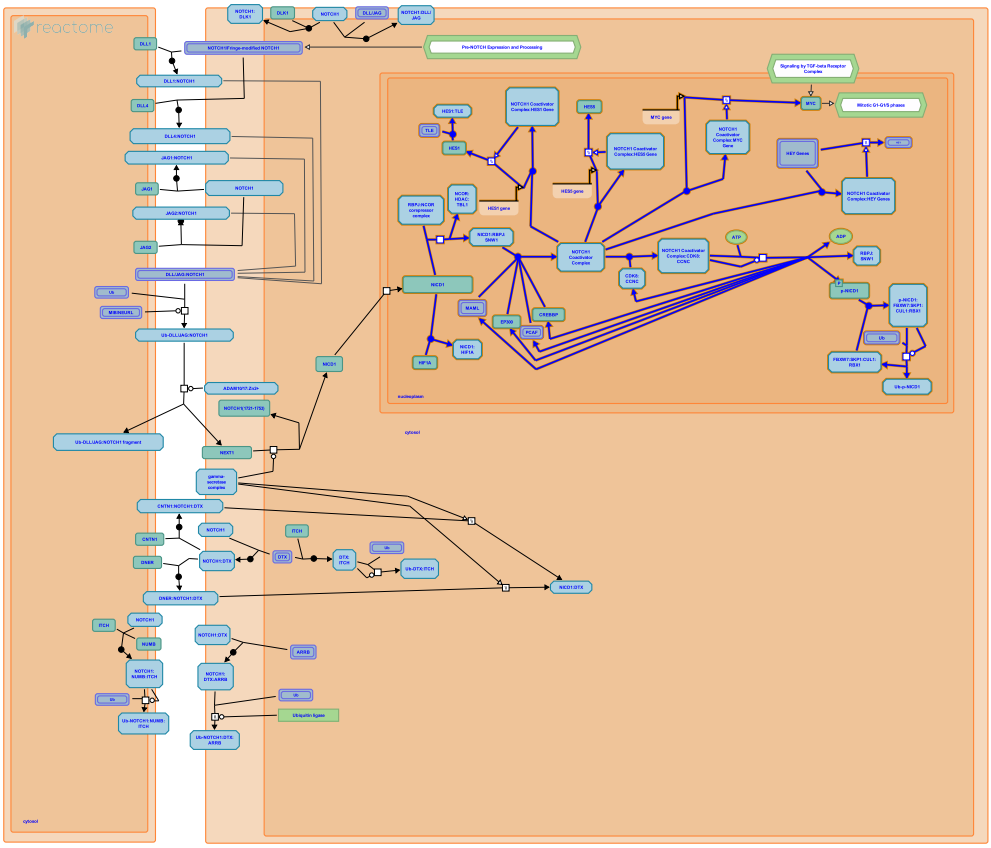
NOTCH1 Intracellular Domain Regulates Transcription



Chuang, LS., D'Eustachio, P., Egan, SE., Haw, R., Ito, Y., Orlic-Milacic, M.

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

22/11/2019

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. ↗

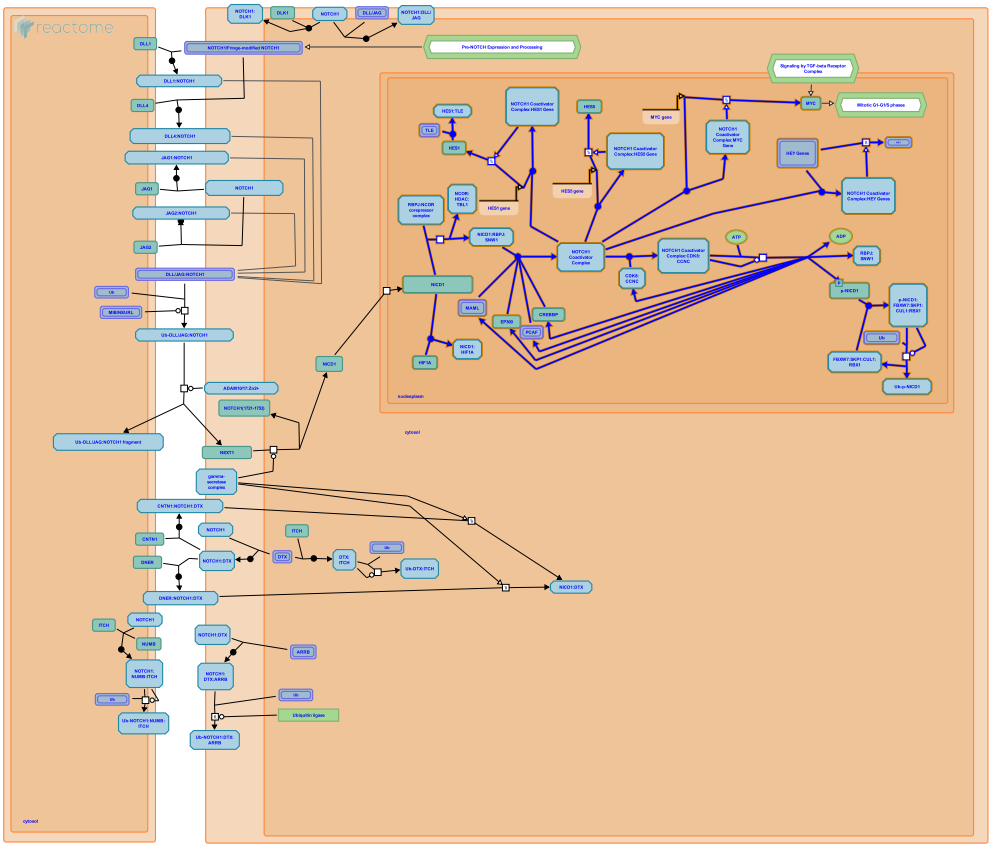
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

NOTCH1 Intracellular Domain Regulates Transcription ↗

Stable identifier: R-HSA-2122947

Compartments: nucleoplasm



NICD1 produced by activation of NOTCH1 in response to Delta and Jagged ligands (DLL/JAG) presented in trans, traffics to the nucleus where it acts as a transcription regulator. In the nucleus, NICD1 displaces the NCOR corepressor complex from RBPJ (CSL). When bound to the co-repressor complex that includes NCOR proteins (NCOR1 and NCOR2) and HDAC histone deacetylases, RBPJ (CSL) represses transcription of NOTCH target genes (Kao et al. 1998, Zhou et al. 2000, Perissi et al. 2004, Perissi et al. 2008). Once the co-repressor complex is displaced, NICD1 recruits MAML (mastermind-like) to RBPJ, while MAML recruits histone acetyltransferases EP300 (p300) and PCAF, resulting in formation of the NOTCH coactivator complex that activates transcription from NOTCH regulatory elements. The minimal functional NOTCH coactivator complex that activates transcription from NOTCH regulatory elements is a heterotrimer composed of NICD, MAML and RBPJ (Fryer et al. 2002, Wallberg et al. 2002, Nam et al. 2006).

NOTCH1 coactivator complex is known to activate transcription of HES1 (Jarriault et al. 1995), HES5 (Arnett et al. 2010), HEY genes (Fischer et al. 2004, Leimeister et al. 2000, Maier et al. 2000, Arnett et al. 2010) and MYC (Palomero et al. 2006) and likely regulates transcription of many other genes (Wang et al. 2011). NOTCH1 coactivator complex on any specific regulatory element may involve additional transcriptional regulatory proteins. HES1 binds TLE proteins, forming an evolutionarily conserved transcriptional corepressor involved in regulation of neurogenesis, segmentation and sex determination (Grbavec et al. 1996, Fisher et al. 1996, Paroush et al. 1994).

