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Telomerase as a possible key to bypass reproductive cost

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Abstract

Telomerase activity and telomere maintenance in certain somatic cells of human adults support the proliferative capacity of these cells and thus contribute to their regenerative potential, and telomerase activity and telomere length are commonly considered lifespan predictors. Eusocial insects provide excellent models for aging research based on their extraordinary caste-related lifespan differences that contradict the typical mammalian fecundity/lifespan trade-off. Telomerase activity is upregulated in the reproductive, long-lived individuals of eusocial insects such as queens and kings, and telomerase activity may act as a key factor in their extended longevity. But, as documented by the presence of telomerase in somatic tissues of numerous invertebrate and vertebrate species, the connection between telomerase activity and the predicted lifespan is not clear. Here, I ask whether somatic telomerase activity in eusocial reproductives may serve its non-canonical function to protect its individuals against the metabolic stress due to reproduction and reflect a more common phenomenon among species. Here, I propose a hypothesis that the presence of telomerase activity in somatic cells reflects a different reproduction strategy of species.

Introduction

Social behavior is a set of interactions among individuals within a species and is displayed in a wide spectrum of forms, and eusociality represents the most intimate and complex degree of social organization. Eusociality is defined by the presence of distinct reproductive and non-reproductive castes, overlapping generations, and cooperative care for the brood within a colony (Engels 1990; Kocher and Paxton 2014). Reproductives (kings and queens) and non-reproductives (workers or soldiers) in the colonies are differentiated morphologically, physiologically, and behaviorally (Wheeler 1907; Wilson 1971; Robinson et al. 1991; Harvell 1994; Sherman et al. 1994; Gräff et al. 2007; Begna et al. 2012; Seeley 2014). Although most well-characterized eusocial species are termites and hymenopteran insect species such as honeybees and ants, eusociality has been reported in several other insect, non-insect, and even vertebrate species (Sherman et al. 1994; Duffy et al. 2000). Although taxonomically rare, eusocial insect species exhibit great ecological importance, as approximately 50% of the world insect biomass is comprised of eusocial insect species (Wilson 1971; Kocher and Paxton 2014).

Eusocial insects offer an appealing opportunity to uncover mechanisms underlying how the social environment can alter the rate of organismal aging (Parker 2010; Lucas and Keller 2014). Due to their extraordinary caste-related lifespan differences, their plasticity in the rate of aging, and their contradiction of the usual fecundity/lifespan trade-off, eusocial insects provide an excellent model system for research on aging (Chapuisat and Keller 2002; Parker 2010; Lucas et al. 2017; Corona et al. 2019; Kohlmeier et al. 2019). This article proposes the possible role of telomerase and telomere biology in life-span regulation as a reproduction strategy of animal species.

Factors driving eusocial insect caste lifespan differences

As aging is linked to increased mortality and decreased reproductive success, the evolutionary theory of aging explains aging as a non-adaptive outcome of individual's declining ability to maintain fitness at older ages, which leads to the accumulation of harmful mutations in old age (Haldane 1941; Medawar 1952; Flatt T and Partridge L 2018). Based on natural selection, theories of evolution attempt to explain how organisms achieve

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maximal genetic contribution to the future genetic pool. However, fitness maximization is limited by certain evolutionary constraints, such as multiple life-history trade-offs (Williams 1957; Stearns 1989). The trade-offs act as negative correlations between the fitness components when an improvement in one component is associated with a decrement in another, based on the competitive allocation of limited resources (Fabian and Flatt 2014). According to the disposable soma theory of aging, one of the major trade-offs is the cost of reproduction, which is the phenomenon by which an increased rate of reproduction reduces soma maintenance and, consequently, longevity (Reznick 1985; Harshman and Zera 2006).

Insect species differ greatly in terms of fecundity and lifespan; lifetime fecundity in insects ranges from less than ten to several million eggs, while adult lifespan varies from days to decades. Most non-social insect species lay tens or hundreds of eggs, and a small fraction lay thousands (Brueland 1995). The highest lifetime fecundity among non-social insects was reported in the Australian ghost moth, *Trictena atripalpis* (Hepialidae), which lays approximately 29,100 eggs (Tindale 1932). The high fecundity in non-social insect species appears to be associated with a risky oviposition strategy and high juvenile mortality (Brueland 1995). When compared to non-social insects, most eusocial insect species have extremely high fecundity as a single queen can lay hundreds of millions of eggs in a lifetime. For example, the honeybee queen, with a lifespan of about 5 years, can lay up to 200,000 eggs per year (Bodenheimer and Nerya 1937); the queen of the army ant *Eciton burchelli* , with a lifespan of up to 30 years, can lay 100,000 eggs in three weeks (Gotwald 1995; Boswell et al. 1998); or the queen of the termite *Macrotermes subhyalinus* can produce 3,600 eggs in 24 hours over her 20-year lifespan (Keller 1998; Khan et al. 2022).

