Investigating the neuroinflammatory role of RIP1 kinase

https://neurodegenerationresearch.eu/survey/investigating-the-neuroinflammatory-role-of-rip1-kinase/

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Country

USA

Title of project or programme

Investigating the neuroinflammatory role of RIP1 kinase

Source of funding information

NIH (NIA)

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€ 1,726,924.77

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15/05/2014

Total duration of award in years

3

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Dementia... Immune System... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): The goal of this proposal is to validate the role and

explore the molecular mechanism of RIP1 kinase as a mediator of inflammatory response in Alzheimer’s disease (AD), a devastating neurodegenerative disorder and the leading cause of dementia of the elderly. Chronic brain inflammation, characterized by the presence of an increased number of microglia and elevated levels of proinflammatory cytokines, is a hallmark of AD. Increased levels of cerebral spinal TNF? were found in patients with mild cognitive impairment (MCI) at risk to develop AD, suggesting that CNS inflammation is an early event during the pathogenesis of AD. The role of inflammation in the pathogenesis of AD was further highlighted by a recent network-based integrative analysis of a large collection of gene expression profiles from patients of late-onset Alzheimer’s disease (LOAD) which discovered the immune/microglia system, including multiple TLR receptors and TNF?, as the molecular system most strongly associated with the pathophysiology of the LOAD. When activated, microglia may release proinflammatory cytokines to drive the chronic progression of AD by exacerbating A? deposition and neuronal death. Identification of the molecular targets in microglia that can be safely modulated to inhibit their inflammatory response may provide new options for the treatment of AD. However, there is a lack of knowledge about the neuroinflammatory mechanism that can be specifically and effectively modulated. We have developed a highly specific and potent inhibitor of RIP1 kinase, 7-Cl-O-Nec-1, a small molecule with excellent oral availability and safety profile, and highly CNS permeable. RIP1 kinase, a death- domain containing Ser/Thr kinase, has an established role in mediating multiple downstream signaling pathways downstream of TNFR1. We found that RIP1 kinase also plays an important role in mediating the production of TNF? by microglia induced by A? in vitro and in PSAPP transgenic mice in vivo which can be effectively inhibited by 7-Cl-O-Nec-1. Furthermore, oral administration of 7-Cl-O-Nec-1 led to the reduction of amyloid plaques and improved behavior and memory of B6.Cg-Tg(APPswe, PSEN1dE9) 85Dbo/J mice (PSAPP) mice, a model for AD. Our study suggests that RIP1 kinase is an important target for inhibiting neuroinflammatory response in AD. This proposal is to test this hypothesis and investigate the mechanism by which RIP1 kinase mediates neuroinflammatory responses in microglia. Specific Aim 1: Investigating the role and mechanism by which RIP1 kinase mediates inflammatory response in microglia activated by oligomeric A? by testing the possible involvement of MKK7 and TLR signaling as downstream mediators of RIP1 signaling. Specific Aim 2: Investigating the role and mechanism of p62 in A? mediated RIP1 kinase activation in microglia by testing the hypothesis that oligomerized p62 provides a platform for mediating RIP1 activation. Specific Aim 3: Genetic confirmation of the role of RIP1 kinase in mediating inflammatory response in AD transgenic mice using a RIP1 kinase dead knockin mouse line.

Lay Summary

PUBLIC HEALTH RELEVANCE: The goal of this proposal is to validate the role and explore the molecular mechanism of RIP1 kinase in mediating inflammatory response in Alzheimer’s disease (AD), a devastating neurodegenerative disorder and the leading cause of dementia of the elderly. Chronic brain inflammation, characterized by the presence of an increased number of microglia and elevated levels of proinflammatory cytokines, is a hallmark of AD. Identification of the molecular targets in microglia that can be safely modulated to inhibit their inflammatory response may provide new options for the treatment of AD.

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

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