Primary Mitochondrial Dysfunction Promotes Mitochondrial DNA Copy Number Upregulation to Maintain Mitochondrial Functionality in Neuronal Models

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Introduction. There is growing evidence supporting the critical role of mitochondrial function in the progression of Alzheimer's Disease (AD), yet the direct mechanisms are still unclear. We predicted that primary mitochondrial dysfunction would cause an upregulation in mitochondrial DNA copy number (mtDNAcn) to maintain protein and energetic homeostasis.

Methods. We generated human SH-SY5Y neuron models of broad and fine-tuned mitochondrial dysfunction using chloramphenicol or a knockdown of PTCD1 (PTCD1-KD), a nuclear-encoded RNA-binding protein essential for mitochondrial translation, respectively to assess alterations in mtDNAcn, respiratory chain and AD-associated targets, and cellular respiration.

Results. Both chloramphenicol and PTCD1-KD treatments showed a significant increase in mtDNAcn. We observed no changes in respiratory chain proteins, ATP5A, UQCRC2, and SDHB, expression for either group, except for a significant reduction of UQCRC2 in chloramphenicol-treated neurons. Total amyloid precursor protein (APP) expression was unchanged in either group, but interesting the non-glycosylated to glycosylated APP ratio was significantly increased. Additionally, APOE mRNA was significantly elevated by 26% in PTCD1-KD cells. Chloramphenicol treatment significantly reduced oxygen consumption (OCR). PTCD1-KD showed no changes respiration function, however, there was a significant reduction in the PTCD1-KD neurons when basal OCR was normalized for mtDNAcn.

Conclusions. In this study, we showed that chloramphenicol and PTCD1-KD produce mitochondrial dysfunction via disruptions to mtDNA translation. When neurons are placed under mtDNA translational stress, they increase mtDNA copy number to attempt to maintain mitochondrial functional homeostasis until it overcomes their adaptive capacity and show alterations to AD-related markers.