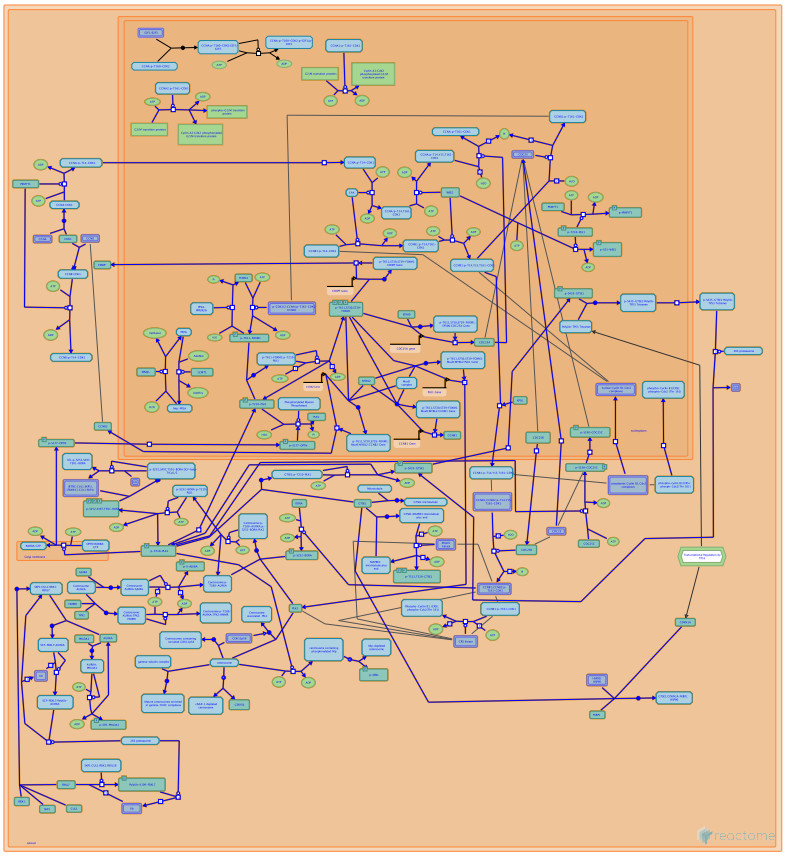
G2/M Transition



Bird, AW., Bruinsma, W., Chen, H., Gillespie, ME., Grant, R., Lee, KS., Lindon, C., Lorca, T., Matthews, L., Maxwell, CA., Merdes, A., Orlic-Milacic, M., Shah, K., Weil, R.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

03/09/2021

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. ↗

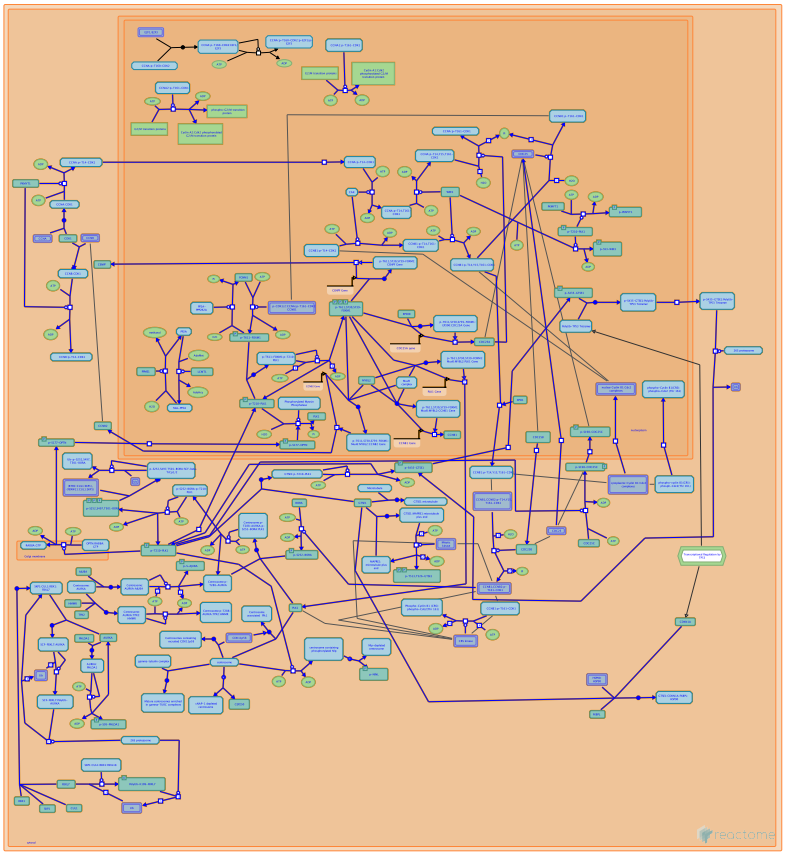
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

