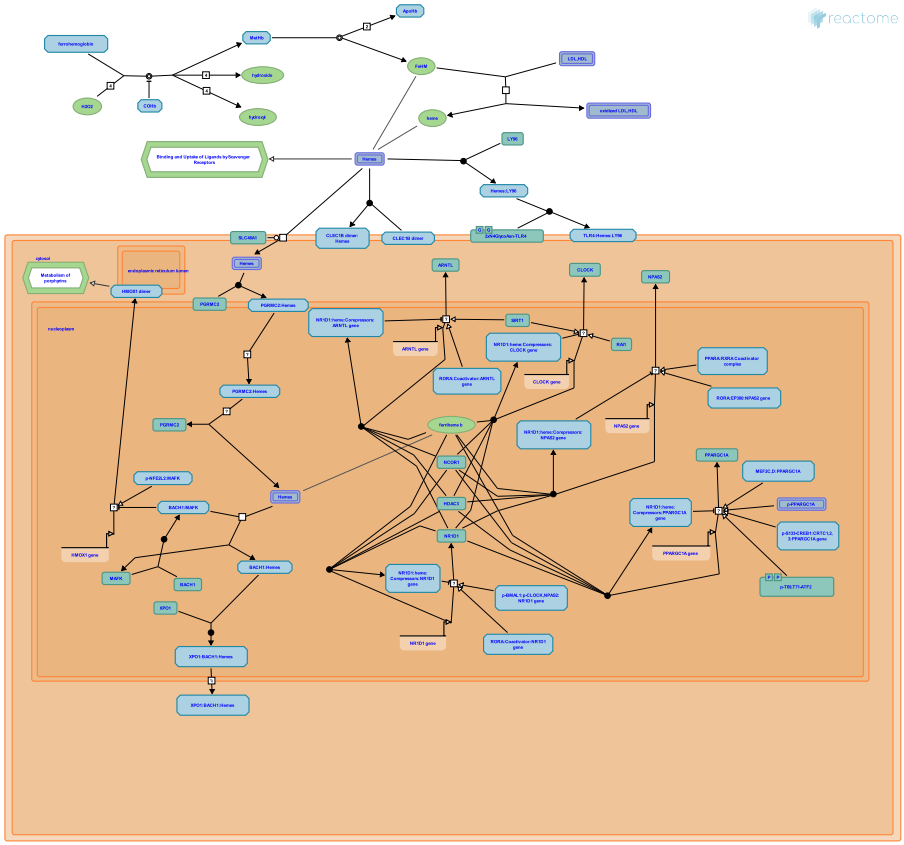
Heme signaling



Albrecht, U., Cuadrado, A., D'Eustachio, P., Delaunay, F., Hirota, T., Jassal, B., Kay, SA., Kersten, S., Lezza, AM., May, B., Rothfels, K., Somers, J., Stephan, R.

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.

25/04/2024

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

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. ↗

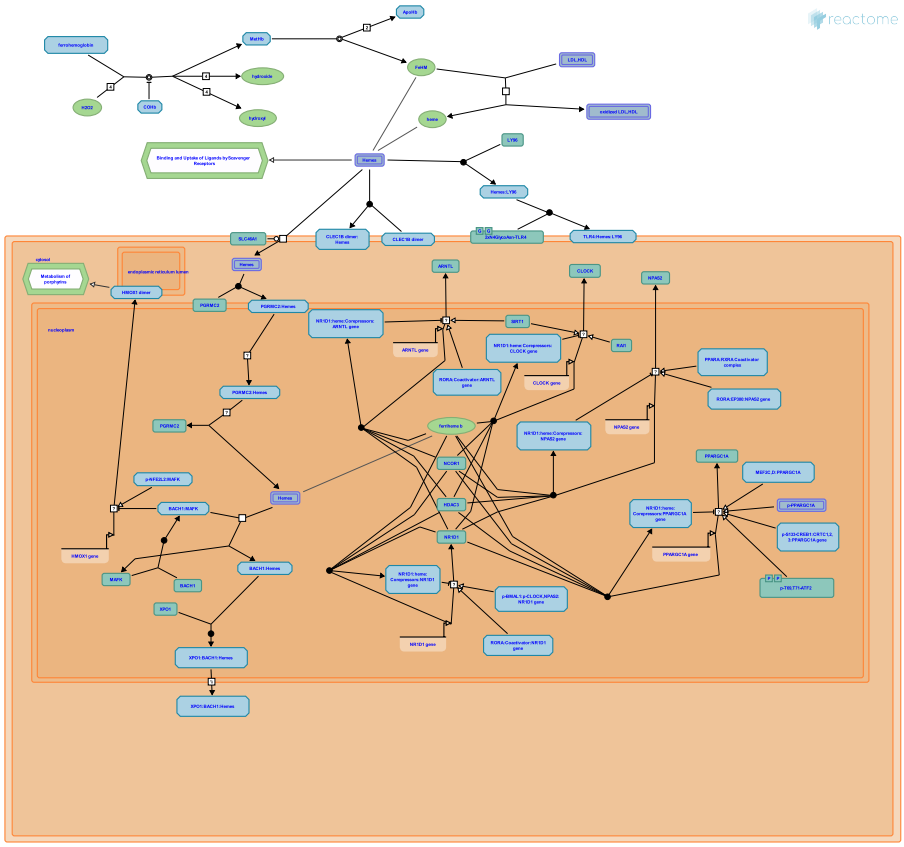
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Heme signaling ↗

Stable identifier: R-HSA-9707616

Compartments: cytosol, extracellular region, nuclear envelope, nucleoplasm, plasma membrane



Extracellular hemoglobin, a byproduct of hemolysis, can release its prosthetic heme groups upon oxidation. Blood plasma contains proteins that scavenge heme. It is estimated that about 2–8% of the heme released in plasma becomes ‘bioavailable’, being internalized by bystander cells. If the heme degradation capacity of a cell, represented by heme oxidase 1 and 2, cannot be ramped up sufficiently then heme signaling and reactivity puts cells under stress. Platelets are activated by heme, and macrophages switch to the inflammatory type (Donegan et al, 2019; Gouveia et al, 2019).

Free (labile) heme accumulates in the blood stream in great amounts under pathological conditions like viral infections and malaria, but also ARDS amd COPD. The locally affected cells' primary reaction is to upregulate heme oxidase 1 (HMOX1) expression. HMOX1 induction in these cells not only removes heme from circulation but also triggers a functional switch toward the anti-inflammatory phenotype (Vijayan et al, 2018). However, heme scavenging and degradation systems may get overwhelmed by the sheer amount of heme present.

Heme promotes platelet activation, complement activation, vasculitis, and thrombosis (Bourne et al, 2020; Merle et al, 2018). Heme was recognized to act as a danger signal, damage-associated molecular pattern (DAMP), or alarmin (Soares and Bozza, 2016) and was shown to activate Toll-like receptor 4 (TLR4) signaling (Figueiredo et al, 2007; Janciauskiene et al, 2020). It also has a role as corepressor in the circadian clock system (Ko and Takahashi, 2006). BACH1 is regulated by heme in a cell, thus placing heme as a signaling molecule in gene expression in higher eukaryotes. The regulation of BACH1 by heme may be important for the stress response in general (Suzuki et al, 2004).

Extracellular hemoglobin, a byproduct of hemolysis, can release its prosthetic heme groups uponoxidation. Due to the reactive nature of free heme, the blood plasma contains proteins that scavenge heme. It is estimated that about 2–8% of the heme released in plasma becomes ‘bioavailable’, being internalized by bystander cells. Failure of nearby cells to sufficientlymetabolize free heme can incite platelet activation, macrophage differentiation, and oxidative stress (Donegan et al, 2019; Gouveia et al, 2019).

Literature references

Ko, CH., Takahashi, JS. (2006). Molecular components of the mammalian circadian clock. *Hum Mol Genet, 15*, R271-7. ↗

Soares, MP., Bozza, MT. (2016). Red alert: labile heme is an alarmin. *Curr Opin Immunol, 38*, 94-100. ↗

Immenschuh, S., Vijayan, V., Janciauskiene, S. (2020). TLR4 Signaling by Heme and the Role of Heme-Binding Blood Proteins. *Front Immunol, 11*, 1964. ↗

Wagener, FADTG., Immenschuh, S., Vijayan, V. (2018). The macrophage heme-heme oxygenase-1 system and its role in inflammation. *Biochem Pharmacol, 153*, 159-167. ↗

Editions

2020-11-12	Authored, Edited	Stephan, R.
2021-01-23	Reviewed	Somers, J.

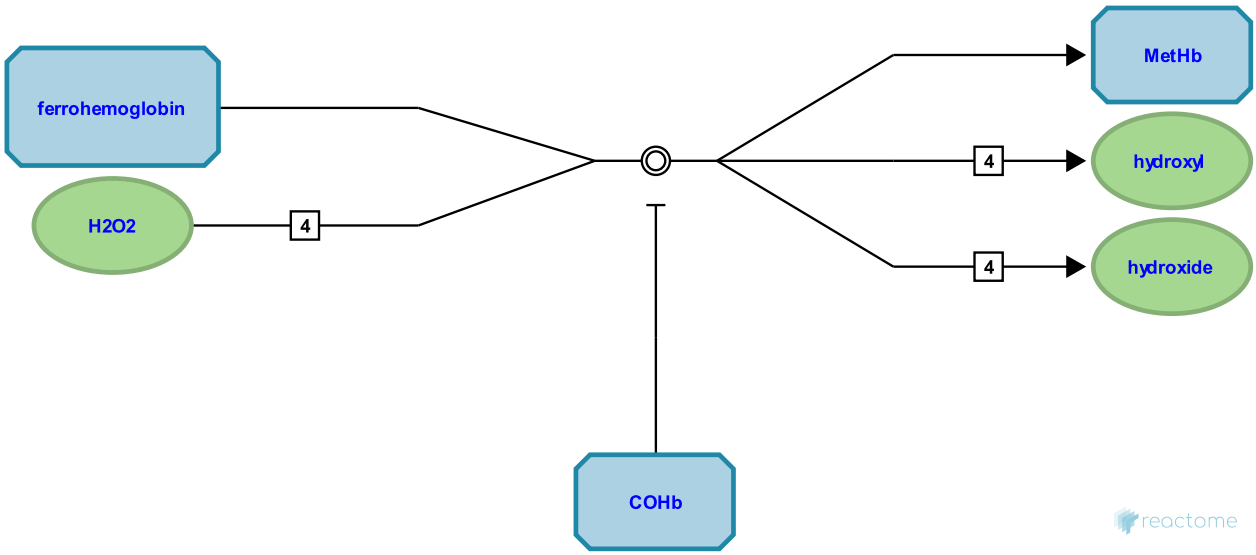
H2O2 oxidises ferrohemoglobin to MetHb ↗

Location: Heme signaling

Stable identifier: R-HSA-9707504

Type: dissociation

Compartments: extracellular region



Extracellular ferrous (Fe2+) hemoglobin (FeHM) is readily oxidized into methemoglobin (MetHb) in the presence of reactive oxygen species (ROS) like hydrogen peroxide (H2O2) (Gouveia et al, 2017; Sadrzadeh et al, 1984).

