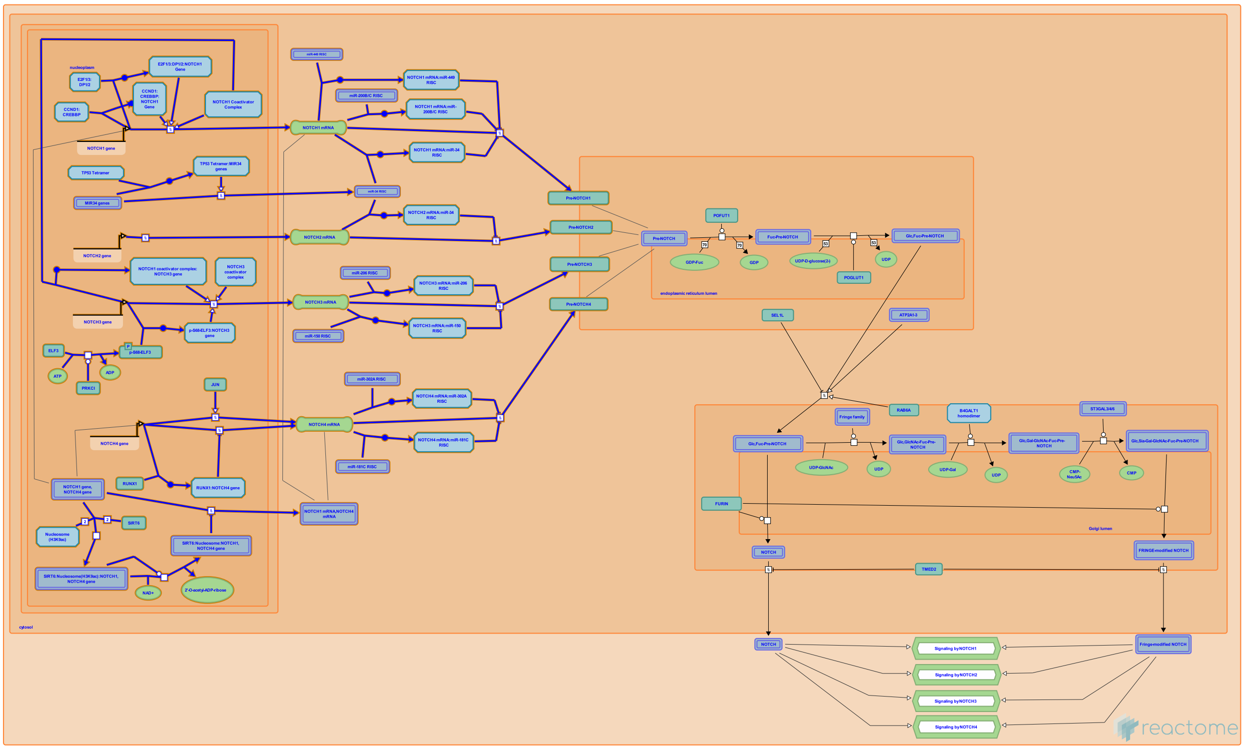
Pre-NOTCH Transcription and Translation



D'Eustachio, P., Egan, SE., Gillespie, ME., Haw, R., Jupe, S., May, B., Orlic-Milacic, M.

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

This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the [Reactome Textbook]().

06/05/2024

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. ↗

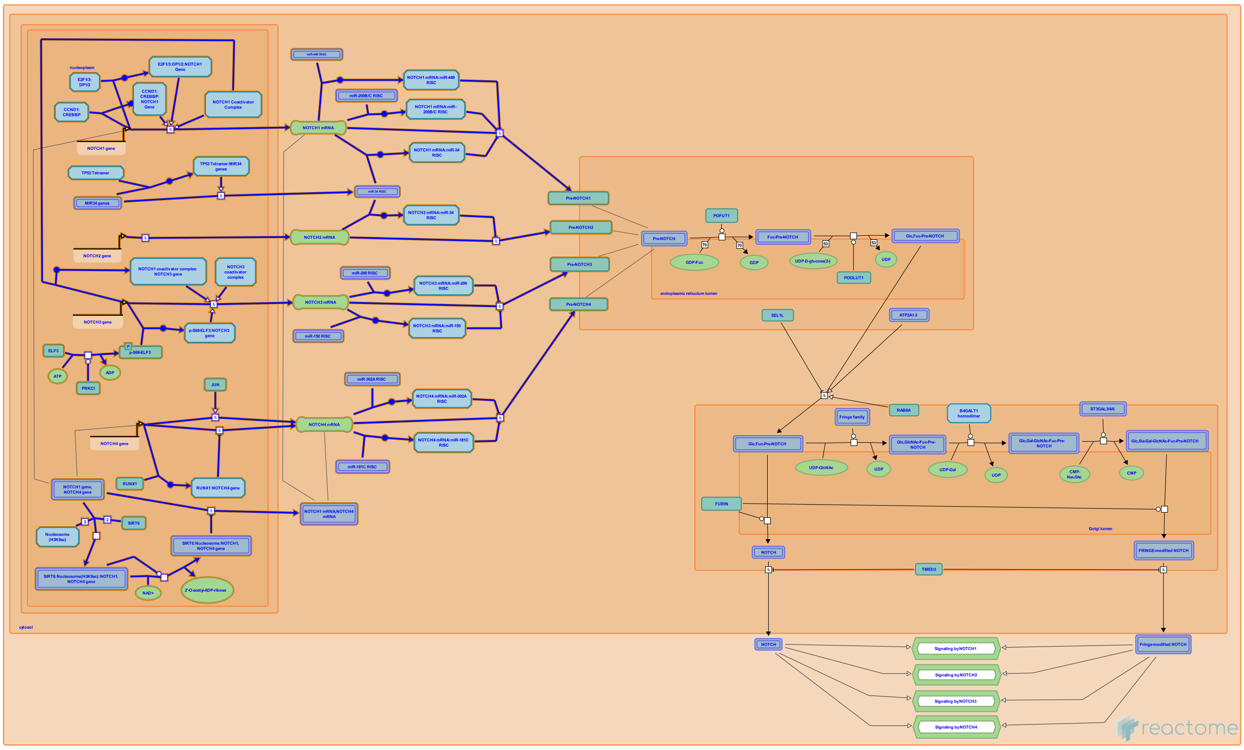
Reactome database release: 88

This document contains 1 pathway and 28 reactions (see Table of Contents)

Pre-NOTCH Transcription and Translation ↗

Stable identifier: R-HSA-1912408

Compartments: nucleoplasm, cytosol, endoplasmic reticulum membrane



In humans, the NOTCH protein family has four members: NOTCH1, NOTCH2, NOTCH3 and NOTCH4. NOTCH1 protein was identified first, as the product of a chromosome 9 gene translocated in T-cell acute lymphoblastic leukemia that was homologous to Drosophila Notch (Ellisen et al. 1991). At the same time, rat Notch1 was cloned (Weinmaster et al. 1991), followed by cloning of mouse Notch1, named Motch (Del Amo et al. 1992). NOTCH2 protein is the product of a gene on chromosome 1 (Larsson et al. 1994). NOTCH2 expression is differentially regulated during B-cell development (Bertrand et al. 2000). NOTCH2 mutations are a rare cause of Alagille syndrome (McDaniell et al. 2006). NOTCH3 is the product of a gene on chromosome 19. NOTCH3 mutations are the underlying cause of CADASIL, cerebral arteriopathy with subcortical infarcts and leukoencephalopathy (Joutel et al. 1996). NOTCH4, the last NOTCH protein discovered, is the product of a gene on chromosome 6 (Li et al. 1998).

MicroRNAs play an important negative role in translation and/or stability of NOTCH mRNAs. MicroRNAs miR-34 (miR-34A, miR-34B and mi-R34C), whose transcription is directly induced by the tumor suppressor protein p53 (Chang et al. 2007, Raver-Shapira et al. 2007, He et al. 2007, Corney et al. 2007) bind and negatively regulate translation of NOTCH1 mRNA (Li et al. 2009, Pang et al. 2010, Ji et al. 2009) and NOTCH2 mRNA (Li et al. 2009). NOTCH1 mRNA translation is also negatively regulated by microRNAs miR-200B and miR-200C (Kong et al. 2010), as well as miR-449A, miR-449B and miR-449C (Marcet et al. 2011). Translation of NOTCH3 mRNA is negatively regulated by microRNAs miR-150 (Ghisi et al. 2011) and miR-206 (Song et al. 2009). Translation of NOTCH4 mRNA is negatively regulated by microRNAs miR-181C (Hashimoto et al. 2010) and miR-302A (Costa et al. 2009).

Nascent NOTCH peptides are co-translationally targeted to the endoplasmic reticulum for further processing, followed by modification in the Golgi apparatus, before trafficking to the plasma membrane. Endoplasmic reticulum calcium ATPases, positively regulate NOTCH trafficking, possibly by contributing to accurate folding of NOTCH precursors (Periz et al. 1999).

Literature references

Meiri, E., Raver-Shapira, N., Moskovits, N., Spector, Y., Rosenfeld, N., Bentwich, Z. et al. (2007). Transcriptional activation of miR-34a contributes to p53-mediated apoptosis. *Mol Cell, 26*, 731-43. ↗

Yeung, WS., Lee, KF., Pang, RT., Chiu, PCN., Leung, CON., Liu, W. et al. (2010). MicroRNA-34a suppresses invasion through downregulation of Notch1 and Jagged1 in cervical carcinoma and choriocarcinoma cells. *Carcinogenesis, 31*, 1037-44. ↗

Arndt, K., Costa, FF., Bischof, JM., Seftor, EA., Soares, MB., Hendrix, MJC. et al. (2009). Epigenetically reprogramming metastatic tumor cells with an embryonic microenvironment. *Epigenomics, 1*, 387-398. ↗

Friedman, C., Banta, AB., Chen, L., Deng, Y., Hood, L., Huang, GM. et al. (1998). Cloning, characterization, and the complete 56.8-kilobase DNA sequence of the human NOTCH4 gene. *Genomics, 51*, 45-58. ↗

Gridley, T., Del Amo, FF., Greenspan, RJ., Gendron-Maguire, M., Smith, DE., McMahon, AP. et al. (1992). Expression pattern of Motch, a mouse homolog of Drosophila Notch, suggests an important role in early postimplantation mouse development. *Development, 115*, 737-44. ↗

Editions

2011-09-27	Edited	Jupe, S.
2011-11-14	Authored	Egan, SE., Orlic-Milacic, M.
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2012-02-09	Edited	Gillespie, ME., May, B.
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2012-05-17	Reviewed	Haw, R.
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2017-11-02	Edited	Orlic-Milacic, M.
2018-04-05	Revised	Orlic-Milacic, M.
2018-05-01	Reviewed	Haw, R.

CCND1:CREBBP binds NOTCH1 promoter ↗

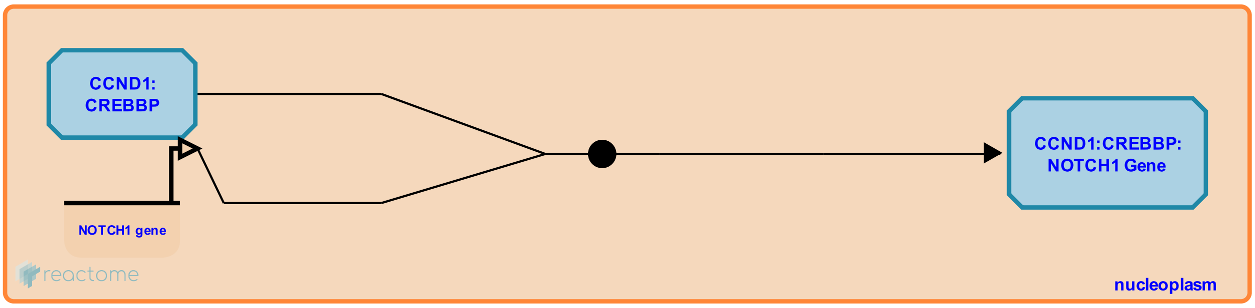
Location: Pre-NOTCH Transcription and Translation

Stable identifier: R-HSA-4395227

Type: binding

Compartments: nucleoplasm

Inferred from: Ccnd1:Crebbp binds Notch1 promoter (Mus musculus)



CCND1 (cyclin D1) forms a complex with CREBBP and binds to the NOTCH1 promoter, stimulating NOTCH1 transcription. The involvement of CCND1 in transcriptional regulation of NOTCH1 was established in mouse retinas and the rat retinal precursor cell line R28 (Bienvenu et al. 2010).

