Organization of telomere and its maintenance

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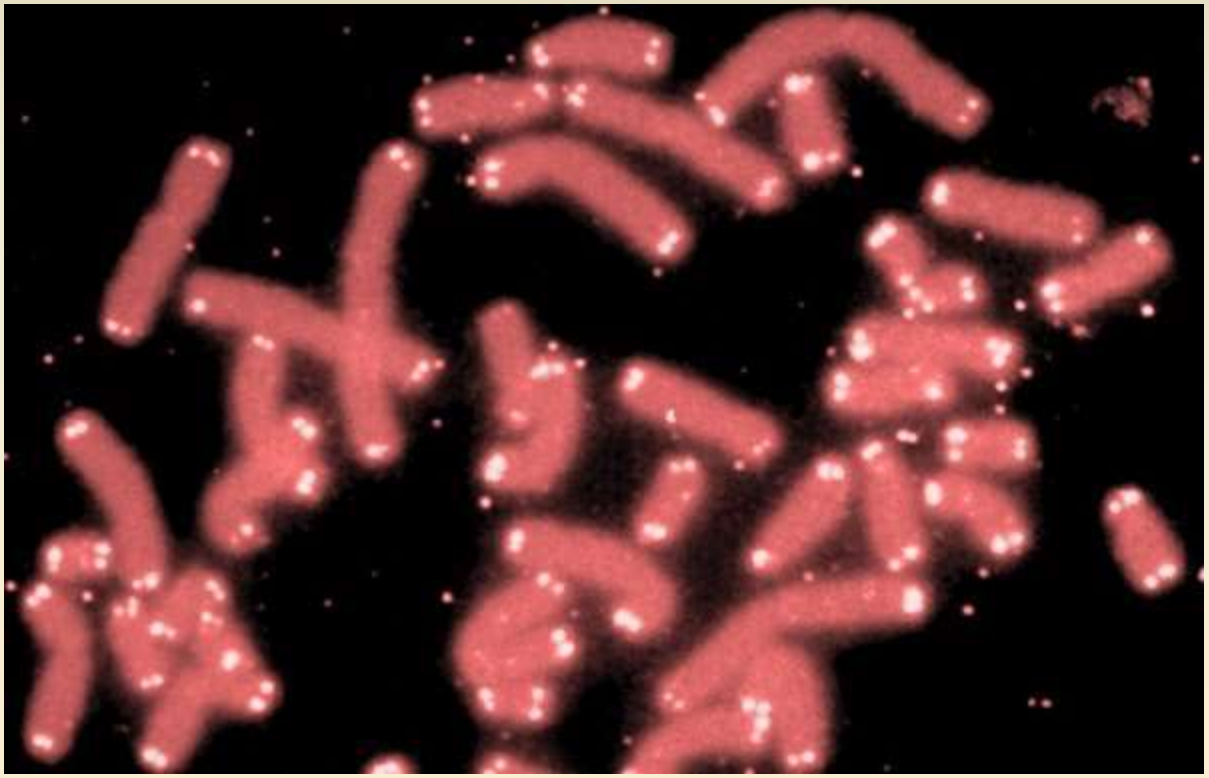
Introduction

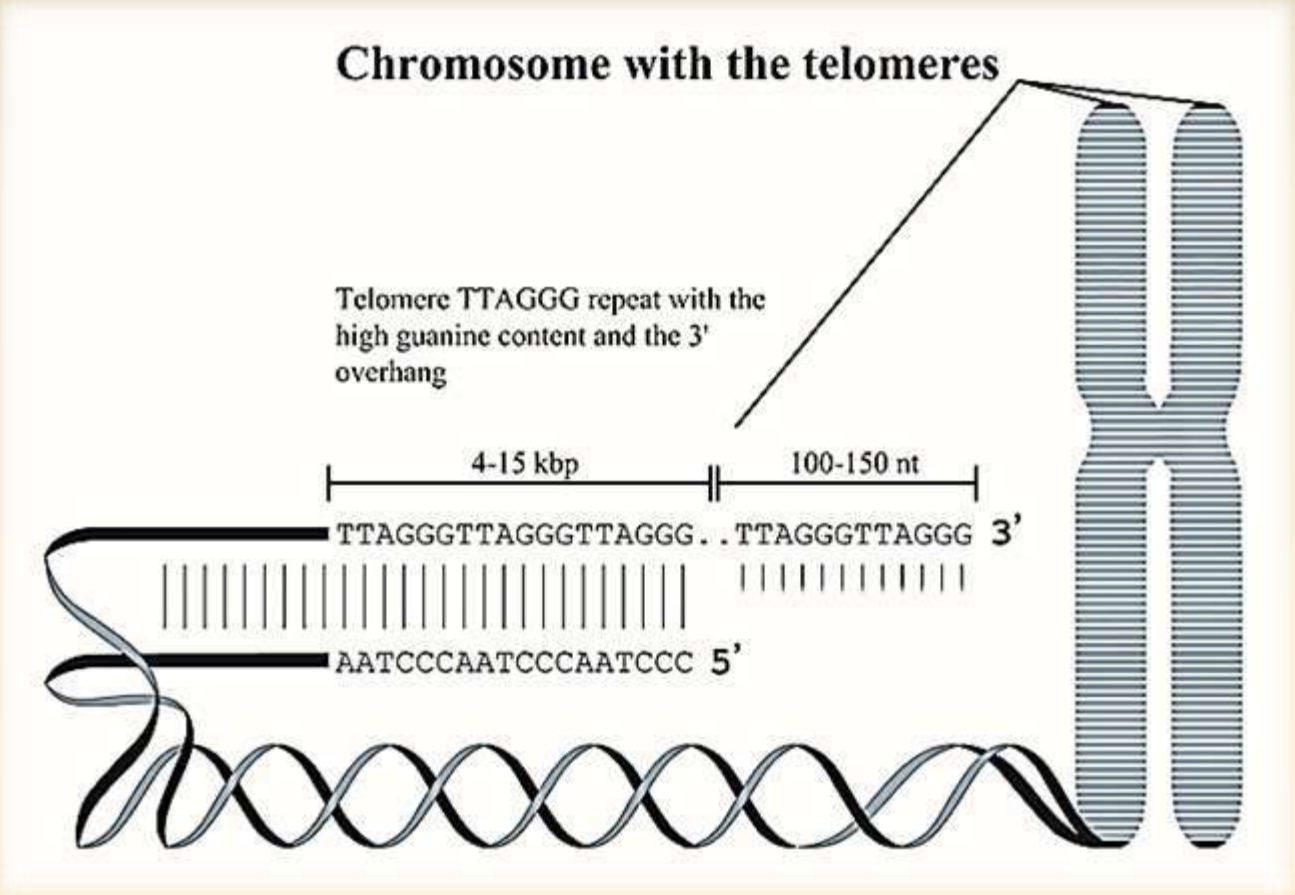
- Telomeres are sections of DNA that are found at both ends of every chromosomes.
- The term telomere is formed of two Greek words ‘telos’ meaning ‘the end’ and ‘meros’ meaning ‘the part’.
- It consists of short tandem repeats which increases in successive cell division during karyokinesis.
- In humans, these repetitive sequence is TTAGGG.
- The telomere sequence may be found in repetition of about 3000 times and even 15,000 bp in length in certain cases (new bron have 8000 to 13000 bp).
- As the ageing of cells progress, 25 to 200 bp length of telomere lost.
- Telomere is formed by an enzyme known as telomerase.
- The telomerase enzymes is found in high level in germ line cells & in cancer cells.
- Most important role of telomere is to protect the ends of our chromosomes by forming a cap, much like the plastic tip on shoelaces.
- Capping attributes of telomere allow the chromosome to be replicated properly during cell division.
- It confers a chromosome stability and integrity.

