Aging across the tree of life: the importance of a comparative perspective for the use of animal models in aging

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Highlights

- Many animals do not age, and physiological mechanisms of aging vary across species
- Nonetheless, conserved aging-related signalling pathways exist
- Aging is thus highly multi-factorial, complex, and particular to each species
- Animal models should include both traditional and non-traditional species
- Results should be interpreted cautiously and within a broad comparative perspective

Abstract

Use of model organisms in aging research is problematic because our ability to extrapolate across the tree of life is not clear. On one hand, there are conserved pathways that regulate lifespan in organisms including yeast, nematodes, fruit flies, and mice. On the other, many intermediate taxa across the tree of life appear not to age at all, and there is substantial variation in aging mechanisms and patterns, sometimes even between closely related species. There are good evolutionary and mechanistic reasons to expect this complexity, but it means that model organisms must be used with caution and that results must always be interpreted through a broader comparative framework. Additionally, it is essential to include research on non-traditional and unusual species, and to integrate mechanistic and demographic research. There will be no simple answers regarding the biology of aging, and research approaches should reflect this.

Keywords

Aging, comparative biology, complexity, disposable soma, diversity, model organism

1. Introduction

This special issue is devoted to animal models of aging. The term "animal model" implies that the final objective is not in fact to understand the species studied for its own sake, but to be able to draw some general conclusions with respect to human aging. Paradoxically, this generates the need for a comparative/ evolutionary perspective in order to identify which animals might have something important to teach us about ourselves. In most cases, this is relatively simple. For example, basic cellular respiration is relatively similar across eukaryotes, so any simple, easy-to-work-with organism such as yeast may serve as a good model [1]. The immune system differs substantially between mammals and other vertebrates, implying that for most questions only mammalian immune models are likely to be pertinent. And for questions such as complex social behavior, the list of potential models might be limited to gregarious primates, carnivores, and cetaceans.

However, in the case of aging, things are not so simple. First, there is no real consensus about what aging is or how to define it [2, 3], though there is increasing agreement that it is at least multi-factorial [4, 5], and potentially an emergent property of a formally complex system [6, 7]. Second, there is conflicting evidence about the extent to which aging is a process that is similar across all organisms or particular to each species [3, 8]. Third, there is reason to expect that aging is systematically different in long-lived and short-lived species, such that in some cases long-lived birds might be better models for human aging than mice (*Mus musculus*), despite the much closer phylogenetic relationship between humans and mice [9, 10]. This obviously presents a challenge for the long-term follow-up of the aging process within individuals. Fourth, there are a wide variety of questions that can be asked about aging, requiring different models.

The goal of this article is to take the view from on high, asking what we know about aging across the entire tree of life and searching for both commonalities and particularities that would point to what organisms are good models for what questions. In some cases, this perspective can be used to identify model organisms that may have unique strategies to combat aging, from which we might learn. In other cases, it is the broad patterns themselves that generate insight into what aging is. More than perhaps any other field in basic biology, a comprehensive understanding of aging will require a multi-faceted back-and-forth between findings in specific model organisms, findings in non-model organisms, a broad comparative perspective, evolutionary theory, and basic principles of biology and physiology.

2. Key concepts to understand the diversity of aging

The diversity of life forms on our planet is so astounding that the familiar concept of aging we know as humans cannot be directly transferred to many other species. Here I introduce several concepts that are important to understand that diversity and how we define aging.

2.1 The germ line-soma distinction

In humans, other vertebrates, and a wide variety of organisms, not all cells have the potential to contribute genetic material to the next generation. The cells that do are called the germ line, while those that do not are called the soma. This is analogous to the situation in eusocial insects, where only the queen and the males reproduce, and the workers serve no function except to aid the reproduction of the queen. August Weismann [11] first pointed out the germ line-soma distinction and noted that this implied that aging should occur only in the soma (otherwise aging would occur across generations and life itself would end). This was further developed by

Kirkwood [4, 12] into the Disposable Soma theory of aging, which posits that the soma sacrifices itself to transmit the germ line, and that constraints on the acquisition and use of energy and other resources would force the soma to trade off between reproduction and maintenance (i.e., survival).

However, not all organisms have a distinct germ line and soma. Unicellular organisms (bacteria, protists, yeasts, etc.) obviously do not. Fungi, and many marine/aquatic invertebrates (including, starfish, hydra, and jellyfish) also do not: they appear to be able to revert apparent somatic cells to a germ line state [13]. Plants were long thought to lack a distinct soma as well, but this is somewhat less clear in light of recent findings suggesting that both long-lived and short-lived plants have similar numbers of cell-divisions before producing germ cells [14]. Species without a distinct soma are not necessarily predicted to age [4], and it thus may be crucial to understand if aging patterns differ systematically between organisms with and without the germ line-soma distinction [15, 16]. Note, however, that an implicit assumption of the importance of the germ line-soma distinction is that aging primarily a cellular phenomenon that scales up to the individual level. If aging is driven primarily by factors at higher organisational levels (tissues, organs, organism), the germ line-soma distinction could be less important or even irrelevant. While the implicit assumption in much of the aging literature is that aging is primarily cellular, there is evidence for both cellular and higher-order processes (e.g. systemic dysregulation, wing damage in insects) [6, 17, 18], and no good evidence as to their relative contributions.

