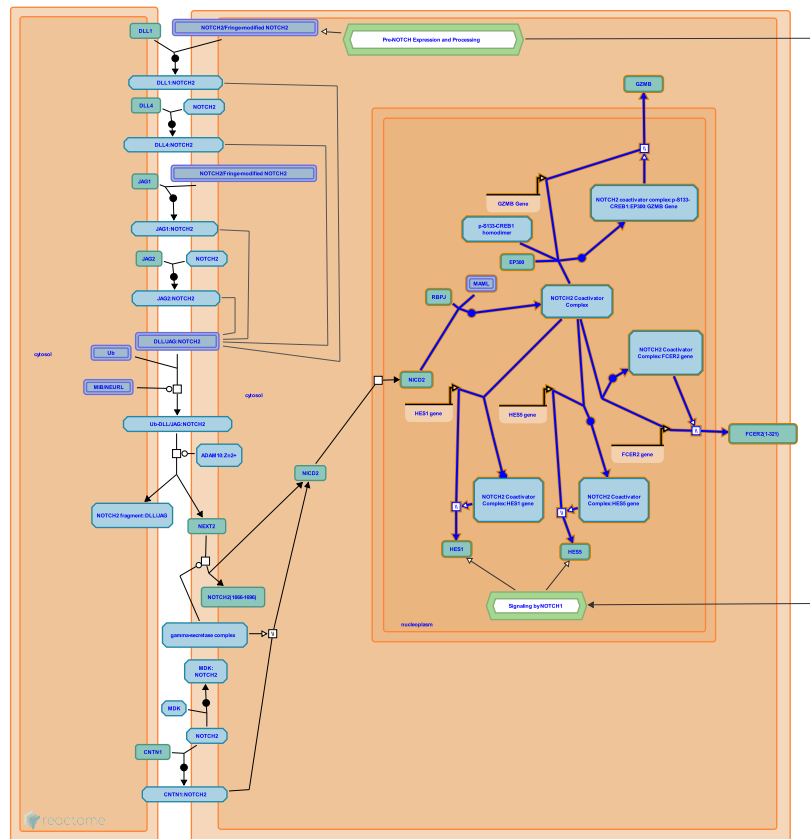


NOTCH2 intracellular domain regulates transcription



Boyle, S., Haw, R., Ilagan, MXG., Orlic-Milacic, M.

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

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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/).

30/04/2024

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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- Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics*, 33, 3461-3467. [↗](#)
- Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res*, 46, D649-D655. [↗](#)
- Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology*, 14, e1005968. [↗](#)

