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Ageing and Neurodegenerative Diseases

Review

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Potential roles of telomeres and telomerase in neurodegenerative diseases

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Abstract

Telomeres, essential DNA-protein complexes located at chromosome ends, play a critical role in preventing chromosome fusion, recombination, and degradation, thus ensuring genomic stability. When telomeres reach a limiting shortened length, they will activate DNA damage checkpoints, stop cell division and trigger replicative senescence. Telomerase is composed of RNA and protein, which can synthesize telomeres repeat sequences, and elongate telomeres. Studies have shown that telomere length (TL) and telomerase activity are closely involved in aging, aging-related degenerative diseases, and tumors. Neurodegenerative diseases (NDDs) are one of the major aging-related diseases caused by both genetic and environmental factors, characterized by insidious onset, difficult diagnosis, irreversible disease progression, and lack of effective treatments, which brings a heavy burden to society and families. Currently, many studies have noted variations in leukocyte telomere length (LTL) and telomerase activity in NDDs, suggesting a vital role for telomeres and telomerase in NDD pathogenesis. This review explores the relationship between TL and NDDs, examines telomerase as a potential therapeutic target, and discusses emerging biomarkers and intervention strategies for NDD diagnosis and treatment.

Keywords: Telomeres, telomerase, neurodegenerative diseases, Alzheimer's disease, Parkinson's disease, aging

INTRODUCTION

Telomeres, special structures at chromosome ends composed of repetitive DNA sequences (TTAGGG) and binding proteins, are crucial for protecting chromosomes from fusion and degradation. They play a significant role in chromosome replication and in controlling cell growth[1,2]. Telomeres are wrapped by a multimeric shelterin complex, including TRF1, TRF2, TPP1, POT1, TIN2, and RAP1, six protein subunits, which avoids their identification as DNA damage[3]. However, linear DNA replication suffers from the end replication problems leading to progressive telomere shortening[4]. Additionally, there is increasing evidence linking oxidative stress to accelerated telomere shortening and dysfunction[5-7]. Telomerase, a ribonucleoprotein complex, includes the telomerase RNA component (TERC), telomerase reverse transcriptase (TERT), and other telomerase-related proteins. TERT can lengthen telomeres by adding telomeric repeat sequences to the 3' end of telomeres using TERC as a template and the 3' end of telomeres as a substrate[8]. Other proteins such as dyskerin, GAR 1, NHP 2, and NOP 10 maintain telomerase complex stability[9]. TERT, the key enzyme regulating telomerase activity, is down-regulated in humans post early embryonic development. Consequently, telomerase activity is undetectable in most normal cells, except in specific cells like stem cells, progenitor cells, germ cells, and certain immune and endothelial cells. It has been found that TERT expression is high in neural stem cells (NSCs) and neural progenitor cells (NPCs), but decreases rapidly when NSCs and NPCs differentiate or die. Thus, high telomerase activity can be detected in embryonic brain tissue but gradually declines after birth. Lee *et al.* detected TERT expression and activity in adult brain tissue, including the hippocampus, olfactory bulb, and subventricular region of the lateral ventricles, which may be due to the abundance of NPCs in these regions[10,11]. However, despite studies confirming that telomerase activity is restricted to stem cell-containing regions of the brain, TERT protein has been found to be present in mature Purkinje neurons[12], and a variety of injuries, including ischaemia-hypoxia, radiation, and glutamate- or N-methyl-D-aspartate (NMDA)-induced excitotoxicity, can also significantly increase TERT level in rodent neurons[12,13].

Neurodegenerative diseases (NDDs) encompass a spectrum of age-related neurological disorders, primarily affecting the central nervous system (CNS) and, to a lesser extent, the peripheral nervous system (PNS). These conditions are marked by a progressive loss of neurons and are characterized by symptoms such as cognitive decline, cerebral atrophy, white matter degeneration, and the buildup of neuropathic proteins. Key examples include Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), and others[14]. The brain has limited nerve repair capacity, but this is insufficient to stop the disease from progressing[15]. If NDDs occur in the CNS, and in fact, most NDDs actually occur in the CNS, then as the disease progresses, other conditions related or unrelated to the nervous system will follow, ultimately leading to the patient's death. The World Health Organization (WHO) reports that approximately 55 million people worldwide currently suffer from NDDs, a figure projected to rise to 139 million by 2050. At this rate, NDDs may replace cancer as the second most common human fatal disease. The survey showed that the largest proportion of NDDs is now AD (77%), followed by PD (15.5%), multiple sclerosis (MS, 3.7%), ALS (1%) and others (2.8%). Despite their prevalence, there is no universally effective treatment for NDDs, and their underlying mechanisms remain largely unknown. Wilson *et al.* have identified eight key hallmarks of NDDs: pathological protein aggregation, synaptic and neuronal network dysfunction, aberrant proteostasis, cytoskeletal abnormalities, altered energy homeostasis, DNA and RNA defects, inflammation, and neuronal cell death[16]. This lays the foundation for elucidating the disease categories, pathogenesis, and personalized targeted therapies for NDDs. Factors such as oxidative stress, immuno-inflammation, mitochondrial dysfunction, aberrant autophagy, and cellular senescence are thought to play significant roles in the pathogenesis of NDDs, with telomeres and telomerase

