Regulation of RUNX2 expression and activity

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**Introduction**

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

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

**Literature references**


Reactome database release: 69

This document contains 1 pathway and 32 reactions (see Table of Contents)

https://reactome.org
Several transcription factors have been implicated in regulation of the RUNX2 gene transcription. Similar to the RUNX1 gene, the RUNX2 gene expression can be regulated from the proximal P2 promoter or the distal P1 promoter (reviewed in Li and Xiao 2007).

Activated estrogen receptor alpha (ESR1) binds estrogen response elements (EREs) in the P2 promoter and stimulates RUNX2 transcription (Kammerer et al. 2013). Estrogen-related receptor alpha (ERRA) binds EREs or estrogen-related response elements (ERREs) in the P2 promoter of RUNX2. When ERRα is bound to its co-factor PPARG1CA (PGC1A), it stimulates RUNX2 transcription. When bound to its co-factor PPARG1CB (PGC1B), ERRα represses RUNX2 transcription (Kammerer et al. 2013).

TWIST1, a basic helix-loop-helix (bHLH) transcription factor, stimulates RUNX2 transcription by binding to the E1-box in the P2 promoter (Yang, Yang et al. 2011). TWIST proteins also interact with the DNA-binding domain of RUNX2 to modulate its activity during skeletogenesis (Bialek et al. 2004). Schnurri-3 (SHN3) is another protein that interacts with RUNX2 to decrease its availability in the nucleus and therefore its activity (Jones et al. 2006). In contrast, RUNX2 and SATB2 interact to enhance the expression of osteoblast-specific genes (Dobreva et al. 2006). Formation of the heterodimer with CBFB (CBF-beta) also enhances the transcriptional activity of RUNX2 (Kundu et al. 2002, Yoshida et al. 2002, Otto et al. 2002).

Transcription of RUNX2 from the proximal promoter is inhibited by binding of the glucocorticoid receptor (NR3C1) activated by dexamethasone (DEXA) to a glucocorticoid receptor response element (GRE), which is also present in the human promoter (Zhang et al. 2012).

NKX3-2 (BAPX1), required for embryonic development of the axial skeleton (Tribioli and Lufkin 1999), binds the distal (P1) promoter of the RUNX2 gene and inhibits its transcription (Lengner et al. 2005).
RUNX2-P1 transcription is also autoinhibited by RUNX2-P1, which binds to RUNX2 response elements in the P1 promoter of RUNX2 (Drissi et al. 2000). In contrast, binding of RUNX2-P2 to the proximal P2 promoter autoactivates transcription of RUNX2-P2 (Ducy et al. 1999). Binding of a homeodomain transcription factor DLX5, and possibly DLX6, to the RUNX2 P1 promoter stimulates RUNX2 transcription (Robledo et al. 2002, Lee et al. 2005). The homeobox transcription factor MSX2 can bind to DLX5 sites in the promoter of RUNX2 and inhibit transcription of RUNX2-P1 (Lee et al. 2005).

Translocation of RUNX2 protein to the nucleus is inhibited by binding to non-activated STAT1 (Kim et al. 2003).

Several E3 ubiquitin ligases were shown to polyubiquitinate RUNX2, targeting it for proteasome-mediated degradation: FBXW7a (Kumar et al. 2015), STUB1 (CHIP) (Li et al. 2008), SMURF1 (Zhao et al. 2003, Yang et al. 2014), WWP1 (Jones et al. 2006), and SKP2 (Thacker et al. 2016).

Literature references


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Activated estrogen receptor alpha (ESR1) binds estrogen response elements in the proximal P2 promoter of the RUNX2 gene (Kammerer et al. 2013).

**Followed by:** RUNX2 gene expression from proximal (P2) promoter is stimulated by ESR1:estrogen, ESRRA:PPARG1CA, TWIST1 and RUNX2-P2, and inhibited by ESRRA:PPARG1CB and DEXA:NR3C1

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ESRRA:PPARG1CA binds the RUNX2 gene promoter

**Location:** Regulation of RUNX2 expression and activity

**Stable identifier:** R-HSA-8939929

**Type:** binding

**Compartments:** nucleoplasm

Estrogen-related receptor alpha (ESRRA), in complex with its co-activator PPARG1CA (PGC1A), binds estrogen response elements (EREs) and/or estrogen-related response elements (ERREs) in the proximal P2 promoter of the RUNX2 gene (Kammerer et al. 2013).

