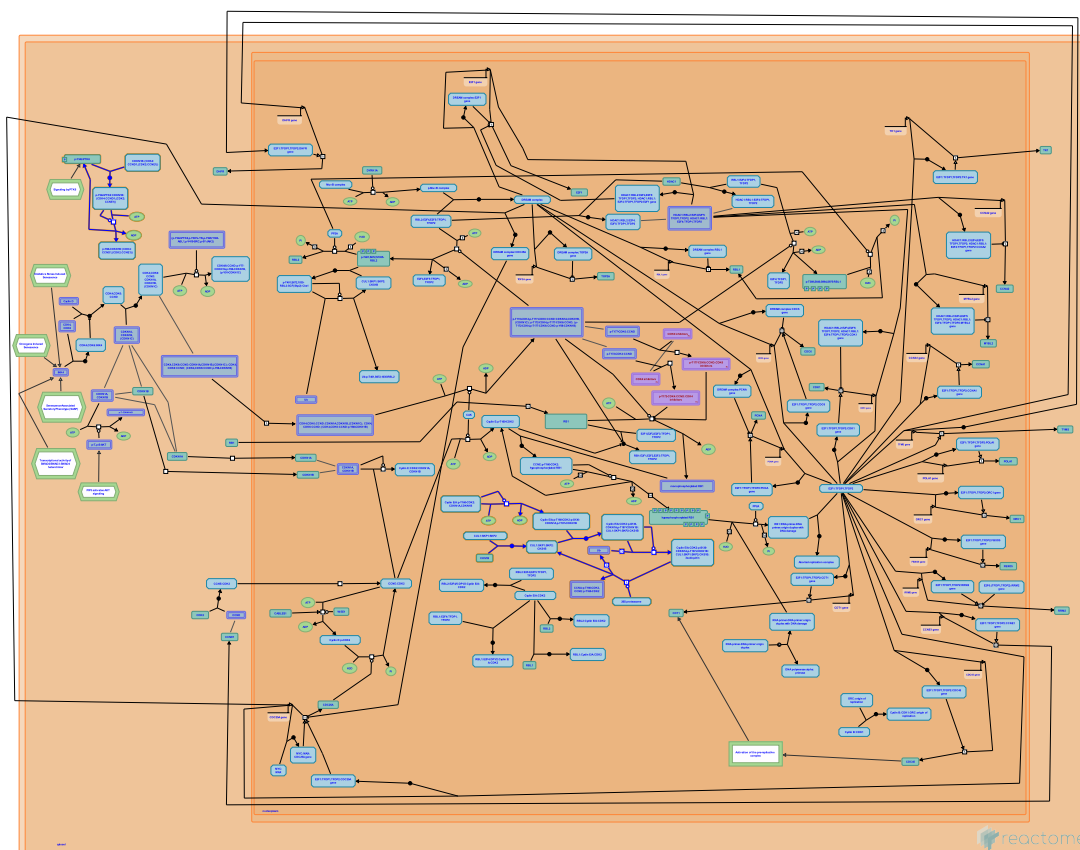


SCF(Skp2)-mediated degradation of p27/p21



Coqueret, O., Matthews, L., Orlic-Milacic, M., Pagano, M., Pires, IM.

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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](https://reactome.org/textbook/).

05/05/2024

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.