being crucial components[17,18]. However, the role of telomere shortening in NDDs remains controversial because there are not only mitotic division-competent cells in the brain (glial cells), but also post-mitotic cells (neurons). Telomere shortening does not work in neurons, but their telomeres are still damaged and induce a DNA damage response (DDR) and senescence. In non-proliferating cells, DDR foci tend to accumulate at telomeres that are not necessarily short[19]. At the same time, DNA damage that occurs within telomeric repeat sequences resists repair, which results in a sustained DDR that can also develop in long telomeres[19,20].

Telomere length (TL) and telomerase activity have been identified as key factors in the development of NDDs. Topiwala *et al*. found that short telomeres increase the risk of neurological and psychiatric disorders, including AD[21]. This comprehensive study, involving over 31,661 participants from the UK Biobank, is notable for its scale and systematic approach. It compared brain MRI results and electronic health records with leukocyte telomere length (LTL). The findings revealed a correlation between LTL and various MRI phenotypes associated with NDDs. Individuals with longer telomeres were found to have healthier brain structures, evidenced by a larger volume of gray matter, more substantial hippocampi, and a thicker cerebral cortex. These traits are indicative of better overall brain health. Conversely, individuals with AD typically exhibit shrinkage in gray matter and the hippocampus, alongside thinning of the cerebral cortex as the disease progresses. These observations underscore the significance of TL as a potential biomarker in understanding and perhaps predicting the risk and progression of NDDs[21]. Recently, researchers from the University of Connecticut Health and the University of Exeter in the United Kingdom published a study in the journal *Aging Cell* suggesting that people with longer leukocyte telomeres may have a lower risk of developing AD and cognitive impairment[22]. The study found that longer LTL was associated with better cognitive performance and lower risk of developing AD, vascular dementia, and their associated brain markers, pointing to TL as a strong indicator of AD development or cognitive impairment. Scarabino *et al.* found that LTL was significantly longer in people with normal cognitive function than in people with mild cognitive impairment (MCI)[23]. In the elderly, the longer the LTL, the lower the risk of MCI[24-26]. Oxidative stress and mitochondrial dysfunction have important effects on NDDs[27-29]. Telomere dysfunction activates p53 and inhibits PGC1α/β, leading to mitochondrial dysfunction and increased oxidative stress[30]. In turn, oxidative stress damages telomeres[31], creating a vicious cycle. 8-oxo-guanine is a guanine oxidation product and telomeres are more susceptible to 8-oxo-guanine because of the TTAGGG repeat sequence[31]. A recent study showed that induction of 8-oxo-guanine on telomeres of human fibroblasts and epithelial cells activated the ATM/ChK2 pathway, thereby activating p53 and leading to cellular senescence[32]. Interestingly, acute 8-oxo-guanine production did not cause telomere shortening, but rather telomere fragility and dysfunction. This suggests a strong link between mitochondrial dysfunction, oxidative stress, and telomeres [Figure 1]. In addition to the canonical telomerase activity, TERT has many non-canonical functions outside telomeres[33]. TERT can exert neuroprotective effects potentially by modulating the expression of neurotrophic factors, synaptic signaling, and plasticity-related genes[34,35]. Ahmed *et al*. found that oxidative stress in human fibroblasts with *hTERT* gene overexpression increased the mitochondrial localization of TERT[36]. Spilsbury *et al*. found that TERT persists in mature human hippocampal neurons and activated microglia, and colocalized with mitochondria during oxidative stress[37]. Miwa *et al.* found that dietary restriction or rapamycin led to the accumulation of TERT protein in the mitochondria of brain tissue from wild-type mice[38]. In addition, rapamycin treatment did not affect reactive oxygen species (ROS) release in TERT-/- mice, suggesting that the effect of ROS reduction is dependent on the presence of TERT in the model. This provides evidence that the TERT protein acts non-canonically in neurons of brain tissue and exerts neuroprotective effects mainly through mitochondrial effects[39]. This demonstrates the potential of TERT as a novel therapeutic target for NDDs[40-42].