Carbon monoxide (CO) tightly binds to free ferrohemoglobin, preventing its oxidation to methemoglobin by reactive oxygen species. The reaction is fast and quickly removes CO from the local environment if free hemoglobin is present (Cera et al, 1987; Sher et al, 2012).

Followed by: FeHM dissociates from MetHb

Literature references

Eaton, JW., Graf, E., Panter, SS., Hallaway, PE., Sadrzadeh, SM. (1984). Hemoglobin. A biologic fenton reagent. *J Biol Chem, 259*, 14354-6. ↗

Acker, JP., Kanias, T. (2010). Biopreservation of red blood cells--the struggle with hemoglobin oxidation. *FEBS J, 277*, 343-56. ↗

Editions

2020-11-12	Authored	Stephan, R.
2020-11-19	Edited	Stephan, R.
2021-01-23	Reviewed	Somers, J.

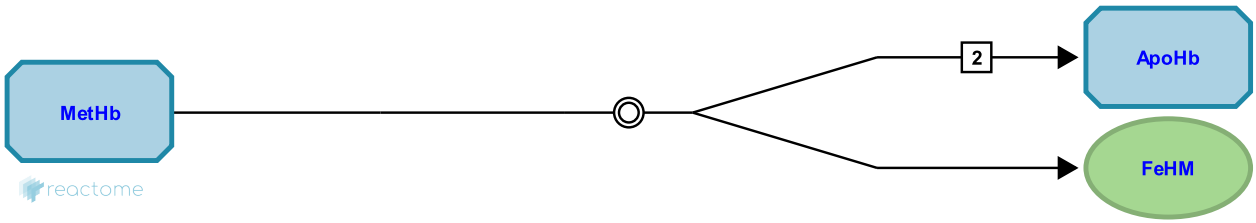
FeHM dissociates from MetHb ↗

Location: Heme signaling

Stable identifier: R-HSA-9707516

Type: dissociation

Compartments: extracellular region



Methemoglobin (MetHb) is highly unstable, releasing free ferriheme (FeHM). The hydrophobic ferriheme, if not scavenged by serum proteins, rapidly intercalates into the plasma membrane of surrounding cells, catalyzing lipid oxidation (Balla et al, 1993).

Preceded by: H2O2 oxidises ferrohemoglobin to MetHb

Followed by: FeHM oxidises LDL,HDL

Literature references

Eaton, JW., Balla, G., Jacob, HS., Vercellotti, GM., Balla, J., Nath, K. (1993). Endothelial-cell heme uptake from heme proteins: induction of sensitization and desensitization to oxidant damage. *Proc Natl Acad Sci U S A, 90*, 9285-9. ↗

Editions

2020-11-12	Authored, Edited	Stephan, R.
2021-01-23	Reviewed	Somers, J.

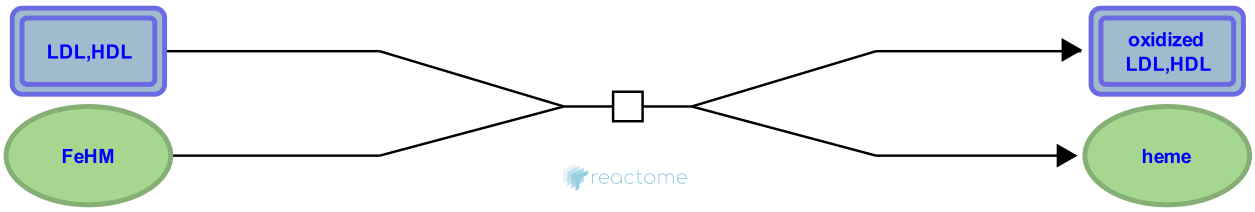
FeHM oxidises LDL,HDL ↗

Location: Heme signaling

Stable identifier: R-HSA-9707586

Type: transition

Compartments: extracellular region



Free heme initially binds to the lipoproteins LDL and HDL which are highly susceptible to oxidation by ferriheme (FeHM). The half-life of the heme:lipoprotein complex is longer than 20 sec. Heme is then transferred to the antioxidants albumin and hemopexin (Miller and Shaklai, 1999; Jeney et al, 2002)

Preceded by: FeHM dissociates from MetHb

Literature references

Shaklai, N., Miller, YI. (1999). Kinetics of hemin distribution in plasma reveals its role in lipoprotein oxidation. *Biochim Biophys Acta, 1454*, 153-64. ↗

Eaton, JW., Jeney, V., Vercellotti, GM., Yachie, A., Balla, G., Varga, Z. et al. (2002). Pro-oxidant and cytotoxic effects of circulating heme. *Blood, 100*, 879-87. ↗

Editions

2020-11-12	Authored, Edited	Stephan, R.
2021-01-23	Reviewed	Somers, J.

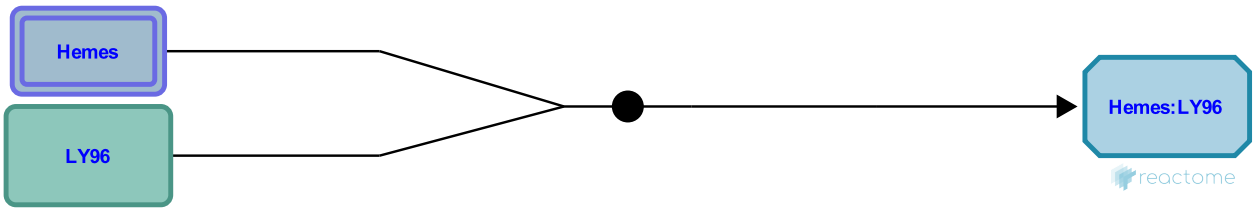
Hemes bind LY96 ↗

Location: Heme signaling

Stable identifier: R-HSA-9707594

Type: binding

Compartments: extracellular region



Secreted LY96 (MD-2) is a large protein that confers lipopolysaccharide (LPS) sensitivity to Toll-like receptor 4 (TLR4). Hemes can bind to secreted LY96 at a different site than LPS, resulting in comparable TLR4 activation (Belcher et al, 2002; Visintin et al, 2001).

Followed by: Hemes:LY96 activates TLR4

Literature references

Belcher, JD., Nath, KA., Kiser, ZM., Nguyen, J., Trent, JO., Zhang, P. et al. (2020). Identification of a Heme Activation Site on the MD-2/TLR4 Complex. *Front Immunol, 11*, 1370. ↗

Editions

2020-11-12	Authored, Edited	Stephan, R.
2021-01-23	Reviewed	Somers, J.

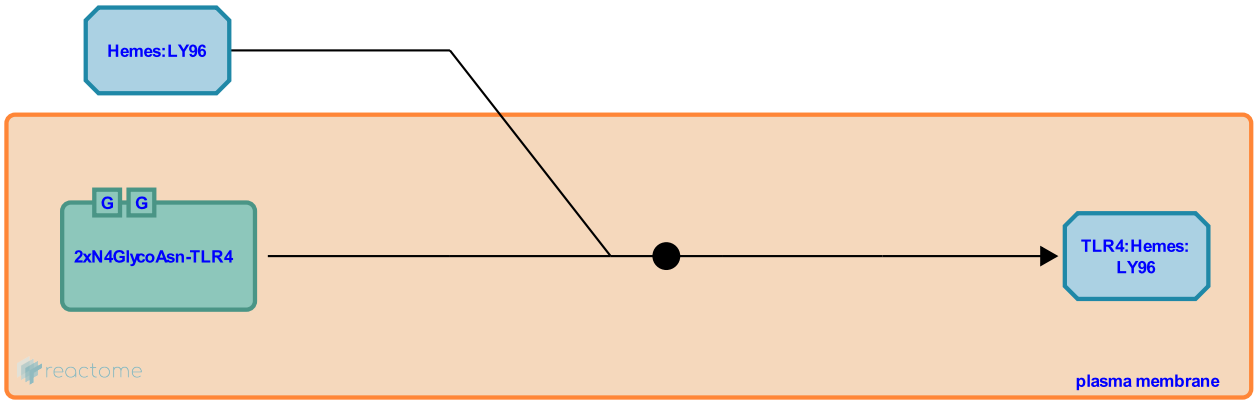
Hemes:LY96 activates TLR4 ↗

Location: Heme signaling

Stable identifier: R-HSA-9707659

Type: binding

Compartments: plasma membrane, extracellular region



Hemes bind and activate TLR4 signaling at amino acids W23 and Y34 on LY96 (MD-2) (Belcher et al, 2002).

Preceded by: Hemes bind LY96

Literature references

Belcher, JD., Nath, KA., Kiser, ZM., Nguyen, J., Trent, JO., Zhang, P. et al. (2020). Identification of a Heme Activation Site on the MD-2/TLR4 Complex. *Front Immunol, 11*, 1370. ↗

Editions

2020-11-12	Authored, Edited	Stephan, R.
2021-01-23	Reviewed	Somers, J.

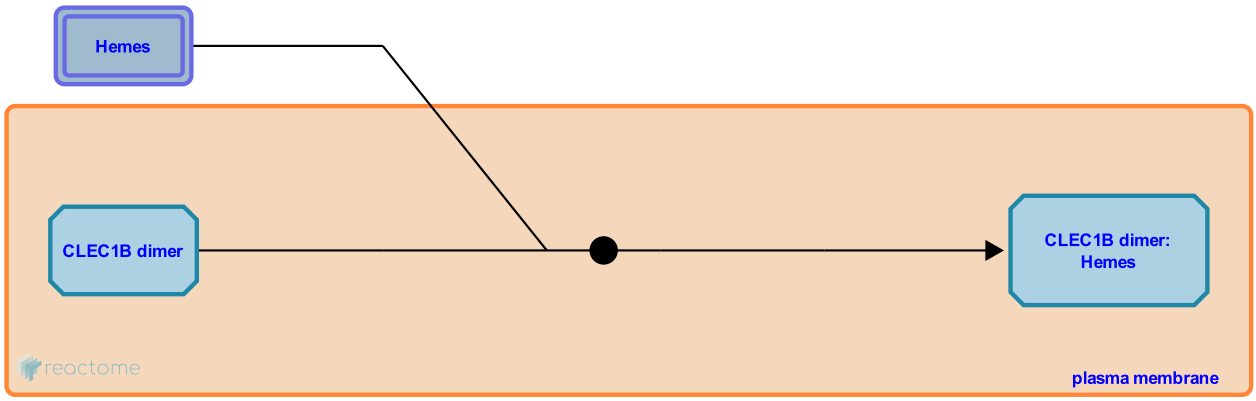
Hemes bind to CLEC1B dimer ↗

Location: Heme signaling

Stable identifier: R-HSA-9707505

Type: binding

Compartments: plasma membrane, extracellular region



Heme is an endogenous agonist for CLEC-2 (CLEC1B) leading to platelet activation through activation of integrin GPIIbIIIa at low concentrations and agglutination at high concentrations (Bourne et al, 2020).