Comparative analysis between the lifespan of eusocial reproductives and solitary insects has indicated that the evolution of eusociality is associated with a roughly 100-fold increase in longevity between queens and solitary females (Keller and Genoud 1997). The reproductive individuals of many termite or ant species may live for many decades (Keller and Genoud 1997; Keller 1998). For example, the mean average lifespans of honeybee queens is 5.6 years, while adults of solitary insect species exhibit lifespans of only 0.1 ± 0.2 years (Keller and Genoud 1997; Keller 1998). As a result, it appears that the reproductive individuals in eusocial insect colonies contradict the reversed reproduction-longevity trade-off because they are both highly fecund and live longer than non-reproductives within their own colonies or solitary insect individuals.

First, it is known that variation in nutrition can have an impact on division of labor and the development of reproductive vs non-reproductive castes in both advanced eusocial insects with morphologically distinct castes and social species where all individuals are capable of mating and reproducing (totipotent at birth), and nutritional stress can be conceptualized as a mechanism to control reproductive potential (Smith et al. 2011; Slater et al. 2020). Further, it has long been suspected that the lifespan disparity in eusocial insects is associated with caste differences in extrinsic mortality risk because workers, unlike reproductives, primarily perform risky tasks and are subjected to a variety of stressful factors (Kramer and Schaible 2013). However, according to recent findings and supporting by the disposable soma theory of ageing (Kirkwood 1977; Kreider et al. 2021), when castes are exposed to antagonistic fitness effects, allocation of limited resources by workers to queens results in accumulation of deleterious mutational effects preferentially in workers. As a result, it appears that extrinsic mortality may be only a minor factor in caste-specific lifespan divergence, and that caste-specific lifespan differences evolved as a result of antagonistic effects caused by reproductive division of labor (Kreider et al. 2021). Furthermore, interspecific variation in queen lifespan and fecundity is linked to differences in alternative reproductive strategies observed in different species, such as polygyny (colonies with multiple reproductive queens) or monogyny (colonies with only one reproductive queen) in ants. Comparison of different ant species revealed that monogynous queens have a longer lifespan than that of polygynous queens, despite having their equal morphology, colony founding mode, and extrinsic mortalities (Keller and Genoud 1997; Schrempf et al. 2011), and that mating has a positive effect on lifespan and the lifetime reproductive success of queens (Schrempf et al. 2005). Finally, contrary to the common observation that reproductive performance declines with age, sociality in insects has been linked to a positive correlation between fecundity and age (Keller and Genoud 1997; Lopez-Vaamonde et al. 2009; Heinze and Schrempf 2012). This demonstrates that the social environment has a significant impact on aging of social insects.

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Telomeres as a component of organismal aging

Aging theories are classified into two types based on the molecular and cellular mechanisms associated with biological aging: non-programmed (stochastic) and programmed (Davidovic et al. 2010; Jin 2010; Fathi et al. 2019). Stochastic theories propose that aging is the result of accumulating random changes that negatively affect biological systems and are a result of natural processes such as effects of toxic byproducts, telomere shortening, various other molecular damage, etc. The programmed theory of aging proposes that aging is the result of a progression of changes in expression of specific genes, such as those of the immune system or telomerase activity, both of which decline over time (Davidovic et al. 2010; Jin 2010; Fathi et al. 2019). Accumulating evidence indicate that stem cell function, regeneration, and organ maintenance, all of which largely contribute to the aging process, are connected to telomere biology.

Telomeres are nucleoprotein structures located at eukaryotic chromosome ends that consist of short DNA repeats with well-defined sequence composition and telomere-specific protein complexes (Blackburn 1990). Through a multiprotein structure called a telomere cap, telomeres allow cells to distinguish natural chromosome ends from chromosome breaks, and formation of telomere caps requires a satisfactory length of telomeric DNA (Blackburn 1991; Capkova Frydrychova et al. 2009; Mason et al. 2011). Due to the limitations of semiconservative DNA replication and the inability of conventional DNA polymerase to fully replicate the end of linear DNA strands, telomere length is shortened with each round of cell division. When telomeres become critically short, a DNA damage checkpoint response induces cell senescence (Greenberg 2005), which not only acts as a major determinant of organismal development (Ulaner and Giudice 1997; Jiang et al. 2007) but also aging and age-related diseases such as dyskeratosis congenita, pulmonary fibrosis, and aplastic anemia (Kong et al. 2007). In a variety of mammal and avian species, a positive correlation has been observed between telomere shortening rate or telomere length early in life and realized lifespan, which is consistent with the fact that critically short telomeres limit replicative potential and, thus, tissue or organ regeneration potential. As a result, telomere length and, more importantly, the rate of telomere shortening may be used to predict lifespan (Heidinger et al. 2011; Whittemore et al. 2019). In this regard, it is worth noting that the species' ability to defend against some DNA damaging agents, such as ultraviolet light or oxidative stress, that can cause telomere shortening correlates with the species' lifespan (Hart and Setlow 1974; Hall et al. 1984; von Zglinicki 2002; Ma et al. 2012). Telomere length has been linked to a variety of stressor exposures, and telomere length is thought to be a potential molecular-level measure of allostatic load, which is the cumulative burden of chronic stress and life events (Law et al. 2016; Guidi et al. 2021). Because allostatic load includes dysregulation of multiple physiological systems, telomere length and attrition rate may provide an index of cumulative damage inputs from multiple regulatory systems and cellular structures (Tomiyama et al. 2012) and can act as somatic integrity biomarkers (Young 2018).