2.2 Asymmetrical division and budding

Many organisms lacking a germ line-soma distinction reproduce by splitting one organism into two (asexual reproduction), rather than by creating a specific seed or egg (usually sexual reproduction). Again, unicellular organisms do this, but also many invertebrates and plants. For example, the hydra, a small freshwater cnidarian, reproduces by budding, a process in which a small mass of cells separates from the body stem and grows into a separate individual [19]. In most of these cases, the division of the individual is not perfectly symmetrical: it is possible to identify a "mother" cell or individual, and a "daughter" cell or individual. This is true even in unicellular organisms such as bacteria and yeast (*Saccharomyces cerevisae*) [4, 20, 21]. Accordingly, it is possible to consider aging in such species as long as it is possible to identify and follow the mother across multiple division/budding events [20].

2.3 Ramets and genets

In organisms such as humans that reproduce only sexually, each individual has a unique genotype and is easy to identify. However, in the case of asexual reproduction, many apparent individuals can share the same genotype. With the exception of unicellular organisms, most species that can reproduce asexually also reproduce sexually. This means that certain aggregates of individuals will be descended asexually from a single, sexually-produced progenitor and will share their genotype [19, 22-24]. Each physically separate organism is called a ramet, and the collection of ramets sharing a genotype is called a genet. Examples include ascidians, hydra, corals, and a great diversity of plants, including entire stands of aspen (*Populus tremuloides*) [25]. Questions of aging in species with both ramets and genets can be particularly tricky because the genet may be essentially immortal once enough ramets are produced, and yet ramets might age in

a programmed fashion that increases the fitness of the genet, particularly in structured colonies [22].

3. What is aging, and how does it vary across the tree of life?

3.1 Demographic aging: Measurement

From a demographic perspective, aging can be defined as an inexorable increase in mortality and/or decrease in fertility with age. Usually, the focus of research is on mortality, though reproductive aging is of particular interest in humans with our long female post-reproductive lifespan [26, 27]. Note that this definition decouples aging from lifespan: some organisms with very high extrinsic mortality due to predation, etc. appear not to age at all (i.e., mortality is unchanged with age, such as in hydra [19]), whereas some very long-lived organisms such as humans show clear aging (i.e., the probability of death increases steadily with age). A note on terminology: some authors refer to this aging-lifespan distinction as the shape vs. the pace of aging [28] or as senescence (decline) vs. aging (progression of time) [3].

There are limits to a purely demographic perspective, particularly when we wish to apply comparative findings to humans. Demographic patterns may or may not clearly reflect the kind of physiological deterioration we tend to associate with the term "aging." In plants in particular, there is now a clear understanding that size is often more important than age in determining mortality risk [29-31], such that demographic patterns of aging (or lack thereof) may not be driven at all by physiological processes of interest from a human perspective. Species with indeterminate growth and/or increasing reproduction with size might be expected to show different aging patterns [32], despite Hamilton's original predictions [33]. Likewise, demographic patterns can depend strongly on environmental conditions. For example, in the

hydra, *Hydra vulgaris* appears to show no aging under standard laboratory conditions, whereas *H. oligactis* can show aging depending on the precise temperature [34]. More broadly, the distinction between intrinsic and extrinsic causes of mortality is falling into disfavor as we begin to understand the importance of internal conditions for determining susceptibility to external causes [35, 36]. This implies that both rates and patterns of demographic aging are highly dependent on environmental conditions that may affect not just mortality rates, but how mortality affects different age classes [36]. Between such environmental influences and methodological questions, it is possible to observe both aging and its apparent absence in different populations of the same species. For example, painted turtles (*Chrysemys picta*) were long thought to be a good example of a species that showed no apparent aging [37]; however, a recent study in a much shorter-lived population appears to show aging [38], and it is not clear whether this reflects a genuine difference between the populations (which would be surprising), a data artefact, or a methodological issue in one or the other study.

Despite these caveats and the challenges of acquiring detailed demographic data for a wide array of taxa, demographic data on aging is currently the most promising path for broad comparisons across the tree of life. Demographic patterns can be standardized and compared across taxa relatively easily, regardless of how complex or varied the underlying mechanisms [28]. (Note that the problem of defining the unit in clonal species is present both for demographic and mechanistic studies.) Because of this potential to standardize, a major effort has been invested in the compilation of these data (outlined below; [39-41]). Additionally, there is an increasing body of theoretical work on the comparative demography of aging. This work shows (a) that we should expect a wide array of patterns, including both absence of aging and "negative senescence" (declining mortality with age) [32, 42, 43]; (b) that it is possible to

169 distinguish the pace of aging (i.e., lifespan) from the shape of aging (how abruptly aging sets in
170 toward the end of the lifespan) [28, 44]; and (c) that understanding aging mechanisms may be
171 critical to understanding variation in aging demography [6, 15, 43, 45]. Thus, while there are
172 certain challenges to the demographic comparative study of aging, these challenges are dwarfed
173 by the challenges related to the comparative physiology of aging.
174
175 *3.2 Demographic aging: Patterns*
176 Perhaps the simplest measure of demographic aging is maximum observed lifespan (Table 1).
177 This measure conflates aging and lifespan and pace vs. shape, as noted above, with the potential
178 for short-lived species not to age and long-lived species to age quickly relative to their lifespan.
179 Nonetheless, exceptionally long-lived species are doing something quite differently from many
180 other species, regardless of whether they can be formally shown not to age, and maximum
181 observed lifespan is available for a wide array of organisms, many of which (particularly
182 vertebrates) are compiled in the AnAge database [46]. The taxonomic bias on the availability of
183 data makes strong inferences problematic; nonetheless, a quick perusal of the longest-lived
184 species is striking for the repetition of closely related taxa: of the 42 vertebrates with 80+ year
185 lifespans, 31 are whales, turtles, rockfish, sturgeon, or oreo fish.
186 More sophisticated analyses including both shape and pace have confirmed the importance of
187 slow, negligible, and negative aging [44]. One of the most striking findings in recent years is that
188 demographic aging appears to be far from universal [3, 39]. The compilation of data for large
189 numbers of species now allows us to see for the first time that non-aging species are not simply
190 rare, weird exceptions, but are rather common across the tree of life (Fig. 1). Some turtles, fish,
191 trees, and marine invertebrates were long suspected not to show aging [47], but it is now possible

