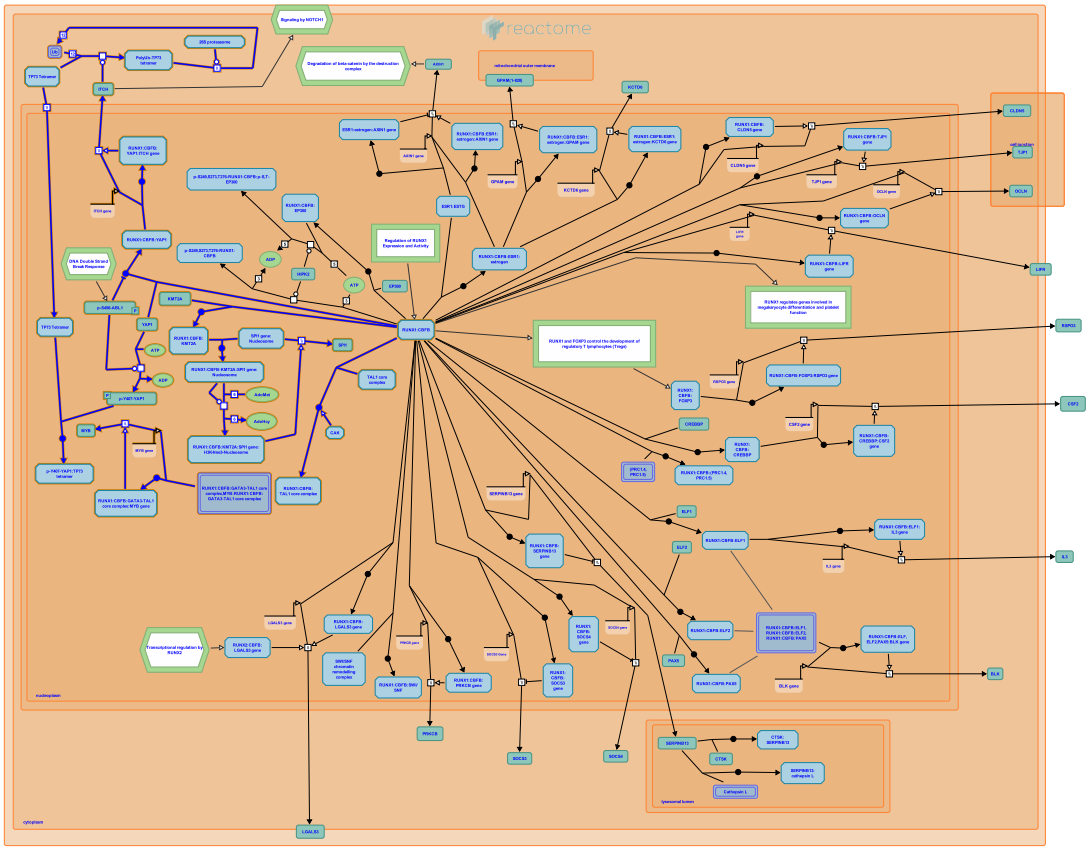
RUNX1 regulates transcription of genes involved in differentiation of HSCs



Chuang, LS., Ito, Y., Orlic-Milacic, M., Skokowa, J.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

12/11/2019

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.

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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. ↗

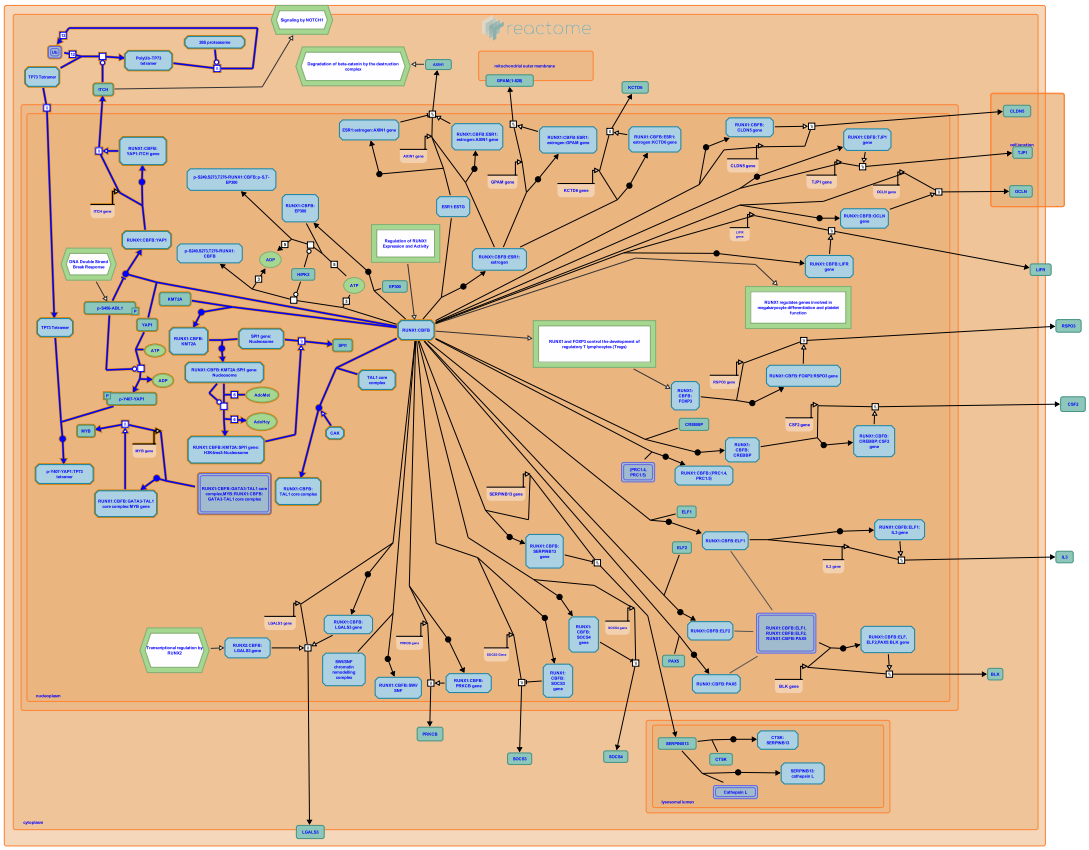
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

RUNX1 regulates transcription of genes involved in differentiation of HSCs ↗

Stable identifier: R-HSA-8939236



The RUNX1:CBFB complex regulates transcription of the SPI1 (PU.1) gene, involved in differentiation of hematopoietic stem cells (HSCs). RUNX1 recruits histone methyltransferase KMT2A (MLL) to the SPI1 gene locus, leading to generation of the activating H3K4Me3 mark on nucleosomes associated with the SPI1 promoter and the upstream regulatory element (Huang et al. 2011). SPI1 transactivation represses self-renewal and proliferation of HSCs (Fukuchi et al. 2008) and is needed for commitment of HSCs to specific hematopoietic lineages (Imperato et al. 2015).

