Sleeping through Aging: Telomere Dynamics and Longevity in *Glis glis*

Honors Thesis

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Abstract

Telomeres are the important repetitive DNA sequences at the end of chromosomes that help them maintain their structure and stability. As cells divide, telomeres may become shortened as they prevent damage to the chromosome, and can help in determining cellular lifespans. While telomere shortening has been well documented within humans, there are other species with telomere dynamics which are less explored. Namely, the European Edible Dormouse (*Glis glis*) demonstrates an atypical lengthening of telomeres in old age, contradictory to the trend seen in humans and many other species. The mechanisms and causes behind this have remained poorly understood and underexplored. With a focus on *Glis glis*, this literature review examines both the lifestyles of edible dormice and their observed telomere dynamics, provided within the context of broader cross-species telomere regulation. Across literature, one behavior which seems to be key to this unique dynamic in dormice is their torpor. Food availability, time spent in euthermy, and telomerase activity are all influenced by torpor, and in turn, affect telomere regeneration. Alternative methods of telomere lengthening and maintenance are also explored, highlighting a complex metabolic relationship between the multiple factors resulting in the observed telomere lengthening seen in dormice. Developing our understanding of this unique characteristic provides an opportunity to uncover new mechanisms behind telomere maintenance within a species that challenges traditional models of aging.

Introduction

The edible dormouse (*Glis glis)* is a small rodent native to regions of Eastern Europe and Western Asia. They live largely arboreal lifestyles in the wild where they gather a variety of nuts

and seeds, especially Beech Mast seeds, to eat. However, they typically spend over half the year (~6-11 months) in a state of hibernation, with varying hibernation durations during reproductive and non-reproductive years[1]. These dormice also possess one of the highest lifespan:body size ratios among rodents (aside from the naked mole rat)[2], living an average of 8.7 years according to the AnAge database[3] , with some having been recorded living up to 13 years [4].

One potential explanation behind this unusually long lifespan has been explored in the form of telomere elongation. Telomeres consist of the end caps of chromosomes; often a series of multiple repeats of the 5'-TTAGGG-3' motif within vertebrates [33]. Telomeres, along with their associated proteins, such as those within the shelterin complex (TRF1, TRF2, RAP1, TIN2, TPP1, and POT1) (Figure 4)[33] protect coding regions of DNA from degradation. In somatic cells, degradation typically occurs during cell division in mitosis due to the end replication problem. DNA polymerase is unable to fully replicate the ends of DNA strands, in this case telomeres, due to the inability of a primer to attach upstream to the final segment of the lagging strand of DNA[5]. Telomere shortening is often believed to be a biological indicator for aging and lifespan, and may speak to genome stability, cancer risk, and life expectancy [6]. In humans and a majority of other observed mammals, telomeres have been found to shorten with age, and often more rapidly in species with high metabolic rates and shorter lifespans [6]. However, in the edible dormouse it has been observed that telomeres are often either maintained or lengthened with age (typically beginning lengthening after ~5.3 years of age) (Figure 1) [7]. This telomere lengthening has also been associated with an increased probability of reproduction with old age (despite sexual maturity being reached around ~1 year of age)(Figure 2) [7].

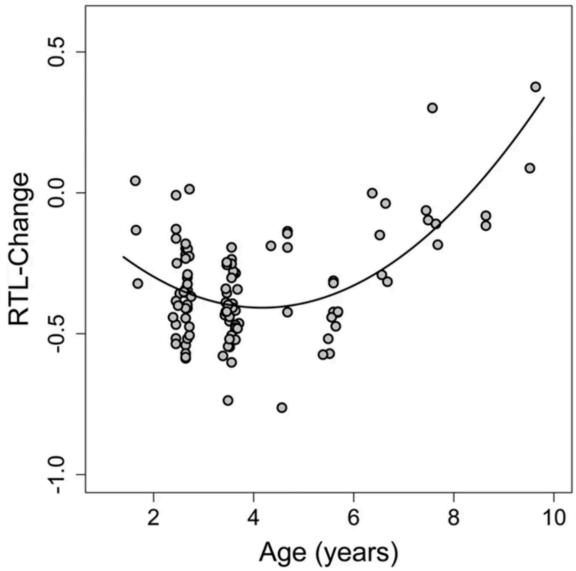

Figure 1. RTL over the lifespan of *Glis glis* in years. Image sourced from *Scientific Reports* (2016).[7]

