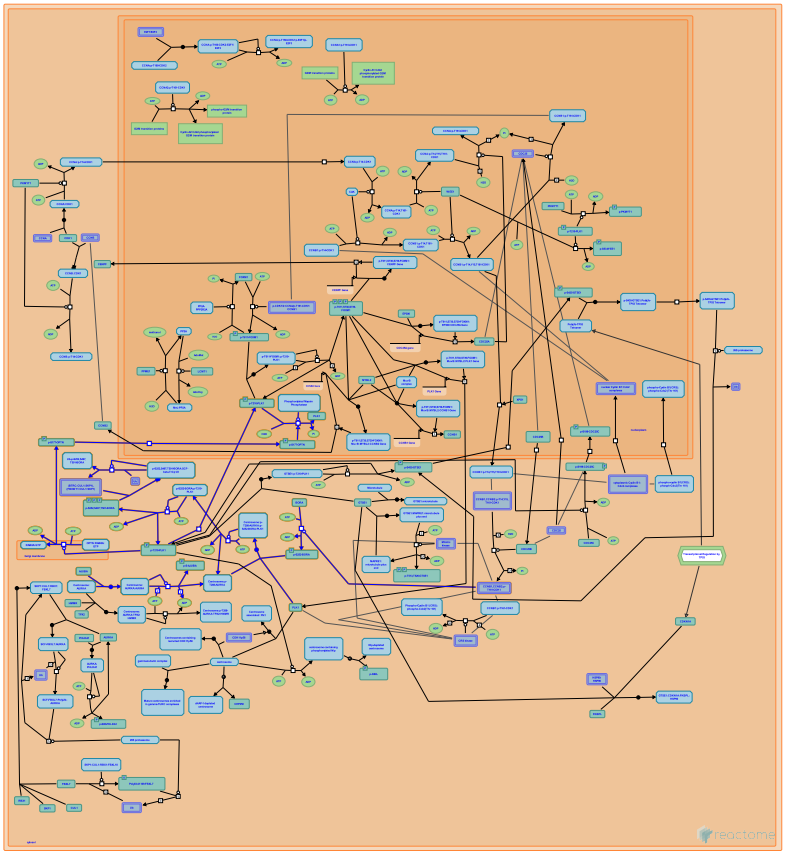
Regulation of PLK1 Activity at G2/M Transition



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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

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. ↗

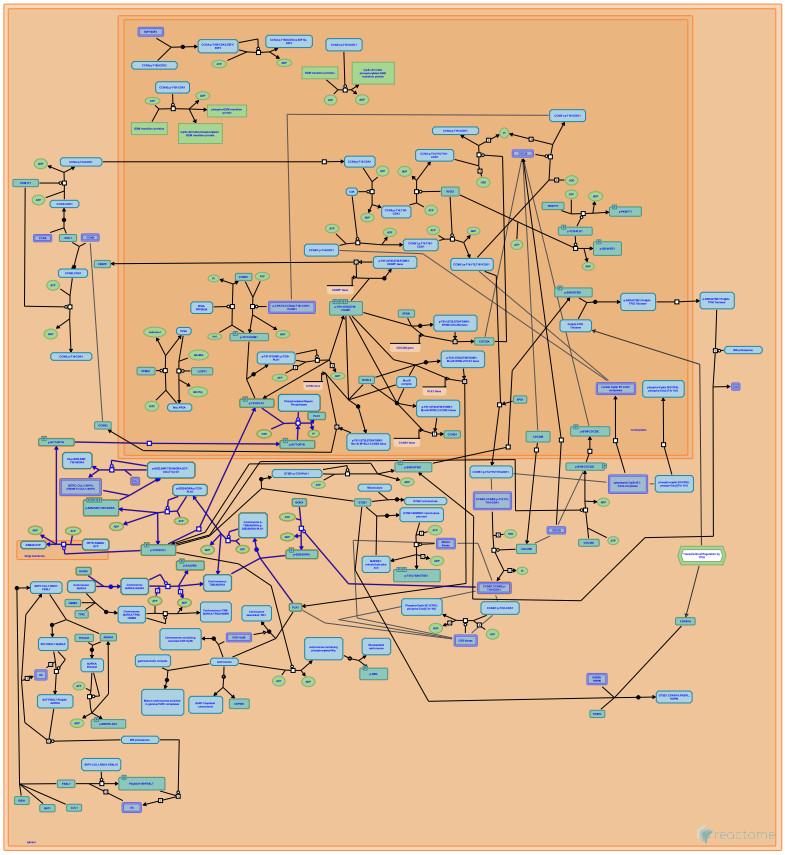
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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 PLK1 Activity at G2/M Transition ↗

Stable identifier: R-HSA-2565942

Compartments: cytosol



The kinase activity of PLK1 is required for cell cycle progression as PLK1 phosphorylates and regulates a number of cellular proteins during mitosis. Centrosomic AURKA (Aurora A kinase), catalytically activated through AJUBA facilitated autophosphorylation on threonine residue T288 at G2/M transition (Hirota et al. 2003), activates PLK1 on centrosomes by phosphorylating threonine residue T210 of PLK1, critical for PLK1 activity (Jang et al. 2002), in the presence of BORA (Macurek et al. 2008, Seki et al. 2008). Once activated, PLK1 phosphorylates BORA and targets it for ubiquitination mediated degradation by SCF-beta-TrCP ubiquitin ligases. Degradation of BORA is thought to allow PLK1 to interact with other substrates (Seki, Coppinger, Du et al. 2008, Seki et al. 2008).

