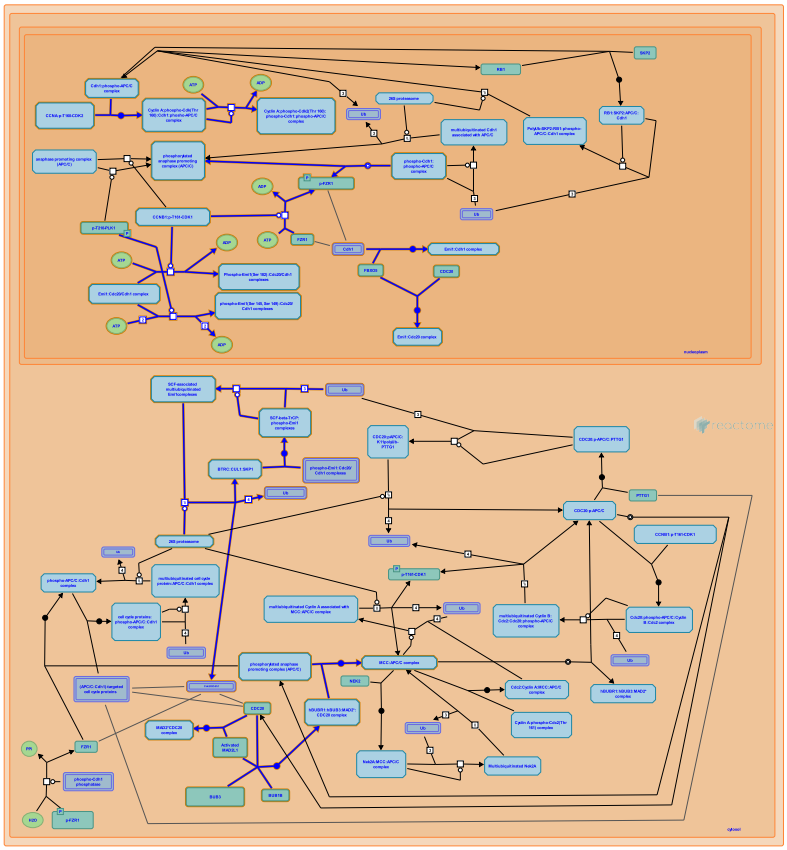
Regulation of APC/C activators between G1/S and early anaphase



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04/05/2024

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. ↗

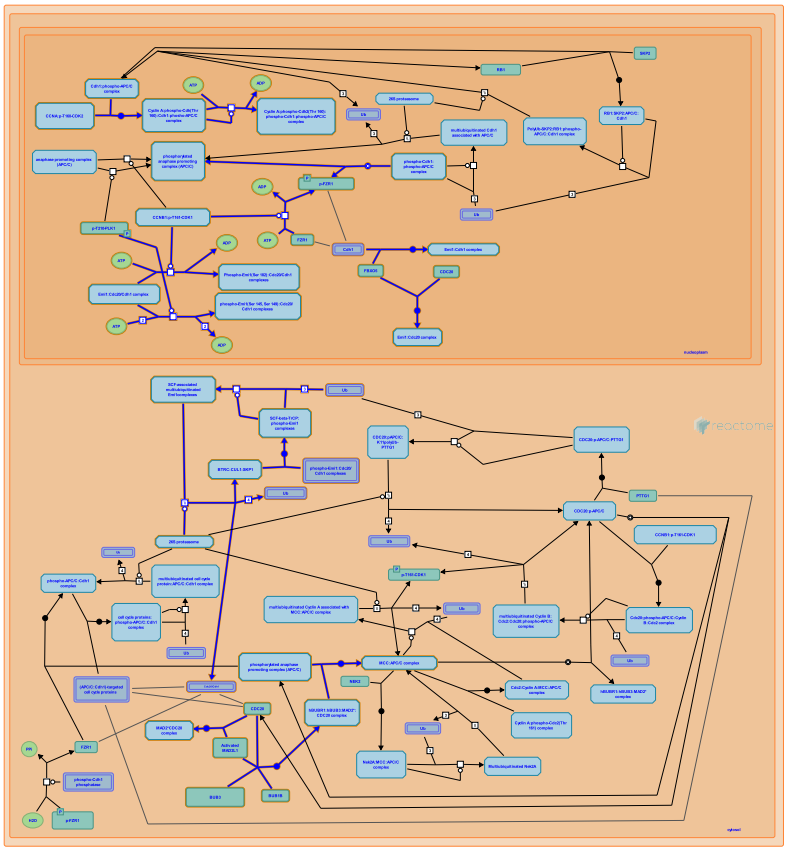
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

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

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.

