Evolutionary Theories of Aging

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Introduction

Demographically, aging is defined as a decline in fitness with increasing chronological age, manifested by an elevated risk of death and a decrease in reproductive success. This demographic change is caused by functional deterioration at multiple levels, providing a mechanical explanation for the manifestation of aging. As to why organisms age, we are faced with an apparent paradox. As aptly articulated by G. C. Williams more than 60 years ago, "It is truly amazing that, after having completed the nearly miraculous feat of embryogenesis, a complex metazoon fails at the seemingly much easier task of simply preserving what was already created" (Williams, 1957). This paradox is best explained by evolutionary theories of aging.

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Why then do organisms age? The foundation for answering this question was laid down between the 1940s and 1960s. During this period, a Modern Synthesis of biological thinking combined Darwin's evolutionary theory, Mendel's findings on heredity and insights from population genetics. Within this framework, the earlier idea that aging was programmed as an adaptation for "the good of the species" (Weismann, 1889) was no longer tenable as it assumed that selection acts at the level of the species rather than individuals.

Medawar (1952) used this framework, and earlier insights of the Modern Synthesis, to establish that alleles with deleterious effects that are expressed only late in life are effectively shielded from natural selection and may spread in a population. This is because, even in the absence of aging (i.e., no increase in the risk of death with age), organisms are mortal, that is, individuals ultimately die from predation, accidents, outbreaks of disease and other catastrophic events. These sources of mortality (termed extrinsic mortality) affect all individuals in a population. Hence, while extrinsic, environmentally related mortality events are not associated with chronological age, they allow aging to evolve through genetic drift. A negligible number of individuals will ever survive to an old age (with the definition of "old age" being contingent upon the risk of extrinsic mortality in particular species) to enable natural selection to effectively purge alleles with deleterious action constrained to that old age from the population.

A further insight into how aging can evolve comes from the work of Williams (1957). Following the same central argument that all organisms have a non-zero risk of death, he extended Medawar's idea and suggested that aging represents a side effect of positive selection for early life fitness. Given that death is unavoidable, irrespective of aging, any investment into early life fitness (such as increased investment into reproduction) should be positively selected, regardless of any potential negative side effects for long-term survival. Hence, an allele that increases reproductive success early in life will be favored by natural selection, regardless of its expression being detrimental later in life. Two decades later, Kirkwood (1977) extended this logic and broadened the arguments from the level of antagonistic actions of single genes to a broader context of functional and physiological trade-offs.

An important aspect of evolutionary perspectives on aging is that aging and lifespan are two different terms that often do not correspond (Baudisch, 2011). Mortality in all organisms has a non-aging component (termed background or baseline mortality) that is defined by the risk of mortality that does not increase with chronological age—represented by extrinsic mortality. It means that short lifespan does not equal rapid aging. Instead, species with a short lifespan may simply experience such a high risk of extrinsic mortality that they never live long enough to experience aging. In contrast, other species may age sharply, despite living long lives. Our own species is the best example; after decades of very low mortality, mortality risk increases sharply in old age. A similar demographic trajectory is experienced by organisms as different from us as *Daphnia*; except that, in this case, the overall pace of life is much quicker and aging develops after weeks of life rather than decades (Jones et al., 2014).

This article aims to review our present understanding of the three standard evolutionary theories of aging. After defining the three theories and providing an overview of their conditions and predictions, I summarize the support and challenges they receive from empirical tests. I then highlight the main recent extensions to the evolutionary theories of aging, and briefly discuss the evolutionary importance of reproductive activities on aging. Finally, I outline situations where current evolutionary theories of aging do not apply and provide an outlook for future research on aging from an evolutionary perspective.

Defining Evolutionary Theories of Aging

Mutation Accumulation

Medawars's Mutation Accumulation (MA) theory (Medawar, 1952) considers aging-related declines in bodily function to be a consequence of alleles with deleterious effects, which spread in the genome because their action is only expressed late in life. Under normal circumstances, only few individuals survive to such an old age to experience their deleterious effects. In addition, those individuals that live long enough to be affected will likely already have repeatedly reproduced, and hence passed the alleles to the next generation. The fitness of their carriers (quantified as their genetic contribution to the next generation), therefore, is at least equal to the population average. By restricting the negative effects to later in life, deleterious mutations are effectively shielded from natural selection and accumulate in the genome.

Under the MA scenario, senescence (aging-related functional decline) is only expressed more widely in the population when environmentally driven mortality is greatly reduced. In humans, contemporary achievements in medical care, vaccination and improved hygiene have enabled individuals to live much longer than in prehistoric times, when natural selection shaped our life history traits. This has exposed our species to the widespread expression of later acting deleterious alleles, manifested as late-life malfunctions. The same logic applies to captive animals shielded from predation and other risks to which natural populations are subjected. This is why we observe senescent decline in captive animals, but only rarely in natural populations.

