Metabolic Regulation of Neurodegeneration in Tauopathy

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Country

USA

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Metabolic Regulation of Neurodegeneration in Tauopathy

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1

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Research Abstract
PROJECT SUMMARY/ABSTRACT Neurodegenerative diseases and metabolic disorders are common in the elderly population. Tauopathies, such as Alzheimer’s disease (AD) and frontotemporal lobar degeneration with tau inclusions, are the most prevalent

neurodegenerative diseases in the US and worldwide. There is no cure, and the few available treatments have limited efficacy. Therefore, novel molecular targets and new therapies are urgently needed. The hallmark of tauopathy is the accumulation of tau, a microtubule-associated protein, in the brain, leading to progressive cognitive decline and neurodegeneration. Tau accumulation in brain regions coincides with areas of glucose hypometabolism, implicating metabolic dysregulation in those areas, and metabolic disorders such as type2 diabetes increase the risk of developing AD. However, it is unclear which signaling pathways are critically involved in metabolic dysregulation in tauopathy brains, whether they contribute to neurodegeneration, and what the underlying molecular mechanisms are. In preliminary studies, I discovered that AMPK—a key energy sensor and regulator in cells—is dysregulated in tauopathy animals, which might contribute to the accumulation of pathogenic tau. This study aims to use multidisciplinary approaches to elucidate how metabolic dysregulation modulates tau-mediated neurodegeneration, focusing on defining the mechanistic role of AMPK in tauopathy models. Specifically, I will determine whether AMPK regulates tau-mediated neurodegeneration in tauopathy mouse models (Aim 1) and dissect the mechanism underlying the neuroprotective effect of AMPK (Aim 2). Based on my preliminary research, I will test the hypothesis that AMPK protects against tau-mediated neurodegeneration by a) inhibiting p300-induced tau acetylation and b) enhancing autophagy, in mouse and fly models. I will assess how metabolic changes effect AMPK- p300/autophagy pathways and tau pathology in tauopathy brain (Aim 3). Finally, I will perform a genetic screen in Drosophila to identify novel genes and pathways that regulate metabolic deficits in tauopathy animals, and investigate the roles of these regulators in tau-mediated neurodegeneration (Aim 4). In the mentored phase, I will continue to use fly genetics and in vitro and in vivo tauopathy models, and acquire additional skills in mouse genetic models and metabolic characterization. This training I receive will enable me to complete the proposed studies and launch an independent research laboratory within 2 years. Completion of my proposed studies will provide a proof of concept for targeting AMPK pathway for tauopathy treatment, and enable me to establish a working system beginning from identification of new regulators of tau-dependent metabolic deficits and neurodegeneration, to mechanistic studies using multi-disciplinary approaches, to provide basis formulating new therapeutic strategies for treating neurodegenerative diseases. The K99/R00 mechanism will provide the support necessary to advance my goal of successfully establishing an NIH R01-funded, independent laboratory to study metabolic regulation of neurodegeneration.

Further information available at:

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