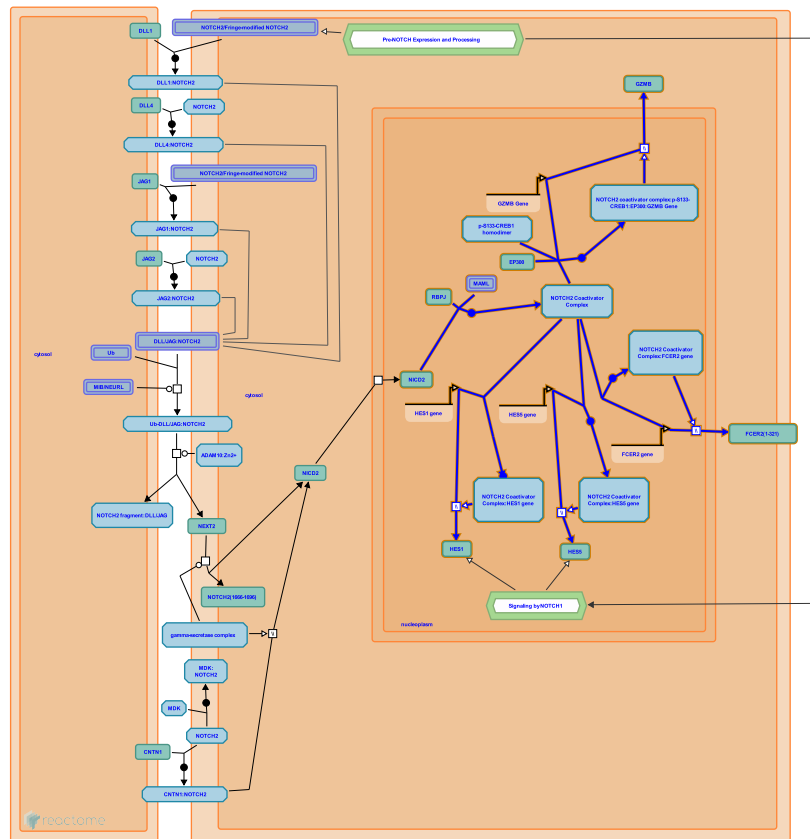
Reactome database release: 88

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

NOTCH2 intracellular domain regulates transcription ↗

Stable identifier: R-HSA-2197563

Compartments: nucleoplasm



In the nucleus, NICD2 forms a complex with RBPJ (CBF1, CSL) and MAML (mastermind). NICD2:RBPJ:MAML complex activates transcription from RBPJ-binding promoter elements (RBEs) (Wu et al. 2000). Besides NICD2, RBPJ and MAML, NOTCH2 coactivator complex likely includes other proteins, shown as components of the NOTCH1 coactivator complex.

NOTCH2 coactivator complex directly stimulates transcription of HES1 and HES5 genes (Shimizu et al. 2002), both of which are known NOTCH1 targets.

The promoter of FCER2 (CD23A) contains several RBEs that are occupied by NOTCH2 but not NOTCH1 coactivator complexes, and NOTCH2 activation stimulates FCER2 transcription. Overexpression of FCER2 (CD23A) is a hallmark of B-cell chronic lymphocytic leukemia (B-CLL) and correlates with the malfunction of apoptosis, which is thought to be an underlying mechanism of B-CLL development. The Epstein-Barr virus protein EBNA2 can also activate FCER2 transcription through RBEs, possibly by mimicking NOTCH2 signaling (Hubmann et al. 2002).

NOTCH2 coactivator complex occupies the proximal RBE of the GZMB (granzyme B) promoter and at the same time interacts with phosphorylated CREB1, bound to an adjacent CRE site. EP300 transcriptional coactivator is also recruited to this complex through association with CREB1 (Maekawa et al. 2008). NOTCH2 coactivator complex together with CREBP1 and EP300 stimulates transcription of GZMB (granzyme B), which is important for the cytotoxic function of CD8+ T-cells (Maekawa et al. 2008).

There are indications that NOTCH2 genetically interacts with hepatocyte nuclear factor 1-beta (HNF1B) in kidney development (Massa et al. 2013, Heliot et al. 2013) and with hepatocyte nuclear factor 6 (HNF6) in bile duct formation (Vanderpool et al. 2012), but the exact nature of these genetic interactions has not been defined.

Literature references

- Desgrange, A., Buisson, I., Vainio, S., Prunskaitė-Hyyryläinen, R., Shan, J., Heliot, C. et al. (2013). HNF1B controls proximal-intermediate nephron segment identity in vertebrates by regulating Notch signalling components and *Irx1/2*. *Development*, 140, 873-85. [↗](#)
- 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. [↗](#)
- Shehata, M., Berger, R., Schwarzmeier, JD., Duechler, M., Hilgarth, M., Hubmann, R. et al. (2002). Notch2 is involved in the overexpression of CD23 in B-cell chronic lymphocytic leukemia. *Blood*, 99, 3742-7. [↗](#)
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- Saito, T., Sakata-Yanagimoto, M., Kurihara, T., Sone, S., Taniuchi, I., Kojima, H. et al. (2008). Notch2 integrates signaling by the transcription factors RBP-J and CREB1 to promote T cell cytotoxicity. *Nat. Immunol.*, 9, 1140-7. [↗](#)

Editions

| | | |
|------------|----------|-------------------------|
| 2013-01-11 | Authored | Orlic-Milacic, M. |
| 2013-01-14 | Edited | Haw, R. |
| 2013-04-25 | Reviewed | Ilagan, MXG., Boyle, S. |