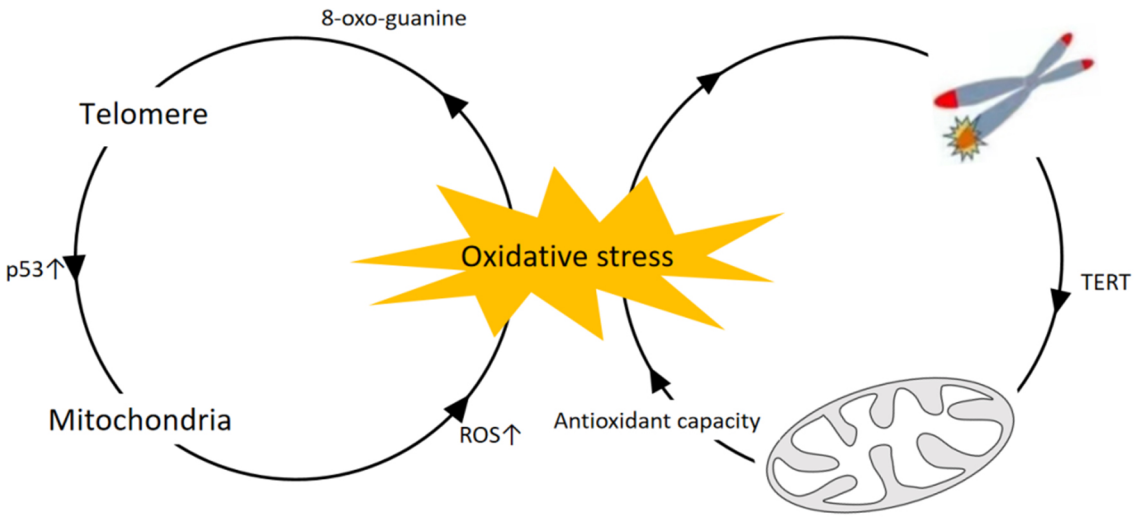

Figure 1. Interaction of telomeres with mitochondria and oxidative stress. TERT: Telomerase reverse transcriptase; ROS: reactive oxygen species.

TELOMERES AND TELOMERASE AND AD

AD is the leading cause of dementia in the elderly and has become one of the most expensive, deadly, and burdensome diseases of this century[43]. Studies in the United States have shown that the percentage of people with AD increases with age and that people aged 65 and over are at higher risk of developing AD[44]. Even up to 33.3 percent of people aged 85 and over suffer from AD[44]. People with AD typically exhibit cognitive dysfunction with impaired emotion regulation and loss of motor skills. Many therapeutic strategies have been explored, but no effective treatment has been found, and the high cost of medical treatment and care for AD patients places a heavy burden on society and families[45-47]. A recent study published by the University of Oxford suggests that brain changes caused by AD are associated with shortened leucocyte telomeres[21]. Ma *et al.* found that peripheral blood LTL was shorter in patients with AD than in normal subjects[48]. A meta-analysis also confirmed the presence of shorter telomeres in multiple individual cell samples from AD patients, especially in leukocytes[49]. Another meta-analysis also found that leukocytes or PBMCs from AD patients had shorter telomeres and a trend of increased telomerase activity[50]. Lee *et al.* reported a notable finding that the annual rate of telomere shortening in peripheral blood leukocytes is higher in patients with AD compared to healthy individuals and those with MCI[51]. This suggests a possible link between TL and AD. Further supporting this, LTL has been positively correlated with better cognitive and memory functions. Individuals with shorter telomeres are at a heightened risk of developing AD[52]. However, the research in this area presents a complex picture. Martínez-González *et al.* conducted studies using a 3xTg-AD mouse model and observed that TL and oxidative stress were influenced by AD progression[53]. Interestingly, changes in blood cell telomeres were more pronounced than in brain tissue, indicating that systemic changes in this AD mouse model might be detectable early in the disease. Despite shorter telomeres being found in the blood cells of AD mouse models compared to wild-type mice, no significant changes in TL were observed in the hippocampus[53]. Contrasting findings have also been reported. Guan *et al.* found normal mean TL in peripheral leukocytes from AD patients and Hinterberger *et al.* observed no association between LTL and the development of AD alone[54,55]. Therefore, whether LTL can be used as a predictor of AD in patients remains to be further investigated. In addition, it has been reported that a *TERT* gene polymorphism of telomerase is linked with an increased risk of developing AD in humans[56]. The three TERC single nucleotide polymorphisms (rs12696304, rs3772190, rs16847897) are all in a linkage disequilibrium because they are located in the same restricted region. The

combination of their genotypes affects the age of onset of AD[56].

