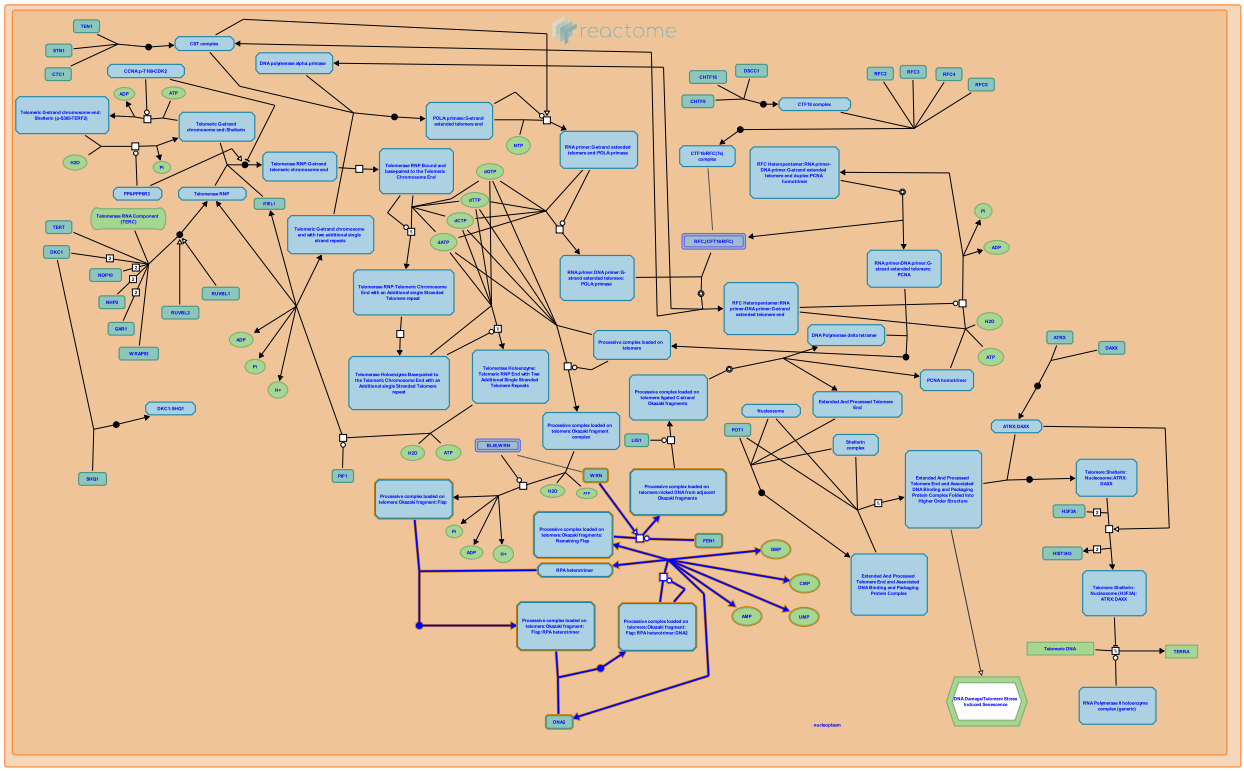
Removal of the Flap Intermediate from the C-strand



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

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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. ↗

