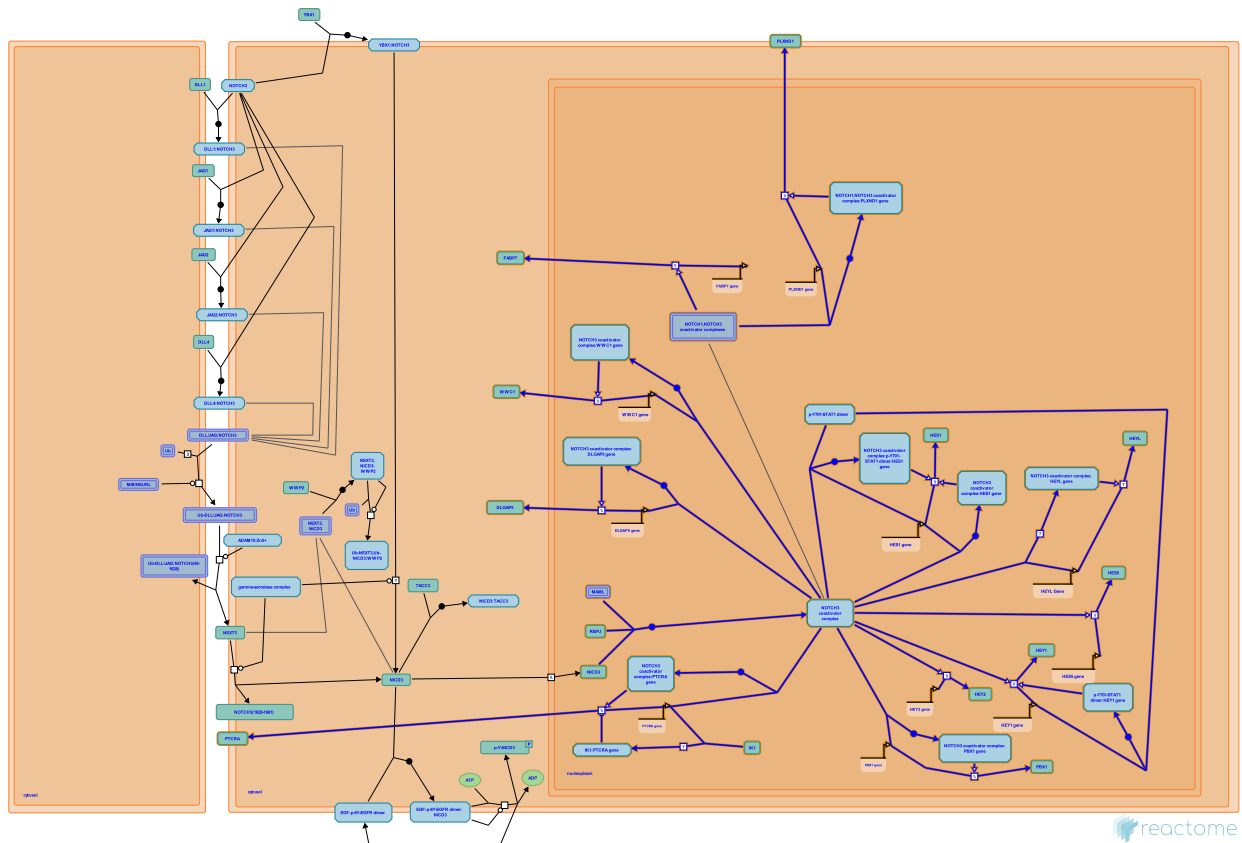


NOTCH3 Intracellular Domain Regulates Transcription



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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](https://reactome.org/textbook/).

04/05/2024

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

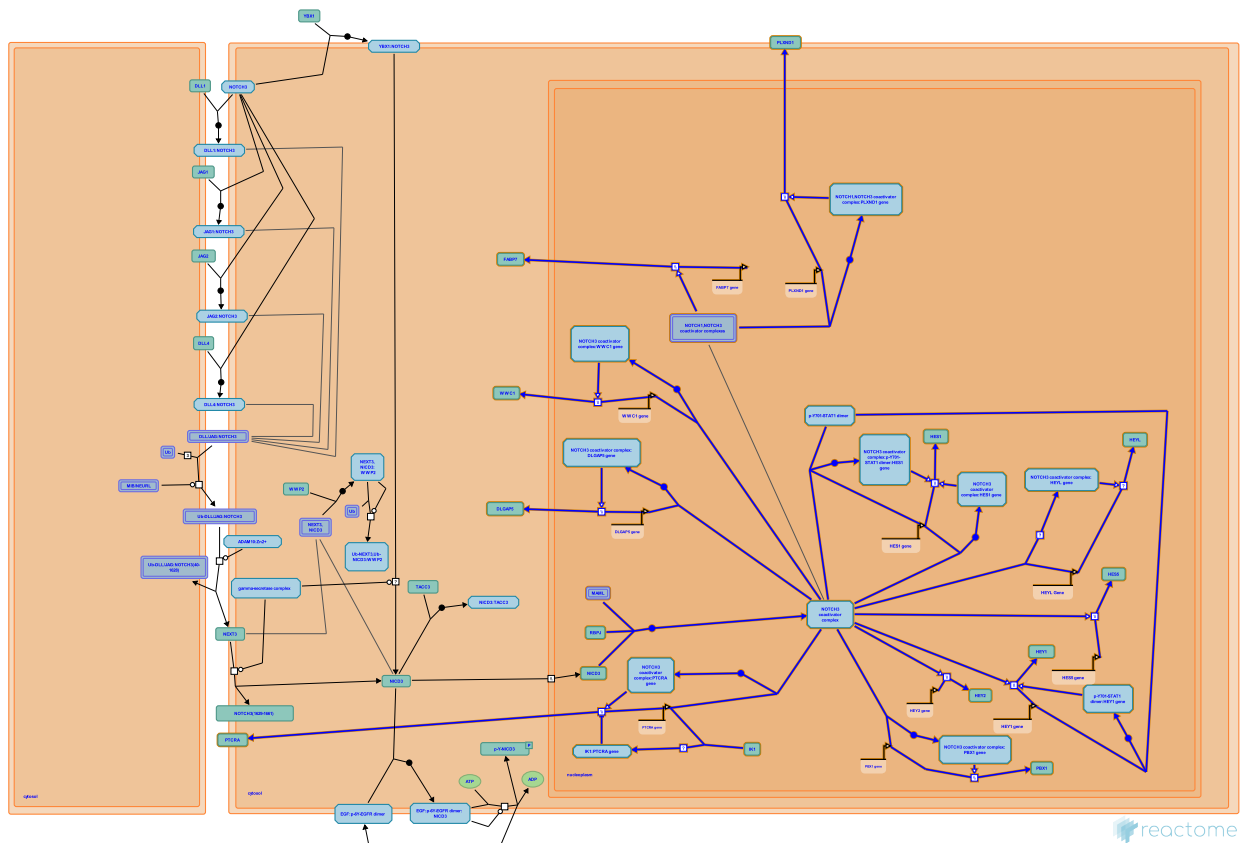
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Reactome database release: 88

This document contains 1 pathway and 22 reactions ([see Table of Contents](#))

NOTCH3 Intracellular Domain Regulates Transcription ↗

Stable identifier: R-HSA-9013508



In the nucleus, NICD3 forms a complex with RBPJ (CBF1, CSL) and MAML (mastermind) proteins MAML1, MAML2 or MAML3 (possibly also MAML1). NICD3:RBPJ:MAML complex, also known as the NOTCH3 coactivator complex, activates transcription from RBPJ-binding promoter elements (Lin et al. 2002). While NOTCH1 prefers paired RBPJ binding sites, NOTCH3 preferentially binds to single RBPJ binding sites (Ong et al. 2006).

NOTCH3 coactivator complex induces transcription of the well established NOTCH target genes HES1 (Lin et al. 2002, Boelens et al. 2014), HEYL (Maier and Gessler 2000, Geimer Le Lay et al. 2014), HES5 (Lin et al. 2002, Shimizu et al. 2002), and HEY2 (Wang et al. 2002).

NOTCH3 positively regulates transcription of the pre-T-cell receptor alpha chain (PTCRA, commonly known as pT-alpha or pre-TCRalpha) (Talora et al. 2003, Bellavia et al. 2007). IK1, splicing isoform of the transcription factor Ikaros (IKZF1), competes with RBPJ for binding to the PTCRA promoter and inhibits PTCRA transcription. NOTCH3, through pre-TCR signaling, stimulates expression of the RNA binding protein HuD, which promotes splicing of IKZF1 into dominant negative isoforms. These dominant negative isoforms of IKZF1 heterodimerize with IK1, preventing its binding to target DNA sequences and thus contributing to sustained transcription of PTCRA (Bellavia et al. 2007, reviewed by Bellavia, Mecarozzi, Campese, Grazioli, Gulino and Screpanti 2007).

NOTCH3-triggered pre-TCR-signaling downregulates the activity of the transcription factor TCF3 (E2A), through ERK-dependent induction of ID1. Inhibition of TCF3-mediated transcription downstream of NOTCH3 contributes to development of T-cell lymphomas in transgenic mice expressing NICD3 (Talora et al. 2003). Activation of ERKs downstream of NOTCH3-stimulated pre-TCR signaling leads to phosphorylation of the transcription factor TAL1, formation of the TAL1:SP1 complex, and activation of cyclin D1 (CCND1) transcription, which stimulates cell division (Talora et al. 2006).