Followed by: NOTCH1 gene transcription

Literature references

Gygi, SP., Liu, XS., Geng, Y., Mizeracka, K., Jirawatnotai, S., Meyer, CA. et al. (2010). Transcriptional role of cyclin D1 in development revealed by a genetic-proteomic screen. *Nature, 463*, 374-8. ↗

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2011-11-14	Authored	Egan, SE., Orlic-Milacic, M.
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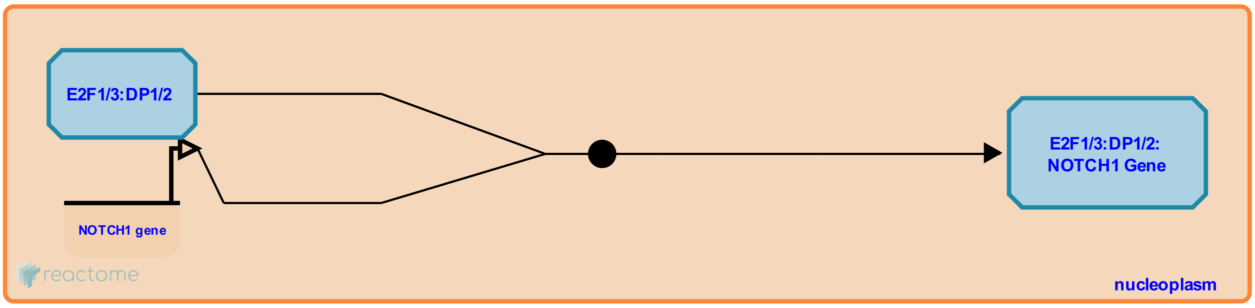
E2F1/3:DP1/2 binds NOTCH1 promoter ↗

Location: Pre-NOTCH Transcription and Translation

Stable identifier: R-HSA-4395231

Type: binding

Compartments: nucleoplasm



E2F1 and E2F3 are able to bind to the NOTCH1 promoter and activate NOTCH1 transcription (Viatour et al. 2011).

Followed by: NOTCH1 gene transcription

Literature references

Saddic, LA., Zmoos, AF., Sylvester, KG., Ehmer, U., Sage, J., Dorrell, C. et al. (2011). Notch signaling inhibits hepatocellular carcinoma following inactivation of the RB pathway. *J Exp Med, 208*, 1963-76. ↗

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2011-11-14	Authored	Egan, SE., Orlic-Milacic, M.
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NOTCH1 gene transcription ↗

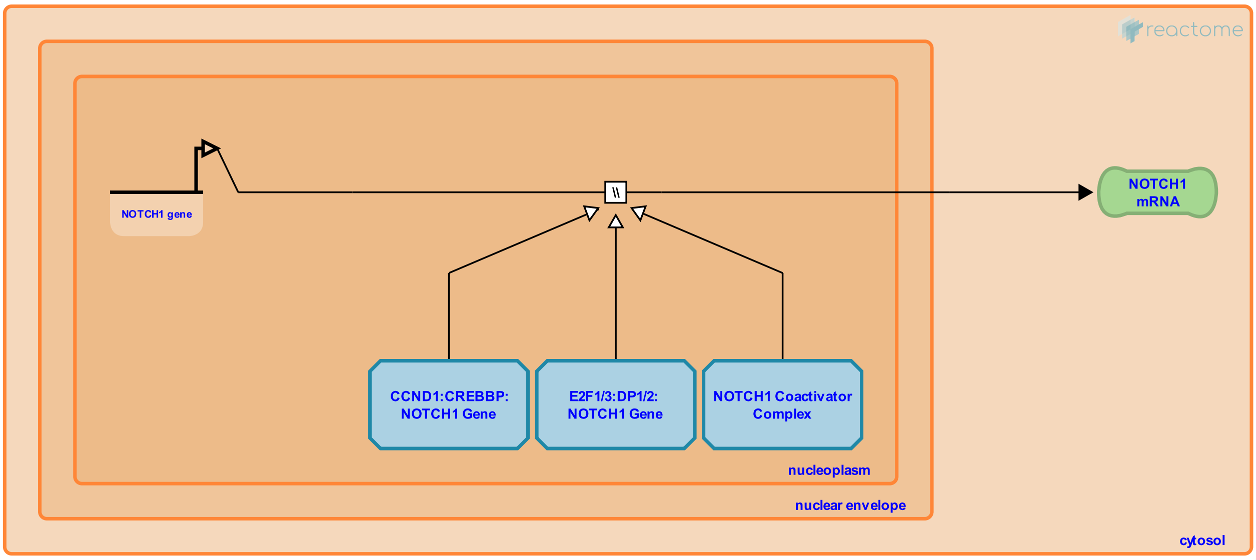
Location: Pre-NOTCH Transcription and Translation

Stable identifier: R-HSA-1912416

Type: omitted

Compartments: nucleoplasm

Inferred from: Notch1 gene transcription (Mus musculus)



NOTCH1 was cloned as a chromosome 9 gene involved in translocation t(7;9)(q34;q34.3) in several T-cell acute lymphoblastic leukemia (T-ALL) patients. The gene was found to be highly homologous to the Drosophila gene Notch and was initially named TAN-1 (translocation-associated Notch homolog). Transcripts of NOTCH1 were detected in many fetal and adult human and mouse tissues, with the highest abundance in lymphoid tissues. The translocation t(7;9)(q34;q34.3) found in a small fraction of T-ALL patients puts NOTCH1 transcription under the control of the T-cell receptor-beta (TCRB) locus, which results in expression of truncated peptides that lack the extracellular ligand binding domain and are constitutively active (reviewed by Grabher et al. 2006). Activating NOTCH1 point mutations, mainly affecting the extracellular heterodimerization domain and/or the C-terminal PEST domain, are found in more than 50% of human T-ALLs (Weng et al. 2004).

Studies of mouse Rbpj knockout embryos and zebrafish Mib (mindbomb) mutants indicate that the NOTCH1 coactivator complex positively regulates NOTCH1 transcription. The RBPJ-binding site(s) that the NOTCH1 coactivator complex normally binds have not been found in the NOTCH1 promoter, however, so this effect may be indirect and its mechanism is unknown (Del Monte et al. 2007).

CCND1 (cyclin D1) forms a complex with CREBBP and binds to the NOTCH1 promoter, stimulating NOTCH1 transcription. The involvement of CCND1 in transcriptional regulation of NOTCH1 was established in mouse retinas and the rat retinal precursor cell line R28 (Bienvenu et al. 2010).

E2F1 and E2F3 are able to bind to the NOTCH1 promoter and activate NOTCH1 transcription (Viatour et al. 2011).

NOTCH1 promoter possesses two putative p53-binding sites. Chromatin immunoprecipitation (ChIP) assays of human primary keratinocytes showed binding of endogenous p53 protein to both sites. Experiments in which p53 was downregulated or overexpressed implicate p53 as a positive regulator of NOTCH1 expression in primary human keratinocytes. It is likely that p53-mediated regulation of NOTCH1 expression involves interplay with other cell-type specific determinants of gene expression (Lefort et al. 2007). In lymphoid cells, NOTCH1 expression may be negatively regulated by p53 (Laws and Osborne 2004). Other proteins implicated in the negative regulation of NOTCH1 transcription are KLF9 (Ying et al. 2011), JARID2 (Mysliwiec et al. 2011, Mysliwiec et al. 2012), KLF4 and SP3 (Lambertini et al. 2010), and p63 (Yugawa et al. 2010).

Preceded by: E2F1/3:DP1/2 binds NOTCH1 promoter, CCND1:CREBBP binds NOTCH1 promoter

Followed by: MIR449 microRNAs bind 3'UTR of NOTCH1 mRNA, MIR200B/C microRNAs bind NOTCH1 mRNA, MIR34 microRNAs bind 3'UTR of NOTCH1 mRNA, NOTCH1 mRNA translation controlled by miRNAs

Literature references

Lee, W., Blacklow, SC., Silverman, LB., Look, AT., Sanchez-Irizarry, C., Aster, JC. et al. (2004). Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. *Science, 306*, 269-71. ↗

von Boehmer, H., Look, AT., Grabher, C. (2006). Notch 1 activation in the molecular pathogenesis of T-cell acute lymphoblastic leukaemia. *Nat Rev Cancer, 6*, 347-59. ↗

Egawa, N., Yoshimatsu, Y., Kiyono, T., Fujita, M., Haga, K., Narisawa-Saito, M. et al. (2010). DeltaNp63alpha repression of the Notch1 gene supports the proliferative capacity of normal human keratinocytes and cervical cancer cells. *Cancer Res., 70*, 4034-44. ↗

Saddic, LA., Zmoos, AF., Sylvester, KG., Ehmer, U., Sage, J., Dorrell, C. et al. (2011). Notch signaling inhibits hepatocellular carcinoma following inactivation of the RB pathway. *J Exp Med, 208*, 1963-76. ↗

Bolós, V., Grego-Bessa, J., González-Rajal, A., De La Pompa, JL., Del Monte, G. (2007). Monitoring Notch1 activity in development: evidence for a feedback regulatory loop. *Dev. Dyn., 236*, 2594-614. ↗

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2011-11-14	Authored	Egan, SE., Orlic-Milacic, M.
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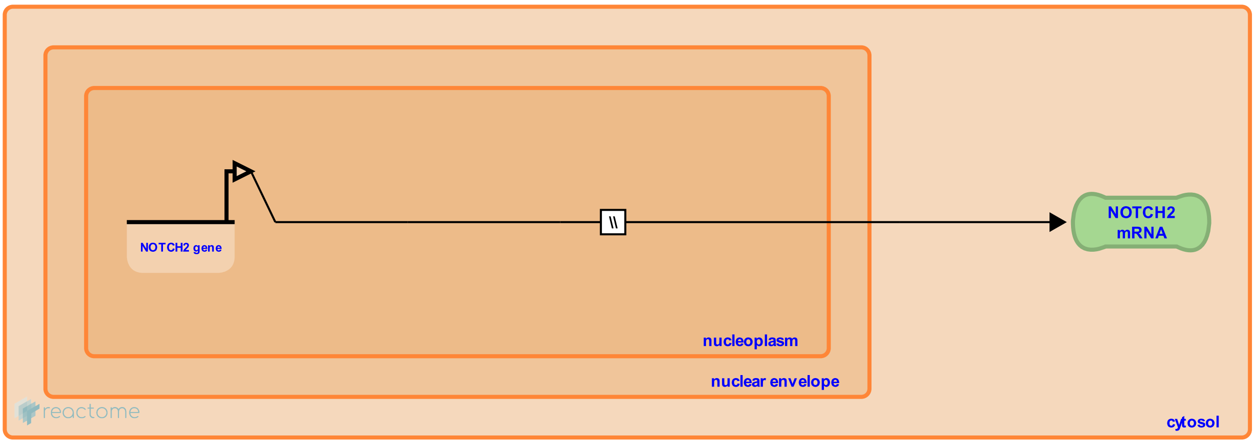
NOTCH2 gene transcription ↗

Location: Pre-NOTCH Transcription and Translation

Stable identifier: R-HSA-1912407

Type: omitted

Compartments: nucleoplasm



The NOTCH2 gene maps to human chromosome 1. NOTCH2 gene expression is differentially regulated during human B-cell development, with NOTCH2 transcripts appearing at late developmental stages. NOTCH2 mutations are a rare cause of Alagille syndrome. Alagille syndrome is a dominant multisystem disorder mainly characterized by hepatic bile duct abnormalities, and is predominantly caused by mutations in JAG1, a NOTCH2 ligand.

