Review

How to live for centuries: common denominators of organisms with exceptional longevity

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ABSTRACT

Organisms vary in their lifespan. Understanding this variation may help us live healthier and longer. Here, we focus on species living twice as long as humans, or more. Out of the 101 multicellular species with a maximum lifespan of 250+ years, 11 are animals and 90 are plants. We surveyed the genetic, transcriptional, proteomic, metabolomic, regeneration-, stress-, and cancer-related components of intraspecific and interspecific lifespan variation, across these species. We examined whether the mechanisms regulating intraspecific lifespan variation across these species are the same or different from mechanisms regulating interspecific lifespan variation. We identified several similarities: both types of variation include mechanisms related to DNA maintenance, stemness, and stress management. Such mechanisms are also typical of early developmental stages and germ cells. Nonetheless, caution should be exercised when attempting to draw robust conclusions based on available data, given the lack of in-depth molecular studies on the healthspan and lifespan across thousands of individuals and species, the methodological variation across published studies, and our partial understanding of the interplay between physiology and the environment across species.

INTRODUCTION

Each species consists of numerous individuals, with some living less than others. Over a dozen different definitions of a species have, historically, been put forward [1–3]. More recently, a unified concept of a species has been introduced, such that a species is a separately evolving population consisting of sub-populations [4]. We use these conventions to refer to specific species in this article. Certain molecular processes shape the lifespan of each species and each individual. Deciphering these processes, which underlie the diversity in lifespan across and within species can help us better understand how they evolved and why. Such knowledge may inform the design of effective strategies towards increasing human and other species' healthspan and lifespan. Healthspan broadly refers to the time that an organism is healthy, i.e., does not suffer from diseases or disabilities, whereas lifespan refers to the time that the organism exists from birth to death [5]. Several studies have investigated the molecular biology of lifespan variation within and across different groups of species (reviewed in [6–11]). However, a survey of recent developments regarding the molecular components regulating the variation in lifespan within and across extremely long-lived (e.g., of at least 250 years old) animal and plant species is lacking.

Here, we consider 101 species that live past 250 years, including the longest-living beings on Earth (Figure 1). Among these species, 90 are plants and only 11 are animals. Some barely reach an age of 250 years, while others live for up to 80,000 years. Few, such as the freshwater planarian and the *Turritopsis dohrnii* jellyfish,

are considered potentially immortal [12, 13]. There are only a handful of species, that live for over 10,000 years. These are mostly animals (four out of the six species, with the rest being plants). None of these species are mammals; indeed, no known mammal lives for over 250 years.

We reviewed the literature on the molecular and cellular mechanisms implicated in lifespan variation within and among extremely long-lived multicellular species. We aimed to examine whether the lifespan-extending mechanisms that extremely long-lived organisms have

