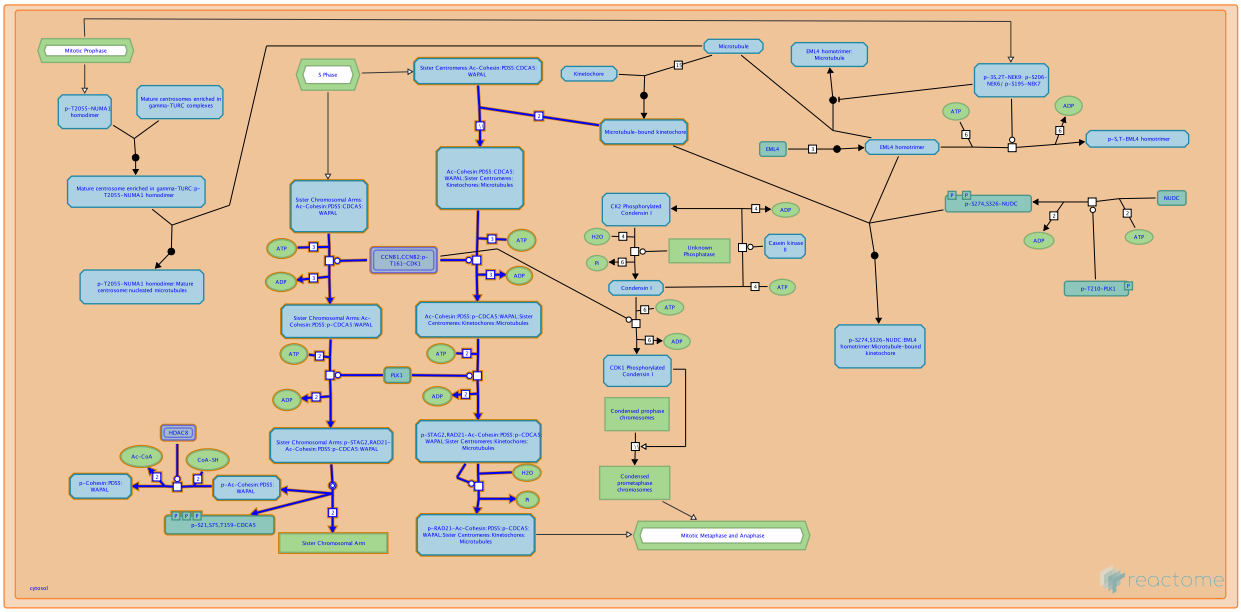
Resolution of Sister Chromatid Cohesion



Gillespie, ME., Lee, KS., Matthews, L., Orlic-Milacic, M., Tanno, Y., Watanabe, Y., Zhang, N.

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

07/09/2021

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. ↗

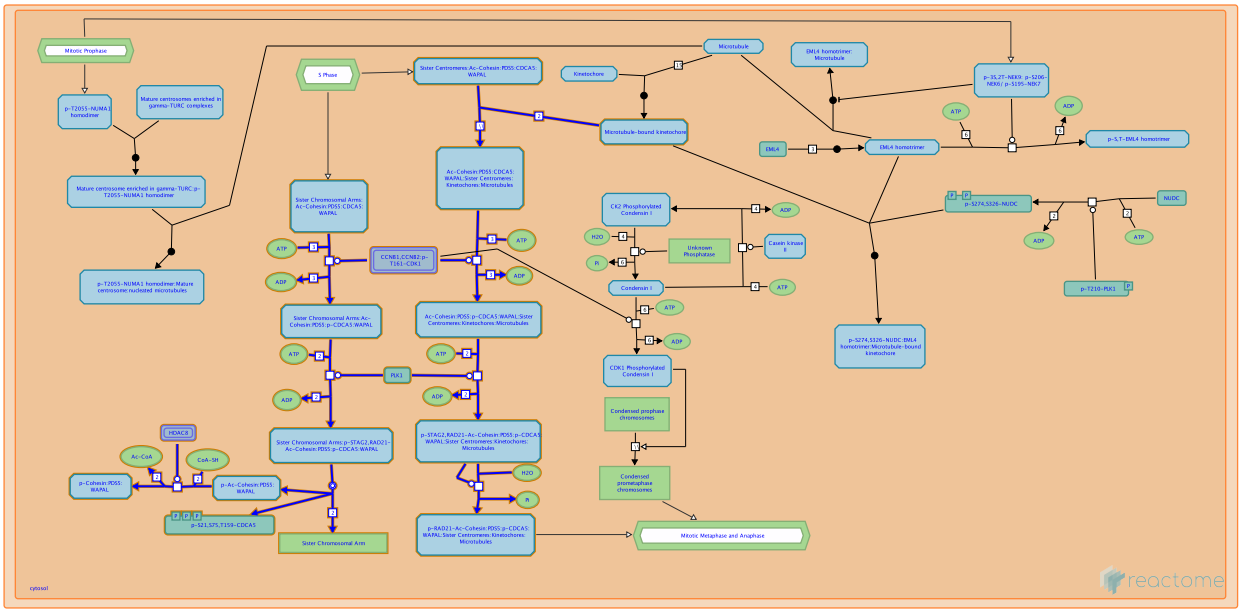
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Resolution of Sister Chromatid Cohesion ↗

Stable identifier: R-HSA-2500257

Compartments: cytosol, chromosome, chromosome, centromeric region



The resolution of sister chromatids in mitotic prometaphase involves removal of cohesin complexes from chromosomal arms, with preservation of cohesion at centromeres (Losada et al. 1998, Hauf et al. 2001, Hauf et al. 2005).

