Role of Mitochondrial dynamics and mitochondrial dysfunction in neurodegeneration

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Abstract: Mitochondria play a critical role in neuronal function and survival and mitochondrial abnormalities and dysfunction have been well characterized in various neurodegenerative diseases including Alzheimer’s disease (AD). In fact, significant advances have recently been made in the understanding of the changes in morphology and distribution of neuronal mitochondria in AD. It is believed that mitochondrial fragmentation, due to impaired fission and fusion balance, likely causes mitochondrial dysfunction that underlies many aspects of neurodegenerative changes in AD. To examine whether and how impaired mitochondrial fission/fusion balance causes neurodegeneration in AD, we developed a transgenic mouse model using the CAMKII promoter to knockout mitofusin 2 (mfn2) in the hippocampus and cortex. Electron micrographs of neurons from these mice show swollen mitochondria with cristae damage and mitochondria membrane abnormalities. Over time the mfn2 KO model demonstrates a progression of neurodegeneration via mitochondrial morphological changes, oxidative stress response, inflammatory changes, cell cycle induction, and loss of MAP2 in dendrites, leading to severe and selective neuronal death. In this model, hippocampal CA1 neurons were affected earlier and resulted in nearly total loss, while cortical neuronal death was associated with fewer neurons and decreased cortical size, but no changes in neuronal density. Hemizygous mfn2 KO mice showed no neurodegeneration, but did display heightened levels of oxidative stress at old age. Finally, knockout of mitofusin 1 (mfn1) did not show any neuronal degeneration, with only subtle changes in mitochondria structure seen by electron microscopic analysis. Overall, our findings indicate that impaired mitochondrial fission and fusion balance can cause many neurodegenerative changes and eventual neurodegeneration that characterize AD in the hippocampus and cortex which makes it a potential target for treatment strategies for AD.

Key Words: Alzheimer’s disease, mitochondrial dynamics, mitochondrial dysfunction, Mfn2, neurodegeneration