# The Role of Shelterin in Cellular Senescense and Systemic Aging

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## Introduction

Telomeres are special heterochromatic structure at the terminal end of eukaryotic chromosomes formed by tandem arrays of TTAGGG repeats bound to six telomere-specific proteins, the complex shelterin.

Telomeres cap the natural chromosome ends and protect them from being detected as DNA double-strand breaks (DBSs) and therefore, targeted by DNA repair pathways which lead to fusion and degradation of chromosome ends.

Due to the "end replication problem", telomeric DNA end in a 3' single-stranded overhang which can fold back and form the t-loop invading the double-stranded telomere helix in order to avoid the recognition of this free end as a DSB.

Shelterin plays a critical role in maintaining the integrity of the t-loop. The destabilization of t-loop either due to the telomeres shortering or loss of shelterin binding activates the DNA damage response (DDR) and induce the cellular senescence.

## Methodology

Literature research on PubMed database using following keywords: Telomere, Shelterin, senescence, stem cells, DNA damage response, aging, cancer, telomerase.
The papers were selected based the date of publication and authors.

## References

de Lange, T. Shelterin: the protein complex that shapes and safeguards human telomeres. *Genes Dev.* **19,** 2100–10 (2005).
Campisi, J. & d'Adda di Fagagna, F. Cellular senescence: when bad things happen to good cells. *Nat. Rev. Mol. Cell Biol.* **8,** 729–40 (2007).
Qian, Y. Senescence Regulation by the p53 Protein Family. *Methods Mol Biol* **965,** 37–61 (2013).

## Shelterin

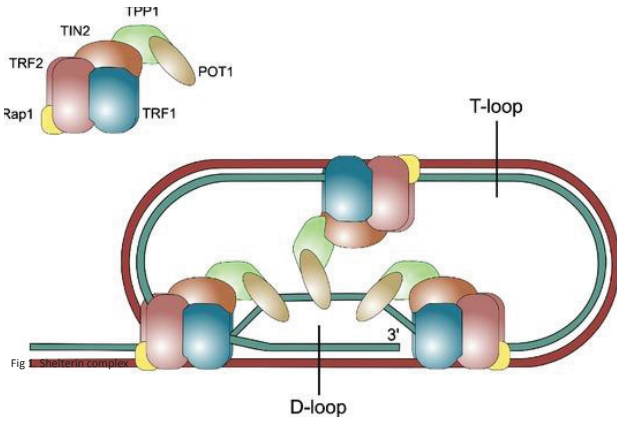


Figure1. The Shelterin complex

TRF1:
✓ DNA binding protein.
✓ Negative regulator of telomere length.
✓ TRF1 over-expresion induces telomere shortering mediated by XPF nuclease.
✓ TRF1 loss increases the telomere fragility but not telomere shortering
✓ Important role in telomere protection
✓ TRF1-deficient mice are embryonic lethal

TRF2:
✓ DNA binding protein.
✓ Negative regulator of telomere length.
✓ TRF2 over-expresion induces telomere shortering mediated by XPF nuclease.
✓ TRF2 inhibites ATM and Non Homologous End Joining (NHEJ).
✓ TRF2 over-expresion induces telomeric extension by HR.
✓ TRF1-deficient mice are embryonic lethal

TIN2:
✓ Tethers TPP1/POT1 to TRF1 and TRF2.
✓ Connects TRF1 and TRF2.
✓ Over-expresion of TIN2 inhibits telomere elongation by changing the telomere structure, which is inaccessible to telomerase.
✓ TIN2 mutation have been associated with bone marrow failure.
✓ TIN2-deficient mice are embryonic lethal.

TPP1:
✓ Deletion of TPP1 result in a loss of POT1.
✓ TPP1-depleted cells show the telomere dysfunction phenotypes.
✓ TPP1-deficient cells show a telomere fragility
✓ TPP1 regulates telomere length by recluting telomerase.
✓ TPP1-deficient mice are embryonic lethal.

