Propagation of Lewy pathology in Parkinsons disease

https://neurodegenerationresearch.eu/survey/propagation-of-lewy-pathology-in-parkinsons-disease/

Principal Investigators

LUK, KELVIN C

Institution

UNIVERSITY OF PENNSYLVANIA

Contact information of lead PI
Country

USA

Title of project or programme

Propagation of Lewy pathology in Parkinsons disease

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,573,394.50

Start date of award

13/03/2015

Total duration of award in years

4

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

alpha synuclein, Lewy Bodies, Parkinson Disease, Neurites, Pathology

Research Abstract

? DESCRIPTION (provided by applicant): The accumulation of misfolded proteins represents a common pathological mechanism of most major neurodegenerative disorders. Neuronal inclusions comprised of aggregated a-Synuclein (aSyn) are known as Lewy bodies (LBs) and

Lewy-neurites (LNs), and represent a key histopathological feature of Parkinson’s disease (PD), and a family of related disorders known as synucleinopathies that affect as many as 1 million individuals in the U.S. alone. Mutations in the SNCA gene encoding aSyn also cause familial PD but while histological and genetic evidence firmly indicate a correlation between aSyn accumulation and disease, how aSyn pathology forms and whether it directly contributes to disease remains unclear. Abnormal aSyn catalyzes the misfolding of the normal protein and it has recently been demonstrated that minute quantities of aSyn aggregates can trigger the formation of toxic LBs/LNs in cultured neurons. Misfolded aSyn also induces the formation of LBs/LNs in healthy non-transgenic mice. In both human PD and animal models, aSyn pathology progressively propagates and spreads to neuroanatomically connected regions, reminiscent of prion diseases. Importantly, animals with LBs/LNs recapitulate the cardinal features of PD, including progressive loss of dopamine-producing neurons and locomotor deficits. This proposed research plan addresses key biological questions posed by these findings, and combines novel in vitro, cell-based, and in vivo tools to further understand how LBs/LNs are form, propagate, and ultimately contribute to neurodegeneration and neurological symptoms. Aim 1 examines whether neurons in multiple brain regions develop LBs/LNs following inoculation with misfolded recombinant aSyn and subsequently undergo cell death. A recently developed tissue processing method will be used to determine if LBs/LNs spread via neuronal projections, as hypothesized for human PD, or by other mechanisms. Behavioral tests will then reveal if specific clinicopathological correlations exist. Aim 2 will define the molecular interactions that govern how abnormal aSyn triggers the conversion of normal aSyn in LBs/LNs, by testing the ability of mutant aSyn sequences to seed pathology in both cells and in vivo following stereotactic injection. Finally, Aim 3 will elucidate the cellular and molecular mechanisms by which aSyn induce intracellular pathology by using cell-based, in vivo, and proteomics approaches to compare LB/LN-inducing and non-inducing aSyn mutants that we have recently discovered. Completion of these studies should provide valuable insights into the potential mechanisms by which aSyn contribute to the progression of PD. Increased understanding of the pathogenesis of this and related synucleinopathies should ultimately result in disease-modifying therapies for this group of incurable disorders.

Lay Summary
PUBLIC HEALTH RELEVANCE: The brains of individuals with Parkinson’s disease gradually develop abnormal protein deposits called Lewy bodies but it is not known how they contribute to disease. This study uses a recently discovered method that causes brain cells to form these lesions, allowing the investigation of how they impair the function and survival of neurons. Better understanding of these processes could lead to the development of new therapies for Parkinson’s disease and other neurodegenerative disorders.

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