**Followed by:** RUNX2 gene expression from proximal (P2) promoter is stimulated by ESR1:estrogen, ESRRA:PPARG1CA, TWIST1 and RUNX2-P2, and inhibited by ESRRA:PPARG1CB and DEXA:NR3C1

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ESRRA:PPARG1CB binds the RUNX2 gene promoter

**Location:** Regulation of RUNX2 expression and activity

**Stable identifier:** R-HSA-8939938

**Type:** binding

**Compartments:** nucleoplasm

Estrogen-related receptor alpha (ESRRA), in complex with its co-activator PPARG1CB (PGC1B), binds estrogen response elements (EREs) and/or estrogen-related response elements (ERREs) in the proximal P2 promoter of the RUNX2 gene (Kammerer et al. 2013).

**Followed by:** RUNX2 gene expression from proximal (P2) promoter is stimulated by ESR1:estrogen, ESRRA:PPARG1CA, TWIST1 and RUNX2-P2, and inhibited by ESRRA:PPARG1CB and DEXA:NR3C1

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TWIST1 binds the RUNX2 gene promoter

**Location:** Regulation of RUNX2 expression and activity

**Stable identifier:** R-HSA-8940032

**Type:** binding

**Compartments:** nucleoplasm

TWIST1 transcription factor binds the proximal P2 promoter of RUNX2. Binding involves the basic helix-loop-helix (bHLH) domain of TWIST1 and E1-box in the P2 promoter of RUNX2 (Yang et al. 2011). TWIST1, a transcriptional target of HIF1A (Yang et al. 2008) and STAT3 (Zhang et al. 2015), induces epithelial-to-mesenchymal transition (EMT) and promotes cancer metastasis (Yang et al. 2004). In zebrafish, Twist-mediated transactivation of runx2 controls skeletal development and dorsoventral patterning (Yang et al. 2011). Twist proteins also interact with the DNA-binding domain of RUNX2 to modulate its activity during skeletogenesis (Bialek et al. 2004).

**Followed by:** RUNX2 gene expression from proximal (P2) promoter is stimulated by ESR1:estrogen, ESRRA:PPARG1CA, TWIST1 and RUNX2-P2, and inhibited by ESRRA:PPARG1CB and DEXA:NR3C1

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Based on studies in mice, glucocorticoid receptor (NR3C1) activated by dexamethasone (DEXA) binds to glucocorticoid receptor response element (GRE) in the proximal (P2) promoter of the RUNX2 gene. NR3C1 may also recruit histone deacetylase HDAC1 to the RUNX2 promoter (Zhang et al. 2012). Similar to the mouse promoter, human RUNX2 P2 promoter also contains GREs.

**Followed by:** RUNX2 gene expression from proximal (P2) promoter is stimulated by ESR1:estrogen, ESRRA:PPARG1CA, TWIST1 and RUNX2-P2, and inhibited by ESRRA:PPARG1CB and DEXA:NR3C1

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RUNX2-P2 binds RUNX2 gene promoter

**Location:** Regulation of RUNX2 expression and activity

**Stable identifier:** R-HSA-9016526

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Runx2-P2 binds to Runx2 gene promoter (Mus musculus)

Based on studies in mice, RUNX2-P2 (RUNX2 variant expressed from the proximal promoter) binds to RUNX2 response elements in the proximal P2 promoter of the RUNX2 gene (Ducy et al. 1999). It is assumed that RUNX2 is associated with at least CBFB and the RUNX2 promoter, although this has not been examined.

**Followed by:** RUNX2 gene expression from proximal (P2) promoter is stimulated by ESR1:estrogen, ESRRA:PPARG1CA, TWIST1 and RUNX2-P2, and inhibited by ESRRA:PPARG1CB and DEXA:NR3C1

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RUNX2 gene expression from proximal (P2) promoter is stimulated by ESR1: estrogen, ESRRA:PPARG1CA, TWIST1 and RUNX2-P2, and inhibited by ESRR-A:PPARG1CB and DEXA:NR3C1 →

Location: Regulation of RUNX2 expression and activity

Stable identifier: R-HSA-8939900

Type: omitted

Compartments: nucleoplasm

Inferred from: Runx2 gene expression from proximal (P2) promoter is stimulated by Runx2-P2 and inhibited by DEXA:Nr3c1 (Mus musculus)

