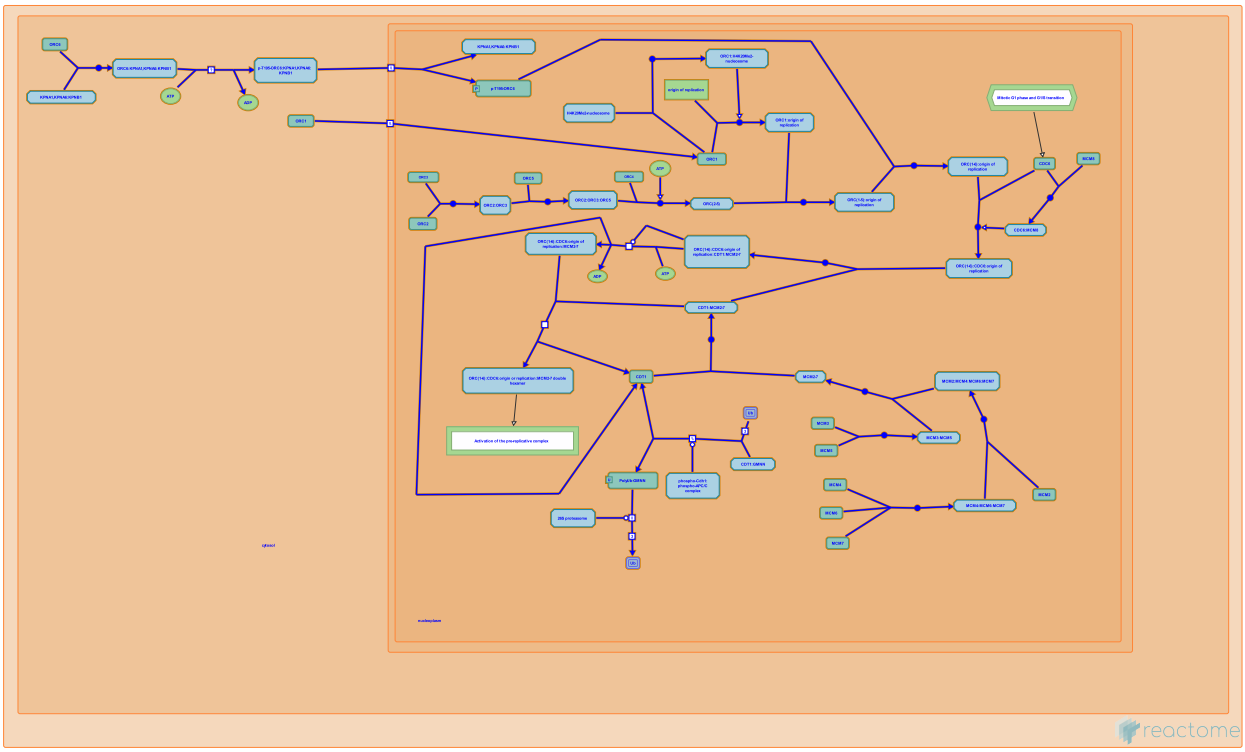
Assembly of the pre-replicative complex



Davey, MJ., Kusic-Tisma, J., Manfredi, JJ., O'Donnell, M., Orlic-Milacic, M., Tye, BK.

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

02/05/2024

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. ↗

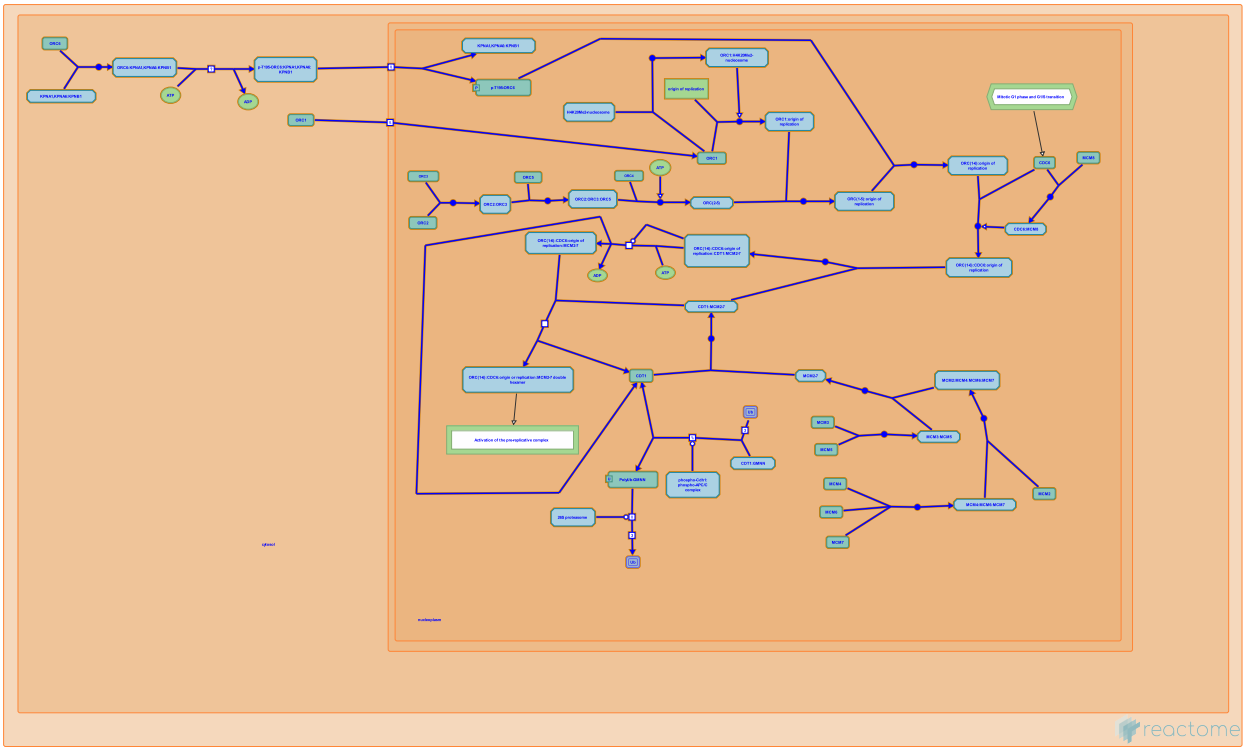
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Assembly of the pre-replicative complex ↗