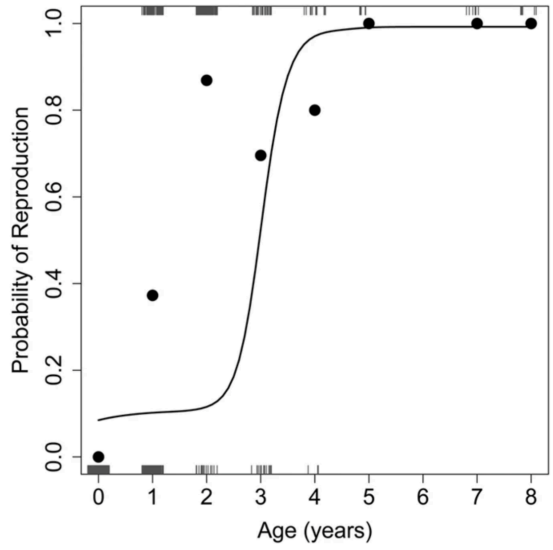

Figure 2. Reproductive probability increases substantially with age in *Glis glis.* Image sourced from *Scientific Reports* (2016).[7]

Torpor and Hibernation

Several hypotheses have been proposed as a potential reason behind this telomere lengthening and conservation. One of which is that long periods of hibernation could help to conserve telomere length, as the low body temperature of the dormice reached during periods of hibernation can halt the cell cycle in the G2 stage [8], thus preventing cellular division and telomere shortening [9]. Such an occurrence has been suspected to be responsible for telomere maintenance (and mild elongation) via the daily torpor of Djungarian hamsters (*Phodopus sungorus*) [10]. However, it was found that over the course of a hibernation season (across a sample size of 15 edible dormice), longer hibernation periods were associated with more advanced telomere shortening [9]. This is likely due to the confounding variable of arousals during hibernation. Longer periods of hibernation often contained more arousals, especially in non-reproductive years when the hibernations carried over into the warm seasons [1], as they did during this study [9]. Higher arousals then showed significant correlation with elevated levels of relative telomere length (RTL) shortening [9].

Rewarming and Telomere Loss

Within ground squirrels (*Citellus erythrogenys*), arousals (defined as 3+ days spent euthermic) and rewarming from states of deep torpor (such as those observed in *Glis glis* whose body temperatures remained around ~5℃ to 15℃ during deep torpor)[9] often correspond with a rapid increase in the rate of mitosis [11]. This increase in mitotic activity is accompanied by increased metabolic processes including the heating of brown adipose tissue and increased ventilation rates [12]. These sudden increases in metabolic activity and oxygen uptake cause a spike in Electron

Transport Chain (ETC) activity, and lead to the creation of more Reactive Oxygen Species (ROS) in which electrons prematurely interact with the sudden excess of oxygen available. This increase in oxidative stress can lead to damage and shortening of telomeres [13]. Telomeres are especially vulnerable to oxidative damage due to the high ratio of Guanine in their 5'-TTAGGG-3' motif . Guanine is sensitive to oxidation, often oxidizing to 8-oxoguanine and potentially Hydantoin Lesions, which can disrupt replication forks [31] (Figure 3) [15]. This can lead to single strand breakage within telomeres, which can cause downstream DNA damage and cellular apoptosis. With increased cellular apoptosis, the remaining cells may be driven to overcompensate by replicating more, further shortening telomeres [14]. It has also been hypothesized that ROS may interfere with the binding sites of the shelterin complex, which help to regulate telomeres [14]. It is important to note that most studies showing this have been carried out in vitro on a tissue-level.

