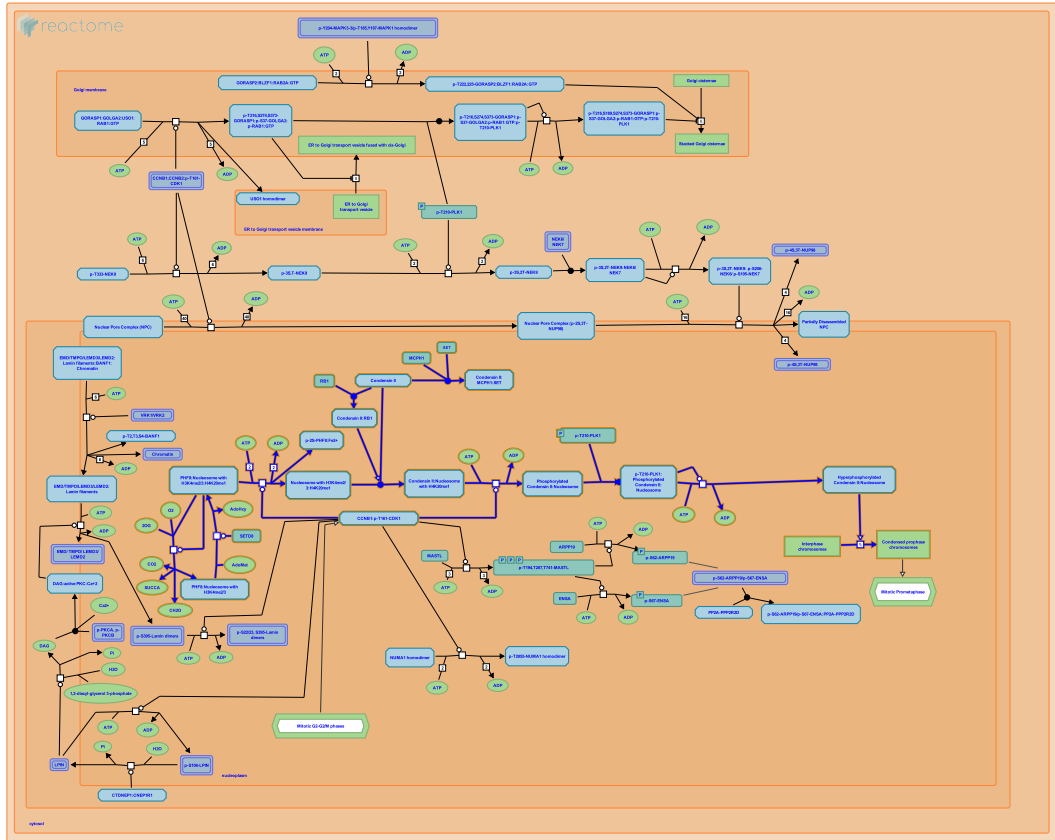


Condensation of Prophase Chromosomes



Gallie, BL., Longworth, MS., Matthews, L., Orlic-Milacic, M.

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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

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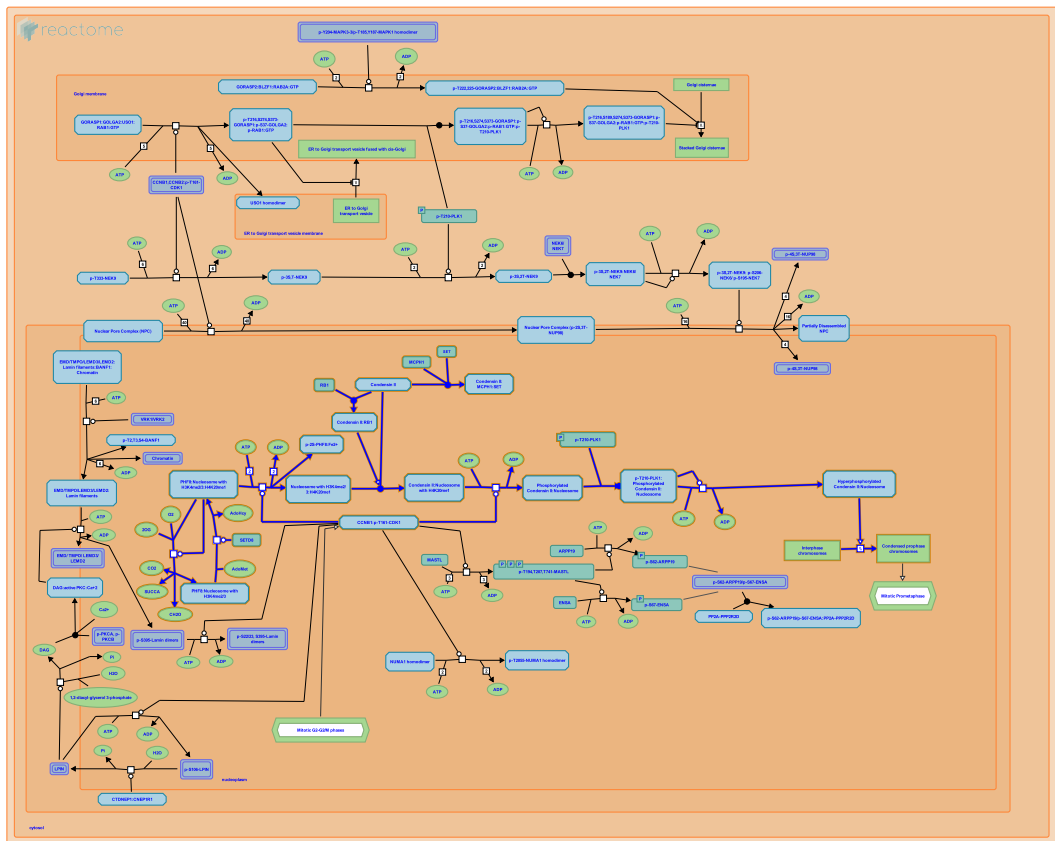
Reactome database release: 70