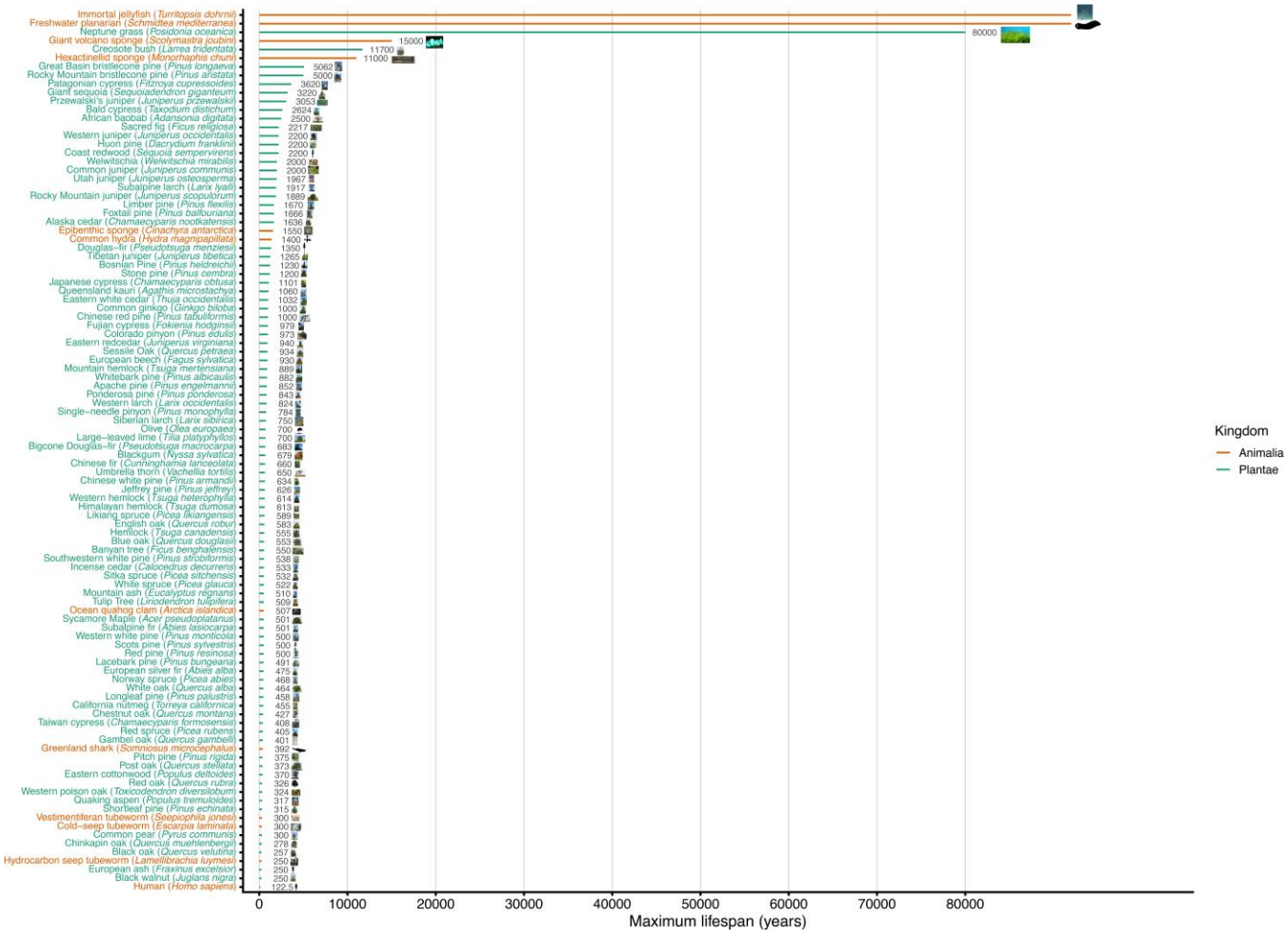

Figure 1. 101 species with a maximum lifespan of at least 250 years. The maximum lifespan of humans is noted for comparison with other species. We obtained most maximum lifespan values from the AnAge database [14]. For the following species, maximum lifespan values were found in the indicated references: *Juglans nigra, Fraxinus excelsior, Pinus sylvestris, Tsuga canadensis, Nyssa sylvatica, Olea europaea, Fagus sylvatica, Agathis microstachya, Pinus cembra, Juniperus communis, Dacrydium franklinii, Quercus velutina*, *Quercus montana*, *Quercus rubra*, *Quercus alba*, *Pinus rigida*, *Pyrus communis* [15], *Fitzroya cupressoides* [16], *Juniperus przewalskii* [17], *Pinus heldreichii, Quercus petraea* [18], *Acer pseudoplatanus* [19], *Liriodendron tulipifera* [20], *Quercus douglasii, Taxodium distichum* [21], *Posidonia oceanica* [22], *Pinus monophylla*, *Pseudotsuga macrocarpa* [23], *Pinus monticola*, *Pinus resinosa*, *Pinus aristata* [24], *Hydra magnipapillata* [25], *Monorhaphis chuni* [26], *Pinus tabuliformis* [27], *Welwitschia mirabilis* [28], *Ficus benghalensis* [29], and *Larrea tridentata* [30]. For the remaining species shown on the figure that lack maximum lifespan values in the AnAge database, we found lifespan data in ref. [31]. Numbers on the side of each bar show the value of maximum lifespan for each species. The freshwater planarian *Schmidtea mediterranea* does not have a reported maximum lifespan in the AnAge database, and is considered potentially immortal [32]. Likewise, the jellyfish *Turritopsis dohrnii* is considered potentially immortal [13]. We obtained the species images included from Phylopic, or from online resources under the creative commons license. Due to unavailability of Creative Commons Licensed images for *Escarpia laminata*, *Cinachyra antarctica* and *Juniperus tibetica*, we used Creative Commons Licensed images of their sister species *Escarpia southwardae*, *Cinachyra australiensis* and *Juniperus virginiana*, respectively. The image of *Scolymastra joubini* is taken from ref. [33]. The image of *Juniperus tibetica* is taken from https://www.inaturalist.org/taxa/135889-Juniperus-tibetica/browse_photos. The figure was generated using *R*.

evolved over millennia are distinct, or bear discernible similarities. Our analysis incorporated available genetic, genomic, transcriptomic and metabolomic data, focusing on findings relevant to telomere maintenance, stress resistance, regeneration, and tumorigenesis processes. These analyses have yielded a wealth of information about the genes and molecules shaping organismal physiology and the adaptations that underlie the variation in lifespan among extremely long-lived individuals.

