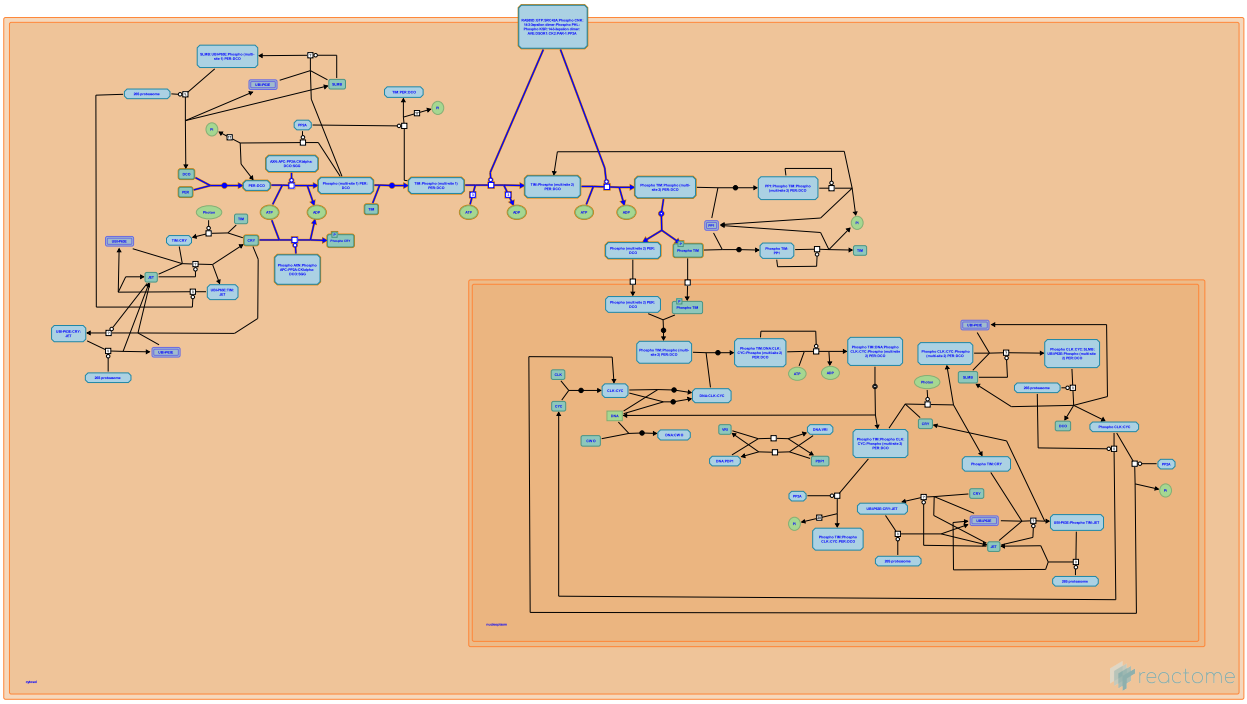
Phosphorylation of PER and TIM



Edery, I., Williams, MG.

