The impact of endocytic protein Tom1 on Alzheimers disease

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Research Abstract

PROJECT SUMMARY/ABSTRACT Alterations in the dichotomy between initiation and resolution of the immune response is a primary contributor to the reduced quality of life reported with aging. As we age, the immune system becomes dysregulated and is characterized by

persistent inflammation. Changes in the immune system contribute to the increased susceptibility of the elderly to innumerous diseases including Alzheimer’s disease (AD). A crucial aspect of this process is a failure to resolve inflammation, which normally involves the suppression of inflammatory cell influx, effective clearance of apoptotic cells, and promotion of inflammatory cell egress. Working under the hypothesize that the failure to properly resolve inflammatory pathways within the brain significantly contribute to the clinical manifestations of AD, our previous studies demonstrate that chronic inflammation mediated by interleukin-1? receptor 1 (IL-1R1), toll-like receptor-4 (TLR4), and tumor necrosis factor-? receptor (TNFR), represents a key mechanism by which ?-amyloid (A?) drives the development of tau pathology and cognitive decline in AD. The potent pro-inflammatory activities of these receptors are counter-regulated by target of Myb1 (Tom1) and its interaction partner toll-interacting protein (Tollip) via endocytosis and lysosomal degradation mechanisms to ensure proper resolution of immune responses. Remarkably, our preliminary data show that levels of Tom1 and Tollip are significantly reduced in human AD brains versus respective aged- matched controls. Further studies using AD model mice, show that reductions in Tom1 and Tollip occur vary early in the disease, prior to tau deposition and cognitive disruption. Therefore, reductions in Tom1 and Tollip may result in excessive expression of inflammatory receptors that in turn lead to exacerbated neuroinflammation, and represent an as yet identified link between A?, tau and cognitive disruption. Here we hypothesize that changes in the resolution of inflammatory receptors are an early A?-triggered event that leads to exacerbated neuroinflammation, which in turn evokes tau pathology, synaptic dysfunction and cognitive decline. To address properly our hypothesis, we will use cutting-edge in vitro and in vivo approaches, such as our novel APPKI-hA?wt that express wild-type human A? under the control of the endogenous mouse APP gene, to establish the connection between A? pathology and changes in Tom1-mediated endocytosis. Lastly, we will investigate the impact of persistent inflammatory receptor activation on tau pathology and cognition by using our innovative wild type human tau model (hTau). This research project will elucidate the underlying molecular mechanisms linking A? to Tom1 signaling, tau pathology and cognitive decline in AD. As we gain a better understanding of the age-related changes in the immune system, our overall goal is to craft therapies to proper activate the resolution of inflammation, with the broader purpose of sharply reducing the number of people suffering and dying from AD.

Further information available at:

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