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Telomere Shortening in Neurological Disorders: An Abundance of Unanswered Questions

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Abstract

Telomeres, ribonucleoprotein complexes that cap eukaryotic chromosomes, typically shorten in leukocytes with aging. Aging is a primary risk factor for neurodegenerative disease (ND), and a common assumption has arisen that leukocyte telomere length (LTL) can serve as a predictor of neurological disease. However, the evidence for shorter LTL in Alzheimer's and Parkinson's patients is inconsistent. The diverse causes of telomere shortening may explain variability in LTL between studies and individuals. Additional research is needed to determine whether neuronal and glial telomeres shorten during aging and in neurodegenerative disorders, if and how LTL is related to brain cell telomere shortening, and whether telomere shortening plays a causal role in or exacerbates neurological disorders.

Telomere length and immunological aging

Telomeres are an evolutionarily conserved DNA sequence at the end of each chromosome that is identical in the entire vertebrate phylum. They consist of six base pair repeats (TTAGGG) that are folded into a T loop structure by a protein complex called shelterin [1]. Telomeres have at least four fundamental roles: sheltering valuable genetic information from erosion during DNA replication; distinguishing and protecting chromosomal ends from DNA damage; serving as a docking site for DNA repair proteins; and providing information on the proliferation history of a given cell [1].

In cultured cells, telomeres typically lose 50–200 base pairs (bps) during each round of DNA replication [2], and leukocyte telomeres (LT) shorten at a rate of ~25 bp/year in adult humans [3]. It has been suggested that LT length (LTL) may serve as a "mitotic clock" indicating cellular age. In contrast, telomere length in hematopoietic stem cells (HSC) and lymphocytes is determined by the balance of elongation by telomerase, an enzyme that

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elongates telomeres and shortening in response to stress, DNA damage, proliferation and trimming (Figure 1) [1]. Telomere trimming is an active shortening of telomeres recently observed in sperm cells, activated lymphocytes and cancer cells; the underlying molecular mechanism is unknown [4]. Telomerase activity and telomere trimming are tightly regulated in lymphocytes during immune responses; for example, activation of T-cells with anti-CD3 antibody induces a 70-fold increase in T-cell telomerase activity [5].

LTL is reduced during normal aging in laboratory animals and humans subjects [3, 6], and considerable inter-individual variation is observed in LT shortening during aging. One possibility for this variation is that LTL reflects the 'biological age' of the cell and the organism, which may differ from chronological age. Genetic factors, lifestyle and disease may alter the biological age of an organism and thus be reflected in LTL. Recent data indicate that regular exercise slows LT erosion [7, 8], while obesity is associated with reductions in LTL [9, 10]. An association between short LTL and chronic disease states including diabetes, cardiovascular disease and arthritis has been reported [10, 11]. Normal aging and chronic disease states involve increased oxidative stress and inflammation, suggesting that reduced LTL may be a consequence of these stressors. While individual reports suggest an association between short telomere length and neurodegenerative disorders (NDs), an overview of the literature reveals a number of studies with findings to the contrary.

In the last decade the role of leukocyte and neural telomere erosion in neurological disorders has become a topic of considerable interest, but fundamental questions remain unresolved. Does reduced LTL occur in NDs such as Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD)? Do changes in telomere length of CNS cell populations occur in NDs and, if so, is such an association consistent enough that LTL can serve as an indicator of CNS telomere length? Are factors associated with NDs such as oxidative stress and inflammation a cause of reduced LTL? (See Outstanding Questions Box). Until such questions are answered, measurement of LTL or other peripheral cell telomere length cannot provide a useful diagnostic for or insight into the contribution of telomere shortening to ND pathology.

Is LTL altered in neurological disorders?

Data from clinical studies suggest that shorter LTL can occur in many diseases including autoimmune and metabolic diseases, cancer, stroke and NDs [11, 12]. Review of the literature investigating LTL in NDs reveals no consistent relationship between LTL in AD and PD, with an almost equal number of studies reporting no change in LTL associated with these diseases as those reporting LTL shortening (summarized in Table 1). A recent study reported longer LTL in PD patients [13]. Compared to AD and PD, a majority of studies examining LTL in psychological stress, cognitive impairment and dementia find shorter LTL is associated with these conditions (Table 1). Most of these studies are cross-sectional, thus inter-individual variation may reduce their statistical power. One longitudinal study did not detect changes in LTL during the progression from mild cognitive impairment (MCI) to AD, but progressive LTL shortening was reported with dementia. Variability in LTL is observed between individuals, with meta-analysis of several large cohorts demonstrating

that LTL is 50–70% heritable [14]. The high variability observed between studies cannot be accounted for by the methods of LTL measurement used (Southern Blot, PCR, FISH) or the ethnicity of the population being examined. Interestingly, similar LTL is found between long-term spouses, suggesting possible roles for environmental factors such as diet, chronic stress, exercise and lifestyle [14].

