Aging

https://doi.org/10.1038/s41684-024-01360-z

Less telomerase slows early aging in *tp53mut* zebrafish

The aging process is characterized by less effective cell replication, with reduced replication stability and reduced preservation of genetic material. Telomeres are complexes composed of proteins and DNA located at the ends of chromosomes. Telomeres are critical for genetic stability, but they shorten with each replication round. This shortening is a consequence of insufficient telomerase activity, the enzyme responsible for the maintenance of the telomere complex. Most telomerase information comes from studies using inbred mouse models of aging. But with zebrafish showing telomere shortening, the *tert*$^{-/-}$ zebrafish model was previously developed. This fish model shows early-onset aging, chronic inflammation and an accelerated cancer rate attributed to telomerase deficiency. Telomerase and *p53* are essential for maintaining the integrity of the genome and suppressing tumor growth. Zebrafish mutants deficient in *tp53* show an increased risk of cancer. The tumor suppressor gene *TP53* acts as a mechanism of defense against cancer, and mutations on this gene have been found in multiple human cancers. However, the relationship between telomerase loss and the *TP53* gene remains unknown. A study in *Scientific Reports* demonstrated that the loss of telomerase in *tp53* mutants reduced cancer incidence and increased life expectancy in zebrafish.

The team compared wild-type animals showing normal aging, telomerase deficiency mutants (*tert*$^{-/-}$), *tp53* mutants (*tp53mut*), and double mutants (*tert*$^{-/-}$ *tp53mut*). The study found that the *tp53* mutation in double mutants, where telomerase is also reduced, rescued male infertility seen in single *tert* mutants while reducing premature aging phenotypes, such as abnormal spine curvature. When the fish carried only the *tp53* mutation, male fertility was only slightly affected during the first 9 months when compared to control animals. Conversely, a *tert* mutation reduced tumor incidence in double mutants while simultaneously increasing the mutant lifespan compared to single *tp53* mutants. However, the presence of *tp53* in double mutants did not impact the increased chronic inflammation rate caused by *tert* deficiency.

A decline in cell proliferation is a hallmark event of aging. The effects of telomerase have been previously described in mice and zebrafish. However, this study further establishes the interdependent connection between telomerase and *tp53* for aging and cancer. These results are important as they shed light on the mechanisms behind aging, which could be explored to develop strategies to prevent complications associated with aging in the future.

Jorge Ferreira

Original reference: Şerifoğlu, N. et al. *Sci. Rep.* **14**, 5382 (2024)