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Mutation Accumulation Aging Theory

Laurence D. Mueller
Department of Ecology and Evolutionary Biology, University of California, Irvine CA, USA

Synonyms

Evolutionary theories of aging; Mutation-selection balance

Definition

Mutation accumulation refers to a process which involves both natural selection and mutation which can lead to senescence. This process assumes there exist deleterious mutations that act in an age-specific fashion and that the strength of natural selection weakens as the age of onset of the mutation increases.

Overview

The timing and pattern of reproduction or life history of an organism will fall into two broad categories: semelparity and iteroparity. A semelparous organism reproduces only once after development and sexual maturation. An iteroparous organism may reproduce multiple times during its adult life-span. For this entry we do not consider the evolutionary forces which favor one of these life history patterns over another. Instead the entry focuses on iteroparous organisms and what causes aging or the gradual increase in age-specific chances of mortality and the decline in age-specific reproductive capacity due to internal physiological deterioration.

Most mutations are deleterious and will be actively removed from populations by natural selection. However, the force of natural selection to remove these deleterious mutations will be opposed by new mutations constantly being added back into the population. An equilibrium is expected to be reached between these two forces. For semelparous organisms that equilibrium can be simply derived. Suppose at a single locus, the A allele mutates to the a allele with frequency μ. For a semelparous organism, fitness is assumed to affect the survival from zygote to reproductive adult. If the A allele is dominant, then the fitness of the AA, Aa, and aa genotypes can be assumed to be 1, 1, and 1-s, respectively, where $0 < s \leq 1$. At equilibrium the deleterious mutant will be at a frequency of $\sqrt{\mu/s}$. This equilibrium frequency increases as the deleterious effects of the mutant decline. For instance, if $\mu = 10^{-6}$ and $s = 0.1$, the equilibrium frequency of the mutant is 0.003. However, if

D. Gu, M. E. Dupre (eds.), *Encyclopedia of Gerontology and Population Aging*,
https://doi.org/10.1007/978-3-319-69892-2_48-1

selection is weak, say $s = 0.001$, then the equilibrium increases to 0.03. Similar results can be obtained when the mutant is not recessive.

In an iteroparous organism, it is often useful to divide the life-span into equally spaced age classes. Thus, $p(x)$ can represent the probability of an individual surviving from age class-x to age class-$(x + 1)$, and $m(x)$ can be the fertility of individuals in age class-x. If there is genetic variation at a single locus that affects survival, then we can represent the genotypic-specific survival at age-x of the two homozygotes as $p_{AA}(x)$ and $p_{aa}(x)$. Then at the mutation-selection equilibrium, the frequency of deleterious, recessive homozygotes (aa) will be:

$$\frac{\mu}{\{[lnp_{AA}(x) - lnp_{aa}(x)]s_{AA}(x)\}}, \qquad (1)$$

where $s_{AA}(x) = \sum_{y=x+1}^{d} e^{-ry} l_{AA}(y) m(y)$, d is the last age where reproduction is possible, and $l_{AA}(x)$ equals $\prod_{y=0}^{x-1} p_{AA}(y)$ (Charlesworth 1994, Eq. 5.5b). The function $s_{AA}(x)$ is a strictly decreasing function of x, for $r \geq 0$. Thus, for a constant survival difference and mutation rate, the equilibrium frequency of the mutant homozygote, Eq. (1) (and mutant allele), will increase, the later the mutant affects survival.

This theory suggests that the equilibrium frequency of deleterious alleles that lower survival will increase as their age of onset increases. Since there are expected to be many loci capable of affecting survival, every individual is expected to have a number of these deleterious alleles, and that number will increase with the age of the mutant's effect. Such a process should lead to an increasing chance of death as we get older or aging. In plants there is often substantial vegetative growth prior to the development of reproductive tissue. It has been suggested that older plants which have undergone more cell divisions during their vegetative growth may pass on more mutations to the germ line and hence lead to reduced longevity of their offspring. However, recent experimental evidence has shown this is not the case (Watson et al. 2016).