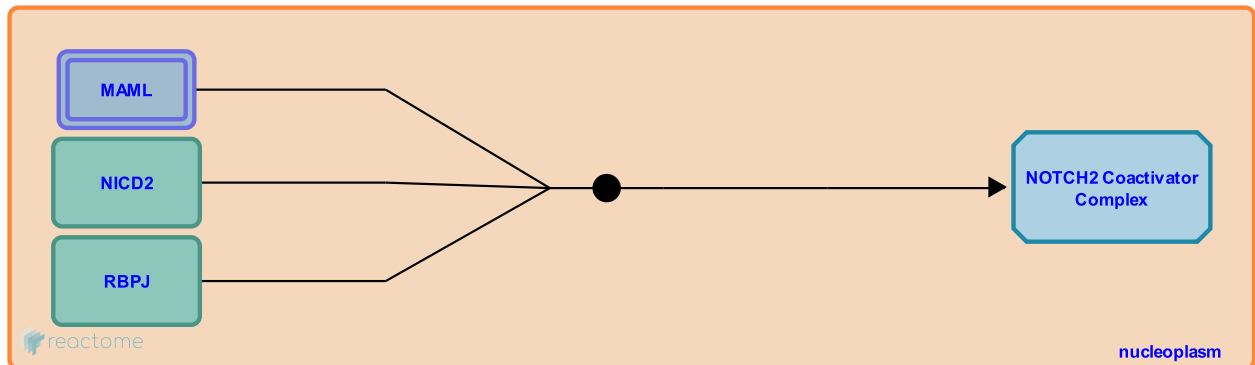
NICD2 binds RBPJ and MAML in the nucleus ↗

Location: [NOTCH2 intracellular domain regulates transcription](#)

Stable identifier: R-HSA-2197588

Type: binding

Compartments: nucleoplasm



In the nucleus, NICD2 forms a complex with RBPJ (CBF1, CSL) and MAML (mastermind). NICD2:RBPJ:MAML complex activates transcription from RBPJ-binding promoter elements (Wu et al. 2000).

Besides NICD2, RBPJ and MAML, NOTCH2 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 NICD2, 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: [NOTCH2 coactivator complex binds HES5 promoter](#), [NOTCH2 coactivator complex and phosphorylated CREB1 bind GZMB promoter](#), [NOTCH2 coactivator complex binds FCER2 promoter](#), [NOTCH2 coactivator complex binds HES1 promoter](#)

Literature references

Blacklow, SC., Pear, WS., Nam, Y., Sliz, P., Aster, JC. (2007). Cooperative assembly of higher-order Notch complexes functions as a switch to induce transcription. *Proc. Natl. Acad. Sci. U.S.A.*, 104, 2103-8. ↗

Blacklow, SC., Artavanis-Tsakonas, S., Aster, JC., Wu, L., Griffin, JD., Lake, R. (2000). MAML1, a human homologue of *Drosophila* mastermind, is a transcriptional co-activator for NOTCH receptors. *Nat Genet*, 26, 484-9. ↗

Editions

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NOTCH2 coactivator complex binds HES1 promoter ↗

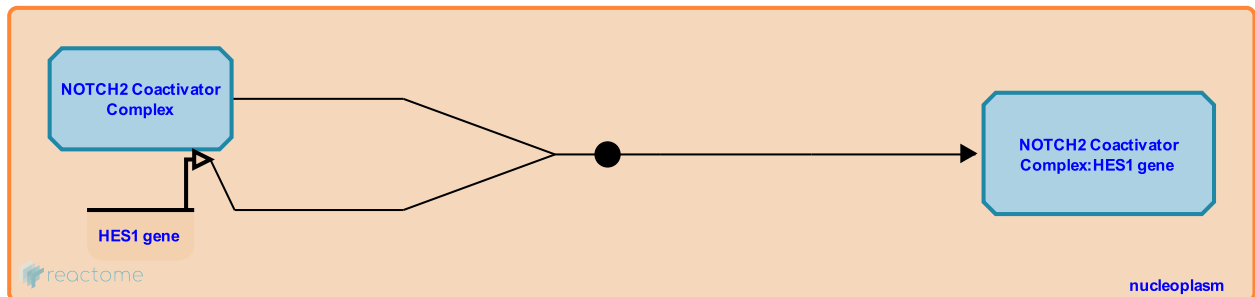
Location: [NOTCH2 intracellular domain regulates transcription](#)

Stable identifier: R-HSA-2976716

Type: binding

Compartments: nucleoplasm

Inferred from: [Notch2 binds Hes1 promoter \(Mus musculus\)](#)



NOTCH2 intracellular domain, NICD2, as a part of the NOTCH2 coactivator complex, binds RBPJ elements in the promoter of HES1 gene (Shimizu et al. 2002).

