Genetic Screens for New Genes Involved in *C. elegans* Aging

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Studies of *C. elegans* and other organisms have identified molecular pathways important in the control of aging. Research in this field has largely been focused on genes that normally function to reduce longevity (a loss of gene function extends lifespan), primarily because of the relative ease of identifying long-lived mutants and of the difficulties in distinguishing accelerated aging from sickness for short-lived mutants.

We are seeking genes that function to delay the aging of *C. elegans*. Loss-of-function mutations in these genes should result in accelerated aging. We performed a genetic screen for mutants that appear to age prematurely, based on their early accumulation of intestinal autofluorescence. We screened 20,000 mutagenized haploid genomes and identified 25 strains that exhibit premature accumulation of gut autofluorescence. We characterized these isolates for lifespan and other aging-related characteristics, including behavioral decline and tissue deterioration.

Three of our mutants are alleles of the gene *kat-1*, which encodes a conserved ketoacyl-CoA thiolase involved in the last step of fatty acid β-oxidation. *kat-1* maps to chromosome II and appears to be important for normal *C. elegans* lifespan and aging. Loss of *kat-1* function results in an early increase in intestinal autofluorescence and fat accumulation, a shortened lifespan and an early decline in pumping and locomotion. We are also characterizing two other highly fluorescent mutants isolated from the screen, *n5150* and *n5153*, which map to chromosome IV and fail to complement each other for increased intestinal autofluorescence. Both *n5150* and *n5153* accumulate more fat than does the wild type, as shown by Nile Red staining.

To understand how KAT-1 functions in the control of aging we are seeking suppressors of the early autofluorescence of *kat-1* mutants. We screened 20,000 mutagenized haploid genomes and identified 31 strains with wild-type intestinal autofluorescence. Some of these mutants suppress only the intestinal autofluorescence, while others suppress both the intestinal autofluorescence and the increased fat accumulation of *kat-1* worms. We are currently mapping these suppressors and characterizing their effects on lifespan and other aging-related characteristics.

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