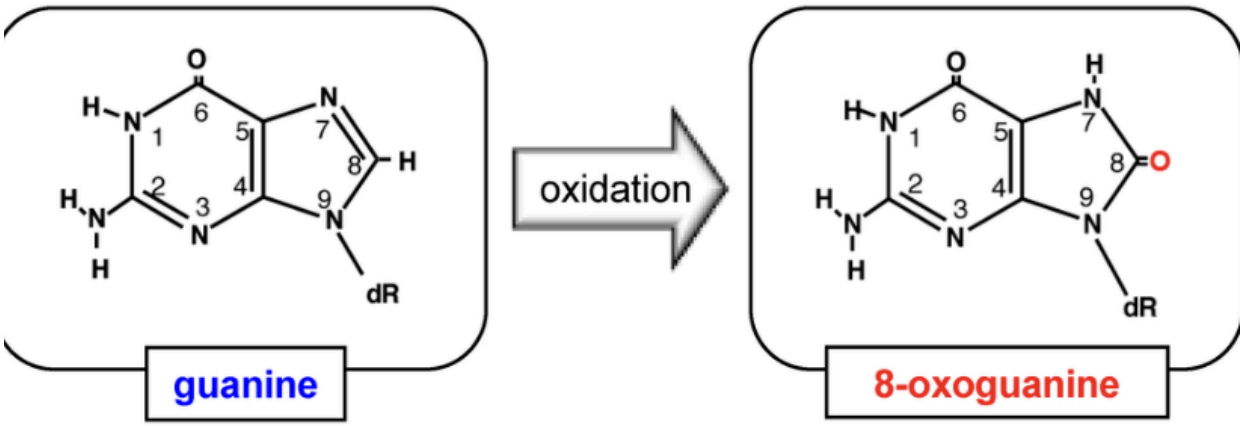

Figure 3. Oxidation of Guanine into 8-oxoguanine. Image sourced from *International Journal of Molecular Sciences* (2014).[15]

Hibernation Factors

Multiple factors appear to affect how torpor and hibernation interact with telomere length, including: general duration of torpor, body temperature during torpor, number of arousals from torpor, and time spent in torpor prior to arousal. Based on one study of *Glis glis*, frequent arousals were directly correlated with a decrease in RTL [9]. This has remained the general consensus of scientific literature, with frequency of arousals during torpor being the most reliable predictor of the extent of RTL shortening following a hibernation season. However Djungarian hamsters, both in shallow (>25 ℃) and deep (<25 ℃) daily torpor, were found to enhance somatic maintenance and undergo RTL conservation or elongation over a 180 day period [10]. Daily torpor refers to the process of torpor within a 24 hour cycle, typically lasting a few hours before arousal, indicating that daily torpor is a process accompanied by frequent (daily) arousals [10]. One potential key difference between the torpor of *Glis glis* and the Djungarian hamster, which has not been ruled out as a contributing factor to the RTL increase in hamsters despite the frequent arousals, is the difference in body temperature during torpor. Within *Glis glis,* torpor temperatures varied between 5℃ to 15℃ [9], while in Djungarian hamsters body temperatures could be upwards of 25 ℃ [10]. However, another study on garden dormice (*Eliomys quercinus*) found that the buccal mucosal cells of the dormice experienced a general increase in telomere length throughout prolonged hibernation (with RTL being measured every 5-8 weeks of hibernation after a period of rewarming) in groups hibernating at both 3 ℃ and 14 ℃ (though warmer temperatures had more extensive RTL lengthening) [16]. It is important to note that dormice who experienced telomere elongation were fed *ad libitum*. These results further highlight the unexpected nature of those in the Djungarian hamster, since they support that RTL elongation can occur even at extremely low body temperatures. This runs in direct contrast with

the previous observation of shortening telomeres over a hibernation season within *Glis glis* [7]. With this, it seems possible that neither frequency of arousals nor depth of/body temperature during torpor alone can be relied upon to explain the RTL shortening during hibernation within *Glis glis*. Of course the difference among species could be a potential explanation for this, however given the conserved nature of results across Djungarian Hamsters to *Eliomys quercinus,* there is strong potential of a similarly conserved mechanism within *Glis glis*. If temperature and depth of torpor has little effect on RTL, and frequency of arousals alone does not provide conclusive evidence as to how much telomeres shorten given daily torpor, then a more complex dynamic involving the duration of time spent in torpor prior to arousal, as well as frequency of arousals may have potential to describe the telomere dynamics at play in all 3 of these studies.

Telomerase Activity

Telomerase is an enzyme which aids in the maintenance and elongation of telomeres. Telomerase contains several subunits, including TERT which synthesizes the new strands of DNA, TERC which acts as a template RNA for the new DNA to be built from, as well as numerous accessory proteins that help to stabilize TERT, such as NOP10 and GAR1 [33] (Figure 4). Within adult humans, telomerase is suppressed in most somatic cells, aside from activated lymphocytes and some stem cell lines [17]. It is also active in human male germ cells and during embryonic development, though tightly regulated [17]. The most frequent place which active telomerase is seen in somatic cells is during oncogenesis and tumor development [20]. Telomerase is also believed to be a prime candidate for the driving factor behind the elongation of telomeres in edible dormice.

