Telomere shortening to a critical length can trigger aging and shorter life spans in mice and humans by a mechanism that involves induction of a persistent DNA damage response at chromosome ends and loss of cellular viability. However, whether telomere length is a universal determinant of species longevity is not known. To determine whether telomere shortening can be a single parameter to predict species longevity, here we measured in parallel the telomere length of a wide variety of species (birds and mammals) with very different life spans and body sizes, including mouse (Mus musculus), goat (Capra hircus), Audouin’s gull (Larus audouinii), reindeer (Rangifer tarandus), griffon vulture (Gyps fulvus), bottlenose dolphin (Tursiops truncatus), American flamingo (Phoenicopterus ruber), and Sumatran elephant (Elephas maximus sumatranus). We found that the telomere shortening rate, but not the initial telomere length alone, is a powerful predictor of species life span. These results support the notion that critical telomere shortening and the consequent onset of telomeric DNA damage and cellular senescence are a general determinant of species life span.

Telomere shortening rate predicts species life span

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Humans have relatively short telomere lengths from 5 to 15 kb (1–3), and yet humans have much longer life spans than mice, which can start with telomere lengths around 50 kb (4, 5). Previous studies have suggested that the telomere shortening rate rather than the initial telomere length is the critical variable that determines species life span (4, 6–10). In particular, we have previously shown that human telomeres shorten at a rate of ~70 bp per y (1), which is in line with the rate published by other authors (3, 11–14), while mice telomeres shorten at a rate of 7,000 bp per y (4). These different rates of telomere shortening between human and mice could explain the different longevity of mice and humans. However, the telomere shortening rate has been investigated to date in few species (4, 6–10, 15, 16), and using different techniques, which has prevented side-by-side comparisons of telomere shortening rates in phylogenetically distant species with different body sizes and life spans.

Here, to address whether telomere length and/or telomere shortening rates could explain species longevity, we measured telomere length in peripheral blood mononuclear cells from individuals of different species of birds and mammals at different ages in parallel, and calculated the telomere shortening rate per year in each species. A longitudinal study of telomere length throughput quantitative fluorescence in situ hybridization (HT Q-FISH) technique, which allows to quantify individual telomere lengths in parallel mice (Table S1 and Fig. 1) (17, 18). In particular, we measured, in shortening rates in phylogenetically distant species with different techniques, which has prevented side-by-side comparisons of telomere length dynamics may not be linear during the early stages of life (19). First, we confirmed a very high rate of telomere shortening in our current mouse cohort of 6,420 bp per y (Fig. 1A), similar to that previously described by us (4). Bottlenose dolphins showed a telomere shortening rate of 766 bp per y (SI Appendix, Table S1 and Fig. 1B) and an estimated initial telomere length around 90.7 kb (Fig. 1B). Goats showed a telomere shortening rate of 363 bp per y (Fig. 1C) and an estimated initial telomere length around 10.4 kb. Reindeer showed a telomere shortening rate of 531 bp per y (Fig. 1D) and an estimated initial telomere length of ~19.8 kb. American flamingos showed a telomere shortening rate of 105 bp per y (Fig. 1E) and an estimated initial telomere length around 21.0 kb. Griffon vultures had a telomere shortening rate of 209 bp per y (Fig. 1F) and an estimated initial telomere length around 19.8 kb. Audouin’s gulls had a telomere shortening rate of 771 bp per y (Fig. 1G) and an estimated initial telomere length around 35 kb. Sumatran elephants have a telomere shortening rate of 109 bp per y (Fig. 1H) and an estimated initial telomere length around 36.3 kb. In the case of griffon vultures and Sumatran elephants, we were limited to the few available individuals at the Madrid Zoo; thus, in these cases the values obtained should be considered as a first approximation to the telomere shortening rates in these species.

We next investigated relationships between telomere length, telomere shortening rate, and species life span. For the species maximum life span, we used the AnAge database (20). The average life spans were obtained from various sources (SI Appendix, Table S1). First, we did not find any correlation between the previously shown a rate of telomere shortening of around 7,000 bp per y, which is 100-fold faster than that reported in humans (4). The initial telomere length of the different species under study was estimated by linear regression (Fig. 1). Note that the initial telomere length value is only an estimate and telomere length dynamics may not be linear during the early stages of life (19). The exact causes of aging are still not understood, and it is unclear why some species live less than 1 d, while others can live more than 400 y. Research suggests that telomeres are related to the aging process, but a clear relationship between the life span of a species and initial telomere length has not been observed. Here, we measure the telomere lengths of a variety of different species. We find that, in fact, there is no strong correlation between the life span of a species and initial telomere length. However, we find a strong correlation between the telomere shortening rate and the life span of a species.