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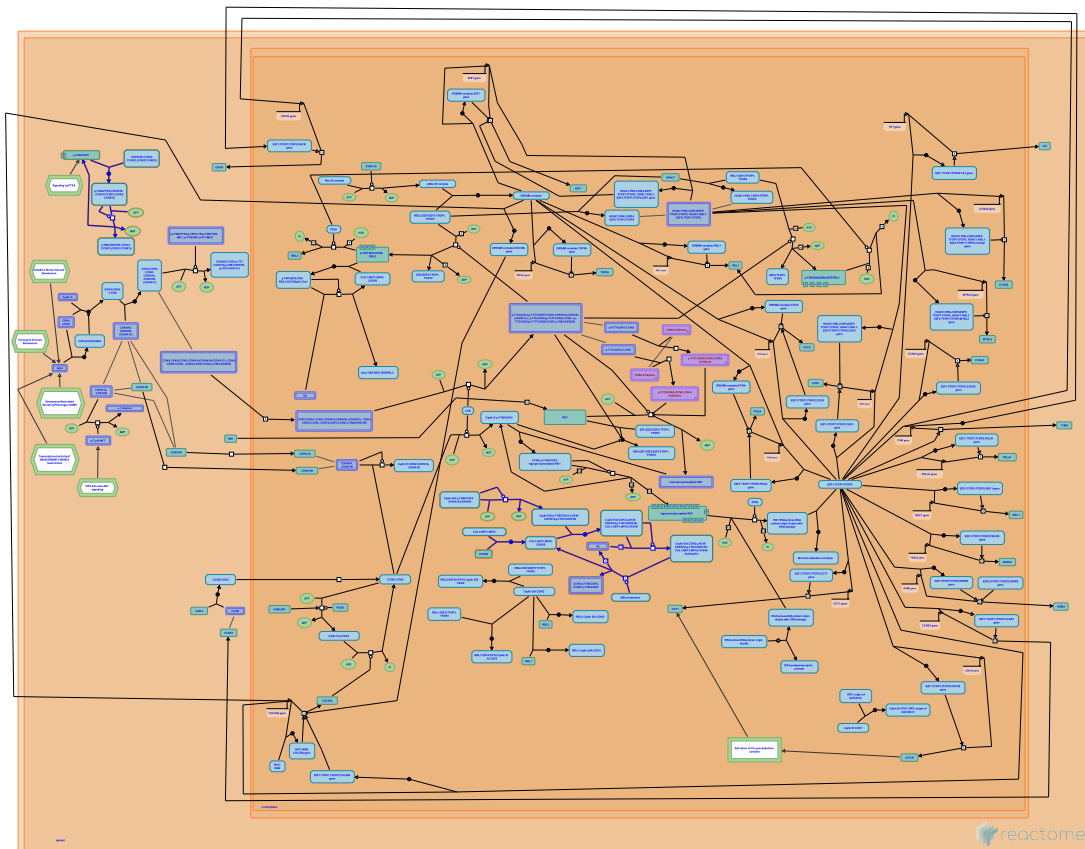
Reactome database release: 88

This document contains 1 pathway and 7 reactions ([see Table of Contents](#))

SCF(Skp2)-mediated degradation of p27/p21 ↗

Stable identifier: R-HSA-187577

Compartments: nucleoplasm



During G1, the activity of cyclin-dependent kinases (CDKs) is kept in check by the CDK inhibitors (CKIs) p27 and p21, thereby preventing premature entry into S phase (see Guardavaccaro and Pagano, 2006). These two CKIs are degraded in late G1 phase by the ubiquitin pathway (Pagano et al., 1995; Bloom et al., 2003) involving the ubiquitin ligase SCF(Skp2) (Tsvetkov et al., 1999; Carrano et al., 1999; Sutterluty et al., 1999; Bornstein et al., 2003) and the cell-cycle regulatory protein Cks1 (Ganoth et al., 2001; Spruck et al 2001; Bornstein et al., 2003). Recognition of p27 by SCF(Skp2) and its subsequent ubiquitination is dependent upon Cyclin E/A:Cdk2- mediated phosphorylation at Thr 187 of p27 (Montagnoli et al., 1999). There is evidence that Cyclin A/B:Cdk1 complexes can also bind and phosphorylate p27 on Th187 (Nakayama et al., 2004). Degradation of polyubiquitinated p27 by the 26S proteasome promotes the activity of CDKs in driving cells into S phase. (Montagnoli et al., 1999; Tsvetkov et al., 1999, Carrano et al 1999). The mechanism of SCF(Skp2)-mediated degradation of p21 is similar to that of p27 in terms of its requirements for the presence of Cks1 and of Cdk2/cyclin E/A (Bornstein et al.,2003; Wang et al., 2005). In addition, as observed for p27, p21 phosphorylation at a specific site (Ser130) stimulates its ubiquitination. In contrast to p27, however, ubiquitination of p21 can take place in the absence of phosphorylation, although with less efficiency (Bornstein et al.,2003). SCF(Skp2)-mediated degradation of p27/p21 continues from late G1 through M-phase. During G0 and from early G1 to G1/S, Skp2 is degraded by the anaphase promoting complex/Cyclosome and its activator Cdh1 [APC/C(Cdh1)] (Bashir et al, 2004; Wei et al, 2004). The tight regulation of APC/C(Cdh1) activity ensures the timely elimination Skp2 and, thus, plays a critical role in controlling the G1/S transition. APC/C(Cdh1) becomes active in late M-phase by the association of unphosphorylated Cdh1 with the APC/C. APC/C(Cdh1) remains active until the G1/S phase at which time it interacts with the inhibitory protein, Emi1 (Hsu et al., 2002). Inhibition of APC/C(Cdh1) activity results in an accumulation of cyclins, which leads to the phosphorylation and consequently to a further inactivation of Cdh1 at G1/S (Lukas et al., 1999). Finally, to make the inactivation of APC/C(Cdh1) permanent, Cdh1 and its E2, namely Ubc10, are eliminated in an auto-ubiquitination event (Listovsky et al., 2004; Rape and Kirschner, 2004). At G1/S, Skp2 reaccumulates as Cdh1 is inactivated, thus allowing the ubiquitination of p21 and p27 and resulting in a further increase in CDK activity.