Literature references

Rayes, J., Watson, SP., Roumenina, LT., Slater, A., Dimitrov, JD., Martin, E. et al. (2020). Heme induces human and mouse platelet activation through C-type-lectin-like receptor-2. *Haematologica*. ↗

Editions

2020-11-12	Authored, Edited	Stephan, R.
2021-01-23	Reviewed	Somers, J.

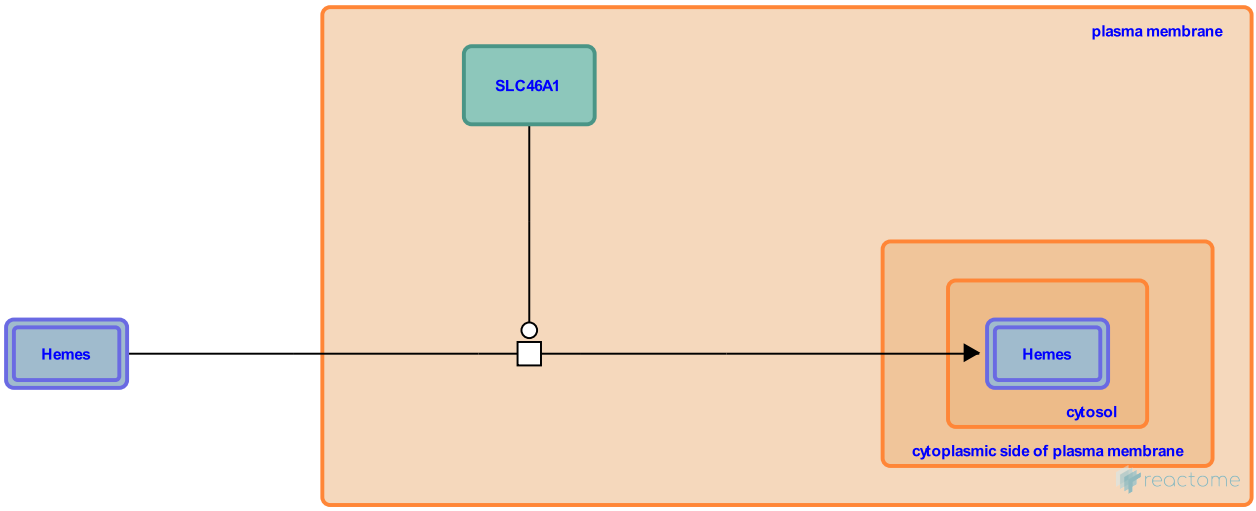
SLC46A1 transports hemes from extracellular region to cytosol ↗

Location: Heme signaling

Stable identifier: R-HSA-917870

Type: transition

Compartments: plasma membrane



Uptake of iron from meat happens mostly in the form of ferriheme (FeHM), and via the same transporter that is used for folate. The process is more effective than taking up iron ions (Shayeghi M et al, 2005). In general, heme transporters do not differentiate between ferroheme and ferriheme.

Literature references

Simpson, RJ., McKie, AT., Shayeghi, M., Latunde-Dada, GO., Laftah, AH., Halliday, N. et al. (2005). Identification of an intestinal heme transporter. *Cell, 122*, 789-801. ↗

Editions

2010-07-01	Authored	Stephan, R.
2010-07-30	Edited	Jassal, B.
2010-11-05	Reviewed	D'Eustachio, P.
2021-01-23	Reviewed	Somers, J.

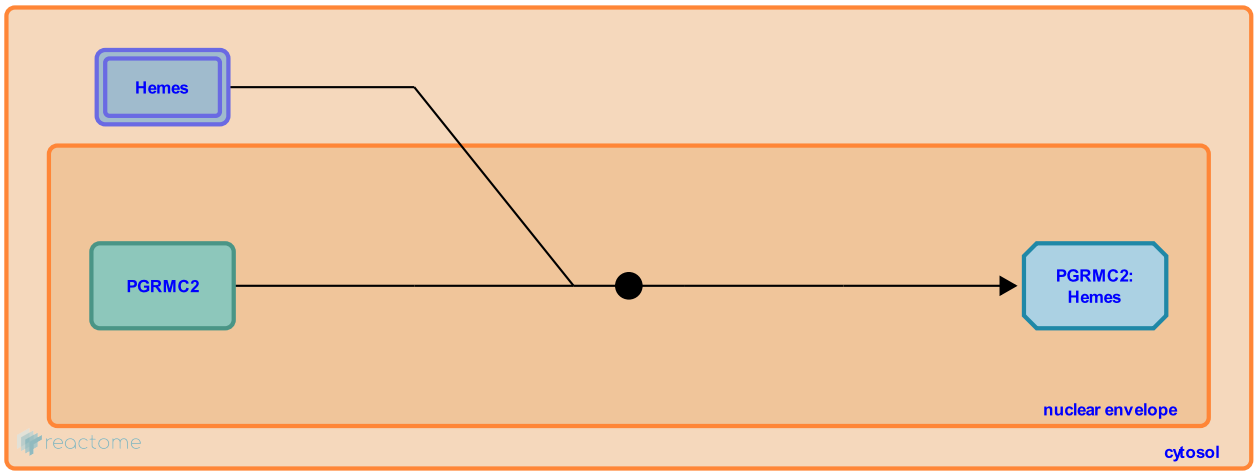
PGRMC2 binds Hemes ↗

Location: Heme signaling

Stable identifier: R-HSA-9707683

Type: binding

Compartments: nuclear envelope, cytosol



Mitochondria-bound PGRMC1 transfers heme to ER-bound PGRMC2, which delivers heme to proteins in the ER and nucleus, including heme-responsive transcription factors such as Rev-Erbα (Parker et al, 2017; Galmozzi et al, 2020).

Followed by: PGRMC2:Hemes translocate to the nucleus

Literature references

Cintron-Colon, R., Mosure, S., Kojetin, D., Montenegro-Burke, JR., Godio, C., Siuzdak, G. et al. (2019). PGRMC2 is an intracellular haem chaperone critical for adipocyte function. *Nature, 576*, 138-142. ↗

Sasaki, K., Correia, BE., Lawrence, RM., Joslyn, CM., Johnson, SR., Wang, Y. et al. (2017). Ligand and Target Discovery by Fragment-Based Screening in Human Cells. *Cell, 168*, 527-541.e29. ↗

Editions

2020-11-12	Authored, Edited	Stephan, R.
2021-01-23	Reviewed	Somers, J.

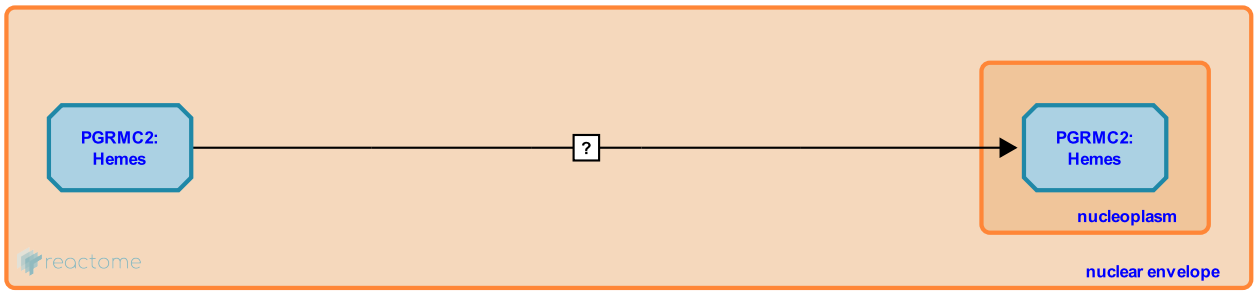
PGRMC2:Hemes translocate to the nucleus ↗

Location: Heme signaling

Stable identifier: R-HSA-9707606

Type: uncertain

Compartments: nuclear envelope, nucleoplasm



PGRMC2 binds heme reversibly. Also, PGRMC2 can bind to AAAS, a subunit of the nuclear pore complex, suggesting nuclear import of the PGRMC2:heme complex through the NPC takes place (Jühlen et al, 2016; Parker et al, 2017; Galmozzi et al 2020).

Preceded by: PGRMC2 binds Hemes

Followed by: Hemes bind to BACH1:MAFK, PGRMC2:Hemes dissociates

Literature references

Jühlen, R., Landgraf, D., Koehler, K., Huebner, A. (2016). Identification of a novel putative interaction partner of the nucleoporin ALADIN. *Biol Open, 5*, 1697-1705. ↗

Editions

2020-11-12	Authored, Edited	Stephan, R.
2021-01-23	Reviewed	Somers, J.

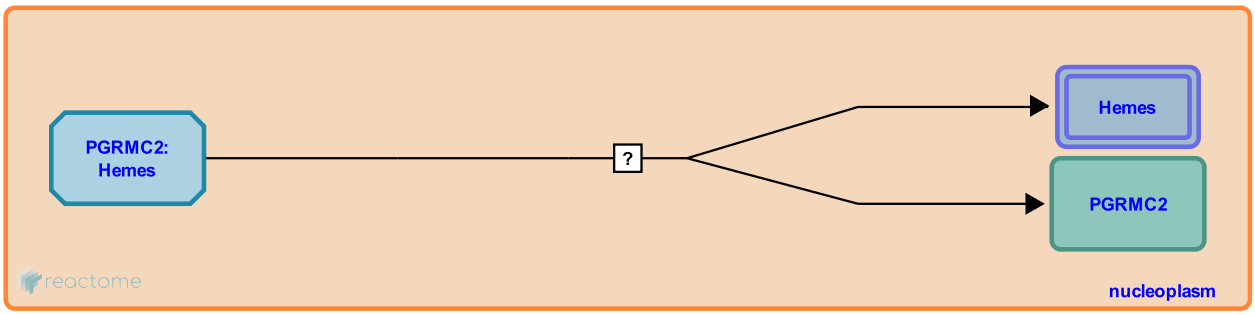
PGRMC2:Hemes dissociates ↗

Location: Heme signaling

Stable identifier: R-HSA-9707856

Type: uncertain

Compartments: nucleoplasm



Free heme behaves differently in the nucleus, in the absence of PGRMC2. This implies that heme may separate from the PGRMC2:heme complex. The exact conditions under which dissociation might occur are unknown (Galmozzi et al, 2019).