Environmental adverse stressors and stress-related signals such as cytokines and hormones can alter LTL (Figure 1) [15]. Variability in stress and inflammation among individuals and cohorts of patients with NDs may induce variability in LTL between studies. The interaction between environmental factors and genotype can also play a role, as at least one study found that patients that are homozygous for ApoE4 have significantly shorter LTL than those with only one ApoE4 copy or other ApoE alleles [16]. The ApoE4 protein is a less efficient antioxidant compared to ApoE2 or ApoE3, and one possible mechanism for LTL shortening in ApoE4 homozygous individuals is a higher level of oxidative stress in leukocytes [17]. The interaction between genetics and environment may influence LTL shortening independent of ND status (Figure 1). Before a meaningful association between NDs and LTL can be made, the potential causes of telomere shortening (discussed below) must be examined simultaneously with LTL to account for variability.

Causes of telomere damage and shortening

Oxidative stress

Oxidative stress contributes to the telomere shortening that occurs in leukocytes and other mitotic cells during aging and in chronic disease states. The 5′-TTAGGG-3′ repeats in the telomere sequence are prone to oxidative damage (8-oxodG) and ROS-induced DNA breaks [18]. Telomere shortening in lymphocytes is induced by chronic exposure to oxidative stress [19]. Markers of oxidative stress are also elevated in association with shorter LTL in patients with rheumatoid arthritis [20] and type 2 diabetes [21]. Telomere shortening due to oxidative stress is accelerated due to the fact that DNA damage in telomeres is highly stable and not readily repaired [22]. In addition to oxidative DNA damage, impaired calcium homeostasis in AD patient lymphocytes can also induce telomere erosion [23, 24]. Oxidative stress can cause release of calcium from the mitochondria which then triggers a viscous cycle of telomere shortening, mitochondrial dysfunction and elevated ROS that leads to DNA damage which exacerbates telomere shortening.

Neurons and glial cells experience increased oxidative stress during normal aging and in NDs [25, 26]. In addition to the ROS generated by their own dysfunctional mitochondria, neurons are subjected to large amounts of H_2O_2 and NO produced by activated microglia and macrophages, which increases the oxidative load further and could lead to telomere shortening [27]. It is unknown if oxidative stress causes telomere erosion in CNS cell populations, nor is it known if ROS-induced telomere shortening in neurons and glia are a causal or contributing factor in neurological diseases.

Inflammation and immune exhaustion

Chronic systemic inflammation, characterized by elevated levels of tumor necrosis factor (TNFα) and interleukin-6 (IL-6), occurs in NDs. In addition, innate and adaptive immune

cells infiltrate into the CNS during injury and disease [27]. Immune cell activation results in an increased demand for new cells, which arise from hematopoietic stem cells (HSC). This demand for lymphocytes results in their clonal proliferation and this increased proliferation of HSCs and lymphocytes increases telomerase activity, but not to an extent that counteracts LT erosion [5]. Thus, the increase in cell proliferation induced by chronic inflammation may be one cause of LT erosion in NDs.

Chronic stress

Another prominent feature of normal aging, NDs and psychiatric disorders is the excessive activation of the hypothalamic-pituitary-adrenal (HPA) axis and the consequent chronic elevation of the adrenal glucocorticoid cortisol [28]. Chronic exaggerated activation of the HPA contributes to the onset and progression of NDs, and also to impaired immune function. LTL is correlated with elevated levels of stress response hormones such as norepinephrine, epinephrine, cortisol and IGF-1 [15, 29, 30]. Excessive HPA activation results in reduced blood levels of growth hormone (GH), which has an effect on telomere maintenance [31]. The stress response also results in a reduction in dehydroepiandrosterone (DHEA), although a role for DHEA in telomere maintenance remains to be determined.