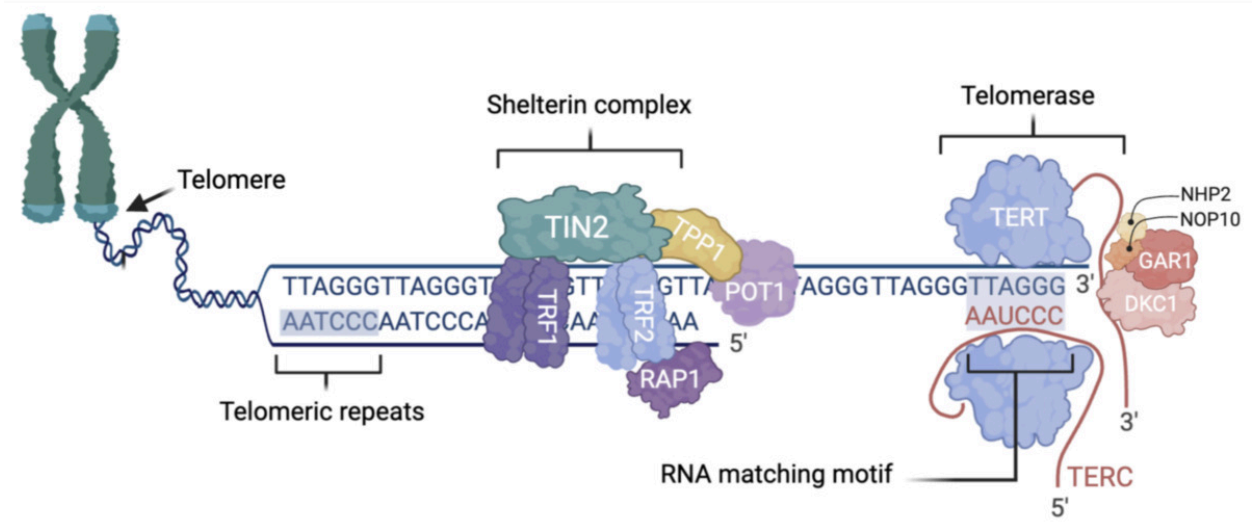

Figure 4. Telomerase subunits and Shelterin Complex domains. Image sourced from *Archives of Medical Science* (2026). [32]

Previous studies in telomere length had not focused on the measurement of telomerase activity levels, due to the constraints of acquiring and measuring it in a timely manner with wild populations. The situation is further complicated by a limited understanding of the timing and level of telomerase activity required to produce a detectable increase in RTL. From previous studies, two main hypotheses arose regarding the timing of telomere extension: it occurs either right before the start of hibernation or immediately after waking from hibernation and entering a prolonged state of euthermia [20]. The former had been believed to be unlikely due to the process of lipogenesis also occurring before the start of hibernation [20]. In 2023, a group of researchers measured the telomerase activity during different seasons of a garden dormouse's (*Eliomys quercinus*) year. Over 200 dormice had their telomerase activity measured via TRAP assay during 4 behavioral seasons: active, prehibernation, hibernation, and IBE (short arousal periods

during hibernation) [20]. Each assay was carried out with one of two different extension phase temperatures: 25 ℃ and 5 ℃ [20].

Several key findings arose from this study. Firstly, it was found that telomerase activity was significantly higher in assays conducted as 25 ℃ than those that were conducted at 5 ℃ (Figure 5) [20]. Secondly, telomerase activity was present across all four seasons, including hibernation (Figure 6) [20]. Telomerase activity was significantly lower during the prehibernation season when compared to all other seasons, with IBE periods having the highest telomerase activity. However, the resulting RTL was only significantly smaller in the prehibernation season when compared to the active season (Figure 6) [20]. This indicates that telomerase activity peaks during periods of euthermia and arousal, even when these periods have not been as prolonged as during the active season. However, RTL is longest during the active season, potentially due to the effect of higher telomerase activity over a longer period of time than compared to that of IBE. This would suggest that telomere lengthening does not occur right before hibernation, but rather immediately after becoming euthermic.