G2/M Transition ↗

Stable identifier: R-HSA-69275



Together with two B-type cyclins, CCNB1 and CCNB2, Cdc2 (CDK1) regulates the transition from G2 into mitosis. CDK1 can also form complexes with Cyclin A (CCNA1 and CCNA3). CDK1 complexes with A and B type cyclins are activated by dephosphorylation of CDK1 threonine residue T14 and tyrosine residue Y15. Cyclin A:CDK1 and Cyclin B:CDK1 complexes phosphorylate several proteins involved in mitotic spindle formation and function, the breakdown of the nuclear envelope, and chromosome condensation that is necessary for the ~2 meters of DNA to be segregated at mitosis (Nigg 1998, Nilsson and Hoffmann 2000, Salaun et al. 2008, Fisher et al. 2012).

Literature references

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Fisher, D., Krasinska, L., Coudreuse, D., Novák, B. (2012). Phosphorylation network dynamics in the control of cell cycle transitions. *J. Cell. Sci., 125*, 4703-11. ↗

Salaun, P., Rannou, Y., Prigent, C. (2008). Cdk1, Plks, Auroras, and Neks: the mitotic bodyguards. *Adv. Exp. Med. Biol., 617*, 41-56. ↗

Nigg, EA. (1998). Polo-like kinases: positive regulators of cell division from start to finish. *Curr. Opin. Cell Biol., 10*, 776-83. ↗

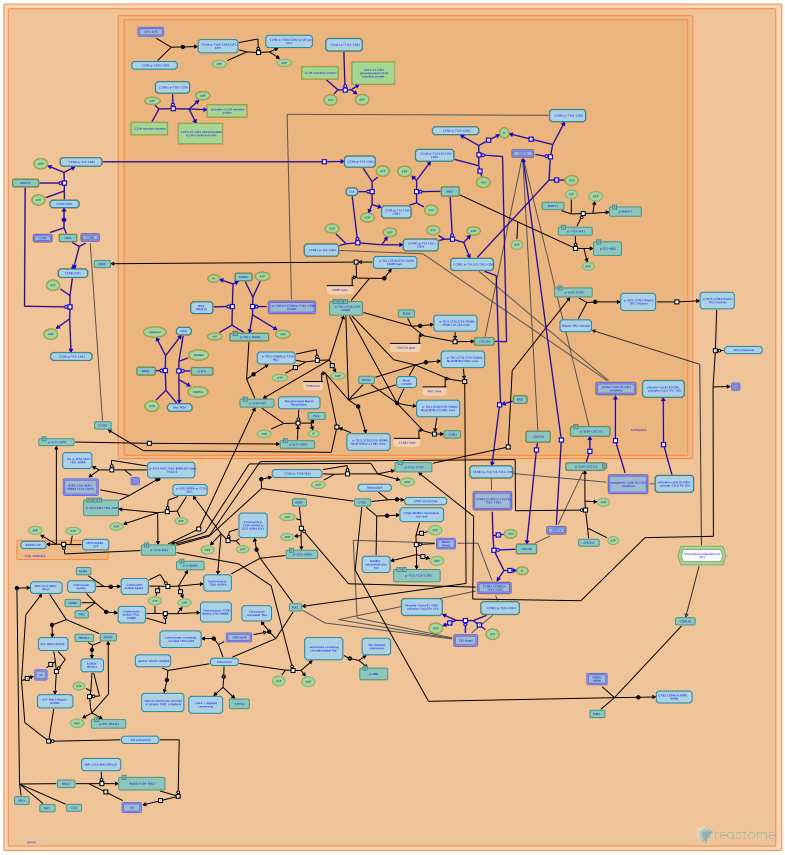
Editions

2005-10-10	Reviewed	Lorca, T.
2017-03-25	Edited	Orlic-Milacic, M.

Cyclin A/B1/B2 associated events during G2/M transition ↗

Location: G2/M Transition

Stable identifier: R-HSA-69273



Cell cycle progression is regulated by cyclin-dependent protein kinases at both the G1/S and the G2/M transitions. The G2/M transition is regulated through the phosphorylation of nuclear lamins and histones (reviewed in Sefton, 2001).

The two B-type cyclins localize to different regions within the cell and are thought to have specific roles as CDK1-activating subunits (see Bellanger et al., 2007). Cyclin B1 is primarily cytoplasmic during interphase and translocates into the nucleus at the onset of mitosis (Jackman et al., 1995; Hagting et al., 1999). Cyclin B2 colocalizes with the Golgi apparatus and contributes to its fragmentation during mitosis (Jackman et al., 1995; Draviam et al., 2001).

