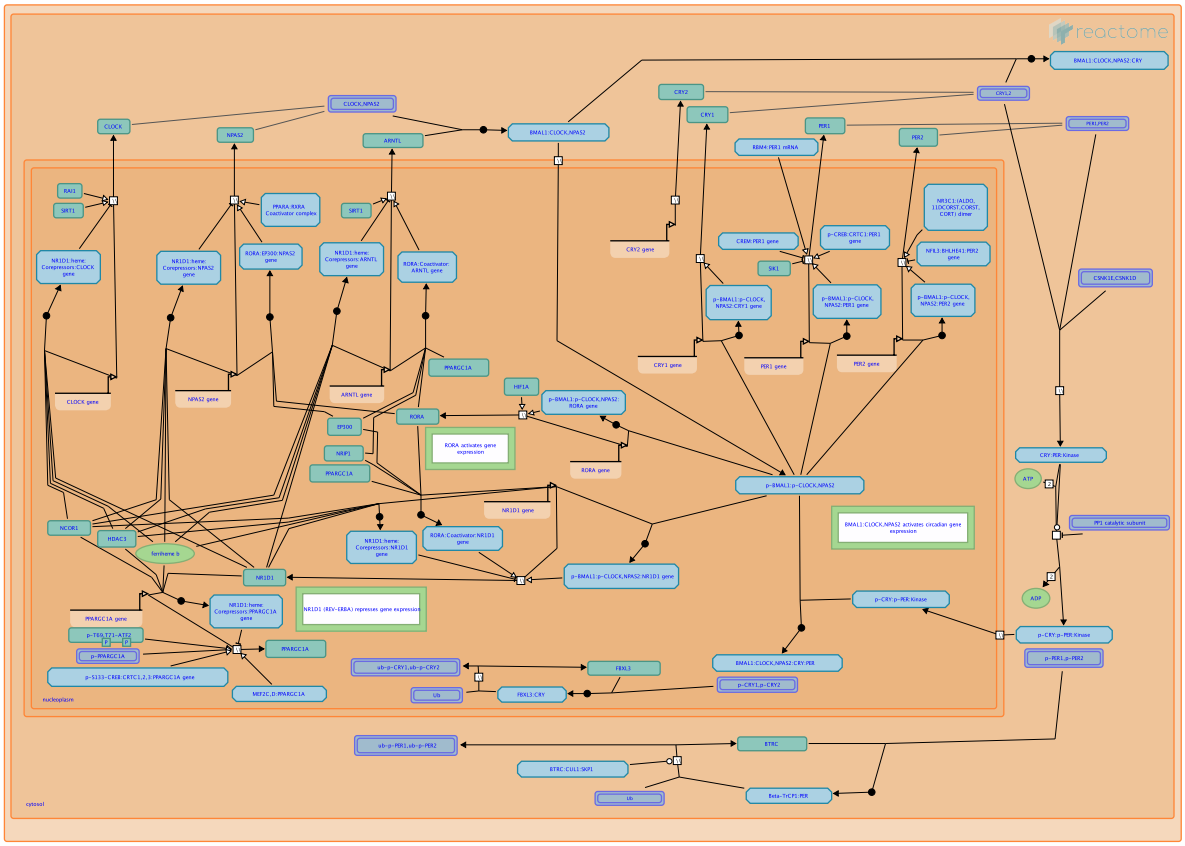
Circadian Clock



Albrecht, U., D'Eustachio, P., Delaunay, F., Hirota, T., Kay, SA., Kersten, S., Lezza, AM., May, B., Somers, J.

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07/09/2021

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

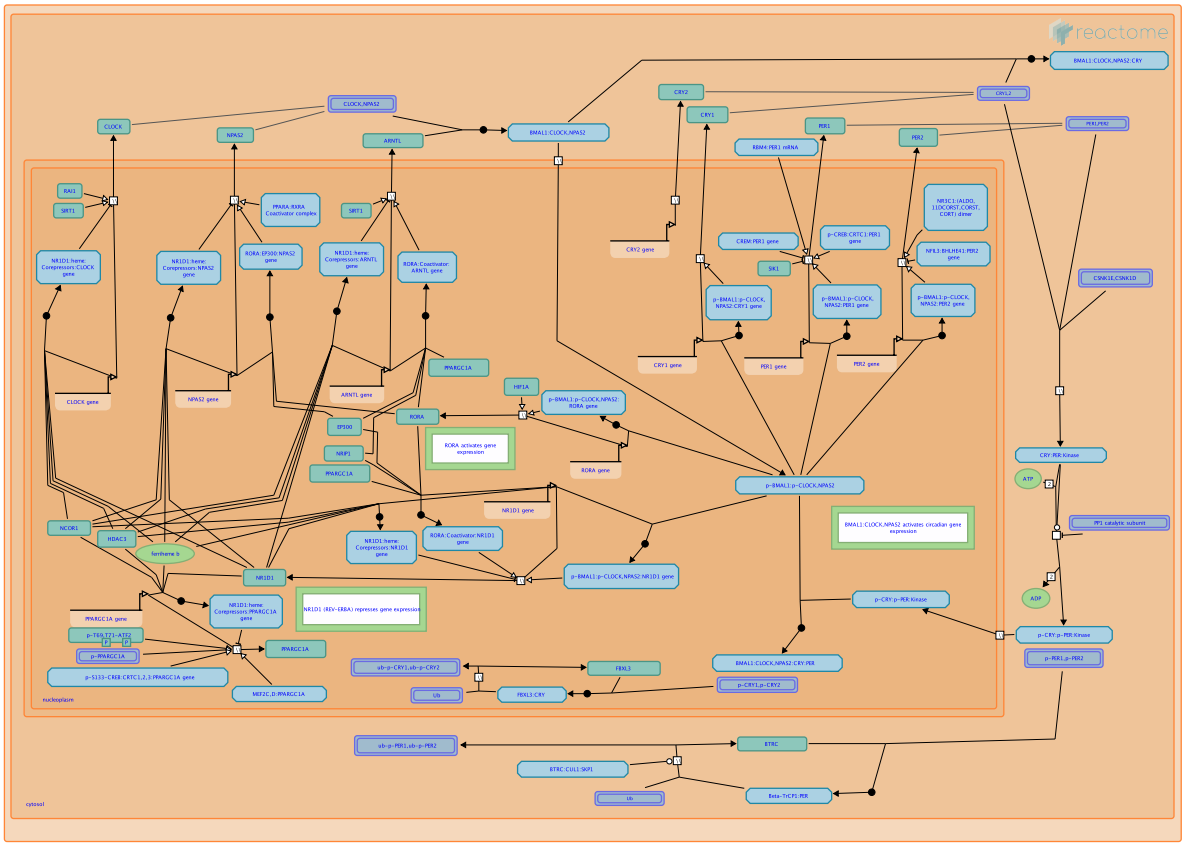
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Circadian Clock ↗

Stable identifier: R-HSA-400253

Compartments: nucleoplasm, cytosol



At the center of the mammalian circadian clock is a negative transcription/translation-based feedback loop: The BMAL1:CLOCK/NPAS2 (ARNTL:CLOCK/NPAS2) heterodimer transactivates CRY and PER genes by binding E-box elements in their promoters; the CRY and PER proteins then inhibit transactivation by BMAL1:CLOCK/NPAS2. BMAL1:CLOCK/NPAS2 activates transcription of CRY, PER, and several other genes in the morning. Levels of PER and CRY proteins rise during the day and inhibit expression of CRY, PER, and other BMAL1:CLOCK/NPAS2-activated genes in the afternoon and evening. During the night CRY and PER proteins are targeted for degradation by phosphorylation and polyubiquitination, allowing the cycle to commence again in the morning.

Transcription of the BMAL1 (ARNTL) gene is controlled by ROR-alpha and REV-ERBA (NR1D1), both of which are targets of BMAL1:CLOCK/NPAS2 in mice and both of which compete for the same element (RORE) in the BMAL1 promoter. ROR-alpha (RORA) activates transcription of BMAL1; REV-ERBA represses transcription of BMAL1. This mutual control forms a secondary, reinforcing loop of the circadian clock. REV-ERBA shows strong circadian rhythmicity and confers circadian expression on BMAL1.

BMAL1 can form heterodimers with either CLOCK or NPAS2, which act redundantly but show different tissue specificity. The BMAL1:CLOCK and BMAL1:NPAS2 heterodimers activate a set of genes that possess E-box elements (consensus CACGTG) in their promoters. This confers circadian expression on the genes. The PER genes (PER1, PER2, PER3) and CRY genes (CRY1, CRY2) are among those activated by BMAL1:CLOCK and BMAL1:NPAS2. PER and CRY mRNA accumulates during the morning and the proteins accumulate during the afternoon. PER and CRY proteins form complexes in the cytosol and these are bound by either CSNK1D or CSNK1E kinases which phosphorylate PER and CRY. The phosphorylated PER:CRY:kinase complex is translocated into the nucleus due to the nuclear localization signal of PER

and CRY. Within the nucleus the PER:CRY complexes bind BMAL1:CLOCK and BMAL1:NPAS2, inhibiting their transactivation activity and their phosphorylation. This reduces expression of the target genes of BMAL1:CLOCK and BMAL1:NPAS2 during the afternoon and evening.

PER:CRY complexes also traffic out of the nucleus into the cytosol due to the nuclear export signal of PER. During the night PER:CRY complexes are polyubiquitinated and degraded, allowing the cycle to begin again. Phosphorylated PER is bound by Beta-TrCP1, a cytosolic F-box type component of some SCF E3 ubiquitin ligases. CRY is bound by FBXL3, a nucleoplasmic F-box type component of some SCF E3 ubiquitin ligases. Phosphorylation of CRY1 by Adenosine monophosphate-activated kinase (AMPK) enhances degradation of CRY1. PER and CRY are subsequently polyubiquitinated and proteolyzed by the 26S proteasome.

The circadian clock is cell-autonomous and some, but not all cells of the body exhibit circadian rhythms in metabolism, cell division, and gene transcription. The suprachiasmatic nucleus (SCN) in the hypothalamus is the major clock in the body and receives its major input from light (via retinal neurons) and a minor input from nutrient intake. The SCN and other brain tissues determine waking and feeding cycles and influence the clocks in other tissues by hormone secretion and nervous stimulation. Independently of the SCN, other tissues such as liver receive inputs from signals from the brain and from nutrients.

Literature references

Takahashi, JS., Hong, HK., Ko, CH., McDearmon, EL. (2008). The genetics of mammalian circadian order and disorder: implications for physiology and disease. *Nat Rev Genet, 9*, 764-75. ↗

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

Green, CB., Takahashi, JS., Bass, J. (2008). The meter of metabolism. *Cell, 134*, 728-42. ↗

Hastings, MH., Maywood, ES., O'Neill, JS. (2008). Cellular circadian pacemaking and the role of cytosolic rhythms. *Curr Biol, 18*, R805-R815. ↗

Editions

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

Expression of CLOCK ↗

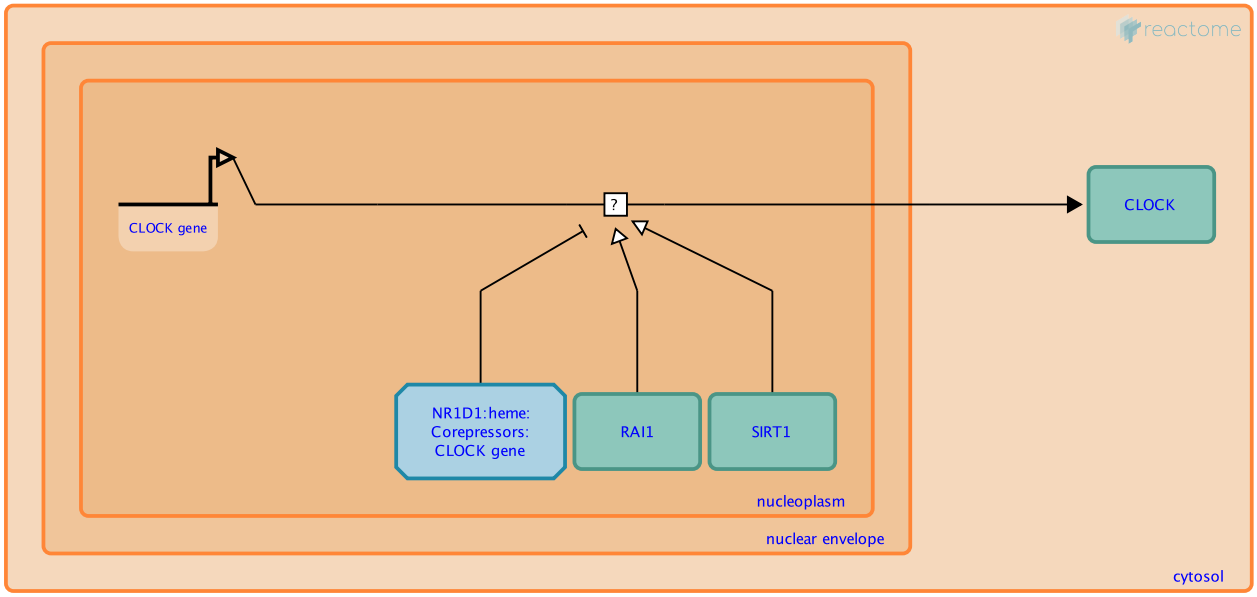
Location: Circadian Clock

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.

Followed by: BMAL1 binds CLOCK,NPAS2 forming BMAL1:CLOCK,NPAS2 heterodimer

Literature references

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

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

Editions

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

BMAL1 binds CLOCK,NPAS2 forming BMAL1:CLOCK,NPAS2 heterodimer ↗

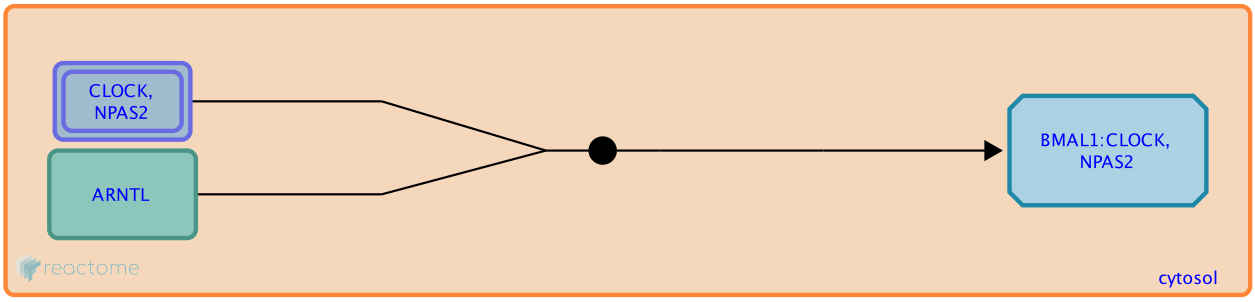
Location: Circadian Clock

Stable identifier: R-HSA-400228

Type: binding

Compartments: cytosol

Inferred from: Bmal1 binds Clock,Npas2 forming Bmal1:Clock,Npas2 heterodimer (Mus musculus)



BMAL1 (ARNTL), CLOCK, and NPAS2 are basic helix-loop-helix transcription factors. In humans BMAL1 has been demonstrated to form a heterodimer with CLOCK. In mouse, BMAL1 can form a heterodimer with either CLOCK or NPAS2. By analogy with other basic helix-loop-helix proteins the basic domain binds DNA, in this case the E-box motif, and the helix-loop-helix domains interact to form the heterodimer. BMAL1 and CLOCK/NPAS2 are codependently phosphorylated by unknown kinases after dimerization. The phosphorylation enhances transactivation activity and is inhibited by PER:CRY complexes. Both CLOCK and NPAS2 are expressed in the suprachiasmatic nucleus of the hypothalamus and act redundantly there. The tissue distributions of CLOCK and NPAS2 do not entirely overlap, however. For example, NPAS2 but not CLOCK is found in forebrain.