This document contains 1 pathway and 10 reactions ([see Table of Contents](#))

Condensation of Prophase Chromosomes ↗

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., Sarma, K., Steward, R., Reinberg, D., 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. ↗
- Longworth, MS., Herr, A., Ji, JY., Dyson, NJ. (2008). RBF1 promotes chromatin condensation through a conserved interaction with the Condensin II protein dCAP-D3. *Genes Dev.*, 22, 1011-24. ↗
- Abe, S., Nagasaka, K., Hirayama, Y., Kozuka-Hata, H., Oyama, M., Aoyagi, Y. 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. ↗

Liu, W., Tanasa, B., Tyurina, OV., Zhou, TY., Gassmann, R., Liu, WT. et al. (2010). PHF8 mediates histone H4 lysine 20 demethylation events involved in cell cycle progression. *Nature*, 466, 508-12. [↗](#)

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

Editions

2013-04-11	Authored	Gallie, BL.
2013-04-22	Authored	Orlic-Milacic, M.
2013-04-23	Edited	Matthews, L.
2013-10-14	Reviewed	Longworth, MS.

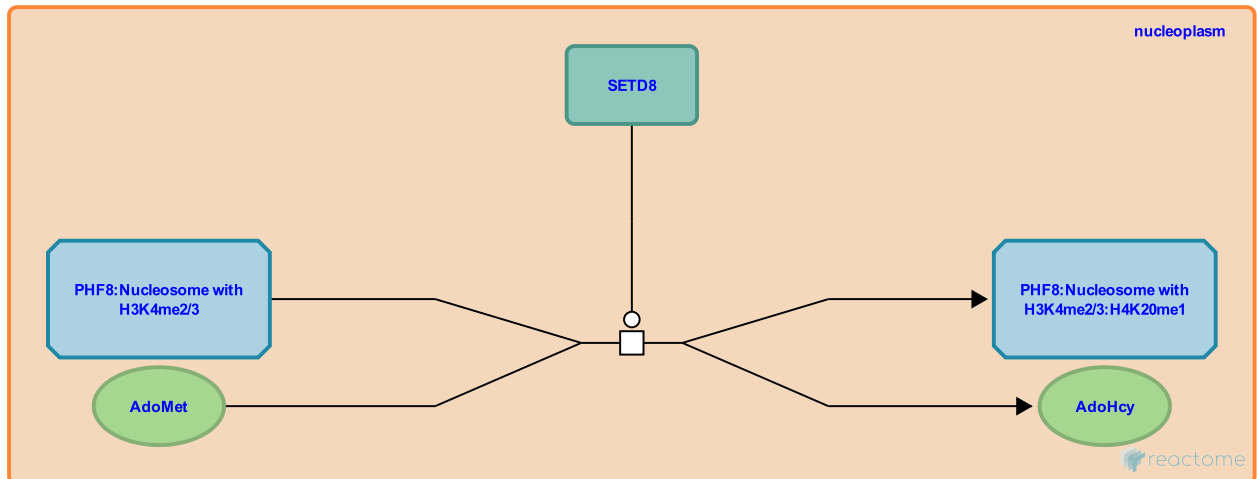
SETD8 monomethylates histone H4 ↗

Location: [Condensation of Prophase Chromosomes](#)

Stable identifier: R-HSA-2301205

Type: transition

Compartments: nucleoplasm



SETD8 is a protein-lysine N-methyltransferase that monomethylates H4 histone to produce H4K20me1 (Nishioka et al. 2002, Wu et al. 2010). SETD8 levels peak at G2/M transition, and regulated SETD8 activity is required for normal cell cycle progression (Rice et al. 2002, Wu et al. 2010).

