Journal of Thermal Biology 123 (2024) 103913

Contents lists available at ScienceDirect

Journal of Thermal Biology

journal homepage: www.elsevier.com/locate/jtherbio

Understanding seasonal telomere length dynamics in hibernating species

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ARTICLE INFO

Keywords:
Telomere length
Ageing
Hibernation
Oxidative stress
Seasonal species
Evolutionary physiology

ABSTRACT

Oxidative stress is thought to be one of the main causes of ageing as it progressively damages cell components throughout life, eventually causing cellular failure and apoptosis. In many organisms, telomeres shorten throughout life under the effect of, amongst other factors, oxidative stress, and are therefore commonly used as marker of biological ageing. However, hibernators, which are regularly exposed to acute oxidative stress when rewarming from torpor, are unexpectedly long-lived. In this review, we explore the causes of oxidative stress associated with hibernation and its impact on telomere dynamics in different taxa, focussing on hibernating rodents. We then speculate on the adaptive mechanisms of hibernators to compensate for the effects of oxidative stress, which may explain their increased longevity. Because winter hibernation appears to be associated with high oxidative stress, hibernators, particularly rodents, may periodically invest in repair mechanisms and antioxidant defences, resulting in seasonal variations in telomere lengths. This research shows how species with a slow life-history strategy deal with large changes in oxidative stress, unifying evolutionary and physiological theories of ageing. Because of the marked seasonal variation in telomere length, we also draw attention when using telomeres as markers for biological aging in seasonal heterotherms and possibly in other highly seasonal species.

1. Introduction

The complex process of ageing can be considered from many points of view across the biological field. Recently, Le Maître and colleagues (2024) proposed a unified framework for evolutionary and physiological theories of ageing. The disposable soma theory allows a link between the evolutionary and physiological/molecular mechanisms of ageing in organisms (Kirkwood, 1977; Lemaître et al., 2024). Based on this theory ageing results from damage accumulation to cell components over time due to energy allocation trade-offs that can vary across species (Kirkwood, 1977). Hence many studies aim to identify the cellular causes of ageing, which has led to the creation of a list of markers, known as the hallmarks of ageing, shown to correlate with chronological age (López-Otín et al., 2023).

Telomere length as one of these hallmarks correlates with chronological age across different taxa (López-Otín et al., 2023; Whittemore et al., 2019). It has also been suggested to be a key mediator of resource allocation trade-offs between growth, reproductive effort and somatic maintenance (Young, 2018). Telomeres are non-coding repeated sequences at the end of eukaryotic chromosomes that protect coding DNA strands from attrition after replication. Telomeres are shortened after each cell division (Chan and Blackburn, 2004), especially under the effect of oxidative stress, *i.e.*, an imbalance between reactive oxygen species (ROS) production and antioxidant capacity. Under oxidative stress, oxidative damage caused by ROS leads to the alteration of cellular macromolecules, such as DNA via strand breaks (Armstrong and Boonekamp, 2023; Proctor and Kirkwood, 2002). However, repair mechanisms, such as the activation of telomerase enzyme (Chan and Blackburn, 2004) or the alternative lengthening of telomeres (Neumann et al., 2013), can repair DNA strands and prevent critical shortening of telomeres (see, though, the anticancer hypothesis (Tian et al., 2018). Telomeres can therefore be used as a marker of somatic maintenance,

Abbreviations: ROS, Reactive Oxygen Species; T_a, Ambient temperature; T_b, Body temperature; CIRP, cold-induced RNA-binding Protein.

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https://doi.org/10.1016/j.jtherbio.2024.103913
Received 14 February 2024; Received in revised form 26 June 2024; Accepted 27 June 2024
Available online 5 July 2024

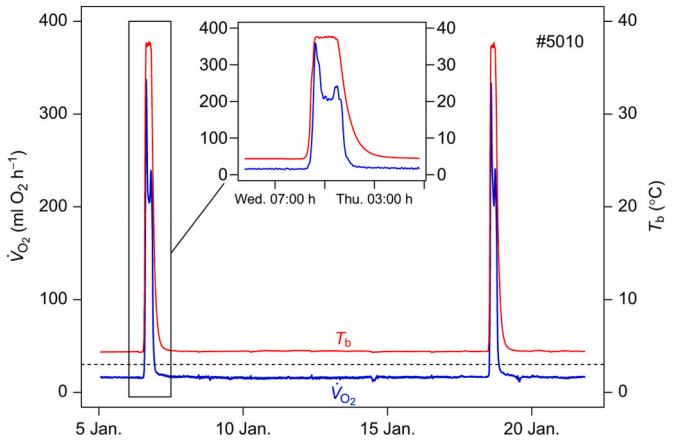

Fig. 1. Example of oxygen consumption (VO_2) during torpor and two arousals (with interbout euthermia) in the garden dormouse (*Eliomys quercinus*), adapted from Ruf et al. (2021). In this review, "torpor" refers to the phase where body temperature (T_b) and VO_2 are low and constant, and both "rewarming" and "arousal" refer to the rewarming from torpor until euthermic T_b.

since they shorten under the effect of oxidative stress, but can lengthen through repair mechanisms if sufficient energy is available (Hoelzl et al., 2016).