Antagonistic Pleiotropy

The theory of Antagonistic Pleiotropy (AP) (Williams, 1957) argues that aging may be a common by-product of natural selection. Alleles that improve early-life fitness, for example, by increasing fecundity in females or the number of mating partners in males, will be positively selected for, despite their negative action in later life. Alleles with pleiotropic effects, including negative (antagonistic) pleiotropy, are very common (reviewed in (Austad and Hoffman, 2018)). Within the framework of AP, aging can be compared to

other traits that increase reproductive success at the expense of long-term survival, be it an elaborated sexually selected ornament, aggressive behaviour that increases mating success or a particular hormonal profile with long-term costs to survival but immediate reproductive benefits.

In contrast to MA, senescent functional declines evolved via AP are predicted to be more often encountered in natural populations. Though they are still expressed later in individual's life, they may be a relatively common source of mortality. Under the AP scenario, aging should respond to variation in the strength of natural selection for particular life history components. Specifically, significant changes to the extrinsic mortality regime should lead to changes in the cost-benefit ratio related to expression of particular alleles, to which the population should respond through evolution towards different trade-off equilibrium. With an increase in predation pressure, for example, investment into rapid fitness payoffs (e.g., early reproduction) becomes more strongly favored over survival (and hence investment into future reproduction by surviving over more reproductive cycles). Consequently, alleles that support early maturation are positively selected and increase in frequency, despite more rapid deterioration later in adulthood.

Disposable Soma

The Disposable Soma (DS) theory proposed by Kirkwood (1977) is centred on the same argument as AP, that is, there is a trade-off between somatic maintenance and reproduction. The way the DS theory approaches this trade-off goes beyond the actions of single genes and considers optimal allocation of limited resources at the organismal level. The DS scenario assumes dynamic allocation of resources over an individual's lifetime in response to the environmental and developmental conditions it experiences, thereby maximizing the potential for a fitness benefit. It embraces phenotypic plasticity (i.e., the potential of particular genotypes to express alternative phenotypic variants) as an important part of life history trade-offs. It also provides an explanation as to the existence of individual adjustments to life history trade-offs on the basis of individually experienced environmental conditions under the umbrella of evolutionary theories of aging. Hence, the DS theory is not rooted in the principles of quantitative population genetics (as are the MA and AP theories) but uses optimality approach arguments.

Conditions for Evolutionary Theories of Aging

Evolutionary theories of aging are based on particular assumptions initially articulated by Williams (1957). These were extended and clarified by Hamilton (1966), Charlesworth (1993), and Abrams (1993) and recently reviewed by Gaillard and Lemaître (2017). It must be stressed that evolutionary theories of aging were originally defined for those systems that satisfied those assumptions.

1. There is a clear distinction between the soma and germ line. The germ line is the only source of genetic variants transmitted to the next generation. While the soma is required for reproduction, somatic mutations perish with individual death. As discussed below, this condition is relaxed in many plants and problematic in many unicellular organisms.
2. Natural selection acts on competing alleles. This is a cornerstone of current evolutionary thinking and does not exclude any taxa.
3. At least some alleles have pleiotropic effects. This condition is also firmly supported by our current understanding of evolution and development.
4. Reproductive value decreases with individual age. This is based on the logic that death is inevitable, regardless of aging. There is some debate regarding its generalization (Vaupel et al., 2004); however, this is beyond the scope of this article and I recommend (Shefferson et al., 2017) for a more detailed discussion.
5. Populations are age-structured. This requires distinction between parent(s) and offspring. Note that cell division (budding, fission) in unicellular organisms can be asymmetric, with one cell determined as the offspring.

It is very important to note that these assumptions leave ample scope for the existence of non-aging cells and organisms and their occurrence does not invalidate evolutionary theories of aging. At the same time, it is clear that current evolutionary theories of aging cannot explain all variation in the perpetuity of particular lineages, their longevity, aging, death and extinction. As an example, germ lines, by definition, represent non-aging cell lineages inside aging bodies. I will return to lineages that deviate from these assumptions in "**Situations Beyond the Evolutionary Theories of Aging**" section 6.

Predictions of the Three Evolutionary Theories of Aging

The three evolutionary theories of aging outlined above are complementary and it is very likely that each of them contributes to the prevalence of aging in nature. While they share the basic assumptions, they postulate different predictions. Most notably, the AP theory (and by extension, the DS theory) predicts that there is a negative correlation between early and late-life fitness, that is, allelic variants supporting early fitness are likely to be related to decreased survival or reproduction later in life. In contrast, the MA theory does not predict a correlation between early and late life fitness. The AP theory predicts that aging can be observed in natural populations, as it is a by-product of an adaptive trait under positive selection. The MA theory postulates that aging is primarily manifested when survival dramatically increases (e.g., in captivity) and it only occurs exceptionally in natural populations. Finally, the AP theory predicts dynamic bidirectional changes in lifespan and aging among closely related species (and populations of those species) as a predictable response to selection. The MA theory does not exclude evolution of extended or shortened lifespans, but requires substantially longer timeframes. Accumulation of deleterious mutations by genetic drift

(MA) should result in greater variability in genes that cause late-life malfunctions, while certain metabolic pathways are likely to be repeatedly subjected to selection for early/late fitness (AP). In addition, the AP theory predicts that there are many genes with alleles acting in an antagonistically pleiotropic manner and that natural selection acts on their representation in a population. The DS theory predicts that the dynamics of lifespan and aging can be mediated within existing allelic representation, expressed as phenotypic plasticity within a reaction norm and responding to actual developmental and environmental conditions. In other words, the DS theory predicts a plastic and more rapid response to changing conditions, with selection acting on reaction norms rather than on allelic variants.