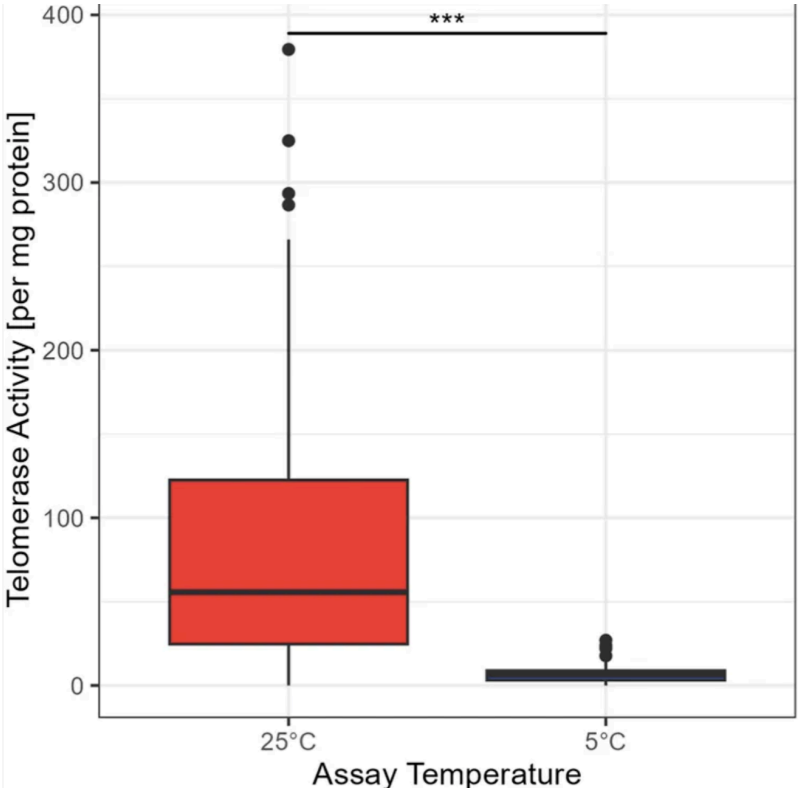

Figure 5. Telomerase activity at different temperatures of TRAP assay. Image sourced from *Frontiers in Physiology, Galindo-lalana et. al* (2023). [20]

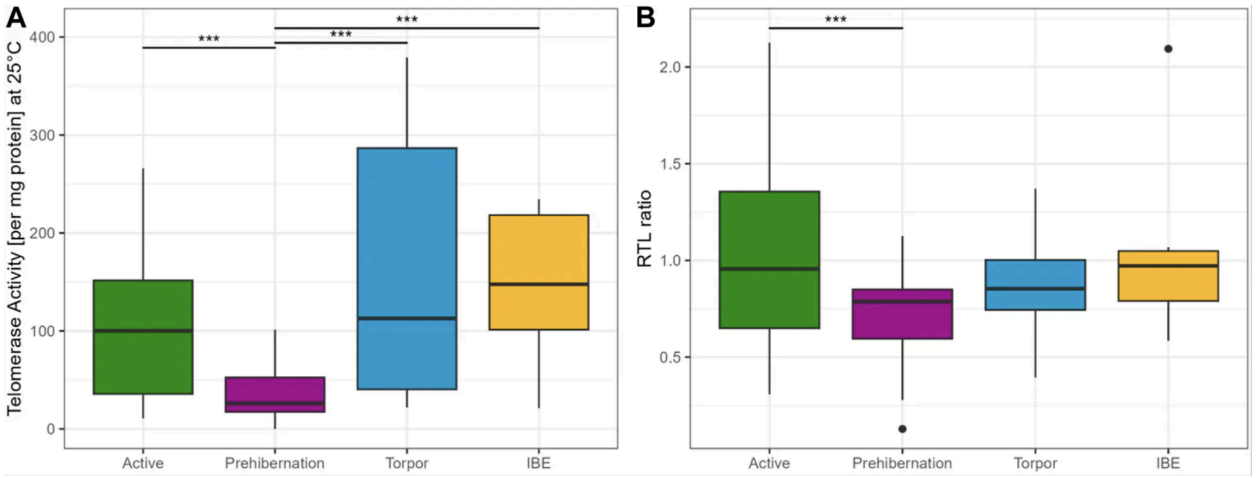

Figure 6. Telomerase activity and resulting RTL during different seasons of *Eliomys quercinus*. Image sourced from *Frontiers in Physiology, Galindo-lalana et. al* (2023). [20]