Literature references

Sefton, BM. (2001). Overview of protein phosphorylation. *Curr Protoc Cell Biol, 14*, Unit 14.1. ↗

Bellanger, S., de Gramont, A., Sobczak-Thépot, J. (2007). Cyclin B2 suppresses mitotic failure and DNA re-replication in human somatic cells knocked down for both cyclins B1 and B2. *Oncogene, 26*, 7175-84. ↗

Jackman, M., Firth, M., Pines, J. (1995). Human cyclins B1 and B2 are localized to strikingly different structures: B1 to microtubules, B2 primarily to the Golgi apparatus. *EMBO J, 14*, 1646-54. ↗

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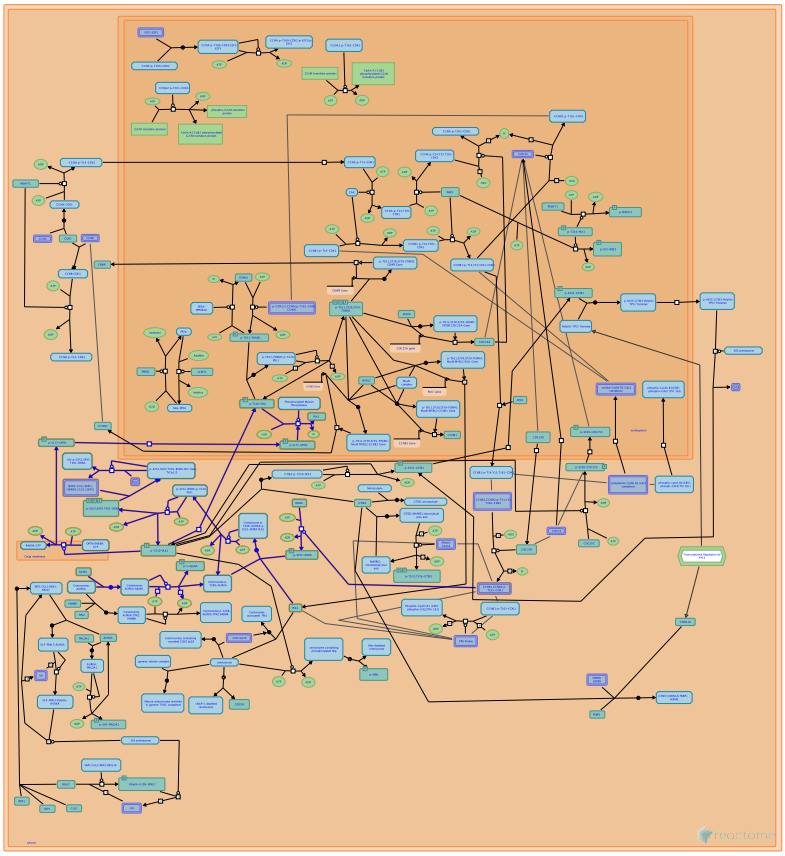
Regulation of PLK1 Activity at G2/M Transition ↗

Location: 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

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Hirota, T., Kunitoku, N., Sasayama, T., Marumoto, T., Zhang, D., Nitta, M. 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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Editions

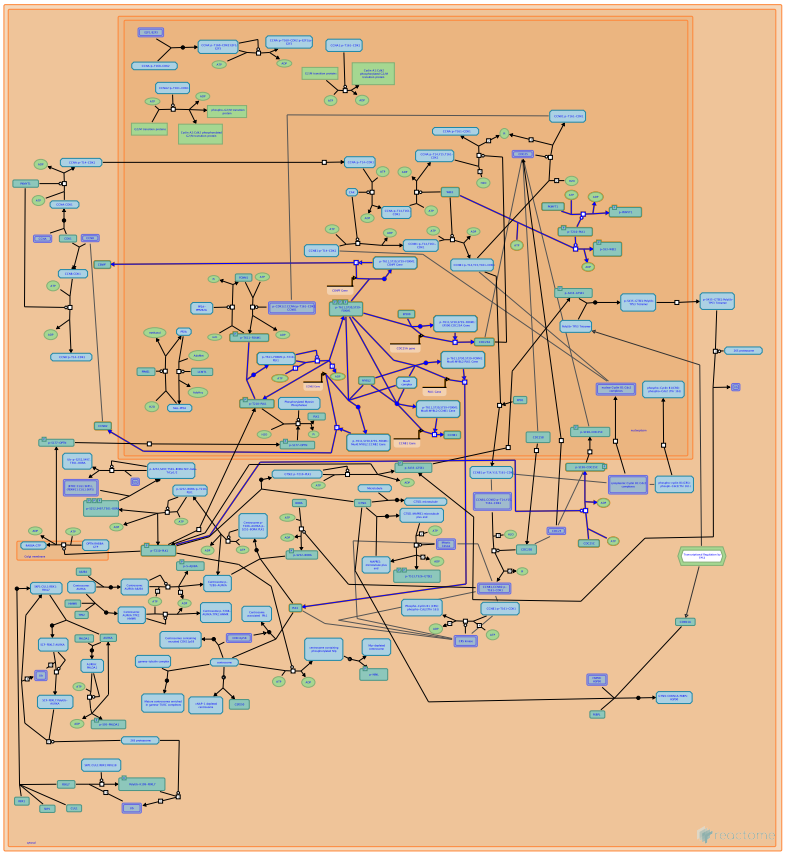
2013-01-29	Authored	Orlic-Milacic, M.
2013-01-30	Edited	Orlic-Milacic, M.
2013-02-07	Reviewed	Weil, R.
2013-08-21	Reviewed	Bruinsma, W.