NOTCH3 signaling can activate NF-kappaB (NFKB)-mediate transcription either indirectly, through activation of pre-TCR signaling, or directly, through association of NOTCH3 with IKKA. NFKB is constitutively active in T lymphoma cells derived from NOTCH3 transgenic mice (Vacca et al. 2006).

Transcription of the PLXND1 gene, encoding the semaphorin receptor Plexin D1, is directly stimulated by NOTCH1 and NOTCH3 coactivator complexes. PLXND1 is involved in neuronal migration and cancer cell invasiveness

(Rehman et al. 2016). Expression of FABP7 (BLBP) in radial glia is positively regulated by NOTCH1 and NOTCH3 during neuronal migration (Anthony et al. 2005, Keilani and Sugaya 2008).

NOTCH3 gene is frequently amplified in ovarian cancer (Park et al. 2006). NOTCH3 coactivator complex directly stimulates DLGAP5 transcription. DLGAP5 is involved in G2/M transition and is overexpressed in ovarian cancer cells. (Chen et al. 2012). Another gene overexpressed in ovarian cancer whose transcription is directly stimulated by NOTCH3 is PBX1 (Park et al. 2008). The NOTCH3 coactivator complex directly stimulates WWC1 gene transcription. WWC1 gene encodes protein Kibra, involved in Hippo signaling. NOTCH3-mediated induction of WWC1 positively regulates Hippo signaling and inhibits epithelial-to-mesenchymal transition (EMT) in triple negative breast cancer cells (Zhang et al. 2016).

Literature references

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- Vacca, A., Pascucci, M., Cialfi, S., Gulino, A., Frati, L., Palermo, R. et al. (2006). Cross talk among Notch3, pre-TCR, and Tal1 in T-cell development and leukemogenesis. *Blood*, 107, 3313-20. [↗](#)
- Oyama, T., Nagase, T., Lin, SE., Kitagawa, M., Harigaya, K. (2002). Identification of new human mastermind proteins defines a family that consists of positive regulators for notch signaling. *J. Biol. Chem.*, 277, 50612-20. [↗](#)
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- Shimizu, K., Hirai, H., Kumano, K., Hamada, Y., Saito, T., Chiba, S. (2002). Functional diversity among Notch1, Notch2, and Notch3 receptors. *Biochem Biophys Res Commun*, 291, 775-9. [↗](#)

Editions

2017-09-20	Authored	Orlic-Milacic, M.
2017-10-30	Reviewed	Haw, R.
2017-11-02	Edited	Orlic-Milacic, M.

NICD3 binds RBPJ and MAML in the nucleus ↗

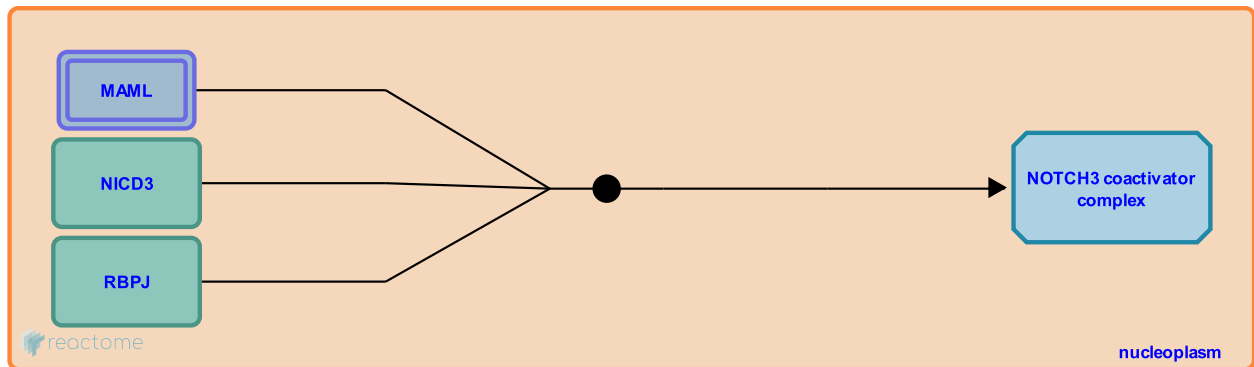
Location: [NOTCH3 Intracellular Domain Regulates Transcription](#)

Stable identifier: R-HSA-9013631

Type: binding

Compartments: nucleoplasm

Inferred from: [NICD3 binds RBPJ and MAML in the nucleus \(Homo sapiens\)](#)



In the nucleus, NICD3 forms a complex with RBPJ (CBF1, CSL) and MAML (mastermind) proteins MAML1, MAML2 or MAML3 (possibly also MAMLD1). NICD3:RBPJ:MAML complex activates transcription from RBPJ-binding promoter elements (Lin et al. 2002).

Besides NICD3, RBPJ and MAML, NOTCH3 coactivator complex likely includes other proteins shown as components of the NOTCH1 coactivator complex. Since disruption of the RBPJ:NCOR corepressor and MAML-mediated recruitment of transcriptional activators has not been studied in the context of NICD3, it is not shown here. More details are available in the pathway [Signaling by NOTCH1](#).

Many NOTCH-regulated genes have paired RBPJ-binding sites in their promoters, in head-to-head arrangement, and require cooperative formation of dimeric NOTCH transcription complexes for transcriptional activation (Nam et al. 2007).

Followed by: [NOTCH3 coactivator complex binds HEYL gene promoter](#), [HEY1 gene expression is positively regulated by NOTCH3 and STAT1](#), [NOTCH3 coactivator complex binds HES1 gene promoter](#), [NOTCH3 coactivator complex binds the PTCRA gene promoter](#), [HEY2 gene expression is positively regulated by NOTCH3](#), [NOTCH3 coactivator complex binds PBX1 gene promoter](#), [HES5 gene expression is stimulated by NOTCH3](#), [FABP7 gene expression is positively regulated by NOTCH1 and NOTCH3](#), [NOTCH3 coactivator complex and STAT1 bind HES1 gene promoter](#), [NOTCH3 coactivator complex binds DLGAP5 gene promoter](#), [NOTCH1,NOTCH3 coactivator complex binds PLXND1 gene promoter](#), [NOTCH3 coactivator complex binds WWC1 \(Kibra\) gene promoter](#)

Editions

2017-08-09	Edited	Orlic-Milacic, M.
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NOTCH3 coactivator complex binds HES1 gene promoter ↗

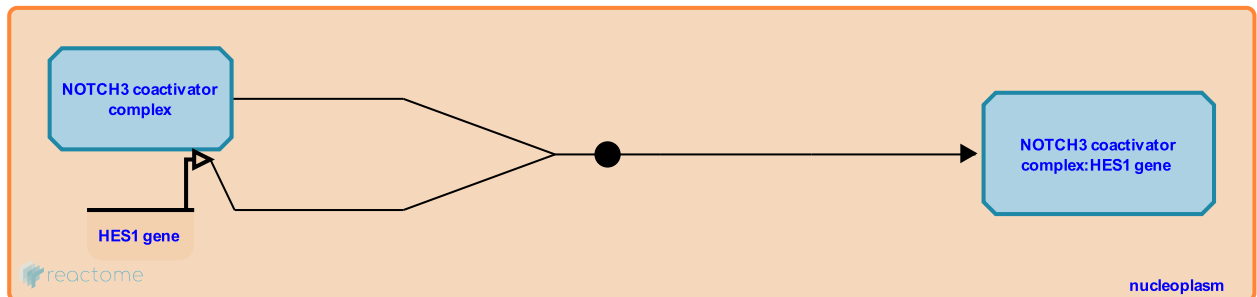
Location: [NOTCH3 Intracellular Domain Regulates Transcription](#)

Stable identifier: R-HSA-9013652

Type: binding

Compartments: nucleoplasm

Inferred from: [Notch3 coactivator complex binds Hes1 gene promoter \(Homo sapiens\)](#)



NOTCH3 coactivator complex, composed of at least NICD3 (NOTCH3 intracellular domain), RBPJ and MAML (MAML1, MAML2 or MAML3; possibly MAMLD1), directly binds to RBPJ elements in the HES1 gene promoter (Lin et al. 2002).

Preceded by: [NICD3 binds RBPJ and MAML in the nucleus](#)

Followed by: [HES1 gene expression is stimulated by NOTCH3 and STAT1](#)

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2017-09-20	Authored	Orlic-Milacic, M.
2017-10-30	Reviewed	Haw, R.
2017-11-02	Edited	Orlic-Milacic, M.