While different theoretical predictions make it plausible to separate the strength of particular evolutionary theories of aging, comparisons of their relative importance remain challenging. First, we can never be certain that a particular late-acting deleterious allele has no positive impact on early-life fitness—a lack of evidence may does not equal a lack of effect. Positive early-life effects can be minor; hence, while a 1% increase in early-life survival or reproductive success may be strong enough to be selected for in large populations, it could be very difficult to detect empirically (Arbuthnott et al., 2016). A late-acting detrimental allele supposedly persisting in a population under the MA regime, therefore, can actually be maintained in the population due to its pleiotropic effects on early life (AP), which may be so minor that it cannot be reliably detected. Second, evolutionary lineages share common ancestry. As aging evolved in the evolutionary past so late-acting deleterious mutations (MA) will have accumulated over time. As such, they may actually be shared across diverse taxa, despite the prediction of higher variability than under the AP scenario. Finally, recent insights from genomics and transcriptomics demonstrate that a substantial part of genetic variation among taxa is accomplished by regulating gene expression rather than through variation in the gene sequence. This calls for a reappraisal of the predictions of the MA, AP, and DS theories, and suggests that testing the relative contributions of the three theories as regards the prevalence of aging in nature has little relevance.

Empirical Tests for the Evolutionary Theories of Aging

Predictions of the evolutionary theories of aging have been empirically tested using different approaches and at a range of scales. While the tests have largely supported the theories, they have highlighted a number of issues that has led further investigation in order to refine our understanding of why and how aging evolves.

Ecological Correlates of External Mortality: Broad Taxonomic Comparisons

Demographic associations

At the broadest scale, comparative analyses have firmly established that evolutionary lineages or species with particular adaptations that eliminate the risk of environmentally related mortality live substantially longer (reviewed in (Furness and Reznick, 2017)). The most famous example contrasts flying and non-flying taxa. Flight is considered to minimize the risk of predation. Accordingly, flying birds live longer than non-flying mammals of the same body size, and bats, a rare example of flying mammals, live longer than similarly sized mammals that are not capable of flying. Another source of protection from predation, the presence of poison glands, is also correlated with a longer lifespan, especially in reptiles and amphibians. Likewise, the presence of protective shells in turtles and bivalves coincides with the extended lifespans of these groups compared with their closest relatives (Furness and Reznick, 2017). Subterranean life can also effectively protect individuals from predation. In naked mole rats (*Heterocephalus glaber*), this has led to a longer lifespan compared to their ground-living relatives. Most notably, naked mole rats also display slower aging (rather than simply having a longer lifespan) due to specific adaptations that maintain DNA and protein integrity (Buffenstein, 2005). Overall, evolutionary theories of aging are well supported by large-scale comparative analyses, though most current support comes at the level of longer lifespans than reduced aging.

Comparative genomics

A new generation of comparative studies have begun to play a major role in our understanding of the evolution of aging. For a long time, many of the techniques used to study functional senescence were only available for the study of laboratory animals; however, these same techniques have recently become more accessible for use on wild animals. These include protocols and resources for measuring telomeres, hormonal levels, gene expression and plasma parameters (Valenzano et al., 2017), all of which allow the completion of longitudinal studies.

Most notably, genomic and transcriptomic resources are accumulating at an ever increasing rate. The question of whether unrelated long-lived animals share common adaptations to protect them from aging-related morbidity can now be answered by comparing genomes and transcriptomes of unrelated very long-lived bowhead whale (*Balaena mysticetus*), African elephant (*Loxodonta africana*) or naked mole rats with those of exceptionally short lived species such as the turquoise killifish (*Nothobranchius furzeri*) (Ma and Gladyshev, 2017). At a smaller scale, *Sebastes* rockfishes from the Pacific Ocean display remarkable variation in lifespans, from as little as 12 years in the Calico rockfish (*S. dalli*) to over 200 years in the rougheye rockfish (*S. aleutianus*) (Cailliet et al., 2001), making them perfect candidates for comparative transcriptomics. There is no doubt that genomics and transcriptomics will become a rich source of information for comparative studies on the evolution of aging.

Ecological Correlates of External Mortality: Intraspecific Contrasts

Support from intraspecific contrasts

Different populations of a species often experience a range of environmental conditions associated with the risk of mortality. Whenever those conditions are repeatable across generations, we may predict inter-population differences in lifespan and aging rate. The first empirical comparative evidence for evolutionary theories of aging at the intraspecific level comes from a comparison between island and mainland populations of the Virginia opossum (*Didelphis virginiana*), a Nearctic marsupial. The island opossum population, which has probably been separated from the continent for at least 4000 years, enjoys an environment with very limited predation risk compared to the continental population. These island opossums live almost 25% longer and display reduced reproductive and physiological aging (Austad, 1993), supporting predictions from the evolutionary theories of aging. Other contrasts within species (or between closely related species) have established that lifespan limitations due to habitat seasonality (i.e., extrinsic mortality) are mirrored in the intrinsic lifespan of species in a benign laboratory environment (i.e., where extrinsic mortality has been removed). Hence, grasshoppers, *Daphnia* and annual killifishes from short-season environments have all evolved shorter lives than populations from long-season environments (Tatar et al., 1997), with annual killifishes also evolving slower senescence at the functional level (Blažek et al., 2017).

