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What can long-lived mutants tell us about mechanisms causing aging and lifespan variation in natural environments?

Michael Briga *, Simon Verhulst

Groningen Institute for Evolutionary Life Sciences, University of Groningen, 9747 AG Groningen, the Netherlands

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ABSTRACT

Long-lived mutants of model organisms have brought remarkable progress in our understanding of aging mechanisms. However, long-lived mutants are usually maintained in optimal standardized laboratory environments (SLEs), and it is not obvious to what extent insights from long-lived mutants in SLEs can be generalized to more natural environments. To address this question, we reviewed experiments that compared the fitness and lifespan advantage of long-lived mutants relative to wild type controls in SLEs and more challenging environments in various model organisms such as yeast *Saccharomyces cerevisiae*, the nematode worm *Caenorhabditis elegans*, the fruitfly *Drosophila melanogaster* and the mouse *Mus musculus*. In competition experiments over multiple generations, the long-lived mutants had a lower fitness relative to wild type controls, and this disadvantage was the clearest when the environment included natural challenges such as limited food (N = 6 studies). It is well known that most long-lived mutants have impaired reproduction, which provides one reason for the fitness disadvantage. However, based on 12 experiments, we found that the lifespan advantage of long-lived mutants is diminished in more challenging environments, often to the extent that the wild type controls outlive the long-lived mutants. Thus, it appears that information on aging mechanisms obtained from long-lived mutants in SLEs may be specific to such environments, because those same mechanisms do not extend lifespan in more natural environments. This suggests that different mechanisms cause variation in aging and lifespan in SLEs compared to natural populations.

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1. Introduction

Aging is the decline in physiological function with age, associated with decreasing survival probability and reproduction. Remarkable progress in our understanding of aging mechanisms has been achieved through the study of model organisms such as yeast *Saccharomyces cerevisiae*, the nematode worm *Caenorhabditis elegans*, the fruitfly *Drosophila melanogaster* and the mouse *Mus musculus* (e.g. Sprott and Austad, 1996). An important tool in the study of aging mechanisms is the use of genetic mutants with an extended lifespan (Gems and Partridge, 2013; Kenyon, 2005, 2010; Partridge, 2010). The effect of these genetic mutations can be enormous, with for example some mutants living up to 10 times longer than wild type controls

* Corresponding author.
E-mail addresses: michbriga@gmail.com (M. Briga), s.verhulst@rug.nl (S. Verhulst).

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(Ayyadevara et al., 2009). Aging pathways identified in this way include those involved in stress responses and nutrient sensing such as the 'insulin/insulin-like growth factor 1 signaling' (IIS) pathway and the 'target of rapamycin' (TOR) pathway (Fontana et al., 2010; Gems and Partridge, 2013; Kenyon, 2005, 2010). The study of long-lived mutants has thus provided insight into key mechanisms that affect aging and lifespan.

Long-lived mutants are usually studied in standardized laboratory environments (SLEs), characterized by a constant climate, minimal exposure to pathogens, no opportunity to reproduce (depending on the species) and *ad libitum* food that can be obtained with little or no physical effort. Standardizing the environment has the advantage that it may reduce environmentally caused variation in aging and lifespan. More importantly, when the SLE provides an optimal environment, the animals may achieve a lifespan that is close to their maximum, determined only by intrinsic causes. On the other hand, an intrinsic aging phenotype can only be defined against the background of the environment, because intrinsic aging factors interact with the environment to determine intrinsic aging rate (Flatt et al., 2013; Stearns, 1992). Thus the lifespan achieved by long-lived mutants in SLEs is only one of the many phenotypes that characterize the specific long-lived mutant genotype, and mechanisms causing an extended lifespan in SLEs may not have a similar effect in more natural environments.

How the aging phenotype of a long-lived mutant varies between environments will depend on the physiological mechanism through which the extended lifespan is achieved. Given that SLEs lack most challenges faced by organisms in natural environments, the optimality theory of aging (Partridge and Barton, 1993), an umbrella covering the antagonistic pleiotropy (Williams, 1957) and disposable soma (Kirkwood, 1977) hypotheses, suggests that the extended lifespan of long-lived mutants may at least in part be due to a reallocation of resources saved on mechanisms that enhance fitness in natural environments (e.g. immune function, foraging, reproduction) to increased maintenance and repair (Fig. 1). If extended lifespans are achieved by saving resources that animals could not afford to save under more natural conditions, it is not clear how knowledge of the mechanisms giving these mutants an extended lifespan in SLEs will help understand variation in lifespan or the causes of aging in natural populations (including humans) where there would be strong natural selection against such savings. We thus question whether the mechanisms modulating lifespan in SLEs would be the same as those that explain variation in lifespan in the wild.

