

MOLECULAR AND CELL BIOLOGY

Dysfunctional mitochondria during accelerated senescence and their impact on Alzheimer's disease neuropathology

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Abstract

Background: Although aging is the leading risk factor for Alzheimer's disease (AD), the exact mechanisms through which aging becomes pathogenic and triggers neurodegeneration have not yet been identified. Recent evidence suggests that AD is tightly correlated with the appearance of senescent cells and that mitochondrial dysfunction is a pathological feature occurring during senescence and AD. Additionally, studies have suggested that mitochondrial dysfunction and altered mitophagy might lead to A β accumulation. Our goal was to explore if a reduced removal of dysfunctional mitochondria during aging is a key contributor to amyloid pathology and neurodegeneration in AD.

Method: Since telomere shortening is a known trigger of cellular senescence, a telomerase-deficient mouse model was used: *Terc*^{-/-}. The brain proteome of *Terc*^{-/-} mice was evaluated to validate classical and novel markers of senescence and investigate the alteration of key cellular pathways. Primary cultures and brain tissue from *Terc*^{-/-} mice were evaluated for mitochondrial function/content and mitophagy alterations. Then, we explored the relationship between amyloid pathology and mitochondrial dysfunction by crossing the *Terc*^{-/-} mice with an AD-related amyloid mouse model (5xFAD) and exploring mitophagy alterations and amyloid- β (A β) accumulation in disease-vulnerable regions.

Result: Proteomic analysis revealed changes in proteins related to autophagy and mitochondrial functions during accelerated senescence. The mitophagy modulator BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3) was found down-regulated in *Terc*^{-/-} mice. We evidenced the presence of mitochondrial dysfunction and accumulation in senescent neurons. Additionally, we observed that senescence induces intraneuronal A β accumulation in specific brain regions (e.g., the subiculum) of an AD mouse model and we suggest that mitochondrial dysfunction and altered mitophagy might lead to A β accumulation.

Conclusion: Our results indicate that dysfunctional mitochondria accumulate during pathological aging due to a mitophagy impairment, which might contribute to AD neuropathology.