Telomere localization



Telomeres (seen as bright white dots) cap and protect the ends of chromosomes like the caps on shoelaces.
Wood M. 2016. UChicago Medicine Forefront Biological Sciences

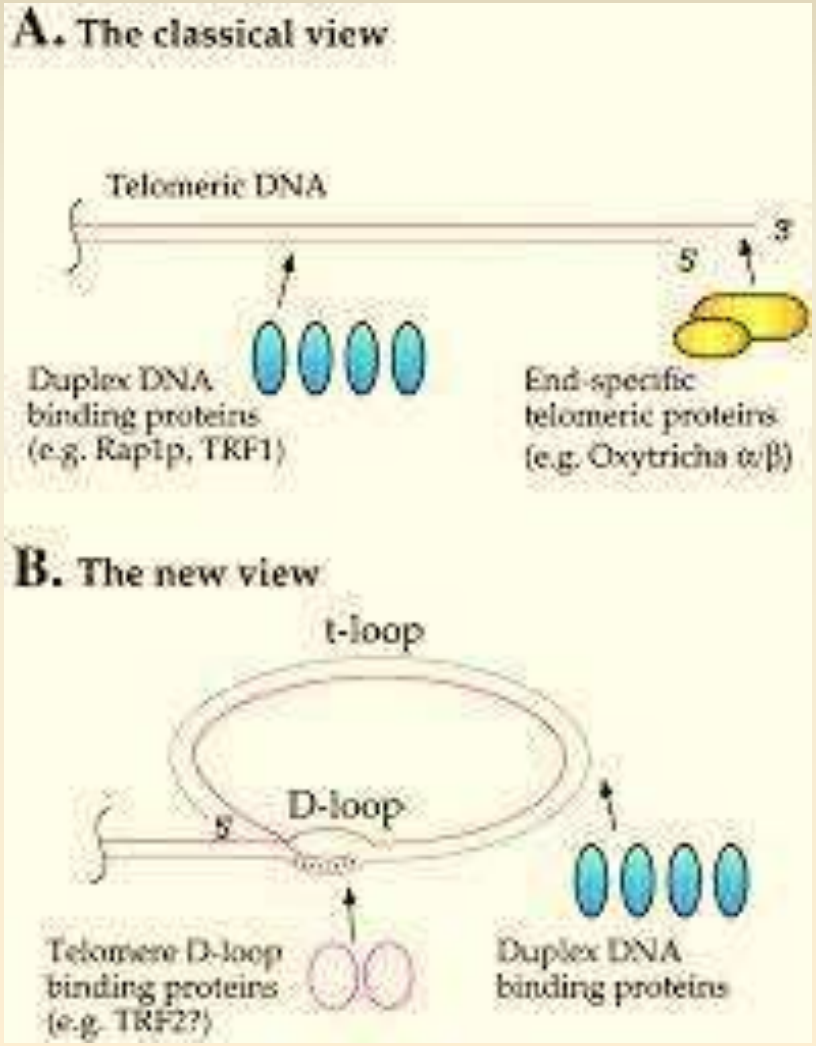
Structure of telomere



Telomeres are located at the end of chromosomes, where they help protect against loss of DNA during replication.