Polo-like kinase mediated events ↗

Location: G2/M Transition

Stable identifier: R-HSA-156711

Compartments: nucleoplasm



At mitotic entry, Plk1 phosphorylates and activates Cdc25C phosphatase, whereas it phosphorylates and down-regulates Wee1A (Watanabe et al. 2004). Plk1 also phosphorylates and inhibits Myt1 activity (Sagata 2005). Cyclin B1-bound Cdc2, which is the target of Cdc25C, Wee1A, and Myt1, functions in a feedback loop and phosphorylates the latter components (Cdc25C, Wee1A, Myt1). The Cdc2- dependent phosphorylation provides docking sites for the polo-box domain of Plk1, thus promoting the Plk1-dependent regulation of these components and, as a result, activation of Cdc2-Cyclin B1.

PLK1 phosphorylates and activates the transcription factor FOXM1 which stimulates the expression of a number of genes needed for G2/M transition, including PLK1, thereby creating a positive feedback loop (Laoukili et al. 2005, Fu et al. 2008, Sadasivam et al. 2012, Chen et al. 2013).

Literature references

Watanabe, N., Arai, H., Nishihara, Y., Taniguchi, M., Watanabe, N., Hunter, T. et al. (2004). M-phase kinases induce phospho-dependent ubiquitination of somatic Wee1 by SCFbeta-TrCP. *Proc Natl Acad Sci U S A, 101*, 4419-24. ↗

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Sadasivam, S., Duan, S., DeCaprio, JA. (2012). The MuvB complex sequentially recruits B-Myb and FoxM1 to promote mitotic gene expression. *Genes Dev., 26*, 474-89. ↗

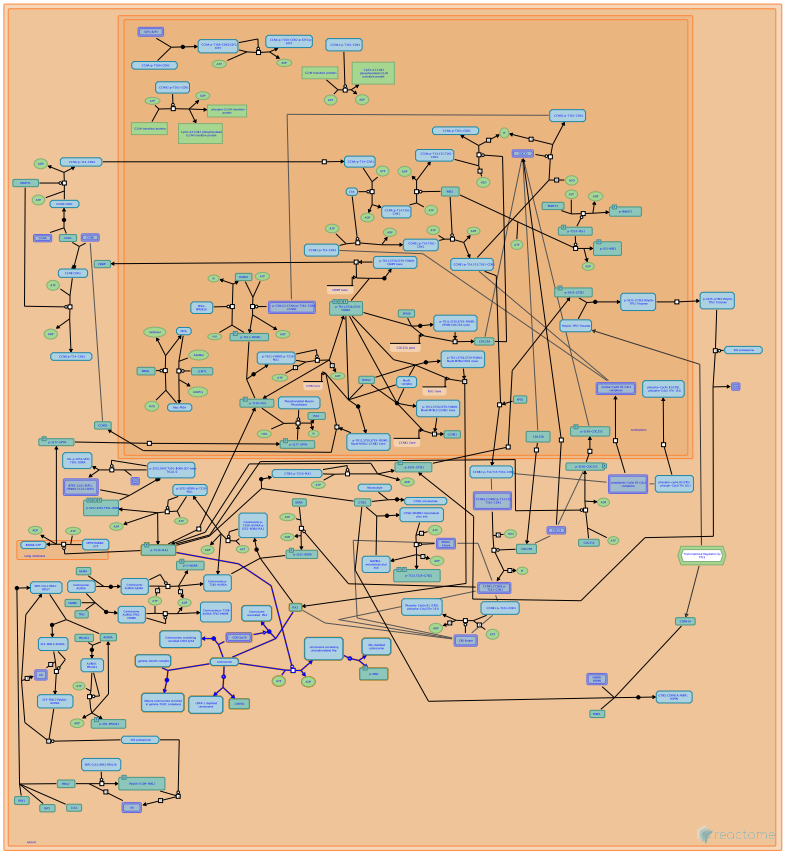
Editions

2004-12-09	Authored	Lee, KS.
2013-08-21	Reviewed	Bruinsma, W.
2021-05-18	Edited	Gillespie, ME.