Amyloid plaques formed by extra-neural deposition of the β-amyloid peptide (Aβ) in the brain and neurofibrillary tangles (NFTs) formed by intracellular accumulation/deposition of hyperphosphorylated tau proteins are two neuropathological hallmarks of AD. Hu *et al.* observed early and persistent microglia proliferation in CLEC7A$^+$, CD11C$^+$, or MHCII$^+$ cells in APP/PS1 mice, a well-established mouse model of genetical AD, that exhibited telomere shortening, increased senescence-associated β-galactosidase activity, which are consistent with disease-associated microglia (DAM) and senescent microglia features found in AD patients[57]. Meanwhile, they found that inhibition of early microglia proliferation in the AD model prevented microglia senescence and ameliorated amyloid-related pathology. This suggests that Aβ-induced microglia overproliferation may induce DAM production and promote amyloid-related pathology through replicative senescence[57]. Raj *et al.* demonstrated the consequences of TERC knockouts on microglia in mice[58]. These microglia showed telomere shortening and decreased proliferation efficiency, resulting in an enhanced proinflammatory response to lipopolysaccharide (LPS). This condition in microglia with shortened telomeres leads to increased production of inflammatory cytokines and ROS, impairing phagocytosis in the brain and potentially accelerating neurodegeneration. Wang *et al.* found that aggregated forms of Aβ (Aβ1-40 and Aβ1-42), but not Aβ monomers, inhibit telomerase activity both *in vitro* and in living cells[59]. The β fragment structure is crucial for Aβ-induced inhibition of telomerase. Aβ oligomers interfere with telomerase activity by binding to DNA-RNA hybrids formed by telomeric DNA and the RNA template of telomerase, blocking telomerase's elongation of telomeric DNA. Additionally, intracellular Aβ localizes to telomeres, inducing telomere shortening. These findings suggest that Aβ oligomers could act as natural telomerase inhibitors and play a role in Aβ-induced cytotoxicity. TERT protein may be protective against pathological tau proteins in the adult brain, while direct evidence is lacking. Spilsbury *et al.* demonstrated that TERT had anti-oxidative stress capacity in primary embryonic mouse neurons transduced with pathological tau proteins, whereas neurons without TERT had higher levels of ROS and peroxides[37]. Whittemore *et al.* found that both old wild-type and third-generation Tert-/- mice exhibited neurodegeneration[60]. The former is due to natural aging, and the latter is due to short telomeres resulting from telomerase absence. They also showed that introducing the telomerase gene into these mice's brains ameliorated some neurodegenerative symptoms. Shim *et al.* observed that increased TERT levels significantly reduced Aβ levels in neurons in an AD mouse model and in cultured human iPSCs derived from AD donors with APP gene duplication[35]. TERT stimulates the β-catenin/TCF7 complex, upregulating key neuronal genes controlling synaptic signaling and learning pathways, independently of its catalytic capacity or telomerase RNA. Moreover, TERT activation by small molecules like GV1001 and AGS-499 has been shown to be neuroprotective. GV1001, a vaccinia peptide derived from TERT's active site, protects against Aβ oligomer-induced neurotoxicity in rat NSCs[61]. In addition, Park *et al.* demonstrated that GV1001 induced cell proliferation, counteracted β-amyloid toxicity, and inhibited apoptosis, senescence, and oxidative stress in NSCs[61]. AGS-499, a novel synthetic compound, enhances the survival of the NSC-34 cell line, a motor neuron-like cell model, under oxidative stress[62]. Baruch-Eliyahu *et al.* demonstrated AGS-499 increases *TERT* gene expression in primary hippocampal cell cultures and protects neurons from Aβ-induced degradation[34]. TERT activates the Wnt/β-catenin pathway, elevates neurotrophic factor levels (NGF, BDNF), boosts neuronal plasticity gene expression, and offers neuroprotection against Aβ-induced cytotoxicity. These findings highlight TERT's potential as a therapeutic target in AD treatment.