Literature references

Hershko, A., Bornstein, G., Pagano, M., Bloom, J., Nakayama, K., Sitry-Shevah, D. (2003). Role of the SCFSkp2 ubiquitin ligase in the degradation of p21Cip1 in S phase. *J Biol Chem*, 278, 25752-7. ↗

Del Sal, G., Yew, PR., Draetta, GF., Beer-Romero, P., Rolfe, M., Theodoras, AM. et al. (1995). Role of the ubiquitin-proteasome pathway in regulating abundance of the cyclin-dependent kinase inhibitor p27. *Science*, 269, 682-5. [↗](#)

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Editions

2006-09-19	Edited	Matthews, L.
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2006-10-06	Reviewed	Coqueret, O.

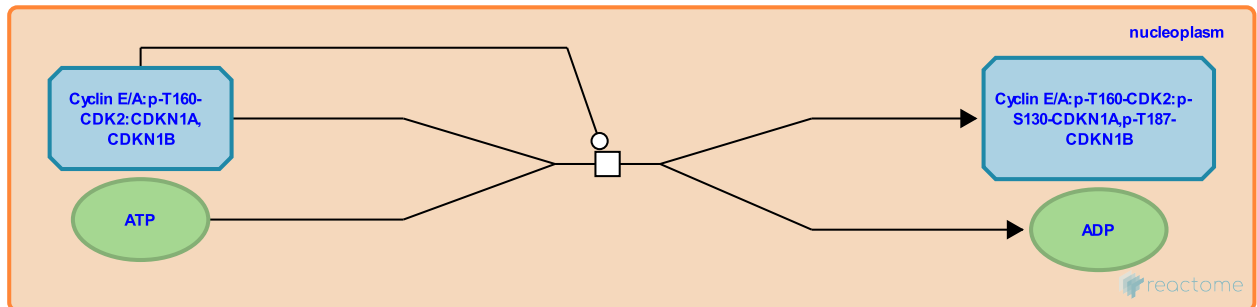
Cyclin E/A:Cdk2-mediated phosphorylation of p27/p21 ↗

Location: SCF(Skp2)-mediated degradation of p27/p21

Stable identifier: R-HSA-187520

Type: transition

Compartments: nucleoplasm



The interaction between the Skp2 subunit of the SCF(Skp2) complex and p27 is dependent upon Cdk2:Cyclin A/E mediated phosphorylation of p27 at Thr 187 (Carrano et al, 1999; Tsvetkov et al, 1999). There is evidence that Cyclin A/B:Cdk1 can also bind and phosphorylate p27 on Thr 187 (Nakayama et al., 2004). This phosphorylation is also essential for the subsequent ubiquitination of p27.

Followed by: [Binding of phospho-p27/p21:Cdk2:Cyclin E/A to the SCF\(Skp2\):Cks1 complex](#)

Literature references

- Eytan, E., Hershko, A., Pagano, M., Carrano, AC. (1999). SKP2 is required for ubiquitin-mediated degradation of the CDK inhibitor p27. *Nat Cell Biol*, 1, 193-9. ↗
- Eytan, E., Draetta, GF., Hershko, A., Montagnoli, A., Pagano, M., Carrano, AC. et al. (1999). Ubiquitination of p27 is regulated by Cdk-dependent phosphorylation and trimeric complex formation. *Genes Dev*, 13, 1181-9. ↗
- Sun, H., Zhang, H., Tsvetkov, LM., Lee, SJ., Yeh, KH. (1999). p27(Kip1) ubiquitination and degradation is regulated by the SCF(Skp2) complex through phosphorylated Thr187 in p27. *Curr Biol*, 9, 661-4. ↗