NOTCH3 coactivator complex and STAT1 bind HES1 gene promoter ↗

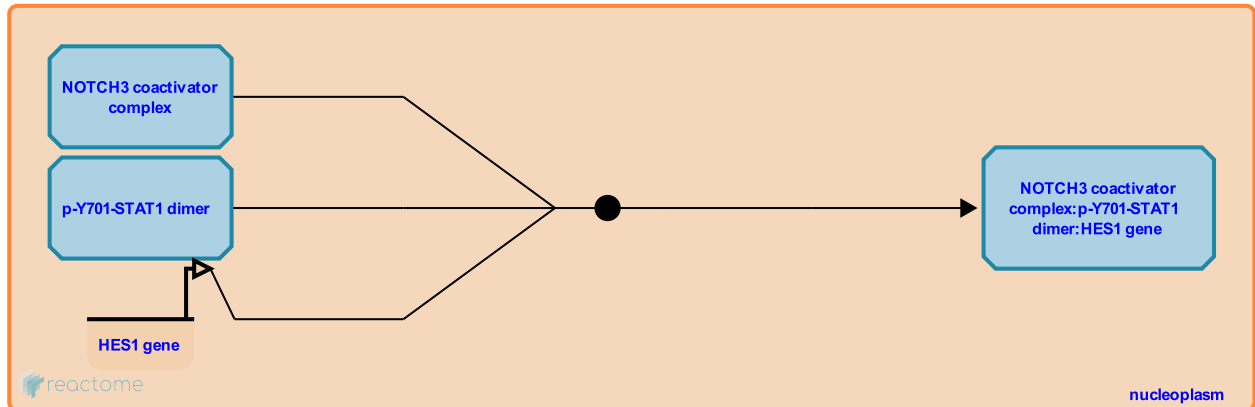
Location: [NOTCH3 Intracellular Domain Regulates Transcription](#)

Stable identifier: R-HSA-9021325

Type: binding

Compartments: nucleoplasm

Inferred from: [Notch3 coactivator complex binds Hes1 gene promoter \(Homo sapiens\)](#)



NOTCH3 coactivator complex, composed of at least NICD3 (NOTCH3 intracellular domain), RBPJ and MAML (MAML1, MAML2 or MAML3; possibly MAMLD1), directly binds to RBPJ elements in the HES1 gene promoter (Lin et al. 2002). STAT1 can bind to STAT response elements in the HES1 gene promoter and enhance HES1 transcription induced by NICD3. In breast cancer, stromal cells secrete RNA-containing exosomes. Upon uptake of exosomes by breast cancer cells, STAT1-dependent antiviral signaling is initiated. Stromal cells also express JAG1 ligand on their surface and, in parallel to STAT1 signaling, activate NOTCH3 signaling in NOTCH3-expressing breast cancer cells. Synergistic activation of NOTCH3 and STAT1 increases breast cancer radiation resistance (Boelens et al. 2014).

Preceded by: [NICD3 binds RBPJ and MAML in the nucleus](#)

Followed by: [HES1 gene expression is stimulated by NOTCH3 and STAT1](#)

Literature references

Wiemann, BZ., Qiu, Y., Nabet, BY., Ishwaran, H., Wu, TJ., Slingerland, J. et al. (2014). Exosome transfer from stromal to breast cancer cells regulates therapy resistance pathways. *Cell*, 159, 499-513. ↗

Editions

2017-09-20	Authored	Orlic-Milacic, M.
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HES1 gene expression is stimulated by NOTCH3 and STAT1 ↗

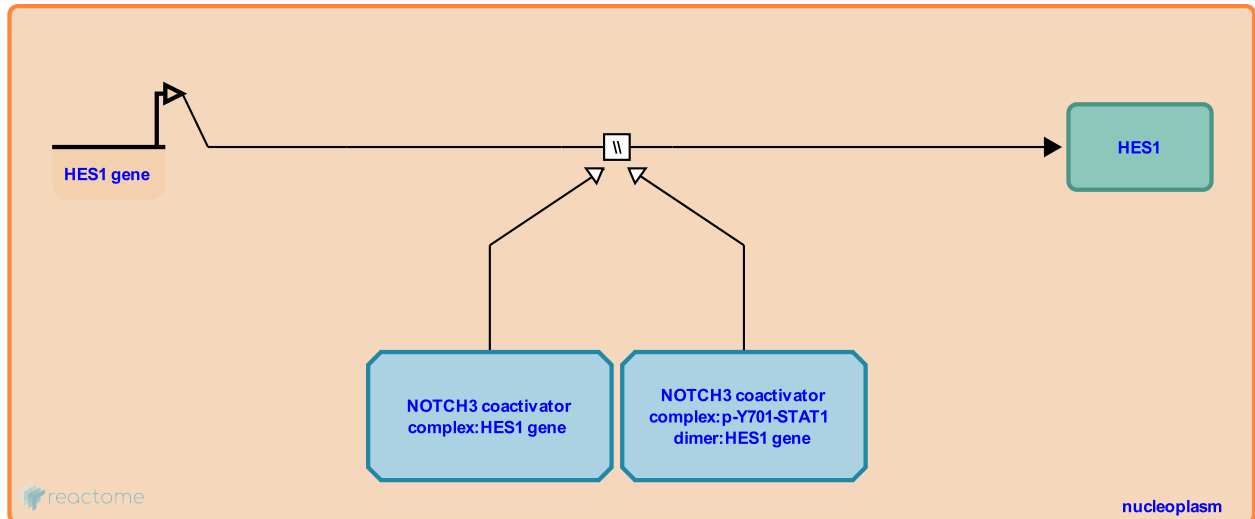
Location: [NOTCH3 Intracellular Domain Regulates Transcription](#)

Stable identifier: R-HSA-9013567

Type: omitted

Compartments: nucleoplasm

Inferred from: [Hes1 gene expression is stimulated by Notch3 \(Homo sapiens\)](#)



Based on studies in a mouse system, HES1 gene expression is directly stimulated by the NOTCH3 coactivator complex (Lin et al. 2002, Shimizu et al. 2002). Activated STAT1 directly enhances HES1 transcription induced by NICD3 (Boelens et al. 2014).

Preceded by: [NOTCH3 coactivator complex binds HES1 gene promoter](#), [NOTCH3 coactivator complex and STAT1 bind HES1 gene promoter](#)

Literature references

Shimizu, K., Hirai, H., Kumano, K., Hamada, Y., Saito, T., Chiba, S. (2002). Functional diversity among Notch1, Notch2, and Notch3 receptors. *Biochem Biophys Res Commun*, 291, 775-9. ↗

Oyama, T., Nagase, T., Lin, SE., Kitagawa, M., Harigaya, K. (2002). Identification of new human mastermind proteins defines a family that consists of positive regulators for notch signaling. *J. Biol. Chem.*, 277, 50612-20. ↗

Wiemann, BZ., Qiu, Y., Nabet, BY., Ishwaran, H., Wu, TJ., Slingerland, J. et al. (2014). Exosome transfer from stromal to breast cancer cells regulates therapy resistance pathways. *Cell*, 159, 499-513. ↗

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NOTCH3 coactivator complex binds HEYL gene promoter ↗

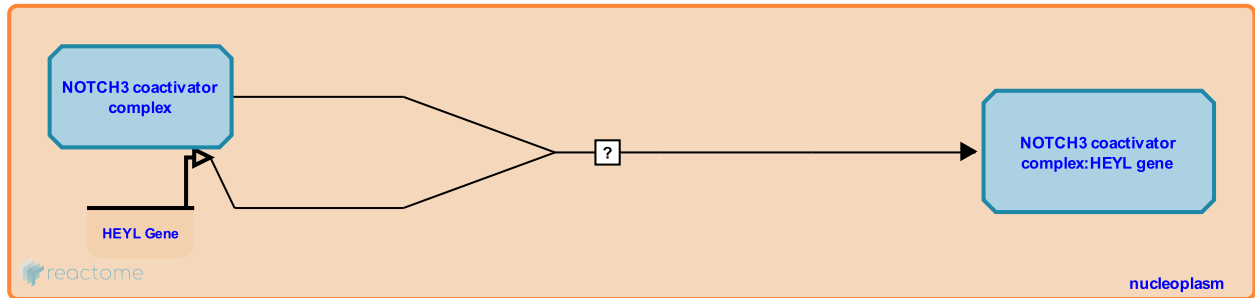
Location: [NOTCH3 Intracellular Domain Regulates Transcription](#)

Stable identifier: R-HSA-9017398

Type: uncertain

Compartments: nucleoplasm

Inferred from: [Notch3 coactivator complex binds the Heyl gene promoter \(Mus musculus\)](#)



Based on the findings that the NOTCH3 coactivator complex component RBPJ (CSL) binds to RBPJ response elements in the promoter of the HEYL gene (Geimer Le Lay et al. 2014) and that HEYL gene expression is stimulated by NOTCH3 (Maier and Gessler 2000) and overlaps with NOTCH3 expression in vascular smooth muscle cells and the thymus (Leimeister et al. 2000), it can be concluded that the NOTCH3 coactivator complex binds the promoter of the HEYL gene.

Preceded by: [NICD3 binds RBPJ and MAML in the nucleus](#)

Followed by: [HEYL gene expression is stimulated by NOTCH3](#)

Editions

2017-09-20	Authored	Orlic-Milacic, M.
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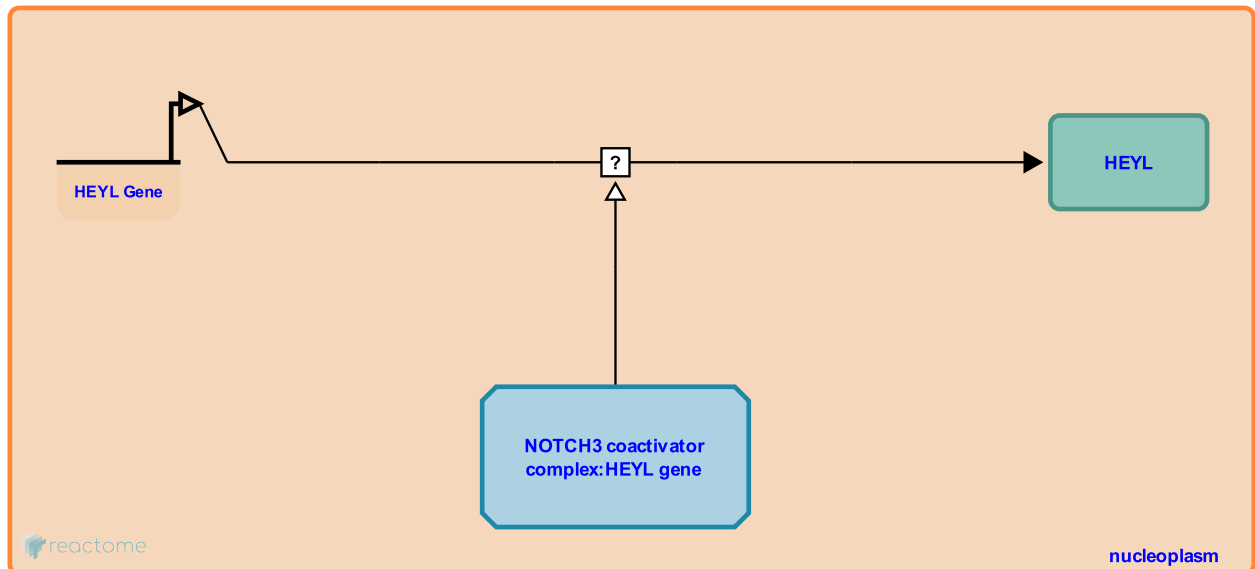
HEYL gene expression is stimulated by NOTCH3 [↗](#)

