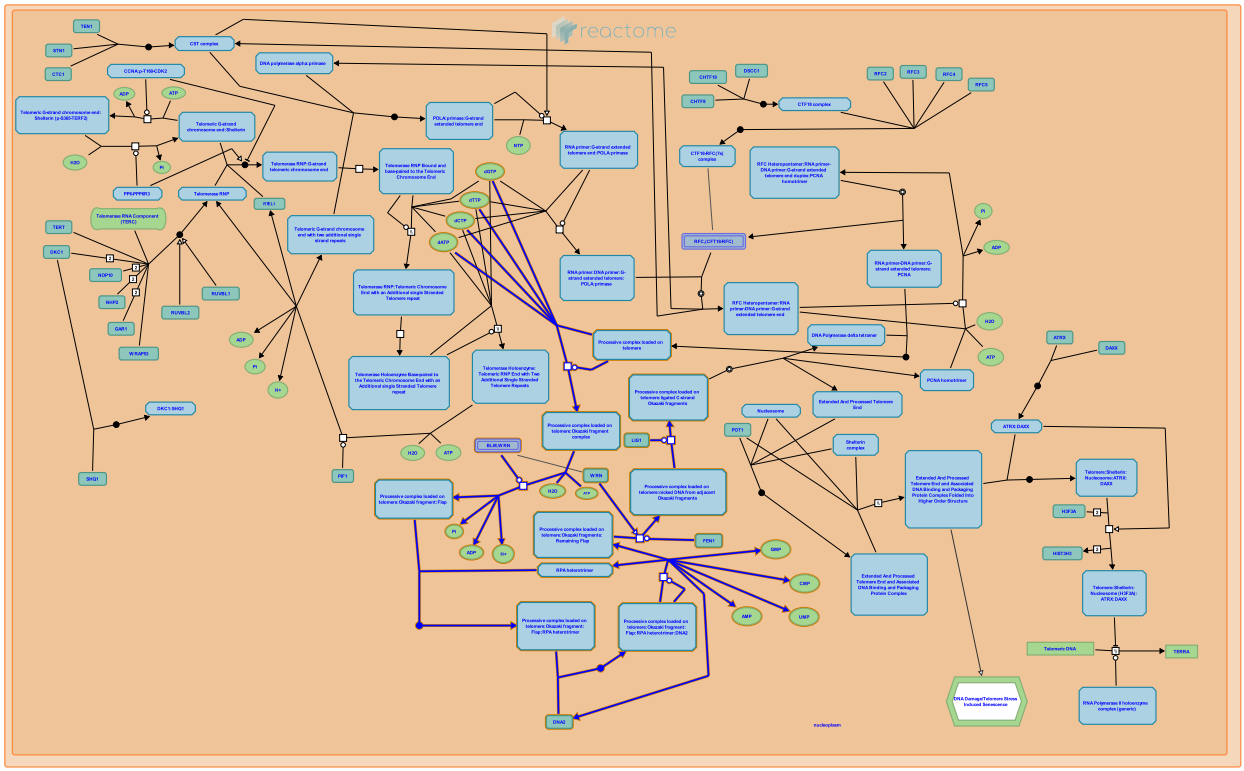
Processive synthesis on the C-strand of the telomere



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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.