Activated estrogen receptor alpha (ESR1) directly stimulates the RUNX2 gene transcription by binding to estrogen response elements in the proximal P2 promoter of RUNX2. Estrogen-related receptor alpha (ESRRA) binds to estrogen response elements (EREs) or estrogen-related response elements (ERREs) in the proximal P2 promoter of the RUNX2 gene. In the presence of its PPARG1CA co-factor, ESRRA stimulates RUNX2 transcription. In the presence of another co-factor, PPARG1CB, ESRRA inhibits RUNX2 transcription (Kammerer et al. 2013).

Transcription of RUNX2 is stimulated by binding of TWIST1 transcription factor to the E1-box in the proximal P2 promoter of RUNX2 (Yang et al. 2011).

Studies in mice have shown that RUNX2-P2 can autoactivate its own expression by binding to the proximal P2 promoter of the RUNX2 gene (Ducy et al. 1999).

Based on studies in mice, transcription of RUNX2 from the proximal promoter is inhibited by binding of the glucocorticoid receptor (NR3C1) activated by dexamethasone (DEXA) to a glucocorticoid receptor response element (GRE), which is also present in the human promoter (Zhang et al. 2012). The complex of DEXA and NR3C1 may also inhibit RUNX2 activity by directly binding to the RUNX2 protein (Koromila et al. 2013).

Preceded by: Activated ESR1 binds the RUNX2 gene promoter, ESRRA:PPARG1CA binds the RUNX2 gene promoter, ESRRA:PPARG1CB binds the RUNX2 gene promoter, TWIST1 binds the RUNX2 gene promoter, DEXA:NR3C1 complex binds RUNX2 gene proximal promoter, RUNX2-P2 binds RUNX2 gene promoter

Followed by: RUNX2 binds STAT1, RUNX2 binds to HIVEP3 and WWP1, RUNX2 binds STUB1, RUNX2 translocates to the nucleus
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NKX3-2 binds RUNX2 gene promoter

**Location:** Regulation of RUNX2 expression and activity

**Stable identifier:** R-HSA-8985293

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Nkx3-2 binds Runx2 gene promoter (Mus musculus)

Based on studies in mice, the homeobox protein NKX3-2 (BAPX1), required for embryonic development of the axial skeleton (Tribioli and Lufkin 1999), binds the distal (P1) promoter of the RUNX2 gene (Lengner et al. 2005). NKX3-2 binding sites are conserved in the human RUNX2 promoter.

**Followed by:** RUNX2 gene expression from distal (P1) promoter is inhibited by NKX3-2, MSX2 and RUNX2-P1, and stimulated by DLX5,(DLX6)

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RUNX2-P1 binds RUNX2 gene promoter

**Location:** Regulation of RUNX2 expression and activity

**Stable identifier:** R-HSA-9008345

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Runx2-P1 binds to Runx2 gene promoter (Mus musculus)

Based on studies in mice, RUNX2-P1 (RUNX2 variant expressed from the distal promoter) binds to RUNX2 response elements in the distal promoter of the RUNX2 gene, which are conserved in rat and human RUNX2 promoters (Drissi et al. 2000). It is assumed that RUNX2 is associated with at least CBFB and the RUNX2 promoter, although this has not been examined.

**Preceded by:** RUNX2 translocates to the nucleus

**Followed by:** RUNX2 gene expression from distal (P1) promoter is inhibited by NKX3-2, MSX2 and RUNX2-P1, and stimulated by DLX5,(DLX6)

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**DLX5,(DLX6) binds RUNX2 gene promoter**

**Location:** Regulation of RUNX2 expression and activity

**Stable identifier:** R-HSA-9007707

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Dlx5,(Dlx6) binds Runx2 gene promoter (Mus musculus)

Based on studies in mice, in response to BMP2 signaling, a homeodomain transcription factor DLX5 binds to three sites in the distal (P1) promoter of the RUNX2 gene (Lee et al. 2005). DLX5 binding sites are conserved in the human RUNX2 promoter.

