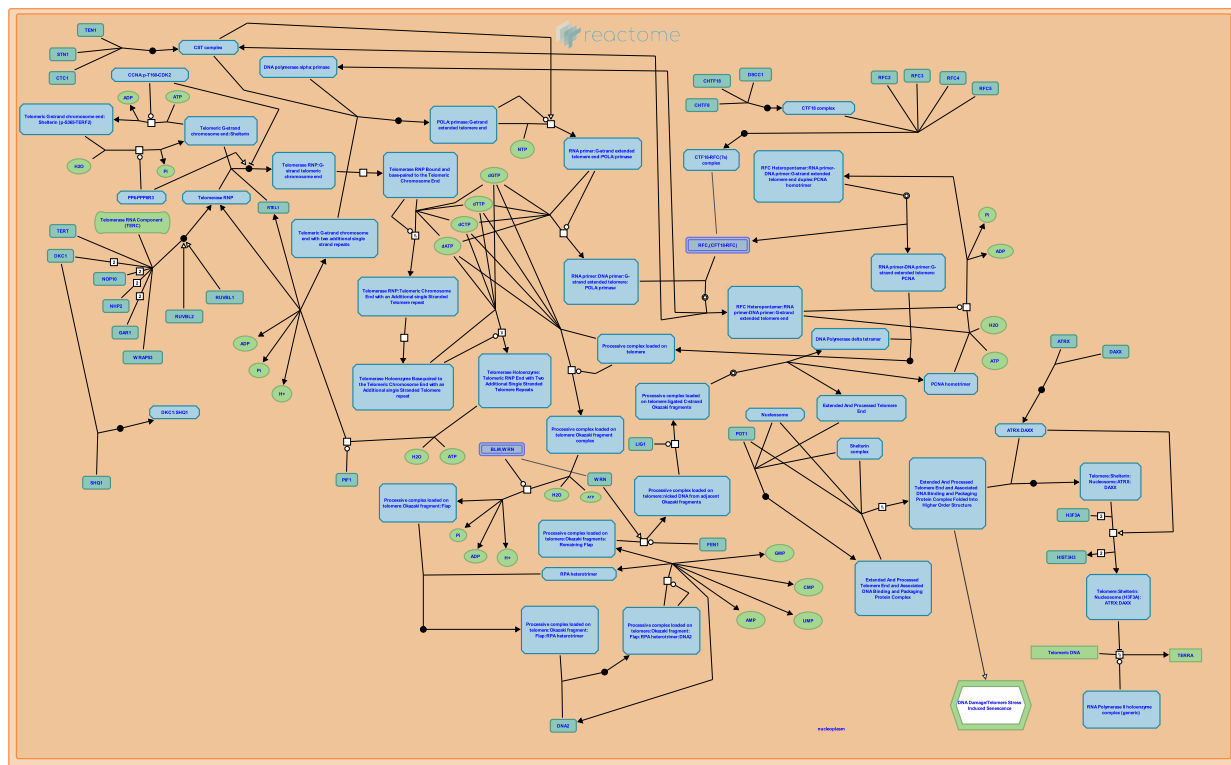


# Telomere Maintenance



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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](https://reactome.org/faq).

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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.

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## 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. [↗](#)

