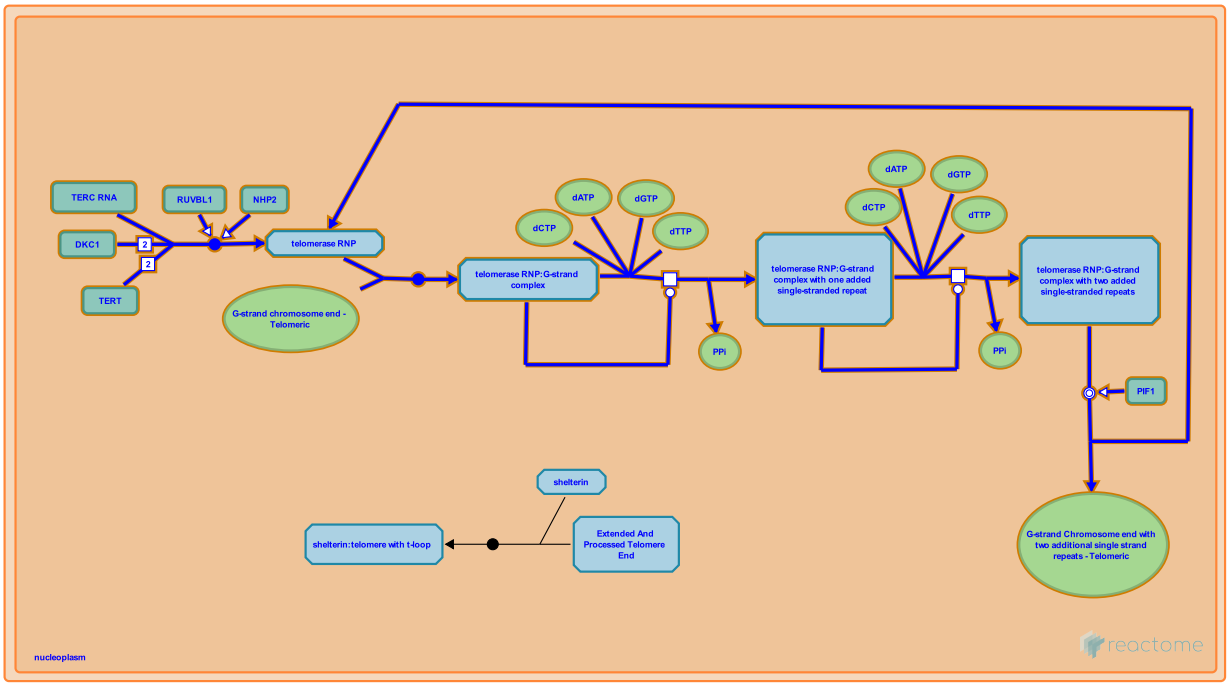
# Assembly of telomerase and telomere extension