to see that a large fraction of the tree of life does not appear to show aging. So far, all mammals and birds appear to age [48, 49]; perhaps it is our bias as mammals that led us to consider this the default state of most organisms. Across the rest of the tree, examples of aging and non-aging species are often closely interspersed, with even closely related taxa showing differing patterns. Some plants age, others do not [16, 24, 39]. Some arthropods age, others do not [39]. Some reptiles and amphibians age, others do not [39]. Some fish age, others do not [46, 50]. Some fungi age, others do not [23]. Some organisms with distinct somas age, others do not [39]. Some organisms without distinct somas age [16], others do not [19]. Moreover, changes in mortality with age often show more complex patterns, not just monotonic increases or flat, unchanging levels [39]. Generally, aging patterns can be classified using the schema in Table 2, with broad representation for most patterns.

This finding is crucial and paradigm-shifting because it implies that there is no single, universal aging pathway. At most, there might be a pathway that is shared when aging is present but can be turned off. However, this would imply that aging is programmed, which does not appear to be the case (see below), and does not address the distinct possibility that non-aging is the default state, with aging evolving independently multiple times across the tree of life. Moreover, the taxonomic distribution of aging patterns observed so far does not appear to agree with predictions made based on aging as a programmed phenomenon [51]. The finding also presents challenges for the Disposable Soma theory, which does not provide a way to understand why some organisms with distinct somas could avoid aging, nor to understand why some organisms without distinct somas would age [15].

3.3 Programmed aging: the rare exception

Most researchers studying the evolution of aging consider aging to be non-adaptive in the sense that it appears to be a by-product or side effect of other biological and evolutionary processes rather than an end in itself [51-53]. In this sense, aging is also seen as non-programmed: not the result of a specific pathway that has evolved in order to carry out the aging process. The multiplicity of mechanisms and their heterogeneity across species (see below) confirms this. While most of what we call aging follows this non-programmed paradigm, there are a small number of exceptions where aging is clearly programmed. For example, the colonial marine invertebrate *Botryllus schlosseri* kills off its modules through programmed senescence prior to replacing them [22], an excellent example of ramet but not genet aging. The catastrophic aging observed in semelparous organisms such as annual plants, Pacific salmon (*Oncorhynchus* spp.), and even some mammals may also be an example of programmed aging, though this is not fully clear [52-55]. These examples are interesting both ecologically, and as a contrast that reinforces the conclusion that most aging is non-programmed [52]. Nonetheless, their relevance for understanding aging in humans specifically or in animals generally is somewhat limited, precisely because most aging does not appear programmed in this way.

3.4 Physiological aging: mechanisms

Physiological aging here refers to the myriad mechanisms and processes that lead to inexorable organism-level declines in functional capacity and/or health state. Overall physiological aging is generally non-programmed, though some portions of it may include molecular programs that exist for other purposes [51]. Physiological aging encompasses structural wear and tear (e.g. insect wings, tooth wear), cellular processes, tissue and organ processes, and organism-level processes. In 1990, Medvedev listed hundreds of mechanistic processes [2], and a brief survey of

the literature will turn up numerous semi-competing, semi-complementary theories: oxidative stress, inflammation, telomere shortening, cellular senescence, mitochondrial dysfunction, and accumulation of misfolded proteins, to name some of the most popular. A recent review proposed nine hallmarks of aging: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication [5], though the authors noted that the choice reflected a mammal-centric perspective and that the precise list could be discussed. For example, epigenetic alterations might be expected to at least partially underlie almost any of the other hallmarks.

All of this goes to show that there is very little consensus on what the basic mechanisms of aging are, or their relative importance. Personally I think an effort to identify hallmarks is premature, with the proposed list excluding or simplifying many important processes (e.g. inflammation), as well as giving a false sense that the hallmarks are independent. However, efforts like this are useful to the extent that they demonstrate an increasing consensus that aging is multifactorial. Indeed, the aging phenotype is surprisingly heterogeneous both among individuals within species and across species. Taking the familiar example of humans, each individual has a unique aging profile in terms of diseases, affected organ systems, molecular profiles, etc. Unlike for many other biological phenomena, no single biomarker appears to have a particularly strong correlation with human age, with even telomere length only correlating at $|r| < 0.5$ [56]. While the complex nature of the aging phenotype does not exclude the possibility of a simpler upstream cause, our failure to identify such a universal cause to date makes its existence seem increasingly less likely.

The majority of research on the biological mechanisms of aging occurs at the cellular level, and there is indeed good evidence for cellular aging processes and the contribution of these processes to the aging of the organism [17, 57]. Nonetheless, there is no *a priori* reason to suspect that all or even most of physiological aging can be explained by cellular processes. For example, the accumulation of chronic stress and related allostatic load appear to have numerous consequences for the aging phenotype, but are organism-level phenomena [58]. Likewise, structural wear and tear may affect the ability to forage and thereby nutritional state or other aspects of the aging process [59]. Indeed, the cellular machinery of most organisms is relatively similar, despite differences in lifespan approaching 1 million-fold [60].