Bulk lymphocyte proliferation and markers of oxidative damage are elevated during a typical stress response [29], which may also contribute to stress-induced LT erosion. However, telomerase activity in cultured cells can be enhanced by stress hormones including cortisol, suggesting the possibility of an adaptive response to the telomere shortening effects of chronic stress [15, 29, 30].

Mice with short telomeres exhibit an anxiety phenotype [32]. It is not yet clear whether this anxiety-like behavior is a direct consequence of shorter telomeres or a secondary effect of the overall accelerated aging phenotype, although the anxiety phenotype was present in third generation mice where a mild accelerated aging phenotype was observed. The association of short LTL with anxiety [33, 34] and other psychiatric disorders should motivate further study to determine whether telomere length plays a causal role in conditions of psychological stress. Further research is required to clarify the roles of individual cytokines and stress hormones in LTL maintenance and erosion. Another factor to consider is that leukocyte subtypes might have different responses to oxidative stress, inflammatory cytokines and stress hormones.

Different leukocyte subtypes have different telomere lengths

Leukocytes include diverse cell populations that play complementary roles in tissue homeostasis and responses to infection and disease. Three major classifications of leukocytes are granulocytes, lymphocytes and monocytes, which can be further subdivided into distinct cell populations based on their phenotypes and functions (Figure 2). These leukocyte subpopulations have different telomere lengths and erosion rates as the result of differences in telomerase activity, proliferation history and telomere trimming [1]. In healthy adults the leukocyte population consists of 36–66% neutrophils, 24–44% lymphocytes and 4–10% monocytes. Studies of LTL typically do not distinguish between subpopulations, and one potential explanation for the high LTL variability between individuals is individual

differences in leukocyte composition. The few studies that compared telomere length between leukocyte types found substantial differences (Table 2). These differences are due in part to different erosion rates as lymphocytes and granulocytes have similar telomere length in young individuals, with lymphocytes demonstrating a 1.5 faster erosion rate than granulocytes during aging [35].

Memory T-cells (CD4 and CD8) have significantly (~2.5 Kbp or 30%) shorter telomeres than naïve lymphocytes, possibly reflecting proliferation history [35–37]. Despite this observed decrease, telomerase activity is elevated in lymphocytes during immune responses and this may serve as an adaptive response to protect lymphocytes from telomere shortening. Telomeres are also elongated during the maturation of naïve B-cells to germ-center B-cells or memory B cells (Figure 2) [36, 38]. Differences in average telomere length among leukocyte subpopulations would not mask the overall reduction in telomere length that occurs during aging. Moreover, the age-related increase in the percentage of leukocytes with short telomeres is also bolstered by a general population shift towards cells with relatively short telomeres including natural killer cells, tregs and memory lymphocytes [39]. Thus the shorter average LTL may not reflect stress but rather a cell population shift.

This explanation may also apply to NDs as pathology may cause shifts in cell populations that result in shorter average telomere length. In AD, lymphocyte and basophil populations are reduced while monocyte and neutrophil populations increase [40]. The observation that dietary restriction and exercise inhibit LT erosion [7, 41] supports the leukocyte subpopulation explanation, as changes in immune cell composition are more malleable than telomere elongation. Most measurements of telomere length in leukocyte subpopulations have been performed by FLOW-FISH, which enables the simultaneous detection of cell type and telomere length, although this method has not been applied to ND patient samples.

Effects of short LTL on neurodegeneration

Shortening of telomeres in leukocytes and microglia may indirectly affect neuronal health by compromising the normal functions of these immune cells within the brain [38, 42]. The roles of the immune system in the initiation and progression of NDs are being actively investigated [43]. As of yet, the contribution of impaired leukocyte and microglial function due to shortened telomeres to NDs is unclear. Short telomeres in immune cells, astrocytes and neurons could enhance oxidative stress-dependent senescence and the associated secretion of pro-inflammatory mediators (senescence-associated secretory phenotype) that may enhance the disease progression [6, 38, 44]. Based on the existing literature it appears that the shortest telomeres within a cell have the most pronounced effect on cell phenotype and senescence [45, 46]. At present it is unclear whether median telomere length as measured in all real-time PCR and in most Southern blot studies serves as a good indicator of cellular phenotype.