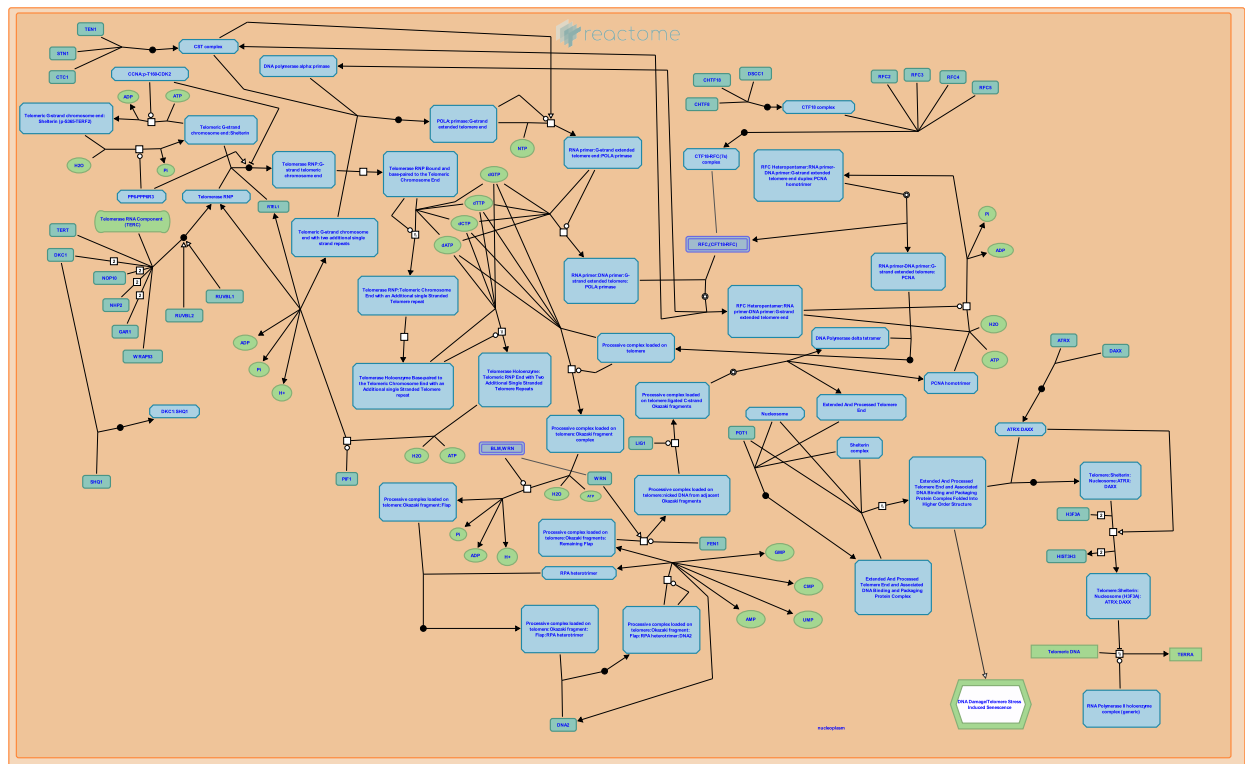
Reactome database release: 90

This document contains 4 pathways ([see Table of Contents](#))

# Telomere Maintenance ↗

**Stable identifier:** R-HSA-157579

**Compartments:** nucleoplasm



Telomeres are protein-DNA complexes at the ends of linear chromosomes that are important for genome stability. Telomeric DNA in humans, as in many eukaryotic organisms, consists of tandem repeats (Blackburn and Gall 1978; Moyzis et al. 1988; Meyne et al. 1989). The repeats at human telomeres are composed of TTAGGG sequences and stretch for several kilobase pairs. Another feature of telomeric DNA in many eukaryotes is a G-rich 3' single strand overhang, which in humans is estimated to be approximately 50-300 bases long (Makarov et al. 1997; Wright et al. 1997; Huffman et al. 2000). Telomeric DNA isolated from humans and several other organisms can form a lasso-type structure called a t-loop in which the 3' single-strand end is presumed to invade the double stranded telomeric DNA repeat tract (Griffith et al. 1999). Telomeric DNA is bound by multiple protein factors that play important roles in regulating telomere length and in protecting the chromosome end from recombination, non-homologous end-joining, DNA damage signaling, and unregulated nucleolytic attack (reviewed in de Lange 2005).

DNA attrition can occur at telomeres, which can impact cell viability. Attrition can occur owing to the "end-replication problem", a consequence of the mechanism of lagging-strand synthesis (Watson 1972; Olovnikov 1973). Besides incomplete replication, nucleolytic processing also likely contributes to telomere attrition (Huffman et al. 2000). If telomeres become critically shortened, replicative senescence can result (Harley et al. 1990). Thus, in order to undergo multiple divisions, cells need a mechanism to replenish the sequence at their chromosome ends.

The primary means for maintaining the sequence at chromosome ends in many eukaryotic organisms, including humans, is based on telomerase (Greider and Blackburn, 1985; Morin 1989). Telomerase is a ribonucleoprotein complex minimally composed of a conserved protein subunit containing a reverse transcriptase domain (telomerase reverse transcriptase, TERT) (Lingner et al. 1997; Nakamura et al. 1997) and a template-containing RNA (telomerase RNA component, TERC, TR, TER) (Greider and Blackburn, 1987; Feng et al 1995). Telomerase uses the RNA template to direct addition of multiple tandem repeats to the 3' G-rich single strand overhang. Besides extension by telomerase, maintenance of telomeric DNA involves additional activities, including C-strand synthesis, which fills in the opposing strand, and nucleolytic processing, which likely contributes to the generation of the 3' overhang.