The interaction of PLK1 with OPTN (optineurin) provides a negative-feedback mechanism for regulation of PLK1 activity. Phosphorylated PLK1 binds and phosphorylates OPTN associated with the Golgi membrane GTPase RAB8, promoting dissociation of OPTN from Golgi and translocation of OPTN to the nucleus. Phosphorylated OPTN facilitates the mitotic phosphorylation of the myosin phosphatase subunit PPP1R12A (MYPT1) and myosin phosphatase activation (Kachaner et al. 2012). The myosin phosphatase complex dephosphorylates threonine residue T210 of PLK1 and inactivates PLK1 (Yamashiro et al. 2008).

Literature references

Seki, A., Coppinger, JA., Yates, JR., Jang, CY., Fang, G. (2008). Bora and the kinase Aurora a cooperatively activate the kinase Plk1 and control mitotic entry. *Science, 320*, 1655-8. ↗

Hirota, T., Hatakeyama, K., Nitta, M., Sasayama, T., Saya, H., Kunitoku, N. et al. (2003). Aurora-A and an interacting activator, the LIM protein Ajuba, are required for mitotic commitment in human cells. *Cell, 114*, 585-98. ↗

Laplantine, E., Bennett, KL., Superti-Furga, G., Weil, R., Kachaner, D., Israel, A. et al. (2012). Plk1-dependent phosphorylation of optineurin provides a negative feedback mechanism for mitotic progression. *Mol. Cell, 45*, 553-66. ↗

Clouin, C., Medema, RH., Taylor, SS., Freire, R., Lampson, MA., Klompmaker, R. et al. (2008). Polo-like kinase-1 is activated by aurora A to promote checkpoint recovery. *Nature, 455*, 119-23. ↗

Erikson, RL., Ma, S., Jang, YJ., Terada, Y. (2002). Phosphorylation of threonine 210 and the role of serine 137 in the regulation of mammalian polo-like kinase. *J. Biol. Chem., 277*, 44115-20. ↗

Editions

2013-01-29	Authored	Orlic-Milacic, M.
2013-01-30	Edited	Orlic-Milacic, M.
2013-02-07	Reviewed	Weil, R.
2013-08-21	Reviewed	Bruinsma, W.

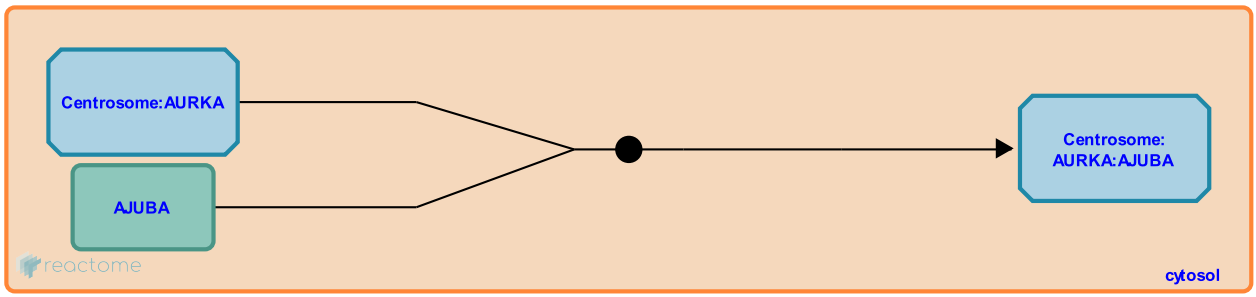
AJUBA binds centrosome-associated AURKA ↗

Location: Regulation of PLK1 Activity at G2/M Transition

Stable identifier: R-HSA-2574845

Type: binding

Compartments: cytosol



AJUBA, a LIM domain-containing protein, binds centrosome-associated AURKA (Aurora A kinase) through interaction of LIM-2 and LIM-3 domains of AJUBA with the N-terminus of AURKA (Hirota et al. 2003).

Followed by: AJUBA facilitates AURKA autophosphorylation

Literature references

Hirota, T., Hatakeyama, K., Nitta, M., Sasayama, T., Saya, H., Kunitoku, N. et al. (2003). Aurora-A and an interacting activator, the LIM protein Ajuba, are required for mitotic commitment in human cells. *Cell, 114*, 585-98. ↗

