Antagonistically pleiotropic allele increases lifespan and late-life reproduction at the cost of early-life reproduction and individual fitness

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Abstract

Evolutionary theory of ageing maintains that increased allocation to early-life reproduction results in reduced somatic maintenance, which is predicted to compromise longevity and late-life reproduction. This prediction has been challenged by the discovery of long-lived mutants with no loss of fecundity. The first such long-lived mutant was found in the nematode worm *Caenorhabditis elegans*. Specifically, partial-loss-of-function mutation in the *age-1* gene, involved in the nutrient-sensing insulin/insulin-like growth factor (IIS) signalling pathway, confers longevity, as well as increased resistance to pathogens and to temperature stress without appreciable fitness detriment. Here we show that the long-lived *age-1(hx546)* mutant has reduced fecundity and offspring production in early-life but increased fecundity, hatching success and offspring production in late-life compared to wild-type worms under standard conditions. However, reduced early-life performance of long-lived mutant animals was not fully compensated by improved performance in late-life and resulted in reduced individual fitness. These results suggest that the *age-1(hx546)* allele has opposing effects on early-life versus late-life fitness in accordance with antagonistic pleiotropy and disposable soma theories of ageing. These findings support the theoretical conjecture that experimental studies based on standing genetic variation underestimate the importance of antagonistic pleiotropy in the evolution of ageing.

1. Introduction

Ageing is a progressive deterioration of organismal function leading to reduced reproduction and/or increased probability of death with increasing age [1]. Despite the presence of cellular repair systems, ageing affects nearly all organisms and reduces Darwinian fitness in natural populations [2-4]. The evolutionary theory of ageing rests on the basic assumption that the lifespan of individual organisms in nature is inescapably curtailed by environmental hazards (e.g. predation, parasitism, starvation, drought or extreme temperatures) and accidents. Because of such environment-driven mortality, deleterious mutations whose effects are concentrated in late-life are partially shielded from selection and can accumulate in the population to cause an age-specific decline in organismal performance (mutation accumulation theory (MA); [5-7]). Moreover, alleles with beneficial effects on early-life can be positively selected despite their negative effects on late-life (antagonistic pleiotropy theory, AP;[8]). The "disposable soma" theory of ageing (DS) [9-11], which can be seen as a physiological account of quantitative genetic AP theory, specifically posits that organisms evolve to optimally allocate their limited metabolic resources between reproduction and somatic maintenance.

Empirical evidence suggests that standing genetic variation for ageing and longevity can be dominated by mutations with positively pleiotropic effects across the life stages supporting the MA theory (reviewed in [12]). Nevertheless, it has often been argued that quantitative genetic approaches may underestimate the importance of antagonistic pleiotropy because AP alleles would rapidly go to fixation [1]. Increased somatic maintenance manifested in high-fidelity DNA repair, better clearance of damaged proteins from the cells, and stronger immune response can safeguard the organism

against genome and proteome damage, as well as against parasites, and extend its projected lifespan (reviewed in [13]). However, when such measures hinder growth and impair reproduction, increased longevity can be detrimental to fitness, resulting in rapid fixation of alleles that boost early-life performance at the cost of reduced longevity and accelerated ageing. Because of the possible rapid fixation of adaptive AP alleles, there could be relatively little standing AP genetic variation for fitness in populations [1]. However, the occurrence of *de novo* mutations that increase somatic maintenance leading to improved longevity and stress resistance but result in reduced early-life growth and/or reproductive performance and compromised net individual fitness would provide support for AP and DS theories ageing. There are few examples of such mutations in model organisms, including mutations in *daf-2* [14], *nuo-6* and *isp-1* [15] genes in *C. elegans* and three mutations in IIS pathway in mice [16], where increased lifespan as associated with reduced reproductive performance [reviewed in 17, 18].