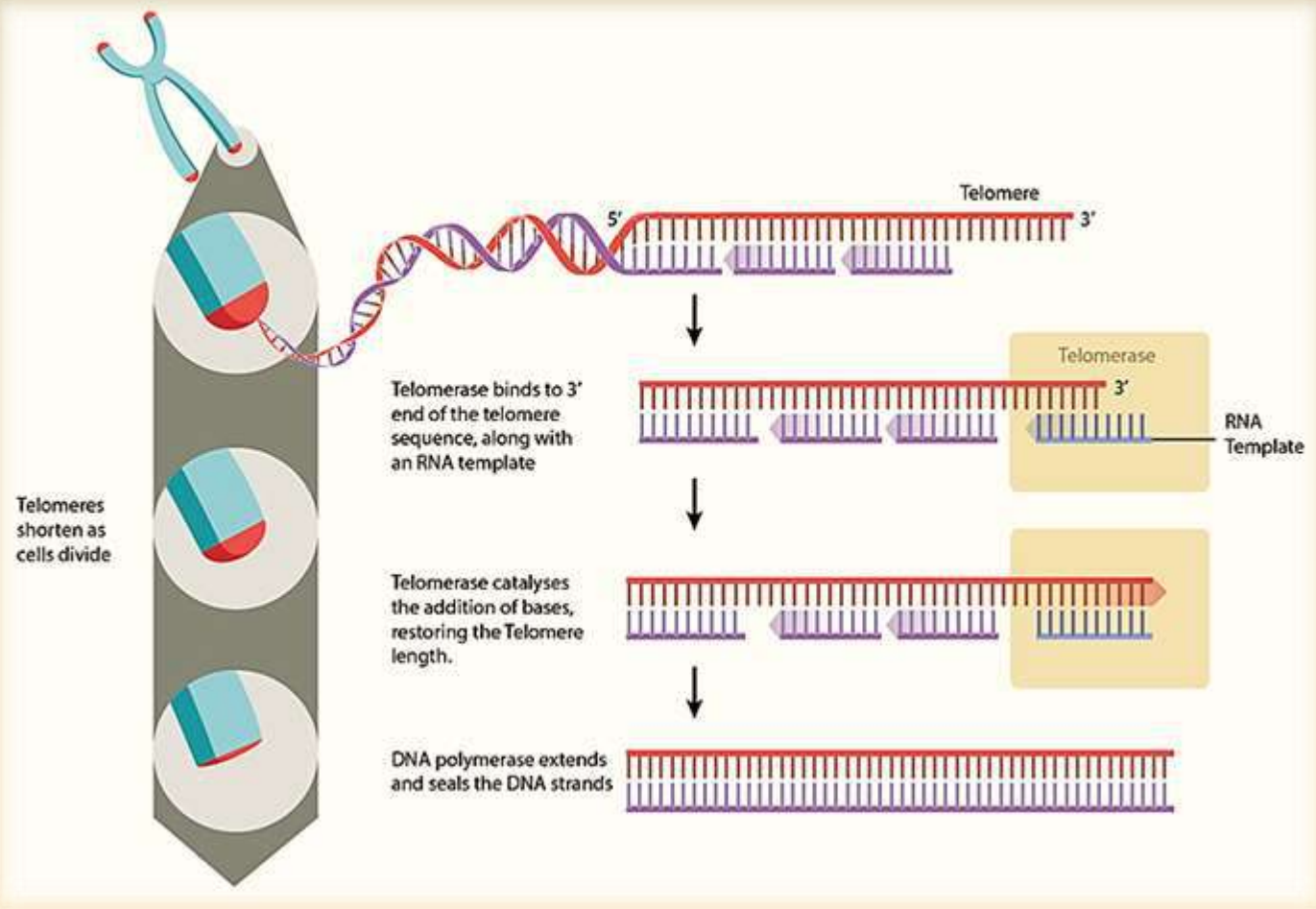
Structure of telomere

- Telomeres have large terminal loops rather than linear DNA endings as previously thought.
- There are two loos in the telomere, namely three-stranded DNA displacement loops or D-loops and RNA displacement loop or R-loops also known as telomere loops or t-loops.
- The long stretches of the double-stranded telomere DNA are looped around, and the single-stranded terminus is tucked back inside the double-stranded DNA molecule thus protecting the chromosome terminus



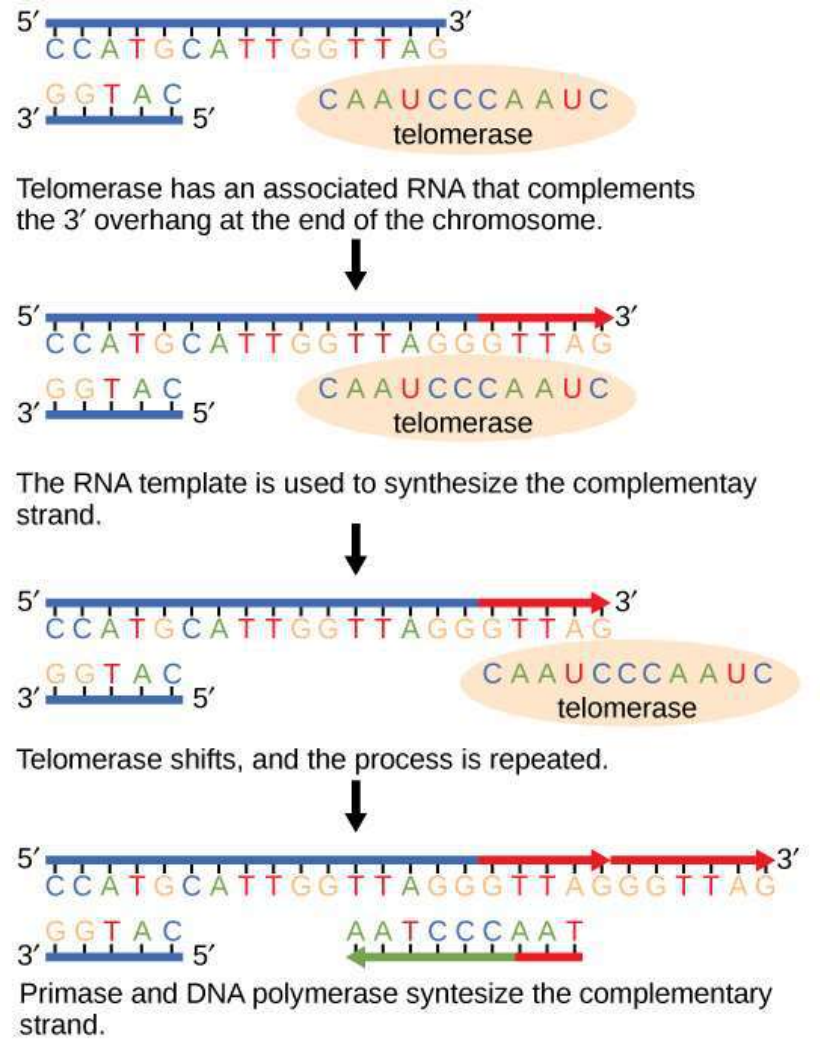
Greider C.W. Cell 1999; 97(4): P419-422.

