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SPECIAL LECTURE: CARDIOLIPIN AND MITOCHONDRIAL QUALITY CONTROL IN AGING

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A progressive decline in mitochondrial oxidative phosphorylation (OxPhos) is a fundamental feature of aging and a strong predictor of mobility loss, cognitive decline, and dementia. (1-4) Work from the Baltimore Longitudinal Study of Aging and complementary cohorts demonstrates that reduced skeletal muscle mitochondrial OxPhos, assessed in vivo by ^31P-MRS, precedes and predicts deterioration in walking performance, cardiorespiratory fitness, brain structural integrity, and risk of mild cognitive impairment and dementia. These associations suggest that mitochondrial dysfunction represents a shared biological mechanism underlying both physical and cognitive aging.This project focuses on cardiolipin, a signature phospholipid of the mitochondrial inner membrane that is essential for respiratory chain supercomplex assembly, proton handling, and efficient ATP synthesis. Cardiolipin is highly susceptible to oxidative damage, and emerging evidence indicates that oxidized cardiolipin is poorly repaired, promotes inflammation and apoptosis, and compromises mitochondrial quality control. We hypothesize that aging is characterized by the accumulation of oxidized cardiolipin due to impaired remodeling and insufficient availability of key lipid precursors, particularly lysophosphatidylcholine species containing oleic (18:1) and linoleic (18:2) acids. To test this hypothesis, we integrate longitudinal human phenotyping with advanced metabolomics, lipidomics, and “in vivo” imaging. We have identified lipid metabolites linking mitochondrial OxPhos to mobility and cognition and developed a highly sensitive method to quantify native and oxidized cardiolipin species in human skeletal muscle. Preliminary data indicate that higher levels of tetralinoleoyl cardiolipin are associated with better physical and cognitive performance, whereas a greater proportion of oxidized cardiolipin predicts worse outcomes. Ongoing efforts aim to extend these findings to the brain using novel PET radioligands and advanced MRS techniques. Together, this work positions cardiolipin remodeling and mitochondrial quality control as central mechanisms of aging and promising targets for interventions to preserve physical and cognitive function in late life.

Keywords: *mitochondria, quality control, oxidative phosphorylation, aging, mobility, dementia.*