Stable identifier: R-HSA-68867

Compartments: cytosol, nucleoplasm



DNA replication pre-initiation in eukaryotic cells begins with the formation of the pre-replicative complex (pre-RC) during the late M phase and continues in the G1 phase of the mitotic cell cycle, a process also called DNA replication origin licensing. The association of initiation proteins (ORC, Cdc6, Cdt1, Mcm2-7) with the origin of replication in both *S. cerevisiae* and humans has been demonstrated by chromatin immunoprecipitation experiments. In *S. cerevisiae*, pre-replicative complexes are assembled from late M to G1. In mammalian cells as well, pre-replicative complexes are assembled from late M to G1, as shown by biochemical fractionation and immunostaining. There are significant sequence similarities among some of the proteins in the pre-replicative complex. The ORC subunits Orc1, Orc4 and Orc5 are homologous to one another and to Cdc6. The six subunits of the Mcm2-7 complex are homologous to one another. In addition, Orc1, Orc4, Orc5, Cdc6, and the Mcm2-7 subunits, are members of the AAA+ superfamily of ATPases. Since the initial identification of these pre-RC components other factors that participate in this complex have been found, including Cdt1 in human, *Xenopus*, *S. pombe*, and *S. cerevisiae* cells.

Literature references

Mendez, J., Stillman, B. (2000). Chromatin association of human origin recognition complex, cdc6, and minichromosome maintenance proteins during the cell cycle: assembly of prereplication complexes in late mitosis. *Mol Cell Biol, 20*, 8602-12. ↗

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Editions

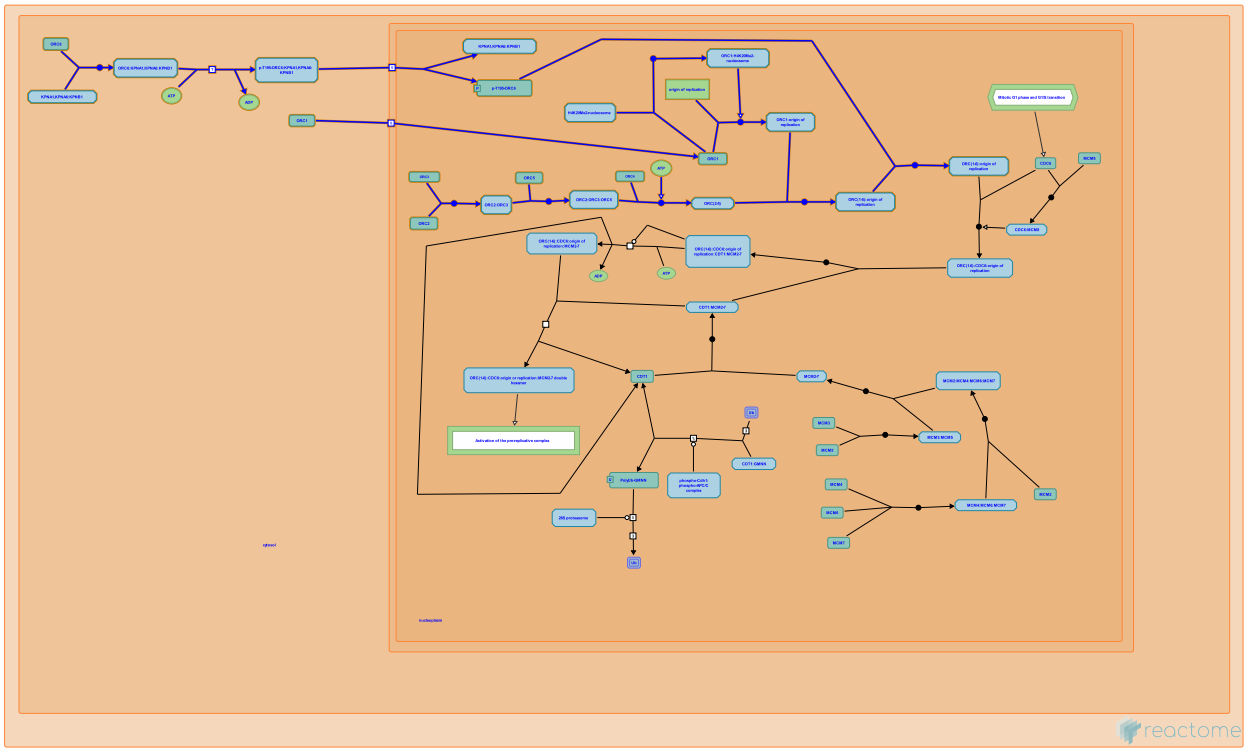
2006-03-17	Authored	Davey, MJ., O'Donnell, M., Tye, BK.
2018-07-10	Reviewed	Manfredi, JJ.
2021-10-27	Authored, Revised	Kusic-Tisma, J.
2021-11-03	Edited	Orlic-Milacic, M.

Assembly of the ORC complex at the origin of replication ↗

Location: Assembly of the pre-replicative complex

Stable identifier: R-HSA-68616

Compartments: nucleoplasm



Human ORC1 can associate with DNA origin of replication sites independently of other origin of replication complex (ORC) subunits (Hoshina et al. 2013; Eladl et al. 2021). ORC1 localizes to condensed chromosomes during early mitosis (M phase) and serves as a nucleating center for the assembly of the ORC and, subsequently, the pre-replication complex. ORC1 remains associated with late replication origins throughout late G1. Upon S phase entry, ORC1 undergoes ubiquitin-mediated degradation, leading to dissociation of the ORC from chromatin (Kara et al. 2015).

Most human replication origins contain guanine (G)-rich sequences which may form G-quadruplex (G4) structures (Besnard et al. 2012) and these G4 structures may mediate the recognition of replication origins by ORC1 (Hoshina et al. 2013; Eladl et al. 2021). Besides binding to nucleosome-free replication origin DNA, ORC1 interacts with neighboring nucleosomes (Hizume et al. 2013), in particular with nucleosomes containing histone H4 dimethylated at lysine 21 (H4K20me2 mark), which is enriched at replication origins. Binding of ORC1 to H4K20me2 facilitates ORC1 binding to replication origins and ORC chromatin loading (Kuo et al. 2012, Zhang et al. 2015).

