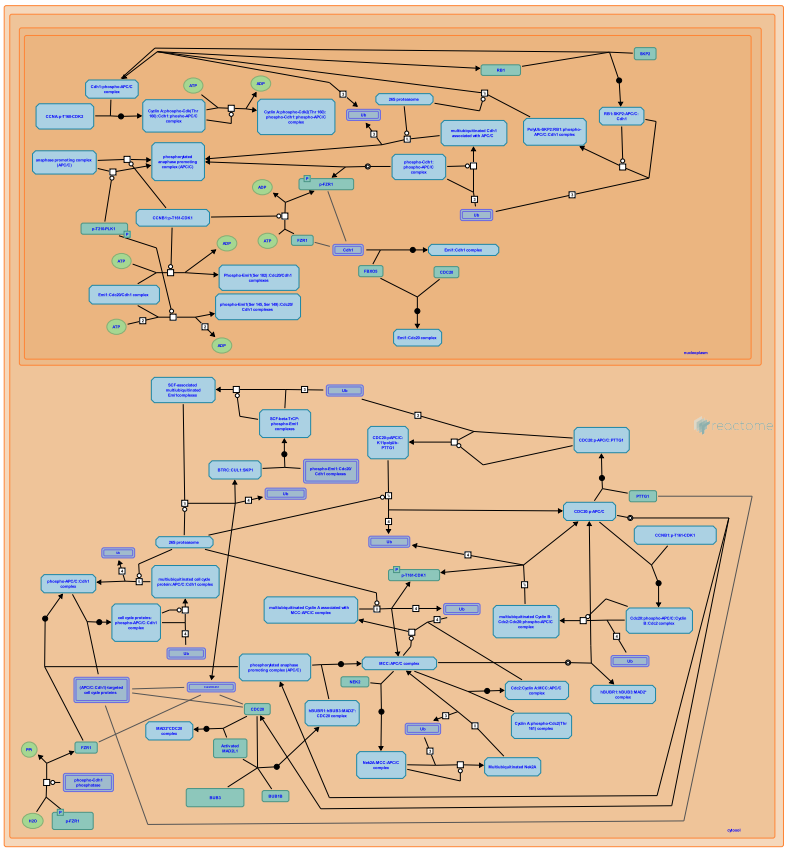
Regulation of mitotic cell cycle



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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.

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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

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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. ↗

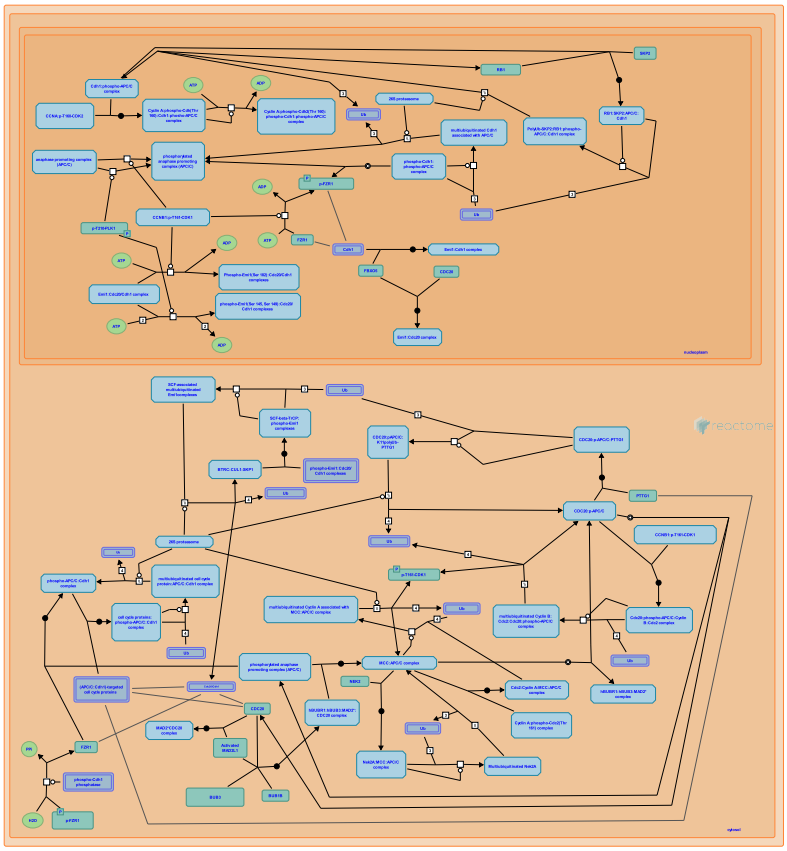
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 2 pathways (see Table of Contents)

Regulation of mitotic cell cycle ↗

Stable identifier: R-HSA-453276



Regulation of mitotic cell cycle currently covers APC/C-mediated degradation of cell cycle proteins.

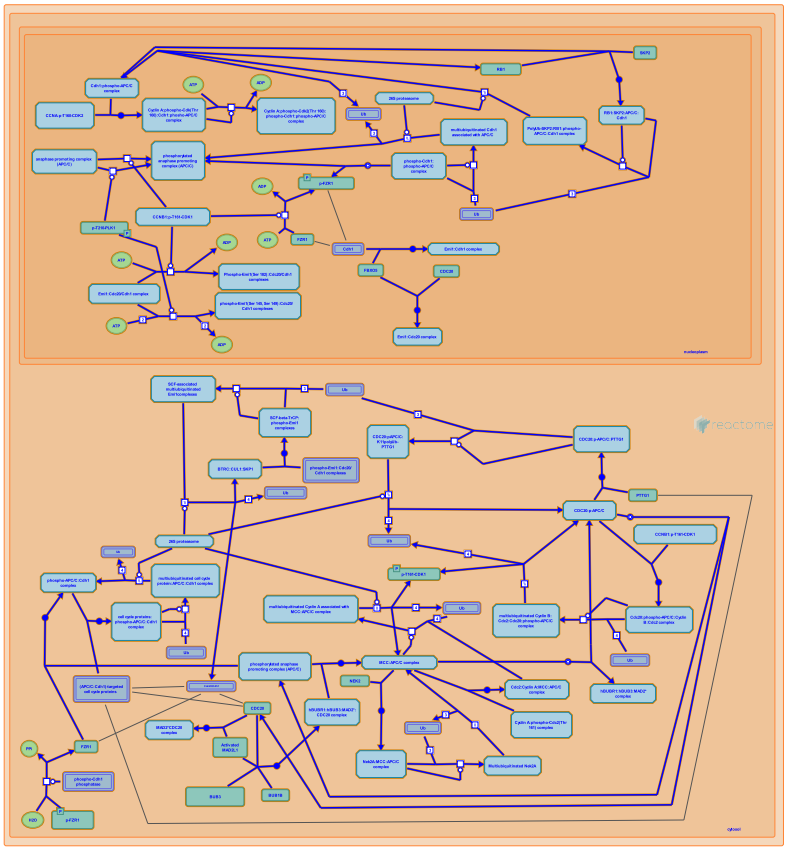
Editions

2010-01-19	Edited	Matthews, L.
2018-07-10	Reviewed	Manfredi, JJ.

APC/C-mediated degradation of cell cycle proteins ↗

Location: Regulation of mitotic cell cycle

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

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Editions

2006-01-26	Authored	Lorca, T., Castro, A.
2006-01-30	Edited	Matthews, L.
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