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Telomeres shorten more slowly in slow-aging wild animals than in fast-aging ones

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ABSTRACT

Research on the physiological causes of senescence aim to identify common physiological mechanisms that explain age-related declines in fitness across taxonomic groups. Telomeres are repetitive nucleotide sequences found on the ends of eukaryotic chromosomes. Past research indicates that telomere attrition is strongly correlated with inter-specific rates of aging, though these studies cannot distinguish whether telomere attrition is a cause or consequence of the aging process. We extend previous research on this topic by incorporating recent studies to test the hypothesis that telomeres shorten more slowly with age in slow-aging animals than in fast-aging ones. We assembled all studies that have quantified cross-sectional (i.e. between-individual) telomere rates of change (TROC) over the lifespans of wild animals. This included 22 estimates reflecting absolute TROC (TROCabs, bp/yr, primarily measured using the terminal restriction fragment length method), and 10 estimates reflecting relative TROC (TROCrel, relative telomere length/yr, measured using qPCR), from five classes (Aves, Mammalia, Bivalvia, Reptilia, and Actinopterygii). In 14 bird species, we correlated between-individual (i.e. cross-sectional) TROCabs estimates with both maximum lifespan and a phylogenetically-corrected principle component axis (pcPC1) that reflected the slow-fast axis of life-history variation. Bird species characterized by faster life-histories and shorter maximum lifespans had faster TROCabs. In nine studies, both between-individual and within-individual TROC estimates were available ($n = 8$ for TROCabs, $n = 1$ for TROCrel). Within-individual TROC estimates were generally greater than between-individual TROC estimates, which is indicative of selective disappearance of individuals with shorter telomeres. However, the difference between within- and between-individual TROC estimates was only significant in two out of nine studies. The relationship between within-individual TROCabs and maximum lifespan did not differ from the relationship of between-individual TROCabs and maximum lifespan. Overall, our results provide additional support for the hypothesis that TROC is correlated with inter-specific rates of aging and complement the intra-specific research that also find relationships between telomere attrition and components of fitness.

1. Introduction

Senescence or aging is the process of cellular and physiological deterioration that causes age-related decreases in performance, survival, and/or reproduction. Senescence may have important ecological and evolutionary effects (Roach and Carey, 2014) and it is therefore not surprising that evolutionary biologists have been interested in documenting its existence in natural populations for quite some time. Despite some initial skepticism about its existence (Kirkwood and Austad, 2000; Hayflick, 2000) and some recent evidence that the fitness costs of senescence are low (Bouwhuis et al., 2012), declines in survival and reproduction with age are now well-documented in wild animals (Nussey et al., 2013). However, the study of the actual molecular or physiological causes of senescence in wild animals is still in its infancy compared to similarly focused studies in laboratory animals. One of the remaining challenges in the study of senescence is connecting evolutionary biologists that study the ultimate causes of variation in senescence in natural populations with those studying proximate causes of senescence (Flatt and Schmidt, 2009; Hughes and Reynolds, 2005; Partridge and Gems, 2006; Ackermann and Pletcher, 2007; Vleck et al., 2007; Roach and Carey, 2014; Holmes and Martin, 2009).

Age-related declines in fitness are caused by physiological deterioration (Williams et al., 2006). In order to unify and simplify examinations of age-related physiological deterioration, researchers have attempted to identify over-arching physiological mechanisms ("public mechanisms of aging") that explain age-related declines in fitness that apply across

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diverse taxonomic groups, including humans (Partridge and Gems, 2002, 2006). This research has focused primarily on documenting the physiological changes that occur within individuals as they age (using a cross-sectional or longitudinal approach) or differences among taxa with differential maximum, median, or mean lifespans. Recent studies in this search for common mechanisms contributing to aging have focused on a few key physiological systems. Specifically, increases in the activity of the hypothalamic-pituitary adrenal axis that produces glucocorticoid stress hormones (Sapolsky et al., 1986; Lupien et al., 1994; Sapolsky, 1999; Boonstra et al., 2014; Hämäläinen et al., 2015) and the levels of insulin-signaling (van Heemst et al., 2005; Pawlikowska et al., 2009; Stuart and Page, 2010; Dantzer and Swanson, 2012; Swanson and Dantzer, 2014) may be correlated with lifespan. Other studies have focused on age-related declines in the immune system (Miller, 1996; Franceschi et al., 2000; Larbi et al., 2008) or differences in metabolic rate (Wiersma et al., 2007; Williams et al., 2010; Londoño et al., 2015) or how the production of reactive oxygen species (Short et al., 2005; Yu and Chung, 2001; Monaghan et al., 2009; Selman et al., 2012) can contribute to senescence.

