SL03 **Mitochondrial Degeneration in Aging and Neurodegenerative Disease**

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Mitochondria are central players in cellular function with roles in sustaining cell survival, maintaining energy metabolism, balancing reactive oxygen species (ROS), and mediating cell death pathway. The concept of mitochondrial dysfunction has been set forth as a central theme in multiple aging-related disease states, including cancer, diabetes, and neurodegenerative diseases. In particular, the aging process has been noted to involve deterioration in mitochondrial function and alterations in mitochondrial dynamics. Neurons are vulnerable to mitochondrial dysfunction due to their high energy demands and dependence on respiration to generate ATP. Mitochondrial dysfunction may, therefore, drive or mediate neurodegeneration and neurodegenerative diseases including Alzheimer's disease (AD). Neuronal mitochondria show age-dependent increase in mitochondrial permeability transition pore (MPTP), cyclophilin D expression, and oxidative stress, as well as decline in calcium capacity. In amyloid beta peptide (Aβ)-enriched mitochondria, neuronal mitochondria revealed a greater degree of age dependent accumulation of Aβ and mitochondrial alterations. The neuronal mitochondrial pool of Aβ was detected at an age as young as 4 month, well before the onset of nonsynaptic mitochondrial and extensive extracellular Aβ accumulation. Aβ-insulted neuronal mitochondria revealed early deficits in mitochondrial function, as shown by increased mitochondrial permeability transition, decline in both respiratory function and activity of cytochrome c oxidase, and increased mitochondrial oxidative stress. Furthermore, a low concentration of Aβ significantly perturbed mitochondrial function, distribution, and trafficking in axons. Blockade of cyclophilin D mediated MPTP by genetic depletion of CypD or pharmacological inhibitor significant attenuates aberrant mitochondrial function and synaptic and cognitive function in AD mouse model. These data suggest that targeting specific process in mitochondria could provide beneficial therapeutic options.