ORC1 binding sites are universally associated with transcription start sites (TSSs) of coding and non-coding RNAs. Replication origins associated with moderate to high transcription level TSSs (belonging to coding RNAs) fire in early S phase, while those associated with low transcription level TSSs (belonging to non-coding RNAs) fire throughout the S phase (Dellino et al. 2013).

ORC2 forms a heterodimer with ORC3, which is a prerequisite for the association of ORC5 and, subsequently, ORC4 (Ranjan and Gossen 2006; Siddiqui and Stillman 2007). ORC1 binds to the ORC(2-5) complex in the nucleus to form a stable ORC(1-5) complex (Radichev et al. 2006; Ghosh et al. 2011). ORC1 is necessary for the association of the ORC(2-5) complex to chromatin (Radichev et al. 2006). The ORC(2-5) complex exhibits a tightly autoinhibited conformation, with the winged-helix domain (WHD) of ORC2 completely blocking the central DNA-binding channel. Binding of ORC1 remodels the WHD of ORC2, moving it away from the central channel and partially relieving the autoinhibition (Cheng et al. 2020, Jaremko et al. 2020). ORC6 associates with the ORC(1-5) complex to form the ORC(1-6) complex (Ghosh et al. 2011). The association of ORC6 with the ORC(1-5) complex is weak and it frequently does not co-immunoprecipitate with the other ORC(1-5) subunits. ORC4 is the only ORC(1-5) subunit that was shown to directly bind to ORC6 (Radichev et al. 2006). Some ORC6 mutations reported in Meier-Gorlin syndrome were shown to interfere with ORC6 incorporation into the ORC (Balasov et al. 2015).

Literature references

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Balasov, M., Akhmetova, K., Chesnokov, I. (2015). Drosophila model of Meier-Gorlin syndrome based on the mutation in a conserved C-Terminal domain of Orc6. *Am J Med Genet A, 167*, 2533-40. ↗

Siddiqui, K., Stillman, B. (2007). ATP-dependent assembly of the human origin recognition complex. *J Biol Chem, 282*, 32370-83. ↗

Song, J., Gozani, O., Zhang, W., Sankaran, S. (2015). A Meier-Gorlin syndrome mutation impairs the ORC1-nucleosome association. *ACS Chem Biol, 10*, 1176-80. ↗

Editions

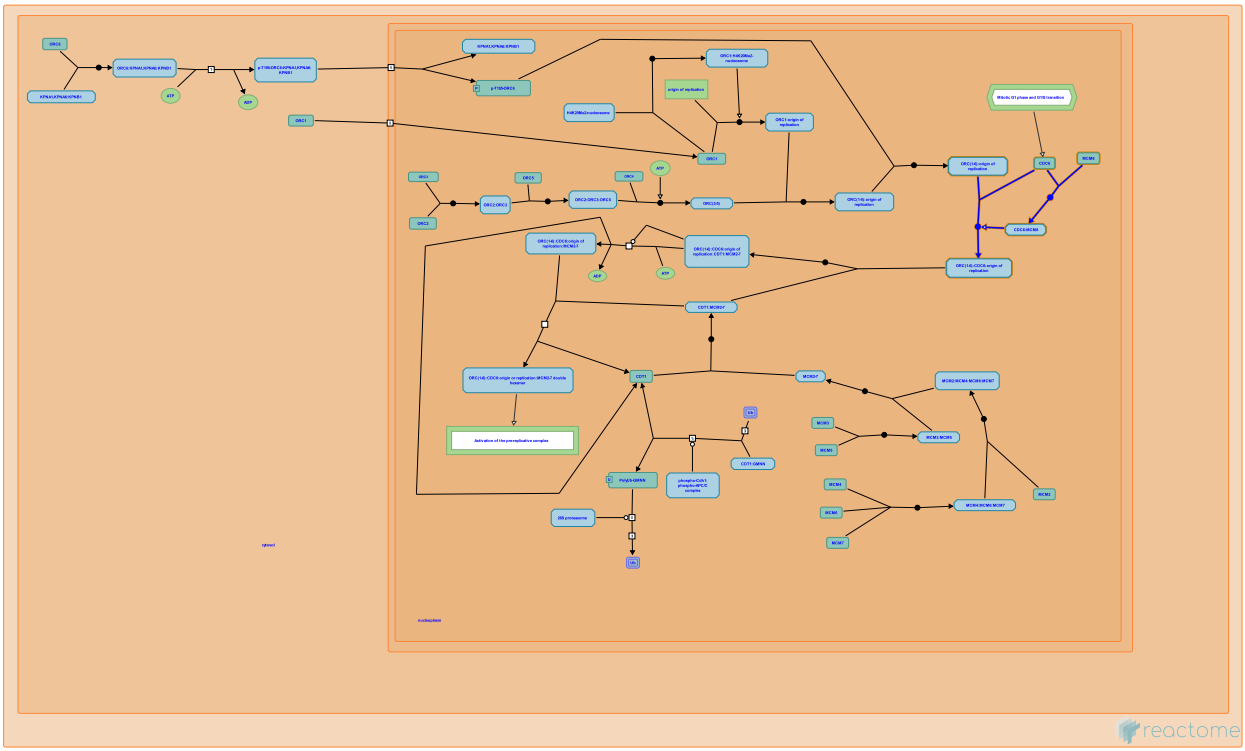
2003-06-05	Authored	Davey, MJ., O'Donnell, M.
2021-07-30	Authored, Revised	Kusic-Tisma, J.
2021-08-16	Edited	Orlic-Milacic, M.

CDC6 association with the ORC:origin complex ↗

Location: Assembly of the pre-replicative complex

Stable identifier: R-HSA-68689

Compartments: nucleoplasm



Cdc6 is a regulator of DNA replication initiation in both yeasts and human cells (Mendez and Stillman 2000), but its mechanism of action differs between the two systems. Genetic studies in budding yeast (S. cerevisiae) and fission yeast (S. pombe) indicate that the normal function of Cdc6 protein is required to restrict DNA replication to once per cell cycle. Specifically, Cdc6 may function as an ATPase switch linked to Mcm2-7:Cdt1 association with the Cdc6:ORC:origin complex (Lee and Bell 2000). In S. cerevisiae, Cdc6 protein is expressed late in the M phase of the cell cycle and, in cells with a prolonged G1 phase, late in G1. This protein has a short half-life, and is destroyed by ubiquitin-mediated proteolysis, mediated by the SCF complex (Piatti et al. 1995, Drury et al. 1997, Drury et al. 2000, Perkins et al. 2001). Human Cdc6 protein levels are reduced early in G1 but otherwise are constant throughout the cell cycle (Petersen et al. 2000). Some reports have suggested that after cells enter S phase, Cdc6 is phosphorylated, excluded from the nucleus and subject to ubiquitination and degradation (Saha et al. 1998, Jiang et al. 1999, Petersen et al. 1999). Replenishing Cdc6 protein levels during G1 appears to be regulated by E2F transcription factors (Yan et al. 1998).