Preceded by: [NICD2 binds RBPJ and MAML in the nucleus](#)

Followed by: [NOTCH2 stimulates HES1 transcription](#)

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. ↗

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NOTCH2 stimulates HES1 transcription ↗

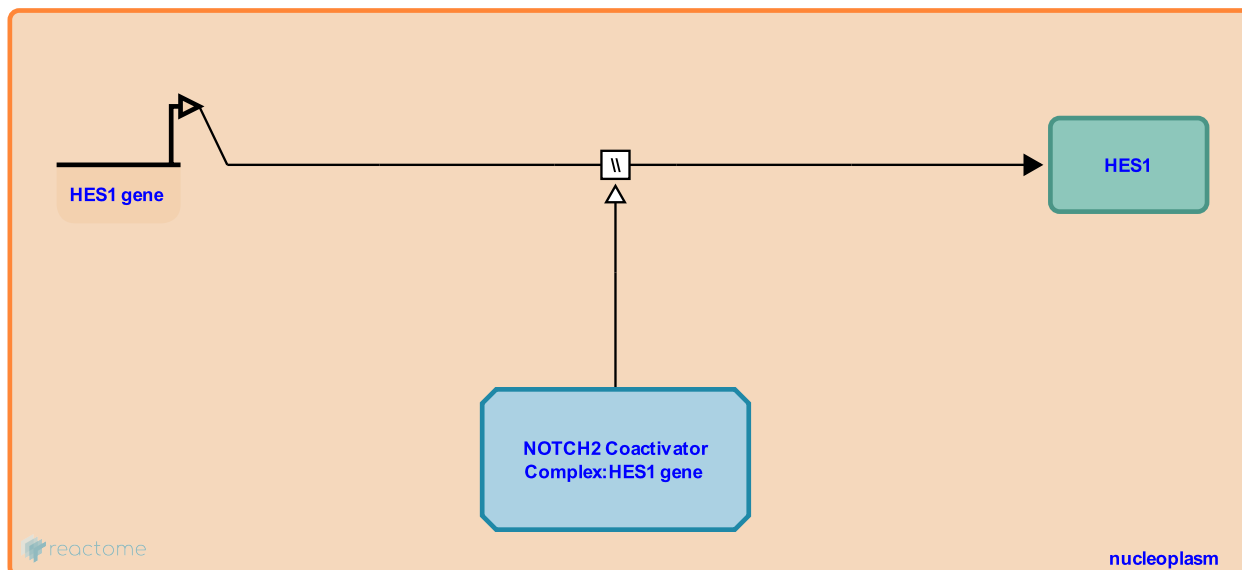
Location: [NOTCH2 intracellular domain regulates transcription](#)

Stable identifier: R-HSA-2197562

Type: omitted

Compartments: nucleoplasm

Inferred from: [Notch2 stimulates Hes1 transcription \(Mus musculus\)](#)



NOTCH2 coactivator complex bound to RBPJ elements in the promoter of HES1 gene stimulates HES1 transcription (Shimizu et al. 2002).

