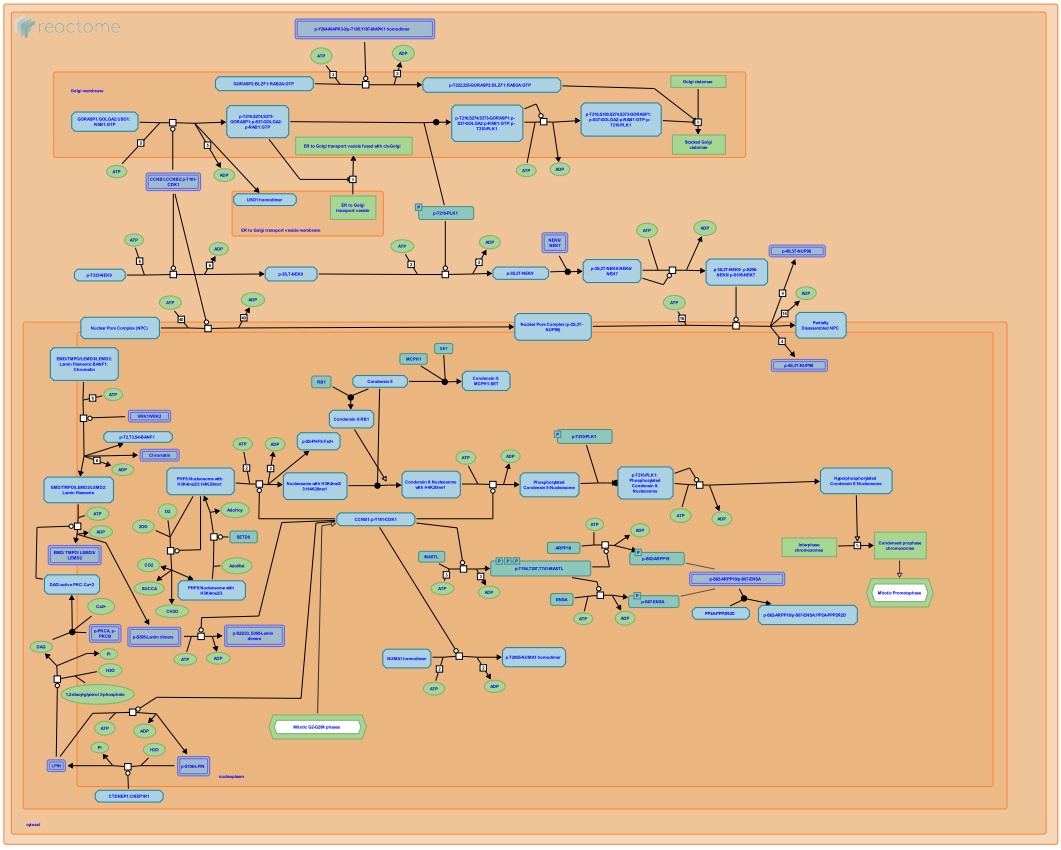
Mitotic Prophase



Burgess, A., Colanzi, A., Gallie, BL., Gillespie, ME., Gorjánácz, M., Longworth, MS., Malhotra, V., Mattaj, IW., Matthews, L., Merdes, A., Mochida, S., Orlic-Milacic, M., Wang, Y.

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

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.

17/05/2024

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.
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. ↗

