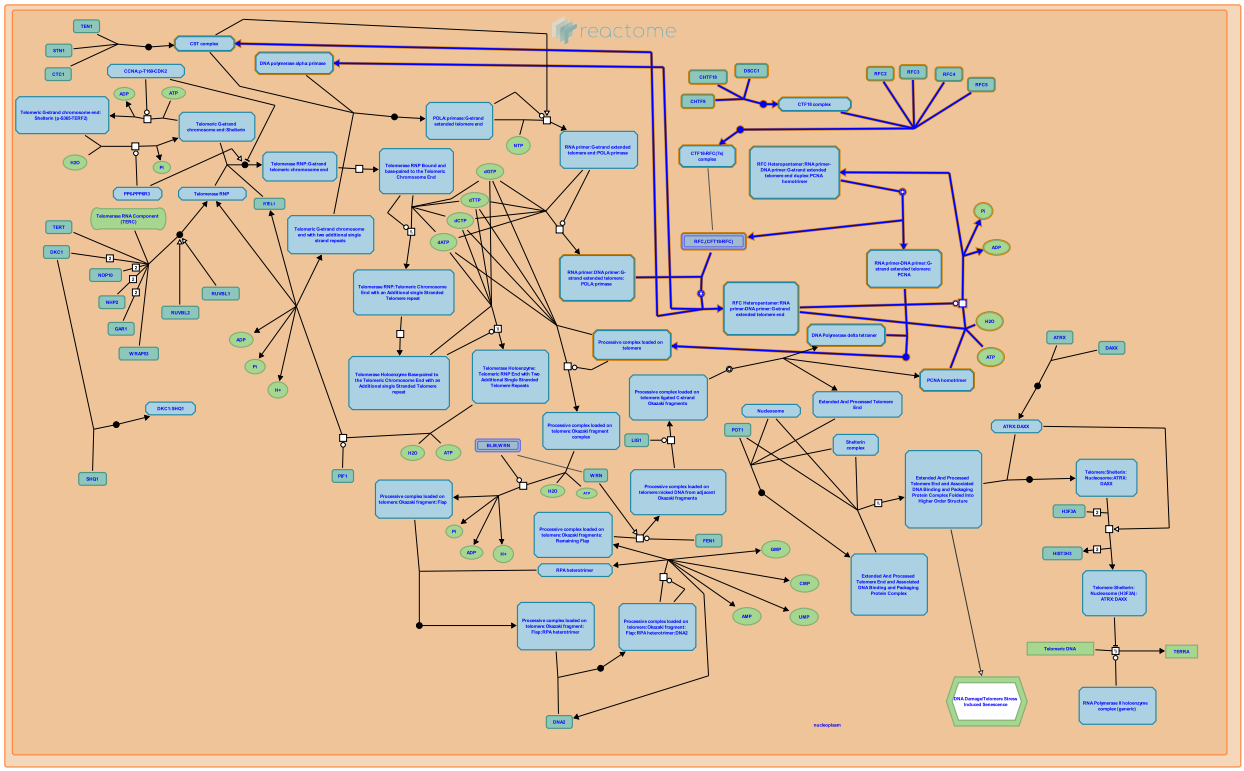
Polymerase switching on the C-strand of the telomere



Blackburn, EH., D'Eustachio, P., Gillespie, ME., Hayashi, MT., Orlic-Milacic, M., Price, C., Seidel, J.

