SIRT1 Limits Microglial Toxicity in Alzheimers Disease

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Country

USA

Title of project or programme

SIRT1 Limits Microglial Toxicity in Alzheimers Disease

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NIH (NIA)

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01/08/2012

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5

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... Genetics... Immune System... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): Microglial activation has long been proposed to

contribute to the pathogenesis of Alzheimer’s disease (AD). Besides causing direct toxic effects on neuronal and synaptic functions, accumulation of amyloid beta (Aß) and/or tau stimulates microglial activation and expression of inflammatory cytokines, which can induce further neuronal damage. Blocking the toxic pathway in microglial activation could effectively protect against neurodegeneration. However, the molecular mechanisms modulating the microglial loop remain elusive. Our previous studies in primary cortical cultures suggest that NF-?B activation in microglia plays a critical role in microglial-mediated Aß toxicity. Inhibition of NF-?B by SIRT1, a member of the sirtuin family of histone deacetylases, protected against microglia toxicity in Aß-treated primary cultures. In AD brains, SIRT1 levels were markedly reduced. SIRT1 expression in cultured microglia was significantly diminished by Aß treatment. Based on these findings, we hypothesize that SIRT1 reduction is a key event leading to microglial toxicity in AD and that microglial SIRT1 limits Aß-mediated neuronal deficits by suppressing NF-?B activation. To test this hypothesis, we propose three Specific Aims. In Aim 1, we will inactivate SIRT1 in microglia of mice expressing human amyloid precursor protein (hAPP) and systematically examine how microglial SIRT1 inactivation affects inflammatory responses and Aß-related neuronal/behavioral deficits. In Aim 2, to determine if microglial SIRT1 exerts neuroprotection by suppressing NF-?B activation, we will determine if constitutive activation of canonical NF-?B signaling in microglia of hAPP mice exacerbates the deficits in a manner similar to SIRT1 deletion. In complementary experiments, we will determine if inhibiting NF-?B signaling will ameliorate Aß-associated neuronal deficits by infusing a potent NF-?B inhibitor in the brain or injection of a viral vector that inhibits NF-?B in microglia. In Aim 3, to determine the mechanism by which microglial SIRT1 inhibits NF-?B, we will systematically examine if SIRT1 inhibits NF-?B by deacetylating RelA and/or by reducing RelA phosphorylation in myeloid cells. Using chromatin immunoprecipitation (ChIP) analyses, we will then determine if SIRT1- induced suppression of NF-?B activation involves deacetylation of histones (H3K56Ac) in myeloid cells. Completion of the proposed studies will provide new insight into the molecular mechanisms modulating the microglial loop in neurodegeneration. These studies will also lay the foundation for our long-term goal of developing SIRT1-enhancing strategies as a new therapeutic approach for AD.

Lay Summary
This projects aims at investigating mechanisms regulating the proinflammatory responses and microglial toxicity in Alzheimer’s disease. This study may provide new therapeutic avenue for treating this devastating disease.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

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2016

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