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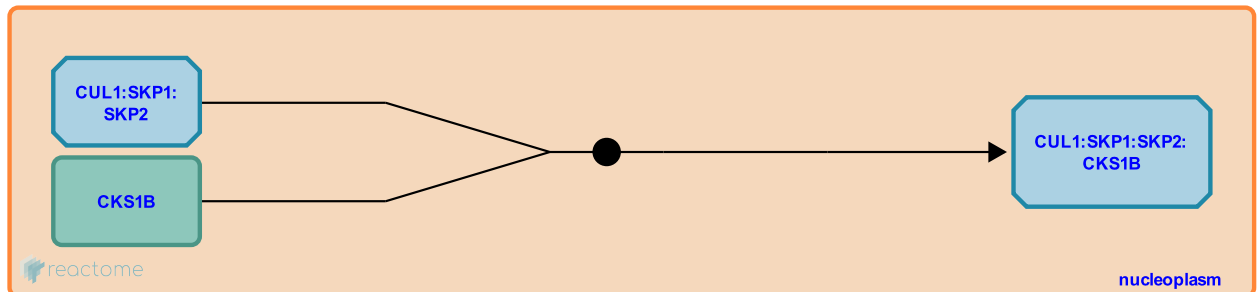
Association of Cks1 with SCF(Skp2) complex ↗

Location: SCF(Skp2)-mediated degradation of p27/p21

Stable identifier: R-HSA-187545

Type: binding

Compartments: nucleoplasm



The accessory protein, Cks1 promotes efficient interaction between phosphorylated p27 and the SCF (Skp2) complex (Ganoth et al., 2001; Spruck et al., 2001). Cks1 binds to Skp2 in the leucine-rich repeat (LRR) domain and C-terminal tail (Hao et al., 2005). The phosphorylated Thr187 side chain of p27 associates with a phosphate binding site on Cks1, and the side chain containing Glu185 is positioned in the interface between Skp2 and Cks1 where it interacts with both (Hao et al., 2005).

Followed by: [Binding of phospho-p27/p21:Cdk2:Cyclin E/A to the SCF\(Skp2\):Cks1 complex](#)

Literature references

Ko, TK., Ganoth, D., Hershko, A., Bornstein, G., Tyers, M., Pagano, M. et al. (2001). The cell-cycle regulatory protein Cks1 is required for SCF(Skp2)-mediated ubiquitinylation of p27. *Nat Cell Biol*, 3, 321-4. ↗

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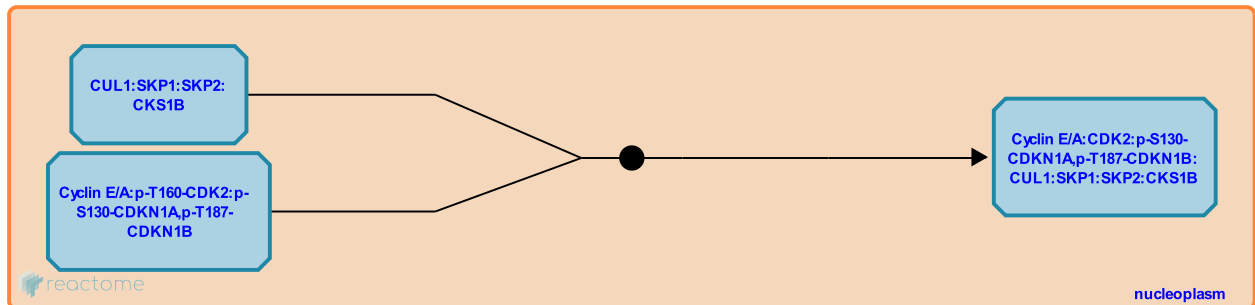
Binding of phospho-p27/p21:Cdk2:Cyclin E/A to the SCF(Skp2):Cks1 complex ↗

Location: SCF(Skp2)-mediated degradation of p27/p21

Stable identifier: R-HSA-187552

Type: binding

Compartments: nucleoplasm



The association of Cks1 with both Skp2 and phosphorylated p27 promotes a tight interaction between p27 and the SCF complex (Hao et al., 2005).