Centrosome maturation ↗

Location: G2/M Transition

Stable identifier: R-HSA-380287



The centrosome is the primary microtubule organizing center (MTOC) in vertebrate cells and plays an important role in orchestrating the formation of the mitotic spindle. Centrosome maturation is an early event in this process and involves a major reorganization of centrosomal material at the G2/M transition. During maturation, centrosomes undergo a dramatic increase in size and microtubule nucleating capacity. As part of this process, a number of proteins and complexes, including some that are required for microtubule nucleation and anchoring, are recruited to the centrosome while others that are required for organization of interphase microtubules and centrosome cohesion are lost (reviewed in Schatten, 2008; Raynaud-Messina and Merdes 2007).

Literature references

Schatten, H. (2008). The mammalian centrosome and its functional significance. *Histochem Cell Biol, 129*, 667-86. ↗

Raynaud-Messina, B., Merdes, A. (2007). Gamma-tubulin complexes and microtubule organization. *Curr Opin Cell Biol, 19*, 24-30. ↗

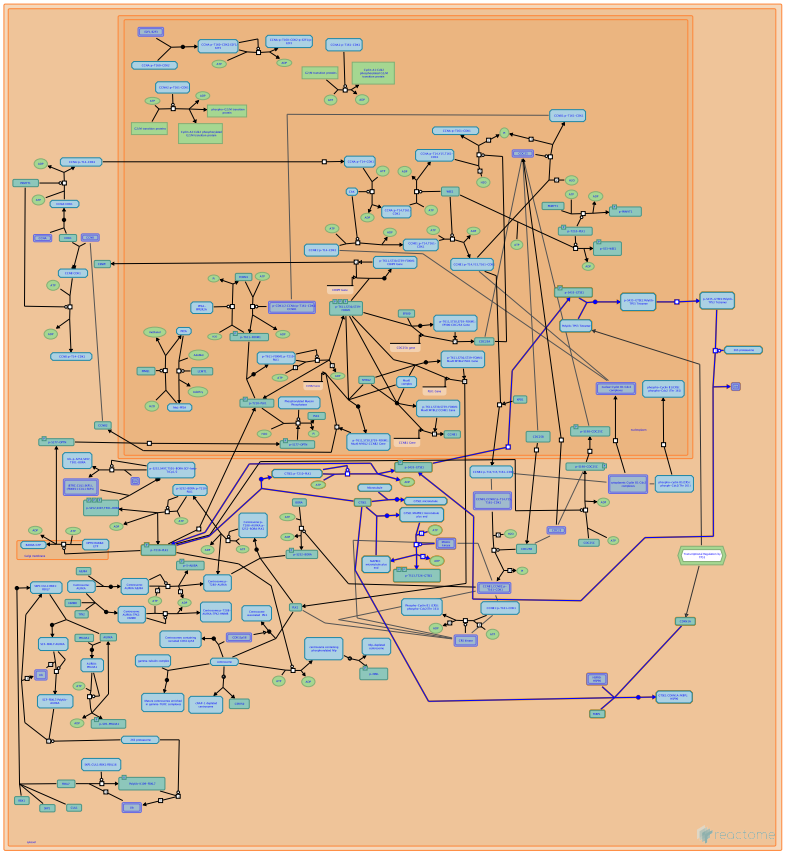
Editions

2008-11-11	Authored	Matthews, L.
2008-11-17	Reviewed	Merdes, A.
2008-11-24	Edited	Matthews, L.

The role of GTSE1 in G2/M progression after G2 checkpoint ↗

Location: G2/M Transition

Stable identifier: R-HSA-8852276



GTSE1 (B99) was identified as a microtubule-associated protein product of the mouse B99 gene, which exhibits both a cell cycle regulated expression, with highest levels in G2, and DNA damage triggered expression under direct control of TP53 (p53) (Utrera et al. 1998, Collavin et al. 2000). Human GTSE1, similar to the mouse counterpart, binds to microtubules, shows cell cycle regulated expression with a peak in G2 and plays a role in G2 checkpoint recovery after DNA damage but is not transcriptionally regulated by TP53 (Monte et al. 2003, Monte et al. 2004, Scolz et al. 2012).

