIN3B), PRMT6 and HDAC1 bind the ITGA2B promoter

**Location:** RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

**Stable identifier:** R-HSA-8935730

**Type:** binding

**Compartments:** nucleoplasm

The transcriptional co-repressor SIN3A (and possibly SIN3B) can bind to the RUNX1:CBFB complex at the promoter of the ITGA2B (CD41) gene, encoding Integrin alpha IIb. Binding of SIN3A (and probably SIN3B) to RUNX1 is inhibited by PRMT1-mediated arginine methylation of RUNX1 arginine residues R206 and R210 (Zhao et al. 2008). In addition to SIN3A, the RUNX1-containing transcriptional repressor complex at the ITGA2B promoter also includes histone arginine methyltransferase PRMT6 and histone deacetylase HDAC1 (Herglotz et al. 2013). Dimethylation of histone H3 on lysine residue K4 (K5 when taking into account the initiator methionine), known as the H3K4me2 mark, is characteristic of nucleosomes associated with megakaryocyte specific promoters, including the ITGA2B gene, prior to the onset of differentiation (Herglotz et al. 2013).

**Preceded by:** RUNX1 binds SIN3A,(SIN3B) co-repressor

**Followed by:** PRMT6 arginine methylates H3K4me2-Nucleosome at the ITGA2B gene promoter

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**PRMT6 arginine methylates H3K4me2-Nucleosome at the ITGA2B gene promoter**

**Location:** RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

**Stable identifier:** R-HSA-8936584

**Type:** transition

**Compartments:** nucleoplasm

The histone arginine methyltransferase PRMT6 asymmetrically dimethylates histone H3 on arginine residue R2 (R3 when taking into account the initiator methionine), thus creating the H3R2me2a mark on nucleosomes at the ITGA2B gene promoter. Histone H3 arginine methylation by PRMT6 interferes with methylation of H3K4me2 to generate the activating H3K4me3 mark at the ITGA2B gene promoter, thus contributing to transcriptional repression (Herglotz et al. 2013).

**Preceded by:** RUNX1:CBFB, SIN3A(SIN3B), PRMT6 and HDAC1 bind the ITGA2B promoter

**Followed by:** ITGA2B gene transcription is stimulated by the complex of RUNX1, GATA1 and PRMT1 and inhibited by the complex of RUNX1, SIN3A and PRMT6

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ITGA2B gene transcription is stimulated by the complex of RUNX1, GATA1 and PRMT1 and inhibited by the complex of RUNX1, SIN3A and PRMT6

**Location:** RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

**Stable identifier:** R-HSA-8935731

**Type:** omitted

**Compartments:** nucleoplasm, plasma membrane

The RUNX1:CBFB complex binds the promoter of the ITGA2B (CD41) gene, encoding Integrin alpha IIb, and stimulates ITGA2B transcription. Transcription of ITGA2B is significantly upregulated by PRMT1-dependent arginine methylation of RUNX1, which interferes with the recruitment of the SIN3A (or, possibly, SIN3B) co-repressor (Zhao et al. 2008). The transcription activator complex at the ITGA2B promoter includes the RUNX1:CBFB complex, PRMT1, the GATA1:ZFPM1 complex, histone acetyltransferases p300 (EP300) and PCAF (KAT2B), and the WDR5-containing histone methyltransferase MLL complex. The MLL complex produces the activating H3K4me3 mark on nucleosomes associated with the ITGA2B gene promoter (Herglotz et al. 2013).

The transcription repressor complex at the ITGA2B promoter is formed when the SIN3A (or possibly SIN3B) co-repressor binds to the RUNX1:CBFB complex along with histone arginine methyltransferase PRMT6 and histone deacetylase HDAC1. Histone H3 arginine methylation by PRMT6 interferes with methylation of H3K4me2 to generate the activating H3K4me3 mark at the ITGA2B gene promoter, thus contributing to transcriptional repression (Herglotz et al. 2013).

ITGA2B, involved in platelet aggregation, is only expressed in maturing megakaryocytes and platelets and is a model gene for megakaryocyte specific expression (Block and Poncz 1995, Jackson 2007).