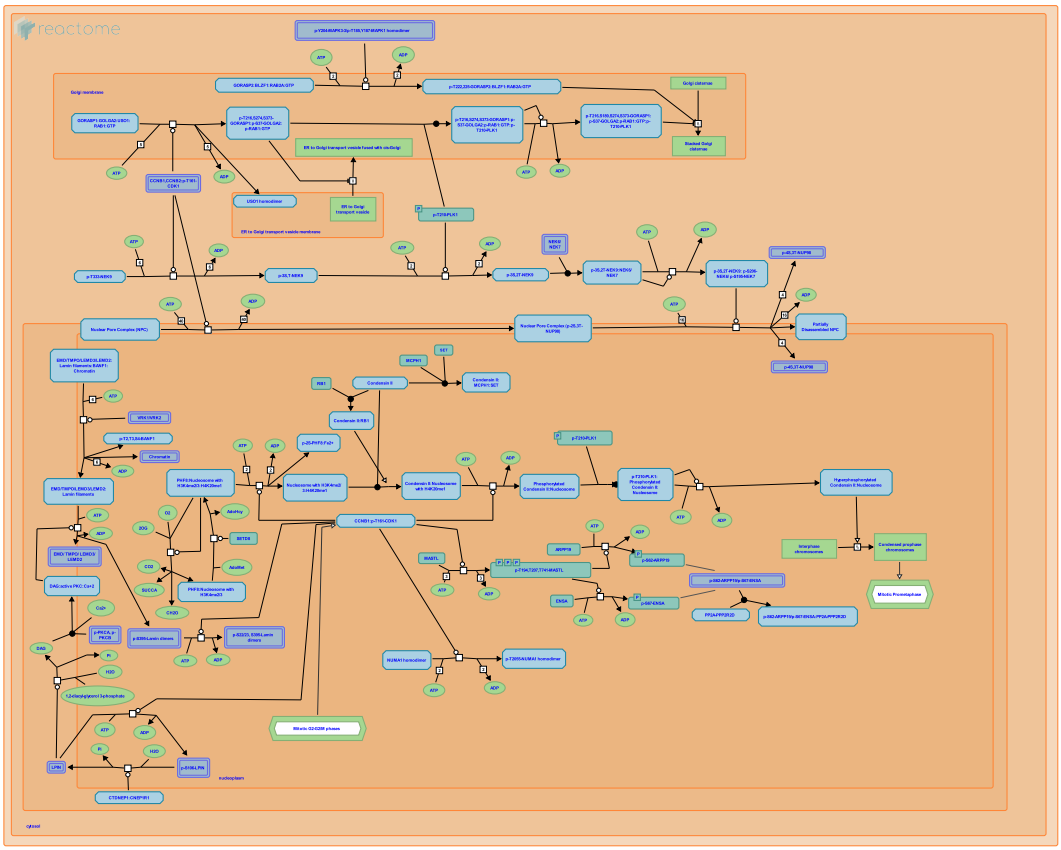
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 5 pathways and 1 reaction (see Table of Contents)

Mitotic Prophase ↗

Stable identifier: R-HSA-68875



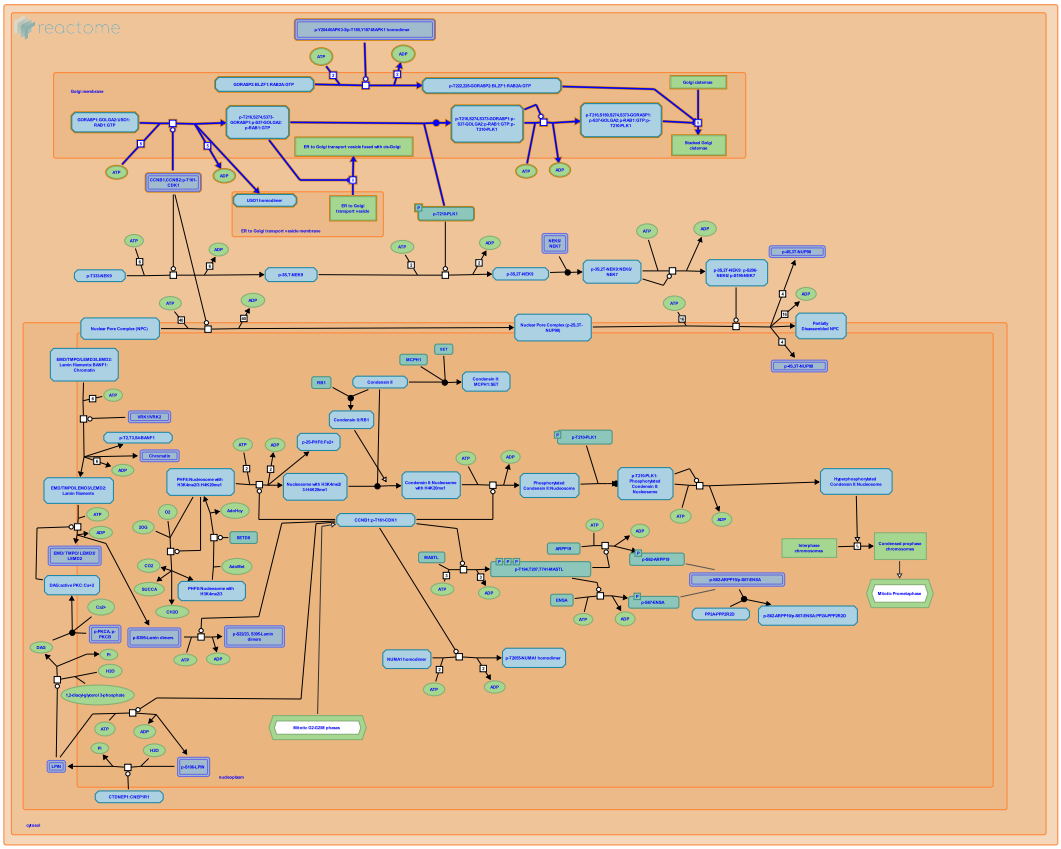
During prophase, the chromatin in the nucleus condenses, and the nucleolus disappears. Centrioles begin moving to the opposite poles or sides of the cell. Some of the fibers that extend from the centromeres cross the cell to form the mitotic spindle.