Followed by: [PHF8 demethylates histone H4K20me1](#), [CDK1 phosphorylates PHF8](#)

Literature references

Nishioka, K., Rice, J.C., Sarma, K., Erdjument-Bromage, H., Werner, J., Wang, Y. 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, J.C., Nishioka, K., Sarma, K., Steward, R., Reinberg, D., Allis, C.D. (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. ↗

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

Editions

2013-04-22	Authored	Orlic-Milacic, M.
2013-04-23	Edited	Matthews, L.
2013-10-14	Reviewed	Longworth, M.S.

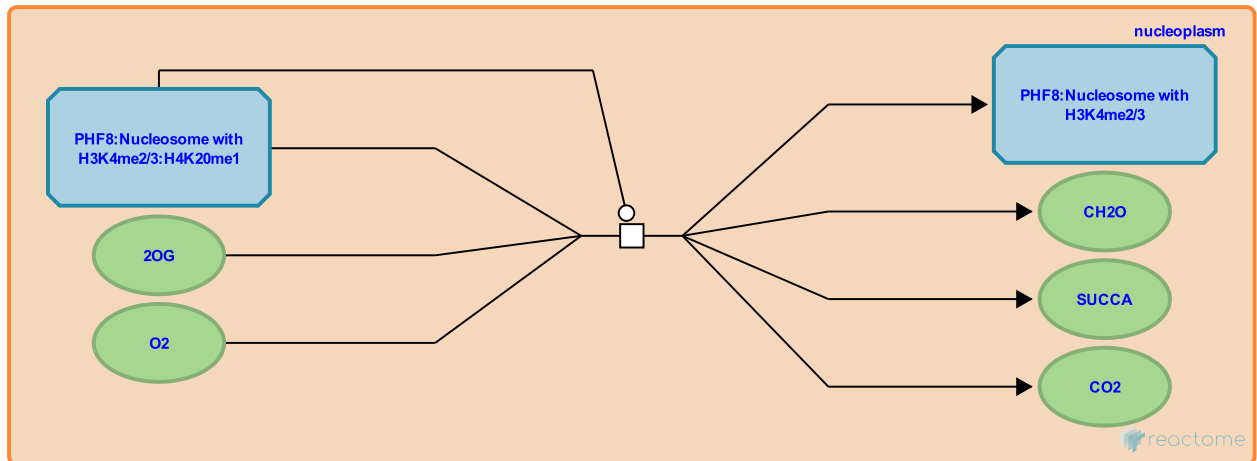
PHF8 demethylates histone H4K20me1 [↗](#)

Location: [Condensation of Prophase Chromosomes](#)

Stable identifier: R-HSA-2172678

Type: transition

Compartments: nucleoplasm



PHF8, a PHD and Jumonji C domain-containing protein, is recruited to chromatin by binding to dimethylated or trimethylated histone H3 - H3K4me2 and/or H3K4me3. PHF8 demethylates monomethylated histone H4, H4K20me1, a docking site for the condensin II complex (Liu et al. 2010).

Preceded by: [SETD8 monomethylates histone H4](#)

Literature references

Liu, W., Tanasa, B., Tyurina, OV., Zhou, TY., Gassmann, R., Liu, WT. et al. (2010). PHF8 mediates histone H4 lysine 20 demethylation events involved in cell cycle progression. *Nature*, 466, 508-12. [↗](#)

Editions

2013-04-22	Authored	Orlic-Milacic, M.
2013-04-23	Edited	Matthews, L.
2013-10-14	Reviewed	Longworth, MS.