Telomere shortening can be circumvented by the extension of telomeric DNA via special telomere maintenance mechanisms such as the activity of telomerase, retrotransposition of special telomeric elements, or gene conversion (Mason et al. 2011, 2016), and the most common mechanism of telomere elongation involves telomerase activity. Telomerase is a specialized reverse transcriptase that uses an RNA template to repeatedly synthesize a short telomeric sequence onto the chromosome ends (Blackburn 2005; Mason et al. 2015). Telomerase activity is tightly regulated. In humans, telomerase activity is highest during embryogenesis and gradually decreases in most somatic cells later in development, suggesting that telomerase may play a role in fetal tissue differentiation and development (Wright et al. 1996; Ulaner and Giudice 1997). In adult humans, most somatic cell types are telomerase-negative; telomerase activity is primarily present in germ, stem, and cancer cells. In contrast to germ and cancer cells, the level of telomerase in most stem cells of human adults is low and insufficient to prevent cell senescence (Hiyama and Hiyama 2007; Choudhary et al. 2012). Telomerase in adult humans is, however, upregulated in cells with high reproducible activity, such as hematopoietic progenitor cells, endometrial and intestinal cells, activated lymphocytes, or keratinocytes (Wright et al. 1996; Razgonova et al. 2020). In contrast to other cell types, embryonic stem cells and cancer cells are, due to their high telomerase activity, considered immortal having the capacity of indefinite self-renewal and proliferation (Hiyama and Hiyama 2007).

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Telomerase is upregulated in the long-lived eusocial reproductives

The common presumption that telomerase activity is a marker of aging and advancing organismal development, even in insects, is supported by observations in hemimetabolous insects such as cockroaches and termites (Korandová et al. 2014; Koubová et al. 2021a). Hemimetabolous insects exhibit incomplete metamorphosis, where ontogenetic development lacks larval and pupal stages and instead includes several nymphal stages that eventually molt into adults. Recent phylogenetic studies indicate that termites evolved from cockroaches, and along with cockroaches, they form the order Blattodea (Inward et al. 2007). But, in contrast to cockroaches, termites are eusocial insects. Both cockroaches and termites exhibit upregulated telomerase activity in young instars, which gradually declines during development. However, there were two exceptions for the decline: germline cells in both insects and somatic tissues in the long-lived reproductives (Korandová et al. 2014; Koubová et al. 2021a). Telomerase activity is also increased in adult somatic tissues of long-lived honeybee queens (Korandová and Frydrychová 2016; Koubová and Čapková Frydrychová 2021) and ant queens (our unpublished data), both of which are holometabolous insects with adult growth largely determined by metamorphosis. These findings suggest that telomerase upregulation is important in caste differentiation in eusocial insects (both holometabolous and hemimetabolous) and in the extended longevity of their reproductive individuals.

It is well established that where telomerase is required for the maintenance of telomeres, it is active during DNA replication stage (S-phase), and while high levels of telomerase activity are found in S-phase, telomerase activity is virtually absent in G2/M or G0 phases (Zhu et al. 1996; Holt et al. 1997). Surprisingly, no DNA synthesis was detected in telomerase-positive somatic tissues of honeybee queens (Koubová and Čapková Frydrychová 2021) or the termite*Prorhinotermes simplex* (our unpublished data). Furthermore, there were no differences in telomere length between the long-lived and short-lived castes of honeybees or the tested ant (*Lasius niger*) or termite (*P. simplex*) (Jemielity et al. 2007; Korandová and Frydrychová 2016).