Maintenance of telomere



- *Telomeres can be restored by the enzyme telomerase.*
- High level of telomerase activity is found in cells that undergo regular division.

Role of telomerase in telomere replication



Source: https://bio.libretexts.org

C-rich strand acts as template for leading-strand (5′→3′) synthesis.

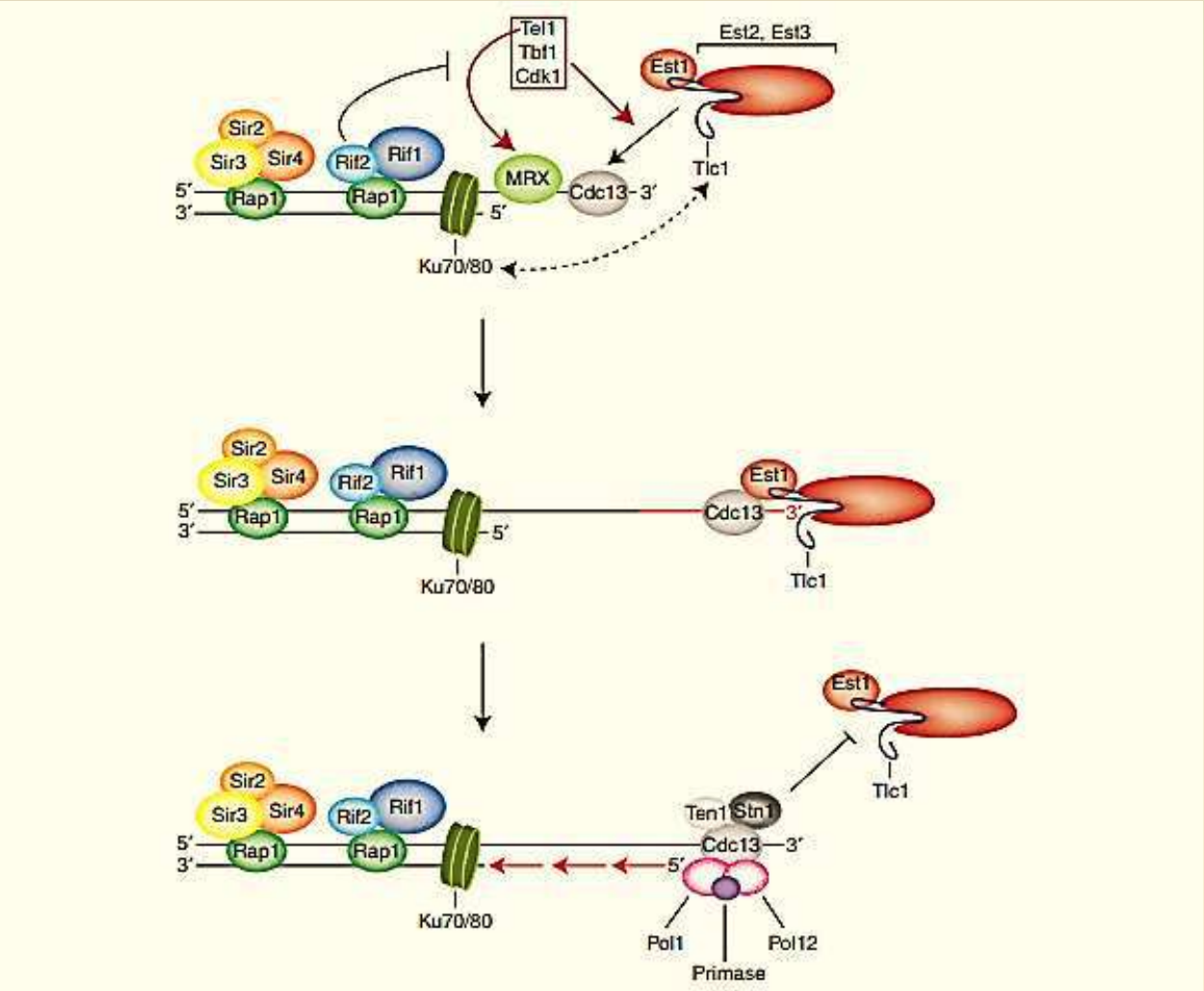
G-rich strand acts as template for lagging-strand (3′→5′) synthesis.

Telomerase extends telomeres in late S phase after DNA replication.