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19/05/2024

# 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. ↗

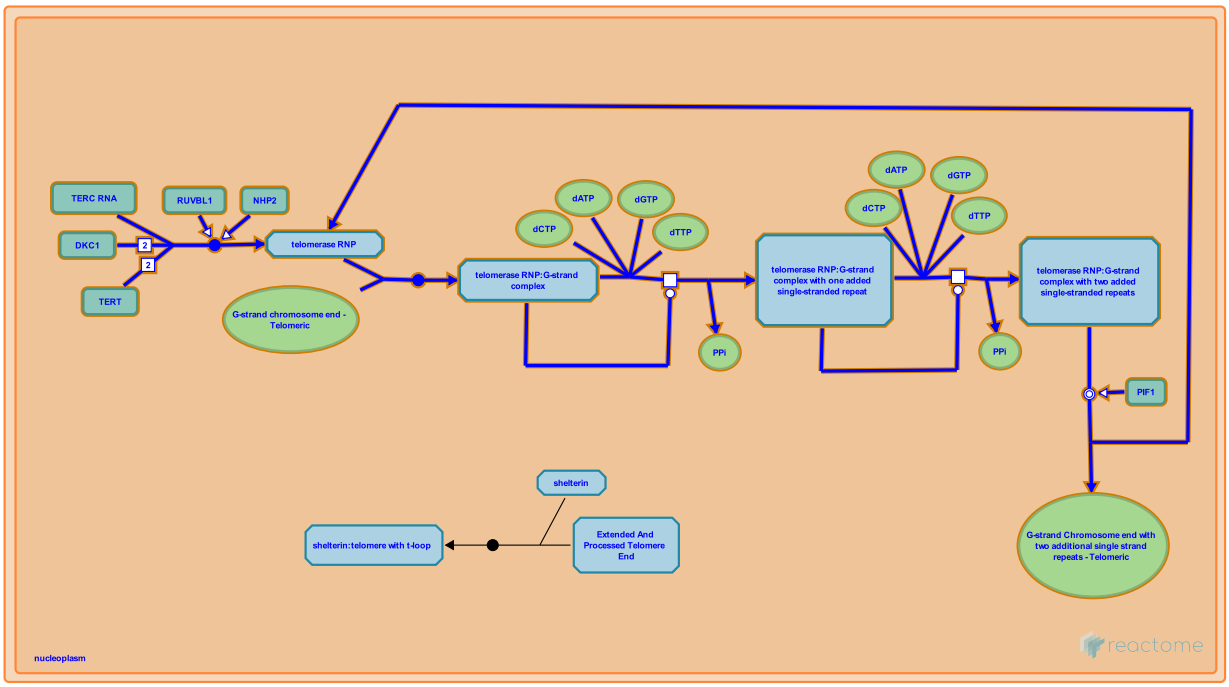
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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 telomerase and telomere extension ↗

**Stable identifier:** R-GGA-417076

**Compartments:** nucleoplasm




Telomerase activity has been demonstrated in a variety of chicken cells in vivo and in vitro including primary, differentiated, aging, immortalized and transformed cell types (Taylor and Delany 2000; Swanberg and Delany 2003; O'Hare and Delany 2005; Hrdlickova et al. 2006).

The telomerase ribonucleoprotein complex is formed in the nucleoplasm from the association of TERT and TERC. In human, DKC1 (dyskerin) is also part of the complex, but association of the chicken ortholog with chicken telomerase has not been demonstrated experimentally. The involvement and stoichiometry of DKC1 as a component of the complex in chicken are inferred from studies of purified human telomerase (Cohen et al. 2007).

RUVBL1 (pontin) and RUVBL2 (reptin) are found associated with human telomerase purified from HeLa cells and activities of these proteins are required for telomerase assembly in vitro (Venteicher et al. 2008). Their exact roles in the assembly and function of in vivo telomerase remain unclear. A potential chicken ortholog for RUVBL1 (pontin) has been identified.

NHP2 (NOLA2) is likewise associated with telomerase ribonucleoprotein complexes (Pogacic et al. 2000) and homozygous NHP2 mutations are associated with telomerase failure in humans (Vuillamy et al. 2008). A potential chicken ortholog for NHP2 has been identified.

## Literature references


Venteicher, AS., Veenstra, TD., Artandi, SE., Mason, PJ., Meng, Z. (2008). Identification of ATPases pontin and reptin as telomerase components essential for holoenzyme assembly. *Cell, 132*, 945-57. ↗

Delany, ME., Swanberg, SE. (2003). Dynamics of telomere erosion in transformed and non-transformed avian cells in vitro. *Cytogenet Genome Res, 102*, 318-25. ↗

Filipowicz, W., Pogacic, V., Dragon, F. (2000). Human H/ACA small nucleolar RNPs and telomerase share evolutionarily conserved proteins NHP2 and NOP10. *Mol Cell Biol, 20*, 9028-40. ↗

