RUNX2 regulates osteoblast differentiation

D'Eustachio, P., Ducy, P., Orlic-Milacic, M., Sudol, M.

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23/07/2019
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 24 reactions (see Table of Contents)

https://reactome.org
The complex of RUNX2 and CBFB regulates transcription of genes involved in differentiation of osteoblasts.

RUNX2 stimulates transcription of the BGLAP gene, encoding osteocalcin (Ducy and Karsenty 1995, Ducy et al. 1997). Binding of the RUNX2:CBFB complex to the BGLAP gene promoter is increased when RUNX2 is phosphorylated on serine residue S451 (Wee et al. 2002). Osteocalcin, a bone-derived hormone, is one of the most abundant non-collagenous proteins of the bone extracellular matrix (reviewed in Karsenty and Olson 2016). Association of the activated androgen receptor (AR) with RUNX2 prevents binding of RUNX2 to the BGLAP promoter (Baniwal et al. 2009). When YAP1, tyrosine phosphorylated by SRC and/or YES1, binds to RUNX2 at the BGLAP gene promoter, transcription of the BGLAP gene is inhibited (Zaidi et al. 2004). Signaling by SRC is known to inhibit osteoblast differentiation (Marzia et al. 2000).

Simultaneous binding of RUNX2 and SP7 (Osterix, also known as OSX) to adjacent RUNX2 and SP7 binding sites, respectively, in the UCMA promoter, synergistically activates UCMA transcription. UCMA stimulates osteoblast differentiation and formation of mineralized nodules (Lee et al. 2015).

The SCF(SKP2) E3 ubiquitin ligase complex inhibits differentiation of osteoblasts by polyubiquitinating RUNX2 and targeting it for proteasome-mediated degradation (Thacker et al. 2016). This process is inhibited by glucose uptake in osteoblasts (Wei et al. 2015).

**Literature references**


**Editions**

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Androgen receptor (AR), activated by binding to androgens, forms a complex with RUNX2 (presumably associated with CBFB) in the nucleus. AR inhibits transcriptional activity of RUNX2, which may underlie AR-mediated attenuation of bone turnover. RUNX2 may play a tumor suppressor role in prostate cancer (Baniwal et al. 2009).

The complex of RUNX2 and AR is implicated in stimulation of the PSA gene transcription in response to TGF-beta signaling, but further experimental validation is needed (van der Deen et al. 2010).

**Literature references**


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RUNX2:CBFB binds BGLAP gene promoter

**Location:** RUNX2 regulates osteoblast differentiation

**Stable identifier:** R-HSA-9008877

**Type:** binding

**Compartments:** nucleoplasm

RUNX2 binds the OSE2 element in the promoter of the BGLAP (osteocalcin, OC) gene (Ducy and Karsenty 1995, Ducy et al. 1997). The affinity of the RUNX2:CBFB complex for the BGLAP gene promoter is increased when RUNX2 is phosphorylated on serine residue S451 (Wee et al. 2002), or on serine residues S294 and S312, which correspond to mouse Runx2-P1 residues S472, S301 and S319 (Ge et al. 2009). Formation of the complex between the activated androgen receptor (AR) and RUNX2 prevents RUNX2 from binding the BGLAP promoter (Baniwal et al. 2009). Twist proteins and Schnurri-3 also interact with RUNX2 to decrease BGLAP expression (Bialek et al. 2004, Jones et al. 2006). In contrast, RUNX2 and SATB2 interact to enhance the expression of osteoblast-specific genes (Dobreva et al. 2006).

**Preceded by:** Activated ERKs phosphorylate RUNX2

**Followed by:** BGLAP gene expression is stimulated by RUNX2, WWTR1 and RB1 and inhibited by AR, YAP1 and ZNF521

**Literature references**


RUNX2 binds MAF

Location: RUNX2 regulates osteoblast differentiation

Stable identifier: R-HSA-8984994

Type: binding

Compartments: nucleoplasm

Inferred from: Runx2 binds Maf (Mus musculus)

Based on studies in mice, RUNX2 forms a complex with the transcription factor MAF. It is unknown whether MAF participates in this complex as a homodimer or a monomer. It is also unknown whether RUNX2 is bound to CBFB when in complex with MAF (Nishikawa et al. 2010).

