MODEL ORGANISMS

Short-lived excitement

A collection of genomic tools helps researchers exploit a short-lived fish species as a model for human aging.

The systemic decline that overtakes the body during aging underlies many human diseases, including such leading killers as cancer, heart disease and Alzheimer's. Unfortunately, the processes of human aging—and potential determinants of human longevity—remain difficult to study. Worms and flies are useful and easy to work with but represent greatly oversimplified models, whereas closer relatives such as rats and mice have lifespans that make natural aging studies impractical.

Stanford University researchers led by Anne Brunet have now assembled a valuable set of resources for the study of vertebrate aging, centered on the turquoise killifish. This species has an extremely short lifespan of 4–6 months, during which it experiences the same processes of age-related physical decline that take place in mammals at a proportionally compressed timescale. Scientists have long been aware of this fish's potential as a model but lacked the genetic tools to render it completely useful, and so Brunet and colleagues began by sequencing and annotating the turquoise killifish genome. Drawing on the gene models developed through this process, the researchers designed a collection of guide RNAs that could be used for genomic editing via the clustered, regularly interspaced, short palindromic repeats (CRISPR)-Cas9 system.

As an initial proof of concept, the team disrupted the gene encoding TERT, the protein component of the telomerase enzyme. These mutant fish appeared healthy in early adulthood but subsequently acquired signs of atrophy in tissues that undergo extensive cellular proliferation, such as the intestinal lining and reproductive organs. The defects were even more prominent in the offspring from these fish; the researchers found that the loss of TERT resulted in considerable shortening of the telomeres in this second generation. This genome-editing process also made it possible to alter gene function with far tinier changes, including single-nucleotide mutations and short insertions.

This entire collection of tools—including the genome sequence, gene annotations and guide RNA designs—will be made available to the general research community, along with an initial set of mutant fish lines generated with these resources. "This platform should allow high-throughput studies on aging and longevity in vertebrates," the authors write, "as well as longitudinal modeling of human diseases."

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RESEARCH PAPERS

Harel, I. *et al.* A platform for rapid exploration of aging and diseases in a naturally short-lived vertebrate. *Cell* **160**, 1013–1026 (2015).