Vulnerability to cellular, tissue and organismal stress may also change the lifespan of organisms through a complex network of molecular and cellular interactions [34–37]. For example, oxidative stress responses involve over 70 molecular pathways, including apoptosis, mitophagy, FoxO signaling, JAK-STAT signaling, Toll-like receptor signaling, and HIF-1 signaling [38]. In addition, the ability of cells to regenerate gradually diminishes in aging organisms. This decline is thought to be an evolutionary adaptation preventing uncontrollable cell over-proliferation, e.g., cancer [39]. Thus, understanding potential intraspecific and interspecific variations in the regulation of regenerative downfall can aid in understanding intraspecific and interspecific variations in lifespan of extremely long-lived individuals. It is important to examine these mechanisms in extremely long-lived species, given their known role in lifespan variation across long-lived species (reviewed in [10]). For example – across various species of mammals, birds, or fish – long-lived species have a higher ratio of tumor suppressor gene:oncogene copies [40], lower somatic mutation rates [41], less telomere shortening [42], shorter telomeres [43, 44], longer telomeres [45], no significant difference in telomere length compared to shorter-lived species [46], higher concentrations of antioxidants [47], lower concentrations of reactive oxygen species [47], higher resistance to stress [48], fewer polyunsaturated triacylglycerols [49], and increased levels of mono-unsaturated fatty acids [50].

Finally, we discuss the translatability and the implications of studies involving species of exceptional longevity on human health and aging. We also note that the mechanisms regulating lifespan variation within and between ≥250-year-old species are somewhat similar. Key features of extremely long-lived organisms are enhanced regeneration and DNA maintenance capacity, as well as better resistance to stress, oxidative damage, and cancer. Further studies with many more individuals and species, consistent methodology, and inclusion of environmental parameters could strengthen our understanding of intra- and inter-species lifespan variation.

Components of intraspecific lifespan variation

Genomic analyses

Studies of the genetic variation among individuals of extremely long-lived species found some genetic variation, selection for stress-related genes, and chromosomal rearrangements, depending on the species (Table 1). For example, a genomic region of 12 cytochrome b sequences was sequenced from six populations of ocean quahog clams; each population from a different region in northern Europe. Large genetic variation (80%) was detected within the populations, but negligible variation was observed between the populations (2%), indicating that geographic location had a marginal effect on genetic variation [51]. Among the genomes of 545 trees of the species *Ginkgo biloba* from 51 populations across the world, specific genes were selected over evolutionary time. These genes are involved in managing abiotic (e.g., low temperatures, high concentrations of salt, and dehydration) and biotic stress. There was no correlation between diversity at the genetic level versus variation in morphology, or their geographical distance [52]. In freshwater planarians, large chromosomal rearrangements possibly regulate lifespan. Comparison of the asexual (which is also considered immortal) and sexual *Schmidtea mediterranea* show that the former has a translocated chromosome, whereas the latter does not have this rearrangement [53, 54]. Specifically, in the asexual strain, a fragment from one of the 1st pair of chromosomes has moved to one of the 3rd pair of chromosomes [53]. It is worth noting that these studies are an important initial step in understanding what regulates the variation in lifespan within extremely long-lived species. However, they do not establish a direct causal link between specific genetic components and lifespan regulation, within these species.

Transcriptomics

Comparisons of transcriptomic data between individuals, within two potentially immortal species, show that differences in the regulation of DNA maintenance and stemness pathways may play an important role in lifespan variation, within these species. The jellyfish *Turritopsis dohrnii* can reverse its development and become larvae again, potentially achieving immortality [6, 13]. Matsumoto and colleagues compared the transcriptome of multiple jellyfish individuals at different developmental stages. Animals at the cyst stage (early in development) overexpressed genes related to DNA repair, telomere maintenance, and telomere organization, and underexpressed genes related to aging, compared to other stages. For example,

Table 1. Indicative characteristics of long- versus short-lived individuals, within extremely long-lived species.

Species	Sample size (# individuals in all experimental conditions of an assay)	Experimental approach	Characteristic features	Reference
Arctica islandica	18-180 depending on the assay	Molecular	No significant differences in the metabolic rate nor activity of antioxidant enzymes	[55]
Arctica islandica	at least 50 per assay	Metabolomics	Less accumulation of lipofuscin	[56]
Arctica islandica	62 or 25 depending on the assay	Molecular	No significant differences in the length of telomeres nor in the activity of telomerase	[57]
Arctica islandica	51 per assay	Molecular	No significant differences in the activity of the mitochondrial electron transfer chain, or in the susceptibility of mitochondria to oxidative damage	[58]
Pinus longaeva	7-9 depending on the assay	Molecular	Longer telomeres and increased activity of telomerase in the roots; no significant differences in the length of telomeres and lower activity of telomerase in needles	[24]
Schmidtea mediterranea	17 or 20 depending on the assay	Molecular	Better maintenance of telomeres	[12]
Schmidtea mediterranea	at least 24	Cytogenetics	Chromosomal translocations	[53, 54]