Preceded by: Expression of ARNTL (BMAL1), Expression of NPAS2, Expression of CLOCK

Followed by: BMAL1:CLOCK,NPAS2 heterodimer is phosphorylated and translocates to the nucleus, CRY proteins stabilize unphosphorylated BMAL1:CLOCK,NPAS2

Literature references

Hogenesch, JB., Gu, YZ., Jain, S., Bradfield, CA. (1998). The basic-helix-loop-helix-PAS orphan MOP3 forms transcriptionally active complexes with circadian and hypoxia factors. *Proc Natl Acad Sci U S A, 95*, 5474-9. ↗

Gekakis, N., Staknis, D., Nguyen, HB., Davis, FC., Wilsbacher, LD., King, DP. et al. (1998). Role of the CLOCK protein in the mammalian circadian mechanism. *Science, 280*, 1564-9. ↗

Reick, M., Garcia, JA., Dudley, C., McKnight, SL. (2001). NPAS2: an analog of clock operative in the mammalian forebrain. *Science, 293*, 506-9. ↗

Rutter, J., Reick, M., Wu, LC., McKnight, SL. (2001). Regulation of clock and NPAS2 DNA binding by the redox state of NAD cofactors. *Science, 293*, 510-4. ↗

Editions

2009-05-18	Authored	May, B.
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2009-06-02	Edited	May, B.
2010-06-23	Reviewed	Hirota, T., Kay, SA., Delaunay, F., Albrecht, U.

BMAL1:CLOCK,NPAS2 heterodimer is phosphorylated and translocates to the nucleus ↗

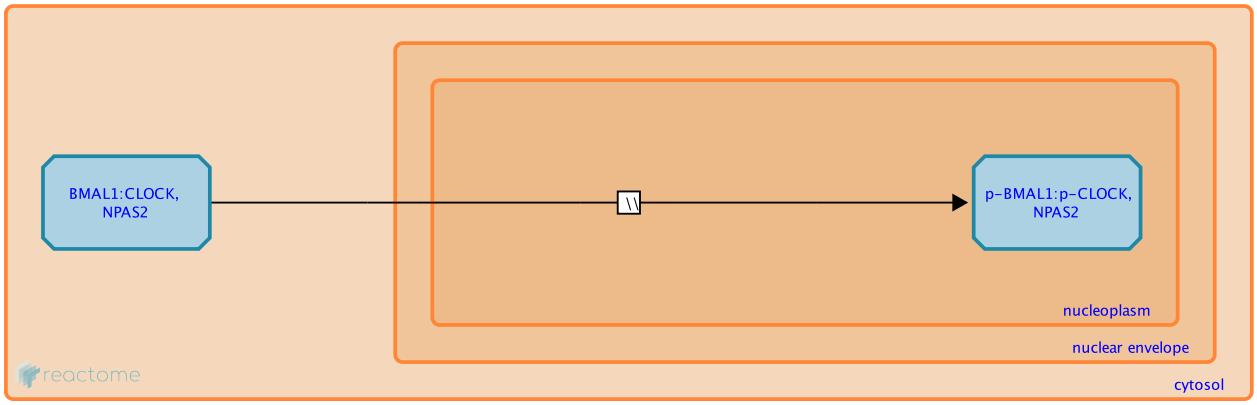
Location: Circadian Clock

Stable identifier: R-HSA-421320

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Bmal1:Clock,Npas2 heterodimer is phosphorylated and translocates to the nucleus (Mus musculus)



As inferred from mouse, BMAL1 (ARNTL), CLOCK, and NPAS2 are phosphorylated by unknown kinases. The phosphorylation is dependent on the heterodimerization of BMAL1 with CLOCK or NPAS2. Phosphorylated BMAL1:CLOCK/NPAS2 is a much stronger transactivator of gene expression than is unphosphorylated BMAL1:CLOCK/NPAS2.

Preceded by: BMAL1 binds CLOCK,NPAS2 forming BMAL1:CLOCK,NPAS2 heterodimer

Followed by: p-BMAL1:p-CLOCK,NPAS2 binds PER2 gene, Expression of CRYPTOCHROME-2, p-BMAL1:p-CLOCK,NPAS2 binds PER1 gene, p-BMAL1:p-CLOCK,NPAS2 binds CRY1 gene, p-BMAL1:p-CLOCK,NPAS2 binds NR1D1 gene, p-BMAL1:p-CLOCK,NPAS2 binds RORA gene, CRY:PER heterodimer binds the BMAL1:CLOCK/NPAS2 heterodimer

Editions

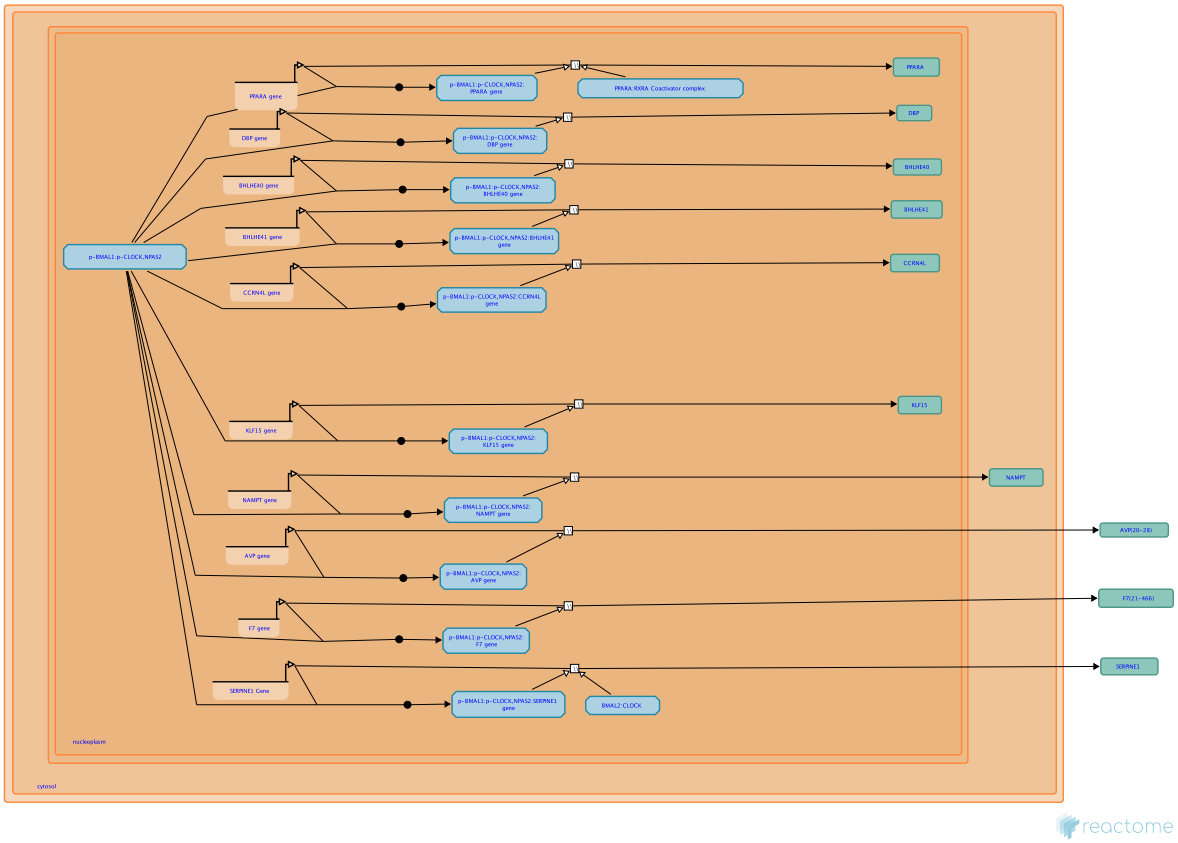
2009-05-18	Authored	May, B.
2009-05-27	Reviewed	D'Eustachio, P.
2009-06-02	Edited	May, B.
2010-06-23	Reviewed	Hirota, T., Kay, SA., Delaunay, F., Albrecht, U.

BMAL1:CLOCK,NPAS2 activates circadian gene expression ↗

Location: Circadian Clock

Stable identifier: R-HSA-1368108

Compartments: nucleoplasm, extracellular region, endoplasmic reticulum lumen, cytosol



As inferred from mouse, BMAL1:CLOCK (ARNTL:CLOCK) and BMAL1:NPAS2 (ARNTL:NPAS2) heterodimers bind to sequence elements (E boxes) in the promoters of target genes and enhance transcription (Gekakis et al. 1998, reviewed in Munoz and Baler 2003).

Literature references

Muñoz, E., Baler, R. (2003). The circadian E-box: when perfect is not good enough. *Chronobiol Int, 20*, 371-88. ↗

Gekakis, N., Staknis, D., Nguyen, HB., Davis, FC., Wilsbacher, LD., King, DP. et al. (1998). Role of the CLOCK protein in the mammalian circadian mechanism. *Science, 280*, 1564-9. ↗

Editions

2009-05-27	Reviewed	D'Eustachio, P.
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2011-06-22	Authored, Edited	May, B.
2015-01-17	Revised	May, B.

p-BMAL1:p-CLOCK,NPAS2 binds CRY1 gene ↗

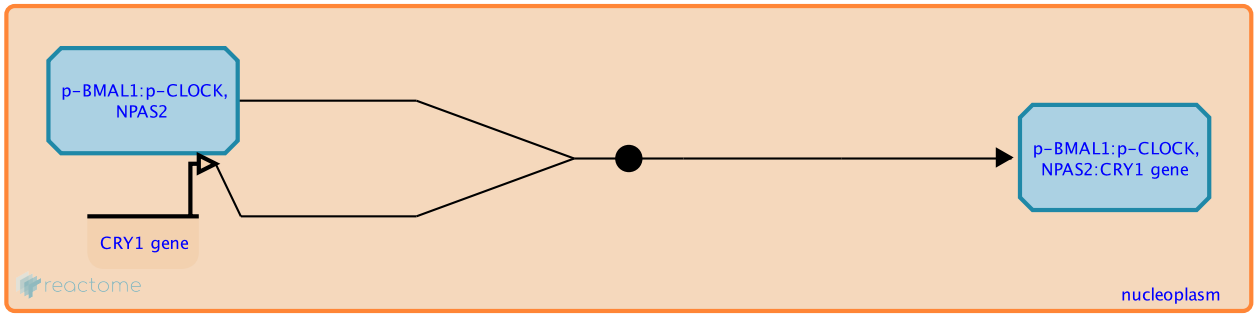
Location: Circadian Clock

Stable identifier: R-HSA-5663120

Type: binding

Compartments: nucleoplasm

Inferred from: p-Bmal1:p-Clock,Npas2 binds Cry1 gene (Mus musculus)



The phosphorylated BMAL1:CLOCK (ARNTL:CLOCK) heterodimer binds an E-box in the promoter of the CRY1 gene and activates transcription of CRY1. NPAS2 is predicted to act redundantly with CLOCK.

Preceded by: BMAL1:CLOCK,NPAS2 heterodimer is phosphorylated and translocates to the nucleus

Followed by: Expression of CRYPTOCHROME-1

Literature references

Nakamura, K., Inoue, I., Takahashi, S., Komoda, T., Katayama, S. (2008). Cryptochrome and Period Proteins Are Regulated by the CLOCK/BMAL1 Gene: Crosstalk between the PPARs/RXRalpha-Regulated and CLOCK/BMAL1-Regulated Systems. *PPAR Res, 2008*, 348610. ↗

Editions

2009-05-27	Reviewed	D'Eustachio, P.
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2015-01-15	Authored, Edited	May, B.

Expression of CRYPTOCHROME-1 ↗

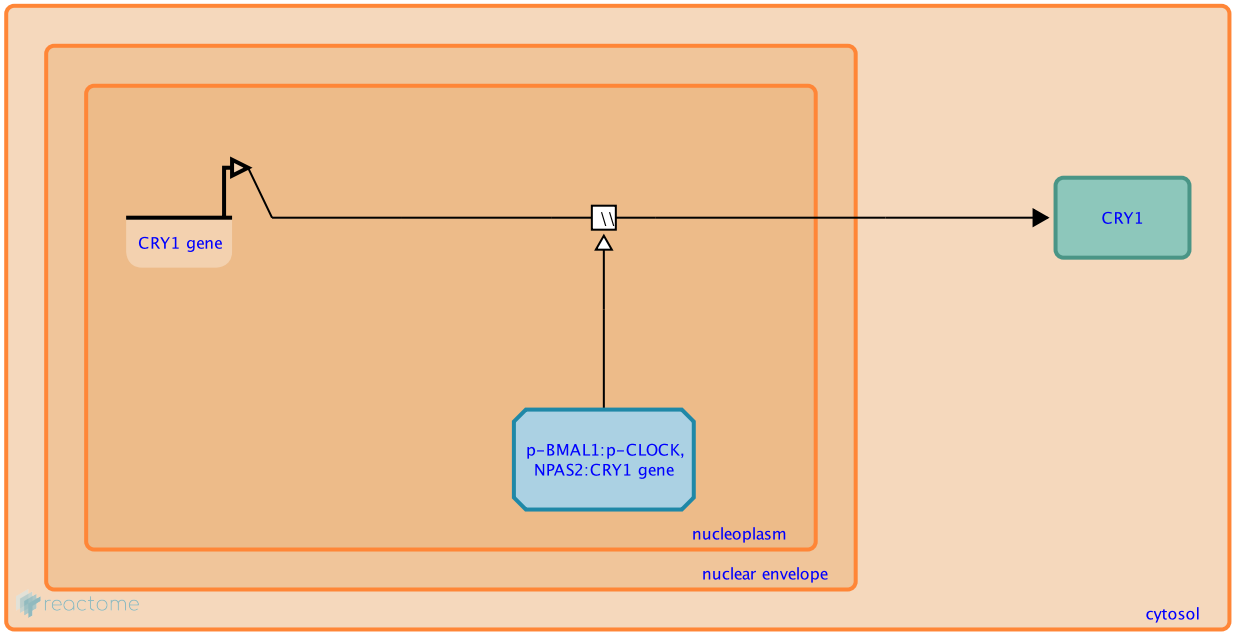
Location: Circadian Clock

Stable identifier: R-HSA-549467

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Expression of Cryptochrome-1 (Cry1) (Mus musculus)



The CRYPTOCHROME-1 (CRY1) gene is transcribed to yield mRNA and the mRNA is translated to yield CRY1 protein (van der Spek et al. 1996, Thompson et al. 2003, also inferred from mouse homologs). CRY1 mRNA and protein show circadian expression. The promoter of the CRY1 gene contains an E-box which is bound by the BMAL1:CLOCK (ARNTL:CLOCK) heterodimer (and probably also the BMAL1:NPAS2 heterodimer), which activates transcription of CRY1.