**Preceded by:** RUNX1 and GATA1 bind the promoter of the ITGA2B gene, PRMT6 arginine methylates H3K4me2-Nucleosome at the ITGA2B gene promoter

**Literature references**

RUNX1:CBFB, SIN3A(SIN3B), PRMT6 and HDAC1 bind the GP1BA promoter

Location: RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

Stable identifier: R-HSA-8936599

Type: binding

Compartments: nucleoplasm

The transcriptional co-repressor SIN3A (and possibly SIN3B) can bind to the RUNX1:CBFB complex at the promoter of the GP1BA (CD42b) gene, encoding Platelet glycoprotein Ib alpha chain. Binding of SIN3A (and probably SIN3B) to RUNX1 is inhibited by PRMT1-mediated arginine methylation of RUNX1 arginine residues R206 and R210 (Zhao et al. 2008). In addition to SIN3A, the RUNX1-containing transcriptional repressor complex at the GP1BA promoter also includes histone arginine methyltransferase PRMT6 and histone deacetylase HDAC1 (Herglotz et al. 2013). Dimethylation of histone H3 on lysine residue K4 (K5 when taking into account the initiator methionine), known as the H3K4me2 mark, is characteristic of nucleosomes associated with megakaryocyte specific promoters, including the GP1BA gene, prior to the onset of differentiation (Herglotz et al. 2013).

Followed by: PRMT6 arginine methylates H3K4me2-Nucleosome at the GP1BA gene promoter

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PRMT6 arginine methylates H3K4me2-Nucleosome at the GP1BA gene promoter

**Location:** RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

**Stable identifier:** R-HSA-8936608

**Type:** transition

**Compartments:** nucleoplasm

The histone arginine methyltransferase PRMT6 asymmetrically dimethylates histone H3 on arginine residue R2 (R3 when taking into account the initiator methionine), thus creating the H3R2me2a mark on nucleosomes at the GP1BA gene promoter. Histone H3 arginine methylation by PRMT6 interferes with methylation of H3K4me2 to generate the activating H3K4me3 mark at the GP1BA gene promoter, thus contributing to transcriptional repression (Herglotz et al. 2013).

**Preceded by:** RUNX1:CBFB, SIN3A(SIN3B), PRMT6 and HDAC1 bind the GP1BA promoter

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RUNX1 and GATA1 bind the promoter of the GP1BA gene

Location: RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

Stable identifier: R-HSA-8936616

Type: binding

Compartments: nucleoplasm

The RUNX1:CBFB complex can bind to the promoter of the GP1BA (CD42b) gene, encoding Platelet glycoprotein Ib alpha chain. Based on the analogy with the ITGA2B gene transcription (Zhao et al. 2008), the PRMT1-mediated arginine-methylation increases transcriptional activity of the RUNX1:CBFB complex at the GP1BA promoter (Herglotz et al. 2013). In addition to the RUNX1:CBFB complex, the complex of GATA1 and ZFPM1 (FOG1) (Freson et al. 2003) is also recruited to the GP1BA promoter (Herglotz et al. 2013), likely through the interaction between GATA1 and RUNX1 (Elagib et al. 2003). The zinc finger domain of GATA1 is involved in binding to RUNX1 (Xu et al. 2006). Along with RUNX1 and GATA1, histone acetyltransferases p300 (EP300) and PCAF (KAT2B), as well as the WDR5-containing histone methyltransferase MLL complex are also recruited to the GP1BA promoter. Dimethylation of histone H3 on lysine residue K4 (K5 when taking into account the initiator methionine), known as the H3K4me2 mark, is characteristic of nucleosomes associated with megakaryocyte specific promoters, including the GP1BA gene, prior to the onset of differentiation (Herglotz et al. 2013).

Preceded by: PRMT1 arginine-methylates RUNX1

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Core MLL complex methylates H3K4Me2-Nucleosome at the GP1BA gene promoter

**Location:** RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

**Stable identifier:** R-HSA-8936621

**Type:** transition

**Compartments:** nucleoplasm

The WDR5-containing histone methyltransferase MLL complex, recruited to the GP1BA promoter via RUNX1 (and possibly GATA1), methylates histone H3 on dimethylated lysine residue K4 (K5 when taking into account the initiator methionine), producing the H3K4me3 mark. The H3K4me3 mark is characteristic of nucleosome associated with transcriptionally active promoters of megakaryocyte-specific genes (Herglotz et al. 2013).