Followed by: MIR34 microRNAs bind 3'UTR of NOTCH2 mRNA, NOTCH2 mRNA translation controlled by miRNAs

Literature references

Larsson, C., White, I., Lardelli, M., Lendahl, U. (1994). The human NOTCH1, 2, and 3 genes are located at chromosome positions 9q34, 1p13-p11, and 19p13.2-p13.1 in regions of neoplasia-associated translocation. *Genomics, 24*, 253-8. ↗

Eckfeldt, CE., Bertrand, FE., LeBien, TW., Lysholm, AS. (2000). Notch-1 and Notch-2 exhibit unique patterns of expression in human B-lineage cells. *Leukemia, 14*, 2095-102. ↗

Krantz, ID., Sanchez-Lara, PA., Spinner, NB., Pai, A., Warthen, DM., Piccoli, DA. et al. (2006). NOTCH2 mutations cause Alagille syndrome, a heterogeneous disorder of the notch signaling pathway. *Am J Hum Genet, 79*, 169-73. ↗

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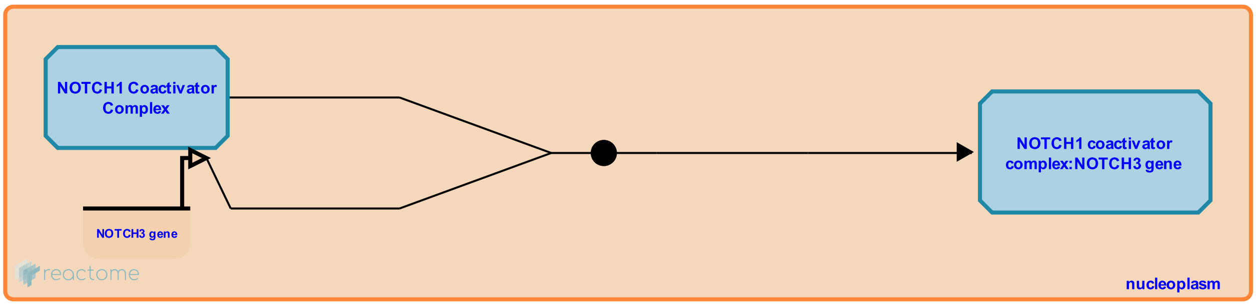
NOTCH1 coactivator complex binds NOTCH3 gene ↗

Location: Pre-NOTCH Transcription and Translation

Stable identifier: R-HSA-9017835

Type: binding

Compartments: nucleoplasm



NOTCH1 and RBPJ (CSL), likely in the form of the NOTCH1 coactivator complex, bind to the RBPJ response elements in the second intron of the NOTCH3 gene (Ohashi et al. 2010).

Followed by: NOTCH3 gene transcription

Literature references

Katz, JP., Kalman, RA., Nakagawa, M., Klein-Szanto, AJ., Yashiro-Ohtani, Y., Wu, L. et al. (2010). NOTCH1 and NOTCH3 coordinate esophageal squamous differentiation through a CSL-dependent transcriptional network. *Gastroenterology, 139*, 2113-23. ↗

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2017-09-20	Authored	Orlic-Milacic, M.
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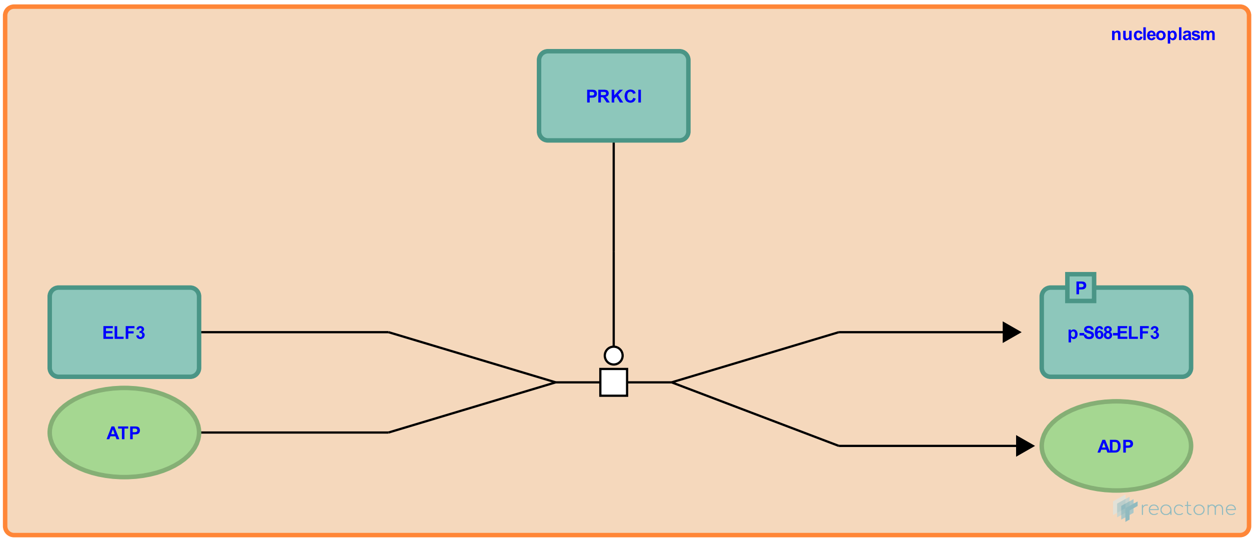
PRKCI phosphorylates ELF3 ↗

Location: Pre-NOTCH Transcription and Translation

Stable identifier: R-HSA-9021357

Type: transition

Compartments: nucleoplasm



PRKCI (protein kinase C iota), activated in response to KRAS signaling, phosphorylates transcription factor ELF3 on serine residue S68. PRKCI-mediated phosphorylation of ELF3 promotes transcriptional activity of ELF3, probably by stimulating nuclear retention or import of ELF3 (Ali et al. 2016).

Followed by: ELF3 binds NOTCH3 gene promoter

Literature references

Jamieson, L., Justilien, V., Murray, NR., Ali, SA., Fields, AP. (2016). Protein Kinase Cι Drives a NOTCH3-dependent Stem-like Phenotype in Mutant KRAS Lung Adenocarcinoma. *Cancer Cell, 29*, 367-78. ↗

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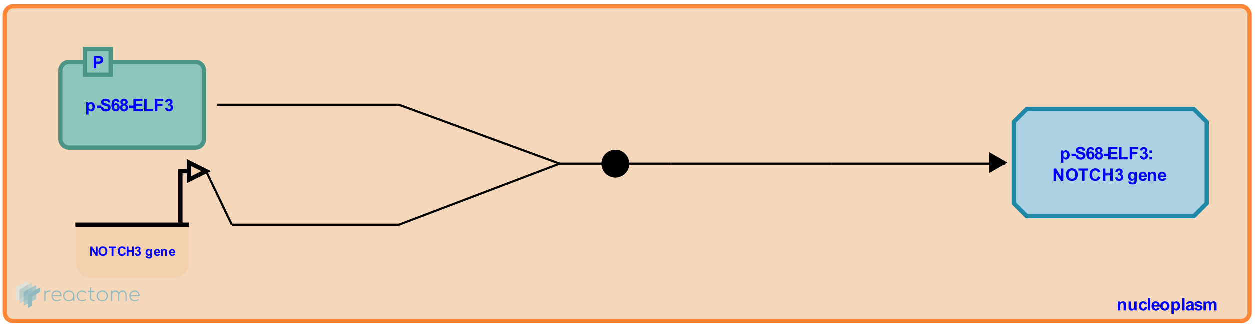
ELF3 binds NOTCH3 gene promoter ↗

Location: Pre-NOTCH Transcription and Translation

Stable identifier: R-HSA-9021364

Type: binding

Compartments: nucleoplasm



ELF3, phosphorylated by PRKCI (protein kinase C iota) on serine residue S68, binds multiple ELF3-binding sites in the NOTCH3 gene promoter (Ali et al. 2016).

Preceded by: PRKCI phosphorylates ELF3

Followed by: NOTCH3 gene transcription

Literature references

Jamieson, L., Justilien, V., Murray, NR., Ali, SA., Fields, AP. (2016). Protein Kinase Cι Drives a NOTCH3-dependent Stem-like Phenotype in Mutant KRAS Lung Adenocarcinoma. *Cancer Cell, 29*, 367-78. ↗

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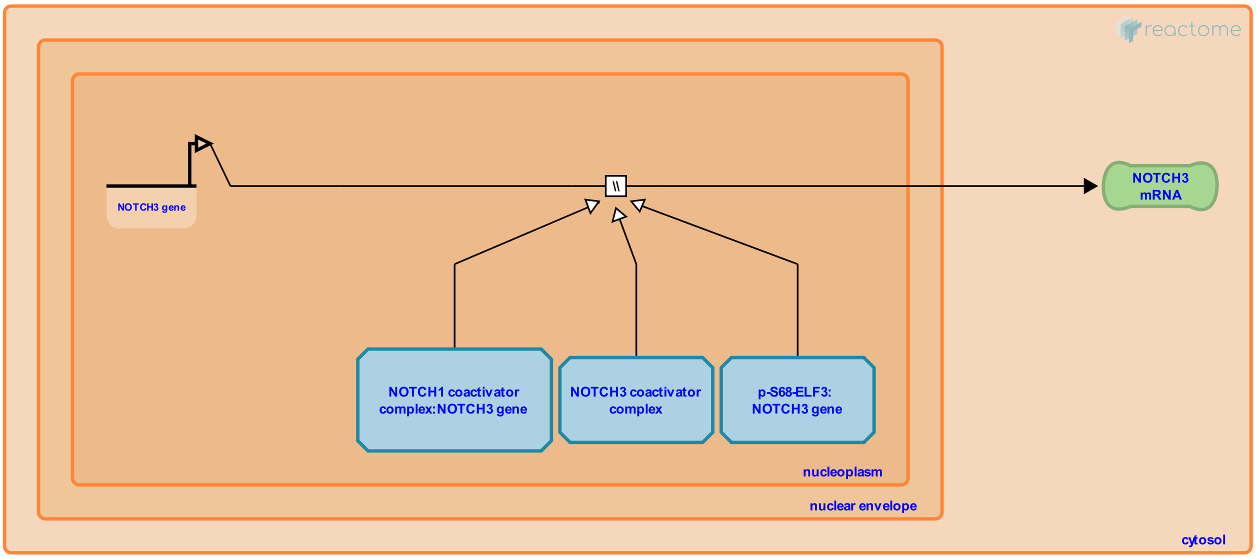
NOTCH3 gene transcription ↗

Location: Pre-NOTCH Transcription and Translation

Stable identifier: R-HSA-1912415

Type: omitted

Compartments: nucleoplasm



The NOTCH3 gene maps to human chromosome 19. NOTCH3 transcript is ubiquitously expressed in fetal and adult human tissues. Mutations in NOTCH3 are found in cerebral arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), an autosomal dominant progressive disorder of small arterial vessels of the brain characterized by migraines, strokes, and white matter lesions, with the onset in early adulthood (Joutel et al. 1996).

NOTCH3 gene transcription is stimulated by the NOTCH3 coactivator complex but it is not known whether this effect is direct, or indirect (Liu et al. 2009).

NOTCH3 gene transcription is directly stimulated by the NOTCH1 coactivator complex and NOTCH1-mediated regulation of NOTCH3 is involved in differentiation of esophageal squamous cells (Ohashi et al. 2009).

NOTCH3 transcription is directly stimulated by transcription factor ELF3, activated by PRKCI (protein kinase C iota)-mediated phosphorylation downstream of KRAS signaling. The PRKCI-ELF3-NOTCH3 signaling controls the tumor-initiating cell phenotype in KRAS-mediated lung adenocarcinoma (Ali et al. 2016).