the cyst stage expressed 831 transcripts related to DNA repair whereas the other life stages expressed 574-742 DNA-repair-related transcripts [59]. In another extremely long-lived organism, hydra, the transcription factor FoxO has been implicated in maintaining the organism's ability to regenerate and reach potential immortality. Specifically, transcriptomic comparison of hydra individuals, with silenced versus non-silenced foxO gene, showed that the former had fewer terminally differentiated cells in the foot region of the hydra and more stem cell proliferation than the latter. FoxO regulates the expression of genes, such as *cniwi*, and *cniwi* is differentially expressed in somatic versus stem cells. Mature nematocytes of hydra do not express *cniwi*, whereas their interstitial stem cells do [60].

Metabolomics

Studies between individuals of *Arctica islandica* that varied in their lifespans showed that metabolic rate did not explain a significant amount of variation in the individuals' lifespans. By contrast, shorter-lived individuals had higher levels of an aging-related marker, compared to longer-lived individuals. Specifically, when studying different populations of *Arctica islandica*, Basova and colleagues found that while metabolic rate could not explain the variation in lifespan of the examined individuals, the levels of the autofluorescent age pigment lipofuscin that accumulates in lysosomes of old cells, are higher in the mantle and gills of individuals with shorter lifespan compared to those with longer lifespan [55, 56]. This points to the potential ability of longer-lived *Arctica islandica* individuals to withstand aging-related damage.

Telomere maintenance

The length of telomeres and telomerase activity does not seem to consistently explain the variation in lifespan among individuals of extremely long-lived species. For example, the telomere length and telomerase activity among individuals of *Arctica islandica* did not correlate significantly with the different lifespans of these individuals [57]. Among different trees of the species *Pinus longaeva*, ranging from 20 to 3,500 years old, the length of telomeres and the activity of telomerase varied depending on the tissue of the tree. The roots of old trees had longer telomeres, compared to the roots of young trees, whereas the needles of old and younger trees did not show significant telomere length differences. The roots of old trees appeared to have an increased activity of telomerase, whereas the needles and the core samples of the old trees had lower activity of telomerase relative to younger trees [24]. When comparing the length of telomeres over time in asexual versus sexual strains of the freshwater planarian *Schmidtea mediterranea*, asexual strains which are considered immortal are better able to maintain the ends of their telomeres, compared to the sexually reproducing strains [12].

Stress resistance

Individuals of exceptionally long-lived species that vary in their lifespan do not show significant variation in the

way they handle oxidative stress. Out of all the types of stresses, only oxidative stress is mentioned here, given the absence of relevant literature on associations between intraspecific lifespan variation and other types of stresses, in extremely long-lived species. The activity of antioxidant enzymes was not significantly correlated with age, in a study where different individuals of the species *Arctica islandica* were examined [55]. The activity of the electron transport system in mitochondria, and the susceptibility of the mitochondrial membrane to damage caused by reactive oxygen species did not differ significantly among young versus old *Arctica islandica* individuals [58]. In addition, although hypoxia resistance has often been linked to longevity [61], varying oxygen concentrations did not increase the lifespan of *Arctica islandica* individuals, compared to normoxia [55].

Components of interspecific lifespan variation

Genomic analyses

Across diverse species, comparisons including extremely long-lived species have almost always shown that longer-lived species are characterized by a higher number of genes involved in DNA maintenance, and abiotic and biotic stress resistance, compared to shorter-lived species. In studies of animals, for example, it has been shown that the extremely long-lived *Lamellibrachia luymesi* has more copies of SOD genes, which are involved in protecting cellular damage from oxidative stress, than other shorter-lived species of Lophotrochozoa [62]. Three SOD2 proteins were detected in a proteomic analysis of *Lamellibrachia luymesi* [62], though it is unknown whether the extra SOD2 gene copies provide increased resistance to oxidative stress in this species. *Arctica islandica* has the highest percentage of repeats and a higher total number of genes, relatively to other shorter-lived bivalve species [63]. Additionally, by comparing the dN/dS ratio of short- versus long-lived bivalve species, Iannello and colleagues [64] found evolutionary convergence in many genes of long-lived species. These genes are involved in pathways regulating DNA damage repair, the resistance to viruses, and environmental insults, as well as pathways regulating apoptosis, and tumor suppression. The same study also identified 43 genes that were episodically positively selected in long-lived versus short-lived species of bivalves. These genes are involved in protein homeostasis, protein folding, the response to hypoxia, oxidative stress resistance, and apoptosis. *Turritopsis dohrnii* has more copies of replication regulating, DNA damage repair, oxidative stress resistance, and apoptosis-regulating genes, compared to the non-immortal *Turritopsis rubra*. Specifically, some of these genes included the DNA polymerase delta and alpha, DNA topoisomerase III beta, X-ray repair cross complementing 5, RAD51 paralog C, gene endonuclease homolog 1, thioredoxin, glutathione reductase GSR, presenilin 1, and bone morphogenetic protein 7 [65]. The number of expressed gene copies is higher in *Turritopsis dohrnii* than *Turritopsis rubra* [65]. However, it is unknown whether in *Turritopsis dohrnii* the corresponding protein levels are higher than *Turritopsis rubra*, and whether this increased gene copy number leads to improved DNA replication and repair, resistance to oxidative stress, and tighter regulation of apoptosis, in *Turritopsis dohrnii*, compared to *Turritopsis rubra.*