After NOTCH1 coactivator complex is assembled on a NOTCH-responsive promoter, MAML (mastermind-like) recruits CDK8 in complex with cyclin C, triggering phosphorylation of conserved serine residues in TAD and PEST domains of NICD1 by CDK8. Phosphorylated NICD1 is recognized by the E3 ubiquitin ligase FBXW7 which ubiquitinates NICD1, leading to degradation of NICD1 and downregulation

of NOTCH1 signaling. FBXW7-mediated ubiquitination and degradation of NOTCH1 depend on C-terminally located PEST domain sequences in NOTCH1 (Fryer et al. 2004, Oberg et al. 2001, Wu et al. 2001). The PEST domain of NOTCH1 and the substrate binding WD40 domain of FBXW7 are frequent targets of mutations in T-cell acute lymphoblastic leukemia - T-ALL (Welcker and Clurman 2008).

NICD1, which normally has a short half-life, can be stabilized by binding to the hypoxia-inducable factor 1-alpha (HIF1A) which accumulates in the nucleus when oxygen levels are low. This results in HIF1A-induced inhibition of cellular differentiation that is NOTCH-dependent (Gustafsson et al. 2005).

Literature references

Fryer, CJ., White, JB., Jones, KA. (2004). Mastermind recruits CycC:CDK8 to phosphorylate the Notch ICD and coordinate activation with turnover. *Mol Cell, 16*, 509-20. ↗

Wu, G., Lyapina, S., Das, I., Li, J., Gurney, M., Pauley, A. et al. (2001). SEL-10 is an inhibitor of notch signaling that targets notch for ubiquitin-mediated protein degradation. *Mol Cell Biol, 21*, 7403-15. ↗

Gustafsson, MV., Zheng, X., Pereira, T., Gradin, K., Jin, S., Lundkvist, J. et al. (2005). Hypoxia requires notch signaling to maintain the undifferentiated cell state. *Dev Cell, 9*, 617-28. ↗

Perissi, V., Aggarwal, A., Glass, CK., Rose, DW., Rosenfeld, MG. (2004). A corepressor/coactivator exchange complex required for transcriptional activation by nuclear receptors and other regulated transcription factors. *Cell, 116*, 511-26. ↗

Zhou, S., Fujimuro, M., Hsieh, JJ., Chen, L., Miyamoto, A., Weinmaster, G. et al. (2000). SKIP, a CBF1-associated protein, interacts with the ankyrin repeat domain of NotchIC To facilitate NotchIC function. *Mol Cell Biol, 20*, 2400-10 . ↗

Editions

2011-11-14	Authored	Egan, SE., Orlic-Milacic, M.
2012-02-06	Edited	D'Eustachio, P.
2012-02-06	Reviewed	Haw, R.
2012-02-10	Edited	Orlic-Milacic, M.

NICD1 displaces co-repressor complex from RBPJ (CSL) ↗

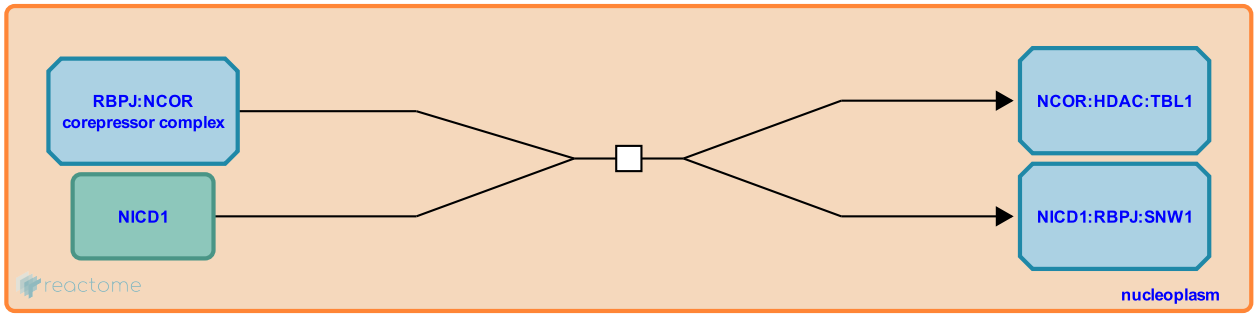
Location: NOTCH1 Intracellular Domain Regulates Transcription

Stable identifier: R-HSA-1912388

Type: transition

Compartments: nucleoplasm

Inferred from: NICD1 displaces NCOR co-repressor complex from CSL (Cercopithecus aethiops)



In the absence of NICD1, RBPJ (CSL) is bound to a co-repressor complex that includes NCOR proteins, NCOR1 and/or NCOR2 (also known as SMRT) and HDAC histone deacetylases. Both NCOR and HDAC proteins interact with RBPJ (CSL) through a repression domain in RBPJ. When bound to the co-repressor complex, RBPJ (CSL) represses transcription of NOTCH target genes (Kao et al. 1998). The co-repressor complex also contains SNW1 (SKIP), which interacts with RBPJ (CSL) in a repression-domain independent way (Zhou et al. 2000), TBL1X (TBL1) and TBL1XR1 (TBLR1) (Perissi et al. 2004). NICD1 binds to RBPJ (CSL) and SNW1 (SKIP) and displaces NCOR and HDAC proteins (Kao et al. 1998). TBL1X and TBL1XR1 facilitate displacement of NCOR and HDAC and positively regulated NOTCH-mediated transcription probably by recruiting the ubiquitin/19S proteasome complex that degrades transcriptional repressors (Perissi et al. 2004, Perissi et al. 2008). SNW1 facilitates NICD1 interaction with RBPJ and NOTCH-mediated transcription (Zhou et al. 2000). It is possible that the co-repressor complex contains additional proteins not described here. Loss-of-function mutations in RBPJ typically result in phenotypes associated with reduced NOTCH function, suggesting that RBPJ activation complex (i.e. NOTCH coactivator complex) is more important than RBPJ repressor complex in control of normal development and homeostasis (Oka et al. 1995).

Followed by: NICD1 in complex with RBPJ (CSL) recruits MAML

Literature references

Kao, HY., Ordentlich, P., Koyano-Nakagawa, N., Tang, Z., Downes, M., Kintner, CR. et al. (1998). A histone deacetylase corepressor complex regulates the Notch signal transduction pathway. *Genes Dev, 12*, 2269-77. ↗

Zhou, S., Fujimuro, M., Hsieh, JJ., Chen, L., Miyamoto, A., Weinmaster, G. et al. (2000). SKIP, a CBF1-associated protein, interacts with the ankyrin repeat domain of NotchIC To facilitate NotchIC function. *Mol Cell Biol, 20*, 2400-10 . ↗

Perissi, V., Scafoglio, C., Zhang, J., Ohgi, KA., Rose, DW., Glass, CK. et al. (2008). TBL1 and TBLR1 phosphorylation on regulated gene promoters overcomes dual CtBP and NCoR/SMRT transcriptional repression checkpoints. *Mol Cell, 29*, 755-66. ↗