Preceded by: [NOTCH2 coactivator complex binds HES1 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. ↗

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NOTCH2 coactivator complex binds HES5 promoter ↗

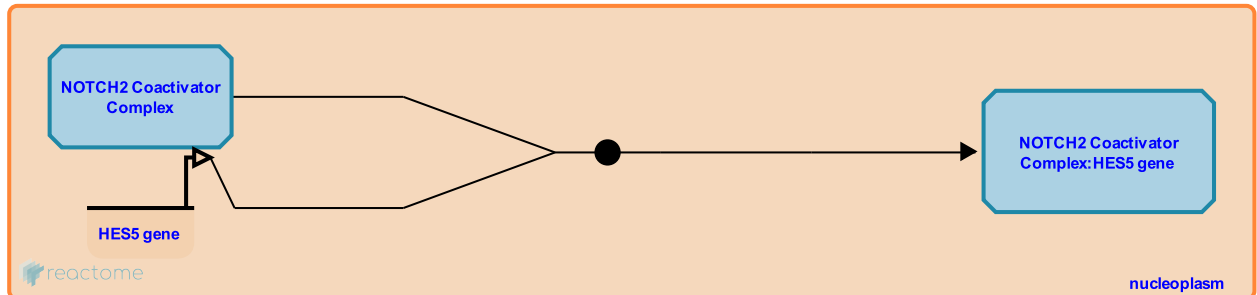
Location: [NOTCH2 intracellular domain regulates transcription](#)

Stable identifier: R-HSA-2976726

Type: binding

Compartments: nucleoplasm

Inferred from: [Notch2 binds Hes5 promoter \(Mus musculus\)](#)



NOTCH2 intracellular domain, NICD2, as a part of the NOTCH2 coactivator complex, binds RBPJ elements in the promoter of HES5 gene (Shimizu et al. 2002).

Preceded by: [NICD2 binds RBPJ and MAML in the nucleus](#)

Followed by: [NOTCH2 stimulates transcription of HES5](#)

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. ↗

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NOTCH2 stimulates transcription of HES5 ↗

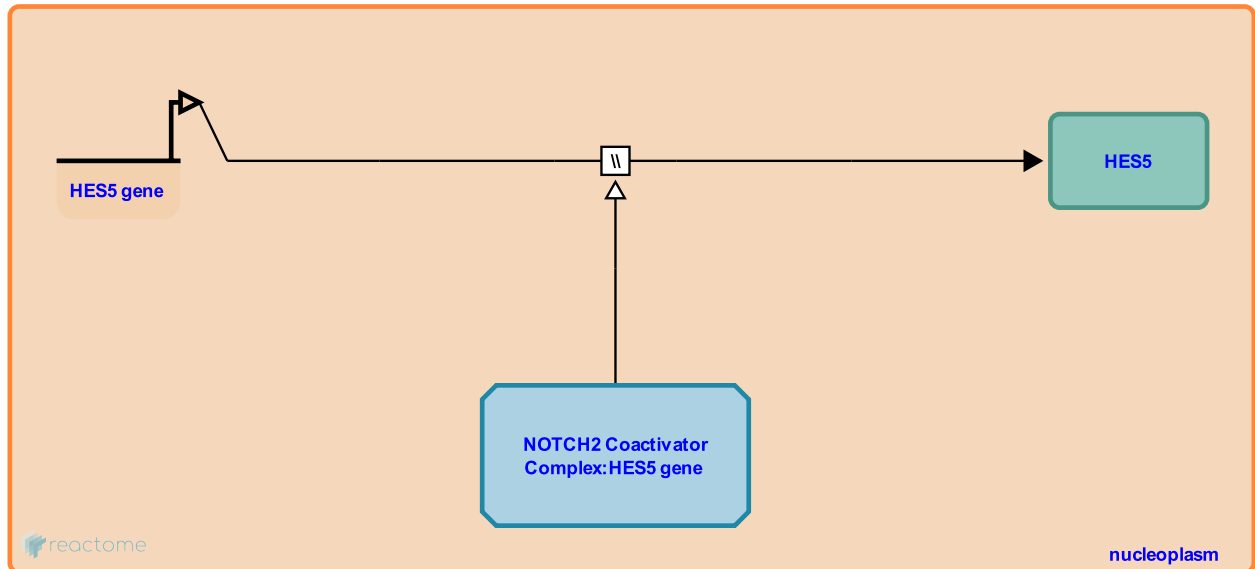
Location: [NOTCH2 intracellular domain regulates transcription](#)

Stable identifier: R-HSA-2197564

Type: omitted

Compartments: nucleoplasm

Inferred from: [Notch2 stimulates transcription of Hes5 \(Mus musculus\)](#)



NOTCH2 coactivator complex bound to HES5 promoter stimulates HES5 transcription (Shimizu et al. 2002).

