Explain the role of telomerase in cellular aging and NAD metabolism

Telomerase is an enzyme that maintains and elongates telomeres—the protective caps at the ends of chromosomes—which is a critical factor in cellular aging. Shortened or dysfunctional telomeres trigger cellular senescence (growth arrest), apoptosis, and can amplify age-related diseases and inflammation, making telomerase activity central to cellular longevity.[1] [2] [3] [4] [5] [6]

Telomerase in Cellular Aging

- Telomerase replenishes telomere sequences lost during DNA replication, allowing cells to divide repeatedly without losing vital genetic material.[3] [5] [1]
- In most somatic cells, telomerase is silenced, leading to gradual telomere shortening—a molecular clock for aging.[6] [1]
- Critically short telomeres activate DNA damage responses, promote cell cycle exit, and induce senescence, contributing to tissue dysfunction and aging phenotypes.[2] [5] [3] [6]
- Cells with shortened telomeres also exhibit increased ROS (reactive oxygen species), mitochondrial dysfunction, and a pro-inflammatory profile, exacerbating the aging process.[7] [2]

Telomerase and NAD Metabolism

- Cellular studies and animal models reveal that telomere dysfunction and short telomeres—often due to reduced telomerase activity—lead to disturbed NAD metabolism.[8] [9] [10] [7]
- Short telomeres can increase the activity of CD38, an enzyme that breaks down NAD+, contributing to loss of NAD+ homeostasis and impairing NAD-dependent enzymes such as sirtuins and PARPs.[10] [7]
- NAD+ depletion, in turn, weakens sirtuin function, which is important for DNA repair, mitochondrial health, and anti-senescence signaling—creating a feedback loop between telomere integrity and cellular metabolism.[9] [11] [10]
- Clinical models suggest that restoring NAD+ levels with precursors like NMN and NR boosts sirtuin activity and may help stabilize telomeres, reduce DNA damage at chromosome ends, and ameliorate cellular aging.[11] [8] [9] [7] [10]

Key Mechanistic Connections

- Telomerase maintains telomere length, preserving genome stability and delaying senescence.[5] [12] [3]
- Telomere dysfunction reduces NAD+ via increased CD38, which then impairs sirtuin/PARP function and worsens cellular aging.[7] [10] [11]
- Boosting NAD+ with NMN/NR or CD38 inhibition can partially reverse metabolic and telomere abnormalities in cells and animal models with telomerase defects, supporting a dynamic telomere-NAD metabolic axis.[9] [10] [11] [7]

Telomerase is therefore deeply intertwined with both cellular lifespan and metabolic health via regulation of telomere length and NAD+ homeostasis. Dysfunction in either system accelerates aging and promotes age-associated disease.[10] [11] [9] [7]

⁂

1. https://pubmed.ncbi.nlm.nih.gov/18391173/
2. https://www.frontiersin.org/journals/aging/articles/10.3389/fragi.2024.1339317/full
3. https://www.spandidos-publications.com/10.3892/mmr.2020.11274
4. https://embryo.asu.edu/pages/telomeres-and-telomerase-cellular-aging-senescence
5. https://pmc.ncbi.nlm.nih.gov/articles/PMC1933587/
6. https://www.nature.com/articles/s41556-022-00842-x
7. https://www.frontiersin.org/journals/aging/articles/10.3389/fragi.2021.785171/full
8. https://www.aboutnad.com/blogs/blog/re-balancing-nad-metabolism-blunts-the-impact-of-telomere-dysfunction-in-human-cells-mice
9. https://www.embopress.org/doi/10.15252/embj.2019103420
10. https://pmc.ncbi.nlm.nih.gov/articles/PMC9261345/
11. https://www.nature.com/articles/s42003-025-08567-x
12. https://febs.onlinelibrary.wiley.com/doi/10.1016/j.febslet.2010.07.042
13. https://learn.genetics.utah.edu/content/basics/telomeres/
14. https://www.sciencedirect.com/science/article/pii/S0753332223013513
15. https://www.nad.com/news/new-study-combining-nr-with-nac-may-slow-telomere-shortening
16. https://www.sciencedirect.com/science/article/pii/S2468501118300063
17. https://www.sciencedirect.com/science/article/pii/S0753332224005274
18. https://pmc.ncbi.nlm.nih.gov/articles/PMC7275989/
19. https://academic.oup.com/jcem/article/110/11/e3656/8069815