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16/05/2024

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. ↗

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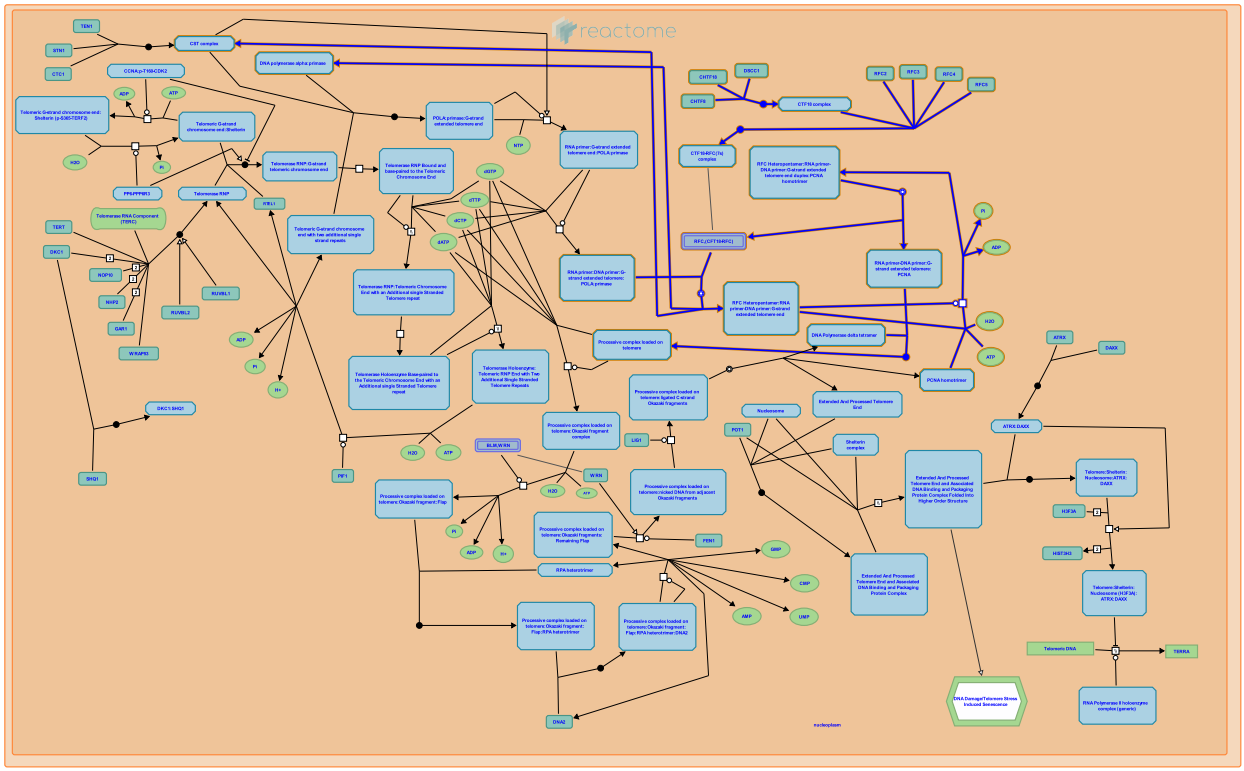
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Polymerase switching on the C-strand of the telomere ↗

Stable identifier: R-HSA-174411

Compartments: nucleoplasm



After the primers are synthesized on the G-Rich strand, Replication Factor C binds to the 3'-end of the initiator DNA to trigger polymerase switching. The non-processive nature of pol alpha catalytic activity and the tight binding of Replication Factor C to the primer-template junction presumably lead to the turnover of the pol alpha:primase complex. After the Pol alpha-primase primase complex is displaced from the primer, the proliferating cell nuclear antigen (PCNA) binds to form a "sliding clamp" structure. Replication Factor C then dissociates, and DNA polymerase delta binds and catalyzes the processive synthesis of DNA.

Literature references

Stillman, B., Tsurimoto, T. (1990). Functions of replication factor C and proliferating-cell nuclear antigen: functional similarity of DNA polymerase accessory proteins from human cells and bacteriophage T4. *Proc Natl Acad Sci U S A, 87*, 1023-7. ↗

Hurwitz, J., Kwong, AD., Pan, ZQ., Lee, SH. (1991). Studies on the activator 1 protein complex, an accessory factor for proliferating cell nuclear antigen-dependent DNA polymerase delta. *J Biol Chem, 266*, 594-602. ↗

Stillman, B., Tsurimoto, T. (1991). Replication factors required for SV40 DNA replication in vitro. II. Switching of DNA polymerase alpha and delta during initiation of leading and lagging strand synthesis. *J Biol Chem, 266*, 1961-8. ↗

Editions

2006-03-10	Authored	Blackburn, EH., Seidel, J.
2006-07-13	Reviewed	Price, C.
2009-06-03	Revised	D'Eustachio, P.
2019-12-02	Revised	Orlic-Milacic, M.
2020-04-29	Reviewed	Hayashi, MT.
2020-05-04	Edited	Orlic-Milacic, M.

