

# Abstract

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## Telomere shortening reduces Alzheimer's disease amyloid pathology in mice.

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**BACKGROUND:** Alzheimer's disease is a neurodegenerative disorder of the elderly and advancing age is the major risk factor for Alzheimer's disease development. Telomere shortening represents one of the molecular causes of ageing that limits the proliferative capacity of cells, including neural stem cells. Studies on telomere lengths in patients with Alzheimer's disease have revealed contrary results and the functional role of telomere shortening on brain ageing and Alzheimer's disease is not known.

**OBJECTIVE:** Here, we have investigated the effects of telomere shortening on adult neurogenesis and Alzheimer's disease progression in mice.

**METHODS AND RESULTS:** The study shows that aged telomerase knockout mice with short telomeres (G3Terc<sup>-/-</sup>) exhibit reduced dentate gyrus neurogenesis and loss of neurons in hippocampus and frontal cortex, associated with short-term memory deficit in comparison to mice with long telomere reserves (Terc<sup>(+)</sup>(+)). In contrast, telomere shortening improved the spatial learning ability of ageing APP23 transgenic mice, a mouse model for Alzheimer's disease. Telomere shortening was also associated with an activation of microglia in ageing amyloid-free brain. However, in APP23 transgenic mice, telomere shortening reduced both amyloid plaque pathology and reactive microgliosis.

**CONCLUSIONS:** Together, these results provide the first experimental evidence that telomere shortening, despite impairing adult neurogenesis and maintenance of post-mitotic neurons, can slow down the progression of amyloid plaque pathology in Alzheimer's disease, possibly involving telomere-dependent effects on microglia activation.

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