Preceded by: PGRMC2:Hemes translocate to the nucleus

Literature references

Cintron-Colon, R., Mosure, S., Kojetin, D., Montenegro-Burke, JR., Godio, C., Siuzdak, G. et al. (2019). PGRMC2 is an intracellular haem chaperone critical for adipocyte function. *Nature, 576*, 138-142. ↗

Editions

2020-11-20	Authored, Edited	Stephan, R.
2021-01-23	Reviewed	Somers, J.

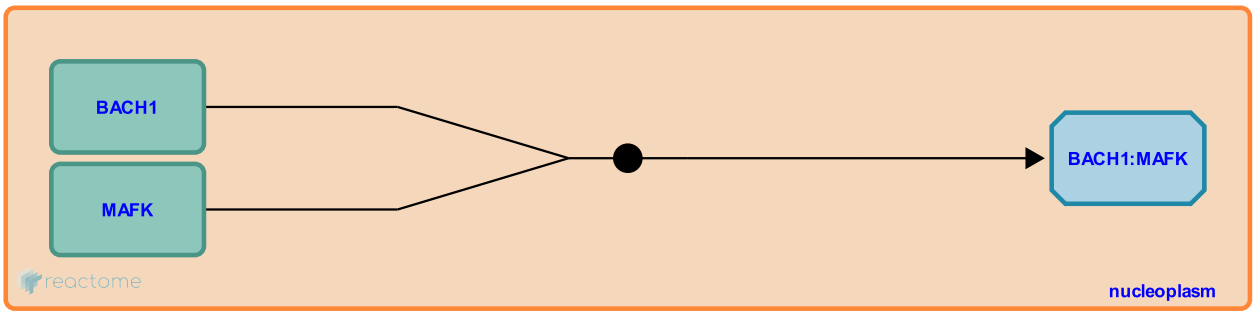
BACH1 binds MAFK ↗

Location: Heme signaling

Stable identifier: R-HSA-9707690

Type: binding

Compartments: nucleoplasm



Members of the small Maf family (MAFK, MAFF, and MAFG) can function as transcriptional activators or repressors, depending on the dimer compositions of their DNA binding forms. Transcription regulator protein BACH1 is a heterodimerization partner of MAFK (Oyake et al, 1996).

Followed by: Hemes bind to BACH1:MAFK, HMOX1 gene produces HMOX1 dimer

Literature references

Yamamoto, M., Motohashi, H., Oyake, T., Hayashi, N., Igarashi, K., Itoh, K. et al. (1996). Bach proteins belong to a novel family of BTB-basic leucine zipper transcription factors that interact with MafK and regulate transcription through the NF-E2 site. *Mol Cell Biol, 16*, 6083-95. ↗

Editions

2020-11-12	Authored, Edited	Stephan, R.
2021-01-23	Reviewed	Somers, J.

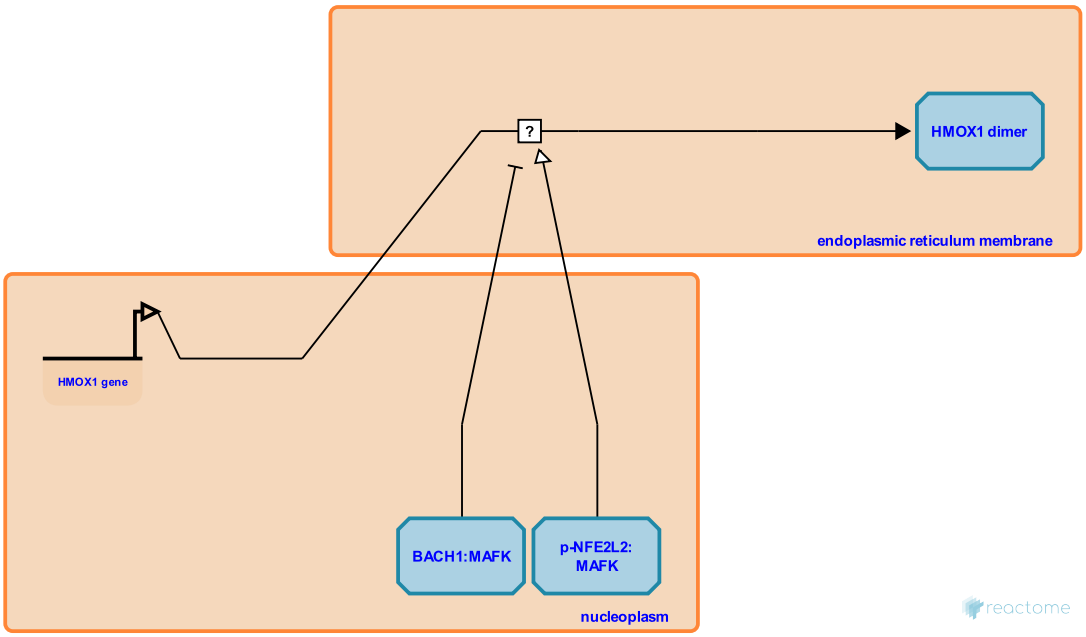
HMOX1 gene produces HMOX1 dimer ↗

Location: Heme signaling

Stable identifier: R-HSA-9707645

Type: uncertain

Compartments: endoplasmic reticulum membrane, nucleoplasm



Transcription regulator protein BACH1 is a critical physiological repressor of heme oxygenase 1 (HMOX1). BACH1 binds to the multiple Maf recognition elements (MAREs) of HMOX1 enhancer MafK in vitro and represses its activity in vivo. BACH1 is inducible by hypoxia and IFN-gamma (Kitamuro et al, 2003; Sun et al, 2002).

NFE2L2 (nuclear factor erythroid 2-related factor 2) is a transcription factor that activates transcription of a battery of cytoprotective genes by binding to the ARE (antioxidant response element). It is considered not only as a cytoprotective factor regulating the expression of genes coding for anti-oxidant, anti-inflammatory and detoxifying proteins, but it is also a powerful modulator of species longevity. HMOX1 is one of the genes whose expression it activates (Huang et al, 2000; Reichard et al, 2007).

Preceded by: BACH1 binds MAFK

Literature references

Sun, J., Muto, A., Takaku, K., Suzuki, H., Takahashi, S., Taketo, MM. et al. (2002). Hemoprotein Bach1 regulates enhancer availability of heme oxygenase-1 gene. *EMBO J, 21,* 5216-24. ↗

Sun, J., Takeda, K., Shirato, K., Nakayama, M., Shibahara, S., Fujita, H. et al. (2003). Bach1 functions as a hypoxia-inducible repressor for the heme oxygenase-1 gene in human cells. *J Biol Chem, 278*, 9125-33. ↗

Editions

2020-11-12	Authored, Edited	Stephan, R.
2021-01-23	Reviewed	Somers, J.
2022-02-23	Reviewed	Cuadrado, A.
2022-02-24	Revised	Rothfels, K.

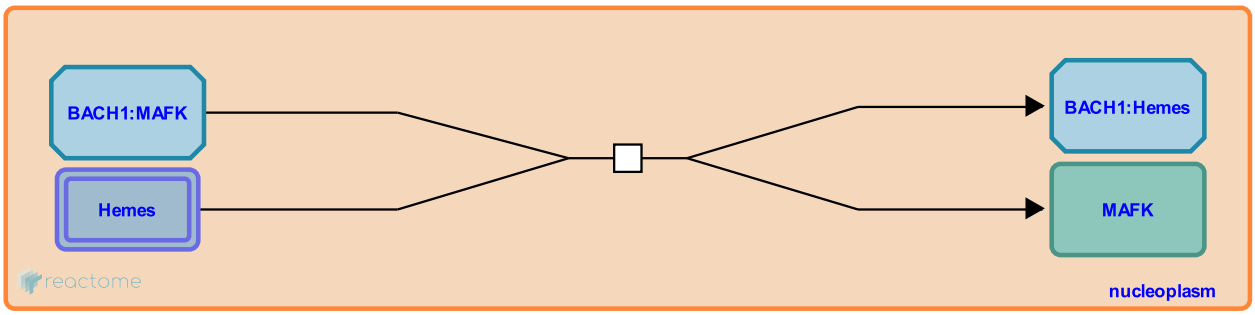
Hemes bind to BACH1:MAFK ↗

Location: Heme signaling

Stable identifier: R-HSA-9707523

Type: transition

Compartments: nucleoplasm



Heme binds to four cysteine-proline motifs in the C-terminal region of BACH1 and inhibits the DNA-binding activity of BACH1-MAFK heterodimers resulting in HMOX1 induction. MAFK separates from the complex, and heme recruits nuclear exporters for BACH1 (Yoshida et al, 1988; Ogawa et al, 2001; Suzuki et al, 2004).

Preceded by: BACH1 binds MAFK, PGRMC2:Hemes translocate to the nucleus

Followed by: XPO1 (CRM1) binds to BACH1:Hemes

Literature references

Nishitani, C., Sassa, S., Nakajima, O., Taketani, S., Shibahara, S., Yamamoto, M. et al. (2001). Heme mediates derepression of Maf recognition element through direct binding to transcription repressor Bach1. *EMBO J, 20*, 2835-43. ↗

Yoshida, T., Müller, RM., Biro, P., Shibahara, S., Cohen, T. (1988). Human heme oxygenase cDNA and induction of its mRNA by hemin. *Eur J Biochem, 171*, 457-61. ↗

Sun, J., Hira, S., Yamazaki, C., Yoshida, M., Igarashi, K., Ikeda-Saito, M. et al. (2004). Heme regulates gene expression by triggering Crm1-dependent nuclear export of Bach1. *EMBO J, 23*, 2544-53. ↗

Editions

2020-11-12	Authored, Edited	Stephan, R.
2021-01-23	Reviewed	Somers, J.

