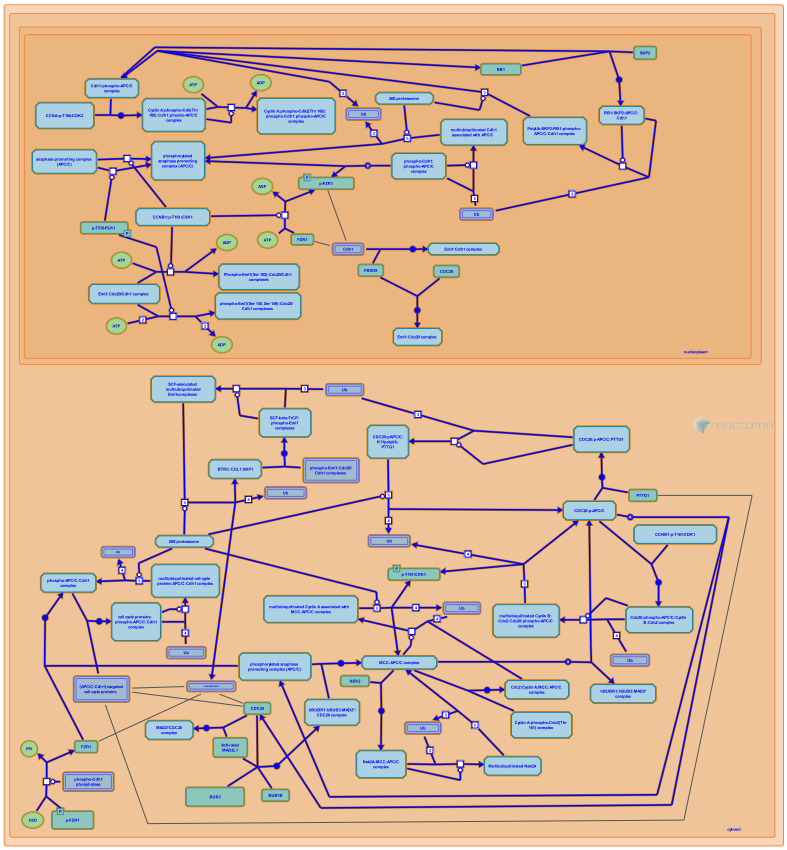
APC/C-mediated degradation of cell cycle proteins



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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.

19/09/2024

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. ↗

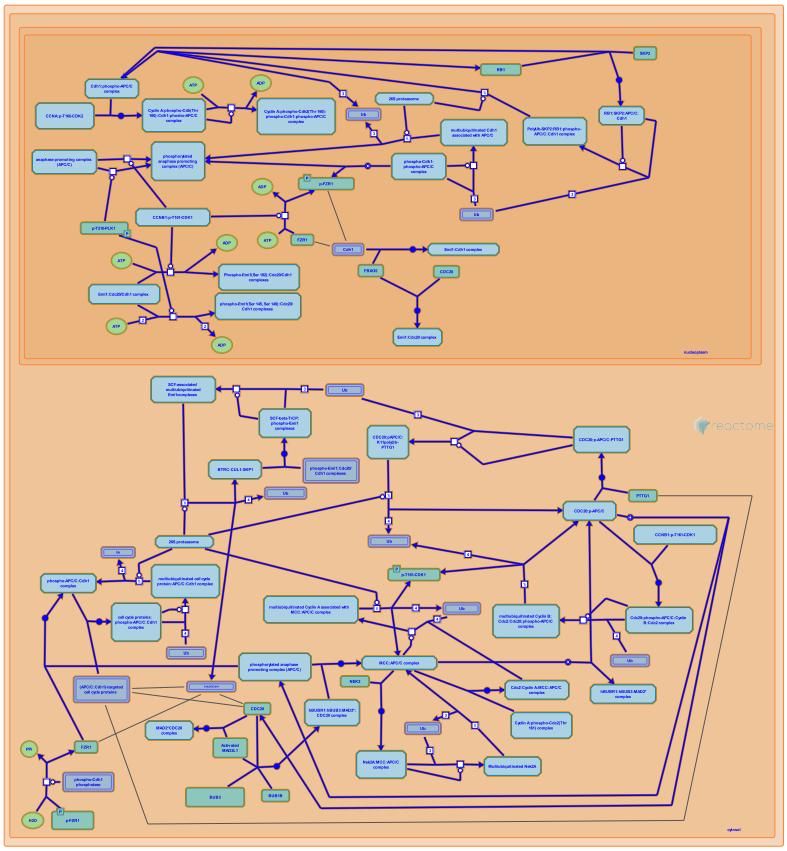
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 89