TELOMERES AND TELOMERASE AND PD

PD is the second most prevalent NDD after AD, characterized as a chronic, progressive movement disorder often accompanied by cognitive, psychiatric, and autonomic problems[63]. The two primary histopathological features of PD are the loss of dopaminergic neurons in the substantia nigra compacta[64]

and the accumulation of cytoplasmic inclusions (Lewy bodies), predominantly comprised of α-synuclein, in surviving neurons[65]. The pathogenesis of PD is not fully understood but is linked to increased oxidative stress and neuroinflammation, which can lead to telomere shortening[31]. Armstrong *et al.* found increased oxidative stress and telomere shortening in the brain tissue of PD patients[5]. However, no potential causal relationship between LTL and PD was found in a Mendelian randomization study[66]. In a study by Guan *et al*, only patients with PD had a mean peripheral blood LTL shorter than 5 kb and an accelerated rate of telomere shortening compared to age-matched controls[67]. Scheffold *et al.* found that brainstem neuronal cells in a Terc knockout mouse model of PD showed telomere shortening[68]. Telomere shortening promoted disease progression as evidenced by decreased locomotor activity and increased formation of α-synuclein aggregates, as well as damage to brainstem microglia at the end stage of the disease. This suggests that telomere shortening may increase α-synuclein by decreasing microglia function[68]. Martin-Ruiz *et al.* discovered significant telomere shortening in newly diagnosed PD patients in comparison to age-matched controls[69]. Levstek *et al.* found that PD patients with shorter TL in peripheral blood cells had a higher risk of dementia and that TL influenced the time to onset of motor complications post initiation of levodopa therapy[70]. Wan *et al.* found that telomerase activators increased TERT levels in the brains of PD model mice, leading to substantial improvements in motor functions[71]. Importantly, they observed no alteration in TL in the regions analyzed. The treatment not only reduced phosphorylated and aggregated α-synuclein but also the total α-synuclein levels in the hippocampus and neocortex, correlating with enhanced autophagy markers. This suggests that degradation of toxic α-synuclein is improved by telomerase activator-induced elevated TERT levels, possibly by activating autophagy or by preventing or delaying degradation mechanism impairment during disease progression[71]. These findings provide valuable insights into the relationship between telomere biology and PD, offering potential avenues for developing new therapeutic strategies for this debilitating disease.

TELOMERES AND TELOMERASE AND ALS

ALS is a rapidly progressive and fatal NDD primarily affecting motor neurons in the motor cortex, brainstem, and spinal cord, with predominantly sporadic cases and inheritance in about 10% of cases[72]. Characterized by motor neuron death and dysfunction, it often presents with gliosis at lesion sites, thinning of spinal nerve anterior roots, axonal breaks, and demyelination[14]. The prevalence of ALS increases with age, being highest between the ages of 60 and 79, and there are gender differences, showing a male to female ratio of 1.35[73]. Globally, its incidence varies geographically, with an overall rate of 1.68 per 100,000 person-years[74]. A mendelian randomization study of LTL in ALS revealed a negative association between longer leukocyte telomeres and ALS risk, which was primarily driven by rs 940209 which is a polymorphism localized at the oligosaccharide-binding fold containing 1 (OBFC1) locus, suggesting a potential role for the OBFCl in ALS[75]. The OBFC1 protein associates with the TPP1 protein which is a component of the shelterin complex and is involved in maintaining telomere integrity and down-regulating telomerase action[76,77]. These findings imply that longer leukocyte telomeres might reduce ALS risk, highlighting the importance of preserving TL in preventing and treating the disease. Geng *et al.* showed that repeated amplification of C9orf72 hexanucleotide repeats, which is common in ALS, forms stable G-quadruplexes that can reduce telomeres integrity and cause DNA damage and neurodegeneration[78]. Furthermore, the protective effect of LTL against ALS may be influenced by other mechanisms, including sex differences in TL[79,80]. In part, this is due to the direct activation of the telomerase promoter by estrogen[81] and enhanced telomerase activity via the phosphatidylinositol 3-kinase/Akt[82] and nitric oxide pathways[83], decelerating telomere shortening. This aligns with the higher prevalence of ALS in men compared to women, suggesting that estrogen supplementation might benefit ALS treatment[74]. Animal studies with 17β-estradiol have shown promising effects on ALS, improving locomotor performance in male SOD1 (G93A) mice[84] and delaying disease progression in ovariectomized mice[85]. Although estrogen replacement therapy has been