The study of telomeres in hibernators, showing high longevity despite experiencing large changes in oxidative stress, would provide a better understanding of the role of telomeres in somatic maintenance. Hibernating species show a longer lifespan compared to non-hibernators of the same body size, which especially applies to rodents (Wilkinson and South, 2002; Turbill et al., 2011; Constant et al., 2020). Also, torpor use correlates positively with lifespan and telomere length in daily hibernators (Lyman et al., 1981; Turbill et al., 2011). However, to date, the mechanisms underlying the positive effect of hibernation on lifespan remain unclear. In large mammals, telomerase activity is usually inhibited in somatic tissue, probably to reduce the risk of cells becoming immortal and thus avoiding cancer (Seluanov et al., 2007). However, somatic telomerase activity is common among rodents as well as some hibernating bats (Gorbunova et al., 2008; Wang et al., 2011), and telomere lengthening has been reported as well in hibernating bears (Kirby et al., 2019). The longer lifespan observed in hibernators could therefore be related to telomerase expression and telomere maintenance.

Small hibernating species such as bats and rodents typically perform multi-day torpor bouts during the winter (Fig. 1), via lowering metabolic rate, body temperature (T_b), and heart rate, enabling them to save energy during several months of unfavourable conditions (Geiser, 2013). During hibernation, torpor in small (<5 kg) species is regularly interrupted by periodic phases of arousal or rewarming where organism reaches euthermic T_b (~36–38 °C) within a few hours, followed by a brief (8–72h) period of constant euthermia, before individual re-enters torpor for several days or weeks (Heldmaier, 2004; Geiser 2013; Ruf et al., 2021). In large (>10 kg) hibernators such as bears, T_b during torpor drops only for a few degrees reaching torpid values ~30–34 °C for four to six months without periodic arousals (Folk et al., 1976; Hissa et al., 1994). Since hibernators experience a longer lifespan compared to non-hibernators, hibernation is seen as a state slowing down ageing processes. However, periodic arousals as seen in small species during hibernation constitute a major source of oxidative stress for the organism (Turbill et al., 2013; Hoelzl et al., 2016; Nowack et al., 2019; Charlanne et al., 2022; Duffy and Staples, 2022). Oxidative stress is known to inhibit telomerase activity via the formation of 8-hydroxy-2--deoxyguanosine (8-OHdG) on telomere sequences (Smith, 2018), thus preventing repairs after DNA replication and leading to further telomere shortening (for overview, see Table 1). However, such oxidative damage only occurs when ROS production exceeds antioxidant capacity (Sies, 2000). The use of enzymatic and non-enzymatic antioxidant defences is an efficient strategy used across many different taxa to counteract an increase in ROS production (Costantini, 2010; Hermes-Lima et al., 2001; Tøien et al., 2001; Stier et al., 2019; Corsolini et al., 2001; Chazarin et al., 2019; Morin and Storey, 2007). The exceptional longevity of hibernators could therefore be explained by (1) an enhanced antioxidant capacity during winter preventing or limiting oxidative damages, (2) an increased investment in repair mechanisms such as telomerase to compensate for damages experienced during hibernation, or (3) a combination of both mechanisms. Such findings are likely to lead to a more complete and integrative understanding of ageing in wild seasonal species, where telomere length dynamics are probably much more complex than initially expected.

In this review, we summarize the current knowledge on ageing across different, mostly rodents, hibernating species (1) to understand

Table 1
Summary of the different observations (on the left column), and the possible associated explanations for each case. References are indicated for each explanation. 8OH-dG stands for of 8-hydroxyguanosine (see introduction). Stars (*) indicate hypothetical explanations, even though based on the associated references.

Observation	Tentative explanations			
Telomere length dynamics	Metabolism	Telomerase	Telomerase + CIRP	Metabolic telomere attrition
Telomere shortening during hibernation Giroud et al. (2014) Hoelzl et al. (2016a) Nowack et al. (2019)	Oxidative stress during arousal Carey et al. (2000) Storey (2010) Morin and Storey (2007)	Inhibited by 8OH-dG Smith (2018)	T_b is too low for CIRP effect to be observed or its effect is masked by oxidative costs* Zhong and Huang (2017)	High energy demand leads to high AMP/ATP ratio causing telomere shortening during arousals* Casagrande and Hau (2019)
Telomere lengthening during daily torpor or hibernation at mild temperature Turbill et al. (2012) Nowack et al. (2019) Giroud et al. (2023) Galindo-Lalana et al. (2023)	Lower oxidative stress because of lower degree of rewarming Karpovich et al. (2009) Nowack et al. (2019)	Residual activity because of higher temperature and reduced oxidative stress* Smith (2018)	CIRP activated by low T_b allows for a higher telomerase activity, notably during interbout euthermia* Zhang et al. (2016) Sano et al. (2015) Galindo-Lalana et al. (2023)	Food availability allows for low AMP/ATP ratio leading to more telomere lengthening during IBE* Casagrande and Hau (2019)
Telomere lengthening over summer Turbill et al. (2013) Hoelzl et al. (2016b) Tissier et al. (2022)	Enough energy available for somatic maintenance Hoelzl et al. (2016b) Tissier et al. (2022)	Active in somatic tissues in small mammals Seluanov et al. (2007)	Consequences of CIRP activity might still be observed at the beginning of summer* Zhong and Huang (2017) Sano et al. (2015)	Energy availability during summer allows for a low AMP/ATP ratio and causes telomere lengthening* Casagrande and Hau (2019)
Telomere shortening over summer Turbill et al. (2013)	High costs of growth and reproduction on telomeres in sub-adults* Smith et al. (2022) Monaghan (2024)	Masked by oxidative stress associated with active metabolism* Smith (2018) Monaghan (2024)	CIRP is not activated at euthermic T_b* Zhong and Huang (2017) Sano et al. (2015)	High AMP/ATP ratio due to costs associated with growth and reproduction causes telomere shortening* Casagrande and Hau (2019)

