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Review

# From cellular senescence to Alzheimer's disease: The role of telomere shortening

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ABSTRACT

The old age population is increasing worldwide as well as age related diseases, including neurodegenerative disorders, such as Alzheimer's disease (AD), which negatively impacts on the health care systems. Aging represents *per se* a risk factor for AD. Thus, the study and identification of pathways within the biology of aging represent an important end point for the development of novel and effective disease-modifying drugs to treat, delay, or prevent AD. Cellular senescence and telomere shortening represent suitable and promising targets. Several studies show that cellular senescence is tightly interconnected to aging and AD, while the role of telomere dynamic and stability in AD pathogenesis is still unclear. This review will focus on the linking mechanisms between cellular senescence, telomere shortening, and AD.


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## 1. Introduction

Alzheimer's disease (AD) is the major cause of dementia in old age subjects, affecting more than 40% of individuals over the age of 85 (Hebert et al., 2003; Selkoe, 2012). Along with population aging, by 2050 AD is predicted to affect 1 out of 85 people worldwide (Brookmeyer et al., 2007; Selkoe, 2012), with a consequent heavy impact on health care systems.

Aging is a natural process characterized by a progressive functional decline of tissues, organs, and organ systems, which leads to an increased susceptibility to age-related diseases and, ultimately, to death. A persistently DNA damage response (DDR), known as "cellular senescence", is one of the main contributing factor to age-associated tissue dysfunction, reduced regenerative capacity, and age-related diseases (Hayflick, 1976; Collado et al., 2007). Upon generation of a DNA damage, cells activate a DDR to coordinate the DNA repair and the transient arrest of cell-cycle progression until DNA damage has been removed. If the DNA damage remains unrepaired, cells enter in a permanent growth arrest, associated with a permanent active DDR. Senescent cells accumulate along with aging in many tissues (Collado et al., 2007; Herbig et al., 2006;

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Jeyapalan et al., 2007), but little is known about the appearance of DDR expressing cells in the brain. However, it has been suggested that brain senescence may contributes to AD pathogenesis and may represent a link between the aging process and disease development.

Telomeres, evolutionarily conserved DNA sequences located at the end of chromosomes, shorten with each cell division, and replication event in most human tissues (Baird and Kipling, 2004; Campisi, 2005). From recent reports telomere shortening is emerging as a potential contributor to AD pathogenesis (reviewed in Eitan et al., 2014). However, results from studies in subjects suffering from AD are contradictory: while telomere shortening is observed in peripheral blood cells (Zhang et al., 2003; Panossian et al., 2003), opposite results have been obtained from hippocampus of AD brain (Thomas et al., 2008). Telomere shortening might also contribute to cognitive impairment in patients with AD (Jenkins et al., 2006), although a recent study in a murine AD model demonstrated that shorter telomeres are associated with a better cognitive status (Rolyan et al., 2011).

Whether telomere shortening is a cause or a consequence of AD is unknown and the linking mechanism between telomere shortening, AD pathology, and cognitive impairment remains unclear. This review aims at investigating the role of the more recent findings on cellular senescence and the emerging role of telomere maintenance in AD pathogenesis.

## 2. Replicative cellular senescence and telomere shortening

Cellular senescence has been described more than 50 years ago as a process that limits the growth of normal human cells in culture. Cellular senescence is closely interconnected with aging, longevity, and age related diseases by sharing common genes, regulators, and multiple signaling pathways (Tacutu et al., 2011). Cells do not have the ability to proliferate indefinitely, but they arrest irreversibly after a limited number of divisions, phenomenon known as “Hayflick limit” (reviewed in Campisi and d’Adda di Fagagna, 2007). A senescent cell changes its morphology, becomes flatter and wider, increases β-galactosidase activity expression, p16 levels, and heterochromatin foci (dense puncta of DNA observed *in vitro* following senescence) that, all together, represent validate biomarkers of cellular senescence. However, senescence is not restricted to the loss of cell replicative ability, but involves complex changes in cellular metabolism, gene expression, and epigenetic regulation (reviewed in Tan et al., 2014). In fact, disruption of energy metabolism is frequently observed in senescent cells. Here, the mitochondria are abnormally elongated, likely due to increased expression of mitochondrial fusion proteins which may confer protection against oxidative stress (Mai et al., 2010). Again, gene expression profiles suggest that senescence is a tightly regulated process, with consistent alterations in heterochromatin foci across tissues. In addition, senescent cells acquire the ability to express a senescence-associated secretory phenotype (SASP) characterized by the secretion of many inflammatory cytokines, growth factors, and proteases (Coppe et al., 2010a,b,b). Indeed, emerging and novel evidences suggest that specific gene expression and epigenetic mechanisms allow senescent cells to effect on microenvironment and, through SASP, to mediate organism-wide phenotypes, such as systemic inflammation. The fact that a recent network analysis of age related genes revealed multiple connections to cellular senescence and systemic inflammation, further support the role of senescence in organismal aging (Tacutu et al., 2011).