In G1 cells, GTSE1 is found at the microtubule lattice, likely due to direct binding to tubulin. An evolutionarily conserved interaction between GTSE1 and MAPRE1 (EB1), a microtubule plus end protein, promotes GTSE1 localization to the growing tip of the microtubules, which contributes to cell migration and is likely involved in cancer cell invasiveness. Highly invasive breast cancer cell lines exhibit high GTSE1 levels in G1, while GTSE1 levels in G1 are normally low. At the beginning of mitotic prometaphase, GTSE1 is phosphorylated by mitotic kinase(s), possibly CDK1, in proximity to the MAPRE1-binding region, causing GTSE1 dissociation from the plus end microtubule ends (Scolz et al. 2012).

During G2 checkpoint recovery (cell cycle re-entry after DNA damage induced G2 arrest), GTSE1 relocates to the nucleus where it binds TP53 and, in an MDM2-dependent manner, promotes TP53 cytoplasmic translocation and proteasome mediated degradation (Monte et al. 2003, Monte et al. 2004). Relocation of GTSE1 to the nucleus in G2 phase depends on PLK1-mediated phosphorylation of GTSE1 (Liu et al. 2010).

GTSE1-facilitated down-regulation of TP53 in G2 allows cells to avoid TP53 mediated apoptosis upon DNA damage and to re-enter cell cycle (Monte et al. 2003). While TP53 down-regulation mediated by GTSE1 in G2 correlates with decreased expression of TP53 target genes involved in apoptosis and cell cycle arrest,

GTSE1 can also increase the half-life of the TP53 target p21 (CDKN1A). GTSE1-mediated stabilization of CDKN1A involves interaction of GTSE1 with CDKN1A and its chaperone complex, consisting of HSP90 and FKBPL (WISp39), and may be involved in resistance to paclitaxel treatment (Bublik et al. 2010).

Literature references

Utrera, R., Collavin, L., Lazarević, D., Delia, D., Schneider, C. (1998). A novel p53-inducible gene coding for a microtubule-localized protein with G2-phase-specific expression. *EMBO J., 17*, 5015-25.

Collavin, L., Monte, M., Verardo, R., Pfleger, C., Schneider, C. (2000). Cell-cycle regulation of the p53-inducible gene B99. *FEBS Lett., 481*, 57-62.

Monte, M., Benetti, R., Buscemi, G., Sandy, P., Del Sal, G., Schneider, C. (2003). The cell cycle-regulated protein human GTSE-1 controls DNA damage-induced apoptosis by affecting p53 function. *J. Biol. Chem., 278*, 30356-64.

Monte, M., Benetti, R., Collavin, L., Marchionni, L., Del Sal, G., Schneider, C. (2004). hGTSE-1 expression stimulates cytoplasmic localization of p53. *J. Biol. Chem., 279*, 11744-52.

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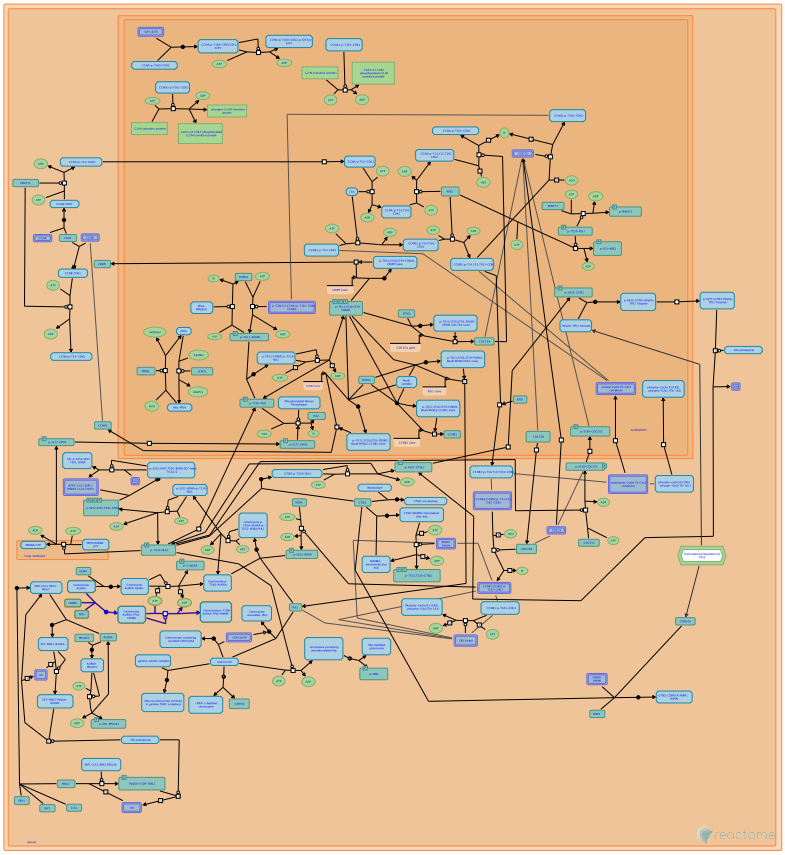
Editions

2016-01-15	Authored, Edited	Orlic-Milacic, M.
2016-01-22	Reviewed	Bird, AW.