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

01/05/2024

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

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

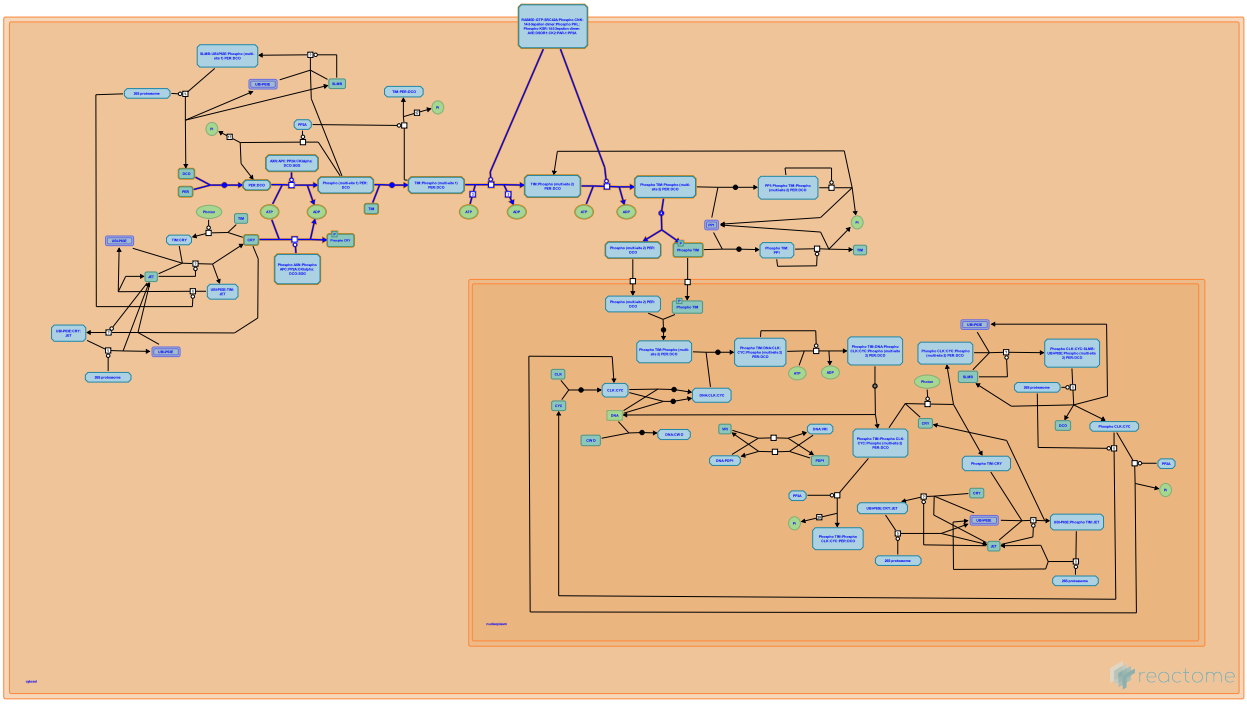
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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

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

Phosphorylation of PER and TIM ↗

Stable identifier: R-DME-432553



Spatzle (SPZ) dimer binding leads to Toll (TL) receptor homodimerisation and activation.

Literature references

Hardin, PE. (2005). The circadian timekeeping system of Drosophila. *Curr Biol, 15*, R714-22. ↗

Editions

2009-08-13	Authored	Williams, MG.
2009-08-14	Edited	Williams, MG.
2010-07-06	Reviewed	Edery, I.

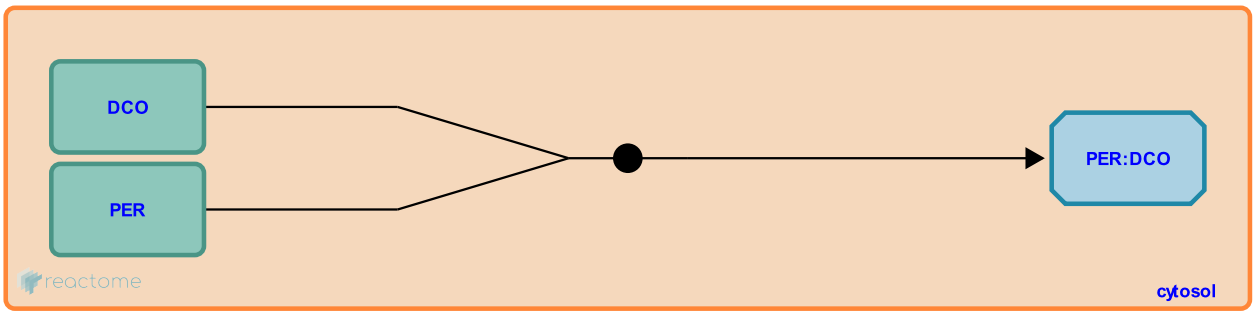
PER binds to DCO ↗

Location: Phosphorylation of PER and TIM

Stable identifier: R-DME-538835

Type: binding

Compartments: cytosol



The Casein kinase 1epsilon orthologue, Discs Overgrown (DCO) aka Double-time (DBT) forms a complex with Period (PER).