Golgi Cisternae Pericentriolar Stack Reorganization ↗

Location: Mitotic Prophase

Stable identifier: R-HSA-162658

Compartments: cytosol, ER to Golgi transport vesicle membrane, Golgi membrane



The pericentriolar stacks of Golgi cisternae undergo extensive fragmentation and reorganization in mitosis.

In mammalian cells, Golgi apparatus consists of stacked cisternae that are connected by tubules to form a ribbon-like structure in the perinuclear region, in vicinity of the centrosome. Reorganization of the Golgi apparatus during cell division allows both daughter cells to inherit this organelle, and may play additional roles in the organization of the mitotic spindle.

First changes in the structure of the Golgi apparatus likely start in G2 and are subtle, involving unlinking of the Golgi ribbon into separate stacks. These changes are required for the entry of mammalian cells into mitosis (Sutterlin et al. 2002). This initial unlinking of the Golgi ribbon depends on GRASP proteins and on CTBP1 (BARS) protein, which induces the cleavage of the tubular membranes connecting the stacks (Hidalgo Carcedo et al. 2004, Colanzi et al. 2007), but the exact mechanism is not known. Activation of MEK1/2 also contributes to unlinking of the Golgi ribbon in G2 (Feinstein and Linstedt 2007).

From prophase to metaphase, Golgi cisternae undergo extensive fragmentation that is a consequence of unstacking of Golgi cisternae and cessation of transport through Golgi. At least three mitotic kinases, CDK1, PLK1 and MEK1, regulate these changes. CDK1 in complex with cyclin B phosphorylates GOLGA2 (GM130) and GORASP1 (GRASP65), constituents of a cis-Golgi membrane complex (Lowe et al. 1998, Preisinger et al. 2005). Phosphorylation of GOLGA2 prevents binding of USO1 (p115), a protein localizing to the membrane of ER (endoplasmic reticulum) to Golgi transport vesicles and cis-Golgi, thereby impairing fusion of these vesicles with cis-Golgi cisternae and stopping ER to Golgi transport (Lowe et al. 1998, Seeman et al. 2000, Moyer et al. 2001). Phosphorylation of GORASP1 by CDK1 enables further phosphorylation of GORASP1 by PLK1 (Sutterlin et al. 2001, Preisinger et al. 2005). Phosphorylation of GORASP1 by CDK1 and PLK1 impairs stacking of Golgi cisternae by interfering with formation of GORASP1 trans-oligomers that would normally link the Golgi cisternae together (Wang et al. 2003, Wang et al. 2005, Sengupta and Linstedt 2010).

In the median Golgi, GORASP2 (GRASP55), a protein that forms a complex with BLFZ1 (Golgin-45) and RAB2A GTPase and contributes to cisternae stacking and Golgi trafficking (Short et al. 2001), is also phosphorylated in

mitosis. Phosphorylation of GORASP2 by MEK1/2-activated MAPK1 (ERK2) and/or MAPK3-3 (ERK1b in human, Erk1c in rat) contributes to Golgi unlinking in G2 and fragmentation of Golgi cisternae in mitotic prophase (Acharya et al. 1998, Jesch et al. 2001, Colanzi et al. 2003, Shaul and Seger 2006, Duran et al. 2008, Feinstein and Linstedt 2007, Feinstein and Linstedt 2008, Xiang and Wang 2010).