The discovery of long-lived mutants that combine longevity and stress resistance with normal reproduction challenged the inevitability of a resource allocation trade-off between reproduction and somatic maintenance [18-21]. The first long-lived mutant was discovered in the nematode worm *Caenorhabditis elegans*, where partial-loss-of-function mutation in the *age-1* gene encoding a catalytic subunit of the PI3 kinase results in downregulation of the nutrient-sensing insulin/insulin-like growth factor signalling (IIS) pathway [19, 22]. Initially, the longevity of *age-1* mutants was associated with severe reduction in fecundity [22]. However, it was later discovered that fecundity deficit was caused by a different co-segregating allele, while fecundity of *age-1(hx546)* worms was considered normal [23]. Because the finding of a long-lived mutant with

normal fecundity contradicted the prediction from AP and DS theories, later studies focussed at testing the performance of *age-1(hx546)* mutant animals under different environmental conditions. Thus, mutant worms were found to perform worse than wild-type under nutritional stress signifying that the trade-off between longevity and starvation resistance could explain the prevalence of the *age-1(+)* wild-type allele [24]. However, *age-1(hx546)* worms outperform *age-1(+)* wild-type counterparts in resistance to a range of bacterial pathogens [25], as well as in resistance to cold stress [26] and heat stress [27, 28] suggesting that the *age-1(+)* allele may not necessarily confer advantage under ecologically relevant environmental conditions [28, 29]. Moreover, a recent study combined the effects of starvation and heat stress to show that the *age-1(hx546)* mutation confers a selective advantage when periodic starvation is encountered together with temperature fluctuations, suggesting that environmental heterogeneity can favour long-lived mutants over their short-lived wild-type counterparts [28]. Thus, while several long-lived mutants in different model organisms were found to perform poorly under more natural conditions [17], *age-1(hx546)* animals seem to thrive under a range of ecologically relevant environments.

Here we studied age-specific reproduction and survival of the long-lived and stress resistant *age-1(hx546)* mutant to test two non-mutually exclusive hypotheses that could explain the reported lack of fitness loss in response to increased investment into somatic maintenance under standard conditions. First, we hypothesised that the long-lived genotype has reduced early-life reproductive performance, which can be compensated by improved performance in late-life. If so, individual rate-sensitive fitness of long-lived worms will be reduced. The rate-sensitive estimates of fitness should be

particularly relevant for longevity evolution under natural conditions where high environmental mortality due to predation and the ephemeral nature of their food sources can place higher priority on early-life reproduction than in the laboratory selection experiments.

Second, it is possible that long-lived worms invest less into protection and repair of their germline reducing the quality of their gametes rather than their quantity. Germline maintenance is costly, and a recent study have found that increased investment into germline stem cells can accelerate somatic ageing in nematodes [30]. To this end, we used an established technique to test the ability of the worms to repair the germline damage by subjecting them to low-dose ionizing radiation [31]. Because somatic cells of *C. elegans* nematodes are post-mitotic, they are highly resistant to radiation, while their germline stem cells are easily affected [31-33]. The germline that is damaged by exposure to low-dose ionizing radiation has the capacity to recover, either partially or fully [31], as long as some of the germline stem cells survive. We used both hatching success and total offspring production following low-dose ionizing radiation relative to baseline level of these variables in untreated control animals as an indicator of investment into germline protection, repair and recovery.

2. Methods

Nematode strains and experimental procedures

We used *Caenorhabditis elegans* strains Bristol N2 wild-type [34] and TJ1052 *age-1(hx546)* [35]. We confirmed the genotype of the *age-1 (hx546)* mutant by PCR using primers 261 age1F, 5'-GATGTTATCCATAACTTCGA-3', and 262 age1R, 5'-

TTACCTCCGTGGAAATGAAG-3', followed by sequencing. The populations were recovered and maintained under standard laboratory conditions at 20°C and 60% RH on NGM agar plates [34] that also contained kanamycin, streptomycin and nystatin following Lionaki and Tavernarakis [36], to prevent bacterial and fungal growth and fed with OP50-1 *E. coli* obtained from J. Ewbank from Centre d'Immunologie de Marseille-Luminy, which are resistant to these antibiotics. The population was synchronised by bleaching [37].

For life-history assays (lifespan and fecundity), we only used nystatin to prevent fungal contamination and worms were fed standard OP50 *E. coli* in these assays. In lifespan assays, 50 individual L4 worms per plate were placed on 35 mm agar plates and checked daily until death. Some worms were lost resulting in slightly reduced final sample sizes (see Table S4). The worms were transferred every second day to a new plate seeded with 0.1 ml *E. coli* OP50 grown in LB supplemented with 10 ug/ul nystatin. In reproduction assays, we followed the same procedure but individually kept worms were transferred to new plates every day until day seven, when reproduction has virtually ceased. Plates were saved for counting developed larvae and eggs 2.5 days later. Offspring were killed by placing them in a 40°C chamber for 2 h prior to counting.