This document contains 6 pathways (see Table of Contents)

APC/C-mediated degradation of cell cycle proteins ↗

Stable identifier: R-HSA-174143



The Anaphase Promoting Complex or Cyclosome (APC/C) functions during mitosis to promote sister chromatid separation and mitotic exit through the degradation of mitotic cyclins and securin. This complex is also active in interphase insuring the appropriate length of the G1 phase (reviewed in Peters, 2002). The APC/C contains at least 12 subunits and functions as an ubiquitin-protein ligase (E3) promoting the multiubiquitination of its target proteins (see Gieffers et al., 2001).

In the ubiquitination reaction, ubiquitin is activated by the formation of a thioester bond with the (E1) ubiquitin activating enzyme then transferred to a cysteine residue within the ubiquitin conjugating enzyme (E2) and ultimately to a lysine residue within the target protein, with the aid of ubiquitin-protein ligase activity of the APC/C. The ubiquitin chains generated are believed to target proteins for destruction by the 26S proteasome (Reviewed in Peters, 1994)

The activity of the APC/C is highly periodic during the cell cycle and is controlled by a combination of regulatory events. The APC/C is activated by phosphorylation and the regulated recruitment of activating subunits and is negatively regulated by sequestration by kinetochore-associated checkpoint proteins. The Emi1 protein associates with Cdh1 and Cdc20, inhibiting the APC/C between G1/S and prophase. RSSA1 may play a similar role in ihibiting the APC during early mitosis.

Following phosphorylation of the APC/C core subunits by mitotic kinases, the activating subunit, Cdc20 is recruited to the APC/C and is responsible for mitotic activities, including the initiation of sister chromatid separation and the timing of exit from mitosis (See Zachariae and Nasmyth, 1999). Substrates of the Cdc20:APC/C complex, which are recognized by a motif known as the destruction box (D box) include Cyclin A, Nek2, Securin and Cyclin B. Degradation of Securin and Cyclin B does not occur until the mitotic spindle checkpoint has been satisfied (see Castro et al. 2005).

Cdc20 is degraded late in mitosis (Reviewed in Owens and Hoyt, 2005). At this time the activating subunit, Cdh1, previously maintained in an inactive phosphorylated state by mitotic kinases, is dephosphorylated and associates with and activates the APC/C. The APC/C:Cdh1 complex recognizes substrates containing a D box, a KEN box (Pfleger and Kirschner, 2000) or a D box activated (DAD) domain (Castro et al., 2002) sequence and promotes the ordered degration of mitotic cyclins and other mitotic proteins culminating with its own ubiquitin-conjugating enzyme (E2) subunit UbcH10 (Rape et al., 2006). This ordered degradation promotes the stability of Cyclin A at the end of G1. This stabilization, in turn, promotes the phosphorylation of Cdh1 and its abrupt dissociation from the APC/C, allowing accumulation of cyclins for the next G1/S transition (Sorensen et al., 2001).

Literature references

Peters, JM. (2002). The anaphase-promoting complex: proteolysis in mitosis and beyond. *Mol Cell, 9*, 931-43. ↗

Lorca, T., Bernis, C., Vigneron, S., Castro, A., Labbe, JC. (2005). The anaphase-promoting complex: a key factor in the regulation of cell cycle. *Oncogene, 24*, 314-25. ↗