Aging is thus clearly multi-factorial. It is also likely to be complex, in the formal sense that it is an emergent property of a complex dynamic system. The molecular regulatory networks that maintain homeostasis at levels ranging from intracellular to whole-organism are a textbook example of a complex dynamic system [6]. Unlike ecological networks or climate systems, biological systems are directed complex systems, in the sense that they have been shaped by evolution for the express purpose of maintaining and adjusting homeostasis [61]. To achieve this, they can rely only on structural properties of the regulatory network itself (redundancy, feedback loops, etc.); should homeostasis be lost to the point where the network cannot correct itself, there is no external "reset" mechanism (with the exception of modern medicine). Any such complex system has a certain tolerance to variation in external and internal conditions, but the tolerance is not infinite, and there are structural trade-offs between high tolerance to common conditions and broad tolerance to rare conditions [7]. This implies that the regulatory networks are subject to dysregulation, which, when system tolerance is exceeded, could manifest either as sudden death

or as a gradual decline in system performance where dysregulation in one part of the system engenders other dysregulation elsewhere in the system [6].

The multiplicity of aging mechanisms, their diverse manifestations even among individuals within a species, and the apparent complex interactions and feedback loops among the mechanisms [62] all suggest a major challenge for the use of animal models in the context of aging. On the one hand, the complexity of the phenomenon means that animal models will be particularly important, while on the other hand it means that the lessons to be drawn are not always straightforward, and the ecological and evolutionary context of the organism will need to be carefully considered before drawing broad conclusions.

4. Conserved aging-related signalling pathways

Some readers may at this point be confused: isn't it well known that there are conserved aging-related signalling pathways present in organisms ranging from yeast to mammals? And indeed there are [63], most notably insulin/insulin-like growth factor 1 (IGF-1) signalling [64], mechanistic target of rapamycin (mTOR) signalling [65], and nicotinamide adenine dinucleotide (NAD+)-dependent sirtuins [66]. The challenge is to reconcile these conserved pathways with the diversity of demographic and physiological aging/non-aging patterns. Part of the answer almost certainly stems from the ecological/evolutionary function of these pathways. They appear to be related to caloric restriction and nutrient sensing, with the function of helping organisms decide whether to invest in current reproduction at a potential cost to survival (when resources are sufficient), or to invest in physiological maintenance/diapause at the expense of reproduction, thereby helping the organism survive to reproduce another day [67]. Much as is the case with conservation of eye development across the animal kingdom, the upstream control

mechanism has been conserved, but the downstream impacts of that control vary, allowing each species to experience "private" impacts of the regulation tailored to its physiological and ecological context [67].

Still, the challenge is larger than this. The impact of these pathways on lifespan (increases of more than 100% in some model systems [64]) is notable from an intraspecific perspective, but is minimal from an interspecific perspective, where lifespans can range from several days to hundreds of years, without even considering all the species that do not age at all [60]. Model organisms are also chosen specifically for their short lifespans, meaning that, in contrast to humans, they may have substantial margin for regulatory up-regulation of lifespan. Furthermore, as noted above, some aging mechanisms such as wear and tear would seem to be largely independent of these pathways. Other mechanisms, such as inflammation and systemic dysregulation, might be subject to some degree of modulation by the conserved pathways, but would likely contribute to aging to some extent regardless of how down-regulated they were by conserved pathways. In other words, conserved pathways clearly control certain aging mechanisms and have the potential to affect aging rates, but it seems highly unlikely that, even taken together, they represent a sufficient mechanistic explanation for aging. They also do not explain why some organisms do not age.

Despite their relatively modest effects on individual lifespan (as viewed from a comparative perspective), it is also likely that these conserved pathways play at least some role in modulating lifespan over evolutionary time [68]. For example, IGF-1 appears to mediate much of the variation in lifespan across dog breeds, perhaps because an IGF-1 allele affecting body size (which is strongly selected for via artificial selection) also produces marked effects on lifespan pleiotropically [69].

5. An integrative understanding of variation in aging across the tree of life

Combining the insights that conserved aging-related signalling pathways explain a modest but non-negligible portion of the aging process, and that aging is both mechanistically and demographically quite heterogeneous across the tree of life, the inescapable but rather unsatisfying conclusion is that aging is highly particular: that each species will have evolved aging patterns that reflect a combination of the physiological constraints imposed by its evolutionary history and its current environment and selection pressures. In some taxa, this may include the possibility of non-aging, and in others aging may be inevitable. When aging exists, it may exist for very different reasons in different taxa.

While there are not necessarily any universal aging mechanisms, some mechanisms might be present in a wide range of species. For example, it is possible that oxidative stress is one mechanism among many in species ranging from plants [70] to yeast [71] to mice [72]. However, naked mole rats (*Heterocephalus glaber*), which are very closely related to mice compared to plants or yeast, have extremely long lifespans despite high levels of oxidative damage [73], implying that the importance of oxidative stress as an aging mechanism can shift over relatively short evolutionary timescales. Extrapolating this example, we should expect substantial complexity in patterns of aging mechanisms across the tree of life. Some mechanisms may only exist in one or a few closely related species that have a particular physiological vulnerability or ecological situation. Some mechanisms may be broadly important within a large taxon, but not outside the taxon. Some mechanisms may appear more or less frequently across the entire tree of life. In most or all cases, aging will be the result not of a single mechanism but of the confluence

of a large number of mechanisms, in combinations that vary markedly across the tree of life and even sometimes among closely related species.