Gamma-irradiation treatment was conducted using a Caesium source at Rudbeck laboratory, Uppsala University. All worms (including non-irradiated controls) were transported simultaneously to Rudbeck and back. Half of the plates were irradiated at 90Gy (97.7min at estimated 0.9214 Gy/min) by being randomly placed in one layer inside the Caesium source.

Statistical analyses

Survival was analysed in Cox proportional hazard models with Gaussian random effects implemented in the *coxph* package for *R 3.2.2*. The two worm strains (wild-type N2 and TJ1052 *age-1(hx546)*) and the treatments (control and irradiation) were modelled as crossed fixed factors.

We fitted the mortality data to the Gompertz family of four nested models (Gompertz, Gompertz-Makeham, Logistic and Logistic-Makeham) using maximum likelihood approach in WinModest software and the best fit was decided based on likelihood ratio tests [38]. The fullest model is Logistic-Makeham, where $\mu_x = c + \alpha e^{\beta}x / [1 + (\alpha s/\beta)\,(e^{\beta}x - 1)]$, where μx is the mortality hazard at age x, c is the constant mortality, α is the baseline mortality rate, *β* is the rate of increase in mortality with age (Gompertz rate-of-senescence), and *s* is the rate of deceleration in mortality late in life (late-life-deceleration). When c and *s* parameters equal zero, the model is reduced to the simplest two-parameter Gompertz equation ($\mu_x = \alpha e^{\beta}x$).

Fecundity (eggs produced) and offspring production (larvae alive after 2 days) were analysed in separate mixed models using the *lme4* package in *R*. Response variables were log transformed after adding a small constant (0.01) to meet the assumptions of normality and avoid infinite values. Strain, treatment, age and age^2 were modelled as crossed fixed factors, and female ID as random factor, to control for repeated measures. To investigate the effects of early and late reproduction, we also analysed the total reproduction between adult day 1-3 and 4-6 for every individual that survived this time period. These data were analysed in separate ANOVAs with strain and treatment as crossed fixed factors.

Hatching success was analysed in a generalized mixed model with binomial error structure. Strain, treatment, age and age^2 were modelled as crossed fixed factors, and female ID as random factor, to control for repeated measures. To test and control for overdispersion, we also added an individual–level observation effect (ILOE) as a random factor. We compared models with and without the ILOE using the *DHARMa* package in *R*. Inspection of the scaled residuals and testing for overdispersion showed that none of the models was significantly overdispersed (with ILOE: p = 1.0, without ILOE: p = 0.46) The dispersion-parameters of the models were calculated using the *blmeco* package in *R* (with ILOE: 0.595, without ILOE: 0.995).

Individual fitness (λ_{ind}) is a rate-sensitive measure of fitness and was calculated from the life table of age-specific daily reproduction from the Euler-Lotka equation following Brommer et al. [39]. Individual fitness and lifetime reproductive success (LRS) was only calculated for individuals surviving at least six days (13 individuals excluded), which encompasses the absolute majority of reproduction. Individual fitness and total reproduction were analysed in separate ANOVAs, using strain and treatment as crossed fixed factors. LRS was log transformed prior to the analysis.

3. Results and Discussion

Mutant *age-1(hx546)* worms indeed lived longer than wild-type, while there was no significant effect of ionizing radiation on longevity and no interaction between strain and radiation effects. Similar results were also obtained if worms dying of matricide (internal hatching of eggs) were treated as dead instead of excluded (Fig. 1, Table 1). However, radiation increased early-life mortality resulting in difference in age-specific mortality rates (Fig. 1, Table S1). The *age-1(hx546)* mutant had significant late-life deceleration

in mortality with the Logistic-Makeham model being the best fit (Table S1), while the best fit for wild-type worms was the Gompertz-Makeham model suggesting zero late-life deceleration in mortality rate in this cohort. Irradiated mutant animals lived longer than control wild-type individuals (Fig.1; χ^2 = 25.2 , df = 1, p < 0.001) further supporting increased stress resistance and longevity of *age-1(hx546)* worms. Interestingly, the cohort of irradiated mutant worms had lower rate-of-senescence than non-irradiated controls (-2*ΔLLR = 8.201, df = 1, p = 0.004; Table S1).

