Role of microRNAs as modulators of neuroinflammation in Alzheimer disease

https://www.neurodegenerationresearch.eu/survey/role-of-micrornas-as-modulators-of-neuroinflammation-in-alzheimer-disease/

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Research Abstract

? DESCRIPTION (provided by applicant): Patients with Alzheimer’s disease (AD) develop two main pathological changes in their brains: deposits of abnormally aggregated amyloid ß-protein (Aß) and abnormal aggregates (neurofibrillary tangles, NFTs) of hyperphosphorylated tau protein. Fibrillar Aß deposits in the brain are accompanied with inflammation characterized by

activated microglia and increased levels of cytokines. Many lines of evidence support the notion that activated microglia, innate immune cells in the central nervous system (CNS), play pivotal, dual roles in AD progression: either clearing Aß deposits by phagocytosis and promoting neuron survival and plasticity or releasing cytotoxic chemicals, inflammatory cytokines, exacerbating Aß load and neurodegeneration. Thus, activating microglia with a beneficial phenotype should have clinically vital importance in AD therapy and prevention. Aß aggregates activate microglia through interaction with certain toll- like receptors (TLRs) including TLR4. TLRs are a class of pattern-recognition receptors in the innate immune system. One of the important roles of TLRs is to activate microglia in response to pathogens and damaged host cells, and to clear pathogens, damaged tissues, and accumulated wastes. Activation of microglia through certain TLRs markedly boosts ingestion and clearance of Aß. Indeed, treatments of AD mouse models with certain TLR agonists activates microglia and decreases cerebral Aß deposits, NFTs and improve cognitive deficits. Low levels of certain TLR agonists, however, induce hyporesponsiveness to subsequent higher levels of TLR agonist challenge (endotoxin/TLR tolerance). Because Aß aggregates are a weak TLR agonist, we hypothesize that chronic exposure of microglia to Aß aggregates induces Aß/TLR tolerance, leading to decreased clearance of Aß aggregates and reduced neuronal survival and plasticity in AD and its animal models. Our preliminary results show that an AD mouse model is hyper-responsive to a TLR4 agonist, lipopolysaccharide (LPS), prior to cerebral Aß deposition but hypo-responsive after cerebral Aß deposition. We also found that certain biomarkers of TLR tolerance are upregulated in an AD mouse model after the development of Aß deposition in the brain. Because microRNA-146a modulates TLR tolerance and its expression is altered in AD mouse models as well as AD patients, we hypothesize that miR-146a induces Aß/TLR tolerance in microglia leading to reduced Aß clearance and neuronal survival in AD and their mouse models. This hypothesis will be tested by carrying out the following Specific Aims: (Aim 1) Enhance microRNA- 146a activity in microglia and determine cerebral Aß load, neuroinflammation and cognitive functions in an AD mouse model and (Aim 2) knockdown microRNA-146a expression in microglia and determine cerebral Aß load, neuroinflammation and cognitive functions in an AD mouse model. The long-term goals of this project are to determine the role of microRNA-146a in the pathogenesis of AD and to develop new preventive and therapeutic strategies for AD.

Further information available at:

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