As a component of the TAL1 transcription factor complex, involved in acute T cell lymphoblastic leukemia (T-ALL), RUNX1 can promote growth and inhibit apoptosis of hematopoietic stem cells by stimulating transcription of the MYB gene and possibly the TRIB2 gene (Sanda et al. 2012, Mansour et al. 2014).

Literature references

Huang, G., Zhao, X., Wang, L., Elf, S., Xu, H., Zhao, X. et al. (2011). The ability of MLL to bind RUNX1 and methylate H3K4 at PU.1 regulatory regions is impaired by MDS/AML-associated RUNX1/AML1 mutations. *Blood, 118*, 6544-52. ↗

Fukuchi, Y., Ito, M., Shibata, F., Kitamura, T., Nakajima, H. (2008). Activation of CCAAT/enhancer-binding protein alpha or PU.1 in hematopoietic stem cells leads to their reduced self-renewal and proliferation. *Stem Cells, 26*, 3172-81. ↗

Imperato, MR., Cauchy, P., Obier, N., Bonifer, C. (2015). The RUNX1-PU.1 axis in the control of hematopoiesis. *Int. J. Hematol., 101*, 319-29. ↗

Sanda, T., Lawton, LN., Barrasa, MI., Fan, ZP., Kohlhammer, H., Gutierrez, A. et al. (2012). Core transcriptional regulatory circuit controlled by the TAL1 complex in human T cell acute lymphoblastic leukemia. *Cancer Cell, 22*, 209-21. ↗

Mansour, MR., Abraham, BJ., Anders, L., Berezovskaya, A., Gutierrez, A., Durbin, AD. et al. (2014). Oncogene regulation. An oncogenic super-enhancer formed through somatic mutation of a noncoding intergenic element. *Science , 346*, 1373-7. ↗

Editions

2016-09-14	Authored	Orlic-Milacic, M.
2016-12-20	Reviewed	Ito, Y., Chuang, LS.
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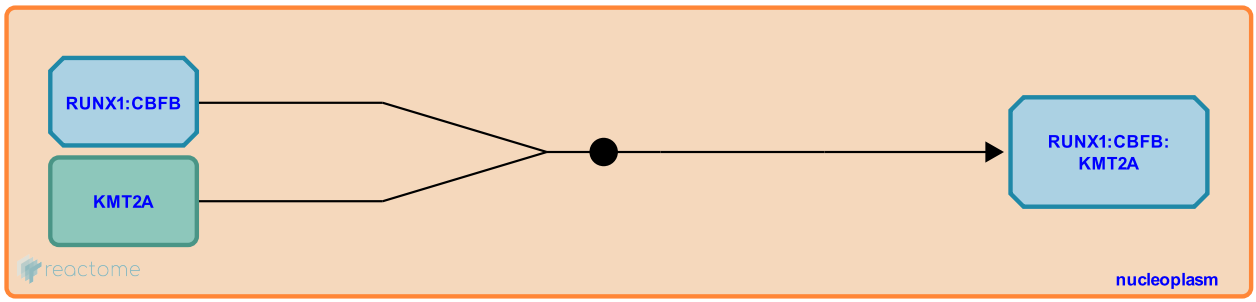
KMT2A (MLL) binds RUNX1 ↗

Location: RUNX1 regulates transcription of genes involved in differentiation of HSCs

Stable identifier: R-HSA-8865482

Type: binding

Compartments: nucleoplasm



Histone methyltransferase KMT2A (MLL) binds to RUNX1 (AML1) both in the presence and absence of CBFB (Huang et al. 2011).

Followed by: RUNX1:CBFB:KMT2A binds SPI1 (PU.1) gene

Literature references

Huang, G., Zhao, X., Wang, L., Elf, S., Xu, H., Zhao, X. et al. (2011). The ability of MLL to bind RUNX1 and methylate H3K4 at PU.1 regulatory regions is impaired by MDS/AML-associated RUNX1/AML1 mutations. *Blood, 118*, 6544-52. ↗

Editions

2016-09-14	Authored	Orlic-Milacic, M.
2016-12-20	Reviewed	Ito, Y., Chuang, LS.
2017-05-09	Edited	Orlic-Milacic, M.

RUNX1:CBFB:KMT2A binds SPI1 (PU.1) gene ↗

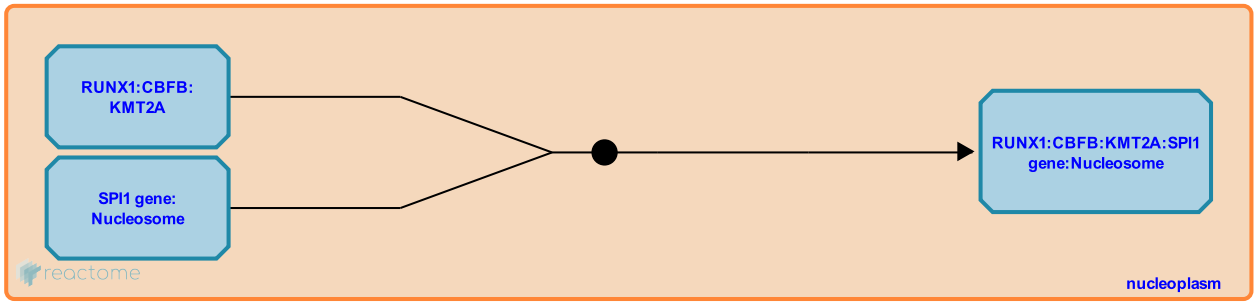
Location: RUNX1 regulates transcription of genes involved in differentiation of HSCs

Stable identifier: R-HSA-8865491

Type: binding

Compartments: nucleoplasm

Inferred from: RUNX1 recruits KMT2A to the Spi1 gene (Homo sapiens)



RUNX1 recruits histone methyltransferase KMT2A (MLL) to the SPI1 (PU.1) gene locus (Huang et al. 2011). This interaction was demonstrated by using endogenous mouse proteins and DNA, as well as by expressing recombinant human KMT2A and RUNX1 in mouse myeloid progenitor cell line 416B.

Preceded by: KMT2A (MLL) binds RUNX1

Followed by: KMT2A trimethylates nucleosomes at the SPI1 gene locus producing H3K4Me3 mark

Literature references

Huang, G., Zhao, X., Wang, L., Elf, S., Xu, H., Zhao, X. et al. (2011). The ability of MLL to bind RUNX1 and methylate H3K4 at PU.1 regulatory regions is impaired by MDS/AML-associated RUNX1/AML1 mutations. *Blood, 118*, 6544-52. ↗

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2017-05-09	Edited	Orlic-Milacic, M.