AURKA Activation by TPX2 ↗

Location: G2/M Transition

Stable identifier: R-HSA-8854518



TPX2 binds to aurora kinase A (AURKA) at centrosomes and promotes its activation by facilitating AURKA active conformation and autophosphorylation of the AURKA threonine residue T288 (Bayliss et al. 2003, Xu et al. 2011, Giubettini et al. 2011, Dodson and Bayliss 2012).

Literature references

Bayliss, R., Sardon, T., Vernos, I., Conti, E. (2003). Structural basis of Aurora-A activation by TPX2 at the mitotic spindle. *Mol. Cell, 12*, 851-62. ↗

Giubettini, M., Asteriti, IA., Scrofani, J., De Luca, M., Lindon, C., Lavia, P. et al. (2011). Control of Aurora-A stability through interaction with TPX2. *J. Cell. Sci., 124*, 113-22. ↗

Xu, X., Wang, X., Xiao, Z., Li, Y., Wang, Y. (2011). Two TPX2-dependent switches control the activity of Aurora A. *PLoS ONE, 6*, e16757. ↗

Dodson, CA., Bayliss, R. (2012). Activation of Aurora-A kinase by protein partner binding and phosphorylation are independent and synergistic. *J. Biol. Chem., 287*, 1150-7. ↗

Editions

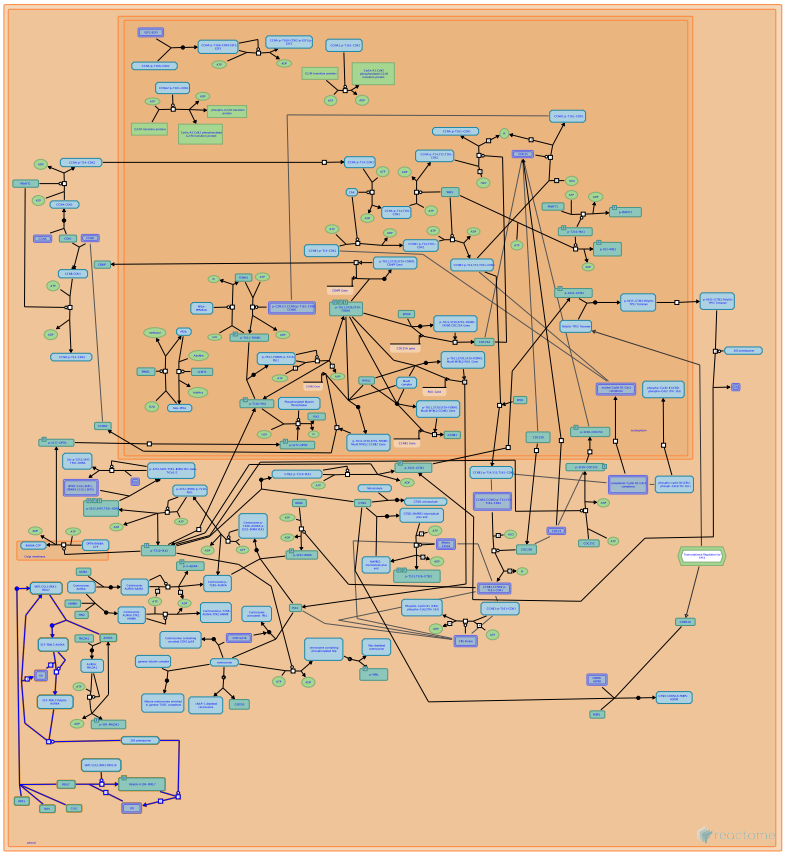
2016-01-27	Authored, Edited	Orlic-Milacic, M.
2016-02-16	Reviewed	Maxwell, CA., Chen, H.

FBXL7 down-regulates AURKA during mitotic entry and in early mitosis ↗

Location: G2/M Transition

Stable identifier: R-HSA-8854050

Compartments: cytosol



The protein levels of aurora kinase A (AURKA) during mitotic entry and in early mitosis can be reduced by the action of the SCF-FBXL7 E3 ubiquitin ligase complex consisting of SKP1, CUL1, RBX1 and FBXL7 subunits. FBXL7 is the substrate recognition subunit of the SCF-FBXL7 complex that associates with the centrosome-bound AURKA, promoting its ubiquitination and proteasome-mediated degradation. Overexpression of FBXL7 results in G2/M cell cycle arrest and apoptosis (Coon et al. 2011).