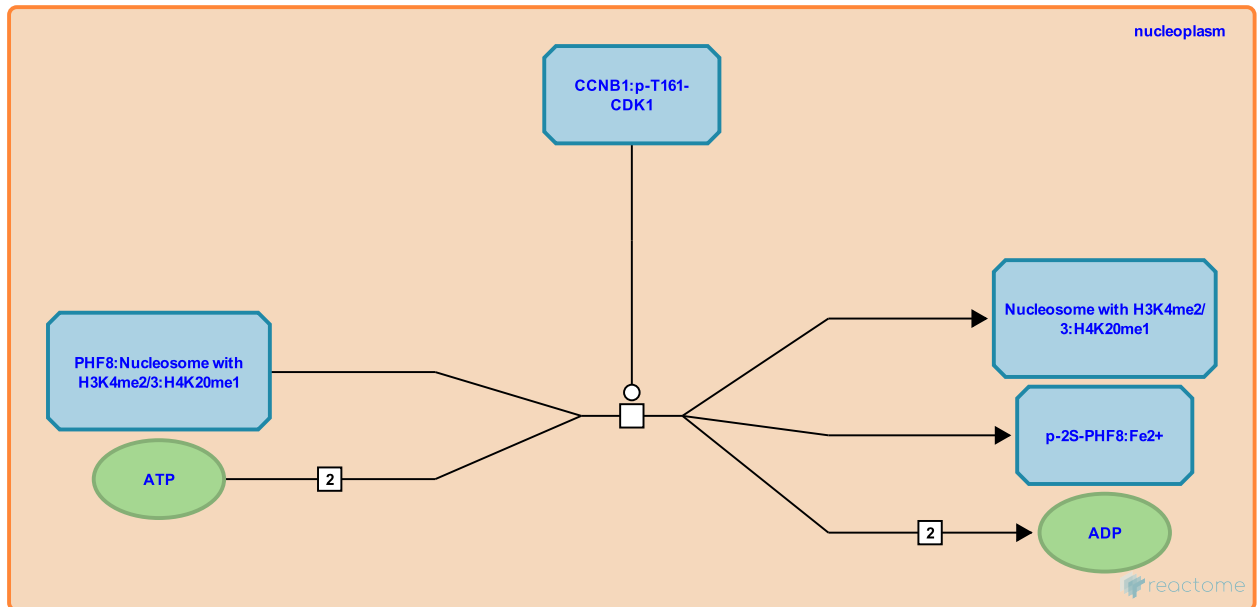
CDK1 phosphorylates PHF8 ↗

Location: [Condensation of Prophase Chromosomes](#)

Stable identifier: R-HSA-2245218

Type: transition

Compartments: nucleoplasm



Increased activity of CDK1:CCNB1 during the cell cycle promotes PHF8 dissociation from chromatin, while the inhibition of CDK activity promotes binding of PHF8 to chromatin during mitosis. CDK1:CCNB1 complex phosphorylates PHF8 in vitro on serine residues S33 and S84. Mutation of PHF8 phosphorylation sites impairs the dissociation of PHF8 from chromatin and the accumulation of H4K20me1 in prophase (Liu et al. 2010). Positions of CDK1-phosphorylated serine residues in PHF8, S33 and S84, are based on the sequence of PHF8 splicing isoform 2, which was used in the experiments of Liu et al. In PHF8 splicing isoforms 1 and 3, serine residues S69 and S120 are annotated as targets of CDK1-mediated phosphorylation.

Preceded by: [SETD8 monomethylates histone H4](#)

Followed by: [Condensin II complex binds H4K20me1-containing nucleosomes](#)

Literature references

Liu, W., Tanasa, B., Tyurina, OV., Zhou, TY., Gassmann, R., Liu, WT. et al. (2010). PHF8 mediates histone H4 lysine 20 demethylation events involved in cell cycle progression. *Nature*, 466, 508-12. ↗

Editions

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2013-04-23	Edited	Matthews, L.
2013-10-14	Reviewed	Longworth, MS.

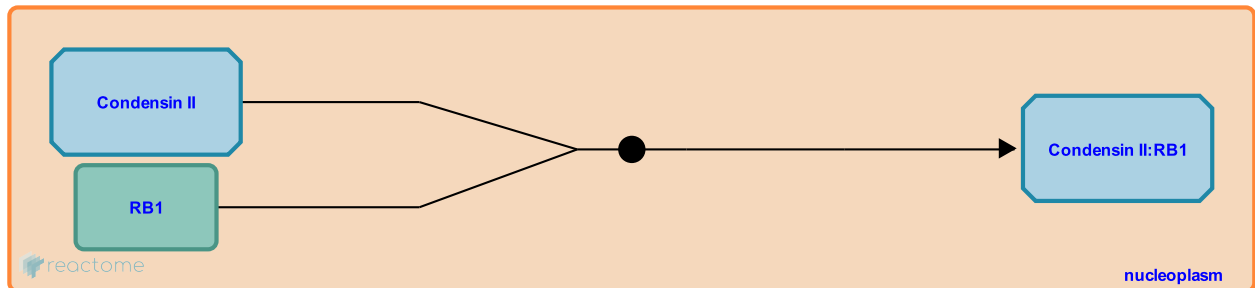
RB1 binds condensin II ↗

Location: [Condensation of Prophase Chromosomes](#)

Stable identifier: R-HSA-2172666

Type: binding

Compartments: nucleoplasm



RB1 binds the condensin II complex through interaction with the NCAPD3 subunit of condensin II. This interaction is E2F independent and is important for targeting of the condensin II complex to chromatin (Longworth et al. 2008). RB1 may be particularly important for targeting of the condensin II complex to centromeres (Manning et al. 2010). RB1 deficient cells exhibit chromosome condensation defects and are prone to aneuploidy caused by aberrant chromosomal segregation. Therefore, tumor suppressor role of RB1 is based both on E2F-dependent control of G1/S transition, as well as on E2F-independent maintenance of genomic stability through regulation of mitotic chromosome condensation (Longworth et al. 2008, Coschi et al. 2010, Manning et al. 2010).