## Literature references

de Lange, T. (2005). Shelterin: the protein complex that shapes and safeguards human telomeres. *Genes Dev*, 19, 2100-10. ↗

- Vega, LR., Mateyak, MK., Zakian, VA. (2003). Getting to the end: telomerase access in yeast and humans. *Nat Rev Mol Cell Biol*, 4, 948-59. [↗](#)
- Olovnikov, AM. (1973). A theory of marginotomy. The incomplete copying of template margin in enzymic synthesis of polynucleotides and biological significance of the phenomenon. *J Theor Biol*, 41, 181-90. [↗](#)
- Watson, JD. (1972). Origin of concatemeric T7 DNA. *Nat New Biol*, 239, 197-201. [↗](#)
- Greider, CW., Blackburn, EH. (1985). Identification of a specific telomere terminal transferase activity in Tetrahymena extracts. *Cell*, 43, 405-13. [↗](#)

## Editions

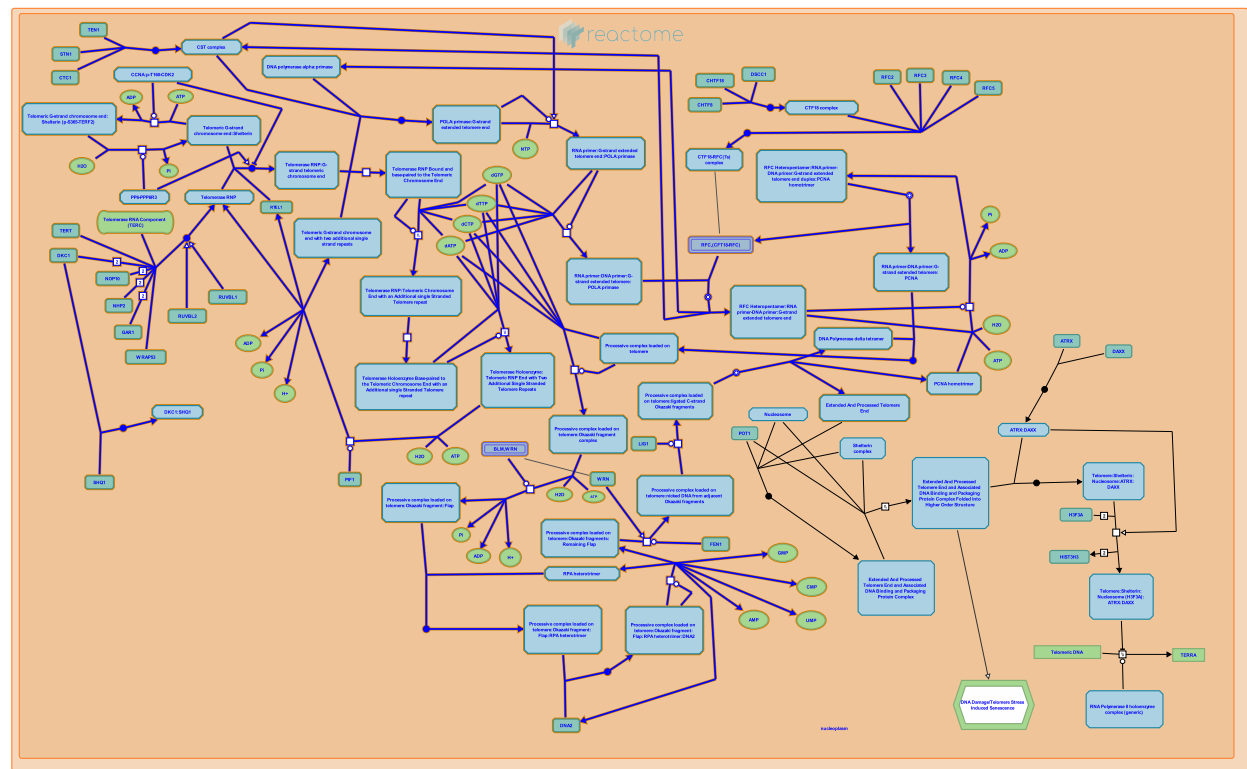
2006-03-10	Authored	Blackburn, EH., Seidel, J.
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Extension of Telomeres ↗

Location: [Telomere Maintenance](#)

Stable identifier: R-HSA-180786

Compartments: nucleoplasm



Telomerase acts as reverse transcriptase in the elongation of telomeres (Smogorzewska and de Lange 2004).