Location: [NOTCH3 Intracellular Domain Regulates Transcription](#)

Stable identifier: R-HSA-9013488

Type: uncertain

Compartments: nucleoplasm



HEYL gene expression is stimulated by NOTCH3 (Maier and Gessler 2000). In developing mouse embryos, Notch3 expression overlaps with HeyL expression in vascular smooth muscle cells and in the thymus (Leimeister et al. 2000).

Preceded by: [NOTCH3 coactivator complex binds HEYL gene promoter](#)

Literature references

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

Editions

2017-09-20	Authored	Orlic-Milacic, M.
2017-10-30	Reviewed	Haw, R.
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HES5 gene expression is stimulated by NOTCH3 ↗

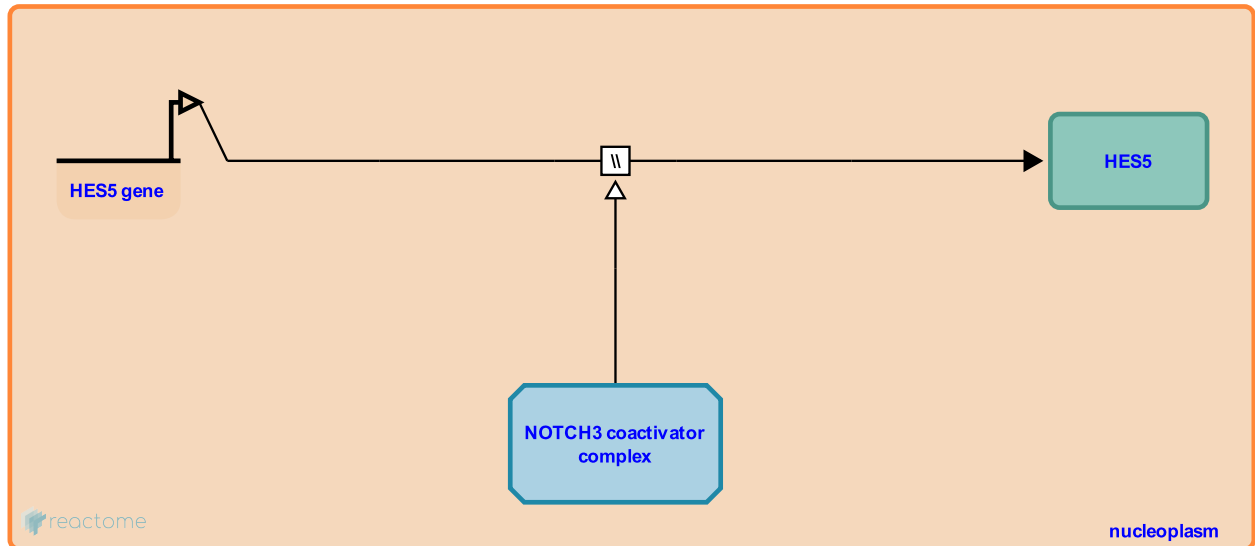
Location: [NOTCH3 Intracellular Domain Regulates Transcription](#)

Stable identifier: R-HSA-9013568

Type: omitted

Compartments: nucleoplasm

Inferred from: [Hes5 gene expression is stimulated by Notch3 \(Mus musculus\)](#)



Based on studies in mouse, NOTCH3 intracellular domain (NICD3), likely in complex with RBPJ and MAML (MAML1, MAML2 or MAML3), positively regulates transcription from the HES5 gene promoter. While HES5 promoter contains RBPJ binding elements, direct binding of the NOTCH3 coactivator complex to the HES5 promoter has not been demonstrated (Lin et al. 2002, Shimizu et al. 2002). Studies in rats suggest that NOTCH3-mediated upregulation of HES5 plays a key role in the development of pulmonary arterial hypertension. NOTCH3 and HES5 are both expressed in vascular smooth muscle cells of small pulmonary arteries of human and rat lungs, with NOTCH3 and HES5 levels increased in hypertensive human and rat lung tissues (Li et al. 2009).

Preceded by: [NICD3 binds RBPJ and MAML in the nucleus](#)

Literature references

Shimizu, K., Hirai, H., Kumano, K., Hamada, Y., Saito, T., Chiba, S. (2002). Functional diversity among Notch1, Notch2, and Notch3 receptors. *Biochem Biophys Res Commun*, 291, 775-9. ↗

Editions

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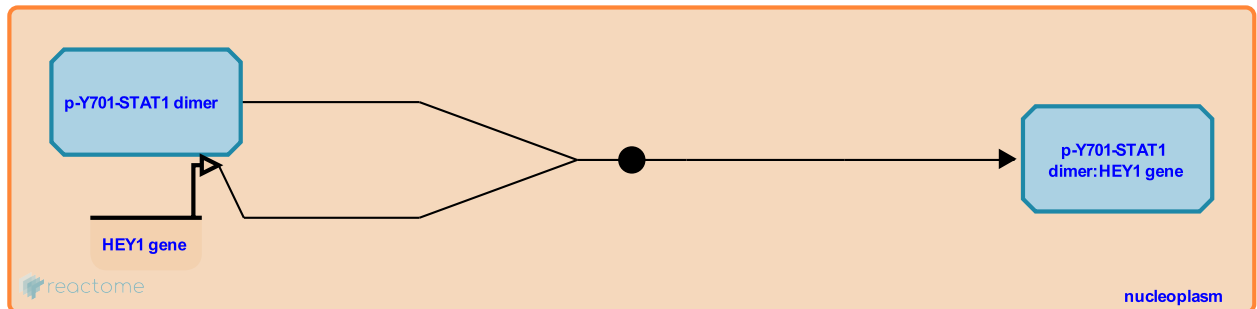
STAT1 binds HEY1 gene promoter ↗

Location: [NOTCH3 Intracellular Domain Regulates Transcription](#)

Stable identifier: R-HSA-9021334

Type: binding

Compartments: nucleoplasm



STAT1 can bind to STAT response elements in the HEY1 gene promoter and enhances HEY1 transcription induced by NICD3 (Boelens et al. 2014).

Followed by: [HEY1 gene expression is positively regulated by NOTCH3 and STAT1](#)

Literature references

Wiemann, BZ., Qiu, Y., Nabet, BY., Ishwaran, H., Wu, TJ., Slingerland, J. et al. (2014). Exosome transfer from stromal to breast cancer cells regulates therapy resistance pathways. *Cell*, 159, 499-513. ↗

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HEY1 gene expression is positively regulated by NOTCH3 and STAT1 ↗

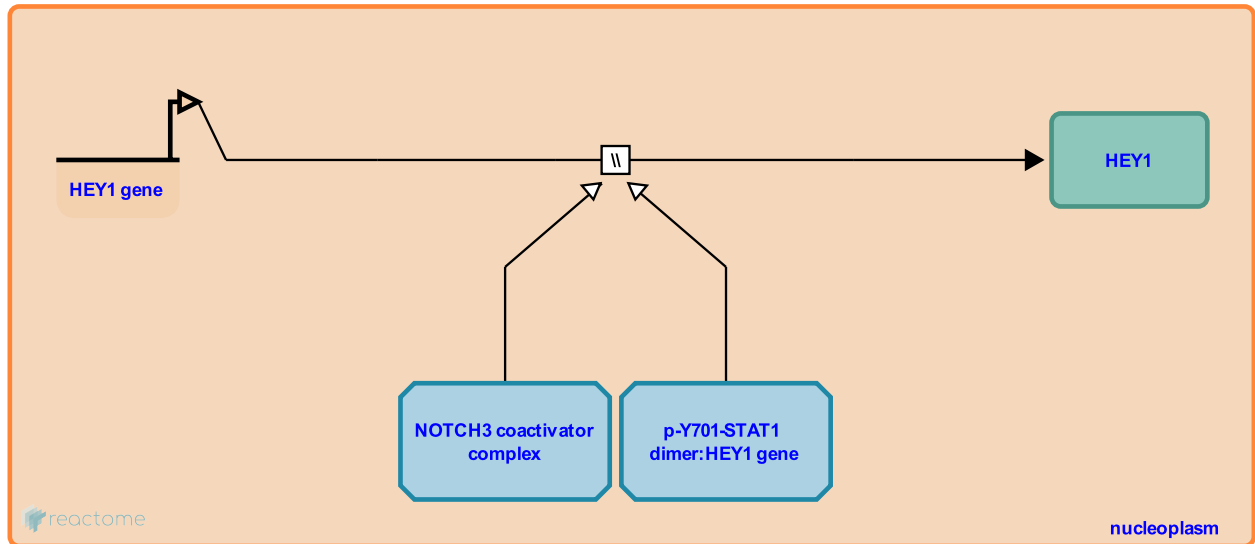
Location: [NOTCH3 Intracellular Domain Regulates Transcription](#)

Stable identifier: R-HSA-9014129

Type: omitted

Compartments: nucleoplasm

Inferred from: [Hey1 gene expression is positively regulated by Notch3 \(Mus musculus\)](#)



Based on a study involving mouse and rat proteins and DNA, NOTCH3 coactivator complex positively regulates transcription of HEY1 (HRT1). Direct binding of NOTCH3 to the HEY1 gene promoter has not been demonstrated (Wang et al. 2002). STAT1 directly enhances HEY1 gene transcription induced by NICD3. In breast cancer, stromal cells secrete RNA-containing exosomes. Upon uptake of exosomes by breast cancer cells, STAT1-dependent antiviral signaling is initiated. Stromal cells also express JAG1 ligand on their surface and, in parallel to STAT1 signaling, activate NOTCH3 signaling in NOTCH3-expressing breast cancer cells. Synergistic activation of NOTCH3 and STAT1 increases breast cancer radiation resistance (Boelens et al. 2014).

