A TELOscopic View of Neuroinflammation

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Deterioration of physiological integrity that is observed with age is a primary risk factor for associated pathologies. Telomere shortening and chronic inflammation are two of such prominent cellular changes associated with ageing. Telomeres, the repeat sequences at chromosomal ends, are considered as the determinants of biological age. The ability of telomeres to predict cellular senescence has sparked a keen interest in understanding its role in age-related disorders. The highly interdependent relationship between the telomere biology and inflammation has been comprehensively described by Zhang and Rane, et al. A growing epidemic of chronic low grade inflammation seems to be a common denominator for many age-related diseases. Neuro-inflammation leading to neurodegeneration is considered as the primary cause of age-associated neurological disorders. Increasing studies indicate a link between telomere length (TL) and dementia or cognitive impairment, however, the role of telomeres in neurodegenerative disorder still remains ambiguous. The question of whether telomeres are cause or consequence of disease still remains. Nevertheless, in a recent report employing Mendelian randomization technique, TL has been causally linked to risk of Alzheimer’s disease. These results suggested that telomere might be a part of an active mechanism leading to the development of the disease. Telomeres thus provide an entirely new dimension to the understanding neurodegenerative disorders.

Keywords: Telomere; telomerase; inflammation; neurodegeneration


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Telomeres are nucleo-protein structures that cap the ends of eukaryotic chromosomes. In humans, the telomeric sequence is TTAGGG and is bound by specific complex of proteins called the shelterin complex. These shelterin proteins include, telomeric repeat-binding factor 1 and 2 (TRF1 and TRF2), TRF1-interacting protein 2 (TINF2 or TIN2), TPP1 and protection of telomeres protein 1 (POT1) and repressor-activator protein 1 (RAP1) [¹]. While telomeres

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are required to maintain chromosome stability, the length of telomeres decreases with age. When a critical minimum length is reached, telomeres become dysfunctional and trigger a persistent DNA damage response leading to cellular senescence. Senescent cells, although lack replicative potential, are metabolically active with extensive gene expression alterations [2]. In fact, these cells can adversely affect tissue microenvironment through release of pro-inflammatory signals (such as IL6, chemokines) termed as senescence associated secretory phenotype (SASP). This leads to chronic inflammation and is often associated with ageing and can lead to development of disease. Interestingly, persistent DNA damage signaling, that is also observed due to telomere dysfunction, is associated with inflammatory cytokine secretion very similar to SASP [3, 4]. In addition, in chronic inflammation models, telomere dysfunction is highly exacerbated as compared to controls [5]. Conversely, elevated chronic inflammation is found in animal models of telomere dysfunction.