Followed by: RUNX2:MAF complex binds the BGLAP gene promoter

Literature references


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RUNX2: MAF complex binds the BGLAP gene promoter

**Location:** RUNX2 regulates osteoblast differentiation

**Stable identifier:** R-HSA-8877918

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Runx2:Maf binds the Bglap gene promoter (Mus musculus)

RUNX2 binds the OSE2 element in the promoter of the BGLAP (osteocalcin, OC) gene. Formation of the complex between the activated androgen receptor (AR) and RUNX2 prevents RUNX2 from binding the BGLAP gene promoter (Baniwal et al. 2009). Based on studies in mice, RUNX2 binds to the BGLAP promoter in complex with the MAF transcription factor, and RUNX2 and MAF act synergistically to induce BGLAP transcription (Nishikawa et al. 2010). RUNX2 binding sites are conserved in the human BGLAP gene promoter.

**Preceded by:** RUNX2 binds MAF

**Followed by:** BGLAP gene expression is stimulated by RUNX2, WWTR1 and RB1 and inhibited by AR, YAP1 and ZNF521

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[https://reactome.org](https://reactome.org)
**WWTR1 (TAZ) binds RUNX2**

**Location:** RUNX2 regulates osteoblast differentiation

**Stable identifier:** R-HSA-2064932

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Wwtr1 (Taz) binds Runx2 (Mus musculus)

In the nucleus the WWTR1 (TAZ) transcriptional coactivator can bind the RUNX2 transcription factor to form a complex. This interaction has not been experimentally characterized in human cells but is inferred from properties of the homologous mouse proteins. The stoichiometry of this complex is unknown (Cui et al. 2003).

Formation of the RUNX2:WWTR1 complex is implicated in promotion of luminal breast cancer progression through regulation of E-cadherin (CDH1) and cross-talk with ERBB2 (HER2) signaling (Brusgard et al. 2015).

**Followed by:** The complex of RUNX2 and WWTR1 (TAZ) binds the BGLAP gene promoter

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The complex of RUNX2 and WWTR1 (TAZ) binds the BGLAP gene promoter

Location: RUNX2 regulates osteoblast differentiation

Stable identifier: R-HSA-8985227

Type: binding

Compartments: nucleoplasm

Inferred from: Runx2:Wwtr1 binds the Bglap gene promoter (Mus musculus)

Based on studies in mouse cells, the complex of RUNX2 and WWTR1 (TAZ) binds to the promoter of the BGLAP gene, encoding osteocalcin (Hong et al. 2005). Catalytically active protein tyrosine kinase ABL1 promotes association of RUNX2 and WWTR1 and transcription of the BGLAP gene (Matsumoto et al. 2016). RUNX2 binding sites are conserved in the human BGLAP gene promoter.

Preceded by: WWTR1 (TAZ) binds RUNX2

Followed by: BGLAP gene expression is stimulated by RUNX2, WWTR1 and RB1 and inhibited by AR, YAP1 and ZNF521

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RUNX2 binds RB1

Location: RUNX2 regulates osteoblast differentiation

Stable identifier: R-HSA-8985460

Type: binding

Compartments: nucleoplasm

Inferred from: Runx2 binds RB1 (Homo sapiens)

RUNX2 forms a complex with the tumor suppressor RB1. The C-terminus and B-pocket of RB1 are needed for the interaction (Thomas et al. 2001).

Followed by: RUNX2 and RB1 bind the COL1A1 gene promoter, RUNX2 and RB1 bind the BGLAP gene promoter

Literature references

RUNX2 and RB1 bind the BGLAP gene promoter

**Location:** RUNX2 regulates osteoblast differentiation

**Stable identifier:** R-HSA-8985485

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Runx2:RB1 binds the BGLAP gene promoter (Homo sapiens)

The complex of RUNX2 and RB1 binds the promoter of the BGLAP gene, encoding osteocalcin (Thomas et al. 2001, Calo et al. 2010).

**Preceded by:** RUNX2 binds RB1

**Followed by:** BGLAP gene expression is stimulated by RUNX2, WWTR1 and RB1 and inhibited by AR, YAP1 and ZNF521

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Activated ERKs phosphorylate RUNX2

**Location:** RUNX2 regulates osteoblast differentiation

**Stable identifier:** R-HSA-9009208

**Type:** transition

**Compartments:** nucleoplasm

**Inferred from:** Activated ERKs phosphorylate Runx2 (Homo sapiens)

RUNX2 is phosphorylated by activated ERKs (MAPK3 and MAPK1) on at least two conserved serine residues. ERK-mediated phosphorylation is not known to affect binding of RUNX2 to CBFB and is therefore shown to happen in the context of the RUNX2:CBFB complex. RUNX2 phosphorylated by ERKs shows enhanced binding to RUNX2 response elements in the osteocalcin (BGLAP) gene promoter, resulting in increased BGLAP gene transcription (Ge et al. 2009).