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GP1BA gene transcription is stimulated by the complex containing RUNX1, PRMT1 and GATA1 and inhibited by the complex of RUNX1, SIN3A and PRMT6

**Location:** RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

**Stable identifier:** R-HSA-8936628

**Type:** omitted

**Compartments:** nucleoplasm, plasma membrane

The RUNX1:CBFB complex binds the promoter of the GP1BA (CD42b) gene, encoding Platelet glycoprotein Ib alpha chain, and stimulates GP1BA transcription. Based on analogy with the ITGA2B gene transcription, transcription of GP1BA is significantly upregulated by PRMT1-dependent arginine methylation of RUNX1, which interferes with the recruitment of the SIN3A (or, possibly, SIN3B) co-repressor (Zhao et al. 2008). The transcription activator complex at the GP1BA gene promoter includes the RUNX1:CBFB complex, PRMT1, the GATA1:ZFPM1 complex, histone acetyltransferases p300 (EP300) and PCAF (KAT2B), and the WDR5-containing histone methyltransferase MLL complex. The MLL complex produces the activating H3K4me3 mark on nucleosomes associated with the GP1BA gene promoter (Herglotz et al. 2013).

The transcription repressor complex at the GP1BA promoter is formed when the SIN3A (or possibly SIN3B) co-repressor binds to the RUNX1:CBFB complex along with histone arginine methyltransferase PRMT6 and histone deacetylase HDAC1. Histone H3 arginine methylation by PRMT6 interferes with methylation of H3K4me2 to generate the activating H3K4me3 mark at the GP1BA gene promoter, thus contributing to transcriptional repression (Herglotz et al. 2013).

Platelet glycoprotein Ib (GP-Ib) alpha chain, encoded by the GP1BA gene, is expressed at the cell surface membrane of platelets and participates in the formation of platelet plugs (Cauwenberghs et al. 2000, Jilma-Stohlwaletz et al. 2003). Gp-Ib protein is first detected on the plasma membrane of maturing megakaryocytes (Debili et al. 1990).

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RUNX1 and GATA1 bind the promoter of the THBS1 gene

Location: RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

Stable identifier: R-HSA-8936979

Type: binding

Compartments: nucleoplasm

The RUNX1:CBFB complex can bind to the promoter of the THBS1 (TSP-1) gene, encoding Thrombospondin-1. Based on the analogy with the ITGA2B gene transcription (Zhao et al. 2008), the PRMT1-mediated arginine-methylation increases transcriptional activity of the RUNX1:CBFB complex at the THBS1 promoter (Herglotz et al. 2013). In addition to the RUNX1:CBFB complex, the complex of GATA1 and ZFPM1 (FOG1) (Freson et al. 2003) is also recruited to the THBS1 promoter (Herglotz et al. 2013), likely through the interaction between GATA1 and RUNX1 (Elagib et al. 2003). The zinc finger domain of GATA1 is involved in binding to RUNX1 (Xu et al. 2006). Along with RUNX1 and GATA1, histone acetyltransferases p300 (EP300) and PCAF (KAT2B), as well as the WDR5-containing histone methyltransferase MLL complex are also recruited to the THBS1 promoter. Dimethylation of histone H3 on lysine residue K4 (K5 when taking into account the initiator methionine), known as the H3K4me2 mark, is characteristic of nucleosomes associated with megakaryocyte promoters prior to the onset of differentiation (Herglotz et al. 2013) and is assumed to be present at the THBS1 promoter.

Preceded by: PRMT1 arginine-methylates RUNX1

Followed by: Core MLL complex methylates H3K4Me2-Nucleosome at the THBS1 gene promoter

Literature references


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Core MLL complex methylates H3K4Me2-Nucleosome at the THBS1 gene promoter

**Location:** RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

**Stable identifier:** R-HSA-8937016

**Type:** transition

**Compartments:** nucleoplasm

The WDR5-containing histone methyltransferase MLL complex, recruited to the THBS1 (TSP-1) promoter via RUNX1 (and possibly GATA1), is assumed to methylate histone H3 on dimethylated lysine residue K4 (K5 when taking into account the initiator methionine), producing the H3K4me3 mark. The H3K4me3 mark is characteristic of nucleosome associated with transcriptionally active promoters of megakaryocyte-specific genes (Herglotz et al. 2013) and the appearance of the H3K4me3 mark at the THBS1 promoter coincides with THBS1 transactivation (Michaud-Levesque and Richard 2009).

