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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

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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. Tengfei Wan, Emma J. Weir, Mary Johnson, Viktor I. Korolchuk, Gabriele C. Saretzki, Increased telomerase improves motor function and alpha-synuclein pathology in a transgenic mouse model of Parkinson's disease associated with enhanced autophagy, Progress in Neurobiology, Volume 199, 2021, 101953, ISSN 0301-0082,
2. Martin-Ruiz C, Williams-Gray CH, Yarnall AJ, Boucher JJ, Lawson RA, Wijeyekoon RS, Barker RA, Kolenda C, Parker C, Burn DJ, Von Zglinicki T, Saretzki G. Senescence and Inflammatory Markers for Predicting Clinical Progression in Parkinson's Disease: The ICICLE-PD Study. J J Parkinsons Dis. 2020;10(1):193-206.
3. Martens A, Schmid B, Akintola O, Saretzki G. Telomerase Does Not Improve DNA Repair in Mitochondria upon Stress but Increases MnSOD Protein under Serum-Free Conditions. International Journal of Molecular Sciences. 2020; 21(1):27.

Biography

G Saretzki was born in Berlin, graduated from Sankt Petersburg (Russia) University 1982 and did her PhD at the Department of Genetics at the Humboldt-University Berlin (Germany) in 1990. Since 1990 she was involved in ageing research and worked on telomeres, telomerase, oxidative stress, DNA damage and cellular senescence. Since 2001 she worked at Newcastle University (UK) where she became a lecturer in ageing research in 2002. In particular, her research interests were functions of telomerase in cancer and stem cells as well as non-canonical functions of the telomerase protein TERT in mitochondria. She extended this work to non-canonical functions of TERT in brain with an interest in neurodegenerative diseases. She is now retired but still a visiting lecturer at Newcastle University. She published around 105 papers and has an H-index of 49.

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