Literature references

Smogorzewska, A., de Lange, T. (2004). Regulation of telomerase by telomeric proteins. *Annu Rev Biochem*, 73, 177-208. ↗

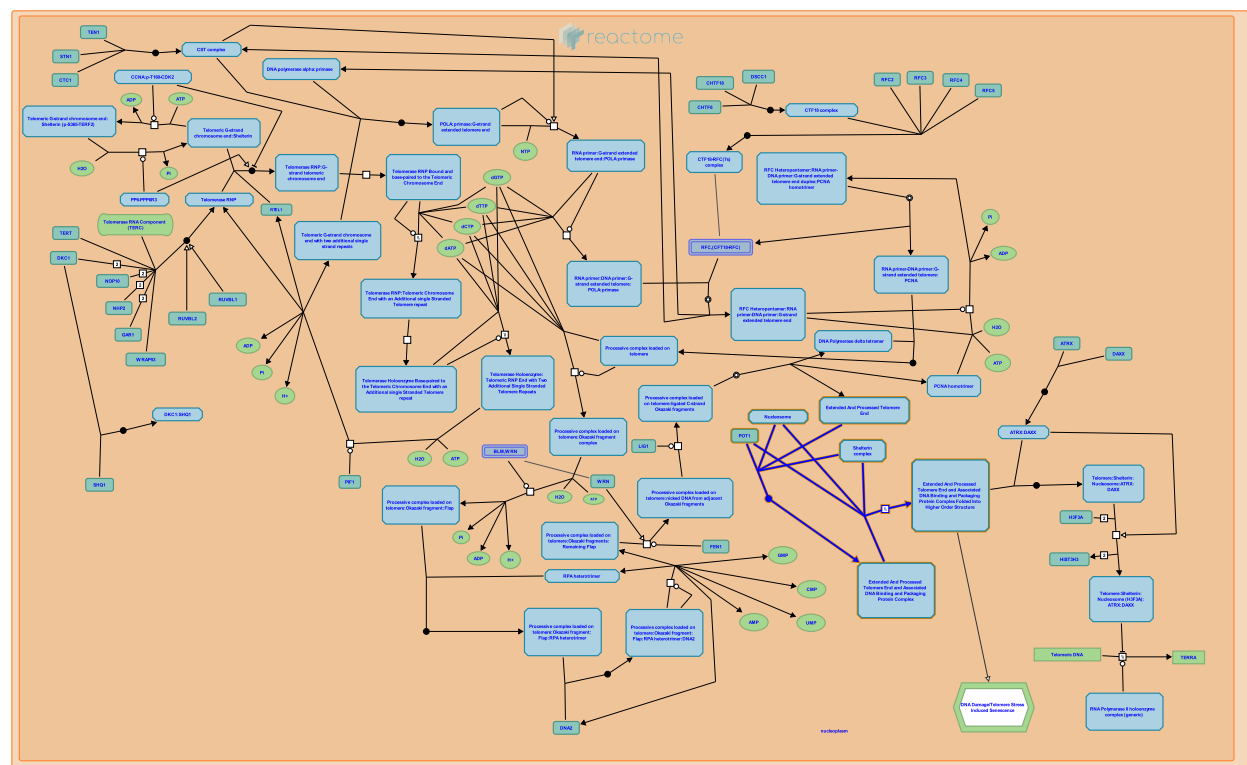
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# Packaging Of Telomere Ends ➤

**Location:** Telomere Maintenance

**Stable identifier:** R-HSA-171306



Multiple steps, including C-strand resection, telomerase-mediated elongation, and C-strand synthesis are involved in processing and maintaining the telomere. Though this module posits a linear transit for the steps, in humans it is not well understood how these steps are coordinated and what other events may be involved.

Telomeric DNA can form higher order structures. Electron microscopy of telomeric DNA isolated from human cells provided evidence for lariat-type structures termed telomeric loops, or t-loops (Griffith et al., 1999). t-loops are proposed to result from the invasion of the 3' G-rich single strand overhang into the double stranded telomeric TTAGGG repeat tract. The function of the t-loop is presumed to be the masking of the 3' telomeric overhang. Multiple protein factors can bind telomeric DNA and likely contribute to dynamic, higher order structures.