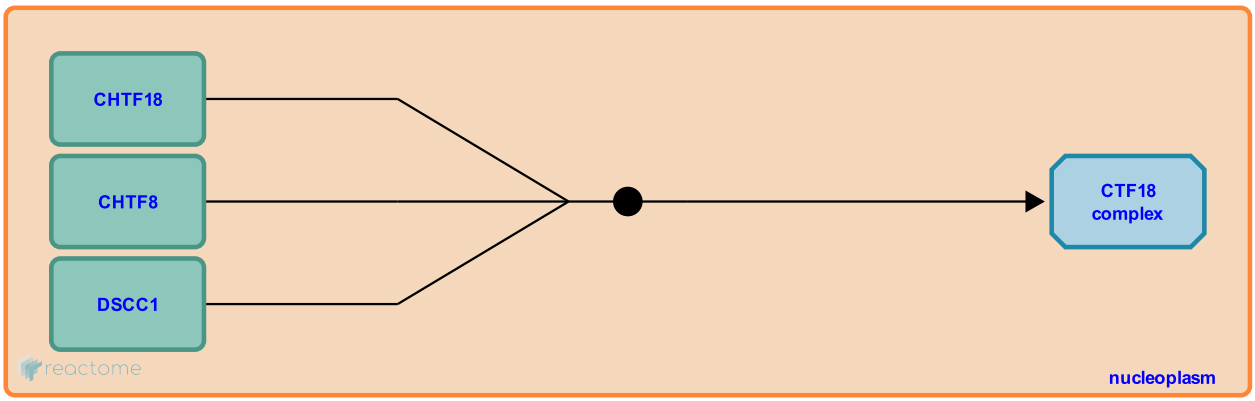
Formation of the CTF18 complex ↗

Location: Polymerase switching on the C-strand of the telomere

Stable identifier: R-HSA-9668904

Type: binding

Compartments: nucleoplasm



CHTF18 (CTF18), a homolog of the RFC complex subunit RFC1, binds to CHTF8 (CTF8) and DSCC1 (DCC1) to form the evolutionarily conserved CTF18 complex (Merkle et al. 2003, Bermudez et al. 2003). Formation of a heterodimer between DSCC1 and CHTF8 may precede formation of a heterotrimer (Bermudez et al. 2003).

Followed by: Formation of the CTF18-RFC(7s) complex

Literature references

Karnitz, LM., Merkle, CJ., Henry-Sánchez, JT., Chen, J. (2003). Cloning and characterization of hCTF18, hCTF8, and hDCC1. Human homologs of a Saccharomyces cerevisiae complex involved in sister chromatid cohesion establishment. *J. Biol. Chem., 278*, 30051-6. ↗

Hurwitz, J., Ozato, K., Yokomori, K., Maniwa, Y., Tappin, I., Bermudez, VP. (2003). The alternative Ctf18-Dcc1-Ctf8-replication factor C complex required for sister chromatid cohesion loads proliferating cell nuclear antigen onto DNA. *Proc. Natl. Acad. Sci. U.S.A., 100*, 10237-42. ↗

Editions

2019-12-02	Authored	Orlic-Milacic, M.
2020-04-29	Reviewed	Hayashi, MT.
2020-05-04	Edited	Orlic-Milacic, M.