To explain the role of telomerase in the caste system of eusocial insects and to identify its possible engagement in the disparity between fertility and life expectancy, research was further conducted examining the bumblebee *Bombus terrestris* (Koubová et al. 2019). Bumblebees are members of the group of insects possessing a primitive social organization, and there are significant differences in the life expectancies of their female castes. Workers of the bumblebee species*B. terrestris* typically live for 2-3 months, however, the queens can live up to one year. Nevertheless, the lifespan comparison is not unbiased, as bumblebee queens spend the majority of their lives (approximately 6-9 months) in diapause, in which most biological processes take place at only low-cost levels. Thus, bumblebee queens cannot provide an example of a full-bodied extension of life expectancy, or at least they cannot provide it in the way that exists in advanced eusocial species. In contrast to eusocial reproductive individuals, the only adult somatic tissue of *B. terrestris* showing upregulated telomerase was the fat body of very young and pre-diapause queens (Koubová et al. 2019). Additionally, telomerase activity in fat body was co-localized with the DNA endoreduplication cycles that were followed by a massive increase in fat body mass and nutrient content, which suggests that the upregulation of telomerase activity in the fat body is tightly linked to the ability of queens to survive upcoming diapause (Koubová et al. 2019). A similar observation was obtained in honeybee workers, where telomerase activity, DNA synthesis, and nutrient content were reinforced in the fat body cells of winter-generation workers (Koubová et al. 2021b).

As there is very little cell turnover or DNA synthesis in most adult insect soma, we can expect that the caste-related differences in telomerase activity in eusocial insects such as honeybees or termites are not linked to telomere maintenance mechanisms, and instead, they can be associated with some non-canonical telomerase role, i.e. a role of telomerase without the typical telomerase catalytic activity that directly serves to elongate telomeres.

Non-canonical functions of telomerase in oxidative defense

Although organisms have evolved a set of stress responses to protect against adverse environmental conditions, protracted stressful conditions and long-term activation of the stress response negatively impact health

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and lifespan (Monaghan 2014). It is now broadly accepted that chronic stress and lifestyle factors such as oxidative stress, psychosocial stress, and improper health conditions can affect telomere dynamics (Epel et al. 2004; Kotrschal et al. 2007; Lin et al. 2012; Monaghan 2014; Korandová et al. 2018). DNA represents an important target of oxidative damage in cells, and the most common DNA damage caused by free oxygen radicals is oxidative modifications of DNA bases such as the formation of 8-oxoguanine. Oxidative DNA lesions are largely associated with single-strand breaks that are induced directly or as an intermediate step in the repair of oxidative base modifications. Due to their high content of guanine, telomeres are highly sensitive to oxidative damage and production of single-strand breaks that interfere with the replication fork and thus lead to telomere attrition (von Zglinicki 2002; Houben et al. 2007; Coluzzi et al. 2019).

An increasing body of evidence indicates that non-canonical telomerase functions participate in a variety of biological pathways related to the regulation of cell cycle, apoptosis, DNA repair, gene expression, or protection of cells against oxidative stress (Geserick et al. 2006; Saretzki 2009; Mukherjee et al. 2011; Ségal-Bendirdjian et al. 2019; Zheng et al. 2019). The impact of telomere biology on the cell functions under oxidative stress conditions is documented by the crosstalk between telomeres/telomerase and mitochondria (Zheng et al. 2019). It was discovered that mitochondrial dysfunction accelerates telomere shortening, implying that mitochondrial ROS (reactive oxygen species) may act as a determinant of telomere-dependent senescence (Liu et al. 2002; Passos et al. 2007), or that telomere shortening and dysfunction can lead to alterations in mitochondrial functioning (Guo et al. 2011; Sahin et al. 2011). It has also been reported that in response to oxidative stress induced by hyperoxia, 80-90% of TERT (the catalytic subunit of telomerase) is transported from the nucleus into mitochondria, ultimately resulting in a dramatic acceleration of telomere shortening. When the cellular conditions are shifted from hyperoxia back to normoxia, TERT is transported back to the nucleus, and telomere length is restored (Santos et al. 2006; Ahmed et al. 2008; Saretzki 2009). Telomerase may also exert a protective effect on mitochondrial functions. Under oxidative stress it binds to mitochondrial DNA, increases respiratory chain activity, and protects against oxidative stress-induced damage (Haendeler et al. 2009). Consistent with these observations, different tissues of the bank vole *Myodes glareolus* from the Chernobyl Exclusion Zone displayed reduced telomere length but upregulated telomerase activity. The upregulation of telomerase, in this case, appears to be associated with functions other than telomere maintenance, perhaps protection against a stressful environment (Kesäniemi et al. 2019).

The predicted link between telomeres/telomerase and the lifespan is not universally valid