Delany, ME., O'Hare, TH. (2005). Telomerase gene expression in the chicken: Telomerase RNA (TR) and reverse transcriptase (TERT) transcript profiles are tissue-specific and correlate with telomerase activity. *Age (Dordr), 27*, 257-66. ↗

Kirwan, M., Marrone, A., Walne, A., Digweed, M., Beswick, R., Vulliamy, T. et al. (2008). Mutations in the telomerase component NHP2 cause the premature ageing syndrome dyskeratosis congenita. *Proc Natl Acad Sci U S A, 105*, 8073-8. ↗

## Editions

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|---|---|---|
| 2009-04-16 | Edited | D'Eustachio, P. |
| 2010-06-11 | Authored | Delany, ME., Swanberg, SE., O'Hare, TH. |

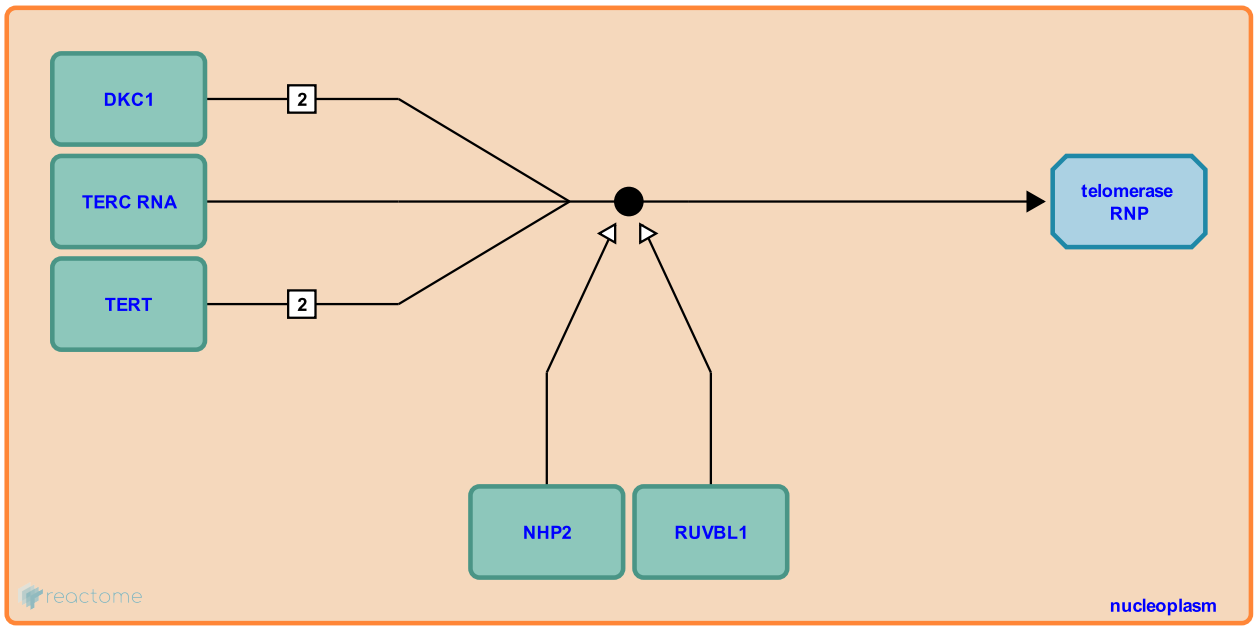
## Assembly of telomerase RNP ↗

**Location:** Assembly of telomerase and telomere extension

**Stable identifier:** R-GGA-417114

**Type:** binding

**Compartments:** nucleoplasm




The telomerase RNP complex is formed in the nucleoplasm from TERT protein, TERC RNA, and DKC1 (dyskerin) protein. The complex has been identified and its activity demonstrated in chicken cells (Hrdlickova et al. 2006). Its stoichiometry and the presence of DKC1 as a component of the complex are inferred from studies of purified human telomerase RNP (Cohen et al. 2007).

