Telomerase in Brain

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Contributor: Gabriele Saretzki

Telomerase is an enzyme that in its canonical function extends and maintains telomeres, the ends of chromosomes. However, telomere-independent functions are known for the telomerase protein TERT like shuttling from the nucleus to mitochondria where it decreases oxidative stress, apoptosis sensitivity and DNA damage. Recently, a protective role of TERT was found in brain where it protects neurons from stress and toxic proteins connected to neurodegenerative diseases. Telomerase activators are able to boost this protection in brain. The entry summarises our current knowledge about telomerase in the brain and highlights possible therapeutic approaches.

Keywords: telomerase ; TERT protein ; brain ; neuron ; neurodegenerative disease ; autophagy

1. Canonical and Non-Canonical Functions of Telomerase

Telomerase an enzyme well-known for elongating telomeres in dividing cells. It consists of two main components: the protein TERT (Telomerase Reverse Transcriptase) with reverse transcriptase function and an RNA component (TR: Telomerase RNA or TERC: Telomerase RNA Component) which contains the template for telomere synthesis de novo. This telomere-maintaining function is the canonical role of telomerase and is also called “telomerase activity” (TA).

While the canonical function of telomerase includes the inherent RNA component (TR/TERC) with the template region for telomere synthesis, during evolution novel properties of the TERT component have developed that are independent of the RNA and telomeres. These are usually called “non-canonical”. One of these non-telomeric functions consists in the ability of the TERT protein to shuttle upon oxidative stress from the nucleus to mitochondria where it can decrease ROS (reactive oxygen species) levels, cellular sensitivity to different drugs and apoptosis sensitivity [1][2].

2. Telomerase and TERT in Brain

The first group to recognise and investigate the role of telomerase/TERT in neuronal cells was Mark Mattson’s. This group pioneered research on telomerase in brain using cultured pheochromocytoma cells and embryonic hippocampal neurons subjected to overexpression and knockdown of TERT. The resulting modifications to telomerase activity demonstrated the importance of telomerase against apoptosis and excitotoxicity [3][4]. Telomerase activity in the brain is mainly associated with neural stem cells in certain areas such as the subventricular zone, the hippocampal dentate gyrus, and a few other regions [5][6].

The mechanism of downregulation of telomerase activity in the brain seems to be different from other somatic tissues. While in human somatic tissues the amount of TERT protein is an important regulator and limiting factor for telomerase activity (TA), the RNA subunit TERC in these tissues is constitutively expressed. In contrast, in human brain, the hTERC component is downregulated at very early stages of development (after postconception week 10) [7] and thus is most likely the factor responsible for the absence of telomerase activity at later stages of development and in adult brain tissue. However, TERT persists in neurons and the brain [8][9][10].

Several groups have shown that adult mammalian hippocampal neurons maintain TERT protein without telomerase activity [9][10]. This also fits well with its non-nuclear localisation in these neurons [9][10]. However, this could be different in other neuron types since telomerase activity was described in mouse Purkinje neurons but not in the granular and molecular layer of the cerebellum [8]. The authors found TERT localisation in the nucleus, cytoplasm and mitochondria, which could be specific to Purkinje neurons and possibly also to mice. External stress such as γ-irradiation in vivo and high glutamate concentration in situ on cerebellar slices increased TERT protein levels in the nucleus and mitochondria, respectively [8].

3. TERT and Neurodegenerative Diseases

Many neurodegenerative diseases such as AD and PD can be either caused genetically by mutations or occur spontaneously as in the majority of cases. There are many facets to brain ageing and the underlying causes of age-related neurodegenerative diseases are not well understood yet and thus no cures are available. However, among the most likely candidates contributing to those diseases are oxidative stress, mitochondrial dysfunction as well as the accumulation of toxic proteins such as amyloid-β, pathological tau and α-synuclein [11]. With increasing evidence of a potential role of telomerase and the TERT protein in the brain, various groups started to analyse different models in order to evaluate a possible beneficial role of telomerase and TERT.

The TERT protein has been demonstrated to provide a protective function for neurons against various stimuli such as oxidative stress, high glutamate and neurodegenerative agents such as amyloid-β and pathological tau [8][9][12]. Neurons lacking TERT protein due to a genetic knock-out develop higher amounts of oxidative stress after being transduced with pathological tau [9].

A study from the Saretzki group on hippocampal tissue from AD brains and age-matched controls did not find a decrease of TERT protein during the development of AD at different Braak stages [9]. Instead, they found a higher amount of TERT protein in mitochondria of hippocampal CA1 neurons at the highest Braak stage compared to healthy aged-matched controls. The study also revealed that pathological tau protein in the form of neurofibrillary threads and tangles in hippocampal neurons at higher Braak stages was mutually exclusive with TERT protein [9]. The study also used isolated and cultured primary embryonic mouse neurons and transduced them lentivirally with mutated tau (p301L) [9]. Employing neurons from wild-type and *Tert* knockout (KO) mice [13], the authors demonstrated clear differences in oxidative stress (higher levels of reactive oxygen species ROS and lipid peroxides) as a result of the p301L transduction [9]. These results suggest that TERT protein might indeed protect neurons from the damaging effects of pathological tau.