ERK-mediated phosphorylation of RUNX2 in response to FGF2 signaling is thought to promote RUNX2 isomerization by PIN1 prolyl isomerase, which facilitates EP300 (p300) mediated acetylation and stabilization of RUNX2 (Yoon et al. 2014).

**Followed by:** RUNX2:CBFB binds BGLAP gene promoter

**Literature references**


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**SRC,YES1 bind YAP1**

**Location:** RUNX2 regulates osteoblast differentiation

**Stable identifier:** R-HSA-8937820

**Type:** binding

**Compartments:** cytosol, plasma membrane

**Inferred from:** Src,Yes1 bind Yap1 (Rattus norvegicus)

Based on studies in rat osteosarcoma cell line, activated SRC and YES1 form a complex with YAP1 (Zaidi et al. 2004).

**Followed by:** SRC,YES1 phosphorylate YAP1

**Literature references**


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SRC,YES1 phosphorylate YAP1

**Location:** RUNX2 regulates osteoblast differentiation

**Stable identifier:** R-HSA-8937844

**Type:** transition

**Compartments:** cytosol, plasma membrane

**Inferred from:** Src,Yes1 phosphorylate Yap1 (Rattus norvegicus)

Based on studies in rat, activated SRC and/or YES1 tyrosine kinases phosphorylate YAP1 on an unknown tyrosine residue (Zaidi et al. 2004).

**Preceded by:** SRC,YES1 bind YAP1

**Followed by:** p-Y-YAP1 translocates to the nucleus

**Literature references**


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p-Y-YAP1 translocates to the nucleus

Location: RUNX2 regulates osteoblast differentiation

Stable identifier: R-HSA-8937856

Type: transition

Compartments: cytosol, nucleoplasm

Inferred from: p-Y-Yap1 translocates to the nucleus (Rattus norvegicus)

Based on studies in rat, YAP1, phosphorylated on an unknown tyrosine residue by SRC and/or YES1, translocates to the nucleus. Tyrosine phosphorylated YAP1 shuffles between the nucleus and the cytosol, and phosphorylation by SRC and/or YES1 does not change the ratio of nuclear and cytosolic YAP1 (Zaidi et al. 2004).

Preceded by: SRC, YES1 phosphorylate YAP1

Followed by: RUNX2 binds tyrosine phosphorylated YAP1

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RUNX2 binds tyrosine phosphorylated YAP1

Location: RUNX2 regulates osteoblast differentiation

Stable identifier: R-HSA-8937864

Type: binding

Compartments: nucleoplasm

Inferred from: Runx2 binds p-Y-Yap1 (Rattus norvegicus)

Based on studies in rat, RUNX2, presumably associated with CBFB, binds YAP1, phosphorylated on an unknown tyrosine residue by SRC and/or YES1. The interaction involves the PY motif of RUNX2 (Zaidi et al. 2004).

Preceded by: p-Y-YAP1 translocates to the nucleus

Followed by: RUNX2:CBFB:p-Y-YAP1 binds the BGLAP gene promoter

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RUNX2:CBFB:p-Y-YAP1 binds the BGLAP gene promoter

**Location:** RUNX2 regulates osteoblast differentiation

**Stable identifier:** R-HSA-8937869

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Runx2:Cbfb:p-Y-Yap1 binds the Bglap gene promoter (Rattus norvegicus)

Based on studies in rat, the complex of RUNX2, presumably associated with CBFB, and tyrosine phosphorylated YAP1 binds to the promoter of the BGLAP (osteocalcin) gene (Zaidi et al. 2004). RUNX2 binding sites are conserved in the human BGLAP gene promoter.

