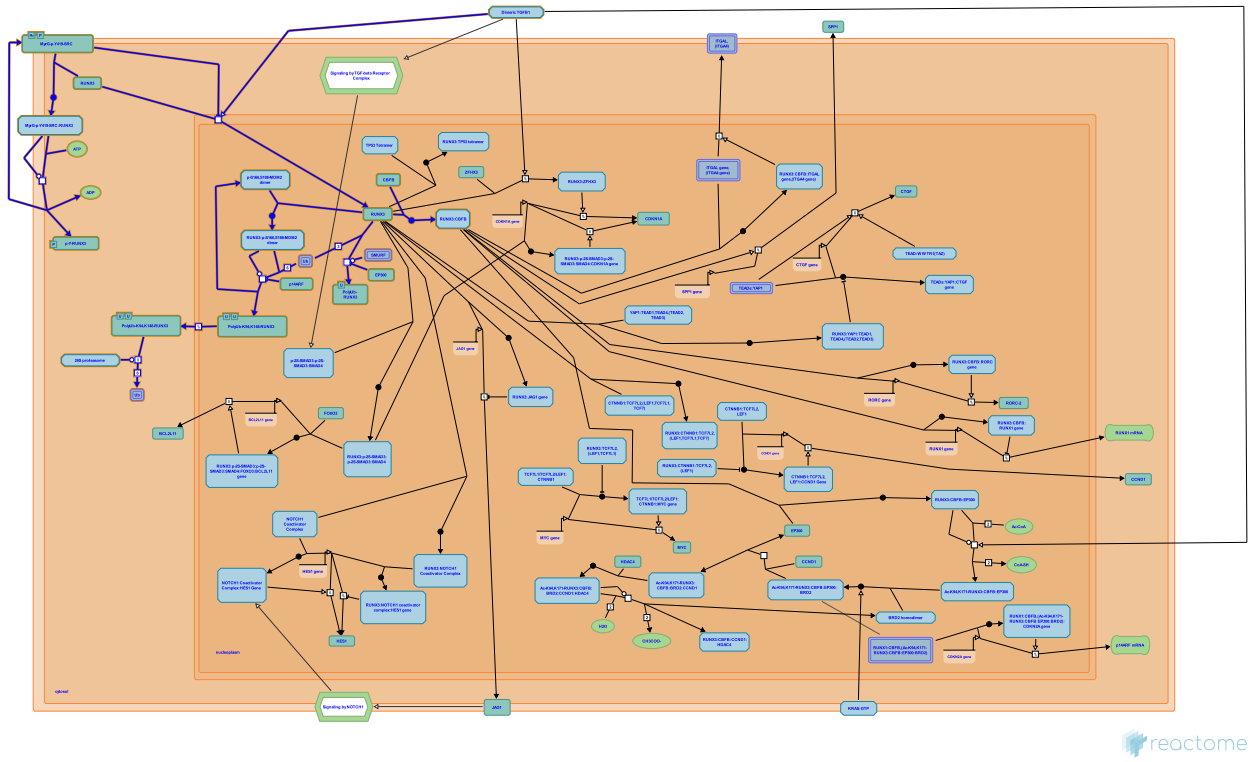
Regulation of RUNX3 expression and activity



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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