01/05/2024

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. ↗

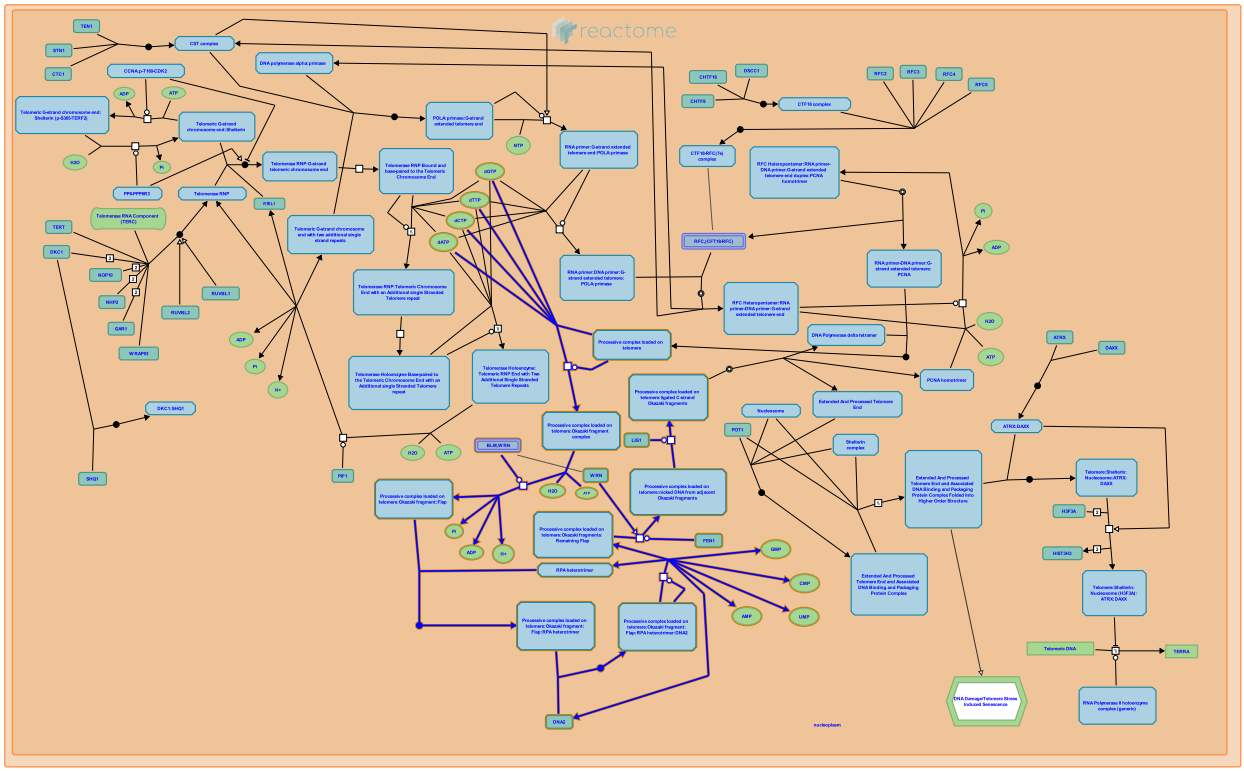
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Processive synthesis on the C-strand of the telomere ↗

Stable identifier: R-HSA-174414

Compartments: nucleoplasm



Once polymerase switching from pol alpha to pol delta is complete the processive synthesis of a short run of DNA called an Okazaki fragment begins. DNA synthesis is discontinuous and as the extending Okazaki fragment reaches the RNA primer, this primer is folded into a single-stranded flap, which is removed by endonucleases. The process of extension is completed by the ligation of adjacent Okazaki fragments.

Literature references

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

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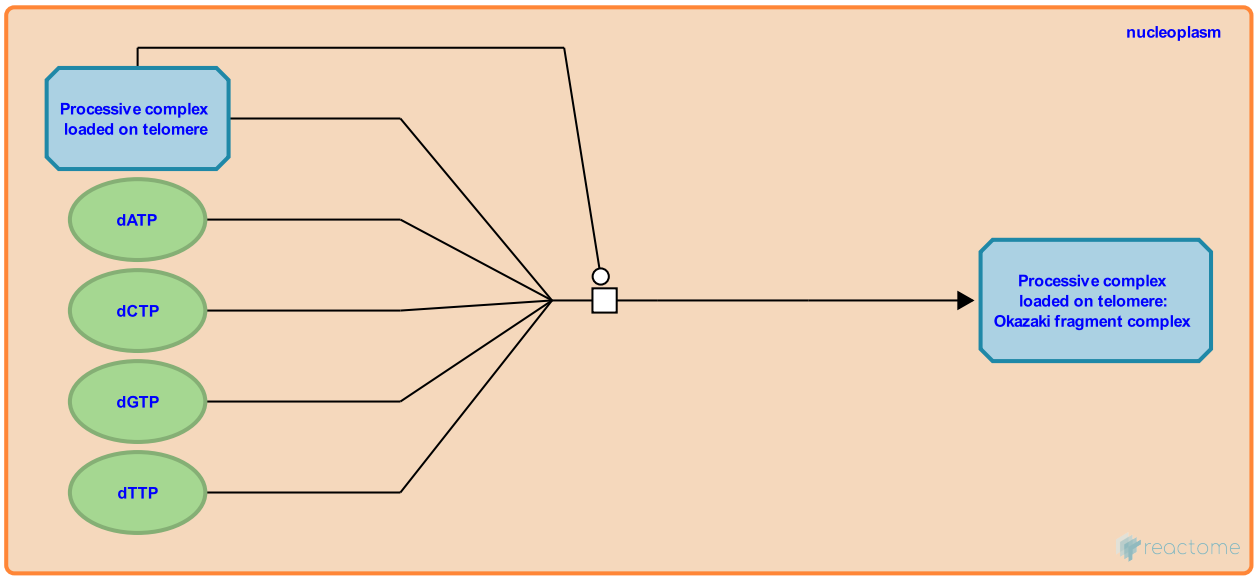
Formation of C-strand Okazaki fragments ↗