Perissi, V., Aggarwal, A., Glass, CK., Rose, DW., Rosenfeld, MG. (2004). A corepressor/coactivator exchange complex required for transcriptional activation by nuclear receptors and other regulated transcription factors. *Cell, 116*, 511-26. ↗

Oka, C., Nakano, T., Wakeham, A., de la Pompa, JL., Mori, C., Sakai, T. et al. (1995). Disruption of the mouse RBP-J kappa gene results in early embryonic death. *Development, 121*, 3291-301. ↗

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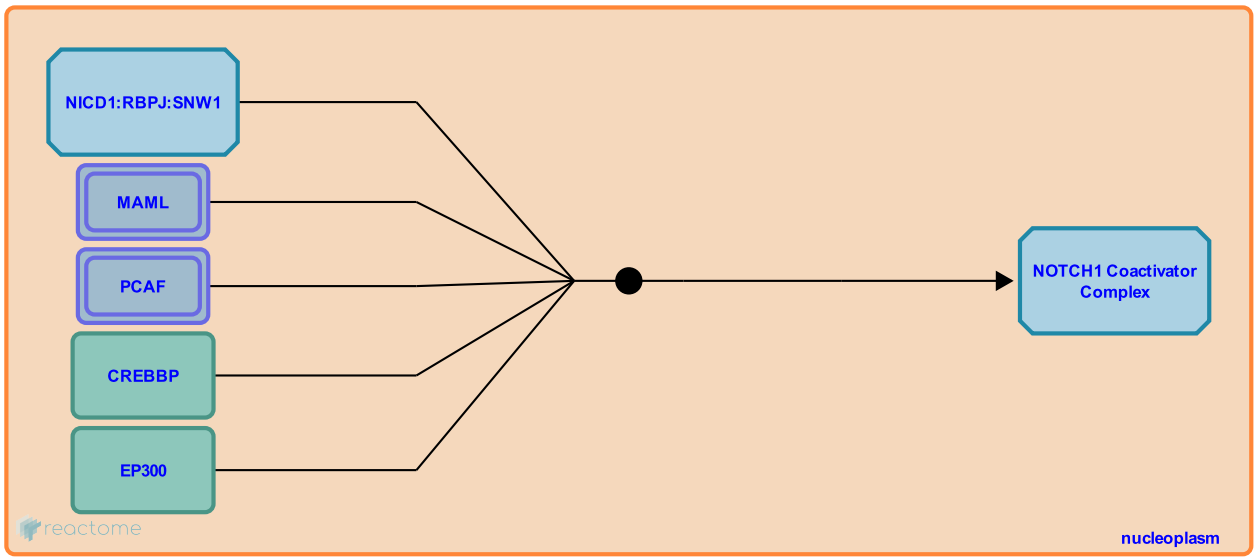
NICD1 in complex with RBPJ (CSL) recruits MAML ↗

Location: NOTCH1 Intracellular Domain Regulates Transcription

Stable identifier: R-HSA-1912394

Type: binding

Compartments: nucleoplasm



The minimal functional NOTCH coactivator complex that activates transcription from NOTCH regulatory elements is a heterotrimer composed of MAML (mastermind-like), NICD (NOTCH intracellular domain) and RBPJ (CSL) (Fryer et al. 2002). Structural studies indicate that NOTCH:RBPJ complexes can be pre-assembled on promoters of NOTCH-target genes and that MAML binds to a composite groove created by RBPJ and the NOTCH ankyrin domain (Nam et al. 2006). MAML is able to interact directly with a histone acetyltransferases EP300 (p300) and CREBBP. The presence of EP300 strongly activates NOTCH1 coactivator complex-mediated transcription and this positive effect is blocked by Lys-CoA, a selective inhibitor of EP300 histone acetyltransferase activity (Fryer et al. 2002). NICD1:RBPJ:MAML-mediated transcription increases threefold in the presence of both EP300 and PCAF, in comparison with the presence of EP300 alone (Wallberg et al. 2002).

Preceded by: NICD1 displaces co-repressor complex from RBPJ (CSL)

Followed by: MAML in complex with NICD1 recruits CDK8, NOTCH1 Coactivator Complex binds HES1 promoter, NOTCH1 Coactivator Complex binds HES5 promoter, NOTCH1 Coactivator Complex binds promoters of HEY genes, NOTCH1 Coactivator Complex binds MYC promoter

Literature references

Fryer, CJ., Lamar, E., Turbachova, I., Kintner, C., Jones, KA. (2002). Mastermind mediates chromatin-specific transcription and turnover of the Notch enhancer complex. *Genes Dev, 16*, 1397-411. ↗

Wallberg, AE., Pedersen, K., Lendahl, U., Roeder, RG. (2002). p300 and PCAF act cooperatively to mediate transcriptional activation from chromatin templates by notch intracellular domains in vitro. *Mol Cell Biol, 22*, 7812-9. ↗

Nam, Y., Sliz, P., Song, L., Aster, JC., Blacklow, SC. (2006). Structural basis for cooperativity in recruitment of MAML coactivators to Notch transcription complexes. *Cell, 124*, 973-83. ↗

Editions

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2012-02-06	Reviewed	Haw, R.
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NOTCH1 Coactivator Complex binds HES1 promoter ↗

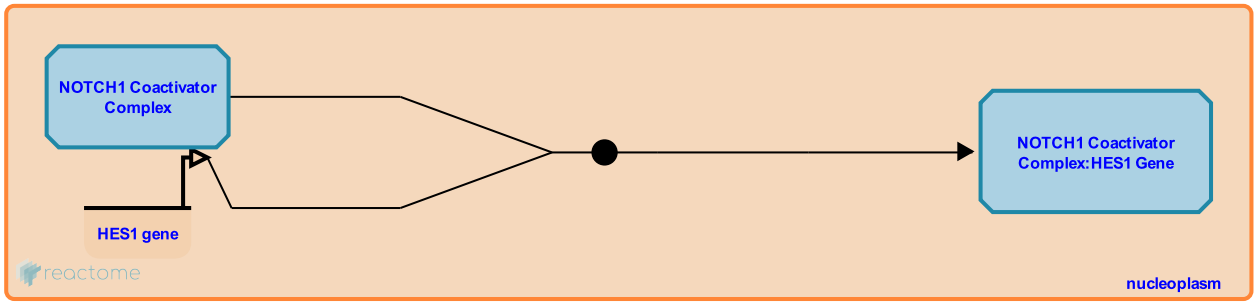
Location: NOTCH1 Intracellular Domain Regulates Transcription

Stable identifier: R-HSA-4396347

Type: binding

Compartments: nucleoplasm

Inferred from: mNICD1 Chimeric Enhancer Complex binds Hes1 promoter (Homo sapiens)



NOTCH1 coactivator complex binds the promoter of HES1 gene and directly stimulates HES1 transcription (Jarriault et al. 1995).

Preceded by: NICD1 in complex with RBPJ (CSL) recruits MAML

Followed by: NOTCH1 stimulates HES1 transcription

Literature references

Jarriault, S., Brou, C., Logeat, F., Schroeter, EH., Kopan, R., Israel, A. (1995). Signalling downstream of activated mammalian Notch. *Nature, 377*, 355-8. ↗

Editions

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2012-02-10	Edited	Orlic-Milacic, M.
2017-01-31	Reviewed	Ito, Y., Chuang, LS.
2017-01-31	Edited	Orlic-Milacic, M.