The role of RB1 in the maintenance of genomic stability is supported by studies of the childhood eye cancer retinoblastoma and its precursor, retinoma. Retinoma, a quiescent precursor of malignant retinoblastoma with functional loss of both RB1 alleles, is genomically unstable (Dimaras et al. 2008). Also, while the majority of retinoblastoma tumors are caused by the loss-of-function of the tumor suppressor gene RB1, ~2% of retinoblastoma tumors in unilaterally affected patients are initiated by a high level amplification of MYCN gene, in the presence of two functional, unmutated RB1 alleles. These tumors, with normal RB1 and amplified MYCN show a much lower level of genomic instability than retinoblastoma tumors with RB1 loss-of-function (Rushlow et al. 2013).

Followed by: [Condensin II complex binds H4K20me1-containing nucleosomes](#)

Literature references

- Longworth, MS., Herr, A., Ji, JY., Dyson, NJ. (2008). RBF1 promotes chromatin condensation through a conserved interaction with the Condensin II protein dCAP-D3. *Genes Dev*, 22, 1011-24. ↗
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Editions

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

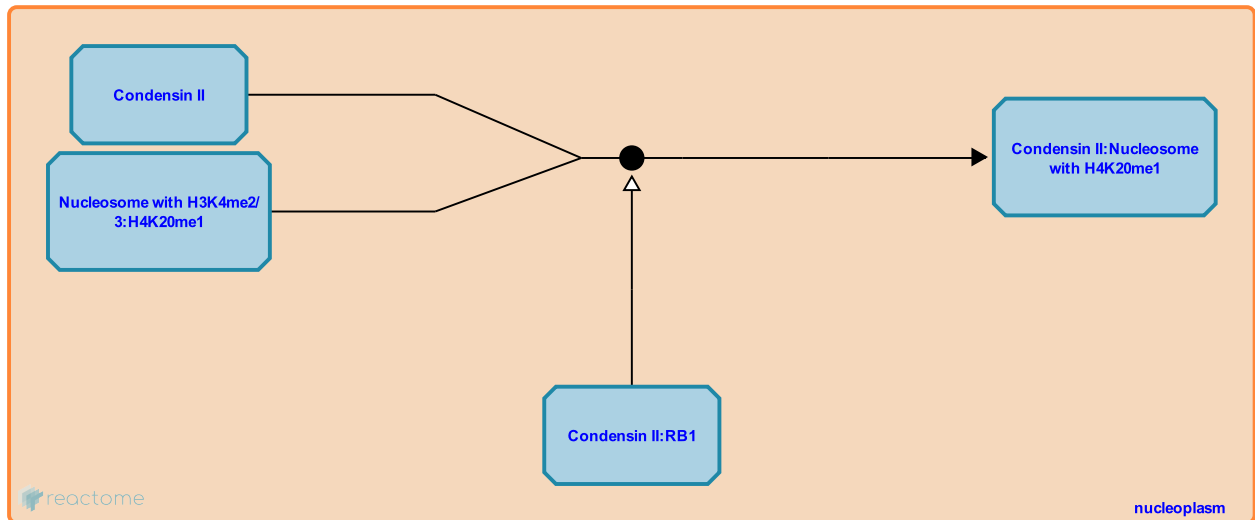
Condensin II complex binds H4K20me1-containing nucleosomes ↗

Location: [Condensation of Prophase Chromosomes](#)

Stable identifier: R-HSA-2288097

Type: binding

Compartments: nucleoplasm



Accumulation of monomethylated histone H4 (H4K20me1) is necessary for loading of the condensin II complex on chromatin. Condensin II binds H4K20me1 through HEAT repeats of two condensin II subunits, NCAPD3 and NCAPG2 (Liu et al. 2010). RB1 is required, at least partially, for the successful association of condensin II with chromatin (Longworth et al. 2008). The precise role of RB1 in condensin II loading and the connection, if any, between histone H4 monomethylation and RB1-facilitated loading of the condensin II complex on chromatin has not, however, been elucidated. RB1 family proteins are known to interact with H4K20 trimethylating enzymes Suv4-20h1 and Suv4-20h2 and promote H4K20 trimethylation at pericentric and telomeric heterochromatin (Gonzalo et al. 2005).

Preceded by: [RB1 binds condensin II](#), [CDK1 phosphorylates PHF8](#)

Followed by: [CDK1 phosphorylates condensin II subunit NCAPD3](#)

Literature references

Liu, W., Tanasa, B., Tyurina, OV., Zhou, TY., Gassmann, R., Liu, WT. et al. (2010). PHF8 mediates histone H4 lysine 20 demethylation events involved in cell cycle progression. *Nature*, 466, 508-12. ↗

Longworth, MS., Herr, A., Ji, JY., Dyson, NJ. (2008). RBF1 promotes chromatin condensation through a conserved interaction with the Condensin II protein dCAP-D3. *Genes Dev*, 22, 1011-24. ↗