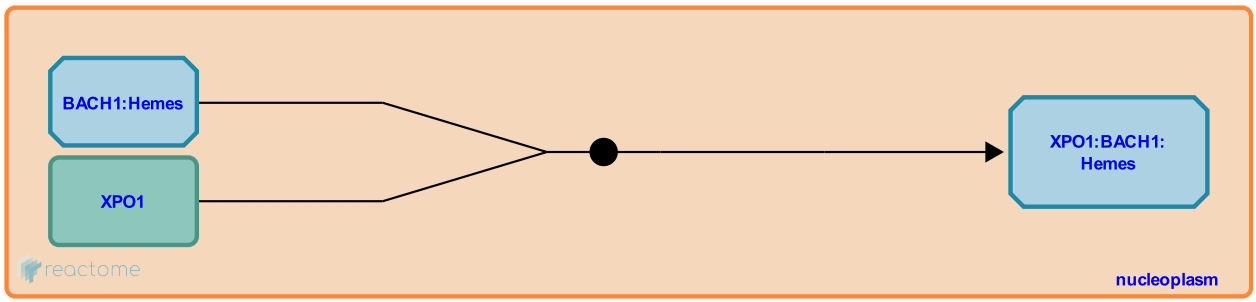
XPO1 (CRM1) binds to BACH1:Hemes ↗

Location: Heme signaling

Stable identifier: R-HSA-9708430

Type: binding

Compartments: nucleoplasm



A small but significant fraction of XPO1 (CRM1) binds to BACH1. Several cysteine–proline (CP) dipeptide sequence in BACH1 are involved in heme binding, they also contain a nuclear export signal. The simplest model is that this region is involved in a heme-regulated interaction with XPO1 that mediates nuclear export. While XPO1 bound to BACH1 in GST pull-down assays, the nature of this interaction has yet to be extensively characterized (Suzuki et al, 2004).

Preceded by: Hemes bind to BACH1:MAFK

Followed by: XPO1:BACH1:Hemes are transported out of the nucleus

Literature references

Sun, J., Hira, S., Yamazaki, C., Yoshida, M., Igarashi, K., Ikeda-Saito, M. et al. (2004). Heme regulates gene expression by triggering Crm1-dependent nuclear export of Bach1. *EMBO J, 23*, 2544-53. ↗

Editions

2020-11-23	Authored, Edited	Stephan, R.
2021-01-23	Reviewed	Somers, J.

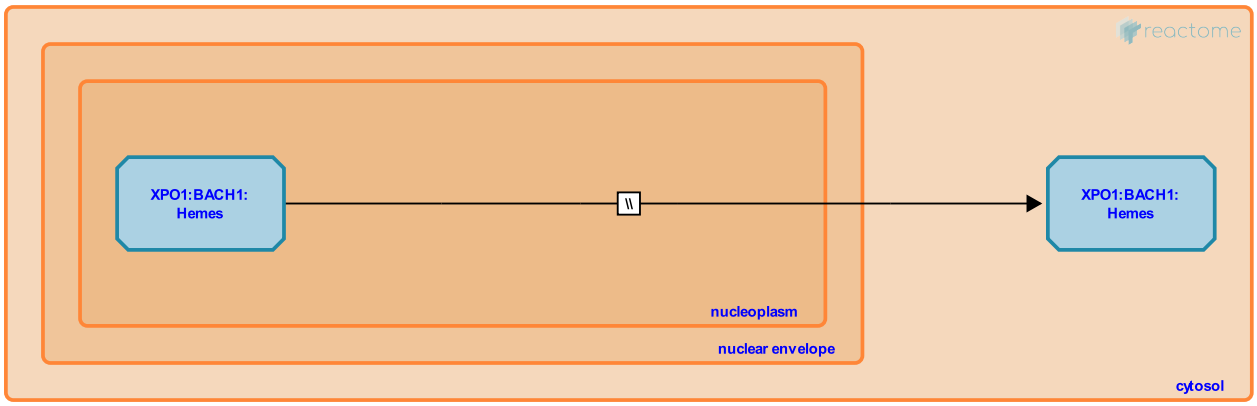
XPO1:BACH1:Hemes are transported out of the nucleus ↗

Location: Heme signaling

Stable identifier: R-HSA-9708423

Type: omitted

Compartments: nucleoplasm, cytosol



Heme regulates transcription by affecting the nucleocytoplasmic shuttling of nuclear protein. Inhibition of heme synthesis enhances the nuclear accumulation of BACH1, whereas treating cells with hemin results in nuclear exclusion of BACH1. A specific region on BACH1 functions as a heme-regulated NES dependent on the exporter Crm1 (XPO1) (Suzuki et al, 2004).

Preceded by: XPO1 (CRM1) binds to BACH1:Hemes

Literature references

Sun, J., Hira, S., Yamazaki, C., Yoshida, M., Igarashi, K., Ikeda-Saito, M. et al. (2004). Heme regulates gene expression by triggering Crm1-dependent nuclear export of Bach1. *EMBO J, 23*, 2544-53. ↗

Editions

2020-11-23	Authored, Edited	Stephan, R.
2021-01-23	Reviewed	Somers, J.

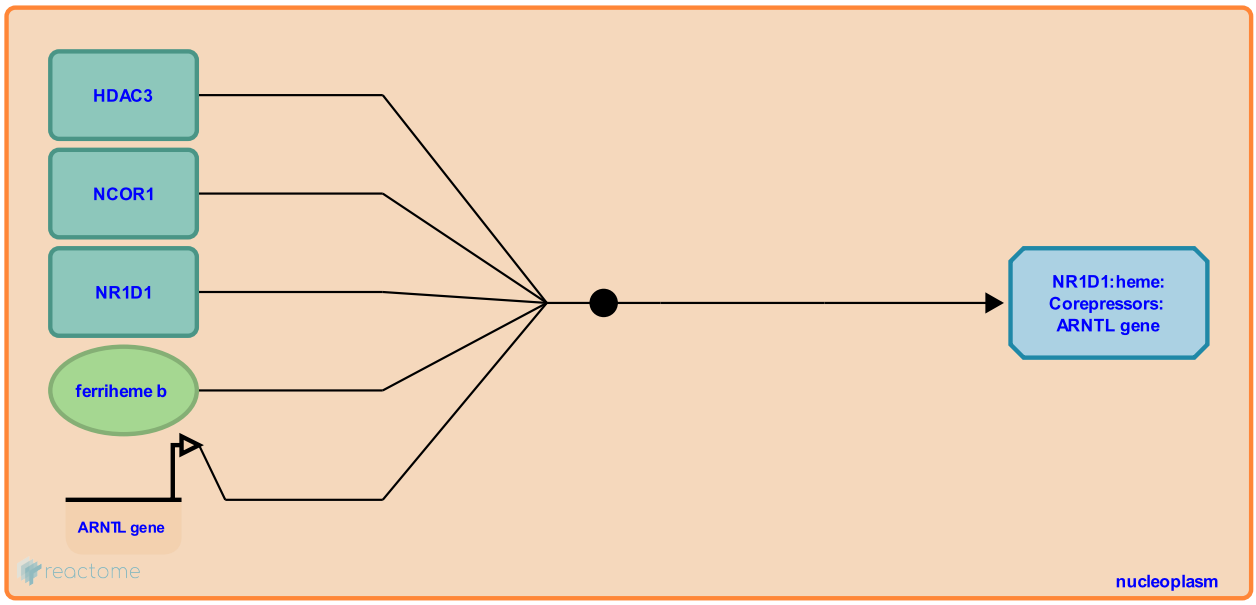
NR1D1 (REV-ERBA) binds heme, the ARNTL gene, and recruits corepressors.

Location: Heme signaling

Stable identifier: R-HSA-1368069

Type: binding

Compartments: nucleoplasm



NR1D1 (REV-ERBA) binds heme. The NR1D1:heme complex is then able to recruit the corepressors NCoR and HDAC3. Corepressors do not bind NR1D1 in the absence of heme. NR1D1:heme binds a RRE element in the promoter of the ARNTL (BMAL1) gene, recruits corepressors, and represses transcription.

Preceded by: Expression of NR1D1 (REV-ERBA)

Literature references

Lazar, MA., Nolte, RT., Broderick, TM., Phelan, CA., Williams, SP., Hu, X. et al. (2010). Structure of Rev-erbalpha bound to N-CoR reveals a unique mechanism of nuclear receptor-co-repressor interaction. *Nat Struct Mol Biol, 17* , 808-14.

Lazar, MA., Waitt, GM., Qatanani, M., Curtin, JC., Pearce, KH., Parks, DJ. et al. (2007). Rev-erbalpha, a heme sensor that coordinates metabolic and circadian pathways. *Science, 318*, 1786-9.

Burris, LL., Khorasanizadeh, S., Huang, P., McClure, DB., Stayrook, KR., Burris, TP. et al. (2007). Identification of heme as the ligand for the orphan nuclear receptors REV-ERBalpha and REV-ERBbeta. *Nat Struct Mol Biol, 14*, 1207-13.

Lazar, MA., Yin, L. (2005). The orphan nuclear receptor Rev-erbalpha recruits the N-CoR/histone deacetylase 3 corepressor to regulate the circadian Bmal1 gene. *Mol Endocrinol, 19*, 1452-9.

Editions

2011-06-22	Authored, Edited	May, B.
2012-01-28	Reviewed	Delaunay, F.
2021-01-23	Reviewed	Somers, J.

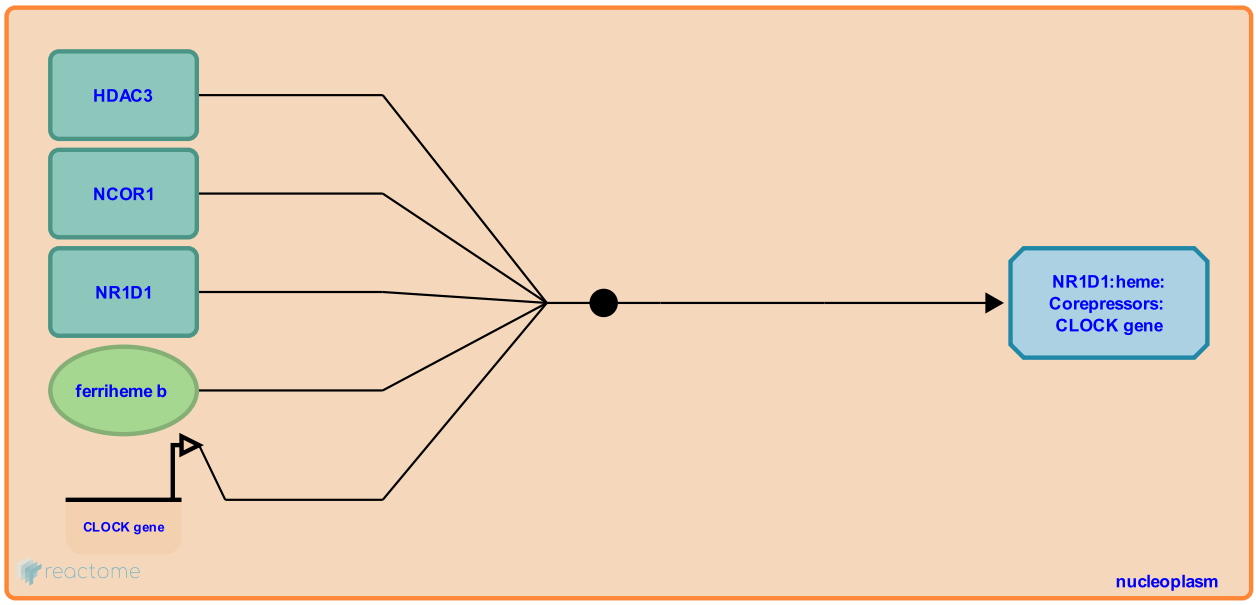
NR1D1 (REV-ERBA) binds heme, the CLOCK gene, and recruits corepressors ↗

Location: Heme signaling

Stable identifier: R-HSA-5663271

Type: binding

Compartments: nucleoplasm



NR1D1 (REV-ERBA) binds the promoter of the CLOCK gene and recruits corepressors to repress transcription. Recruitment of repressors appears to depend on the binding of heme by NR1D1.