the underlying mechanisms of telomere length dynamics in hibernators, and (2) to suggest new research avenues in the physiology of ageing considering the seasonal regulations of telomere length dynamics occurring in hibernators.

2. Telomere length dynamics according to hibernating lifestyle

2.1. Torpor use and telomere attrition

Telomere length either stays constant (Turbill et al., 2013; Giroud et al., 2014) or shortens over winter (Giroud et al., 2014; Hoelzl et al., 2016a; Nowack et al., 2019) in the garden dormouse (*Eliomys quernicus*) and the edible dormouse (*Glis glis)* hibernating at low temperatures without extra-energy reserves. These studies revealed that both the time spent euthermic, and the arousal frequency negatively affect telomere length (Giroud et al., 2014; Hoelzl et al., 2016a; Nowack et al., 2019). The production of ROS during periodic arousals appears as the cause of these observations (Turbill et al., 2013; Duffy and Staples, 2022). The fast increase in metabolic rate (Fig. 1) causes tissues to receive too high oxygen delivery, similar to a situation of ischemia/reperfusion, greatly damaging cells and macromolecules due to the burst of ROS production (Duffy and Staples, 2022; Kalogeris et al., 2016). Antioxidant mechanisms are known to prevent oxidative damage in a large range of taxa (Costantini, 2010; Hermes-Lima et al., 2001). In brown bears (*Ursus arctos*), the upregulation of antioxidant enzymes has been associated with overall reduction of oxidative damage during hibernation (Chazarin et al., 2019). However, hibernation in brown bears is associated with a mild T_b reduction of a few degrees Celsius and does not require periodic arousals (Folk et al., 1976; Hissa et al., 1994), hence the need for antioxidant defences during hibernation might be lesser compared to rodents. In the arctic ground squirrel (*Spermophilus parryii*), ascorbate has a protective effect against oxidative stress during arousals in metabolically active tissues such as liver and spleen (Toien et al., 2001; Drew et al., 2002). Antioxidant enzymes are also upregulated in brown adipose tissue and skeletal muscle, but not in liver of ground squirrels, *Spermophilus citellus* (Vucetic et al., 2013). Finally, an increase in both enzymatic and non-enzymatic antioxidant defences in the brain of hibernating bats appears to prevent major cerebral oxidative damage (Yin et al., 2016). Although such responses are partially protecting organs and tissues against oxidative damage during arousals, data regarding the actual efficiency of these shedding mechanisms is lacking. Indeed, oxidative damage occurs despite the upregulation of protection mechanisms (Carey et al., 2000; Storey, 2010; Morin and Storey, 2007), indicating a lack of optimal protection against oxidative damage during hibernation. As possible explanation, the energetic cost of antioxidant mechanisms might constitute a limitation during a period of restricted food availability (Pamplona and Costantini, 2011). Hence, a balance could exist between the allocation of sufficient energy to antioxidant mechanisms and the need for energy saving during hibernation and for the subsequent early active season. Also, the burst in ROS production occurring before T_b is high enough to allow for an optimal activity for antioxidant enzymes, and levels of antioxidant enzymes, even upregulated, are being limited compared to the burst in ROS production. Further studies are warranted to that respect.