KMT2A trimethylates nucleosomes at the SPI1 gene locus producing H3K4Me3 mark

↗

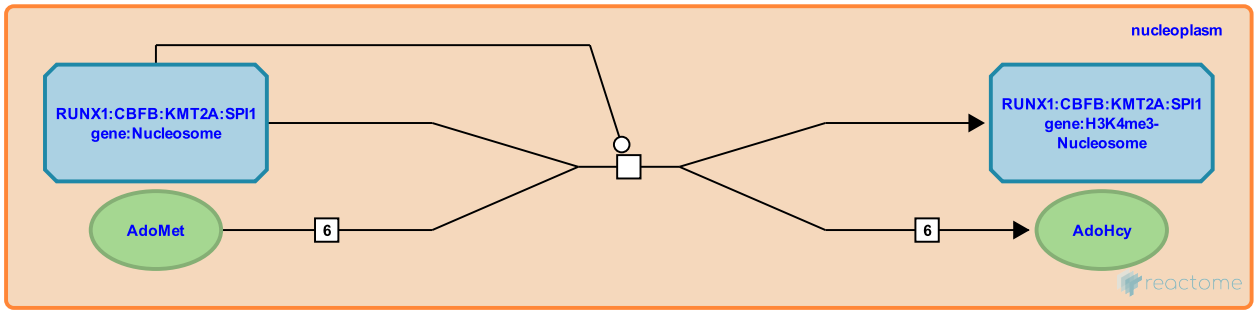
Location: RUNX1 regulates transcription of genes involved in differentiation of HSCs

Stable identifier: R-HSA-8865498

Type: transition

Compartments: nucleoplasm

Inferred from: KTM2A trimethylates nucleosomes at the Spi1 gene locus producing H3K4Me3 mark (Homo sapiens)



Once recruited to the SPI1 (PU.1) gene locus, KMT2A (MLL) histone methyltransferase trimethylates nucleosomes associated with the SPI1 promoter and the upstream regulatory element. KMT2A creates the H3K4Me3 mark on histone H3 at the SPI1 gene, a characteristic of transcriptionally active chromatin (Huang et al. 2011).

Preceded by: RUNX1:CBFB:KMT2A binds SPI1 (PU.1) gene

Followed by: SPI1 (PU.1) gene transcription is stimulated by RUNX1:CBFB:KMT2A

Literature references

Huang, G., Zhao, X., Wang, L., Elf, S., Xu, H., Zhao, X. et al. (2011). The ability of MLL to bind RUNX1 and methylate H3K4 at PU.1 regulatory regions is impaired by MDS/AML-associated RUNX1/AML1 mutations. *Blood, 118*, 6544-52. ↗

Editions

2016-09-14	Authored	Orlic-Milacic, M.
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2017-05-09	Edited	Orlic-Milacic, M.

SPI1 (PU.1) gene transcription is stimulated by RUNX1:CBFB:KMT2A ↗

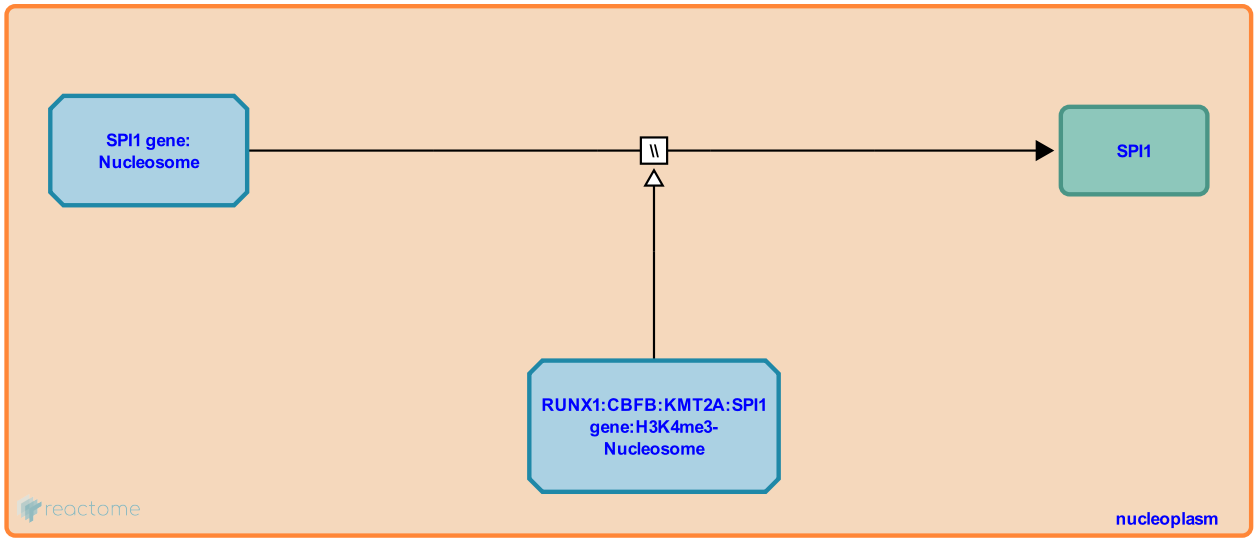
Location: RUNX1 regulates transcription of genes involved in differentiation of HSCs

Stable identifier: R-HSA-8865505

Type: omitted

Compartments: nucleoplasm

Inferred from: Spi1 gene transcription is stimulated by RUNX1:Cbfb:KMT2A (Homo sapiens)



The SPI1 (PU.1) transcription factor represses self renewal and proliferation of HSCs (Fukuchi et al. 2008) and is needed for commitment of HSCs to specific hematopoietic lineages (Imperato et al. 2015), for example differentiation of lymphoid cells. SPI1 gene transcription is directly stimulated by the RUNX1:CBFB transcription factor complex, in the presence of the activating histone methyltransferase KMT2A (MLL) (Huang et al. 2011).

Preceded by: KMT2A trimethylates nucleosomes at the SPI1 gene locus producing H3K4Me3 mark

Literature references

Huang, G., Zhao, X., Wang, L., Elf, S., Xu, H., Zhao, X. et al. (2011). The ability of MLL to bind RUNX1 and methylate H3K4 at PU.1 regulatory regions is impaired by MDS/AML-associated RUNX1/AML1 mutations. *Blood, 118*, 6544-52. ↗

Editions

2016-09-14	Authored	Orlic-Milacic, M.
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2019-03-10	Reviewed	Skokowa, J.

