Neurotropic Viral Infection in CNS Aging and Alzheimers Disease

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Neurotropic Viral Infection in CNS Aging and Alzheimers Disease

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Research Abstract

Project Summary Alzheimer’s disease (AD) is estimated to affect 5.3 million Americans currently and is expected to rise over the next decade. Neuroinflammation is increasingly recognized as

contributing to disorders of the central nervous system (CNS) including AD. Microglial cell surface receptor TREM2 was recently identified from two independent genome-wide association studies to contribute to the risk of developing AD, and previous studies suggested that infectious burden may contribute to the etiopathogenesis of AD. I hypothesize that viral encephalitis may enhance inflammatory events that accelerate the normal processes of CNS aging and contribute to the development of AD pathology. This five-year project has three specific aims that use West Nile virus (WNV) neuroinvasive disease as a model of viral encephalitis. During the K99 mentored phase of this project, Aim 1 will identify mechanisms of microglial-mediated aging processes triggered by WNV encephalitis using a TREM2-/- mouse model. I hypothesize that viral encephalitis triggers neuroinflammatory processes that accelerate replicative senescence in microglia via telomere shortening and inflammatory cytokine expression. Because TREM2 is critical in sensing environmental damage associated molecular patterns, we expect that TREM2-/- microglia will be will be less effective in responding to neuronal damage following viral encephalitis causing increased CNS aging. Aim 2, also during the K99 mentored phase, will identify mechanisms of neuron-mediated aging processes triggered by WNV encephalitis. Data from the Klein lab demonstrate that IL-1 receptor 1 (IL-1R1) signaling is essential for survival from acute neurotropic viral infection. However, inflammatory cytokines including IL-1 and IL-8, which are upregulated via IL-1R1 signaling, contribute to neuronal senescence via DNA damage. Experiments in this Aim will examine the role of IL-1R1 signaling following recovery from WNV encephalitis and during neuronal aging using IL-1R1-/- mice and in vitro primary neuron culture models. During the R00 independent phase of this project, Aim 3 will explore the impact of viral encephalitis on pathological tau accumulation. AD is defined by proteinaceous deposits composed of A? and tau. A? is known to stimulate chronic inflammation; however, less is known about the role of misfolded tau in the neuroinflammatory cascade, and even less is known is about how neuroinflammation can contribute to tau deposition. I hypothesize that an acute episode of neuroinflammation caused by viral encephalitis may predispose an individual to develop AD pathology. Experiments in this Aim will determine whether viral encephalitis increases the rate at which transgenic mice harboring the Mapt P301L mutation develop tau pathology, identify the impact of tau aggregates on the aging processes in primary microglia, and determine whether IL-1? impacts tau aggregation propensity in primary neurons cultures from Mapt P301L embryonic mice. These studies will give new understanding of the impact of viral encephalitis to processes of aging in the CNS and the development of AD.

Further information available at:

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