Preceded by: ELF3 binds NOTCH3 gene promoter, NOTCH1 coactivator complex binds NOTCH3 gene

Followed by: MIR150 microRNA binds 3'UTR of NOTCH3 mRNA, MIR206 microRNA binds 3'UTR of NOTCH3 mRNA, NOTCH3 mRNA translation controlled by miRNAs

Literature references

Jamieson, L., Justilien, V., Murray, NR., Ali, SA., Fields, AP. (2016). Protein Kinase Cι Drives a NOTCH3-dependent Stem-like Phenotype in Mutant KRAS Lung Adenocarcinoma. *Cancer Cell, 29*, 367-78. ↗

Katz, JP., Kalman, RA., Nakagawa, M., Klein-Szanto, AJ., Yashiro-Ohtani, Y., Wu, L. et al. (2010). NOTCH1 and NOTCH3 coordinate esophageal squamous differentiation through a CSL-dependent transcriptional network. *Gastroenterology, 139*, 2113-23. ↗

Cabanis, EA., Chabriat, H., Corpechot, C., Cruaud, C., Maréchal, E., Cécillion, M. et al. (1996). Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature, 383*, 707-10. ↗

Liu, H., Kennard, S., Lilly, B. (2009). NOTCH3 expression is induced in mural cells through an autoregulatory loop that requires endothelial-expressed JAGGED1. *Circ. Res., 104*, 466-75. ↗

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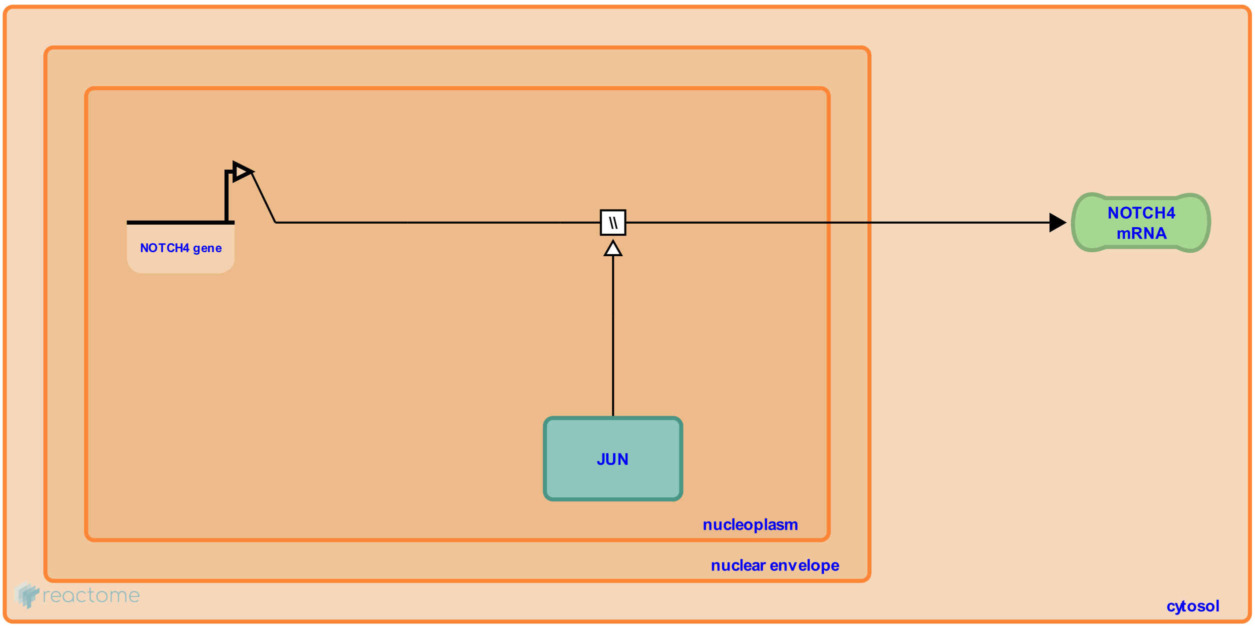
NOTCH4 gene transcription ↗

Location: Pre-NOTCH Transcription and Translation

Stable identifier: R-HSA-1912401

Type: omitted

Compartments: nucleoplasm



The NOTCH4 gene maps to the short arm of human chromosome 6. High levels of NOTCH4 transcript are detectable in adult heart. NOTCH4 mRNA is also found in lung and placenta, and at low levels in liver, skeletal muscle, kidney, pancreas, spleen, thymus, lymph nodes and bone marrow (Li et al. 1998).

In vascular endothelium, NOTCH4 transcription is activated by c-JUN (AP-1) transcription factor. JUN, likely in complex with other transcription factors, binds AP-1 motif(s) in the NOTCH4 promoter and possibly within the first intron (Wu et al. 2005).

Followed by: MIR181C microRNA binds 3'UTR of NOTCH4 mRNA, MIR302A microRNA binds 3'UTR of NOTCH4 mRNA, NOTCH4 mRNA translation controlled by miRNAs

Literature references

Yamamoto, M., Osborne, CS., Grass, JA., Elnitski, L., Ohneda, O., Iwata, F. et al. (2005). Molecular determinants of NOTCH4 transcription in vascular endothelium. *Mol. Cell. Biol., 25*, 1458-74. ↗

Friedman, C., Banta, AB., Chen, L., Deng, Y., Hood, L., Huang, GM. et al. (1998). Cloning, characterization, and the complete 56.8-kilobase DNA sequence of the human NOTCH4 gene. *Genomics, 51*, 45-58. ↗

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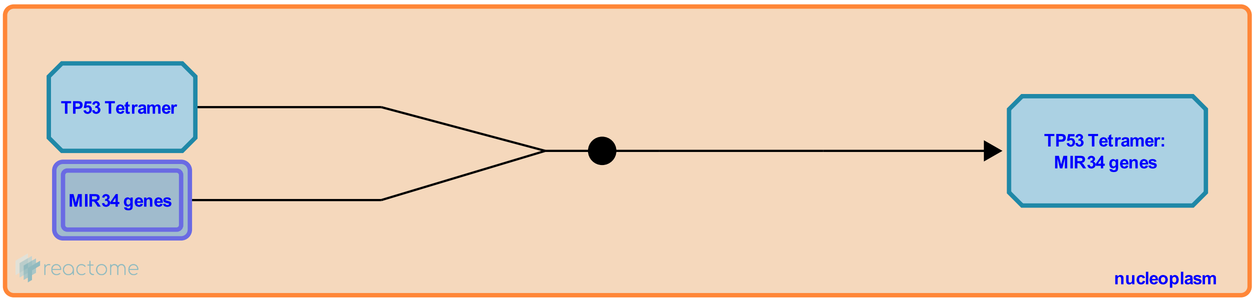
TP53 binds promoters of MIR34 genes ↗

Location: Pre-NOTCH Transcription and Translation

Stable identifier: R-HSA-4395236

Type: binding

Compartments: nucleoplasm



TP53 (p53) binds to the conserved p53 binding site located in the vicinity of the MIR34A transcription start (Chang et al. 2007, Raver-Shapira et al. 2007). TP53 also binds to conserved p53 binding sites in the promoter of clustered MIR34B and MIR34C genes, and the transcription of MIR34B and MIR34C microRNAs is directly positively regulated by p53 (He et al. 2007, Corney et al. 2007).

Followed by: p53 positively regulates transcription of MIR34 microRNAs

Literature references

Meiri, E., Raver-Shapira, N., Moskovits, N., Spector, Y., Rosenfeld, N., Bentwich, Z. et al. (2007). Transcriptional activation of miR-34a contributes to p53-mediated apoptosis. *Mol Cell, 26*, 731-43. ↗

Nikitin, AY., Godwin, AK., Flesken-Nikitin, A., Wang, W., Corney, DC. (2007). MicroRNA-34b and MicroRNA-34c are targets of p53 and cooperate in control of cell proliferation and adhesion-independent growth. *Cancer Res, 67*, 8433-8. ↗

Linsley, PS., Ridzon, D., Xuan, Z., Xue, W., Liang, Y., Lim, LP. et al. (2007). A microRNA component of the p53 tumour suppressor network. *Nature, 447*, 1130-4. ↗

Mendell, JT., Chang, TC., Lee, KH., Kent, OA., Ferlito, M., Mullendore, M. et al. (2007). Transactivation of miR-34a by p53 broadly influences gene expression and promotes apoptosis. *Mol Cell, 26*, 745-52. ↗

Editions

2011-11-14	Authored	Egan, SE., Orlic-Milacic, M.
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2012-02-07	Edited	D'Eustachio, P.
2012-02-11	Edited	Orlic-Milacic, M.

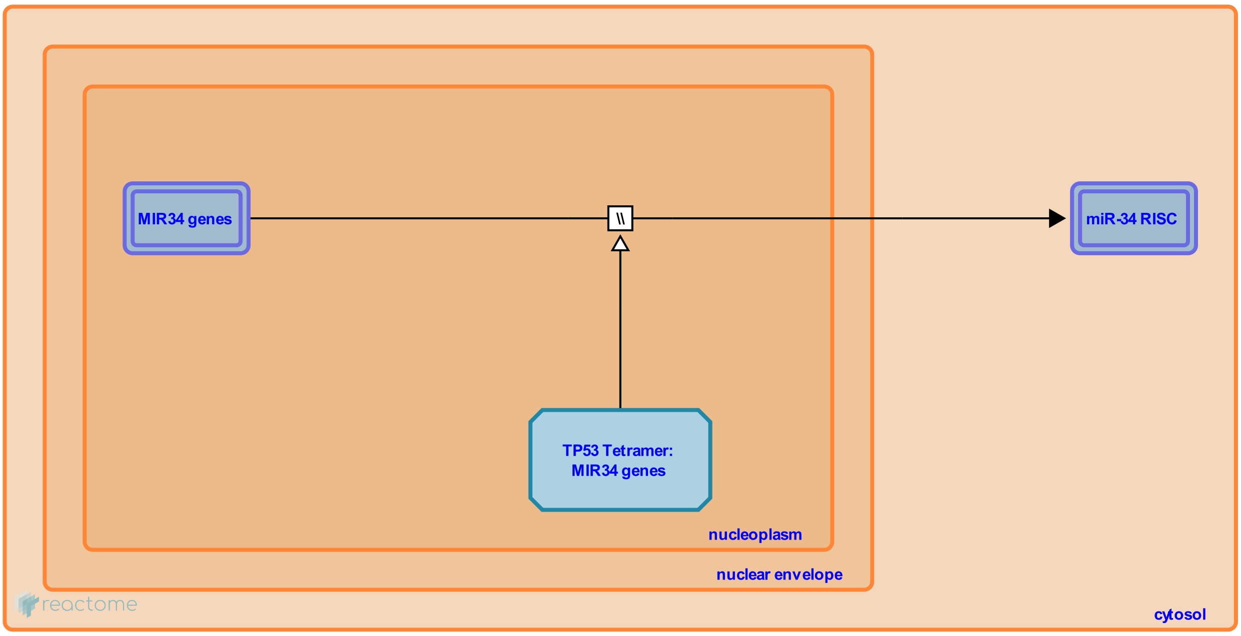
p53 positively regulates transcription of MIR34 microRNAs ↗

Location: Pre-NOTCH Transcription and Translation

Stable identifier: R-HSA-1912406

Type: omitted

Compartments: nucleoplasm



Transcription of microRNA MIR34A is directly induced by the tumor suppressor p53, which binds to the conserved p53 binding site located in the vicinity of the MIR34A transcription start (Chang et al. 2007, Raver-Shapira et al. 2007). Genomic loss of the chromosomal band 1p36, harboring the MIR34A gene, is a frequent event in pancreatic cancer, and MIR34A is considered to act as a tumor suppressor. Conserved p53 binding sites were also mapped to the promoter of clustered MIR34B and MIR34C genes, and the transcription of MIR34B and MIR34C microRNAs was shown to be positively regulated by p53 (He et al. 2007, Corney et al. 2007). The steps involved in processing of pri-microRNA into pre-microRNA have been omitted in this event - please refer to the diagram of Regulatory RNA Pathways for details.

