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Increased Telomerase Improves Motor Function and Alpha-Synuclein Pathology in a Transgenic Mouse Model of Parkinson's Disease Associated with Enhanced Autophagy

Protective effects of the telomerase protein TERT have been shown in neurons and brain. We previously demonstrated that TERT protein can accumulate in mitochondria of Alzheimer's Disease (AD) brains and protect from pathological tau in primary mouse neurons. This prompted us to employ telomerase activators in order to boost telomerase expression in a mouse model of Parkinson's Disease (PD) overexpressing human wild type α-synuclein. Our aim was to test whether increased Tert expression levels were able to ameliorate PD symptoms and to activate protein degradation.

We found increased Tert expression in brain for both activators which correlated with a substantial improvement of motor functions such as gait and motor coordination while telomere length in the analysed region was not changed. Interestingly, only one activator (TA-65) resulted in a decrease of reactive oxygen species from brain mitochondria. Importantly, we demonstrate that total, phosphorylated and aggregated α-synuclein were significantly decreased in the hippocampus and neocortex of activator-treated mice corresponding to enhanced markers of autophagy suggesting an improved degradation of toxic α-synuclein. We conclude that increased Tert expression caused by telomerase activators is associated with decreased α-synuclein protein levels either by activating autophagy or by preventing or delaying degradation mechanisms which are impaired during disease progression. This encouraging preclinical data could be translated into novel therapeutic options for neurodegenerative disorders such as PD.

Recent Publications

1. Saretzki G. Telomerase and neurons: an unusual relationship. Neural Regen Res. 2022 Nov;17(11):2364-2367. doi: 10.4103/1673-5374.336133. PMID: 35535872; PMCID: PMC9120688.
2. Saretzki G, Wan T. Telomerase in Brain: The New Kid on the Block and Its Role in Neurodegenerative Diseases. Biomedicines. 2021 Apr 29;9(5):490. doi: 10.3390/biomedicines9050490. PMID: 33946850; PMCID: PMC8145691.
3. Hapangama DK, Kamal A, Saretzki G. Implications of telomeres and telomerase in endometrial pathology. Hum Reprod Update. 2017 Mar 1;23(2):166-187. doi: 10.1093/humupd/dmw044. PMID: 27979878; PMCID: PMC5850744.

Biography

Gabriele Saretzki has completed her PhD 1990 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 interests are telomeres, telomerase, senescence, ageing, oxidative stress, mitochondria stem cells and brain. 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 87 papers in peer-reviewed journals and is an editorial board member of BMC Biology, PloS One and Oxidative Medicine and longevity.

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