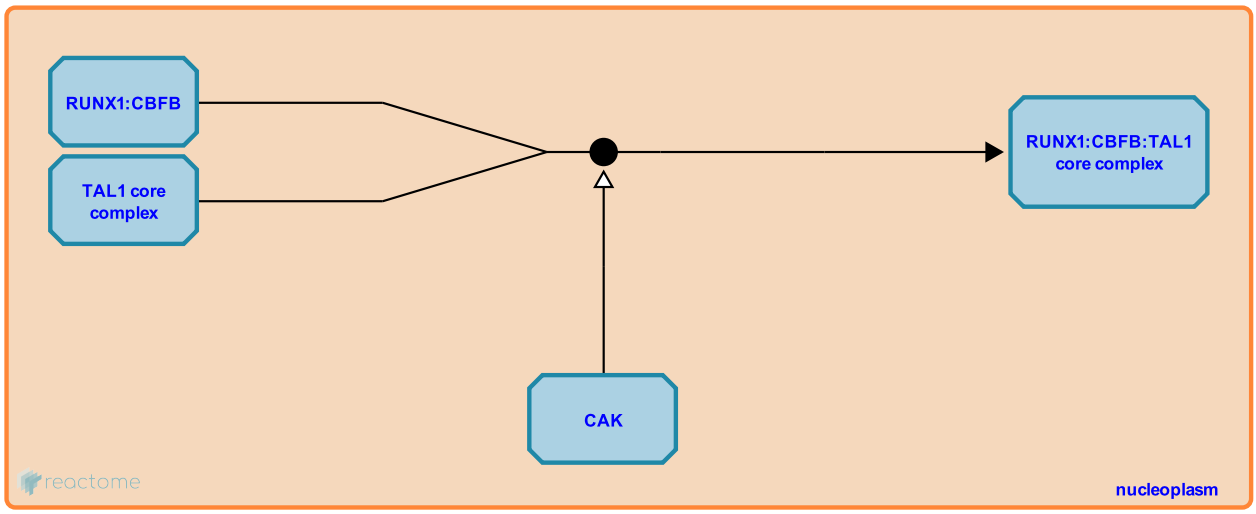
RUNX1 binds the core TAL1 complex ↗

Location: RUNX1 regulates transcription of genes involved in differentiation of HSCs

Stable identifier: R-HSA-8956568

Type: binding

Compartments: nucleoplasm



RUNX1, in complex with CBFB, binds to the core TAL1 complex consisting of TAL1 (SCL), TCF3 (E2A) or TCF12 (HEB), LMO1 or LMO2, LDB1 and GATA1, GATA2 or GATA3 (Wilson et al. 2010, Tijssen et al. 2011, Sanda et al. 2012, Mansour et al. 2014, Hoang et al. 2016). Assembly of the RUNX1- and GATA3-containing TAL1 complex is positively regulated by the CDK7-containing CAK complex (Kwiatkowski et al. 2014).

Followed by: RUNX1-containing TAL1 complex binds the MYB gene enhancer

Literature references

Tijssen, MR., Cvejic, A., Joshi, A., Hannah, RL., Ferreira, R., Forrai, A. et al. (2011). Genome-wide analysis of simultaneous GATA1/2, RUNX1, FLI1, and SCL binding in megakaryocytes identifies hematopoietic regulators. *Dev. Cell, 20*, 597-609. ↗

Sanda, T., Lawton, LN., Barrasa, MI., Fan, ZP., Kohlhammer, H., Gutierrez, A. et al. (2012). Core transcriptional regulatory circuit controlled by the TAL1 complex in human T cell acute lymphoblastic leukemia. *Cancer Cell, 22*, 209-21. ↗

Mansour, MR., Abraham, BJ., Anders, L., Berezovskaya, A., Gutierrez, A., Durbin, AD. et al. (2014). Oncogene regulation. An oncogenic super-enhancer formed through somatic mutation of a noncoding intergenic element. *Science , 346*, 1373-7. ↗

Hoang, T., Lambert, JA., Martin, R. (2016). SCL/TAL1 in Hematopoiesis and Cellular Reprogramming. *Curr. Top. Dev. Biol., 118*, 163-204. ↗

Wilson, NK., Foster, SD., Wang, X., Knezevic, K., Schütte, J., Kaimakis, P. et al. (2010). Combinatorial transcriptional control in blood stem/progenitor cells: genome-wide analysis of ten major transcriptional regulators. *Cell Stem Cell, 7*, 532-44. ↗

Editions

2016-09-14	Authored	Orlic-Milacic, M.
2016-12-20	Reviewed	Ito, Y., Chuang, LS.
2017-05-09	Edited	Orlic-Milacic, M.

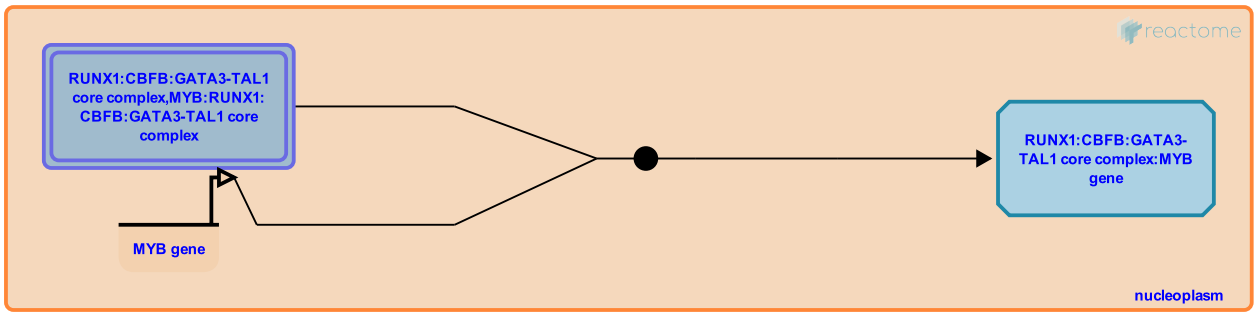
RUNX1-containing TAL1 complex binds the MYB gene enhancer ↗

Location: RUNX1 regulates transcription of genes involved in differentiation of HSCs

Stable identifier: R-HSA-8956586

Type: binding

Compartments: nucleoplasm



The TAL1 complex containing GATA3, RUNX1 and CBFB binds the MYB gene enhancer element (Sanda et al. 2012, Mansour et al. 2014). Binding of the RUNX1-containing TAL1 complex to the MYB gene enhancer can be facilitated by the presence of the MYB transcription factor (Mansour et al. 2014).

Preceded by: RUNX1 binds the core TAL1 complex

Followed by: MYB gene transcription is stimulated by the RUNX1-containing TAL1 complex

Literature references

Sanda, T., Lawton, LN., Barrasa, MI., Fan, ZP., Kohlhammer, H., Gutierrez, A. et al. (2012). Core transcriptional regulatory circuit controlled by the TAL1 complex in human T cell acute lymphoblastic leukemia. *Cancer Cell, 22*, 209-21. ↗

Mansour, MR., Abraham, BJ., Anders, L., Berezovskaya, A., Gutierrez, A., Durbin, AD. et al. (2014). Oncogene regulation. An oncogenic super-enhancer formed through somatic mutation of a noncoding intergenic element. *Science , 346*, 1373-7. ↗

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2016-09-14	Authored	Orlic-Milacic, M.
2016-12-20	Reviewed	Ito, Y., Chuang, LS.
2017-05-09	Edited	Orlic-Milacic, M.

