AGING

Targeting the gut to prevent aging

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The discovery that genetic mutations can expand the lifespan of the microscopic worm *Caenorhabditis elegans* sparked interest in finding interventions for promoting longevity and overall health using different model organisms. Telomere shortening, which leads to the activation of DNA damage and cell senescence signaling pathways, is a major determinant of aging. Telomerase, a specific reverse transcriptase, can counteract telomere shortening, but telomerase expression is insufficient to fully restore telomere erosion throughout the lifespan of vertebrates. In a new study published in *Nature Aging*, a team of scientists from the Institute for Research on Cancer and Aging of Nice shows that tissue-specific expression of telomerase in the gut can reverse premature aging in telomerase-deficient zebrafish, demonstrating the systemic effect of the gut on aging.

The mutant zebrafish strain is known for lacking telomerase, experiencing telomere shortening and early aging. [a]We started working with this telomerase mutant model to understand if there were problems in regeneration, but fin regeneration wasn't affected. Then, we started treating the fish as a whole entity as it would die prematurely. Looking at the choreography of organ failure, we found that the first organ to show problems was the gut[o] says Miguel Godinho Ferreira, the senior author of the study.

The study uses three experimental groups: wild-type (WT) zebrafish, mutant ($tert^{\pm/\pm}$ no Cre) zebrafish without telomerase, and a mutant ($tert^{\pm/\pm}$+ Cre) zebrafish with Cre-inducible telomerase expression in the gut. Here, the $tert^{\pm/\pm}$+ Cre group exhibited several positive outcomes compared to $tert^{-/-}$ no Cre fish, which showed aging defects. [a]The gut was healthy![o], says Godinho Ferreira. Telomeres in the gut of $tert^{\pm/\pm}$+ Cre fish were longer, the DNA damage response was suppressed and senescence was inhibited. Additionally, cell proliferation was restored, resulting in a healthy gut environment with reduced inflammation.

Given the positive impact of telomerase expression observed in the gut, researchers sought to determine whether this effect was extended to other organs. [a]The rest of the animal was wild-type like. Gut was influencing all the other organs, where they recovered even without telomerase being expressed in them. Reproductive capabilities were also back[o], explains Godinho Ferreira.

This study demonstrates that restoring telomerase expression in the gut counteracts systemic aging. Future studies may focus on translating these findings into potential therapeutic strategies targeting the intestine for combating age-related diseases and promoting healthy aging in humans.

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