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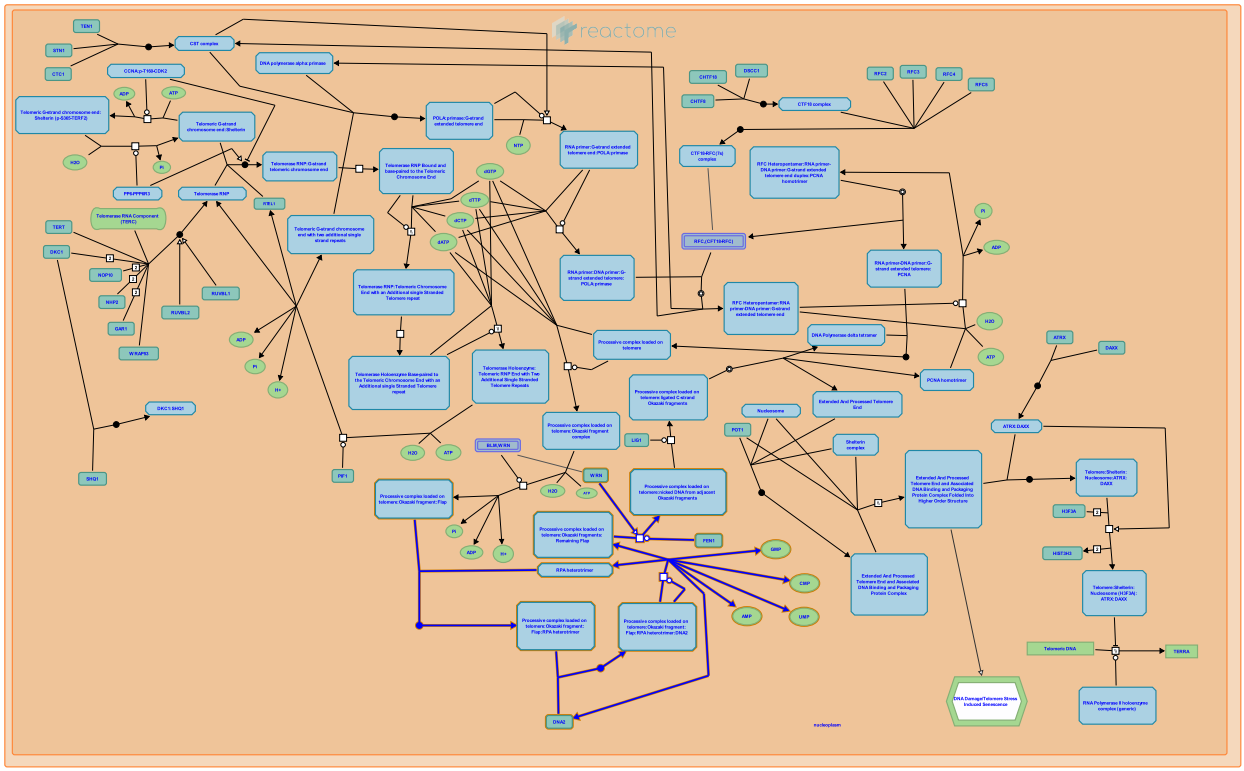
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Removal of the Flap Intermediate from the C-strand ↗

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. ↗

Editions

2006-03-10	Authored	Blackburn, EH., Seidel, J.
2006-07-13	Reviewed	Price, C.
2009-06-03	Revised	D'Eustachio, P.
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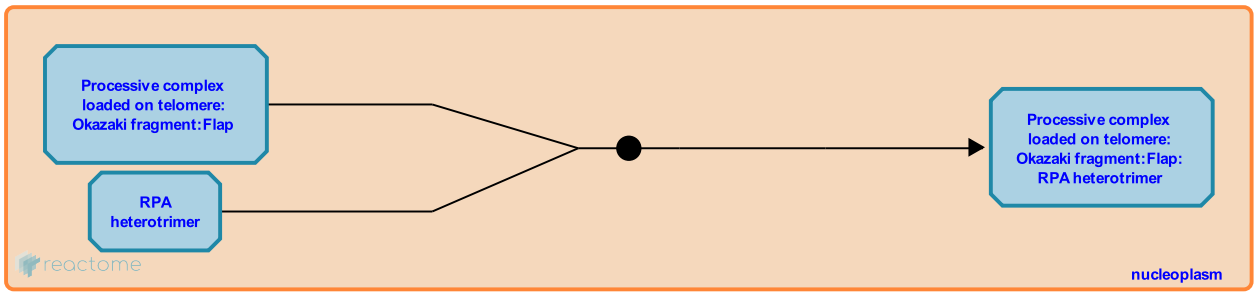
RPA binds to the Flap on the C-strand ↗