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

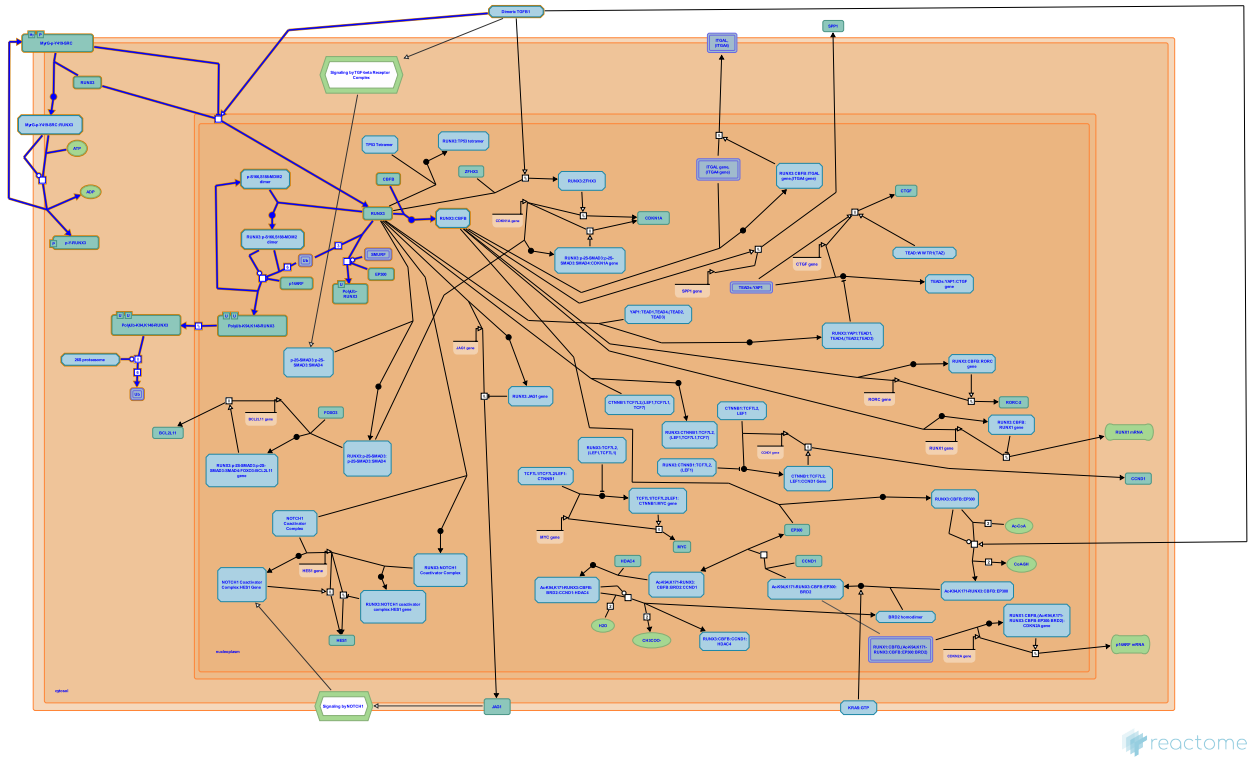
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 1 pathway and 9 reactions (see Table of Contents)

Regulation of RUNX3 expression and activity ↗

Stable identifier: R-HSA-8941858



RUNX3, like other RUNX family members, is transcribed from two promoters - the proximal P2 promoter and the distal P1 promoter. The P2 promoter is positioned within a large CpG island that is frequently methylated in solid tumors, resulting in epigenetic inactivation of the RUNX3 gene (reviewed by Levanon and Groner 2004). RUNX3 transcription is affected by SMAD4 levels. RUNX3 may directly upregulate its own transcription through a positive feedback loop (Whittle et al. 2015). Under hypoxic conditions, RUNX3 transcription is downregulated. Hypoxic silencing of RUNX3 involves hypoxia-induced upregulation of the histone methyltransferase G9a and histone deacetylase HDAC1, which leads to increased dimethylation of histone H3 at lysine residue K9 (K10 when taking into account the initiator methionine) and reduced acetylation of histone H3 at the RUNX3 promoter (Lee et al. 2009).
RUNX3 protein levels are inversely related to the levels of microRNA miR-130b. Based on in silico analysis, RUNX3 is predicted to be the target of miR-130b, but binding assays and 3'UTR reporter assays have not been done to confirm this (Lai et al. 2010, Paudel et al. 2016).
Similar to RUNX1 and RUNX2, RUNX3 forms a transcriptionally active heterodimer with CBFB (CBF-beta) (Kim et al. 2013). RUNX3 activity can be regulated by changes in RUNX3 localization. SRC protein tyrosine kinase phosphorylates RUNX3 on multiple tyrosine residues, inhibiting its translocation from the cytosol to the nucleus and thus inhibiting RUNX3-mediated transcription (Goh et al. 2010). Subcellular localization of RUNX3 may be affected by PIM1-mediated phosphorylation (Kim et al. 2008).
The P1 and P2 promoters regulate RUNX3 transcription in a cell-type/differentiation dependent manner, giving rise to the p44 and p46 isoforms of RUNX3, respectively. Several splicing isoforms have also been reported. One example is the generation of a 33 kDa protein isoform (p33) by alternative splicing. The RUNX3 p33 isoform lacks the Runt domain and is unable to transactivate the regulatory regions of integrin genes. The p33 isoform is induced during maturation of monocyte-derived dendritic cells (MDDC), leading to reduced expression of genes involved in inflammatory responses, such as IL8 (interleukin-8) (Puig-Kroger et al. 2010).
E3 ubiquitin ligases MDM2 (Chi et al. 2009), SMURF1 and SMURF2 (Jin et al. 2004) are implicated in RUNX3 polyubiquitination and degradation.