Aging is characteristically accompanied by a shift from innate immunity to a pro-inflammatory status. It is now widely recognized that age and inflammation play an important role in the development of AD [6, 7]. Activation of the complement system leads to the upregulation of complement activation fragments, including opsonins and anaphylatoxins which stimulate the chronic state of complement activation and chronic inflammation in the Alzheimer’s disease (AD) brain [8, 9]. It is now widely recognized that age and inflammation play an important role in the development of AD [6, 7]. AD is characterized by deposition of amyloid β-peptide (Aβ) and other derivatives of the amyloid precursor protein, leading to degeneration of neurons in brain regions ultimately resulting in progressive cognitive dysfunction [10]. Pro-inflammatory mediators such as TNFα, IL-1β and IL-6 can stimulate synthesis of amyloid precursor protein. In addition, they also can combine with interferon-γ to stimulate the production of Aβ peptides [11]. A dysregulation of the balance between the production and the degradation of Aβ can trigger chronic inflammatory processes in microglial cells and astrocytes. Cumulated over many years, direct and bystander damage from AD chronic inflammatory mechanisms is likely to significantly exacerbate the very pathogenic processes and lead to a perpetuation of this disease [9]. The accumulation of Aβ at sites in microglia enhances expression of RAGE (Receptor for Advanced Glycation End products), which exaggerates neuroinflammation [12]. RAGE is a multi-ligand receptor belonging to immunoglobulin superfamily of cell surface molecules and is known to exacerbate cellular damage and dysfunction in several inflammatory disorders. Initially reports indicated that RAGE mediates Aβ induced neurotoxicity through its role in intra-neuronal transport of Aβ [13, 14]. RAGE is expressed at basal levels in normal tissues but is amplified at sites where its ligands are shown to accumulate [15]. Recent evidence identified amyloid beta as a ligand for RAGE [16, 17]. RAGE was shown to mediate transport of amyloid beta peptide across the blood brain barrier [16]. Perturbation of RAGE-amyloid beta interaction reduced its accumulation in mice brain. Moreover, due to the increased concentration of the ligands, there is overexpression of RAGE, which perpetuates oxidative stress and upregulates NF-κB. The NF-κB activation activates expression of pro-inflammatory cytokines and also upregulates RAGE expression, indirectly prolonging its activation via a positive feedback loop [18]. This increases localized inflammation, which can subsequently lead to cellular damage and cell death. With the recent discovery of RAGE as a mediator of inflammation through the NF-κB signaling pathway, research has been channeled into interventions to block RAGE and measure its effect on neuroinflammation [12]. Neuroinflammation eventually impairs neuronal function and leads to AD pathogenesis. Additionally, many nonsteroidal anti-inflammatory drugs (NSAIDs) have been investigated for their potential influence on amyloid precursor protein processing and the production of Aβ peptides. For example, Ibuprofen, as a commonly over-the-counter used NSAID, decreases cytokine-stimulated Aβ production in human neuronal cells and astrocytes [19]. Therefore, anti-inflammatory agents might protect against neurodegeneration in AD. However previous attempts of RAGE inhibition to curb Alzheimer’s pathogenesis did not prove beneficial [20].

Increase in oxidative stress occurs during normal ageing and more so in neurological disorders along with chronic systemic inflammation which can lead to an increased rate of telomere attrition and cellular senescence. Cross-sectional analyses revealed associations between short leukocyte telomere length (LTL) and Alzheimer’s disease, Parkinson’s disease, cognitive impairment, the ApoE4 gene variant, psychological stress and cognitive function was observed even in neurologically healthy individuals [21-23]. In addition, smaller hippocampal volume, an indicator for cognitive decline, is linked to LTL as well as the ratio of telomerase activity to LTL [24]. A longitudinal study also reported an association of LTL shortening with dementia [25]. Exciting results from a recent study suggests a causal link between TL and risk of Alzheimer’s disease based on Mendelian randomization [26]. Presence of neurological deficits in diseases characterized by excessive telomere shortening and dysfunction and mice models of telomere dysfunction further underscores its role of neurodegenerative disorders [27-29]. However, the association of TL with dementia and its risk factors is not uniformly positive in literature. For instance, some studies either did not observe an association with
Alzheimer’s disease, cognitive impairment, hippocampal volume and APOE status or observed their association with longer LTL [21, 25, 30-32]. A possible explanation for the inconsistency could be inherent variability in TL. Furthermore, the critical minimum length at which cell undergoes senescence may vary between individuals. A high variation in lifestyle as well as diet which in turn affects stress and inflammation could be another possible explanation. Although statistical analysis revealed a causal link between LTL and AD, whether LTL truly reflects the alterations in brain still remains a question. There is a pressing need for a parallel investigation of LTL with neuronal functioning, inflammatory and oxidative stress markers in brain as well as blood.