Literature references

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Diffley, JF., Drury, LS., Perkins, G. (2001). Separate SCF(CDC4) recognition elements target Cdc6 for proteolysis in S phase and mitosis. *EMBO J, 20*, 4836-45. ↗

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Mendez, J., Stillman, B. (2000). Chromatin association of human origin recognition complex, cdc6, and minichromosome maintenance proteins during the cell cycle: assembly of prereplication complexes in late mitosis. *Mol Cell Biol, 20*, 8602-12. ↗

Editions

2006-03-17	Authored	Davey, MJ., O'Donnell, M., Tye, BK.

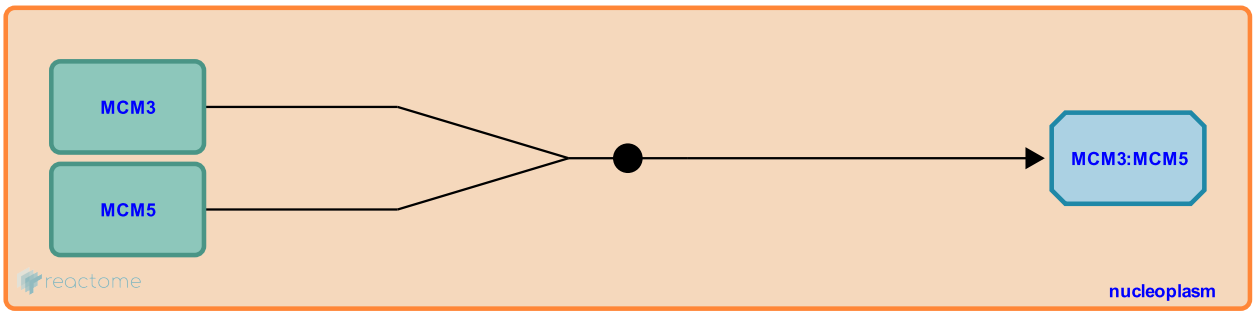
MCM3 binds MCM5 ↗

Location: Assembly of the pre-replicative complex

Stable identifier: R-HSA-9757256

Type: binding

Compartments: nucleoplasm



MCM3 can form a complex with MCM5 in the absence of other MCM complex subunits. This complex does not possess a DNA helicase activity (Sato et al. 2000). The complex of MCM3 and MCM5 was reported to play a role in transcriptional regulation in addition to its involvement in DNA replication (DaFonseca and Zhang 2001).

Followed by: Formation of MCM2-7 complex

Literature references

Ishimi, Y., Gotow, T., Komamura-Kohno, Y., You, Z., Sato, M., Nojima, H. et al. (2000). Electron microscopic observation and single-stranded DNA binding activity of the Mcm4,6,7 complex. *J Mol Biol, 300*, 421-31. ↗

Zhang, JJ., DaFonseca, CJ., Shu, F. (2001). Identification of two residues in MCM5 critical for the assembly of MCM complexes and Stat1-mediated transcription activation in response to IFN-gamma. *Proc Natl Acad Sci U S A, 98*, 3034-9. ↗

Editions

2021-10-27	Authored	Kusic-Tisma, J.
2021-11-03	Edited	Orlic-Milacic, M.

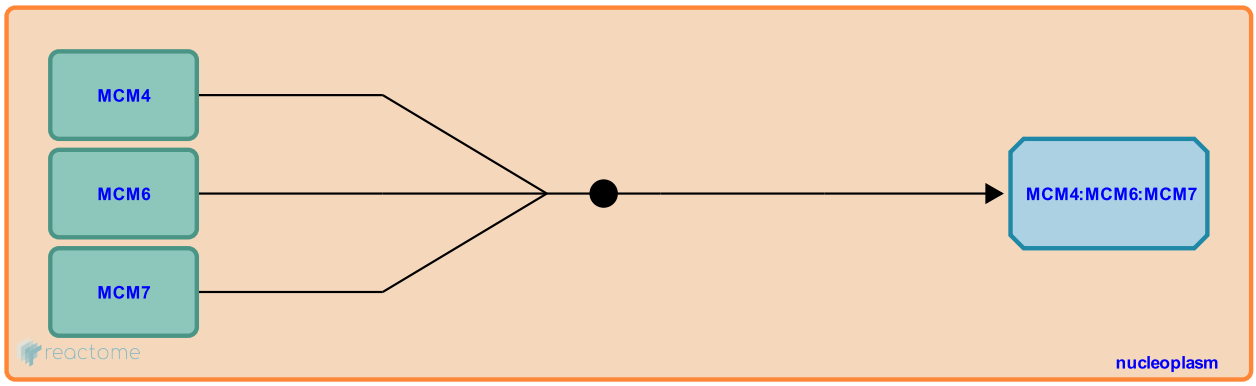
MCM4, MCM6 and MCM7 form a heterotrimer ↗

Location: Assembly of the pre-replicative complex

Stable identifier: R-HSA-9757257

Type: binding

Compartments: nucleoplasm



MCM4, MCM6 and MCM7 form a complex that has a DNA helicase activity (Sato et al. 2000).

Followed by: MCM2 binds MCM4:MCM6:MCM7 heterotrimer

Literature references

Ishimi, Y., Gotow, T., Komamura-Kohno, Y., You, Z., Sato, M., Nojima, H. et al. (2000). Electron microscopic observation and single-stranded DNA binding activity of the Mcm4,6,7 complex. *J Mol Biol, 300*, 421-31. ↗

Editions

2021-10-27	Authored	Kusic-Tisma, J.
2021-11-03	Edited	Orlic-Milacic, M.