**Preceded by:** RUNX1 and GATA1 bind the promoter of the THBS1 gene

**Literature references**


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RUNX1:CBFB, SIN3A(SIN3B), PRMT6 and HDAC1 bind the THBS1 gene promoter

**Location:** RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

**Stable identifier:** R-HSA-8936989

**Type:** binding

**Compartments:** nucleoplasm

The transcriptional co-repressor SIN3A (and possibly SIN3B) can bind to the RUNX1:CBFB complex at the promoter of the THBS1 (TSP-1) gene, encoding Thrombospondin-1. Binding of SIN3A (and probably SIN3B) to RUNX1 is inhibited by PRMT1-mediated arginine methylation of RUNX1 arginine residues R206 and R210 (Zhao et al. 2008). In addition to SIN3A, the RUNX1-containing transcriptional repressor complex at the THBS1 promoter also includes histone arginine methyltransferase PRMT6 and histone deacetylase HDAC1 (Herglotz et al. 2013). Dimethylation of histone H3 on lysine residue K4 (K5 when taking into account the initiator methionine), known as the H3K4me2 mark, is characteristic of nucleosomes associated with megakaryocyte promoters prior to the onset of differentiation (Herglotz et al. 2013), and based on epigenetic modifications that affect transactivation of the THBS1 gene (Michaud-Levesque and Richard 2009), the H3K4me2 mark is assumed to be present at the inactive THBS1 promoter.

**Followed by:** PRMT6 arginine methylates H3K4me2-Nucleosome at the THBS1 gene promoter

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PRMT6 arginine methylates H3K4me2-Nucleosome at the THBS1 gene promoter

Location: RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

Stable identifier: R-HSA-8937022

Type: transition

Compartments: nucleoplasm

The histone arginine methyltransferase PRMT6 asymmetrically dimethylates histone H3 on arginine residue R2 (R3 when taking into account the initiator methionine), thus creating the H3R2me2a mark on nucleosomes at the THBS1 gene promoter. Histone H3 arginine methylation by PRMT6 interferes with generation of the activating H3K4me3 mark at the THBS1 gene promoter, thus contributing to transcriptional repression (Michaud-Levesque and Richard 2009).

Preceded by: RUNX1:CBFB, SIN3A(SIN3B), PRMT6 and HDAC1 bind the THBS1 gene promoter

Literature references


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THBS1 gene transcription is stimulated by the complex containing RUNX1, PRMT1 and GATA1 and inhibited by the complex of RUNX1, SIN3A and PRMT6

**Location:** RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

**Stable identifier:** R-HSA-8936995

**Type:** omitted

**Compartments:** nucleoplasm, plasma membrane

The RUNX1:CBFB complex binds the promoter of the THBS1 (TSP-1) gene, encoding Thrombospondin-1, and stimulates THBS1 transcription. Based on the analogy with the ITGA2B gene transcription, transcription of THBS1 is significantly upregulated by PRMT1-dependent arginine methylation of RUNX1, which interferes with the recruitment of the SIN3A (or, possibly, SIN3B) co-repressor (Zhao et al. 2008). The transcription activator complex at the THBS1 gene promoter includes the RUNX1:CBFB complex, PRMT1, the GATA1:ZFPM1 complex, histone acetyltransferases p300 (EP300) and PCAF (KAT2B), and the WDR5-containing histone methyltransferase MLL complex. The MLL complex produces the activating H3K4me3 mark on nucleosomes associated with RUNX1-regulated megakaryocyte promoters (Herglotz et al. 2013). The presence of the H3K4me3 mark is characteristic of the activated THBS1 promoter (Michaud-Levesque and Richard 2009).

The transcription repressor complex at the THBS1 promoter is formed when SIN3A (or possibly SIN3B) co-repressor binds to the RUNX1:CBFB complex along with histone arginine methyltransferase PRMT6 and histone deacetylase HDAC1. Histone H3 arginine methylation by PRMT6 interferes with methylation of H3K4me2 to generate the activating H3K4me3 mark at RUNX1-regulated megakaryocyte promoters (Herglotz et al. 2013), including THBS1 promoter (Michaud-Levesque and Richard 2009).

