Unfolded Protein Response in Alpha-synucleinopathies

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Principal Investigators

LEE, MICHAEL K

Institution

UNIVERSITY OF MINNESOTA

Contact information of lead PI
Country

USA

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Unfolded Protein Response in Alpha-synucleinopathies

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NIH (NINDS)

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3

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

synucleinopathy, Reticulum, alpha synuclein, Multiple System Atrophy, Parkinson Disease

Research Abstract
DESCRIPTION (provided by applicant): Alpha-synuclein abnormalities are implicated in a number of neurodegenerative diseases; including Parkinson’s disease (PD), Lewy Body Dementia (LBD), and Multiple Systems Atrophy (MSA). Because alpha-synuclein aggregates in

neurons (PD, LBD) and/or oligodendrocytes (MSA) are prominent pathological features of these diseases, they are categorized as alpha-synucleinopathies. Collectively, alpha-synucleinopathies represent the second most common late-onset neurodegenerative disease, next to Alzheimer’s disease (AD). While there are no effective therapies that can slow or stop the progression of neurodegeneration associated with alpha-synucleinopathies, availability of multiple transgenic mouse models of various alpha-synucleinopathies allows us to better understand the genesis of alpha-synuclein abnormalities in vivo and mechanisms of neurodegeneration in brain. These efforts will likely lead to identifying novel therapeutic targets for alpha-synucleinopathies. Presence of intracellular alpha-synuclein aggregates in alpha-synucleinopathy suggest that some aspect of protein degradation/quality control is dysfunctional in the diseases. Consistent with this view, we found that neurodegeneration in cellular and transgenic mouse models of neuronal alpha-synucleinopathy is associated with chronic Endoplasmic Plasmic Reticulum Stress (ERS) with abnormal Unfolded Protein Response (UPR). Our studies indicate that ERS is initiated by translocation and aggregation of alpha-synuclein within the ER. More important, pharmacological treatment with an anti-ERS compound, Salubrinal, significantly delays disease manifestation in rodent model of neuronal alpha-synucleinopathy. These results suggest that ERS response pathway, particularly modulation of phospho-eIF2alpha levels could represent a novel therapeutic target for PD and other alpha-synucleinopathies. However, because of compounds such as Salubrinal may have unknown off-target effects in vivo, a rigorous validation the phospho-eIF2alpha as therapeutic target at molecular levels are needed. Further, it is not clear if all alpha-synucleinopathies shar common neurodegenerative mechanisms. With these issues in mind, we propose following studies. First, we will study whether chronic ERS is a general feature of alpha-synucleinopathy by studying ERS in both neuronal and glial alpha-synucleinopathies (PD, LBD, MSA). Second, we will determine if aging related factors, such as oxidative stress/mitochondrial dysfunction, promotes ER accumulation of alpha-synuclein oligomers. Finally, we will determine whether the genetic alterations in components of the Perk/eIF2alpha arm of the ERS have predictable effects on alpha-synuclein dependent neurodegeneration. These studies will establish the value of ER stress pathway, particularly Perk/eIF2alpha components, as targets for development of novel therapies for PD.

Lay Summary
PUBLIC HEALTH RELEVANCE: Currently, there are no effective therapies for slowing or reversing progressive nature of PD. The proposed studies will use novel models of alpha-synuclein dependent neurodegeneration to rigorously validate ER stress pathways as a potential target for therapy development.

Further information available at:

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Investments > €500k

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United States of America

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