2.2. Effect of hibernating conditions on telomere dynamics

Torpor use and the associated oxidative costs are likely to depend on energetic demand and available resources (Humphries et al., 2003). Thus, environmental conditions during hibernation, such as temperature and food availability, may influence the effect of torpor use on telomere length dynamics. To that respect, dormice hibernating at mild (14 °C) compared to low (3 °C) ambient temperatures (T_a) had longer telomeres while experiencing more frequent arousals (Nowack et al., 2019). This may conflict with previous studies showing higher arousal frequency and longer arousals causing greater telomere shortening over winter (Giroud et al., 2014; Hoelzl et al., 2016a). These results highlight the effect of T_a on the cost of rewarming and telomere length. Indeed, T_b and metabolic rate during torpor are lower when hibernating at low T_a (Nowack et al., 2019; Milsom et al., 1999) as T_b during torpor usually follows T_a in most situations. Artic ground squirrels hibernating at subzero T_a significantly increase their metabolic rate during arousal and the duration of the rewarming phase, as well as their resting metabolic rate during euthermia (Karpovich et al., 2009). The increase in metabolic rate during arousals is lower in squirrels hibernating at a higher T_a, as the rise in T_b required to reach euthermia is lower (Karpovich et al., 2009). The average metabolic rate during inter-bout euthermia would also be lower at higher T_a since maintaining euthermia would then be energetically less demanding. Thus, arousals would be less expensive at high compared to low T_a and accompanied by lower ROS production and therefore less damage to telomeres. These explanations are in line with the positive correlation between torpor duration and telomere length in daily heterotherms that use shorter (<24h) and shallower (~16 °C) torpor bouts compared to small hibernators (Geiser, 2004; Geiser 2020; Heldmaier et al., 2004; Jastroch et al., 2016; Ruf and Geiser, 2015; Turbill et al., 2012). In the fat-tailed dwarf lemur (*Cheirogaleus medius*), hibernating at T_a between 11 °C and 15 °C, telomere length also increases over hibernation (Blanco et al., 2024), supporting the idea that the cost of arousal from low T_b (<8 °C) could be the main driver for shortening of telomeres during hibernation. Nevertheless, in most cases wild hibernators experience low T_a (near or below 0 °C) during winter hibernation. Hence, the positive effect of hypometabolism on ROS production is probably overshadowed by the oxidative stress associated with periodic rewarming from extremely low T_bs.

Food availability during hibernation also affects hibernating patterns through increased arousal frequency and duration, and impact telomere dynamics during winter (Giroud et al., 2023). Food intake allows hibernators to maintain a stable or positive energy balance (Hoelzl et al., 2016a; Giroud et al., 2023) and has a positive effect on telomere length during winter in hibernating garden dormice (Giroud et al., 2023). The mechanism underlying the effect of food availability remains unclear, though it is likely to play a role in the seasonal dynamic of telomere length via its effects on torpor use, hibernation season duration, and energy availability (Humphries et al., 2003; Giroud et al., 2023).

Altogether, telomeres usually shorten for hibernators during the winter, likely due to oxidative stress associated with periodic arousals and despite upregulated antioxidant defences (Carey et al., 2000; Storey, 2010; Morin and Storey, 2007; Staples et al., 2022). According to the *disposable soma theory*, such effect of oxidative stress should lead to a shorter lifespan for hibernators. So how do hibernating (rodent) species live longer than non-hibernators of comparable size? Some compensation mechanisms explaining this apparent paradox may occur during the summer active period.

2.3. Does telomere recovery occur over summer?

Turbill et al. (2013) reported variations of telomere length in edible dormice during the summer depending on individuals' life stage, *i.e.,* juveniles, sub-adults and adults. While juveniles do not reproduce within their first year of life, sub-adults although still growing can reproduce after emerging from their first hibernation, fully-grown adults being sexually mature (Turbill et al., 2013). Only sub-adults experienced telomere shortening over the summer when individuals are active, whereas adult dormice experienced telomere lengthening during the active season (Turbill et al., 2013), suggesting that the cost of being active in summer is not sufficient to explain the observed telomere shortening in sub-adults. Since growth and reproduction are both known to have a cost on telomere length (Monaghan, 2024), it is possible that the simultaneous costs of growth and reproduction in sub-adults would be harder to deal with the cost of growth or reproduction alone, thus explaining telomere shortening in sub-adults but not in adults or juveniles. Older edible dormice, as well as Eastern chipmunks (*Tamias*

striatus), were also able to lengthen their telomeres, thus confirming that telomere lengthening is possible and does occur in hibernating rodents (Hoelzl et al., 2016b; Tissier et al., 2022; Galindo-Lalana et al., 2023). This indicates that telomere length variation is not linear in hibernating rodents and possibly in other hibernating species as well, and likely depends on environmental factors such as environmental temperature and energy availability. Telomere lengthening during the summer would be a very efficient strategy to compensate for the limited efficiency of antioxidant defences during hibernation, thus allowing for an increased lifespan in hibernating species despite a harmful effect of hibernation on cellular maintenance.

Nevertheless, to date, important questions remain: through what mechanisms do dormice and chipmunks, and probably other hibernators, lengthen their telomeres during the summer? Can telomeres still be used as biomarkers of ageing in hibernators despite this seasonal pattern of telomere length variation?

3. Possible mechanisms explaining telomere lengthening in hibernators

3.1. Regulation of telomerase activity

Because telomerase is key in telomere elongation, specific regulations of telomerase activity is necessary to explain the observations occurring in hibernators as discussed above. At first, the effect of food availability on telomere length suggested that energy restriction could lead to a trade-off between energy savings and cellular maintenance: if energy availability is low, energy will be directed to basic cellular functions and somatic maintenance, *i.e.*, telomere repair, will be inhibited. However, there is no empirical evidence of an actual ATP consumption or energetic cost associated with telomerase activity (Smith et al., 2022). This suggests the possibility for telomerase to be affected via other regulatory pathways, *e.g.*, metabolic telomere attrition, linked to energy availability (Casagrande and Hau, 2019). Indeed, telomerase activity is downregulated in liver of garden dormice during the pre-hibernation period, corresponding to the time for accumulation of fat energy reserves (Galindo-Lalana et al., 2023). A simple direct link between food/energy availability and telomere length can therefore be excluded. Instead, this strongly suggests the existence of one or more alternative mechanisms at work.

