CDK4/6:CCND complexes are activated by T-loop phosphorylation of CDK4/6

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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.

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Literature references

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

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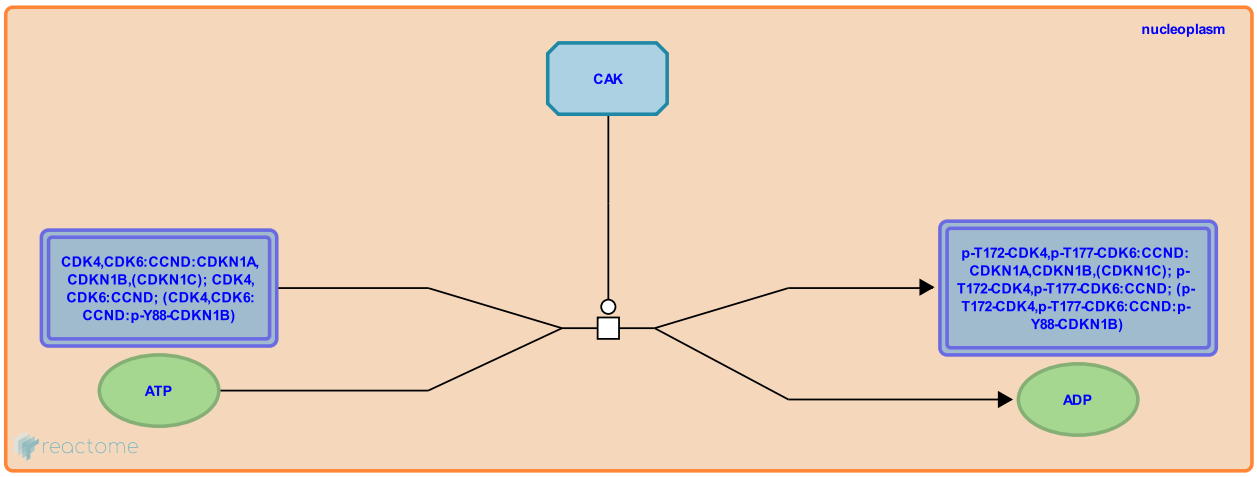
Stable identifier: R-HSA-8942836

Type: transition

Compartments: nucleoplasm



T-loop phosphorylation of CDK4 and CDK6 on threonine residues T172 and T177, respectively, is necessary for catalytic activity of complexes of CDK4 and CDK6 with D-type cyclins (CCND1, CCND2 and CCND3) (Kato, Matsuoka, Strom and Sherr 1994, Merzel-Schachter et al. 2013, Bisteau et al. 2013). These phosphorylations depend on prior D type cyclin binding (Kato, Matsuoka, Polyak et al. 1994, Bockstaele et al. 2006). The T-loop phosphorylation is not precluded by the association of CDK4/6:CCND complexes to Cip/Kip cyclin-dependent kinase (CDK) inhibitors CDKN1A (p21Cip) and CDKN1B (p27Kip1), however high expression levels of CDKN1B reduce the T172 phosphorylation of CDK4 (Kato, Matsuoka, Polyak et al. 1994, Bockstaele et al. 2006, Ray et al. 2009). Phosphorylation at tyrosine residue Y89 of CDKN1B (p27Kip1) bound to CDK4:CCND complexes was found to be necessary for phosphorylation of CDK4 by the CAK complex (composed of CDK7, CCNH and MAT1) in vitro, but not for the phosphorylation by CSK1 of S. pombe (Ray et al. 2009). T-loop phosphorylations of CDK4 and CDK6 are differentially regulated (Bockstaele et al. 2009). Especially, the T172 phosphorylation of CDK4 is strictly controlled by mitogenic and antimitogenic pathways (Paternot and Roger 2009), and it can be differentially regulated in cyclin D1:CDK4 and cyclin D3:CDK4 complexes (reviewed by Paternot et al. 2010). The T-loop T172 phosphorylation motif of CDK4 differs from the other cell cycle CDKs, including CDK6, by the presence of an adjacent proline residue (P173) that is evolutionarily conserved. This proline residue is required for T172 phosphorylation of CDK4 in vivo, but not for its in vitro phosphorylation by CAK. This indicates that CDK4 might be activated by other proline-directed kinases in vivo (Bockstaele et al. 2009). Nevertheless, in HCT116 colon carcinoma cell line, the activity of CDK7 is required for the T172 phosphorylation of CDK4 and the activity of CDK4/6:CCND complexes (Merzel Schachter et al. 2013, Bisteau et al. 2013). T170 phosphorylation of CDK7 facilitates the activity of CAK on CDK4 (Merzel Schachter et al. 2013). However, CDK7 inhibition in HCT116 cells does not preclude the T172 phosphorylation of CDK4:CCND complexes that are not associated with CDKN1A (Bisteau et al. 2013).
Phosphorylation of CDKN1A at serine residue S130 by CDK4/6 and CDK2 has been implicated as a pre-requisite for CAK-mediated phosphorylation of CDKN1A-bound CDK4 (Bisteau et al. 2013). Other kinases involved in phosphorylation of CDK4 at T172 remain to be defined (Bockstaele et al. 2009, Bisteau et al. 2013, reviewed by Paternot et al. 2010).

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Editions

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