Significance

The exact causes of aging are still not understood, and it is unclear why some species live less than 1 d, while others can live more than 400 y. Research suggests that telomeres are related to the aging process, but a clear relationship between the life span of a species and initial telomere length has not been observed. Here, we measure the telomere lengths of a variety of different species. We find that, in fact, there is no strong correlation between the life span of a species and initial telomere length. However, we find a strong correlation between the telomere shortening rate and the life span of a species.
estimated initial telomere length and species longevity (Fig. 2 A–D). In particular, a graph of the species maximum life span versus the estimated initial telomere length resulted in an $R^2$ value of 0.0190 with a linear regression curve (Fig. 2A), and an $R^2$ value of 0.0407 with a power law regression curve (Fig. 2B). A graph of the species’ average life span versus the estimated initial telomere length resulted in an $R^2$ value of 0.125 with a linear regression curve (Fig. 2C), and an $R^2$ value of 0.145 with a power law regression curve (Fig. 2D). Note that there is even a trend for shorter life spans with longer initial telomere lengths with the low $R^2$ values just mentioned, and negative slopes in the regression line equations (Fig. 2A–D). Also note that the inverse correlation between average life span and initial telomere length ($R^2 = 0.125$; Fig. 2C) was better than that between maximum life span and initial telomere length ($R^2 = 0.019$; Fig. 2A). These findings agree with a previous study that compared telomere length in more than 60 different species (21). Although the telomere shortening rate was not measured in that study, the authors concluded that the life span of a species could not be predicted from the initial telomere length and that there was a trend for short-lived species to have longer telomeres (21).

Interestingly, when we plotted maximum life span versus the rate of telomere shortening for the different species, we obtained a power law curve with an $R^2$ value of 0.829 (Fig. 2E). The equation from this curve can be used to predict the life span of a species when given the telomere shortening rate without using any information about the initial telomere length with an $R^2$ value of 0.782 (Fig. 2F). The same graphs can be made using the average life span instead of the maximum life span (Fig. 2G and H), and in this case the power law curve $R^2$ value is 0.934. The observation that life span versus telomere shortening rate fits a power law curve is in agreement with many natural phenomena fitting either a power law or exponential curve such as population growth, temperature cooling/heating, city sizes, species extinction, body mass, individual incomes, and the number of connections to nodes in a scale-free network, among others (22–25).

Alternatively, more linear life span predictions can be made using both the initial telomere length and the rate of telomere shortening. In this case, it seems unlikely that species die when their telomeres are completely eroded since the life spans predicted by complete telomere erosion are longer than the observed life spans for most species (SI Appendix, Table S1). Instead, we find here that
the length of the telomeres when species die at the age of the maximum life span appears to be \(\sim 50\%\) of the original telomere length for that particular species, when considering the average of all of the species measured (SI Appendix, Table S2). Interestingly, when considering the timepoint of the average life span, the telomere length appears to be \(\sim 75\%\) of the original length (SI Appendix, Table S2). Therefore, we can calculate the life span of a species if we assume that telomeres shorten with a constant linear rate and that the time of death will occur once the telomeres have shortened to 50\% or 75\% of the original telomere length. The equation of the estimated life span if telomeres shortened to 50\% of the original length is as follows: 

\[
\text{Estimated life span} = \frac{(\text{Initial telomere length} - 0.5 \times \text{Initial telomere length})}{\text{Telomere shortening rate}}.
\]

A plot of the estimated life span at 50\% original telomere length vs. the maximum life span yields an \(R^2\) of 0.565 (Fig. 3A). The estimated life span at 50\% original telomere length vs. the average life span yields an \(R^2\) of 0.694 (Fig. 3B). Similar graphs are presented for 75\% original telomere length (Fig. 3C and D). With this dataset, the
Although the weight with an $R^2$ value of 0.694. Although the $R^2$ value is the same as the value in Fig. 3B, this graph also has a slope that is closer to a value of 1, indicating a smaller shift between the actual and estimated life spans. Note that better correlation coefficients are obtained with the power law regression curves using the telomere shortening rate without taking the initial telomere length into consideration (Fig. 2 E–H)

Another trait that correlates with life span is body mass (26). In general, larger species such as elephants and whales have longer life spans than small species such as mice and rabbits. One investigation compared the mass and life span of 1,456 different species, and found a trend for longer life span with larger mass ($R^2 = 0.397$) (26). With the species in our dataset, we also observed a correlation between mass and life span (SI Appendix, Table S3). The species telomere shortening rate also correlated with body weight with an $R^2$ of 0.413 (SI Appendix, Fig. S1). Species with higher body weights tend to have lower telomere shortening rates and longer life spans.