Preceded by: [STAT1 binds HEY1 gene promoter](#), [NICD3 binds RBPJ and MAML in the nucleus](#)

Literature references

Wiemann, BZ., Qiu, Y., Nabet, BY., Ishwaran, H., Wu, TJ., Slingerland, J. et al. (2014). Exosome transfer from stromal to breast cancer cells regulates therapy resistance pathways. *Cell*, 159, 499-513. ↗

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HEY2 gene expression is positively regulated by NOTCH3 ↗

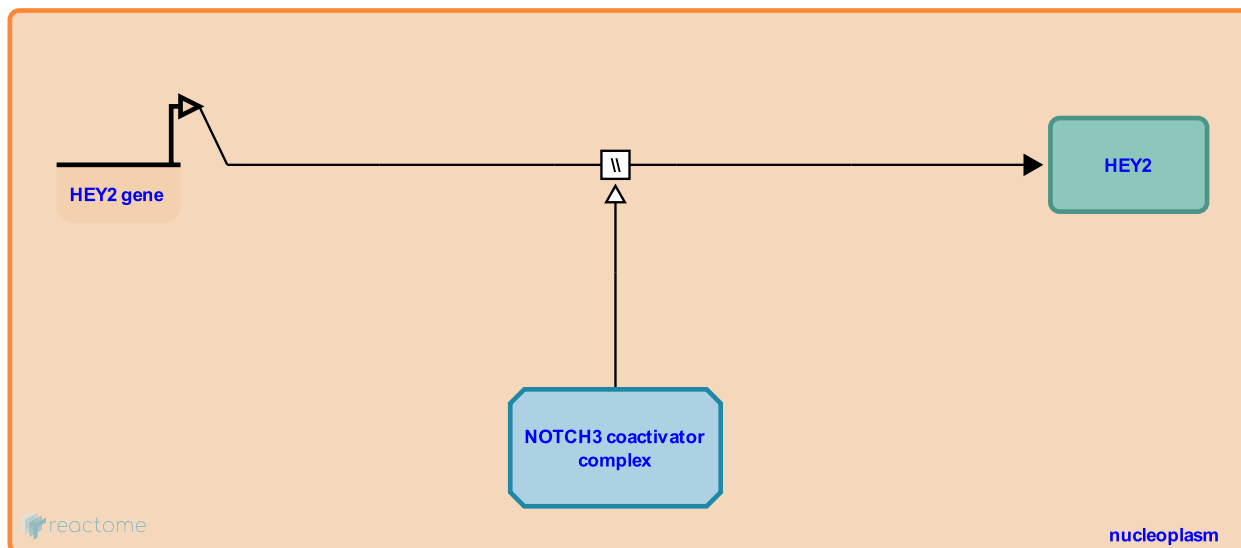
Location: [NOTCH3 Intracellular Domain Regulates Transcription](#)

Stable identifier: R-HSA-9014141

Type: omitted

Compartments: nucleoplasm

Inferred from: [Hey2 gene expression is positively regulated by Notch3 \(Mus musculus\)](#)



Based on a study involving mouse and rat proteins and DNA, NOTCH3 coactivator complex positively regulates transcription of HEY2 (HRT2). Direct binding of NOTCH3 to the HEY2 gene promoter has not been demonstrated (Wang et al. 2002).

Preceded by: [NICD3 binds RBPJ and MAML in the nucleus](#)

Editions

2017-09-20	Authored	Orlic-Milacic, M.
2017-10-30	Reviewed	Haw, R.
2017-11-02	Edited	Orlic-Milacic, M.

FABP7 gene expression is positively regulated by NOTCH1 and NOTCH3 ↗

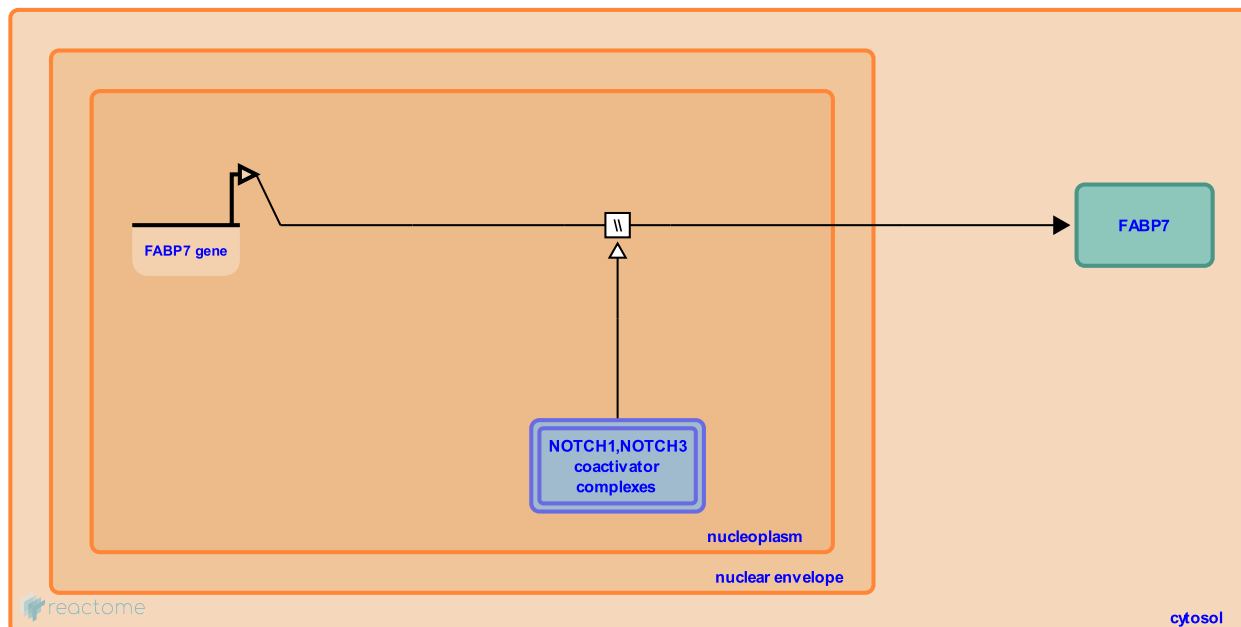
Location: [NOTCH3 Intracellular Domain Regulates Transcription](#)

Stable identifier: R-HSA-9016751

Type: omitted

Compartments: nucleoplasm

Inferred from: [Fabp7 gene expression is positively regulated by Notch1 and Notch3 \(Mus musculus\)](#)



Based on studies in mice, expression of FABP7 (BLBP) in radial glia is positively regulated by NOTCH1 and NOTCH3 during neuronal migration (Anthony et al. 2005, Keilani and Sugaya 2008). The promoter of the mouse Fabp7 gene contains an Rbpj binding site needed for Fabp7 expression (Anthony et al. 2005). Several sites related to the consensus RBPJ binding sequence exist in the human FABP7 gene promoter.

Preceded by: [NICD3 binds RBPJ and MAML in the nucleus](#)

Editions

2017-09-20	Authored	Orlic-Milacic, M.
2017-10-30	Reviewed	Haw, R.
2017-11-02	Edited	Orlic-Milacic, M.

NOTCH3 coactivator complex binds the PTCRA gene promoter ↗

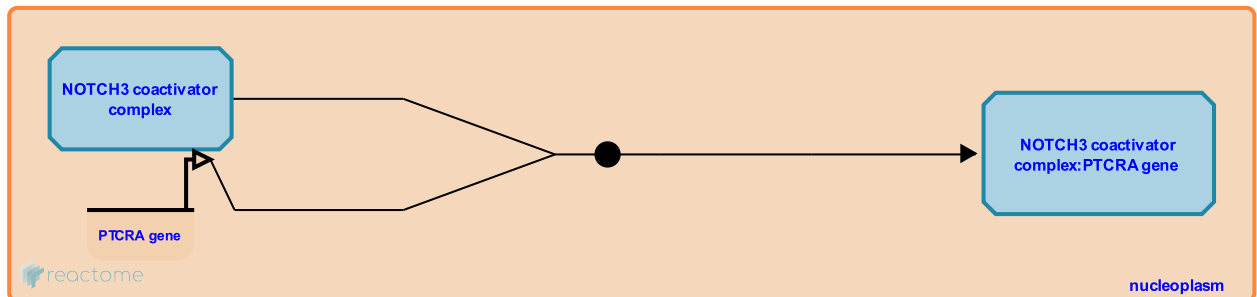
Location: [NOTCH3 Intracellular Domain Regulates Transcription](#)

Stable identifier: R-HSA-9016916

Type: binding

Compartments: nucleoplasm

Inferred from: [Notch3 coactivator complex binds the Ptcra gene promoter \(Mus musculus\)](#)



Based on studies in mice, NOTCH3 coactivator complex binds to RBPJ binding sites in the promoter of the PTCRA gene, encoding pre-TCR-alpha (Bellavia et al. 2007).