Aside from this, the higher expressed levels of telomerase activity during deep torpor and periods of low body temperature poses an interesting dilemma. Telomerase activity was still present when the assay was carried out at 5 ℃, even if to a smaller degree. While animals during this study did not remain in torpor at 5 ℃ [20], *Glis glis* within previous field studies have been found to stay at prolonged torpor temperatures as low as 5 ℃ [9]. Many costly and nonessential metabolic functions are slowed or stopped during periods of torpor to conserve energy. The decreased telomerase activity at 5 ℃ compared to that of 25 ℃ supports that telomerase activity decreases during periods of low body temperature, such as torpor (Figure 5) [20]. However, telomerase activity was not significantly minimized during the torpor season in the group of dormice whose telomerase was given an extension incubation temperature of 25 ℃ when compared to that of the active season (Figure 6) [20]. One potential explanation for this is that the measured telomerase activity at 5 ℃ was a result of activity from IBE being carried over during torpor [20]. However, given the half-life of telomerase at around ~24 hours [20], this is unlikely. While TERC can last longer - up to 5 days with stabilizing elements [21] - TERT degrades much faster and new expression of it would be necessary to see continued telomerase activity several days into deep torpor. The presence of telomerase during a 5 ℃ TRAP assay, no matter how small, also suggests that telomerase activity and even telomere elongation has the potential to be present even at low temperatures. These findings support those of previous studies, which have found telomere maintenance and even elongation during periods of torpor, despite low body temperature [10,16,22].

Other key findings from the study include males having higher telomerase activity than females, but not significantly so. It was also found that juveniles born earlier in the active season

had higher “active season RTL” compared to “prehibernation season RTL” than those born late in active season [20]. This also supports that more time spent in active season correlates with an increased telomere length.

One important note to make about this study is that juvenile garden dormice (*Eliomys quercinus*) (<10 months) were used in the torpor and IBE seasonal telomerase activity readings, whereas adult garden dormice (>10 months) were used to obtain active and prehibernation readings [20]. This could have skewed data collection, especially given the previously observed decrease of telomere length in edible dormice (*Glis glis*) under the age of 5.3 years, and elongation of telomeres in individuals older than 5.3 years old [7].

Alternative Lengthening of Telomeres

Another possibility to explain the lengthening of telomeres in dormice has been Alternative Lengthening of Telomeres (ALT). ALT has been observed in ~10% of cancers, and acts as a means of telomere maintenance and elongation free of telomerase [33]. There are multiple types of ALT, each involving the use of template DNA from elsewhere in the nucleus or from other telomeres to extend and repair damaged telomeres [33]. Since there is no telomerase used in ALT, the standard telomere template strand of RNA - TERC - must be replaced with something else.

Homologous recombination telomere extension describes telomere repair and extension via recombination at the chromosome’s ends between sister chromatids [23]. Break-induced telomere synthesis is more common within somatic cells and can occur after a double-strand break across telomeres, after which the telomere is extended upon by DNA polymerase using

another strand of template DNA from elsewhere in the nucleus [24]. Rolling circle amplification involves taking template DNA from the extrachromosomal t-loops and c-loops formed by telomeres [25]. Overhangs from telomeres may interact with these loops causing DNA polymerase to become "stuck" to the loop, continually using it as a DNA template to replicate the 5'-TTAGGG-3' motif [25]. Many of these processes may be mediated via APBs - ALT-associated promyelocytic leukemia (PML) bodies - which bind to telomeres and assist in their clustering, making APBs a hallmark of ALT [26].

Evidence for ALT activity within non-cancerous somatic cells has been extremely limited. ALT is primarily found within cancerous cell lines and germ cells . However, a 2013 study noted the ability of somatic mouse cells to potentially utilize the ALT pathway for telomere maintenance [27]. Within the study, researchers initially tagged the telomere of chromosome 15 on a mouse embryonic stem cell (ESC) using a Tel tag with an attached fluorescent marker. This ESC was then injected into early-stage developing mouse embryos to test if the tag could be found on the telomeres of other chromosomes later on in the mouse's development [27]. While they found no evidence of telomere copying or ALT activity involving the tagged chromosome within germ lines, they did find evidence of such activity within somatic cells [27]. Within splenocytes, embryonic fibroblasts, and dermal keratinocytes, the telomeres of other chromosomes were found to contain the same fluorescent Tel tag as the original one within chromosome 15 [27]. The highest frequency of this was found within splenocytes, in which ~49% of tested splenocytes displayed at least one other chromosome (aside from 15) whose telomere contained the Tel tag [27]. These findings suggest that telomeres will use other telomeres within the same nucleus as templates for replication of their own telomere material. It is important to note that this study tracked one segment of one telomere on a single chromosome, and as such is likely