NOTCH1 stimulates HES1 transcription ↗

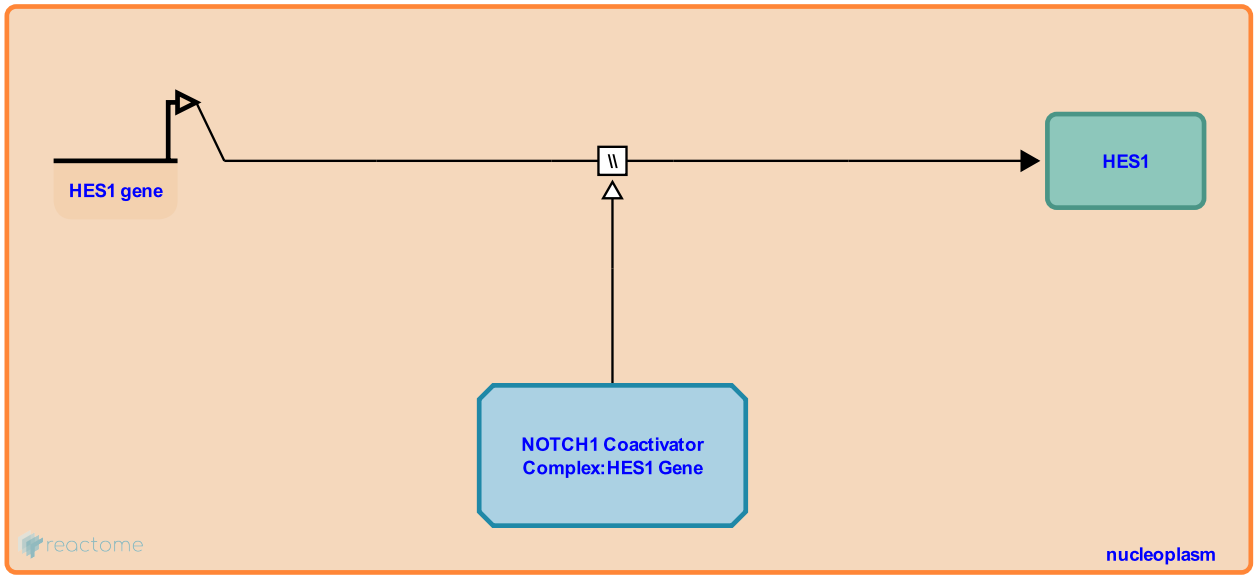
Location: NOTCH1 Intracellular Domain Regulates Transcription

Stable identifier: R-HSA-1980047

Type: omitted

Compartments: nucleoplasm

Inferred from: mNICD1 stimulates Hes1 transcription (Homo sapiens)



NOTCH1 coactivator complex binds the promoter of HES1 gene and directly stimulates HES1 transcription. HES1 belongs to the bHLH family of transcription factors (Jarriault et al. 1995).

Preceded by: NOTCH1 Coactivator Complex binds HES1 promoter

Followed by: HES1 binds TLE

Literature references

Jarriault, S., Brou, C., Logeat, F., Schroeter, EH., Kopan, R., Israel, A. (1995). Signalling downstream of activated mammalian Notch. *Nature, 377*, 355-8. ↗

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HES1 binds TLE ↗

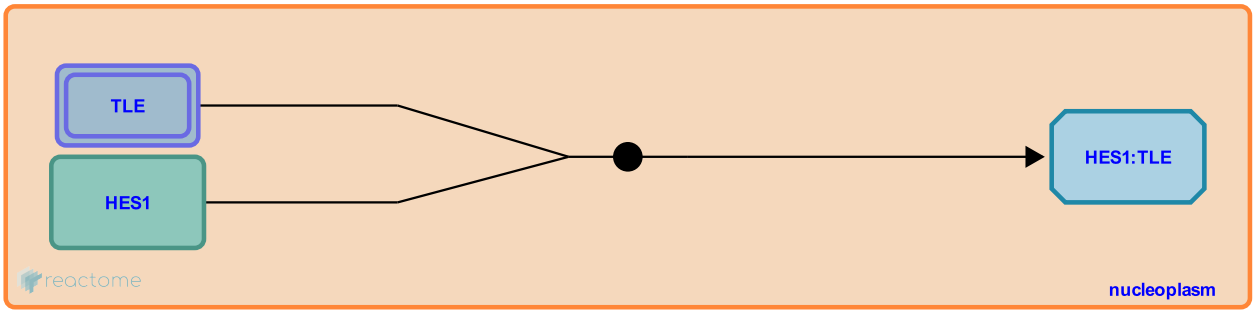
Location: NOTCH1 Intracellular Domain Regulates Transcription

Stable identifier: R-HSA-1912359

Type: binding

Compartments: nucleoplasm

Inferred from: rHes1 binds TLE (Homo sapiens)



Enhancer of split, a Drosophila orthologue of HES, is a basic-helix-loop-helix (bHLH) protein that represses transcription during Drosophila nervous system development. Groucho, the Drosophila homologue of TLE proteins, binds to the WRPW motif of Enhancer of split, resulting in the formation of a transcriptional co-repressor involved in the regulation of neurogenesis, segmentation and sex determination (Paroush et al. 1994). The interaction of HES1 and TLE proteins is conserved in mammals and the WRPW motif of HES1 plays the key role in the formation of HES1:TLE complex (Fisher et al. 1996, Grbavec and Stifani 1996).

Preceded by: NOTCH1 stimulates HES1 transcription

Literature references

Grbavec, D., Stifani, S. (1996). Molecular interaction between TLE1 and the carboxyl-terminal domain of HES-1 containing the WRPW motif. *Biochem Biophys Res Commun, 223*, 701-5. ↗

Fisher, AL., Ohsako, S., Caudy, M. (1996). The WRPW motif of the hairy-related basic helix-loop-helix repressor proteins acts as a 4-amino-acid transcription repression and protein-protein interaction domain. *Mol Cell Biol, 16*, 2670-7. ↗

Paroush, Z., Finley RL, Jr., Kidd, T., Wainwright, SM., Ingham, PW., Brent, R. et al. (1994). Groucho is required for Drosophila neurogenesis, segmentation, and sex determination and interacts directly with hairy-related bHLH proteins. *Cell, 79*, 805-15. ↗

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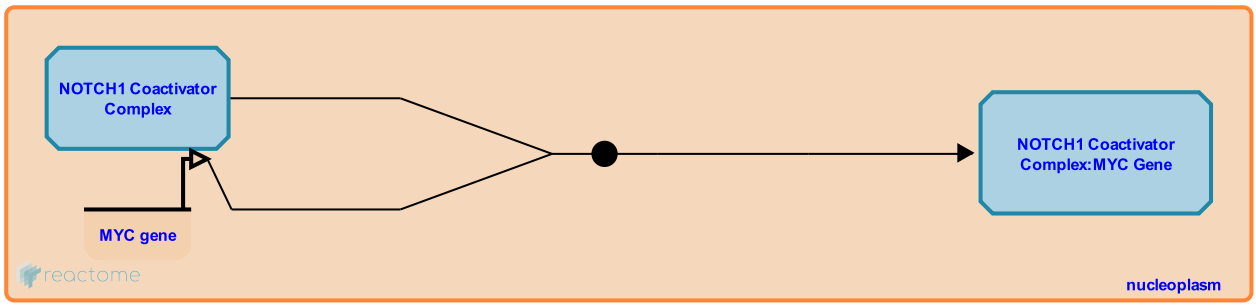
NOTCH1 Coactivator Complex binds MYC promoter ↗

Location: NOTCH1 Intracellular Domain Regulates Transcription

Stable identifier: R-HSA-4396371

Type: binding

Compartments: nucleoplasm



NICD1, as a part of the NOTCH1 Coactivator Complex, binds to the MYC promoter (Palomero et al. 2006).

