The Role of Metaxin 2 in Neurodegenerative Tauopathies

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Alzheimer's disease (AD) affects 6.2 million individuals in the United States and represents a significant neurodegenerative challenge. Tauopathies, characterized by tau protein aggregation within neurons, contribute substantially to AD pathology. Tauopathies involve hyperphosphorylation-induced tau detachment from microtubules, leading to tau aggregate formation and neuronal demise. Mitochondrial dysfunction has emerged as a critical factor in tauopathy, preceding tau aggregation and impacting neuronal health. Despite this association, the mechanisms underlying Tau-mitochondria interaction remain unclear. Here, we identify Metaxin 2 (MTX2) as a novel factor implicated in tauopathy. Unbiased proteomic analysis of hippocampal tissue from PS19 transgenic mice revealed significant upregulation of MTX2 at both early (6-month) and late (9-month) disease stages. Immunohistochemistry confirmed elevated MTX2 levels in both PS19 mice and post-mortem AD patient hippocampi. In vitro, MTX2 upregulation was also observed in HT-22 cells expressing mutant Tau P301L. Proximity Ligation Assays revealed a close spatial association between phosphorylated tau (AT8) and MTX2, suggesting interaction. Functional studies demonstrated that MTX2 knockdown mitigates tau-induced mitochondrial oxidative stress and reduces tau aggregation, as shown by MitoSOX and tau BiFC assays, respectively. Successful completion of this study will establish MTX2 as a crucial player linking mitochondrial dysfunction to neurodegeneration in tauopathy. Furthermore, our findings may identify MTX2 as a novel therapeutic target for ameliorating neuronal toxicity in AD and related tauopathies.

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