Rebalancing Innate Immunity in Alzheimers disease by deleting IRAK-M

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Rebalancing Innate Immunity in Alzheimers disease by deleting IRAK-M

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Research Abstract

PROJECT SUMMARY/ABSTRACT While amyloid plaques and neurofibrillary tangles are Alzheimer’s disease (AD) pathognomonic features, Alzheimer himself originally identified a third pathology–glial inflammation. AD neuroinflammation is characterized by reactive astrocytes and microglia that surround amyloid plaques and chronically secrete low levels of pro-inflammatory

innate immune cytokines. The dominant view for decades has been that all forms of inflammation damage the AD brain. Yet, the simplistic notion that blocking inflammation is beneficial has not held up–non-steroidal anti-inflammatory drugs failed to produce a positive signal for AD primary prevention. This raises a fundamental question: could the innate immune system actually be harnessed as an AD therapeutic? While the focus has squarely been on pro-inflammatory molecules, little attention has been paid to factors that suppress the innate immune response. The unifying theme of our work is that ‘rebalancing’ cerebral innate immunity by releasing immunosuppression will limit AD progression. Our focus on innate immunity in AD has recently been validated by genome-wide association studies, which took the field by storm by identifying a cluster of AD risk alleles belonging to core innate immune and inflammation pathways. Toll-like receptors (TLRs), germline-encoded sensors of invading pathogens and endogenous danger- associated molecular patterns (DAMPs), are largely responsible for innate immune responses. Mounting evidence has shown that amyloid-? acts as a DAMP to provoke microglial TLR signaling. TLRs transduce their signals through interleukin-1 receptor-associated kinases (IRAKs), and IRAK-M is the only IRAK family member that suppresses TLR signaling. Importantly, IRAK-M is selectively expressed by mononuclear phagocytes (e.g., microglia and macrophages). Our preliminary data demonstrate that the IRAK-associated TRAF6/MEKK3 pathway is abnormally elevated in human AD, and IRAK-M deletion licenses A? phagocytosis. In this proposal, we will relieve TLR signaling inhibition by genetic deletion of IRAK-M in the APP/PS1 mouse model of cerebral amyloidosis. Our overarching hypothesis is that releasing IRAK-M inhibition of innate immunity will beneficially activate amyloid-? phagocytosis and restore cognitive function. In Specific Aim 1, cognitive impairment, AD-like pathology and A?/?-amyloid phagocytosis (using our novel q3DISM technology) will be evaluated in APP/PS1 x IRAK-M deficient mice. Further, we will isolate brain monocytes and perform innate immune phenotyping by transcriptomics (RNAseq). In Specific Aim 2, we will determine the relative contribution(s) of peripheral verses central innate immune compartments with bone marrow chimeras. Completion of this project will lead to a deeper, basic understanding of innate immunity in the context of AD.

Further information available at:

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