Preceded by: NICD1 in complex with RBPJ (CSL) recruits MAML

Followed by: NOTCH1 stimulates MYC transcription

Literature references

Palomero, T., Lim, WK., Odom, DT., Sulis, ML., Real, PJ., Margolin, A. et al. (2006). NOTCH1 directly regulates c-MYC and activates a feed-forward-loop transcriptional network promoting leukemic cell growth. *Proc Natl Acad Sci U S A, 103*, 18261-6. ↗

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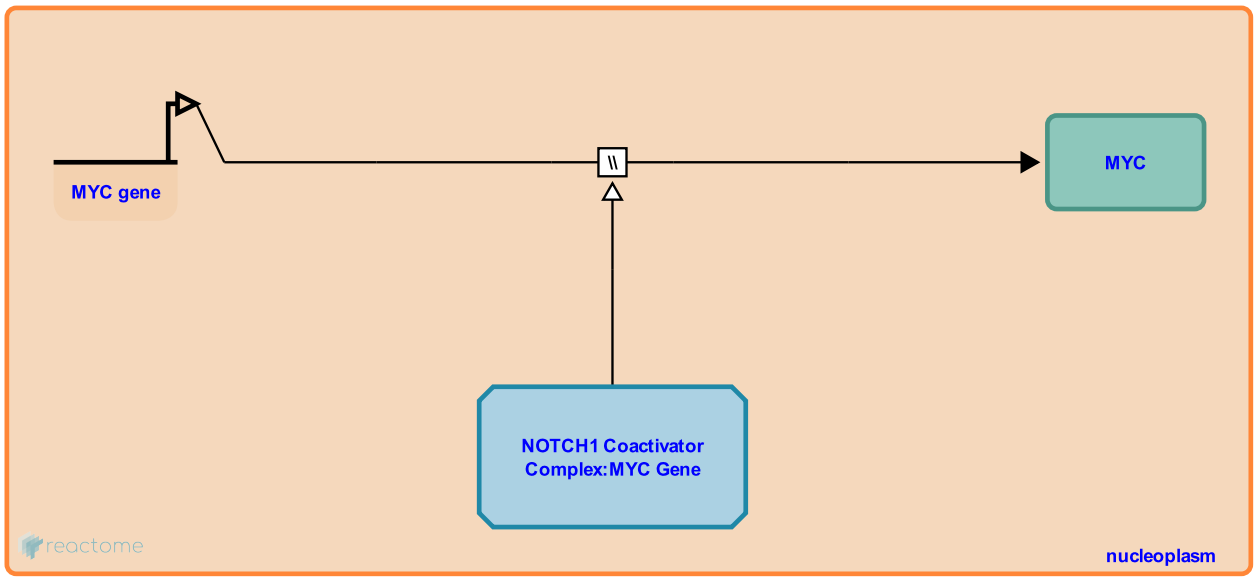
NOTCH1 stimulates MYC transcription ↗

Location: NOTCH1 Intracellular Domain Regulates Transcription

Stable identifier: R-HSA-1980067

Type: omitted

Compartments: nucleoplasm



Binding of the NOTH1 Coactivator Complex to the MYC promoter stimulates MYC transcription (Palomero et al. 2006).

Preceded by: NOTCH1 Coactivator Complex binds MYC promoter

Literature references

Palomero, T., Lim, WK., Odom, DT., Sulis, ML., Real, PJ., Margolin, A. et al. (2006). NOTCH1 directly regulates c-MYC and activates a feed-forward-loop transcriptional network promoting leukemic cell growth. *Proc Natl Acad Sci U S A, 103*, 18261-6. ↗

Editions

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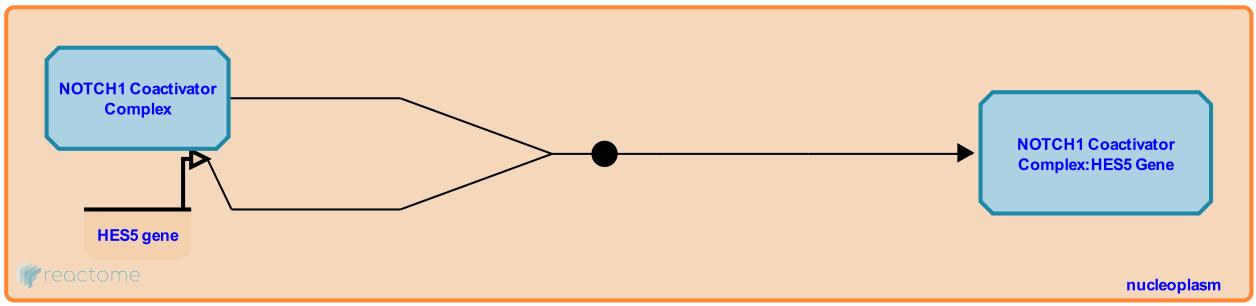
NOTCH1 Coactivator Complex binds HES5 promoter ↗

Location: NOTCH1 Intracellular Domain Regulates Transcription

Stable identifier: R-HSA-4396379

Type: binding

Compartments: nucleoplasm



NICD1, as a part of the NOTCH1 Coactivator Complex, binds to the HES5 promoter (Arnett et al. 2010).

Preceded by: NICD1 in complex with RBPJ (CSL) recruits MAML

Followed by: NOTCH1 stimulates HES5 transcription

Literature references

Arnett, KL., Hass, M., McArthur, DG., Ilagan, MXG., Aster, JC., Kopan, R. et al. (2010). Structural and mechanistic insights into cooperative assembly of dimeric Notch transcription complexes. *Nat Struct Mol Biol, 17*, 1312-7. ↗

Editions

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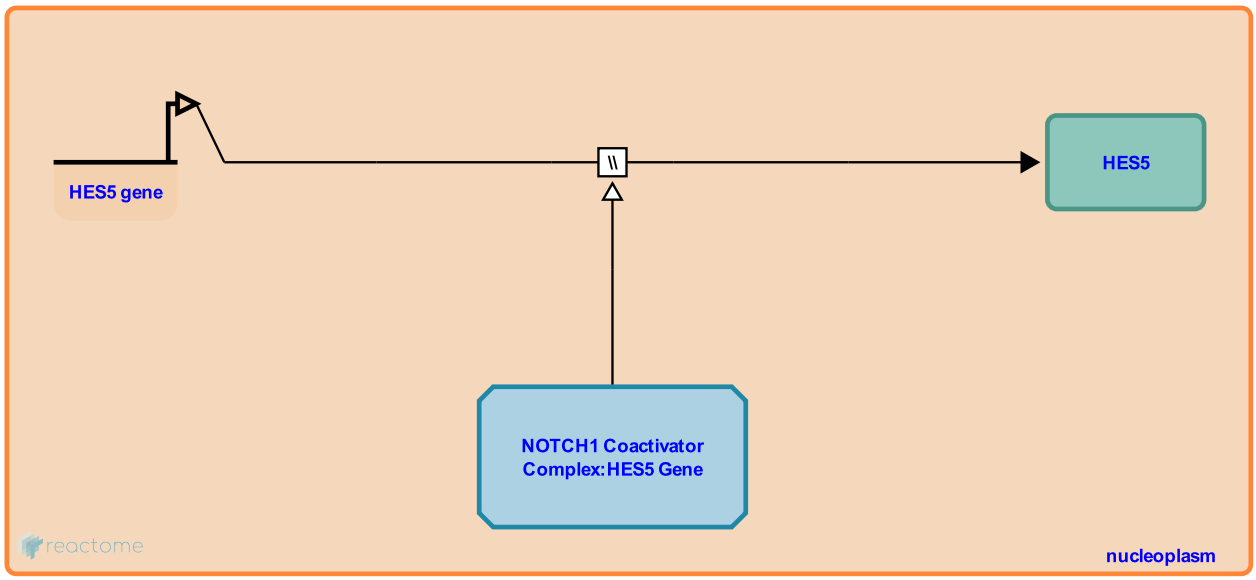
NOTCH1 stimulates HES5 transcription ↗