Most research on telomere length and telomerase activity has been conducted on determinate growers such as mammalian or bird species, and it collectively proposes that (1) telomerase activity and telomere restoration both contribute to cell proliferation and regenerative potential; (2) telomerase is not active in all life stages or tissue types, which causes telomere shortening and replicative senescence in the majority of somatic cells; for this reason, telomerase activity acts as a determinant of organismal development, an anticancer mechanism, and a marker of organismal aging; (3) telomerase activity and telomere length in proliferative cells of adults can be used to predict lifespan (Cong et al. 2002; Blasco 2007; Haussmann et al. 2007; Tan et al. 2012; Hatakeyama et al. 2016; Whittemore et al. 2019). However, from a broad perspective, the connection between the length of telomeres and predicted lifespan or the reason of telomerase activity in somatic tissues of numerous animal species are not clear. Numerous studies have found wide variation in telomere and telomerase dynamics in relation to ectothermy/endothermy (note that ectothermy is frequently associated with indeterminate growth), reproductive mode, the organism's regenerative potential, and environmental conditions (Gomes et al. 2010; Sköld et al. 2011; Sauer et al. 2021; Smith et al. 2021). For example, telomerase activity and telomere length have been studied in sea urchins, which are indeterminate growers, in the context of the long-lived *Strongylocentrotus franciscanus* (live over 100 years) and the short-lived *Lytechinus variegatus* (with an estimated lifespan of only 3-4 years). While both species exhibit telomerase activity in their somatic tissues, *L. variegatus* possessed longer telomeres (average length of approximately 21 kb) compared to those of *S. franciscanus* (average telomere length of approximately 5.5 kb). Moreover, no differences in telomere length were observed between the young and old individuals. This suggests that sea urchins do not utilize telomerase repression as a mechanism to suppress neoplastic transformation (as a decline of telomerase is hypothesized to prevent tumor development, see below), and the continuous telomerase activity

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in somatic tissues of the sea urchins is explained by the indeterminate growth of these organisms throughout their lifespan (Francis et al. 2006). Similarly, somatic telomerase activity is proposed for all species with indeterminate growth, including fungal mycelium, meristematic plant tissue, various invertebrate species, reptiles, amphibia, and fish (Klapper et al. 1998a, b; Gomes et al. 2010; Gruber et al. 2014). Furthermore, numerous studies have shown that telomerase activity is unrelated to telomere length, as reviewed in Smith et al. (2021), or that it remains constant or increases with age in animal species with both determinate and indeterminate growth (Francis et al. 2006; Hartmann et al. 2009; Anchelin et al. 2011; Hoelzl et al. 2016; Korandová and Frydrychová 2016; Koubová et al. 2021a; Sauer et al. 2021). Finally, telomerase and telomere length can be regulated by environmental factors such as stress exposure or seasonal effects (Entringer et al. 2011; Young et al. 2013; Rollings et al. 2014; Mu et al. 2015; Koubová et al. 2021b; Smith et al. 2021).

Telomerase as non-functional phylogenetic relict in small and short-lived animals?

While most mammalian adults, including humans, express telomerase almost exclusively in the germline and a few specialized cell types and have short telomeres ($<$ 25 kb), most rodents express telomerase in both the germline and a wide range of somatic tissues and have long telomeres (25-150 kb) (Gomes et al. 2011). It suggests that rodents do not use telomere length to regulate replicative aging. A similar lack of telomere-based replicative aging is predicted in Lagomorpha (rabbits, pikas, and hares), as prolonged tissue cultures derived from various lagomorph species show no growth arrest or decrease in doubling time but have either very long telomere arrays or detectable telomere activity (Forsyth et al. 2005). Similarly, very long telomeres and expression of telomerase were observed in adult tissues in species of Afrosoricida (golden moles and tenrecs), Didelphimorphia (opossums), and Macroscelidea (elephant shrew) (Gomes et al. 2011). A comparative study of telomerase activity and telomere length revealed that the ancestral mammalian phenotype had human-like telomeres with repressed telomerase activity, and the human-type of telomeres was switched to rodent-type at least 5-7 times during mammalian evolution. Furthermore, it was discovered that telomere length in mammals inversely correlates with lifespan (longer telomeres are found in short-lived mammal species) and telomerase activity in somatic cells inversely correlates with body mass (telomerase activity in somatic cells is found in small mammal species such as small rodents) (Seluanov et al. 2007; Gomes et al. 2010).

Body size and lifespan are factors that influence cancer risk because cancer develops through somatic evolution with genetic and epigenetic instability causing fitness variation among cells. Therefore, one can assume that larger organisms, which typically have longer lifespans, are more susceptible to cancer. In fact, however, there is no correlation between the body size, longevity, and cancer across species (known as Peto's Paradox) (Caulin and Maley 2011).

To explain the Peto's paradox, it has been suggested that larger and longer-lived mammals repress telomerase activity in their somatic cells as protective mechanism against cancer development, and accordingly, small short-lived mammals have telomerase widely active, as there is no need to repress it (Seluanov et al. 2007). On the other hand, this assumption may evoke the idea that telomerase in these species is present only as non-functional phylogenetic relict, and this "presence without purpose' can be questioned regarding why it is worthy for cells to express telomerase (or anything else) if there is no need for it. Furthermore, there is substantial evidence that cancer incidence is a taxonomically widespread phenomenon, observed both in captivity and in wild populations, with no increase in cancer incidence in the long-lived indeterminate growers (Athena Aktipis et al. 2015; Olsson et al. 2018; Kitsoulis et al. 2020). For example, neoplasia was found at necropsy in 2.75 % of mammals, 1.89 % of birds, and 2.19 % of reptiles. Additionally, neoplasia has not been reported in Galapagos giant tortoises (Effron et al. 1977), which live for more than 150 years and, like many other reptile species, are ectotherms with indeterminate growth (Hariharan et al. 2016; Hoekstra et al. 2020). This collectively indicates that the risk of cancer is not elevated in the species with indeterminate growth and somatic telomerase activity, and that the proposed telomerase repression as a cancer protection is less straightforward than was previously believed (Olsson et al. 2018). Finally, a plenty of evidence suggests that numerous anti-cancer mechanisms other than telomere attrition have evolved (Caulin and Maley 2011; Tian et al. 2018).

