Telomeres in Neurons
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Boosting TERT Levels with Telomerase Activators to Counteracts Symptoms of Neurodegeneration
A Possible Link between TERT and Autophagy

Introduction
The enzyme telomerase consists of the two minimal components: telomerase reverse transcriptase (TERT) and the telomerase RNA component (TERC). Using this inherent RNA, it is a reverse transcriptase and an RNA-dependent DNA polymerase. Its main function is to maintain and elongate telomeres which are shortened during cell division due to the so-called “End Replication Problem” (Olovnikov, 1972). This problem occurs during the semi-conservative DNA replication in S-phase when linear chromosome ends can only be completely replicated on one strand (the leading), but not on the lagging one. This telomere-dependent function is the best-described function of telomerase and its canonical role. Linear chromosomes are found in most eukaryotic organisms and with some exceptions, most of those employ telomerase to maintain their chromosomes in dividing cells because critically short telomeres induce senescence and prevent proliferation (Harley et al., 1990).

However, in higher organisms such as mammals, the protein component TERT apparently evolved additional functions that do not require the TERC RNA and are not related to telomeres. For example, it was shown that TERT can shuttle out of the nucleus into the cytoplasm and even reside within mitochondria due to its specific localization sequence (Haendeler et al., 2003; Santos et al., 2004) making it a regulated physiological process. Here the protein has various functions such as decreasing oxidative stress and sensitivity to apoptosis (Ahmed et al., 2008; Haendeler et al., 2009; Singhalop et al., 2013) although the underlying mechanisms are far from known. However, due to its many functions, an involvement of TERT/telomerase in processes such as mitochondrial respiration (Haendeler et al., 2009) and prevention of DNA damage (Masutomi et al., 2005; Singhalop et al., 2013) might explain some of these functions. For more detailed reviews on these non-canonical functions of TERT, please see reviews (for example, Saretzki, 2014; Thompson and Wong, 2020).

While oxidative stress seems to be the best-studied cause for mitochondrial localization of TERT, paradoxically, also other agents that are rather known to decrease oxidative stress such as the mTOR inhibitor rapamycin were shown to promote nuclear exclusion of TERT protein in a cancer cell model (Miwa et al., 2016).

Search Strategy and Selection Criteria
PubMed was searched manually from 2000–2021 using the following keywords/terms: telomerase, TERT, brain, and neurodegenerative disease.

Telomerase in Neurons
More than 20 years ago, Mark Mattson’s group pioneered research on the role of telomerase in cultured neurons. Employing overexpression of telomerase in primary murine hippocampal neurons or inhibition of its activity (using antisense technology) in pheochromocytoma (a neuroendocrine tumor) cells they demonstrated that telomerase is involved in normal brain development, response to neuronal growth factors as well as prevention of apoptosis in response to neurotoxic substances (Fu et al., 2000; Zhu et al., 2000).

Cytoplasmic and mitochondrial localization has recently also been demonstrated in hippocampal neurons while no TERT protein was detected in the nucleus (Tannilli et al., 2013; Spilsbury et al., 2015). This seems to make sense since neurons are postmitotic cells that do not divide in adult tissue and thus have no need for telomere maintenance with telomerase activity. However, it has been shown that processes like cellular senescence still occur in neurons and other postmitotic cells and that telomeres in these cells can still be damaged and emanate DNA damage signals like in dividing cells without any telomere shortening (Jurk et al., 2014). Similar to neurons, astrocytes also do not express telomerase activity but continue to divide and thereby also shorten their telomeres and reach senescence and can thus influence neurodegenerative processes (Bussian et al., 2018).

In contrast, other groups have found telomerase in all neuronal subcellular inclusions such as the nucleus in other neuron types such as Purkinje neurons (Eitan et al., 2012a, 2016). Thus, there could be differences between different neuron types, but only very few of those have so far been analyzed. In general, telomerase activity is maintained only in rare neural stem cells residing in the dentate gyrus and subventricular zone of the brain.

The hippocampus is essential for spatial cognition and is also often involved in neurodegenerative diseases such as AD. While in the mouse brain TERT expression decreases during aging (Miwa et al., 2016) in humans no such decrease has been reported (Ishaq et al., 2016), although systematic studies with larger numbers are still missing. Our group also did not find any decrease in the amount of TERT protein in hippocampal neurons from AD brains compared to age-matched brains from normal controls (Spilsbury et al., 2015). Thus, there seem to be essential differences in telomerase biology in the brain in addition to the well-known differences in telomere biology between rodents and humans as well as other mammals. While telomerase activity is downregulated in the human brain very early during development (approximately around post-conception weeks 8–10) (Ishaq et al., 2016), in mice telomerase activity decreases steadily from embryonic day 13 on, but
has still been detected until early postnatal stages (day 10) (Klapper et al., 2000). In culture, primary mouse embryonic neurons lose telomerase activity around/after days 12–14 (Spilsbury et al., 2015), thus can be used at that stage to analyze non-telomeric functions of the TERT protein.