CDK1-mediated phosphorylation of cohesin-bound CDCA5 (Sororin) at threonine T159 provides a docking site for PLK1, enabling PLK1-mediated phosphorylation of cohesin subunits STAG2 (SA2) and RAD21 (Hauf et al. 2005, Dreier et al. 2011, Zhang et al. 2011). Further phosphorylation of CDCA5 by CDK1 results in dissociation of CDCA5 from cohesin complex, which restores the activity of WAPAL in removing STAG2-phosphorylated cohesin from chromosomal arms (Hauf et al. 2005, Gandhi et al. 2006, Kueng et al. 2006, Shintomi and Hirano 2006, Nishiyama et al. 2010, Zhang et al. 2011).

At centromeres, kinetochore proteins shugoshins (SGOL1 and SGOL2) enable PP2A-B56 (also a kinetochore constituent) to dephosphorylate the STAG2 subunit of centromeric cohesin. Dephosphorylation of STAG2 enables maintenance of centromeric cohesion, thus preventing separation of sister chromatids until anaphase (Salic et al. 2004, Kitajima et al. 2004, Kitajima et al. 2005, Kitajima et al. 2006).

Literature references

Salic, A., Waters, JC., Mitchison, TJ. (2004). Vertebrate shugoshin links sister centromere cohesion and kinetochore microtubule stability in mitosis. *Cell, 118*, 567-78. ↗

Zhang, N., Panigrahi, AK., Mao, Q., Pati, D. (2011). Interaction of Sororin protein with polo-like kinase 1 mediates resolution of chromosomal arm cohesion. *J. Biol. Chem., 286*, 41826-37. ↗

Losada, A., Hirano, M., Hirano, T. (1998). Identification of Xenopus SMC protein complexes required for sister chromatid cohesion. *Genes Dev., 12*, 1986-97. ↗

Kueng, S., Hegemann, B., Peters, BH., Lipp, JJ., Schleiffer, A., Mechtler, K. et al. (2006). Wapl controls the dynamic association of cohesin with chromatin. *Cell, 127*, 955-67. ↗

Hauf, S., Roitinger, E., Koch, B., Dittrich, CM., Mechtler, K., Peters, JM. (2005). Dissociation of cohesin from chromosome arms and loss of arm cohesion during early mitosis depends on phosphorylation of SA2. *PLoS Biol, 3*, e69. ↗

Editions

2012-10-02	Authored	Orlic-Milacic, M.
2012-10-05	Edited	Gillespie, ME., Matthews, L.
2012-10-22	Reviewed	Zhang, N.
2012-11-20	Reviewed	Watanabe, Y., Tanno, Y.

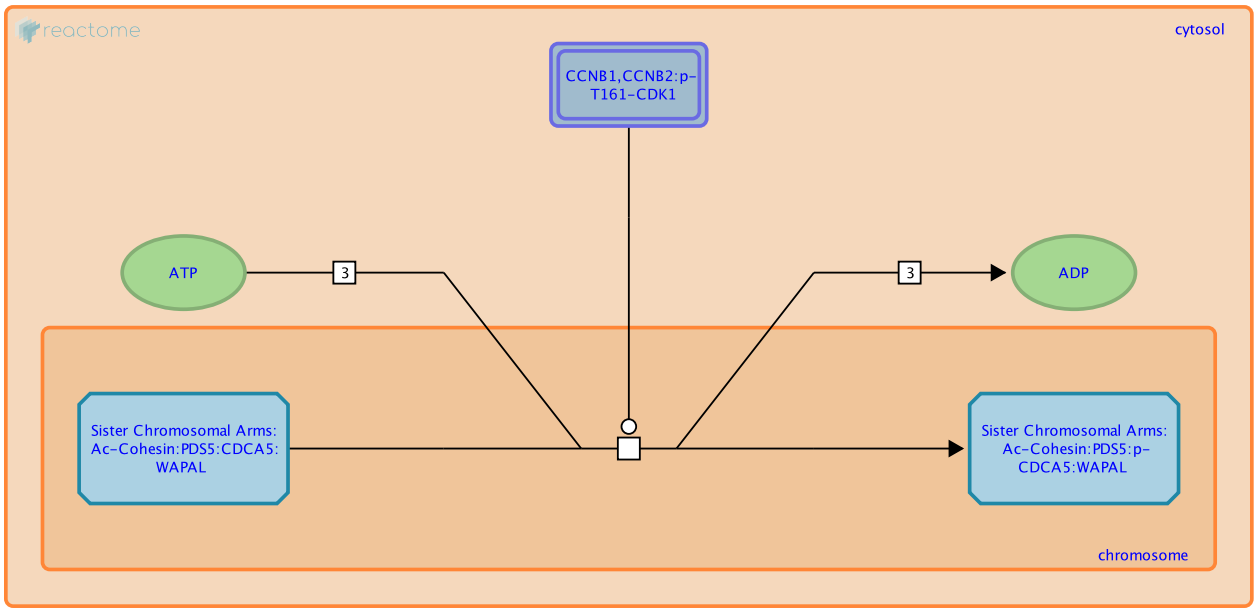
CDK1 phosphorylates CDCA5 (Sororin) at chromosomal arms ↗

Location: Resolution of Sister Chromatid Cohesion

Stable identifier: R-HSA-2468293

Type: transition

Compartments: chromosome, cytosol



Phosphorylation of CDCA5 (Sororin) coincides with dissociation of CDCA5 from chromosomal arms in prometaphase. Several serine and threonine residues in CDCA5 are phosphorylated by CDK1 in prometaphase, but only the three sites that perfectly match the CDK1 consensus phosphorylation sequence are shown here - serines S21 and S75 and threonine T159 (Drier et al. 2011, Zhang et al. 2011).