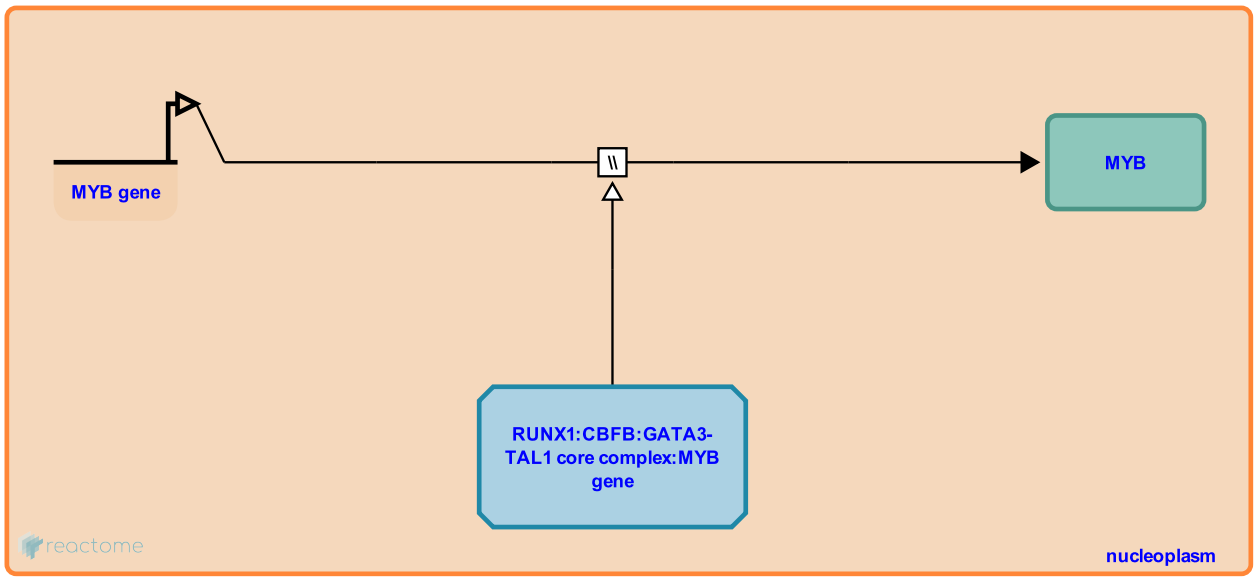
MYB gene transcription is stimulated by the RUNX1-containing TAL1 complex ↗

Location: RUNX1 regulates transcription of genes involved in differentiation of HSCs

Stable identifier: R-HSA-8956608

Type: omitted

Compartments: nucleoplasm



Expression of the MYB gene is stimulated by binding of the RUNX1-containing TAL1 complex to the MYB gene enhancer (Sanda et al. 2012, Mansour et al. 2014). MYB transcription factor encoded by the MYB gene can bind to the RUNX1-containing TAL1 complex at the MYB gene enhancer to further facilitate MYB gene expression, thus creating a positive feedback loop (Mansour et al. 2014). In addition, somatic mutations at the TAL1 gene enhancer enable binding of the TAL1 complex containing MYB, RUNX1 and MYB-associated histone acetyltransferase CBP (CREBBP) to the TAL1 gene enhancer, creating a super-enhancer, which further amplifies the positive feedback loop involved in the MYB gene regulation (Mansour et al. 2014).

Preceded by: RUNX1-containing TAL1 complex binds the MYB gene enhancer

Literature references

Sanda, T., Lawton, LN., Barrasa, MI., Fan, ZP., Kohlhammer, H., Gutierrez, A. et al. (2012). Core transcriptional regulatory circuit controlled by the TAL1 complex in human T cell acute lymphoblastic leukemia. *Cancer Cell, 22*, 209-21. ↗

Mansour, MR., Abraham, BJ., Anders, L., Berezovskaya, A., Gutierrez, A., Durbin, AD. et al. (2014). Oncogene regulation. An oncogenic super-enhancer formed through somatic mutation of a noncoding intergenic element. *Science , 346*, 1373-7. ↗

Editions

2016-09-14	Authored	Orlic-Milacic, M.
2016-12-20	Reviewed	Ito, Y., Chuang, LS.
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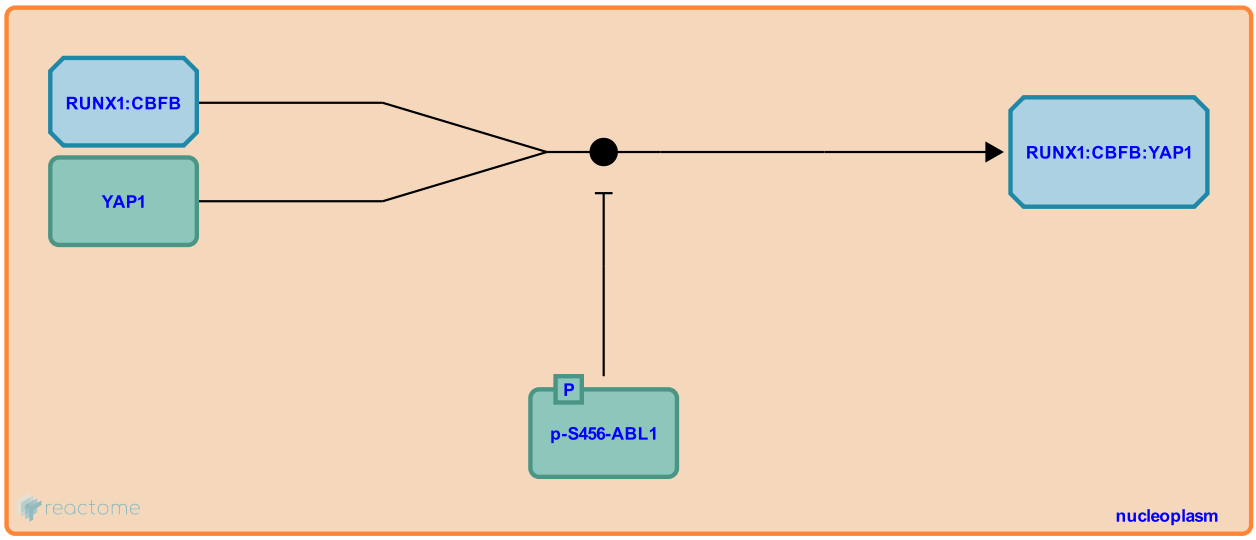
RUNX1 binds YAP1 ↗

Location: RUNX1 regulates transcription of genes involved in differentiation of HSCs

Stable identifier: R-HSA-8956639

Type: binding

Compartments: nucleoplasm



RUNX1, presumably in complex with CBFB, binds to YAP1 (Levy, Adamovich et al. 2008; Levy, Reuven and Shaul 2008). Phosphorylation of YAP1 by ABL1 in response to DNA damage prevents binding of YAP1 to RUNX1 (Levy, Adamovich et al. 2008).

Followed by: The complex of RUNX1 and YAP1 binds the ITCH gene promoter

Literature references

Levy, D., Reuven, N., Shaul, Y. (2008). A regulatory circuit controlling Itch-mediated p73 degradation by Runx. *J. Biol. Chem., 283*, 27462-8. ↗

Levy, D., Adamovich, Y., Reuven, N., Shaul, Y. (2008). Yap1 phosphorylation by c-Abl is a critical step in selective activation of proapoptotic genes in response to DNA damage. *Mol. Cell, 29*, 350-61. ↗

Editions

2016-09-14	Authored	Orlic-Milacic, M.
2016-12-20	Reviewed	Ito, Y., Chuang, LS.
2017-05-09	Edited	Orlic-Milacic, M.