Location: Removal of the Flap Intermediate from the C-strand

Stable identifier: R-HSA-174445

Type: binding

Compartments: nucleoplasm



The first step in the removal of the flap intermediate is the binding of Replication Protein A (RPA) to the long flap structure. RPA is a eukaryotic single-stranded DNA binding protein (Bae et al. 2001). Binding of RPA to the single strand DNA during telomeric strand displacement synthesis is necessary for the recruitment of DNA2. DNA2 is a helicase/endonuclease that resolves G quadruplexes (G4), which are DNA structures that commonly form in polyguanine-rich telomeric DNA sequences (Masuda-Sasa et al. 2008). DNA2 also removes the initiator RNA primers of Okazaki fragments (Bae et al. 2001).

Followed by: Recruitment of DNA2 endonuclease to the C strand

Literature references

Peng, XP., Masuda-Sasa, T., Polaczek, P., Chen, L., Campbell, JL. (2008). Processing of G4 DNA by Dna2 helicase/nuclease and replication protein A (RPA) provides insights into the mechanism of Dna2/RPA substrate recognition. *J. Biol. Chem., 283*, 24359-73. ↗

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2006-03-10	Authored	Blackburn, EH., Seidel, J.
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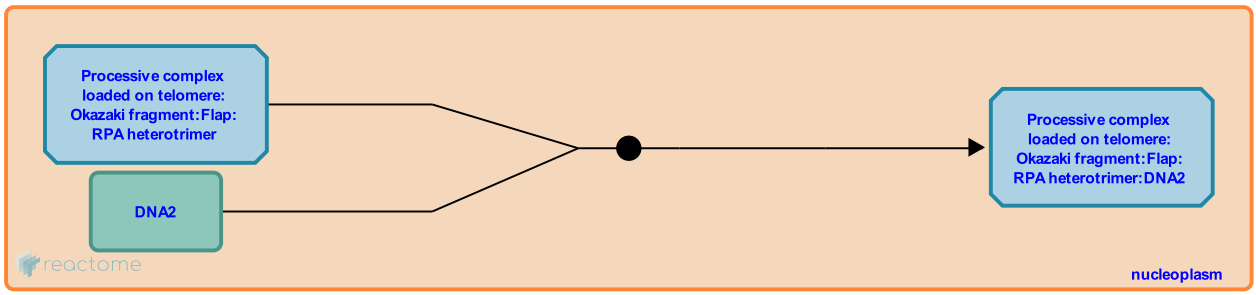
Recruitment of DNA2 endonuclease to the C strand ↗

Location: Removal of the Flap Intermediate from the C-strand

Stable identifier: R-HSA-174451

Type: binding

Compartments: nucleoplasm



After RPA binds the long flap, it recruits the DNA2 helicase/endonuclease which removes the initiator RNA primers of Okazaki fragments (Bae et al. 2001). DNA2 is also needed to resolve G quadruplexes (G4), DNA structures commonly formed by polyguanine-rich telomeric DNA sequences (Masuda-Sasa et al. 2008, Lin et al. 2013).

Preceded by: RPA binds to the Flap on the C-strand

Followed by: Removal of RNA primer and dissociation of RPA and Dna2 from the C-strand

Literature references

Campbell, J., Dai, H., Hu, J., Sampathi, S., Shin-Ya, K., Zheng, L. et al. (2013). Mammalian DNA2 helicase/nuclease cleaves G-quadruplex DNA and is required for telomere integrity. *EMBO J., 32*, 1425-39. ↗

Peng, XP., Masuda-Sasa, T., Polaczek, P., Chen, L., Campbell, JL. (2008). Processing of G4 DNA by Dna2 helicase/nuclease and replication protein A (RPA) provides insights into the mechanism of Dna2/RPA substrate recognition. *J. Biol. Chem., 283*, 24359-73. ↗