Preceded by: [NICD3 binds RBPJ and MAML in the nucleus](#)

Followed by: [PTCRA gene expression is stimulated by NOTCH3 and inhibited by IK1](#)

Editions

2017-09-20	Authored	Orlic-Milacic, M.
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2017-11-02	Edited	Orlic-Milacic, M.

IK1 binds the PTCRA gene promoter ↗

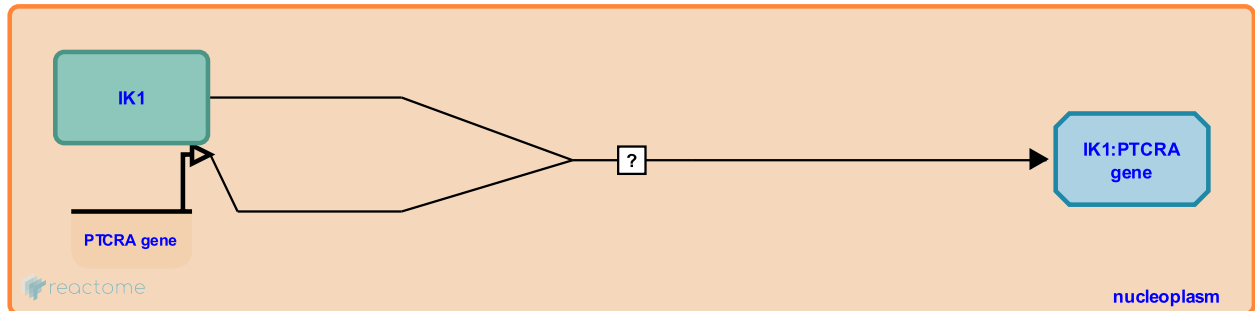
Location: [NOTCH3 Intracellular Domain Regulates Transcription](#)

Stable identifier: R-HSA-9017120

Type: uncertain

Compartments: nucleoplasm

Inferred from: [Ik1 binds the Ptcra gene promoter \(Mus musculus\)](#)



IK1, the splicing isoform 1 of the transcription factor Ikaros (IKZF1), binds to the promoter of the PTCRA gene, encoding pre-TCR-alpha. IK1-binding sites overlap with RBPJ-binding sites. Therefore, IK1 competes with NOTCH3 coactivator complexes for binding to the PTCRA promoter (Bellavia et al. 2007). It is unknown which IK1 heterodimerization partners are involved in binding to the PTCRA promoter.

Followed by: [PTCRA gene expression is stimulated by NOTCH3 and inhibited by IK1](#)

Editions

2017-09-20	Authored	Orlic-Milacic, M.
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PTCRA gene expression is stimulated by NOTCH3 and inhibited by IK1 ↗

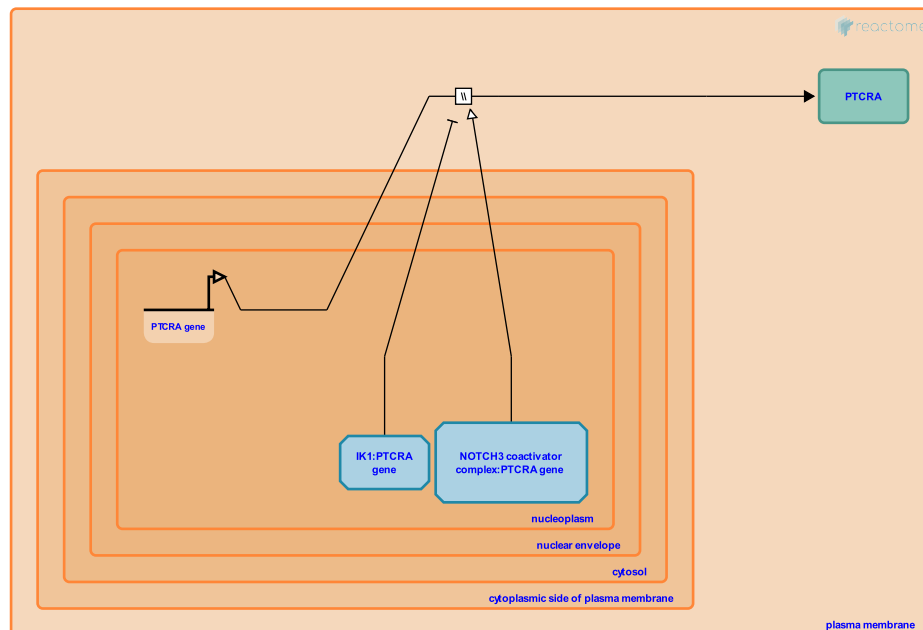
Location: [NOTCH3 Intracellular Domain Regulates Transcription](#)

Stable identifier: R-HSA-9016861

Type: omitted

Compartments: plasma membrane, nucleoplasm

Inferred from: [Ptcra gene expression is positively stimulated by Notch3 and inhibited by Ik1 \(Mus musculus\)](#)



Based on studies in mice, NOTCH3 intracellular domain NICD3 positively regulates transcription of the PTCRA gene, encoding pre-T-cell receptor alpha (pre-TCR-alpha or pTalpha). NICD3-mediated induction of PTCRA transcription is RBPJ and MAML dependent, and the PTCRA promoter contains several RBPJ-binding sites (Talora et al. 2003, Bellavia et al. 2007). IK1, splicing isoform of the transcription factor Ikaros (IKZF1), competes with RBPJ for binding to the PTCRA promoter and inhibits PTCRA transcription. NOTCH3, through pre-TCR signaling, stimulates expression of the RNA binding protein HuD, which promotes splicing of IKZF1 into dominant negative isoforms. These dominant negative isoforms of IKZF1 heterodimerize with IK1, preventing its binding to target DNA sequences and thus contributing to sustained transcription of PTCRA (Bellavia et al. 2007, reviewed by Bellavia, Mecarozzi, Campese, Grazioli, Gulino and Screpanti 2007).

Preceded by: [NOTCH3 coactivator complex binds the PTCRA gene promoter](#), [IK1 binds the PTCRA gene promoter](#)

Editions

2017-09-20	Authored	Orlic-Milacic, M.
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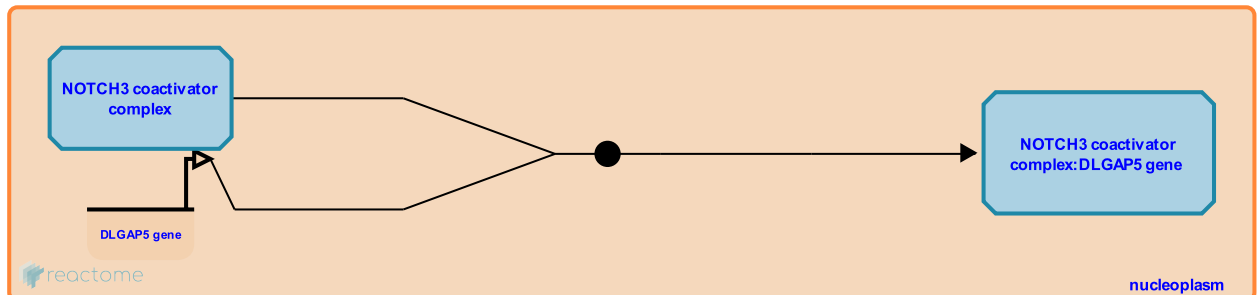
NOTCH3 coactivator complex binds DLGAP5 gene promoter ↗

Location: [NOTCH3 Intracellular Domain Regulates Transcription](#)

Stable identifier: R-HSA-9018542

Type: binding

Compartments: nucleoplasm



NOTCH3 coactivator complex binds the RBPJ (CSL) response elements in the promoter of the DLGAP5 gene. Two adjacent CSL-binding motifs in the DLGAP5 promoter, which are 6 bp apart, are both necessary for NOTCH3-mediated induction of DLGAP5 transcription (Chen et al. 2012).