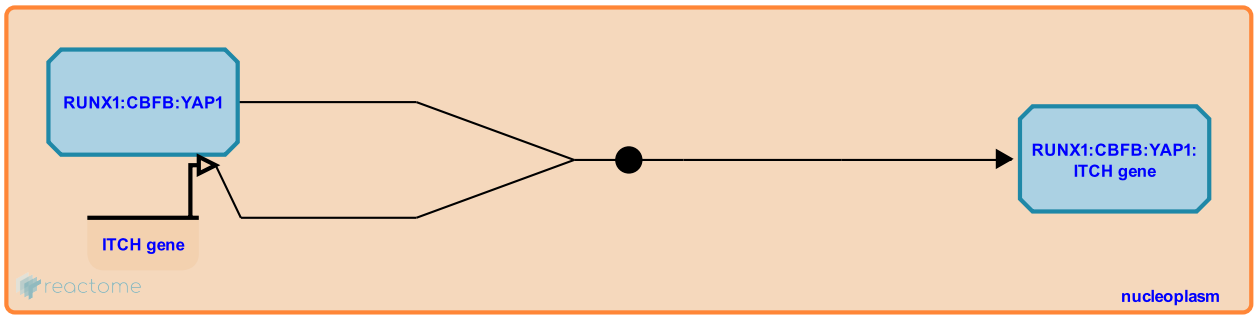
The complex of RUNX1 and YAP1 binds the ITCH gene promoter ↗

Location: RUNX1 regulates transcription of genes involved in differentiation of HSCs

Stable identifier: R-HSA-8956649

Type: binding

Compartments: nucleoplasm



The complex of RUNX1, presumably associated with CBFB, and YAP1 binds the promoter of the ITCH gene, encoding the E3 ubiquitin-protein ligase ITCH (Levy, Reuven and Shaul 2008).

Preceded by: RUNX1 binds YAP1

Followed by: ITCH gene expression is stimulated by RUNX1 and YAP1

Literature references

Levy, D., Reuven, N., Shaul, Y. (2008). A regulatory circuit controlling Itch-mediated p73 degradation by Runx. *J. Biol. Chem., 283*, 27462-8. ↗

Editions

2016-09-14	Authored	Orlic-Milacic, M.
2016-12-20	Reviewed	Ito, Y., Chuang, LS.
2017-05-09	Edited	Orlic-Milacic, M.

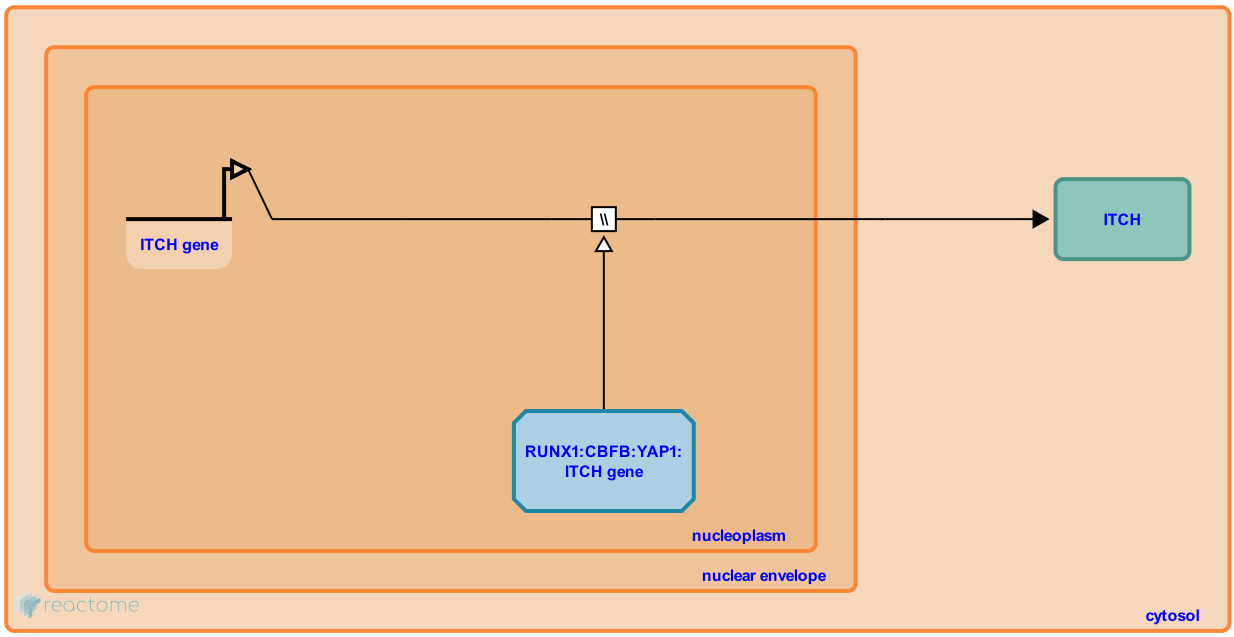
ITCH gene expression is stimulated by RUNX1 and YAP1 ↗

Location: RUNX1 regulates transcription of genes involved in differentiation of HSCs

Stable identifier: R-HSA-8956652

Type: omitted

Compartments: nucleoplasm, cytosol



Expression of the ITCH gene, encoding the E3 ubiquitin-protein ligase ITCH, is directly stimulated by binding of the complex of RUNX1 and YAP1 to the ITCH promoter (Levy, Reuven and Shaul 2008).

ITCH is an important regulator of hematopoietic stem cell (HSC) function and homeostasis. ITCH reduces the proliferation rate of HSCs by downregulating NOTCH1 (Rathinam et al. 2011).

Preceded by: The complex of RUNX1 and YAP1 binds the ITCH gene promoter

Literature references

Levy, D., Reuven, N., Shaul, Y. (2008). A regulatory circuit controlling Itch-mediated p73 degradation by Runx. *J. Biol. Chem., 283*, 27462-8. ↗

Editions

2016-09-14	Authored	Orlic-Milacic, M.
2016-12-20	Reviewed	Ito, Y., Chuang, LS.
2017-05-09	Edited	Orlic-Milacic, M.