Literature references

Oh, BC., Kim, HR., Bae, SC., Choi, JK. (2008). Pim-1 kinase phosphorylates and stabilizes RUNX3 and alters its subcellular localization. *J. Cell. Biochem., 105*, 1048-58. ↗

Lee, KS., Lee, YH., Lee, JW., Bae, SC., Kim, J., Park, WY. et al. (2009). Runt-related transcription factor RUNX3 is a target of MDM2-mediated ubiquitination. *Cancer Res., 69*, 8111-9. ↗

Kim, J., Kim, WH., Lee, YM., Lee, SH. (2009). Hypoxic silencing of tumor suppressor RUNX3 by histone modification in gastric cancer cells. *Oncogene, 28*, 184-94. ↗

Thorsen, SM., DelGiorno, KE., Hruban, RH., Rani, PG., Chang, AE., Hingorani, SR. et al. (2015). RUNX3 Controls a Metastatic Switch in Pancreatic Ductal Adenocarcinoma. *Cell, 161*, 1345-60. ↗

Jeon, EJ., Jin, YH., Lee, YH., Li, QL., Lee, KY., Bae, SC. et al. (2004). Transforming growth factor-beta stimulates p300-dependent RUNX3 acetylation, which inhibits ubiquitination-mediated degradation. *J. Biol. Chem., 279*, 29409-17. ↗

Editions

2016-12-13	Authored	Orlic-Milacic, M.
2017-01-31	Reviewed	Ito, Y., Chuang, LS.
2017-01-31	Edited	Orlic-Milacic, M.

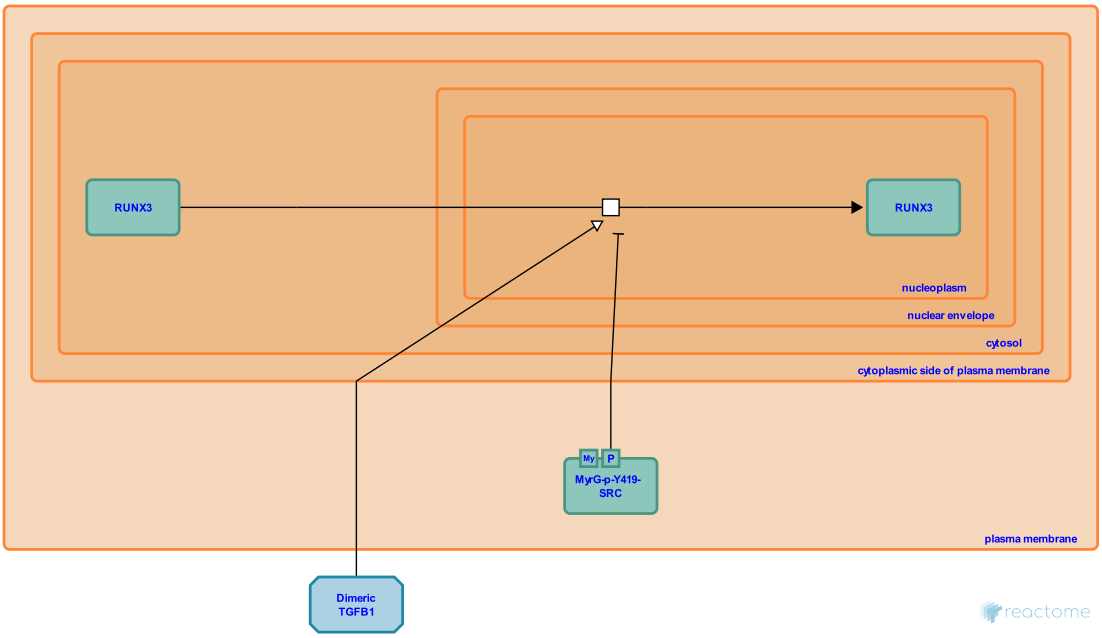
RUNX3 translocates to the nucleus ↗

Location: Regulation of RUNX3 expression and activity

Stable identifier: R-HSA-8937814

Type: transition

Compartments: nucleoplasm, cytosol



Translocation of RUNX3 from the cytosol to the nucleus is stimulated by TGF-beta (TGFB1) treatment (Ito et al. 2005) and inhibited by SRC-mediated phosphorylation of RUNX3 on multiple tyrosine residues (Goh et al. 2010).

