2013-2014 Research Award

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Project Title: Protection of Mitochondrial Function in Neurons from Patients with Parkinson's Disease

Dr. Xin Qi earned her PhD at Hokkaido University, Japan in 2005 and post-doctoral training in Dr. Daria Mochly-Rosen's lab at Stanford University from 2005-2011. In March 2011, she started her own lab in the Department of Physiology and Biophysics at Case Western Reserve University. Dr. Qi is a cell biologist whose research has been focused on understanding the pathogenesis of neurological diseases including Parkinson’s disease (PD), and on identifying potential therapeutics to treat these disorders. Currently she is studying the role of mitochondrial dysfunction in various models of neurological diseases. She has recently developed selective peptide inhibitors of excessive mitochondrial fission, a process involved in mitochondrial morphology regulations and mitochondria-related cell death. Dr. Qi uses a multiple-disciplinary approach in her research, and in addition to in vitro cultured cells and in vivo diseased animals as well as drug design, it also includes the establishment of patient-specific induced pluripotent stem (iPS) cell model and their differentiation into mature cells. Using this cutting-edge technique, she generated PD patient-iPS cell differentiated neurons to determine whether mitochondrial impairment contributes to the pathology of PD in the context of patients’ genotypes.

Objective: The goal of this study is to determine whether inhibition of excessive mitochondrial fission suppresses mitochondrial dysfunction in neurons derived from PD patient LRRK2 G2019S-iPS cells and reduces neuronal degeneration caused by LRRK2 G2019S mutation.

Background: Mitochondria, the power generators of the cell, provide almost all the energy required to maintain function and viability of nerve cells. Mitochondria are highly dynamic and they undergo frequent changes in shape, size, number and location. These dynamic processes can be controlled by mitochondrial fission (which leads to multiple smaller mitochondria) or fusion (which results in larger mitochondria). Recent studies including ours have shown that manipulating these processes has considerable potential for treating human neurological conditions, such as PD, led us to hypothesize that correcting mitochondrial dynamics impairment will be beneficial in controlling PD. LRRK2 G2019S, the most common genetic mutation seen in human PD, induces mitochondrial fragmentation by recruiting primary fission protein Drp1 to the mitochondria.
Our recent work consistently found that Drp1 is translocated to the mitochondria in cells expressing LRRK2 G2019S and in patient fibroblasts carrying this specific mutant. Importantly, we showed that inhibition of Drp1 hyper-activation by a selective Drp1 peptide inhibitor P110 recently developed in my lab reversed LRRK1 G2019S-induced mitochondrial dysfunction and conferred neuroprotection. Further, our recent preliminary study showed that P110 treatment corrected mitochondrial damage and reduced neurite shortening in dopaminergic neurons derived from PD LRRK2 G2019S patient-induced pluripotent stem cells (LRRK2 G2019S-iPS cells). In addition, P110 appears to have minimal effects on mitochondrial function in cells under normal conditions. Thus, the novel Drp1 Peptide inhibitor P119 might be useful for treatment of PD.

Method/Design: Recent success in generating neuronal cell cultures from patients with neurological diseases enables us, for the first time, to study disease mechanisms in the context of cells derived from patients. It also enables testing the ability of drugs to inhibit the neuropathology. Our lab established the model of iPS cells derived from PD-patient fibroblasts carrying LRRK2 G2019S mutation and iPS cell lines from normal subjects. We have been able to differentiate these patient-iPS cells into dopaminergic neurons, which are susceptible in PD. In this study, we plan to utilize Drp1 peptide inhibitor P110 that selectively inhibits mitochondrial fission machinery, and test it in the PD patient-iPS cell-derived neuronal culture. Specifically, we will determine whether treatment with P110 corrects mitochondrial dysfunction in neurons derived from LRRK2 G2019S-iPS cells (Aim 1) and whether inhibition of excessive mitochondrial fission with P110 reduces neuronal degeneration and cell death (Aim 2).

Relevance to Diagnosis/Treatment of Parkinson’s disease: PD is a devastating neurodegenerative disorder. The mechanisms underlying the disease are poorly understood and there is currently no treatment available for PD. Therefore, we are challenged to developed new experimental models for PD and to elucidate novel mechanisms for understanding its pathogenesis, so that we may advance drug development. The human PD iPSC-based neuronal model overcomes the limitation of PD animal models and provides us a powerful tool for studying PD. In this study, utilization of the PD patient-specific iPS cells and differentiated neuronal cells will allow us, for the first time, to discern the crucial role of mitochondrial dynamics and function in this disease in the context of human phenotype with the diseased genotype. Furthermore, development of peptide regulators by selectively targeting excessive mitochondrial fission has the potential to open up a new therapeutic rote for PD and other neurological diseases characterized by impaired mitochondrial functions. If successful, our studies will not only enhance our understanding of PD pathogenesis, but also will accelerate drug development efforts.