Key Research Findings

Theory

J. B. S. Haldane (1941) suggested that alleles with deleterious effects may be subject to genetic modifiers that delay the onset of the deleterious effects. However, as discussed by Charlesworth (1994), the selective advantage of such modifiers is expected to be small. Medawar (1952) gave a verbal description of the broad outline of mutation accumulation. This idea was expanded by Edney and Gill (1968).

A single locus population genetic model of mutation accumulation has been explored by Charlesworth (see Charlesworth 1994, chapter 5). A key result from that work is Eq. (1) above. Charlesworth (1990) has also shown that the accumulation of mutations in a quantitative genetic model can lead to senescence. More recent theoretical results deal with a relatively new demographic pattern called mortality plateaus (Carey et al. 1992; Curtsinger et al. 1992).

Aging is often defined with reference to increasing rates of mortality with age. However, research has shown in a number of organisms that at very advanced ages, mortality rates tend to level off and reach a plateau. Among the species showing such plateaus are the medfly *Ceratitis capitata* (Carey et al. 1992), the commonly studied laboratory fruit fly *Drosophila melanogaster* (Curtsinger et al. 1992), the Mexican fruit fly *Anastrepha ludens* (Vaupel et al. 1998), a parasitoid wasp *Diachasmimorpha longicaudata* (Vaupel et al. 1998), the nematode *Caenorhabditis elegans* (Brooks et al. 1994), the baker's yeast *Saccharomyces cerevisiae* (Vaupel et al. 1998), and the beetle *Callosobruchus maculatus* (Tatar et al. 1993).

One explanation for these late-life mortality plateaus suggests they are a consequence of natural selection and genetic drift. Mueller and Rose (1996) studied models of antagonistic pleiotropy and mutation accumulation using computer simulations. Their argument was that at very advanced ages, the force of natural selection is so weak that drift is the major determinant of allele frequency variation. Thus, deleterious, late-acting mutations that increase mortality may rise to high frequency

but will not show any age-dependent pattern as they would be expected to show from Eq. (1).

Charlesworth (2001) developed a quantitative genetic model of mutation accumulation. Charlesworth found that when mutations had deleterious age-specific effects and pleiotropic effects on all adult ages or all juvenile ages, then mortality rates would increase exponentially over most of the adult life-span and then plateau at late life. Wachter et al. (2013) generalize the results of Charlesworth by relaxing his linear analysis.

Experimental Tests

Additive genetic variance: phenotypes that are under the control of many loci typically show variation for these traits in natural populations. This variation can be broadly divided into an environmental component and a genetic component. The genetic component of variation can be further divided into an additive component and other components that do not act additively, e.g., those due to dominance and epistasis. If natural or artificial selection is applied to the trait, then the rate of change in the trait will be proportional to the additive genetic variation for the trait. If selection is very strong, the additive variation may be eliminated in which case no further changes in the phenotype due to selection will be possible.

As discussed earlier selection is expected to be weak at advanced ages. Thus, all other things being equal might be expected that the level of additive genetic variation for mortality will increase with age due to the variation generated by mutations. Charlesworth (1990) has theoretically demonstrated conditions under which this might occur. Although the discussion of mutation accumulation has focused on mortality, this process is expected to affect other age-specific fitness components like fertility. Rose and Charlesworth (1981) measured genetic variance components for age-specific female fecundity in *Drosophila melanogaster*. They found no increase in additive genetic variance with age. However, as pointed out by Rose (1991), this test may not be conclusive if other genetic mechanisms, like antagonistic pleiotropy, maintain genetic variation at early ages but not later in life.

Kosuda (1985) studied male mating activity in fruit flies by counting the number of females a single male inseminated in 24 h. Kosuda used males that had been made homozygous for their entire second chromosome which makes up about 30% of the genome. Kosuda found that the coefficient of variation was much greater for old males than young males. However, since additive genetic variation was not explicitly measured, it is not clear how much support these observations provide for mutation accumulation.

