Regulation of mitochondrial motility and mitophagy by LRRK2.

https://neurodegenerationresearch.eu/survey/regulation-of-mitochondrial-motility-and-mitophagy-by-lrrk2/

Principal Investigators

WANG, XINNAN

Institution

STANFORD UNIVERSITY

Contact information of lead PI
Country

USA

Title of project or programme

Regulation of mitochondrial motility and mitophagy by LRRK2.

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,796,574.31

Start date of award

30/09/2014

Total duration of award in years

3

The project/programme is most relevant to:

Parkinson's disease and PD-related disorders

Keywords

LRRK2 gene, parkin gene, , ,

Research Abstract
DESCRIPTION (provided by applicant): Anterograde mitochondrial transport in neuronal axons is mediated by a primary motor/adaptor complex which includes motor protein KHC (kinesin heavy chain), and two mitochondrial adaptors milton and Miro (Glater et al., 2006). In the

current model, Miro, an outer mitochondrial membrane (OMM) protein, binds to milton which in turn binds to KHC, to recruit mitochondria to motors and microtubules (Guo et al., 2005, Fransson et al., 2006, Glater et al., 2006). During my postdoctoral training, I discovered that two PD proteins PINK1 and Parkin target Miro for degradation to promote damage-induced mitophagy (Wang et al., 2011). This is consistent with our preliminary observation conducted in my own laboratory that mutant Parkin fibroblasts from one PD patient are failed to degrade Miro after mitochondrial damage and are impaired in mitophagy. The most common genetic form of hereditary PD is caused by a G2019S mutation in the LRRK2 gene. LRRK2 encodes a multi-domain Ser/Thr kinase with unknown functions and unconfirmed substrates. Surprisingly, we found that Miro is also retained on damaged mitochondria in fibroblasts from one PD patient with LRRK2G2019S. In addition, we have preliminary evidence that in LRRK2G2019S iPSC (inducible pluripotent stem cells)-derived neurons from two PD patients, damaged mitochondria fail to stop and to undergo mitophagy, reminiscent of those found in mutant PINK1 or Parkin rodent models (Wang et al., 2011). Therefore, LRRK2G2019S, just like PINK1 or Parkin mutations, prevents Miro protein from degradation on damaged mitochondria, disrupting mitochondrial motility and mitophagy. However, there has been no evidence directly linking LRRK2 to Miro and mitochondrial transport. What is the mechanism underlying the same phenotype caused by distinct PD mutations? In this proposal, we aim to unravel this puzzle. We hypothesize that LRRK2 and PINK1/Parkin operate in parallel pathways but eventually converge on the common substrate Miro. In an alternative model, LRRK2 may not directly phosphorylate Miro, but rather it could genetically or physically interact with and regulate PINK1 or Parkin to control damaged mitochondrial transport and clearance by influencing turn-over of Miro. The molecular mechanism we will define in this research proposal will provide insight into LRRK2-related PD pathogenesis, especially for patients with LRRK2G2019S, which represents about 5-6% of the total cases (Bonifati, 2006). In addition to its relevance to PD, we also expect our results elucidating the mechanisms underlying neuronal mitochondrial transport and clearance to illuminate basic principles of mitochondrial biology and neurobiology. Thus, we propose to use a combination of Drosophila genetics, cultured cells, and even PD patient fibroblasts and derived neurons to pursue the following Specific Aims. Aim 1: To determine the mechanism by which LRRK2 influences the turnover of Miro. Aim 2: To determine the physical relationship between LRRK2 and Miro. Aim 3: To dissect the relationship between LRRK2 and the PINK1/Parkin pathway.

Lay Summary

PUBLIC HEALTH RELEVANCE: Parkinson’s disease (PD), one of the most common neurodegenerative diseases, afflicts millions of people worldwide with tremendous global economic and societal burdens. An effective treatment is desperately needed but the underlying molecular and cellular mechanisms of PD’s destructive path remain poorly understood. This proposal aims to dissect the cellular functions of a gene implicated in PD, LRRK2, and is therefore relevant to public health and the mission of the NIH, as it will illuminate the pathological causes of PD and provide novel targets for therapeutic intervention.

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