Location: Processive synthesis on the C-strand of the telomere

Stable identifier: R-HSA-174444

Type: transition

Compartments: nucleoplasm



After RFC initiates the assembly of the primer recognition complex, the complex of pol delta and PCNA is responsible for incorporating the additional nucleotides prior to the position of the next downstream initiator RNA primer. On the lagging strand, short discontinuous segments of DNA, called Okazaki fragments, are synthesized on RNA primers. The average length of the Okazaki fragments is 100 nucleotides. Polymerase switching is a key event that allows the processive synthesis of DNA by the pol delta and PCNA complex (Lee and Hurwitz 1990, Tsurimoto and Stillman 1991, Nethanel et al. 1992, Brown and Campbell 1993, Waga et al.1994, Bambara et al. 1997). PCNA increases the processivity of the DNA polymerase delta during telomeric C-strand synthesis in a human telomere replication model, but it does not eliminate the DNA polymerase delta stalling on the G-rich template (Lormand et al. 2013).

Followed by: Formation of the Flap Intermediate on the C-strand

Literature references

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. ↗

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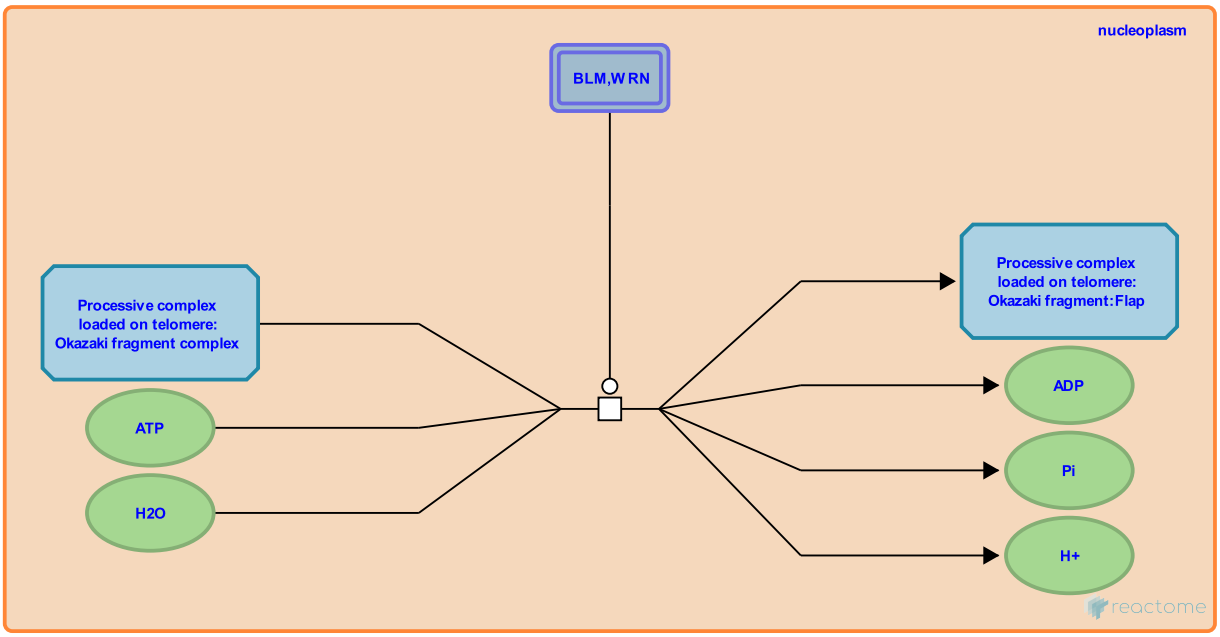
Formation of the Flap Intermediate on the C-strand ↗