Dlx5 deficient mice show a mild delay in ossification of long bones and close to normal Runx2 expression. Mice that are double knockouts for Dlx5 and Dlx6 genes show severe defects in the formation of limbs, cranium and axial skeleton and die after birth. Dlx5/6 double knockouts show reduction in the number of Runx2-expressing chondrocytes (Robledo et al. 2002). As DLX6 is suggested by several studies to be redundant with DLX5 in the regulation of RUNX2 expression (Robledo et al. 2002, Holleville et al. 2007, Barron et al. 2011), although direct binding of DLX6 to the RUNX2 gene promoter has not been tested, DLX6 is shown as a candidate transcriptional regulator of RUNX2.

**Followed by:** RUNX2 gene expression from distal (P1) promoter is inhibited by NKX3-2, MSX2 and RUNX2-P1, and stimulated by DLX5,(DLX6)

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**MSX2 binds RUNX2 gene promoter**

**Location:** Regulation of RUNX2 expression and activity

**Stable identifier:** R-HSA-9007759

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Msx2 binds Runx2 gene promoter (Mus musculus)

Based on studies in mice, homeobox transcription factor MSX2 binds to DLX5 sites in the distal (P1) promoter of the RUNX2 gene, which are conserved between mice and humans, and antagonizes DLX5 binding (Lee et al. 2005).

**Followed by:** RUNX2 gene expression from distal (P1) promoter is inhibited by NKX3-2, MSX2 and RUNX2-P1, and stimulated by DLX5,(DLX6)

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RUNX2 gene expression from distal (P1) promoter is inhibited by NKX3-2, MSX2 and RUNX2-P1, and stimulated by DLX5,(DLX6)

**Location:** Regulation of RUNX2 expression and activity

**Stable identifier:** R-HSA-9007686

**Type:** omitted

**Compartments:** nucleoplasm

**Inferred from:** Runx2 gene transcription is repressed by Nkx3-2 and Ms2, and activated by Dlx5,(Dlx6) (Mus musculus)

Based on studies in mice, RUNX2 transcription is repressed by binding of the transcriptional repressor NKX3-2 (BAPX1) to the distal (P1) RUNX2 gene promoter (Lengner et al. 2005, Provot et al. 2006). RUNX2 itself can autoregulate through a negative feedback mechanism by binding of the RUNX2-P1 isoform to the evolutionarily conserved RUNX2 response elements in the distal P1 promoter (Drissi et al. 2000).

Based on studies in mice, transcription of RUNX2 from the distal (P1) promoter is directly stimulated by DLX5 (and possibly DLX6). Binding of DLX5 to the RUNX2 promoter is antagonized by MSX2. Once bound to the RUNX2 promoter, MSX2 inhibits RUNX2 transcription (Lee et al. 2005). DLX5 is activated by BMP2 signaling through an unknown mechanism.

Transcription of RUNX2 from the P1 promoter may be inhibited by the transcriptional repressor GFI1, which is essential for hematopoiesis (D'Souza et al. 2011).

**Preceded by:** NKX3-2 binds RUNX2 gene promoter, RUNX2-P1 binds RUNX2 gene promoter, DLX5,(DLX6) binds RUNX2 gene promoter, MSX2 binds RUNX2 gene promoter

**Followed by:** RUNX2 binds STAT1, RUNX2 binds to HIVEP3 and WWP1, RUNX2 binds STUB1, RUNX2 translocates to the nucleus

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RUNX2 binds STAT1

**Location:** Regulation of RUNX2 expression and activity

**Stable identifier:** R-HSA-9008015

**Type:** binding

**Compartments:** cytosol

**Inferred from:** Runx2 binds Stat1 (Mus musculus)

Based on studies in mice, RUNX2 forms a complex with non-active (unphosphorylated) STAT1 in the cytosol. The interaction between the two proteins involves the DNA binding and linker domain of STAT1 and the Runt domain of RUNX2. Binding to STAT1 prevents translocation of RUNX2 to the nucleus and thus interferes with activation of RUNX2 target genes. STAT1 phosphorylation diminishes its interaction with RUNX2. Stat1 knockout mice exhibit increased bone mass and accelerated osteoblast differentiation, accompanied by enhanced Runx2 activity (Kim et al. 2003).