Preceded by: p-BMAL1:p-CLOCK,NPAS2 binds CRY1 gene

Followed by: CRY proteins stabilize unphosphorylated BMAL1:CLOCK,NPAS2, Formation of CRY:PER:Kinase complex

Literature references

van der Spek, PJ., Kobayashi, K., Bootsma, D., Takao, M., Eker, AP., Yasui, A. (1996). Cloning, tissue expression, and mapping of a human photolyase homolog with similarity to plant blue-light receptors. *Genomics, 37*, 177-82. ↗

Thompson, CL., Bowes Rickman, C., Shaw, SJ., Ebright, JN., Kelly, U., Sancar, A. et al. (2003). Expression of the blue-light receptor cryptochrome in the human retina. *Invest Ophthalmol Vis Sci, 44*, 4515-21. ↗

Editions

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2010-06-23	Reviewed	Hirota, T., Kay, SA., Delaunay, F., Albrecht, U.

Expression of CRYPTOCHROME-2 ↗

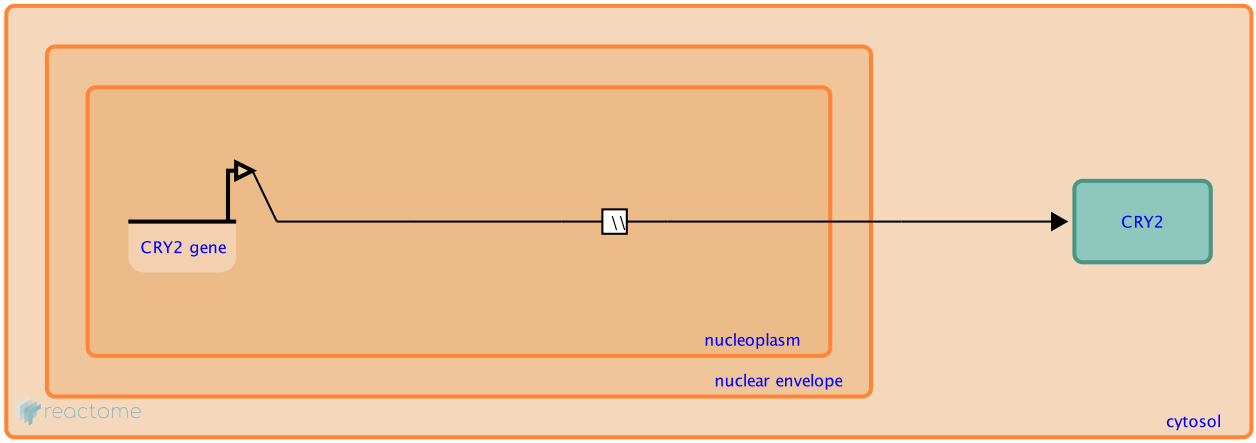
Location: Circadian Clock

Stable identifier: R-HSA-549470

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Expression of Cryptochrome-2 (Cry2) (Mus musculus)



The CRYPTOCHROME-2 (CRY2) gene is transcribed to yield mRNA and the mRNA is translated to yield CRY2 protein (Kobayashi et al. 1998, Thompson et al. 2003, also inferred from mouse homologs). As inferred from mouse, the CRY2 protein shows circadian rhythm in the suprachiasmatic nucleus (SCN) and in peripheral tissues. The mRNA shows circadian rhythm in muscle but not in the SCN. Expression is dependent on CLOCK.

Preceded by: BMAL1:CLOCK,NPAS2 heterodimer is phosphorylated and translocates to the nucleus

Followed by: CRY proteins stabilize unphosphorylated BMAL1:CLOCK,NPAS2, Formation of CRY:PER:Kinase complex

Literature references

Kobayashi, K., Kanno, S., Smit, B., van der Horst, GT., Takao, M., Yasui, A. (1998). Characterization of photolyase/blue-light receptor homologs in mouse and human cells. *Nucleic Acids Res, 26*, 5086-92. ↗

Thompson, CL., Bowes Rickman, C., Shaw, SJ., Ebright, JN., Kelly, U., Sancar, A. et al. (2003). Expression of the blue-light receptor cryptochrome in the human retina. *Invest Ophthalmol Vis Sci, 44*, 4515-21. ↗

Editions

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Expression of PERIOD-1 ↗

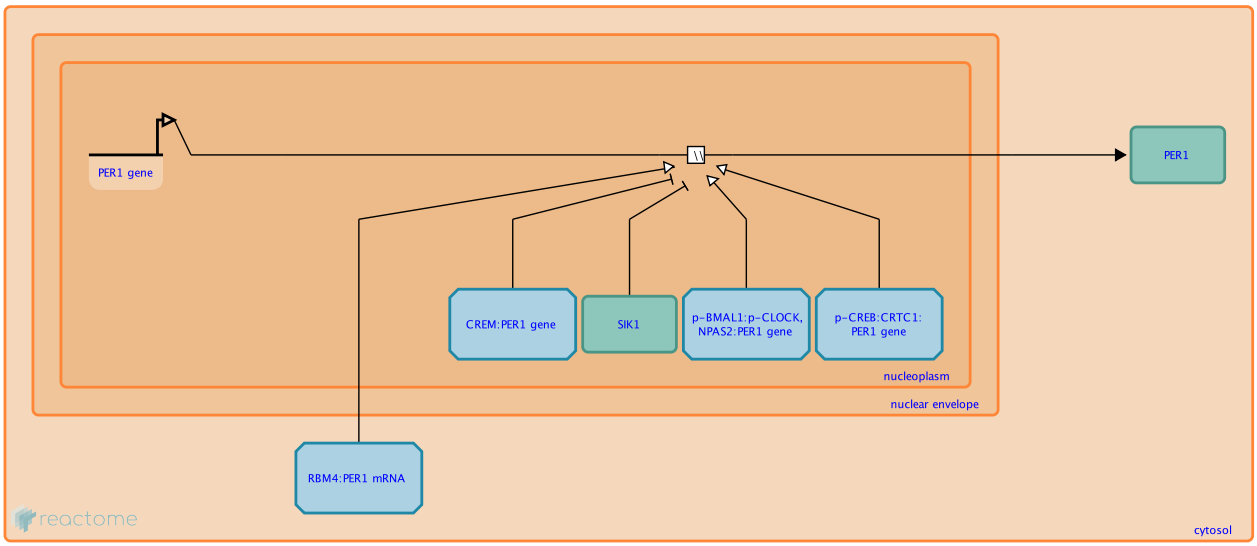
Location: Circadian Clock

Stable identifier: R-HSA-549533

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Expression of Period-1 (Per1) (Mus musculus)



The PERIOD-1 (PER1) gene is transcribed to yield mRNA and the mRNA is translated to yield PER1 protein (Shearman et al. 1997, Tei et al. 1997, Miyazaki et al. 2004, Motzkus et al. 2007, also inferred from mouse homologs). The promoter of the PER1 gene contains E-boxes which are bound by the BMAL1:CLOCK (ARNTL:CLOCK) heterodimer (and probably also the BMAL1:NPAS2 (ARNTL:NPAS2) heterodimer). The BMAL1:CLOCK heterodimer activates transcription of PER1.

Preceded by: p-BMAL1:p-CLOCK,NPAS2 binds PER1 gene

Followed by: Formation of CRY:PER:Kinase complex

Literature references

Motzkus, D., Loumi, S., Cadenas, C., Vinson, C., Forssmann, WG., Maronde, E. (2007). Activation of human period-1 by PKA or CLOCK/BMAL1 is conferred by separate signal transduction pathways. *Chronobiol Int, 24*, 783-92. ↗

Miyazaki, K., Nagase, T., Mesaki, M., Narukawa, J., Ohara, O., Ishida, N. (2004). Phosphorylation of clock protein PER1 regulates its circadian degradation in normal human fibroblasts. *Biochem J, 380*, 95-103. ↗

Shearman, LP., Zylka, MJ., Weaver, DR., Kolakowski LF, Jr., Reppert, SM. (1997). Two period homologs: circadian expression and photic regulation in the suprachiasmatic nuclei. *Neuron, 19*, 1261-9. ↗

Tei, H., Okamura, H., Shigeyoshi, Y., Fukuhara, C., Ozawa, R., Hirose, M. et al. (1997). Circadian oscillation of a mammalian homologue of the Drosophila period gene. *Nature, 389*, 512-6. ↗

Editions

2009-05-27	Reviewed	D'Eustachio, P.
2010-03-11	Authored, Edited	May, B.
2010-06-23	Reviewed	Hirota, T., Kay, SA., Delaunay, F., Albrecht, U.

p-BMAL1:p-CLOCK,NPAS2 binds PER1 gene ↗

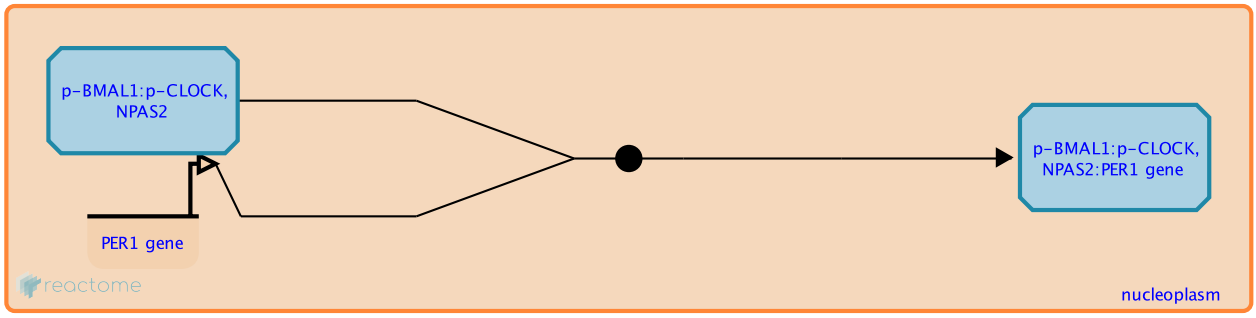
Location: Circadian Clock

Stable identifier: R-HSA-5663174

Type: binding

Compartments: nucleoplasm

Inferred from: p-Bmal1:p-Clock,Npas2 binds Per1 gene (Mus musculus)



The phosphorylated BMAL1:CLOCK (ARNTL:CLOCK) heterodimer binds E-boxes in the promoter of the PER1 gene and activates transcription of PER1. NPAS2 is predicted to act redundantly with CLOCK.

Preceded by: BMAL1:CLOCK,NPAS2 heterodimer is phosphorylated and translocates to the nucleus

Followed by: Expression of PERIOD-1

Literature references

Motzkus, D., Loumi, S., Cadenas, C., Vinson, C., Forssmann, WG., Maronde, E. (2007). Activation of human period-1 by PKA or CLOCK/BMAL1 is conferred by separate signal transduction pathways. *Chronobiol Int, 24*, 783-92. ↗

Miyazaki, K., Nagase, T., Mesaki, M., Narukawa, J., Ohara, O., Ishida, N. (2004). Phosphorylation of clock protein PER1 regulates its circadian degradation in normal human fibroblasts. *Biochem J, 380*, 95-103. ↗

Shearman, LP., Zylka, MJ., Weaver, DR., Kolakowski LF, Jr., Reppert, SM. (1997). Two period homologs: circadian expression and photic regulation in the suprachiasmatic nuclei. *Neuron, 19*, 1261-9. ↗

Tei, H., Okamura, H., Shigeyoshi, Y., Fukuhara, C., Ozawa, R., Hirose, M. et al. (1997). Circadian oscillation of a mammalian homologue of the Drosophila period gene. *Nature, 389*, 512-6. ↗

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2015-01-15	Authored, Edited	May, B.

p-BMAL1:p-CLOCK,NPAS2 binds PER2 gene ↗

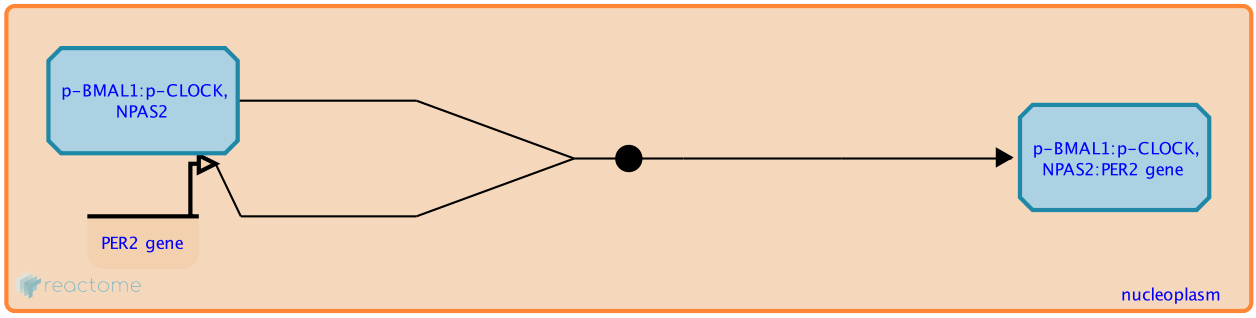
Location: Circadian Clock

Stable identifier: R-HSA-5663118

Type: binding

Compartments: nucleoplasm

Inferred from: p-Bmal1:p-Clock,Npas2 binds Per2 gene (Mus musculus)



As inferred from mouse, the phosphorylated BMAL1:CLOCK (ARNTL:CLOCK) heterodimer binds a non-canonical E-box in the promoter of the PER2 gene and activates transcription of PER2. NPAS2 is predicted to act redundantly with CLOCK.

Preceded by: BMAL1:CLOCK,NPAS2 heterodimer is phosphorylated and translocates to the nucleus

Followed by: Expression of PERIOD-2

Literature references

Nakamura, K., Inoue, I., Takahashi, S., Komoda, T., Katayama, S. (2008). Cryptochrome and Period Proteins Are Regulated by the CLOCK/BMAL1 Gene: Crosstalk between the PPARs/RXRalpha-Regulated and CLOCK/BMAL1-Regulated Systems. *PPAR Res, 2008*, 348610. ↗

Shearman, LP., Zylka, MJ., Weaver, DR., Kolakowski LF, Jr., Reppert, SM. (1997). Two period homologs: circadian expression and photic regulation in the suprachiasmatic nuclei. *Neuron, 19*, 1261-9. ↗

Editions

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2010-06-23	Reviewed	Hirota, T., Kay, SA., Delaunay, F., Albrecht, U.
2015-01-15	Authored, Edited	May, B.

