Longevity Regulation by Drosophila Rpd3 Deacetylase and Caloric Restriction

Blanka Rogina,1 Stephen L. Helfand,1 Stewart Frankel2*

Genetic studies of single gene mutations are revealing mechanisms and pathways that regulate longevity across distant species (1). One such mechanism is an alteration in histone deacetylase activity. Abolishing expression of the Rpd3 deacetylase (2) or increasing expression of the Sir2 deacetylase (1) increases life-span in yeast; Sir2 mediates increased nematode longevity as well (1). Caloric restriction is an intervention that increases life-span in mammals, insects, nematodes, and yeast (1, 3). Although the molecular pathways underlying the response to caloric restriction are yielding to genetic analysis in yeast (1), there is little information on how this response is regulated in metazoans. We investigated the relationship between histone deacetylases, caloric restriction, and longevity in Drosophila.

Greatly reduced Rpd3 levels are lethal in Drosophila (4), but partial reduction of Rpd3 levels has not been evaluated for its effect on life-span. We found that males heterozygous for either a hypomorphic (partial loss-of-function) or null mutation of rpd3 have life-span extension of 33% and 41 to 47%, respectively (Fig. 1A). Females heterozygous for the hypomorphic allele have a 52% increase in life-span, whereas females carrying the null mutation have only modest changes in life-span (maximum but not median life-spans are increased). The presence of large increases in life-span for males carrying both types of allele indicates that the effect is specific to the rpd3 locus. The different results for females may indicate a greater sensitivity to the predicted lower levels of Rpd3 in individuals carrying the null mutation compared with individuals carrying the hypomorphic allele.

To further explore the parallels between life extension in yeast and Drosophila, we examined the effect of caloric restriction on normal-lived control and long-lived rpd3 mutants. Longevity is increased to approximately the same extent in control flies fed a low-calorie diet and rpd3 mutants fed a normal diet (Fig. 1B). In addition, caloric restriction of the rpd3 mutants shows no further extension of life-span (Fig. 1B). The lack of an additive increase in longevity is not due to a physiological cap for life-span extension, because rpd3 females that were kept as virgins did have a further extension of longevity [see (14) in supporting online material (SOM)] (5). Furthermore, at least one other mutation in Drosophila, Indy, increases life-span to a greater extent (>90%) (6). It has previously been demonstrated that caloric restriction of flies leads to a moderate but significant down-regulation of Rpd3, analogous to the decreases obtained in heterozygotes carrying rpd3 mutations (7, 8). The data suggest that life-span extension by the rpd3 mutation is within a pathway related to caloric restriction.

Given the evidence connecting histone deacetylases to life-span extension, we wanted to determine whether Drosophila longevity was generally responsive to changes in histone acetylation. Increased acetylation (9) was achieved by mutating an independent locus, Su(var)2-101. This had virtually no effect upon life-span (5). The effects of Rpd3 therefore appear to be specific, mediated by its targeting to particular genes and/or histone residues. The life-span extension obtained by feeding the drug phenylbutyrate to adult Drosophila may operate by a similar mechanism (10).

Studies in yeast have implicated Sir2 as an important element in the life-extending effects of caloric restriction (1). We found that under our two life-extending conditions, rpd3 mutants fed normal food and wild-type flies fed low-calorie food, Sir2 expression was increased twofold (Fig. 1C). Our results highlight the conservation of longevity regulation across distant species boundaries and suggest a genetic pathway that begins with caloric restriction and proceeds to down-regulation of Rpd3, followed by Sir2-independent regulation of longevity effector genes (gene activation) and/or increased Sir2 levels and Sir2-dependent modulation of longevity effector genes (gene silencing).

References and Notes
5. Supplementary online material is available on Science Online.
8. S. Pletcher, personal communication.

Supporting Online Material
www.sciencemag.org/cgi/full/298/5599/1745/DC1
Materials and Methods Table S1

1Department of Genetics and Developmental Biology, School of Medicine, University of Connecticut Health Center, Farmington, CT 06030, USA. 2Department of Pediatrics, Boyer Center for Molecular Medicine, Yale University School of Medicine, 295 Congress Avenue, New Haven, CT 06536, USA.

*To whom correspondence should be addressed. E-mail: stewart.frankel@yale.edu
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