Followed by: Phosphorylation of cohesin by PLK1 at chromosomal arms

Literature references

Zhang, N., Panigrahi, AK., Mao, Q., Pati, D. (2011). Interaction of Sororin protein with polo-like kinase 1 mediates resolution of chromosomal arm cohesion. *J. Biol. Chem., 286*, 41826-37. ↗

Dreier, MR., Bekier, ME., Taylor, WR. (2011). Regulation of sororin by Cdk1-mediated phosphorylation. *J. Cell. Sci., 124*, 2976-87. ↗

Editions

2012-10-02	Authored	Orlic-Milacic, M.
2012-10-05	Edited	Gillespie, ME., Matthews, L.
2012-10-22	Reviewed	Zhang, N.
2012-11-20	Reviewed	Watanabe, Y., Tanno, Y.

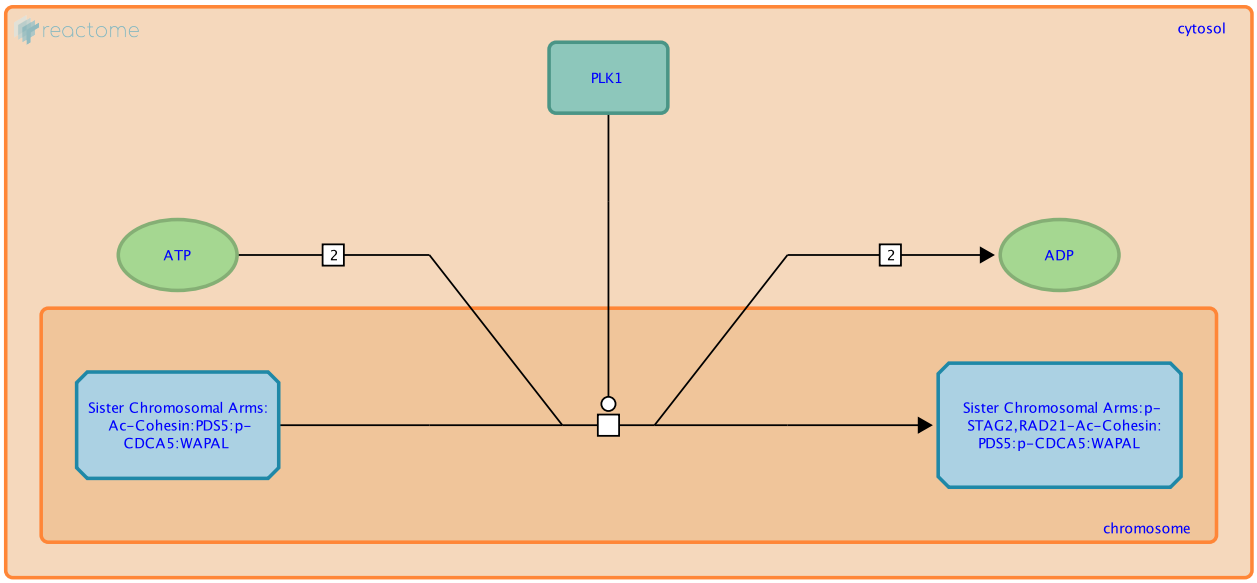
Phosphorylation of cohesin by PLK1 at chromosomal arms ↗

Location: Resolution of Sister Chromatid Cohesion

Stable identifier: R-HSA-2466068

Type: transition

Compartments: chromosome, cytosol



Prior to anaphase onset, sister-chromatids are held together by cohesin complexes. PLK1-dependent phosphorylation of the cohesin subunit STAG2 (SA2) (Hauf et al. 2005) promotes dissociation of cohesins from chromosomal arms in prometaphase (Hauf et al. 2001). Besides phosphorylating STAG2, PLK1 also phosphorylates RAD21 cohesin subunit, but the phosphorylation of RAD21 is not required for the dissociation of cohesin from chromosomal arms in early mitosis (Hauf et al. 2005). There are several potential PLK1 phosphorylation sites in STAG2 and RAD21, but the exact positions of in vivo phosphorylation of STAG2 and RAD21 by PLK1 have not been explicitly established (Hauf et al. 2005). It is likely that the phosphorylation of cohesin-bound CDCA5 (Sororin) by CDK1 creates a docking site for PLK1 at threonine T159 of CDCA5, thus enabling PLK1 to phosphorylate cohesin subunits (Zhang et al. 2011).