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A role of telomerase to eliminate the cost of reproduction depending on the type of reproduction strategy

The telomere-related function of telomerase requires passage into S phase, and appears to be coupled to cell proliferation (Blasco 2007). Regrettably, most of the non-model organism studies mentioned above did not provide detailed information relating telomerase activity to DNA replication or tissue proliferation status, and the presence of telomerase in post-mitotic tissues, if observed, was explained by a non-canonical, and yet unknown, function of telomerase (reviewed in Gomes et al. 2010). In this regard, it is useful to mention that a wide range of TERT alternatively spliced variants were discovered in a variety of animal species, and TERT alternative splicing is thought to be linked to non-canonical telomerase functions such as those in cell proliferation, cancer development, or regeneration process (Yi et al. 2001; Hrdličková et al. 2012; Listerman et al. 2013; Lai et al. 2017; Slusher et al. 2020; Penev et al. 2022). The investigation of the evolutionary history of TERT across different metazoan taxa revealed that the selection of exons for alternative splicing appears to be highly variable between taxa, indicating diverse functions of TERT involved in animal life histories (Lai et al. 2017). Based on this and the data I am presenting below it is tempting to ask whether telomerase may act as one of reproductive fitness traits.

Reproduction is an energetically costly activity that increases metabolic rates, ROS production, and susceptibility to oxidative stress, and it is hypothesized that oxidative stress may represent a mechanistic link for the inverse relationship between reproduction and lifespan in both vertebrate and invertebrate models that acts independently of energy allocation (Alonso-Alvarez et al. 2004; Wiersma et al. 2004; Krůček et al. 2015; Sharick et al. 2015; Colominas-Ciuró et al. 2017; Costantini 2018). Resistance to oxidative stress plays a significant role in shaping fecundity; for instance, higher fecundity rates were observed in individuals with higher oxidative protection (Bize et al. 2008). It is well established that oxidative stress in humans is implicated in pathological processes in the reproductive tract that contribute to infertility and poor pregnancy outcomes, and treatments based on strategies to boost the exhausted antioxidant defense of the reproductive microenvironment have been suggested (Adeoye et al. 2018). Furthermore, in passerine birds, it has been demonstrated that resistance to oxidative stress is decreased during their reproduction and that breeding activity increases susceptibility to oxidative stress (Alonso-Alvarez et al. 2004; Wiersma et al. 2004). In agreement with the assumption that breeding individuals are more susceptible to oxidative damage, engaging organisms in reproduction accelerates telomere loss (Kotrschal et al. 2007; Heidinger et al. 2011; Bauch et al. 2013).

On the other hand, there are numerous studies showing that increased breeding constraints or reproductive status appear to prioritize self-maintenance as documented by the increased lifespan expectancy, telomere length, telomerase activity, or antioxidant defense. It has been demonstrated that (1) workers in many eusocial insect species restore their ability to reproduce if the queen in the colony has been lost, and the transition of the workers into reproductive state is associated with their substantial lifespan extension (Hartmann and Heinze 2003; Dixon et al. 2014; Kohlmeier et al. 2017; Kuszewska et al. 2017; Majoe et al. 2021) and improved resilience to oxidative stress (Schneider et al. 2011; Lucas and Keller 2018; Negroni et al. 2019; Majoe et al. 2021). (2) It has been shown that in contrast to the decline of antioxidant protection during mating in the short-lived passerine birds (Alonso-Alvarez et al. 2004; Wiersma et al. 2004; Kotrschal et al. 2007; Heidinger et al. 2011; Bauch et al. 2013), the long-lived Adélie penguins exhibited an increased antioxidant defense and unchanged telomere length in response to breeding efforts (Beaulieu et al. 2011). (3) The positive correlation between telomere length (and presumably telomerase activity), age and reproduction effort were observed in the edible dormice (*Glis glis*), a hibernating long-lived rodent with a lifespan reaching 13 years. Although telomere length in this species is shortened over the hibernation season during periods of rewarming, which is associated with increased oxidative stress, it is elongated during the summer active season, when the animals mate. Longitudinal telomere length measurements revealed that the telomere-length re-elongation resulted in a gradual telomere lengthening with age of the individuals together with the likelihood of their reproduction (Hoelzl et al. 2016). (4) A lifelong somatic activity of telomerase accompanied by steady or even increasing reproduction rate with advancing age is observed in numerous reptile or fish species with indeterminate growth (Gomes et al. 2010; Schwartz and Bronikowski 2011). For instance, bigmouth buffalo