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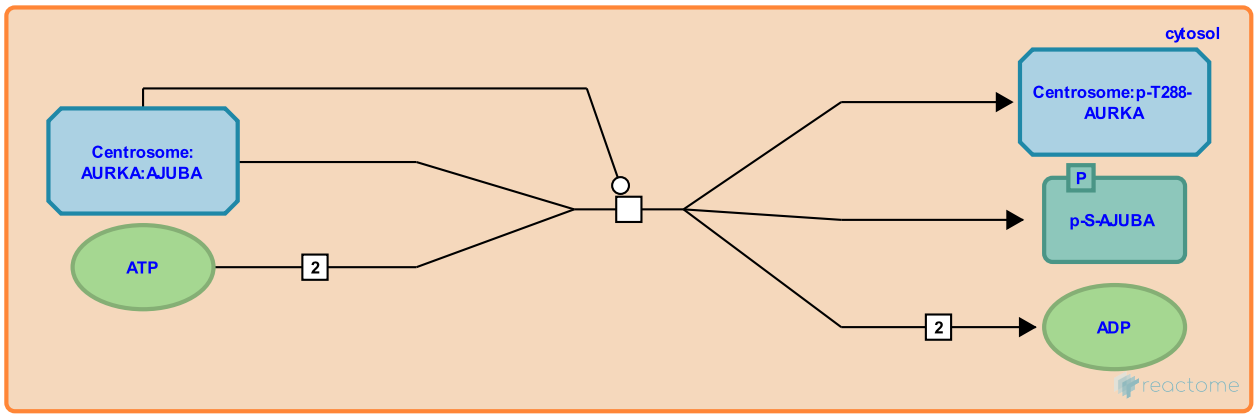
AJUBA facilitates AURKA autophosphorylation ↗

Location: Regulation of PLK1 Activity at G2/M Transition

Stable identifier: R-HSA-2574840

Type: transition

Compartments: cytosol



AURKA (Aurora A kinase) activation through autophosphorylation of threonine T288 is facilitated by AJUBA binding. AJUBA is also phosphorylated by AURKA on an unidentified serine or threonine residue (Hirota et al. 2003).

Preceded by: AJUBA binds centrosome-associated AURKA

Followed by: BORA binds PLK1 and AURKA

Literature references

Hirota, T., Hatakeyama, K., Nitta, M., Sasayama, T., Saya, H., Kunitoku, N. et al. (2003). Aurora-A and an interacting activator, the LIM protein Ajuba, are required for mitotic commitment in human cells. *Cell, 114*, 585-98. ↗

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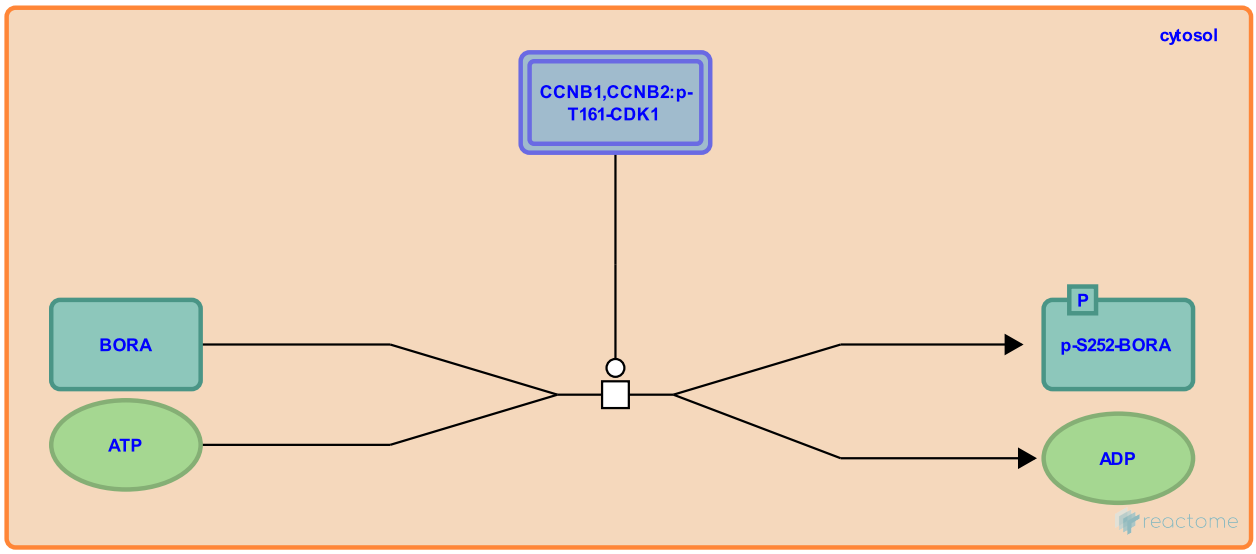
CDK1 phosphorylates BORA ↗

Location: Regulation of PLK1 Activity at G2/M Transition

Stable identifier: R-HSA-4086410

Type: transition

Compartments: cytosol



CDK1 phosphorylates both human and Drosophila BORA protein (Hutterer et al. 2006) on an evolutionarily conserved serine residue - S252 in human BORA (Chan et al. 2008), providing a docking site for PLK1.