Telomere attrition is one possible mechanism that may be associated with age-related declines in physiological function and therefore fitness. Telomeres are repetitive nucleotide sequences found on the ends of eukaryotic chromosomes (Blackburn, 2000, 2001; Monaghan and Haussmann, 2006). Telomeres shorten in length each time a cell divides thereby shortening with age (Harley et al., 1990). They can also experience attrition due to exposure to oxidative stress (Blackburn, 1991; von Zglinicki, 2002; Kawanishi and Oikawa, 2004; Monaghan, 2014). Once the telomeres in a cell become too short, the cells themselves can stop dividing, and undergo apoptosis (i.e., the Hayflick limit: Hayflick and Moorhead, 1961; Olovnikov, 1996). This process of cellular death may be beneficial in terms of inhibiting the proliferation and longevity of cancer cells (Campisi, 2001; Blasco, 2005; Finkel et al., 2007), but may also come at a cost by contributing to age-related declines in survival or reproduction (von Zglinicki and Martin-Ruiz, 2005; reviewed by Monaghan, 2010). The presence of cells with very short telomere lengths may also contribute to the aging process by increasing local inflammation (Campisi et al., 2001; Campisi, 2005), reducing vascular function (Sharpless and DePinho, 2004), as well as by causing genomic instability (Capper et al., 2007; Kong et al., 2013), immuno-senescence (Effros, 2011), and an overall decline in physical capabilities and health (Sharpless and DePinho, 2004; Donate and Blasco, 2011; Armanios and Blackburn, 2012). The enzyme telomerase can repair and elongate telomeres (Greider and Blackburn, 1985; McEachern and Blackburn, 1995), prolonging the period of normal cell functioning (Bodnar et al., 1998; Blackburn, 2001; López-Otín et al., 2013; Xie et al., 2015). While these studies suggest that shortened telomeres may in fact contribute to the aging process, it must also be noted that age-related changes in telomere lengths may simply be a biological consequence of the aging process that does not itself contribute to senescence (Hornsby, 2006; Simons, in press).

Studies in taxa other than laboratory animals and humans, including wild animals, also provide some evidence that the rate of telomere attrition may play an important role in the aging process. Over 10 years ago, Vleck et al. (2003) and Haussmann et al. (2003a) suggested that the rate of change in telomere lengths was an over-arching mechanism that causes aging across taxa. Presenting the same data, Vleck et al. (2003) and Haussmann et al. (2003a) showed that species-specific telomere rate of change (TROC, bp/yr) was a very strong predictor ($r^2 = 0.99$) of the maximum lifespan of five bird species (3 free-living, 2 captive; hereafter, we cite Haussmann et al. (2003a) to refer to this relationship). Haussmann et al. (2003a) also performed this analysis for mammals. They found that the slope and the proportion of the variation explained, were similar to the results from their analysis on birds. In these analyses, humans and species where there was a non-significant relationship between TROC and age were excluded. Unfortunately, Haussmann et al. (2003a) did not correct for phylogeny, though they urged future analyses to do so. To our knowledge, the findings of Haussmann et al. (2003a) suggested that telomere attrition is the best inter-specific predictor of aging that has been developed to date (see also Gomes et al., 2011).

Considerable research on how the length of telomeres change with age has been published on wild animals since Haussmann et al. (2003a). Here, we retest their basic conclusion that telomeres shorten more slowly in species with long maximum lifespans than in species with short maximum lifespans. We compiled all TROC estimates from wild animals (Table 1) and performed a phylogenetically corrected comparative analysis relating TROC and maximum lifespan using all TROC estimates from birds. In birds, we also examined the relationship between TROC and a composite measure of the slow-fast axis of life-history variation (see also Gaillard et al., 1989; Martin, 1996; Ricklefs, 1998; Wiersma et al., 2007). Composite variables reflecting life-history variation may provide new insights into how the process of growth, reproduction, and survival are associated with TROC. Estimates of TROC based on cross-sectional (i.e. between-individual) versus longitudinal (i.e. within-individual) studies designs may differ because of the selective disappearance of individuals with short telomeres in advanced ages (Vaupel et al., 1979; van de Pol and Verhulst 2006). In a reduced number of species where both within-individual and between-individual estimates were available, we investigated differences between these two types of TROC estimates and examined whether the type of estimate (i.e. within- or between-individual) influenced the relationship between TROC and maximum lifespan.

2. Materials and methods

2.1. Obtaining telomere rate of change (TROC) values from the literature

We restricted our literature search to studies on free-living animals that examined the relationship between telomere length and age. We focused exclusively on wild animals because TROC estimates from captivity are likely biased because standard laboratory conditions ameliorate sources of stress or infection that can affect the rate of telomere attrition (von Zglinicki, 2002; Kawanishi and Oikawa, 2004; Kotrschal et al., 2007; Ilmonen et al., 2008; Hau et al., 2015). This could therefore alter the inter-specific relationship between TROC and our aging variables and we chose to only include TROC estimates from natural populations. The majority of studies were obtained using a Web of Science search (performed on 7-April-2015), using the following keywords: telomere, age, ecology, and evolution. From all the studies that contained relevant data, we searched for additional studies using backward (i.e. literature cited) and forward (i.e. papers citing the studies) searches. In most studies, the age of animals was known because they were permanently marked by researchers early in their lives. However, in some studies, the age of animals was determined by morphological features that can be used to infer chronological age (otoliths — Almroth et al., 2012; tail vertebra growth rings — Bronikowski, 2008; shell rings — Gruber et al., 2014; tooth rings — Pauli et al., 2011). We excluded studies that used size, or the size of a morphological trait, as a surrogate for age (Scott et al., 2006; Godwin et al., 2011; Izzo et al., 2014) because of the possible inaccurate age estimates it may produce.

We obtained telomere length data from individuals with known ages in multiple ways. In most cases, data were digitized from figures presenting telomere length vs. age using the R package, digitize (Poisot, 2011). Raw data were also obtained from consulting archived or supplementary data or contacting corresponding authors directly. The corresponding author of Barrett et al. (2013) informed us that they mistakenly reported their telomere length values in kilo base pairs (kbp), when in fact they were in bp (D. Richardson, pers. comm.).

Telomere lengths were reported in two ways: 1) absolute telomere length in bp and 2) relative telomere length (RTL). Absolute measures were primarily obtained by using the terminal restriction fragment (TRF) method on a gel. However, two studies generated absolute