Expression of PERIOD-2 ↗

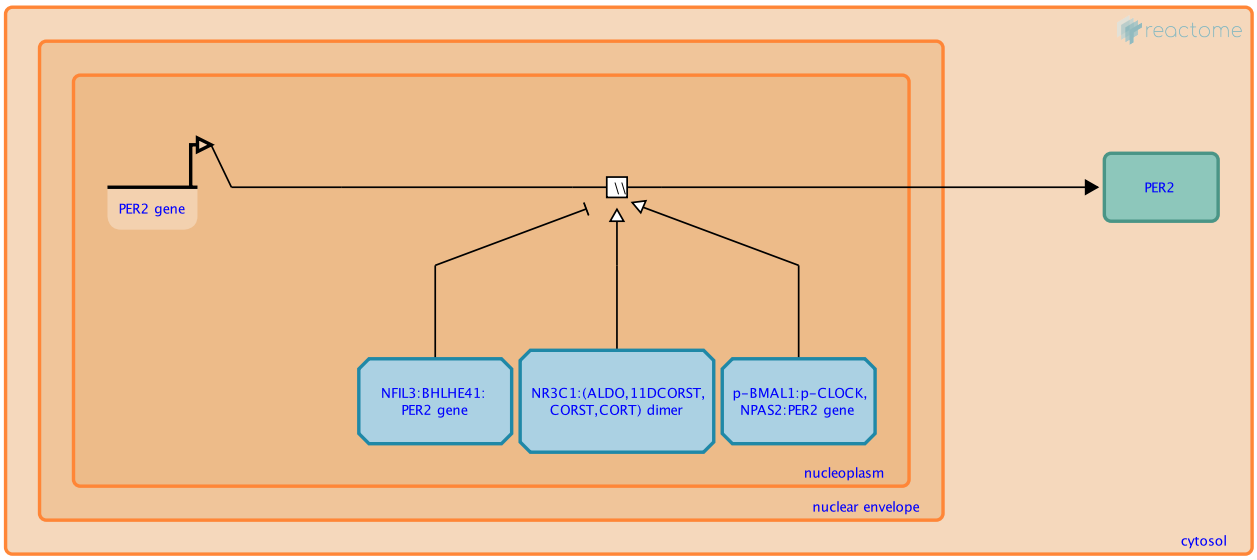
Location: Circadian Clock

Stable identifier: R-HSA-549493

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Expression of Period-2 (Per2) (Mus musculus)



The PERIOD-2 (PER2) gene is transcribed to yield mRNA and the mRNA is translated to yield PER2 protein (Shearman et al. 1997, Nakamura et al. 2008, also inferred from mouse homologs). The promoter of the PER2 gene contains an E-box which binds the BMAL1:CLOCK (ARNTL:CLOCK) heterodimer (and probably also the BMAL1:NPAS2 (ARNTL:NPAS2) heterodimer). The BMAL1:CLOCK heterodimer activates transcription of PER2.

Preceded by: p-BMAL1:p-CLOCK,NPAS2 binds PER2 gene

Followed by: Formation of CRY:PER:Kinase complex

Literature references

Nakamura, K., Inoue, I., Takahashi, S., Komoda, T., Katayama, S. (2008). Cryptochrome and Period Proteins Are Regulated by the CLOCK/BMAL1 Gene: Crosstalk between the PPARs/RXRalpha-Regulated and CLOCK/BMAL1-Regulated Systems. *PPAR Res, 2008*, 348610. ↗

Shearman, LP., Zylka, MJ., Weaver, DR., Kolakowski LF, Jr., Reppert, SM. (1997). Two period homologs: circadian expression and photic regulation in the suprachiasmatic nuclei. *Neuron, 19*, 1261-9. ↗

Editions

2009-05-27	Reviewed	D'Eustachio, P.
2010-03-11	Authored, Edited	May, B.
2010-06-23	Reviewed	Hirota, T., Kay, SA., Delaunay, F., Albrecht, U.

p-BMAL1:p-CLOCK,NPAS2 binds NR1D1 gene ↗

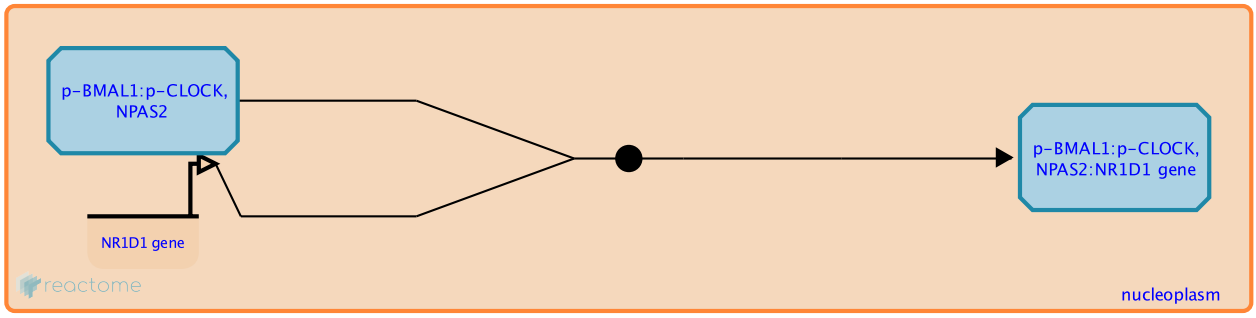
Location: Circadian Clock

Stable identifier: R-HSA-5663155

Type: binding

Compartments: nucleoplasm

Inferred from: p-Bmal1:p-Clock,Npas2 binds Nr1d1 gene (Mus musculus)



Activation of NR1D1 (REV-ERBA) expression by phosphorylated BMAL1:CLOCK (ARNTL:CLOCK) is inferred from mouse. NPAS2 is predicted to act redundantly with CLOCK.

Preceded by: BMAL1:CLOCK,NPAS2 heterodimer is phosphorylated and translocates to the nucleus

Followed by: Expression of NR1D1 (REV-ERBA)

Editions

2009-05-27	Reviewed	D'Eustachio, P.
2010-06-23	Reviewed	Hirota, T., Kay, SA., Delaunay, F., Albrecht, U.
2015-01-15	Authored, Edited	May, B.

p-BMAL1:p-CLOCK,NPAS2 binds RORA gene ↗

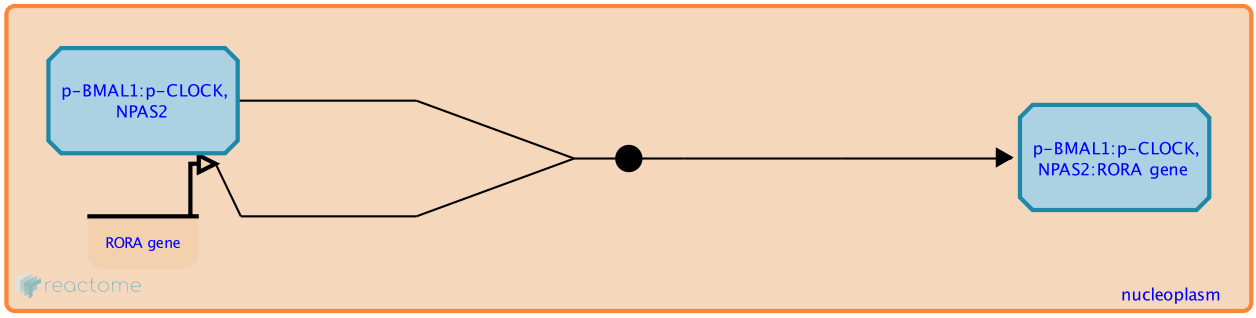
Location: Circadian Clock

Stable identifier: R-HSA-5669302

Type: binding

Compartments: nucleoplasm

Inferred from: p-Bmal1:p-Clock,Npas2 binds Rora gene (Mus musculus)



As inferred from mouse homologs, the p-BMAL1:p-CLOCK,NPAS2 heterodimer binds the promoter of the RORA gene and activates transcription.

Preceded by: BMAL1:CLOCK,NPAS2 heterodimer is phosphorylated and translocates to the nucleus

Followed by: Expression of RORA (ROR-alpha)

Editions

2009-05-27	Reviewed	D'Eustachio, P.
2010-06-23	Reviewed	Hirota, T., Kay, SA., Delaunay, F., Albrecht, U.
2015-02-02	Authored, Edited	May, B.

Expression of RORA (ROR-alpha) ↗

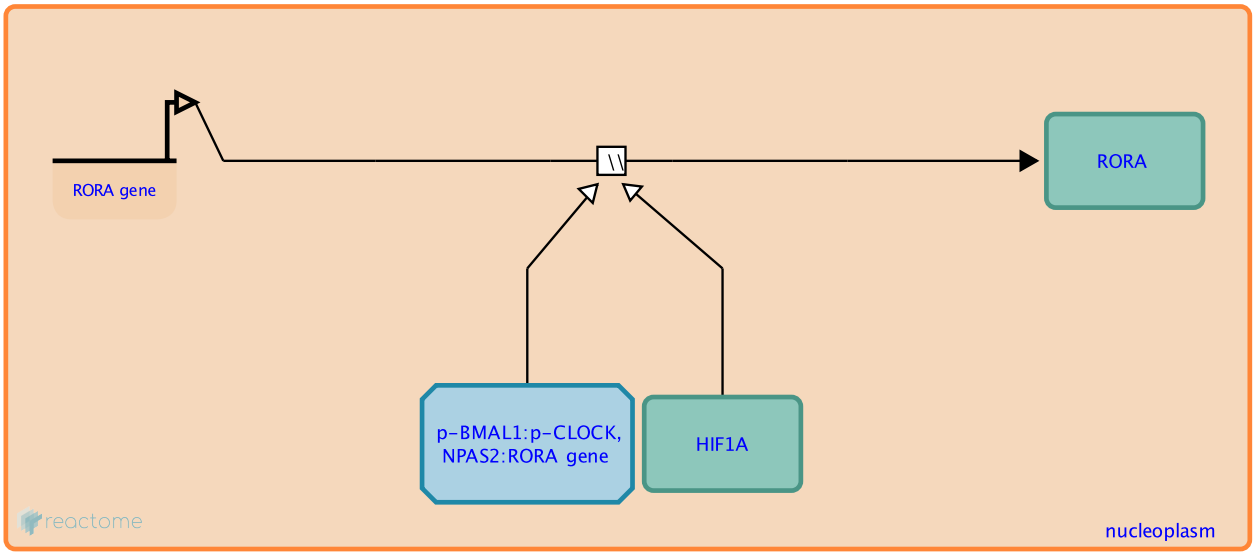
Location: Circadian Clock

Stable identifier: R-HSA-1368133

Type: omitted

Compartments: nucleoplasm

Inferred from: Expression of Rora (Mus musculus)



The RORA gene is transcribed to yield mRNA and the mRNA is transcribed to yield RORA protein (Giguere et al. 1994, also inferred from mouse homologs).

Preceded by: p-BMAL1:p-CLOCK,NPAS2 binds RORA gene

Followed by: RORA, EP300 bind NPAS2 gene, RORA, EP300, PPARGC1A bind NR1D1 gene, RORA, EP300, PPARGC1A, NRIP1 bind ARNTL (BMAL1) gene

Literature references

Giguère, V., Tini, M., Flock, G., Ong, E., Evans, RM., Otulakowski, G. (1994). Isoform-specific amino-terminal domains dictate DNA-binding properties of ROR alpha, a novel family of orphan hormone nuclear receptors. *Genes Dev, 8*, 538-53. ↗

Editions

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

CRY proteins stabilize unphosphorylated BMAL1:CLOCK,NPAS2 ↗

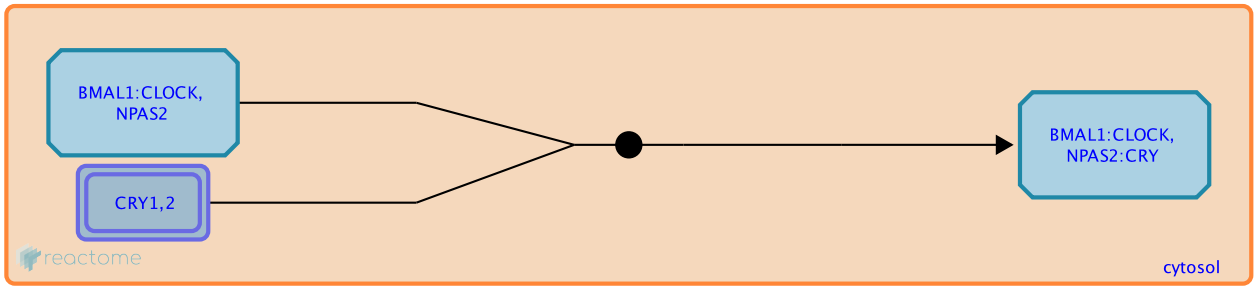
Location: Circadian Clock

Stable identifier: R-HSA-549355

Type: binding

Compartments: cytosol

Inferred from: Cry proteins stabilize unphosphorylated Bmal1:Clock,Npas2 (Mus musculus)



CRY1 and CRY2 bind the unphosphorylated BMAL1:CLOCK (ARNTL:CLOCK) heterodimer (and by homology the BMAL1:NPAS2 (ARNTL:NPAS2) heterodimer) and prolong its half-life. The unphosphorylated BMAL1:CLOCK heterodimer only weakly activates transcription and is therefore believed to competitively reduce transcription by phosphorylated BMAL1:CLOCK heterodimer. The complex of unphosphorylated BMAL1:CLOCK with CRY may contain additional components and may traffic into the nucleus.

Preceded by: Expression of CRYPTOCHROME-1, Expression of CRYPTOCHROME-2, BMAL1 binds CLOCK,NPAS2 forming BMAL1:CLOCK,NPAS2 heterodimer

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.

Formation of CRY:PER:Kinase complex ↗

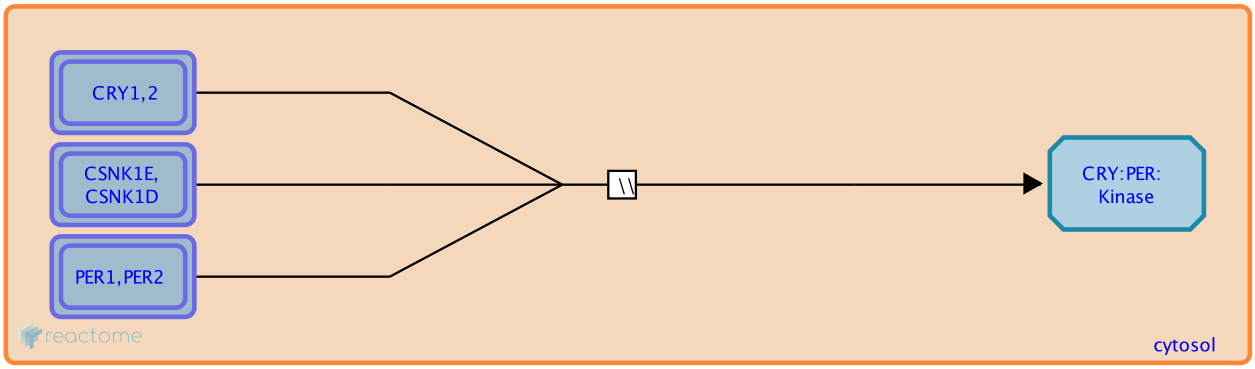
Location: Circadian Clock

Stable identifier: R-HSA-1856948

Type: omitted

Compartments: cytosol

Inferred from: Formation of Cry:Per:Kinase complex (Mus musculus)



CRYPTOCHROME, PERIOD, and a kinase (CKIepsilon or CKIdelta) form a ternary complex in the cytosol.