Preceded by: CDK1 phosphorylates CDCA5 (Sororin) at chromosomal arms

Followed by: Resolution of sister chromatids

Literature references

Hauf, S., Waizenegger, IC., Peters, JM. (2001). Cohesin cleavage by separase required for anaphase and cytokinesis in human cells. *Science, 293*, 1320-3. ↗

Hauf, S., Roitinger, E., Koch, B., Dittrich, CM., Mechtler, K., Peters, JM. (2005). Dissociation of cohesin from chromosome arms and loss of arm cohesion during early mitosis depends on phosphorylation of SA2. *PLoS Biol, 3*, e69. ↗

Zhang, N., Panigrahi, AK., Mao, Q., Pati, D. (2011). Interaction of Sororin protein with polo-like kinase 1 mediates resolution of chromosomal arm cohesion. *J. Biol. Chem., 286*, 41826-37. ↗

Editions

2004-12-09	Authored	Lee, KS.
2005-04-12	Edited	Gillespie, ME.
2012-10-02	Revised	Orlic-Milacic, M.
2012-10-22	Reviewed	Zhang, N.
2012-11-20	Reviewed	Watanabe, Y., Tanno, Y.

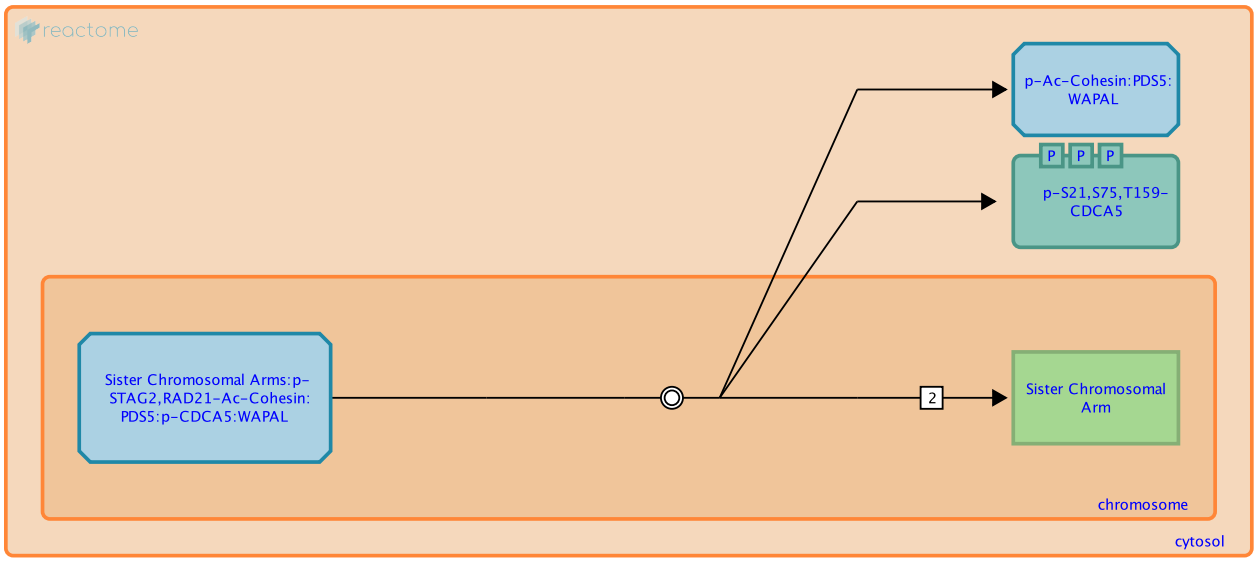
Resolution of sister chromatids ↗

Location: Resolution of Sister Chromatid Cohesion

Stable identifier: R-HSA-2467794

Type: dissociation

Compartments: chromosome, cytosol



Cohesin complexes dissociate from chromosomal arms in prometaphase, leading to sister chromatid resolution. Sister chromatid resolution involves separation of sister chromosomal arms while cohesion at sister centromeres persists (Losada et al. 1998, Hauf et al. 2001, Hauf et al. 2005). Cohesin and CDCA5 (Sororin) simultaneously dissociate from chromosomal arms in prometaphase (Nishiyama et al. 2010, Zhang et al. 2011). This process, triggered by CDK1-mediated phosphorylation of CDCA5 (Dreier et al. 2011, Zhang et al. 2011) and PLK1-mediated phosphorylation of the STAG2 cohesin subunit (Hauf et al. 2005), is controlled by WAPAL (Gandhi et al. 2006, Kueng et al. 2006, Shintomi and Hirano 2009). WAPAL controls cohesion of sister chromatids likely through competing with CDCA5 for binding to cohesin-associated PDS5 (PDS5A and PDS5B) (Nishiyama et al. 2010). While the interaction of WAPAL with PDS5 depends on CDCA5 (Nishiyama et al. 2010), WAPAL maintains its association with cohesin through interaction with cohesin subunits (Kueng et al. 2006, Shintomi and Hirano 2009).

Preceded by: Phosphorylation of cohesin by PLK1 at chromosomal arms

Followed by: Deacetylation of cohesin

Literature references

Shintomi, K., Hirano, T. (2009). Releasing cohesin from chromosome arms in early mitosis: opposing actions of Wapl-Pds5 and Sgo1. *Genes Dev., 23*, 2224-36. ↗

Kueng, S., Hegemann, B., Peters, BH., Lipp, JJ., Schleiffer, A., Mechtler, K. et al. (2006). Wapl controls the dynamic association of cohesin with chromatin. *Cell, 127*, 955-67. ↗

Gandhi, R., Gillespie, PJ., Hirano, T. (2006). Human Wapl is a cohesin-binding protein that promotes sister-chromatid resolution in mitotic prophase. *Curr. Biol., 16*, 2406-17. ↗

Nishiyama, T., Ladurner, R., Schmitz, J., Kreidl, E., Schleiffer, A., Bhaskara, V. et al. (2010). Sororin mediates sister chromatid cohesion by antagonizing Wapl. *Cell, 143*, 737-49. ↗

Hauf, S., Waizenegger, IC., Peters, JM. (2001). Cohesin cleavage by separase required for anaphase and cytokinesis in human cells. *Science, 293*, 1320-3. ↗

Editions

2012-10-02	Authored	Orlic-Milacic, M.
2012-10-05	Edited	Gillespie, ME., Matthews, L.
2012-10-22	Reviewed	Zhang, N.
2012-11-20	Reviewed	Watanabe, Y., Tanno, Y.