RUVBL1 (pontin) and RUVBL2 (reptin) are found associated with human telomerase RNPs purified from HeLa cells, and activities of these proteins are required for telomerase RNP assembly in vivo (Venteicher et al. 2008). The exact roles of these proteins in the assembly and function of telomerase RNP in vivo remain unclear, however, so the one protein, RUVBL1 (pontin), for which a chicken ortholog has been identified is annotated simply as positively regulating telomerase RNP formation.

NHP2 (NOLA2) is likewise associated with telomerase ribonucleoprotein complexes (Pogacic et al. 2000) and homozygosity for NHP2 mutations is associated with telomerase failure (dyskeratosis congenital) in humans (Vuillamy et al. 2008). The molecular function of NHP2 remains unclear, however, so its chicken ortholog is annotated simply as positively regulating telomerase RNP formation.

The chicken TERC gene has been identified, based on its content of conserved TERC sequence elements (Chen et al. 2000) and the phenotypes of DT40 cells heterozygous for a null allele of the gene (Faure et al. 2008). Both a full-length the chicken TERT mRNA and numerous shorter mRNAs generated by alternative splicing have been described, but only the full-length form encodes a catalytically active protein (Chang and Delaney 2006; Hrdlickova et al. 2006).

**Followed by:** Recruitment of telomerase RNP to a telomeric chromosome end

## Literature references

Venteicher, AS., Veenstra, TD., Artandi, SE., Mason, PJ., Meng, Z. (2008). Identification of ATPases pontin and reptin as telomerase components essential for holoenzyme assembly. *Cell, 132*, 945-57. ↗

Filipowicz, W., Pogacic, V., Dragon, F. (2000). Human H/ACA small nucleolar RNPs and telomerase share evolutionarily conserved proteins NHP2 and NOP10. *Mol Cell Biol, 20*, 9028-40. ↗

Kirwan, M., Marrone, A., Walne, A., Digweed, M., Beswick, R., Vulliamy, T. et al. (2008). Mutations in the telomerase component NHP2 cause the premature ageing syndrome dyskeratosis congenita. *Proc Natl Acad Sci U S A, 105*, 8073-8. ↗

Hrdlickova, R., Liss, AS., Bose, HR., Nehyba, J. (2006). Mechanism of telomerase activation by v-Rel and its contribution to transformation. *J Virol, 80*, 281-95. ↗

Reddel, RR., Lovrecz, GO., Bache, N., Graham, ME., Cohen, SB., Robinson, PJ. (2007). Protein composition of catalytically active human telomerase from immortal cells. *Science, 315*, 1850-3. ↗

## Editions

| | | |
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## Recruitment of telomerase RNP to a telomeric chromosome end ↗

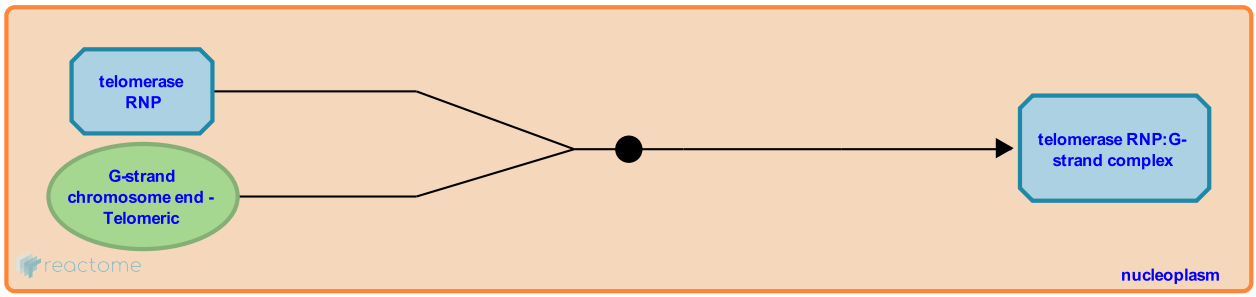
**Location:** Assembly of telomerase and telomere extension