However, this complexity in not completely intractable: clear patterns exist. For example, within relatively large taxa such as birds, mammals, bats, and marsupials, there are clear relationships between aging rate and factors such as body size, extrinsic mortality, and metabolic rate [74-78]. This implies that aging rate is under coherent genetic control in ways that permit it to respond to selection pressures. This explains variation in lifespan among dog (*Canis familiaris*) breeds, for example: lifespan might be difficult to select on independently of factors such as body size and personality [69, 79], but it nonetheless can be altered dramatically by selection over relatively short evolutionary timescales. Indeed, it is likely that the conserved aging-related signalling pathways discussed above play an important role in allowing selection to act coherently on aging rate [68]. Such upstream mechanisms might be crucial to canalize physiological complexity, which would otherwise prove intractable evolutionarily [61].

Nonetheless, there is also good reason to suspect that the conserved aging-related signalling pathways identified so far are not the only upstream control mechanisms that selection targets to adjust aging rate. First, as noted above, experimental manipulation of these pathways does not seem to account for sufficient variation in lifespan. Second, there are likely to be taxon-specific control mechanisms that are adapted to a taxon's ecological context. For example, in eusocial insects, queens often have lifespans that are orders of magnitude longer than workers [80]. Control of lifespan across castes in these species appears to be at least partially regulated by normal insect hormones (vitellogenin and juvenile hormone) that have been somewhat repurposed with altered roles in this context [81]. Third, control mechanisms can be emergent properties of the underlying regulatory network such that they are hard to trace to a single

molecule or pathway. Although this has yet to be demonstrated for evolutionarily conserved control mechanisms, it appears to be the case for variation in some aging mechanisms within individuals [82], and similar principles are likely to apply for evolutionary control.

6. Implications for the use of model organisms in aging

The integrative understanding of aging presented above implies on the one hand that a diversity of model organisms will be essential to achieve a full understanding of the aging process, and on the other that extreme caution will be needed in their interpretation. For example, the finding that insulin/IGF signalling is important in yeast, nematodes, fruit flies, and mice has been interpreted as proof of the (near) universality of this aging-related signalling pathway, but this is contradicted by the absence of aging in many species nested within the clade containing these conserved pathways (hydra, some turtles, some fish, etc.). Of course, it is possible that the trait of aging was lost repeatedly, but there is no current evolutionary explanation for why this would happen in this particular pattern. Here I present several approaches to the use of model organisms in aging research based on the above perspective. Many of my suggestions have been previously discussed by Steve Austad, perhaps the foremost champion of the use of unusual animal models in aging research [60, 76, 83-90].

6.1 Identification of unique anti-aging strategies in long-lived species

Some species are exceptionally long-lived, either in general or for their taxonomic group, and this implies that they may have evolved specific mechanisms to avoid aging. Understanding these mechanisms might generate potential benefits for human health, and might help understand the ecological, evolutionary, and physiological context of extreme lifespans. For example, the

longest-lived known non-colonial animal is a small, coldwater clam, *Arctica islandica*. Its record lifespan is 507 years, and it demonstrates a number of unique features, including marked stress resistance and proteostasis throughout its lifespan [91-93]. Understanding the basis of this proteostasis might provide avenues for the prevention or treatment of Alzheimer's disease. Similarly, the naked mole-rat is the only eusocial mammal, with a social system like many ants, bees, and wasps. As in eusocial insects, the queens have much longer lifespans than the workers, living for 30+ years. Surprisingly, despite their long lifespan, naked mole-rats accumulate oxidative damage at rates similar to mice and have rather poor oxidative defence systems [73]. Rather, it seems they have evolved mechanisms to tolerate high levels of macromolecular damage, such as increased proteasome activity [94].

These are important, fascinating findings, but again we must be cautious about their interpretation, given what is known about the complexity of aging. Other, undiscovered aging mechanisms may also be involved in determining the extreme lifespans of these species, and it is not clear that interventions designed to replicate these mechanisms in humans would have the desired effect without replicating the entire physiological context of these organisms more broadly. Long lifespan likely requires evolution of mechanisms to mitigate many potential underlying processes. It will also be important to develop a large number of such model organisms to understand the diversity of strategies that might be adopted. Based on these two well-known examples, it appears that each has chosen a different strategy.

6.2 Generation of broad, comparative data

Which aging mechanisms are universal within certain taxa, such as mammals? Which aging mechanisms covary with lifespan across species, and which do not? How variable is

demographic aging within and across taxa at different levels? All of these questions and more require an enormous effort to collect data in a relatively standardized or comparable way across large numbers of species. It is precisely such efforts that have led to recent demographic insights. A parallel effort for biological mechanisms is needed. The challenge is that data is often collected by many different laboratories in ways that are not easily standardized. Curated databases such as AnAge might provide an excellent vehicle to encourage such efforts [46].