Followed by: PER is phosphorylated by DCO

Literature references

Saez, L., Young, MW., Rothenfluh, A., Kloss, B. (2001). Phosphorylation of period is influenced by cycling physical associations of double-time, period, and timeless in the Drosophila clock. *Neuron, 30*, 699-706. ↗

Wesley, CS., Price, JL., Saez, L., Young, MW., Rothenfluh, A., Blau, J. et al. (1998). The Drosophila clock gene double-time encodes a protein closely related to human casein kinase Iepsilon. *Cell, 94*, 97-107. ↗

Editions

2010-03-08	Authored	Williams, MG.
2010-07-06	Reviewed	Edery, I.
2014-05-20	Edited	Williams, MG.

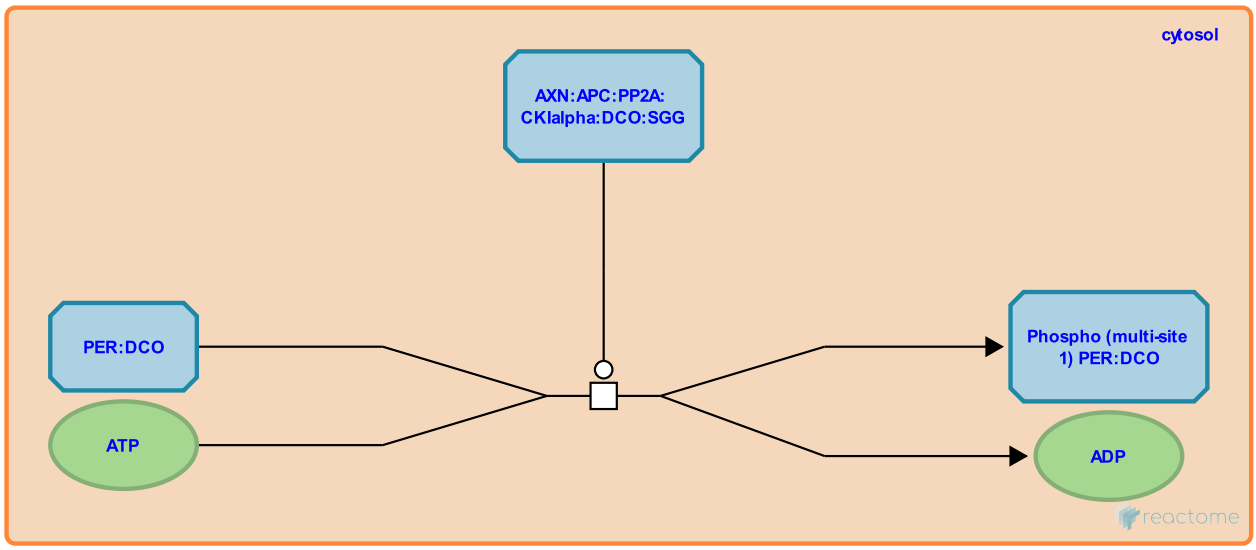
PER is phosphorylated by DCO ↗

Location: Phosphorylation of PER and TIM

Stable identifier: R-DME-432559

Type: transition

Compartments: cytosol



Period (PER) is phosphorylated on between 15-20 individual serine and threonine sites by Casein kinase 1epsilon orthologue, Discs Overgrown (DCO) aka Double-time (DBT). During the day, when light activated regulation of Timeless (TIM) occurs and its levels are low, phosphorylated PER is susceptible to supernumerary limbs (SLMB) mediated ubiquitination and degradation. Ser47 and possibly other phosphorylated residues nearby are key phospho-signals on PER mediating the binding of SLMB to PER.

Preceded by: PER binds to DCO

Followed by: Phosphorylated PER binds to TIM

Literature references

Grima, B., Lamouroux, A., Limbourg-Bouchon, B., Papin, C., Rouyer, F., Chélot, E. (2002). The F-box protein slimb controls the levels of clock proteins period and timeless. *Nature, 420*, 178-82. ↗

Vanselow, JT., Edery, I., Kramer, A., Chiu, JC. (2008). The phospho-occupancy of an atypical SLIMB-binding site on PERIOD that is phosphorylated by DOUBLETIME controls the pace of the clock. *Genes Dev, 22*, 1758-72. ↗

Jiang, J., Edery, I., Ko, HW. (2002). Role for Slimb in the degradation of Drosophila Period protein phosphorylated by Doubletime. *Nature, 420*, 673-8. ↗

Editions

2009-08-13	Authored	Williams, MG.
2010-07-06	Reviewed	Edery, I.
2014-05-20	Edited	Williams, MG.