In plants, the extreme lifespan of some species may be partly explained by increased copies of genes related to DNA damage response and stress resistance, but not to genome size or ploidy. Specifically, when comparing the genomes of 61 plant species, Aoyagi Blue and colleagues [66] found that certain extremely long-lived species have more copies of PARP genes, which are involved in responding to DNA damage. Specifically, *Pseudotsuga menziesii*, *Pinus sylvestris*, and *Malus domestica* had the highest copy number of PARPs [66]. A genomic comparison of three plant species, with *Sequoiadendron giganteum* being the longest-lived among the three, showed that *Sequoiadendron giganteum* has relatively more genes involved in the synthesis of flavonoids or tannins [67]. These tannins may help this species resist fires and thus help it live longer. Positive selection of genes, related to abiotic (e.g., osmosis, dehydration) and biotic (e.g., pathogens) stress resistance, in the extremely long-lived *Ficus benghalensis* and *Ficus religiosa* relative to other angiosperm species, may explain the extreme longevity of these two species [68]. The extremely long-lived *Ginkgo biloba* has almost five times more copies of genes related to the synthesis of metabolites, such as terpenes and flavonoids, involved in defenses against pathogens, than the shorter-lived *Arabidopsis thaliana* [69, 70]. However, genome size did not seem to explain the variation in the lifespans of plant species [71]. Polyploidy also does not appear to be associated with longevity in a study of hundreds of gymnosperm species [72].

Metabolomics

The ability to recycle proteins and the levels of oxidative stress resistance-related proteins do not appear to explain the variation in longevity among species. However, in some species the increased production of metabolites, such as monoterpenes, may help increase their lifespan. Longer-lived species are expected to be

better able to eliminate damaged proteins. To test whether the longer-lived species *Arctica islandica* are better at eliminating damaged proteins, compared to the shorter-lived *Mercenaria mercenaria*, Ungvari et al. compared the activity of three proteasome proteases in these two species. In the adductor muscle, the baseline activities of the three proteases did not differ significantly between the two species. In the gills, two out of the three proteases did not have significantly different activity between the two species, but surprisingly the activity of caspase was higher in the shorter-lived species than the longer-lived species. Thus, the extreme longevity of *Arctica islandica* relative to *Mercenaria mercenaria* cannot be clearly attributed to enhanced ability to recycle proteins [73]. The Greenland shark does not differ significantly in terms of the levels of glutathione peroxidase, an enzyme that protects cells from oxidative damage, in its red blood cells and muscles, compared with other, shorter-lived vertebrate species [74]. Moving to the plant kingdom, *Pinus longaeva* has higher maximum lifespan, compared to *Pinus balfouriana* and *Pinus flexilis*, and also displays a higher concentration of monoterpenes than the other two species [75]. Monoterpenes help plants defend themselves against pathogens [76, 77]. Thus, monoterpenes may be contributing to the increased longevity of *Pinus longaeva* relative to *Pinus balfouriana* and *Pinus flexilis*.

Stress resistance

Extremely long-lived species of some trees appear to have stronger stress responses, and, similarly, extremely long-lived clams appear to have properties that minimize the accumulation of oxidative damage in comparison to shorter-lived species. The extremely long-lived tree *Tilia platyphyllos* appears to have a much stronger response to the stress of urban life than other shorter-lived species. Specifically, comparing the stress responses of three plant species, *Celtis occidentalis*, *Platanus hispanica,* and the extremely long-lived *Tilia platyphyllos,* living in roads with lots of traffic versus less traffic, showed that, out of all the antioxidant enzymes (APX, CAT) and biomarkers of oxidative stress (TBARS, proline, GSH) measured, *Tilia platyphyllos* had a significantly higher concentration of all these compounds in the urban, versus the low traffic environment, whereas the other two species did not show a significant increase in all of these tested compounds [78]. Considering animals, *Arctica islandica* produce much lower amounts of the toxic H_2O_2 than the relatively shorter-lived clam *Mya arenaria* [79]. *Arctica islandica* has comparatively very low peroxidation index of its mitochondrial membrane. This indicates that this species may have a relatively better ability to prevent damage of its mitochondrial membranes, and thus this may, in part, explain this species' relatively longer lifespan [80]. *Arctica islandica* are also relatively more resistant to death from stressors, such as DNA methylation and alkylation agents, in comparison to *Mercenaria mercenaria* [81].