Preceded by: Expression of NR1D1 (REV-ERBA)

Literature references

Crumbley, C., Burris, TP. (2011). Direct regulation of CLOCK expression by REV-ERB. *PLoS One, 6,* e17290. ↗

Editions

2012-01-28	Reviewed	Delaunay, F.
2015-01-16	Authored, Edited	May, B.
2021-01-23	Reviewed	Somers, J.

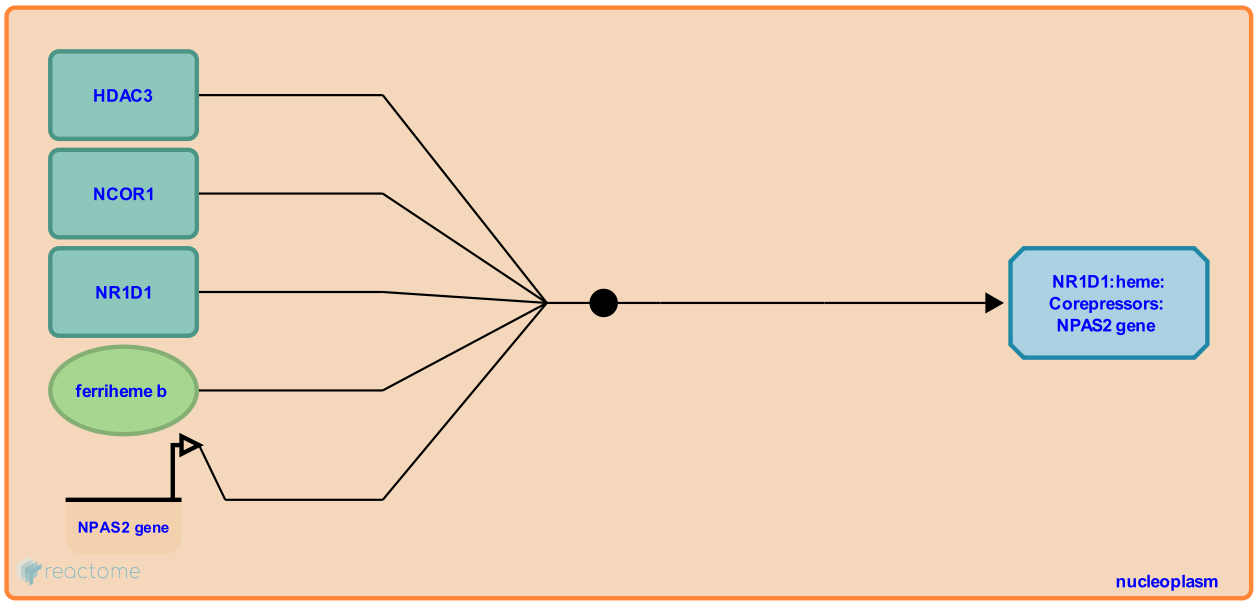
NR1D1 (REV-ERBA) binds heme, the NPAS2 gene, and recruits corepressors ↗

Location: Heme signaling

Stable identifier: R-HSA-5663245

Type: binding

Compartments: nucleoplasm



NR1D1 (REV-ERBA) binds the promoter of the NPAS2 gene and recruits corepressors to repress transcription. Recruitment of repressors appears to depend on the binding of heme by NR1D1.

Preceded by: Expression of NR1D1 (REV-ERBA)

Literature references

Kojetin, DJ., Crumbley, C., Burris, TP., Wang, Y. (2010). Characterization of the core mammalian clock component, NPAS2, as a REV-ERBalpha/RORalpha target gene. *J Biol Chem, 285*, 35386-92. ↗

Editions

2012-01-28	Reviewed	Delaunay, F.
2015-01-16	Authored, Edited	May, B.
2021-01-23	Reviewed	Somers, J.

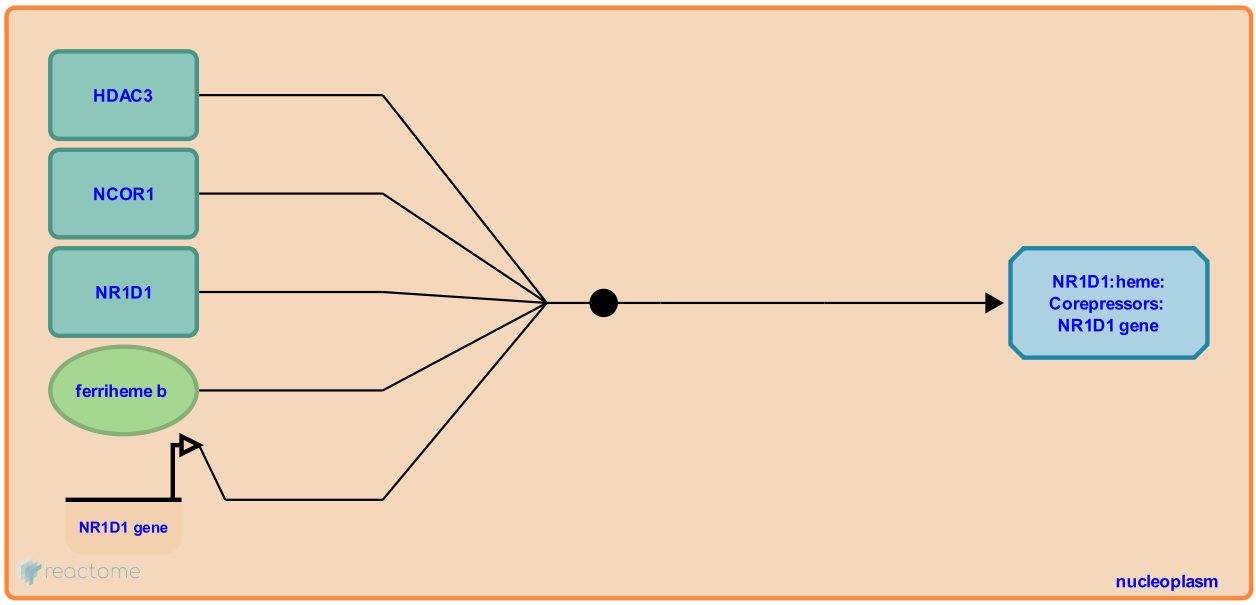
NR1D1 (REV-ERBA) binds heme, the NR1D1 gene, and recruits corepressors ↗

Location: Heme signaling

Stable identifier: R-HSA-5663265

Type: binding

Compartments: nucleoplasm



NR1D1 (REV-ERBA) binds its own promoter and represses its own expression.

Preceded by: Expression of NR1D1 (REV-ERBA)

Literature references

Stéhelin, D., Adelmant, G., Laudet, V., Bègue, A. (1996). A functional Rev-erb alpha responsive element located in the human Rev-erb alpha promoter mediates a repressing activity. *Proc Natl Acad Sci U S A, 93*, 3553-8. ↗

Editions

2012-01-28	Reviewed	Delaunay, F.
2015-01-16	Authored, Edited	May, B.
2021-01-23	Reviewed	Somers, J.

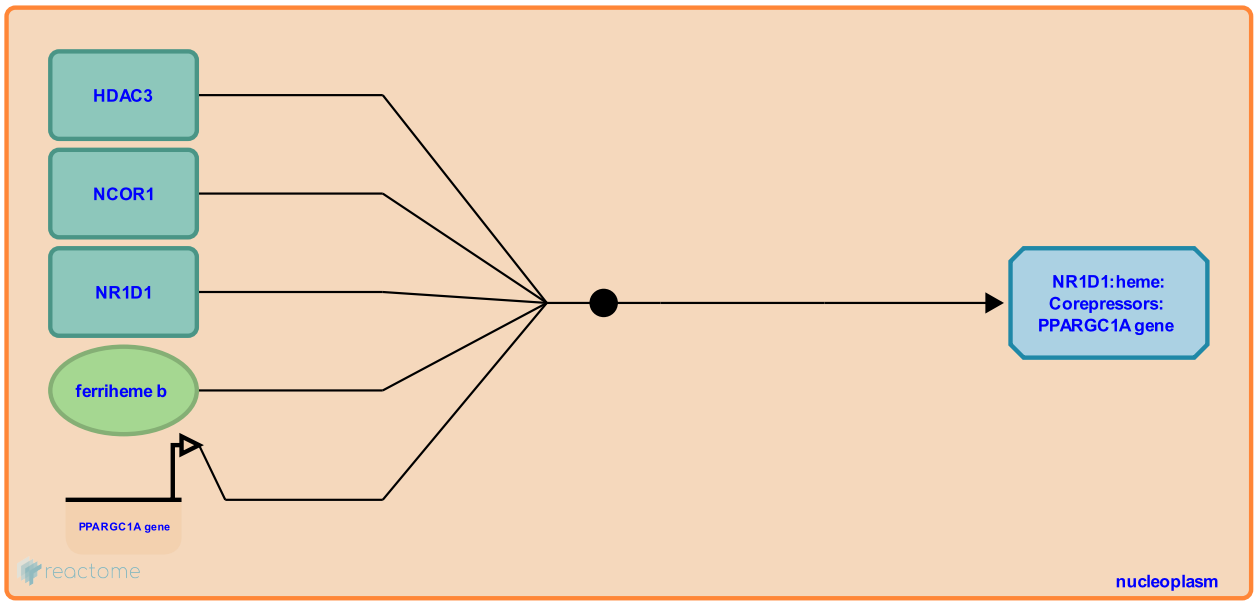
NR1D1 (REV-ERBA) binds heme, the PPARGC1A gene, and recruits corepressors ↗

Location: Heme signaling

Stable identifier: R-HSA-5663258

Type: binding

Compartments: nucleoplasm



NR1D1 (REV-ERBA) binds heme and the promoter of the PGC-1alpha (PPARGC1A) gene. The REV-ERBA:heme complex recruits the corepressors NCoR and HDAC3 and represses transcription.