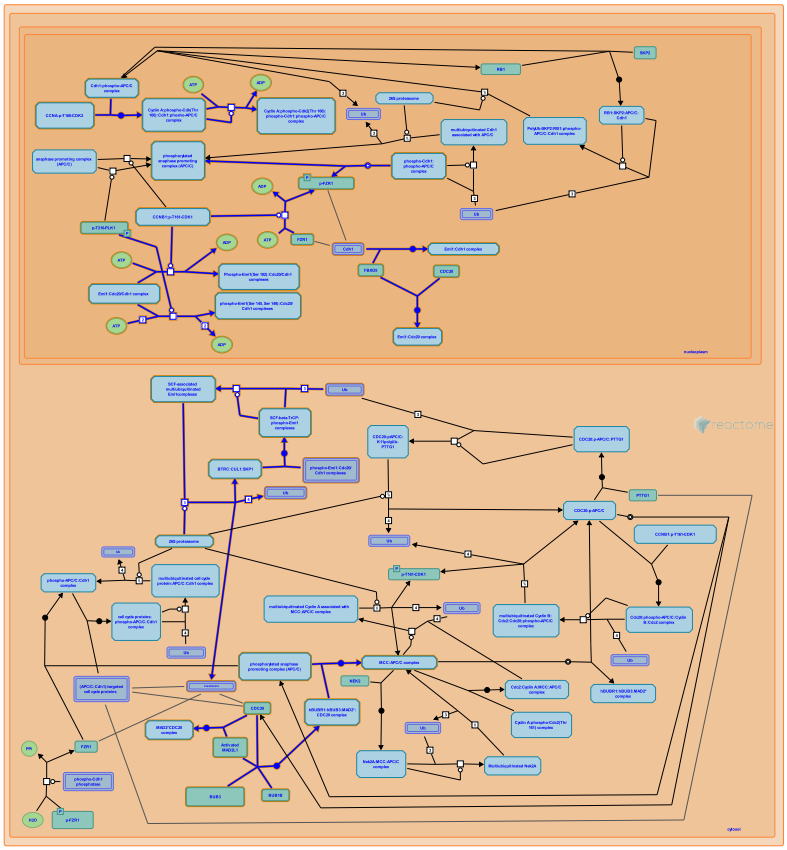
Editions

2006-01-26	Authored	Lorca, T., Castro, A.
2006-01-30	Edited	Matthews, L.
2006-03-28	Reviewed	Peters, JM.

Regulation of APC/C activators between G1/S and early anaphase ↗

Location: APC/C-mediated degradation of cell cycle proteins

Stable identifier: R-HSA-176408



The APC/C is activated by either Cdc20 or Cdh1. While both activators associate with the APC/C, they do so at different points in the cell cycle and their binding is regulated differently (see Zachariae and Nasmyth, 1999). Cdc20, whose protein levels increase as cells enter into mitosis and decrease upon mitotic exit, only associates with the APC/C during M phase. Cdh1 associates with the APC/C in G1. This interaction is inhibited at other times by Cdk1 phosphorylation.

Literature references

Peters, JM., Buschhorn, BA. (2006). How APC/C orders destruction. *Nat Cell Biol, 8*, 209-11. ↗

Peters, JM. (2002). The anaphase-promoting complex: proteolysis in mitosis and beyond. *Mol Cell, 9*, 931-43. ↗

Lorca, T., Bernis, C., Vigneron, S., Castro, A., Labbe, JC. (2005). The anaphase-promoting complex: a key factor in the regulation of cell cycle. *Oncogene, 24*, 314-25. ↗

Burton, JL., Solomon, MJ., Harper, JW. (2002). The anaphase-promoting complex: it's not just for mitosis any more. *Genes Dev, 16*, 2179-206. ↗