Regeneration

The ability of some extremely long-lived species to regenerate and maintain a non-aging population of stem cells may contribute to their extreme longevity. In comparison to other species, sponges, corals, hydra, jellyfish, and planaria display remarkable ability to regenerate and maintain an active population of stem cells [6]. These properties likely enable them to live so long [6]. This is similar to the ability of germ cells to be transferred from one generation to the next, and to minimize aging-related damage, thus, almost achieving immortality. For example, hydra regularly (approximately every 20 days) replaces all of its cells, including aged cells [82]. *Turritopsis dohrnii* shows a unique capacity to reverse to a younger developmental stage [6]. The neoblasts of planaria are stem cells that circulate around the body of the flatworm and are able to generate any cell type [83], even after the worm has been cut into 279 pieces [84]. Furthermore, although the pluripotency of cells in the meristem region in the roots of the short-lived plant species *Arabidopsis thaliana* decays as they age [85], this decay does not appear in the longer-lived *Pinus sylvestris* and *Ginkgo biloba* [86, 87].

Tumorigenesis

Tumors are not very common in extremely long-lived species (Figure 1), relative to others, and cancer in these species has never been reported. Tumors have been found in several cacti [88], but no case of cancer has been reported in extremely long-lived plants [89, 90]. Tumors are also uncommon in *Arctica islandica* and *Margaritifera margaritifera* [91] relative to other bivalves [92]. Nevertheless, tumors that grew spontaneously have been found in lab strains of hydra [93]. In planaria, tumors have not been observed to develop spontaneously. The capacity of these planaria to not develop as many tumors as expected, based on their lifelong regenerative ability, has been attributed to enhanced DNA repair mechanisms [94], as well as, oncogenes and tumor suppressors, such as PTEN, AKT, p53, and Rb, that also regulate stem cell division [95–99]. However, tumors in planaria can be induced using mammalian carcinogens [100, 101]. The sparsity of reported tumors in these extremely long-lived species indicates that these species may have evolved anticancer mechanisms worthy of future investigations for human anticancer treatments. Other studies,

analyzing a range of vertebrate species, well below the 250-year maximum lifespan with ≥20 individual necropsy records per species, also support potential enhanced anticancer mechanisms in long-lived species, as indicated by the absence of a correlation between maximum lifespan and cancer prevalence [102–105] or cancer risk [106].

Caveats and next steps

As is evident from the studies described above, the molecular processes determining the variation in longevity within and across species have not been systematically investigated across a large number of species on the tree of life, or a large number of individuals within a given species. Therefore, our knowledge is fragmented, at best. For example, Iannello and colleagues [64] emphasized that they based their analyses on only a few genes. Apart from speculations about the remarkable ability of potentially immortal species to regenerate, it is not fully understood exactly why some species have extremely long lifespans or are potentially immortal. In other words, it is not known what particular molecular mechanisms position these species to have a variation in their life history traits that is shifted towards extreme longevity. Future studies, when more and higher quality genome sequences of extremely long-lived species become available, will allow more methodical genomic and transcriptomic analyses towards untangling the molecular mechanisms that enable organisms to live extremely long. Such a broader-scale investigation across species would increase statistical power as highlighted by Rechsteiner and colleagues [10], and would reveal whether the mechanisms that determine the variation in longevity, within and across species, are clade specific or apply to species across the tree of life. Unfortunately, there is very limited molecular mechanistic information for extremely long-lived plants and separately for extremely long-lived animals to allow conclusions about potential differences in the cellular and molecular mechanisms underlying longevity of extremely long-lived species between these two kingdoms. There are few studies per kingdom, and in some cases, there is no information at all about extremely long-lived plants. It remains to be found whether the processes that are thought to be essential for extreme longevity in some immortal species (e.g., regular regeneration in hydra, sponges, and planaria) are also essential for other extremely long-lived species for which relatively less research has been conducted (e.g., some extremely long-lived plants and the hexactinellid sponge).

While there is a lot of data on maximum longevity that allows examining the variation in maximum lifespan across species (the AnAge database; [14]), there is no similar database of healthspan records within and across species. Future studies aiming to build such a database would be useful, as they could, perhaps, reveal new molecular pathways/components that contribute to increased healthspan. This is particularly important given the ongoing efforts to find ways of increasing healthspan in humans [107, 108].