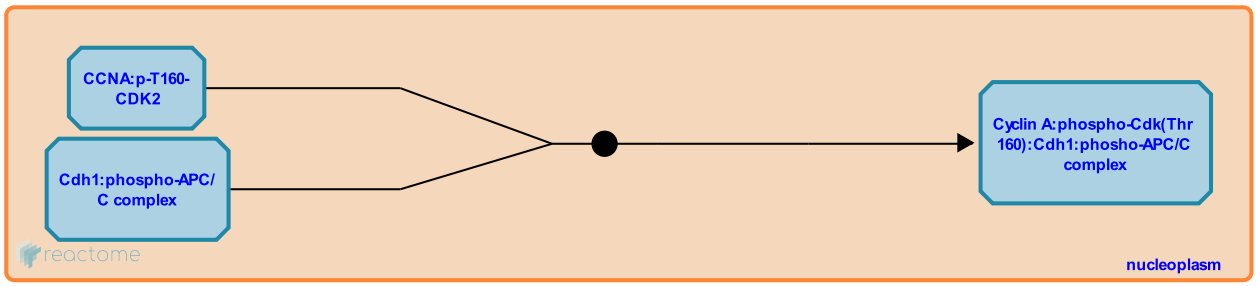
Association of Cyclin A:Cdk2 with Cdh1 ↗

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

Stable identifier: R-HSA-188371

Type: binding

Compartments: nucleoplasm



Cyclin A-Cdk2 prevents unscheduled APC reactivation during S phase by binding and subsequently phosphorylating Cdh1. Phosphorylation-dependent dissociation of the Cdh1-activating subunit inhibits the APC/C.

Followed by: Phosphorylation of Cdh1 by Cyclin A:Cdk2

Literature references

Lukas, J., Peters, JM., Kramer, ER., Sorensen, CS., Lukas, C. (2001). A conserved cyclin-binding domain determines functional interplay between anaphase-promoting complex-Cdh1 and cyclin A-Cdk2 during cell cycle progression. *Mol Cell Biol, 21*, 3692-703. ↗

Editions

2006-10-10	Authored	Lorca, T., Castro, A.
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2006-10-10	Reviewed	Peters, JM.

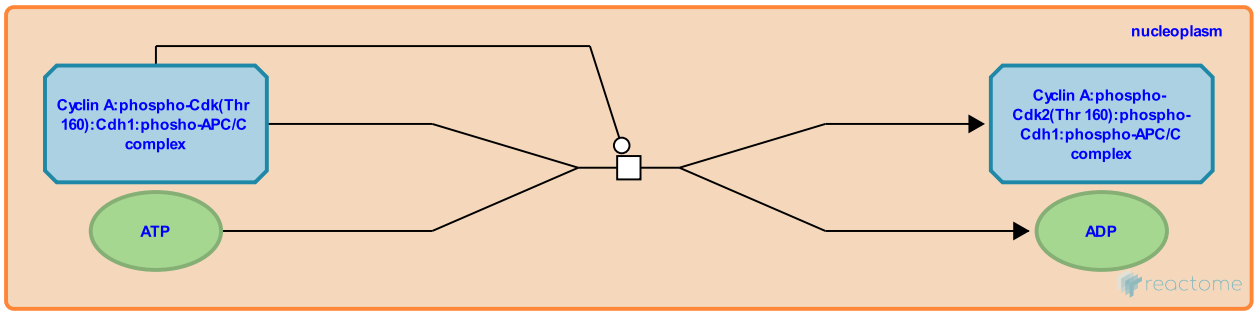
Phosphorylation of Cdh1 by Cyclin A:Cdk2 ↗

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

Stable identifier: R-HSA-174079

Type: transition

Compartments: nucleoplasm



At the G1/S transition, the Cdh1 subunit of the APC:Cdh1 complex is phosphorylated by Cyclin A:Cdk2 and dissociates from APC/C. This inactivates APC/C and permits the accumulation of cell cycle proteins required for DNA synthesis and entry into mitosis.