Preceded by: Expression of CRYPTOCHROME-1, Expression of CRYPTOCHROME-2, Expression of PERIOD-1, Expression of PERIOD-2

Followed by: CSNK1E,CSNK1D phosphorylate CRY and PER proteins

Literature references

Keesler, GA., Camacho, F., Guo, Y., Virshup, D., Mondadori, C., Yao, Z. (2000). Phosphorylation and destabilization of human period I clock protein by human casein kinase I epsilon. *Neuroreport, 11*, 951-5. ↗

Camacho, F., Cilio, M., Guo, Y., Virshup, DM., Patel, K., Khorkova, O. et al. (2001). Human casein kinase Idelta phosphorylation of human circadian clock proteins period 1 and 2. *FEBS Lett, 489*, 159-65. ↗

Editions

2010-06-23	Reviewed	Hirota, T., Kay, SA., Delaunay, F., Albrecht, U.
2011-10-29	Authored, Edited	May, B.

CSNK1E,CSNK1D phosphorylate CRY and PER proteins ↗

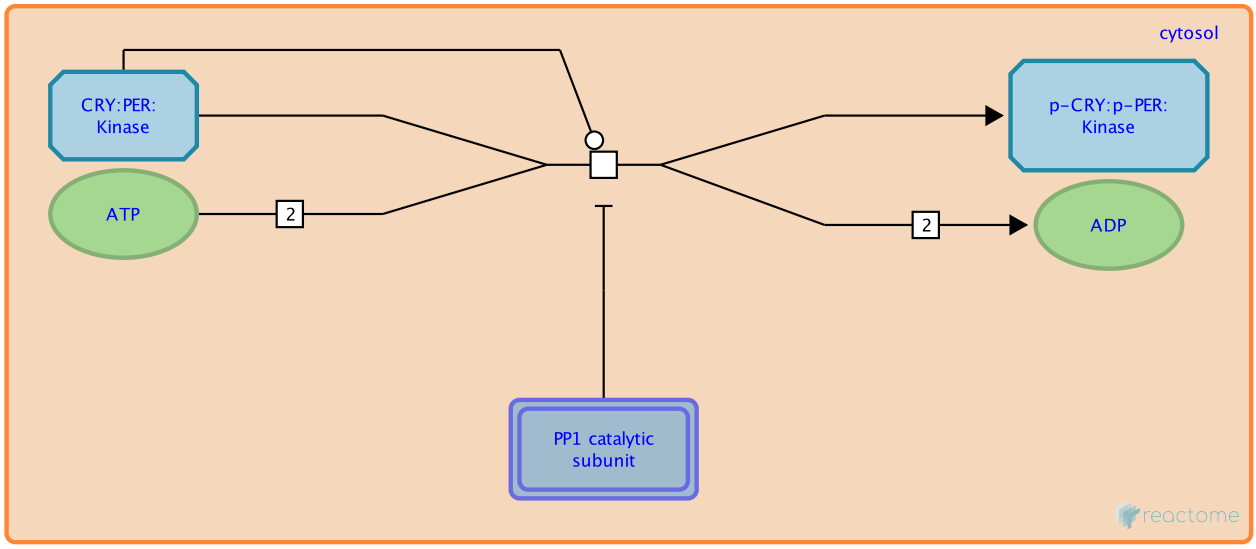
Location: Circadian Clock

Stable identifier: R-HSA-400382

Type: transition

Compartments: cytosol

Inferred from: Csnk1e,Csnk1d phosphorylate Cry and Per proteins (Mus musculus)



In the cytosol the kinases CSNK1D (casein kinase I delta) and CSNK1E (casein kinase I epsilon) phosphorylate PER1, PER2, CRY1, and CRY2 at multiple sites. Evidence indicates that PER:CRY complexes form a stable ternary complex with either CSNK1E or CSNK1D. Both kinases are able to bind and phosphorylate PER proteins. CSNK1E has been shown to phosphorylate CRY proteins only when they are complexed with PER proteins.

PER proteins contain a nuclear localization sequence and a nuclear export sequence allowing their movement into and out of the nucleus. Phosphorylation is required for transit of PER:CRY:kinase complexes into the nucleus and for interaction of PER proteins with the ubiquitin-mediated degradation process in the cytoplasm.

A mutation at Serine662 of PER2 is responsible for familial advanced phase sleep syndrome, however the particular kinase responsible for phosphorylating Serine662 is unknown.

Preceded by: Formation of CRY:PER:Kinase complex

Followed by: CRY:PER:Kinase complex translocates to the nucleus

Literature references

Miyazaki, K., Nagase, T., Mesaki, M., Narukawa, J., Ohara, O., Ishida, N. (2004). Phosphorylation of clock protein PER1 regulates its circadian degradation in normal human fibroblasts. *Biochem J, 380*, 95-103. ↗

Isojima, Y., Nakajima, M., Ukai, H., Fujishima, H., Yamada, RG., Masumoto, KH. et al. (2009). CKIepsilon/delta-dependent phosphorylation is a temperature-insensitive, period-determining process in the mammalian circadian clock. *Proc Natl Acad Sci U S A, 106*, 15744-9. ↗

Xu, Y., Toh, KL., Jones, CR., Shin, JY., Fu, YH., Ptácek, LJ. (2007). Modeling of a human circadian mutation yields insights into clock regulation by PER2. *Cell, 128*, 59-70. ↗

Toh, KL., Jones, CR., He, Y., Eide, EJ., Hinz, WA., Virshup, DM. et al. (2001). An hPer2 phosphorylation site mutation in familial advanced sleep phase syndrome. *Science, 291*, 1040-3. ↗

Camacho, F., Cilio, M., Guo, Y., Virshup, DM., Patel, K., Khorkova, O. et al. (2001). Human casein kinase Idelta phosphorylation of human circadian clock proteins period 1 and 2. *FEBS Lett, 489*, 159-65. ↗

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.

CRY:PER:Kinase complex translocates to the nucleus ↗

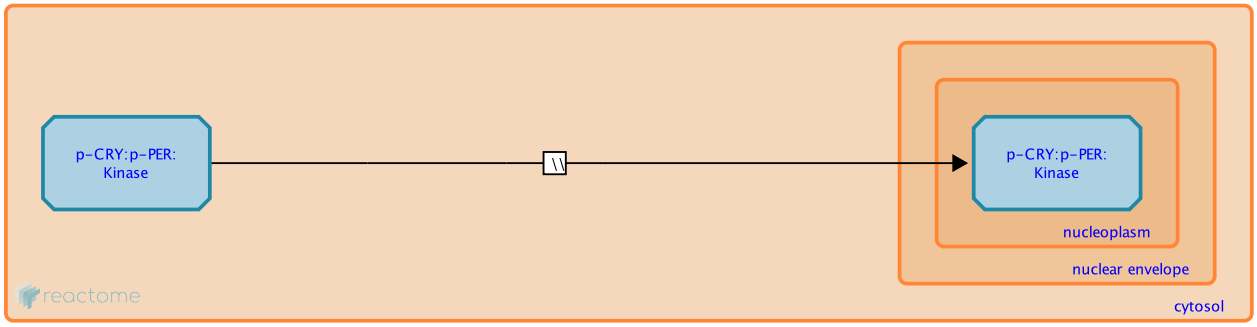
Location: Circadian Clock

Stable identifier: R-HSA-549385

Type: omitted

Compartments: cytosol, nucleoplasm

Inferred from: Phosphorylated Cry:Per:Kinase complex translocates to the nucleus (Mus musculus)



The ternary complex containing phosphorylated CRY and PER proteins with a kinase (CSNK1D or CSNK1E) is translocated to the nucleus. Phosphorylation controls transfer to the nucleus and retention in the nucleus.

Preceded by: CSNK1E,CSNK1D phosphorylate CRY and PER proteins

Followed by: CRY:PER heterodimer binds the BMAL1:CLOCK/NPAS2 heterodimer

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.

CRY:PER heterodimer binds the BMAL1:CLOCK/NPAS2 heterodimer ↗

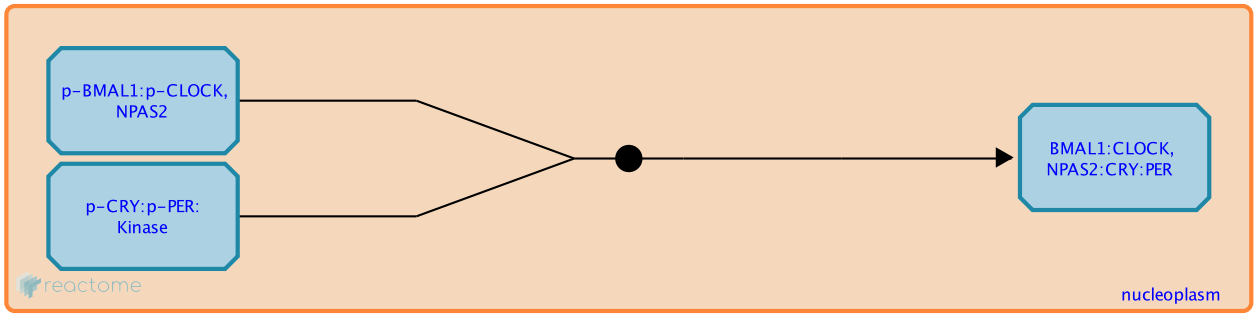
Location: Circadian Clock

Stable identifier: R-HSA-400256

Type: binding

Compartments: nucleoplasm

Inferred from: Cry:Per heterodimer binds Bmal1:Clock,Npas2 heterodimer (Mus musculus)



CRY (CRY1 and CRY2) and PER (PER1, PER2, PER3) proteins form complex in the cytoplasm where they are phosphorylated by CSNK1D and CSNK1E kinases. CRY:PER complexes appear to form stable complexes with a kinase. Because of the nuclear localization signals of PER and CRY, the complexes are translocated to the nucleus where they bind BMAL1:CLOCK/NPAS2 (ARNTL:CLOCK/NPAS2) heterodimers and inhibit the transactivation activity of BMAL1:CLOCK/NPAS2.

CRY and PER proteins are themselves transcriptionally activated by BMAL1:CLOCK/NPAS2 thus they participate in a negative loop inhibiting their own synthesis and the synthesis of other targets of BMAL1:CLOCK/NPAS2.

Experiments with two-hybrid interactions and in vitro associations show that CRY1, CRY2, and PER2 bind BMAL1 at two different sites on BMAL1. PER2 but not CRY1 or CRY2 binds CLOCK. Different combinations of PER and CRY proteins in PER:CRY complexes have different inhibitory activities.

Preceded by: CRY:PER:Kinase complex translocates to the nucleus, BMAL1:CLOCK,NPAS2 heterodimer is phosphorylated and translocates to the nucleus

Followed by: FBXL3 binds phosphorylated CRY proteins, Beta-TrCP1 binds phosphorylated PER proteins

Literature references

Sato, TK., Yamada, RG., Ukai, H., Baggs, JE., Miraglia, LJ., Kobayashi, TJ. et al. (2006). Feedback repression is required for mammalian circadian clock function. *Nat Genet, 38*, 312-9. ↗

Griffin EA, Jr., Staknis, D., Weitz, CJ. (1999). Light-independent role of CRY1 and CRY2 in the mammalian circadian clock. *Science, 286*, 768-71. ↗

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.

Beta-TrCP1 binds phosphorylated PER proteins ↗

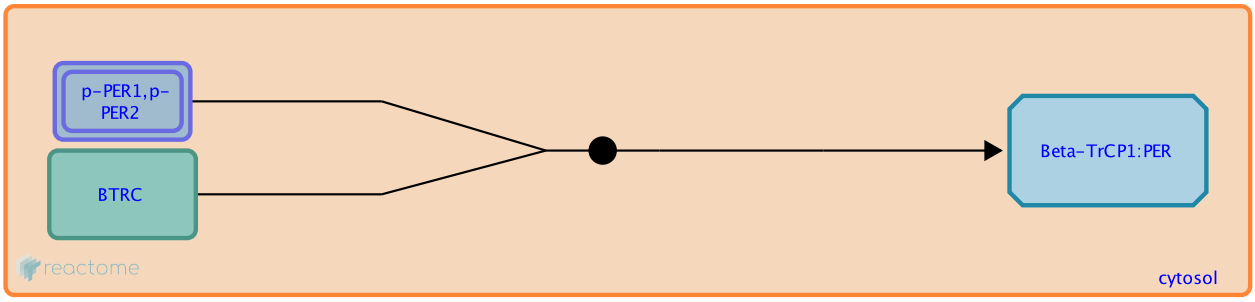
Location: Circadian Clock

Stable identifier: R-HSA-400219

Type: binding

Compartments: cytosol

Inferred from: Beta-TrCP (Btrc) binds phosphorylated Per (Mus musculus)



Beta-TrCP1 is an F-box type component of a particular SKP/CUL/F-Box (SCF) E3 ubiquitin ligase. Beta-TrCP1 interacts specifically with phosphorylated PER proteins and directs their polyubiquitination.

Preceded by: CRY:PER heterodimer binds the BMAL1:CLOCK/NPAS2 heterodimer

Followed by: BTRC:CUL1:SKP1 (SCF-beta-TrCP1) ubiquitinylates PER proteins

Literature references

Shirogane, T., Jin, J., Ang, XL., Harper, JW. (2005). SCFbeta-TRCP controls clock-dependent transcription via casein kinase 1-dependent degradation of the mammalian period-1 (Per1) protein. *J Biol Chem, 280*, 26863-72. ↗

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.

FBXL3 binds phosphorylated CRY proteins ↗

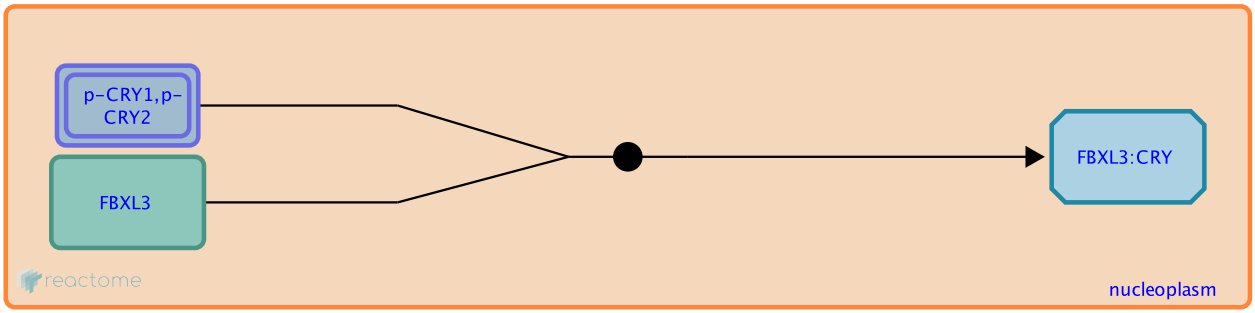
Location: Circadian Clock

Stable identifier: R-HSA-400272

Type: binding

Compartments: nucleoplasm

Inferred from: Fbxl3 binds phosphorylated Cry proteins (Mus musculus)



FBXL3 is an F-box type component of a particular SKP/CUL/F-Box E3 ubiquitin ligase. FBXL3 interacts specifically with CRY1 and CRY2 in the cytosol to direct the polyubiquitination of CRY1 and CRY2. It is unknown if FBXL3 requires phosphorylation or other modification of CRY proteins in order to bind and ubiquitinate them. Phosphorylation of CRY by Adenosine monophosphate-dependent kinase increases degradation of CRY, apparently by increasing association of CRY with FBXL3 Polyubiquitination of CRY proteins directs them to the 26S proteasome for degradation.