Editions

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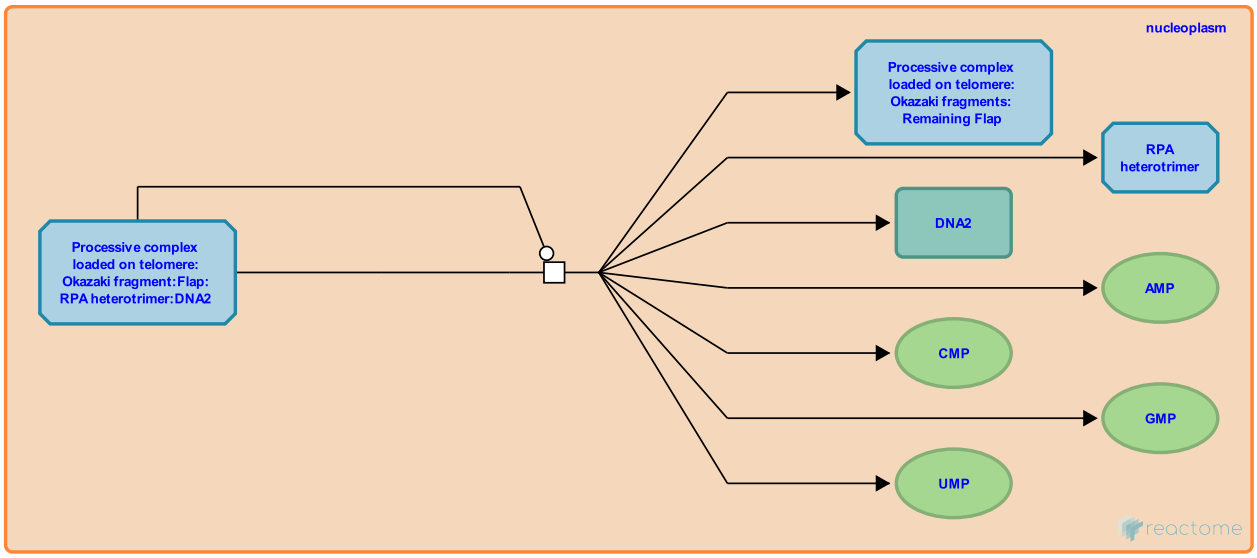
Removal of RNA primer and dissociation of RPA and Dna2 from the C-strand ↗

Location: Removal of the Flap Intermediate from the C-strand

Stable identifier: R-HSA-174441

Type: transition

Compartments: nucleoplasm



The DNA2 endonuclease removes the initiator RNA along with several downstream deoxyribonucleotides. The cleavage of the single-stranded RNA substrate results in the disassembly of RPA and DNA2. The current data for the role of the DNA2 endonuclease has been derived from studies of yeast (Budd et al. 2000, Bae et al. 2001) and Xenopus DNA2 (Liu et al. 2000, Liao et al. 2008). DNA2-mediated cleavage of G-quadruplexes (G4), DNA structures commonly formed by polyguanine-rich telomeric DNA sequences, is necessary for completion of telomeric DNA synthesis (Masuda-Sasa et al. 2008, Lin et al. 2013).

Preceded by: Recruitment of DNA2 endonuclease to the C strand

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

Literature references

Campbell, J., Dai, H., Hu, J., Sampathi, S., Shin-Ya, K., Zheng, L. et al. (2013). Mammalian DNA2 helicase/nuclease cleaves G-quadruplex DNA and is required for telomere integrity. *EMBO J., 32*, 1425-39. ↗

Peng, XP., Masuda-Sasa, T., Polaczek, P., Chen, L., Campbell, JL. (2008). Processing of G4 DNA by Dna2 helicase/nuclease and replication protein A (RPA) provides insights into the mechanism of Dna2/RPA substrate recognition. *J. Biol. Chem., 283*, 24359-73. ↗