Consistent with the Hayflick’s proposal, it has been demonstrated that, along with the expansion of human cells in culture, telomeres progressively shorten, ultimately leading the cells to stop dividing and become senescent (phenomena identified as replicative cellular senescence). Telomeres are a nucleoprotein complex located at the very end of linear chromosomes, whose primary function is to prevent cells from sensing the linear chromosome ends as “damaged”, and so maintaining the genome stability. In vertebrates, telomeres are composed of tandem repeats of the TTAGGG sequence bound by a set of specialized proteins, known as “shelterin complex” (Sfeir et al., 2005; de Lange, 2002). In the absence of a compensatory elongating mechanism, telomeres get shorter with each cell division due to the so-called “end replication problem” (Harley et al., 1990). This problem derives from three features of DNA replication. First, replication is bidirectional (replication proceeds in both 5′ and 3′ direction from an origin of replication); second, DNA polymerases are unidirectional, polymerizing exclusively in 5′–3′ direction; and third, DNA polymerases require a primer, which is supplied as a short tract of RNA. Due to the end replication problem, DNA polymerases cannot fully complete the replication of the 3′ end of linear DNA, resulting in a gap of 50–200 base pairs of telomeric DNA which leads telomeres to shorten progressively with repeated cell divisions. Short and dysfunctional telomeres cannot be repaired by any of the known DNA repair mechanisms and consequently trigger a persistent DNA damage response (DDR), which leads a cell to senescence (Sfeir et al., 2005; de Lange, 2002, reviewed in Klement and Goodarzi., 2014). Considering that DNA damage generated at telomeres is resistant to repair, shorter telomeres are favourite targets of persistent DDR activation during ageing process (Hewitt et al., 2012; Fumagalli et al., 2012). Most importantly, persistent DDR has been observed with ageing also in non dividing cells, whose telomeres are not necessary short, such as primates neurons and liver hepatocytes (Fumagalli et al., 2012, 2014).

Telomerase is a multi-protein complex containing a reverse transcriptase catalytic subunit (TERT) and an associated telomerase RNA template (TERC). As a reverse transcriptase, telomerase adds DNA repeats to chromosome ends, counteracting telomere shortening associated with replication and degrading activities (Blackburn, 2000). However, immediately after birth, telomerase is silenced in most of somatic cells and telomeres progressively start their countdown to senescence (Masutomi et al., 2003). The dependence of replicative senescence on telomere shortening is evident from its bypass by the ectopic expression of the catalytic subunit of the telomerase holoenzyme (hTERT), which elongates telomeres, thereby, abrogating the effect of the end replication problem (Bodnar et al., 1998). But a very recent study performed in budding yeast demonstrated that early telomerase inactivation leads to accelerated aging also through a mechanism independent from senescence caused by telomere shortening (Xie et al., 2015).

Senescence may contribute to organismal aging and aging phenotype expression *in vivo*. In fact, as in culture, markers of senescence have been found to increase progressively with age in most organisms, including mouse and human tissues (Herbig and Sedivy, 2006; Jeyapalan et al., 2007; Jeyapalan and Sedivy, 2008). However, little is known about the potential role of senescent cells in brain aging and/or in neurodegenerative disorders, such as AD.

### 2.1. Cellular senescence in aging brain

The brain is basically composed of two different kinds of cells: glial cells (astrocytes and microglia) and neurons. Astrocytes are involved in the modulation of synaptic neuronal function and plasticity (Ota et al., 2013), while microglia work as resident macrophages (Streit, 2002a,b,b), providing immune surveillance and mediating innate immune responses to pathogens or injuries. Neurons are terminally-differentiated post-mitotic cells while glia, particularly microglia, are the only adult cell type in the central nervous system (CNS) that exhibit a significant mitotic potential, and are susceptible to telomere shortening. Increasing evidences