Rechsteiner and colleagues concluded that “no current genetic model fully explains the variation observed across species” [10]. One explanation for this limitation could be that the variation in each study's approaches, scope, and number of species is preventing us from detecting a common genetic model of lifespan variation that could be applied across species. Previous studies aiming to discern the molecular mechanisms of lifespan variation, within and across species, have not all investigated the same species, nor used the same methods. The type of tissue sampled in each experiment may have had a large confounding effect on the interpretation of results from comparative studies. For example, a study comparing the markers of longevity across individuals and species, based on collected liver samples may show very different molecular markers, compared to a study of collected epithelial samples. Each tissue may likely be expressing different molecular markers at a given time point in different individuals and different species. Therefore, variation in the results of these studies could emerge due to methodological differences and examination of different species. Future studies ought to address this issue by using many more species and using consistent methodology to examine whether similarities or differences in the molecular and cellular mechanisms linked to longevity, truly contribute to longevity or have been associated to it due to other confounding variables. Unless we try to minimize this noise coming from attempting to compare dissimilar studies that employ different methodologies, it will be difficult to conclude with confidence whether or not a particular genetic/physiological model can fully capture the variation observed across species. Moreover, the molecular mechanisms explaining the variation in longevity within and across species may be slightly or largely different between laboratory-maintained, versus wild species. Various parameters in laboratory conditions may be different in the wild, and these parameters may affect which genes are expressed, and to what extent, in each environment, thus, affecting individual and species maximum lifespan. Therefore, future studies should carefully take into account the environmental conditions, where these organisms have been living, in order to more accurately pinpoint the components that affect lifespan.

The exact effective population size of every species and the evolutionary pressures that species experience is largely unknown. Therefore, the evolutionary forces that shape the lifespan of each species are unclear. It would be important to unravel these evolutionary forces in order to understand the life trajectory that each organism is likely to follow at the molecular level and, thus, improve strategies that prevent the development of age-related diseases in these organisms. Several environmental components may be affecting the lifespan of exceptionally long-lived species. For example, extreme cold temperatures may have led to unique temperature-dependent molecular pathways contributing to lifespan extension in some species; e.g., the bivalve species *Arctica islandica* found in arctic waters live up to 507 years and the Greenland shark lives up to 392 years. However, we must be cautious with generalizing the impact of environmental factors on physiology to all species, since, obviously, the same environmental conditions do not have the same effect on all species. The cold-sensitive *Hydra oligactis* ages at low temperatures (around 10° C), whereas it is considered immortal at higher temperatures (around 22° C) [109, 110]. By investigating the life-time records of extremely long-lived species, we could identify environmental conditions that extended their lifespans in specific periods and thus elucidate new interactions between the environment and molecular processes that increase the likelihood of living, in any given year. In the case of plants, environmental changes can be tracked by inspecting the rings of the trunks of long-lived trees [17]. The growth of the bivalve *Arctica islandica* each year for hundreds of years can be tracked by measuring the thickness of lines on its shell [111]. Understanding what environmental conditions extend the growth of this bivalve consistently in several years, and if a particular sequence of line thickness is linked to some individuals living longer than others, can reveal new environmental factors that contribute to lifespan extension. Overall, the interplay between environmental pressures and molecular biology leading to the evolution of extreme lifespans is largely unknown and worthy of future research.

Finally, research on extremely long-lived species may inform efforts to extend healthspan and lifespan of other species. Understanding the molecular and cell biology of extreme longevity, may facilitate translational approaches targeting human pathophysiology. Indeed, ginkgo tree root and leaves extracts are already used to prevent and treat aging-related diseases [112]. Leaf extracts from the extremely long-lived *Larrea tridentata* have anti-apoptotic effects on human neuroblastoma cells [113]. Additionally, olive oil from the extremely long-lived *Olea europaea* has shown many anti-aging benefits for humans and is integral to the Mediterranean diet which has been associated with longevity and increased healthspan [114, 115]. Expression of the elephant *TP53* gene in human cancer cells increases apoptosis of these cells [116]. This indicates that expressing tumor-suppressor genes, found in multiple copies in extremely long-lived species relative to shorter-lived species, in human cells might have anti-aging effects in human cells.

CONCLUSIONS

Here, we reviewed the available literature on the molecular mechanisms associated with the variation in lifespan within and across extremely long-lived species. These studies converge to indicate that, at least for the species investigated, variations in the lifespan of individuals within a particular species is largely not due to variation in the length of telomeres, the activity of telomerase, the metabolic rates, the capacity to handle oxidative stress, or other large genetic changes. By contrast, the variation in lifespan within species seems to be mostly due to selection for specific stress-related genes and small chromosomal rearrangements, differences in how the DNA is maintained, and the expression of certain genes regulating stemness. When comparing extremely long-lived to shorter-lived species, we find that longer-lived species are often characterized by better DNA maintenance, improved ability to withstand abiotic and biotic stress, to minimize the effect of oxidative damage, to regenerate and maintain a minimally-aging population of stem cells, and to suppress cancer development (Table 2). Hence, the underpinnings of lifespan variation within and across extremely long-lived organisms show specific similarities. Both types of variation include mechanisms related to DNA maintenance, stemness, and stress resistance-related pathways. These pathways are all also characteristic of early developmental stages and germ cells. Living young appears to be a strategy of living long. These processes are ancient and have likely persisted over billions of years from LUCA (Last Universal Common Ancestor) to extant organisms [117, 118]. However, the vast majority of species with extremely long lifespans shown in Figure 1 are under-studied in terms of the molecular biology sustaining their long lifespans.