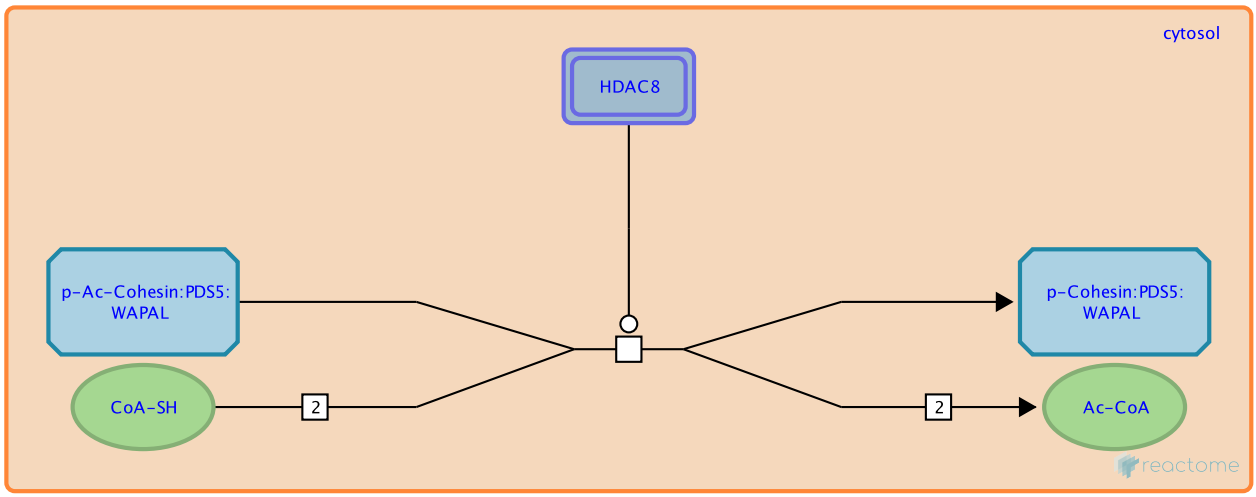
Deacetylation of cohesin ↗

Location: Resolution of Sister Chromatid Cohesion

Stable identifier: R-HSA-2545253

Type: transition

Compartments: cytosol



HDAC8 deacetylates cohesin in prometaphase, after cohesin dissociates from chromosomal arms (Deardorff et al. 2012).

Preceded by: Resolution of sister chromatids

Literature references

Deardorff, MA., Bando, M., Nakato, R., Watrin, E., Itoh, T., Minamino, M. et al. (2012). HDAC8 mutations in Cornelia de Lange syndrome affect the cohesin acetylation cycle. *Nature, 489*, 313-7. ↗

Editions

2012-10-02	Authored	Orlic-Milacic, M.
2012-10-05	Edited	Gillespie, ME., Matthews, L.
2012-10-22	Reviewed	Zhang, N.
2012-11-20	Reviewed	Watanabe, Y., Tanno, Y.