Preceded by: Association of Cyclin A:Cdk2 with Cdh1

Followed by: Dissociation of phospho-Cdh1 from the APC/C complex

Literature references

Lukas, J., Lindeneg, C., Peters, JM., Sorensen, CS., Kramer, E., Lukas, C. et al. (1999). Accumulation of cyclin B1 requires E2F and cyclin-A-dependent rearrangement of the anaphase-promoting complex. *Nature, 401*, 815-8. ↗

Editions

2006-01-26	Authored	Lorca, T., Castro, A.
2006-01-30	Edited	Matthews, L.
2006-03-28	Reviewed	Peters, JM.
2006-10-10	Revised	Matthews, L.

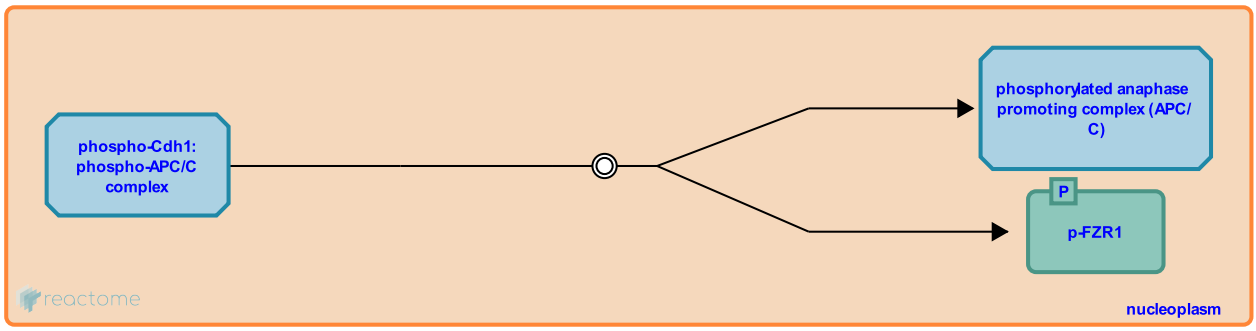
Dissociation of phospho-Cdh1 from the APC/C complex ↗

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

Stable identifier: R-HSA-174139

Type: dissociation

Compartments: nucleoplasm



Following its phosphorylation, Cdh1 dissociates from the APC/C, rendering the APC/C inactive. This allows the stabilization of proteins required for subsequent cell cycle progression.

Preceded by: Phosphorylation of Cdh1 by Cyclin A:Cdk2

Literature references

Lukas, J., Lindeneg, C., Peters, JM., Sorensen, CS., Kramer, E., Lukas, C. et al. (1999). Accumulation of cyclin B1 requires E2F and cyclin-A-dependent rearrangement of the anaphase-promoting complex. *Nature, 401,* 815-8. ↗