Location: NOTCH1 Intracellular Domain Regulates Transcription

Stable identifier: R-HSA-1980078

Type: omitted

Compartments: nucleoplasm



Binding of the NOTCH1 Coactivator Complex to the HES5 promoter stimulates HES5 transcription (Arnett et al. 2010).

Preceded by: NOTCH1 Coactivator Complex binds HES5 promoter

Literature references

Arnett, KL., Hass, M., McArthur, DG., Ilagan, MXG., Aster, JC., Kopan, R. et al. (2010). Structural and mechanistic insights into cooperative assembly of dimeric Notch transcription complexes. *Nat Struct Mol Biol, 17*, 1312-7. ↗

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NOTCH1 Coactivator Complex binds promoters of HEY genes ↗

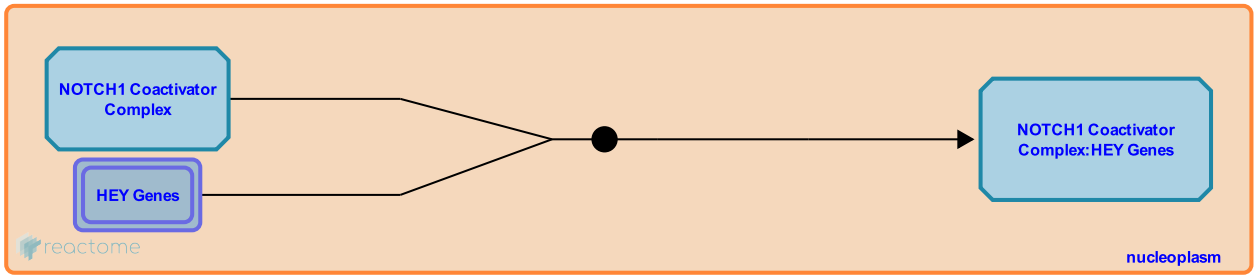
Location: NOTCH1 Intracellular Domain Regulates Transcription

Stable identifier: R-HSA-4396382

Type: binding

Compartments: nucleoplasm

Inferred from: mNOTCH1 coactivator complex bind promoters of Hey genes (Mus musculus)



RBPJ binding sites in the promoters of HEY1, HEY2 and HEYL genes are conserved between humans and mice (Maier and Gessler 2000), and human NICD1 was directly shown to bind human HEY2 and HEYL promoters (Arnett et al. 2010).

Preceded by: NICD1 in complex with RBPJ (CSL) recruits MAML

Followed by: NOTCH1 stimulates HEY transcription

Literature references

Maier, MM., Gessler, M. (2000). Comparative analysis of the human and mouse Hey1 promoter: Hey genes are new Notch target genes. *Biochem Biophys Res Commun, 275*, 652-60. ↗

Arnett, KL., Hass, M., McArthur, DG., Ilagan, MXG., Aster, JC., Kopan, R. et al. (2010). Structural and mechanistic insights into cooperative assembly of dimeric Notch transcription complexes. *Nat Struct Mol Biol, 17*, 1312-7. ↗

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2012-02-10	Edited	Orlic-Milacic, M.

NOTCH1 stimulates HEY transcription ↗

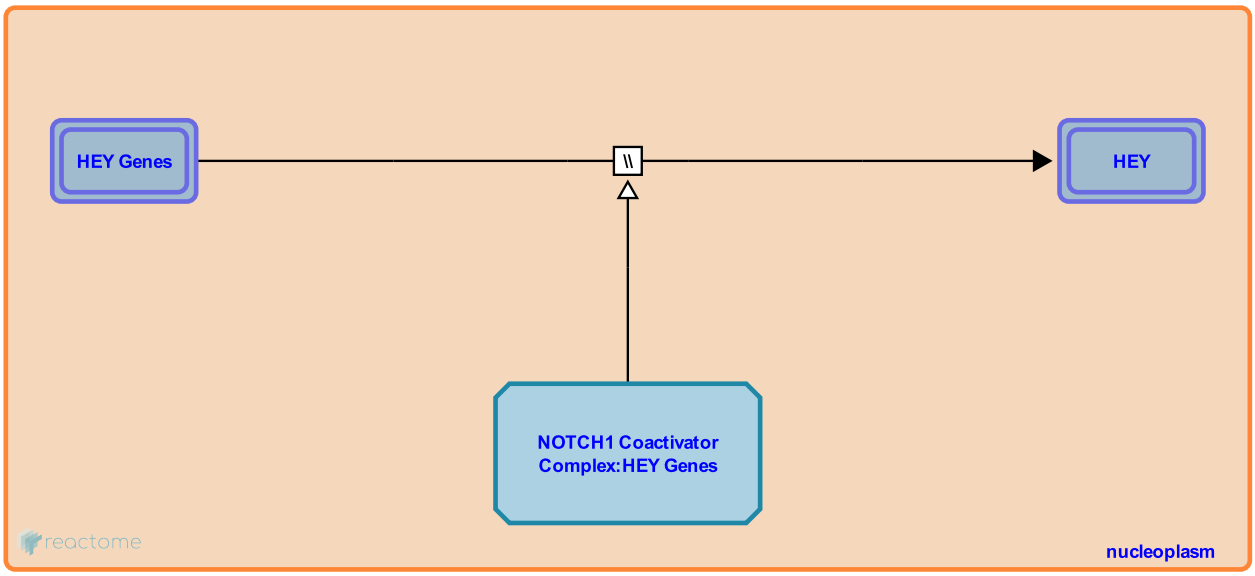
Location: NOTCH1 Intracellular Domain Regulates Transcription

Stable identifier: R-HSA-1980065

Type: omitted

Compartments: nucleoplasm

Inferred from: mNOTCH1 coactivator complex positively regulates transcription of Hey1, Hey2 and Heyl (Mus musculus)



RBPJ binding sites in the promoters of HEY1, HEY2 and HEYL genes are conserved between humans and mice (Maier and Gessler 2000), and expression of human NICD1 was directly shown to activate transcription from human HEY2 and HEYL promoters (Arnett et al. 2010). Based on the evolutionary conservation of RBPJ sites and the existing findings from human and mouse studies, NOTCH1 is expected to directly stimulate transcription of HEY1, HEY2 and HEYL (Fischer et al. 2004, Leimeister et al. 2000).