Literature references

Linstedt, AD., Ahn, NG., Lewis, TS., Jesch, SA. (2001). Mitotic phosphorylation of Golgi reassembly stacking protein 55 by mitogen-activated protein kinase ERK2. *Mol. Biol. Cell, 12*, 1811-7. ↗

Seemann, J., Jokitalo, EJ., Warren, G. (2000). The role of the tethering proteins p115 and GM130 in transport through the Golgi apparatus in vivo. *Mol. Biol. Cell, 11*, 635-45. ↗

Bossard, C., Kinseth, M., Wu, CC., Zimmerman, T., Duran, JM., Yates, J. et al. (2008). The role of GRASP55 in Golgi fragmentation and entry of cells into mitosis. *Mol. Biol. Cell, 19*, 2579-87. ↗

Seemann, J., Warren, G., Wang, Y., Shorter, J., Pypaert, M. (2003). A direct role for GRASP65 as a mitotically regulated Golgi stacking factor. *EMBO J., 22*, 3279-90. ↗

Satoh, A., Warren, G., Wang, Y. (2005). Mapping the functional domains of the Golgi stacking factor GRASP65. *J. Biol. Chem., 280*, 4921-8. ↗

Editions

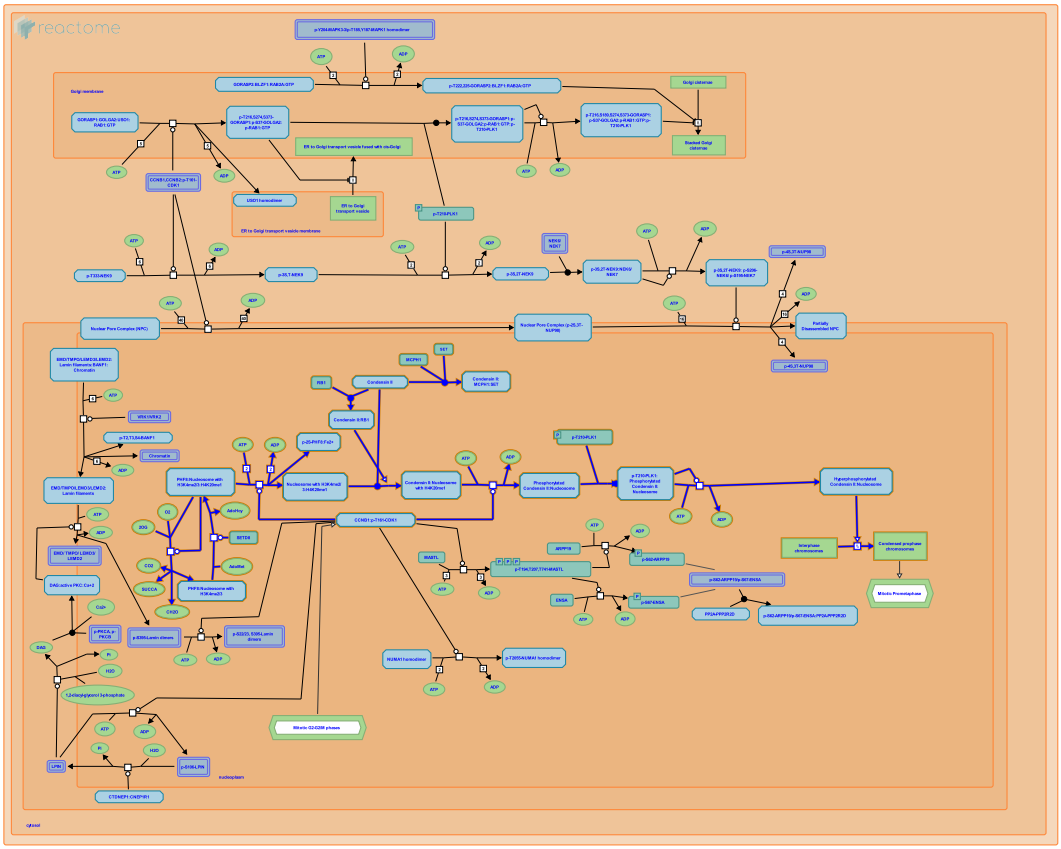
2005-04-04	Authored	Gillespie, ME.
2012-07-20	Revised	Orlic-Milacic, M.
2012-08-15	Reviewed	Malhotra, V.
2012-08-19	Reviewed	Wang, Y.
2012-08-21	Reviewed	Colanzi, A.