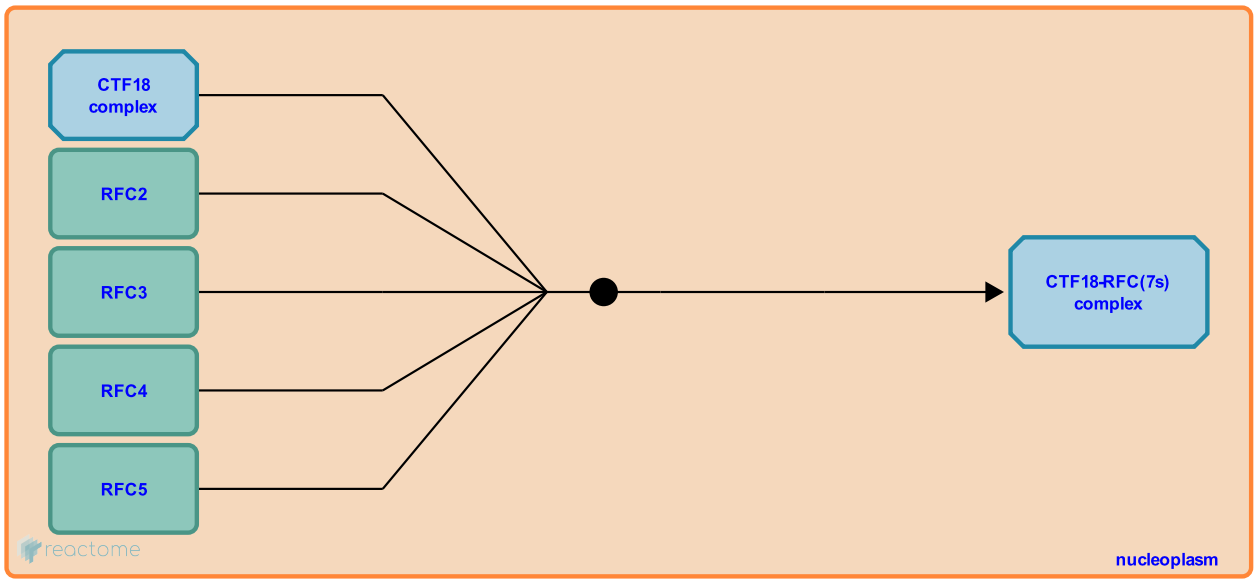
Formation of the CTF18-RFC(7s) complex ↗

Location: Polymerase switching on the C-strand of the telomere

Stable identifier: R-HSA-9668902

Type: binding

Compartments: nucleoplasm



The CTF18 complex, composed of RFC1 homolog CHTF18 (CTF18), CHTF8 (CTF8) and DSCC1 (DCC1) binds to RFC2, RFC3, RFC4 and RFC5 to form the evolutionarily conserved heteroheptameric CTF18-RFC complex (CTF18-RFC(7s)), in which the RFC1 subunit of the RFC complex is replaced with the CTF18 complex (Bermudez et al. 2003, Merkle et al. 2003). CHTF18 is able to form a heteropentameric CTF18-RFC complex (CTF18-RFC(5s)) with RFC2, RFC3, RFC4 and RFC5 in the absence of CHTF8 and DSCC1 (Bermudez et al. 2003, Shiomi et al. 2004).

Preceded by: Formation of the CTF18 complex

Followed by: RFC binding displaces Pol Alpha on the C-strand of the telomere

Literature references

Karnitz, LM., Merkle, CJ., Henry-Sánchez, JT., Chen, J. (2003). Cloning and characterization of hCTF18, hCTF8, and hDCC1. Human homologs of a Saccharomyces cerevisiae complex involved in sister chromatid cohesion establishment. *J. Biol. Chem., 278*, 30051-6. ↗

Hurwitz, J., Ozato, K., Yokomori, K., Maniwa, Y., Tappin, I., Bermudez, VP. (2003). The alternative Ctf18-Dcc1-Ctf8-replication factor C complex required for sister chromatid cohesion loads proliferating cell nuclear antigen onto DNA. *Proc. Natl. Acad. Sci. U.S.A., 100*, 10237-42. ↗

Shinozaki, A., Tsurimoto, T., Obuse, C., Sugimoto, K., Usukura, J., Shiomi, Y. (2004). The reconstituted human Chl12-RFC complex functions as a second PCNA loader. *Genes Cells, 9*, 279-90. ↗

Editions

2019-12-02	Authored	Orlic-Milacic, M.
2020-04-29	Reviewed	Hayashi, MT.
2020-05-04	Edited	Orlic-Milacic, M.