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(*Ictiobus cyprinellus*), which displays some of the longest lifespans among vertebrates (> 100 years), has indeterminate growth and fecundity that increases with size and thus with age of individuals. In contrast to the common expectation, no telomere length decline was observed in old individuals of this species, along with declines in other physiological systems such as stress response and immune function; instead, all the tested parameters improved their efficiencies with age (Sauer et al. 2021). (5) It is well-known that the fertility rate of termite queens increases with age along with their body mass, which, based on the evidence shown above, appears to be consistent with their increasing somatic telomerase activity (Adams and Atkinson 2008; Adams et al. 2008; Nozaki and Matsuura 2019; Koubová et al. 2021a).

It is widely known that body mass in terrestrial mammals is negatively correlated with the fecundity rate of the species (Allainé et al. 1987; Werner and Griebeler 2011), which is reflected by the litter size, interlitter intervals, or gestation length. Based on this assumption, we can ask whether the necessity to maintain telomerase activity in somatic cells of small but highly fecund mammal species observed by Gomes et al. (2010) reflects a different reproduction strategy of the species and their specific demands during reproduction rather than their body size. The somatic telomerase activity or longer telomeres (> 25kb) do tend to be correlated with shorter gestation periods, as observed in Eulipotyphia, Chiroptera, and even two Carnivora species (steppe polecat and tiger); in Rodentia, Lagomorpha, Afrosoricida, and Macroscelidea they are associated with short gestation periods along with multiple litters per year, and in some cases also with the increased litter size (Figure 1). Despite the lack of telomerase activity, Diprotodontia have short gestation periods (Figure 1), which, however, might reflect that youngs in the species are born at a precocious stage of development.

Based on this observation, it is tempting to speculate that somatic telomerase activity in eusocial insect reproductives, as well as in the small mammals or potentially other animal or plant species, may serve a non-canonical function of protecting individuals against reactive oxygen species produced due to exacerbated metabolic stress during reproduction, and may simply reflect a more widespread phenomenon.

Although validity of this hypothesis needs to be tested, we can infer from all the data that telomerase expression patterns differ greatly across species, life stages, and conditions, implying that telomerase is involved in the organism's adaptive potential and individual fitness, and that telomerase expression might co-evolved as a pleiotropic regulator involved in the life-history trade-offs between growth, maintenance, and reproduction. More precise information connecting telomerase activity to distinct reproductive strategies and lifespan expectancies, along with different cellular, physiological, and ecological features in various species across the animal and plant kingdoms, would help us better understand the role of telomerase in this aspect. We can assume that resolving the connections between these trade-offs would lead to new and intriguing directions for ecology and evolutionary biology study.

Conflicts of Interest Statement Author declares no conflict of interest.

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Data availability statement

Data sharing not applicable to this article as no data sets were generated or analyzed during the current study.

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Figure 1. Comparing reproductive strategy to telomerase activity and telomere length in mammalian species. Data on telomerase activity were got from Gomes et al. 2011, except for the data on pig that were got from Fradiani et al. 2004. Data on gestation period, litters per year, and litter sizes were obtained from the ANAGE data-base (The Animal Ageing & Longevity Database. http://genomics. senescence.info/species/). The data on telomeres and telomerase were obtained from cultured cells derived from fibroblasts from skin, kidney, lung or cornea of the species (Gomes et al. 2011), or from spleen, lymph node, lung, and kidney (Fradiani et al. 2004). For more details on telomerase activities see Gomes et al. 2011. * The gestation periods in tiger and steppe polecat are 36 and 105 days, respectively, in contrast to the other Carnivora species with the gestation period ranging from 110 – 259 days. Accordingly, steppe polecat and tiger have the largest litter sizes (9.4 and 2.5, respectively), in contrast to the other Carnivora species where litter sizes ranging from 2 to 1.5. Discontinuous telomeres are abbreviated as “d”.