Interestingly, Ianniilli et al. (2013) found that the TERT protein can form complexes with RNA particles and the cell cycle inhibitor p15 in the in vitro setting. In the case of oxidative stress, the complex is resolved and the different components are released to fulfill their various functions. Increased mitochondrial localization of TERT protein in neurons was also described after increased glutamate stress, while other types of stress such as irradiation transiently upregulated TERT levels (Eitan et al., 2016).

Telomerase/TERT and Neurodegenerative Diseases

It has been well documented that the number of people with neurodegenerative diseases is steadily increasing in our aging population. Unfortunately, there are currently no cures available to combat these devastating diseases that target not only the patients, but also their families and carers. Consequently, a better understanding of the molecular mechanisms is imperative in order to develop new therapies in the future.

The connection between telomerase and the brain is a relatively new field and seemed surprising initially. However, due to its potential importance to ameliorate neurodegenerative diseases, there is intensive research underway to elucidate the potential of TERT localization in the brain and neurons in particular. As mentioned above, agents such as rapamycin seem to be capable of decreasing oxidative stress in brain mitochondria in a TERT-dependent manner. Miwa et al. (2016) have demonstrated in cell models in vitro as well as in a mouse model in vivo that a beneficial effect of rapamycin on oxidative stress and brain mitochondrial localization of TERT protein in cells without TERT or when cytoplasmic localization of TERT was prevented using the sr-kinase inhibitor bosutinib, the effect of rapamycin on decreasing reactive oxygen species (ROS) was diminished. Likewise, only wild-type mice but not TERT KO mice responded to rapamycin treatment with a decreased ROS level in their brain tissue (Miwa et al., 2016). Similarly, Crews et al., (2010) demonstrated a beneficial effect of rapamycin on the brains of a mouse model of PD. Rapamycin as an mTOR inhibitor is able to activate autophagy, which plays an important role in neurodegeneration by degrading various toxic brain proteins, such as pathological tau and aggregated α-synuclein. In addition, other protein degradation processes, such as proteasomal degradation, are also involved in degrading toxic proteins in the brain.

Our group was the first to report a potential connection between TERT protein and hippocampal neurons in AD. While, as stated before, we did not find a decrease of TERT protein in AD hippocampus compared to age-matched controls we found a significant increase of TERT protein within mitochondria in hippocampal neurons of Braak stage 6 AD brains compared to normal controls (Spilsbury et al., 2015). With our knowledge of TERT entering mitochondria under increased oxidative stress (Ahmed et al., 2008; Haendeler et al., 2006; Jia et al., 2020), we interpret this data as an attempt to decrease oxidative stress, which is characteristic for AD neurons (Tobone, 2019). This suggestion was also strengthened by an observation that in normal brains TERT protein was predominantly found in neurons which diminished as hyperphosphorylation of tau or α-synuclein accumulated with increasing Braak stages (Spilsbury et al., 2015). However, using just steady-state brain tissue, we were not able to discriminate mechanistically between TERT protein being displaced by accumulating pathological tau protein or high amounts of TERT protein actively preventing TERT from accumulation from occurring. By performing experiments with primary embryonal mouse neurons which were transduced with pathological tau we were able to confirm that neurons from TERT KO mice had a higher ROS level in neuronal dendrites as well as higher lipid peroxidation in neuronal bodies compared to neurons from wild-type mice harboring TERT protein. In addition, an oxidative challenge actively promoted a mitochondrial localization of TERT protein in TERT wild-type neurons (Spilsbury et al., 2015). These results clearly demonstrated a protective effect of TERT protein in a model of tau-related pathology. Similar experiments were recently performed by another group using a model of cultured neurons treated with wild-type amyloid-β (Aβ) (Baruch-Eliyahu et al., 2019). This treatment resulted in the expected neurotoxicity, which could be reversed by increasing TERT levels. This data will be described in the next heading.