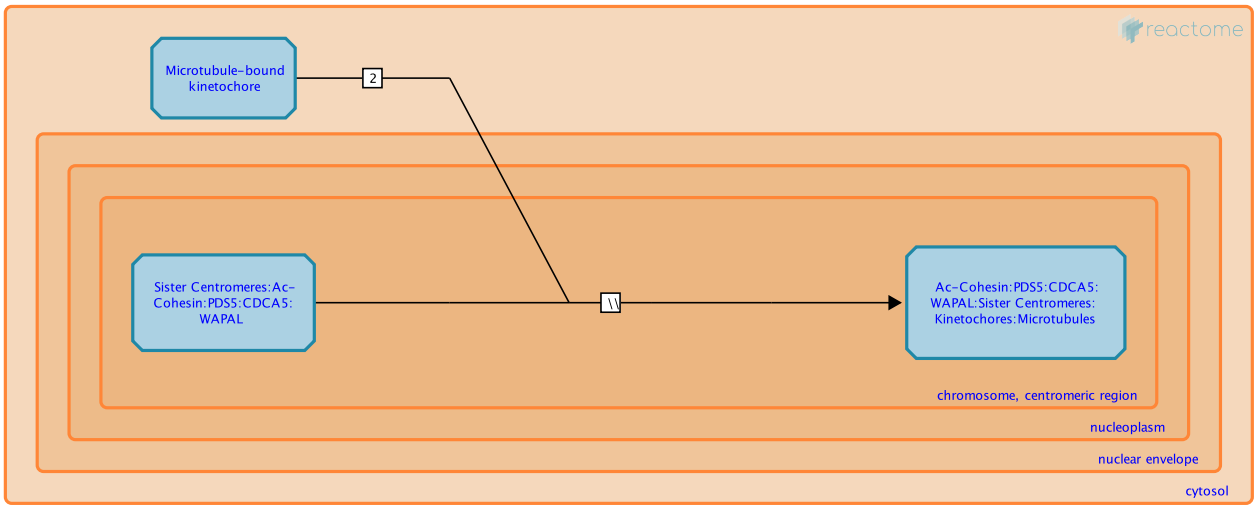
Kinetochore assembly ↗

Location: Resolution of Sister Chromatid Cohesion

Stable identifier: R-HSA-2484822

Type: omitted

Compartments: chromosome, centromeric region, cytosol



The kinetochore assembly on centromeres of replicated chromosomes is completed by mitotic prometaphase. Some kinetochore components are associated with centromeres throughout the cell cycle while others associate with centromeres during mitosis. The sequential kinetochore assembly and kinetochore dynamics is not shown here. For a review of this process, please refer to Cheeseman and Desai 2008.

Followed by: CDK1 phosphorylates CDCA5 (Sororin) at centromeres

Literature references

Cheeseman, IM., Desai, A. (2008). Molecular architecture of the kinetochore-microtubule interface. *Nat Rev Mol Cell Biol, 9*, 33-46. ↗

Editions

2012-10-02	Authored	Orlic-Milacic, M.
2012-10-05	Edited	Gillespie, ME., Matthews, L.
2012-10-22	Reviewed	Zhang, N.
2012-11-20	Reviewed	Watanabe, Y., Tanno, Y.

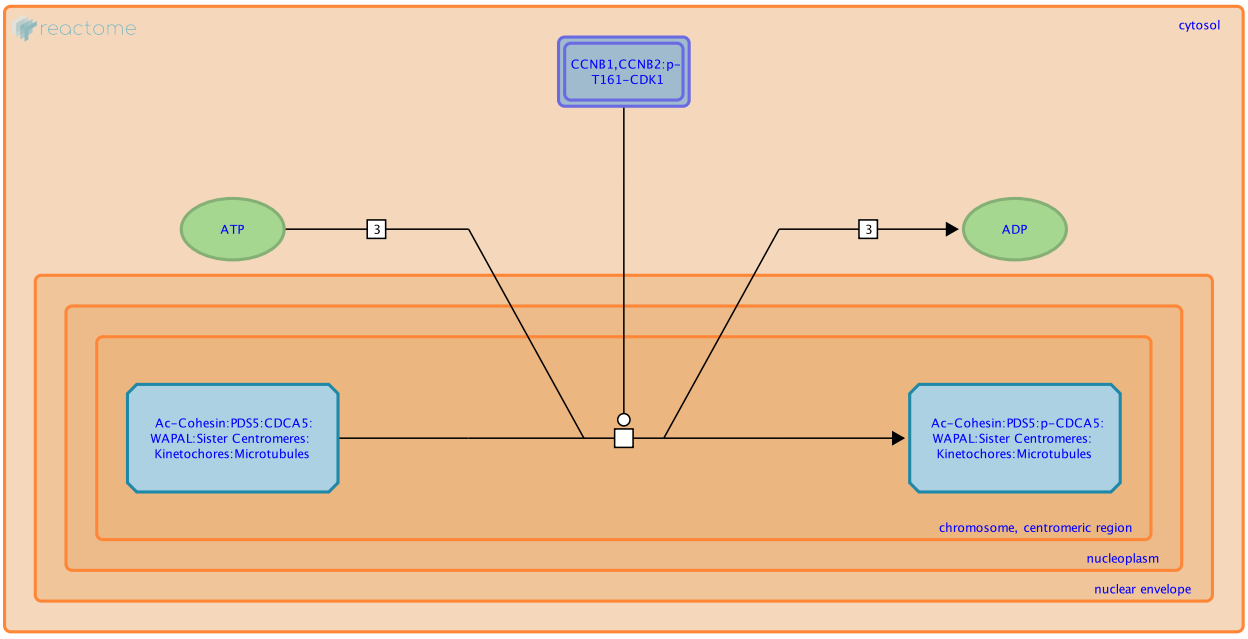
CDK1 phosphorylates CDCA5 (Sororin) at centromeres ↗

Location: Resolution of Sister Chromatid Cohesion

Stable identifier: R-HSA-2468287

Type: transition

Compartments: chromosome, centromeric region, cytosol



Phosphorylation of CDCA5 (Sororin) coincides with dissociation of CDCA5 from chromosomal arms in prometaphase, but phosphorylated CDCA5 persists on centromeres throughout prophase and metaphase. Several serine and threonine residues in CDCA5 are phosphorylated by CDK1 in prometaphase, but only the three sites that perfectly match the CDK1 consensus phosphorylation sequence are shown here - serines S21 and S75 and threonine T159 (Drier et al. 2011, Zhang et al. 2011).

Preceded by: Kinetochore assembly

Followed by: Phosphorylation of cohesin by PLK1 at centromeres

Literature references

Zhang, N., Panigrahi, AK., Mao, Q., Pati, D. (2011). Interaction of Sororin protein with polo-like kinase 1 mediates resolution of chromosomal arm cohesion. *J. Biol. Chem., 286*, 41826-37. ↗

Dreier, MR., Bekier, ME., Taylor, WR. (2011). Regulation of sororin by Cdk1-mediated phosphorylation. *J. Cell. Sci., 124*, 2976-87. ↗

Editions

2012-10-02	Authored	Orlic-Milacic, M.
2012-10-05	Edited	Gillespie, ME., Matthews, L.
2012-10-22	Reviewed	Zhang, N.
2012-11-20	Reviewed	Watanabe, Y., Tanno, Y.

