Roles of heat shock protein 110 in modulating amyloid neurotoxicity

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Research Abstract

PROJECT ABSTRACT The Hsp110 molecular chaperone is increasingly being recognized as a potent regulator of amyloidogenesis as well as a potential pathogenic modifier for multiple protein misfolding disorders including cystic fibrosis, Alzheimer’s disease and Huntington’s disease (HD). However, few systematic studies have been carried out on metazoan Hsp110 to examine its physiological roles, particularly in long-lived neurons that are more susceptible to protein misfolding and aggregate formation, largely due to lack of suitable metazoan model. In

addition, Hsp110 has been determined at the biochemical level to function both as a chaperone “holdase” and as a Hsp70 nucleotide exchange factor (NEF). However, how these two distinct activities contribute to its neuronal protective role is unknown. In this R21 application, we propose to generate Drosophila lines with designed mutations in the sole fly Hsp110 ortholog (dHsp110) that specifically abolish holdase or NEF activities, and use established Drosophila HD models to test the hypothesis that Hsp110 acts as an activator of Hsp70 cycling in concert with Hsp40, and/or as a stand-alone chaperone holdase to sequester amyloidogenic proteins and prevent aggregation and associated toxicity. Completion of this project will establish the feasibility of future pharmacological exploitation of Hsp110 in the nervous system to combat morbidity and mortality arising from proteopathies in the aging population.

Further information available at:

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