Boosting TERT Levels with Telomerase Activators to Counteracts Symptoms of Neurodegeneration

When Baruch-Eliyahu and colleagues (2019) employed a synthetic telomerase activator (Tri-aryl derivative) on their Aβ-treated neuronal cultures, they found an increase of TERT expression as well as of neurotrophic factors, such as nerve growth factor and brain-derived neurotrophic factor, as well as several plasticity genes counteracting the neurotoxic effects of Aβ treatment. A similar effect was also observed, when they performed a short-term treatment (12 hours) of wild-type mice (Baruch-Eliyahu et al., 2019). The same group had demonstrated previously on a mouse model of amyotrophic lateral sclerosis that disease symptoms could be significantly delayed when applying the same AG699 telomerase activator (Eitan et al., 2012b).

In addition to AGS-499, there are at least two more telomerase activators from the American Company TA Science Inc. One is a purified plant extract TA-65 (cycloastragenol, Harley et al., 2011) from mongolian milkvetch (Astragalus membranaceus) and the other a synthetic derivative GRN510 (Le Saux et al., 2013). Our group has used both of those activators on 2-year-old wild type mice in an oral treatment for 3 months and found an increase of TERT expression in brain tissue as well as an improvement of motor properties, such as a decrease of the latency on the rotarod due to treatment with both activators (Wan et al., 2021). In addition, we used a mouse model of PD which has been developed by E. Masliah’s group (Masliah et al., 2000) and overexpresses human wild-type α-synuclein, predominantly in the hippocampus, neocortex, and olfactory bulb. These mice accumulate α-synuclein around the age of 12 months, which coincided with an increase in disease severity of PD-like symptoms (Amschi et al., 2013). Treating those mice for 14 months starting at 4 months with a daily dose of 25 mg/kg body weight for TA-65 and 10 mg/kg body weight the study found, similar to the wild type mice, a significant increase in the TERT expression in brain tissue as well as with both activators (Wan et al., 2021). Analyzing different parameters related to PD symptoms, the study demonstrated a gender-specific effect on balance on a Rota-rod which measures time on the rod, speed (which is increased incrementally) as well as distance traveled by each mouse. While males showed no significant improvement of TERT levels in their brains, females generally improved, for example in gene expression. Such sexual dimorphism after using both activators was described previously in a study (Eyrjofson et al., 2020). In contrast, a simple stride length test, similar to that used in human PD patients in order to measure gait, showed a substantial improvement in stride length, width as well as a decrease in variability in both sexes with both activators (Wan et al., 2021). Other tests, such as general activity (cylinder test) or novel object recognition test, were less conclusive.

Regarding a possible danger of oncogenicity of increased TERT expression, no tumors have been identified up to 18 months of daily local treatment with TA-65 in the study of Wan and co-workers although this occurrence cannot be entirely excluded at a higher age. However, it is well known that most tumors acquire a higher telomerase activity and enhanced TERT levels via genetic (mutations) and epigenetic (methylation and miRNA) events in vivo (Harley et al., 2011). While telomerase activators act on the physiological level of TERT expression rather moderately. Consequently, no major side-effects of an exacerbated tumorigenesis are expected for telomerase activation via a plant-derived activator, such as TA-65 whose applied daily dose in humans is also much less than that used in animal experiments in rodents (Harley et al., 2011; Salvador et al., 2016).

A Possible Link between TERT and Autophagy

Intriguingly, when the study from Wan et al. (2021) analyzed brain pathology, it found a significant decrease of total, phosphorylated and aggregated α-synuclein levels in the hippocampus as well as the neocortex with both activators. It is well known that important mechanisms of combating the accumulation of toxic brain proteins such as amyloid-β, hyperphosphorylated tau or aggregated α-synuclein, are protein degradation processes (Ciechanova and Kwon, 2015). Thus, a possible hypothesis for the decrease of different forms of α-synuclein in the brains of PD model mice has been that autophagy is an important degradation mechanism which was promoted by increasing TERT. Consequently, the study analyzed p62, an adaptor protein for autophagy, as well as a protein on the membrane of autopahosomes LC3B (microtubule-associated protein 1A/1B-light chain 3-B) in hippocampal and neocortical regions of the hTERT promoter (Leao et al., 2018), while telomerase activators act on the hTERT promoter (12 hours) of wild-type mice (Baruch-Eliyahu et al., 2019). The same group had demonstrated previously on a mouse model of amyotrophic lateral sclerosis that disease symptoms could be significantly delayed when applying the same AG699 telomerase activator (Eitan et al., 2012b).