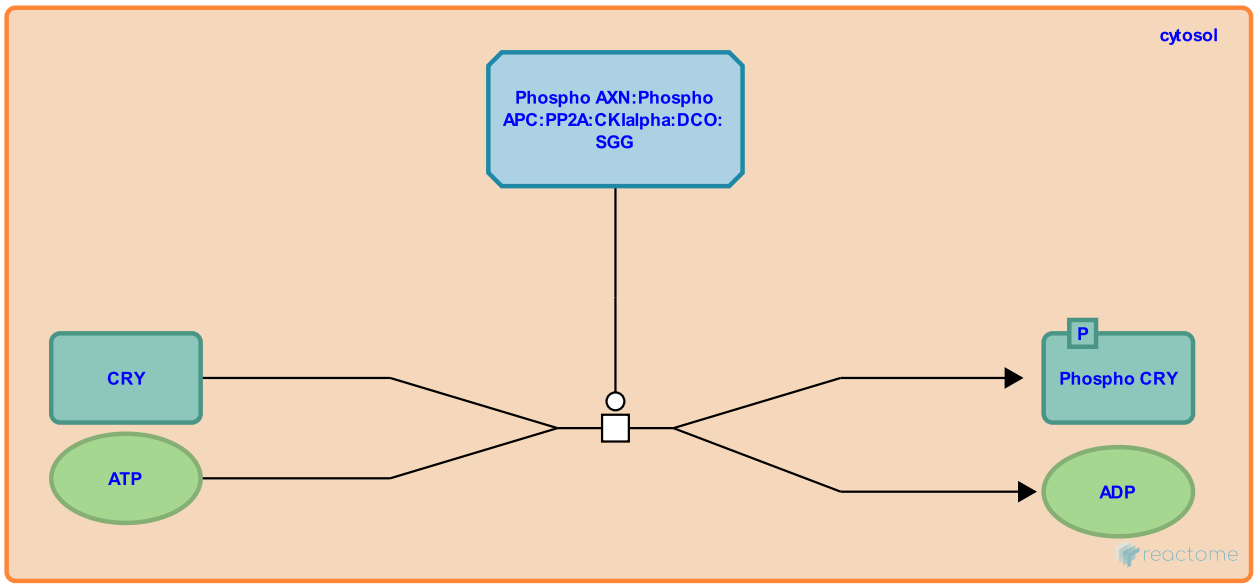
CRY is phosphorylated by SGG ↗

Location: Phosphorylation of PER and TIM

Stable identifier: R-DME-881988

Type: transition

Compartments: cytosol



The blue-light photoreceptor cryptochrome (CRY) is phosphorylated on unknown serine/threonine residues by GSK3beta kinase orthologue, Shaggy (SGG). Phosphorylation appears to attenuate the function of CRY and it doesn't degrade Timeless (TIM). Earlier studies suggested that the effect of SGG on the light-mediated degradation of TIM was due to direct phosphorylation of TIM by SGG (Martinek et al., 2001), however, more recent experiments suggest the actual target of SGG in this pathway is CRY (Storelu et al., 2007).

Literature references

Menet, JS., Nawathean, P., Stoleru, D., Fernández, MP., Rosbash, M., Ceriani, MF. (2007). The Drosophila circadian network is a seasonal timer. *Cell, 129*, 207-19. ↗

Inonog, S., Young, MW., Manoukian, AS., Martinek, S. (2001). A role for the segment polarity gene shaggy/GSK-3 in the Drosophila circadian clock. *Cell, 105*, 769-79. ↗

Editions

2010-06-28	Authored	Williams, MG.
2010-07-06	Reviewed	Edery, I.
2014-05-20	Edited	Williams, MG.