Editions

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

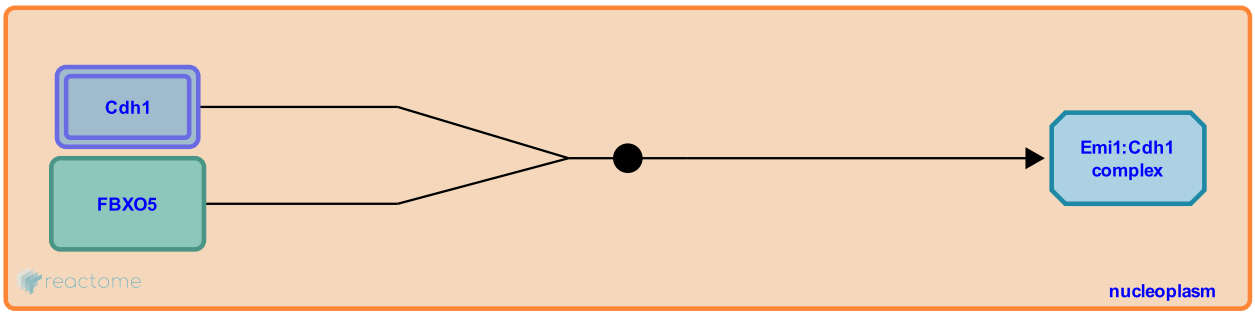
Association of Emi1 with Cdh1 ↗

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

Stable identifier: R-HSA-174097

Type: binding

Compartments: nucleoplasm



Emi1 promotes the accumulation of Cyclin A and entry into S phase by associating with and inhibiting the APC/C:Cdh1 complex at G1/S.

Followed by: Phosphorylation of Emi1

Literature references

Reimann, JD., Lukas, J., Hsu, JY., Sorensen, CS., Jackson, PK. (2002). E2F-dependent accumulation of hEmi1 regulates S phase entry by inhibiting APC(Cdh1). *Nat Cell Biol, 4*, 358-66. ↗

Editions

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2006-03-28	Reviewed	Peters, JM.

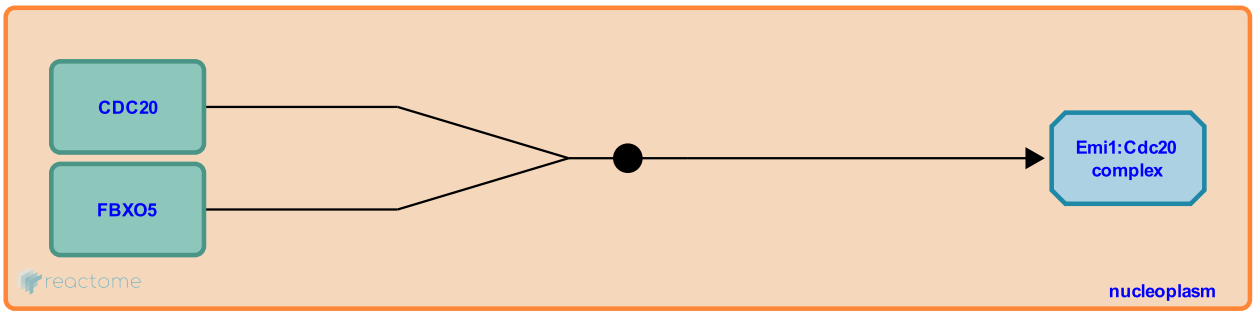
Association of Emi1 with Cdc20 ↗

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

Stable identifier: R-HSA-174235

Type: binding

Compartments: nucleoplasm



In addition to its association with Cdh1 in G1 phase, Emi1 further contributes the inactivation of the APC/C between G2 and prophase by associating with another APC/C activator, Cdc20.

Followed by: Phosphorylation of Emi1

Literature references

Choi, EJ., Kim, JW., Lim, DS., Lee, H., Choi, N., Kirschner, MW. et al. (2004). The tumour suppressor RASSF1A regulates mitosis by inhibiting the APC-Cdc20 complex. *Nat Cell Biol, 6*, 129-37. ↗

Reimann, JD., Lukas, J., Hsu, JY., Sorensen, CS., Jackson, PK. (2002). E2F-dependent accumulation of hEmi1 regulates S phase entry by inhibiting APC(Cdh1). *Nat Cell Biol, 4*, 358-66. ↗