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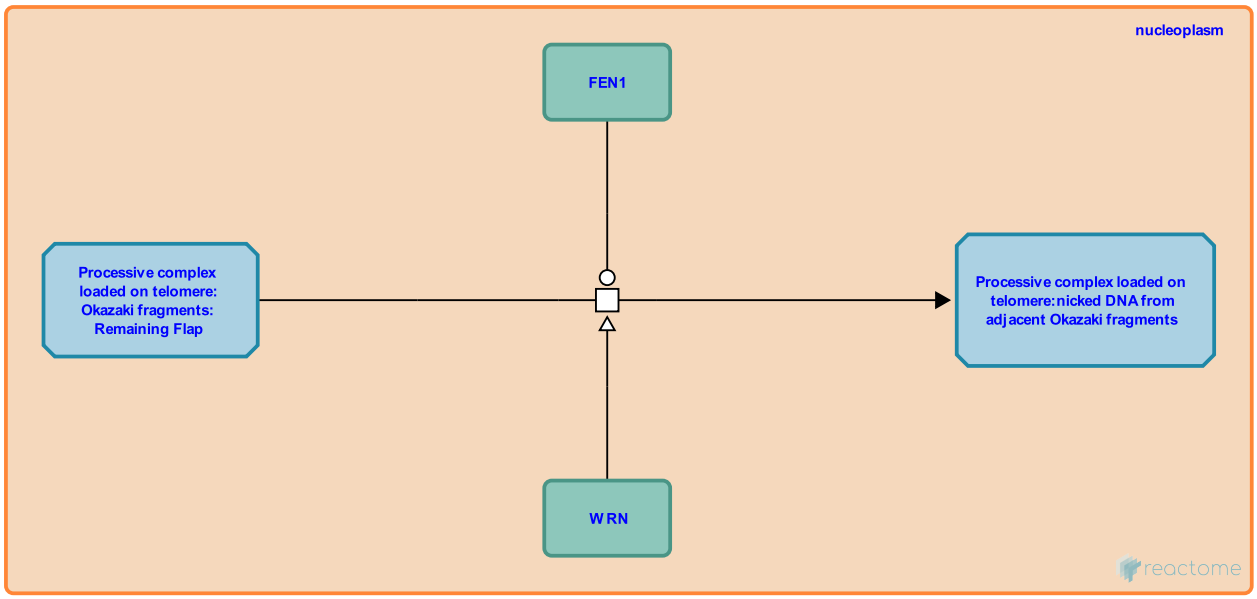
Removal of remaining Flap from the C-strand ↗

Location: Removal of the Flap Intermediate from the C-strand

Stable identifier: R-HSA-174446

Type: transition

Compartments: nucleoplasm



The remaining flap, which is too short to support RPA binding, is then processed by FEN1. There is evidence that binding of RPA to the displaced end of the RNA-containing Okazaki fragment prevents FEN1 from accessing the substrate. FEN1 is a structure-specific endonuclease that cleaves near the base of the flap at a position one nucleotide into the annealed region. Biochemical studies have shown that the preferred substrate for FEN1 consists of a one-nucleotide 3'-tail on the upstream primer in addition to the 5'-flap of the downstream primer (Harrington and Lieber 1994, Harrington and Lieber 1995, Murante et al. 1996, Lieber 1997, Kaiser et al. 1999, Xu et al. 2000, Kao et al. 2002). The interaction of FEN1 with WRN, a RECQ family DNA helicase, is needed for successful flap cleavage during telomeric strand displacement synthesis (Saharia et al. 2010, Li et al. 2017).

Preceded by: Removal of RNA primer and dissociation of RPA and Dna2 from the C-strand

Literature references

Chiappinelli, KB., Teasley, DC., Saharia, A., Dao, B., Stewart, SA., Duxin, JP. (2010). FEN1 ensures telomere stability by facilitating replication fork re-initiation. *J. Biol. Chem., 285*, 27057-66. ↗

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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