Followed by: SMURFs ubiquitinate RUNX3, MDM2 binds RUNX3, CBFB binds RUNX3

Literature references

Cinghu, S., Lee, KS., Lee, YS., Kim, JH., Goh, YM., Hong, ET. et al. (2010). Src kinase phosphorylates RUNX3 at tyrosine residues and localizes the protein in the cytoplasm. *J. Biol. Chem., 285*, 10122-9. ↗

Yano, T., Salto-Tellez, M., Ida, H., Ito, K., Ito, Y., Peh, BK. et al. (2005). RUNX3, a novel tumor suppressor, is frequently inactivated in gastric cancer by protein mislocalization. *Cancer Res., 65*, 7743-50. ↗

Editions

2016-12-13	Authored	Orlic-Milacic, M.
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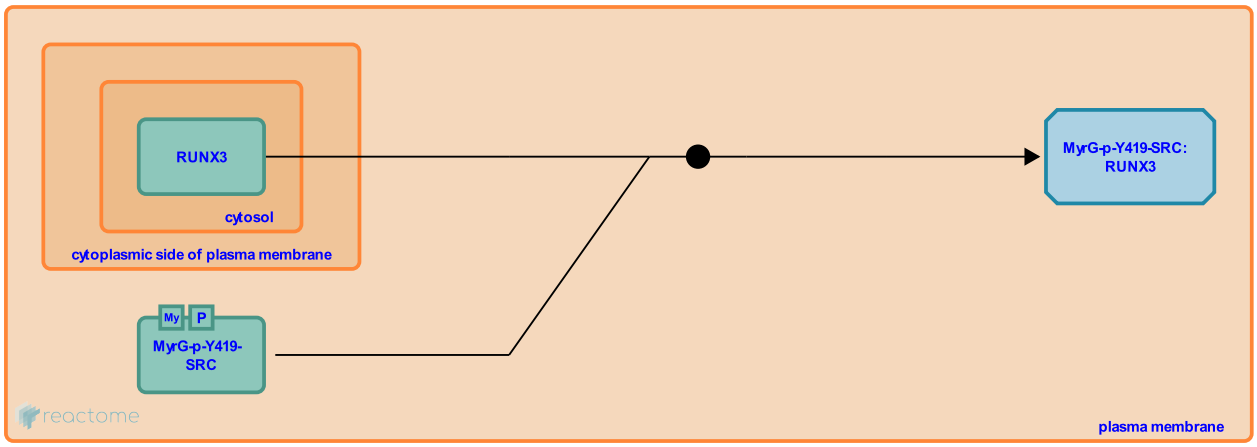
RUNX3 binds SRC ↗

Location: Regulation of RUNX3 expression and activity

Stable identifier: R-HSA-8937792

Type: binding

Compartments: plasma membrane, cytosol



Activated SRC binds to RUNX3 in the cytosol. The interaction involves the Runt domain of RUNX3 (Goh et al. 2010).

Followed by: SRC phosphorylates RUNX3

Literature references

Cinghu, S., Lee, KS., Lee, YS., Kim, JH., Goh, YM., Hong, ET. et al. (2010). Src kinase phosphorylates RUNX3 at tyrosine residues and localizes the protein in the cytoplasm. *J. Biol. Chem., 285*, 10122-9. ↗

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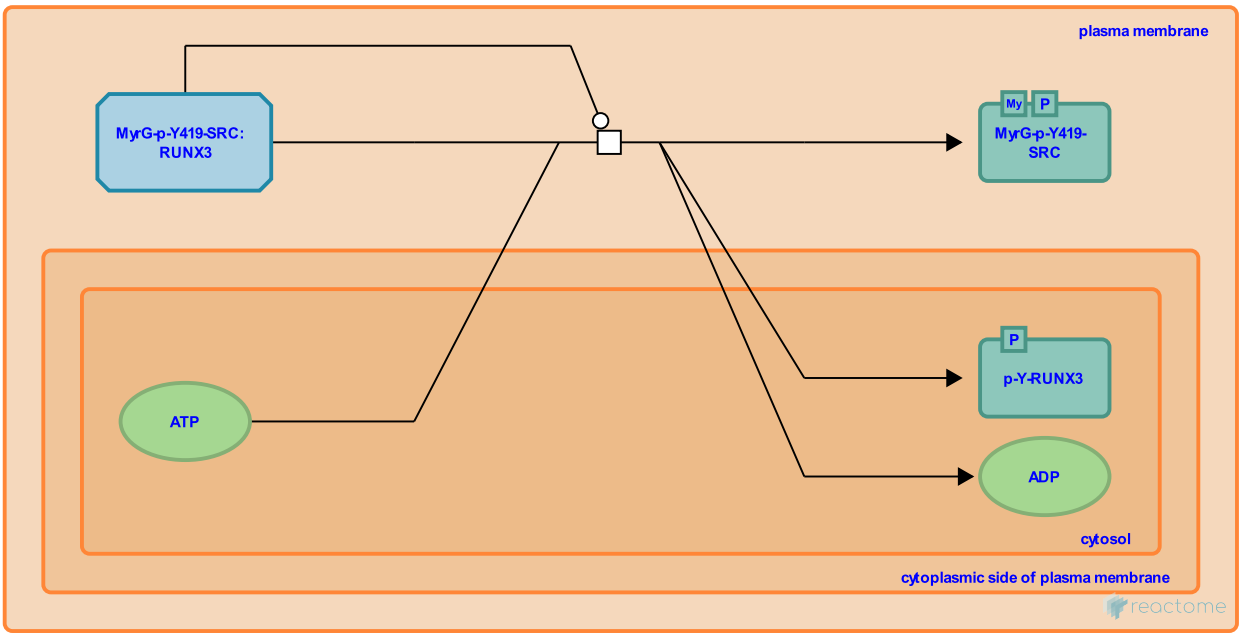
SRC phosphorylates RUNX3 ↗

