Proteostasis and secondary proteinopathy in AD and FTD

https://neurodegenerationresearch.eu/survey/proteostasis-and-secondary-proteinopathy-in-ad-and-ftd/

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Country

USA

Title of project or programme

Proteostasis and secondary proteinopathy in AD and FTD

Source of funding information

NIH (NIA)

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Start date of award

01/05/2015

Total duration of award in years

2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease Related Dementias (ADRD)... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Dementia... Frontotemporal Dementia (FTD)... Neurodegenerative... Neurosciences... Pick's Disease... Rare Diseases

Research Abstract

DESCRIPTION (provided by applicant): One of the major gaps in our understanding of the evolution of Alzheimer's disease is how the deposition of amyloid triggers tauopathy. Moreover, it is now widely recognized that it is common for the CNS of individuals with a neurodegenerative phenotype to develop multiple pathologic abnormalities. The basis for the preponderance of mixed pathology is poorly understood. We hypothesize that insults that compromised function of the proteostasis network may lay the foundation for the development of mixed proteinopathies. The basic concept here is that high levels of misfolded proteins produce an added burden on the proteostatic network by occupying various activities required to dissociate such aggregates and degrade the misfolded proteins. This concept was first uncovered in C. elegans models, where the expression of proteins that produce intracellular inclusions leads to the secondary misfolding of by-stander proteins that are particularly dependent upon the proteostatic network. Recently, we have extended this concept to mammalian model systems. In proteomic studies of brain from mice with high levels of Alzheimer-amyloidosis, Drs. Xu and Borchelt identified a number of cytosolic proteins that appeared to lose solubility – a finding that is consistent with the hypothesis that amyloid deposition can, by some manner, impinge on the function of the proteostatic network to cause ""secondary"" misfolding. The Lewis laboratory also recently found that two independent lines of mice that model tau pathology also develop cytoplasmic TDP-43 immunoreactive inclusion pathology. Thus, in our mouse models, we are beginning to uncover evidence that the accumulation of one misfolded protein, can by some manner, impact on the folding of others. Our central hypothesis is that these secondary pathologies are the consequence, at least in part, of a disturbance in the cellular protein quality control network, or proteostasis network, to cause collateral misfolding. In the present application, we propose 3 Aims that seek to determine the contribution of proteostatic network dysfunction to the evolution of AD-related pathology. Aim 1 will create a novel paradigm in which mutant tau expression is induced in a preexisting environment of amyloid pathology and disturbed proteostatic function. Aim 2 will determine how the mixed pathology of AD may synergize to produce by-stander misfolding and whether the severity of such misfolding produces functional deficits in critical cellular processes (e.g. energy metabolism). Aim 3 will determine whether augmentation of proteostatic networks mitigates by-stander misfolding. Collectively, these studies will provide new insight into how AD-related pathology impacts CNS protein homoeostasis and whether augmentation of the network in later stages of disease may provide significant benefit.

Lay Summary

PUBLIC HEALTH RELEVANCE: A myriad of activities work in concert as a network (proteostasis network) to produce, fold, and degrade the proteins that constitute the essential effectors of cellular function. In studies prior to this application, we have uncovered evidence that the deposition of amyloid plaques, the first pathology to appear in Alzheimer's disease, may diminish the function of the proteostasis network in nerve cells, laying the foundation of a cascade of events that produce memory loss. The proposed studies seek to explore the relationships between amyloid, diminished proteostasis function, and the evolution of the full spectrum of Alzheimer brain pathology.

Further information available at:

Types:

Investments > €500k

Member States:

United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

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