ABSTRACT

Elucidating the Mechanisms of Microglia-Mediated Neurodegeneration in Alzheimer's Disease

by

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Genetic studies have implicated microglia, the brain's primary immune cells, as a leading causal cell type in Alzheimer's disease (AD), a neurodegenerative disease for which there remains no definitive cure. This unmet therapeutic need has intensified efforts to clarify the role of microglia in disease progression, with contradictory findings on microglial mediation: while they protect the brain against the pathological hallmarks of AD, they also exacerbate neurodegeneration. This functional heterogeneity of microglia, alongside their molecular heterogeneity, supports a framework in which distinct, molecularly defined microglial subsets differentially contribute to neuroprotection or neurodegeneration. Identifying and mechanistically characterizing potentially neurodegenerative microglia subsets would provide actionable targets for the treatment of AD. Recently, a distinct subset of electron-dense "dark microglia" has come into focus due to their indicators of cellular stress and consistent presence in conditions modeling AD, features that suggest an association between microglial stress and neurodegenerative function. Building on this association, in this doctoral thesis I identify a neurodegenerative subset of microglia characterized by the activation of the conserved stress signaling pathway, the integrated stress response (ISR). Using mouse models to manipulate ISR, specifically in microglia, I demonstrate that AD pathologies, including amyloid burden, tau accumulation, and synapse loss, are largely regulated by microglial stress levels. This regulatory relationship also extends to dark microglia, and notably, microglial ISR activation is sufficient to induce the dark microglia phenotype in the absence of any pathology. Mechanistically, I found that ISR-activated microglia secrete toxic lipids that disrupt neuronal and glial homeostasis and survival, as well as promote synapse loss. The collective findings in this dissertation elucidate stressed microglia as a neurodegenerative subset and pinpoint microglial ISR, together with its downstream toxic lipid secretion, as compelling targets for therapeutic intervention in AD.