Chronic inflammation can also induce proliferation-dependent immune senescence, which increases the susceptibility to infectious diseases with age and may contribute to mood disorders [29, 38]. It has been suggested that neurodegenerative symptoms appear as a result of immune failure to fight the pathology [43] such that LT erosion reflects immune cell

'exhaustion'. This hypothesis is reinforced by the prion-like progression of many NDs [47], which indicates that extracellular factors are crucial for the disease progression. While it is tempting to speculate that immune senescence resulting from shorter telomeres is one reason why age is a major risk factor for many NDs, evidence supporting this view is limited. Prospective studies found that short LTL predicts dementia [48, 49], cognitive decline [50–52] and mortality [49, 53], but not the progression from mild cognitive impairment (MCI) to AD [54, 55]. Further prospective studies are needed to evaluate the predictive nature of short LTL.

Humans deficient in telomerase (dyskeratosis congenita patients) present with memory deficits and psychiatric symptoms, and 7% of patients develop cerebellar hypoplasia [56]. While the cognitive phenotype invites comparison to anxiety and impaired cognition in telomerase-deficient mice, systemic complications in dyskeratosis congenita such as bone marrow dysfunction, cancer and a shortened lifespan (30 years) should be taken into consideration. These systemic aspects of the disease could indirectly impact cognitive performance.

Telomere shortening might also indirectly impact progression of NDs by altering the HSC response by impairing their self-renewal and skewing differentiation [57]. Wang et al. recently demonstrated that HSCs derived from third generation telomerase knockout mice or irradiated mice have significantly reduced proliferation and that differentiation was skewed toward lymphoid progenitors ($CD150^{low}IL7^{+}$). This effect is BATF- and P21-dependent [57]. It is reasonable to suggest that telomere length impacts HSC differentiation and it may alter the differentiation of immune cell populations, such as lymphocytes. A more speculative hypothesis is that telomere erosion rate controls the duration of the immune response, and different telomere erosion rates between distinct immune cell populations temporally coordinate the response. Thus, LT shortening may change the efficacy and duration of the immune response during NDs.

Is there an association between LTL and telomere length of CNS cells?

LTL has been heavily studied in human subjects because blood is easily accessible. Cross-sectional studies of peripheral tissues such as skin, synovial tissue, subcutaneous fat and skeletal muscle suggest age-related telomere regression similar to leukocytes (25–29 bp/year) [58, 59]. One report found telomere erosion rates in mouse liver, kidney and brain were similar to each other, but different than in testis [60]. While these observations suggest that in a subset of peripheral organs telomere erosion occurs at a consistent rate, investigations of other tissues including the CNS demonstrate variability in telomere erosion.

Proliferation can account for differences in telomere erosion rates. For example, buccal cells have shorter telomeres than lymphocytes due to a higher turnover rate, and fibroblasts have a longer telomere length than lymphocytes [61]. This contrasts with age-related telomere lengthening in sperm cells [60] and a relative lack of telomere erosion in cells of different brain regions [62]. *In-vitro* data from fibroblasts [2], microglia and astrocytes [63] suggest that telomere erosion is influenced by proliferation rate. Shorter telomeres are found in the

CNS with the progression of gestation [62], raising the possibility that the shift from mitotic neural stem cells (NSCs) to post-mitotic neurons and slowly proliferating glia could alter telomere erosion rates compared to peripheral tissues.

Another study compared telomere length in the hippocampus of AD patients to LTL and found LTL erosion contrasted with longer hippocampal cell telomere length [64], although a smaller study found evidence of telomere erosion in AD-patient hippocampus [65]. Telomere lengths in the cerebellum of AD patients was similar to that of peripheral blood leukocytes in one study [66]. This variability between findings could be accounted for by regional differences within the CNS or differences in the leukocyte extraction method.

Does telomere length of brain cells reflect aging and neurological disease status?

Three studies examined age-associated changes in telomere length in postmortem brain tissue samples from human subjects, with telomere erosion rates of 0 to 10 bp/year being reported [62, 67, 68]. A significant negative correlation was reported between age and telomere length (~10 bp/year) in the occipital lobe white and gray matter of 31 subjects (0–80 years-old), while the same study reported a positive correlation with age (longer telomeres) in 40 older (80–100 year-old) subjects [67]. Increased telomere length in older populations may reflect a selection bias for individuals with a longer lifespan, as reflected by a positive association between shorter telomere length and mortality in humans over 60 years [69]. Another potential confounding factor is that human CNS tissue is acquired at autopsy from patients who have often suffered a prolonged agonal state.