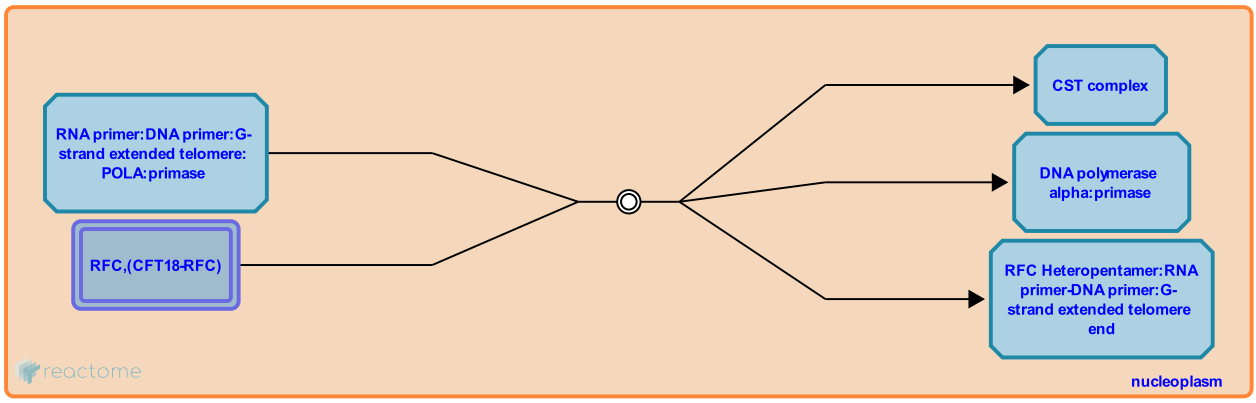
RFC binding displaces Pol Alpha on the C-strand of the telomere ↗

Location: Polymerase switching on the C-strand of the telomere

Stable identifier: R-HSA-174452

Type: dissociation

Compartments: nucleoplasm



Once the RNA-DNA primer is synthesized, replication factor C (RFC) initiates a reaction called "polymerase switching"; pol delta, the processive enzyme, replaces pol alpha, the priming enzyme. RFC binds to the 3'-end of the RNA-DNA primer on the Primosome, to displace the pol alpha primase complex. The binding of RFC triggers the binding of the primer recognition complex (Tsurimoto and Stillman 1991, Maga et al. 2000, Mossi et al. 2000). RFC is recruited to telomeres via interaction with 5'-phosphate ends of a telomere repeat sequence (Uchiumi et al. 1996, Uchiumi et al. 1999). In budding yeast, the alternative evolutionarily conserved RFC complex in which the RFC1 subunit is substituted with the CTF18 complex (composed of CHTF18, CHTF8 and DSCC1) plays a critical role in telomere maintenance (Hiraga et al. 2006, Gao et al. 2014). The CTF18-RFC complex is also implicated in telomere maintenance in fission yeast (Khair et al. 2010). It was shown that the human CTF18-RFC complex has a redundant function with the RFC pentamer in PCNA loading and DNA replication (Bermudez et al. 2003), but its role in human telomere maintenance has not been studied. Mouse CFT18 complex is necessary for proper development of germ cells (Berkowitz et al. 2012).

Preceded by: Formation of the CTF18-RFC(7s) complex

Followed by: Loading of PCNA - Sliding Clamp Formation on the C-strand of the telomere

Literature references

Tanuma, S., Uchiumi, F., Ohta, T. (1996). Replication factor C recognizes 5'-phosphate ends of telomeres. *Biochem. Biophys. Res. Commun., 229*, 310-5. ↗

Tanuma, Si., Uchiumi, F., Watanabe, M. (1999). Characterization of telomere-binding activity of replication factor C large subunit p140. *Biochem. Biophys. Res. Commun., 258*, 482-9. ↗

Editions

2006-03-10	Authored	Blackburn, EH., Seidel, J.
2006-07-13	Reviewed	Price, C.
2019-12-18	Revised	Orlic-Milacic, M.
2020-01-03	Reviewed	Gillespie, ME.
2020-04-29	Reviewed	Hayashi, MT.
2020-05-04	Edited	Orlic-Milacic, M.

