The role of inflammasome signaling in tauopathies

https://neurodegenerationresearch.eu/survey/the-role-of-inflammasome-signaling-in-tauopathies/

Principal Investigators

BHASKAR, KIRAN

Institution

UNIVERSITY OF NEW MEXICO HEALTH SCIS CTR

Contact information of lead PI
Country

USA

Title of project or programme

The role of inflammasome signaling in tauopathies

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,213,829.36

Start date of award

01/03/2014

Total duration of award in years

3

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Tauopathies, tau Proteins, hTau Mice, neuroinflammation, Interleukin-1

Research Abstract

DESCRIPTION (provided by applicant): Tangle pathology is one of the major pathological hallmarks of Alzheimer’s disease (AD) and related tauopathies, where microtubule associated protein – tau (or tau) acquires a pathological protein conformation, accumulates as

neurofibrillary tangles (NFTs) and coincides with neurodegeneration. Increasing evidence suggests that age-related alterations in inflammatory processes also closely associated with NFT pathology in the brains of individuals with human and mouse models of tauopathies. While it is hypothesized that accumulation misfolded proteins released from injured neurons and synapses may trigger neuroinflammation, it is not clear how misfolding of proteins intrinsic to neurons, such NFTs, trigger neuroinflammation. Previous studies have documented that neurodegenerative lesions caused by truncation of human tau promoted inflammatory response including upregulation of numerous immune molecules and morphological activation of microglial cells in a rat model of tauopathy. Furthermore, NFT lesions in this model also promoted infiltration and recruitment of peripheral leukocytes into the brain parenchyma. In another study, microglial activation preceded NFT pathology in P301S mouse model of tauopathy. We have recently demonstrated a progressive and age-dependent neuroinflammation in hTau mouse model of tauopathy. First, robust microglial activation was observed in 12 month and 18 month old hTau mice compared to 18 month old non-transgenic controls. Second, a significant increase in mRNA levels for inflammatory molecules such as nitric-oxide synthase-2 (NOS2) and monocyte chomoattractant protein (MCP1 or CCL2) was observed in the brains of much younger, 6 month old hTau mice. Finally, enhancing microglia-specific neuroinflammation accelerated tau phsphorylation, aggregation and behavioral impairment in hTau mouse model of tauopathy. Notably, the interleukin-1 (IL-1) released by reactive microglia induces tau phosphorylation via activating neuronal IL-1 receptor (IL-1R) and p38 mitogen activated protein kinase pathway. While these studies suggested that microglial activation and IL-1 signaling is involved in accelerating tau pathology and neurodegeneration, the factor(s) driving microglial activation and/or secretion of IL-1 is unclear. In our preliminary studies, we have observed that misfolded tau could act as ‘danger signal’ to stimulate secretion of IL-1¿ via assembly of a multiprotein complex called “”inflammasome””, which includes ASC as a key component of inflammasome complex. Based on this novel phenomenon from our preliminary studies, we propose to determine whether misfolded tau trigger inflammasome assembly/maturation of IL-1¿ and lead to microglial activation in vitro (Specific Aims 1) and in rTg4510 regulatable mouse model of tauopathy (Specific Aim 2). We also propose to determine whether blocking inflammasome assembly via genetic deficiency of ASC prevents IL-1¿ activation, microglial neuroinflammation and block tau pathology in hTau mice crossed to ASC-/- and ASCfl/fl mice (Specific Aim 3). The outcome of these studies will provide greater understanding of the tau pathology and innate immune responses mediated by inflammasome/IL-1¿ and present opportunities in identifying novel therapeutic targets against tauopathies.

Lay Summary

PUBLIC HEALTH RELEVANCE: Increasing number of research studies suggests that brain inflammation is strongly associated with neurodegeneration in Alzheimer’s disease and related tauopathies. A recent study from our group has provided compelling evidence that microglia-specific neuroinflammation accelerates microtubule-associated protein tau (or tau) pathology and cognitive impairment in humanized mouse model of tauopathy (hTau). Notably, interneukin-1? (IL-1?) released from activated microglia is responsible for upregulating neuronal p38 mitogen activated protein kinase and tau hyperphosphorylation via IL1 receptor (IL-1R) signaling pathway. In the current study, we propose to utilize cell culture system and transgenic (rTg4510 and hTau) and knockout (Asc-/- and Ascfl/fl) mouse models to determine; 1) Whether or not variety of pathologically altered tau is responsible for triggering the IL-1? activation in oth

neuron and microglia to result in microglial activation, tau pathology and neurodegeneration; 2) Whether blocking pathological tau expression (in rTg4510 mice) will prevent neuroinflammation and IL-1? activation. 3) Test if genetic deficiency of ASC (total or cell-specific) – key protein required for IL-1? activation will prevent microglial neuroinflammation, tau pathology, cognitive impairment and neurodegeneration in hTau mouse model of tauopathy. The outcome of this study will provide direct evidence whether pathological tau act as initial trigger to induce neuroinflammation in tauopathies. Furthermore, our study also provides mechanistic insights into IL-1? / inflammasome as potential therapeutic target against tauopathies.

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

Database Tags:
N/A