POT1:
✓ POT1 binds to the 3' overhang and stabilizes the t-loop.
✓ Blocks the XPF nuclease.
✓ Inhibites the telomerase access, the ATR signaling pathway and NHEJ repair.
✓ POT-1-deficient mice are embryonic lethal

Rap1:
✓ Rap1 binds to TRF2
✓ Rap1 over-expresion induce telomere extension.
✓ Blocks the NHEJ repair.
✓ Rap1-deficient mice are viable.

## DNA Damage Response

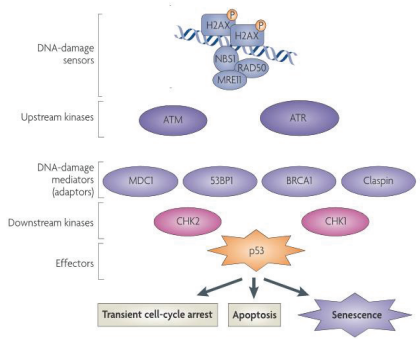


Figure 2. The DNA damage response

1. When t-loop is destabilized, DSB locus is recongnized by sensors of DNA damage response.
2. These sensors reclute ATM / ATR kinases
3. Activation of ATM / ATR kinases by autophosphorylation at Ser 1981.
4. Activated ATM / ATR kinases phosporylate the variant of histone H2AX
5. Phosphorylated H2AX reclutes mediators that bring to the DSB locus dowstream kinases
6. The dowstream kinases phosphorylates P53 and active it.

## Cellular Senescence

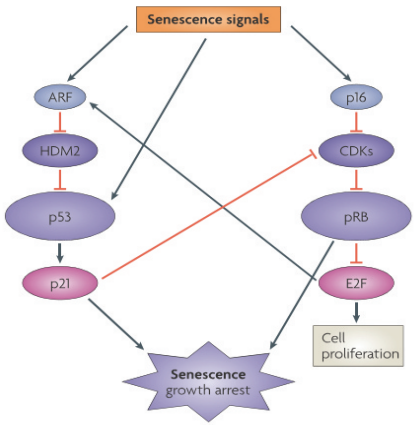


Figure 3. Senescence controlled by the p53 and the p16 pathways

Celular senescence is controlled by a functional p53 and p16. Without p53, cell that reach the replicative senescense (M1) bypass the cell cycle checkpoint and telomeres continue to short resulting in crisis (M2). M2 is caracterized by a chromosome end-fusions and genomic instability where cells undergo massive apoptosis.

## Systemic Aging

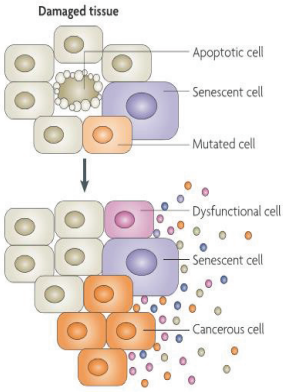


Figure4. Potential deleterious efects of senescent cells

- Senescent cells secrete factors that can alter the neighbouring cells' funtion and spoil the surrounding tissue.

- They can also stimulate the proliferation and malignant progresion of premalignant cells.

- Accumulation of senescent cells can compromise surrounding tissue's funtion

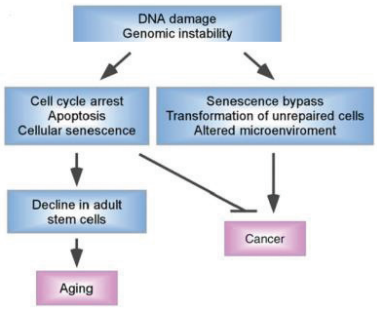


Figura 5. The correlation between cancer and aging

## Conclusions:

1. The shelterin complex plays a crucial role in telomere structure maintaince and protection.
2. Shelterin can reclute other telomere associated proteins in order to modulate the telomere structure and length
3. The telomeric end must be protected by the t-loop in order to avoid the DNA damage response.
4. In eActivation of P53 and p16 leads to senescence but protect the organismal from cancer
5. arly age, senescense is considered as a tumor supressor mechanism while in old age, it contributes to aging.
6. Stem cell ageing is the major problem of loss regeneration ability in tissues.