Condensation of Prophase Chromosomes ↗

Location: Mitotic Prophase

Stable identifier: R-HSA-2299718

Compartments: nucleoplasm



In mitotic prophase, the action of the condensin II complex enables initial chromosome condensation.

The condensin II complex subunit NCAPD3 binds monomethylated histone H4 (H4K20me1), thereby associating with chromatin (Liu et al. 2010). Binding of the condensin II complex to chromatin is partially controlled by the presence of RB1 (Longworth et al. 2008).

Two mechanisms contribute to the accumulation of H4K20me1 at mitotic entry. First, the activity of SETD8 histone methyltransferase peaks at G2/M transition (Nishioka et al. 2002, Rice et al. 2002, Wu et al. 2010). Second, the complex of CDK1 and cyclin B1 (CDK1:CCNB1) phosphorylates PHF8 histone demethylase at the start of mitosis, removing it from chromatin (Liu et al. 2010).

Condensin II complex needs to be phosphorylated by the CDK1:CCNB1 complex, and then phosphorylated by PLK1, in order to efficiently condense prophase chromosomes (Abe et al. 2011).

Literature references

Rice, JC., Nishioka, K., Lis, JT., Tempst, P., Werner, J., Allis, CD. et al. (2002). PR-Set7 is a nucleosome-specific methyltransferase that modifies lysine 20 of histone H4 and is associated with silent chromatin. *Mol. Cell, 9*, 1201-13. ↗

Rice, JC., Yokomori, K., Wu, S., Wang, W., Kirschner, MW., Congdon, LM. et al. (2010). Dynamic regulation of the PR-Set7 histone methyltransferase is required for normal cell cycle progression. *Genes Dev., 24*, 2531-42. ↗

Liu, W., Glass, CK., Desai, A., Ohgi, KA., Aggarwal, AK., Benner, C. et al. (2010). PHF8 mediates histone H4 lysine 20 demethylation events involved in cell cycle progression. *Nature, 466*, 508-12. ↗

Nagasaka, K., Hirota, T., Aoyagi, Y., Abe, S., Kozuka-Hata, H., Obuse, C. et al. (2011). The initial phase of chromosome condensation requires Cdk1-mediated phosphorylation of the CAP-D3 subunit of condensin II. *Genes Dev., 25*, 863-74. ↗

Rice, JC., Nishioka, K., Reinberg, D., Steward, R., Sarma, K., Allis, CD. (2002). Mitotic-specific methylation of histone H4 Lys 20 follows increased PR-Set7 expression and its localization to mitotic chromosomes. *Genes Dev., 16*, 2225-30. ↗

Editions

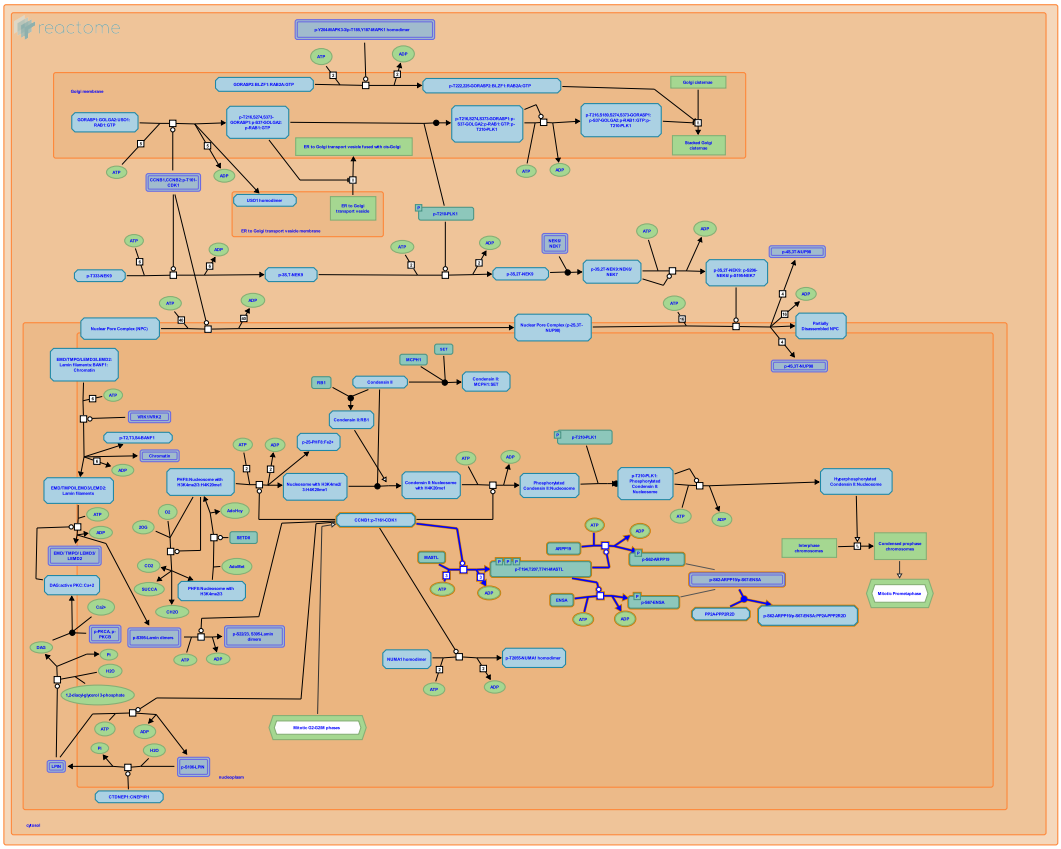
2013-04-11	Authored	Gallie, BL.
2013-04-23	Edited	Matthews, L.
2013-04-23	Authored	Orlic-Milacic, M.
2013-10-14	Reviewed	Longworth, MS.

