LRRK2, KIF5A and Parkinson disease

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USA

Title of project or programme

LRRK2, KIF5A and Parkinson disease

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NIH (NINDS)

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5

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

LRRK2 gene, Kinesin, Parkinson Disease, Family member, Lewy Bodies

Research Abstract

Abstract: Mutations in the leucine-rich repeat kinase 2 (LRRK2) cause a genetic form of Parkinson’s disease (PD) with pleomorphic pathology, and constitute one of the most common known causes of PD. LRRK2 is a large protein whose normal functions are still largely unknown although it has kinase and GTPase activities. Most though not all LRRK2 mutations alter GTPase or kinase activities. We have identified KIF5A (kinesin family member 5A) as a novel

LRRK2 interactor in a yeast two-hybrid screen. KIF5A is a microtubule-associated force-producing motor protein that drives intracellular organelle transport. Our preliminary studies suggest that KIF5A alters LRRK2-induced neuronal degeneration and protein aggregation. Thus, investigation of the KIF5A/LRRK2 interaction could provide novel insight into the mechanisms of LRRK2 PD pathogenesis. In this proposal, we will test the hypothesis that the interaction of mutant LRRK2 with KIF5A impairs cellular transport and contributes to neuronal degeneration resulting in PD pathology. Our proposed Aims are as follows: Aim 1. We will further characterize the newly identified KIF5A and LRRK2 interaction using in vitro and in vivo models. Aim 2. We will examine whether KIF5A protects against LRRK2-induced neuronal toxicity. Aim 3. We will determine whether mutant LRRK2 alters KIF5A-mediated axon transport. Aim 4. We will investigate the roles of LRRK2 and KIF5A interaction in relation to Lewy body pathology and cellular aggregation pathways. These studies will provide new insights into LRRK2 functions and potential novel mechanisms underlying LRRK2- linked protein aggregation and neurodegeneration, and may have broader implications for neurological diseases related to impairment of cellular transport. Thus, these studies have the potential for significant impact and benefit the population suffering from PD and other neurodegenerative diseases. The understanding of transport-related pathogenesis may provide new targets for development of novel disease- modifying therapeutic strategies.

Lay Summary
Project Narrative: We propose to study the novel functions of LRRK2 and a newly identified interaction partner protein, KIF5A, in neurons, and their relationship towards the development of Parkinson’s disease (PD). These studies will provide new insights into the molecular mechanisms underlying LRRK2-induced neuronal degeneration and help identify potentially novel therapeutic targets for PD intervention.

Further information available at:

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Investments > €500k

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United States of America

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Parkinson's disease & PD-related disorders

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