Preceded by: [NOTCH2 coactivator complex binds HES5 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. ↗

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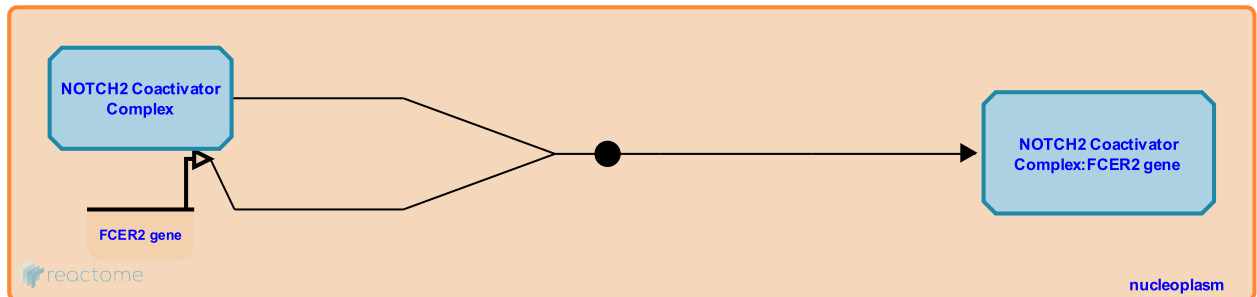
NOTCH2 coactivator complex binds FCER2 promoter ↗

Location: [NOTCH2 intracellular domain regulates transcription](#)

Stable identifier: R-HSA-2976742

Type: binding

Compartments: nucleoplasm



The promoter of FCER2 (CD23A) contains several RBPJ (CSL i.e. CBF) binding sites that are occupied by RBPJ transcription complexes that contain NICD2, but not NICD1. The association of NICD2 with RBPJ promoter elements of FCER2 gene was demonstrated by electromobility shift assays on nuclear extracts of human B-cell chronic lymphocytic leukemia (B-CLL) cells (Hubmann et al. 2002).

Preceded by: [NICD2 binds RBPJ and MAML in the nucleus](#)

Followed by: [NOTCH2 stimulates transcription of FCER2 \(CD23A\)](#)

Literature references

Shehata, M., Berger, R., Schwarzmeier, JD., Duechler, M., Hilgarth, M., Hubmann, R. et al. (2002). Notch2 is involved in the overexpression of CD23 in B-cell chronic lymphocytic leukemia. *Blood*, 99, 3742-7. ↗

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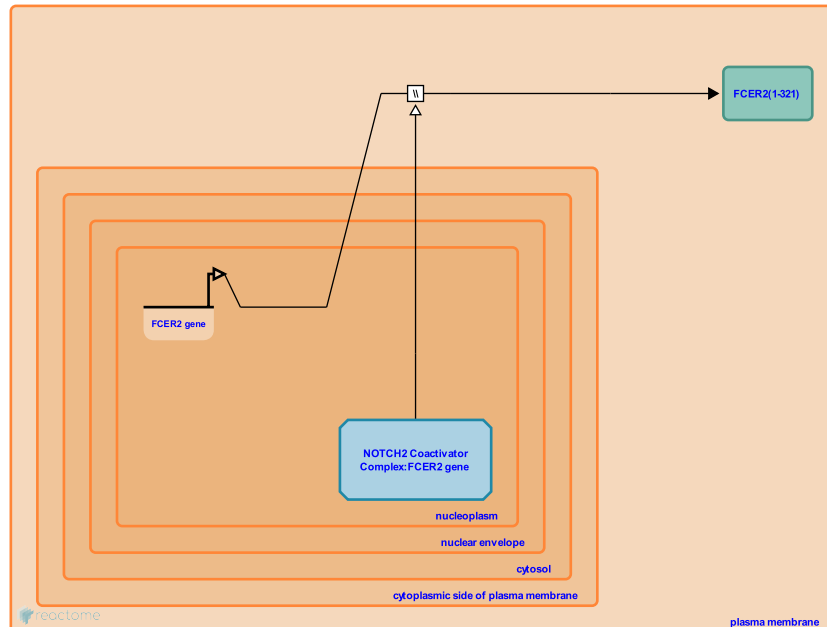
NOTCH2 stimulates transcription of FCER2 (CD23A) ↗