Gonzalo, S., García-Cao, M., Fraga, MF., Schotta, G., Peters, AH., Cotter, SE. et al. (2005). Role of the RB1 family in stabilizing histone methylation at constitutive heterochromatin. *Nat. Cell Biol.*, 7, 420-8. ↗

Editions

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

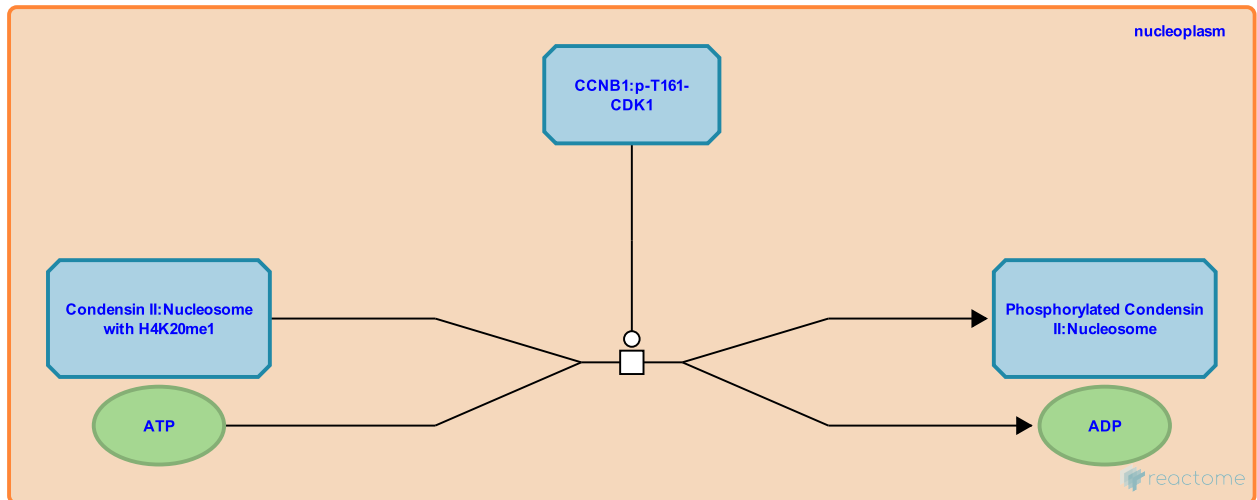
CDK1 phosphorylates condensin II subunit NCAPD3 ↗

Location: [Condensation of Prophase Chromosomes](#)

Stable identifier: R-HSA-2294600

Type: transition

Compartments: nucleoplasm



Phosphorylation of the threonine residue T1415 of condensin II subunit NCAPD3 is required for chromosome condensation in prophase. In vivo, phosphorylation of NCAPD3 threonine residue T1415 is blocked when cells are treated with CDK1 inhibitors. In addition, it was shown that CDK1 in complex with cyclin B1 (CDK1:CCNB1) phosphorylates NCAPD3 at T1415 in vitro (Abe et al. 2011).

Preceded by: [Condensin II complex binds H4K20me1-containing nucleosomes](#)

Followed by: [PLK1 binds phosphorylated condensin II complex](#)

Literature references

Abe, S., Nagasaka, K., Hirayama, Y., Kozuka-Hata, H., Oyama, M., Aoyagi, Y. 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. ↗

Editions

2013-04-22	Authored	Orlic-Milacic, M.
2013-04-23	Edited	Matthews, L.
2013-10-14	Reviewed	Longworth, MS.

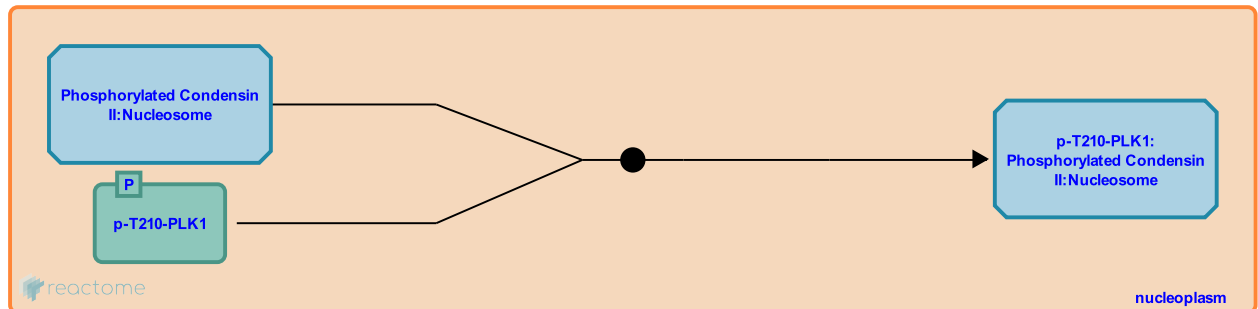
PLK1 binds phosphorylated condensin II complex ↗

Location: [Condensation of Prophase Chromosomes](#)

Stable identifier: R-HSA-2294590

Type: binding

Compartments: nucleoplasm



Phosphorylated threonine T1415 of NCAPD3 condensin II subunit serves as a docking site for PLK1 (Abe et al. 2011).