3.2. The metabolic telomere attrition hypothesis

One possible mechanism to explain the effect of food availability on telomere length variation would be the *metabolic telomere attrition* hypothesis. This recent hypothesis considers telomere length as a signal transductor of energy metabolism and suggests that telomerase, and thus telomere length, could be regulated by cellular AMP/ATP ratio (Casagrande and Hau, 2019). This ratio can be used as an indicator for cellular energy consumption: if the cell has high energy consumption, then ATP is quickly consumed and the AMP/ATP ratio is high, whereas if the cell has low energy consumption, ATP accumulates and the AMP/ATP ratio is low (Hardie, 2003). According to the *metabolic telomere attrition* hypothesis, telomeres would shorten when the AMP/ATP ratio is high, *i.e.* in case of energy deficit, and lengthen when AMP/ATP ratio is low, *i.e.* in case of high energy availability (Fig. 2).

This would explain the effect of food availability on telomere length observed by Hoelzl et al. (2016a) in active edible dormice during the summer and by Giroud et al. (2023) in hibernating garden dormice during winter. When food is available, the AMP/ATP ratio could be maintained at a low level during the active season, allowing telomere lengthening in the summer (Table 1). During hibernation, AMP/ATP

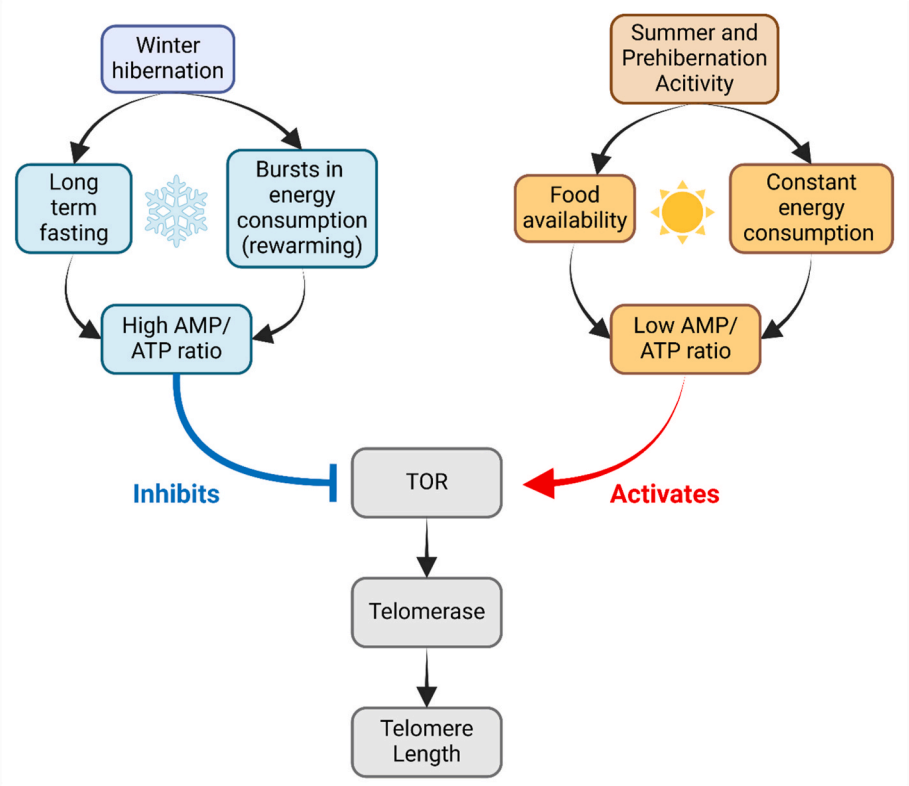

Fig. 2. Diagram representing the effect of season on telomere length dynamics in light of the *metabolic telomere attrition* hypothesis. Under normal physiological conditions, TOR promotes telomerase leading to telomere elongation. During hibernation, caloric restriction and bursts in energy consumption associated with arousals lead to a high AMP/ATP ratio, inhibiting TOR and thus preventing telomere lengthening. During summer, food availability and moderate energy consumption allow for a lower AMP/ATP ratio, activating TOR and leading to telomere lengthening. See Casagrande and Hau, 2019 for more details.

ratio appears to remain overall unchanged (Abnous and Storey, 2021), although it could temporarily increase during arousals, the most energetically costly phases of hibernation. This may explain telomere shortening with increasing arousal frequency during hibernation as observed by Hoelzl et al. (2016) in edible dormice, and the lengthening of telomeres reported in garden dormice hibernating with food (Giroud et al., 2023). It could also explain why sub-adult edible dormice experience telomere shortening during the summer. The combination of high energetic costs associated with both growth (absent in adults) and reproduction (not occurring in juveniles), results in high AMP/ATP ratio leading to a decrease in telomere length (Table 1). However, some results seem to contradict this hypothesis. The accumulation of energy reserves during pre-hibernation would be expected to increase *in vitro* telomerase activity causing telomere lengthening, while the opposite is observed in liver samples from pre-hibernating garden dormice (Galindo-Lalana et al., 2023). The *metabolic telomere attrition* hypothesis may explain part of telomere dynamics in hibernators, but more research is needed to test the different predictions formulated by this theory and the other possible mechanisms at work.

