Molecular Mechanism of LRRK2 Biology and Pathology in Parkinsons Disease

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Country

USA

Title of project or programme

Molecular Mechanism of LRRK2 Biology and Pathology in Parkinsons Disease

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 836,816.51

Start date of award

01/12/2007

Total duration of award in years

2

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

LRRK2 gene, Parkinson Disease, Pathology, Biology, Synaptic Vesicles

Research Abstract

DESCRIPTION (provided by applicant): The overarching goal of this renewal R01 is to advance our understanding of the biology and pathology of Leucine-Rich Repeat Kinase 2 (LRRK2),

whose mutations are the most common genetic cause of Parkinson’s disease (PD). LRRK2 encodes a large and complex protein (285kD) including a kinase and a GTPase domain. Previously multiple lines of evidence have led to a “”gain-of-function”” hypothesis that LRRK2 pathogenic mutations cause increased kinase activity that is attributable to the neurotoxicity. Recent studies in cell cultures implicate LRRK2 in vesicle trafficking, neurite outgrowth, cytoskeletal dynamics, protein translation and degradation, mitochondria dynamics and inflammatory response. Importantly, the study of genetic animal models show that the pathogenic LRRK2 mutations impair dopamine transmission without causing neurodegeneration, suggesting a pathophysiological role of LRRK2 in neurotransmission at early disease stage prior to neurodegeneration. Emerging evidence has also linked LRRK2 to neuroinflammation that is a contributing factor to neurodegeneration in PD. But the precise mechanisms whereby LRRK2 mutant mediate the neural dysfunction and neurotoxicity remain unclear. Therefore, we hypothesize that (1) LRRK2 regulates SV protein functions and neurotransmission that is impaired by LRRK2 pathogenic mutations; 2) LRRK2 plays a critical role in neuroinflammatory response in glial cells; LRRK2 mutants deregulate glial inflammatory pathway and cause neurotoxicity in PD. Our specific aims are to (1) determine the pathogenic role of LRRK2 in SV traffic and neurotransmission; (2) examine dysfunctional LRRK2 in glial neuroinflammatory response. A major challenge of LRRK2 research is the lack of well-defined neurodegeneration models of LRRK2 that are relevant to the PD pathogenesis. In fact, the incomplete disease penetrance of the common mutation G2019S suggests a significant contribution of environmental factors to PD pathogenesis. Our third aim is then to test the hypothesis in animal models that LRRK2 causes neurodegeneration in PD through genetic lesion and environmental toxin-linked neuroinflammation. Successful completion of the study not only will gain insight into LRRK2 biology and pathophysiology, but also will deliver valuable cell and animal models for interrogating neurodegenerative pathways in PD and developing platforms for LRRK2 inhibitor screening.

Lay Summary

PUBLIC HEALTH RELEVANCE: Our application will investigate potential pathogenic pathways mediated by LRRK2 in Parkinson’s disease. We seek to develop two-hit LRRK2 neurodegeneration model for PD by combining LRRK2 genetic lesions and environmental toxin exposure. If successful, our study not only will gain insight into molecular and cellular mechanism for the pathogenesis of PD, but also will establish valuable cell and animal models for developing therapeutic strategies to treat PD.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Parkinson's disease & PD-related disorders

Years:
2016

Database Categories:
N/A

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N/A