**Stable identifier:** R-GGA-417077

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Alignment Of The RNA Template On The Telomeric Chromosome End (Homo sapiens), Recruitment of Telomerase RNP to the Telomeric Chromosome End (Homo sapiens)




The telomerase RNP complex associates specifically with 3' G-rich single-stranded ends of linear DNA sequences at telomeres and its RNA component anneals to the chromosomal G-rich DNA. This process has been extensively studied in humans and yeast; the orthologous chicken event is inferred based on data from these other systems.

**Preceded by:** Assembly of telomerase RNP

**Followed by:** Elongation and translocation of the telomeric chromosome end

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## Elongation and translocation of the telomeric chromosome end ↗

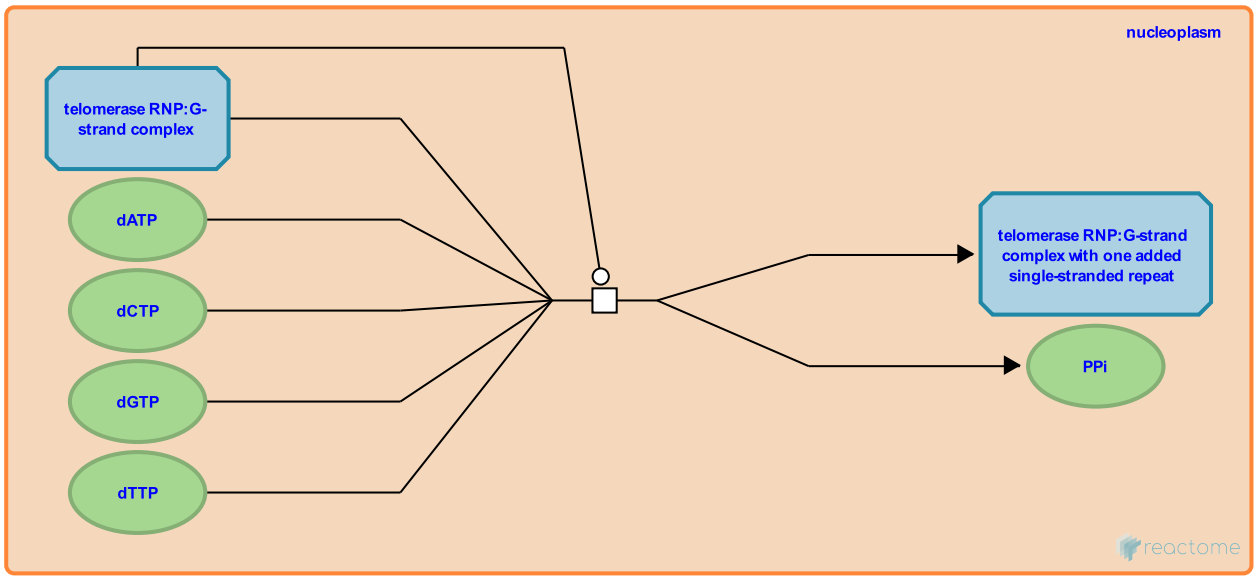
**Location:** Assembly of telomerase and telomere extension

**Stable identifier:** R-GGA-417122

**Type:** transition

**Compartments:** nucleoplasm

**Inferred from:** Elongation Of The Telomeric Chromosome End (Homo sapiens), Translocation Of Telomerase RNP And Alignment Of RNA Template (TERC) To Extended Single Stranded Telomeric Chromosome-End (Homo sapiens)




TERC directs the sequential addition of nucleotides to the 3' telomeric DNA end. After each addition, the template must move relative to the telomerase active site to bring the next template residue into the active site. The product of these additions and translocations is a chromosomal single-stranded end extended by one repeat unit (complementary to the TERC template sequence), positioned on the template so as to allow repetition of the process. The template region of TERC is perfectly conserved between humans and chickens (Chen et al. 2000). The molecular details of the process have been studied in humans; the orthologous chicken event is inferred from those data.

