Unfolded protein response activation protects neurons against pathological tau

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USA

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Unfolded protein response activation protects neurons against pathological tau

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Research Abstract

? DESCRIPTION (provided by applicant): Neuronal lesions containing abnormal aggregated tau protein are one of the diagnostic hallmarks of Alzheimer’s disease (AD), related tauopathy disorders, and advanced aging of the brain. How aggregated tau leads to the dysfunction and loss of neurons in AD patients remains enigmatic, although neuronal dysfunction and loss clearly causes dementia. To better understand how abnormal tau contributes to neurodegeneration in AD and other tauopathies, we established a transgenic model in C.

elegans for neurodegeneration driven by human tau aggregation. Through investigation of the genes involved in tau neurotoxicity, we have identified XBP1, the master transcriptional regulator of the unfolded protein response (UPR). ER stress and activation of the UPR have clearly been implicated in human tauopathy disorders by other laboratories although the functional consequences of UPR activation on tau pathology remain unclear. We have leveraged our C. elegans model of tauopathy to dissect the functional role of the UPR in tau pathology. While C. elegans lacking XBP1 function are viable under normal conditions, when challenged with ER stress they die. Likewise C. elegans expressing human tau but lacking XBP1 are not viable. These findings suggest tau pathology induces ER stress, and UPR activation protects against tauopathy. To test this hypothesis, we upregulated the UPR in the absence of ER stress specifically in neurons using a constitutively active XBP1 transgene. Preliminary data indicates constitutively active XBP1 suffices to protect against tauopathy related phenotypes bolstering the argument for the UPR acting to protect against tauopathy. The data gathered to date do not address the mechanism of how UPR activation protects against tauopathy. Given the high level of conservation of the UPR system between mammals and C. elegans, we propose to utilize the existing model and transgenes to dissect the mechanism by which the UPR protects against tau neurotoxicity. While the mechanism appears to be mediated through XBP1 target genes, the molecular underpinnings remain unclear. The Specific Aims of this project are to: identify which XBP1 target genes modulate tau mediated neuronal dysfunction and neurodegeneration, dissect the mechanism by which these target genes regulate tauopathy, and determine whether or not there is comprehensive engagement of all three branches of the UPR in protecting against tau toxicity. Completion of the project as proposed will identify specific genes and pathways normally functioning to detoxify tau pathology. Identification of new regulators of tauopathy will provide the field with additional points of intervention in tauopathy which will set the stage for future translational studies of ta mediated neurodegeneration and UPR mediated neuroprotection in mouse models.

Further information available at:

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