Preceded by: CRY:PER heterodimer binds the BMAL1:CLOCK/NPAS2 heterodimer

Followed by: CRY proteins are ubiquitinylated

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.

CRY proteins are ubiquitinylated ↗

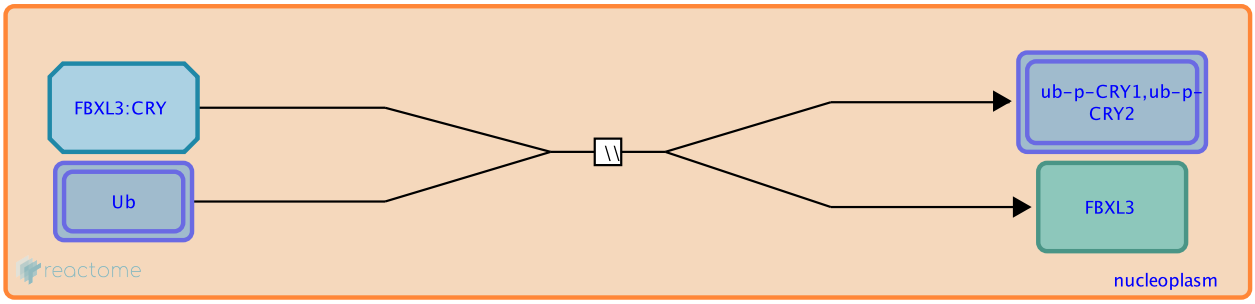
Location: Circadian Clock

Stable identifier: R-HSA-400282

Type: omitted

Compartments: nucleoplasm

Inferred from: Cry proteins are ubiquitinylated (Mus musculus)



Polyubiquitination of CRY proteins is directed by the FBXL3 component of SCF E3 ubiquitin ligase. The polyubiquitinated CRY proteins are recognized and degraded by the 26S proteasome. Degradation of CRY proteins occurs during the night and is necessary to allow new transcription of BMAL1:CLOCK/NPAS2 (ARNTL:CLOCK/NPAS2) targets in the morning during the circadian cycle.

Preceded by: FBXL3 binds phosphorylated CRY proteins

Editions

2009-05-18	Authored	May, B.
2009-05-27	Reviewed	D'Eustachio, P.
2009-06-02	Edited	May, B.
2010-02-20	Edited	May, B.
2010-06-23	Reviewed	Hirota, T., Kay, SA., Delaunay, F., Albrecht, U.

BTRC:CUL1:SKP1 (SCF-beta-TrCP1) ubiquitinylates PER proteins ↗

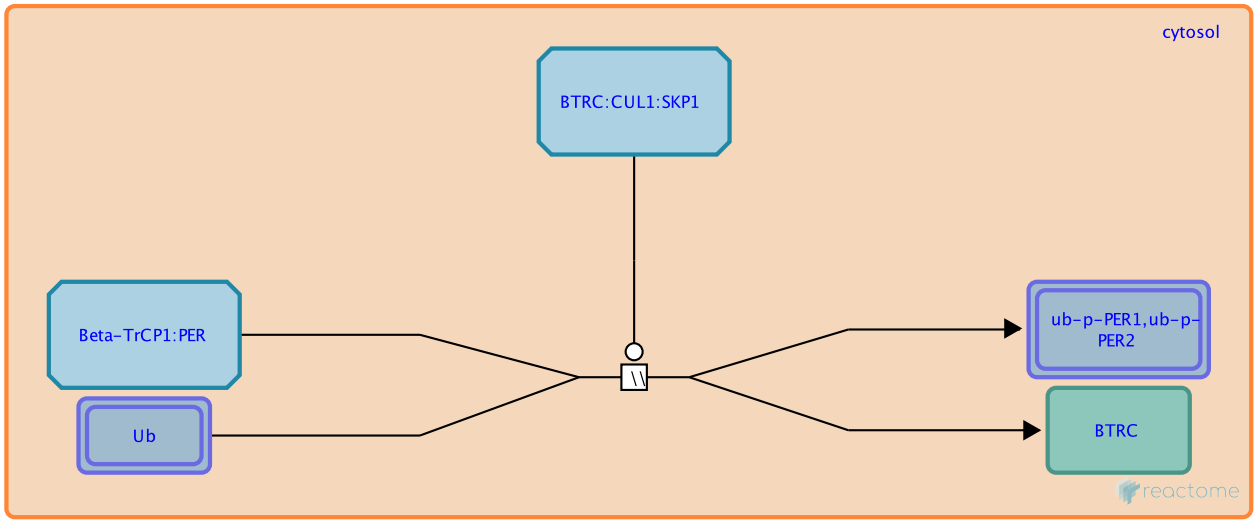
Location: Circadian Clock

Stable identifier: R-HSA-400267

Type: omitted

Compartments: cytosol

Inferred from: Per proteins are ubiquitinylated (Mus musculus)



Polyubiquitination of PER proteins is directed by the Beta-TrCP1 component of SCF E3 ubiquitin ligase. The polyubiquitinated PER proteins are recognized and degraded by the 26S proteasome. Degradation of PER proteins occurs during the night and is necessary to allow new transcription of BMAL1:CLOCK/NPAS2 (ARNTL:CLOCK/NPAS2) targets in the morning during the circadian cycle.

Preceded by: Beta-TrCP1 binds phosphorylated PER proteins

Editions

2009-05-18	Authored	May, B.
2009-05-27	Reviewed	D'Eustachio, P.
2009-06-02	Edited	May, B.
2010-02-20	Edited	May, B.
2010-06-23	Reviewed	Hirota, T., Kay, SA., Delaunay, F., Albrecht, U.

Expression of PPARGC1A (PGC-1alpha) ↗

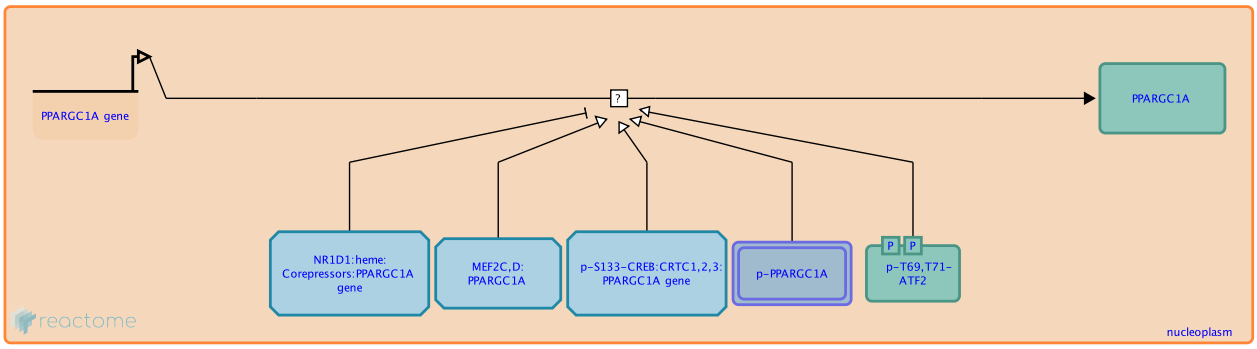
Location: Circadian Clock

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.

Followed by: RORA, EP300, PPARGC1A bind NR1D1 gene, RORA, EP300, PPARGC1A, NRIP1 bind ARNTL (BMAL1) gene

Literature references

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

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

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

Editions

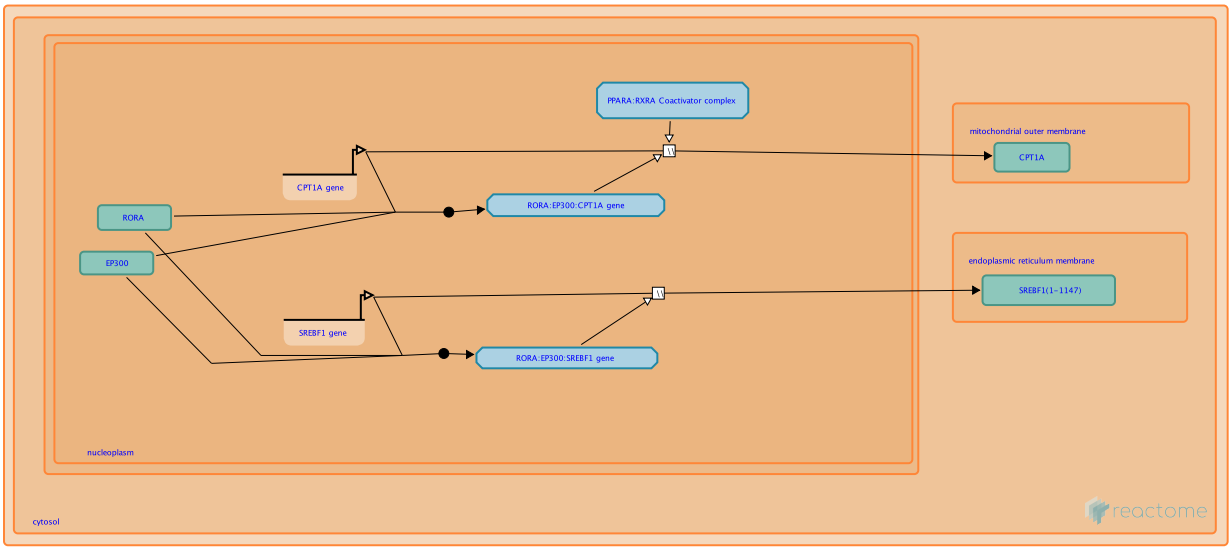
2011-06-22	Authored, Edited	May, B.
2013-12-07	Reviewed	Lezza, AM.
2021-01-23	Reviewed	Somers, J.

RORA activates gene expression ↗

Location: Circadian Clock

Stable identifier: R-HSA-1368082

Compartments: nucleoplasm, plasma membrane, endoplasmic reticulum membrane



As inferred from mouse, RORA binds ROR elements (ROREs) in DNA and recruits the coactivators PPARGC1A (PGC-1alpha) and p300 (EP300, a histone acetylase) to activate transcription.

Literature references

Giguère, V., Tini, M., Flock, G., Ong, E., Evans, RM., Otulakowski, G. (1994). Isoform-specific amino-terminal domains dictate DNA-binding properties of ROR alpha, a novel family of orphan hormone nuclear receptors. *Genes Dev, 8*, 538-53. ↗

Editions

2011-06-22	Authored, Edited	May, B.
2012-01-28	Reviewed	Delaunay, F.
2015-01-17	Revised	May, B.

RORA, EP300, PPARGC1A, NRIP1 bind ARNTL (BMAL1) gene ↗

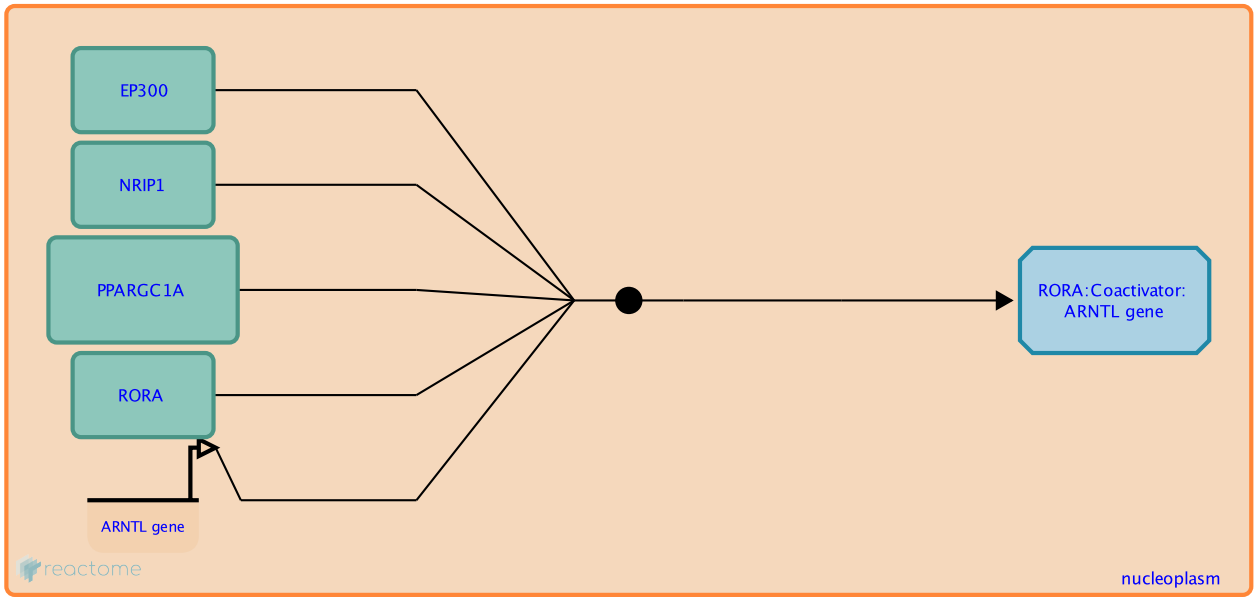
Location: Circadian Clock

Stable identifier: R-HSA-1368087

Type: binding

Compartments: nucleoplasm

Inferred from: Rora, Ep300, Ppargc1a bind Arntl (Bmal1) gene (Mus musculus)



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.