Long-lived *age-1(hx546)* mutant animals laid fewer eggs than wild-type worms both under irradiated and control conditions (Table 2), and this difference in fecundity was driven by lower egg-laying rates during the first three days of life (Fig. 2a, b, Table S2). However, *age-1(hx546)* worms had higher hatching success than wild-type worms during the second part of their reproductive life (days four to six) (Fig.2c, d; Table 3). Because the *age-1(hx546)* long-lived mutant had similar fecundity but higher hatching success in late-life, they also had higher offspring production during the last three days of reproduction (Fig. 2e, f; Table S3).

Thus, long-lived *age-1(hx546)* mutants have lower fecundity and lower offspring production in early life, but higher hatching success and higher offspring production in late life, while irradiation has a negative effect on reproduction in both strains. The interactions between irradiation, strain and age for offspring production (Table 2) suggest that the effect of irradiation on this trait was somewhat stronger in wild-type worms in early-life (Fig.2e, f). Because the worms produce most of their eggs and offspring during the first three days of life (Fig.2a, b, e and f, Table S2-S3), it is not surprising that both lifetime reproductive success and rate-sensitive individual fitness

(λ_{ind}) of wild-type worms are higher than those of the long-lived strain (Fig. 3a, b, Table 3).

These results are fully in line with AP and DS theories of ageing, and suggest that *age-1(hx546)* is an antagonistically pleiotropic allele that increases longevity, stress resistance and late-life reproductive performance at the cost of early-life reproduction and net fitness. These findings thus provide support for the hypothesis that ageing evolved as an optimal life-history strategy [1], where alleles that increase fitness are fixed by selection even when they accelerate ageing and reduce lifespan.

Several previous studies exploited standing genetic variation for ageing to test for the trade-offs between early-life and late-life fitness but produced mixed results [reviewed in 12]. The general problem with such studies is that standing genetic variation for age-specific fitness is not very informative as a test of the evolutionary theories of ageing, because beneficial alleles will become fixed by selection, while detrimental alleles can become fixed by drift [1]. Thus, even if AP alleles do play a key role in shaping the evolution of ageing in any given species or population, it may be difficult to reveal this using quantitative genetic approaches based on standing genetic variation. Mutation accumulation studies can provide a useful alternative but they are also not conclusive because AP alleles can be rare. Indeed, several mutations that increase longevity in model organisms also cause major reductions in fitness [17, 40, 41], suggesting that they would be rapidly selected against if occurred under natural conditions. Therefore, the discovery of an *age-1* (*hx546*) allele that substantially increased longevity, as well as stress resistance, of *C. elegans* nematodes that maintain normal development, locomotion and fecundity [24, 28] was surprising and remains one of the hallmarks of

the idea that lifespan extension can be relatively cost-free [19, 42]. Moreover, recent studies suggest that heat-shock resistance can confer substantial evolutionary advantage to *age-1 (hx546)* worms under starvation [28], the only condition to date where these long-lived mutants were shown to suffer in comparison to the wild-type [24]. Here we analysed survival and age-specific reproduction of *age-1 (hx546)* long-lived worms and found that they suffer from substantial reproductive deficiencies in early life, which are not sufficiently compensated by their improved late-life performance. Mutations such as *age-1 (hx526)*, which are beneficial for long life and slow ageing but detrimental for individual fitness, are directly predicted by AP theory of ageing and support the notion that standing genetic variation approaches may underestimate the importance of AP in the evolution of ageing

It has been suggested in recent years that energy trade-offs between reproduction and soma can be uncoupled and, therefore, are not necessarily decisive in the evolution of ageing and longevity [18, 20, 21, 29, 42, 43]. Here we show that the long-lived *age-1* mutant previously reported to lack the fecundity deficit suffers from early-life reduction in fecundity and net individual fitness under standard conditions supporting the hypothesis of the reproduction-longevity trade-off. Future research should focus on understanding the mechanistic basis of the reduced early-life reproduction and improved late-life reproduction and longevity of the *age-1 (hx546)* mutant. Recent studies suggest that there is a trade-off between germline cell maintenance and longevity in *C. elegans* nematodes [13, 44-46], and that germline removal, or arrest of germline development increases protection and repair of the proteome in the somatic cells [45, 47]. It is possible that long-lived *age-1(hx546)* mutant animals have either smaller or slower

developing germlines and, therefore, have more resources available for the

maintenance of the somatic cells resulting in slower reproductive ageing and increased

longevity.