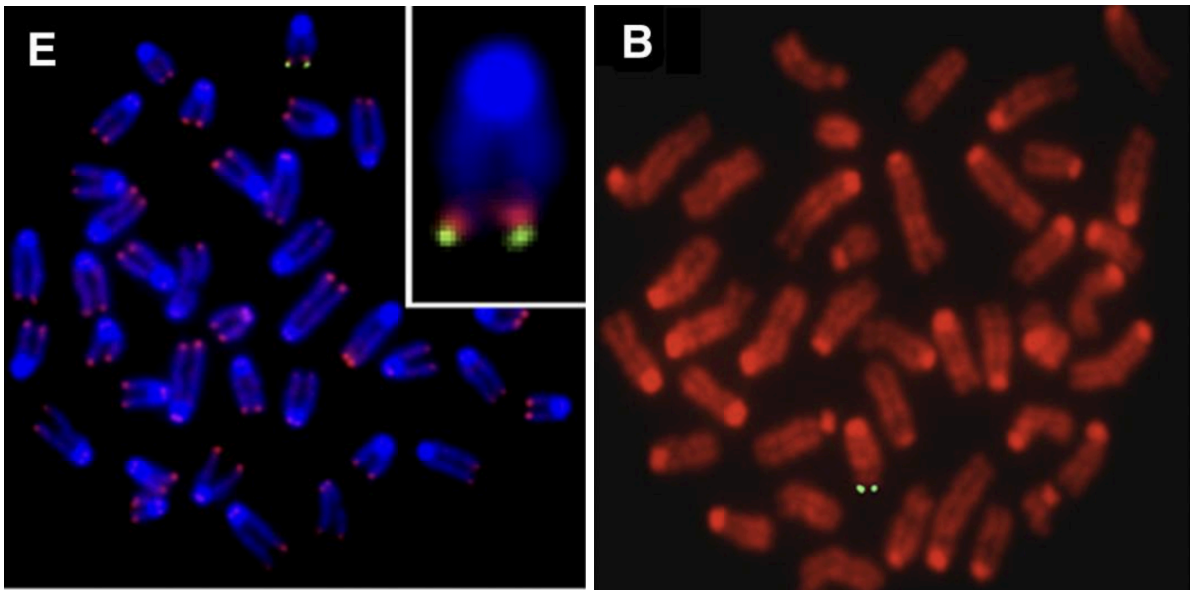

Figure 7. Initial tagging of Tel, shown in green, onto chromosome 15. Images by *Cheng, et. al.* (2024).[28]

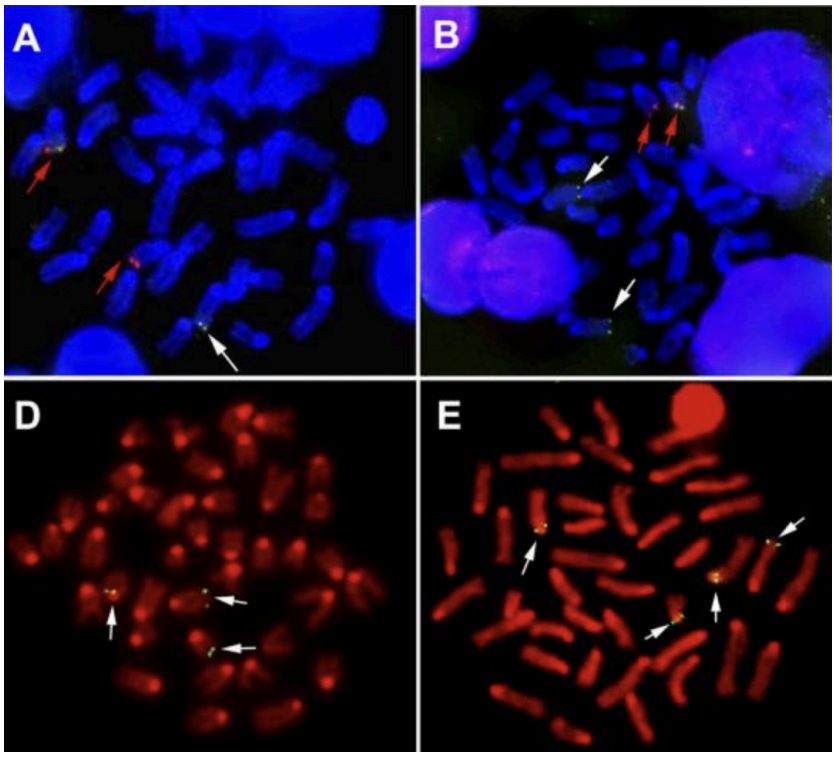

Figure 8. Tel-tagged telomeres on other chromosomes within mouse Splenocytes. Red arrows on A and B indicate chromosome 15. Images by *Research Square*, *Cheng, et. al.* (2024).[28]

representative of a much smaller amount than the total number of cross-telomere templating events occurring within the nucleus. This study is especially applicable in the study of dormice due to the ALT activity being observed in mouse (*Mus musculus*) somatic cells which still expressed telomerase, as certain *Glis glis* somatic cells do [20]. In most cases ALT has been observed in the absence of telomerase, making its observation alongside telomerase within mice [28] crucial for understanding the potential of ATL within other non-cancerous and telomerase-positive environments.