Preceded by: Expression of PPARGC1A (PGC-1alpha), Expression of RORA (ROR-alpha)

Followed by: Expression of ARNTL (BMAL1)

Literature references

Poliandri, AH., Gamsby, JJ., Christian, M., Spinella, MJ., Loros, JJ., Dunlap, JC. et al. (2011). Modulation of clock gene expression by the transcriptional coregulator receptor interacting protein 140 (RIP140). *J. Biol. Rhythms, 26*, 187-99. ↗

Editions

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

Expression of ARNTL (BMAL1)

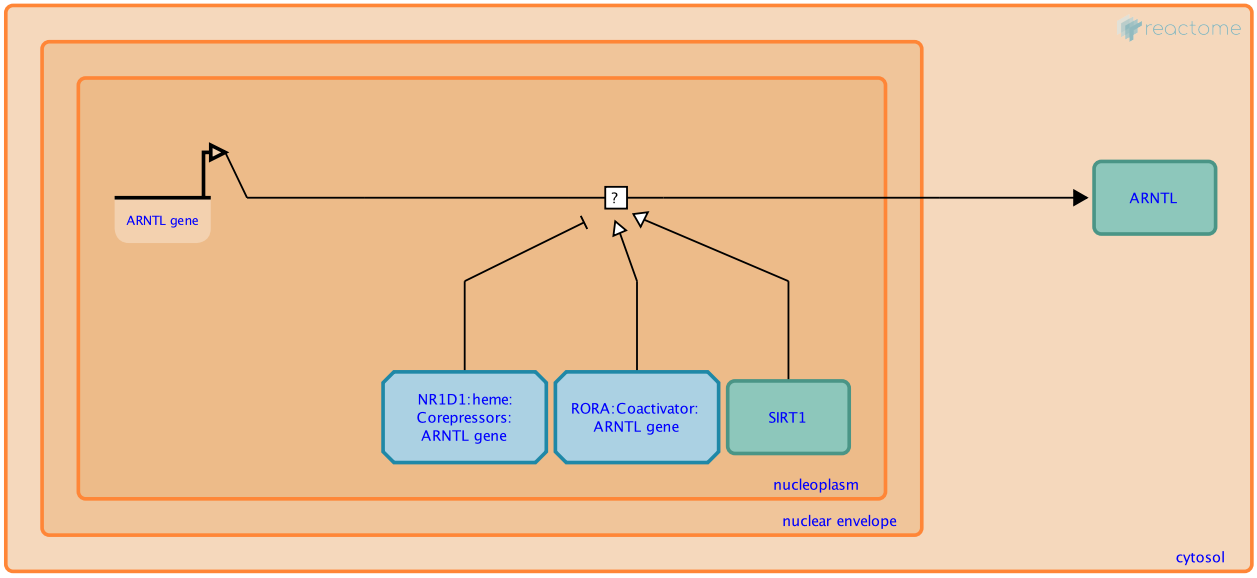
Location: Circadian Clock

Stable identifier: R-HSA-400342

Type: uncertain

Compartments: nucleoplasm, cytosol

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



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.

Preceded by: RORA, EP300, PPARGC1A, NRIP1 bind ARNTL (BMAL1) gene

Followed by: BMAL1 binds CLOCK,NPAS2 forming BMAL1:CLOCK,NPAS2 heterodimer

Literature references

Ikeda, M., Nomura, 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.

Hogenesch, JB., Chan, WK., Jackiw, VH., Brown, RC., Gu, YZ., Pray-Grant, M. 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.

RORA, EP300 bind NPAS2 gene ↗

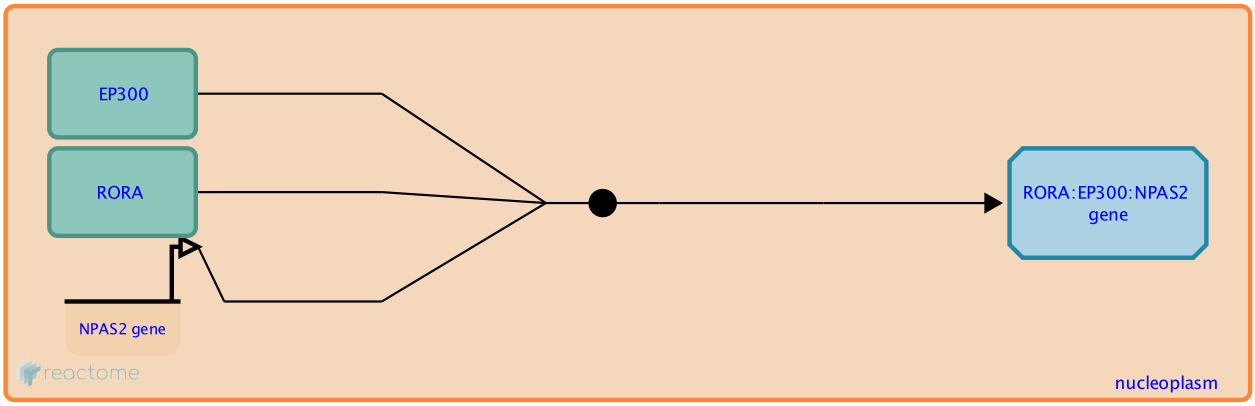
Location: Circadian Clock

Stable identifier: R-HSA-5663246

Type: binding

Compartments: nucleoplasm

Inferred from: Rora, Ep300 bind Npas2 gene (Mus musculus)



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.

Preceded by: Expression of RORA (ROR-alpha)

Followed by: Expression of NPAS2

Literature references

Matsumura, R., Matsubara, C., Node, K., Takumi, T., Akashi, M. (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

2012-01-28	Reviewed	Delaunay, F.
2015-01-16	Authored, Edited	May, B.

Expression of NPAS2 ↗

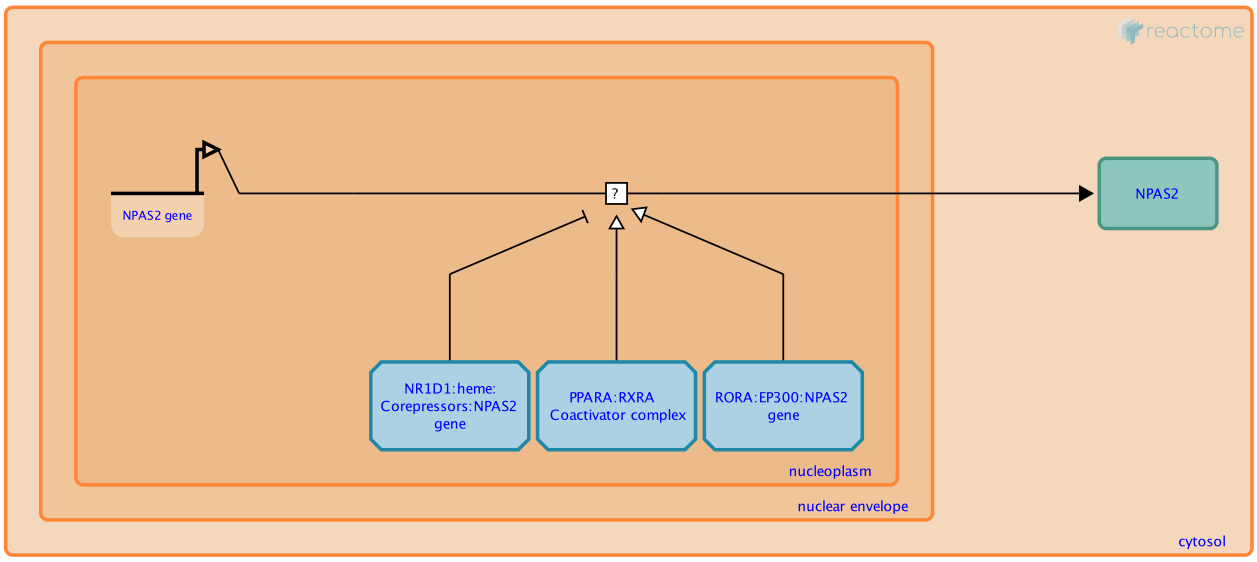
Location: Circadian Clock

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.

Preceded by: RORA, EP300 bind NPAS2 gene

Followed by: BMAL1 binds CLOCK,NPAS2 forming BMAL1:CLOCK,NPAS2 heterodimer

Literature references

Zhou, YD., Barnard, M., Tian, H., Li, X., Ring, HZ., 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. ↗

Matsumura, R., Matsubara, C., Node, K., Takumi, T., Akashi, M. (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.

RORA, EP300, PPARGC1A bind NR1D1 gene ↗

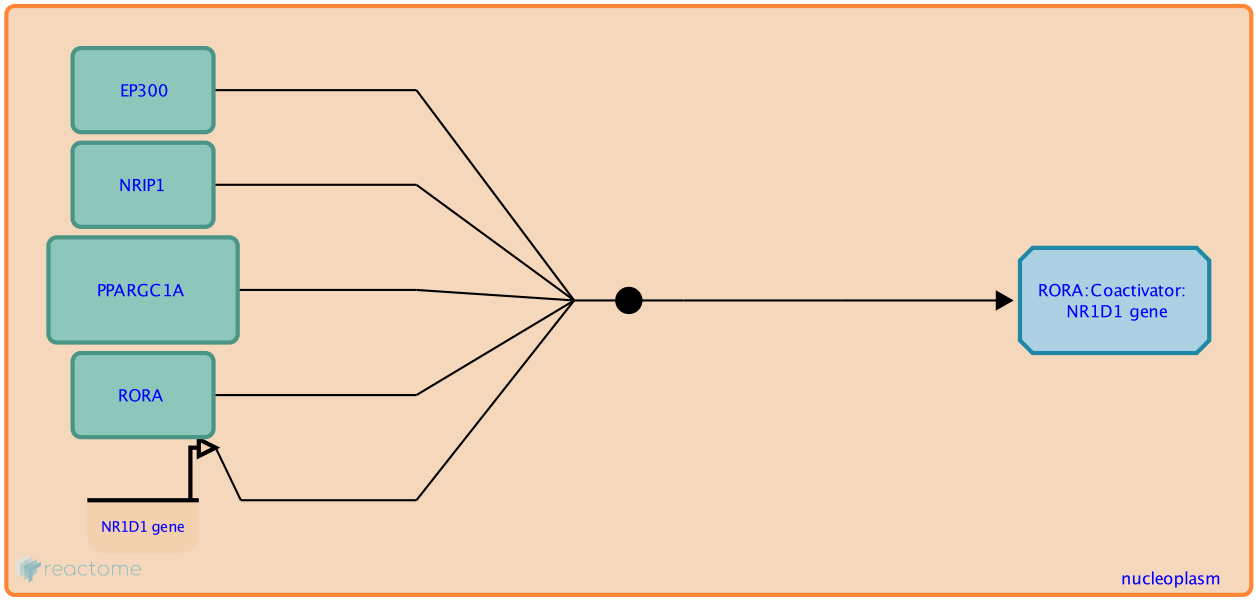
Location: Circadian Clock

Stable identifier: R-HSA-5663273

Type: binding

Compartments: nucleoplasm

Inferred from: Rora, Ep300, Ppargc1a bind Nr1d1 gene (Mus musculus)



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.

Preceded by: Expression of PPARGC1A (PGC-1alpha), Expression of RORA (ROR-alpha)

Followed by: Expression of NR1D1 (REV-ERBA)

Literature references

Raspè, E., Mautino, G., Duval, C., Fontaine, C., Duez, H., Barbier, O. et al. (2002). Transcriptional regulation of human Rev-erbalpha gene expression by the orphan nuclear receptor retinoic acid-related orphan receptor alpha. *J Biol Chem, 277*, 49275-81. ↗

Editions

2012-01-28	Reviewed	Delaunay, F.
2015-01-16	Authored, Edited	May, B.

Expression of NR1D1 (REV-ERBA) ↗

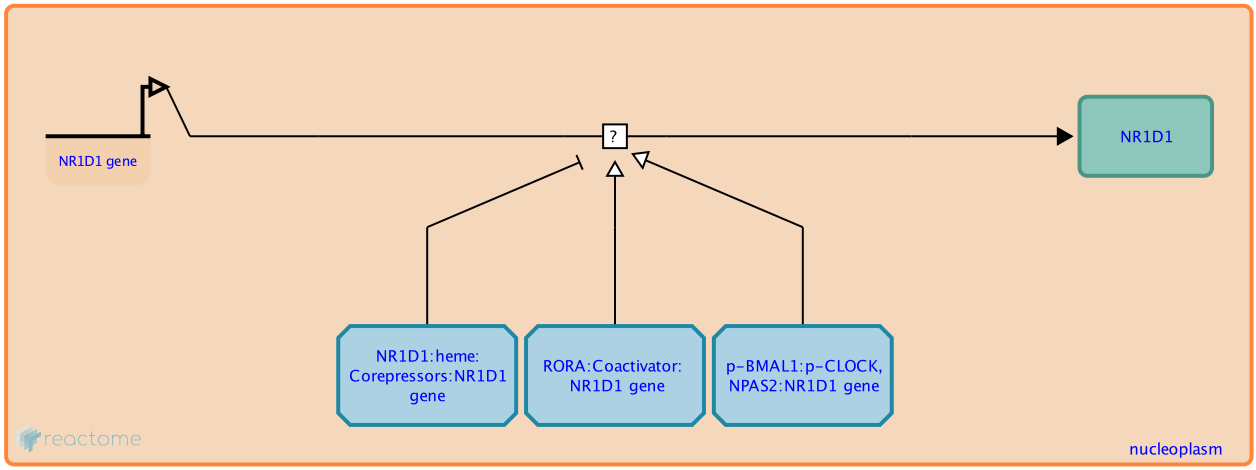
Location: Circadian Clock

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).

Preceded by: p-BMAL1:p-CLOCK,NPAS2 binds NR1D1 gene, RORA, EP300, PPARGC1A bind NR1D1 gene

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

Miyajima, N., Horiuchi, R., Shibuya, Y., Fukushige, S., Matsubara, K., Toyoshima, K. 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. ↗

Adelmant, G., Bègue, A., Stéhelin, D., Laudet, V. (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

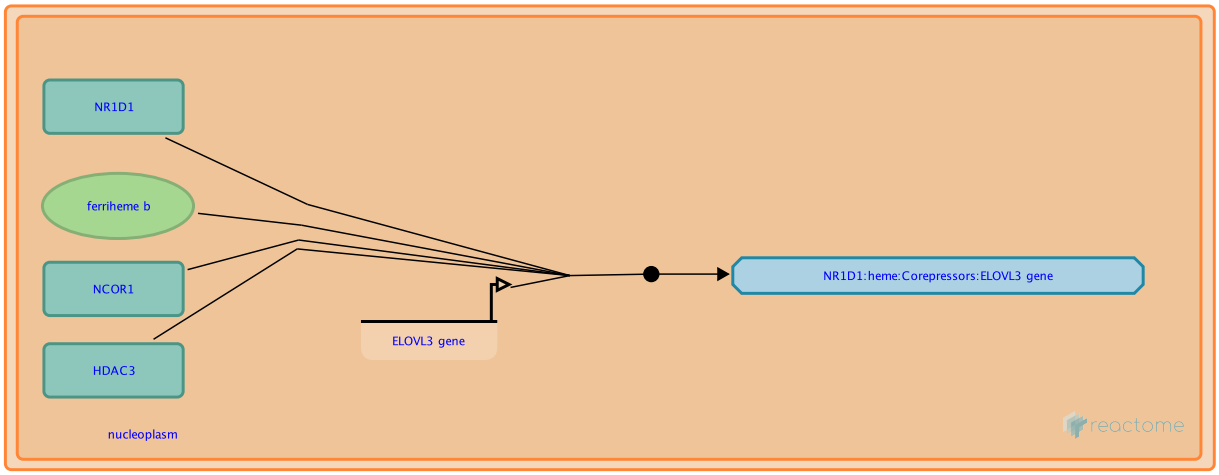
2009-05-27	Reviewed	D'Eustachio, P.
2010-03-19	Authored, Edited	May, B.
2010-06-23	Reviewed	Hirota, T., Kay, SA., Delaunay, F., Albrecht, U.
2021-01-23	Reviewed	Somers, J.

