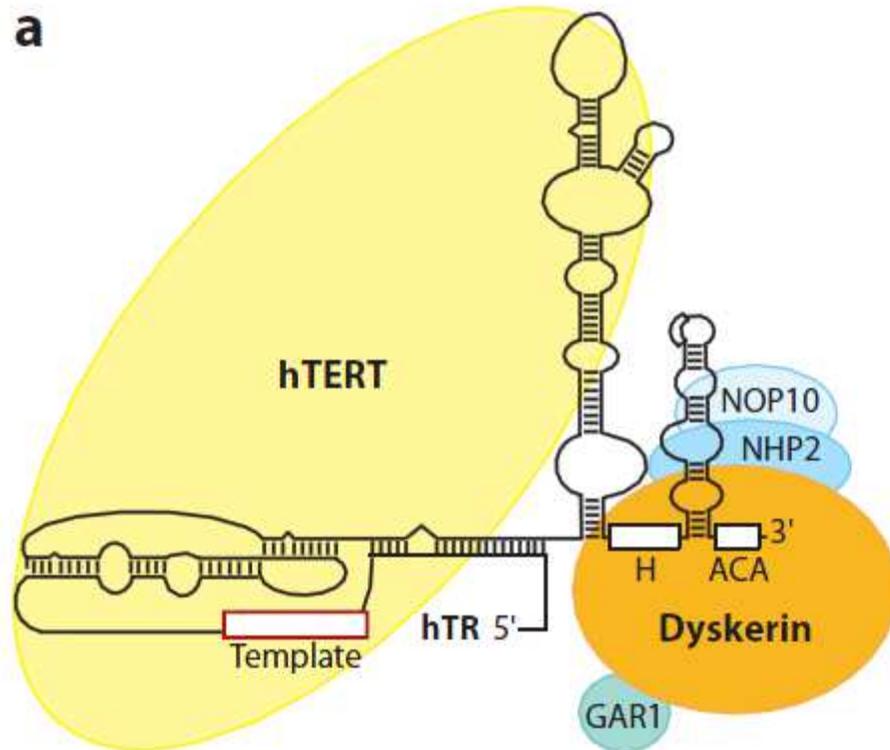


TELOMERI

# Complessi macromolecolari associati alla Telomerasi



The ribonucleoprotein **dyskerin** (DKC1 gene) is important for the RNA component folding and stability.

NOP10, NHP2, and GAR are other proteins that associate with the telomerase complex; these proteins are important for TERC molecule stabilization and also play a role in ribosome biogenesis and messenger RNA processing.

Mutations in telomerase and telomere components lead to syndromes of telomere shortening.

(a) The essential telomerase components. hTERT utilizes the template provided by hTR to add new telomeres onto the ends of chromosomes.