Preceded by: [NICD3 binds RBPJ and MAML in the nucleus](#)

Followed by: [DLGAP5 gene transcription is stimulated by NOTCH3](#)

Literature references

Chen, X., Gao, M., Xuan, J., Chen, L., Wang, TL., Stoeck, A. et al. (2012). Defining NOTCH3 target genes in ovarian cancer. *Cancer Res.*, 72, 2294-303. ↗

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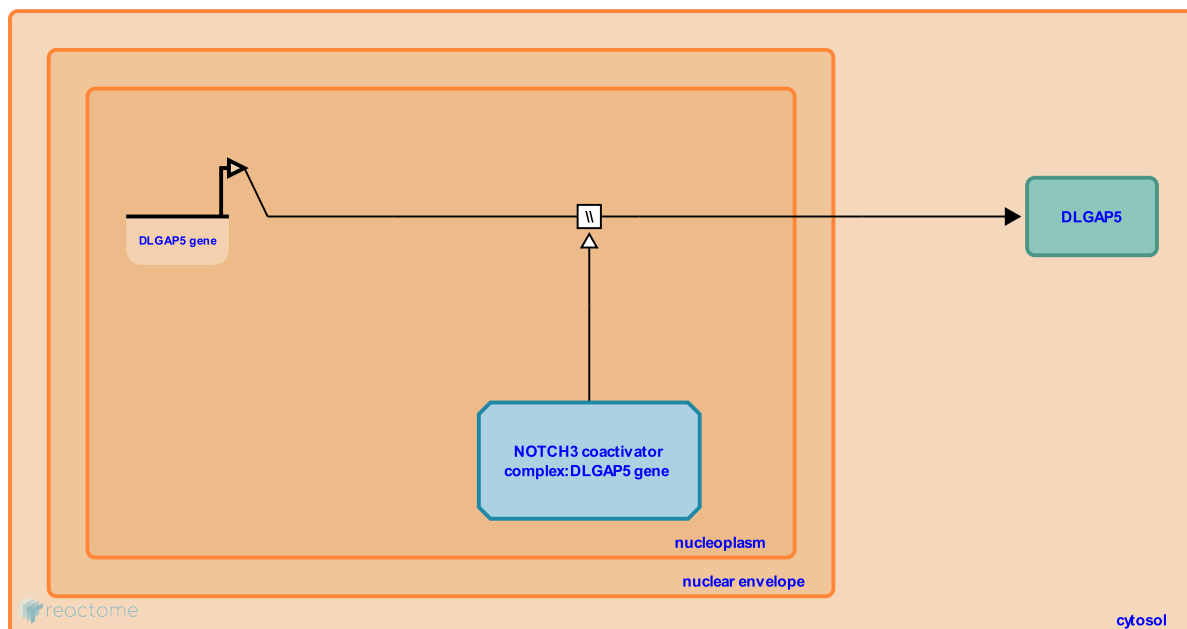
DLGAP5 gene transcription is stimulated by NOTCH3 ↗

Location: [NOTCH3 Intracellular Domain Regulates Transcription](#)

Stable identifier: R-HSA-9018538

Type: omitted

Compartments: nucleoplasm, cytosol



Binding of the NOTCH3 coactivator complex to RBPJ response elements in the promoter of the DLGAP5 gene stimulates DLGAP5 transcription. DLGAP5 is involved in G2/M transition and is overexpressed in ovarian cancer cells. NOTCH3 gene is frequently amplified in ovarian cancer (Chen et al. 2012).

Preceded by: [NOTCH3 coactivator complex binds DLGAP5 gene promoter](#)

Literature references

Chen, X., Gao, M., Xuan, J., Chen, L., Wang, TL., Stoeck, A. et al. (2012). Defining NOTCH3 target genes in ovarian cancer. *Cancer Res.*, 72, 2294-303. ↗

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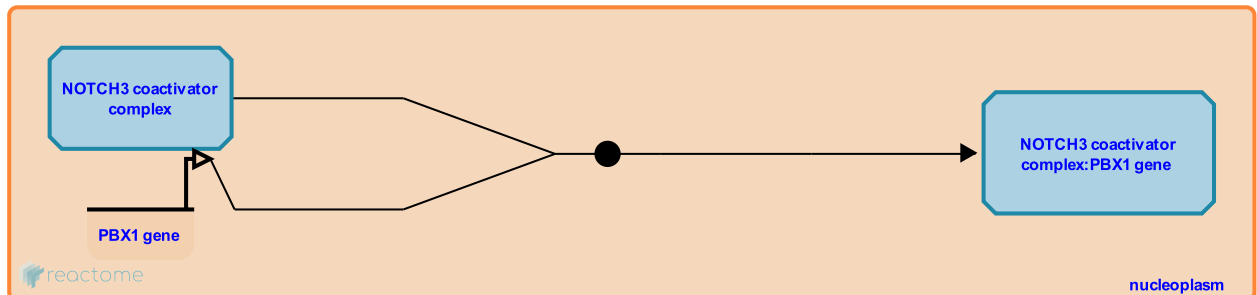
NOTCH3 coactivator complex binds PBX1 gene promoter ↗

Location: [NOTCH3 Intracellular Domain Regulates Transcription](#)

Stable identifier: R-HSA-9021406

Type: binding

Compartments: nucleoplasm



NOTCH3 coactivator complex binds to RBPJ-binding element in the promoter region of the PBX1 gene (Park et al. 2008).

Preceded by: [NICD3 binds RBPJ and MAML in the nucleus](#)

Followed by: [PBX1 gene expression is stimulated by NOTCH3](#)

Literature references

Park, JT., Wang, TL., Shih, IeM. (2008). Identification of Pbx1, a potential oncogene, as a Notch3 target gene in ovarian cancer. *Cancer Res.*, 68, 8852-60. ↗

Editions

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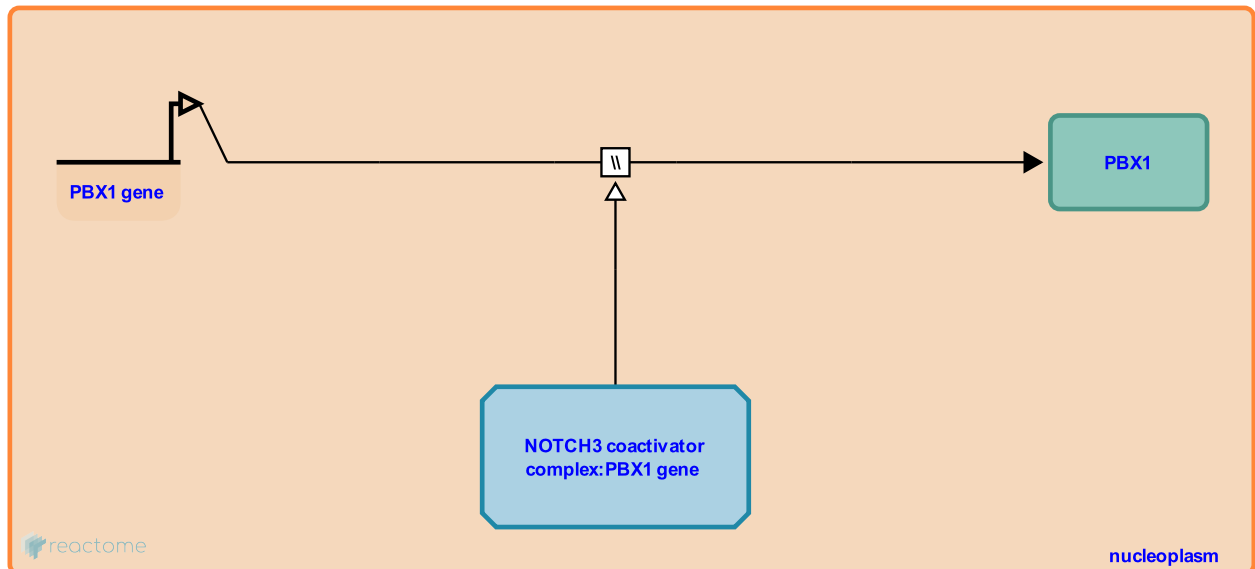
PBX1 gene expression is stimulated by NOTCH3 [↗](#)

Location: [NOTCH3 Intracellular Domain Regulates Transcription](#)

Stable identifier: R-HSA-9021412

Type: omitted

Compartments: nucleoplasm



PBX1 gene transcription is directly stimulated by the NOTCH3 coactivator complex (Park et al. 2008). NOTCH3 gene is amplified in high-grade ovarian serous carcinoma and NOTCH3 overexpression contributes to cancer cell growth (Park et al. 2006). Overexpression of NOTCH3 in high-grade ovarian serous carcinoma correlates with overexpression of PBX1 (Park et al. 2006, Park et al. 2008). PBX1 gene encodes a homeodomain transcription factor PBX1 which is a B cell leukemia (B-ALL) oncogene (Nourse et al. 1990, Kamps et al. 1991) and is also overexpressed in melanoma (Shiraishi et al. 2007).

Preceded by: [NOTCH3 coactivator complex binds PBX1 gene promoter](#)

Literature references

Park, JT., Wang, TL., Shih, IeM. (2008). Identification of Pbx1, a potential oncogene, as a Notch3 target gene in ovarian cancer. *Cancer Res.*, 68, 8852-60. [↗](#)

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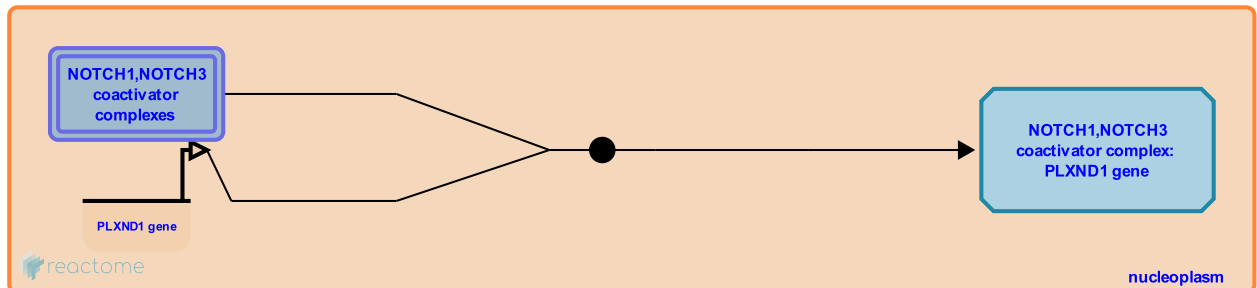
NOTCH1,NOTCH3 coactivator complex binds PLXND1 gene promoter ↗

Location: [NOTCH3 Intracellular Domain Regulates Transcription](#)

Stable identifier: R-HSA-9021451

Type: binding

Compartments: nucleoplasm



PLXND1 gene promoter possesses an RBPJ-binding site which is necessary for NOTCH1 and NOTCH3-mediated induction of PLXND1 transcription. It is therefore concluded that NOTCH1 and NOTCH3 co-activator complexes directly bind to the PLXND1 gene promoter (Rehman et al. 2016).