Preceded by: Association of Cks1 with SCF(Skp2) complex, Cyclin E/A:Cdk2-mediated phosphorylation of p27/p21

Followed by: Ubiquitination of phospho-p27/p21

Literature references

- Traganos, F., Zhu, XH., Koff, A., Nguyen, H., Halicka, HD. (2004). Noncatalytic requirement for cyclin A-cdk2 in p27 turnover. *Mol Cell Biol*, 24, 6058-66. ↗
- Pavletich, NP., Miller, JJ., Wu, G., Schulman, BA., Pagano, M., Zheng, N. et al. (2005). Structural basis of the Cks1-dependent recognition of p27(Kip1) by the SCF(Skp2) ubiquitin ligase. *Mol Cell*, 20, 9-19. ↗
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- Sun, H., Zhang, H., Tsvetkov, LM., Lee, SJ., Yeh, KH. (1999). p27(Kip1) ubiquitination and degradation is regulated by the SCF(Skp2) complex through phosphorylated Thr187 in p27. *Curr Biol*, 9, 661-4. ↗

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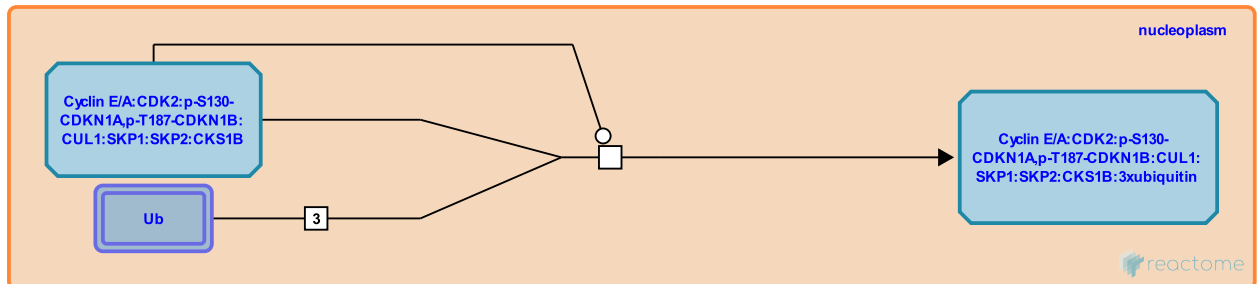
Ubiquitination of phospho-p27/p21 ↗

Location: SCF(Skp2)-mediated degradation of p27/p21

Stable identifier: R-HSA-187575

Type: transition

Compartments: nucleoplasm



Once in tight contact with the SCF (Skp2):Cks1 complex, phosphorylated p27/p21 is ubiquitinated.

Preceded by: Binding of phospho-p27/p21:Cdk2:Cyclin E/A to the SCF(Skp2):Cks1 complex

Followed by: Degradation of ubiquitinated p27/p21 by the 26S proteasome

Literature references

Ko, TK., Ganoth, D., Hershko, A., Bornstein, G., Tyers, M., Pagano, M. et al. (2001). The cell-cycle regulatory protein Cks1 is required for SCF(Skp2)-mediated ubiquitinylation of p27. *Nat Cell Biol*, 3, 321-4. ↗