shown to be associated with attenuation of motor symptoms in ALS in animal studies, high-quality clinical trials are needed to validate these findings in human ALS treatments. The telomerase activator AGS-499 has shown potential in ALS treatment, increasing telomerase activity and TERT protein levels in mouse brain and spinal cord. It delayed the onset and progression of ALS disease in SOD1 transgenic mice and resulted in a 60% increase in motor neuron survival in SC after the onset of ALS[62]. Beyond pharmacological interventions, lifestyle factors like stress reduction and a high-quality diet may also play a role in retarding telomere shortening and are worth exploring as potential ALS treatment strategies[86].

TELOMERES AND TELOMERASE AND HD

HD is an autosomal dominant, progressive neurodegenerative disorder caused by a CAG trinucleotide repeat amplification in the first exon of the Huntington (*HTT*) gene, which encodes the Huntington protein. Huntington proteins are ubiquitous proteins involved in transcriptional regulation[87]. HD is characterized by movement disorder as well as cognitive and psychiatric symptoms. Studies demonstrated that HD patients have shorter LTL than healthy controls[88-90]. Scarabino *et al.* observed the presence of significant LTL shortening in HD patients and that LTL in pre-manifest HD (pre-HD) patients started to shorten significantly with increasing CAGs and age, along with disease progression[91]. In their other study, a relational analysis between LTL in pre-HD patients and the estimated time to clinical diagnosis showed that LTL in pre-HD patients could be used as an indicator of the time to clinical onset[92]. They also showed that the number of CAGs increased leukocyte telomere shortening in pre-HD patients and found that an LTL value > 0.70 T/S could indicate a premanifest phase approximately 3 years before clinical symptoms, whereas an LTL < 0.70 T/S could indicate impending clinical symptoms. This suggests that short LTL can be a feature of disease progression in pre-HD patients. Castaldo *et al.* found that peripheral blood mononuclear cells from both pre-HD and HD patients showed shorter telomeres compared to healthy controls[93]. They also observed a significant increase in γ-H2A.X. The γ-H2A.X is produced by phosphorylation of histone H2A.X present at the DNA which is caused by DNA damage and is a DNA damage marker. The levels of γ-H2A.X were strongly associated with the presence of the mutated *HTT* gene in both pre-HD and HD patients and could be used to characterize disease progression in patients with established HD. Treatments aimed at reducing T cell-driven inflammation have shown promise in delaying or preventing episodes in HD[94]. This is particularly relevant as telomere shortening in HD may be linked to oxidative stress[88]. Since TERT plays a critical role in maintaining TL and has antioxidant effects[37], it emerges as a potential therapeutic target for alleviating HD symptoms and warrants further investigation[14].

TELOMERES AND TELOMERASE AND MS

MS is a chronic disease characterized by both autoimmune and degenerative processes in the CNS[95]. It involves multiple inflammatory demyelinating plaques in the CNS's white matter during the acute phase, and calcified plaques due to glial fiber proliferation in old lesions, which occur in the optic nerves, spinal cord, and brainstem, and are more common in females than in males[95,96]. The etiology of MS is unknown and has been associated with genetic factors, viral infection, and autoimmunity[96]. Hinsinger *et al.* have found that shortened telomeres are associated with higher levels of chitinase-3-like protein 1 (CHI3L1), which is a protein that is associated with a higher level of the enzyme chitinase-3[97]. CHI3L1 was found in cerebrospinal fluid and serum at different disease stages of MS and was associated with a higher rate of conversion from clinically isolated syndrome to relapsing-remitting MS (RRMS). A cross-sectional study revealed a decrease in LTL over time in both RRMS and primary-progressive MS (PPMS) patients. Patients with shorter LTL at baseline had a higher likelihood of transitioning from RRMS to secondary-progressive MS (SPMS)[98]. Krysko *et al.* found that shorter LTL in MS patients was associated with greater disability, lower brain volume, higher relapse rates, and a faster conversion from relapsed to progressive MS after adjusting for age, disease duration, and gender at baseline[99]. By assessing the mean TL in peripheral blood