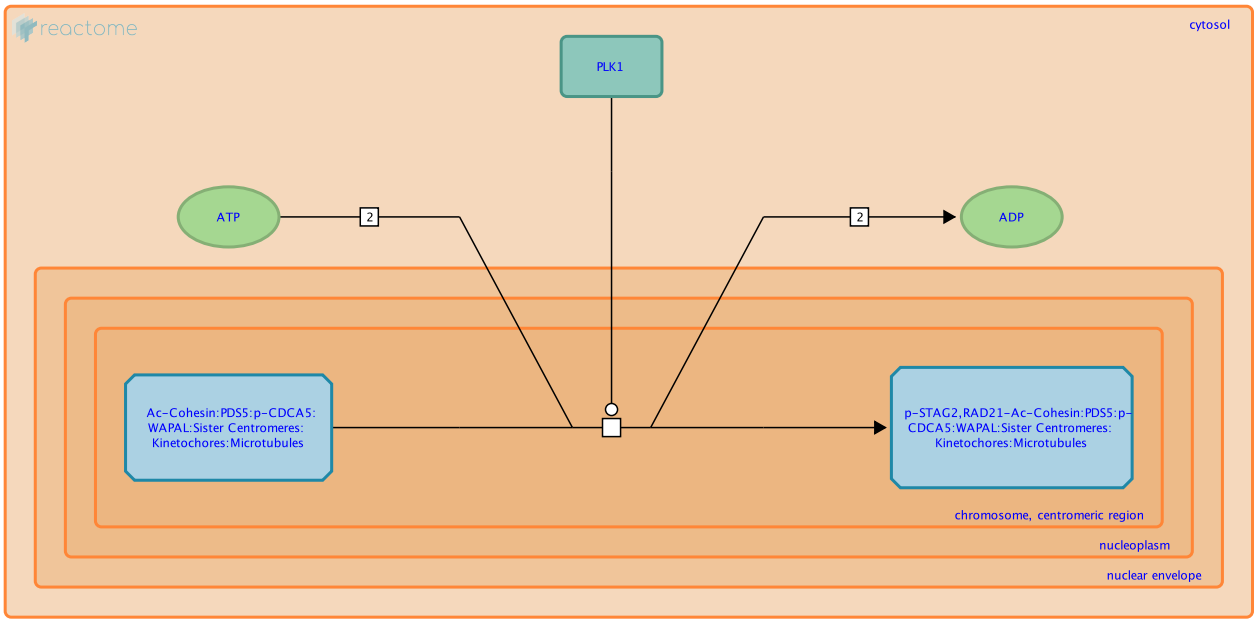
Phosphorylation of cohesin by PLK1 at centromeres ↗

Location: Resolution of Sister Chromatid Cohesion

Stable identifier: R-HSA-1638803

Type: transition

Compartments: chromosome, centromeric region, cytosol



Prior to anaphase onset, sister-chromatids are held together by cohesin complexes distributed along chromosomal arms and at centromeres. In prometaphase, PLK1, likely recruited to cohesin complexes by binding to CDK1-phosphorylated CDCA5 (Sororin) (Zhang et al. 2011), phosphorylates cohesin subunits STAG2 (SA2) and RAD21 (Hauf et al. 2005). PLK1-mediated phosphorylation of cohesin subunits at centromeres is counteracted by the phosphatase activity of PP2A complex (containing the regulatory subunit B56 i.e. PPP2R5), which is recruited to the kinetochore by shugoshin proteins, SGOL1 and SGOL2 (Kitajima et al. 2006). Therefore, while cohesin complexes dissociate from chromosomal arms in prometaphase (Hauf et al. 2001), they remain bound to centromeres until anaphase onset (Hauf et al. 2001, Hauf et al. 2005, Kitajima et al. 2006). When separase is activated after its inhibitor securin is degraded by APC/C at the onset of anaphase, RAD21 is cleaved by separase. Phosphorylation of RAD21 by PLK1 facilitates subsequent cleavage of RAD21 by separase (Hauf et al. 2005). There are several potential PLK1 phosphorylation sites in STAG2 and RAD21, but the exact positions of in vivo phosphorylation of STAG2 and RAD21 by PLK1 have not been explicitly established (Hauf et al. 2005).

Preceded by: CDK1 phosphorylates CDCA5 (Sororin) at centromeres

Followed by: PP2A-B56 dephosphorylates centromeric cohesin

Literature references

Hauf, S., Waizenegger, IC., Peters, JM. (2001). Cohesin cleavage by separase required for anaphase and cytokinesis in human cells. *Science, 293*, 1320-3. ↗

Hauf, S., Roitinger, E., Koch, B., Dittrich, CM., Mechtler, K., Peters, JM. (2005). Dissociation of cohesin from chromosome arms and loss of arm cohesion during early mitosis depends on phosphorylation of SA2. *PLoS Biol, 3*, e69. ↗

Kitajima, TS., Sakuno, T., Ishiguro, K., Iemura, S., Natsume, T., Kawashima, SA. et al. (2006). Shugoshin collaborates with protein phosphatase 2A to protect cohesin. *Nature, 441*, 46-52. ↗

Editions

2004-12-09	Authored	Lee, KS.
2005-04-12	Edited	Gillespie, ME.
2012-10-02	Revised	Orlic-Milacic, M.
2012-10-22	Reviewed	Zhang, N.
2012-11-20	Reviewed	Watanabe, Y., Tanno, Y.