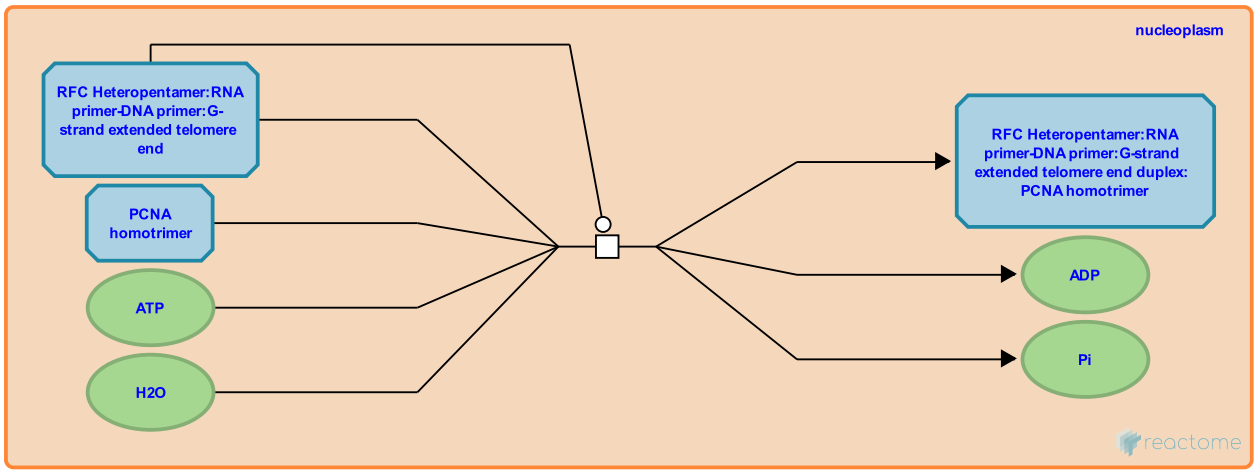
Loading of PCNA - Sliding Clamp Formation on the C-strand of the telomere ↗

Location: Polymerase switching on the C-strand of the telomere

Stable identifier: R-HSA-174439

Type: transition

Compartments: nucleoplasm



The binding of the primer recognition complex involves the loading of the proliferating cell nuclear antigen (PCNA). Replication Factor C (RFC) transiently opens the PCNA toroid in an ATP-dependent reaction, and then allows PCNA to re-close around the double helix adjacent to the primer terminus. This leads to the formation of the "sliding clamp" (Tsurimoto et al. 1990, Mossi and Hubscher 1998). In a human telomere replication model, RFC-mediated PCNA loading increases the processivity of telomeric C-strand synthesis, but does not eliminate polymerase delta stalling on the G-rich template (Lormand et al. 2013).
Interaction of RTEL1 with PCNA is needed for telomere replication and maintenance of telomere integrity (Vannier et al. 2013).

Preceded by: RFC binding displaces Pol Alpha on the C-strand of the telomere

Followed by: RFC dissociates after sliding clamp formation on the C-strand of the telomere

Literature references

Ding, H., Petalcorin, MI., Sandhu, S., Boulton, SJ., Wu, X., Vannier, JB. et al. (2013). RTEL1 is a replisome-associated helicase that promotes telomere and genome-wide replication. *Science, 342*, 239-42. ↗

Opresko, PL., Kaur, P., Wang, H., Kunkel, TA., Buncher, N., Lee, MY. et al. (2013). DNA polymerase δ stalls on telomeric lagging strand templates independently from G-quadruplex formation. *Nucleic Acids Res., 41*, 10323-33. ↗

Editions

2006-03-10	Authored	Blackburn, EH., Seidel, J.
2006-07-13	Reviewed	Price, C.
2020-04-29	Reviewed	Hayashi, MT.
2020-05-04	Edited	Orlic-Milacic, M.

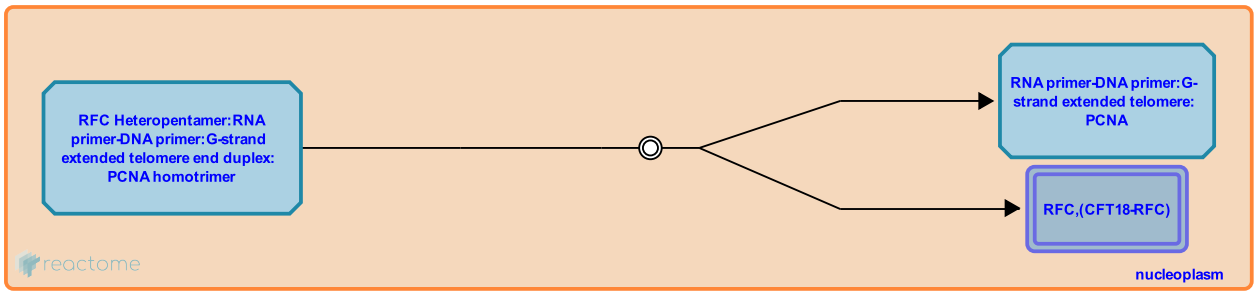
RFC dissociates after sliding clamp formation on the C-strand of the telomere ↗

Location: Polymerase switching on the C-strand of the telomere

Stable identifier: R-HSA-174447

Type: dissociation

Compartments: nucleoplasm



It is assumed that, as shown for generic DNA replication (Podust et al. 1998), the RFC complex dissociates from PCNA following sliding clamp formation at the telomere, and the DNA toroid alone tethers pol delta to the DNA.