In contrast to the studies described in the preceding paragraph, several studies have failed to find correlations of CNS telomere length with aging or disease state. One study found no significant changes in telomere length in different CNS regions when comparing tissue from different ages [62]. Zhang et al. compared telomere length in different brain regions of patients with major depression, schizophrenia and bipolar disorder and found no difference between disease state or age [68]. Other studies have observed no difference between cerebellar cell telomere length in AD patients and age-matched healthy controls [66]. A similar negative finding was observed for substantia nigra cell telomere length between PD patients and age-matched controls [70]. This inter-study variability makes it unclear if CNS cell telomere length is significantly shortened during aging and if telomere erosion is altered in regions where neurons degenerate.

Do specific cell populations within the brain undergo telomere shortening and by which mechanism? Experiments in cultured neurons suggest that telomere damage can trigger cell death [44, 71], and activation of telomerase may reduce neuronal vulnerability [72, 73]. If telomere shortening occurs in mitotic glial cells or neurons during aging and in NDs does it play a functional role in neuronal dysfunction and degeneration? Does a shift away from telomere maintenance in these cell populations contribute to disease progression?

Conclusions and future directions

The etiologies of NDs are complex but involve oxidative stress, inflammation and impaired adaptive stress responses, which may all accelerate LT erosion [18, 38, 79]. Our review of the literature suggests that at present no reliable conclusions can be drawn regarding the contribution of LTL to AD or PD, either as a biomarker for disease or as an indicator of the telomere length of CNS cell populations. The contribution of telomere erosion to the progression NDs, either directly from CNS cell populations or indirectly from peripheral tissues, remains unknown due to variability between studies. We also find no supporting evidence for the idea that LTL correlates with and can serve as an indicator of CNS telomere length.

To address the issue of inter-study variability, we pose key outstanding questions (Box 2) and propose a series of experiments and methodological improvements (Box 3) that will provide greater insight into the potential contribution of telomere erosion to neurodegenerative disease. The association between telomere erosion and components of NDs such as oxidative damage also suggests the possibility that telomere erosion could serve as a novel therapeutic target. Until these questions are addressed, the potential of utilizing LTL as an early biomarker for NDs as well as a therapeutic avenue remain uncertain.

Box 2

Outstanding questions

- Do changes in telomere length of CNS cell populations occur in NDs and is such an association consistent enough that LTL can serve as an indicator of CNS telomere length?
- Do specific cell populations within the brain undergo telomere shortening and by which mechanism? If telomere shortening occurs in mitotic glial cells or post-mitotic neurons during aging and in NDs, does it play an active role in neuronal dysfunction and degeneration?
- Are factors associated with NDs such as oxidative stress and inflammation a cause of shorter LTL?
- Do leukocyte and/or neural cell telomere dynamics observed during aging and in ND reflect cellular dysfunction or a shift in cell populations?
- What is a better indicator of cellular biological age, average LTL or shorter LTL?

Box 3

The way forward

- Examine telomere length in leukocyte subpopulations in NDs, and the relationships between average LT length and leukocyte population distributions.

- Use animal models to examine the dynamics of telomeres in different brain cell populations and in leukocyte subpopulations during healthy aging and in ND models.
- Test the neurological consequences of short LT by transplanting bone marrow cells with short telomeres into ND animal models. Disease progression and severity as well as behavioral deficits should be measured.
- The rapidly increasing number of clinical studies on telomere length in different diseases and its association with symptoms and biomarkers should be organized in one database. This will enable the determination of the variability between studies and may help establish or rule out cause – effect relationships. Such a database would help avoid inaccurate speculation based on limited datasets.

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Glossary

Alzheimer's disease (AD)	A fatal age-related neurodegenerative disorder characterized by progressive dysfunction and degeneration of neurons in brain regions involved in cognition and emotional control. The affected brain regions exhibit accumulation of diffuse and fibrillar aggregates of amyloid β-peptide (Aβ) outside of cells, and the accumulation of hyperphosphorylated Tau (a microtubule-associated protein) inside of neurons
Leukocyte	Any of the many different types of white blood cells that includes neutrophils, monocytes and T- and B-lymphocytes. All leukocytes are derived from hematopoietic stem cells within the bone marrow
Parkinson's disease	A progressive fatal age-related neurodegenerative disorder characterized by the dysfunction and degeneration of neurons in the brainstem, substantia nigra (dopaminergic neurons) and cerebral cortex, resulting in loss of autonomic and motor control, often accompanied by cognitive impairment in late stages of the disease
Telomerase	A reverse transcriptase that catalyzes the addition of TTAGGG DNA repeats onto the ends of chromosomes thereby increasing telomere length
Telomere	The end of eukaryotic chromosome which consists of repeats of the six-base DNA repeat TTAGGG folded into a T-loop structure by a protein complex called shelterin. Telomeres protect the chromosomes by preventing their erosion during DNA replication. In addition, some telomere-associated proteins play important roles in DNA repair