Followed by: BORA binds PLK1 and AURKA

Literature references

Nigg, EA., Chan, EH., Santamaria, A., Silljé, HH. (2008). Plk1 regulates mitotic Aurora A function through betaTrCP-dependent degradation of hBora. *Chromosoma, 117*, 457-69. ↗

Hutterer, A., Zigman, M., Knoblich, JA., Schleiffer, A., Wirtz-Peitz, F., Berdnik, D. (2006). Mitotic activation of the kinase Aurora-A requires its binding partner Bora. *Dev. Cell, 11*, 147-57. ↗

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2013-01-29	Authored	Orlic-Milacic, M.
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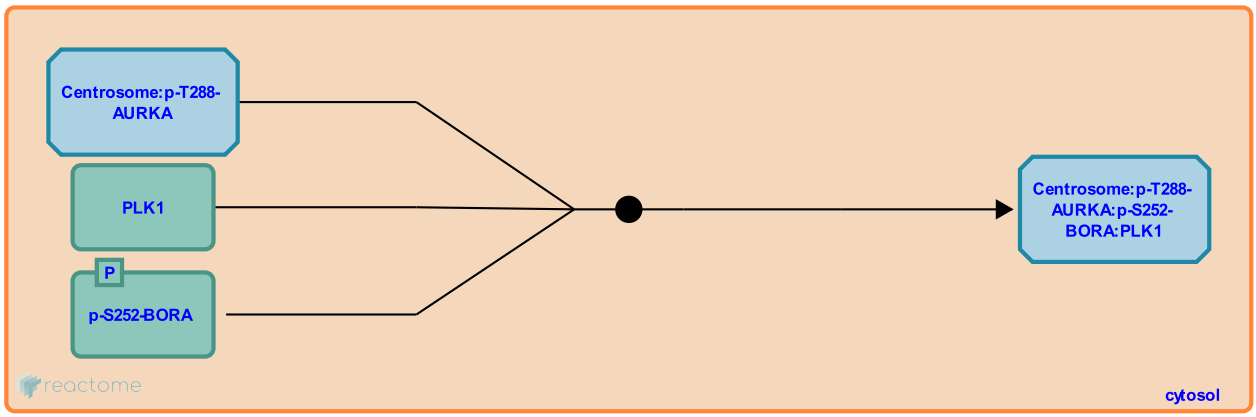
BORA binds PLK1 and AURKA ↗

Location: Regulation of PLK1 Activity at G2/M Transition

Stable identifier: R-HSA-3000319

Type: binding

Compartments: cytosol



BORA is able to interact with both AURKA (Aurora A kinase) and PLK1. Binding of BORA to PLK1 increases the accessibility of PLK1 threonine residue T210 and also brings PLK1 in proximity to AURKA, enabling AURKA to phosphorylate T210 of PLK1 and thereby activate PLK1 (Seki et al. 2008). While BORA is required for mitotic activation of AURKA in Drosophila (Hutterer et al. 2006), it does not significantly activate AURKA in human cells (Seki et al. 2008). AURKA is able to phosphorylate BORA in vitro, but the functional significance of this modification has not been determined (Hutterer et al. 2006).

Preceded by: AJUBA facilitates AURKA autophosphorylation, CDK1 phosphorylates BORA

Followed by: AURKA phosphorylates PLK1

Literature references

Seki, A., Coppinger, JA., Yates, JR., Jang, CY., Fang, G. (2008). Bora and the kinase Aurora a cooperatively activate the kinase Plk1 and control mitotic entry. *Science, 320*, 1655-8. ↗

Hutterer, A., Zigman, M., Knoblich, JA., Schleiffer, A., Wirtz-Peitz, F., Berdnik, D. (2006). Mitotic activation of the kinase Aurora-A requires its binding partner Bora. *Dev. Cell, 11*, 147-57. ↗

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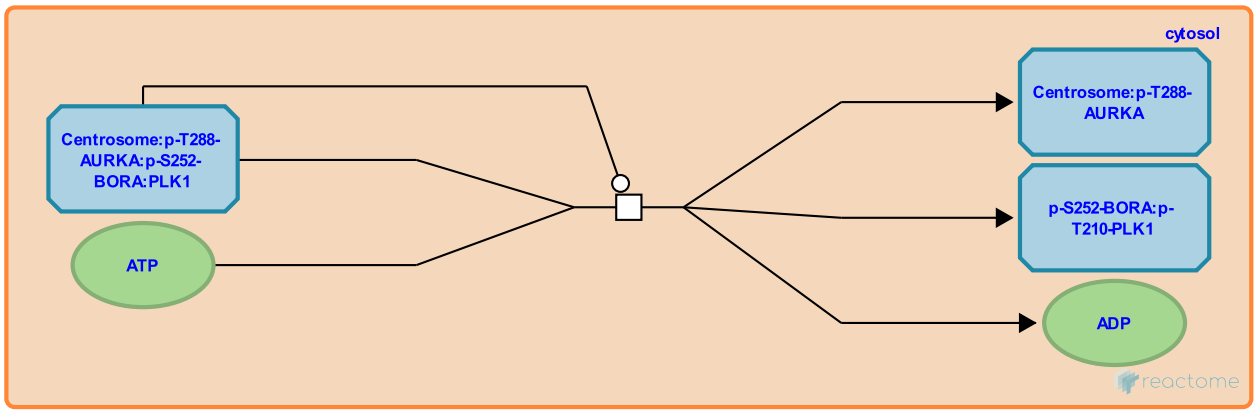
AURKA phosphorylates PLK1 ↗

Location: Regulation of PLK1 Activity at G2/M Transition

Stable identifier: R-HSA-3000310

Type: transition

Compartments: cytosol



AURKA (Aurora A kinase) phosphorylates PLK1 on threonine residue T210 that lies in the conserved aurora kinase consensus site (Seki et al. 2008). PLK1 needs to be phosphorylated on T210 to become catalytically active (Jang et al. 2002). BORA, but not other AURKA co-activators, facilitate PLK1 phosphorylation by AURKA (Macurek et al. 2008, Seki et al. 2008).