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	Telomere length (kb)	Telomerase activity	Gestation period (days)	Litters per year	Litter size
Cetartiodactyla					
Grey whale (*Eschrichtius robustus*)	< 25	(-)	> 110	≤ 1	1
Bowhead whale (*Balaena mysticetus*)	< 25	(-)	> 110	≤ 1	1
Bottle nosed dolphin (*Tursiops truncatus*)	< 25	(-)	> 110	≤ 1	1
Pygmy hippopotamus (*Hexaprotodon liberiensis*)	< 25	(-)	> 110	≤ 1	1
Giraffe (*Giraffa camelopardalis*)	< 25	(-)	> 110	≤ 1	1
Cow (*Bos taurus*)	< 25	(-)	> 110	≤ 1	1
Pig (*Sus scrofa*)	< 25	(+)	> 110	≤ 1	> 1
Indian muntjac (*Muntiacus muntjak*)	< 25	(-)	> 110	≤ 1	1
Camel (*Camelus dromedarius*)	< 25	(+)	> 110	≤ 1	1
Perissodactyla					
White rhinoceros (*Ceratotherium simum*)	< 25	(-)	> 110	≤ 1	1
Malasian tapir (*Tapirus indicus*)	< 25	(-)	> 110	≤ 1	1
Horse (*Equus caballus*)	< 25	(-)	> 110	≤ 1	1
Grevy's zebra (*Equus grevyi*)	< 25	(-)	> 110	≤ 1	1
Carnivora*					
Spotted hyena (*Crocuta crocuta*)	< 25	(-)	> 110	≤ 1	> 1
Tiger (*Panthera tigris*)	> 25	(+)	< 110	≤ 1	> 1
Polar bear (*Ursus maritimus*)	< 25	(-)	> 110	≤ 1	> 1
California sea lion (*Zalophus californianus*)	< 25	(-)	> 110	≤ 1	1
Red panda (*Ailurus fulgens*)	< 25	(-)	> 110	≤ 1	> 1
Steppe polecat (*Mustela eversmanii*)	> 25	(+)	< 110	≤ 1	> 1
Chiroptera					
Flying fox (*Pteropus rodricensis*)	< 25	(-)	> 110	≤ 1	1
Big brown bat (*Eptesicus fuscus*)	> 25	(+)	< 110	≤ 1	1
Little brown bat (*Myotis lucifugus*)	> 25	(+)	< 110	≤ 1	1
Brazilian Free-tail Bat (*Tadarida brasiliensis*)	> 25	(+)	< 110	≤ 1	1
Eulipotyphla					
Four-toed hedgehog (*Atelerix albiventris*)	> 25	(+)	< 110	≤ 1	> 1
Soricidae sp.	> 25	(+)	< 110	≤ 1	> 1
Rodentia*					
House mouse (*Mus musculus*)	> 25	(+)	< 110	> 1	> 1
Norway rat (*Rattus norvegicus*)	> 25	(+)	< 110	> 1	> 1
Deer mouse (*Peromyscus maniculatus*)	< 25	(+)	< 110	> 1	> 1
Naked mole rat (*Heterocephalus glaber*)	< 25	(+)	< 110	> 1	> 1
Eastern gray squirrel (*Sciurus carolinensis*)	> 25	(+)	< 110	> 1	> 1
Mountain beaver (*Aplodontia rufa*)	< 25	(-)	< 110	≤ 1	> 1
American beaver (*Castor canadensis*)	< 25	(-)	> 110	≤ 1	> 1
Lagomorpha					
European white rabbit (*Oryctolagus cuniculus*)	> 25	(-)	< 110	> 1	> 1
Black-tailed jack rabbit (*Lepus californicus*)	> 25	(-)	< 110	> 1	1
Swamp rabbit (*Sylvilagus aquaticus*)	> 25	(-)	< 110	> 1	> 1
North American pika (*Ochotona princeps*)	> 25	(+)	< 110	> 1	> 1
Primata					
Ring-tailed lemur (*Lemur catta*)	< 25	(-)	> 110	≤ 1	1
Spider Monkey (*Ateles geoffroyi*)	< 25	(-)	> 110	≤ 1	1
Squirrel Monkey (*Saimiri sciureus*)	< 25	(-)	> 110	≤ 1	1
Orangutang (*Pongo pygmaeus*)	< 25	(-)	> 110	≤ 1	1
Bonobo (*Pan paniscus*)	< 25	(-)	> 110	≤ 1	1
Human (*Homo sapiens*)	< 25	(-)	> 110	≤ 1	1
Xenartha					
Two-toed Sloth (*Choloepus hoffmanni*)	< 25	(-)	> 110	≤ 1	1
Giant anteater (*Myrmecophaga tridactyla*)	< 25	(-)	> 110	≤ 1	1
Afrosoricida					
Greater hedgehog tenrec (*Setifer setosus*)	> 25	(+)	< 110	> 1	> 1
Macroscelidea					
Elephant shrew (*Macroscelides proboscideus*)	> 25	(+)	< 110	> 1	1
Elephant shrew (*Petrodromus tetradactylus*)	> 25	(+)	< 110	> 1	1
Hyracoidea					
Rock hyrax (*Procavia capensis*)	< 25	(-)	> 110	≤ 1	> 1
Proboscidea					
Indian Elephant (*Elephas maximus*)	< 25	(-)	> 110	≤ 1	1
African Elephant (*Loxodonta africana*)	< 25	(-)	> 110	≤ 1	1
Diprotodontia					