Preceded by: TP53 binds promoters of MIR34 genes

Followed by: MIR34 microRNAs bind 3'UTR of NOTCH2 mRNA, MIR34 microRNAs bind 3'UTR of NOTCH1 mRNA

Literature references

Meiri, E., Raver-Shapira, N., Moskovits, N., Spector, Y., Rosenfeld, N., Bentwich, Z. et al. (2007). Transcriptional activation of miR-34a contributes to p53-mediated apoptosis. *Mol Cell, 26*, 731-43. ↗

Nikitin, AY., Godwin, AK., Flesken-Nikitin, A., Wang, W., Corney, DC. (2007). MicroRNA-34b and MicroRNA-34c are targets of p53 and cooperate in control of cell proliferation and adhesion-independent growth. *Cancer Res, 67*, 8433-8. ↗

Linsley, PS., Ridzon, D., Xuan, Z., Xue, W., Liang, Y., Lim, LP. et al. (2007). A microRNA component of the p53 tumour suppressor network. *Nature, 447*, 1130-4. ↗

Mendell, JT., Chang, TC., Lee, KH., Kent, OA., Ferlito, M., Mullendore, M. et al. (2007). Transactivation of miR-34a by p53 broadly influences gene expression and promotes apoptosis. *Mol Cell, 26*, 745-52. ↗

Editions

2011-11-14	Authored	Egan, SE., Orlic-Milacic, M.
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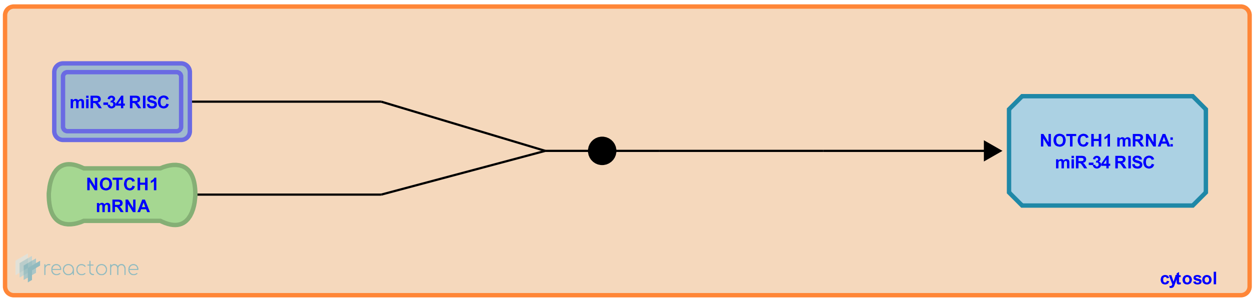
MIR34 microRNAs bind 3'UTR of NOTCH1 mRNA ↗

Location: Pre-NOTCH Transcription and Translation

Stable identifier: R-HSA-1606682

Type: binding

Compartments: cytosol



Translation of NOTCH1 mRNA is inhibited by MIR34 microRNAs (MIR34A, MIR34B and MIR34C), which bind to the 3'UTR of NOTCH1 mRNA. Expression of MIR34 microRNAs is directly regulated by the p53 (TP53) tumor suppressor gene (Chang et al. 2007, Raver-Shapira et al. 2007), and MIR34-mediated downregulation of NOTCH1 signaling is thought to negatively regulate cell survival, motility and maintenance of an undifferentiated state.

Preceded by: NOTCH1 gene transcription, p53 positively regulates transcription of MIR34 microRNAs

Literature references

Meiri, E., Raver-Shapira, N., Moskovits, N., Spector, Y., Rosenfeld, N., Bentwich, Z. et al. (2007). Transcriptional activation of miR-34a contributes to p53-mediated apoptosis. *Mol Cell, 26*, 731-43. ↗

Yeung, WS., Lee, KF., Pang, RT., Chiu, PCN., Leung, CON., Liu, W. et al. (2010). MicroRNA-34a suppresses invasion through downregulation of Notch1 and Jagged1 in cervical carcinoma and choriocarcinoma cells. *Carcinogenesis, 31*, 1037-44. ↗

Mendell, JT., Chang, TC., Lee, KH., Kent, OA., Ferlito, M., Mullendore, M. et al. (2007). Transactivation of miR-34a by p53 broadly influences gene expression and promotes apoptosis. *Mol Cell, 26*, 745-52. ↗

Guessous, F., DiPierro, C., Kefas, B., Li, Y., Schiff, D., Johnson, E. et al. (2009). MicroRNA-34a inhibits glioblastoma growth by targeting multiple oncogenes. *Cancer Res, 69*, 7569-76. ↗

DeSano, JT., Lawrence, TS., Meng, Y., Fan, D., Bommer, GT., Fearon, ER. et al. (2009). MicroRNA miR-34 inhibits human pancreatic cancer tumor-initiating cells. *PLoS One, 4*, e6816. ↗

Editions

2011-09-27	Edited	Jupe, S.
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2012-02-11	Edited	Orlic-Milacic, M.

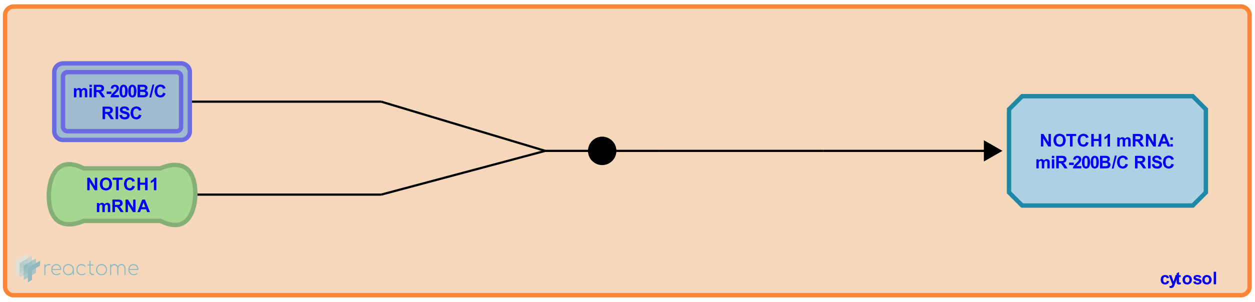
MIR200B/C microRNAs bind NOTCH1 mRNA ↗

Location: Pre-NOTCH Transcription and Translation

Stable identifier: R-HSA-1912363

Type: binding

Compartments: cytosol



Translation of NOTCH1 mRNA is inhibited by microRNAs miR-200B and miR-200C, which bind to the 3'UTR of NOTCH1 mRNA. Levels of miR-200B and miR-200C are decreased in pancreatic cancer cells with an EMT (epithelial to mesenchymal transition) phenotype, and the EMT phenotype is reversed by exogenous overexpression of miR-200B/C microRNAs, suggesting that miR-200B and mir-200C may be acting as tumor suppressors.

Preceded by: NOTCH1 gene transcription

Literature references

Li, Y., Kong, D., Sarkar, FH., Sethi, S., Wang, Z., Banerjee, S. et al. (2010). Epithelial to mesenchymal transition is mechanistically linked with stem cell signatures in prostate cancer cells. *PLoS One, 5*, e12445. ↗

Editions

2011-09-27	Edited	Jupe, S.
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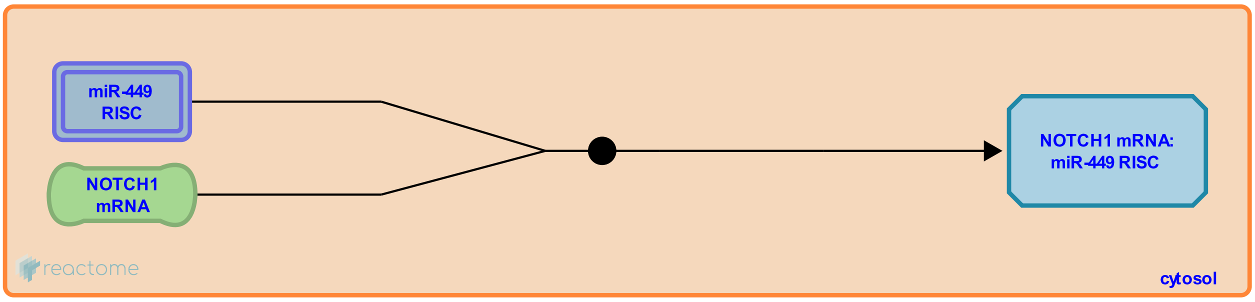
MIR449 microRNAs bind 3'UTR of NOTCH1 mRNA ↗

Location: Pre-NOTCH Transcription and Translation

Stable identifier: R-HSA-1606561

Type: binding

Compartments: cytosol



Translation of NOTCH1 mRNA is negatively regulated by MIR449 microRNAs (MIR449A, MIR449B and MIR449C), which bind to the 3'UTR of NOTCH1. Downregulation of NOTCH1 signaling by the MIR449 cluster appears to be an evolutionarily conserved mechanism involved in regulation of vertebrate multiciliogenesis. DLL1 mRNA is also a target of the MIR449 cluster.

Preceded by: NOTCH1 gene transcription

Literature references

Moreilhon, C., Coraux, C., Robbe-Sermesant, K., Kodjabachian, L., Barbry, P., Waldmann, R. et al. (2011). Control of vertebrate multiciliogenesis by miR-449 through direct repression of the Delta/Notch pathway. *Nat Cell Biol, 13*, 693-9. ↗

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2011-09-27	Edited	Jupe, S.
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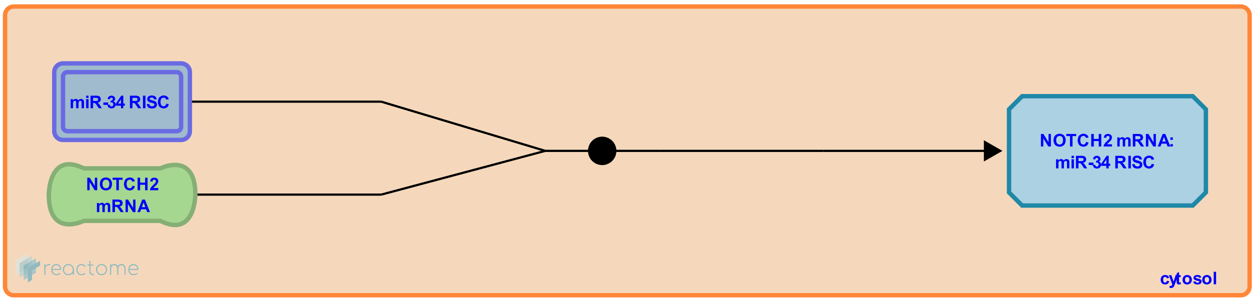
MIR34 microRNAs bind 3'UTR of NOTCH2 mRNA ↗

Location: Pre-NOTCH Transcription and Translation

Stable identifier: R-HSA-1912367

Type: binding

Compartments: cytosol



Translation of NOTCH2 mRNA is inhibited by MIR34 microRNAs (MIR34A, MIR34B and MIR34C), which bind to the 3'UTR of NOTCH2 mRNA.

Preceded by: p53 positively regulates transcription of MIR34 microRNAs, NOTCH2 gene transcription

Literature references

Guessous, F., DiPierro, C., Kefas, B., Li, Y., Schiff, D., Johnson, E. et al. (2009). MicroRNA-34a inhibits glioblastoma growth by targeting multiple oncogenes. *Cancer Res, 69*, 7569-76. ↗

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2012-02-11	Edited	Orlic-Milacic, M.