**Preceded by:** Recruitment of telomerase RNP to a telomeric chromosome end

**Followed by:** Elongation and translocation of the extended telomeric chromosome end

## Literature references

Greider, CW., Chen, JL., Blasco, MA. (2000). Secondary structure of vertebrate telomerase RNA. *Cell, 100*, 503-14. ↗

## Editions

| | | |
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| 2009-04-16 | Edited | D'Eustachio, P. |
| 2010-06-11 | Authored | Delany, ME., Swanberg, SE., O'Hare, TH. |

## Elongation and translocation of the extended telomeric chromosome end ↗

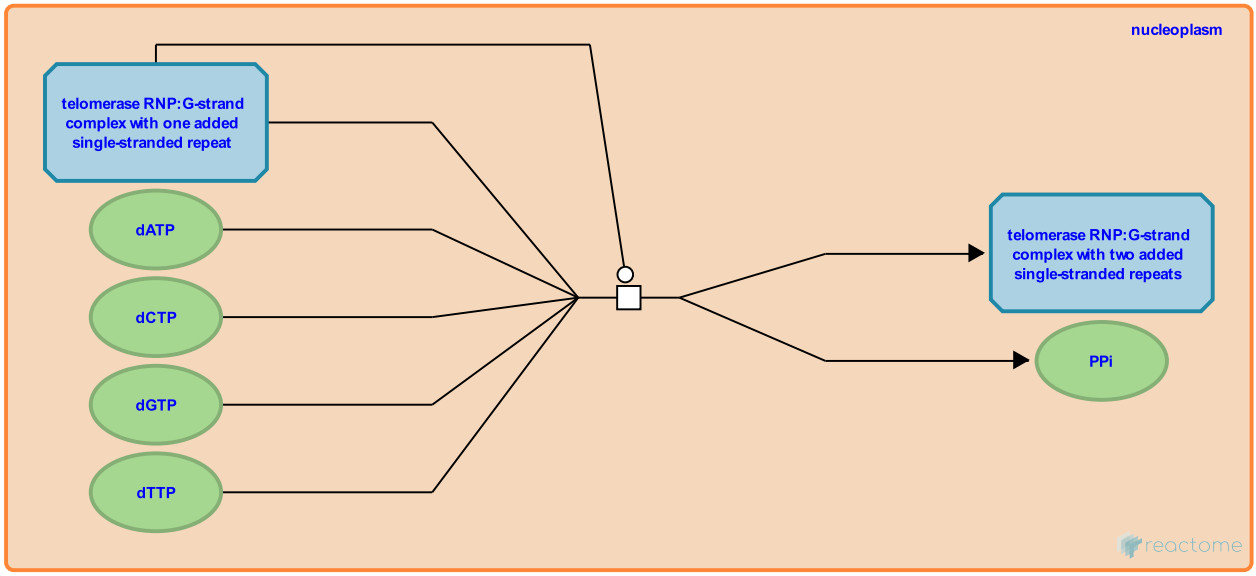
**Location:** Assembly of telomerase and telomere extension

**Stable identifier:** R-GGA-417127

**Type:** transition

**Compartments:** nucleoplasm

**Inferred from:** Elongation of Extended Telomeric Chromosome End (Homo sapiens)




TERC directs the sequential addition of nucleotides to the 3' end of a chromosomal DNA strand with one added telomere repeat. After each addition, the template must move relative to the telomerase active site to bring the next template residue into the active site. The product of these additions and translocations is a chromosomal single-stranded end extended by two repeat units (each complementary to the TERC template sequence), positioned on the template so as to allow repetition of the process. The template region of TERC is perfectly conserved between humans and chickens (Chen et al. 2000). The molecular details of the process have been studied in humans; the orthologous chicken event is inferred from those data.