cells of MS patients, Guan *et al.* showed that PPMS patients had a shorter mean TL in peripheral blood mononuclear cells on average (6.5 kb in males and 7.0 kb in females) than controls (8.4 kb in males and 10.1 kb in females), whereas patients with RRMS and SPMS did not have a significant difference in TL from controls[100]. They also found significantly higher levels of urinary 8-iso-prostaglandin $F_{2\alpha}$ (PGF 2α, a marker of lipid peroxidation) and reduced antioxidant capacity of plasma low-density lipoprotein (LDL) in patients with MS, especially those with PPMS. This suggests that telomere shortening and enhanced oxidative stress are more pronounced in the most severe stages of MS[100]. The relationship between telomere attrition in MS patients and oxidative stress and inflammation remains to be fully elucidated. Furthermore, studies have shown that antioxidant therapies, such as vitamin E supplementation[101], can mitigate enhanced oxidative levels and help maintain TL in MS patients. This suggests that antioxidant therapy could be a significant direction for future interventions in MS treatment.

TELOMERES AND TELOMERASE AND ATAXIA-TELANGIECTASIA

Ataxia-telangiectasia (AT) is a rare, autosomal recessive disorder characterized by cerebellar ataxia, ocular and cutaneous telangiectasia, genomic instability, heightened radiosensitivity, and a predisposition to tumor development[102]. The prevalence of AT ranges from 1 in 40,000 to 1 in 1.1 million[102]. The gene mutation of ataxia telangiectasia mutant protein (ATM) is the only causative gene for AT[103,104]. The ATM protein is a downstream kinase of the DDR. It uses its kinase activity to catalyze the phosphorylation of a variety of functionally important substrate proteins such as tumor suppressor proteins CtIP, the catalytic subunit of DNA-dependent protein kinase(DNA-PKcs), and Artemis (the protein defective in patients with RS-SCID), and to repair DNA damage by homologous recombination (HR) and non-homologous end-joining (NHEJ)[105,106]. Studies have shown that ATM is a member of the PI3K family, and its function is related to the maintenance of TL[107], so AT is also categorized as a secondary telomeres disease[108]. Telomere fusion is often observed in the mid-mitotic phase of AT patients, which may be due to short telomeres or altered chromosome structure. Current evidence suggests that the telomere-binding protein TRF1, which binds to double-stranded DNA repeats at telomeres, is one of the substrates for the action of ATM proteins[109] in the regulation of telomeres and mitotic progression of cells, and that high level of TRFI accelerates telomere shortening, whereas decreased expression of TRF1 lengthens telomeres, suggesting that TRF1 is a negative regulator of TL[110]. Transfection of two dominant inactivating mutants of TRF1 separately into AT cells increased TL, restored G2/M checkpoint defects, and reduced cellular radiosensitivity in AT cells[111], indicating TRF1's involvement in DNA damage repair and cell cycle signaling regulation mechanisms linked to ATM[111]. It has been shown that genetic mutations in ATM are responsible for the increased risk of AT and telomere shortening[112]. Wood *et al.* demonstrated that expression of the *hTERT* gene in fibroblasts of primary AT patients rescued the premature senescence phenotype and did not stimulate malignant transformation[113]. Pintado-Berninches *et al.* found that the AT cell lines (AT-3189 and AT-719) had approximately 40% lower levels of telomerase activity and TERT expression than control cells (C-736)[114]. Consistent with the results for telomerase activity, the average TL in the AT cell lines was approximately 6 kb shorter than in the control cells. A genetic suppressor element 24-2 (GSE24-2) is a peptide corresponding to an internal domain of dyskerin[115]. Since expression of GSE4 (composed of the 11 N-terminal amino acids of GSE24.2) can increase telomerase activity in X-linked dyskeratosis congenita cells[116], the authors tested their function in AT cells. They found that increased expression of the GSE4 peptide in AT cells counteracted the cellular effects of the high ROS levels produced in AT cells and also increased telomerase activity and promoted cell proliferation[114]. This demonstrates that GSE4 has the function of increasing telomerase activity and is expected to be used for AT intervention.