Preceded by: BORA binds PLK1 and AURKA

Followed by: PLK1 phosphorylates OPTN, PLK1 phosphorylates BORA

Literature references

Seki, A., Coppinger, JA., Yates, JR., Jang, CY., Fang, G. (2008). Bora and the kinase Aurora a cooperatively activate the kinase Plk1 and control mitotic entry. *Science, 320*, 1655-8. ↗

Erikson, RL., Ma, S., Jang, YJ., Terada, Y. (2002). Phosphorylation of threonine 210 and the role of serine 137 in the regulation of mammalian polo-like kinase. *J. Biol. Chem., 277*, 44115-20. ↗

Clouin, C., Medema, RH., Taylor, SS., Freire, R., Lampson, MA., Klompmaker, R. et al. (2008). Polo-like kinase-1 is activated by aurora A to promote checkpoint recovery. *Nature, 455*, 119-23. ↗

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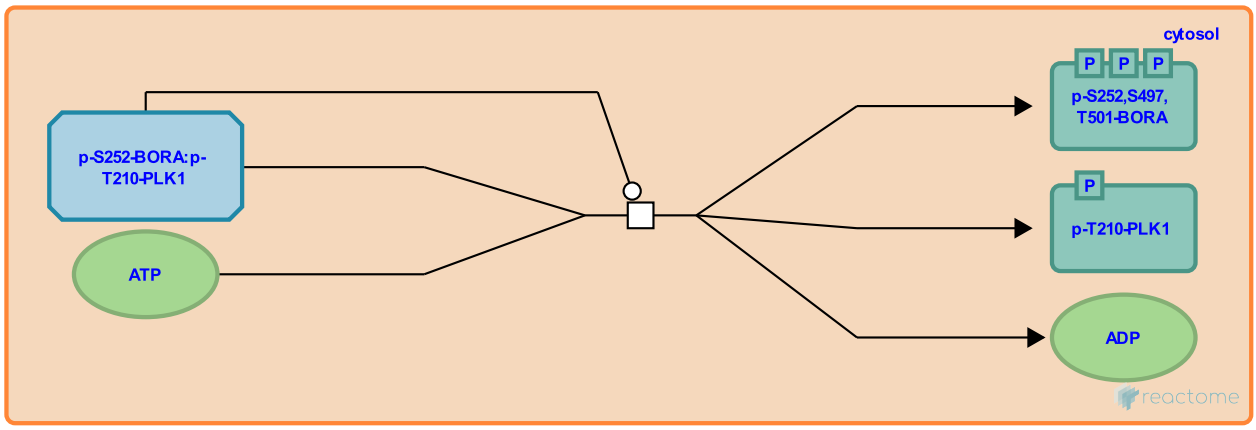
PLK1 phosphorylates BORA ↗

Location: Regulation of PLK1 Activity at G2/M Transition

Stable identifier: R-HSA-3000327

Type: transition

Compartments: cytosol



PLK1 phosphorylates BORA on serine residue S497 and threonine residue T501 that both lie in the DSGYNT degron recognized by beta-TrCP F-box proteins (Seki et al. 2008).

Preceded by: AURKA phosphorylates PLK1

Followed by: Phosphorylated BORA binds SCF-beta-TrCp1/2, Cytosolic PLK1 translocates to the nucleus

Literature references

Seki, A., Coppinger, JA., Yates, JR., Jang, CY., Fang, G., Du, H. (2008). Plk1- and beta-TrCP-dependent degradation of Bora controls mitotic progression. *J. Cell Biol., 181*, 65-78. ↗

Editions

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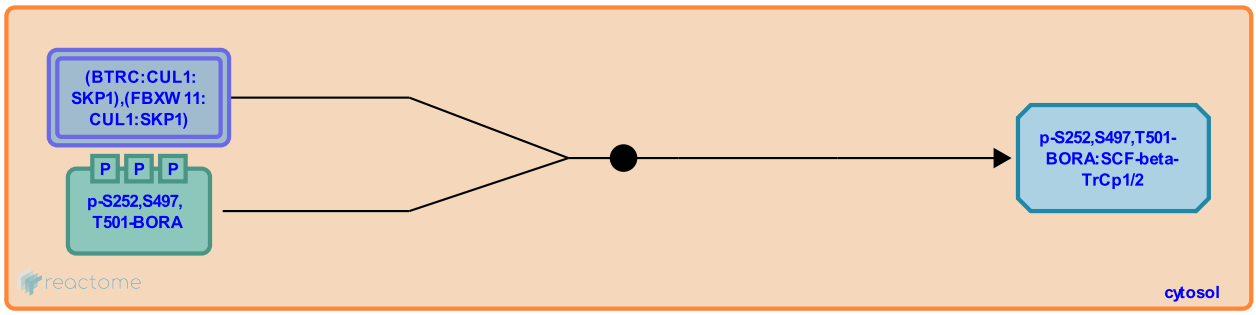
Phosphorylated BORA binds SCF-beta-TrCp1/2 ↗

Location: Regulation of PLK1 Activity at G2/M Transition

Stable identifier: R-HSA-3000339

Type: binding

Compartments: cytosol



The substrate recognition subunits beta-TrCP (BTRC) and beta-TrCP2 (FBXW11) of SCF-beta-TrPC1 and SCF-beta-TrPC2 ubiquitin ligases, respectively, bind the phosphorylated DSGYNT motif of BORA (Seki et al. 2008).

