Northwestern Medicine
Feinberg School of Medicine

Mesulam Center for Cognitive
Neurology and Alzheimer's Disease

26th Annual Alzheimer Day

Aging primes microglia for aberrant antigen presentation and initiation of persistent cognitive decline

Rogan A Grant,[1] Satoshi Watanabe,[1] Yuan-Shih Hu,[2] Constance E Runyan,[1] Mariana Maciel,[1] Ziyan Lu,[1] Hiam Abdala-Valencia,[1] Yuliya Politanska,[1] Richard I Morimoto,[3] GR Scott Budinger,[1] Alexander V Misharin[1]

[1]Department of Medicine, Division of Pulmonary and Critical Care Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, 60611, USA
[2] Ken and Ruth Davee Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, 60611, USA
[3]Department of Molecular Biosciences, Northwestern University, Evanston, IL 60208

Abstract
Multiple lines of clinical evidence establish a link between infection, aging, and dementia, including Alzheimer's disease (AD). Pneumonia, in particular, is associated with the initiation of cognitive decline in the elderly, and may worsen trajectories of decline in patients with existing cognitive impairment. Notably, modest levels of neuroinflammation are observed in aging and dementia. As the tissue-resident macrophages and key immune cells of the central nervous system, microglia have been implicated as likely mediators of this phenomenon and disruption of microglial complement and pro-inflammatory signaling has been shown to worsen progression in AD models. This has led to the proposal that aging and previous inflammatory events "prime" microglia for a shift toward a persistent neurotoxic state after pneumonia. We have developed a mouse model of pneumonia to study this phenomenon, using intratracheal infection of Influenza A virus (A/WSN/33 H1N1; IAV). In support of the priming hypothesis, IAV infection in old animals (18-29 months) leads to increases in antigen presentation in microglia, concomitant with decreases in the expression of the anti-inflammatory cytokine *Cxcl1* and plasticity-associated genes in bulk brain tissue. Microglia from old, naïve animals also exhibit broad reductions in molecular chaperone gene expression, in addition to a strong upregulation of complement components and pro-inflammatory cytokines, suggesting that deficits in microglial proteostasis may play a role in neuroimmune priming. We now extending these findings to the 5XFAD mouse model of AD, with the hypothesis that microglial responses to IAV will be strongly potentiated in AD mice, leading to accelerated disease progression. Additionally, we are testing the hypothesis that the restoration of microglial proteostasis can ameliorate neurotoxic inflammation in aged animals and 5xFAD mice, using genetic and pharmacological intervention.

Summary for community members

While many key genetic and environmental risk factors for dementia have been identified, the ways in which individuals transition from being “at risk” to actually developing dementia remain largely unknown. We are therefore investigating the link between severe infection, such as pneumonia, and the development of cognitive impairment in vulnerable populations.

This research was presented as part of the 26th Annual Alzheimer Day hosted by the Northwestern University Mesulam Center for Cognitive Neurology and Alzheimer Disease on September 24, 2020.

brain.northwestern.edu