6.3 Disadvantages of standard laboratory model organisms

There can be no doubt that standard laboratory model organisms – yeast, nematodes (*Caenhorabditis elegans*), fruit flies (*Drosophila melanogaster*), and mice – have generated major advances in our understanding of aging, including the identification of conserved pathways. However, the limits of such model organisms are also more pronounced in the field of aging than in many other contexts [89]. This is in large part because aging is a highly plastic phenotype that depends heavily on the environment, both at the individual level in terms of how it evolves. Here are several major challenges/limits of typical model organisms in a laboratory context:

1) **Short lifespans**. Laboratory organisms are chosen because of their short generation times and concomitant short lifespans. Because the pace and shape of life are not necessarily linked, it should be possible to choose short-lived non-aging species as model organisms (e.g. hydra). Nonetheless, all the standard model organisms have both short lifespans and fast aging. Just as there might be some shared biological features of long-lived organisms across very different taxa, there may also be some shared features of fast-aging organisms that make them more similar to each other than to other members of their respective taxa

[89]. There may also be particularities of their aging processes. For example, telomerase is not expressed in human somatic tissues, but is expressed in mouse tissues. Though this appears to be attributable to body size differences more than lifespan [9], it still suggests that the aging process in mice may differ from that in many other mammals in important ways. One crucial impact of the use of fast-aging models is that they may have more room to express increases in lifespan. For example, if evolution has modulated insulin signalling pathways to generate short lifespans in mice and long lifespans in humans (within the basic constraints of mammalian physiology), it is possible that even though manipulation of this pathway markedly extends lifespan in mice [95], it might have little to no effect in humans, which may have already maxed out the potential of this pathway in order to generate their current life histories.

2) **Genetic homogeneity** [96]. Laboratory animals, particularly mice, are often highly inbred, for the good reason that this minimizes the impact of genetic variation on results. However, it also creates problems for research on aging. Results are based on a single genotype that may have many particularities, and thus results may not be generalizable. The inbreeding process itself may create unexpected forms of selection, and near-universal homozygosity may have important biological consequences.

3) **Selection for laboratory survival and reproduction**. All environments create selective pressures, including the laboratory environment. Long-lived mutants that have been identified in lab populations only rescue the phenotype of wild populations [97]. There may be behavioural and physiological adaptations [96], both of which may impact lifespan and aging [79]. Also, relaxation of selective pressures present in the wild may cause important changes relative to the wild phenotype. For example, the primary cause

of mortality in wild mice is cold exposure (i.e., insufficient thermogenesis) [98], and pathogen exposure is presumably another main cause, meaning selection will be very strong. Neither cold exposure nor pathogens is a major cause of laboratory mortality, implying that laboratory mice could differ substantially from their wild counterparts in terms of immune function and energy metabolism, both known to be important in aging.

4) **Lack of ecological context**. Organisms are adapted for their particular ecological niches, and taking them out of this context can produce major impacts on their demography and physiology. For example, a mutation that increases longevity without apparent costs to reproduction in a lab may or may not have a similar effect in the wild: the mutation might increase susceptibility to pathogens, might decrease real-world reproductive success (e.g. obtaining a mate in a competitive environment), or might even accelerate physiological aging under realistic conditions such as variable nutrition and/or high pathogen exposure.

Of course, none of these limitations is a reason to abandon or disparage studies of model organisms; rather, they are factors to consider both in the planning and interpretation of such studies, and they are reasons to complement research on model organisms with other research from a broad comparative perspective [89].

7. Conclusions

Aging remains one of the most complex known biological processes. While it is still poorly understood, there is now clear evidence that aging is multi-factorial, probably formally complex, and varies across the tree of life not just in the specifics of its mechanisms but in whether or not it exists in anything like the form we know it as humans. For these reasons, the choice and use of model organisms is particularly challenging. Familiar model organisms – yeast, nematodes, fruit

flies, and mice – will continue to have important roles, but a wide variety of other organisms will also be needed in specific contexts. It will be important to study very slow-aging and long-lived organisms to understand their particularities, and to study broad comparative patterns. Aging appears to be heavily dependent on evolutionary history, a species' ecological context, and an organism's particular environment, and results must therefore be interpreted with caution and always in a comparative context. The mysteries of aging will only be unravelled through continued use of a multi-pronged strategy including standard laboratory models, unusual laboratory models, wild models, and comparative physiological and demographic data.

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Figure legends

Figure 1. Relative mortality (red) and fertility (blue) as functions of age, from maturity to the age when only 5% of the adult population is still alive; mortality and fertility are scaled relative to their means. Subplots are arranged in order of decreasing relative mortality at the terminal age. Survivorship (on a log scale) from maturity is depicted by the shaded areas. Broken lines, for trajectories derived from projection matrices, start at the age when cohorts have converged to within 5% of their quasi-stationary distribution. Reprinted by permission from Macmillan Publishers Ltd: Nature Publishing Group (Jones, O.R. *et al*., Nature 505, 169–173), copyright (2013).

