

## Stress resistance and longevity in selected lines of *Drosophila melanogaster*<sup>☆</sup>

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Received 16 June 1999; received in revised form 25 August 1999; accepted 3 September 1999

### Abstract

Five independent populations (lines) of *Drosophila melanogaster* were selected for female starvation resistance. Females and males from the selected lines were relatively starvation resistant when compared to flies from five control lines. Moreover, flies from selected lines were resistant to other stresses: desiccation, acetone fumes, ethanol fumes, and paraquat (a source of oxygen radicals). Data from a variety of previous studies indicate an association between stress resistance and longevity. In this context, the present study addressed the question of whether flies from the stress-resistant lines were relatively long-lived. Replicate population cages from each selected and control line were used to assess longevity. Neither females nor males from the selected lines were relatively long-lived. In at least some cases, stress resistance may be necessary, but not sufficient, for longevity. © 1999 Elsevier Science Inc. All rights reserved.

*Keywords:* *Drosophila melanogaster*; Longevity; Stress resistance; Selection; Selected lines

### 1. Introduction

A body of data suggest an association between stress resistance and longevity. Support for a genetic basis for this relationship is derived from selection experiments, mutation analysis, and studies of differential gene expression. Selection experiments using *Drosophila melanogaster* have implicated a relationship between stress and longevity. Rose [41] selected for late-life reproduction, which increased longevity as a correlated response to selection. Flies from these selected lines were also found to be resistant to a variety stresses [45]. Specifically, Males and females from the selected lines were resistant to starvation, desiccation, and vapor from 15% ethanol. Conversely, selection for desiccation resistance or starvation resistance resulted in increased longevity [42].

Mutational analysis of longevity has been based on three model organisms: a yeast (*Saccharomyces cerevisiae*), a nematode (*Caenorhabditis elegans*) and a fly (*D. melanogaster*). Induced mutations in these model organisms indicate a correlation between longevity and stress resistance.

For example, yeast mutations characterized by stress resistance may exhibit a longer replicative life span [25]. A *D. melanogaster* P-element insertion mutation characterized by extended longevity was also relatively resistant to oxidative stress (paraquat), starvation, and high temperature [28]. A suite of nematode genes control entry into the *dauer* larval state, and mutations in some of these genes confer greater longevity [26]. Nematode mutations that increase longevity tend to be multiple-stress resistant [9,23].

Investigation of gene expression during the aging process, and studies based on differential expression of genes by using transgenic organisms, also indicate a genetic relationship between stress resistance and longevity. Relatively old yeast show elevated expression of the *RAS2* gene and, perhaps accordingly, transgenic over expression of *RAS2* delays replicative senescence in yeast [25,48]. *RAS2* plays a general role in environment-mediated cell signaling and can mediate responses to nutritional status and various stresses, including starvation, exposure to ultraviolet light, heat shock, and oxidative damage [22,25]. *D. melanogaster* has proven to be useful in this area of investigation. In aging muscle tissue, Wheeler et al. [52] documented increased expression of heat shock protein 70 (*hsp70*) and increased mRNA abundance of the *hsp22* and *hsp23* genes. Tatar et al. [50] determined that a transgenic strain of *D. melanogaster* with extra copies of the *hsp70* gene exhibited an increased

<sup>☆</sup> This research project was supported by National Institute on Aging (NIA) AG08761.

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life span. Also in *D. melanogaster*, transgenic over expression of a superoxide dismutase (SOD) gene resulted in increased resistance to oxidative damage and increased life span in one study, but not in a second study [34,39]. Simultaneous over expression of catalase and SOD apparently increased life span [35,47]. In an inducible *D. melanogaster* gene expression system, catalase over-expression did not extend life span, but SOD over-expression increased life span ~50% [49].