Contradictions from intraspecific contrasts

In some cases, the relationship between mortality risk and aging can be reversed. The best example comes from comparative work on Trinidadian guppies (*Poecilia reticulata*). In the wild, guppy populations repeated colonized habitats upstream of waterfalls where the main predators of the original lowland populations are absent. In the high-predation guppy populations, the probability of surviving half a year was 20–30 times lower than in the low-predation guppy populations. Contrary to theoretical predictions, however, guppies from the high-predation populations (i.e., with a high extrinsic mortality) evolved longer rather than shorter lives. While their physiological performance declined with age at a steeper rate than guppies from the low-predation populations (which is consistent with theoretical predictions of more rapid senescence), the difference arose solely from their higher peak performance. Later in life, surviving guppies from either population showed no difference in physiological performance, measured as the ability to escape predator attack (Reznick et al., 2004).

The importance of condition-dependent survival

Support for evolutionary theories of aging from intraspecific comparative work is mixed and ambiguous. The key point appears to be the source of mortality in natural populations. If mortality is condition-independent (i.e., the impact on all individuals in the population is at the same strength)—which is in accordance with the original assumptions—then population-level contrasts support the theoretical predictions. However, if mortality is condition-dependent (e.g., predation that can be avoided by escape), then the population can experience much stronger selection for overall physical performance, and ultimately evolve longer lifespans as selection for high performance is related to condition in old age (Williams et al., 2006). This is very important as extrinsic mortality in nature is often realized in a condition-dependent manner and some individuals are less likely to escape predation, survive famine, cold weather or a virulent infection. Importantly, variation in individual condition is contingent upon genetic variation within the population. Consequently, condition-dependent survival emerges as an important component in the evolution of lifespan and aging, and may alter the original predictions (Williams et al., 2006).

Contrasts Between Castes in Eusocial Animals

Eusocial insects

Eusociality in ants, termites and bees is associated with a 100-fold increase in maximum lifespan compared to other insects (Keller and Genoud, 1997). This is a further example of a lowered rate of extrinsic mortality leading to a longer lifespan, alongside protective shells, subterranean lifestyles and an ability to fly. At the same time, it represents perhaps the most striking example of variation in lifespan within a species. This notable species-level lifespan extension can largely be ascribed to the very long lifespans of the reproductive caste in such colonies. While sharing the same genome, the well-protected kings and queens considerably outlive members of the working and soldier castes. In the black garden ant (*Lasius niger*), for example, workers never live for longer than 2 years (and typically considerably less), even in a protected captive environment, while the queens can live for up to 29 years (Hölldobler and Wilson, 1990). This is a striking example of where the same genetic background can produce alternative phenotypes with contrasting longevities. Undoubtedly, research on eusocial insects will contribute greatly to our understanding of aging mechanisms, and especially as regards the links between aging and reproductive effort and between differential gene expression and aging.

Complex vertebrate societies

In the naked mole rat, the best known example of a eusocial mammal with dominant and subordinate individuals, no lifespan differences have been reported between reproductive and non-reproductive individuals. In *Fukomys*, a sister linage of mole rats with comparable social structure, reproductive individuals live twice as long as their non-reproductive counterparts (Dammann, 2017). On the one hand, reproduction is costly to females; on the other, reproduction in the colony is mainly (although not exclusively) accomplished by the dominant pair, a situation similar to that of eusocial insects. It would be interesting to compare

longevity and associated demographic and life history parameters in other group-living mammals (e.g., meerkats, *Suricata suricatta*), birds (e.g., the common bubbler, *Turdoides caudata*) or fishes (e.g., the Tanganyikan cichlid, *Neolamprologus pulcher*) and their close relatives in order to assess the role of social lifestyle on aging. Likewise, comparing individuals within social groups could illuminate our understanding of the role of reproductive effort and social dominance on lifespan and aging. In meerkats, reproducing dominants age faster but outlive subordinates due to safer life style.

Artificial Selection and Experimental Evolution

Testing antagonistic pleiotropy and longevity-reproduction trade-offs

The outcomes of selection experiments on established laboratory models, and on the fruit fly (*Drosophila melanogaster*) in particular, have provided firm evidence that lifespan and aging can respond to selection. Contrasting high (99%) and low (19%–36%) levels of extrinsic mortality (experimentally imposed and applied randomly within a population), Stearns et al. (Stearns et al., 2000) bred replicated lines of *D. melanogaster* under the two selection regimes. After 90 generations, flies with negligible external mortality lived considerably shorter lives in the high-mortality selection lines. In the low-mortality lines, flies lived longer but had reduced fertility, providing strong support for the AP/DS theories. Many other approaches have been used to test the predictions of the AP theory, including mutant and transgenic lines and natural polymorphism, confirming that the central prediction of extended lifespan comes with the cost of decreased early-life fecundity. Nevertheless, disparate results from particular experiments, especially as regards the link between survival and reproduction, have demonstrated that benign laboratory conditions are suboptimal for testing longevity-reproduction trade-offs. In essence, a challenging natural environment is needed to fully expose populations to such trade-offs (Austad and Hoffman, 2018).