In our article, we also strived to highlight areas that are only partially covered by available findings and require further investigation. First, collecting more molecular and healthspan data from many more individuals and species across the tree of life will contribute towards discovering potentially new anti-aging mechanisms. Second, we ought to be watchful of methodological differences, including effects of growing organisms in the lab versus species in the wild, when attempting to

Table 2. Indicative characteristics of extremely long-lived, compared to shorter-lived species.

Species	Sample size (# species)	Experimental approach	Characteristic features	Reference
Lamellibrachia luymesi vs. shorter-lived species of Lophotrochozoa	at least 40	Genomics analyses	Increased SOD gene copy number (protection from oxidative damage)	[62]
Somniosus microcephalus vs. other vertebrate species	24	Proteomics analyses	No significantly higher levels of glutathione peroxidase in red blood cells and muscles	[74]
Arctica islandica vs. shorter-lived bivalves	10	Genomics analyses	Higher percentage of DNA repeats and higher gene number	[63]
Arctica islandica vs. *Mercenaria mercenaria*	2	Proteomics analyses	No significant difference in the capacity to recycle proteins	[73]
Arctica islandica vs. *Mya arenaria*	2	Molecular genetics	Lower concentration of H_2O_2	[79]
Tilia platyphyllos vs. *Celtis occidentalis* and *Platanus* × *hispanica*	3	Molecular genetics	Higher concentrations of all tested antioxidant enzymes and oxidative stress biomarkers in conditions of high traffic	[78]
Arctica islandica vs. *Mercenaria mercenaria*	2	Phenotypic characterization	Elevated resistance against death from alkylating (e.g., methyl methanesulfonate) and methylating (e.g., nitrogen mustard) agents	[81]
Arctica islandica and *Margaritifera margaritifera* vs. other bivalve species	at least 11	Observational characterization, Histology	Less tumor formation	[91, 92]
33 bivalve species, including the long-lived *Arctica islandica*, *Margaritifera margaritifera*, *Elliptio complanata*, and *Lampsilis siliquoidea*	33	Transcriptomics analyses	Convergent genetic pathways for DNA damage repair, tumor suppression, apoptosis, protein homeostasis, protein folding, hypoxia and oxidative stress resistance, defense against viruses and environmental stressors	[64]
61 plant species, including gymnosperms, angiosperms, perennial and annual herbs, and algae	61	Genomics analyses	Higher number of PARP genes (DNA damage repair)	[66]
Plant species, including *Ginkgo biloba*, *Sequoiadendron giganteum,* and *Pinus tabuliformis*	1,224	Genomics analyses	Similar genome size	[71]
Gymnosperms	614	Cytogenetics	Similar ploidy	[72]
Metasequoia glyptostroboides, *Sequoia sempervirens*, and *Sequoiadendron giganteum*	3	Genomics analyses	Higher number of genes involved in flavonoid/tannin synthesis	[67]
Ficus benghalensis and *Ficus religiosa* vs. other angiosperm species	52	Genomics	Genes related to abiotic and biotic stress resistance are positively selected	[68]
Ginkgo biloba vs. *Arabidopsis thaliana*	2	Genomics analyses	Nearly five times more genes involved in terpene and flavonoid biosynthesis	[69, 70]
Turritopsis dohrnii vs. *Turritopsis rubra*	2	Genomics analyses	Higher number of genes involved in DNA replication and repair, oxidative stress responses, and apoptosis	[65]
Pinus longaeva vs. *Pinus balfouriana* and *Pinus flexilis*	3	Metabolomics analyses	Higher concentration of monoterpenes	[75]
Pinus sylvestris and *Ginkgo biloba* vs. shorter-lived plants	3	Transcriptomics analyses, Molecular genetics, Epigenomics analyses	Lower decay of cell pluripotency in the meristem during aging	[85–87]

draw conclusions from different studies. Third, we should investigate the role of the environment in more detail, including the effect of variation in species' population sizes, over evolutionary time scales, on age-related genes. Finally, we suggest that our options of increasing human healthspan and lifespan could be expanded by investing in research that translates findings from extremely long-lived species to human physiology.

AUTHOR CONTRIBUTIONS

S.E.K. and N.T. conceptualized the work, S.E.K. wrote the draft of the manuscript and prepared the display items. N.T. revised and edited the manuscript.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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