Review

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Telomere shortening in neurological disorders: an abundance of unanswered questions

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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 (see Glossary) are an evolutionarily conserved DNA sequence at the end of each chromosome that is identical in the entire vertebrate phylum. They consist of 6 bp 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 bp during each round of DNA replication [2], and leukocyte telomeres (LTs) 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. By contrast, telomere length in hematopoietic stem cells (HSCs) and lymphocytes is determined by the balance of elongation by telomerase, an enzyme that 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 (Box 1) and humans [3,6], and considerable interindividual 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], whereas obesity is

Glossary

Alzheimer's disease (AD): a fatal age-related ND 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 Aβ peptide 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 HSCs within the bone marrow.
Parkinson's disease: a progressive fatal age-related ND 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 the 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 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 into the length distribution. Southern blots were used by a significant proportion 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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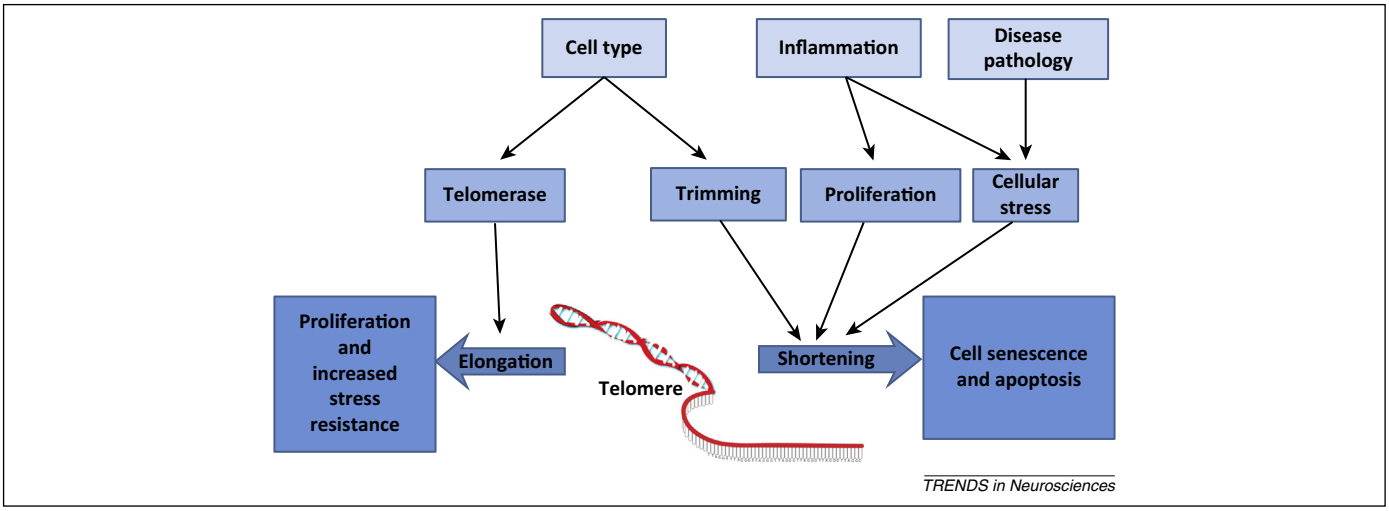

Figure 1. Causes of telomere shortening. Telomerase is a reverse transcriptase that can maintain telomere length by adding the TTAGGG sequence to the telomere. High levels of telomerase are present in stem cells and may contribute to their 'immortal' phenotype. A reduction in telomerase expression contributes 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.

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. Although 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 past decade the role of leukocyte and neural cell 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 central nervous system (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? (Box 2). 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.

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) [75]. Telomeres are also shorter with age in mouse subventricular zone (SVZ) NSCs [76]. 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 in main text) [76,77]. Late generation telomerase-deficient mice have neuronal loss in the hippocampal CA1 region and frontal cortex, short-term memory deficits [42], impaired olfaction [77], and anxiety-like behaviors [32]. Reactivation of telomerase in adult mice not only delays but can also reverse many aging-related phenotypes [77]. However, $APP23^{V171}$ knock-in mice with short telomeres have fewer amyloid β (Aβ) plaques and improved spatial learning abilities compared with $APP23^{V171}$ 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 mutant 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 [78]. 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 with humans and wild mice (10 kb) [79]. Therefore, any translation of studies from mouse models to humans should be cautiously approached until appropriate animal models are developed.

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]. A 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 with AD and PD, a majority of studies examining LTL in psychological stress, cognitive impairment, and dementia found that 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-analyses of several large