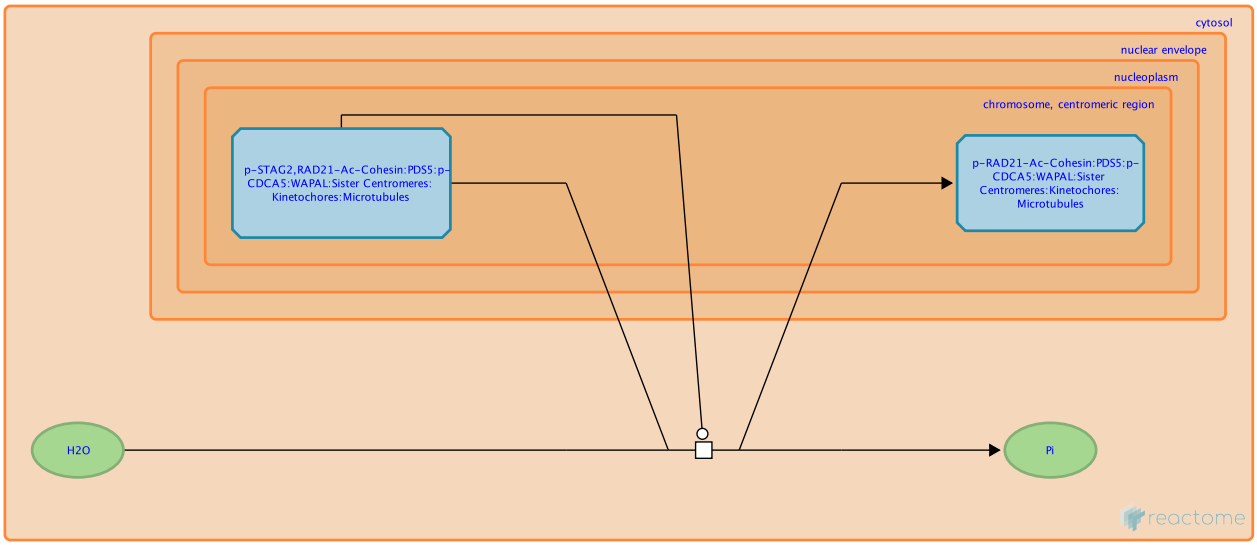
PP2A-B56 dephosphorylates centromeric cohesin ↗

Location: Resolution of Sister Chromatid Cohesion

Stable identifier: R-HSA-1638821

Type: transition

Compartments: cytosol, chromosome



PLK1-mediated phosphorylation of the STAG2 subunit of centromeric cohesin (Hauf et al. 2005) is counteracted by the kinetochore PP2A phosphatase, containing the 56 kDa regulatory B subunit (PP2A-B56 i.e. PP2A-PPP2R5). PP2A-B56 is recruited to the centromeric cohesin complex by shugoshin proteins (SGOL1 and SGOL2) (Kitajima et al. 2006), which are also kinetochore constituents (Cheeseman and Desai 2008). SGOL1 localization to centromeres is sustained by the interaction with histone H2A possessing the phosphorylation of T120 which is introduced by the protein kinase BUB1, and heterochromatin protein HP1 (Kitajima et al. 2005, Kawashima et al. 2010, Yamagishi et al. 2008). Shugoshin- and PP2A-B56-regulated dephosphorylation of centromeric STAG2 ensures that the cohesin complex remains bound to centromeres throughout prometaphase and metaphase, thereby preventing premature separation of sister chromatids (Salic et al. 2004, Kitajima et al. 2004, Kitajima et al. 2005, Kitajima et al. 2006).

Preceded by: Phosphorylation of cohesin by PLK1 at centromeres

Literature references

Kitajima, TS., Sakuno, T., Ishiguro, K., Iemura, S., Natsume, T., Kawashima, SA. et al. (2006). Shugoshin collaborates with protein phosphatase 2A to protect cohesin. *Nature, 441*, 46-52. ↗

Kitajima, TS., Kawashima, SA., Watanabe, Y. (2004). The conserved kinetochore protein shugoshin protects centromeric cohesion during meiosis. *Nature, 427*, 510-7. ↗

Kitajima, TS., Hauf, S., Ohsugi, M., Yamamoto, T., Watanabe, Y. (2005). Human Bub1 defines the persistent cohesion site along the mitotic chromosome by affecting Shugoshin localization. *Curr. Biol., 15*, 353-9. ↗

Salic, A., Waters, JC., Mitchison, TJ. (2004). Vertebrate shugoshin links sister centromere cohesion and kinetochore microtubule stability in mitosis. *Cell, 118*, 567-78. ↗

Hauf, S., Roitinger, E., Koch, B., Dittrich, CM., Mechtler, K., Peters, JM. (2005). Dissociation of cohesin from chromosome arms and loss of arm cohesion during early mitosis depends on phosphorylation of SA2. *PLoS Biol, 3*, e69. ↗

Editions

2012-10-02	Authored	Orlic-Milacic, M.
2012-10-05	Edited	Gillespie, ME., Matthews, L.
2012-10-22	Reviewed	Zhang, N.
2012-11-20	Reviewed	Watanabe, Y., Tanno, Y.

Table of Contents