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Telomerase activators improve motor function and protein degradation in a mouse model of Parkinson's disease

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While telomerase maintains telomeres in dividing cells, its protein component TERT (telomerase reverse transcriptase) has various non-canonical functions such as localisation to mitochondria resulting in decreased oxidative stress, apoptosis and DNA damage. TERT protein persist in adult neurons while telomerase activity is downregulated early during development. We recently demonstrated increased mitochondrial TERT protein in hippocampal neurons from Alzheimer's disease brains and mutual exclusion of pathological tau and TERT. Transduction of mutated tau into cultivated neurons confirmed that TERT decreases mitochondrial oxidative stress and lipid oxidation. Mitochondrial dysfunction is also involved in the development of other neurodegenerative diseases. Treatment of Parkinson's disease (PD) model mice overexpressing human wild-type alpha-synuclein with 2 telomerase activators resulted in increased TERT expression in brain and amelioration of PD symptoms by significantly improving balance, gait and motor function as well as mitochondrial function. Analysing levels of total and phosphorylated alpha-synuclein we found a substantial decrease of both proteins in the hippocampus and neocortex suggesting a better protein degradation after telomerase activator treatment. Interaction of TERT with proteasomal and autophagy pathways has been described recently. Accordingly, we found a decrease in poly-ubiquitinated proteins and the autophagy receptor p62 and analyse the involvement of these degradation pathways currently. We also present data on DNA damage, telomere-associated foci (TAFs), BDNF, MnSOD, mitochondrial proteins and aggregated alpha synuclein in different brain regions. Thus, our results suggest that telomerase activators might form novel treatment options for better degradation of toxic proteins in neurodegenerative diseases such as PD and AD.

Biography

Gabriele Saretzki has completed her PhD at Humboldt University, Berlin and performed most of her Postdoctoral studies at the Institute for Ageing and Health in Newcastle upon Tyne (UK) where she is a Lecturer in Ageing Research since 2002. Her main research interests include "Telomeres, telomerase, senescence, ageing, oxidative stress and mitochondria". She has pioneered work on non-canonical functions of the telomerase protein TERT shifting her focus recently to brain ageing and neurodegenerative diseases. She has published more than 84 papers in peer-reviewed journals and is an Editorial Board Member of *BMC Biology, PLOS One and Oxidative Medicine and Cellular longevity*.

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