Preceded by: [CDK1 phosphorylates condensin II subunit NCAPD3](#)

Followed by: [PLK1 hyperphosphorylates Condensin II complex](#)

Literature references

Abe, S., Nagasaka, K., Hirayama, Y., Kozuka-Hata, H., Oyama, M., Aoyagi, Y. 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. ↗

Editions

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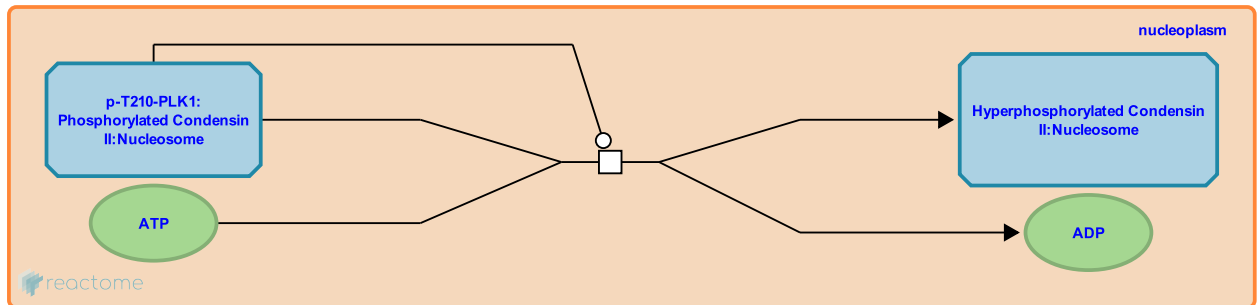
PLK1 hyperphosphorylates Condensin II complex ↗

Location: [Condensation of Prophase Chromosomes](#)

Stable identifier: R-HSA-2294580

Type: transition

Compartments: nucleoplasm



Once PLK1 is recruited to the chromatin-bound condensin II complex, it phosphorylates the NCAPD3 subunit of condensin II on serine residue S1419, and possibly other residues. In addition to phosphorylating NCAPD3, PLK1 phosphorylates other condensin II subunits, NCAPG2 and NCAPH2. However, the phosphorylation sites have not yet been determined. PLK1-mediated phosphorylation of the condensin II complex facilitates condensation of prophase chromosomes (Abe et al. 2011).

Preceded by: [PLK1 binds phosphorylated condensin II complex](#)

Followed by: [Condensin II-mediated condensation of prophase chromosomes](#)

Literature references

Abe, S., Nagasaka, K., Hirayama, Y., Kozuka-Hata, H., Oyama, M., Aoyagi, Y. 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. ↗

Editions

2013-04-22	Authored	Orlic-Milacic, M.
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2013-10-14	Reviewed	Longworth, MS.

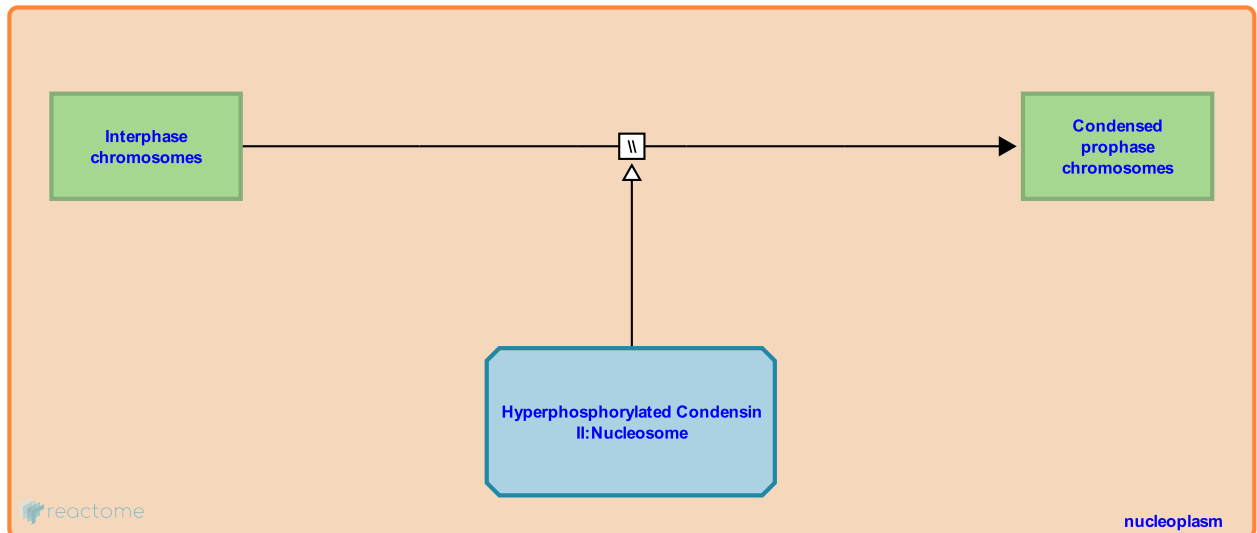
Condensin II-mediated condensation of prophase chromosomes ↗

Location: [Condensation of Prophase Chromosomes](#)

Stable identifier: R-HSA-2294574

Type: omitted

Compartments: nucleoplasm



Condensation of chromosomes in prophase is mediated by chromatin-bound hyperphosphorylated condensin II complex.

