Mechanisms of LRRK2 Mediated Dopaminergic Axonal Degeneration and Synaptic Transmission Deficits

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Principal Investigators

ZHANG, HUI

Institution

THOMAS JEFFERSON UNIVERSITY

Contact information of lead PI
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Research Abstract

Mechanisms of LRRK2 Mediated Dopaminergic Axonal Degeneration and Synaptic Transmission Deficits Emerging evidence suggests that synaptic dysfunction of dopamine (DA) neurons is an early event in the pathogenesis of Parkinson disease (PD) occurring prior to the

onset of symptoms. Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene are the most prevalent causes of familial and sporadic PD, demonstrating an unprecedented significant role in PD pathogenesis. Recently a transgenic mouse model with over- expression of human LRRK2-R1441G has been shown to recapitulate motor behavioral, neurochemical and pathological features of PD, and we have found age-dependent deficits in DA release in the striatum in this model. Both genetic and environmental causes of PD have highlighted the importance of mitochondrial dysfunction in the pathogenesis of PD. Essentially, synaptic mitochondria play a critical role in the function and organization of synaptic vesicle pools and in neurotransmitter release. However, behavior of synaptic mitochondria in mutant LRRK2 associated-PD has not been well studied. Moreover, it is unknown why DA neurons in the substantia nigra pars compacta (SNc) and their terminals in the dorsal striatum (dSTR) are specifically vulnerable to degeneration due to pathogenic LRRK2 mutations. Therefore, it is important to understand the role of synaptic mitochondria in DA release and DAergic axon degeneration in LRRK2 transgenic mouse models. We hypothesize that mutant LRRK2 impairs mitochondrial function at the pre-synaptic terminals, which in turn diminishes local ATP synthesis for normal DA release and increase oxidation level which will lead to axonal degeneration in the end. We will utilize a combination of fast cyclic voltammetry recording and two-photon imaging in living brain slices, induced pluripotent stem cells (iPSCs) and mouse genetics to uncover mechanisms underlying DAergic transmission deficit in PD. These findings will likely provide new insights into pathogenesis of PD and open new avenues for therapeutic intervention.

Further information available at:

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