Telomeres are special heterochromatic structure at the terminal end of submetacentric 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 (DSBs) 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 shortening or loss of shelterin binding activates the DNA damage response (DDR) and induces the cellular senescence.

The shelterin complex plays a crucial role in telomere structure maintenance and protection. DNA binding protein. Negative regulator of telomere length. TRF1 over-expression induces telomere shortening mediated by XPF nuclease. TRF1 loss increases the telomere fragility but not telomere shortening. Important role in telomere protection. TRF1-deficient mice are embryonic lethal.


Rap1: Rap1 binds to TRF2. Rap1 over-expression induces telomere extension. Blocks the NHEJ repair. Rap1-deficient mice are viable.

Conclusions:
1. The shelterin complex plays a crucial role in telomere structure maintenance and protection.
2. Shelterin can recluster 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. Inactivation of TRF2 and p16 leads to senescence but protect the organism from cancer.
5. In early age, senescence is considered as a tumor suppressor mechanism while in old age, it contributes to aging.
6. Stem cell aging is the major problem of loss regeneration ability in tissues.

References