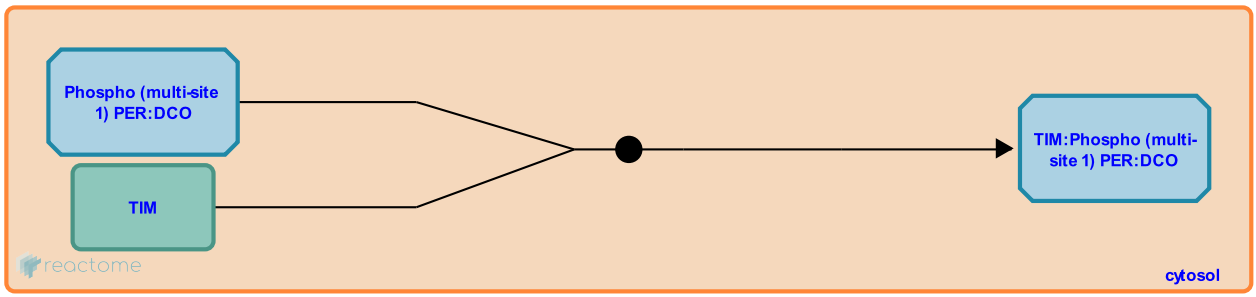
Phosphorylated PER binds to TIM ↗

Location: Phosphorylation of PER and TIM

Stable identifier: R-DME-432647

Type: binding

Compartments: cytosol



After dusk, *per* and *tim* genes continue to be transcribed and their mRNAs reach peak levels between during the early part of the night. Timeless (TIM) protein is stable in the dark and so begins to accumulate and forms a complex with Period (PER) and Casein kinase 1epsilon orthologue, Discs Overgrown (DCO) aka Double-time (DBT). TIM stabilises PER despite the continuous attentions of casein kinase II (CK2) and DCO. As a result, PER and TIM accumulate to high levels during the middle of the night.

Preceded by: PER is phosphorylated by DCO

Followed by: Phosphorylated PER is phosphorylated by CK2

Literature references

Myers, MP., Qian, Z., Rosbash, M., Zeng, H. (1996). A light-entrainment mechanism for the Drosophila circadian clock. *Nature, 380*, 129-35. ↗

Bae, K., Itsukaichi, T., Edery, I., Lee, C., Parikh, V. (1996). Resetting the Drosophila clock by photic regulation of PER and a PER-TIM complex. *Science, 271*, 1740-4. ↗

Saez, L., Young, MW., Rothenfluh, A., Kloss, B. (2001). Phosphorylation of period is influenced by cycling physical associations of double-time, period, and timeless in the Drosophila clock. *Neuron, 30*, 699-706. ↗

Myers, MP., Delahaye-Brown, AM., Sehgal, A., Saez, L., Young, MW., Weitz, CJ. et al. (1995). Isolation of timeless by PER protein interaction: defective interaction between timeless protein and long-period mutant PERL. *Science, 270*, 811-5. ↗

Saez, L., Young, MW., Meyer, P. (2006). PER-TIM interactions in living Drosophila cells: an interval timer for the circadian clock. *Science, 311*, 226-9. ↗

Editions

2009-08-13	Authored	Williams, MG.
2010-07-06	Reviewed	Edery, I.
2014-05-20	Edited	Williams, MG.

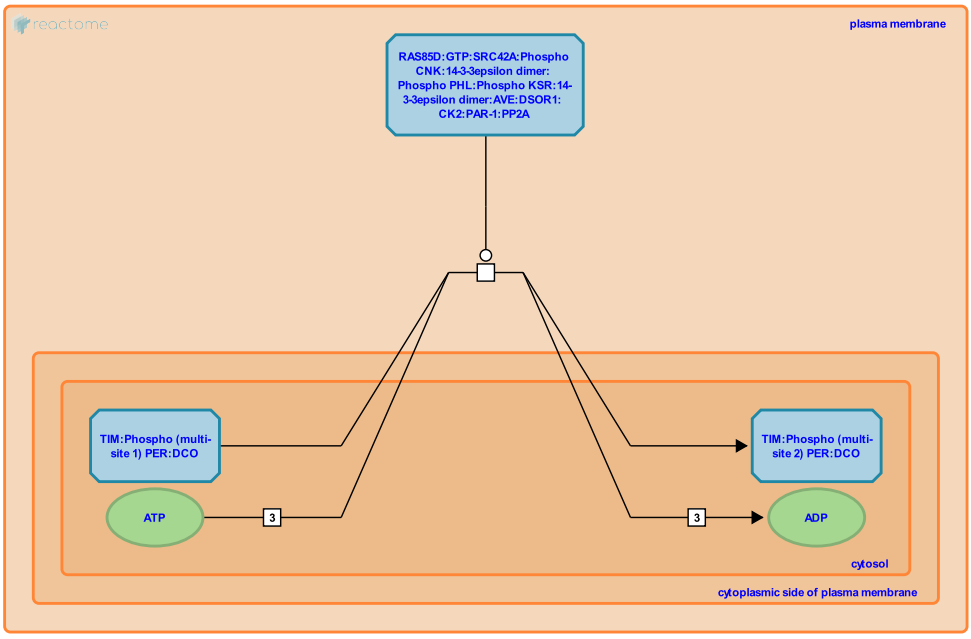
Phosphorylated PER is phosphorylated by CK2 ↗