**Preceded by:** RUNX2 binds tyrosine phosphorylated YAP1

**Followed by:** BGLAP gene expression is stimulated by RUNX2, WWTR1 and RB1 and inhibited by AR, YAP1 and ZNF521

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RUNX2 binds ZNF521 and HDAC3

**Location:** RUNX2 regulates osteoblast differentiation

**Stable identifier:** R-HSA-9008137

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Runx2 binds Znf521 and Hdac3 (Mus musculus)

Based on studies in mice, RUNX2 forms a complex with ZNF521 (ZNP521) and a histone deacetylase HDAC3. Binding to ZNF521 does not inhibit RUNX2 binding to target genes, such as the BGLAP (Osteocalcin) gene promoter, but inhibits RUNX2-mediated activation of these genes. HDAC3 is needed for ZNF521 to inhibit RUNX2-mediated transcription from the BGLAP promoter. Action of ZNF521 antagonizes RUNX2 during mesenchymal commitment to the osteoblast lineage and during osteoblast maturation (Hesse et al. 2010).

**Followed by:** BGLAP gene expression is stimulated by RUNX2, WWTR1 and RB1 and inhibited by AR, YAP1 and ZNF521

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RUNX2 binds HEY1,HEY2,HES1

**Location:** RUNX2 regulates osteoblast differentiation

**Stable identifier:** R-HSA-9008177

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Runx2 binds Hey1,Hey2,Hes1 (Mus musculus)

Based on studies in mice, RUNX2 forms a complex with HEY2 (HRT2), a product of the NOTCH1 target gene. Binding to HEY2 inhibits RUNX2-mediated transcriptional activation of the BGLAP (Osteocalcin) gene (Garg et al. 2005). Other NOTCH1 targets, HEY1 and HES1, can also bind to RUNX2 and inhibit RUNX2 transcriptional activity (Hilton et al. 2008). NOTCH1 mutations cause severe aortic valve calcification in humans, which may be due to impaired repression of RUNX2-mediated transcription (Garg et al. 2005). NOTCH-mediated inhibition of RUNX2 transcriptional activity is also implicated in the maintenance of mesenchymal progenitors in the bone marrow by suppression of osteoblast differentiation (Hilton et al. 2008).

NOTCH1 may also inhibit RUNX2-mediated activation of target promoters by formation of a complex between RUNX2 and NOTCH1 intracellular domain (NICD1) (Engin et al. 2008).

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BGLAP gene expression is stimulated by RUNX2, WWTR1 and RB1 and inhibited by AR, YAP1 and ZNF521

Location: RUNX2 regulates osteoblast differentiation

Stable identifier: R-HSA-8877922

Type: omitted

Compartments: nucleoplasm, endoplasmic reticulum lumen

Inferred from: Bglap gene expression is negatively regulated by Znf521 (Mus musculus), Bglap gene expression is negatively regulated by Yap1 (Rattus norvegicus), Bglap gene expression is stimulated by the complex of Runx2 and Maf, or the complex of Runx2 and Wwtr1 (Taz) (Mus musculus)

Binding of RUNX2 to the OSE2 element in the promoter of the BGLAP (osteocalcin, OC) gene stimulates BGLAP transcription (Ducy and Karsenty 1995, Ducy et al. 1997). When RUNX2 binds the OSE2 element in complex with the MAF transcription factor, BGLAP transcription is enhanced (Nishikawa et al. 2010). BGLAP gene transcription is also directly stimulated by the complex of RUNX2 and WWTR1 (TAZ) (Hong et al. 2005), as well as the complex of RUNX2 and RB1 (Thomas et al. 2001). Phosphorylation of RUNX2, in the context of the RUNX2:CBFB complex, increases its association with the BGLAP promoter and enhances BGLAP transcription (Wee et al. 2002, Ge et al. 2009). Osteocalcin, a bone-derived hormone, is one of the most abundant non-collagenous proteins of the bone extracellular matrix (reviewed in Karsenty and Olson 2016).

Association of the activated androgen receptor (AR) with RUNX2 prevents binding of RUNX2 to the BGLAP promoter (Baniwal et al. 2009). Based on studies in rat, when YAP1, phosphorylated on an unknown tyrosine residue by SRC and/or YES1, is present in the complex with RUNX2 at the BGLAP gene promoter, transcription of the BGLAP gene is inhibited (Zaidi et al. 2004). Signaling by SRC is known to inhibit osteoblast differentiation (Marzia et al. 2000). Based on studies in mice, binding to ZNF521 (ZNP521) inhibits RUNX2-mediated activation of target promoters, such as BGLAP. HDAC3 is needed for ZNF521 to inhibit RUNX2-mediated transcription from the BGLAP promoter. Action of ZNF521 antagonizes RUNX2 during mesenchymal commitment to the osteoblast lineage and during osteoblast maturation (Hesse et al. 2010).