**Preceded by:** RUNX2 gene expression from distal (P1) promoter is inhibited by NKX3-2, MSX2 and RUNX2-P1, and stimulated by DLX5,(DLX6), RUNX2 gene expression from proximal (P2) promoter is stimulated by ESR1:estrogen, ESRRA:PPARG1CA, TWIST1 and RUNX2-P2, and inhibited by ESRR-A:PPARG1CB and DEXA:NR3C1

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**RUNX2 translocates to the nucleus**

**Location:** Regulation of RUNX2 expression and activity

**Stable identifier:** R-HSA-9007999

**Type:** omitted

**Compartments:** cytosol, nucleoplasm

**Inferred from:** Runx2 translocates to the nucleus (Mus musculus)

Based on studies in mice, binding of RUNX2 to cytosolic STAT1 inhibits RUNX2 translocation to the nucleus (Kim et al. 2003).

**Preceded by:** RUNX2 gene expression from distal (P1) promoter is inhibited by NKX3-2, MSX2 and RUNX2-P1, and stimulated by DLX5,(DLX6), RUNX2 gene expression from proximal (P2) promoter is stimulated by ESR1:estrogen, ESRRA:PPARG1CA, TWIST1 and RUNX2-P2, and inhibited by ESRR-A:PPARG1CB and DEXA:NR3C1

**Followed by:** RUNX2 binds GSK3B, SCF(SKP2) complex binds RUNX2, RUNX2-P1 binds RUNX2 gene promoter

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</table>
RUNX2 binds to HIVEP3 and WWP1

Location: Regulation of RUNX2 expression and activity

Stable identifier: R-HSA-9008036

Type: binding

Compartments: cytosol

Inferred from: Runx2 binds to Hivep3 and Wwp1 (Mus musculus)

Based on studies in mice, HIVEP3 (also known as SHN3 or Schnurri-3), a zinc finger adapter protein, binds to RUNX2 together with the E3 ubiquitin ligase WWP1. Hivep3 knockout mice exhibit increased bone mass, due to increased bone formation by osteoblasts, which is accompanied by increased expression of Runx2 target genes (Jones et al. 2006).

Preceded by: RUNX2 gene expression from distal (P1) promoter is inhibited by NKX3-2, MSX2 and RUNX2-P1, and stimulated by DLX5,(DLX6), RUNX2 gene expression from proximal (P2) promoter is stimulated by ESR1:estrogen, ESRR:A:PPARG1CA, TWIST1 and RUNX2-P2, and inhibited by ESRR-A:PPARG1CB and DEXA:NR3C1

Followed by: WWP1 polyubiquitinitates RUNX2

Literature references


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</table>
**WWP1 polyubiquitinates RUNX2**

**Location:** Regulation of RUNX2 expression and activity

**Stable identifier:** R-HSA-9008076

**Type:** transition

**Compartments:** cytosol

**Inferred from:** Wwp1 polyubiquitinates Runx2 (Mus musculus)

Studies in mice have shown that once HIVEP3 (SHN3, Schnurri-3) and WWP1 are bound to RUNX2, WWP1, an E3 ubiquitin ligase, polyubiquitinates RUNX2, targeting it for proteasome-mediated degradation. HIVEP3 overexpression in human embryonic kidney 293T cells leads to a dose-dependent decrease in RUNX2 protein levels (Jones et al. 2006).

**Preceded by:** RUNX2 binds to HIVEP3 and WWP1

**Followed by:** Proteasome degrades polyubiquitinated RUNX2

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</table>
Proteasome degrades polyubiquitinated RUNX2

Location: Regulation of RUNX2 expression and activity

Stable identifier: R-HSA-9008110

Type: omitted

Compartments: cytosol

Inferred from: Proteasome degrades polyubiquitinated Runx2 (Mus musculus)

Based on studies in mice, proteasome degrades RUNX2 polyubiquitinated by WWP1 in the context of the complex of RUNX2, HIVEP3 (SHN3, Schnurri-3) and WWP1 (Jones et al. 2006).

Preceded by: WWP1 polyubiquitinates RUNX2

Literature references


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RUNX2 binds GSK3B

**Location:** Regulation of RUNX2 expression and activity

**Stable identifier:** R-HSA-9008476

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Runx2 binds GSK3B (Mus musculus)

RUNX2 forms a complex with a serine/threonine kinase GSK3B. Since GSK3B can localize to both cytosol and nucleus, this reaction is shown to occur in the nucleoplasm, although this has not been experimentally tested (Kugimiya et al. 2007, Kumar et al. 2015).

