Structure and Function of the Parkinsons disease associated protein LRRK2

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Country

USA

Title of project or programme

Structure and Function of the Parkinsons disease associated protein LRRK2

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NIH (NINDS)

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01/04/2015

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4

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

LRRK2 gene, Parkinson Disease, Guanosine Triphosphate Phosphohydrolases, magnesium ion, Structure

Research Abstract
? DESCRIPTION (provided by applicant): Here we seek to understand how structure and

interactions between the domains of LRRK2 regulate its activities, and also how Parkinson’s disease-associated mutations affect these processes. Those areas of study are significant because LRRK2 holds the strongest promise for developing effective treatments for Parkinson’s disease (PD), for which there is currently none. Mutations in LRRK2 leading to disease clearly perturb LRRK2 kinase activity; however, the mechanism in doing so is complex as mutation sites remote from the kinase domain also exert similar effects on kinase activity. The major roadblock in unraveling these mechanisms had been the lack of protein samples amenable for detail biochemical and biophysical studies. We have overcome that by developing procedures that yield highly purified samples amenable for detail studies. Here we use these samples to study the structure and function of LRRK2, to tease out how its activities are regulated, and to define its mechanism in disease pathogenesis. The three areas to be investigated in this project are: 1. To determine the effects of PD-associated mutations on the structure and function of the Roc domain of LRRK2. We have shown that the PD-mutation R1441H impairs GTPase activity of the Roc domain of LRRK2. This impairment occurs through distorting the active-site, altering the conformation of the switch regions, or impeding the binding of magnesium ions. 2. To determine the GTPase activation domain of Roc and to define the structural basis for GTPase regulation. We have shown that the Roc domain of LRRK2 has low intrinsic GTPase activity, and we have seen that it could be activated 30-fold by an unknown domain within LRRK2. We will use a combination of biochemical and structural studies to identify and define this activation mechanism. 3. To define global structural interactions between the domains within LRRK2. Mutations are found in various parts of LRRK2, but they all affect kinase activity which can be several domains away from the mutation sites, thus indicating that these domains interact with one another working in concert to exert a common function. We will map the spatial arrangement of all domains within LRRK2 to gain insight into how they work together.

Lay Summary
PUBLIC HEALTH RELEVANCE: This study addresses several issues of central importance to the cause of Parkinson’s disease and development of treatments. Those include: how mutations affect LRRK2 activity and lead to disease, the mechanism of how LRRK2 is normally regulated and how disease-associated mutations alter those, and define specific locations on LRRK2 for drug targeting. These studies will show a pathway for Parkinson’s disease and how to treat it.

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

Years:
2016

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N/A

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