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Microglia in AD Pathogenesis

Microglia are the primary innate immune effector cells in the brain, and their dysfunction has been linked to a variety of central nervous system disorders. These inflammatory cells are constantly surveying their external environment and rapidly respond to a variety of molecules that signal changes in CNS homeostasis. In response to these signals, microglia influence neuronal connections, modulate the functions of other glia, and mediate inflammatory responses to disease or injury. Recent studies implicate microglia in AD pathogenesis. Garden's group has been examining a number of molecular pathways that influence microglia behavior and response patterns, with a focus on specific transcriptional regulators that are induced by oxidative stress and microRNAs with demonstrated roles in modulating the behavior of macrophages.

The microRNAs miR-155 and miR-146a have been shown to modulate microglia inflammatory phenotypes. Specifically, the interaction of amyloid beta (Ab) fibrils with different receptor complexes at the cell membrane of microglia and astrocytes leads to both cellular internalization and phagocytosis, as well as activation of standard MyD88-mediated inflammatory pathways, culminating in the activation of nuclear factor kappa B (NF- κ B) and c-Jun. While c-Jun activity upregulates the expression of miR-155 contributing to suppressor of cytokine signaling 1 (SOCS-1) inhibition and consequent propagation of inflammation, NF- κ B-derived miR-146a upregulation can generate an immunomodulatory effect. Considering its confirmed targets, IL-1R-associated kinase 1 (IRAK1) and TNFR-associated factor 6 (TRAF6) miR-146a may act as a negative regulatory feedback mechanism by interfering with TNFR/IL1R and TLR pathways, as well as with NF- κ B activation and retinoic acid-inducible gene I dependent type I IFN production [Jurkin et al. *J Immunol* May 1, 2010, 184 (9) 4955-4965] [Cardoso et al 2016 *Current Opinion in Pharmacology*].

Garden discussed the implications of the existence of adult microglia progenitors, a completely new class of cell. Cd11b⁺ cells obtained from the adult brain include microglia progenitors. Compared to freshly isolated adult microglia, cultured CD11b⁺ cells express less microglia specific mRNA and more stem cell marker mRNA [Elmore et al. *Neuron*, 2014;82: 380-397]. The adult microglia progenitor population seems to have a physiological role. In fact, microglia progenitors can be induced to divide by

physiological stimuli. Specifically, microglia and microglia progenitors divide in response to ischemia/reperfusion. And, ischemia/reperfusion yields increased microglia number and volume. Furthermore, adult microglia progenitors can be isolated by *ex vivo* FACS. Adult microglia progenitors express unique surface markers; and microglia progenitors contribute to the normal adult microglia population.

Current questions of interest for the Garden Lab: Is there replicative senescence of progenitors? Does experience (exposure to prior inflammatory signals) have epigenetic impact on subsequent generations of microglia? How might this process interact with AD pathogenesis? Is AD associated with altered microglia maturation? Does Trem2-R47H inhibit microglia maturation?

Future UW studies of the role of microglia in AD pathogenesis will merge genetics with cellular phenotypes. Garden's group is focused on the AD f(x)ome Project. Leveraging the ADRC Rapid Autopsy protocol, they will use cell type specific transcriptomics and open chromatin mapping on prefrontal cortex tissue and functional assays on meningeal cells made into iPSCs.