Relaxing selection in late life: if selection were completely removed from late life, then any deleterious allele that affected survival or any other fitness component in late life would now be neutral. Over a sufficiently long period of time, some of these now neutral mutations could rise to high frequency by random genetic drift, and their presence might be detected by appropriate crosses. This idea was used by Mueller (1987). Mueller studied replicate populations of *D. melanogaster* that had been kept for 120 generations at a breeding population size of 50. These fruit flies were only allowed to reproduce early in life, and hence any late-acting deleterious mutations were rendered neutral. When female fecundity of these flies was compared to a large population that was allowed to reproduce until natural death, there was no difference in the fecundity of young flies, but at advanced ages, the small populations with only early reproduction showed depressed fecundity suggesting an accumulation of deleterious alleles in these populations.

Borash et al. (2007) did an experiment that was similar to Mueller (1987) with some important differences. In this experiment all populations were maintained using the same breeding numbers of about 1000 per population. There was an early and late-reproducing population. Thus, the relevant question was whether the early-reproducing population showed any elevation of deleterious alleles. To test this idea, both the fecundity and male mating activity of the flies at various ages were compared in each of five replicate populations to hybrids of the early-reproducing populations. The reason for using hybrids is that we expect many of these deleterious late-acting alleles to be recessive. Independent drifting populations are unlikely to

raise to high frequency the same initially rare, late-acting deleterious allele. Thus, hybrid flies are expected to be heterozygous for most of these deleterious alleles and should be cured of the deleterious effects. Borash et al. found no evidence of mutation accumulation for fecundity but strong evidence for male mating activity.

Reverse selection: if individuals are only allowed to reproduce late in life, then there will be strong selection for high fitness at older ages. Such selection should result in the purging of deleterious, late-acting alleles that are present in the population. If those genetic changes result in phenotypic changes, like an increase in longevity, then if the culturing of these populations is changed such that they only reproduce early in life, a process called reverse selection, we would expect no change in the altered phenotypes in the short run since all the deleterious alleles have been purged.

Rose (1984) subjected populations of *D. melanogaster* to different age-specific selection by allowing one set of replicate populations to reproduce at young ages only and a second set of populations to reproduce only at late ages. The late-reproducing populations evolved greater longevity, reduced early fecundity, increased ethanol tolerance, and increased desiccation and starvation resistance relative to the early-reproducing populations. When the late-reproducing populations were subjected to reverse selection for 22 generations by forcing them to reproduce when they were young, they showed an increase in early fecundity and a decrease in starvation resistance (Service et al. 1988). However, ethanol and desiccation resistance did not change. This observation was initially concluded to be consistent with mutation accumulation (Service et al. 1988). However, a later test after 100 generations of reverse selection showed that ethanol tolerance and desiccation resistance had declined (Graves et al. 1992). This latter result might reflect the actual appearance of new mutations over the 100 generations that lowered the phenotypic value of these traits. Alternatively, there may have been a much slower change in allele frequencies originally affected by antagonistic pleiotropy. The original selection process may have sufficiently changed the genetic architecture that during reverse selection, there was substantially reduced selection pressure to reduce ethanol and desiccation resistance (Teotonio and Rose 2001).

Future Directions of Research

The current status of the mutation accumulation hypothesis based on the most intensively studied organism, *D. melanogaster*, is that there is evidence of both mutation accumulation and antagonistic pleiotropy as contributors to senescence. Genomics should be able to contribute to our understanding of the genetic mechanisms involved in senescence and the postponement of senescence in experimental populations. Early genomic studies have indicated that this evolution doesn't typically proceed by sweeps of beneficial mutants as is often observed in microbial genetics (Burke et al. 2010). Recently, genome-wide association studies have been used to suggest there is evidence of mutation accumulation in humans that affects disease and senescence (Rodríguez et al. 2017). However, as previously mentioned, many phenotypes evolve in response to selection for high fitness at later ages. Thus, one major problem facing genomic analysis will be identifying the gene regions associated with changes in specific phenotypes (although some progress has been made along these lines (Mueller et al. 2018)).

Summary

Mutation accumulation and antagonistic pleiotropy are two major genetic mechanisms that have been proposed to explain senescence. Currently in the best-studied experimental organism, *D. melanogaster*, there is evidence for both mechanisms although it has not been possible to apportion the relative contribution of each mechanism to overall aging. Future empirical research will certainly benefit from the ability to collect genomic data on a large scale although many technical issues still need to be resolved in the interpretation of these data.

Cross-References

- Aging Theories
- Antagonistic Pleiotropy

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