Thrombospondin-1, encoded by the THBS1 gene, forms homotrimers which can be detected in many different cell types and are very abundant in platelet alpha granules. While THBS1 is not necessary for platelet aggregation, it contributes to stabilization of the platelet aggregate (Bonnefoy and Hoylaerts 2008).

**Literature references**


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</table>
RUNX1 and GATA1 bind the promoter of the MIR27A gene

**Location:** RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

**Stable identifier:** R-HSA-8937037

**Type:** binding

**Compartments:** nucleoplasm

The RUNX1:CBFB complex can bind to the promoter of the MIR27A gene, encoding microRNA miR-27A (Ben-Ami et al. 2009). Based on analogy with the ITGA2B gene transcription (Zhao et al. 2008), the PRMT1-mediated arginine-methylation increases transcriptional activity of the RUNX1:CBFB complex at the MIR27A gene promoter (Herglotz et al. 2013). In addition to the RUNX1:CBFB complex, the complex of GATA1 and ZFPM1 (FOG1) (Freson et al. 2003) is also recruited to the MIR27A promoter (Herglotz et al. 2013), likely through the interaction between GATA1 and RUNX1 (Elagib et al. 2003). The zinc finger domain of GATA1 is involved in binding to RUNX1 (Xu et al. 2006). Along with RUNX1 and GATA1, histone acetyltransferases p300 (EP300) and PCAF (KAT2B), as well as the WDR5-containing histone methyltransferase MLL complex are also recruited to the MIR27A promoter. Dimethylation of histone H3 on lysine residue K4 (K5 when taking into account the initiator methionine), known as the H3K4me2 mark, is characteristic of nucleosomes associated with megakaryocyte specific promoters, including the MIR27A gene, prior to the onset of differentiation (Herglotz et al. 2013).

**Preceded by:** PRMT1 arginine-methylates RUNX1

**Literature references**


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Core MLL complex methylates H3K4Me2-Nucleosome at the MIR27A gene promoter

Location: RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

Stable identifier: R-HSA-8937050

Type: transition

Compartments: nucleoplasm

The WDR5-containing histone methyltransferase MLL complex, recruited to the MIR27A promoter via RUNX1 (and possibly GATA1), methylates histone H3 on dimethylated lysine residue K4 (K5 when taking into account the initiator methionine), producing the H3K4me3 mark. The H3K4me3 mark is characteristic of nucleosome associated with transcriptionally active promoters of megakaryocyte-specific genes (Herglotz et al. 2013).

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RUNX1:CBFB, SIN3A(SIN3B), PRMT6 and HDAC1 bind the MIR27A gene promoter

Location: RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

Stable identifier: R-HSA-8937118

Type: binding

Compartments: nucleoplasm

The transcriptional co-repressor SIN3A (and possibly SIN3B) can bind to the RUNX1:CBFB complex at the promoter of the MIR27A gene, encoding microRNA miR-27a (Ben-Ami et al. 2009, Herglotz et al. 2013). Binding of SIN3A (and probably SIN3B) to RUNX1 is inhibited by PRMT1-mediated arginine methylation of RUNX1 arginine residues R206 and R210 (Zhao et al. 2008). In addition to SIN3A, the RUNX1-containing transcriptional repressor complex at the MIR27A promoter also includes histone arginine methyltransferase PRMT6 and histone deacetylase HDAC1 (Herglotz et al. 2013). Dimethylation of histone H3 on lysine residue K4 (K5 when taking into account the initiator methionine), known as the H3K4me2 mark, is characteristic of nucleosomes associated with megakaryocyte specific promoters, including the MIR27A gene, prior to the onset of differentiation (Herglotz et al. 2013).