753 **Table 1: Notable non-model animals in aging research**

Common name	Scientific name	Taxon	Maximum lifespan	Reason
Hydra	*Hydra magnipapillata*	Cnidarians	None	Best example of a non-aging species [19]
Sea squirt (one kind)	*Botryllus schlosseri*	Tunicates	None	Programmed aging ramets and non-aging genets [22]
American lobster	*Homarus americanus*	Arthropods	100	Longest-lived arthropod [46]
Black garden ant	*Lasius niger*	Arthropods	29 (queen)	Eusocial, extreme queen lifespan [81]
Honeybees	*Apis mellifera*	Hymenoptera	8 (queen)	Eusocial, well-characterized [46]
Ocean quahog clam	*Arctica islandica*	Molluscs	507	Longest-lived non-colonial animal [91, 93]
Red sea urchin	*Strongylocentrotus franciscanus*	Echinoderms	200	Extreme lifespan for its size [46]
Greenland shark	*Somniosus microcephalus*	Chondrichthyes	500	Longest lived fish [99]
Lake sturgeon	*Acipenser fulvescens*	Actinopterygii	152	Long lifespan [46]
Rougheye rockfish	*Sebastes aleutianus*	Actinopterygii	205	Long lifespan [46]
Olm	*Proteus anguinus*	Amphibia	102	Longest-lived amphibian [46]
Japanese giant salamander	*Andrias japonicus*	Amphibia	55	Long lifespan [46]
African bullfrog	*Pyxicephalus adspersus*	Amphibia	45	Long lifespan [46]
Galapagos tortoise	*Geochelone nigra*	Reptiles	177	Longest-lived reptile [46]
Eastern box turtle	*Terrapene carolina*	Reptiles	138	Extreme lifespan and manageable in captivity [46]
Tuatara	*Sphenodon punctatus*	Reptiles	90	Long lifespan [46]
American alligator	*Alligator mississippiensis*	Reptiles	73	Long lifespan [46]
Broad-tailed hummingbird	*Selasphorus platycercus*	Birds	14	Extreme lifespan for its mass and metabolic rate [46]
Pink cockatoo	*Cacatua leadbeateri*	Birds	83	Long lifespan [46]
Andean condor	*Vultur gryphus*	Birds	79	Long lifespan [46]
Royal albatross	*Diomedea epomophora*	Birds	58	Long lifespan [46]
Japanese quail	*Coturnix japonica*	Birds	6	CJ is one of the shortest lived birds; marked lifespan difference for congeners [46]
Common quail	*Coturnix coturnix*	Birds	14.6	
Naked mole-rat	*Heterocephalus glaber*	Rodents	31	Exceptional rodent lifespan, eusocial [100]
American beaver	*Castor canadensis*	Rodents	23.4	Contrast with mouse [46]

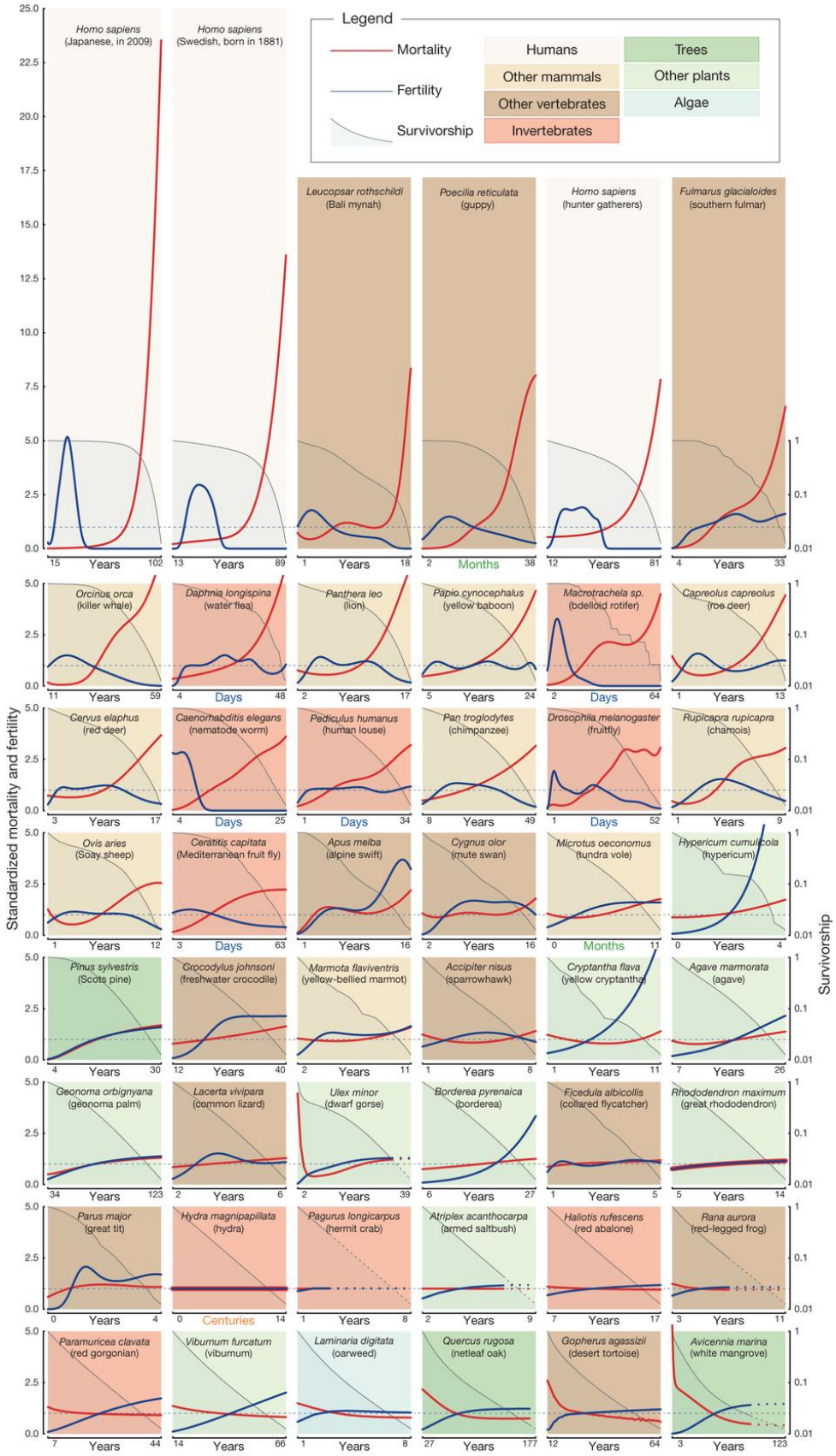
North American Porcupine	*Erethizon dorsatus*	Rodents	23.4	Contrast with mouse [9, 101]
Little brown bat	*Myotis lucifugus*	Chiroptera	34	Contrast with each other; LBB exceptionnaly long-lived for its mass and metabolic rate [87]
Evening bat	*Nycticeius humeralis*	Chiroptera	6	
Bowhead whale	*Balaena mysticetus*	Cetaceans	211	Longest-lived mammal [46]
Killer whale	*Orcinus orca*	Cetaceans	90	Very long-lived; highly social with menopause analog [46]
Common marmoset	*Callithrix jacchus*	Primates	16	Short-lived for a primate [87]
Fat-tailed dwarf lemur	*Cheirogaleus medius*	Primates	23	Hibernation in a primate [101, 102]
Gray mouse lemur	*Microcebus murinus*	Primates	18	Photoperiod/torpor effects; model of brain aging [101, 103]