Location: Processive synthesis on the C-strand of the telomere

Stable identifier: R-HSA-174438

Type: transition

Compartments: nucleoplasm



When the polymerase delta:PCNA complex reaches a downstream Okazaki fragment, strand displacement synthesis occurs. The primer containing 5'-terminus of the downstream Okazaki fragment is folded into a single-stranded flap (Podust et al. 1995, Bae et al. 2001, Maga et al. 2001). The helicase activity of either WRN (Werner syndrome protein) or BLM (Bloom syndrome helicase) is needed for DNA polymerase delta progression and strand displacement synthesis across G-rich telomeric repeats during lagging strand (C-strand) synthesis (Li et al. 2017).

Preceded by: Formation of C-strand Okazaki fragments

Followed by: Removal of the Flap Intermediate from the C-strand

Literature references

Reddy, S., Li, B., Comai, L. (2017). The Werner Syndrome Helicase Coordinates Sequential Strand Displacement and FEN1-Mediated Flap Cleavage during Polymerase δ Elongation. *Mol. Cell. Biol., 37*. ↗

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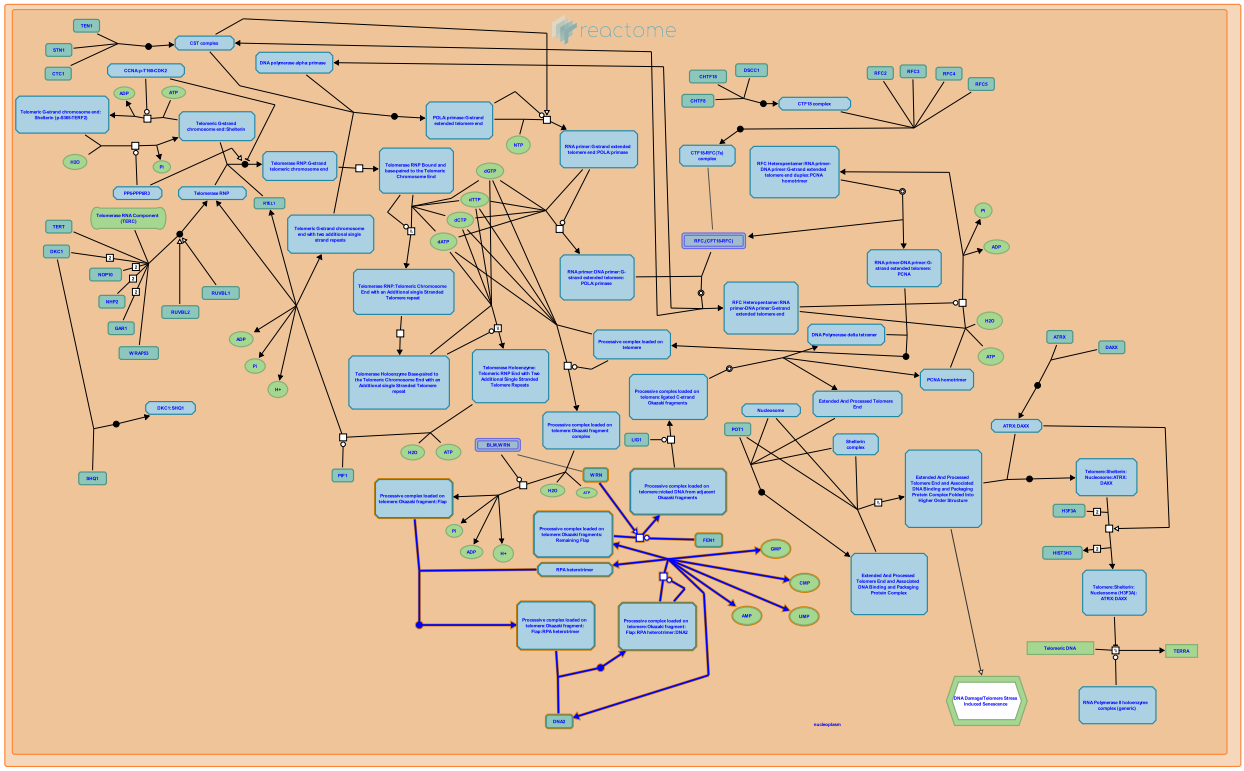
Removal of the Flap Intermediate from the C-strand ↗