**Preceded by:** RUNX2 translocates to the nucleus

**Followed by:** GSK3B phosphorylates RUNX2

**Literature references**


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</table>
GSK3B phosphorylates RUNX2

Location: Regulation of RUNX2 expression and activity

Stable identifier: R-HSA-9008480

Type: transition

Compartments: nucleoplasm

Inferred from: GSK3B phosphorylates Runx2 (Homo sapiens)

GSK3B phosphorylates RUNX2 on three serine residues in an evolutionarily conserved motif SPPWSYDQS, which decreases the DNA binding ability of RUNX2 (Kugimiya et al. 2007, Kumar et al. 2015).

Preceded by: RUNX2 binds GSK3B

Followed by: FBXW7 binds RUNX2 and GSK3B

Literature references


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</table>
FBXW7 binds RUNX2 and GSK3B

**Location:** Regulation of RUNX2 expression and activity

**Stable identifier:** R-HSA-9008478

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Fbxw7 binds Runx2 and Gsk3b (Mus musculus)

FBXW7alpha, a component of an SCF ubiquitin ligase complex, binds to RUNX2 in the presence of GSK3B, probably after GSK3B phosphorylates RUNX2 (Kumar et al. 2015). The presence of other SCF complex components, besides FBXW7alpha, is assumed, although it has not been tested whether they co-immunoprecipitate with RUNX2 and GSK3B.

**Preceded by:** GSK3B phosphorylates RUNX2

**Followed by:** FBXW7 polyubiquitinates RUNX2

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</table>
The E3 ubiquitin ligase FBXW7alpha, a component of an SCF ubiquitin ligase complex, polyubiquitinates RUNX2, targeting it for degradation. The presence of GSK3B, and probably prior phosphorylation of RUNX2 by GSK3B, is required for FBXW7alpha-mediated polyubiquitination of RUNX2 (Kumar et al. 2015).

**Preceded by:** FBXW7 binds RUNX2 and GSK3B

**Followed by:** Proteasome degrades polyubiquitinated RUNX2

**Literature references**


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RUNX2, polyubiquitinated by FBXW7alpha in a GSK3B-dependant manner, is degraded by the proteasome (Kumar et al. 2015).

**Preceded by:** FBXW7 polyubiquitinates RUNX2

**Literature references**

RUNX2 binds STUB1

Location: Regulation of RUNX2 expression and activity

Stable identifier: R-HSA-9009309

Type: binding

Compartments: cytosol

RUNX2 binds to STUB1 (CHIP), an E3 ubiquitin ligase (Li et al. 2008).

Preceded by: RUNX2 gene expression from distal (P1) promoter is inhibited by NKX3-2, MSX2 and RUNX2-P1, and stimulated by DLX5,(DLX6), RUNX2 gene expression from proximal (P2) promoter is stimulated by ESR1:estrogen, ESRR:A:PPARG1CA, TWIST1 and RUNX2-P2, and inhibited by ESRR-A:PPARG1CB and DEXA:NR3C1

Followed by: STUB1 polyubiquitinates RUNX2

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</table>
**STUB1 polyubiquitinates RUNX2**

**Location:** Regulation of RUNX2 expression and activity

**Stable identifier:** R-HSA-9009308

**Type:** transition

**Compartments:** cytosol

STUB1 (CHIP), an E3 ubiquitin ligase, promotes polyubiquitination of RUNX2, targeting it for proteasome-mediated degradation (Li et al. 2008).

**Preceded by:** RUNX2 binds STUB1

**Followed by:** Proteasome degrades PolyUb-RUNX2

**Literature references**


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</table>
RUNX2 binds SMURF1 gene

**Location:** Regulation of RUNX2 expression and activity

**Stable identifier:** R-HSA-9009451

**Type:** binding

**Compartments:** nucleoplasm

RUNX2, presumably in complex with CBFB, binds RUNX2 binding elements in the promoter of the SMURF1 gene, encoding an E3 ubiquitin ligase SMURF1 (Yang et al. 2014).

**Followed by:** SMURF1 gene expression is stimulated by RUNX2

**Literature references**


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</table>
SMURF1 gene expression is stimulated by RUNX2

**Location:** Regulation of RUNX2 expression and activity

**Stable identifier:** R-HSA-9009452

**Type:** omitted

**Compartments:** nucleoplasm, cytosol

Binding of RUNX2, presumably in complex with CBFB, to the SMURF1 gene promoter stimulates SMURF1 transcription. As SMURF1 is an E3 ubiquitin ligase which targets RUNX2 for degradation, this creates a negative feedback loop (Yang et al. 2014).