Location: Phosphorylation of PER and TIM

Stable identifier: R-DME-432590

Type: transition

Compartments: plasma membrane, cytosol



Phosphorylated Period (PER) is phosphorylated on serine residues 149, 151, 153, by casein kinase II (CK2). CK2 phosphorylation appears to be important for subsequent nuclear entry of PER.

Preceded by: Phosphorylated PER binds to TIM

Followed by: TIM is phosphorylated by CK2

Literature references

Vanselow, JT., Edery, I., Kramer, A., Chiu, JC. (2008). The phospho-occupancy of an atypical SLIMB-binding site on PERIOD that is phosphorylated by DOUBLETIME controls the pace of the clock. *Genes Dev, 22*, 1758-72. ↗

Kilman, VL., Allada, R., Paddock, B., Emery-Le, M., Rosbash, M., Lin, JM. et al. (2002). A role for casein kinase 2alpha in the Drosophila circadian clock. *Nature, 420*, 816-20. ↗

Allada, R., Lin, JM., Schroeder, A. (2005). In vivo circadian function of casein kinase 2 phosphorylation sites in Drosophila PERIOD. *J Neurosci, 25*, 11175-83. ↗

Raabe, T., Kim, EY., Edery, I., Genova, GK., Akten, B., Jackson, FR. et al. (2003). A role for CK2 in the Drosophila circadian oscillator. *Nat Neurosci, 6*, 251-7. ↗

Kilman, VL., Allada, R., Lin, JM., Meissner, RA. (2008). TIMELESS is an important mediator of CK2 effects on circadian clock function in vivo. *J Neurosci, 28*, 9732-40. ↗

Editions

2009-08-13	Authored	Williams, MG.
2010-07-06	Reviewed	Edery, I.
2014-05-20	Edited	Williams, MG.