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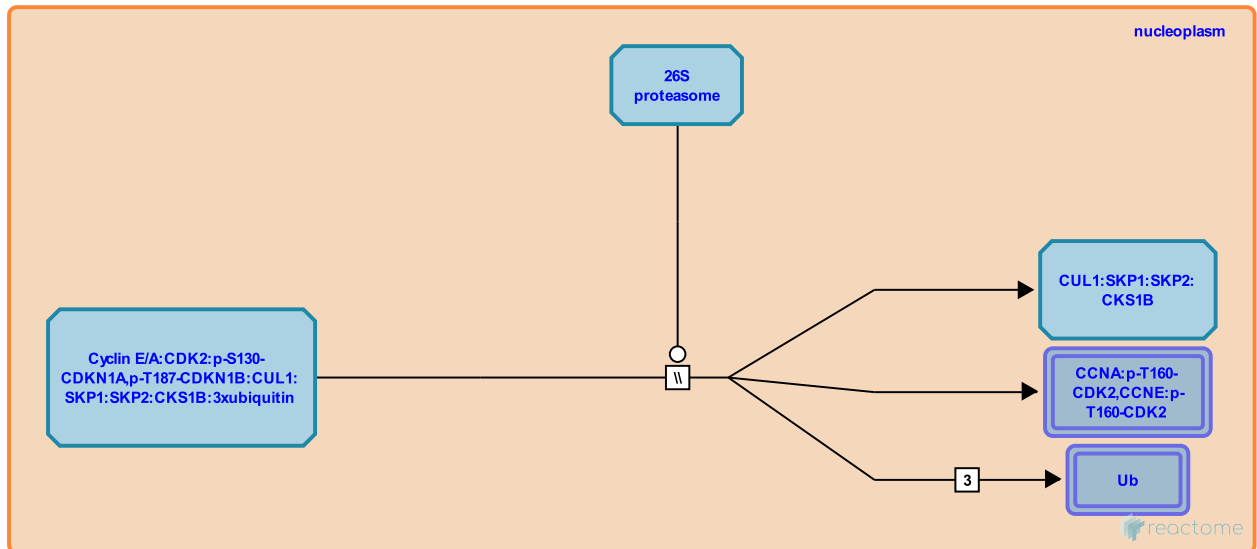
Degradation of ubiquitinated p27/p21 by the 26S proteasome ↗

Location: SCF(Skp2)-mediated degradation of p27/p21

Stable identifier: R-HSA-187574

Type: omitted

Compartments: nucleoplasm



Following ubiquitination by the SCF(Skp2):Cks1 complex, phospho-p27/p21 is degraded by the 26S proteasome.

Preceded by: Ubiquitination of phospho-p27/p21

Literature references

Eytan, E., Hershko, A., Pagano, M., Carrano, AC. (1999). SKP2 is required for ubiquitin-mediated degradation of the CDK inhibitor p27. *Nat Cell Biol*, 1, 193-9. ↗

Sun, H., Zhang, H., Tsvetkov, LM., Lee, SJ., Yeh, KH. (1999). p27(Kip1) ubiquitination and degradation is regulated by the SCF(Skp2) complex through phosphorylated Thr187 in p27. *Curr Biol*, 9, 661-4. ↗

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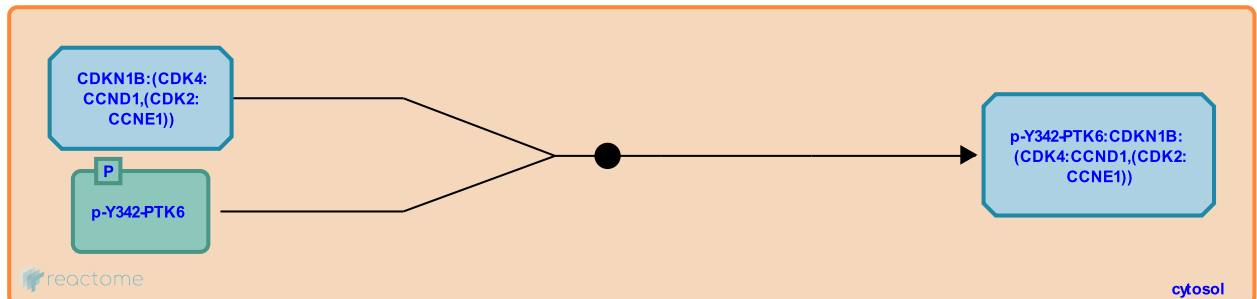
Activated PTK6 binds CDKN1B ↗

Location: SCF(Skp2)-mediated degradation of p27/p21

Stable identifier: R-HSA-8848414

Type: binding

Compartments: cytosol



Activated PTK6 (BRK) binds to CDKN1B (p27KIP1) that is in a complex with CDK4 and cyclin D1 (CCND1). Since PTK6 increases cyclin E1 (CCNE1) levels downstream of ERBB2 while decreasing CDKN1B levels, PTK6 probably also associates with CDKN1B bound to the complex of CCNE1 and CDK2 (Xiang et al. 2008).

