30. Telomeres and Telomerase in Aging and Cancer

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End-Replication Problem

- DNA polymerases cannot fully replicate chromosome ends.
- Results in progressive telomere shortening with each division.
- Predicted by Olovnikov (1971) and Watson (1972).

End-Protection Problem

- Chromosome ends must be distinguished from double-strand breaks.
- Telomeres are capped by the **shelterin complex** (TRF1, TRF2, POT1, TIN2, TPP1, RAP1).
- Shelterin prevents degradation, recombination, and fusion.
- Loss of protection triggers DNA damage signaling and genomic instability.

Telomeres and Telomerase: Structure, Function, and Regulation

- **Telomeres**: TTAGGG repeats, specialized chromatin, and t-loop architecture.
- **Telomerase**: reverse transcriptase (TERT) + RNA template (TERC/TER).
- **Activation**: High in germline, stem, and immune cells; repressed in most somatic cells.
- In ~85–90% of cancers, telomerase is reactivated, often via **TERT promoter mutations** (glioblastoma, melanoma, bladder cancer).

Cellular Aging and Senescence

- Telomere shortening activates checkpoints → replicative senescence.
- Serves as a tumor suppressor barrier.
- Contributes to aging via accumulation of senescent cells and SASP.

Telomere Length in Human Aging

- Declines with age in leukocytes and many tissues.
- Influenced by oxidative stress, inflammation, and genetics.
- Short telomeres are linked to cardiovascular disease, diabetes, and mortality.

Telomeropathies

- Disorders from mutations in telomerase (TERT, TERC, DKC1) or shelterin (TINF2).
- Symptoms: bone marrow failure, pulmonary fibrosis, liver disease, nail dystrophy, abnormal pigmentation.
- Underscore telomere maintenance as critical for stem cell renewal.

Telomerase in Cancer and Therapeutic Targeting

- Telomerase reactivation drives replicative immortality.
- **Clinical approaches**:
  - **Imetelstat (GRN163L)**: oligonucleotide inhibitor in clinical trials.
  - Small molecules, vaccines, and immunotherapies under development.
- **Challenges**: delayed effect, stem/progenitor cell toxicity.
- **Strategies**: transient inhibition or combinations with DNA-damaging agents.

Biology and Hallmarks of ALT

- **Definition**: A telomerase-independent telomere maintenance pathway (~10–15% of cancers).
- **Basis**: Homologous recombination–mediated extension, often linked to ATRX/DAXX loss.
- **Hallmarks**:
  - ALT-associated PML bodies (APBs).
  - C-circles as diagnostic markers.
  - Telomere length heterogeneity.
  - Elevated telomeric recombination and break-induced replication–like events.
- **Mechanisms**: HR between telomeres, BIR-like DNA synthesis, and replication stress.

ALT in Cancer and Therapy

- **Context**: Common in sarcomas, glioblastomas, osteosarcomas, pancreatic neuroendocrine tumors; correlated with ATRX/DAXX deficiency.
- **Function**: Provides immortality without telomerase.
- **Therapeutic directions**:
  - No approved ALT-specific drugs.
  - Target APBs, HR proteins (RAD51, BLM, FANCM), or replication stress (ATR/FANCM inhibitors).
  - C-circle assays in development as ALT biomarkers.

Paper for Discussion:

- Tesmer VM, Brenner KA, Nandakumar J. Human POT1 protects the telomeric ds-ss DNA junction by capping the 5' end of the chromosome. Science. 2023 Aug 18;381(6659):771-778. doi: 10.1126/science.adi2436. Epub 2023 Aug 17. PMID: 37590346.

Paper for Review : Lazzerini-Denchi, E and Sfeir, A. Stop pulling my strings — what telomeres taught us about the DNA damage response. Nat Rev Mol Cell Biol. 2016, 7, 364-78.