MASTL Facilitates Mitotic Progression ↗

Location: Mitotic Prophase

Stable identifier: R-HSA-2465910

Compartments: nucleoplasm



The activity of MASTL, also known as the Greatwall kinase (GWL), is necessary for the entry and progression of mitosis. MASTL is activated by phosphorylation of several key residues during mitotic entry. Phosphorylation on the serine residue S875 (S883 in Xenopus), likely through autophosphorylation (Blake-Hodek et al. 2012) appears to be critical (Vigneron et al. 2011). Several other sites, including putative CDK1 targets T194, T207 and T741, contribute to the full activation of MASTL (Yu et al. 2006, Blake-Hodek et al. 2012). Other kinases, such as PLK1 (Vigneron et al. 2011) and other MASTL phosphorylation sites may also be functionally important (Yu et al. 2006, Blake-Hodek et al. 2012).

Activated MASTL phosphorylates ARPP19 and ENSA on serines S62 and S67, respectively, enabling them to bind to and inhibit the phosphatase activity of PP2A complexed with the regulatory subunit PPP2R2D (B55-delta). Inhibition of PP2A-PPP2R2D activity by ARPP19 or ENSA prevents dephosphorylation of CDK1 targets, hence allowing entry and maintenance of mitosis (Mochida et al. 2010, Gharbi-Ayachi et al. 2010, Burgess et al. 2010).

Literature references

Skehel, M., Mochida, S., Hunt, T., Maslen, SL. (2010). Greatwall phosphorylates an inhibitor of protein phosphatase 2A that is essential for mitosis. *Science, 330*, 1670-3. ↗

Yu, J., Li, Z., Goldberg, ML., Galas, S., Zhao, Y. (2006). Greatwall kinase participates in the Cdc2 autoregulatory loop in Xenopus egg extracts. *Mol. Cell, 22*, 83-91. ↗

Lorca, T., Burgess, A., Van-Dorsselaer, A., Vigneron, S., Strub, JM., Gharbi-Ayachi, A. et al. (2010). The substrate of Greatwall kinase, Arpp19, controls mitosis by inhibiting protein phosphatase 2A. *Science, 330*, 1673-7. ↗

Lorca, T., Burgess, A., Vigneron, S., Raymond, AA., Gharbi-Ayachi, A., Castro, A. et al. (2011). Characterization of the mechanisms controlling Greatwall activity. *Mol. Cell. Biol., 31*, 2262-75. ↗

Chen, W., Castilho, PV., Williams, BC., Mao, Y., Goldberg, ML., Blake-Hodek, KA. et al. (2012). Determinants for activation of the atypical AGC kinase Greatwall during M phase entry. *Mol. Cell. Biol., 32,* 1337-53. ↗