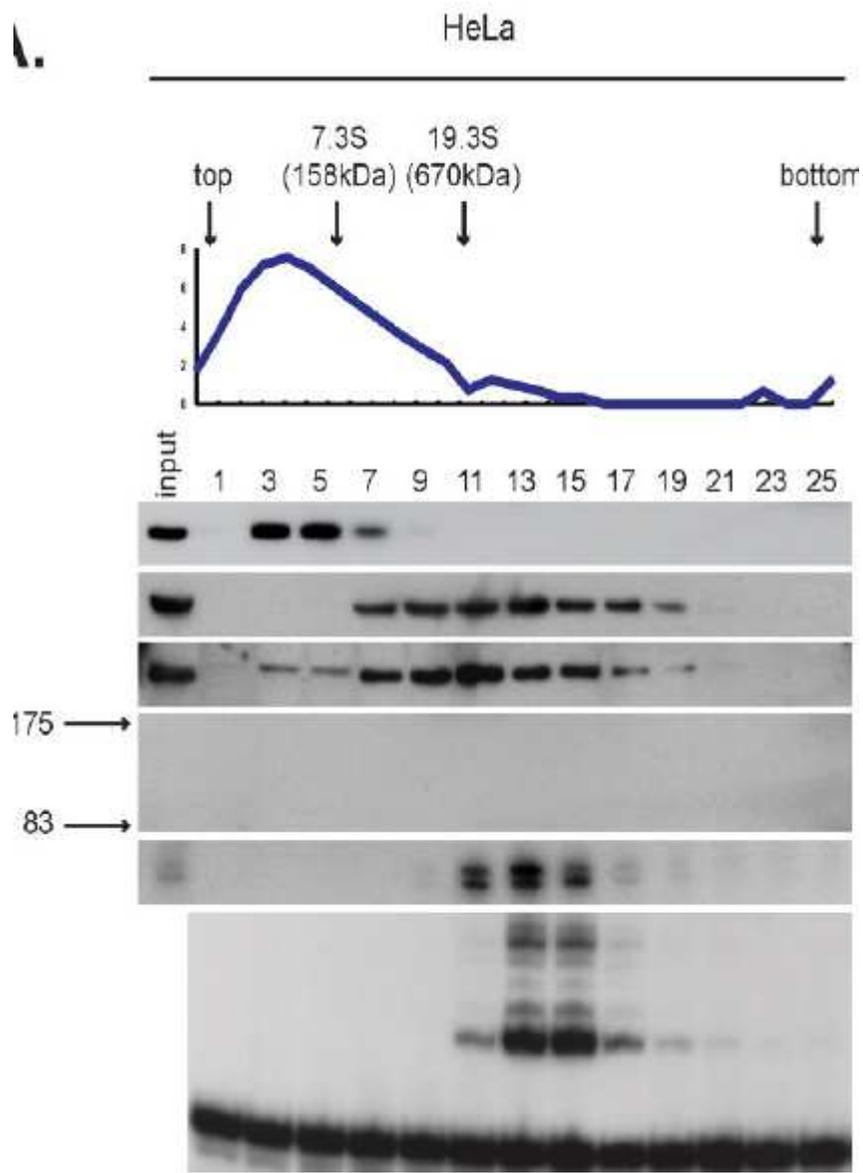
hTR is a 451-nucleotide RNA which contains a box H/ACA motif at its 3' end. The box H/ACA motif is essential for hTR stability and for its assembly with hTERT. These functions are mediated by the presence of the box H/ACA-binding dyskerin complex, which is composed of four proteins: dyskerin, NOP10, NHP2 and GAR1.

Loss-of-function mutations in hTR, hTERT, DKC1, and likely NOP10 and NHP2 lead to a decrease in available telomerase dose and accelerated telomere shortening.

Few other proteins are known to be required for human telomerase function, significantly limiting our understanding of both telomerase regulation and mechanisms of telomerase action.

The ATPases **pontin and reptin** are telomerase components as indicated by Affinity purification of TERT from human cells.