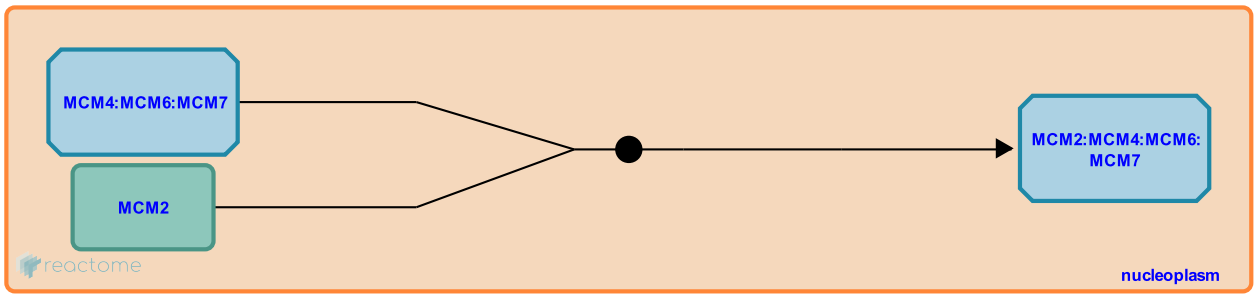
MCM2 binds MCM4:MCM6:MCM7 heterotrimer ↗

Location: Assembly of the pre-replicative complex

Stable identifier: R-HSA-9757258

Type: binding

Compartments: nucleoplasm



MCM2 binds to the complex of MCM4, MCM6 and MCM7 and inhibits its DNA helicase activity (Sato et al. 2000). Association of the complex of MCM4, MCM6 and MCM7 with the complex of MCM3 and MCM5 inhibits the DNA helicase activity (Sato et al. 2000).

Preceded by: MCM4, MCM6 and MCM7 form a heterotrimer

Followed by: Formation of MCM2-7 complex

Literature references

Ishimi, Y., Gotow, T., Komamura-Kohno, Y., You, Z., Sato, M., Nojima, H. et al. (2000). Electron microscopic observation and single-stranded DNA binding activity of the Mcm4,6,7 complex. *J Mol Biol, 300*, 421-31. ↗

Editions

2021-10-27	Authored	Kusic-Tisma, J.
2021-11-03	Edited	Orlic-Milacic, M.

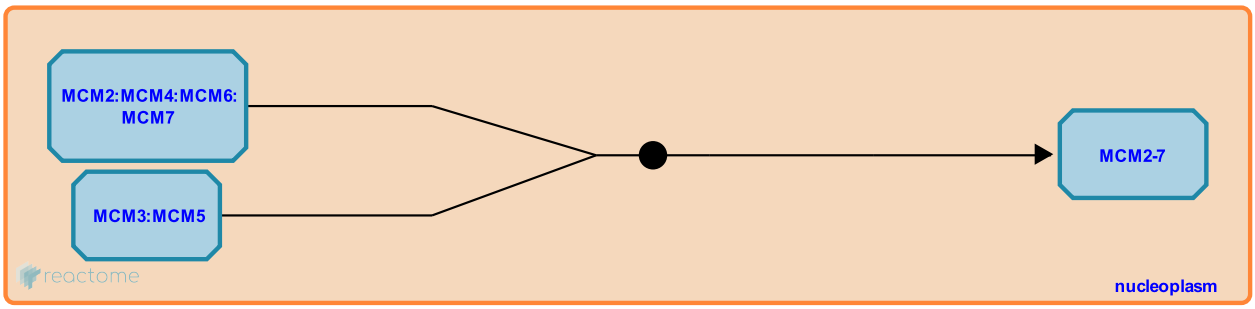
Formation of MCM2-7 complex ↗

Location: Assembly of the pre-replicative complex

Stable identifier: R-HSA-9749253

Type: binding

Compartments: nucleoplasm



Six homologous minichromosome maintenance proteins, MCM2, MCM3, MCM4, MCM5, MCM6 and MCM7, form the evolutionarily conserved MCM2-7 complex, which functions as the core eukaryotic replicated DNA helicase. The structure of the complex is conserved from yeast (Li et al. 2015) to humans (Boskovic et al. 2016), representing an open hexameric ring, with a gate between subunits MCM2 and MCM5. The gate is thought to close and open the MCM2-7 ring to encircle DNA. Each MCM subunit contains an N-terminal DNA interacting and assembly domain and a C-terminal ATP-binding domain.

Preceded by: MCM2 binds MCM4:MCM6:MCM7 heterotrimer, MCM3 binds MCM5

Followed by: CDT1 binds MCM2-7

Literature references

Saligram Prabhakar, B., Méndez, J., Boskovic, J., Montoya, G., Bragado-Nilsson, E., Martínez-Gago, J. et al. (2016). Molecular architecture of the recombinant human MCM2-7 helicase in complex with nucleotides and DNA. *Cell Cycle, 15*, 2431-40. ↗

Yang, M., Gao, N., Tye, BK., Zhai, Y., Li, N., Lei, J. et al. (2015). Structure of the eukaryotic MCM complex at 3.8 Å. *Nature, 524*, 186-91. ↗

Editions

2021-10-27	Authored	Kusic-Tisma, J.
2021-11-03	Edited	Orlic-Milacic, M.

