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Review

Neuroprotective effects of the catalytic subunit of telomerase: A potential therapeutic target in the central nervous system

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ABSTRACT

Senescence plays an important role in neurodegenerative diseases and involves key molecular changes induced by several mechanisms such as oxidative stress, telomere shortening and DNA damage. Potential therapeutic strategies directed to counteract these molecular changes are of great interest for the prevention of the neurodegenerative process. Telomerase is a ribonucleoprotein composed of a catalytic subunit (TERT) and a RNA subunit (TERC). It is known that the telomerase is involved in the maintenance of telomere length and is a highly expressed protein in embryonic stages and decreases in adult cells. In the last decade, a growing number of studies have shown that TERT has neuroprotective effects in cellular and animal models after a brain injury. Significantly, differences in TERT expression between controls and patients with major depressive disorder have been observed. More recently, TERT has been associated with the decrease in reactive oxygen species and DNA protection in mitochondria of neurons. In this review, we highlight the role of TERT in some neurodegenerative disorders and discuss some studies focusing on this protein as a potential target for neuroprotective therapies.

Contents

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1. Introduction

Senescence is a process of mitotic arrest of the cell cycle, which is started in the G1/S check-point (Muller, 2009). During this state the cell experiences several modifications, such as changes in morphology, metabolism and expression of cytokines and growing factors. These changes result in what is known as the Senescence-Associated Secretory Phenotype (SASP) (Fridlyanskaya et al., 2015). It has been considered that senescence might be caused by a series of biological processes, including telomere shortening, oxidative stress, DNA damage, calcium dysregulation, misfolded proteins and oncogene expression (Liu, 2014). Senescence is divided into replicative senescence, Stress-Induced Premature Senescence (SIPS) and oncogene-induced senescence, being SIPS the most important for the central nervous system (CNS) (Tan et al., 2014). Premature senescence caused by stress can involve telomere-dependent or telomere-independent mechanisms (Muller, 2009). Mitochondria play an important role in senescence, as they are among the organelles that produce more oxidative stress and their dysfunction has been associated with high levels of reactive oxygen species (ROS) in senescent cells (Correia-Melo and Passos, 2015) and during aging (Melo et al., 2011). Moreover, the increase in ROS leads to telomere shortening. Telomeres are G-rich sequences, which are sensitive to oxidation and therefore ROS can induce DNA damage in telomeres (Oikawa and Kawanishi, 1999). In addition, repair mechanisms of telomeric DNA seem to be particular and need to be studied in more detail. For example, a study found that after UV irradiation the repair was absent in fibroblasts (Rochette and Brash, 2010), whereas in oxidative guanine damage in mouse cells the base excision repair (BER) pathway participated in oxidative base repair in telomeres (Wang et al., 2010).

Strategies directed to counteract the molecular changes in senescent cells have been explored. Several studies have found that telomerase has neuroprotective effects in the brain and it has been shown that its expression and activity are increased after injury (Table 1). Telomerase is a ribonucleoprotein responsible for telomere length maintenance, and it has been demonstrated that its protein component (Telomerase Reverse Transcriptase, TERT) has extra-telomeric functions, which are important for post-mitotic cells such as neurons (Spilsbury et al., 2015). TERT overexpression is associated with decreased ROS levels (Spilsbury et al., 2015) and with the reduction of excitotoxicity induced by NMDA in neurons (Kang et al., 2004). TERT has effects on neuronal survival because it regulates Bcl2/Bax expression (Li et al., 2013). Therefore, TERT could be considered as a key protective protein since it may decrease some secretory phenotypes of senescence in the brain, which have been associated with the onset of neurodegenerative diseases (Tan et al., 2014).