FBXL7 protein levels are down-regulated by the action of the SCF-FBXL18 E3 ubiquitin ligase complex, consisting of SKP1, CUL1, RBX1 and the substrate recognition subunit FBXL18. FBXL18 binds to the FQ motif of FBXL7, targeting it for ubiquitination and proteasome-mediated degradation, counteracting its pro-apoptotic activity (Liu et al. 2015). Cell cycle stage-dependency of down-regulation of FBXL7 by FBXL18 is unknown.

Literature references

Coon, TA., Glasser, JR., Mallampalli, RK., Chen, BB. (2012). Novel E3 ligase component FBXL7 ubiquitinates and degrades Aurora A, causing mitotic arrest. *Cell Cycle, 11*, 721-9. ↗

Liu, Y., Lear, T., Zhao, Y., Zhao, J., Zou, C., Chen, BB. et al. (2015). F-box protein Fbxl18 mediates polyubiquitylation and proteasomal degradation of the pro-apoptotic SCF subunit Fbxl7. *Cell Death Dis, 6*, e1630. ↗

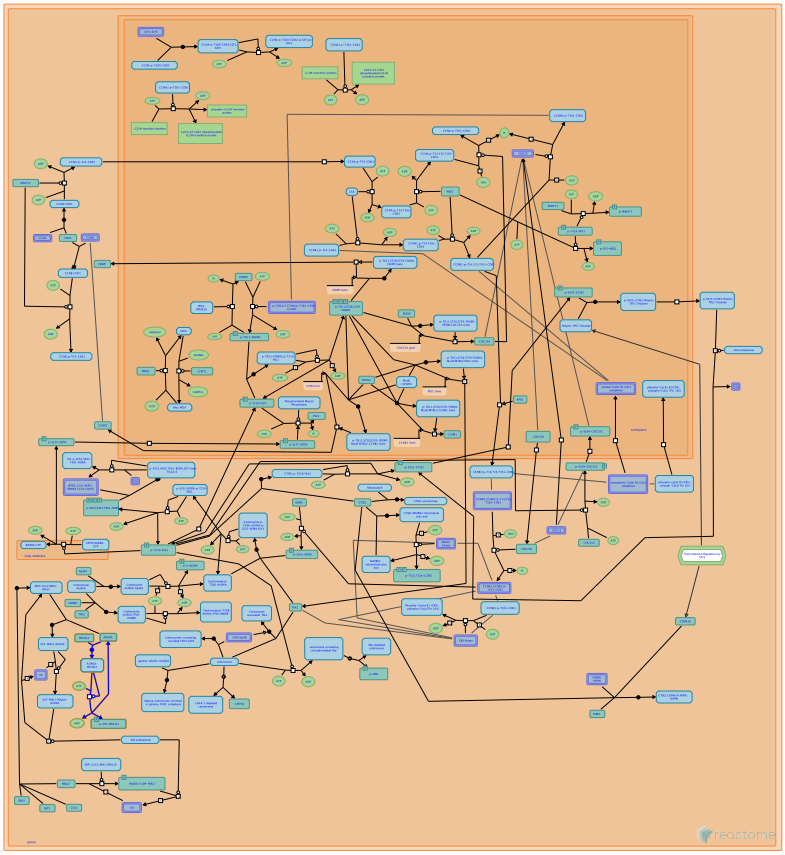
Editions

2016-01-27	Authored, Edited	Orlic-Milacic, M.
2016-05-13	Reviewed	Lindon, C., Grant, R.

Interaction between PHLDA1 and AURKA ↗

Location: G2/M Transition

Stable identifier: R-HSA-8854521



PHLDA1 (TDAG51), the product of a gene involved in breast cancer progression, interacts with aurora kinase A (AURKA). While unphosphorylated PHLDA1 promotes AURKA ubiquitination and degradation, AURKA-mediated phosphorylation of PHLDA1 results in down-regulation of PHLDA1 protein levels. Ectopic expression of PHLDA1 strongly antagonizes AURKA-triggered oncogenic phenotypes, suggesting PHLDA1 downregulation as one of the key mechanisms by which AURKA promotes breast cancer (Johnson et al. 2011).

Literature references

Johnson, EO., Chang, KH., de Pablo, Y., Ghosh, S., Mehta, R., Badve, S. et al. (2011). PHLDA1 is a crucial negative regulator and effector of Aurora A kinase in breast cancer. *J. Cell. Sci., 124*, 2711-22. ↗

Editions

2016-01-29	Authored, Edited	Orlic-Milacic, M.
2016-02-04	Reviewed	Shah, K.

Table of Contents