Some authors have shown an inverse correlation between life span and heart rate, a variable related to organismal metabolism (27, 28), although more extensive studies do not seem to support this notion (29). Here, we set to address a potential correlation between heart rate and telomere length. First, we observed a correlation between life span and heart rate with our dataset (SI Appendix, Table S3). We also found a linear correlation between the telomere shortening rate and the heart rate with an $R^2$ of 0.974 (SI Appendix, Fig. S2 A and B).

Next, to investigate the effect of the multiple variables on life span when combined into the same model, we performed a multivariate linear regression. The input variables of telomere shortening rate, initial telomere length, body mass, and heart rate were fit to either the average life span or the maximum life span. The data used for the regression are presented in SI Appendix, Table S4. The log value of all of the data points was used for the regression

![Graph showing species life span predictions with telomere parameters II](image)

**Fig. 3.** Species life span predictions with telomere parameters II. (A) The estimated life span if telomeres shortened to 50% of the original length vs. the maximum life span. (B) The estimated life span if telomeres shortened to 50% of the original length vs. the average life span. (C) The estimated life span if telomeres shortened to 75% of the original length vs. the maximum life span. (D) The estimated life span if telomeres shortened to 75% of the original length vs. the average life span. The estimated life span is calculated using the following equation: (“Telomere length original” – “Telomere length original” × “percent of original length”)/“Telomere shortening rate.” (E) Graphical illustration which shows the main finding from this paper, which is that faster telomere shortening rates result in shorter species life spans.

instead of the original values. Each variable vs. the average life span or maximum life span had either a higher linear $R^2$ correlation coefficient when using log-transformed data, or there was no noticeable change in the correlation coefficient in the case of the initial telomere length variable. The model fit to the average life span resulted in an $R^2$ value of 0.997 and an adjusted $R^2$ value of 0.992 (SI Appendix, Table S5), demonstrating that these variables can predict the average life span. The $P$ values (listed in the Pr(>|t|) column) were statistically significant for all variables. The telomere shortening rate was the most statistically significant variable ($P = 0.00042$). The model fit to the maximum life span resulted in an $R^2$ value of 0.950 and an adjusted $R^2$ value of 0.884 (SI Appendix, Table S6), demonstrating that the variables can also predict the maximum life span. In this case, only the telomere shortening rate variable was statistically significant ($P = 0.0218$).

Again, we found an inverse relation between average life span and initial telomere length with a $P$ value of $P = 0.0302$, with short-lived species having initial longer telomeres (SI Appendix, Table S5). Also, in the multivariate analysis, the relationship between the initial telomere length and the maximum life span was not significant in agreement with a weaker inverse correlation between initial telomere length and maximum life span compared with average life span (Fig. 2A and C). Thus, these findings confirm that the telomere shortening rate (negative correlation), initial telomere length (negative correlation), body weight (positive correlation), and heart rate (positive correlation) and all species can span and among these variables, the variable with the greatest power to predict the life span is the telomere shortening rate.

Finally, one caveat of studies with animals of different ages is that an effect can occur in which old animals with short telomeres selectively disappear due to death, and these telomeres are consequently not measured at older ages. Therefore, the telomere length could be artificially high at the older ages since only the animals with longer telomeres continue to survive at these ages. However, the fact that telomere shortening with age fits a linear regression in the majority of the species studied indicated that this phenomenon is not very disturbing in our current study. Also, such disappearance of animals would only be expected to occur at very late ages, and the majority of the animals in this study were not extremely old (Methods).

**Conclusions**

Although a number of previous studies measured telomere length in different species (30-35), few of them determined the telomere shortening rates (4, 6-10, 15, 16). In this regard, some studies found a correlation between telomere shortening rate and species’ life spans, including previous work from our group in mice and humans (1, 4, 6-10); however, these studies did not compare side-by-side telomere shortening rates in phylogenetically distant species by using a single technique to measure telomeres.

In our current study, telomere length and the rate of telomere shortening from multiple species with very different life spans, including birds and mammals, was acquired in the same laboratory by using the sensitive HT Q-FISH technique which allows to determine absolute telomere length values in units of base pairs as well as individual telomere signals. A limitation of the current study is, however, the few available individuals for some species.

The results shown here indicate that the telomere shortening rate of a species can be used to predict the life span of that species, at least with the current dataset (Fig. 3E). We observed that mean telomere length at birth does not correlate with species life span since many short-lived species had very long telomeres, and long-lived species had very short telomeres. Future studies warrant determination of telomere shortening rate in species such as cellular senescence, may be the critical factor determining species longevity. In this regard, some studies correlate DNA repair ability to species longevity (37-39). In particular, the ability to repair UV-induced damage positively correlates with life span in different species, including primates (37, 38). Also, DNA repair rates are higher in longer living rodent species compared with rodent species with a shorter life span (39).