**Preceded by:** RUNX2 binds SMURF1 gene

**Followed by:** RUNX2 binds SMURF1

**Literature references**


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</table>
RUNX2 binds SMURF1

Location: Regulation of RUNX2 expression and activity

Stable identifier: R-HSA-9009401

Type: binding

Compartments: cytosol

Inferred from: Runx2 binds Smurf1 (Mus musculus)

SMURF1, an E3 ubiquitin ligase, binds to RUNX2 (Zhao et al. 2003). While the direct interaction was demonstrated in mouse cells, it was shown that in human cells RUNX2 stability is increased upon SMURF1 knockdown while RUNX2 ubiquitination is decreased (Yang et al. 2014).

Preceded by: SMURF1 gene expression is stimulated by RUNX2

Followed by: SMURF1 polyubiquitinates RUNX2

Literature references


SMURF1 polyubiquitinates RUNX2

Location: Regulation of RUNX2 expression and activity

Stable identifier: R-HSA-9009403

Type: transition

Compartments: cytosol

Inferred from: Smurf1 polyubiquitinates Runx2 (Mus musculus)

Based on studies in mice, SMURF1 polyubiquitinates RUNX2, targeting it for degradation (Zhao et al. 2003). In human cells, RUNX2 ubiquitination is decreased upon SMURF1 knockdown (Yang et al. 2014).

Preceded by: RUNX2 binds SMURF1

Followed by: Proteasome degrades PolyUb-RUNX2

Literature references


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Proteasome degrades PolyUb-RUNX2

Location: Regulation of RUNX2 expression and activity

Stable identifier: R-HSA-9009362

Type: omitted

Compartments: cytosol

Inferred from: Proteasome degrades polyubiquitinated Runx2 (Mus musculus)

RUNX2 polyubiquitinated by STUB1 (CHIP) (Li et al. 2008) or SMURF1 (Zhao et al. 2003, Yang et al. 2014) is degraded by the proteasome.

Preceded by: STUB1 polyubiquitinates RUNX2, SMURF1 polyubiquitinates RUNX2

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SCF(SKP2) complex binds RUNX2

**Location:** Regulation of RUNX2 expression and activity

**Stable identifier:** R-HSA-8939688

**Type:** binding

**Compartments:** nucleoplasm

The E3 ubiquitin ligase complex SCF binds RUNX2 through direct interaction between SKP2 subunit of the SCF complex and RUNX2 (Thacker et al. 2016). This process is inhibited by glucose uptake in osteoblasts (Wei et al. 2015).

**Preceded by:** RUNX2 translocates to the nucleus

**Followed by:** SCF(SKP2) polyubiquitinates RUNX2

**Literature references**


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SCF(SKP2) polyubiquitinates RUNX2

Location: Regulation of RUNX2 expression and activity

Stable identifier: R-HSA-8939706

Type: transition

Compartments: nucleoplasm

The SCF(SKP2) E3 ubiquitin ligase complex polyubiquitinates RUNX2 on unknown lysine residues, targeting it for proteasome-mediated degradation. SKP2-triggered RUNX2 degradation negatively regulates osteogenesis by inhibiting differentiation of osteoblasts (Thacker et al. 2016). This process is inhibited by glucose uptake in osteoblasts (Wei et al. 2015).

Preceded by: SCF(SKP2) complex binds RUNX2

Followed by: 26S proteasome degrades PolyUb-RUNX2

Literature references


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26S proteasome degrades PolyUb-RUNX2

Location: Regulation of RUNX2 expression and activity

Stable identifier: R-HSA-8939801

Type: omitted

Compartments: nucleoplasm

Polyubiquitinated RUNX2 is degraded by the proteasome. As it has not been examined whether SCF(SKP2)-mediated polyubiquitination of RUNX2 leads to translocation of PolyUb-RUNX2 to the cytosol (Thacker et al. 2016), proteasome mediated degradation is assumed to happen in the nucleus. This process is inhibited by glucose uptake in osteoblasts (Wei et al. 2015).

Preceded by: SCF(SKP2) polyubiquitinates RUNX2

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https://reactome.org
26S proteasome degrades PolyUb-RUNX2