Pathological role of c-Abl in alpha-synucleinoapathy

https://www.neurodegenerationresearch.eu/survey/pathological-role-of-c-abl-in-alpha-synucleinoapathy/

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Country

USA

Title of project or programme

Pathological role of c-Abl in alpha-synucleinoapathy

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,999,822.94

Start date of award

15/04/2016

Total duration of award in years

5

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

c-abl Proto-Oncogenes, ABL1 gene, synucleinopathy, TP53 gene, Autophagocytosis

Research Abstract

? DESCRIPTION (provided by applicant): PD is a progressive neurodegenerative disease involving a variety of neuronal population. Other then symptomatic therapies, there are no ways to stop the progression of underlying neurodegeneration in PD. Unfortunately, other then

symptomatic therapies, there are no ways to stop the progression of underlying neurodegeneration in PD. Currently, abnormalities in ?-synuclein (?S) is considered as a critical pathogenic agent in PD and other related diseases classified as ?-synucleinopathies. Thus, understanding how ?S abnormalities occur and cause neurodegeneration in brain appears critical for development of disease modifying therapies for PD. To understand the how ?-synucleinopathy leads to neurodegeneration, we are studying a transgenic (Tg) mouse model where the expression of the A53T mutant human ?S (Hu??S) leads to adult-onset fatal neurodegenerative disease. The affected mice exhibit many features of human ?-synucleinopathies, including ?S aggregation and neurodegeneration of multiple neuronal population. Our studies show that a stress activated kinase, c-Abl, is activated with the disease in the Hu??S(A53T) Tg mice. We propose that activation of c-Abl contributes to neurodegeneration in PD by activation of p53 and inhibition of autophagy. Specifically, we propose that c-Abl activation leads to inhibition of mdm2 and abnormal activation of cytosolic p53. Significantly, in addition to the established role of p53 in promoting apoptosis, abnormal metabolism of p53 can also inhibit autophagy. Thus, inhibitors of c-Abl may be used to attenuate the progressive neurodegeneration caused by ?S pathology. Given the therapeutic implications for multiple neurodegenerative diseases, we propose following aims to fully define the role of c-Abl activation in ?-synucleinopathy. 1) Determine the pathologic specificity of c-Al in ?-synucleinopathy using c-Abl knockout mice; 2) Determine whether mdm2/p53 pathway is involved in ?-synucleinopathy and regulation of autophagy; and 3) Determine the role of IRE1? and mTOR function in the regulation of autophagy by c-Abl/p53. By using genetic models, results of the proposed studies will provide unambiguous test of c-Abl as a therapeutic target for PD and other ?-synucleinopathies. Further, our results will provide a novel mechanistic link between c-Abl, p53, autophagy, and ?-synucleinopathy in vivo.

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 c-Abl pathways as a potential target for therapy development. Information and animal models generated here will have direct impact on future efforts aimed at developing therapies for PD.

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