Tyrosine kinases phosphorylate Cip/Kip inhibitors bound to CDK4/6:CCND complexes

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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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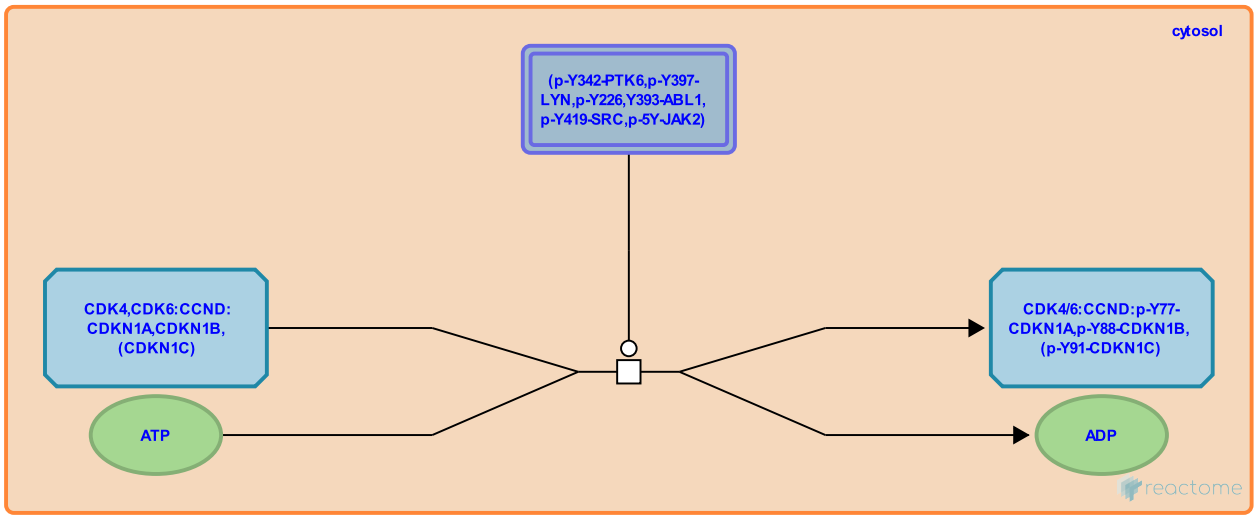
Stable identifier: R-HSA-8942607

Type: transition

Compartments: cytosol



Phosphorylation of Cip/Kip cyclin-dependent kinase (CDK) inhibitors CDKN1A (p21Cip), CDKN1B (p27Kip1) and CDKN1C (p57Kip2) on conserved tyrosine residues Y77, Y88 and Y91, respectively, can convert them from bound inhbitors to bound non-inhibitors of CDK4 or CDK6 complexes with D cyclins by dislodging them from the active site of CDK4 or CDK6. This mechanism was studied in most detail on the example of CDKN1B associated with the CDK2:CCNA complex (Grimmler et al. 2007) and the CDK4:CCND1 complex (James et al. 2008, Patel et al. 2015). For a review of this topic, please refer to Blain 2008.
CDKN1A can be phosphorylated at tyrosine residue Y77 by protein tyrosine kinase ABL1 (Hukkelhoven et al. 2012). CDKN1B can be phosphorylated at tyrosine residue Y88, and probably also at the adjacent Y89, by protein tyrosine kinases ABL1 (Grimmler et al. 2007, James et al. 2008, Ray et al. 2009, Ou et al. 2011), LYN (Grimmler et al. 2007), SRC (Larrea et al. 2008), JAK2 (Jakel et al. 2011) and PTK6 (Patel et al. 2015). CDKN1C can be phosphorylated at tyrosine residue Y91 by protein tyrosine kinase ABL1 (Borriello et al. 2011).
Dislodgment of the tyrosine phosphorylated 3-10 helix of Cip/Kip CDK inhibitors from the active site of cyclin D-bound CDK4 or CDK6 results in increased catalytic activity of CDK4 or CDK6 by allowing ATP binding to the active site, but also by enabling activating phosphorylation of the T-loop of CDK4 or CDK6 phosphorylation by CDK7 in complex with cyclin H (Ray et al. 2009).
SRC-mediated phosphorylation of CDKN1B on tyrosine residue Y88 was shown to reduce protein stability of CDKN1B (Chu et al. 2007).
Without overexpression of BCR-ABL or SRC-family tyrosine kinases in several cell systems, tyrosine phosphorylated p27 is either undetectable or a very low abundance species (Ishida et al. 2000, Jaimes et al. 2008, Grimmler et al. 2007) that does not bind preferentially to CDK4 (Jaimes et al. 2008). Therefore, tyrosine phosphorylation of p27 is unlikely to be the sole explanation of the full activity of p27-bound CDK4:CCND complexes reported in previous studies (Blain et al. 1997, Coulonval et al. 2003, Bockstaele et al. 2006). It has been proposed that stoichiometry of the Cip/Kip complex with CDK4 or CDK6 and cyclin D, in addition to or alternative to tyrosine phosphorylation of Cip/Kip CDK inhibitors, determines their inhibitory role where binding of more than one molecule of CDKN1A, CDKN1B or CDKN1C would be needed to achieve inhibition of the CDK4/6:CCND complex (reviewed by Paternot et al. 2010).

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Editions

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