Pontin interacts with both TERT and dyskerin,



1

Total protein

IB:  $\alpha$ -tubulin

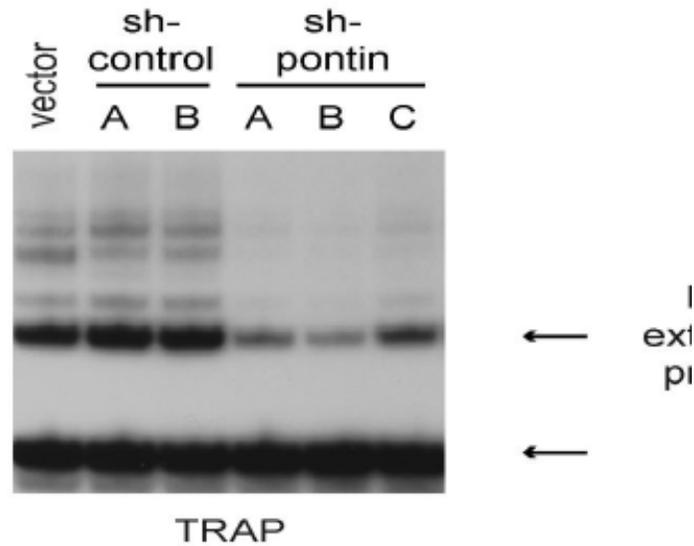
IB: pontin

IB: reptin

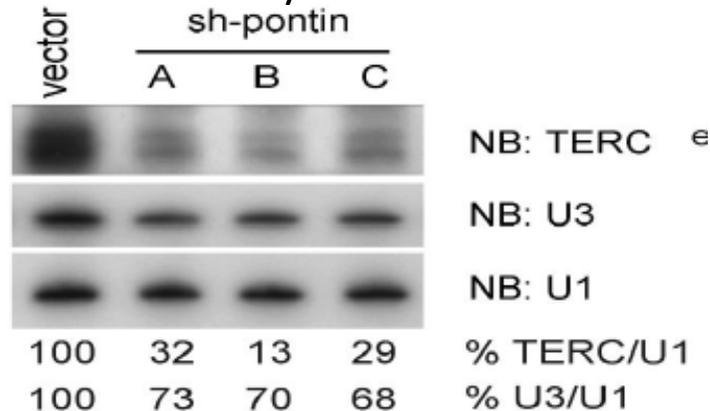
NB: TERC

TRAP

## Depletion of pontin and reptin markedly impairs telomerase activity



Depletion of pontin and reptin markedly impairs accumulation of the telomerase RNP, indicating an essential role in telomerase assembly.