Potential evidence of ALT-like mechanisms being utilized to maintain telomeres exists within the genus of *Myotis* bats [29]. *Myotis myotis* possess some of the highest lifespan:body size ratios of any mammals, with the oldest being found at over 41 years old [29]. Similar to dormice, telomere length was one aspect investigated in *Myotis myotis* as a potential explanation to this incredibly long lifespan. While other genuses of bats had a negative correlation between age and RTL, *Myotis* bats were found to have had little to no significant correlation between their age and RTL [29], and typically experienced little telomere shortening with age. Additionally *Myotis myotis,* similar to humans, was found to express no TERT within blood and fibroblast cells, indicating their maintenance of telomeres is performed in another way aside from telomerase activity [29]. When a series of key telomere-regulation genes were compared across mammalian species, it was found that *Myotis myotis* expressed significantly higher levels of both ATM (Ataxia-Telangiectasia Mutated) and SETX [28]. ATM is an important gene that encodes for ATM Serine/Threonine kinase which aids in DNA damage detection, specifically in recognizing double-strand breaks [30]. SETX encodes for the helicase protein Senataxin, which aids in DNA damage repair and replication fork formation [30, 34]. While this does not prove that *Myotis myotis*

is undergoing ALT activity as a form of DNA repair, it does indicate that the bat utilizes another mechanism to maintain telomere length over a long lifespan, and that this mechanism could involve increased expression of key DNA damage repair genes. A key difference to note between *Myotis myotis* and *Glis glis*, aside from being somewhat phylogenetically distant, is their approach to telomere maintenance. Telomere preservation and maintenance is favored by *Myotis myotis*, whereas edible dormice experience multiple occurrences of drastic telomere shortening and quick rebuilding following periods of torpor throughout their lifespans. *Glis glis* mechanisms focus less on telomere preservation and more on telomere recovery.

An important caveat is that very little research has been done regarding ALT on *Glis glis* directly. Research regarding the use of ALT in various species with different levels of relation to *Glis glis* have supported its involvement in somatic maintenance. However, it cannot be confirmed that any of these results fully translate over to edible dormice without studies on *Glis glis* themselves confirming so.

Conclusion/Discussion

In conclusion, our understanding of the telomere dynamics and its relationship to the lifespan of *Glis glis* is limited. Glis glis is a unique species as its telomere dynamics appear to focus on periods of rapid depletion followed by rapid rebuilding, as opposed to a steady, long-term preservation. It is not clear yet the long-term consequences of this specific mode of telomere maintenance.

Long periods of hibernation and torpor appear to play a key role as life history traits, with the changing of RTL and telomerase activity seeming to revolve around them. Most

recently (2023), the observation of telomerase activity, as opposed to simply just RTL, has marked a crucial step forward in our understanding of the dormouse lifespan. Surprisingly, evidence gathered shows that telomerase activity and RTL experience a steep drop during the pre-hibernation series, followed by a gradual increase during torpor, IBE, and the following active season. Continued research around telomerase activity could include further testing to confirm its ongoing expression and activation during points of deep torpor and low body temperatures, which may also be important to understanding the telomere dynamics of multiple other species. Ideally, this would include specific research into TERT and TERC levels within the broader telomerase readings. Additionally, more research into the relationship of time spent in deep torpor prior to arousal would be beneficial to add nuance to the current understanding that more frequent arousals equal shorter telomere length.

While *Glis glis* has numerous related species with various similarities (*Phodopus sungorus*, *Heterocephalus glaber, Myotis myotis*), none seem to fully express both the long lifespan and hibernation patterns observed within *Glis glis.* This has made research around the longevity of this specific species limited, with heavy supplementary information based around model organisms required. As such, much of what can be gathered is speculative. Potential ALT mechanisms are especially speculative, with little to no research with them in edible dormice specifically. Even research of ALT in non-cancerous mammalian cells is limited. However, some key examples and past studies (specifically within *Mus musculus* and *Myotis myotis*) have given evidence that ALT-like mechanisms may be at work in the somatic maintenance of telomeres. Further research into ALT and its potential co-opted machinery within *Glis glis* and other unusually long-lived species would be another important step forward given our current knowledge base.

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