Replication of telomere

- Replication of telomere is carried out by specialized enzyme known as telomerase during late S phase.
- Telomerase is ribonucleoprotein reverse transcriptase which consists of protein subunit (TERT) and an integral RNA component (TER).
- RNA component (TER) is is utilized by protein component (TERT) to add multiple, identical repeats of DNA, i.e., telomeres to the end of the chromosome.
- First, recognition of the shortest telomeres by telomerase is mediated with the help of Tel1 which specifically recruited to the shortest telomeres by MRX protein (MRX complex).
- Another protein Tfb1 also recognizes short telomere and binds to 5′ TTAGGG 3′ repeats that are present in the subtelomeric region of the yeast telomere (Koering et al. 2000).
- Short telomeres replicate normally in S phase. Replication in S phase gives more time for telomerase to mediate extension of the shortest telomeres (Bianchi and Shore 2007).
- Synthesis of telomeric sense strand or leading strand or G-strand is performed by recruitment of telomerase at Okazaki fragments continuously.
- Synthesis of telomeric antisense strand or lagging strand or C-strand is performed by recruitment of polyα-primase.
- There may be switch between G- to C-strand synthesis by polyα-primase.

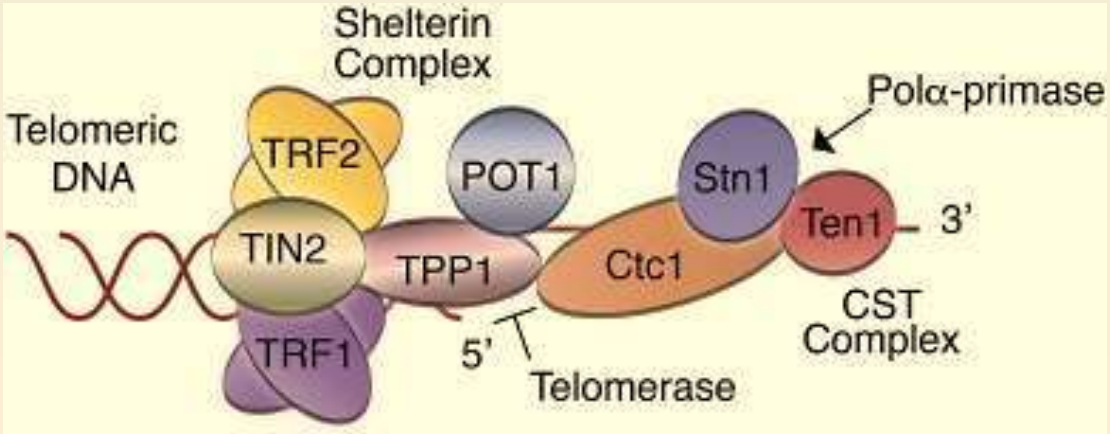
Replication of telomere



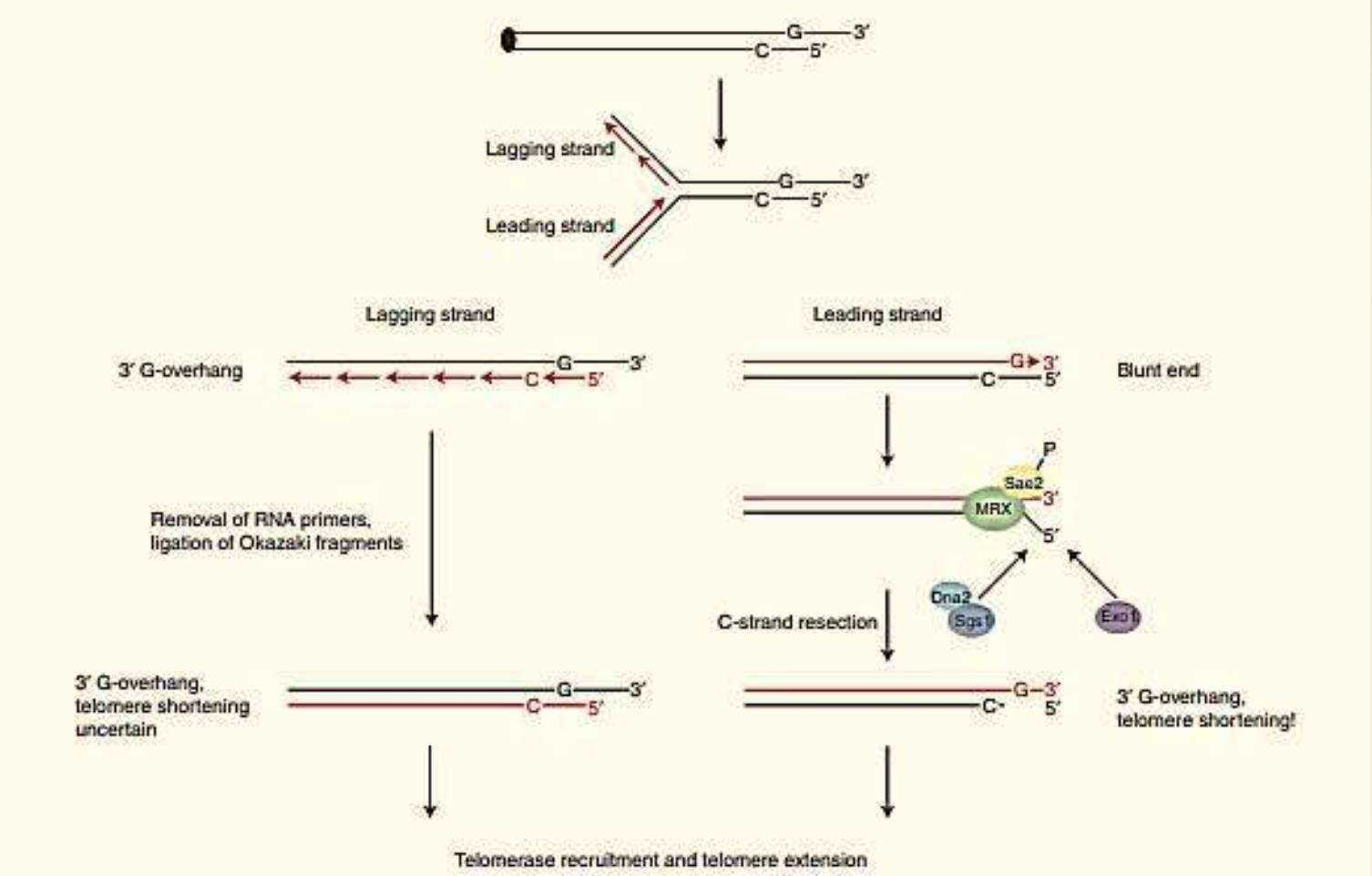
Replication of telomere

- Short telomeres replicate earlier in S phase which confer more time for telomerase to mediate extension of the shortest telomeres (Bianchi and Shore 2007).
- Telomere extension depend on a physical interaction between Cdc13 that binds to the telomeric 30 overhang and the telomerase subunit Est1 (Evans and Lundblad 1999).
- Cdk1 contributes to the cell-cycle dependent recruitment of telomerase through phosphorylation of Cdc13.