Followed by: PTK6 phosphorylates CDKN1B

Literature references

Wagner, R., Patel, P., Asbach, B., Blain, SW., Coltoff, A., Shteyn, E. et al. (2015). Brk/Protein tyrosine kinase 6 phosphorylates p27KIP1, regulating the activity of cyclin D-cyclin-dependent kinase 4. *Mol. Cell. Biol.*, 35, 1506-22. ↗

Muthuswamy, SK., Xiang, B., Lakshmi, B., Yu, M., Miller, WT., Krasnitz, A. et al. (2008). Brk is coamplified with ErbB2 to promote proliferation in breast cancer. *Proc. Natl. Acad. Sci. U.S.A.*, 105, 12463-8. ↗

Editions

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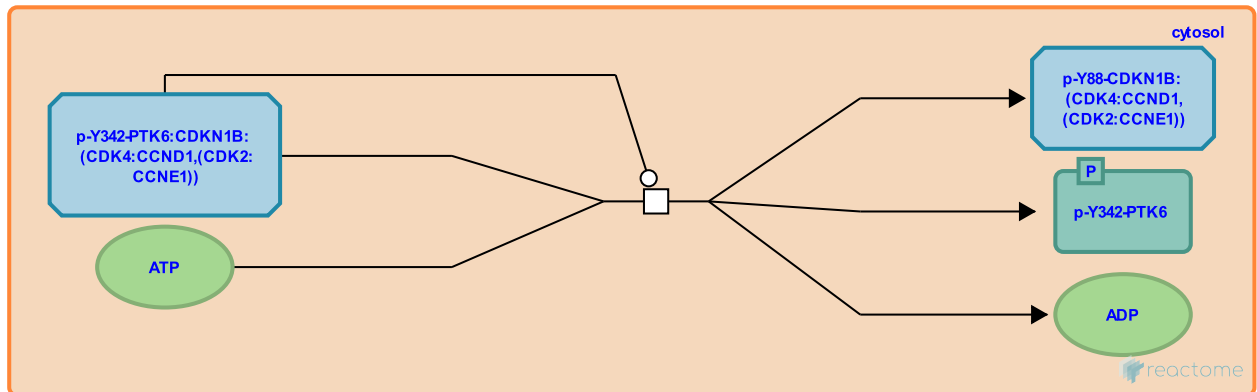
PTK6 phosphorylates CDKN1B ↗

Location: SCF(Skp2)-mediated degradation of p27/p21

Stable identifier: R-HSA-8848436

Type: transition

Compartments: cytosol



PTK6 (BRK) phosphorylates CDKN1B (p27KIP1) bound to the complex of CDK4 and CCND1 (cyclin D1) on tyrosine residue Y88 and possibly other tyrosines (e.g. Y89) (Patel et al. 2015). Based on the finding that PTK6 promotes ERBB2-induced increase in cyclin E1 (CCNE1) levels and decrease in CDKN1B levels (Xiang et al. 2008), and supported by the analogy with other SRC family kinases that phosphorylate CDKN1B (Grimmler et al. 2007), PTK6 is likely to also phosphorylate CDKN1B bound to the complex of CCNE1 and CDK2. Phosphorylation of CDKN1B (p27KIP1) on tyrosine residue Y88 by SRC family kinases dislodges the 3-10 helix of CDKN1B from the active site of CDK2 or CDK4, thus converting CDKN1B from a bound inhibitor to a bound non-inhibitor (Grimmler et al. 2007, Ray et al. 2009).

Preceded by: Activated PTK6 binds CDKN1B

Literature references

Wagner, R., Patel, P., Asbach, B., Blain, SW., Coltoff, A., Shteyn, E. et al. (2015). Brk/Protein tyrosine kinase 6 phosphorylates p27KIP1, regulating the activity of cyclin D-cyclin-dependent kinase 4. *Mol. Cell. Biol.*, 35, 1506-22. ↗

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Table of Contents

Introduction	1
☒ SCF(Skp2)-mediated degradation of p27/p21	2
↳ Cyclin E/A:Cdk2-mediated phosphorylation of p27/p21	4
↳ Association of Cks1 with SCF(Skp2) complex	5
↳ Binding of phospho-p27/p21:Cdk2:Cyclin E/A to the SCF(Skp2):Cks1 complex	6
↳ Ubiquitination of phospho-p27/p21	7
↳ Degradation of ubiquitinated p27/p21 by the 26S proteasome	8
↳ Activated PTK6 binds CDKN1B	9
↳ PTK6 phosphorylates CDKN1B	10
Table of Contents	11