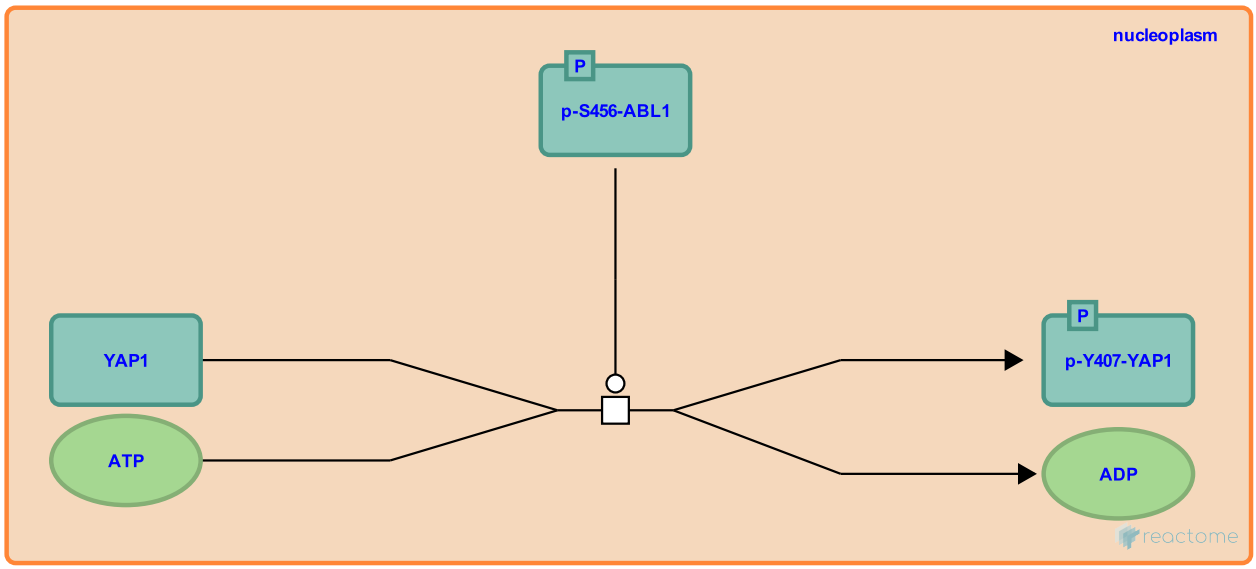
ABL1 phosphorylates YAP1 ↗

Location: RUNX1 regulates transcription of genes involved in differentiation of HSCs

Stable identifier: R-HSA-8956659

Type: transition

Compartments: nucleoplasm



In response to DNA damage, ABL1 phosphorylates YAP1 on tyrosine residue Y407 (corresponds to Y357 in the YAP1 splicing isoform 3, known as YAP1-1beta, which was used in the study by Levy, Adamovich et al. 2008).

Followed by: YAP1 binds TP73

Literature references

Levy, D., Adamovich, Y., Reuven, N., Shaul, Y. (2008). Yap1 phosphorylation by c-Abl is a critical step in selective activation of proapoptotic genes in response to DNA damage. *Mol. Cell, 29*, 350-61. ↗

Editions

2016-09-14	Authored	Orlic-Milacic, M.
2016-12-20	Reviewed	Ito, Y., Chuang, LS.
2017-05-09	Edited	Orlic-Milacic, M.

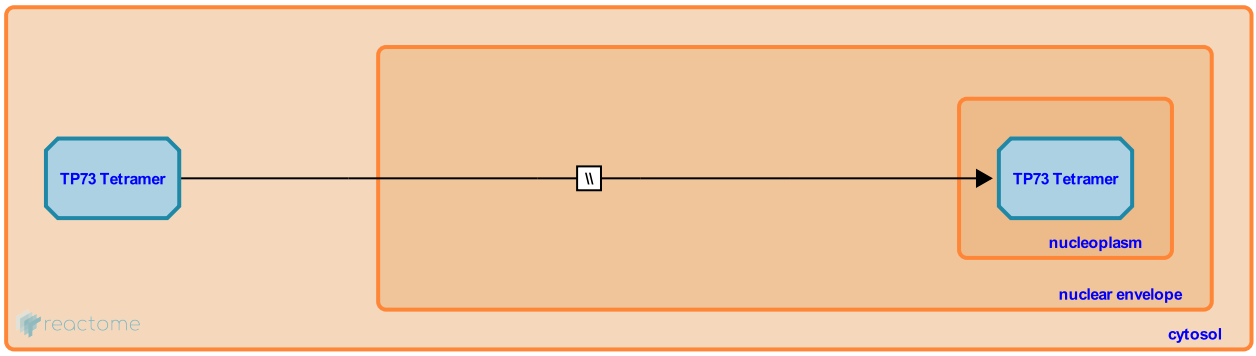
TP73 tetramer translocates to the nucleus ↗

Location: RUNX1 regulates transcription of genes involved in differentiation of HSCs

Stable identifier: R-HSA-8957241

Type: omitted

Compartments: nuclear envelope



TP73 (p73) possesses both a nuclear localization signal (NLS) and a nuclear export signal (NES) and can shuttle between the nucleus and the cytosol (Inoue et al. 2002).

Followed by: YAP1 binds TP73

Literature references

Inoue, T., Stuart, J., Leno, R., Maki, CG. (2002). Nuclear import and export signals in control of the p53-related protein p73. *J. Biol. Chem., 277*, 15053-60. ↗

Editions

2016-09-14	Authored	Orlic-Milacic, M.
2016-12-20	Reviewed	Ito, Y., Chuang, LS.
2017-05-09	Edited	Orlic-Milacic, M.

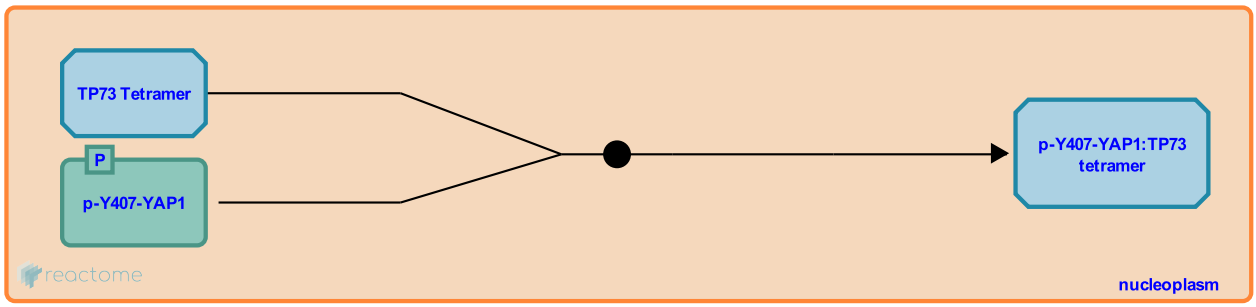
YAP1 binds TP73 ↗

Location: RUNX1 regulates transcription of genes involved in differentiation of HSCs

Stable identifier: R-HSA-8956676

Type: binding

Compartments: nucleoplasm



YAP1, phosphorylated on tyrosine residue Y407 (Y357 in the splicing isoform 3, known as YAP1-1beta) by the protein tyrosine kinase ABL1, activated in response to DNA damage, forms a complex with TP73. ABL1-phosphorylated YAP1 can no longer bind RUNX1 (Levy, Adamovich et al. 2008; Levy, Reuven and Shaul 2008). Binding of phosphorylated YAP1 to TP73 may target TP73 to promoters of pro-apoptotic target genes instead of cell cycle arrest genes (Levy, Adamovich et al. 2008).