Editions

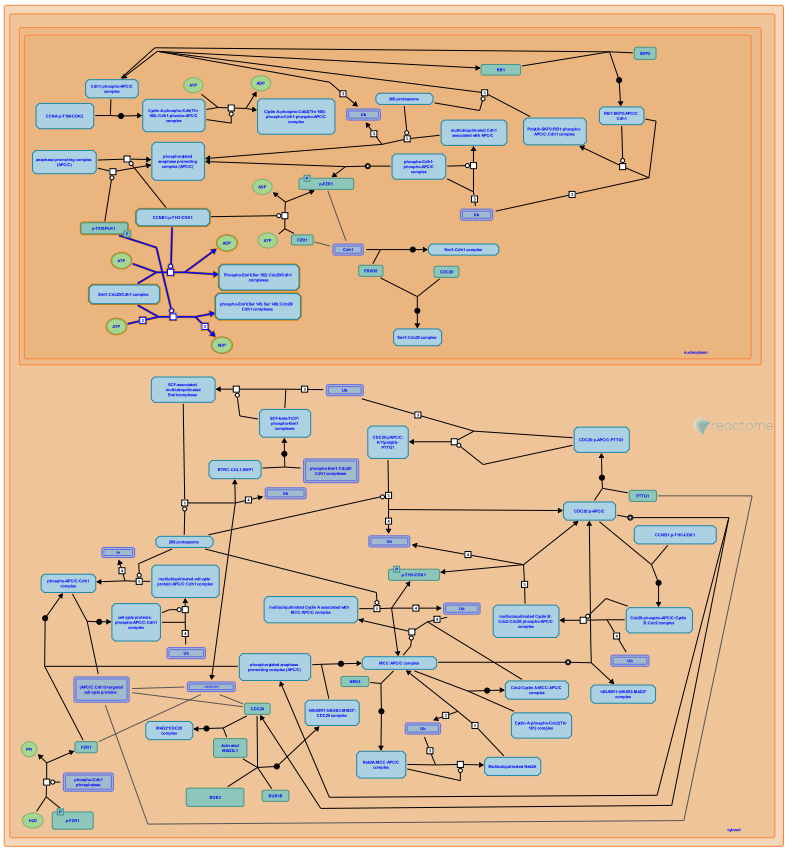
2006-01-26	Authored	Lorca, T., Castro, A.
2006-01-30	Edited	Matthews, L.
2006-03-28	Reviewed	Peters, JM.

Phosphorylation of Emi1 ↗

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

Stable identifier: R-HSA-176417

Compartments: nucleoplasm



The phosphorylation of Emi1, which is required for its degradation in mitosis, appears to involve both Plk1 and Cdk1.

Editions

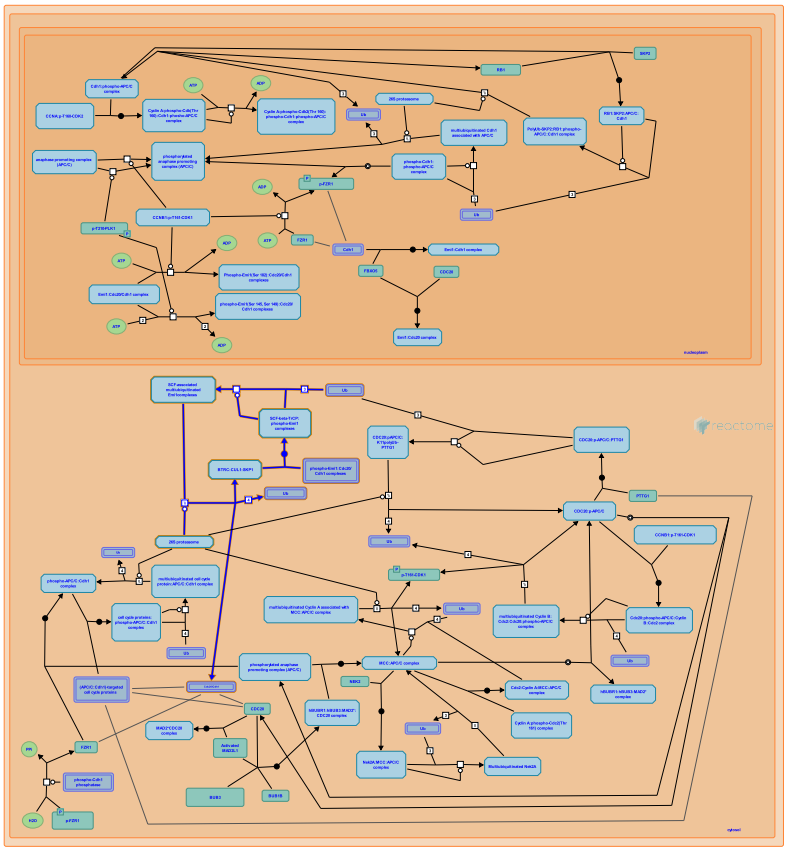
2006-01-26	Authored	Lorca, T., Castro, A.
2006-03-28	Reviewed	Peters, JM.