Testing accumulation of mutations

Some specific predictions derived from the MA theory have been tested using the tools of experimental evolution. As an example, the negative effects of inbreeding depression should be alleviated in old age as late-onset alleles should be more common in populations under the MA scenario. The power and logic of an early experimental support of this prediction (Charlesworth and Hughes, 1996) were later questioned (summarized (Kirkwood and Austad, 2000)). The MA theory predicts a sudden and very steep increase in mortality at very old age (the "wall of death"), when reproduction (or more precisely, contribution to fitness) decreases to zero. Yet, aside from semelparous species' displaying a single burst of reproduction (e.g., Pacific salmon or bamboo), this is not observed. It appears that MA may contribute to aging but is very unlikely to be the main reason for late life increases in mortality.

Insight to particular genetic pathways

The quest to disentangle the effects of MA and AP on the evolution of aging has led to a better understanding of the genetics of senescent decline. While many deleterious mutations appear species-specific, or even population-specific (in agreement with predictions of the MA theory), others are surprisingly evolutionary conserved (Partridge et al., 2018). Genes underlying nutrient sensing pathways (most notably the insulin signaling and target-of-rapamycin pathways) have been recognized as major regulators of growth, reproduction and aging across taxa. Many interventions that successfully alter aging patterns (such as dietary restriction and/or specific chemical compounds) directly interfere with nutrient sensing (Partridge et al., 2018; Flatt and Partridge, 2018). Analysis of long-lived mutants has provided further support for the importance of nutrient sensing pathways, with ongoing experimental elaborations using advances in genetic engineering directly testing the effect of particular genes and their expression. Current research on model species, and especially the nematode worms *Caenorhabditis elegans* and *D. melanogaster*, has provided a solid background for testing these advances in aging research on a broader collection of organisms. New insights from quantitative genetics, comparative genomics and transgenesis promise to unravel the role of particular genetic pathways in the aging process.

Testing the role of condition-dependent survival

A recent experimental evolution study on a nematode worm, *Caenorhabditis remanei*, has helped clarify an emerging conundrum of the effect of condition-dependence in mortality on the evolution of lifespan and aging. Within a single experimental design, Chen and Maklakov (2012) allowed replicate lines of *C. remanei* to evolve under either condition-independent mortality (as earlier experimental evolution studies did) or under a condition-dependent mortality regime. Condition-independent mortality was applied by a haphazard removal of individuals from the population, while condition-dependent mortality was accomplished using a heat-shock that killed a large fraction of the population, the survivors being rescued through superior expression of heat-shock proteins. After 12 generations, elevated condition-independent extrinsic mortality produced worms that had higher aging rates and shorter lifespans, in accordance with the evolutionary theories of aging. However, in lines selected under elevated condition-dependent mortality, worms evolved slower aging and longer lifespans. This clearly demonstrates experimentally that the source and mode of extrinsic mortality is important for evolutionary trajectories of aging and associated life history traits, a prediction noted by Abrams (1993) and Williams and Day (2003) but neglected from mainstream research on the evolution of aging.

Extensions and Modifications of Standard Evolutionary Theories of Aging

Condition Dependence

In retrospect, ignoring the source of mortality in the mainstream discussion on evolutionary trajectories in aging rate would appear fallacious. However, by definition, each model is a simplification of reality and points that are overly simplified may only be seen in hindsight. Condition-dependence in survival and reproduction is the key component of natural selection on which the Modern Synthesis is based. In fact, many theoretical treatments of the evolutionary theories of aging (e.g., Abrams, 1993; Williams and Day, 2003) have repeatedly highlighted the role of condition-dependent mortality and demonstrated how it can produce a diverse set of evolutionary outcomes, depending on the relative strength of the condition-dependent effects.

Williams and Day (2003), in modeling how predictions from the AP theory are affected by explicit interactions between individual condition (performance) and mortality from extrinsic factors, demonstrated that the strength of selection for physiological condition declines with chronological age. However, a stronger link between condition and survival translates into intensified selection against aging in early life and relaxed selection (and more rapid decline) at a later age. It would be interesting to extend these arguments to the interspecific level. For example, birds live longer than similarly sized mammals, but experience much sharper terminal declines in condition and stronger demographic aging (Jones et al., 2008). The intriguing possibility that the ability to fly imposes much stronger selection on individual condition could extend the logic of condition-dependency from within-species contrasts (Reichard, 2017); however, this has yet to be investigated.

Positive Pleiotropy and the Modified Mutation Accumulation Theory

Positive pleiotropy describes the positive association between early and late life performance. While negative associations between reproduction and survival are widely documented, positive association has also strong empirical support. In such cases, particular individuals within a population remain more successful throughout their lives (Rose, 1994). In addition to abundant support from natural populations (Maklakov et al., 2015), a lack of any direct trade-off between fecundity and lifespan has been experimentally demonstrated in *D. melanogaster* (Kimber and Chippindale, 2013).