Location: Regulation of RUNX3 expression and activity

Stable identifier: R-HSA-8937807

Type: transition

Compartments: plasma membrane, cytosol



Activated SRC phosphorylates RUNX3 in the cytosol, on multiple tyrosine residues. There are eleven tyrosine residues in RUNX3, but SRC target sites have not been determined. SRC-mediated phosphorylation of RUNX3 inhibits translocation of RUNX3 to the nucleus and is the underlying cause of cytosolic localization of RUNX3 in gastric and breast cancer (Goh et al. 2010).

Preceded by: RUNX3 binds SRC

Literature references

Cinghu, S., Lee, KS., Lee, YS., Kim, JH., Goh, YM., Hong, ET. et al. (2010). Src kinase phosphorylates RUNX3 at tyrosine residues and localizes the protein in the cytoplasm. *J. Biol. Chem., 285*, 10122-9. ↗

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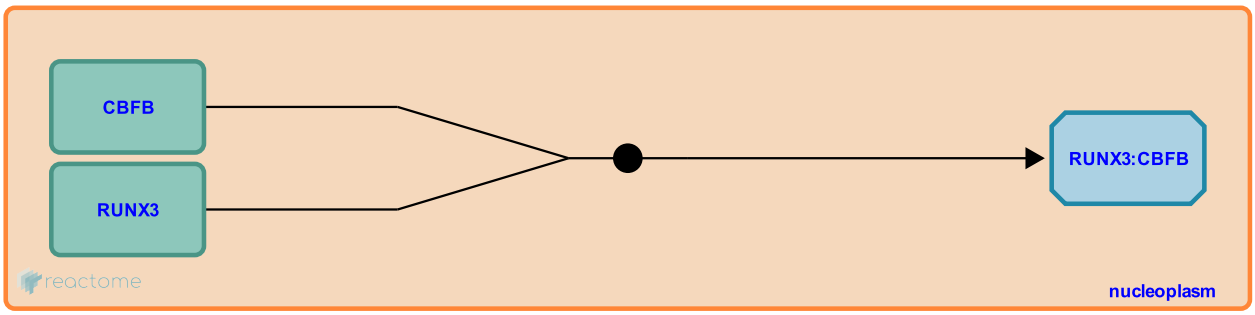
CBFB binds RUNX3 ↗

Location: Regulation of RUNX3 expression and activity

Stable identifier: R-HSA-8865454

Type: binding

Compartments: nucleoplasm



CBFB binds the transcription factor RUNX3, interacting with its Runt domain, which is highly similar to Runt domains of RUNX1 and RUNX2 (Kim et al. 2013). RUNX3 is implicated in neurogenesis, thymopoiesis and stomach development (Inoue et al. 2002, Levanon et al. 2002, Levanon et al. 2003). RUNX3 and CBFB are frequently downregulated in gastric cancer (Sakakura et al. 2005).