Telomere length measurement by Southern blot	For many years the Southern blot method was the gold standard for measurement of telomere length. In this method the subtelomeric region is cut with a restriction enzyme (usually HinfI) and detected using a probe for the telomere sequence. This method enables absolute measurement of telomere length and some insight on the length distribution. Southern blots was used by a significant fraction of the studies described in the present review article, but has been largely replaced by real-time PCR technology
Telomere length measurement by RT-PCR	The reverse transcriptase polymerase chain reaction method measures the ratio between telomeres and a single gene amplification and results in only relative telomere length. Its relative simplicity and requirement for only small amounts of input DNA make this method attractive for large population studies

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Box 1

Telomere function in the brain: lessons from mice

Animal studies can help address the potential confound of tissue quality and selection bias inherent in studies of postmortem human tissue. Cells of the cerebellum and cortex of aged rats (152 days) exhibit significantly shorter telomeres than young rats (21 days) [74]. Telomeres are also shorter with age in mouse subventricular zone (SVZ) NSCs [75]. In telomerase-deficient mice several generations are required for premature aging phenotypes that are similar to telomerase-deficient humans. Neurological phenotypes in these mice include reduction in NSC proliferation, neurogenesis and oligodendrocyte differentiation (Figure 2) [75, 76]. Late generation telomerase-deficient mice have neuronal loss in the hippocampal CA1 region and frontal cortex, short-term memory deficits [42], impaired olfaction [76] and anxiety-like behaviors [32]. Reactivation of telomerase in adult mice not only delays, but can also reverse, many aging-related phenotypes [76]. However, $APP23^{V17I}$ knock-in mice with short telomeres have fewer Aβ plaques and improved spatial learning abilities compared to $APP23^{V17I}$ knock-in mice with normal telomere length. Microglia with shorter telomeres demonstrate an activated phenotype with chronic microglial activation potentially resulting in exhaustion of microglia [42]. Presenilin-1 knock-in mice have an impaired immune response that could feedback to alter telomere length in the CNS and peripheral tissues, providing a secondary route for an AD-related mutation to alter telomere length [77]. Telomere damage in neurons may alter their function and viability, whereas telomere shortening in glial cells may have adverse or beneficial effects on neurons in a disease process-specific manner. It is important to note that most of these studies were performed on laboratory mice which possess long telomeres (40 kb) compared to human and wild mice (10 kb) [78]. Therefore, any translation of studies from mouse models to humans should be approached cautiously until appropriate animal models are developed.

Highlights

- Leukocyte telomere length (LTL) typically shortens with increased age
- Aging is a primary risk factor for neurodegenerative disease (ND)
- Evidence for LTL as a predictor of neuronal/glial telomere length and ND is mixed
- We suggest possible explanations for variability in studies examining LTL-ND relationship