NR1D1 (REV-ERBA) represses gene expression ↗

Location: Circadian Clock

Stable identifier: R-HSA-1368071

Compartments: nucleoplasm



REV-ERBA binds DNA elements very similar to those bound by the transcription activator RORA. RORAREV-ERBA bound to DNA and heme recruits the corepressors NCoR and HDAC3 to repress transcription. Thus REV-ERBA and RORA appear to compete to repress or activate genes, repectively.

Literature references

Raghuram, S., Stayrook, KR., Huang, P., Rogers, PM., Nosie, AK., McClure, DB. 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. ↗

Phelan, CA., Gampe RT, Jr., Lambert, MH., Parks, DJ., Montana, V., Bynum, J. 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. ↗

Yin, L., Wu, N., Lazar, MA. (2010). Nuclear receptor Rev-erbalpha: a heme receptor that coordinates circadian rhythm and metabolism. *Nucl Recept Signal, 8*, e001. ↗

Yin, L., Wu, N., Curtin, JC., Qatanani, M., Szwergold, NR., Reid, RA. et al. (2007). Rev-erbalpha, a heme sensor that coordinates metabolic and circadian pathways. *Science, 318*, 1786-9. ↗

Editions

2011-06-22	Authored, Edited	May, B.
2012-01-28	Reviewed	Delaunay, F.
2015-01-17	Revised	May, B.

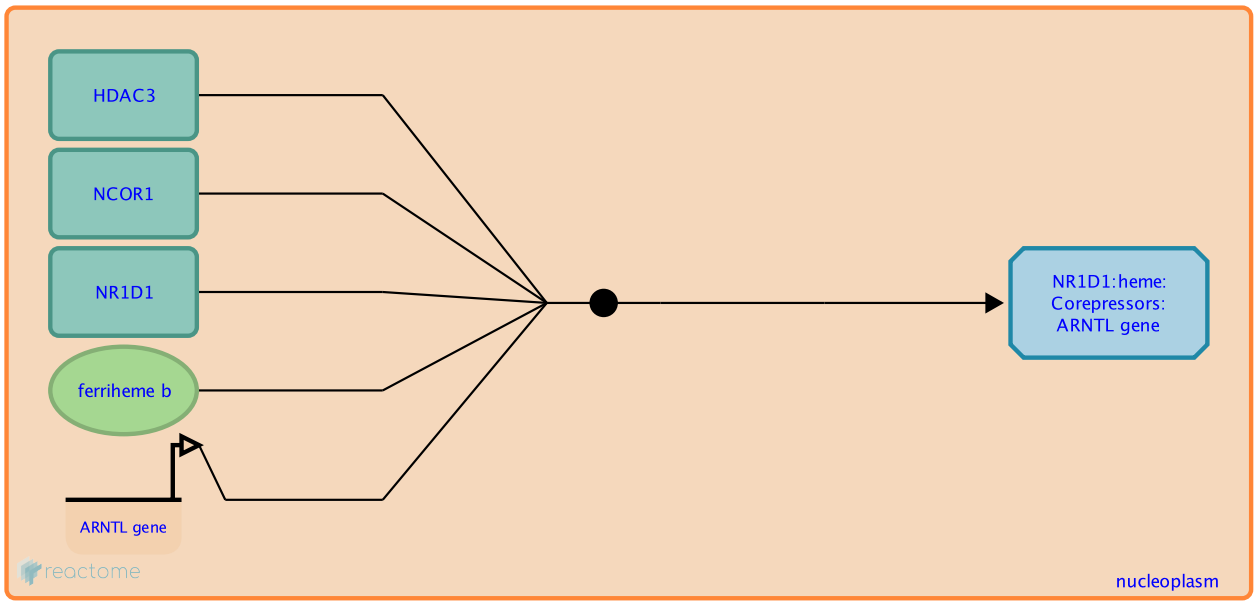
NR1D1 (REV-ERBA) binds heme, the ARNTL gene, and recruits corepressors.

Location: Circadian Clock

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

Raghuram, S., Stayrook, KR., Huang, P., Rogers, PM., Nosie, AK., McClure, DB. 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.

Phelan, CA., Gampe RT, Jr., Lambert, MH., Parks, DJ., Montana, V., Bynum, J. 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.

Yin, L., Lazar, MA. (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.

Yin, L., Wu, N., Curtin, JC., Qatanani, M., Szwergold, NR., Reid, RA. et al. (2007). Rev-erbalpha, a heme sensor that coordinates metabolic and circadian pathways. *Science, 318*, 1786-9.

Editions

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

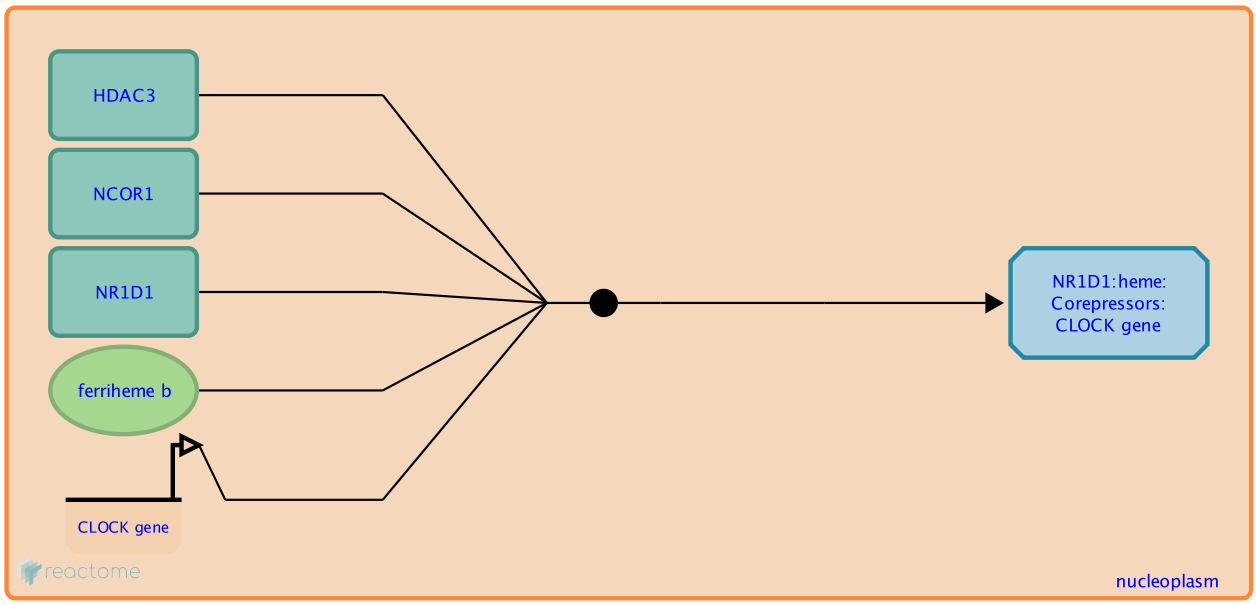
NR1D1 (REV-ERBA) binds heme, the CLOCK gene, and recruits corepressors ↗

Location: Circadian Clock

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.

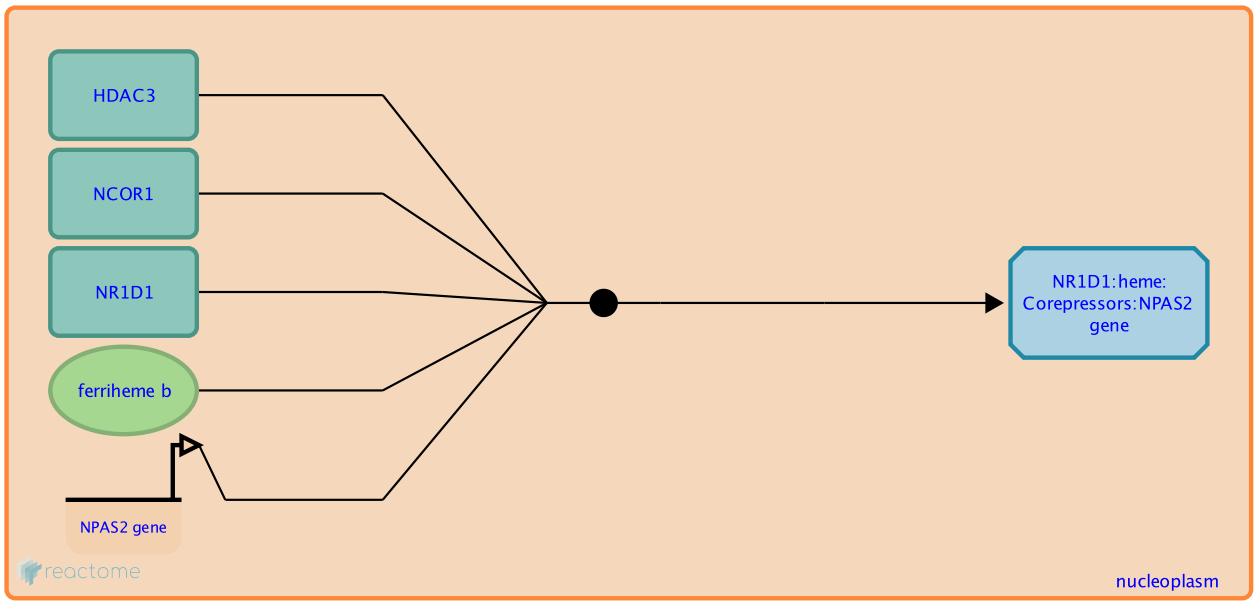
NR1D1 (REV-ERBA) binds heme, the NPAS2 gene, and recruits corepressors ↗

Location: Circadian Clock

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

Crumbley, C., Wang, Y., Kojetin, DJ., Burris, TP. (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.

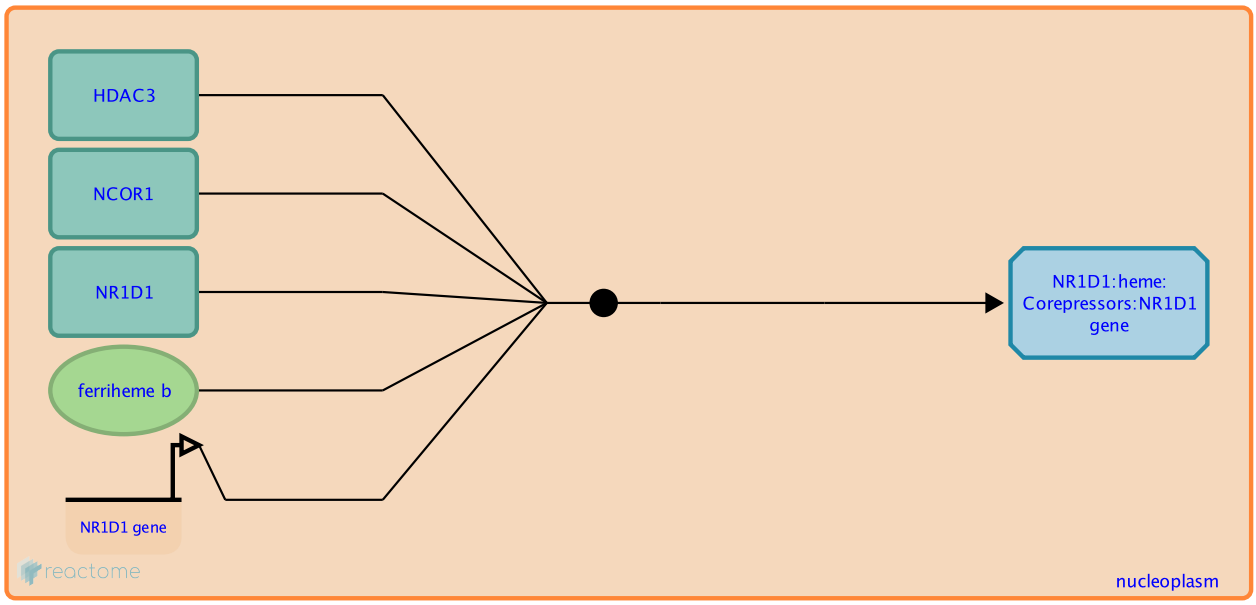
NR1D1 (REV-ERBA) binds heme, the NR1D1 gene, and recruits corepressors ↗

Location: Circadian Clock

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

Adelmant, G., Bègue, A., Stéhelin, D., Laudet, V. (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.

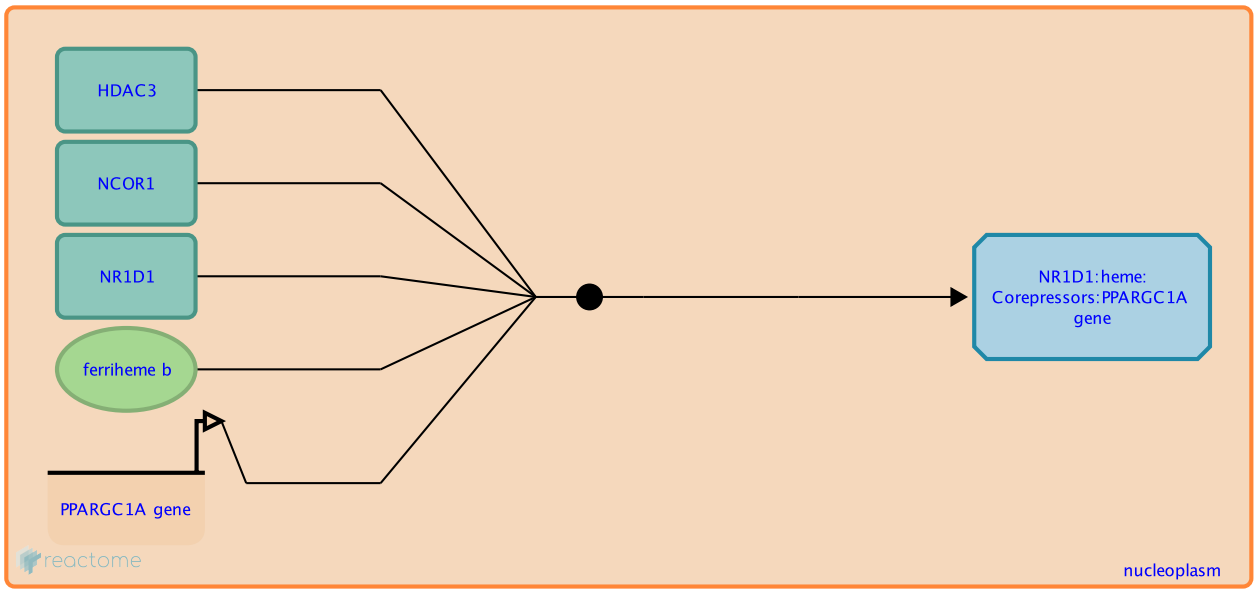
NR1D1 (REV-ERBA) binds heme, the PPARGC1A gene, and recruits corepressors ↗

Location: Circadian Clock

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

Wu, N., Yin, L., Hanniman, EA., Joshi, S., Lazar, MA. (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.

Table of Contents