Preceded by: RUNX3 translocates to the nucleus

Literature references

Hartley, PD., Mann, S., Gross, JD., Krogan, NJ., Kim, DY., Crosby, DC. et al. (2013). CBFβ stabilizes HIV Vif to counteract APOBEC3 at the expense of RUNX1 target gene expression. *Mol. Cell, 49,* 632-44. ↗

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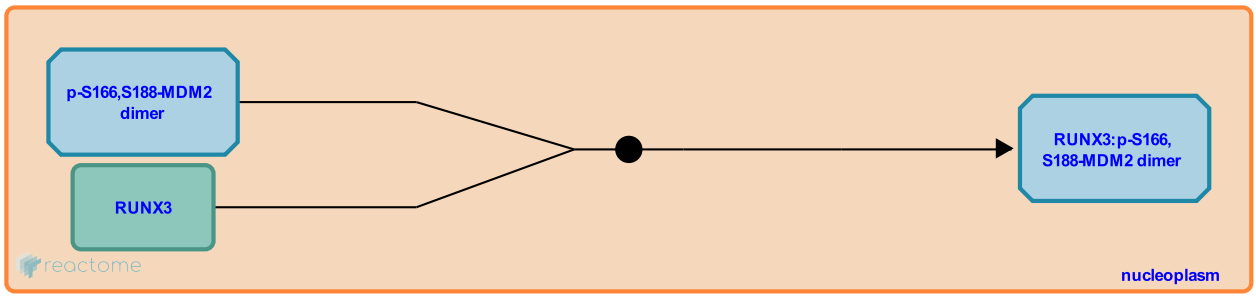
MDM2 binds RUNX3 ↗

Location: Regulation of RUNX3 expression and activity

Stable identifier: R-HSA-8952371

Type: binding

Compartments: nucleoplasm



MDM2 and RUNX3 form a complex in the nucleus. Association of RUNX3 with CBFB does not interfere with binding of MDM2 to RUNX3. The interaction involves the acidic domain of MDM2 and the Runt domain of RUNX3 (Chi et al. 2009).

Preceded by: RUNX3 translocates to the nucleus

Followed by: MDM2 polyubiquitinates RUNX3

Literature references

Lee, KS., Lee, YH., Lee, JW., Bae, SC., Kim, J., Park, WY. et al. (2009). Runt-related transcription factor RUNX3 is a target of MDM2-mediated ubiquitination. *Cancer Res., 69*, 8111-9. ↗

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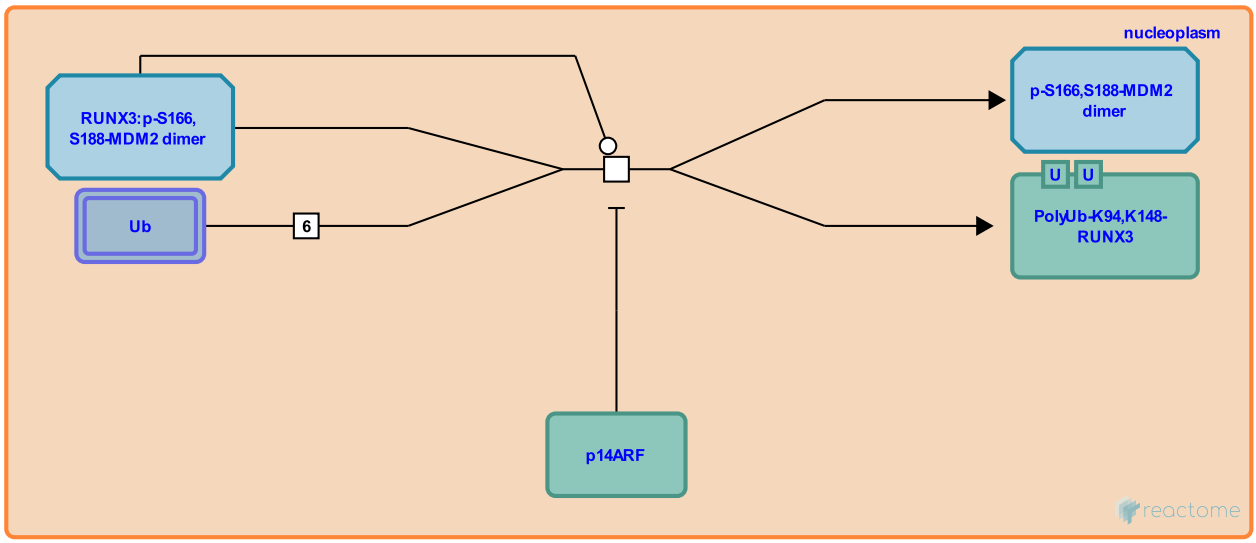
MDM2 polyubiquitinates RUNX3 ↗

Location: Regulation of RUNX3 expression and activity

Stable identifier: R-HSA-8952382

Type: transition

Compartments: nucleoplasm



MDM2 polyubiquitinates RUNX3 on lysine residues K94 and K148. MDM-mediated ubiquitination of RUNX3 is inhibited by p14-ARF (Chi et al. 2009).