4. The use of telomerase activators to boost TERT levels in brain and in models of neurodegeneration

Both, natural and synthetic telomerase activators have been employed in order to boost TERT levels in the brain. Esther Priel's group used a synthetic telomerase activator (aryl compound, AGS-499) directly on a model of Amyotrophic Lateral Sclerosis (ALS). They demonstrated an improvement of disease scores in a mouse model of ALS using subcutaneous injection of the compound and suggested a better survival of affected motor neurons as underlying mechanism [14].

In a recent study, the same group used cultured primary hippocampal mouse cells consisting of both neurons and astrocytes and exposed them to amyloid-b in order to create a cellular model for AD [12]. Ab treatment induced neurotoxicity, and compromised gene expression of factors involved in neuronal survival and plasticity. In contrast, the increase of TERT levels with the synthetic telomerase activator showed protection from the toxic effects of Ab and the resulting neuronal damage [12]. The authors identified the involvement of the Wnt/beta-catenin pathway and an increased expression of neurotrophic factors such as BDNF and NGF as well as neuronal plasticity genes as the underlying mechanisms of protection by TERT [12].

There are currently two more telomerase activators under investigation: TA-65 and GRN510 from TA Science Inc. (USA). TA-65 is a highly purified plant extract from the Mongolian milkvetch (Astragalus membranaceus). A recent study by Wan and colleagues applied both activators on two year old female mice for 3 months which resulted in a significant increase of *mTert* expression in brain tissue [15]. Analysing motor coordination as a read-out for age-related brain function, the study found a significant improvement of strength and coordination in a static rod test where both treatments increased the time on the rod similarly to that of adult (10 months old) mice while only that for GRN510 was statistically significant [15]. These results are similar to those described by Eyolfson and co-authors who treated rats for one month with TA-65 before inflicting a brain injury. The authors found an increase in *Tert* expression as well as an improvement in motor coordination in the treated rats compared to controls [16].

5. Effects of telomerase activators on a mouse model of Parkinson's disease (PD)

Until recently, there was not much known about a possible role of TERT or telomerase in PD. A recently published study from the Saretzki group used TA-65 and GRN510 on a transgenic mouse model of Parkinson's disease (PD). This model was generated by Elizier Masliah and overexpresses human wild-type a-synuclein under a PDGF promoter [17]. These mice accumulate a-synuclein in the hippocampus, neocortex and olfactory bulb at an age of around one year and have decreased levels of dopamine and tyrosine hydroxylase in the substantia nigra [18]. In addition to PD-like pathology, these

mice show behavioural deficits which resemble motor symptoms of PD [17][18]. The fact that a-synuclein accumulation takes around one year to peak in the transgenic mouse model strongly suggests an age-dependency of disease progression similar to that of many neurodegenerative diseases.

Both activators significantly increased *mTert* gene expression in both sexes after 14 months of treatment starting at 4 months. Additionally, *in vitro* experiments on cultured primary embryonic mouse neurons at a time point where these neurons were no longer positive for telomerase activity [9] confirmed specifically that neurons were able to upregulate *mTert* expression after activator treatment [15].

Since impaired motor coordination is an important symptom for PD, behavioural tests for motor activity such as the rotarod test, gait test and walking speed were employed to characterise treatment effects [15]. Interestingly, results from the rotarod test showed some striking sex specificities: while in females only TA-65 improved motor parameters, in males a significant improvement was achieved exclusively with GRN510. Others have described similar effects with TA-65 previously and speculate about the involvement of sex hormones such as estrogen [19] which is involved in *TERT* transcriptional regulation. However, in the Wan et al. study other tests measuring walking speed for bradykinesia and gait identified no such sex-differences. Gait analysis measures stride length and width as well as variations therein and is similar to clinical tests used on PD patients [20]. Both activators greatly improved the walking speed as well as the length and width of strides, with a reduction in stride variation [15].

In order to identify possible mechanisms for TERT's protective effects, the authors measured forward and reverse electron flow in brain mitochondria but found an improvement only for TA-65, but not for GRN510. Possibly the more heterogenous nature of the natural plant extract, which is 95% pure but also contains around 5% other compounds [21][22], could be an explanation for this difference.

In addition to behavioural tests the study of Wan and co-authors analysed the levels of various forms of a-synuclein in brains from the PD mouse model. Intriguingly, they found a striking decrease of total, phosphorylated (S129) as well as aggregated a-synuclein in the three analysed brain regions: hippocampal regions CA1 and CA3 as well as neocortex. Both activators decreased total a-synuclein levels, while only TA-65 decreased phosphorylated a-synuclein levels in all three regions significantly [15].

Importantly, aggregated a-synuclein was decreased significantly by both activators in all three brain regions [15]. As expected for postmitotic neurons, the study did not detect any changes in telomere length in neurons from the hippocampal region CA1.

