

Relationship Between Catalase and Life Span in Recombinant Inbred Strains of *Caenorhabditis elegans*

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Abstract: Johnson and Wood constructed recombinant inbred strains of *Caenorhabditis elegans* with life spans ranging from 10 to 31 days. Using these strains, we have demonstrated previously that hyperoxia and methyl viologen inhibited development at rates inversely correlated with life span. The growth rates of the short-lived recombinant inbred strains were more profoundly inhibited by oxidative stress than were those of the long-lived strains. Here we report a positive correlation between life span and catalase levels in these same strains. Specifically, when compared to short-lived strains at 10 days after fertilization, the long-lived strains possessed higher levels of total enzymatic catalase. Northern blots indicated a similar relationship between life span and *cat-1*mRNA (the cytosolic catalase). This suggests that at least some of the polygenes that influence life span are also responsible for regulating gene expression of catalase, an important defense component against oxidative stress.

Key words: aging, catalase, *Caenorhabditis elegans*, life span, oxidative stress, recombinant inbreds.

There is perhaps no biological process for which genetics and the environment are so entwined as aging. *Caenorhabditis elegans* has proven particularly useful and popular for unraveling the relative contributions of “nature” and “nurture” to the dynamics and mechanisms of organismal aging. This is numerically evidenced by the proliferation of review articles, currently numbering more than 60, that encompass all or various elements of aging and life-span determination in the free-living nematode (e.g., Finch and Ruvkun, 2001; Guarente and Kenyon, 2000; Johnson et al., 2001).

One of the most striking relationships to have emerged from these investigations is that between life span and resistance to oxidative stress. Specifically, long-lived strains usually show heightened resistance to various presentations of oxidative stress, whereas some short-lived strains are hypersensitive to oxidative stress. For example, loss-of-function mutations in *mev-1* and *gas-1* shorten life span and render animals hypersensitive to oxidative stress (Hartman et al., 2001; Ishii et al., 1998). Both encode subunits of complexes of the electron transport system, and mutations in *mev-1* directly increase superoxide anion production (Senoo-Matsuda et al., 2001). Long-lived mutants show increased resistance rather than sensitivity to various presentations of oxidative stress (reviewed in Johnson et al., 2001). This is consistent with the theory that aging is a deleterious response to oxidative stress, a popular notion originally espoused by Harman (1956). It is clear that the mechanisms regulating superoxide anion and catalase levels are central to life-span determination. For example, *age-1* mutations that extend life span result in elevated superoxide dismutase and catalase levels in

geriatric worms (Larsen, 1993; Vanfleteren, 1993). In addition, dauer larvae can survive for months longer than other larval stages and have been recently shown to possess elevated levels of superoxide dismutase and catalase (Henthoofd and Vanfleteren, pers. comm.).

Most efforts have focused on investigating single-gene mutations that influence life span. However, the polygenic nature of aging in *C. elegans* has also received some attention (Ebert et al., 1996; Hartman et al., 1995; Johnson and Wood, 1982). Such analyses began by crossing different wild-type animals to generate recombinant inbred (RI) strains. Owing to independent assortment and genetic recombination, each RI will contain a more or less random mixture of the two parental genomes. This approach was first employed to create, in the absence of any selection, RIs with mean life spans from 10 to 31 days (Johnson and Wood, 1982). The mean life spans of the two parents were about 18 days. The analysis of RIs has, among other things, illuminated the role of oxidative stress in life-span determination. Ebert et al. (1996) exposed a heterogeneous population consisting of many different RI strains to an otherwise toxic level of hydrogen peroxide and identified among the survivors a specific parental chromosomal region that was over-represented, suggesting it conferred resistance to reactive oxygen species (ROS). Hartman et al. (1995) determined that there was a negative correlation between RI life span and the growth-rate inhibition imposed by either hyperoxia or methyl viologen. Thus, at least some of the same polygenes that contribute to life span also control oxidative stress responses. In this report, we extend this second approach by examining the expression of catalase in the RI strains. While there are currently more than 80 RI strains available in the Johnson laboratory alone, we choose to examine the same strains that we had employed previously (Hartman et al., 1995). Our results indicate that catalase levels correlate positively with life span, providing the first molecular linkage between the polygenetic basis of life-span determination and oxidative stress resistance in *C. elegans*.

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