LRRK in Autophagy Function and Dopaminergic Neuron Survival

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Country

USA

Title of project or programme

LRRK in Autophagy Function and Dopaminergic Neuron Survival

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 2,252,875.23

Start date of award

01/07/2010

Total duration of award in years

3

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

LRRK2 gene, dopaminergic neuron, Autophagocytosis, FRAP1 gene, mouse LRRK2 protein

Research Abstract

DESCRIPTION (provided by applicant): Parkinson’s disease (PD) is an age-related neurodegenerative disorder characterized by resting tremor, rigidity and bradykinesia. These clinical features are thought to arise from reduced dopaminergic input to the striatum, which is

caused by the degeneration of dopaminergic neurons in the substantia nigra. Mutations in LRRK2 are the most common genetic cause of late-onset PD, but the normal physiological role of mammalian LRRK2 remains to be elucidated. We previously reported that inactivation of LRRK2 causes age-dependent impairment of autophagy function and protein degradation pathways, leading to striking accumulation and aggregation of proteins including alpha-synuclein and increases of apoptotic cell death, inflammatory responses and oxidative damage in aged mice. Intriguingly, these PD-like phenotypes were observed in the LRRK2-/- kidney but not in the brain. Since LRRK2 has a functional homologue, LRRK1, which is also a ROCO protein containing GTPase and kinase domains, we reasoned that the lack of similar phenotypes in LRRK2-/- brains is due to the relatively high expression of LRRK1 in the brain, which could compensate for the loss of LRRK2, whereas the kidney expresses the highest level of LRRK2. Thus, it is important to determine whether loss of both LRRKs causes age-dependent autophagy impairment and dopaminergic degeneration in the brain. In this application, we propose two Specific Aims to investigate the role of LRRK in the regulation of autophagy and age-dependent survival of dopaminergic neurons, and to explore the molecular mechanisms by which LRRK controls autophagy function. The completion of the proposed studies will further our understanding of LRRK2 biology, define molecular mechanisms by which LRRK regulates autophagy function, and provide insight into the pathogenic mechanism underlying LRRK2 mutations. The identified molecular targets of LRRK2 may be used as novel therapeutic targets or pharmacodynamic biomarkers.

Lay Summary

PUBLIC HEALTH RELEVANCE: Parkinson’s disease (PD) is the most common movement disorder, and mutations in the LRRK2 gene are the most common genetic cause for late-onset PD. In this application, we propose to investigate the mechanisms by which mutations in LRRK2 cause PD by determining the physiological role of LRRK2 in the regulation of autophagy function and protein degradation pathways. Completion of our proposed study will provide insights into PD pathogenesis and may identify novel therapeutic targets for development of more effective drugs.

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

Database Tags:
N/A