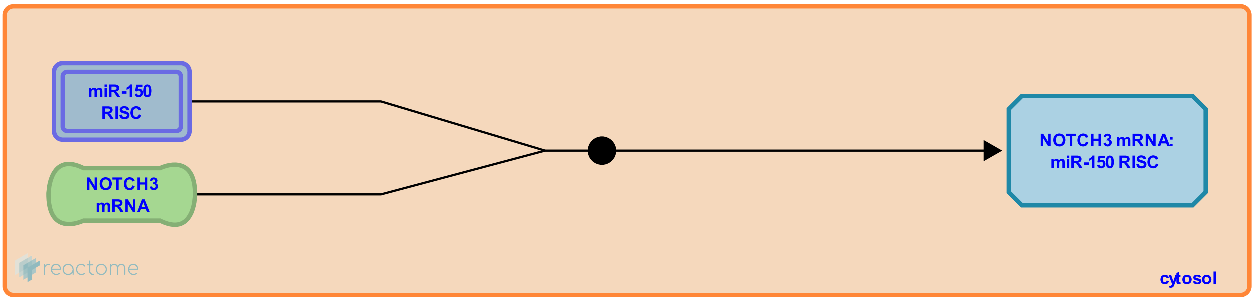
MIR150 microRNA binds 3'UTR of NOTCH3 mRNA ↗

Location: Pre-NOTCH Transcription and Translation

Stable identifier: R-HSA-1912362

Type: binding

Compartments: cytosol



Translation of NOTCH3 mRNA is inhibited by miR-150 microRNA which binds to the 3'UTR of NOTCH3 mRNA. miR-150 is involved in regulation of differentiation of B-cells and T-cells.

Preceded by: NOTCH3 gene transcription

Literature references

Bronte, V., Indraccolo, S., Basso, G., Gerosa, G., D'Agostino, DM., Amadori, A. et al. (2011). Modulation of microRNA expression in human T-cell development: targeting of NOTCH3 by miR-150. *Blood, 117*, 7053-62. ↗

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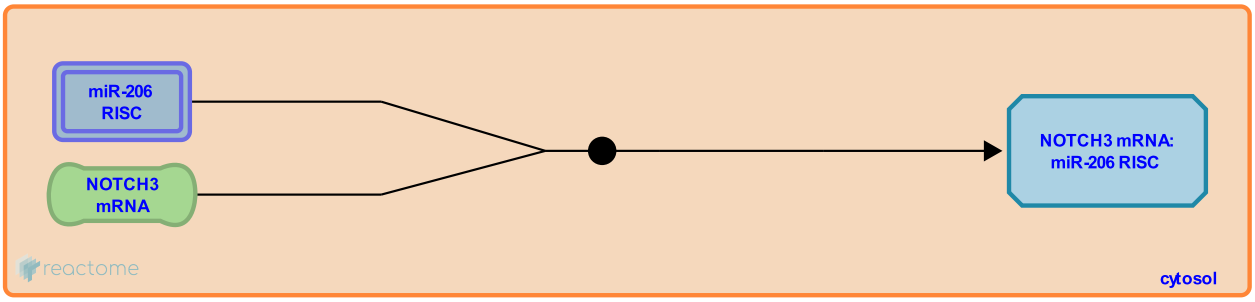
MIR206 microRNA binds 3'UTR of NOTCH3 mRNA ↗

Location: Pre-NOTCH Transcription and Translation

Stable identifier: R-HSA-1912366

Type: binding

Compartments: cytosol



Translation of NOTCH3 mRNA is inhibited by microRNA miR-206 which binds to the 3'UTR of NOTCH3 mRNA.

Preceded by: NOTCH3 gene transcription

Literature references

Song, G., Wang, L., Zhang, Y. (2009). MicroRNA-206 targets notch3, activates apoptosis, and inhibits tumor cell migration and focus formation. *J Biol Chem, 284*, 31921-7. ↗

Editions

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2012-02-09	Edited	Gillespie, ME., May, B.
2012-02-11	Edited	Orlic-Milacic, M.

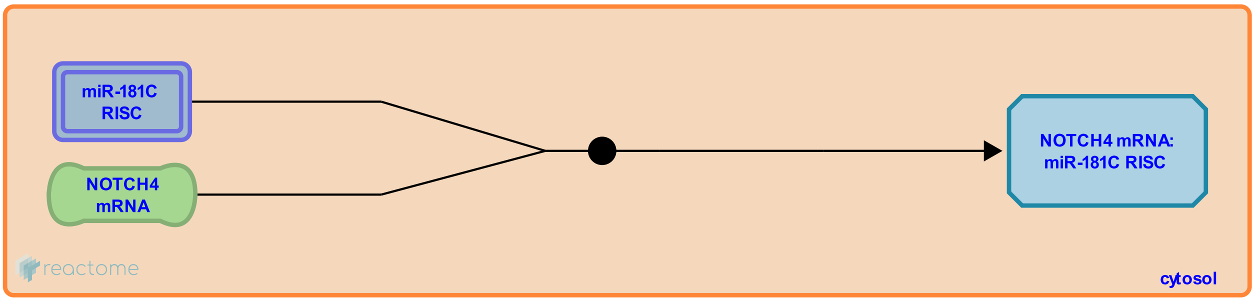
MIR181C microRNA binds 3'UTR of NOTCH4 mRNA ↗

Location: Pre-NOTCH Transcription and Translation

Stable identifier: R-HSA-1912364

Type: binding

Compartments: cytosol



miR-181C microRNA inhibits translation of NOTCH4 mRNA by binding to its 3'UTR. miR181c is a candidate tumor suppressor in gastric cancer.

Preceded by: NOTCH4 gene transcription

Literature references

Yuasa, Y., Akiyama, Y., Shimada, S., Hashimoto, Y., Otsubo, T. (2010). Involvement of epigenetically silenced microRNA-181c in gastric carcinogenesis. *Carcinogenesis, 31*, 777-84. ↗

Editions

2011-09-27	Edited	Jupe, S.
2011-11-14	Authored	Egan, SE., Orlic-Milacic, M.
2012-02-06	Reviewed	Haw, R.
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2012-02-09	Edited	Gillespie, ME., May, B.
2012-02-11	Edited	Orlic-Milacic, M.

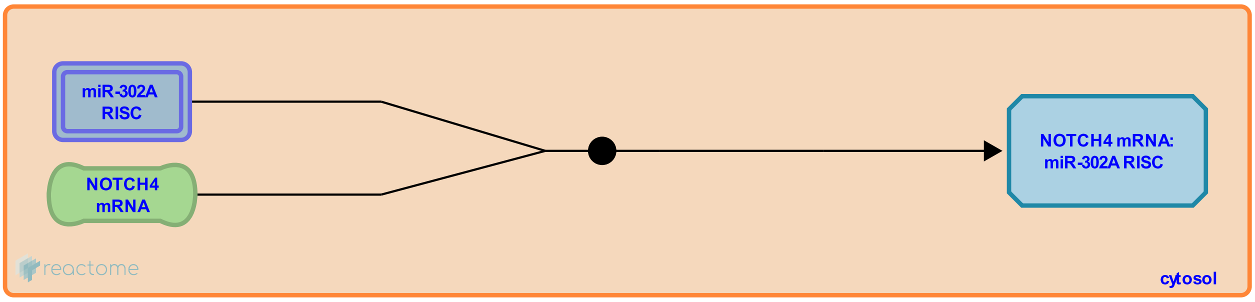
MIR302A microRNA binds 3'UTR of NOTCH4 mRNA ↗

Location: Pre-NOTCH Transcription and Translation

Stable identifier: R-HSA-1912368

Type: binding

Compartments: cytosol



MicroRNA miR-302A, upregulated in melanoma, binds the 3'UTR of NOTCH4, resulting in inhibition of NOTCH4 mRNA translation.

Preceded by: NOTCH4 gene transcription

Literature references

Arndt, K., Costa, FF., Bischof, JM., Seftor, EA., Soares, MB., Hendrix, MJC. et al. (2009). Epigenetically reprogramming metastatic tumor cells with an embryonic microenvironment. *Epigenomics, 1*, 387-398. ↗

Editions

2011-09-27	Edited	Jupe, S.
2011-11-14	Authored	Egan, SE., Orlic-Milacic, M.
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2012-02-07	Edited	D'Eustachio, P.
2012-02-09	Edited	Gillespie, ME., May, B.
2012-02-11	Edited	Orlic-Milacic, M.

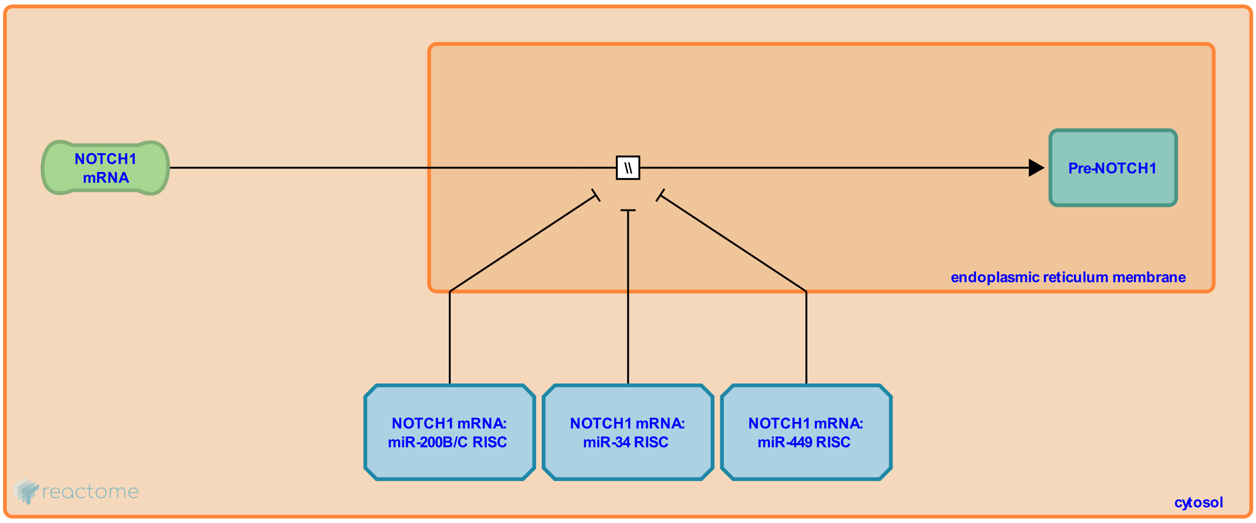
NOTCH1 mRNA translation controlled by miRNAs ↗

Location: Pre-NOTCH Transcription and Translation

Stable identifier: R-HSA-1912412

Type: omitted

Compartments: endoplasmic reticulum membrane, cytosol



Translation of NOTCH1 mRNA is negatively regulated by microRNAs miR-200B and miR200C (Kong et al. 2010), miR-34 (Li et al. 2009, Ji et al. 2009) and miR-449 (Marcet et al. 2011). These miRNAs bind and cause degradation of NOTCH1 mRNA, resulting in decreased level of NOTCH1 protein product.

Preceded by: NOTCH1 gene transcription

Literature references

Moreilhon, C., Coraux, C., Robbe-Sermesant, K., Kodjabachian, L., Barbry, P., Waldmann, R. et al. (2011). Control of vertebrate multiciliogenesis by miR-449 through direct repression of the Delta/Notch pathway. *Nat Cell Biol, 13*, 693-9. ↗

Li, Y., Kong, D., Sarkar, FH., Sethi, S., Wang, Z., Banerjee, S. et al. (2010). Epithelial to mesenchymal transition is mechanistically linked with stem cell signatures in prostate cancer cells. *PLoS One, 5*, e12445. ↗

Guessous, F., DiPierro, C., Kefas, B., Li, Y., Schiff, D., Johnson, E. et al. (2009). MicroRNA-34a inhibits glioblastoma growth by targeting multiple oncogenes. *Cancer Res, 69*, 7569-76. ↗

DeSano, JT., Lawrence, TS., Meng, Y., Fan, D., Bommer, GT., Fearon, ER. et al. (2009). MicroRNA miR-34 inhibits human pancreatic cancer tumor-initiating cells. *PLoS One, 4*, e6816. ↗

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2011-09-27	Edited	Jupe, S.
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2012-02-11	Edited	Orlic-Milacic, M.

