76. A Genetic Screen for New Genes Involved in Aging

Ala Berdichevsky[1], Leonard Guarente[2], Bob Horvitz[1]
[1]HHMI, Dept. Biology, MIT, Cambridge, MA 02139, USA
[2]Dept. Biology, MIT, Cambridge, MA 02139, USA

Over the last decade, studies of *C. elegans* and other organisms have resulted in progress towards understanding molecular mechanisms of aging. Mutations in genes involved in the insulin-like pathway or in mitochondrial function significantly affect *C. elegans* lifespan. Research in the field has largely focused on genes that normally function to reduce longevity, that is, genes that when mutated extend lifespan. This focus is primarily a consequence of the difficulties in distinguishing accelerated aging from sickness in short-lived mutants. Recently, Garigan *et al.*(1) and Herndon *et al.*(2) described characteristics of aging *C. elegans*, including decline in locomotion, muscle deterioration, and accumulation of autofluorescence in the intestine of aging animals. Such observations help distinguish aged from sick worms and therefore facilitate the study of the aging process in *C. elegans*.

We are interested in identifying and studying genes that function to prevent or delay the aging of *C. elegans*. Loss-of-function mutations of such genes should result in accelerated aging, similar to human progeria. We are performing a genetic screen for mutants that age prematurely, using accumulation of intestinal autofluorescence as a marker.

The accumulation of a lipofuscin-like fluorescent pigment in the gut of old worms has long been known to be a marker of aging. The amount of pigment is consistent among wild-type animals of the same age and gradually increases throughout adulthood. We measured the spectrum of the autofluorescence of old worms and found that emission peaks at 420 nm upon excitation at 350 nm. We are using a filter set with similar excitation and emission values to visualize lipofuscin and to screen for mutants showing early accumulation of this pigment.

So far we have screened worms corresponding to 20,000 mutagenized haploid genomes and identified 12 isolates that exhibit premature accumulation of gut autofluorescence. Eight of these isolates have significantly shorter lifespans than the wild type. We are currently mapping the mutations and characterizing the mutants with respect to other aging-related characteristics, such as behavioral decline and tissue deterioration.

1. Garigan, Hsu, Fraser, Kamath, Ahringer and Kenyon, Genetics **161**: 1101-1112 (2002).
2. Herndon, Schmeissner, Dudaronek, Brown, Listner, Sakano, Paupard, Hall and Driscoll, Nature **419**: 808-814 (2002).