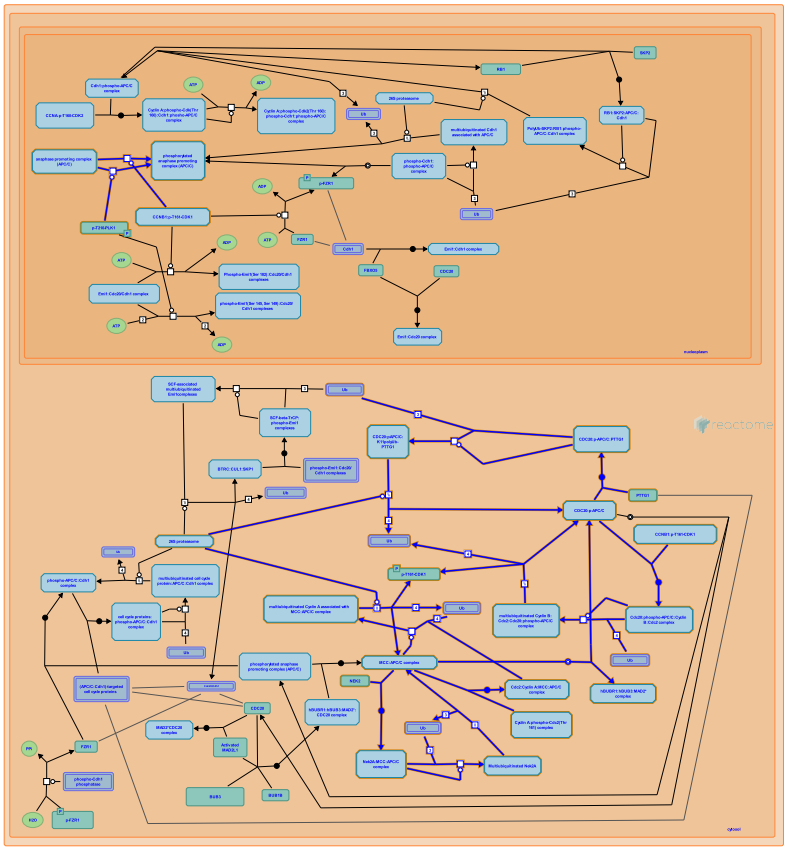
Editions

2006-03-28	Reviewed	Peters, JM.

Activation of APC/C and APC/C:Cdc20 mediated degradation of mitotic proteins ↗

Location: APC/C-mediated degradation of cell cycle proteins

Stable identifier: R-HSA-176814



APC/C:Cdc20 is first activated at the prometaphase/metaphase transition through phosphorylation of core subunits of the APC/C by mitotic kinases as well as recruitment of the APC/C activator protein Cdc20. APC/C:Cdc20 promotes the multiubiquitination and ordered degradation of Cyclin A and Nek2 degradation in prometaphase followed by Cyclin B and securin in metaphase (Reviewed in Castro et al., 2005).

Literature references

Lorca, T., Bernis, C., Vigneron, S., Castro, A., Labbe, JC. (2005). The anaphase-promoting complex: a key factor in the regulation of cell cycle. *Oncogene, 24*, 314-25. ↗

Editions

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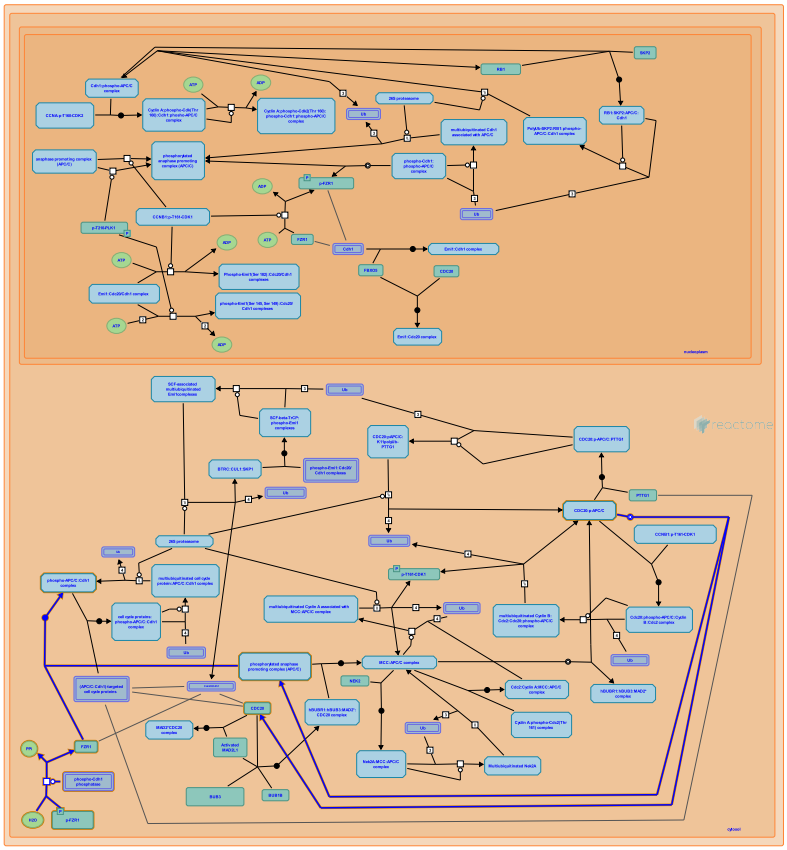
2006-03-28	Reviewed	Peters, JM.