Preceded by: PLK1 phosphorylates BORA

Followed by: SCF-beta-TrCp1/2 ubiquitinates phosphorylated BORA

Literature references

Seki, A., Coppinger, JA., Yates, JR., Jang, CY., Fang, G., Du, H. (2008). Plk1- and beta-TrCP-dependent degradation of Bora controls mitotic progression. *J. Cell Biol., 181,* 65-78. ↗

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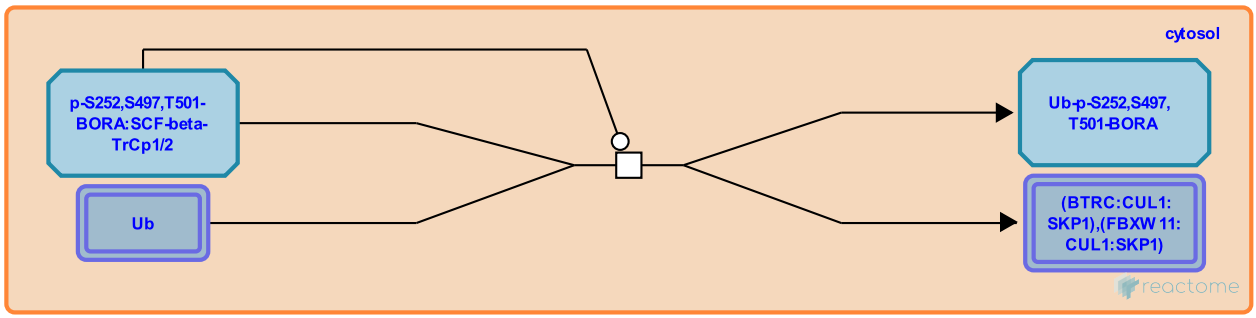
SCF-beta-TrCp1/2 ubiquitinates phosphorylated BORA ↗

Location: Regulation of PLK1 Activity at G2/M Transition

Stable identifier: R-HSA-3000335

Type: transition

Compartments: cytosol



SCF-beta-TrCP ubiquitin ligases promote ubiquitination and degradation of BORA phosphorylated by PLK1, and this is required for timely mitotic progression (Seki et al. 2008).

Preceded by: Phosphorylated BORA binds SCF-beta-TrCp1/2

Literature references

Seki, A., Coppinger, JA., Yates, JR., Jang, CY., Fang, G., Du, H. (2008). Plk1- and beta-TrCP-dependent degradation of Bora controls mitotic progression. *J. Cell Biol., 181*, 65-78. ↗

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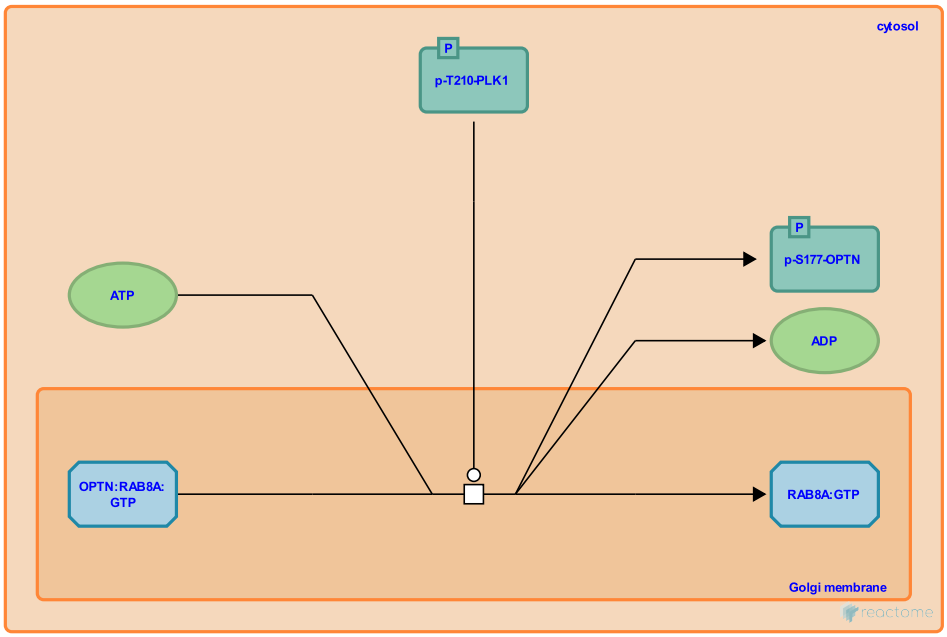
PLK1 phosphorylates OPTN ↗

Location: Regulation of PLK1 Activity at G2/M Transition

Stable identifier: R-HSA-2562526

Type: transition

Compartments: Golgi membrane, cytosol



Activated PLK1 phosphorylates OPTN (optineurin) on serine residue S177. Phosphorylation at S177 disrupts OPTN binding to Golgi-membrane localized RAB8A (Kachaner et al. 2012).