**Preceded by:** Elongation and translocation of the telomeric chromosome end

**Followed by:** Dissociation of telomerase RNP from the extended chromosomal end

## Literature references

Greider, CW., Chen, JL., Blasco, MA. (2000). Secondary structure of vertebrate telomerase RNA. *Cell, 100*, 503-14. ↗

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## Dissociation of telomerase RNP from the extended chromosomal end ↗

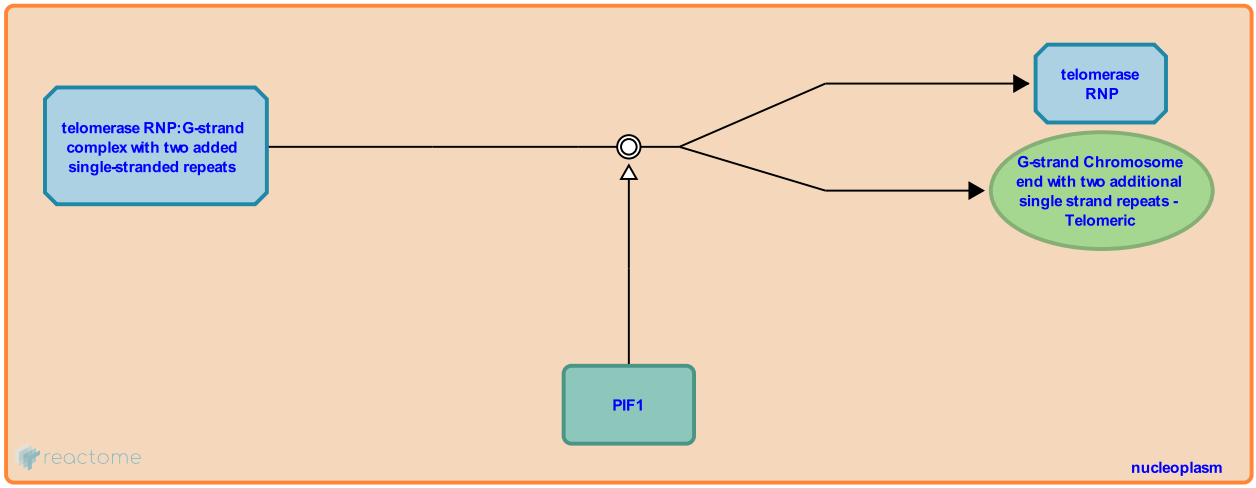
**Location:** Assembly of telomerase and telomere extension

**Stable identifier:** R-GGA-418082

**Type:** dissociation

**Compartments:** nucleoplasm

**Inferred from:** Disassociation of Telomerase RNP and the Chromosome End (Homo sapiens)




The process by which extension of a telomere is terminated has not been characterized in chicken cells, but is inferred from the human system. Human telomerase RNP has low processivity and can dissociate from the primer after addition of single nucleotides or whole repeat units in vitro. Regulation of this process is not well understood, but PIF1 protein, a helicase, can promote dissociation in vitro and its expression levels are inversely correlated with telomere length in some tissue culture systems (Boule et al. 2005; Zhang et al. 2006). On this basis, PIF1 is annotated here as a positive regulator of telomere – telomerase dissociation.

**Preceded by:** Elongation and translocation of the extended telomeric chromosome end

## Literature references


Huang, Y., Xu, LX., Zhou, B., Zhang, DH., Zhou, JQ. (2006). The human Pif1 helicase, a potential Escherichia coli RecD homologue, inhibits telomerase activity. *Nucleic Acids Res, 34*, 1393-404. ↗

Vega, LR., Boule, JB., Zakian, VA. (2005). The yeast Pif1p helicase removes telomerase from telomeric DNA. *Nature, 438*, 57-61. ↗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