3.3. The cold-induced RNA-binding protein hypothesis

Another possible regulator of telomere length could be the Cold Induced RNA-binding Protein (CIRP). Under most situations, telomerase activity is expected to drop during phases of low temperatures due to the Arrhenius effect. However, it has been observed that telomerase expression increases over the course of hibernation in horseshoe bats (*Rhinolophus ferrumequinum*), possibly explaining the telomere lengthening observed toward the end of hibernation in this species (Power et al., 2023), as well as in garden dormice (Nowack et al., 2019). Further, Galindo-Lalana et al. (2023) recently reported preserved *in vitro* telomerase activity at 25 °C in liver tissues of hibernating dormice during both torpor and interbout euthermia compared to the active season, despite a drop of *in vitro* activity during the pre-hibernation season. The cause of the decrease of *in vitro* telomerase activity during pre-hibernation remains unknown although likely resulting from the cost of lipogenesis that occurs during that period (Galindo-Lalana et al., 2023). However, *in vitro* telomerase activity returning to its normal levels (*i.e.*, the active season levels) during hibernation, despite its downregulation during pre-hibernation, suggests a reactivation of the expression of TERT during hibernation (Galindo-Lalana et al., 2023). CIRP appears to be a good candidate for such a mechanism (Table 1). CIRP is expressed in a large variety of tissues, very well-conserved among species and is known to have a positive effect on telomerase activity, as shown in cultured cells exposed to a temperature of 32 °C (Zhong and Huang, 2017; Zhang et al., 2016).

Even though CIRP expression patterns are similar between summer and winter, CIRP mRNA has been found to be alternatively spliced in hearts of torpid Syrian hamsters (*Mesocricetus auratus*) to produce its active form, which would be a much more effective acclimation mechanism because of a rapid activation (Sano et al., 2015). CIRP could then be activated during torpor, when T_b is low, without necessarily having immediate observable consequences on telomerase activity and telomere length due to (1) the Arrhenius effect demonstrated by Galindo-Lalana et al. (2023), and (2) the oxidative stress associated with arousals that could impair the activity of telomerase (Smith, 2018, Fig. 3). It is only during interbout euthermia, or at the beginning of summer, that the CIRP effect on telomerase would be observed, when T_b increases again to 36–38 °C: telomerase upregulated by CIRP during hypothermia, and then working at an optimal temperature, could counterbalance the telomere erosion that occurs during hibernation (Figs. 3 and 4A). This increased telomerase activity could also allow for telomere lengthening observed in daily heterotherms and in garden dormice hibernating at milder temperature and/or when food is available (Fig. 4B–Turbill et al., 2012; Nowack et al., 2019; Giroud et al., 2023; Galindo-Lalana et al., 2023).

CIRP has also been shown to be upregulated in brown bears and is thought to affect overall cellular maintenance (Chazarin et al., 2019). During hibernation, telomere shortening despite CIRP activity could be explained by the high oxidative stress associated with arousals (Carey et al., 2000) preventing the activity of telomerase because of the formation of 8-OHdG (Smith, 2018). We still lack evidence whether CIRP is indeed regulating telomerase activity in hibernating species, or if it is simply regulating telomerase activity at hibernating T_b. The implications of such a mechanism in regulating telomerase activity and telomeres dynamics in hibernators and other seasonal species would constitute an interesting avenue to explore.