SCF-beta-TrCP mediated degradation of Emi1 ↗

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

Stable identifier: R-HSA-174113

Compartments: cytosol



Emi1 destruction in early mitosis requires the SCF beta-TrCP ubiquitin ligase complex. Binding of beta-TrCP to Emi1 occurs in late prophase and requires phosphorylation at the DSGxxS consensus motif as well as Cdk mediated phosphorylation. A two-step mechanism has been proposed in which the phosphorylation of Emi1 by Cdc2 occurs after the G2-M transition followed soon after by binding of beta-TrCP to the DSGxxS phosphorylation sites. Emi1 is then poly-ubiquitinated and degraded by the 26S proteasome.

Literature references

Reimann, JD., Loktev, A., Hsu, JY., Jackson, PK., Margottin-Goguet, F., Hsieh, HM. (2003). Prophase destruction of Emi1 by the SCF(betaTrCP/Slimb) ubiquitin ligase activates the anaphase promoting complex to allow progression beyond prometaphase. *Dev Cell, 4,* 813-26. ↗

Editions

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

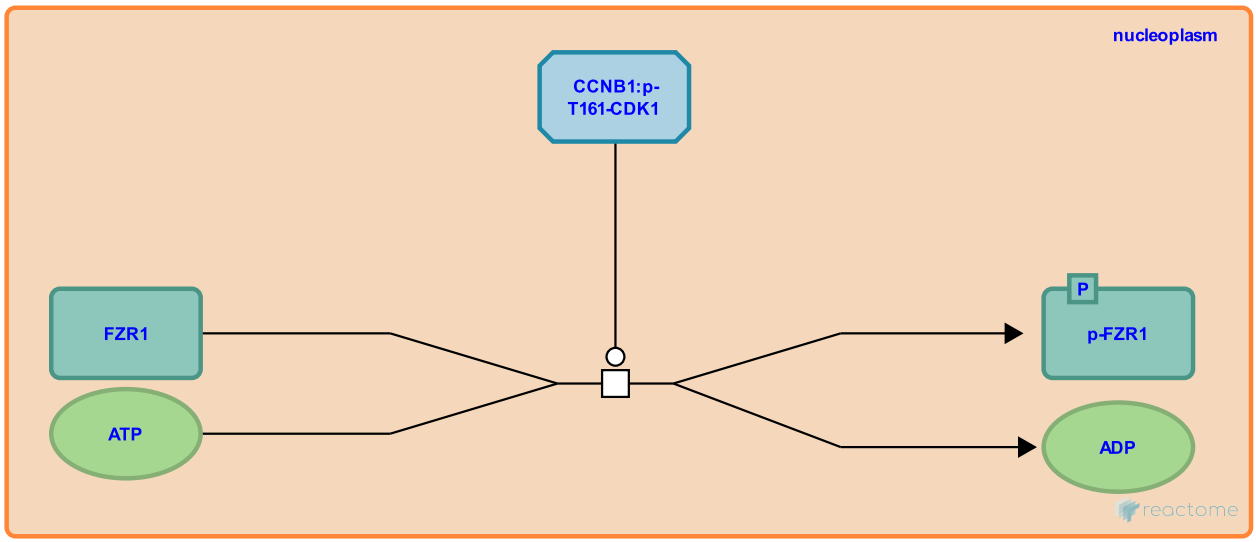
Phosphorylation of Cdh1 by Cyclin B1:Cdc2 ↗

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

Stable identifier: R-HSA-174251

Type: transition

Compartments: nucleoplasm



At the onset of mitosis, Cdh1 is phosphorylated by Cyclin B-Cdc2 resulting in a conformational change that prevents Cdh1 from activating the APC/C.