Preceded by: [PLK1 hyperphosphorylates Condensin II complex](#)

Literature references

Abe, S., Nagasaka, K., Hirayama, Y., Kozuka-Hata, H., Oyama, M., Aoyagi, Y. 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. ↗

Longworth, MS., Herr, A., Ji, JY., Dyson, NJ. (2008). RBF1 promotes chromatin condensation through a conserved interaction with the Condensin II protein dCAP-D3. *Genes Dev*, 22, 1011-24. ↗

Editions

2013-04-22	Authored	Orlic-Milacic, M.
2013-04-23	Edited	Matthews, L.
2013-10-14	Reviewed	Longworth, MS.

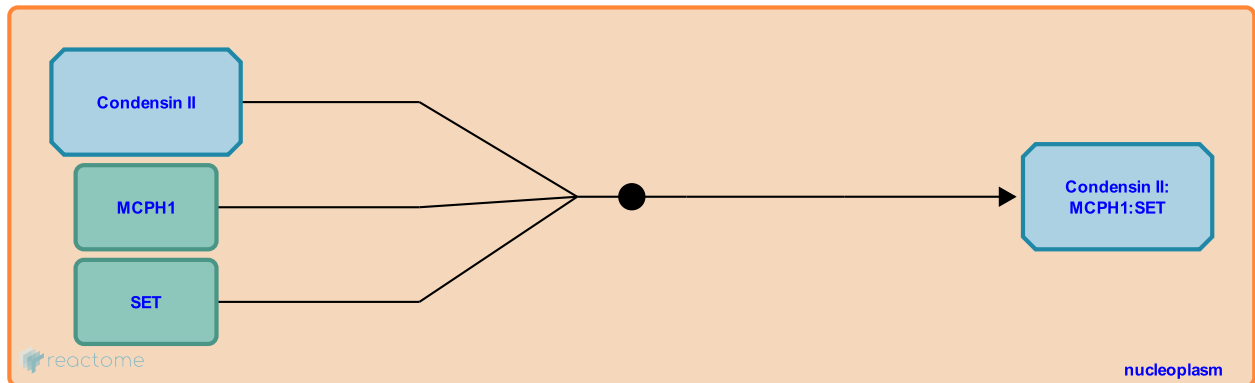
MCPH1 sequesters condensin II [↗](#)

Location: [Condensation of Prophase Chromosomes](#)

Stable identifier: R-HSA-2429719

Type: binding

Compartments: nucleoplasm



MCPH1 (microcephalin) binds condensin II complex through direct interaction with NCAPG2 and possibly NCAPD3 condensin II subunits (Wood et al. 2008, Yamashita et al. 2011). MCPH1 binding sequesters condensin II by preventing loading of condensin II on chromatin. Simultaneous binding of MCPH1 to the SET oncogene may contribute to condensin II sequestering (Leung et al. 2011). Mutations in MCPH1 are a cause of microcephaly inherited in an autosomally recessive manner. MCPH1 deficient cells show premature chromosome condensation (PCC) phenotype, with metaphase-like chromosomes apparent in prophase, before nuclear envelope breakdown (Wood et al. 2008).

Literature references

- Yamashita, D., Shintomi, K., Ono, T., Gavvovidis, I., Schindler, D., Neitzel, H. et al. (2011). MCPH1 regulates chromosome condensation and shaping as a composite modulator of condensin II. *J. Cell Biol.*, 194, 841-54. [↗](#)
- Wood, JL., Liang, Y., Li, K., Chen, J. (2008). Microcephalin/MCPH1 associates with the Condensin II complex to function in homologous recombination repair. *J. Biol. Chem.*, 283, 29586-92. [↗](#)
- Leung, JW., Leitch, A., Wood, JL., Shaw-Smith, C., Metcalfe, K., Bicknell, LS. et al. (2011). SET nuclear oncogene associates with microcephalin/MCPH1 and regulates chromosome condensation. *J. Biol. Chem.*, 286, 21393-400. [↗](#)

Editions

2013-04-22	Authored	Orlic-Milacic, M.
2013-04-23	Edited	Matthews, L.
2013-10-14	Reviewed	Longworth, MS.

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