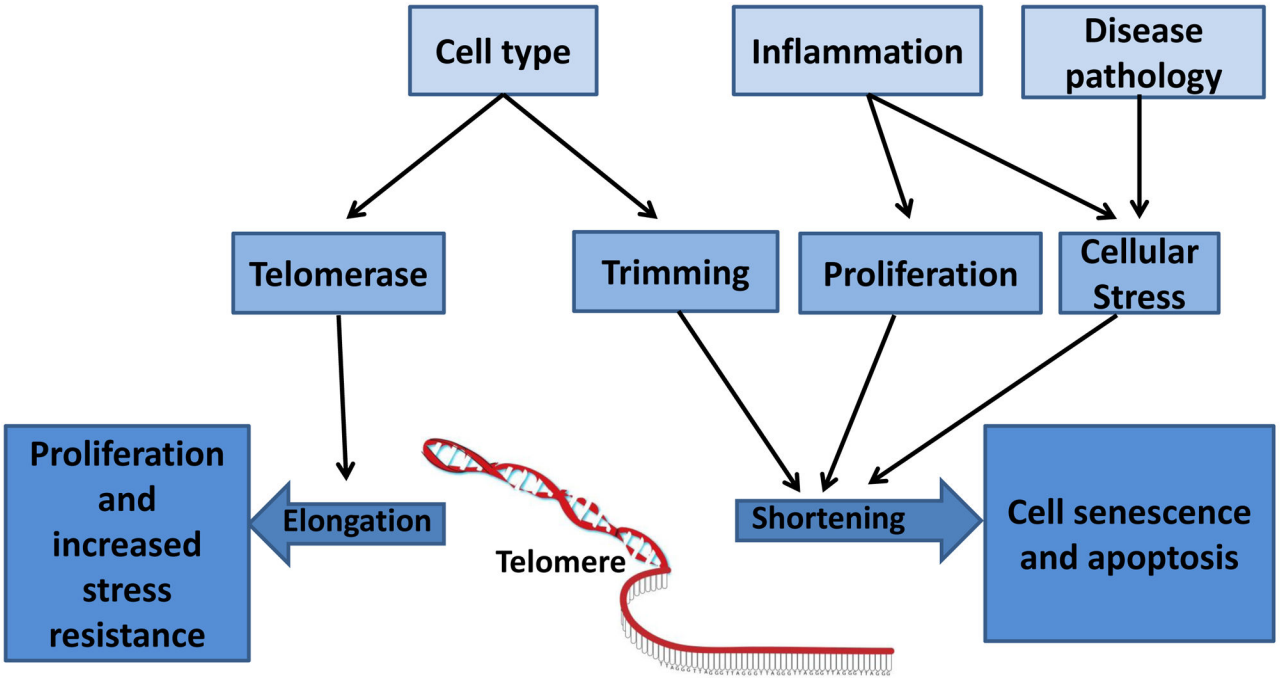

Figure 1.

Causes of telomere shortening. Telomerase is a reverse transcriptase that can maintain telomere length by adding the TTAGGG sequence to the telomere. High levels of telomerase are present in stem cells and may contribute to their 'immortal' phenotype. A reduction in telomerase expression contributes to telomere shortening in mitotic cells. Telomere trimming occurs in dividing cells and involves homologous recombination-mediated removal of telomere loops. Inflammation can accelerate telomere shortening by enhancing cell proliferation and by causing oxidative damage to telomere-associated proteins and telomeric DNA. As a consequence of telomere shortening, cells may undergo senescence or apoptosis.