Location: NOTCH2 intracellular domain regulates transcription

Stable identifier: R-HSA-2127285

Type: omitted

Compartments: plasma membrane, nucleoplasm



Transient transfection of a human pre-B-cell line REH with a vector encoding recombinant rat NICD2 induces endogenous FCER2 transcription. Overexpression of FCER2 (CD23A) is a hallmark of B-cell chronic lymphocytic leukemia (B-CLL) and correlates with the malfunction of apoptosis, which is thought to be an underlying mechanism of B-CLL development. The Epstein-Barr virus protein EBNA2 can also activate FCER2 transcription through RBPJ promoter elements, possibly by mimicking NOTCH2 signaling (Hubmann et al. 2002).

Preceded by: NOTCH2 coactivator complex binds FCER2 promoter

Literature references

Shehata, M., Berger, R., Schwarzmeier, J.D., Duechler, M., Hilgarth, M., Hubmann, R. et al. (2002). Notch2 is involved in the overexpression of CD23 in B-cell chronic lymphocytic leukemia. *Blood*, 99, 3742-7. ↗

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NOTCH2 coactivator complex and phosphorylated CREB1 bind GZMB promoter ↗

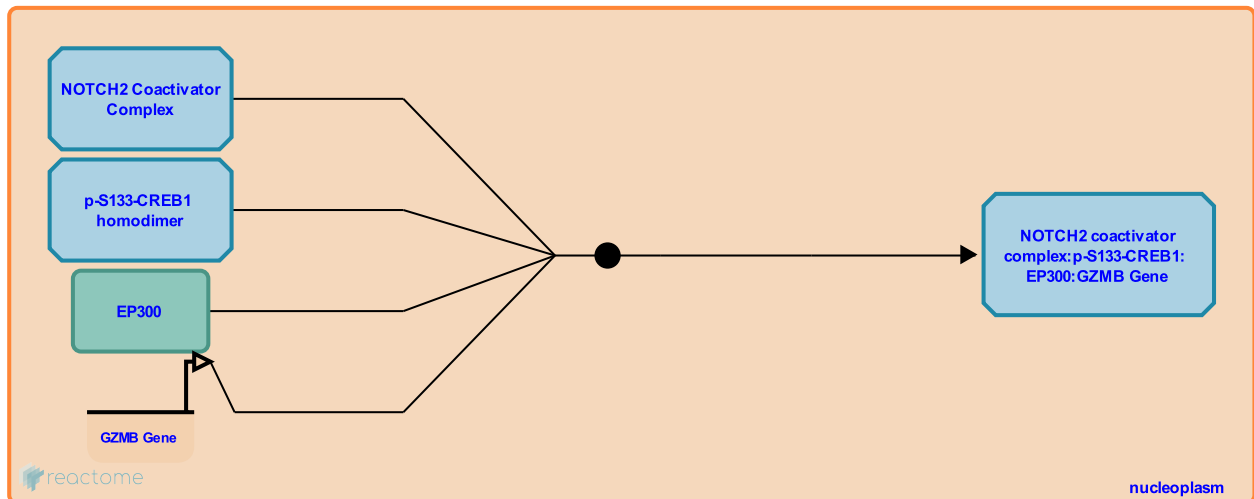
Location: [NOTCH2 intracellular domain regulates transcription](#)

Stable identifier: R-HSA-2976563

Type: binding

Compartments: nucleoplasm

Inferred from: [Notch2 and phosphorylated Creb1 bind Gzmb promoter \(Mus musculus\)](#)



GZMB (granzyme B) promoter contains several RBPJ binding elements (RBEs). NOTCH2 coactivator complex occupies the proximal RBE and at the same time interacts with phosphorylated CREB1, bound to an adjacent CRE site. EP300 transcriptional coactivator is also recruited to this complex through association with CREB1 (Maekawa et al. 2008).