- Telomerase extension is terminated upon formation of the CST complex in yeast and by Shelterin compex in vertebrates, which promotes recruitment of DNA Pol a-primase for fill-in synthesis.

✓ *CST complex is a multiprotein complex composed Cdc13, Stn1, and Ten1 in yeast and proteins CTC1, STN1, and TEN1 in mammals.*



Telomere replication and DNA end resection



The blunt end intermediate at the leading-strand telomere is processed by 5′ end resection in order to recreate a 3′ overhang resulting in shortening of the telomere.

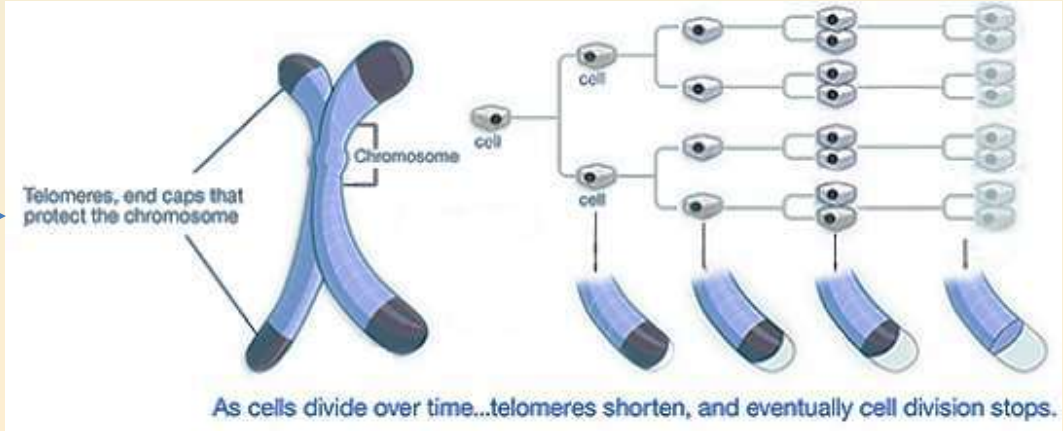
Dysfunction of telomerase maintenance

- Telomere loss and uncapping provokes progressive tissue atrophy, stem cell depletion, organ system failure, and impaired tissue injury responses.
- Telomerase is also diminished over successive cell division that results in fewer telomerase in somatic cells.
- Loss of telomere trigger deregulation in cell division through the impaired regulation of cell division.
- the telomeres of these cells become too short to prevent NHEJ (Non Homologous End Joining) and HR(Homologous Recombination) of chromosome ends, causing a state known as crisis. (Counter C.M. et al., 1992, EMBO).
- Telomerase reactivation has been found to reduce DNA damage signaling and associated cellular checkpoint responses, allows resumption of proliferation (Jaskelioff M, et. al. 2011)

Telomere and ageing

- Telomere play an indispensable role in ageing process happening due to shortening of its length (25 – 200 bases lost in every cell division).
- This loss is due to two main factors, i.e., “end replication problem” accounting for loss of 20 bp), and “oxidative stress” accounting for loss of 50 – 100 bp).
- When the telomere becomes too short to reach a critical length, it is no longer replicated.
- Critical length play a signal/sensor for the cell to die by a process called programmed cell death or apoptosis.
- Therefore, telomere length can be said as our biological age as opposed to our chronological age.