Preceded by: NOTCH1 Coactivator Complex binds promoters of HEY genes

Literature references

Fischer, A., Schumacher, N., Maier, M., Sendtner, M., Gessler, M. (2004). The Notch target genes Hey1 and Hey2 are required for embryonic vascular development. *Genes Dev, 18*, 901-11. ↗

Leimeister, C., Schumacher, N., Steidl, C., Gessler, M. (2000). Analysis of HeyL expression in wild-type and Notch pathway mutant mouse embryos. *Mech Dev, 98*, 175-8. ↗

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Editions

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2012-02-06	Reviewed	Haw, R.
2012-02-10	Edited	Orlic-Milacic, M.

MAML in complex with NICD1 recruits CDK8 ↗

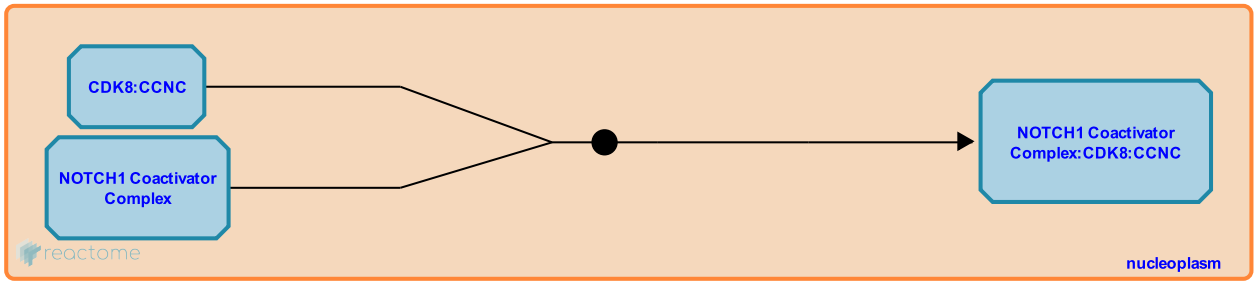
Location: NOTCH1 Intracellular Domain Regulates Transcription

Stable identifier: R-HSA-1912393

Type: binding

Compartments: nucleoplasm

Inferred from: MAML recruits CDK8:CCNC to xNICD1 (Homo sapiens)



After NOTCH1 coactivator complex is assembled on a NOTCH-target promoter, MAML (mastermind-like) recruits CDK8 in complex with cyclin C (CDK:CCNC) (Fryer et al. 2004).

Preceded by: NICD1 in complex with RBPJ (CSL) recruits MAML

Followed by: NICD1 is phosphorylated by CDK8

Literature references

Fryer, CJ., White, JB., Jones, KA. (2004). Mastermind recruits CycC:CDK8 to phosphorylate the Notch ICD and co-ordinate activation with turnover. *Mol Cell, 16*, 509-20. ↗

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NICD1 is phosphorylated by CDK8 ↗

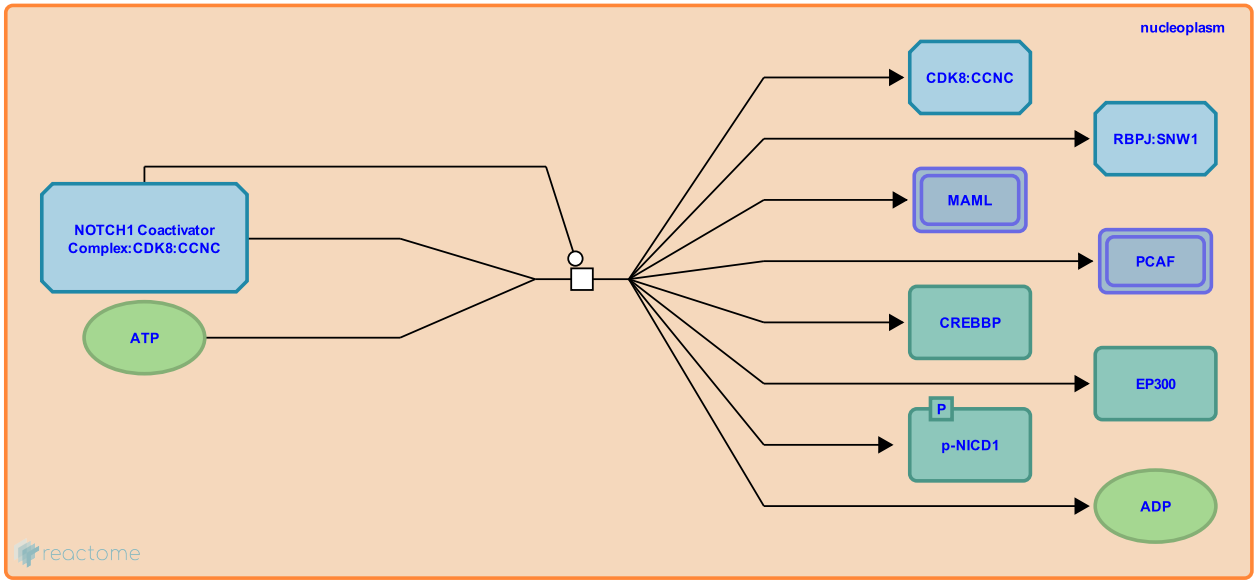
Location: NOTCH1 Intracellular Domain Regulates Transcription

Stable identifier: R-HSA-1912391

Type: transition

Compartments: nucleoplasm

Inferred from: CDK8 phosphorylates xNICD1 (Homo sapiens)



CDK8 phosphorylates conserved serine residues in the TAD and PEST domains of NICD1. Phosphorylation targets NICD1 for ubiquitination and degradation, ultimately terminating transcriptional activity of NOTCH1 (Fryer et al. 2004).

Preceded by: MAML in complex with NICD1 recruits CDK8

Followed by: Phosphorylated NICD1 binds FBXW7

Literature references

Fryer, CJ., White, JB., Jones, KA. (2004). Mastermind recruits CycC:CDK8 to phosphorylate the Notch ICD and coordinate activation with turnover. *Mol Cell, 16*, 509-20. ↗

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Phosphorylated NICD1 binds FBXW7 ↗

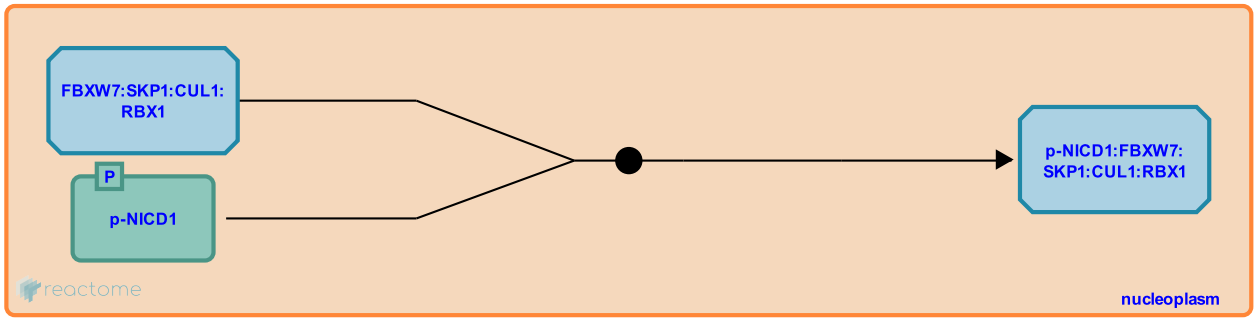
Location: NOTCH1 Intracellular Domain Regulates Transcription

Stable identifier: R-HSA-1912385

Type: binding

Compartments: nucleoplasm

Inferred from: FBXW7 binds phosphorylated NICD1 (Homo sapiens)



The E3 ubiquitin ligase FBXW7, a homologue of C. elegans sel-10, binds phosphorylated NOTCH1 intracellular domain, p-NICD1 (Oberg et al. 2001, Fryer et al. 2004, Wu et al. 2001). FBXW7 is a substrate recognition component of an E3 ubiquitin-protein ligase complex that also contains SKP1, CUL1 and RBX1. FBXW7 has three transcriptional isoforms, known as FBXW7 alpha, FBXW7 beta and FBXWT gamma. While FBXW7 beta is cytosolic, FBXW7 alpha and gamma are nuclear, with FBXW7 gamma localizing to the nucleolus. FBXW7 alpha is the most abundant isoform and the one directly shown to interact with NICD1 (Welcker and Clurman 2008).