Conversion from APC/C:Cdc20 to APC/C:Cdh1 in late anaphase ↗

Location: APC/C-mediated degradation of cell cycle proteins

Stable identifier: R-HSA-176407



The activity of the APC/C must be appropriately regulated during the cell cycle to ensure the timely degradation of its substrates. Of particular importance is the conversion from APC/C:Cdc20 to APC/C:Cdh1 in late anaphase. Phosphorylation of both the APC/C complex and Cdh1 regulate this conversion. During mitosis, several APC/C subunits are phosphorylated increasing the activity of APC/C:Cdc20. However, phosphorylation of Cdh1 by mitotic Cyclin:Cdk complexes prevents it from activating the APC/C. Dephosphorylation of Cdh1 in late anaphase by Cdc14a results in the activation of APC/C:Cdh1 (reviewed in Castro et al, 2005).

Literature references

Lorca, T., Bernis, C., Vigneron, S., Castro, A., Labbe, JC. (2005). The anaphase-promoting complex: a key factor in the regulation of cell cycle. *Oncogene, 24*, 314-25. ↗

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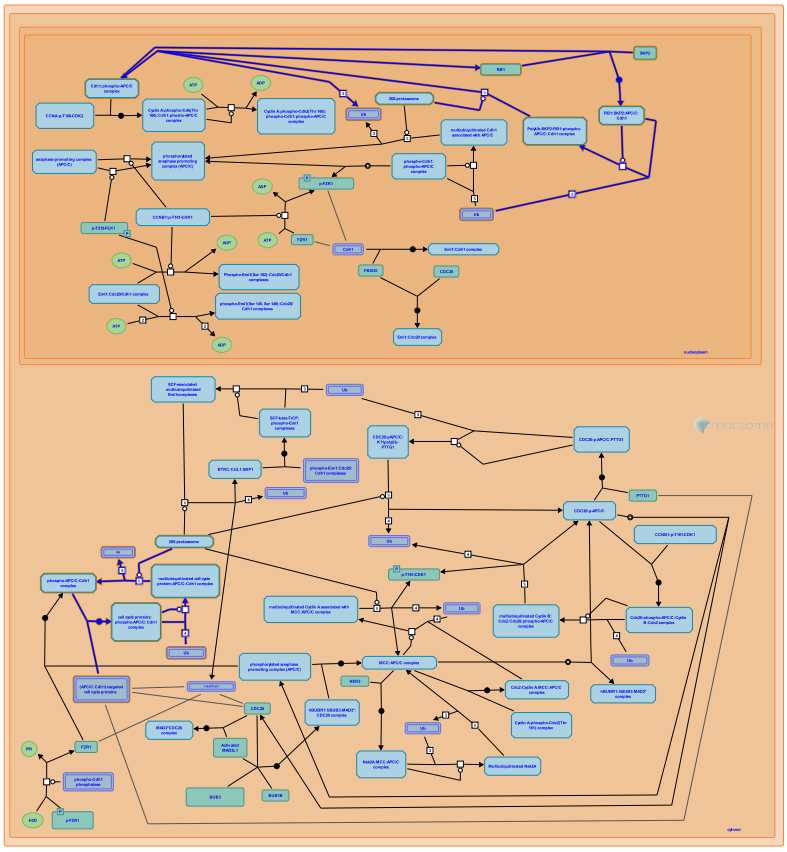
2006-02-17	Edited	Matthews, L.
2006-03-28	Reviewed	Peters, JM.