Evidence is emerging that many mutations with measurably detrimental effects in later life are expressed throughout the lifespan, another tenet of condition-dependent survival effects on the evolution of aging (Maklakov et al., 2015). While these alleles are expressed early in life, their detrimental impact remains minor until old age. Importantly, there is no positive (hence inconsistent with the AP) or neutral (hence inconsistent with the MA) effect in early life; the effect is consistently negative. The minor level of this effect enables them to persist in a population and respond to changing selection regimes. With an increase in random extrinsic mortality, fewer individuals survive to old age to experience negative effects of those mildly deleterious alleles, freeing them from the weak negative selection. This enables them to increase in the population in the same way as the standard MA theory predicts. However, when increase in extrinsic mortality is condition-dependent, the individuals with mildly deleterious alleles are preferentially removed, leading to the evolution of slower aging as those alleles are purged from the population (Maklakov et al., 2015). The relative importance of positive pleiotropy on aging remains to be examined, but represents a stimulating modification of the original evolutionary theories of aging.

Indeterminate Growth

Evolutionary theories of aging assume that the force of natural selection declines with age, as a consequence of decreasing reproductive value of an individual. This assumption is relaxed when fecundity increases steeply with chronological age. There are plenty of taxa where indeterminate growth is common, including fish, reptiles and bivalves. In these organisms, female fecundity is strongly positively correlated with body size, thus fecundity increases over the individual's entire lifespan. Consequently, much stronger investment into somatic maintenance is predicted because future reproduction will yield much higher reproductive success. At the same time, strong selection for incessant growth competes for resources that could be allocated to superior maintenance. Importantly, growth in these taxa is not linear but reaches an asymptote and increments to body size and body mass in older age are relatively minor. While this leads to the evolution of very low aging rates, current evidence demonstrates that indeterminately growing organisms do not escape aging (Reichard, 2017).

Tortoises and turtles are well-known examples of extreme longevities, combining indeterminate growth with protective adaptations that shield them from many predators (shells, partly subterranean life). Long considered an example of non-aging vertebrates, long-term datasets revealed that turtles do age, despite their considerable longevities (Warner et al., 2016). Fishes, another well-researched example of indeterminate growth, also experience aging-related physiological changes and associated increases in mortality (Wootton and Smith, 2015). Finally, some bivalves, such as the ocean quahog (*Arctica islandica*), are reported to live for over 500 years. However, such a long lifespan is only achieved in extremely cold subpolar waters. In the warmer Baltic Sea, populations of the ocean quahog grow much quicker and have lives an order of magnitude shorter (Blier et al., 2017). Given that "indeterminate" growth is always asymptotic, fecundity increase in very old age cannot keep up with its initial rate. Hence, while they live long lives, indeterminate growing organisms may live long lives but do age (Reichard, 2017).

The Relationship Between Aging and Reproduction

Aging describes the decline in fitness function with chronological age, with the fitness function combining survival and reproductive success. From an evolutionary perspective, survival simply represents the potential for future reproduction, as successful reproduction is what counts in evolutionary terms. This is a critical difference in the perception of the term "aging" by gerontologists and evolutionary biologists. This section deals with trade-offs between reproduction and survival.

Reproductive Senescence

The reproductive value of an individual can decline with age, with or without an associated increase in mortality (Jones et al., 2014). Reproductive senescence describes age-related declines in fertility, fecundity, mate attraction, probability of breeding, quality of parental care, offspring survival and any other trait related to reproductive success. Most importantly, aging can be manifested as reproductive senescence, regardless of an increase in mortality. In birds and mammals, progressive erosion of the finite pool of primary oocytes through ovulation and atresia is implicated as a key factor in reproductive decline of females (Lemaître and Gaillard, 2017), while in taxa such as fishes, oocytes can be produced continuously throughout their life (Wootton and Smith, 2015).

Reproductive senescence is often non-monotonous. In mammals and birds, reproductive success peaks at prime age, sometimes well after sexual maturity. The increase in fecundity with age is especially strong in taxa that continue growing after sexual maturity. As discussed in "**Indeterminate Growth**" and "**Situations Beyond the Evolutionary Theories of Aging**" sections, many organisms appear to escape aging because there is no increase in mortality. Nevertheless, any decrease in reproductive success over their enormous lifespans would qualify them for the evolutionary definition of aging (Reichard, 2017).

Generalized Trade-Offs Between Aging and Reproduction

The assumption that limited resources are partitioned between different life history traits is the core of the Disposable Soma theory. Any increase in investment to reproductive function removes resources from functional maintenance and repair. At an interspecific comparative level, species with high reproductive effort (e.g., litter/clutch size or short inter-brood interval) live shorter lives than species with low reproductive effort (Jones et al., 2008). At the individual level, there is widespread evidence from natural vertebrate populations that limited resource availability leads individuals to trade somatic maintenance later in life for high allocation to reproduction early in life (Lemaître et al., 2015). Laboratory assays sometimes fail to observe such trade-offs. A decoupling of reproduction and longevity has been suggested for some long-lived *C. elegans* and *D. melanogaster* mutants displaying mutations in specific metabolic pathways (Flatt and Partridge, 2018; Partridge and Gems, 2002). Dietary restriction and medical interference to metabolic pathways can also decrease aging, with no decrease in reproductive success. Unlimited access to resources in the laboratory environment may explain the lack of reproduction-longevity trade-offs in such cases (Flatt and Partridge, 2018) and long-lived mutant lines are quickly driven to extinction when competing in a natural environment. While making this approach to aging less relevant from an evolutionary point of view, the uncoupling of reproduction-longevity trade-offs remains highly relevant for mitigating aging-associated declines in human populations, especially as many interventions for decreasing aging can be administered during the post-reproductive lifespan.