Preceded by: AURKA phosphorylates PLK1

Followed by: Phosphorylated OPTN translocates to the nucleus

Literature references

Laplantine, E., Bennett, KL., Superti-Furga, G., Weil, R., Kachaner, D., Israel, A. et al. (2012). Plk1-dependent phosphorylation of optineurin provides a negative feedback mechanism for mitotic progression. *Mol. Cell, 45*, 553-66. ↗

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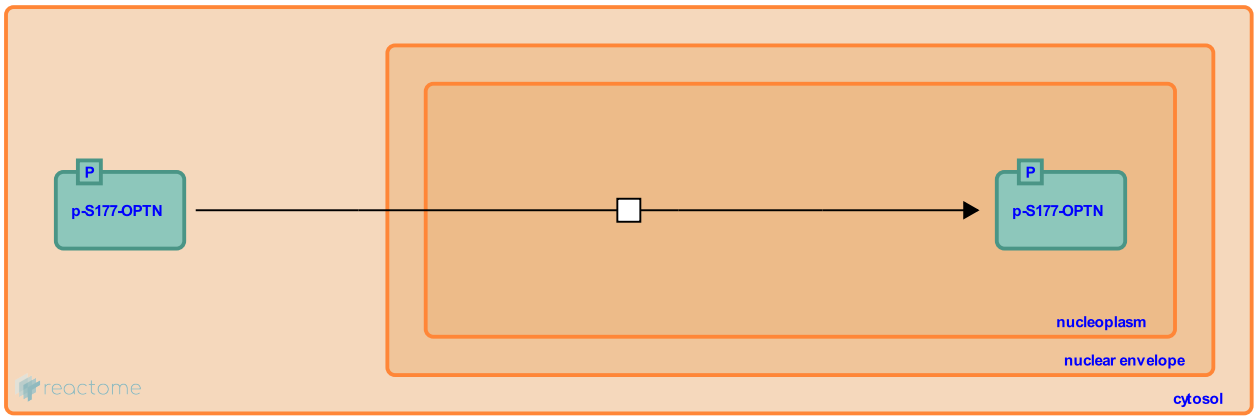
Phosphorylated OPTN translocates to the nucleus ↗

Location: Regulation of PLK1 Activity at G2/M Transition

Stable identifier: R-HSA-2562594

Type: transition

Compartments: nucleoplasm, cytosol



Phosphorylation of OPTN (optineurin) on serine S177 by PLK1 promotes translocation of OPTN to the nucleus (Kachaner et al. 2012).

Preceded by: PLK1 phosphorylates OPTN

Followed by: Myosin phosphatase dephosphorylates PLK1

Literature references

Laplantine, E., Bennett, KL., Superti-Furga, G., Weil, R., Kachaner, D., Israel, A. et al. (2012). Plk1-dependent phosphorylation of optineurin provides a negative feedback mechanism for mitotic progression. *Mol. Cell, 45*, 553-66. ↗

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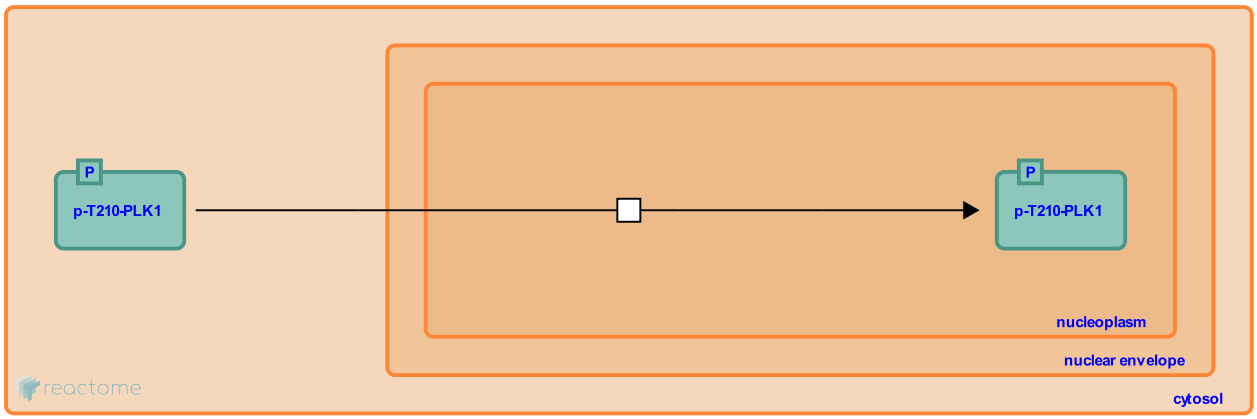
Cytosolic PLK1 translocates to the nucleus ↗

Location: Regulation of PLK1 Activity at G2/M Transition

Stable identifier: R-HSA-3002798

Type: transition

Compartments: nucleoplasm, cytosol



PLK1 is induced in S phase and can be find in both cytosol and nucleus in S and G2 phases of the cell cycle. PLK1 possesses a bipartite nuclear localization signal (NLS) that enables it to enter the nucleus (Taniguchi et al. 2002).

