Dissertation Defense Announcement

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"IDENTIFICATION AND MECHANISTIC ANALYSES OF GENETIC AND ENVIRONMENTAL RISK FACTORS ASSOCIATED WITH PARKINSON'S DISEASE USING A CAENORHABDITIS ELEGANS MODEL"

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ABSTRACT: The etiology of Parkinson's disease (PD) has long been thought to involve both genetic and environmental factors. There exists a common theme across the etiological spectrum of PD, where these factors have the ability to cause nigrostriatal dopaminergic (DA) cell death by interfering with mitochondrial function, inducing oxidative stress and altering proteosomal function. The protein α-synuclein (α-syn) that forms characteristic inclusions termed Lewy bodies in familial or sporadic forms of PD is thought to play a central role in PD pathology. Due to the absence of an effective treatment for PD progression, it is necessary to identify various genetic or environmental modifiers to advance drug discovery and therapeutic development.

Animal models like *Caenorhabditis elegans* are often preferable for experimental research in the study of neurodegenerative diseases as this microscopic nematode combines ease of handling and manipulation, high reproductive rates and facilitation of large-scale experiments. Reminiscent of the situation observed in PD patients, expression of PD associated genetic factors or exposure to environmental neurotoxicants causes various phenotypes in worms such as, robust cell-type specific DA neurodegeneration, occurrence of protein misfolding/aggregates and associated behavioral/locomotion defects. These parameters can be analyzed and quantified, thus rendering the nematode model useful for uncovering mechanistic aspects of PD pathology, including genetic or environmental factors, or interactions affecting neurodegeneration.

Using *C. elegans* as an environmental model system, we elucidated the toxicological effects and mechanism for two different classes of bacterial metabolites in causing neurodegeneration/PD related phenotypes. We demonstrated that a previously identified bacterial neurotoxic metabolite produced by *Streptomyces spp.* caused neuronal cell death as a result of mitochondrial dysfunction and oxidative stress in worms. Interestingly, the neurotoxic effect of this metabolite was enhanced in the presence of α-syn, indicating a functional association. Our study highlights the toxic phenotypes of another group of bacterial products, phenazines, which enhanced α-syn-induced protein aggregation and neurodegeneration in worms. We also determined that phenazine compounds upregulated cellular stress responses in the ER and mitochondria, thus representing a potential PD-related environmental risk factor. Finally, using C. elegans as a genetic model system for PD, we have reported a previously uncharacterized neuroprotective gene product, RTCB-1 that has the ability to regulate xbp-1 mRNA splicing in the unfolded protein response pathway (UPR). Using cell-specific RNA interference (RNAi), we have shown that RTCB-1 rescues α-syn-induced DA neurodegeneration by regulating XBP-1 signaling and activating downstream chaperones in the UPR; thus mitigating the toxic effects caused by accumulation of unwanted proteins.

The combined outcomes of this research represent mechanistic advances in our understanding of factors, both heritable and environmental, that exert an influence on neurodegeneration. The evolutionarily conserved pathways and functional targets revealed through this work highlight the expeditious manner by which *C. elegans* can be exploited to accelerate the path toward attenuating devastating diseases like PD.