TELOMERES AND TELOMERASE AND HYPOXIC-ISCHEMIC ENCEPHALOPATHY

Apoptosis is the main form of neuronal cell death in hypoxic-ischemic encephalopathy (HIE)[117]. When hypoxic-ischemic injury occurs in brain tissues, it induces dysfunction of the energy metabolism, failure of Na^+-K^+-ATP pumps on cell membranes, and large amounts of sodium and calcium ions will flow inwards. The mitochondrial membrane permeability transition pores open abnormally. The apoptosis-inducing factor (AIF) and cytochrome C are released, and large amounts of oxygen free radicals and excitatory amino acids are produced, leading to apoptotic cell death[118]. Apoptosis occurs within ten minutes after hypoxic-ischemic injury, peaks at 24-72 h, and can last for seven days[119]. Taking effective measures to block its pathophysiological process can avoid or reduce neuronal apoptosis and alleviate brain injury. Therefore, apoptosis has become an important target for the pharmacological treatment of HIE. Wang *et al.* demonstrated that multiple risk factors for ischemic stroke are associated with LTL shortening and may be used as risk and prognostic indicators for ischemic stroke[120]. TERT has been shown to inhibit apoptosis in neuronal cells. TERT can exert neuroprotective effects by resisting the excitatory neurotoxic effects of NMDA, improving mitochondrial function, and inhibiting oxygen free radical production, among other mechanisms[12,37,121]. Inhibition of TERT expression significantly enhanced trophic factor deficiency-induced neuronal apoptosis[122]. Li *et al.* simulated *in vivo* cerebral hypoxia-ischemia injury by subjecting primary cultured neurons to hypoxia and glucose deprivation (OGD) for 3 h followed by reperfusion[123]. Ultimately, it was found that the neuronal TERT level increased 8 h after OGD, while the OGD-induced protease cleaved caspase 3 (CC3) level and neuronal apoptosis were detectable. The researchers then inhibited TERT expression and found a decrease in Bcl-2/Bax expression, an increase in ROS production, a decrease in the mitochondrial membrane potential, and enhanced apoptosis. Inhibition of apoptosis by TERT with Bcl-2/Bax has been demonstrated in previous studies in cancer cells[124,125]. It was suggested that TERT protects neurons from apoptosis induced by various stresses including cerebral hypoxia-ischemia by increasing the expression rate of Bcl-2/Bax and decreasing ROS production[123]. Zhang *et al.* verified that rapid nuclear stimulation of the cerebellum could achieve neuroprotection by upregulating the expression of TERT, and then increasing telomerase activity, in adult male SD rats[126]. Kwon *et al.* demonstrated the neuroprotective effect of GV1001 against focal cerebral ischemia-reperfusion injury and OGD/reoxygenation-induced injury in NSCs and cortical neurons in rats[127]. GV1001 reduces neuronal apoptosis and attenuates brain damage by inducing cell proliferation, maintaining mitochondrial function, as well as anti-apoptotic, anti-aging, and antioxidant effects.

CONCLUSION AND FUTURE PROSPECTS

NDDs are closely related to aging. Their pathogenesis is complex, and early features are inconspicuous, combining multiple neurological signs and symptoms, making it difficult to diagnose and differentiate between them. There are almost no treatment options, and the existing methods can only alleviate the disease, which imposes a heavy burden on society and families, and urgently requires searching for appropriate molecular biomarkers and targets for intervention. There is increasing evidence that telomeres and telomerase are significant factors in the pathogenesis and progression of NDDs, but the exact mechanism remains unclear. Telomere shortening leading to cellular senescence may be a means of preventing the accumulation of cancer cells in the nervous system. Studies have shown that LTL correlates well with the risk of NDDs. Even in post-mitotic cells such as neurons where telomere shortening is absent, telomere function remains impaired and induces DDR and senescence when oxidative stress occurs. Meanwhile, the association of telomeres with mitochondrial dysfunction and oxidative stress provides new perspectives on the pathogenesis and treatment of NDDs. A variety of telomerase activators exist as potential therapies for the treatment of NDDs, which are largely based on the non-canonical function of TERT outside of telomeres. This suggests that telomeres and telomerase could be novel biomarkers and intervention targets for NDDs. Although most studies have shown that peripheral blood LTL increases the

risk of NDDs, some studies have observed that leukocyte telomeres in patients with NDDs are not significantly different from those of healthy controls. However, DNA damage induced by oxidative stress, mitochondrial dysfunction, *etc.*, may not lead to significant telomere shortening, resulting in telomere fragility and dysfunction and contributing to the progression of NDDs. In addition, most of the current TERT-based therapies are animal experiments and are small in number, which need to be validated by more animal experiments and clinical trials. Meanwhile, the safety of TERT therapy should also be emphasized as it has a large impact range. In summary, we believe that telomeres and telomerase have a broad application prospect in the diagnosis and treatment of NDDs, and look forward to more relevant studies in the future.

DECLARATIONS

Authors' contributions

Literature search, writing, and original draft preparation: Shao J, Wang J
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