In addition to laboratory conditions, a positive association between reproductive success and lifespan is sometimes observed in natural populations (Flatt and Partridge, 2018; Maklakov et al., 2015). Importantly, this may simply represent an apparent phenotypic correlation, arising from individual variation in condition. Individuals in superior condition are capable of accumulating more resources overall and may supply both higher reproductive effort and higher maintenance. The causal negative link between reproductive effort and aging may yet remain valid, however, with the link detectable through experimental manipulation. For example, Boonekamp et al. (2014) used brood size manipulation in a natural population of jackdaws (*Corvus monedula*) to demonstrate that aging of birds with experimentally enlarged broods was three times higher than that in birds with reduced broods.

Cost of Gamete Production and Germ Line Maintenance

Egg production is energetically costly. The eggs often contain energetically rich substances that sustain embryo development and increase its condition after hatching. Likewise, while often assumed otherwise, sperm is also costly to produce. Despite the minor expense required for development of a single spermatic cell, male gametes are usually required in great numbers. In addition, Maklakov and Immler (2016) recently highlighted that the cost of germ line maintenance (and especially its strict protection from genome instability) is much higher than has been assumed. The high costs associated with germ line protection, rather than the physiological costs of reproduction itself, may represent the primary reason for reproductive senescence (Maklakov and Immler, 2016). There is some support for extended longevity in mutants and individuals in which gamete production is prevented, and for the idea that germ line ablation, rather than functional castration, is required for life extension (Maklakov and Immler, 2016). Clearly, this branch of aging science will continue to provide new insights into our evolutionary and mechanistic understanding of aging.

Sexual Selection

Sexual selection is a component of natural selection that specifically emphasizes the role of reproductive success in natural selection. Traits evolved to gain access to successful reproduction, which may be as diverse as physical bodily armament, aggressive behaviour or an ability to attract partners via elaborate signals, have strong negative consequences for immediate and long-term survival. In addition, sexual selection diverts resources from maintenance to reproduction. Sexual selection is often disproportionally imposed on one sex (almost always males), probably leading to sexual dimorphism in aging and longevity.

Sexual Conflict

As the sexes share a major part of the genome, there is ample scope for sexual conflict on the expression of particular traits. For example, sexually selected ornaments are beneficial for male fitness gain (advertising male presence and attracting more potential partners) but detrimental for female function. This leads to intra-locus sexual conflict (i.e., conflict over trait expression) and results in a suboptimal lifespan in both sexes. Inter-locus sexual conflicts involve direct male-female interactions, and may involve the transfer of seminal fluid during copulation. These protein-based substances manipulate partner behaviour and can even directly decrease the female's lifespan. For example, transfer of seminal fluid by the male *D. melanogaster* increases his reproductive success by decreasing female re-mating rate (which would lead to a loss of paternity) while its enzymatic activity also directly decreases the female's lifespan.

Situations Beyond the Evolutionary Theories of Aging

Evolutionary theories of aging apply in situations that satisfy a number of basic assumptions, and may not apply when those assumptions are not met. There must be a distinction between the soma and germ lines and between parent and offspring, and reproductive value must decrease with individual age. This leaves plenty of scope where predictions of the current theories cannot be formulated. Here, I briefly outline the most notable cases.

The Lack of a Clear Distinction Between the Germ and Somatic Lines

In animals, the germ cell line separates from other cells (the somatic line) very early in individual development. Somatic cells invest a lot of resources to protect the genomic stability of germ cells. Germ cells recruited to reproductive cells are also likely to undergo stringent "quality control" to minimize recruitment of cells with mutations. Germ cells represent "the immortal lineage" with minimal mutation load, though they undergo regular recombination in most organisms to form a new individual during sexual reproduction. This, in addition to rare mutations, is the major source of genetic variation that natural selection acts upon.

Unicellular organisms

Unicellular prokaryotic organisms, such as bacteria and archaea, have no germ lines. Their reproduction is accomplished by budding or fission. Fission produces two identical copies and, in addition to the lack of a clearly separated germ line, there is no obvious distinction between the parent and offspring. Hence, there is no age structure in populations of prokaryotic organisms and evolutionary theories of aging cannot apply. Does this mean that prokaryotes do not senesce? Perhaps they don't, in a similar manner to germ cell lines in eukaryotic organisms. After all, prokaryotes represent a very different form of life when it comes to reproduction (e.g., frequent horizontal exchange of genes) and life history traits. On the other hand, there is some evidence that cell division by fission can be asymmetric, with one daughter cell receiving an uneven share of damaged organelles and intracellular matter (Stewart et al., 2005). This suggests that aging may yet apply to prokaryotic organisms.

