

Therapeutic potential of GMF suppresssion in inflammation and neurodegeneration

<https://www.neurodegenerationresearch.eu/survey/therapeutic-potential-of-gmf-suppresssion-in-inflammation-and-neurodegeneration/>

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Country

USA

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Therapeutic potential of GMF suppresssion in inflammation and neurodegeneration

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NIH (NIA)

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15/09/2015

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2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

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Research Abstract

? DESCRIPTION (provided by applicant): Alzheimer's disease (AD) is the most common form of dementia among elderly, affecting 5 million Americans and over 25 million individuals worldwide. AD is an age-related neurodegenerative disease, with approximately 7% of people older than 65 years and about 40% of people older than 80 years being affected in industrialized countries. AD is characterized by the accumulation of amyloid plaques (APs) and neurofibrillary tangles (NFTs) leading to eventual neuronal death. Studies have shown that NFTs, a defining feature correlated well with the clinical expression of dementia in AD. The role of astrocytes and microglia in mounting an inflammatory response could contribute to the pathogenesis of the disease. Such inflammatory response involves the production of cytokines that are intricately linked to the oxidative stress and stress-activated signal transduction events. The symptoms of AD are characterized by loss of memory, progressive impairment of cognition, and various behavioral and neuropsychiatric disturbances. The etiology of AD remains unknown, but the risk factors include genetic, biological and environmental factors. However, there is no definite treatment yet available for AD. Current proposal builds on our previous work that has provided support for our hypothesis that glia maturation factor (GMF) is involved in neuronal degeneration associated with neurodegenerative diseases, especially AD. We propose to investigate the hypothesis that intracellular GMF is associated with the pathophysiology of AD, as well as investigating the effectiveness of suppression of endogenous GMF-function as an effective and selective strategy to slow, and perhaps reverse, pathogenic processes. Two Specific Aims will be pursued. In Aim 1, we will test the hypothesis that the progressive AD pathogenesis is associated with the enhanced GMF expression and GMF is preferentially localized to sites of amyloid plaques and neurofibrillary tangles in AD affected brain regions. We will examine brain tissues from clinically diagnosed and neuropathologically confirmed AD cases and age- and gender-matched non-demented controls. We will quantitatively evaluate the regional densities of APs, NFTs, reactive glia (neuroprotective and neurotoxic phenotypes), and determine relationship to the prevalence, distribution and concentration of GMF in AD and age-matched non-demented controls. In Aim 2, we will evaluate the effects of suppression of GMF-functions with (A) GMF-specific shRNA, and (B) GMF-specific antibody in two animal models of AD-relevant pathophysiology: (1) 5XFAD mouse expressing 5 different mutations (3 in APP and 2 in presenilin-1), and (2) rTg4510 mouse model of tauopathy. We will evaluate the GMF-function suppression strategy in the context of inflammation and neurodegeneration; compare the histopathological features, neurochemical changes, and cognitive memory functions. The present study has significant clinical implications, and provides an efficient in vivo approach to test GMF-inhibitors as therapeutic agents for neurodegenerative diseases.

Lay Summary

PUBLIC HEALTH RELEVANCE: Alzheimer's disease (AD) is the most common form of dementia among elderly, affecting 5 million Americans and over 35 million individuals worldwide; and the lack of effective treatments represents a significant gap in the ability to treat this devastating disease. Based on glia maturation factor's (GMF) ability to induce several well-established pro-inflammatory mediators, we hypothesize that GMF is involved in the pathogenesis of AD. The aim of this proposal is to elucidate GMF as a novel candidate for therapeutic intervention in neurodegenerative diseases; therefore, these studies may provide the scientific rationale for the development of novel non-toxic therapy for these devastating illnesses.

Further information available at:

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Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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