Preceded by: Expression of NR1D1 (REV-ERBA)

Literature references

Lazar, MA., Yin, L., Wu, N., Hanniman, EA., Joshi, S. (2009). Negative feedback maintenance of heme homeostasis by its receptor, Rev-erbalpha. *Genes Dev, 23*, 2201-9. ↗

Editions

2012-01-28	Reviewed	Delaunay, F.
2015-01-16	Authored, Edited	May, B.
2021-01-23	Reviewed	Somers, J.

Expression of ARNTL (BMAL1)

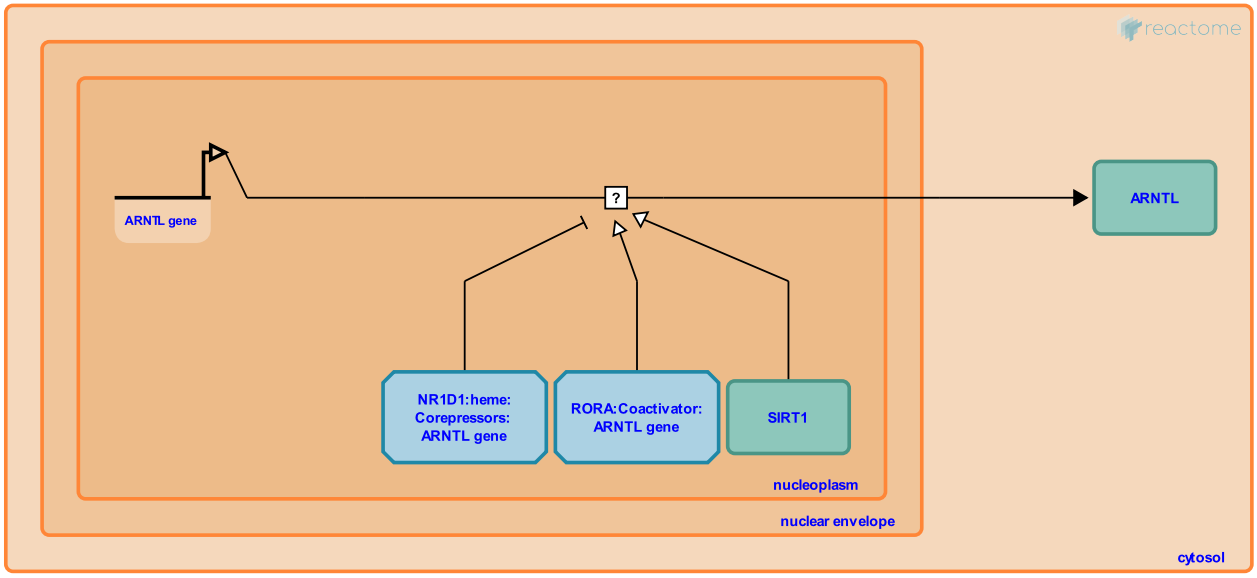
Location: Heme signaling

Stable identifier: R-HSA-400342

Type: uncertain

Compartments: nucleoplasm, cytosol

Inferred from: Expression of Bmal1 (Arntl) (Mus musculus)



NR1D1 (REV-ERBA) binds to the same site in the promoter of the BMAL1 (ARNTL) gene as ROR-alpha (RORA). Whereas ROR-alpha activates transcription of BMAL1, REV-ERBA bound to heme recruits corepressors (NCoR and HDAC3) and inhibits transcription of BMAL1. Both REV-ERBA and ROR-alpha genes are targets of BMAL1:CLOCK/NPAS2 transactivation and they show alternating patterns of maximum protein levels, thus they give BMAL1 transcription circadian expression.
As inferred from mouse, RORA binds RRE DNA elements and recruits the coactivators PGC-1alpha (PPARGC1A), p300 (EP300, a histone acetylase), and NRIP1. Activation of BMAL1 (ARNTL) expression by ROR-alpha (RORA) is inferred from mouse. In mouse, Rora together with coactivators Ep300 and Ppargc1a bind the promoter of Bmal1 and activate transcription.
The ARNTL (BMAL1) gene is transcribed to yield mRNA and the mRNA is translated to yield ARNTL protein (Hogenesch et al. 1997, Ikeda et al. 1997, also inferred from mouse homologs). The ROR-alpha transcription factor binds the RORE element of the BMAL1 (ARNTL) promoter and activates transcription of the BMAL1 gene. The REV-ERBA transcription factor binds the same RORE element and represses transcription of the BMAL1 gene.

Literature references

Nomura, M., Ikeda, M. (1997). cDNA cloning and tissue-specific expression of a novel basic helix-loop-helix/PAS protein (BMAL1) and identification of alternatively spliced variants with alternative translation initiation site usage. *Biochem Biophys Res Commun, 233*, 258-64.

Pray-Grant, M., Perdew, GH., Jackiw, VH., Hogenesch, JB., Brown, RC., Chan, WK. et al. (1997). Characterization of a subset of the basic-helix-loop-helix-PAS superfamily that interacts with components of the dioxin signaling pathway. *J Biol Chem, 272*, 8581-93.

Editions

2009-05-18	Authored	May, B.
2009-05-27	Reviewed	D'Eustachio, P.
2009-06-02	Edited	May, B.
2010-06-23	Reviewed	Hirota, T., Kay, SA., Delaunay, F., Albrecht, U.
2021-01-23	Reviewed	Somers, J.

Expression of CLOCK ↗

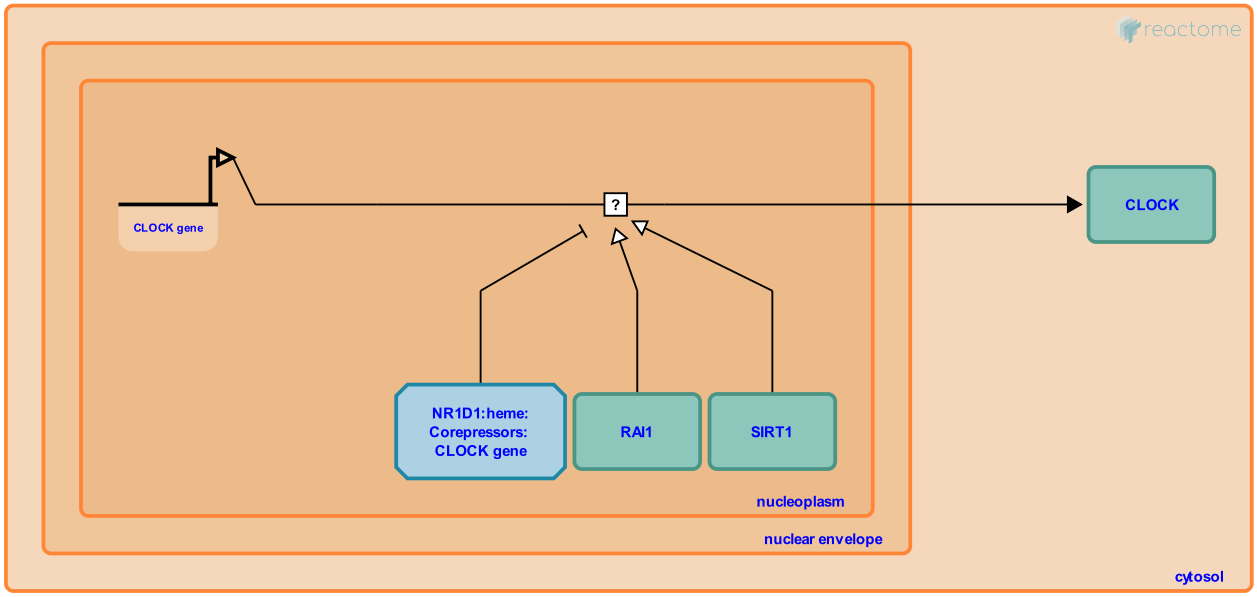
Location: Heme signaling

Stable identifier: R-HSA-1368119

Type: uncertain

Compartments: nucleoplasm, cytosol

Inferred from: Expression of Clock (Mus musculus)



The CLOCK gene is transcribed to yield mRNA and the mRNA is translated to yield CLOCK protein (Steeves et al. 1999, Ueda et al. 2005, also inferred from mouse homologs). Transcription of CLOCK is repressed by REV-ERBA. The promoter of CLOCK contains an RRE element that may bind REV-ERBA and RORA.
Inferred from mouse homologs, RAI1 increases transcription of the CLOCK gene (Williams et al. 2012).

Literature references

Hayashi, S., Hashimoto, S., Iino, M., Chen, W., Machida, M., Shigeyoshi, Y. et al. (2005). System-level identification of transcriptional circuits underlying mammalian circadian clocks. *Nat. Genet., 37*, 187-92. ↗

Bowcock, AM., Zhao, Y., Sangoram, AM., Moore, RY., King, DP., Du, F. et al. (1999). Molecular cloning and characterization of the human CLOCK gene: expression in the suprachiasmatic nuclei. *Genomics, 57*, 189-200. ↗

Editions

2011-06-22	Authored, Edited	May, B.
2012-01-28	Reviewed	Delaunay, F.
2021-01-23	Reviewed	Somers, J.

Expression of NPAS2 ↗

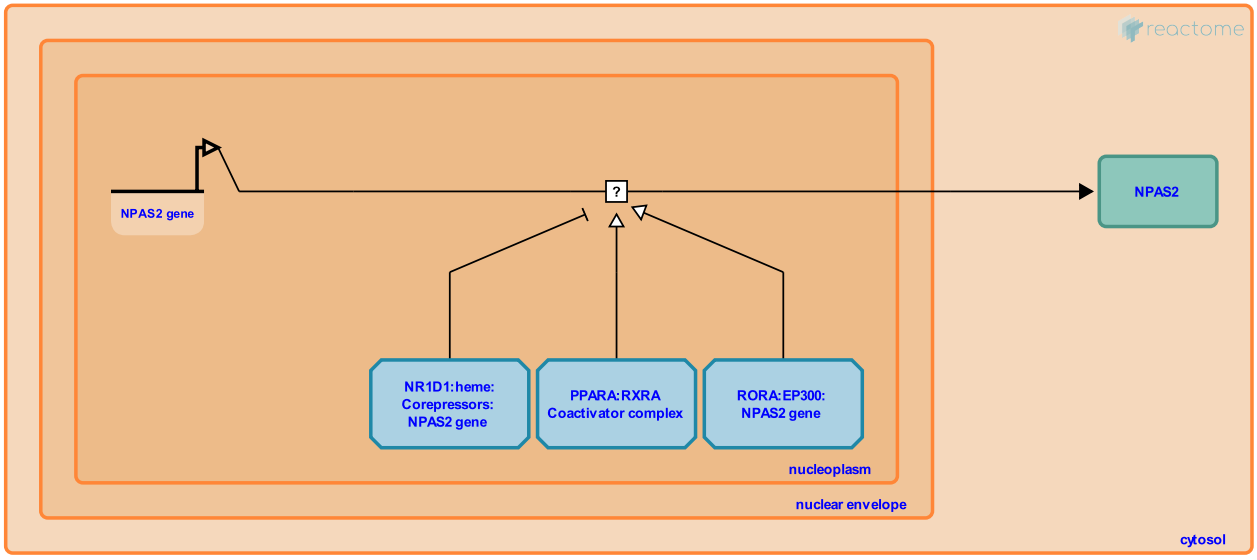
Location: Heme signaling

Stable identifier: R-HSA-1368065

Type: uncertain

Compartments: nucleoplasm, cytosol

Inferred from: Expression of Npas2 (Mus musculus)



The NPAS2 gene is transcribed to yield mRNA and the mRNA is transcribed to yield NPAS2 protein (Zhou et al. 1997, Matsumura et al. 2013, also inferred from mouse homologs). Transcription of NPAS2 is enhanced by the RORA:Coactivator complex and repressed by the REV-ERBA:Corepressor complex.
As inferred from mouse, RORA binds RRE DNA elements and recruits the coactivators PGC-1alpha (PPARGC1A) and p300 (EP300, a histone acetylase). As inferred from mouse, ROR-alpha binds the promoter of the NPAS2 gene and enhances transcription.