It is interesting to note that short telomeres induce DNA damage, and in turn certain types of DNA damage, such as UV irradiation or oxidative stress, can also lead to telomere shortening (40-42).

**Methods**

**Mice.** The mouse strain was >95% C57BL/6 background. All mice were reared and housed in the specific-pathogen-free barrier of the Centro Nacional de Investigaciones Oncológicas (CNIO) institution in Madrid, Spain. After weaning, 5 mice were housed per cage and fed ad libitum with a nonpurified sterilized Teklad 2018 18% protein rodent diet (Harlan; TD.2018S). All animal procedures were approved by the CNIO-Instituto de Salud Carlos III Ethics Committee for Research and Animal Welfare and conducted in accordance to the recommendations of the Federation of European Laboratory Animal Science Associations.

**Blood Samples.** Blood samples were obtained from the Madrid Zoo, with the exception of the mouse samples, which were obtained from the animal facility of CNIO, and the Audouin’s gulls. Only 1 timepoint was measured for each individual, so this is a cross-sectional study. For mice (Mus musculus), blood was sampled from 7 individuals with an age range from 1.4 to 2.6 y. For dolphins (Tursiops truncatus), blood was sampled from 9 individuals with an age range from 8.6 to 50.1 y. For goats (Capra hircus), blood was sampled from 15 individuals with an age range from 0.85 to 10.1 y. For reindeer (Rangifer tarandus), blood was sampled from 8 individuals with an age range from 1.4 to 10.5 y. For African elephants (Loxodonta africana), blood was sampled from 12 individuals with an age range from 0.79 to 38.8 y. For the griffon vulture species (Gypaetus fulvus), blood was sampled from 6 individuals with an age range from 8.06 to 21.4 y. For the Sumatran elephant species (Elephas maximus sumatranus), blood was sampled from 4 individuals with an age range from 6.14 to 24.7 y. The Audouin’s gulls were sampled at the breeding colony of the Ebro Delta (northeast Spain). For this Audouin’s gull species, blood was sampled from 21 individuals ranging from 3-7 y old to 21.2 y old. All blood samples were processed with erythrocyte lysis buffer (Qiagen; catalog no. 79217) according to the manufacturer’s protocol. Therefore, for all species, the telomeres were measured in the leukocyte cells. The samples were then frozen at −80 °C slowly in a Nalgene Cryo Freezing Container (Nalgene; catalog no. 5100-0001).

**HT Q-FISH.** The process for HT Q-FISH has been described previously (1). Briefly, frozen erythrocyte lysis buffer processed blood samples were first thawed quickly and resuspended in complete RPMI media. Cells were attached to the wells (30,000 to 150,000 cells/well) of clear-bottom black-walled 96-well plates (Greiner Bio-One, Inc.; catalog no. 655087), which had been precoated with a general no. P7000-25G) for 15 min at 37 °C. The plate was washed 2 times with 200 μL of blocking reagent [10 g of blocking reagent × 100 mL of maleic acid deionized formamide, 475 mL of blocking reagent × 100 mL of MgCl2 80 °C slowly until the wells were completely dry]. The plate was washed 3 more times. The plate was then fixed by adding 200 μL of fixative solution [3.1 [vol/vol] methanol/acetic acid] slowly to the cells in a chemical hood and incubated for 10 to 15 min. The solution was removed, and this was repeated 3 more times. The plate was then fixed overnight at −20 °C with the fixative solution in the wells.

The fixative solution was then removed, and the plate was dried on a hot plate at 37 °C 1 h in a chemical hood. The wells were rehydrated with 200 μL of PBS. The cells were fixed with 200 μL of 4% formaldehyde in PBS for 2 min at room temperature (RT). The plate was washed 3 × 5 min with PBS. The cell walls were degraded with prewarmed pepsin solution (100 mL of H2O, 100 μL of 37% HCl [10.1 M HCl], and 100 mg of pepsin [Sigma-Aldrich; catalog no. P7000-25G]) for 15 min at 37 °C. The plate was washed 2 × 5 min with 200 μL of PBS, and then dehydrated with a series of 5-min 70%, 90%, and 100% ethanol washes. The plate was dried 1 h at 37 °C or overnight at RT.

Next, 50 μL of the hybridization solution containing the Tel-Cy3 PNA probe was added to the plate (95 μL of 1 M Tris, pH 7.0, 812 μL of MgCl2 solution [25 mM MgCl2, 9 mM citric acid, 82 mM Na2HPO4], 6.65 μL of denaturated formamide, 475 μL of blocking reagent) for 15 min at 37 °C. The plate was washed 2 × 5 min with 200 μL of PBS, and then dehydrated with a series of 5-min 70%, 90%, and 100% ethanol washes. The plate was dried 1 h at 37 °C or overnight at RT.

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