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**RUNX2 and SP7 bind the UCMA gene promoter**

**Location:** RUNX2 regulates osteoblast differentiation

**Stable identifier:** R-HSA-8939852

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Runx2:Cbfb and Sp7 bind the Ucma gene promoter (Mus musculus)

Based on mouse studies, RUNX2, presumably associated with CBFB, and SP7 (also known as Osterix or OSX), bind to adjacent RUNX2 and OSX binding sites, respectively, in the promoter of the UCMA gene. RUNX2 and OSX binding sites in the UCMA promoter are evolutionarily conserved. It is not clear whether RUNX2 and SP7 directly physically interact (Lee et al. 2015).

**Followed by:** UCMA gene expression is stimulated by RUNX2 and SP7

**Literature references**


**Editions**

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UCMA gene expression is stimulated by RUNX2 and SP7

**Location:** RUNX2 regulates osteoblast differentiation

**Stable identifier:** R-HSA-8939870

**Type:** omitted

**Compartments:** nucleoplasm, extracellular region

**Inferred from:** Ucma gene expression is stimulated by Runx2 and Sp7 (Mus musculus)

While RUNX2 and SP7 (OSX), based on mouse studies, can stimulate the UCMA gene expression independently of each other, simultaneous binding of RUNX2 and SP7 to adjacent RUNX2 and SP7 binding sites, respectively, in the UCMA promoter, synergistically activates UCMA transcription. UCMA stimulates osteoblast differentiation and formation of mineralized nodules (Lee et al. 2015).

**Preceded by:** RUNX2 and SP7 bind the UCMA gene promoter

**Literature references**


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RUNX2 binds to SATB2

**Location:** RUNX2 regulates osteoblast differentiation

**Stable identifier:** R-HSA-8985275

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Runx2 binds Satb2 (Mus musculus)

Based on studies in mice, RUNX2 forms a complex with the transcription factor SATB2. SATB2 may promote transcription of RUNX2 targets, including osteocalcin (BGLAP) (Dobreva et al. 2006).

**Literature references**


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**RUNX2 and RB1 bind the COL1A1 gene promoter**

**Location:** RUNX2 regulates osteoblast differentiation

**Stable identifier:** R-HSA-8985627

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Runx2 and Rb1 bind the Col1a1 gene promoter (Mus musculus)

Based on studies in mice, the complex of RUNX2 and RB1 binds to RUNX2-binding elements in the promoter of the COL1A1 gene encoding Collagen alpha-1(I) chain (Kern et al. 2001, Calo et al. 2010). RUNX2 binding sites are conserved in the human COL1A1 gene promoter.

**Preceded by:** RUNX2 binds RB1

**Followed by:** COL1A1 gene expression is stimulated by RUNX2 and RB1

**Literature references**


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COL1A1 gene expression is stimulated by RUNX2 and RB1

**Location:** RUNX2 regulates osteoblast differentiation

**Stable identifier:** R-HSA-8985644

**Type:** omitted

**Compartments:** nucleoplasm, extracellular region

**Inferred from:** Col1a1 gene expression is stimulated by Runx2 and Rb1 (Mus musculus)

Based on mouse studies, binding of the RUNX2:RB1 complex to RUNX2-response elements in the promoter of the COL1A1 gene, encoding Collagen alpha-1(I) chain, stimulates COL1A1 transcription (Kern et al. 2001, Cola et al. 2010).

**Preceded by:** RUNX2 and RB1 bind the COL1A1 gene promoter

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RUNX2 binds GLI3R

**Location:** RUNX2 regulates osteoblast differentiation

**Stable identifier:** R-HSA-9008215

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Runx2 binds Gli3r (Mus musculus)

Based on studies in mice, GLI3R, a repressive form of GLI3 generated in the Hedgehog "off" state, binds to RUNX2 and inhibits binding of RUNX2 to DNA. Cells haploinsufficient for PTCH1 generate less GLI3R, which is associated with increased RUNX2 activity and accelerated osteoblast differentiation (Ohba et al. 2008).

**Literature references**


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RUNX2 binds HDAC6

Location: RUNX2 regulates osteoblast differentiation

Stable identifier: R-HSA-9008389

Type: binding

Compartments: nucleoplasm

Inferred from: Runx2 binds Hdac6 (Rattus norvegicus)

Based on studies in rat osteoblast, RUNX2 forms a complex with the histone deacetylase HDAC6 (Westendorf et al. 2002).

Literature references


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  - SRC,YES1 phosphorylate YAP1  
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