Literature references

Ring, HZ., Barnard, M., Russell, DW., Li, X., Richardson, J., Francke, U. et al. (1997). Molecular characterization of two mammalian bHLH-PAS domain proteins selectively expressed in the central nervous system. *Proc Natl Acad Sci U S A, 94*, 713-8. ↗

Node, K., Akashi, M., Matsubara, C., Takumi, T., Matsumura, R. (2013). Nuclear receptor-mediated cell-autonomous oscillatory expression of the circadian transcription factor, neuronal PAS domain protein 2 (NPAS2). *J. Biol. Chem., 288*, 36548-53. ↗

Editions

2009-06-08	Reviewed	Kersten, S.
2011-06-22	Authored, Edited	May, B.
2012-01-28	Reviewed	Delaunay, F.
2021-01-23	Reviewed	Somers, J.

Expression of NR1D1 (REV-ERBA) ↗

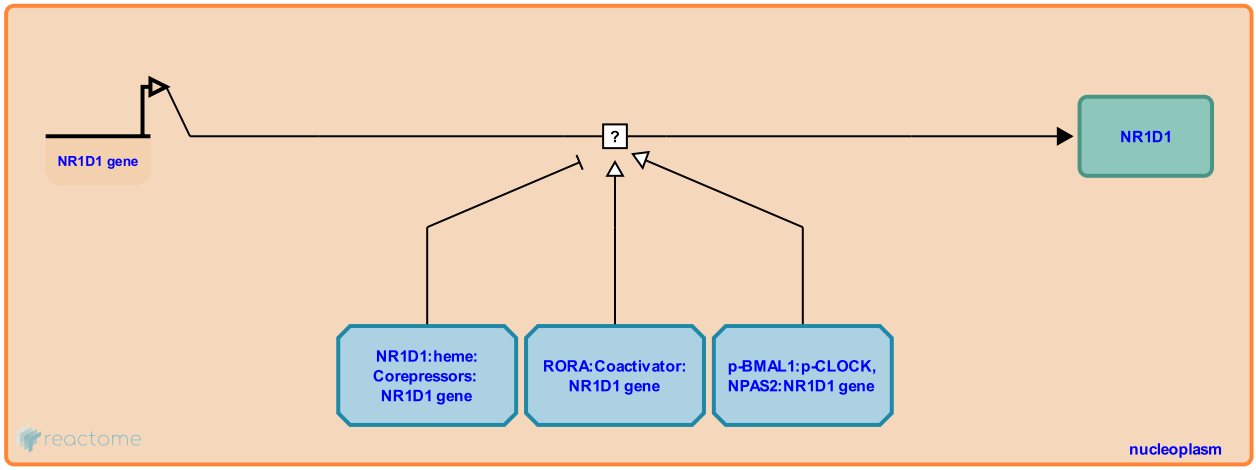
Location: Heme signaling

Stable identifier: R-HSA-549475

Type: uncertain

Compartments: nucleoplasm

Inferred from: Expression of Nr1d1 (Rev-erba) (Mus musculus)



The NR1D1 (REV-ERBA) gene is transcribed to yield mRNA and the mRNA is translated to yield NR1D1 protein (Miyajima et al. 1989, Adelmant et al. 1996, also inferred from mouse homologs). In mouse the Rev-erba gene shows circadian expression due to transactivation by the BMAL1:CLOCK (ARNTL:CLOCK) heterodimer. REV-ERBA binds the promoter of its own gene and represses its own expression (Adelmant et al. 1996).
Activation of NR1D1 (REV-ERBA) expression by phosphorylated BMAL1:CLOCK (ARNTL:CLOCK) is inferred from mouse. NPAS2 is predicted to act redundantly with CLOCK.
As inferred from mouse, RORA binds RRE DNA elements and recruits the coactivators PGC-1alpha (PPARGC1A) and p300 (EP300, a histone acetylase). RORA binds the NR1D1 (REV-ERBA) promoter and activates transcription.

Followed by: NR1D1 (REV-ERBA) binds heme, the NR1D1 gene, and recruits corepressors, NR1D1 (REV-ERBA) binds heme, the CLOCK gene, and recruits corepressors, NR1D1 (REV-ERBA) binds heme, the NPAS2 gene, and recruits corepressors, NR1D1 (REV-ERBA) binds heme, the ARNTL gene, and recruits corepressors., NR1D1 (REV-ERBA) binds heme, the PPARGC1A gene, and recruits corepressors

Literature references

Stéhelin, D., Adelmant, G., Laudet, V., Bègue, A. (1996). A functional Rev-erb alpha responsive element located in the human Rev-erb alpha promoter mediates a repressing activity. *Proc Natl Acad Sci U S A, 93*, 3553-8. ↗

Yamamoto, T., Miyajima, N., Fukushige, S., Matsubara, K., Toyoshima, K., Horiuchi, R. et al. (1989). Two erbA homologs encoding proteins with different T3 binding capacities are transcribed from opposite DNA strands of the same genetic locus. *Cell, 57*, 31-9. ↗

Editions

2009-05-27	Reviewed	D'Eustachio, P.
2010-03-19	Authored, Edited	May, B.
2010-06-23	Reviewed	Hirota, T., Kay, SA., Delaunay, F., Albrecht, U.
2021-01-23	Reviewed	Somers, J.

Expression of PPARGC1A (PGC-1alpha) ↗

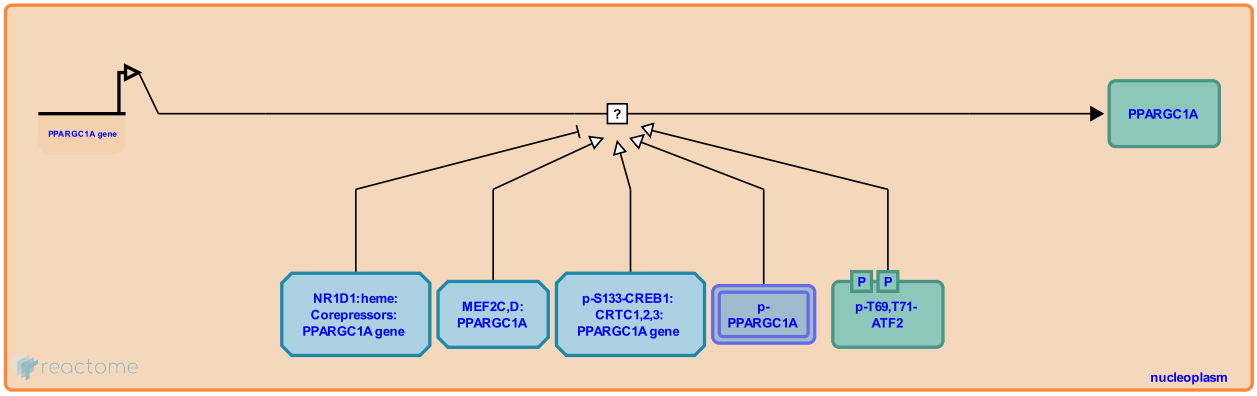
Location: Heme signaling

Stable identifier: R-HSA-1368140

Type: uncertain

Compartments: nucleoplasm

Inferred from: Expression of Ppargc1a (Pgc-1alpha) (Mus musculus)



The PPARGC1A gene is transcribed to yield mRNA and the mRNA is translated to yield PPARGC1A protein (Larrouy et al. 1999, Knutti et al. 2000, Pilegaard et al. 2003). PPARGC1A protein is located in the nucleus where it coactivates transcription.
As inferred from mouse homologs in liver (Herzig et al. 2001) and brown adipose tissue (Cao et al. 2004), phosphorylated CREB enhances expression of PPARGC1A (PGC-1alpha) (Handschin et al. 2003, Yoshioka et al. 2009). CRTC proteins (TORC proteins) coactivate the activation by CREB (Wu et al. 2006). CREB is phosphorylated in response to cAMP
As inferred from mouse, phosphorylated ATF2 binds the PGC-1alpha promoter and enhances expression (Cao et al. 2004, Akimoto et al. 2005, Wright et al. 2007, Akimoto et al. 2008). Intracellular calcium acting via p38 MAPK is believed to activate (phosphorylate) ATF2.
As inferred from mouse, MEF2C or MEF2D with PGC-1alpha activate expression of PGC-1alpha (Handschin et al. 2003).
NR1D1 (REV-ERBA) binds heme and the promoter of the PGC-1alpha (PPARGC1A) gene. The REV-ERBA:heme complex recruits the corepressors NCoR and HDAC3 and represses transcription.
PGC-1alpha (PPARGC1A) enhances expression of its own gene in mouse (Jager et al.2007) and in rat hepatocytes (Lin et al. 2003)

Literature references

Saltin, B., Pilegaard, H., Neufer, PD. (2003). Exercise induces transient transcriptional activation of the PGC-1alpha gene in human skeletal muscle. *J Physiol, 546*, 851-8. ↗

Kralli, A., Kaul, A., Knutti, D. (2000). A tissue-specific coactivator of steroid receptors, identified in a functional genetic screen. *Mol Cell Biol, 20*, 2411-22. ↗

Andreelli, F., Langin, D., Laville, M., Vidal, H., Larrouy, D. (1999). Cloning and mRNA tissue distribution of human PPARgamma coactivator-1. *Int J Obes Relat Metab Disord, 23*, 1327-32. ↗

Editions

2011-06-22	Authored, Edited	May, B.
2013-12-07	Reviewed	Lezza, AM.
2021-01-23	Reviewed	Somers, J.

Table of Contents