Preceded by: [NICD2 binds RBPJ and MAML in the nucleus](#)

Followed by: [NOTCH2 stimulates GZMB transcription](#)

Literature references

Saito, T., Sakata-Yanagimoto, M., Kurihara, T., Sone, S., Taniuchi, I., Kojima, H. et al. (2008). Notch2 integrates signaling by the transcription factors RBP-J and CREB1 to promote T cell cytotoxicity. *Nat. Immunol.*, 9, 1140-7. ↗

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| 2013-04-25 | Reviewed | Ilagan, MXG., Boyle, S. |

NOTCH2 stimulates GZMB transcription [↗](#)

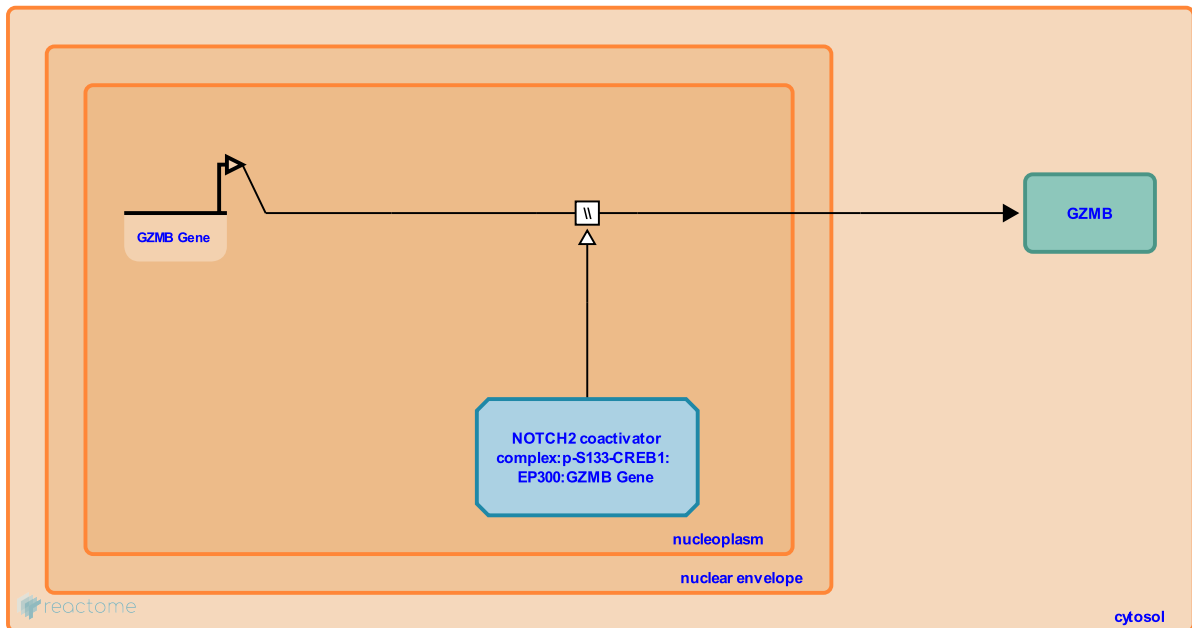
Location: [NOTCH2 intracellular domain regulates transcription](#)

Stable identifier: R-HSA-2976551

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: [Notch2 stimulates Gzmb transcription \(Mus musculus\)](#)



NOTCH2 coactivator complex together with CREB1 and EP300 stimulates transcription of GZMB (granzyme B), which is important for the cytotoxic function of CD8⁺ T-cells (Maekawa et al. 2008).

Preceded by: [NOTCH2 coactivator complex and phosphorylated CREB1 bind GZMB promoter](#)

Literature references

Saito, T., Sakata-Yanagimoto, M., Kurihara, T., Sone, S., Taniuchi, I., Kojima, H. et al. (2008). Notch2 integrates signaling by the transcription factors RBP-J and CREB1 to promote T cell cytotoxicity. *Nat. Immunol.*, 9, 1140-7. [↗](#)

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