The geminin component of geminin:Cdt1 complexes is ubiquitinated, releasing Cdt1

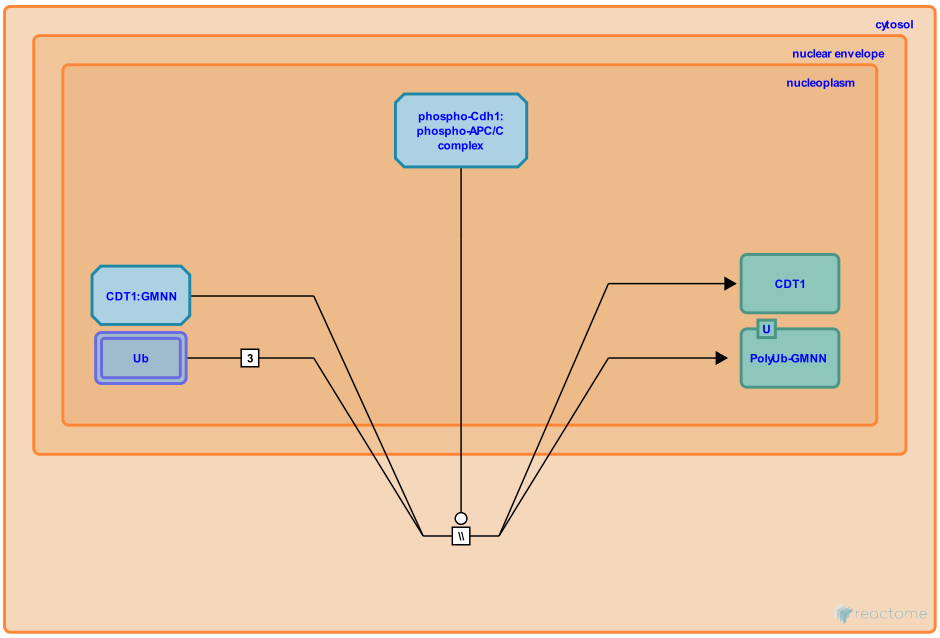
↗

Location: Assembly of the pre-replicative complex

Stable identifier: R-HSA-68712

Type: omitted

Compartments: cytosol



From the end of anaphase and throughout G1, the Cdh1 (FZR1) containing anaphase-promoting complex (APC/C:Cdh1) ubiquitinates geminin (GMNN), targeting it for degradation and enabling release of CDT1 and the subsequent association of CDT1 with the replication origins.The presence of an APC destruction box in geminin and its APC/C-mediated ubiquitination and degradation was first demonstrated in Xenopus egg extracts (McGarry and Kirschner 1998) and was later confirmed in human cells, where it was shown to largely depend on Cdh1 and not Cdc20 component of the APC/C (Pfleger et al. 2001; Di Fiore and Pines 2007; Machida and Dutta 2007). Emi1 (FBXO5) mediated inhibition of the APC/C:Cdh1 complex in S and G2 phases is needed for stabilization of geminin and prevention of re-replication (Di Fiore and Pines 2007; Machida and Dutta 2007).

Followed by: Ubiquitinated geminin is degraded by the proteasome

Literature references

McGarry, TJ., Kirschner, MW. (1998). Geminin, an inhibitor of DNA replication, is degraded during mitosis. *Cell, 93*, 1043-53. ↗

Pfleger, CM., Kirschner, MW., Lee, E. (2001). Substrate recognition by the Cdc20 and Cdh1 components of the anaphase-promoting complex. *Genes Dev, 15*, 2396-407. ↗

Pines, J., Di Fiore, B. (2007). Emi1 is needed to couple DNA replication with mitosis but does not regulate activation of the mitotic APC/C. *J Cell Biol, 177*, 425-37. ↗

Dutta, A., Machida, YJ. (2007). The APC/C inhibitor, Emi1, is essential for prevention of rereplication. *Genes Dev, 21*, 184-94. ↗

Editions

2021-10-30	Revised	Orlic-Milacic, M.
2021-11-05	Reviewed	Kusic-Tisma, J.
2021-11-17	Edited	Orlic-Milacic, M.

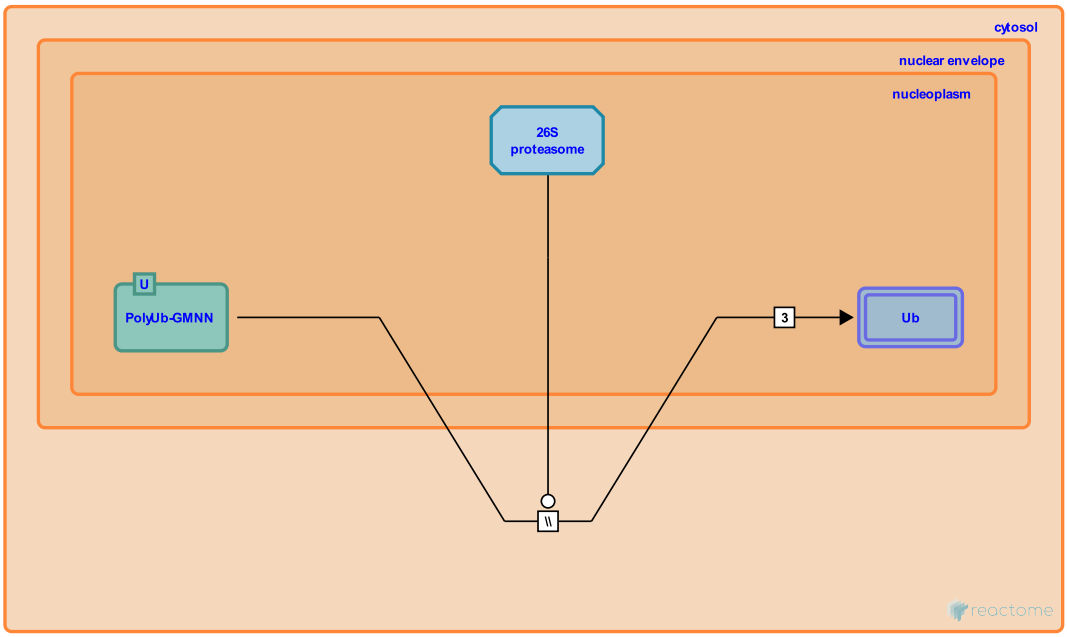
Ubiquitinated geminin is degraded by the proteasome ↗

Location: Assembly of the pre-replicative complex

Stable identifier: R-HSA-68825

Type: omitted

Compartments: cytosol



APC/C-dependent degradation of geminin (GMNN) was first demonstrated in Xenopus (McGarry and Kirschner 1998) and was shown to be proteasome-dependent and sensitive to FBXO5 (Emi1)-mediated inhibition of the APC/C:Cdh1 activity in human cells (Machida and Dutta 2007).

Preceded by: The geminin component of geminin:Cdt1 complexes is ubiquitinated, releasing Cdt1

Literature references

McGarry, TJ., Kirschner, MW. (1998). Geminin, an inhibitor of DNA replication, is degraded during mitosis. *Cell, 93*, 1043-53. ↗

Dutta, A., Machida, YJ. (2007). The APC/C inhibitor, Emi1, is essential for prevention of rereplication. *Genes Dev, 21*, 184-94. ↗

Editions

2021-11-05	Reviewed	Kusic-Tisma, J.
2021-11-17	Edited	Orlic-Milacic, M.