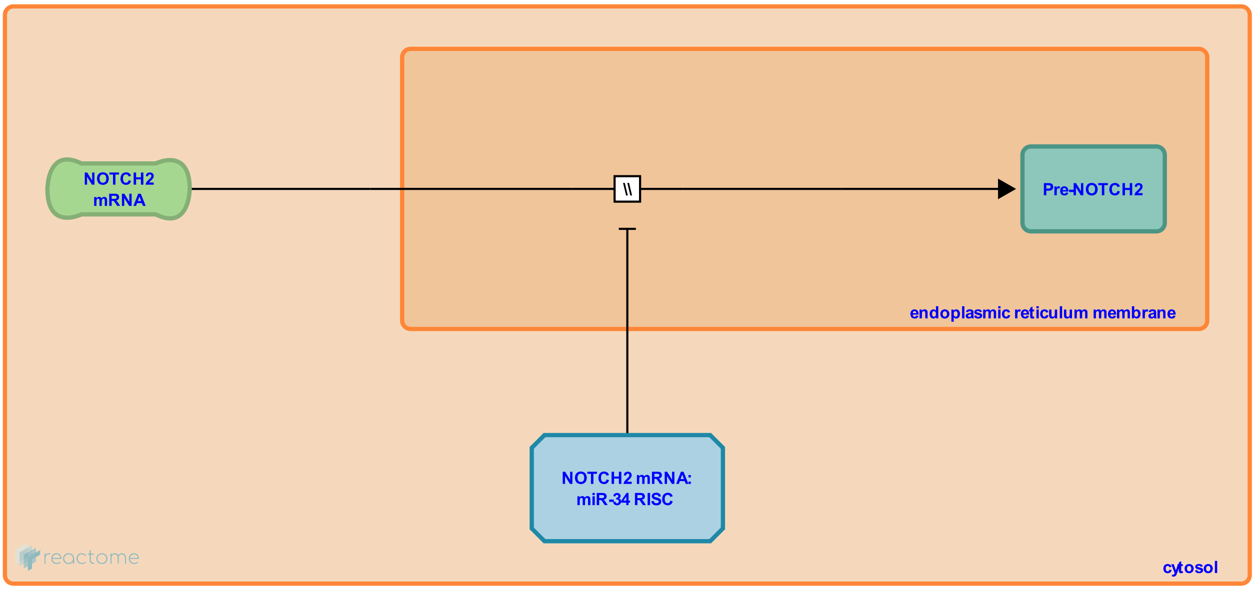
NOTCH2 mRNA translation controlled by miRNAs ↗

Location: Pre-NOTCH Transcription and Translation

Stable identifier: R-HSA-1912413

Type: omitted

Compartments: endoplasmic reticulum membrane, cytosol



Translation of NOTCH2 mRNA is negatively regulated by miR-34 microRNAs (Li et al. 2009). miR-34 miRNAs bind and cause degradation of NOTCH2 mRNA, resulting in decreased level of NOTCH2 protein product.

Preceded by: NOTCH2 gene transcription

Literature references

Guessous, F., DiPierro, C., Kefas, B., Li, Y., Schiff, D., Johnson, E. et al. (2009). MicroRNA-34a inhibits glioblastoma growth by targeting multiple oncogenes. *Cancer Res, 69*, 7569-76. ↗

Editions

2011-09-27	Edited	Jupe, S.
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2012-02-11	Edited	Orlic-Milacic, M.

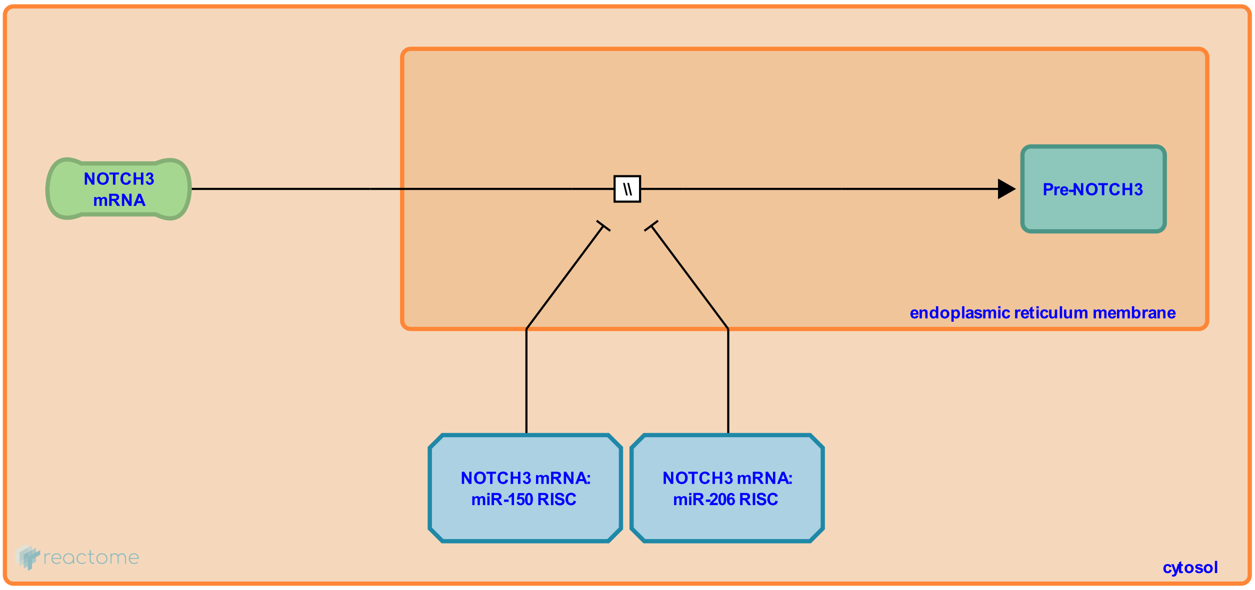
NOTCH3 mRNA translation controlled by miRNAs ↗

Location: Pre-NOTCH Transcription and Translation

Stable identifier: R-HSA-1912409

Type: omitted

Compartments: endoplasmic reticulum membrane, cytosol



Translation of NOTCH3 mRNA is negatively regulated by miR-150 (Ghisi et al. 2011) and miR-206 microRNAs (Song et al. 2009). These miRNAs bind and cause degradation of NOTCH3 mRNA, resulting in decreased level of NOTCH3 protein product.

Preceded by: NOTCH3 gene transcription

Literature references

Song, G., Wang, L., Zhang, Y. (2009). MicroRNA-206 targets notch3, activates apoptosis, and inhibits tumor cell migration and focus formation. *J Biol Chem, 284*, 31921-7. ↗

Bronte, V., Indraccolo, S., Basso, G., Gerosa, G., D'Agostino, DM., Amadori, A. et al. (2011). Modulation of microRNA expression in human T-cell development: targeting of NOTCH3 by miR-150. *Blood, 117*, 7053-62. ↗

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2012-02-11	Edited	Orlic-Milacic, M.

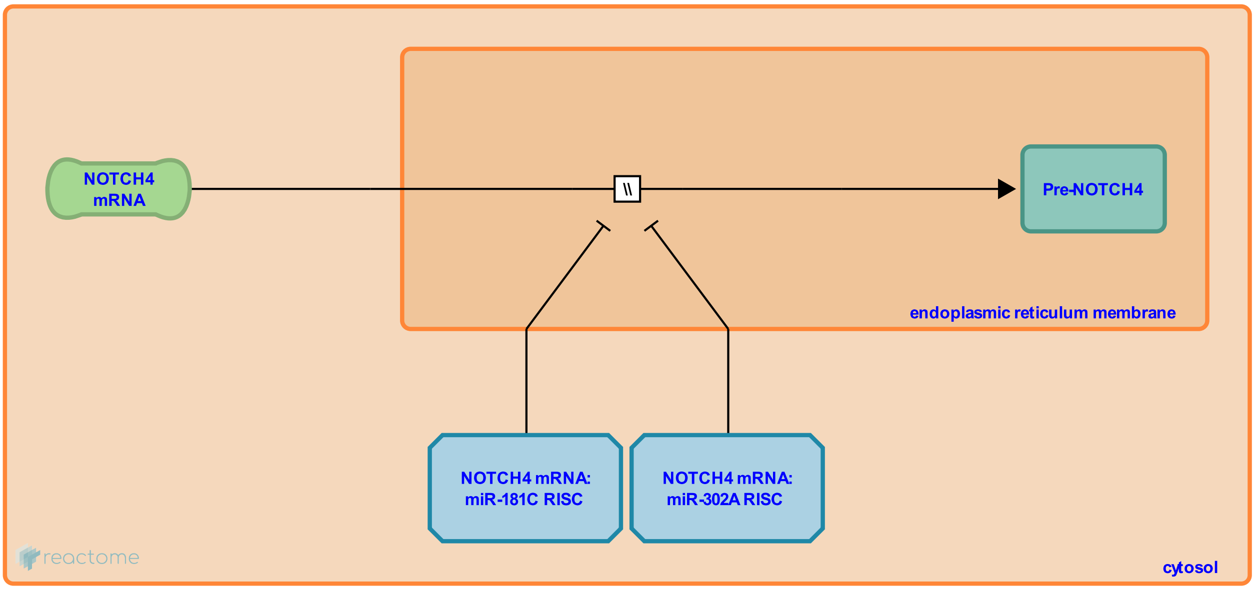
NOTCH4 mRNA translation controlled by miRNAs ↗

Location: Pre-NOTCH Transcription and Translation

Stable identifier: R-HSA-1912410

Type: omitted

Compartments: endoplasmic reticulum membrane, cytosol



Translation of NOTCH4 mRNA is negatively regulated by miR-181c (Hashimoto et al. 2010) and miR-302A microRNAs (Costa et al. 2009). These miRNAs bind and cause degradation of NOTCH4 mRNA, resulting in decreased level of NOTCH4 protein product.

Preceded by: NOTCH4 gene transcription

Literature references

Arndt, K., Costa, FF., Bischof, JM., Seftor, EA., Soares, MB., Hendrix, MJC. et al. (2009). Epigenetically reprogramming metastatic tumor cells with an embryonic microenvironment. *Epigenomics, 1*, 387-398. ↗

Yuasa, Y., Akiyama, Y., Shimada, S., Hashimoto, Y., Otsubo, T. (2010). Involvement of epigenetically silenced microRNA-181c in gastric carcinogenesis. *Carcinogenesis, 31*, 777-84. ↗

Editions

2011-09-27	Edited	Jupe, S.
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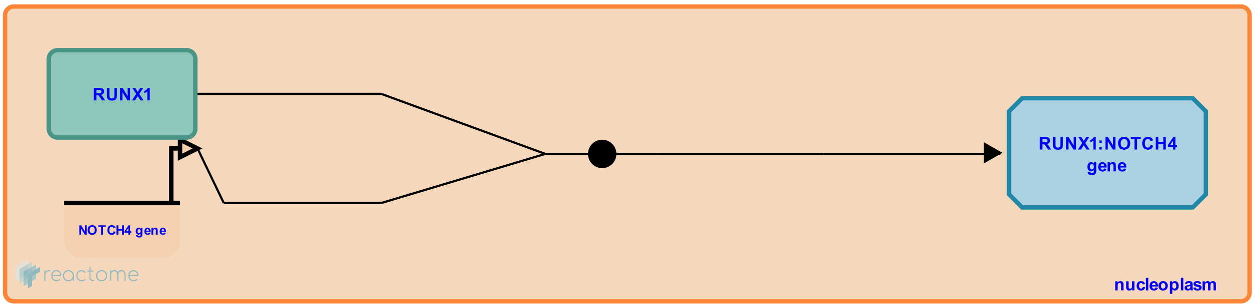
RUNX1 binds NOTCH4 gene ↗

Location: Pre-NOTCH Transcription and Translation

Stable identifier: R-HSA-9604703

Type: binding

Compartments: nucleoplasm



The transcription factor RUNX1 binds to runx response elements in intron 29 of the NOTCH4 gene (Li et al. 2018).