Using *D. melanogaster*, we continue the investigation of the association between stress resistance and longevity. The current study compares five lines selected for starvation resistance with five control lines [16]. The comparison consists of stress-resistance assays and analysis of life span. The stress assays were tests for resistance to desiccation, solvent fumes, oxidation, as well as starvation resistance. Life span was evaluated for all selected and control lines by monitoring daily mortality in population cages. The a priori hypotheses were that flies from the lines selected for starvation resistance were resistant to other stresses and that they were relatively long-lived.

## 2. Method

### 2.1. Selection for starvation resistance and starvation assays

Female starvation resistance has been selected for ~40 generations. The laboratory history of the base population used for selection, rationale for the selection regime, and the response to the first 15 generations of selection are described in Harshman and Schmid [16]. Selection was conducted throughout the duration of the present study, and thus a brief description of the selection experiment immediately follows. There are five selected lines designated Si (Sirius) and five control lines designated W (Wolfskill). Each line is an independent population derived from one base population [16]. For each generation, the procedure was to transfer a total of 800 females from each selected line and 400 females from each control line into empty bottles, at a density of 100 per empty bottle. The bottles were plugged with cotton that was saturated with water. The selection regime was based on differential survival of adult females in the absence of food. Accordingly, the selected-line females were held in empty bottles until ~50% were dead, and the surviving females were aspirated onto fresh food. Control females were subjected to starvation each generation, but the duration of starvation was sublethal. After 24 h without food, control females were transferred onto *Drosophila* medium. Only females were selected because a previous study, based on selection for male and female starvation resistance, documented “striking heterogeneity among replicate populations in male starvation resistance” [2]. The basis of this phenomenon is not yet known, but in some populations all males may be culled

during the selection process, whereas in other populations some males may “escape” selection. For all lines in the present study, the density of larvae in rearing vials was controlled by transferring ~75 eggs to each vial that was used to produce the next generation of adults. After adults emerged, and were allowed ~2–3 days to mate, females were separated from males under light ether anesthesia and then held for a least a day before exposure to starvation conditions for the next cycle of selection.

For the present study, starvation resistance was assessed in the interval from Generations 25 to 35 of the selection experiment. All lines were simultaneously assayed for starvation resistance. After Generation 31 of the selection experiment, using flies reared with the starvation of the parents, we conducted a bottle assay by placing 100 females or 100 males, 4–8 days old, in empty bottles, each with a water saturated cotton plug at room temperature (21–23°C). Two bottles were used for each sex from each line. Mortality was recorded at 8-h intervals until all flies were dead. A vial-based assay was conducted by placing 10 females or 10 males, 4–8 days old, in empty vials, with a water saturated cotton plug, at 22°C. Three vials were used for each sex from each line, and all lines were tested simultaneously. Mortality was recorded at 8-h intervals until a high proportion of the flies from the control lines were dead, at which time the assay was terminated. The starvation assay in vials was conducted twice by using flies from a separate generation for each experiment.

### 2.2. Assays for resistance to solvent fumes, desiccation, and paraquat

Assays were conducted for resistance to acetone fumes, ethanol fumes, elevated temperature, and paraquat. The latter is a compound that generates oxygen radicals that in general are considered to be a significant cause of aging. All lines were simultaneously assayed with replicate vials for each sex and for each line. Flies from selected and control lines were tested after being reared from adults not subjected to starvation. In other words, flies were tested after generational separation from the selection experiment. Adult flies were 4–9 days old at the beginning of these assays. Flies were separated by sex while under light ether anesthesia several days prior to the beginning of an assay. Exposure to each stressor was terminated at the end of an exposure period that killed a relatively high proportion of control flies. Just prior to assays, flies were transferred to otherwise empty vials that were plugged with cotton. Except as noted, for all assays either 10 females or 10 males were placed in empty 8-dr vials with a cotton plug. All lines were tested simultaneously, and repeat experiments of the same type were conducted with flies from different generations.

Assays for resistance to solvent fumes were conducted by holding flies in vials in proximity to the solvent outside the vials but within a closed space. At the termination of exposure to solvent fumes, all flies were transferred from

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