Preceded by: NICD1 is phosphorylated by CDK8

Followed by: Ubiquitination of NICD1 by FBWX7

Literature references

Oberg, C., Li, J., Pauley, A., Wolf, E., Gurney, M., Lendahl, U. (2001). The Notch intracellular domain is ubiquitinated and negatively regulated by the mammalian Sel-10 homolog. *J Biol Chem, 276*, 35847-53. ↗

Fryer, CJ., White, JB., Jones, KA. (2004). Mastermind recruits CycC:CDK8 to phosphorylate the Notch ICD and coordinate activation with turnover. *Mol Cell, 16*, 509-20. ↗

Welcker, M., Clurman, BE. (2008). FBW7 ubiquitin ligase: a tumour suppressor at the crossroads of cell division, growth and differentiation. *Nat Rev Cancer, 8*, 83-93. ↗

Wu, G., Lyapina, S., Das, I., Li, J., Gurney, M., Pauley, A. et al. (2001). SEL-10 is an inhibitor of notch signaling that targets notch for ubiquitin-mediated protein degradation. *Mol Cell Biol, 21*, 7403-15. ↗

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Ubiquitination of NICD1 by FBWX7 ↗

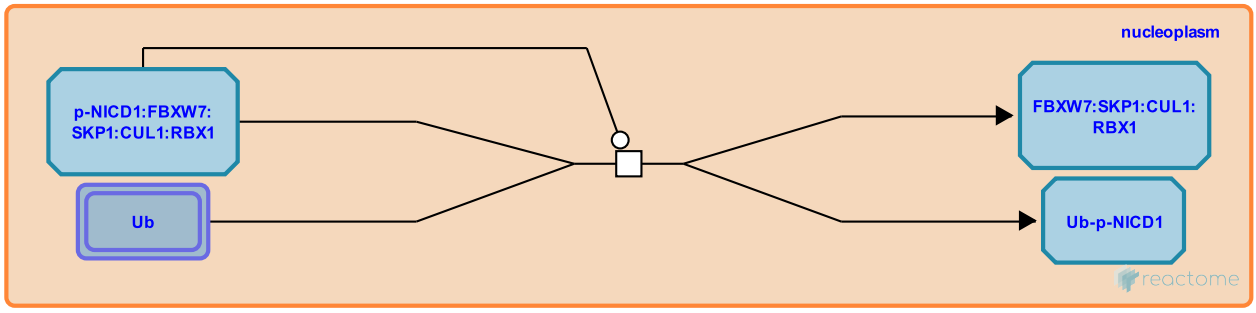
Location: NOTCH1 Intracellular Domain Regulates Transcription

Stable identifier: R-HSA-1852623

Type: transition

Compartments: nucleoplasm

Inferred from: FBXW7 mediates ubiquitination of phosphorylated NICD1 (Homo sapiens)



Once bound to FBXW7, phosphorylated NICD1 is ubiquitinated, which leads to degradation of NICD1 and downregulation of NOTCH1 signaling. FBXW7-mediated ubiquitination and degradation of NOTCH1 depend on the C-terminally located PEST domain of NOTCH1 (Fryer et al. 2004, Oberg et al. 2001, Wu et al. 2001). The PEST domain in NOTCH1 and the substrate binding WD40 domain in FBXW7 are frequent targets of mutations in T-cell acute lymphoblastic leukemia - T-ALL (Welcker and Clurman 2008).

Preceded by: Phosphorylated NICD1 binds FBXW7

Literature references

Fryer, CJ., White, JB., Jones, KA. (2004). Mastermind recruits CycC:CDK8 to phosphorylate the Notch ICD and coordinate activation with turnover. *Mol Cell, 16*, 509-20. ↗

Oberg, C., Li, J., Pauley, A., Wolf, E., Gurney, M., Lendahl, U. (2001). The Notch intracellular domain is ubiquitinated and negatively regulated by the mammalian Sel-10 homolog. *J Biol Chem, 276*, 35847-53. ↗

Wu, G., Lyapina, S., Das, I., Li, J., Gurney, M., Pauley, A. et al. (2001). SEL-10 is an inhibitor of notch signaling that targets notch for ubiquitin-mediated protein degradation. *Mol Cell Biol, 21*, 7403-15. ↗

Welcker, M., Clurman, BE. (2008). FBW7 ubiquitin ligase: a tumour suppressor at the crossroads of cell division, growth and differentiation. *Nat Rev Cancer, 8*, 83-93. ↗

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NICD1 binds HIF1A ↗

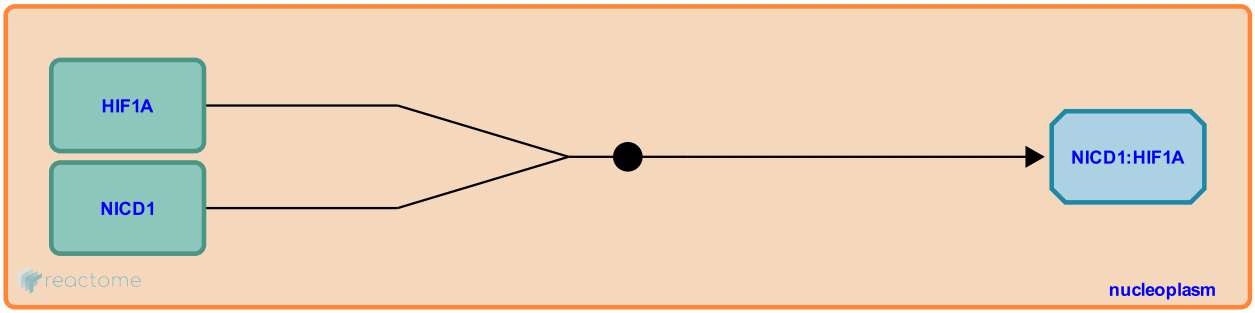
Location: NOTCH1 Intracellular Domain Regulates Transcription

Stable identifier: R-HSA-1912396

Type: binding

Compartments: nucleoplasm

Inferred from: mNICD1 binds HIF1A (Homo sapiens)



When the oxygen supply is low, hypoxia-inducible factor 1-alpha (HIF1A) accumulates in the nucleus where it binds and prolongs the half-life of NICD1, resulting in increased NICD1-mediated transcription and consequent inhibition of cellular differentiation.

Literature references

Gustafsson, MV., Zheng, X., Pereira, T., Gradin, K., Jin, S., Lundkvist, J. et al. (2005). Hypoxia requires notch signaling to maintain the undifferentiated cell state. *Dev Cell, 9*, 617-28. ↗

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