Followed by: NOTCH4 gene transcription is inhibited by RUNX1

Literature references

Gao, Y., Chen, L., Li, Y., Liu, PP., Jin, C., Qin, L. et al. (2018). Human NOTCH4 is a key target of RUNX1 in megakaryocytic differentiation. *Blood, 131*, 191-201. ↗

Editions

2018-04-05	Authored	Orlic-Milacic, M.
2018-05-01	Reviewed	Haw, R.
2018-05-09	Edited	Orlic-Milacic, M.

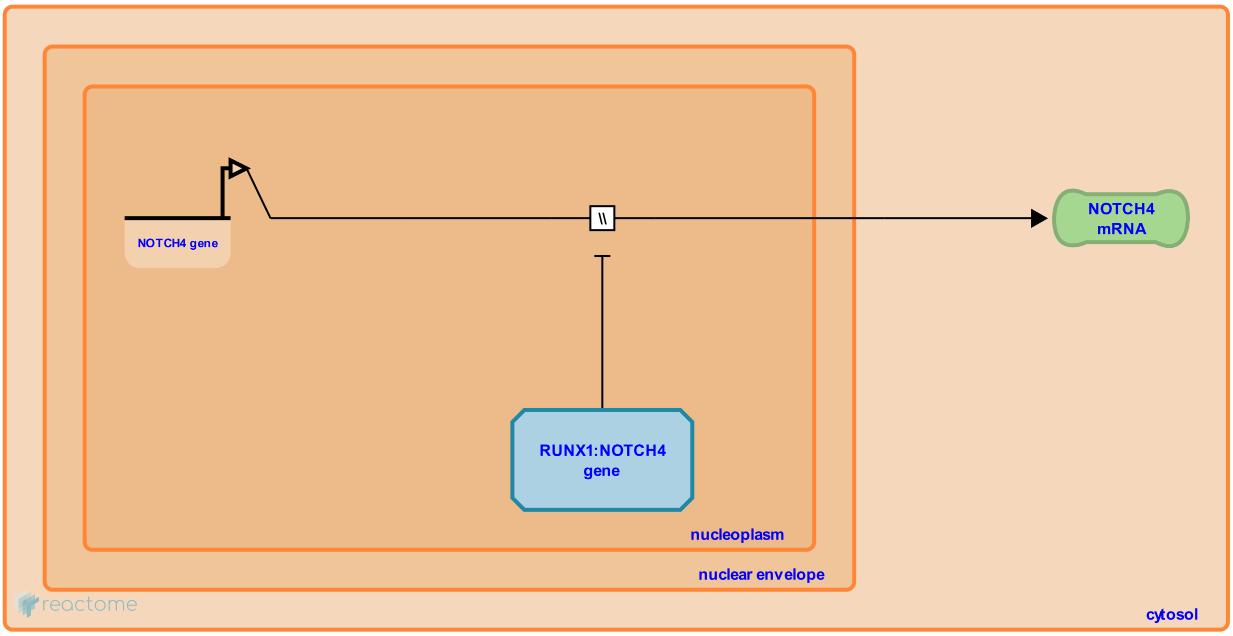
NOTCH4 gene transcription is inhibited by RUNX1 ↗

Location: Pre-NOTCH Transcription and Translation

Stable identifier: R-HSA-9604719

Type: omitted

Compartments: nucleoplasm, cytosol



RUNX1 binding to intron 29 of the NOTCH4 gene represses NOTCH4 transcription. RUNX1-mediated inhibition of NOTCH4 expression contributes to differentiation of human pluripotent stem cells into megakaryocytes (Li et al. 2018).

Preceded by: RUNX1 binds NOTCH4 gene

Literature references

Gao, Y., Chen, L., Li, Y., Liu, PP., Jin, C., Qin, L. et al. (2018). Human NOTCH4 is a key target of RUNX1 in megakaryocytic differentiation. *Blood, 131,* 191-201. ↗

Editions

2018-04-05	Authored	Orlic-Milacic, M.
2018-05-01	Reviewed	Haw, R.
2018-05-09	Edited	Orlic-Milacic, M.

SIRT6 binds to acetylated histones at NOTCH1 and NOTCH4 gene promoters ↗

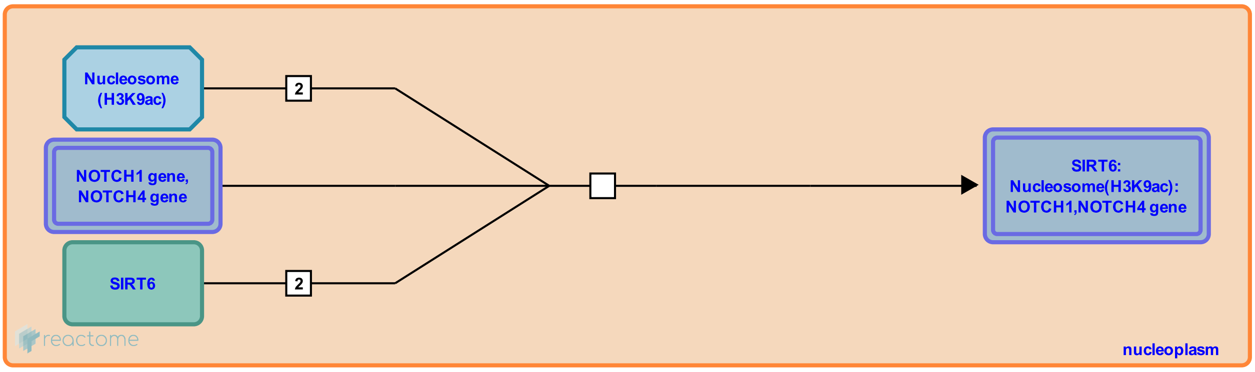
Location: Pre-NOTCH Transcription and Translation

Stable identifier: R-HSA-9604834

Type: transition

Compartments: nucleoplasm

Inferred from: Sirt6 binds to acetylated histones at Notch1 and Notch4 gene promoters (Mus musculus)



Based on studies in mice, histone deacetylase SIRT6 binds to histone H3 acetylated on lysine residue 10 (H3K9Ac epigenetic mark) at promoters of NOTCH1 and NOTCH4 genes (Liu et al. 2017).

Followed by: SIRT6 deacetylates histones at NOTCH1 and NOTCH4 gene promoters

Editions

2018-04-05	Authored	Orlic-Milacic, M.
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2018-05-09	Edited	Orlic-Milacic, M.

SIRT6 deacetylates histones at NOTCH1 and NOTCH4 gene promoters ↗

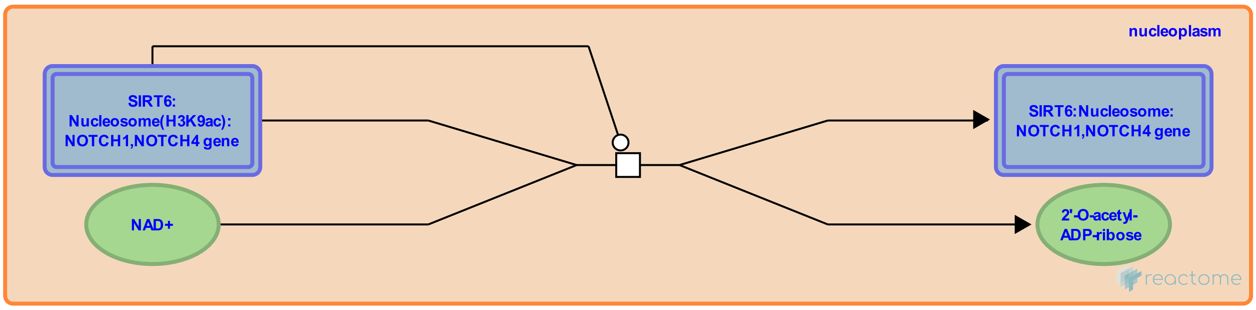
Location: Pre-NOTCH Transcription and Translation

Stable identifier: R-HSA-9604829

Type: transition

Compartments: nucleoplasm

Inferred from: Sirt6 deacetylates histones at Notch1 and Notch4 gene promoters (Mus musculus)



Based on studies in mice, SIRT6 deacetylates H3 histones on lysine residue 10 (removing the H3K9Ac epigenetic mark) at promoters of NOTCH1 and NOTCH4 genes (Liu et al. 2017).

Preceded by: SIRT6 binds to acetylated histones at NOTCH1 and NOTCH4 gene promoters

Editions

2018-04-05	Authored	Orlic-Milacic, M.
2018-05-01	Reviewed	Haw, R.
2018-05-09	Edited	Orlic-Milacic, M.

NOTCH1 and NOTCH4 gene transcription is inhibited by SIRT6 ↗

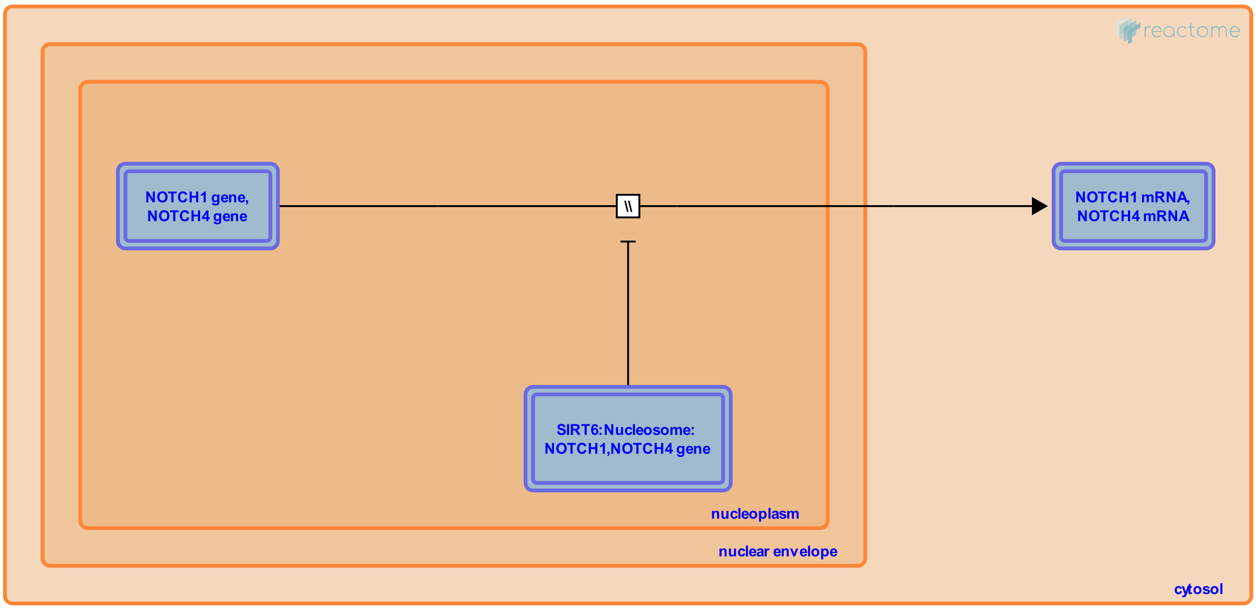
Location: Pre-NOTCH Transcription and Translation

Stable identifier: R-HSA-9604831

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Notch1 and Notch4 gene transcription is inhibited by Sirt6 (Mus musculus)



Based on studies in mice, SIRT6-mediated deacetylation of lysine residue 10 of H3 histones (removal of H3K9Ac epigenetic mark) at promoters of NOTCH1 and NOTCH4 genes inhibits transcription of NOTCH1 and NOTCH4. SIRT6-mediated downregulation of NOTCH1 and NOTCH4 may protect podocytes, kidney cells involved in blood filtering, from injury. SIRT6 is downregulated in podocytes of patients with podocytopathies, such as proteinuric kidney disease, and SIRT6 levels correlate with glomerular filtration rate (Liu et al. 2017).

Editions

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