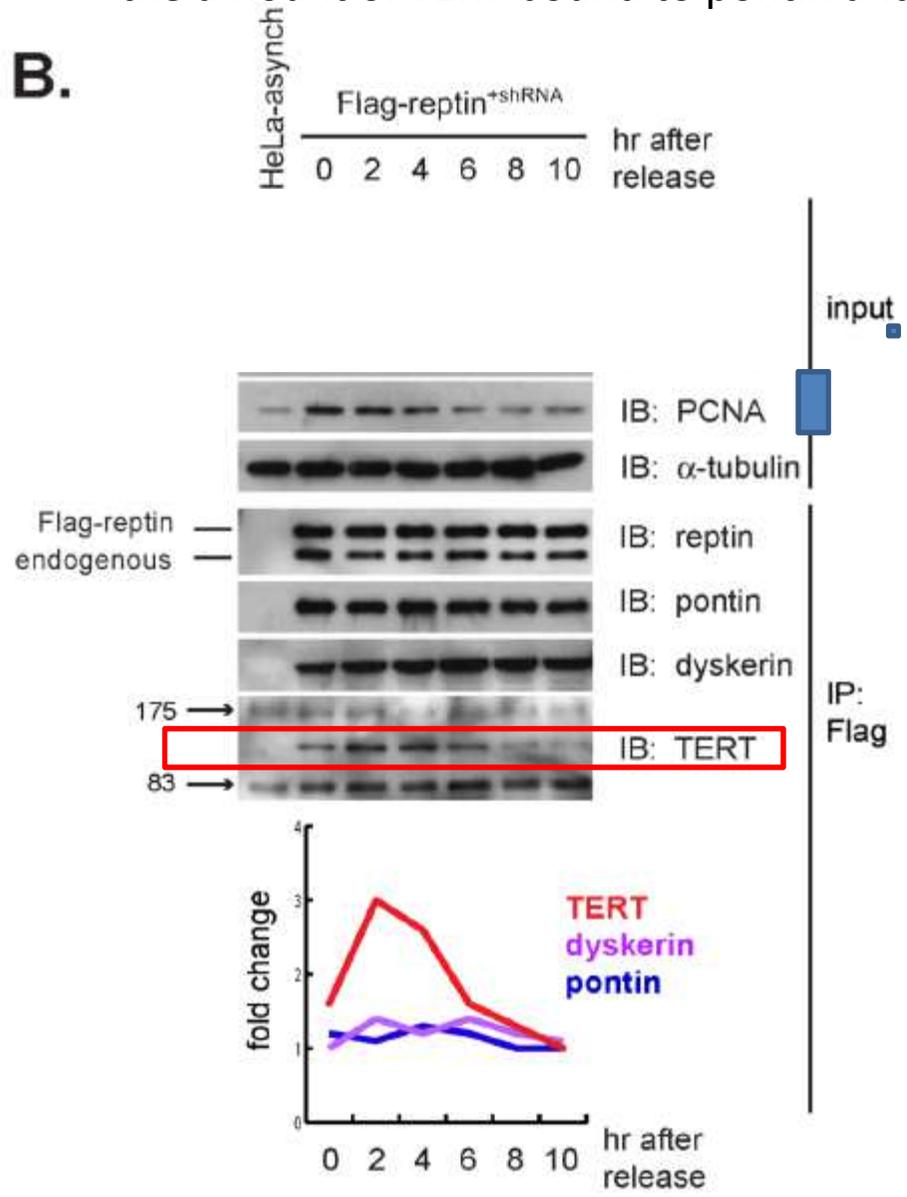


the amount of TERT bound to pontin and reptin peaks in S phase,  
evidence for dynamic cell cycle-dependent regulation of TERT

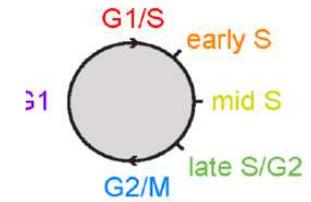
These findings reveal an unanticipated requirement for additional enzymes in telomerase RNP biogenesis and suggest new approaches for inhibiting telomerase in human cancer.