## Literature references

Moss, H., Bianchi, A., de Lange, T., Stansel, RM., Rosenfield, S., Comeau, L. et al. (1999). Mammalian telomeres end in a large duplex loop. *Cell*, 97, 503-14. ➤

## Editions

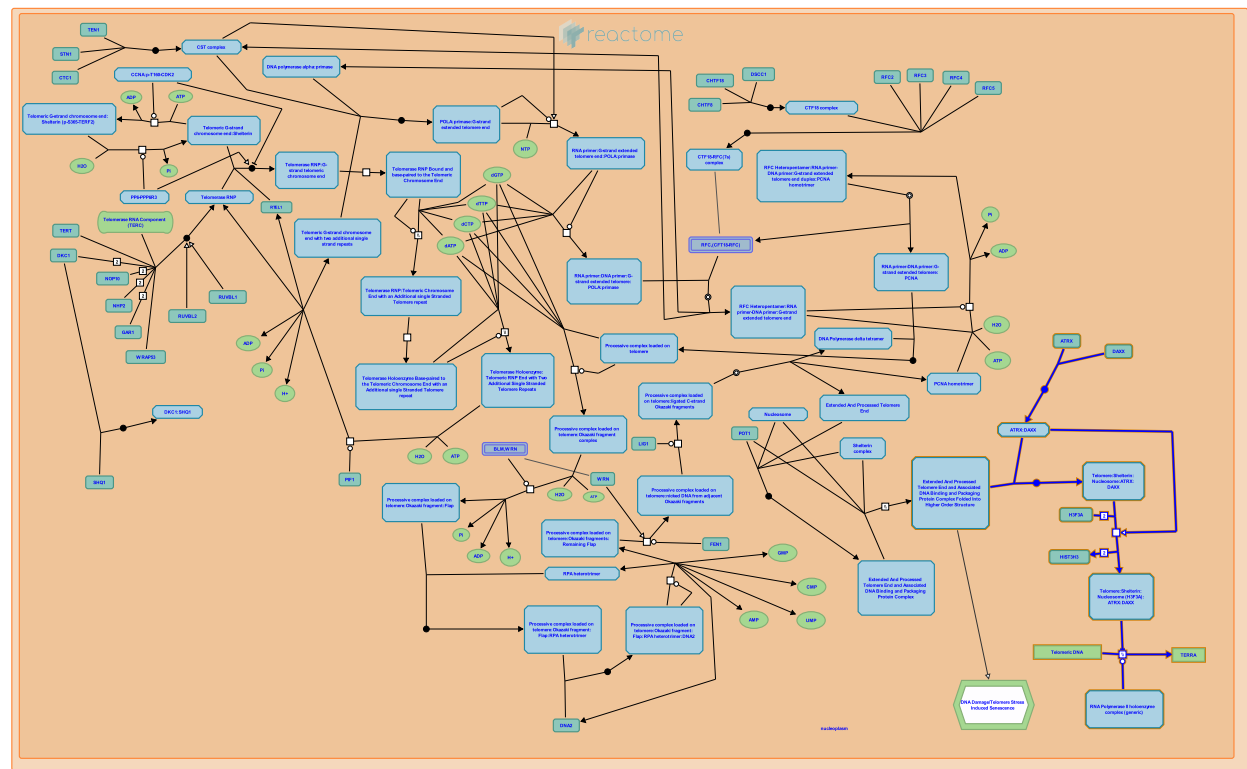
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**Inhibition of DNA recombination at telomere**

**Location:** Telomere Maintenance

**Stable identifier:** R-HSA-9670095

**Compartments:** nucleoplasm



Telomeres resemble double strand DNA breaks (DSBs) and, if not properly packaged and protected, are recognized by the DNA double strand break repair (DSBR) machinery. Initiation of DSB signaling at telomeres due to replicative shortening of telomeres is one of the triggers of cellular senescence, which can also be triggered by other cellular stressors, such as oxidative stress, and oncogenic signaling-induced mitotic arrest. The loss of telomere protection can result in telomere fusions via non-homologous end joining (NHEJ) of microhomology-mediated end joining (MMEJ). Loss of telomere protection accompanied by changes in the organization of telomeric chromatin (O'Sullivan et al. 2014) can trigger extension of telomeres via homologous recombination repair-mediated alternative lengthening of telomeres (ALT). ALT occurs in about 5-15% of cancers and is a telomerase-independent mechanism of replicative immortality. For review, please refer to Arnoult and Karlseder 2015 and Pickett and Reddel 2015.

**Literature references**

Karlseder, J., Schreiber, SL., O'Sullivan, RJ., Kubicek, S. (2010). Reduced histone biosynthesis and chromatin changes arising from a damage signal at telomeres. *Nat. Struct. Mol. Biol.*, 17, 1218-25. [↗](#)

Karlseder, J., Arnoult, N. (2015). Complex interactions between the DNA-damage response and mammalian telomeres. *Nat. Struct. Mol. Biol.*, 22, 859-66. [↗](#)

Reddel, RR., Pickett, HA. (2015). Molecular mechanisms of activity and derepression of alternative lengthening of telomeres. *Nat. Struct. Mol. Biol.*, 22, 875-80. [↗](#)

**Editions**

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