Preceded by: PLK1 phosphorylates BORA

Followed by: Myosin phosphatase dephosphorylates PLK1

Literature references

Nishida, E., Taniguchi, E., Toyoshima-Morimoto, F. (2002). Nuclear translocation of plk1 mediated by its bipartite nuclear localization signal. *J. Biol. Chem., 277*, 48884-8. ↗

Editions

2013-01-29	Authored	Orlic-Milacic, M.
2013-01-30	Edited	Orlic-Milacic, M.
2013-02-07	Reviewed	Weil, R.

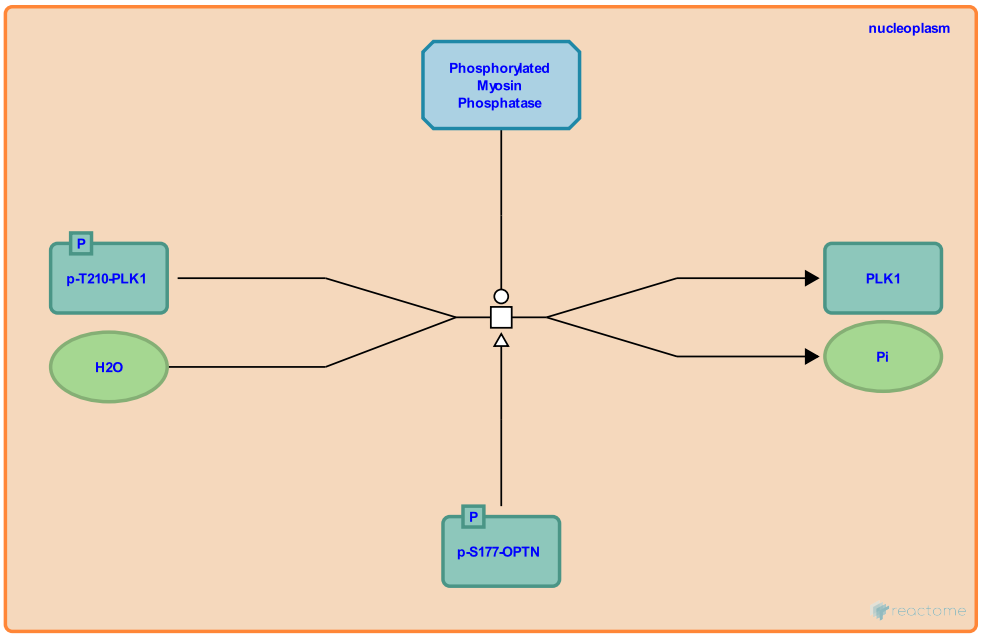
Myosin phosphatase dephosphorylates PLK1 ↗

Location: Regulation of PLK1 Activity at G2/M Transition

Stable identifier: R-HSA-3002811

Type: transition

Compartments: nucleoplasm



The myosin phosphatase complex can dephosphorylate PLK1 threonine residue T210 and inactivate PLK1 (Yamashiro et al. 2008). Myosin phosphatase is activated through phosphorylation of its PPP1R12A (MYPT1) subunit. Several kinases, including CDK1 (Yamashiro et al. 2008) and LATS1 (Chiyoda et al. 2012) have been implicated in myosin phosphatase activation, but the position and temporal order of key PPP1R12A phosphorylations need to be investigated further. Phosphorylated OPTN (optineurin) is able to bind PPP1R12A (MYPT1) and positively regulates PLK1 dephosphorylation by myosin phosphatase, posibly by facilitating PPP1R12A phosphorylation and myosin phosphatase activation (Kachaner et al. 2012).

Preceded by: Phosphorylated OPTN translocates to the nucleus, Cytosolic PLK1 translocates to the nucleus

Literature references

Saya, H., Ishihama, Y., Ito, M., Sugiyama, N., Kuninaka, S., Arima, Y. et al. (2012). LATS1/WARTS phosphorylates MYPT1 to counteract PLK1 and regulate mammalian mitotic progression. *J. Cell Biol., 197*, 625-41. ↗

Laplantine, E., Bennett, KL., Superti-Furga, G., Weil, R., Kachaner, D., Israel, A. et al. (2012). Plk1-dependent phosphorylation of optineurin provides a negative feedback mechanism for mitotic progression. *Mol. Cell, 45*, 553-66. ↗

Goto, H., Kaibuchi, K., Hartshorne, DJ., Totsukawa, G., Matsumura, F., Yamashiro, S. et al. (2008). Myosin phosphatase-targeting subunit 1 regulates mitosis by antagonizing polo-like kinase 1. *Dev. Cell, 14*, 787-97. ↗

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2013-01-30	Edited	Orlic-Milacic, M.
2013-02-07	Reviewed	Weil, R.

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