Given that much of our understanding of the mechanisms of aging comes from studies of long-lived mutants in SLEs, and that the environment can have profound effects on lifespan, we here ask to what extent insights from long-lived mutants in SLEs can be generalized to more natural environments. Is it possible that the longer lifespans of long-lived mutants are achieved at the expense of defenses against natural environmental challenges? And if so, what are the consequences for mechanisms involved in lifespan determination and variation in the wild? These questions are of importance when the aim is to apply insights from long-lived mutants in SLEs to other organisms such as humans, which are invariably exposed to a variety of environmental challenges. To address these questions we reviewed two kinds of studies. Firstly, we reviewed experiments that quantified the performance of long-lived mutants and wild type controls on evolutionary timescales by measuring the fitness of both genotypes in either SLEs or more challenging environments. These studies carried out competition experiments, which consist of mixing two genotypes (the long-lived mutant and the wild type control) in a common environment (SLE or challenging) usually for several generations, after which the relative frequency of each genotype was quantified.

However, fitness (dis)advantages in competition experiments may arise through differences in survival, in reproduction or a combination of the two, and while competition experiments quantify fitness, they rarely quantify survival per se. In the second part, we therefore reviewed studies that quantified the lifespan advantage of long-lived mutants over the wild type controls in SLEs and environments containing more natural challenges. These experiments often last only one generation and exclude competition, i.e. long-lived mutant and wild type populations are not mixed. When the life-extending effect of mutations is largely independent of the environment, this indicates that the underlying mechanisms may be of general importance in causing variation in lifespan. Conversely, a strong dependence of the life extending effect on environmental conditions would give reason to question the generality of the mechanism causing the life extending effect in SLEs.

2. Materials and methods

To find papers that reported competition experiments including long-lived mutants, we searched the Web of Science database using the keywords '*long-lived mutant*' and '*evolution*' (last search on May 31st 2015). This search resulted in 42 articles, of which we selected all articles that had long-lived mutants compete with wild type controls (Delaney et al., 2011; Jenkins et al., 2004; Savory et al., 2014). We then cross-searched all the references and citations of these articles.

For the lifespan studies, articles were only selected if the following criteria were met (i) a long-lived mutant had an extended lifespan in a SLE, (ii) an experimental manipulation of the environment affected the lifespan of either the long-lived mutant or the wild type control and (iii) an estimation of lifespan of the long-lived mutant and the wild type control in both environments. We searched the literature using (i) the above search and (ii) the Web of Science database using the keywords '*long-lived mutant*' and '*environment*' or '*long-lived mutant*' and '*natural*' (last search on May 31st 2015). In addition, we used influential reviews and perspective papers on long-lived mutants and genotype x environment interactions (Flatt et al., 2013; Gems et al., 2002; Partridge and Gems, 2007; Tatar, 2007; Tatar et al., 2014; Van Voorhies et al., 2006). For each of the three searches we searched all the references and citations of these articles before May 31st 2015 in the Web of Science database.

We define a stressor as a factor that shortens the lifespan of wild type controls and/or long-lived mutants relative to the lifespan in a SLE. When examining effects of stressors on lifespan we distinguished between the application of short-term acute stressors (heat stress, UV-radiation, toxic chemicals) that cause more or less immediate death of part of the population (e.g. Barsyte et al., 2001; Clancy et al., 2001), and more moderate long-term stressors that were applied permanently. Long-lived mutants appear more resistant to short-term acute stressors than wild type controls (see e.g. Zhou et al., 2011 for a review). Hence, when an environment is made more challenging by applying short-term acute stressors, the lifespan advantage of the long-lived mutants may increase (Zhou et al., 2011). However, we considered such acute stressors to be generally outside of the range

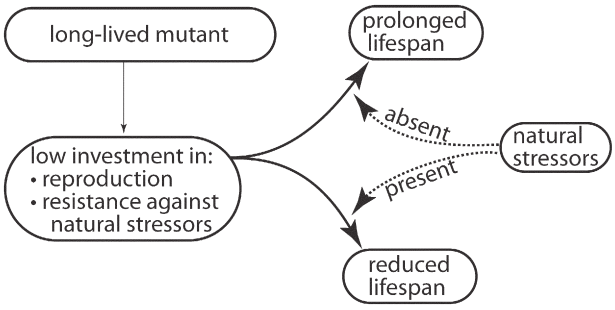

Fig. 1. Hypothesis, based on the optimality theory of aging (Partridge and Barton, 1993) stating that the lifespan advantage of long-lived mutants is diminished in the presence of natural stressors that are as a rule absent from standard laboratory environments.

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