the amount of TERT bound to pontin and reptin peaks in S phase,

**B.**

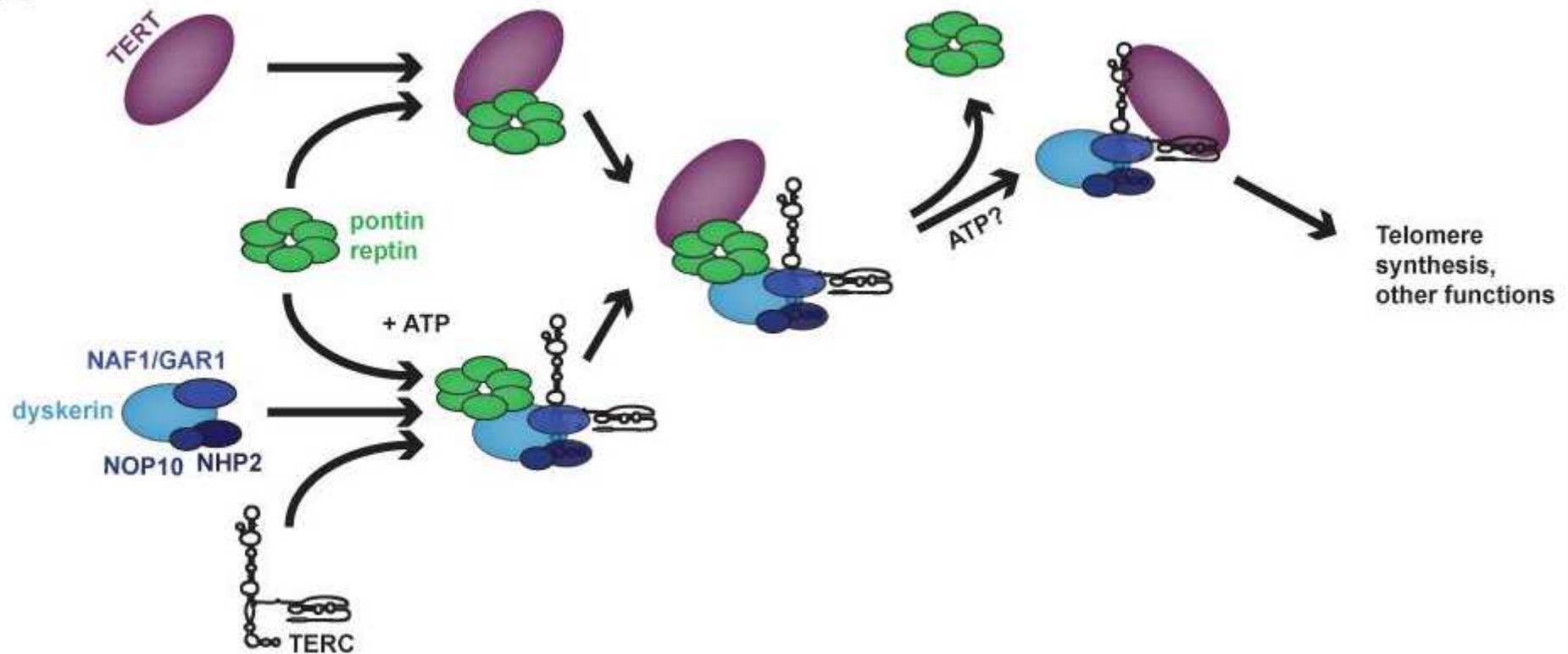


**C.**



evidence for dynamic cell cycle-dependent regulation of TERT.

F.



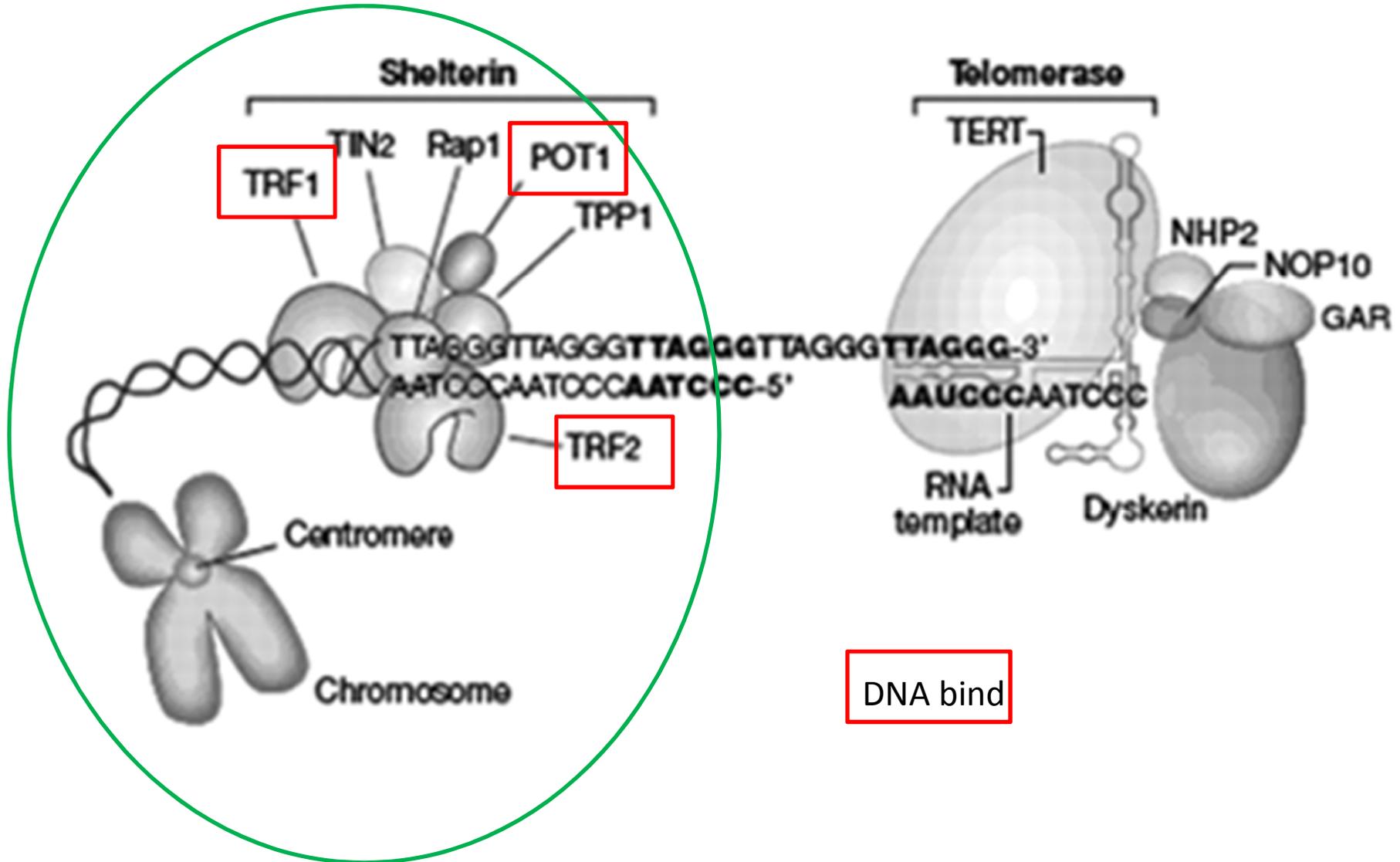
The single-stranded 3' overhang folds back into the telomeric DNA, invades the double-helix, and anneals with the C-rich strand, forming a loop known as T-loop, thus hiding the very ends of chromosomal DNA.