Literature references

Bembenek, J., Yu, H. (2001). Regulation of the anaphase-promoting complex by the dual specificity phosphatase human Cdc14a. *J Biol Chem, 276*, 48237-42. ↗

Editions

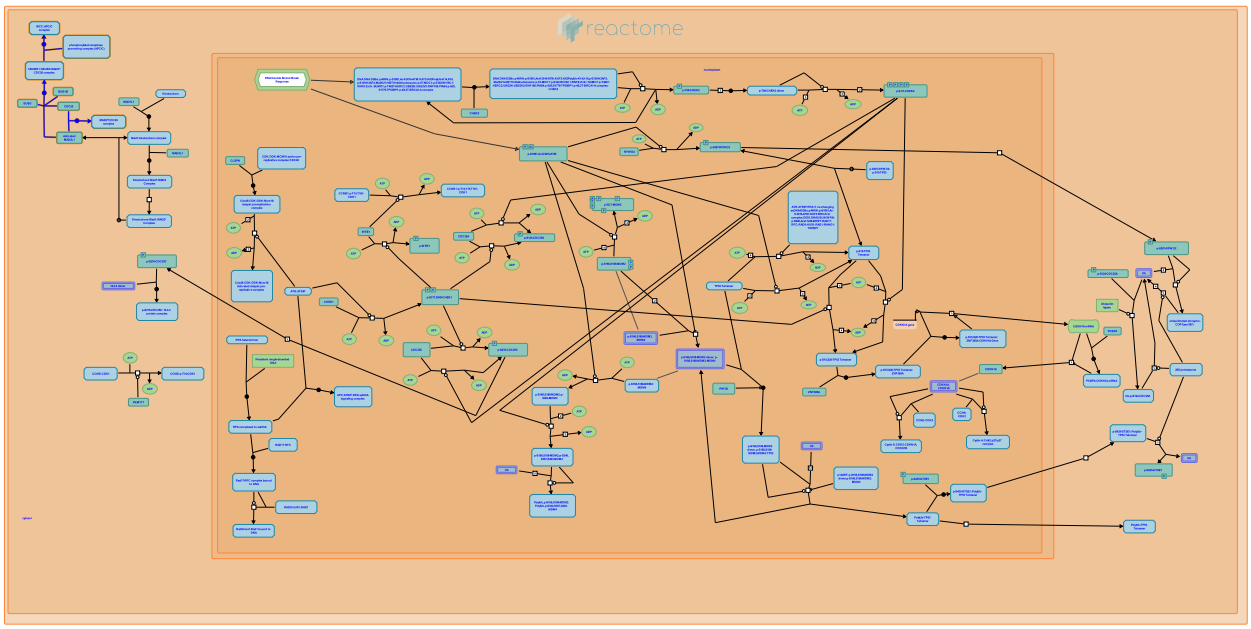
2006-01-26	Authored	Lorca, T., Castro, A.
2006-01-30	Edited	Matthews, L.
2006-03-28	Reviewed	Peters, JM.

Inhibition of the proteolytic activity of APC/C required for the onset of anaphase by mitotic spindle checkpoint components ↗

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

Stable identifier: R-HSA-141405

Compartments: cytosol



The target of the mitotic checkpoint is the Anaphase Promoting Complex/Cyclosome (APC/C) an E3 ubiquitin ligase that targets proteins whose destruction is essential for mitotic exit. Currently, there are two proposed mechanism by which inhibition of the APC/C is achieved. These mechanisms differ depending on the mechanism of signal transduction. The APC/C may be inhibited directly by association with the Mitotic Checkpoint Complex (MCC) or through the sequestration of its activator, Cdc20.

Literature references

Yen, TJ., Chan, GK. (2003). The mitotic checkpoint: a signaling pathway that allows a single unattached kinetochore to inhibit mitotic exit. *Prog Cell Cycle Res, 5*, 431-9. ↗

Editions

2004-05-05	Authored	Yen, TJ.
2006-03-28	Reviewed	Peters, JM.

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