Preceded by: MDM2 binds RUNX3

Followed by: Polyubiquitinated RUNX3 translocates to the cytosol

Literature references

Lee, KS., Lee, YH., Lee, JW., Bae, SC., Kim, J., Park, WY. et al. (2009). Runt-related transcription factor RUNX3 is a target of MDM2-mediated ubiquitination. *Cancer Res., 69*, 8111-9. ↗

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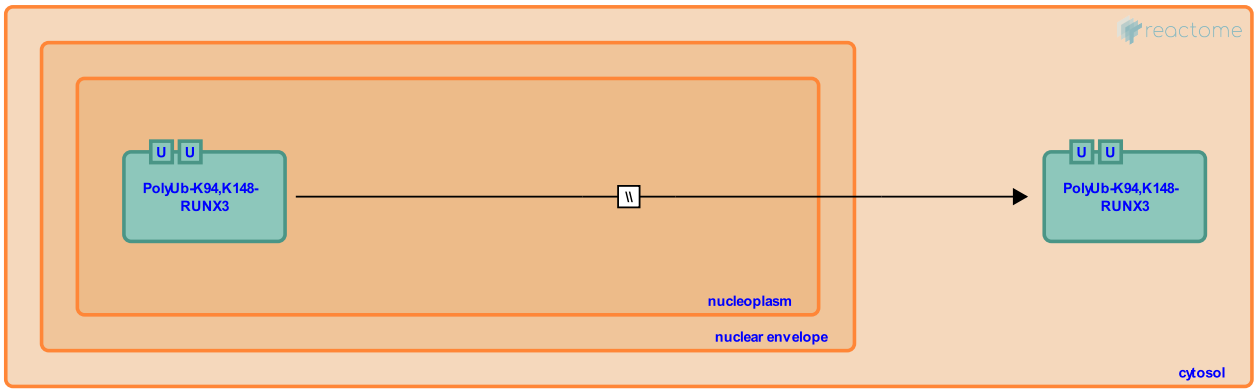
Polyubiquitinated RUNX3 translocates to the cytosol ↗

Location: Regulation of RUNX3 expression and activity

Stable identifier: R-HSA-8952399

Type: omitted

Compartments: nucleoplasm



Polyubiquitination of RUNX3 by MDM2 promotes translocation of RUNX3 from the nucleus to the cytosol (Chi et al. 2009).

Preceded by: MDM2 polyubiquitinates RUNX3

Followed by: Polyubiquitinated RUNX3 is degraded by the proteasome

Literature references

Lee, KS., Lee, YH., Lee, JW., Bae, SC., Kim, J., Park, WY. et al. (2009). Runt-related transcription factor RUNX3 is a target of MDM2-mediated ubiquitination. *Cancer Res., 69*, 8111-9. ↗

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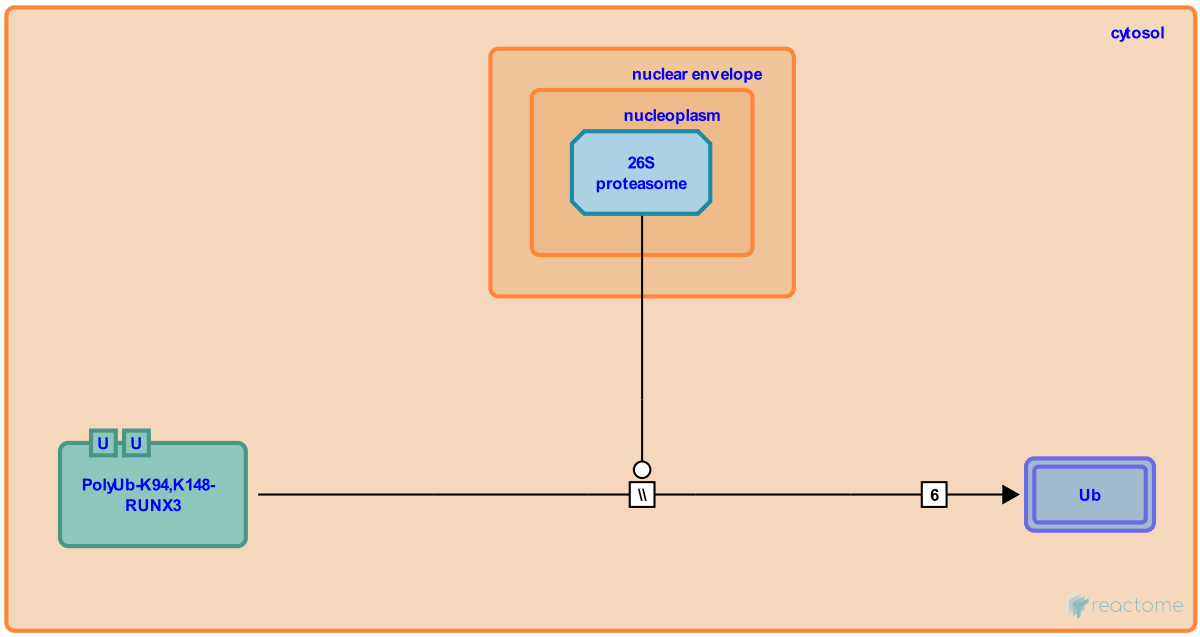
Polyubiquitinated RUNX3 is degraded by the proteasome ↗