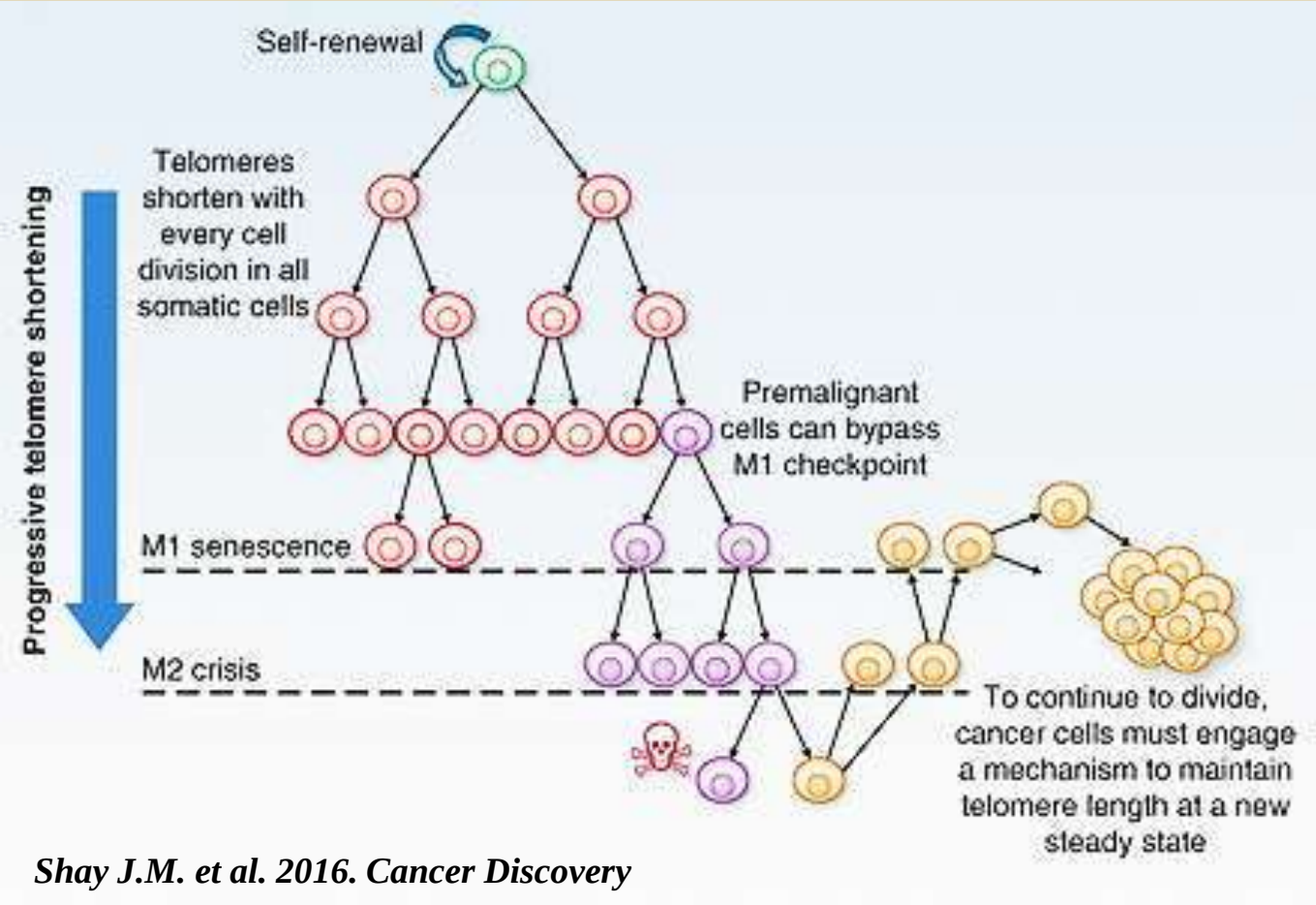
Image showing the successive loss of telomeric fragments in each successive cell division.



Telomere and cancer

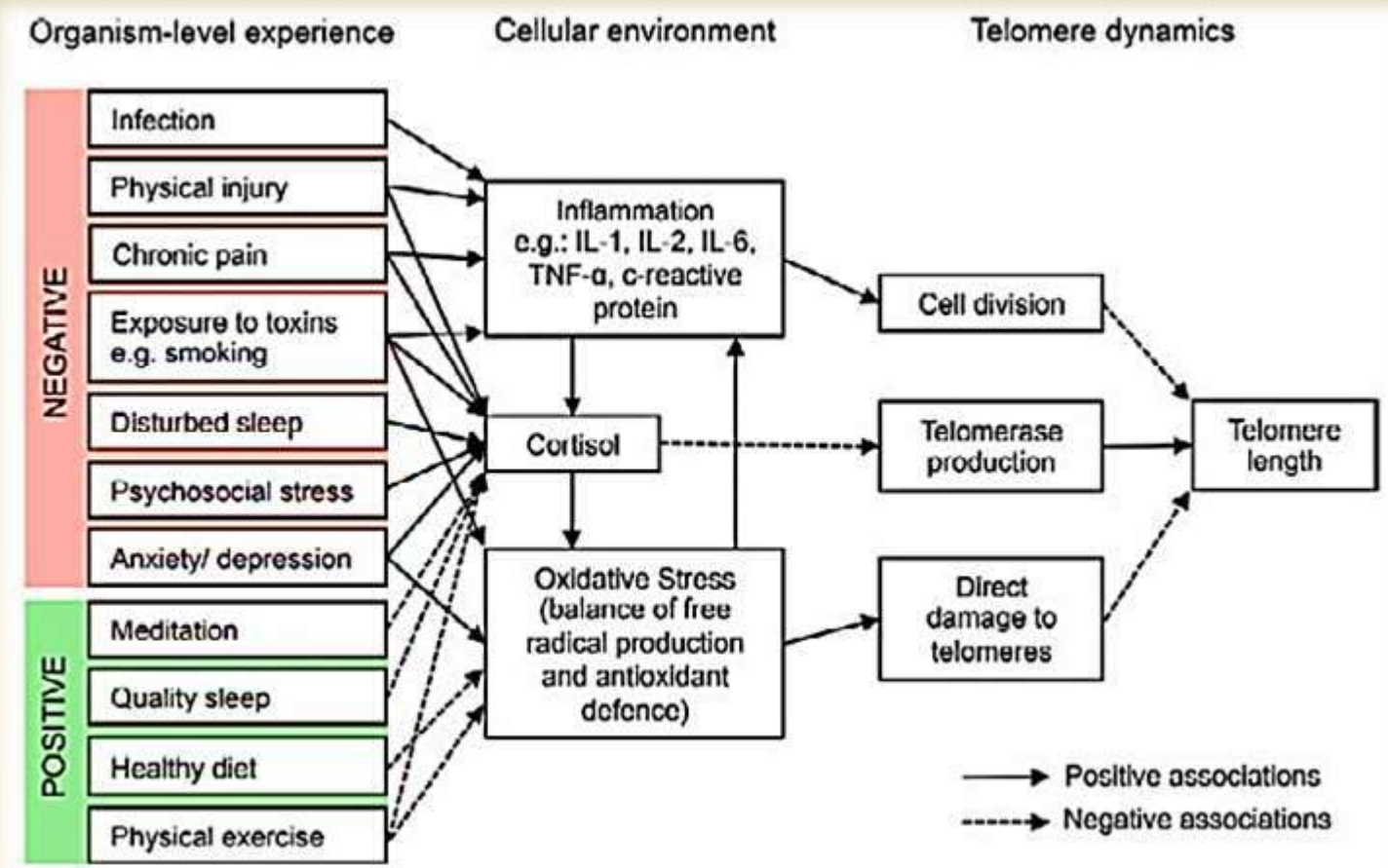
- Cancer cells possess high number of telomere and high titer of telomerase as in germ line cells and stem cells.
- However, some cancer shows shorter telomere length but they have active telomerase which makes them immortal through telomere maintenance.
- Cancer cells enforces telomerase to be activated preventing shortening of their genetic material (about 85% to 95% of human cancer have activates telomerase).
- Thus, cancer cells utilizes two stage model to regulate cell proliferation; first they inactivated DNA damage checkpoint, and second activate telomerase.
- Most study indicates the telomere telomerase through binding proteins Trf1 has major role in cell division as it is found to interact with cell division protein cdc2.
- Several proto-oncogenes and tumor suppressor genes also have been implicated in the regulation of telomerase activity, both directly and indirectly; these include c-Myc, Bcl-2, p21(WAF1), Rb, p53, PKC, Akt/PKB, and protein phosphatase 2A.
- These proteins are important regulator of cell division and cell senescence.