754 This table compiles both species with exceptional potential for aging studies as well as species notable for their longevity within their group. Most
755 records are based on the AnAge database [46], and the taxonomic bias of this resource should be noted: there are records for 4212 species of
756 vertebrate, but only 8 species of arthropod, even though most species on earth are arthropods. This reflects a paucity of high-quality data on these
757 other taxa. The list is intended to be illustrative rather than exhaustive.

Table 2. Common aging profiles found across the tree of life

Profile	Characteristics	Examples
Hamiltonian aging	More-or-less exponential increase in mortality after age at first reproduction timed to coincide with the decreasing force of selection with age; expected concordance between demographic and physiological aging	Most mammals, most birds, garter snakes, guppies, fruit flies, nematodes, some plants
Semeparity/ catastrophic aging	A single reproductive bout followed by a rapid physiological decline and death. The physiological decline can appear programmed (e.g., hormonal cascades) but the actual degree of programming is not clear.	Pacific salmon, marsupial mice (dasyurids), mayflies, annual plants
No aging	Flat mortality rates throughout adult life	Hydra
Negligible aging	Mortality rates are roughly flat or even modestly declining throughout adult life, but are either more variable than the no-aging profile or are not long enough to be sure that eventual aging would not arise. Data series should nonetheless be long enough to ensure that mortality is low when the force of selection is very weak.	Some turtles, some amphibians, many marine invertebrates, some seaweed, some trees, some herbaceaous plants
Size-based mortality patterns	Age contibutes relatively little to prediction of mortality rates beyond a potential correlation with size; clear age structure in mortality may thus be present, but largely as a result of how size impacts mortality.	Many trees, many clonal organisms with distinct ramets, where size is considered the sum of the ramets (colonial marine invertebrates, etc.)
Eusocial aging	Though possibly a subset of Hamiltonian aging, lifespan differs greatly between queens and workers of eusocial species.	Naked mole-rats; many species of ants, bees, and wasps
Other	Many organisms have some combination of the above patterns, such as programmed aging of ramets and negligible aging of genets, or non-monotonic changes in mortality with age. Many organisms have aging patterns that are highly unique and adapted to their particular life histories and environment. Often ignored, this category may actually contain a large portion of the tree of life. Physiological aging may occur but be reversible, or may occur but on timescales much slower than predicted based on selection pressure, etc.	Some tunicates, some birds?, some lizards, many invertebrates and plants

The profiles described here are approximate and are not intended to represent a formal or exhaustive classification, but rather to illustrate the diversity of aging patterns known.


Legend
Mortality
Fertility
Survivorship
Humans
Other mammals
Other vertebrates
Invertebrates
Trees
Other plants
Algae
Homo sapiens (Japanese, in 2009)
Homo sapiens (Swedish, born in 1881)
Leucopsar rothschildi (Bali mynah)
Poecilia reticulata (guppy)
Homo sapiens (hunter gatherers)
Fulmarus glacialoides (southern fulmar)
Orcinus orca (killer whale)
Daphnia longispina (water flea)
Panthera leo (lion)
Papio cynocephalus (yellow baboon)
Macrotrachela sp. (bdelloid rotifer)
Capreolus capreolus (roe deer)
Cervus elaphus (red deer)
Caenorhabditis elegans (nematode worm)
Pediculus humanus (human louse)
Pan troglodytes (chimpanzee)
Drosophila melanogaster (fruitfly)
Rupicapra rupicapra (chamois)
Ovis aries (Soay sheep)
Ceratitis capitata (Mediterranean fruit fly)
Apus melba (alpine swift)
Cygnus olor (mute swan)
Microtus oeconomus (tundra vole)
Hypericum cumulicola (hypericum)
Pinus sylvestris (Scots pine)
Crocodylus johnsoni (freshwater crocodile)
Marmota flaviventris (yellow-bellied marmot)
Accipiter nisus (sparrowhawk)
Cryptantha flava (yellow cryptantha)
Agave marmorata (agave)
Geonoma orbignyana (geonoma palm)
Lacerta vivipara (common lizard)
Ulex minor (dwarf gorse)
Borderea pyrenaica (borderea)
Ficedula albicollis (collared flycatcher)
Rhododendron maximum (great rhododendron)
Parus major (great tit)
Hydra magnipapillata (hydra)
Pagurus longicarpus (hermit crab)
Atriplex acanthocarpa (armed saltbush)
Haliotis rufescens (red abalone)
Rana aurora (red-legged frog)
Paramuricea clavata (red gorgonian)
Viburnum furcatum (viburnum)
Laminaria digitata (oarweed)
Quercus rugosa (netleaf oak)
Gopherus agassizii (desert tortoise)
Avicennia marina (white mangrove)
Years
Months
Days
Centuries
Standardized mortality and fertility
Survivorship
Age