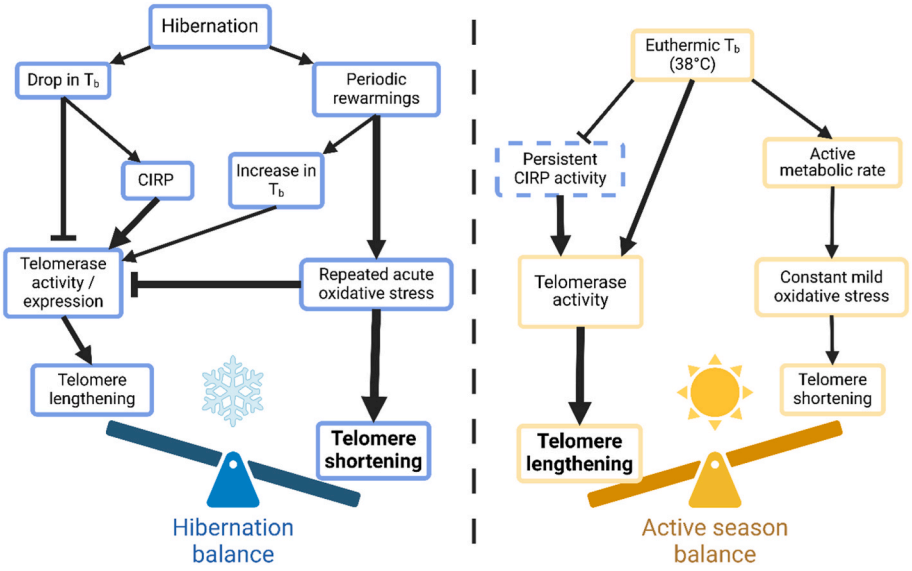

Fig. 3. Diagram of the effect of season on telomere length dynamics in the light of the Cold Induced RNA-binding Protein (CIRP) hypothesis. During hibernation, CIRP is activated and upregulates telomerase to compensate for the drop in T_b, but the oxidative stress associated with arousals usually overshadows the benefits of CIRP activation. During summer, oxidative stress is reduced and the telomerase that has been upregulated during hibernation can efficiently restore telomere length. CIRP could also possibly remain activated for some time after the end of hibernation and have a persistent effect on telomerase activity during early summer.

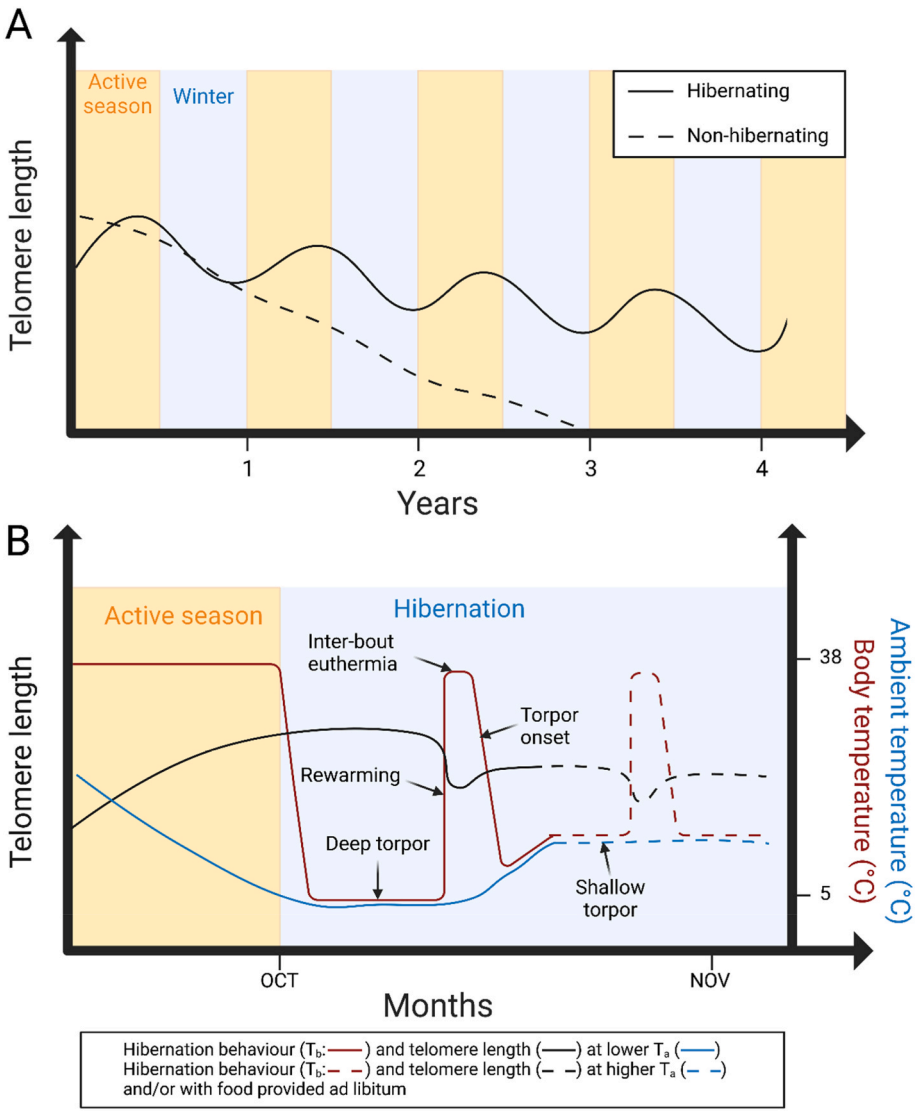

Fig. 4. Illustration of theoretical telomere length varitions. (A) Comparing hibernating (full line) *versus* non-hibernating (dashed line) rodents over years. Hibernating rodents would restore telomere length over summer to compensate for oxidative damages during winter, explaining their longer lifespan compared to non-hibernating rodents, who would experience a more linear, though probably still seasonal, telomere attrition. (B) Theoretical telomere length varitions during the different phases of hibernation. Telomere length would be stable during deep torpor, shorten during rewarming due to oxidative stress and be slightly elongated during inter-bout euthermia. When hibernating at higher temperatures and with food provided *ad libitum*, telomere would shorten less during rewarming and lengthen more during inter-bout euthermia, thus leading to less telomere shortening (or, possibly, telomere lengthening) over hibernation.