Location: Regulation of RUNX3 expression and activity

Stable identifier: R-HSA-8952408

Type: omitted

Compartments: cytosol



Polyubiquitinated RUNX3 is degraded by the proteasome (Chi et al. 2009).

Preceded by: Polyubiquitinated RUNX3 translocates to the cytosol

Literature references

Lee, KS., Lee, YH., Lee, JW., Bae, SC., Kim, J., Park, WY. et al. (2009). Runt-related transcription factor RUNX3 is a target of MDM2-mediated ubiquitination. *Cancer Res., 69*, 8111-9. ↗

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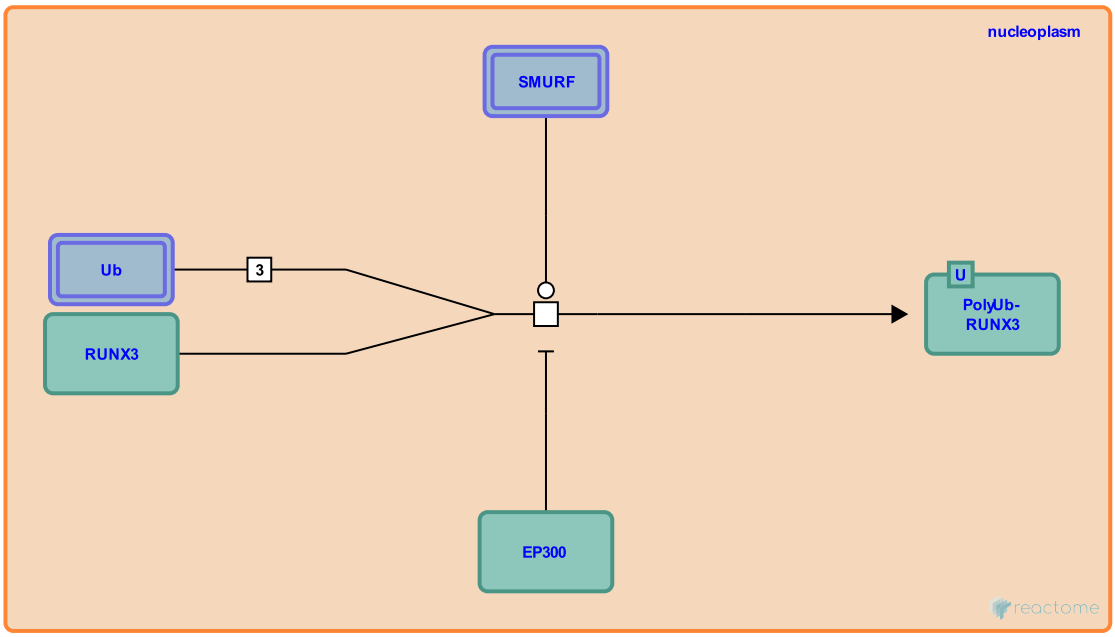
SMURFs ubiquitinate RUNX3 ↗

Location: Regulation of RUNX3 expression and activity

Stable identifier: R-HSA-8952419

Type: transition

Compartments: nucleoplasm



SMURF1 and SMURF2 polyubiquitinate RUNX3 on unknown lysine residues, possibly K148, K186 and K192, targeting it for degradation. The interaction between SMURFs and RUNX3 involves the PY motif of RUNX3 and the WW domain of SMURFs. Acetylation of RUNX3 by EP300 (p300) prevents SMURF-mediated ubiquitination of RUNX3, thus increasing RUNX3 protein stability (Jin et al. 2004).

Preceded by: RUNX3 translocates to the nucleus

Literature references

Jeon, EJ., Jin, YH., Lee, YH., Li, QL., Lee, KY., Bae, SC. et al. (2004). Transforming growth factor-beta stimulates p300-dependent RUNX3 acetylation, which inhibits ubiquitination-mediated degradation. *J. Biol. Chem., 279*, 29409-17. ↗

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