Preceded by: Loading of PCNA - Sliding Clamp Formation on the C-strand of the telomere

Followed by: Formation of Processive Complex on the C-strand of the telomere

Literature references

Podust, VN., Tiwari, N., Stephan, S. (1998). Replication factor C disengages from proliferating cell nuclear antigen (PCNA) upon sliding clamp formation, and PCNA itself tethers DNA polymerase delta to DNA. *J Biol Chem, 273*, 31992-9. ↗

Editions

2006-03-10	Authored	Blackburn, EH., Seidel, J.
2006-07-13	Reviewed	Price, C.
2019-12-18	Revised	Orlic-Milacic, M.
2020-01-03	Reviewed	Gillespie, ME.
2020-04-29	Reviewed	Hayashi, MT.
2020-05-04	Edited	Orlic-Milacic, M.

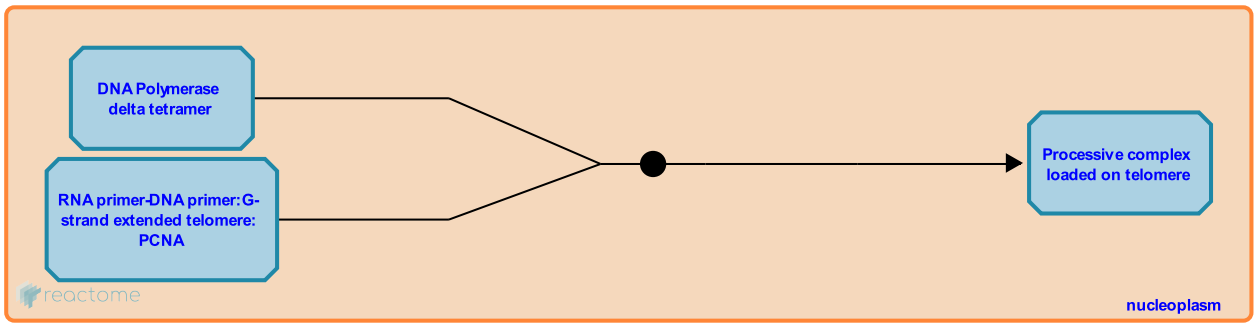
Formation of Processive Complex on the C-strand of the telomere ↗

Location: Polymerase switching on the C-strand of the telomere

Stable identifier: R-HSA-174448

Type: binding

Compartments: nucleoplasm



The loading of proliferating cell nuclear antigen (PCNA) leads to recruitment of pol delta, the process of polymerase switching. Human PCNA is a homotrimer of 36 kDa subunits that form a toroidal structure. The loading of PCNA by RFC is a key event in the transition from the priming mode to the extension mode of DNA synthesis. The processive complex is composed of the pol delta holoenzyme and PCNA (Lee and Hurwitz 1990, Podust et al. 1998). While PCNA increases the processivity of the DNA polymerase delta during telomeric C-strand synthesis in a human telomere replication model, it does not eliminate the DNA polymerase delta stalling on the G-rich template (Lormand et al. 2013).

Preceded by: RFC dissociates after sliding clamp formation on the C-strand of the telomere

Literature references

Podust, VN., Tiwari, N., Stephan, S. (1998). Replication factor C disengages from proliferating cell nuclear antigen (PCNA) upon sliding clamp formation, and PCNA itself tethers DNA polymerase delta to DNA. *J Biol Chem, 273*, 31992-9. ↗

Opresko, PL., Kaur, P., Wang, H., Kunkel, TA., Buncher, N., Lee, MY. et al. (2013). DNA polymerase δ stalls on telomeric lagging strand templates independently from G-quadruplex formation. *Nucleic Acids Res., 41*, 10323-33. ↗

Hurwitz, J., Lee, SH. (1990). Mechanism of elongation of primed DNA by DNA polymerase delta, proliferating cell nuclear antigen, and activator 1. *Proc Natl Acad Sci U S A, 87*, 5672-6. ↗

Editions

2006-03-10	Authored	Blackburn, EH., Seidel, J.
2006-07-13	Reviewed	Price, C.
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