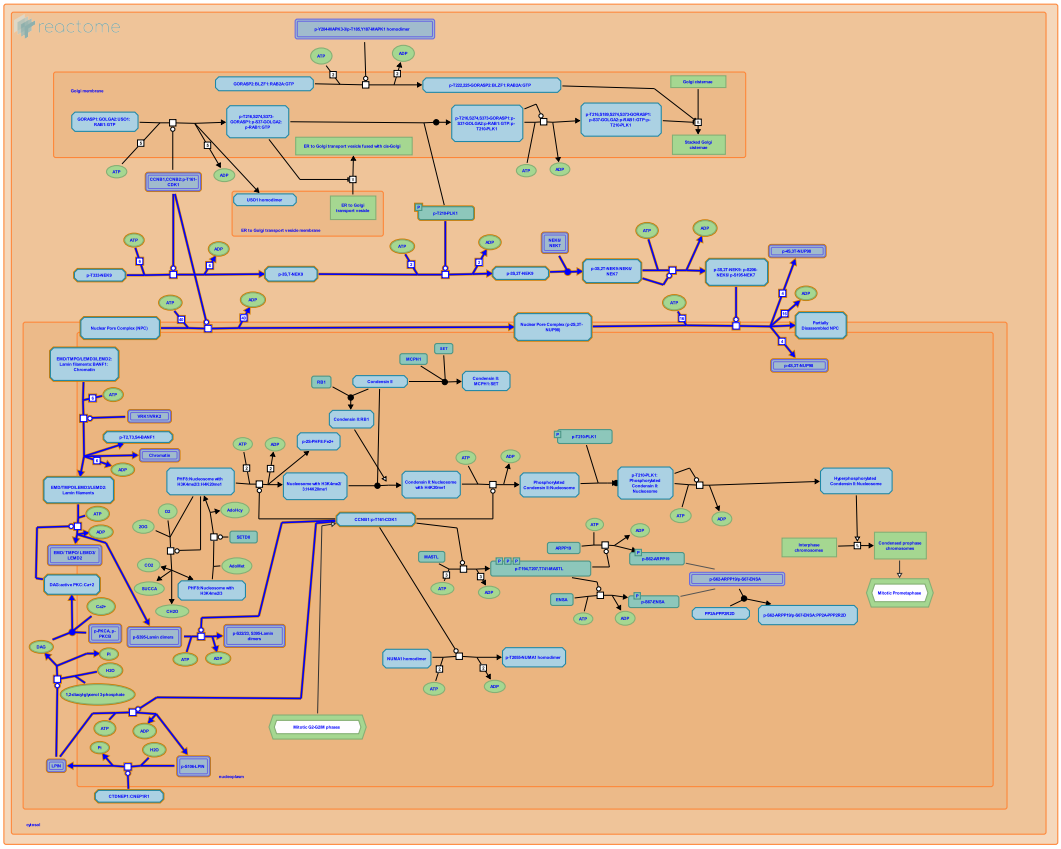
Editions

2012-09-04	Authored	Orlic-Milacic, M.
2012-09-14	Edited	Gillespie, ME.
2012-09-26	Reviewed	Mochida, S.
2012-09-28	Reviewed	Burgess, A.

Nuclear Envelope Breakdown ↗

Location: Mitotic Prophase

Stable identifier: R-HSA-2980766



The nuclear envelope breakdown (NEBD) happens in late prophase of mitosis and involves disassembly of the nuclear pore complex, depolymerization of the nuclear lamina, and clearance of nuclear envelope from chromatin. NEBD allows mitotic spindle microtubules to access condensed chromosomes at kinetochores and enables nuclear division and segregation of genetic material to two daughter cells. For a recent review, please refer to Guttinger et al. 2009.

In mitotic prophase, chromatin detaches from the nuclear envelope, and this contributes to the nuclear envelope breakdown. VRK1 (and possibly VRK2) mediated phosphorylation of BANF1 (BAF), a protein that simultaneously interacts with DNA, LEM-domain inner nuclear membrane proteins, and lamins (Zheng et al. 2000, Shumaker et al. 2001, Haraguchi et al. 2001, Mansharamani and Wilson 2005, Brachner et al. 2005) is considered to be one of the key steps in the detachment of the nuclear envelope from chromatin (Bengtsson and Wilson 2006, Nichols et al. 2006, Gorjanacz et al. 2007).