Followed by: PRMT6 arginine methylates H3K4me2-Nucleosome at the MIR27A gene promoter

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PRMT6 arginine methylates H3K4me2-Nucleosome at the MIR27A gene promoter

Location: RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

Stable identifier: R-HSA-8937113

Type: transition

Compartments: nucleoplasm

The histone arginine methyltransferase PRMT6 asymmetrically dimethylates histone H3 on arginine residue R2 (R3 when taking into account the initiator methionine), thus creating the H3R2me2a mark on nucleosomes at the MIR27A gene promoter. Histone H3 arginine methylation by PRMT6 interferes with generation of the activating H3K4me3 mark at the MIR27A gene promoter, thus contributing to transcriptional repression (Herglotz et al. 2013).

Preceded by: RUNX1:CBFB, SIN3A(SIN3B), PRMT6 and HDAC1 bind the MIR27A gene promoter

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MIR27A gene transcription is stimulated by the complex containing RUNX1, PRMT1 and GATA1 and inhibited by the complex of RUNX1, SIN3A and PRMT6

**Location:** RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

**Stable identifier:** R-HSA-8937097

**Type:** omitted

**Compartments:** nucleoplasm, plasma membrane

The RUNX1:CBFB complex binds the promoter of the MIR27A gene, encoding microRNA miR-27a, and stimulates MIR27A transcription. Based on the analogy with the ITGA2B gene transcription, transcription of MIR27A is significantly upregulated by PRMT1-dependent arginine methylation of RUNX1, which interferes with the recruitment of the SIN3A (or, possibly, SIN3B) co-repressor (Zhao et al. 2008). The transcription activator complex at the MIR27A gene promoter includes the RUNX1:CBFB complex, PRMT1, the GATA1:ZFPM1 complex, histone acetyltransferases p300 (EP300) and PCAF (KAT2B), and the WDR5-containing histone methyltransferase MLL complex. The MLL complex produces the activating H3K4me3 mark on nucleosomes associated with the MIR27A gene promoter (Herglotz et al. 2013).

The transcription repressor complex at the MIR27A promoter is formed when SIN3A (or possibly SIN3B) co-repressor binds to the RUNX1:CBFB complex along with histone arginine methyltransferase PRMT6 and histone deacetylase HDAC1. Histone H3 arginine methylation by PRMT6 interferes with methylation of H3K4me2 to generate the activating H3K4me3 mark at the MIR27A gene promoter, thus contributing to transcriptional repression (Herglotz et al. 2013).

MicroRNA miR-27a binds the 3'UTR of RUNX1 mRNA and inhibits RUNX1 mRNA translation without affecting RUNX1 mRNA stability. RUNX1 and MIR27A thus constitute a negative feedback loop that regulates megakaryocytic differentiation and may be involved in erythroid/megakaryocytic lineage determination (Ben-Ami et al. 2009).

**Literature references**


[https://reactome.org](https://reactome.org)
RUNX1:CBFB binds the PF4 gene promoter

**Location:** RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

**Stable identifier:** R-HSA-8938176

**Type:** binding

**Compartments:** nucleoplasm

The RUNX1:CBFB complex binds to two RUNX1 response elements in the promoter of the PF4 gene, encoding Platelet factor 4 (Aneja et al. 2011).

**Followed by:** PF4 gene transcription is stimulated by RUNX1:CBFB

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The PF4 gene is transcribed by the RUNX1:CBFB complex.

**Location:** RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function.

**Stable identifier:** R-HSA-8938174

**Type:** omitted

**Compartments:** nucleoplasm, platelet alpha granule lumen

Binding of the RUNX1:CBFB complex to the promoter of the PF4 gene stimulates transcription of PF4. The PF4 gene encodes Platelet factor 4, a protein stored in platelet alpha granules. Deficiency of alpha granule proteins, including PF4, is the cause of gray platelet syndrome. PF4 deficiency can be caused by RUNX1 haploinsufficiency (Aneja et al. 2011).

**Preceded by:** RUNX1:CBFB binds the PF4 gene promoter

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RUNX1:CBFB binds the NR4A3 gene promoter

**Location:** RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

**Stable identifier:** R-HSA-8938022

**Type:** binding

**Compartments:** nucleoplasm

The RUNX1:CBFB complex bind the RUNX1 site in the promoter of the NR4A3 gene (Bluteau et al. 2011).