Aging has been well described in unicellular eukaryotic organisms. The budding yeast (*Saccharomyces cerevisiae*), a unicellular fungus, has been used as a model organism across several biological disciplines. It reproduces by budding, with the daughter cell being smaller and receiving an unequal share of intracellular components. The parental cell undergoes a limited number of divisions only, an apparent sign of aging. A similar situation has been described for prokaryotic organisms that reproduce by budding (Petralia et al., 2014).

Plants

In flowering plants (angiosperms), gametes are recruited from somatic cells very late in development; hence, there is no separate germ line to be protected from external environmental risks. Plants alternate between sporophytic and gametophytic generations. The sporophytic generation plays the role of the somatic lineage. Though plant cells are not pluripotent, there is a large group of cell lines in the sporophytic generation that may be recruited as gametophytes, undergo meiosis and eventually become gametes. Hence, the plant "germ line" is only determined after formation of a floral organ. This is just one of many natural history features that makes plants an extremely interesting organism for studying aging.

Fungi

Fungi utilize a huge variety of reproductive systems, from unicellular budding yeasts that undergo aging, despite lacking germ-soma distinction ("**Unicellular organisms**" section), to some filamentous fungi that contain heterokaryotic cells and hyphae (containing two or more unrelated nuclei). Most fungi defy the assumptions of evolutionary theories of aging and, apart from unicellular fungal organisms such as yeast, we have very limited information on their aging processes.

Animals with pluripotent cells

Some animals also lack the formal distinction between the germ and soma lines. Their cells may dedifferentiate and be recruited for gametic cell lineages. This has been reported from basal animal groups such as sponges (Porifera) and cnidarians (e.g., corals and *Hydra*), as well as tunicates (e.g., the colonial star ascidian *Botryllus schlosseri*), a lineage related to the vertebrates. The *Hydra* is capable of asymmetric partitioning of cell waste during somatic cell division. The cell targeted to act in tissue with a rapid cell turnover (such as battery cells in tentacles) receives a disproportional portion of malfunctioning components. This apparently facilitates the avoidance of gradual deterioration of cells with retained pluripotency. With emerging insights into cellular and molecular mechanisms permitting pluripotent cell maintenance, the *Hydra* has gained the popular label of "the organism that completely avoids aging." While these animals represent a fascinating research avenue for understanding the developmental and cellular mechanisms of aging (and especially its avoidance), it must be remembered that simple organisms possess the capacity to replace entire functional elements. This cannot be achieved in complex animals where such elements cannot be entirely replaced during a lifetime, a major constraint for an uncritical reference to human aging. For further discussion on the relationship between organisms that defy aging and aging in complex animals such as humans, see (Reichard, 2017).

Clonal reproduction

Clonal reproduction, a common strategy in asexual reproduction, is widespread in prokaryotes and fungi and relatively common in many plants and animals. During cloning, a genetically identical copy of the parental individual is formed. Clonal progeny may be formed from a germ line, for example, parthenogenesis represents development of an unfertilized egg. In plants, vegetative reproduction is common, with new individuals sprouting from parental somatic cells. This complicates the definition of an individual and entire clonal colonies are sometimes considered to represent one individual. In this sense, large stands of vegetatively reproducing grasses, forests of quaking aspen (*Populus tremuloides*) or massive colonies of reef-building corals all represent long-lived, apparently non-aging individuals. The current lifespan of such colonies (individuals) has been estimated at tens of thousands of years, and they continue producing gametes and contributing to sexual reproduction. Their apparent escape from aging is certainly related to their modular body form and an ability to replace simple bodily components (ramets), thereby combining the advantages of indeterminate growth and pluripotency. While they defy the basic assumptions of the evolutionary theories of aging, the question of whether they have escaped aging has yet to be settled (Reichard, 2017).

Summary and Conclusions

The seeming paradox of why aging has not been eliminated by natural selection when it is apparently detrimental to individual fitness is well embraced by standard evolutionary theories of aging. The theoretical treatments of aging are underpinned by the fact that mortality itself is common in nature, irrespective of aging. This makes survival to a particular chronological age negatively associated with time since birth, enabling aging to evolve as a mere side effect of genetic drift ("**Mutation Accumulation**" section) or a consequence of the trade-off between early and late-life fitness income ("**Antagonistic Pleiotropy**" and "**Disposable Soma**" sections).

Not all organisms and not all cell lineages age. Germ cell lines, most prokaryotic organisms and many eukaryotes show no increase in mortality with chronological age. This is sometimes misleadingly interpreted as a failure of evolutionary theories of aging to incorporate their occurrence into their theoretical underpinning. However, evolutionary theories of aging specifically aim to explain situations where basic assumptions are met and are not relevant in other circumstances. Hence, while the current paradigm for the explanation why does aging sometimes evolve is solid, our understanding of how other taxa escape aging is far from settled. New discoveries, comparative analyses and experimental tests keep producing new insights into the evolutionary perspectives of aging, sometimes leading to clarifications and modifications of the prevailing opinions. In short, evolutionary understanding of aging is itself evolving.

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