Functional analysis of proteins associated with aggregation and neurodegeneration utilizing the model organism *Caenorhabditis elegans*

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Abstract

The common characteristic of many neurodegenerative diseases is protein aggregation and the formation of toxic fibrils. This is definitely the case with proteins alpha-synuclein (α-syn), TAR DNA Binding Protein 43 (TDP-43) and Superoxide Dismutase (SOD1) that contribute to the toxicity of Parkinson's Disease (PD), Frontotemporal Dementia (FTD) and Amyotrophic Lateral Sclerosis (ALS), respectively. Not only do these aggregate-prone proteins influence the demise of the nervous system, there are other genetic and environmental factors that assist in exacerbating the phenotypes of these diseases. Each of these diseases impact older individuals, which strongly correlates with the decline in overall cellular homeostasis. Therefore, with the influence of genetics and environmental factors to aging individuals, there are multiple avenues to explore in search for therapeutics to prevent or slow down the progression of these diseases.

Using model organisms, like *Caenorhabditis elegans* (*C. elegans*), are pivotal as they can be manipulated genetically, exposed to pharmaceuticals, and analyzed quickly due to their short lifespan and high fecundity. They exhibit behaviors and morphological changes that correlate with modifications to their nervous system when perturbed. These model systems have been exploited in finding modifiers of toxicity, as they have expedited the search for the cure in a cost-effective and efficient manner.

Using *C. elegans* as our model system, we have explored the role of GAIP Interacting Protein C-terminus (GIPC) and its role in regulating endocytosis in protecting against α-syn induced neurodegeneration in the DA neurons. Using cell-specific RNAi, we have highlighted the earliest stages of endocytosis (receptor desensitization, internalization and early endosomal trafficking) as factors that assists the worm homolog of GIPC, *C35D10.2*, in the neuroprotection. In addition to the PD model, we have also worked to establish a model of TDP-43 proteinopathy by examining the protein localization of WT and ALS-associated variants, determining if the cytoplasmic mislocalization and/or aggregates is necessary to elicit neuronal toxicity. Finally, using an established ALS worm model, we have demonstrated that the key chaperone, torsinA, has the ability to ameliorate ER stress and locomotive defects associated with mutant SOD1 by promoting ER associated degradation (ERAD).