Protective role of mitochondrial CHCHD10 in tauopathy in Alzheimer's Disease

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Tauopathy is defined by abnormal Tau protein aggregation and hyperphosphorylation, which results in the formation of neurofibrillary tangles within neurons in a variety of neurodegenerative diseases, including Alzheimer's disease (AD) and Frontotemporal lobar degeneration with tau pathology (FTLD-Tau). CHCHD10, a mitochondrial intermembrane space protein, plays a crucial role in regulating diverse mitochondrial functions, such as respiration, genome stability, dynamics, cristae organization, and oxidative phosphorylation. In our study, CHCHD10 was found to be downregulated in the brains of AD, FTLD-Tau, AD-derived neurons, and P301S-Tau mice. Furthermore, either depletion or the presence of CHCHD10-Q95* increases tau seeding activity and tau aggregation in vitro cell lines. Increasing CHCHD10 significantly reduced tau pathology in P301S-Tau mouse brains, human AD fibroblast-converted neurons, and in vitro cell lines. Mechanically, CHCHD10 regulates poly-ubiquitination of tau by recruiting 26s proteasome. Our study provides insights into CHCHD10-associated mechanisms in tauopathy and facilitates the therapeutic potential of increasing CHCHD10 in ameliorating tauopathy in AD and ADRD.

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