Senescence is associated with cellular mechanisms that trigger neurodegenerative diseases and other aging-associated process. It has been shown that senescence involves mitochondrial dysfunction, morphological changes, activation of p38 mitogen-activated protein kinases (p38MAPK) and increased secretion of proteins and factors, such as β-galactosidase and IL-6, by astrocytes and neurons (Bhat et al., 2012; Jurk et al., 2012), in both normal aging and neurodegenerative conditions such as Alzheimer's (AD) and Parkinson's (PD) diseases. Another important factor for senescence is telomere length, although its role in neurological diseases is still controversial. Several studies have found that telomere loss is associated with diseases such as schizophrenia (Polho et al., 2015), depression (Lin et al., 2016) and AD (Tedone et al., 2015). A recent meta-analysis of 13 primary studies (including 860 AD patients and 2022 controls) found shorter telomeres in AD patients (Forero et al., 2016a). Another recent meta-analysis for PD, including 8 primary studies (956 PD patients and 1284 controls), did not find shorter telomeres in samples of leukocytes in PD patients (Forero et al., 2016b). On the other hand, there are different mechanisms by which senescence could affect the brain. For example, SASP of mitotic cells such as microglia, astrocytes, endothelial cells and oligodendrocytes can affect neurons, leading to a pathological state due to the inflammatory factors and loss of trophic support from astrocytes to neurons (Chinta et al., 2015). In the brain there are mitotic (glial cells) and post-mitotic (neurons) cells and therefore senescence in post-mitotic cells does not involve cell cycle arrest, rather it involves a block on re-entering the cell cycle (Campisi and d'Adda di Fagagna, 2007). Interestingly, a study showed that BrdU+ astrocytes expressing Aldh1l1, a protein known to be expressed by mature astrocytes, did not resume proliferation from days 2–7 after focal brain ischemia, demonstrating that mature astroglia do not proliferate as highly as expected following injury (Barreto et al., 2011a,b,c, 2012).

As senescence leads to an alteration in cellular function and structure in the CNS, this process could be considered as the starting point for the search of new treatments against neurodegenerative diseases. Therefore, a therapeutic intervention for senescence in CNS may be associated with an increase of TERT expression and/or telomerase activity (Table 1). Here we discuss the role of TERT in brain pathologies and studies that have explored it as a potential target for neuroprotective therapies.

2. Telomeric complex

2.1. Telomeres

Telomeres are DNA sequences at the end of the chromosomes that consist of a repetition of TTAGGG (G-rich strand) with orientation 5′-3′ towards the terminal portion of the chromosome (Gomez et al., 2012). Telomeres, which are folded into a T loop structure that gives stability to the genome, avoid fusion of nearby chromosomes and serve as binding sites for DNA repair proteins. Telomeres act as a cellular biological clock since their shortening has been observed after each DNA replication (Harley, 1991). When the telomere length reaches a lower limit, then the cell enters apoptosis or senescence. Moreover, telomere shortening is the main cause of replicative senescence, which is triggered by the p53-p21 and DNA-damage response (DDR) pathways (Muller, 2009). On the other hand, several factors such as genetic, epigenetic and environmental variables can lead to shortening of telomeres. During aging telomere loss is observed, however life styles such as smoking, obesity, lack of exercise and an inadequate diet might accelerate the telomere shortening and therefore increase risk for different diseases (Shammas, 2011).

Until now it is unknown the mechanisms by which the telomeres are affected in post-mitotic cells such as neurons, but it is thought that ROS could be involved in telomere shortening, although further studies are needed to elucidate this issue (Eitan et al., 2014). For this reason telomere shortening could be associated with the pathophysiological mechanisms of several diseases (Cai et al., 2013). Interestingly, a study has demonstrated that hydrogen peroxide (H_2O_2) induces DNA damage in the 5′site of 5′-GGG-3′ in the telomere sequence (Oikawa and Kawanishi, 1999). Two methods have been commonly employed to analyze telomere length in large cohorts of neurological patients: the Terminal Restriction Fragment technique, which uses restriction enzymes and Southern blot; and a technique based in quantitative Polymerase Chain Reaction (qPCR), which uses 4 primers binding telomere sequences and a single copy gene (Lustig, 2015; Speck-Hernandez et al., 2015). Furthermore, in several neurological disorders, differences in telomere length are associated with functional genetic variants, which can induce changes in the activity of