Preceded by: ABL1 phosphorylates YAP1, TP73 tetramer translocates to the nucleus

Literature references

Levy, D., Adamovich, Y., Reuven, N., Shaul, Y. (2008). Yap1 phosphorylation by c-Abl is a critical step in selective activation of proapoptotic genes in response to DNA damage. *Mol. Cell, 29*, 350-61. ↗

Levy, D., Reuven, N., Shaul, Y. (2008). A regulatory circuit controlling Itch-mediated p73 degradation by Runx. *J. Biol. Chem., 283*, 27462-8. ↗

Editions

2016-09-14	Authored	Orlic-Milacic, M.
2016-12-20	Reviewed	Ito, Y., Chuang, LS.
2017-05-09	Edited	Orlic-Milacic, M.

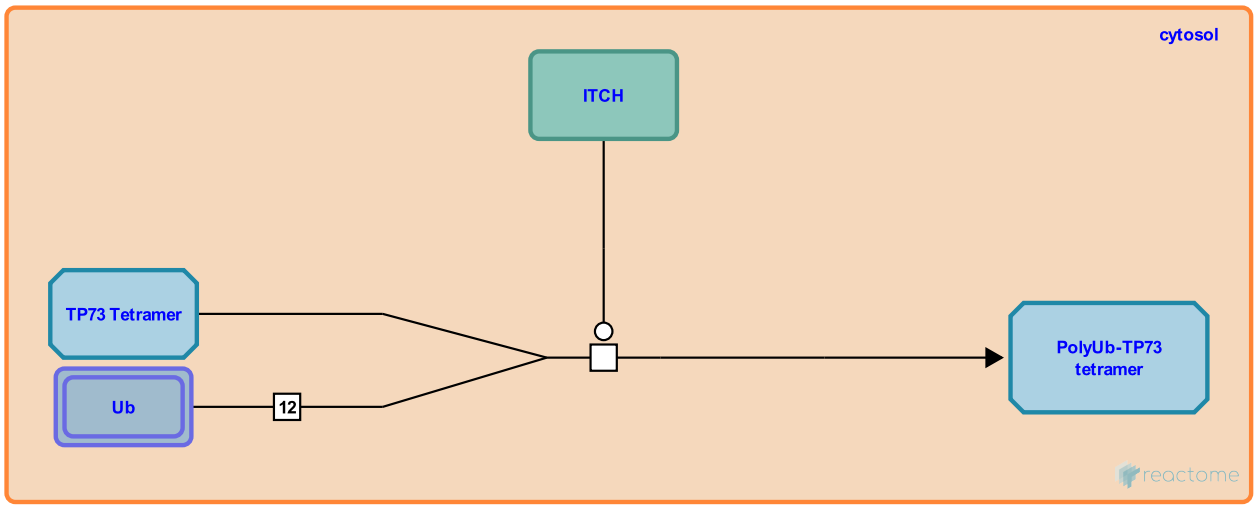
ITCH polyubiquitinates TP73 ↗

Location: RUNX1 regulates transcription of genes involved in differentiation of HSCs

Stable identifier: R-HSA-8956684

Type: transition

Compartments: cytosol



The E3 ubiquitin-protein ligase ITCH polyubiquitinates TP73 (p73), targeting it for degradation. In response to DNA damage, ITCH levels are downregulated, allowing TP73 to accumulate (Rossi et al. 2005). Downregulation of ITCH in response to DNA damage is the consequence of DNA damage-induced phosphorylation of YAP1 by ABL1. YAP1 phosphorylated by ABL1 is no longer able to bind to RUNX1, and the complex of RUNX1 and YAP1 is needed for transcription of the ITCH gene (Levy, Reuven and Shaul 2008).

Followed by: 26S proteasome degrades TP73 polyubiquitinated by ITCH

Literature references

Levy, D., Reuven, N., Shaul, Y. (2008). A regulatory circuit controlling Itch-mediated p73 degradation by Runx. *J. Biol. Chem., 283*, 27462-8. ↗

Rossi, M., De Laurenzi, V., Munarriz, E., Green, DR., Liu, YC., Vousden, KH. et al. (2005). The ubiquitin-protein ligase Itch regulates p73 stability. *EMBO J., 24*, 836-48. ↗

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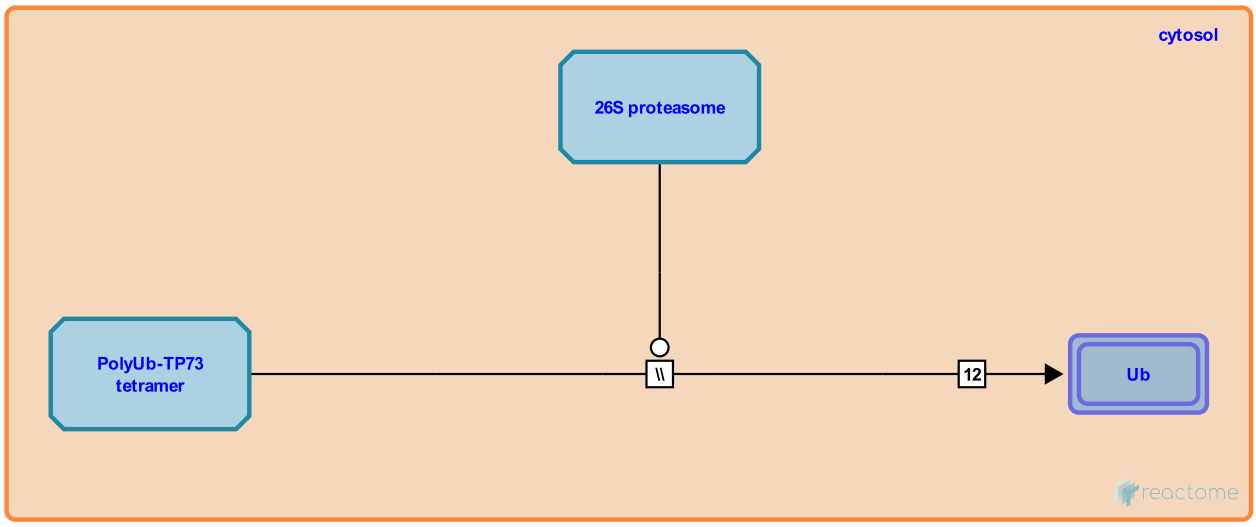
26S proteasome degrades TP73 polyubiquitinated by ITCH ↗

Location: RUNX1 regulates transcription of genes involved in differentiation of HSCs

Stable identifier: R-HSA-8957265

Type: omitted

Compartments: cytosol



ITCH-mediated polyubiquitination of TP73 (p73) targets TP73 for proteasome-mediated degradation (Rossi et al. 2005).

Preceded by: ITCH polyubiquitinates TP73

Literature references

Rossi, M., De Laurenzi, V., Munarriz, E., Green, DR., Liu, YC., Vousden, KH. et al. (2005). The ubiquitin-protein ligase Itch regulates p73 stability. *EMBO J., 24*, 836-48. ↗

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