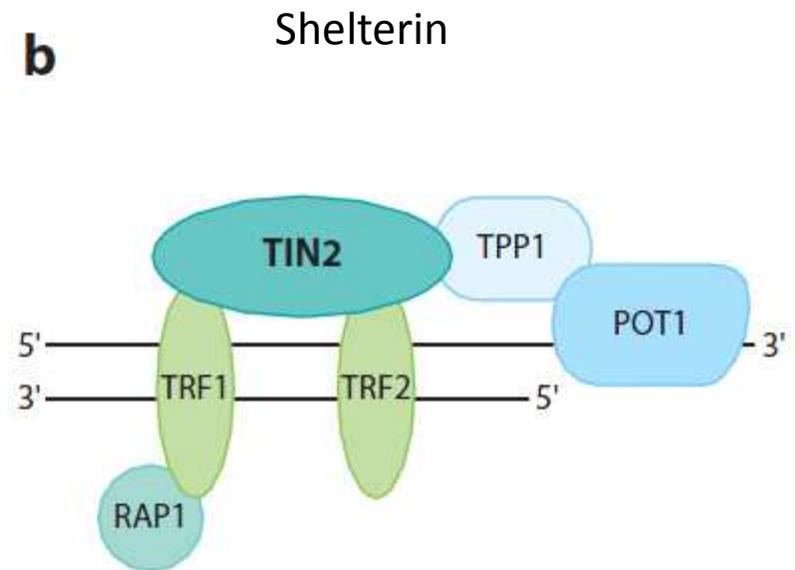
Schematic representation of telomere structure and telomerase complex. Telomeres are at the extremities of chromosomes.

The telomeric 3' end terminates as a single-stranded, G-rich overhang. Telomeres are capped by a protein complex (TRF1, TRF2, TPP1, POT1, TIN2, and Rap1), collectively known as shelterin, that physically shield the DNA

# Complessi macromolecolari associati al Telomero ed alla Telomerasi



# Complessi macromolecolari associati al Telomero



Telomeres are coated by a group of at least six proteins, collectively called **shelterin**

Three proteins, TRF1, TRF2, and POT1(single-stranded repeats) directly recognize and bind to TTAGGG repeats

TIN2 TPP1, and Rap1, interconnect the telomere-binding proteins to form the entire complex

Shelterin serves as a signal that allows the cellular DNA repair machinery to distinguish telomeres from DNA double-stranded breaks

Mutations in telomerase and telomere components lead to syndromes of telomere shortening.

(a) The essential telomerase components. hTERT utilizes the template provided by hTR to add new telomeres onto the ends of chromosomes.

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