Preceded by: [NICD3 binds RBPJ and MAML in the nucleus](#)

Followed by: [PLXND1 gene expression is stimulated by NOTCH1,NOTCH3 coactivator complexes](#)

Literature references

Rehman, M., Gurrapu, S., Capparuccia, L., Tamagnone, L., Cagnoni, G. (2016). PlexinD1 Is a Novel Transcriptional Target and Effector of Notch Signaling in Cancer Cells. *PLoS ONE*, 11, e0164660. ↗

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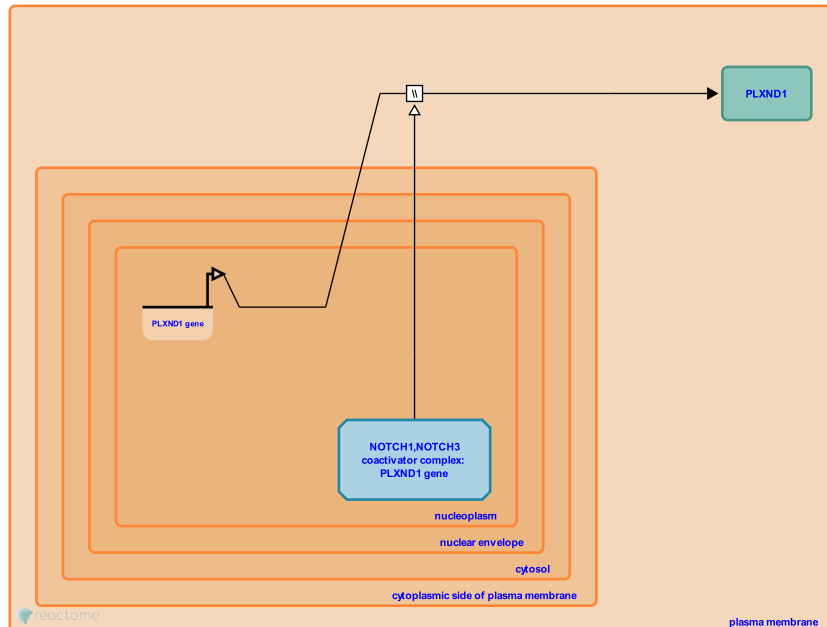
PLXND1 gene expression is stimulated by NOTCH1,NOTCH3 coactivator complexes [↗](#)

Location: [NOTCH3 Intracellular Domain Regulates Transcription](#)

Stable identifier: R-HSA-9021450

Type: omitted

Compartments: plasma membrane, nucleoplasm



PLXND1 gene transcription is stimulated by NOTCH1 and NOTCH3 coactivator complexes. PLXND1 encodes the semaphorin receptor Plexin-D1, involved in neuronal migration as well as cancer cell invasiveness (Rehman et al. 2016).

Preceded by: [NOTCH1,NOTCH3 coactivator complex binds PLXND1 gene promoter](#)

Literature references

Rehman, M., Gurrapu, S., Capparuccia, L., Tamagnone, L., Cagnoni, G. (2016). PlexinD1 Is a Novel Transcriptional Target and Effector of Notch Signaling in Cancer Cells. *PLoS ONE*, 11, e0164660. [↗](#)

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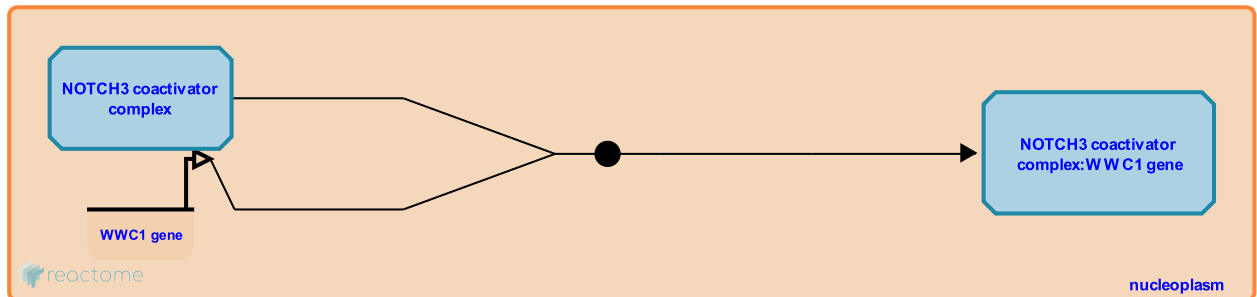
NOTCH3 coactivator complex binds WWC1 (Kibra) gene promoter ↗

Location: [NOTCH3 Intracellular Domain Regulates Transcription](#)

Stable identifier: R-HSA-9021480

Type: binding

Compartments: nucleoplasm



The WWC1 (Kibra) gene promoter region contains two RBPJ-binding sites, one on the sense strand and one on the antisense strand. The NOTCH3 coactivator complex binds to the RBPJ-binding site on the antisense strand (Zhang et al. 2016).

Preceded by: [NICD3 binds RBPJ and MAML in the nucleus](#)

Followed by: [WWC1 \(Kibra\) gene expression is stimulated by NOTCH3](#)

Literature references

Li, Y., Zhang, X., Chen, M., Liu, X., Ye, X., Luo, J. et al. (2016). Notch3 inhibits epithelial-mesenchymal transition by activating Kibra-mediated Hippo/YAP signaling in breast cancer epithelial cells. *Oncogenesis*, 5, e269. ↗

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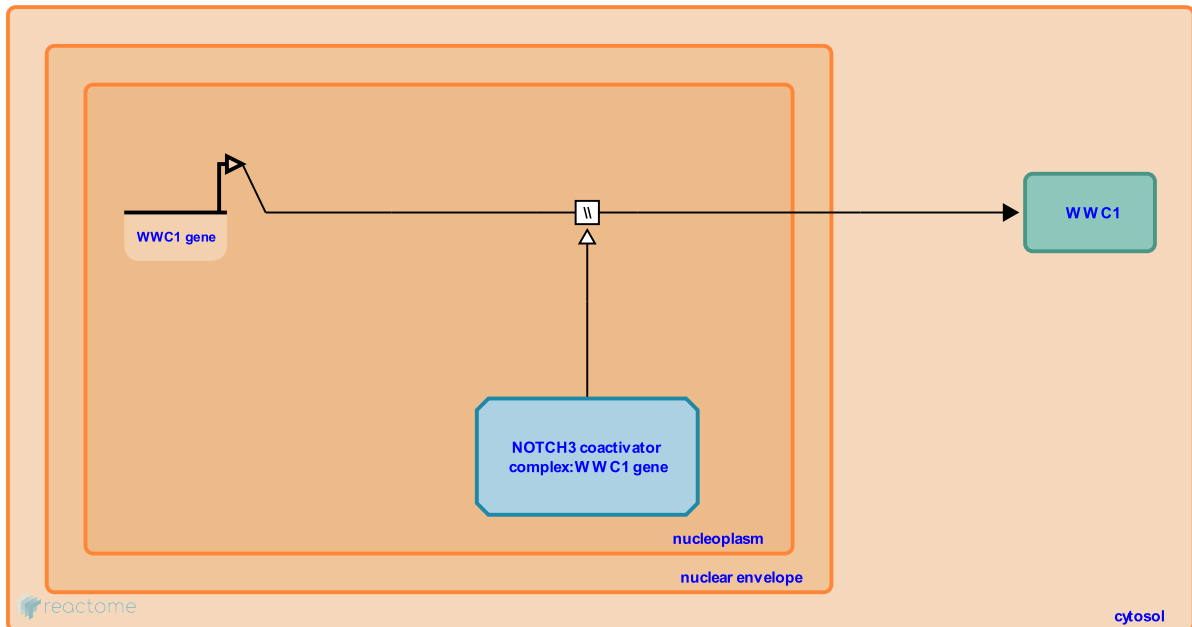
WWC1 (Kibra) gene expression is stimulated by NOTCH3 ↗

Location: [NOTCH3 Intracellular Domain Regulates Transcription](#)

Stable identifier: R-HSA-9021478

Type: omitted

Compartments: nucleoplasm, cytosol



The NOTCH3 coactivator complex directly stimulates WWC1 gene transcription. WWC1 gene encodes the protein Kibra, involved in Hippo signaling. NOTCH3-mediated induction of WWC1 positively regulates Hippo signaling and inhibits epithelial-to-mesenchymal transition (EMT) in triple negative breast cancer cells (Zhang et al. 2016).

Preceded by: [NOTCH3 coactivator complex binds WWC1 \(Kibra\) gene promoter](#)

Literature references

Li, Y., Zhang, X., Chen, M., Liu, X., Ye, X., Luo, J. et al. (2016). Notch3 inhibits epithelial-mesenchymal transition by activating Kibra-mediated Hippo/YAP signaling in breast cancer epithelial cells. *Oncogenesis*, 5, e269. ↗

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