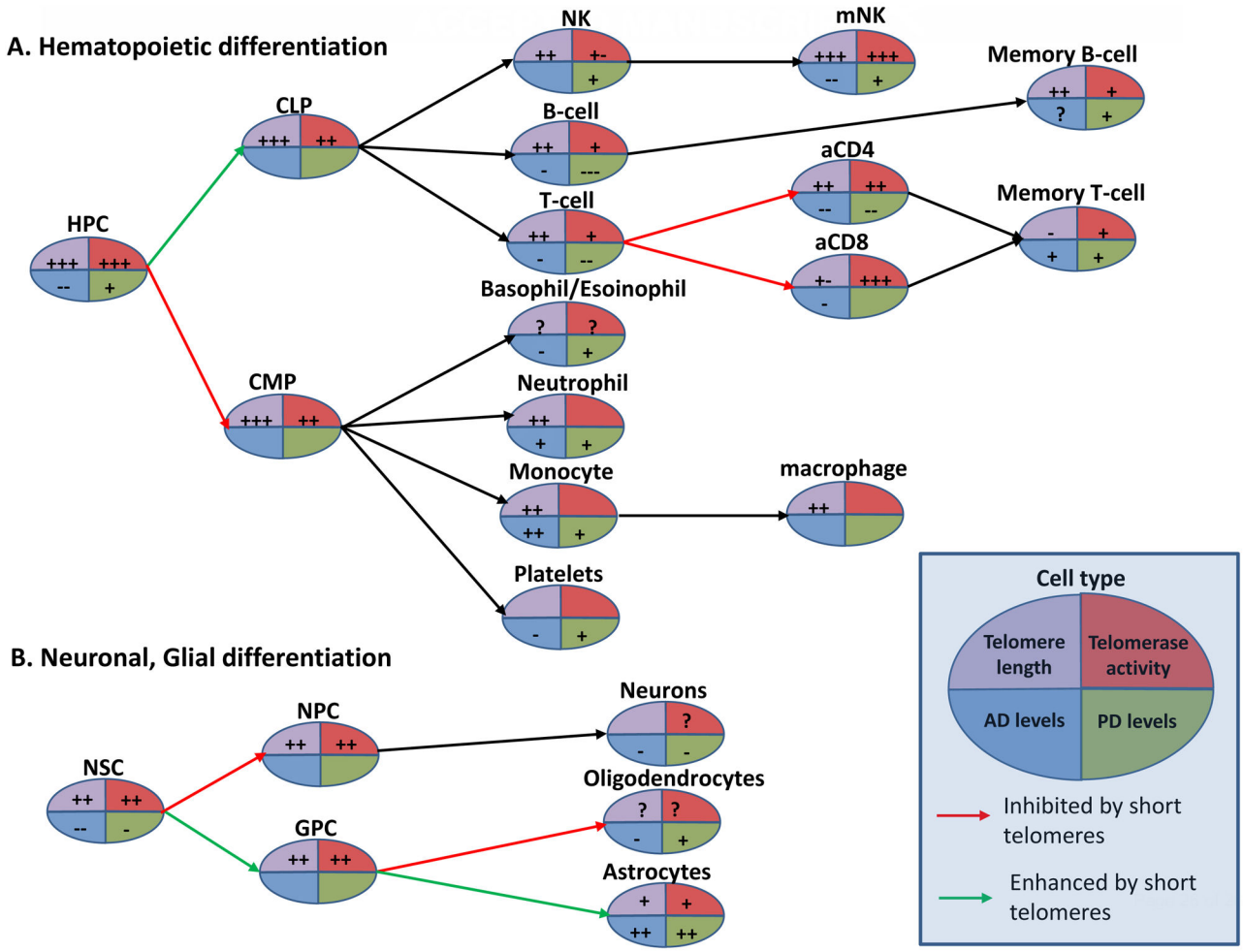

Figure 2.

Impact of telomere length and telomerase activity on hematopoietic stem cells (HSC; panel A) and neural stem cells (NSC; panel B), and their progeny, in the context of Alzheimer's disease (AD) and Parkinson's disease (PD). Telomere length- purple, upper left quadrant; telomerase activity- red up, upper right quadrant; AD- blue, lower left quadrant; PD- green, lower right quadrant. +, increase; −, decrease; ?, unknown; CLP, common lymphocyte progenitor; CMP, common monocyte progenitor; GPC, glial progenitor cell; mNK, mature natural killer cell; NK, natural killer; NPC, neuron progenitor cell; NSC, neural stem cell.

Table 1

Studies of leukocyte telomere length in neurodegenerative disorders.

Disease	TL*	# of studies	N	Method	Remarks	References
AD	S	5	224 P; 274 C	PCR II; SB III	One study examined monocytes and one T cells	[49, 64, 80–83]
	UC	5	238 P; 280 C	PCR II; SB II; FACS	One study examined lymphocytes	[16, 54, 84–86]
PD	S	2	37P; 35C	SB II		[87, 88]
	UC	2	190P; 97C	PCR; SB		[89, 90]
	L	3	609P; 1080C	PCR		[13, 70, 91]
MCI	S	10	871P; 405C	PCR V; SB III; FISH II	Three studies examined T cells	[48–50, 84, 85, 92–96]
	UC	2	122P; 219C	SB; FACS	One study examined monocytes and one lymphocytes	[54, 82]

AD, Alzheimer's disease; C, control subjects; FACS, fluorescence activated cell sorting; FISH, fluorescence in situ hybridization; MCI, mild cognitive impairment; P, patients; PCR, polymerase chain reaction; PD, Parkinson's disease; SB, Southern blot.

*Leukocyte telomere length (TL) in comparison with control subjects. S, shorter; L, longer; UC, unchanged.

Table 2

Impact of age on telomere length in leukocyte subpopulations

Cell type	40 yo	60 yo	80 yo	ADNR	Ref
lymphocyte/granulocyte *	0.97		0.78		[35, 97]
naïve/memory *	1.38	1.64	1.90		[35, 97, 98]
CD4/CD8 *	1.24	1.23	1.22		[97–99]
T cell/B cell *	0.97		0.67		[97–99]
Naïve NK	1.24		1.17		[100]
NK mature/immature				shorter	[101, 102]
CD28+/CD28−				1.45	

The number in the table represents fold-change and was produced by dividing the reported absolute and relative telomere length.

yo, years old; ADNR, age dependency not reported; NK, natural killer cell.

* average of more than one study