Novel Mechanisms of LRRK2-Dependent Neurodegeneration in Parkinsons Disease

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Principal Investigators

MOORE, DARREN JOHN

Institution

VAN ANDEL RESEARCH INSTITUTE

Contact information of lead PI
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USA

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Novel Mechanisms of LRRK2-Dependent Neurodegeneration in Parkinsons Disease

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Parkinson's disease & PD-related disorders

Keywords

LRRK2 gene, Parkinson Disease, Nerve Degeneration, Guanosine Triphosphate Phosphohydrolases, Phosphotransferases

Research Abstract
? DESCRIPTION (provided by applicant): Parkinson’s disease (PD) is a common

neurodegenerative movement disorder caused primarily by the degeneration of dopaminergic neurons in the substantia nigra. Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene cause late-onset, autosomal dominant PD, and LRRK2 genomic variation increases PD risk. LRRK2 has emerged has an important therapeutic target for treating PD and therefore it is critical to understand the molecular mechanisms that lead to LRRK2-dependent neurodegeneration. LRRK2 is a multi- domain protein containing Ras-of-complex (Roc) GTPase and C-terminal-of-Roc (COR) domains, in addition to a protein kinase domain. We have previously shown that familial LRRK2 mutations increase kinase activity (G2019S) or impair GTPase activity (R1441C/G/H or Y1699C) but commonly induce neuronal damage in cultured cells. Our studies have also highlighted an important role for the GTPase domain in regulating LRRK2 kinase activity and neuronal toxicity, highlighting the GTPase domain as a promising target for inhibiting LRRK2. We have also shown that the G2019S mutation, which produces a hyperactive kinase, can induce dopaminergic neuronal degeneration in rats via adenoviral-mediated gene transfer through an unknown mechanism. In the present application, we now propose to explore whether kinase activity is commonly required for dopaminergic neurodegeneration induced by familial PD mutations (R1441C, Y1699C and G2019S) in an adenoviral-based LRRK2 rat model (Aim 1). We hypothesize that certain familial mutations exert their detrimental effects through a kinase-dependent mechanism. Accordingly, genetic and pharmacological inhibition of LRRK2 kinase activity will be evaluated in this adenoviral model for disease- modifying effects. Authentic substrates of LRRK2 kinase activity have not yet been identified in vivo. We recently identified ArfGAP1 as a robust kinase substrate of LRRK2 that is critically required for LRRK2-induced neuronal toxicity in cultures. We now propose to identify the sites of ArfGAP1 phosphorylation by LRRK2 in vitro and in vivo in brain tissue, and evaluate the contribution of ArfGAP1 phosphorylation and expression to LRRK2-induced neuronal damage in primary neuronal and adenoviral-based rat models (Aim 2). Finally, our studies will explore the role of the Roc-COR tandem domain in regulating LRRK2 activity and toxicity (Aim 3). We hypothesize that LRRK2 functions as a GTPase activated by dimerization (GAD) and accordingly we will explore how intermolecular (i.e. COR domain-mediated dimerization) and intramolecular (Roc/COR interactions) interactions contribute to LRRK2 activity and toxicity. We will determine whether disrupting these unique Roc-COR interactions serve to attenuate LRRK2-mediated neurodegeneration. Our proposal is novel, innovative and timely and will provide critical mechanistic insight into the relative contributions of GTPase and kinase activity to LRRK2-mediated neurodegeneration. Our studies will have important implications for the identification of therapeutic strategies for PD based upon attenuating LRRK2 activity and neuronal toxicity.

Lay Summary

PUBLIC HEALTH RELEVANCE: Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene are a common cause of familial Parkinson’s disease (PD), and variation at the LRRK2 genomic locus increases the risk for developing PD. Understanding how these genetic mutations cause neurodegeneration in PD is important for understanding the molecular basis of disease and for the development of disease-modifying therapeutic strategies to slow or halt disease progression. Our studies aim to explore novel mechanisms by which mutant forms of LRRK2 lead to neuronal damage by elucidating the contribution of kinase activity, downstream kinase substrates, and dimerization to the toxic effects of LRRK2 in brain cells indicating that these studies will have important implications for understanding the basis of LRRK2-associated PD and for future drug development efforts.

Further information available at:

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