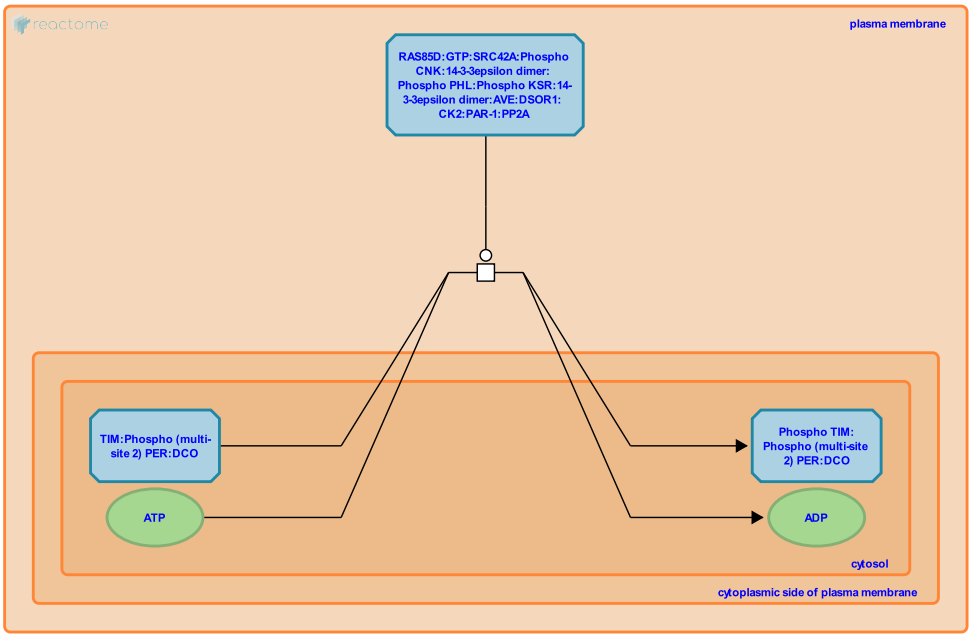
TIM is phosphorylated by CK2 ↗

Location: Phosphorylation of PER and TIM

Stable identifier: R-DME-432535

Type: transition

Compartments: plasma membrane, cytosol



Timeless (TIM) is phosphorylated on unknown serine/threonine residues by casein kinase II (CK2). CK2 phosphorylation appears to be important for subsequent nuclear entry of TIM.

Preceded by: Phosphorylated PER is phosphorylated by CK2

Followed by: Phosphorylated TIM:PER heterodimer dissociate

Literature references

Kilman, VL., Allada, R., Lin, JM., Meissner, RA. (2008). TIMELESS is an important mediator of CK2 effects on circadian clock function in vivo. *J Neurosci, 28*, 9732-40. ↗

Editions

2009-08-13	Authored	Williams, MG.
2010-07-06	Reviewed	Edery, I.
2014-05-20	Edited	Williams, MG.

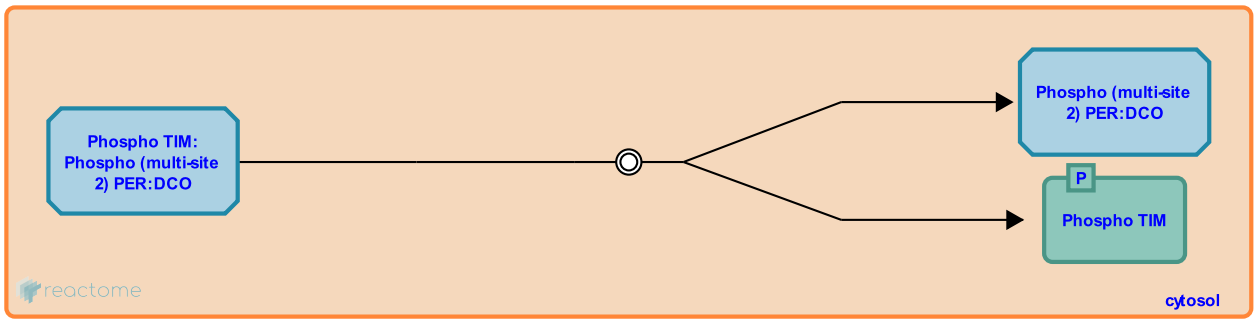
Phosphorylated TIM:PER heterodimer dissociate ↗

Location: Phosphorylation of PER and TIM

Stable identifier: R-DME-432464

Type: dissociation

Compartments: cytosol



The phosphorylation of Timeless (TIM) and Period (PER) by casein kinase II (CK2) appears to be the trigger for their nuclear entry. However, before this occurs, phosphorylated TIM dissociates from the PER:Discs Overgrown (DCO) complex.

Preceded by: TIM is phosphorylated by CK2

Literature references

Saez, L., Young, MW., Meyer, P. (2006). PER-TIM interactions in living Drosophila cells: an interval timer for the circadian clock. *Science, 311*, 226-9. ↗

Truman, JW., Rosbash, M., Shafer, OT. (2002). Sequential nuclear accumulation of the clock proteins period and timeless in the pacemaker neurons of Drosophila melanogaster. *J Neurosci, 22*, 5946-54. ↗

Ashmore, LJ., Schotland, P., Silvestre, DW., Sehgal, A., Sathyanarayanan, S., Emerson, MM. (2003). Novel insights into the regulation of the timeless protein. *J Neurosci, 23*, 7810-9. ↗

Editions

2009-08-13	Authored	Williams, MG.
2010-07-06	Reviewed	Edery, I.
2014-05-20	Edited	Williams, MG.

Table of Contents