6. TERT, mTOR and autophagy in brain

mTOR is a conserved serine/threonine kinase consisting of two protein complexes: mTORC1 and mTORC2. The mTOR pathway regulates cell growth and metabolism in response to nutrient and energy supply. mTOR is an important regulator of autophagy. Both, mTOR and autophagy are critically involved in brain physiology and are increasingly also recognised as important players in neurodegeneration [23][24][25]. Autophagy is prominently involved in the degradation of toxic brain proteins such as misfolded and aggregated a-synuclein in PD [25]. Another mechanism of protein quality control is proteasomal degradation of monomeric and oligomeric toxic proteins in the brain [26].

Two papers recently provided evidence for an involvement of telomerase in promoting these two protein degradation mechanisms in cellular models [27][28]. Im and co-authors demonstrated that an overexpression of *hTERT* promoted assembly of proteasomal subunits and functional improvement of proteasomal degradation in a cancer cell line [27]. Ali et al. described a decrease of mTOR activity through mTORC1 due to overexpression of *hTERT* in human cancer cells which resulted in an increase in autophagy [28]. In contrast, cells lacking *TERT* were unable to execute autophagic flux by autophagosomes.

There have been previous hints on a possible functional as well as physical interaction of TERT with mTOR. Interestingly, these two molecules seem to form a physical complex together with other molecules both in immune cells and cancer cells [29][30].

The first *in vivo* brain model relating to TERT and mTOR was described by Miwa and co-authors in connection with the effects of dietary restriction and rapamycin treatment, both involving decreases in the mTOR pathway resulting in increased autophagy. The authors demonstrated that TERT functionally interacts with the mTOR pathway. Only brain tissue from wild-type mice showed a decrease in ROS levels after rapamycin treatment (which decreases mTORC1) while in *Tert* KO mice this effect was abolished [31]. In an *in vitro* cellular model rapamycin induced a subtle exclusion of a small fraction of TERT protein from the nucleus which correlated to a decrease in ROS levels [31]. In contrast, blocking nuclear

TERT exclusion with a src inhibitor or using *TERT*-knock-out cells abolished the effect of rapamycin in decreasing ROS. Importantly, the study demonstrated the dependence of ROS reduction by rapamycin specifically in the brain but not in liver of wild-type mice while the effect was abolished in *Tert* knockout mice [31].

Wan et al. explored in their study whether autophagy was involved in the effect of telomerase activators on the decrease of a-synuclein in the PD mouse model [15]. The authors analysed the two autophagy parameters p62 (an adaptor protein which decreases when autophagy is induced) and LC3B (a membrane-bound molecule of the autophagosome which decreases when the turnover of these organelles is increased). Both, p62 and LC3B, decreased significantly in the hippocampal CA1 due to telomerase activator treatment [15]. These results suggest that increased TERT levels due to a treatment with telomerase activators might be able to increase protein quality control by autophagy to degrade different a-synuclein forms in the brain, although the authors did not analyse specifically whether the mTOR pathway or increased proteasomal degradation were involved as well. However, Crews et al demonstrated previously in the same mouse model of PD that mTOR and LC3B were increased compared to wild-type mice and importantly, both markers co-localised with a-synuclein [32]. The authors treated the transgenic mice with rapamycin which decreases mTOR, and found an increase in autophagy and decrease in aggregated a-synuclein. This result by Crew et al. emphasises the capability of autophagy to degrade aggregated a-synuclein without studying telomerase/TERT as a possible factor.

7. Conclusions

There is increasing interest in the role of telomerase for brain function, such as cognitive ability, ageing, brain injury as well as neurodegenerative diseases. Various studies have demonstrated a protective function of telomerase/TERT protein in neurons against toxic neurodegenerative proteins including amyloid-b, pathological tau and a-synuclein [9][12][15]. However, the mechanisms for that protection are not entirely clear. Some studies have identified mitochondrial TERT localisation as well as autophagy and the mTOR pathway as possible mechanisms through which TERT might exert its protective function in brain and neurons [31][9][15] while other groups have found specific growth factors and genes involved in brain plasticity to be stimulated by increased TERT levels [12]. The results on a preclinical mouse model of PD are encouraging and suggest that the use of the nutraceutical TA-65 might alleviate PD-related symptoms. This could result in the development of novel therapeutic strategies for the treatment of PD and other neurodegenerative diseases. Studies from various groups using either telomerase activators or other experimental approaches such as adenoviral overexpression of *TERT* for the increase of TERT levels in brain, support this strategy [12][33][34].

Thus, clinical trials with early stages of PD patients or other neurodegenerative diseases such as AD are required to confirm the beneficial effects of increasing telomerase/TERT levels in brains of patients suffering from neurodegenerative diseases. Moreover, due to the already known anti-ageing effects of TA-65 on other organs and cell types (for example blood lymphocytes) such a treatment could also improve different age-related and telomere-dependent health parameters. In addition, preventing senescence and SASP-induced inflammation in various types of brain cells such as neurons, astrocytes and microglia cells [35][36][37][38][39] could be another important mechanism to protect the brain from age-related decline of cognition as well as to ameliorate the development or progression of neurodegenerative diseases. As neurodegenerative diseases are posing an increasing health problem and socio-economic burden for societies all over the world, there is increasing demand for novel therapeutic interventions. Boosting telomerase/TERT level in brain could empower novel treatment strategies for these diseases in the future.

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