Role of PAR-1 Kinase in Synaptogenesis

https://neurodegenerationresearch.eu/survey/role-of-par-1-kinase-in-synaptogenesis/

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Country

USA

Title of project or programme

Role of PAR-1 Kinase in Synaptogenesis

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,840,596.33

Start date of award

01/04/2007

Total duration of award in years

4

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

synaptogenesis, rho GTP-Binding Proteins, Mitochondria, Phosphotransferases, LRRK2 gene

Research Abstract

DESCRIPTION (provided by applicant): Mitochondria play essential roles in normal neuronal physiology, from energy production to Ca2+ buffering to synaptic differentiation and plasticity. The intracellular distribution of mitochondria needs to be precisely matched to the demand for these organelles, a task particularly difficult for neurons due to their highly polarized morpholog and their dynamic patterns of neuronal activity and synaptic plasticity in vivo. Because abnormal

mitochondrial distribution and function has been consistently observed at early stages of neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) as well as neuropsychiatric disorders, understanding the genetic control of mitochondrial distribution in neurons has assumed a high priority in neuroscience research. Unfortunately, progress in this area has been impeded by the lack of identified regulatory molecules governing this process. In the proposed project, we aim to define the role of PAR-1 (partitioning defective 1), an evolutionarily conserved Ser/Thr kinase, in the regulation of neuronal mitochondrial distribution. PAR-1 was initially identified as a gene required for the asymmetric cell division in early C. elegans embryos. Work from our lab and that of others has established a critical role for PAR-1 in regulating synaptic structure and function in Drosophila and mammals. Our most recent work shows that PAR-1 plays an important role in directing neuronal mitochondrial distribution. Additional studies indicate that PAR-1 genetically and physically interacts with mitochondrial rho GTPase (Miro), a conserved key component of the mitochondrial transport machinery, and that PAR-1 regulates the GTPase activity of Miro as well as the interaction between Miro and the mitochondrial fusion regulator mitofusin (Mfn). These findings led logically to the central hypothesis of the current application: that the PAR-1/Miro axis functions as a novel regulatory node through which diverse signals can impact mitochondrial distribution, and that deregulated PAR-1/Miro signaling contributes to the mitochondrial maldistribution and the ensuing synaptic dysfunction and eventual neurodegeneration as occurring in diseases. This hypothesis will be tested by determining the mechanism of how PAR-1/Miro signaling regulates mitochondrial distribution in Drosophila (Aim 1); by testing the effect of restoring PAR-1/Miro-directed mitochondrial distribution on the disease phenotypes of Drosophila models of AD (the Abeta-42 model) and PD (the LRRK2-G2019S model) (Aim 2); and by testing the effect of restoring PAR-1/Miro-directed mitochondrial distribution on the disease phenotypes of patient-specific, Abeta-42 and LRRK2-G2019S-related human neuronal models of AD and PD (Aim 3). Successful completion of these aims will be facilitated by innovative methods and strategies for visualizing and manipulating mitochondrial distribution in vivo in Drosophila and in human neuronal models of AD and PD. We expect that the information to be generated from this project will be fundamental to basic neuroscience research and of high clinical relevance.

Lay Summary

PUBLIC HEALTH RELEVANCE: Proper subcellular distribution of the energy-producing mitochondria is particularly important for the functioning and maintenance of brain cells. Defective mitochondrial distribution has been observed early in the disease process of virtually all neurodegenerative diseases and many neuropsychiatric disorders. How neuronal mitochondria are properly distributed under normal conditions and how this process is impaired in diseased states are poorly understood. This proposal will investigate the role of a conserved signaling pathway in regulating mitochondrial distribution, using both in vivo Drosophila models and human patient-derived neuronal models of neurodegenerative diseases. Results from this study are not only fundamental to basic neuroscience research but also of high significance to the understanding and treatment of neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease, as well as neuropsychiatric disorders, where mitochondrial maldistribution and/or dysfunction have been recognized.

Further information available at:

Types:

Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

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N/A