Ethics Statement

All experiments comply with the laws of Sweden.

Data accessibility statement

The datasets supporting this article have been uploaded as part of the supplementary material.

Competing interests' statement

We have no competing interests.

Authors' contributions statement

AAM, AH and SI conceived, designed and coordinated the study. AM and SI wrote the initial draft. HC, PD and BM conducted the experimental work. MIL and AAM analysed the data. HC, PD, MIL, BM and AH worked on the manuscript. All authors gave final approval for publication.

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Figure legends

Figure 1

Survival curves of Bristol N2 wild-type and TJ1052 age-1(hx546) strains when kept under standard conditions (Intact) or gamma-irradiated at 90Gy (Irradiated). The left panel shows survival when worms that died by matricide (bagging) are excluded, while the right panel shows survival when all worms are included.

Figure 2

Age-specific reproductive performance (fecundity, hatching success, total number of offspring produced) of Bristol N2 wild-type and TJ1052 age-1(hx546) strains when kept under standard conditions (panels A, C, E) or gamma-irradiated at 90Gy (panels B, D, F). N2 worms reproduced better during the first three days, while TJ1052 worms reproduced better during the last three days (see Table 2 and Tables S2 and S3).

Figure 3

Lifetime reproductive success (LRS) and individual fitness (rate-sensitive fitness) of Bristol N2 wild-type and TJ1052 age-1(hx546) strains when kept under standard conditions (Intact) or gamma-irradiated at 90Gy (Irradiated). N2 worms have higher LRS and individual fitness both when intact and irradiated (see Table 3).

Table 1. Survival when matricidal worms (died of internal hatching of eggs early in life) were either excluded or counted as dead.

	Matricide excluded			Matricide as dead		
	z	df	p	z	df	p
Strain	-5.36	3	<0.001	-4.70	3	<0.001
Treatment	-0.98	3	0.33	-0.91	3	0.36
Strain × Treatment	0.86	3	0.39	0.87	3	0.38

Table 2. Total fecundity (eggs laid), viable offspring produced and hatching success. Residual variance is not calculated for binomial mixed effect models (hatching success).

Parameter	Fecundity			Offspring			Hatching success		
	X^2	df	p	X^2	df	p	X^2	df	p
Strain	7.23	1	0.007	17.38	1	<0.001	3.50	1	0.061
Treatment	31.09	1	<0.001	34.98	1	<0.001	538.9	1	<0.001
Age	4684	1	<0.001	5522	1	<0.001	63.61	1	<0.001
Age^2	1981	1	<0.001	2724	1	<0.001	0.01	1	0.944
Strain×Treatment	0.06	1	0.799	3.73	1	0.054	1.49	1	0.222
Strain×Age	12.28	1	<0.001	34.40	1	<0.001	8.14	1	0.004
Treatment×Age	4.99	1	0.026	4.75	1	0.029	102.3	1	<0.001
Strain×Age^2	16.46	1	<0.001	47.07	1	<0.001	48.41	1	<0.001
Treatment×Age^2	14.69	1	<0.001	0.46	1	0.496	29.17	1	<0.001
Strain×Treatment× Age	2.00	1	0.158	8,57	1	0.003	28.99	1	<0.001
Strain×Treatment× Age^2	1.41	1	0.235	9.51	1	0.002	58.37	1	<0.001
Random effects	Var.		Sd.	Var.		Sd.	Var.		Sd.
Female ID (intercept)	0.629		0.793	0.893		0.945	5.661		2.379
Female ID (Age slope)	0.002		0.048	0.004		0.063	0.518		0.713
Residual	2.446		1.564	2.165		1.471			

Table 3. Total reproduction and individual fitness (λ_{ind}).

Parameter	Lifetime reproductive success				Individual fitness (λ_{ind})			
	MS	df	F	p	MS	df	F	p
Strain	1.14	1	8.68	0.004	3.60	1	29.05	<0.001
Treatment	88.81	1	677	<0.001	83.98	1	678	<0.001
Strain×Treatment	0.006	1	0.04	0.835	0.11	1	0.89	0.346
Residuals	24.02	183			22.67	183		