In the midst of limited therapeutic strategies for management of dementia, telomerase research has gained limelight [33]. The reverse transcriptase domain of telomerase, TERT, has protective effects against Aβ toxicity and also reversed neurological dysfunction observed in telomerase deficient mice [28, 34]. Furthermore, telomerase expression negatively correlated with tau pathology in the hippocampus of AD brains [55]. TERT based peptide vaccine has shown promise against Aβ toxicity in neuronal stem cells [36]. In mice lacking the RNA subunit of telomerase (mTERC−/−), immune cells of telomerase deficient mice exhibited elevated chromosome instability which induced inflammation through TLR4 mediated activation of NF-κB [37]. The NF-κB-telomerase-Wnt axis represents a novel mechanism contributing to neurodegeneration and has been discussed extensively in the review by Zhang and Rane et al [38]. NF-κB was shown to be in a feed-forward loop with telomerase levels in cancer cells, although whether this also true in brain cells needs to be established [39]. TERT is also a transcriptional modulator of the Wnt signaling pathway [40]. Wnt signaling plays a role in inflammation and is linked to disorders of the central nervous system [41, 42]. Another intriguing facet of neuroinflammation is Glycogen Synthase Kinase-3 beta (GSK-3 beta) [43, 44]. In brain endothelial cells, GSK-3 beta inhibition decreased expression of

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**Figure 1. Telomeres: A mitotic clock in neurodegeneration fuelled by inflammation.** The key features of brain ageing are indicated in black and the mediators are depicted in green. (SASP – senescence associated secretory phenotype; RAGE – receptor for advanced glycation end products; GSK-3 beta – glycogen synthase kinase 3 beta; Wnt - Wingless, the Drosophila melanogaster segment-polarity gene, and Integrase-1, the vertebrate homologue; NF-κB - Nuclear Factor Kappa B; DP103 – DEAD-box RNA Helicase, DDX20).
proinflammatory cytokines and chemokines \cite{45}. Increased GSK-3 beta activity has been linked to AD \cite{46} and is implicated to play a role in memory formation \cite{47, 48}. Importantly, GSK-3 beta could be a link between Aβ and tau pathology \cite{49}. Aβ exposure increases GSK-3 beta activity \cite{50} which could increase phosphorylation of tau \cite{51}. Of note, phosphorylation of tau by GSK-3 beta is regulated by Presenilin 1, mutations in which are linked to early onset familial AD \cite{52, 53}. As a mediator of NF-κB signaling, GSK-3 beta plays a significant role in neuroinflammation \cite{54, 55}. Inhibition of GSK-3 beta reduced NF-κB activation while upregulated beta-catenin levels in hepatocytes \cite{56}. Interestingly, our group recently showed DP103, a ATP-dependent DEAD-box RNA helicase in a positive feedback with TAK1 promotes constitutive NF-κB activation \cite{57}. DP103 belongs to a family of DEAD box family of proteins that are characterized by conserved Asp-Glu-Ala-Asp (DEAD) motif \cite{58}. A component of survival of motor neuron (SMN) complex \cite{59}, DP103 transcriptionally represses the expression of early growth response 2 (Egr2), a transcription factor required for myelination of peripheral nervous system and development of hindbrain \cite{60}.

In conclusion, chronic inflammation that is observed during ageing works in concert with components of telomere maintenance machinery. Together, they could promote development of diseases associated with age such as dementia (Figure 1). Neuroinflammation is an underlying factor for the development of numerous pathologies associated with neurodegeneration. Inflammation heightens telomere dysfunction which in turn induces cellular senescence that subsequently amplifies inflammation. The cross-talk between inflammation and telomerase has not been studied comprehensively in neurological background. For instance, the role of telomerase in neurological homeostasis has not been systematically characterized. However, given the cancer promoting effect of telomerase, researchers should tread cautiously when considering telomerase as a therapeutic target. Apart from telomerase, the new players in regulation of inflammatory pathways such as RAGE and DEAD-box RNA helicase, DP103, will open a new area for further investigation and development of therapies for neurodegenerative diseases.

**Conflicting interests**

The authors have declared that no conflicts of interests exist.

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**Abbreviations**

Aβ: Amyloid beta; TL: telomere length; AD: Alzheimer’s disease; RAGE: Receptor for Advanced Glycation End products; GSK-3 beta: Glycogen Synthase Kinase-3 beta; Wnt: Wingless, the Drosophila melanogaster segment-polarity gene, and Integrase-1, the vertebrate homologue; NF-κB: Nuclear Factor Kappa B; DP103: DEAD-box RNA Helicase, DDX20.

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