3.4. Further considerations and limitations

Part of explanation for the observed overcompensation in summer observed by Turbill et al. (2012) could also be due to methodological bias. In this study, samples were taken at the end of September, June, and August. The main limitation is then the winter period (September–June) being much longer than the summer season (June–August), variations during winter and summer may be underestimated and overestimated, respectively, even though telomere dynamics still appear seasonal (Fig. 5). This indicates that the sampling dates should be very carefully chosen and considered in the conclusions of future studies. Also, telomere length is likely to differ between tissues because of their different cell turnover rates (Wilbur et al., 2019). In addition, turnover rates for the same tissue may show a seasonal pattern, *i.e.*, differ between summer and winter, as shown for stomach epithelium in fat-storing hibernators (Vinogradova, 1988). It is therefore crucial to be extremely careful when designing a protocol to assess telomere length, in terms of the choice of sampled tissues and sampling dates. This also highlights the need for new methods for telomere length measurement that would allow for a more frequent sampling while limiting the stress on animals. Until then, caution must be taken when interpreting results using telomere length as a biomarker of ageing in hibernators.

4. Conclusion & perspectives

The seasonal telomere dynamics observed in hibernators aligns with (i) the existence of mechanisms to prevent or dampen somatic damage during hibernation, even though these alterations affect cellular and physiological ageing, and (ii) the rate of ageing depending more on the life-history strategy of the species than on the oxidative stress faced by the latter (Fig. 4A). This further highlights the importance of a unified framework for evolutionary genetic and physiological theories of ageing, as proposed by Le Maître et al. (2024), to better understand the process of ageing, its causes and consequences. New hypotheses such as CIRP regulation of telomerase activity or the recent *metabolic telomere attrition* hypothesis could provide a better understanding for the

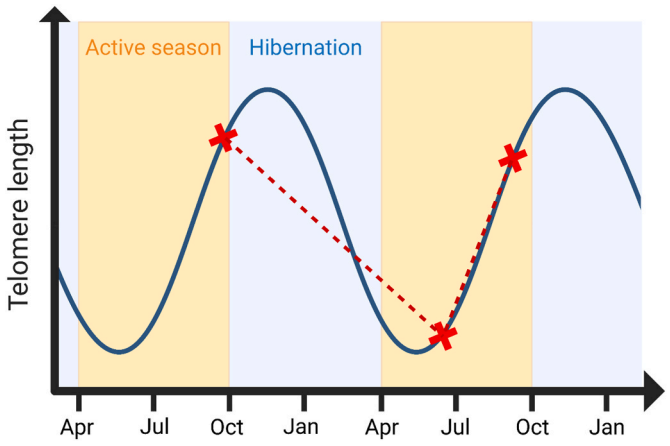

Fig. 5. Theoretical telomere length dynamics and illustration of sampling point bias. Red crosses are hypothetical sampling points, red dashed lines give an idea of telomere length variation rate calculated from these sampling points. In this situation, sampling points for the summer period leads to an overestimation of telomere lengthening rate over the summer, whereas sampling points for the winter period leads to an underestimation of telomere shortening rate over the winter. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

variations in telomere length occurring in hibernating species. However, more work on hibernators other than rodents is necessary to better understand the actual costs and benefits of hibernation across different taxa. For instance, comparing species facing different challenges during hibernation might allow the estimation of the relative costs of these challenges, but also to understand the compensatory mechanisms that evolved. Additionally, these results indicate that telomere length dynamics can proceed at a rapid rate and depend on many environmental factors. Hence, caution must be taken when using telomere length as a biomarker of ageing in hibernators. Understanding the underlying mechanisms of telomere length dynamics including telomerase regulation would greatly benefit the fields of ageing biology, ecology, and environmental physiology, thus leading to ground-breaking discoveries for both medical applications (*e.g.*, in cancer), and species conservation in the context of climate change.

Funding sources

The authors want to thank the Austrian Science Fund (FWF, Grant No. P31577–B25 to SG) and the Austrian-French Agency for International Cooperation in Education and Research (OeAD – Scientific and Technological Cooperation, Grant No. FR September 2020 to SG and CH) for supporting this work.

CRediT authorship contribution statement

Lilian Redon: Writing – review & editing, Writing – original draft, Conceptualization. **Théo Constant:** Writing – review & editing. **Steve Smith:** Writing – review & editing. **Caroline Habold:** Writing – review & editing, Funding acquisition, Conceptualization. **Sylvain Giroud:** Writing – review & editing, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare no competing interest.

Acknowledgements

The authors want to thank the Austrian Science Fund (FWF, Grant No. P31577–B25 to SG) and the Austrian-French Agency for International Cooperation in Education and Research (OeAD – Scientific and Technological Cooperation, Grant No. FR September 2020 to SG and CH) for supporting this work. Figs. 2–5 were made using BioRender.com.

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