Together, these results mean that similar to a direct use of rapamycin to decrease the mTOR pathway and promote autophagy, the decrease of α-synuclein after increasing TERT expression using telomerase activators might be due to increased autophagy which helps to degrade the toxic brain protein (Figure 1). This also fits rather well with the timing of onset of symptoms in the PD mouse model: while during the first 12 months of life, a continuous degradation of α-synuclein takes place with an intact protein quality control system, in older mice α-synuclein is known to accumulate (Perugi et al., 2015). Around this time toxic (phosphorylated and aggregated) α-synuclein starts to accumulate which eventually leads to PD symptoms, possibly triggered by accumulating toxic α-synuclein.?
such as decreased dopamine levels and lower tyrosine hydroxylase activity as well defects in gait and balance (Amschi et al., 2013).

A functional connection between telomerase/TERT and protein degradation mechanisms has recently been described in cellular models where overexpression of TERT promotes both proteasomal degradation as well as autophagy (Ali et al., 2016; Im et al., 2017). Likewise, a physical interaction between TERT and mTOR in a larger protein complex has also been described previously (Kawauchi et al., 2005; Sundin et al., 2013).

Available data suggests that keeping autophagy activity at a high level by whatever mechanism seems to decrease α-synuclein levels (Klyouri et al., 2016) as well as to delay and ameliorate related PD symptoms. At the same time, it might also benefit other neurodegenerative diseases, such as AD, which are also associated with an accumulation of toxic proteins (amyloid-β and hyperphosphorylated tau) as well as general aging. Other authors have used different techniques, such as genetic overexpression of TERT on wild-type mice, and found an improvement of cognition, which counteracted the well-known decline of this important brain function during the normal aging process (Whittemore et al., 2019). However, genomic techniques, even when using adeno viruses to ameliorate neurogeneration, seem technically more challenging than the oral use of a highly purified plant extract or synthetically manufactured telomerase activators like AGS-499 and GRN510.

Moreover, telomerase activators have additional beneficial effects on many aspects of the aging process. Various clinical studies have already demonstrated beneficial effects of telomerase activators, such as TA-65, which has a GRAS (Generally recognized as safe) status (Harley et al., 2011; Salvador et al., 2008). The underlying mechanism for this general anti-aging effect seems to be the predominant extension of very short telomeres, for example in dopaminergic neurons by increased telomerase activity. The additional effect on TERT levels in the brain and neurons seems to be an added value for the telomerase activator. Thus, both functions—the canonical enzymatic role of telomerase, which extends telomeres and the non-canonical function of the TERT protein, seem to complement each other during treatment.

Conclusion

Telomerase is best known for its enzymatic function in extending and maintaining telomeres, special ends of linear chromosomes. However, recently many more non-canonical functions of the telomerase protein component TERT have been described in various tissues and under different conditions. Many of those demonstrate a protective cellular effect on decreasing oxidative stress and resistance to apoptosis and many more.

Neurons in the brain are postmitotic cells, which do not divide and thus their telomeres do not need to be maintained in length. Several groups have described a protective effect of the TERT protein in neurons as well as a mainly extranuclear location of the component. Hippocampal neurons in Braak stage 6 AD brains show an increased mitochondrial TERT localization (Spilsbury et al., 2015), which could be interpreted as an attempt to counteract increased oxidative stress known to be characteristic for brain tissue in various neurodegenerative diseases. Based on such a relation between TERT and neurons in the brain, several groups have described cellular or mouse models of neurodegenerative diseases, for example, ALS and PD where TERT levels were increased with different types of telomerase activators. These activators can exert telomerase activity in tissues where it is present like in lymphocytes where the activators help to extend very short telomeres and thus pose an anti-aging treatment. In addition, cells like hippocampal neurons, which downregulate telomerase activity very early in development, but maintain TERT levels, benefit from telomerase activators by increasing TERT expression while counteracting toxic proteins and ameliorating symptoms of neurodegeneration. In a PD mouse model, two cycloartenol-based telomerase activators were able to improve balance and gait (Wan et al., 2021). A possible underlying mechanism could be the promotion of protein degrading mechanisms, such as autophagy in the brain which are known to decrease during the aging process and might thereby contribute to the accumulation of toxic proteins, such as α-synuclein, Aβ or pathological tau during the development of neurodegenerative diseases (Figure 1).

Consequently, using plant-derived or synthetic telomerase activators could help to counteract and ameliorate the onset and/or progression of these neurodegenerative diseases, which become more and more common in our aging population. Direct clinical trials are indicated to determine details of a treatment regime, such as: effective doses, treatment onset as well as disease stages were best to intervene with the aim to modify neurodegeneration. This also emphasizes the need for an early diagnosis of risk groups and patients to start interventions as soon as possible for best effects in ameliorating symptoms and hopefully to delay disease progression.

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Conflicts of interest: There are no conflicts of interest.

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