**Followed by:** NR4A3 gene expression is stimulated by RUNX1:CBFB

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NR4A3 gene expression is stimulated by RUNX1:CBFB

Location: RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

Stable identifier: R-HSA-8938034

Type: omitted

Compartments: nucleoplasm

Binding of the RUNX1:CBFβ complex to the NR4A3 gene promoter stimulates NR4A3 gene transcription, leading to reduction in the clonogenic potential of hematopoietic progenitors. RUNX1 mutants associated with familial platelet disorders (FPD) and acute myeloid leukemia (AML) are unable to transactivate the NR4A3 gene (Bluteau et al. 2011).

Preceded by: RUNX1:CBFβ binds the NR4A3 gene promoter

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RUNX1:CBFB binds the PRKCQ gene promoter

**Location:** RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

**Stable identifier:** R-HSA-8938150

**Type:** binding

**Compartments:** nucleoplasm

The RUNX1:CBFB complex binds the promoter of the PRKCQ gene, encoding Protein kinase C theta type (Jalagadugula et al. 2011).

**Followed by:** PRKCQ gene expression is stimulated by RUNX1:CBFB

**Literature references**


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</table>
PRKCQ gene expression is stimulated by RUNX1:CBFB

Location: RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

Stable identifier: R-HSA-8938158

Type: omitted

Compartments: nucleoplasm, cytosol

Binding of the RUNX1:CBFB complex to the promoter of the PRKCQ gene, encoding Protein kinase C theta type, stimulates PRKCQ transcription. RUNX1 mutants associated with inherited thrombocytopenia are unable to transactivate the PRKCQ gene. PRKCQ is important for the functioning of megakaryocytes and platelets, but is not megakaryocyte specific (Jalagadugula et al. 2011).

Preceded by: RUNX1:CBFB binds the PRKCQ gene promoter

Literature references


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**RUNX1:CBFB binds the MYL9 gene promoter**

**Location:** RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

**Stable identifier:** R-HSA-8938199

**Type:** binding

**Compartments:** nucleoplasm

The RUNX1:CBFB complex binds to four RUNX1 response elements in the promoter of the MYL9 gene, encoding Myosin regulatory light polypeptide 9, which functions as the regulatory subunit of the myosin complex (Jalagadugula et al. 2010).

**Followed by:** MYL9 gene transcription is stimulated by RUNX1:CBFB

**Literature references**


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MYL9 gene transcription is stimulated by RUNX1:CBFB

Location: RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

Stable identifier: R-HSA-8938201

Type: omitted

Compartments: nucleoplasm, cytosol

Binding of the RUNX1:CBFB complex to the promoter of the MYL9 gene stimulates MYL9 transcription. All four RUNX1 response elements in the MYL9 promoter contribute to transactivation of the MYL9 gene. The MYL9 gene encodes Myosin regulatory light polypeptide, which functions as a regulatory subunit of the myosin complex. Myosin plays an important role in platelet activation and thrombopoiesis. RUNX1 haploinsufficiency is associated with decreased MYL9 expression and myosin light chain phosphorylation, which likely contributes to thrombocytopenia and platelet dysfunction (Jalagadugula et al. 2010).

Preceded by: RUNX1:CBFB binds the MYL9 gene promoter

Literature references


Editions

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**RUNX1:CBFB binds the NFE2 gene promoter**

**Location:** RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

**Stable identifier:** R-HSA-8938328

**Type:** binding

**Compartments:** nucleoplasm

The RUNX1:CBFB complex binds RUNX1 response elements in the promoter of the NFE2 gene, encoding Transcription factor NF-E2 45 kDa subunit (Wang et al. 2010).

**Followed by:** NFE2 gene expression is stimulated by RUNX1:CBFB

**Literature references**


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https://reactome.org
**NFE2 gene expression is stimulated by RUNX1:CBFB**

**Location:** RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function

**Stable identifier:** R-HSA-8938338

**Type:** omitted

**Compartments:** nucleoplasm

Binding of the RUNX1:CBFB complex to the promoter of the NFE2 gene stimulates NFE2 transcription. The NFE2 gene encodes the Transcription factor NF-E2 45 kDa subunit. The NF-E2 transcription factor regulates erythroid and megakaryocytic maturation and differentiation and is overexpressed in myeloproliferative neoplasms (Wang et al. 2010).

**Preceded by:** RUNX1:CBFB binds the NFE2 gene promoter

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