CDT1 binds MCM2-7 ↗

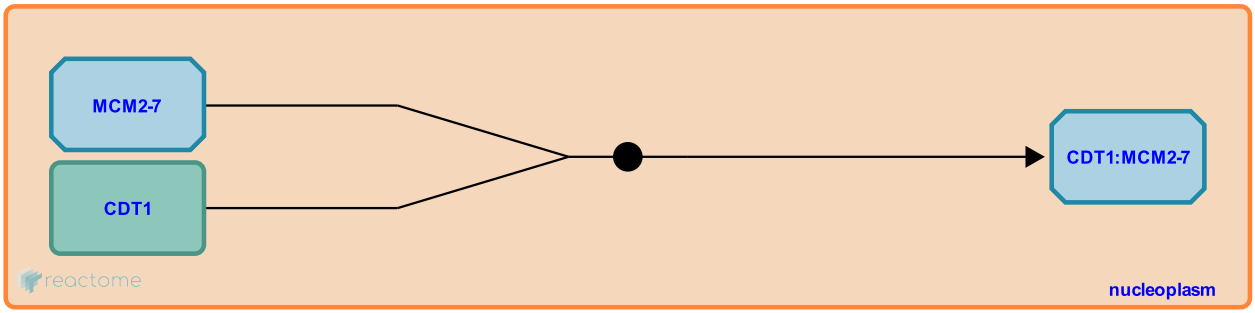
Location: Assembly of the pre-replicative complex

Stable identifier: R-HSA-9749286

Type: binding

Compartments: nucleoplasm

Inferred from: CDT1 binds MCM2-7 complex in budding yeast (Saccharomyces cerevisiae)



While the interaction between CDT1 and the MCM2-7 complex was confirmed in human (Wu et al. 2014) and other mammalian cells (Cook et al. 2004), as well as in the fruit fly (Costa et al. 2011), the mechanism of interaction has only been studied in detail in yeast. From yeast studies, CDT1 binds to the MCM2-7 complex by interacting with its MCM2 and MCM6 subunits (Kawasaki et al. 2006; Remus et al. 2009), resulting in the formation of a hetero-heptameric CDT1:MCM2-7 complex (Sun et al. 2013). CDT1 binding relieves the autoinhibitory action of the MCM6 subunit that prevents association of the MCM2-7 complex with the complex of ORC and CDC6 in the absence of CDT1 (Fernández-Cid et al. 2013, Sun et al. 2013).

Preceded by: Formation of MCM2-7 complex

Followed by: CDT1-mediated loading of MCM2-7 to replication origins

Literature references

Seki, T., Kojima, A., Kawasaki, Y., Kim, HD., Sugino, A. (2006). Reconstitution of Saccharomyces cerevisiae prereplicative complex assembly in vitro. *Genes Cells, 11*, 745-56. ↗

Beuron, F., Remus, D., Tolun, G., Morris, EP., Diffley, JF., Griffith, JD. (2009). Concerted loading of Mcm2-7 double hexamers around DNA during DNA replication origin licensing. *Cell, 139*, 719-30. ↗

Nevins, JR., Chasse, DA., Cook, JG. (2004). The regulated association of Cdt1 with minichromosome maintenance proteins and Cdc6 in mammalian cells. *J Biol Chem, 279*, 9625-33. ↗

Santos, RE., Wu, M., Lu, W., Frattini, MG., Kelly, TJ. (2014). Geminin inhibits a late step in the formation of human pre-replicative complexes. *J Biol Chem, 289*, 30810-30821. ↗

Fernández-Cid, A., Speck, C., Samel, S., Gardenal, E., Winkler, C., Riera, A. et al. (2013). An ORC/Cdc6/MCM2-7 complex is formed in a multistep reaction to serve as a platform for MCM double-hexamer assembly. *Mol Cell, 50*, 577-88. ↗

Editions

2021-10-27	Authored	Kusic-Tisma, J.
2021-11-03	Edited	Orlic-Milacic, M.

CDT1-mediated loading of MCM2-7 to replication origins ↗

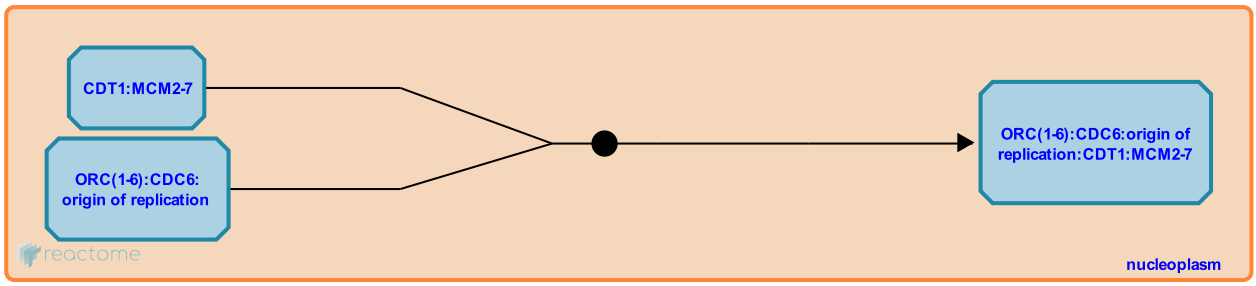
Location: Assembly of the pre-replicative complex

Stable identifier: R-HSA-9749320

Type: binding

Compartments: nucleoplasm

Inferred from: CDT1-mediated loading of MCM2-7 to replication origin in budding yeast (Saccharomyces cerevisiae)



While the simultaneous binding of CDT1 to the MCM2-7 complex and CDC6, as well as the interaction between MCM2-7 and CDC6 at the origin of replication was demonstrated in human cells (Wohlschlegel et al. 2000; Wu et al. 2014), the mechanism has been studied in detail only in the budding yeast (Sun et al. 2013; Fernández-Cid et al. 2013). Based on yeast studies, CDT1 binding to the MCM2-7 complex induces a structural change in the MCM2-7 that relieves MCM2-7 autoinhibition by the C-terminus of its MCM6 subunit, enabling a direct association between MCM2-7 and CDC6 bound to the ORC(1-6) complex at the replication origin (Fernández-Cid et al. 2013). As a result, the OCCM complex is formed, which contains ORC(1-6), CDC6, CDT1 and MCM2-7 bound to the replication origin (Fernández-Cid et al. 2013, Sun et al. 2013). The binding of geminin (GMNN) to CDT1 inhibits CDT1-mediated loading of the MCM2-7 complex to replication origins (Wohlschlegel et al. 2000).