Literature references

Güttinger, S., Laurell, E., Kutay, U. (2009). Orchestrating nuclear envelope disassembly and reassembly during mitosis. *Nat. Rev. Mol. Cell Biol., 10*, 178-91. ↗

Editions

2013-01-23	Edited	Gillespie, ME.
2013-01-23	Authored	Orlic-Milacic, M.
2013-01-30	Reviewed	Mattaj, IW., Gorjánácz, M.

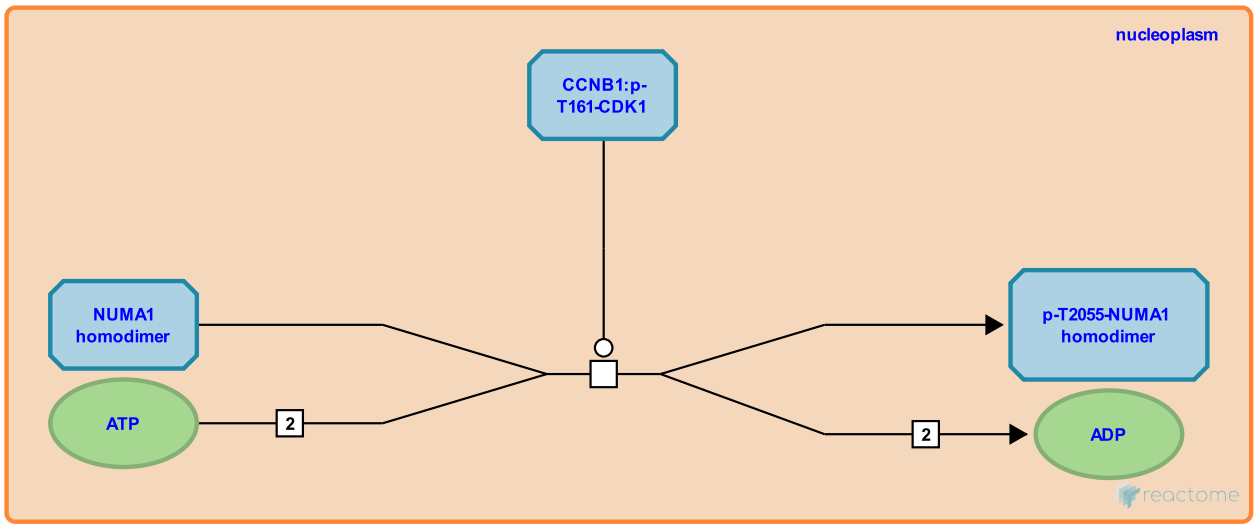
CCNB1:p-T160-CDK1 phosphorylates NUMA1 ↗

Location: Mitotic Prophase

Stable identifier: R-HSA-380278

Type: transition

Compartments: nucleoplasm



After the initiation of DNA condensation in prophase of mitosis, NuMA (NUMA1) is phosphorylated on threonine residue 2055 by the complex of Cdc2 (CDK1) kinase and Cyclin B1 (CCNB1). After the nuclear envelope breakdown, phosphorylated NuMA rapidly moves to the centrosomal region (Compton and Luo 1995, Hsu and Yeh 1996, Kotak et al. 2013). Another phosphorylation event occurs when NuMA associates with the mitotic spindle (Gaglio et al. 1995; Hsu and Yeh 1996). While CCNB1:p-T160-CDK1-dependent phosphorylation appears to plays an essential role in the targeting of NuMA to the spindle apparatus (Compton and Luo 1995, Hsu and Yeh 1996, Kotak et al. 2013), there may be additional protein kinases that promote the release of NuMA from the nuclear compartment at nuclear envelope breakdown (Saredi et al. 1997).

Literature references

Compton, DA., Luo, C. (1995). Mutation of the predicted p34cdc2 phosphorylation sites in NuMA impair the assembly of the mitotic spindle and block mitosis. *J Cell Sci, 108*, 621-33. ↗

Busso, C., Kotak, S., Gönczy, P. (2013). NuMA phosphorylation by CDK1 couples mitotic progression with cortical dynein function. *EMBO J., 32*, 2517-29. ↗

Editions

2008-11-09	Edited	Matthews, L.
2008-11-11	Authored	Matthews, L.
2008-11-17	Reviewed	Merdes, A.

Table of Contents