APC/C:Cdh1 mediated degradation of Cdc20 and other APC/C:Cdh1 targeted proteins in late mitosis/early G1 ↗

Location: APC/C-mediated degradation of cell cycle proteins

Stable identifier: R-HSA-174178



From late mitosis through G1 phase APC/C:Cdh1 insures the continued degradation of the mitotic proteins and during mitotic exit and G1 its substrates include Cdc20, Plk1, Aurora A, Cdc6 and Geminin (see Castro et al., 2005). Rape et al. have recently demonstrated that the order in which APC/C targeted proteins are degraded is determined by the processivity of multiubiquitination of these substrates. Processive substrates acquire a polyubiquitin chain upon binding to the APC/C once and are degraded. Distributive substrates bind, dissociate and reassociate with the APC/C multiple times before acquiring an ubiquitin chain of sufficient length to insure degradation. In addition, distributive substrates that dissociate from the APC/C with short ubiquitin chains are targeted for deubiquitination (Rape et al., 2006).

Literature references

Lorca, T., Bernis, C., Vigneron, S., Castro, A., Labbe, JC. (2005). The anaphase-promoting complex: a key factor in the regulation of cell cycle. *Oncogene, 24*, 314-25. ↗

Kirschner, MW., Rape, M., Reddy, SK. (2006). The processivity of multiubiquitination by the APC determines the order of substrate degradation. *Cell, 124*, 89-103. ↗

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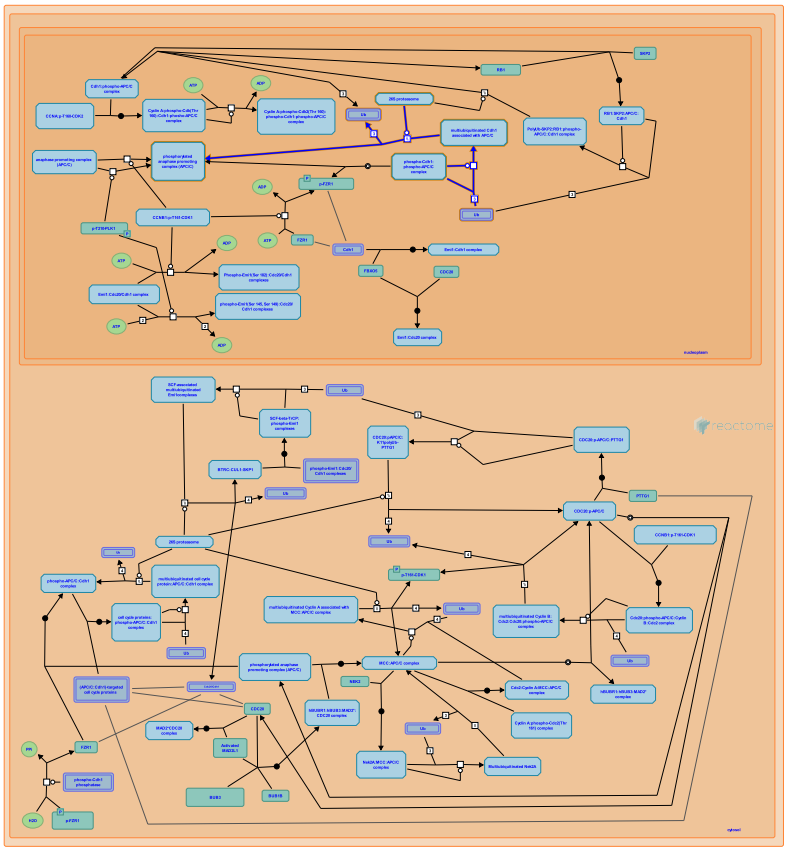
Autodegradation of Cdh1 by Cdh1:APC/C ↗

Location: APC/C-mediated degradation of cell cycle proteins

Stable identifier: R-HSA-174084

Compartments: nucleoplasm



Cdh1 is degraded by the APC/C during in G1 and G0. This auto-regulation may contribute to reducing the levels of Cdh1 levels during G1 and G0 (Listovsky et al., 2004).

Literature references

Listovsky, T., Weiss, AM., Brandeis, M., Lebendiker, M., Mahbubani, HM., Yudkovsky, Y. et al. (2004). Mammalian Cdh1/Fzr mediates its own degradation. *EMBO J, 23*, 1619-26. ↗

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2006-01-30	Edited	Matthews, L.
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