Preceded by: CDT1 binds MCM2-7

Followed by: ATP-dependent release of CDT1 from the OCCM complex

Literature references

Santos, RE., Wu, M., Lu, W., Frattini, MG., Kelly, TJ. (2014). Geminin inhibits a late step in the formation of human pre-replicative complexes. *J Biol Chem, 289*, 30810-30821. ↗

Cvetic, C., Walter, JC., Wohlschlegel, JA., Dwyer, BT., Dutta, A., Dhar, SK. (2000). Inhibition of eukaryotic DNA replication by geminin binding to Cdt1. *Science, 290*, 2309-12. ↗

Editions

2021-10-27	Authored	Kusic-Tisma, J.
2021-11-03	Edited	Orlic-Milacic, M.

ATP-dependent release of CDT1 from the OCCM complex ↗

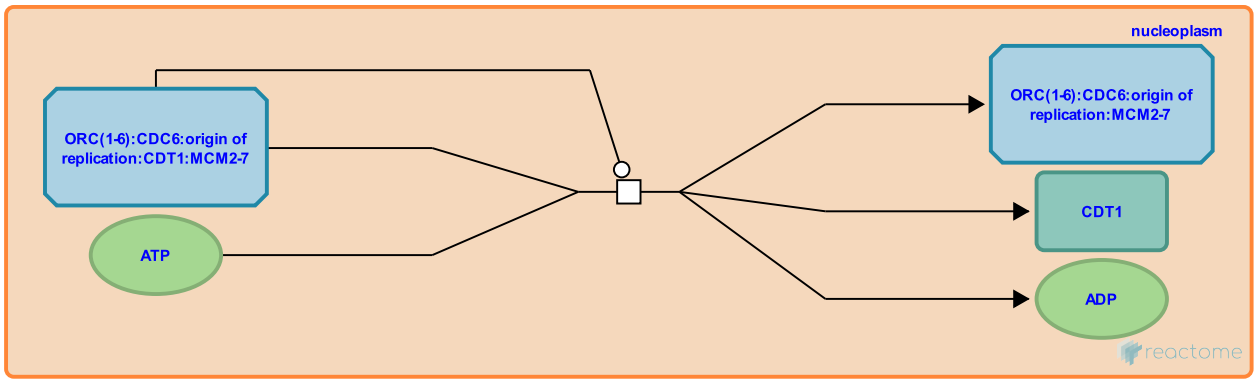
Location: Assembly of the pre-replicative complex

Stable identifier: R-HSA-9749350

Type: transition

Compartments: nucleoplasm

Inferred from: ATP-dependent release of CDT1 from the OCCM complex in budding yeast (Saccharomyces cerevisiae)



Based on studies in budding yeast, once the initial complex of ORC(1-6), CDC6, CDT1 and MCM2-7 (OCCM) is formed, CDT1 is released from DNA in an ATP-dependent manner. The ATPase activity of CDC6 is necessary for CDT1 release, but ATPase activities of other ATPases in the complex (e.g. ORC1) may contribute to CDT1 release. ORC6 is necessary for the retention of MCM2-7 after ATP hydrolysis (Fernández-Cid et al. 2013).

Preceded by: CDT1-mediated loading of MCM2-7 to replication origins

Followed by: CDT1-mediated formation of MCM2-7 double hexamer at the replication origin

Editions

2021-10-27	Authored	Kusic-Tisma, J.
2021-11-03	Edited	Orlic-Milacic, M.

CDT1-mediated formation of MCM2-7 double hexamer at the replication origin ↗

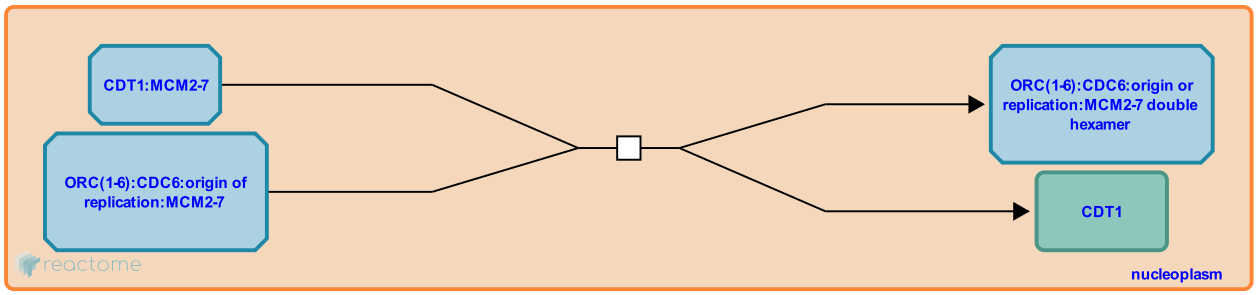
Location: Assembly of the pre-replicative complex

Stable identifier: R-HSA-9749351

Type: transition

Compartments: nucleoplasm

Inferred from: CTD1-mediated formation of MCM2-7 double hexamers at the replication origins in budding yeast (Saccharomyces cerevisiae)



Based on studies in budding yeast, after CDT1-mediated loading of the MCM2-7 complex to CDC6 bound to the ORC(1-6) complex at the replication origin and ATP-dependent release of CDT1, another complex of CDT1 and MCM2-7 is loaded, resulting in the formation of the salt-stable double hexamer of MCM2-7 (Fernández-Cid et al. 2013). MCM2-7 double hexamers are connected head-to-head via their N-terminal rings. DNA runs through a central channel in the double hexamer (Remus et al. 2009). In a study using human proteins, it was suggested that geminin inhibits the formation of salt-resistant pre-replicative complexes (Wu et al. 2014), possibly by interfering with CDT1-mediated loading of the second MCM2-7 hexamer.

Preceded by: ATP-dependent release of CDT1 from the OCCM complex

Editions

2021-10-27	Authored	Kusic-Tisma, J.
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