Telomere and cancer



Shay J.M. et al. 2016. Cancer Discovery

External factors affecting length of telomere



Telomeres are shorter in older cats and in cats with CKD.

In dogs, telomere length correlates with life span.

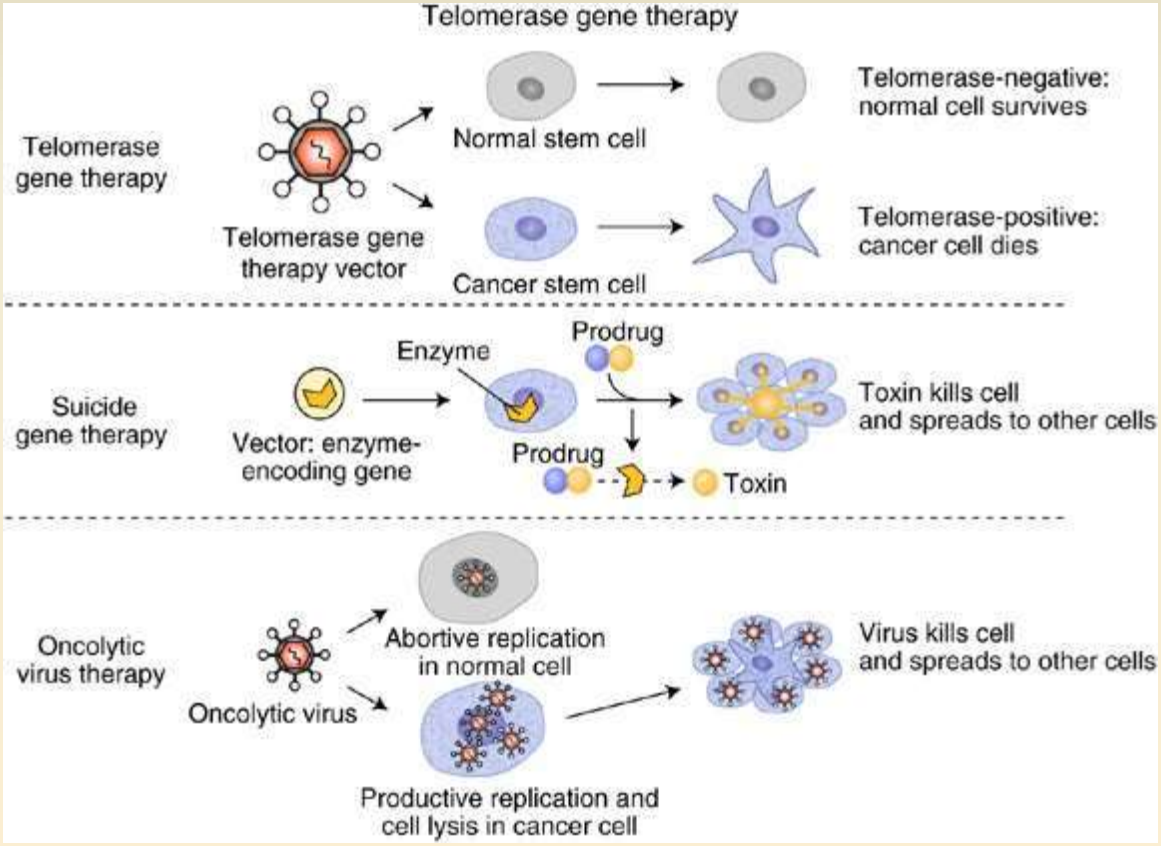
Dietary antioxidants are positively associated with telomere length.

Summary of some of the known relationships between organism level experiences.

Bioessays 2016;38:201-212.

Telomeres in regenerative medicine

- Since loss of telomerase activity makes a cell inactive, stop cell division and eventually signal for cell death.
- Whereas high telomerase activity renders a cell highly proliferative and therefore immortal leading the tumor cells formation.
- Therefore, it has been speculated that drugs that have been shown to inhibit telomerase activity, or kill telomerase-producing cells, may potentially stop and kill tumor cells .



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Further Reading

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