Location: Processive synthesis on the C-strand of the telomere

Stable identifier: R-HSA-174437

Compartments: nucleoplasm



Two endonucleases, Dna2 and flap endonuclease 1 (FEN-1), are responsible for resolving the nascent flap structure (Tsurimoto and Stillman 1991). The Dna2 endonuclease/helicase in yeast is a monomer of approximately 172 kDa. Human FEN-1 is a single polypeptide of approximately 42 kDa. Replication Protein A regulates the switching of endonucleases during the removal of the displaced flap (Tsurimoto et al.1991).

Literature references

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. ↗

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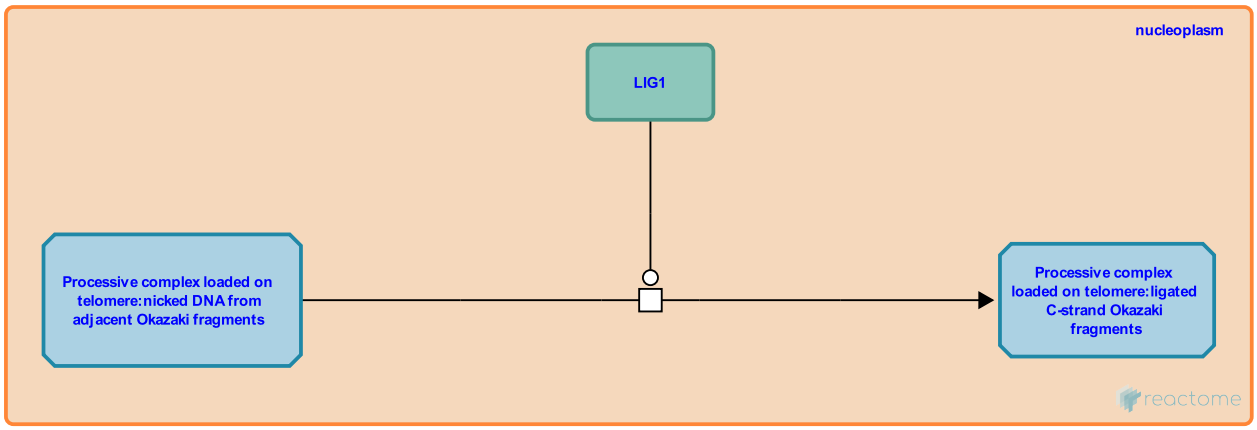
Joining of adjacent Okazaki fragments of the C-strand ↗

Location: Processive synthesis on the C-strand of the telomere

Stable identifier: R-HSA-174456

Type: transition

Compartments: nucleoplasm



Removal of the flap by FEN1 leads to the generation of a nick between the 3'-end of the upstream Okazaki fragment and the 5'-end of the downstream Okazaki fragment. DNA ligase I (LIG1) then seals the nicks between adjacent processed Okazaki fragments to generate intact double-stranded DNA (Turchi and Bambara 1993, Bambara et al. 1997, Waga and Stillman 1998, Levin et al. 2000). LIG1 is necessary for ligation of Okazaki fragments at the lagging telomere DNA strand. LIG1 deficiency results in telomere instability, manifested through telomere sister fusions, which is a consequence of DNA breaks in the lagging strand (C-strand) (Le Chalony et al. 2012).

Literature references

Le Chalony, C., Gross, J., Gauthier, LR., Boussin, FD., Hoffschir, F., Biard, DS. et al. (2012). Partial complementation of a DNA ligase I deficiency by DNA ligase III and its impact on cell survival and telomere stability in mammalian cells. *Cell. Mol. Life Sci., 69*, 2933-49. ↗

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2006-03-10	Authored	Blackburn, EH., Seidel, J.
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