Online Proceedings

POSTER SESSION 2

MGH 241, Easel 137

1:00 PM to 2:30 PM

Linking Inflammatory microRNAs to Behavioral Deficits in a Mouse Model of Alzheimer's Disease

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Mentor: Gwenn Garden, Neurology
Mentor: Macarena Aloi, Pathology

Microglia are the innate immune cells of the central nervous system that exhibit a sustained pro-inflammatory response in the Alzheimer's disease (AD) brain. Regulation of inflammatory gene expression in microglia by microRNA miR-155 modulates transition between distinct phases of the inflammatory response. Though altered expression profiles of miR-155 is seen in other neurodegenerative disorders, the precise role of this microRNA in modulating inflammation and downstream behavioral deficits in mouse models of AD remains unknown. We hypothesize that microglia specific deletion of miR-155 will alter neuroinflammation and behavioral phenotypes in transgenic mice expressing human mutant amyloid precursor protein and presenilin 1 (APP/PS1), an AD model that exhibits Aβ pathology and memory impairments. We generated trigenic (Cx3cr1-Cre^{+}/$-$/Floxed-miR155^{+}/+/APP/PS1^{+}/$-$) to acutely induce microglia specific Cx3cr1 driven Cre-mediated deletion of floxed miR-155 alleles in the APP/PS1 mouse AD model. Changes in inflammatory gene and microRNA expression in microglia 6 and 9 months post miR-155 deletion were assessed by qPCR. We expect that conditional deletion of miR-155 leads to anti-inflammatory gene expression and thus improve cognitive performance. To measure anxiety, spatial memory, and spatial learning, we employ open field chambers with and without novel object recognition and T-maze assessments. Preliminary results support the hypothesis that conditional miR-155 deletion specifically in microglia alters innate immune gene expression and behavioral phenotypes in the APP/PS1 mouse model of AD, further elucidating the impact of the molecular regulators in neuroinflammation in AD.

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Isolating Murine Microglia Progenitors and Identifying Senescence Marker Expression *in vitro*

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Microglia are the resident immune cells of the CNS and are hypothesized to influence aging in the brain. Like somatic cells, microglia can be replaced by self-renewal. Recently, some studies have suggested that new microglia derive from asymmetric cell division of a progenitor population. Microglia progenitor cells have been difficult to study due to a lack of specific molecular markers of this population. However, the Garden lab has recently identified novel candidate markers. We hypothesize that in neurodegenerative disorders associated with advanced age, microglia progenitor senescence may contribute to disease pathology. To efficiently study the senescence of microglia progenitors, we turned to neonatal mixed glia cultures, in which the presence of microglia progenitors has long been inferred. In these cultures, microglia are harvested from cells floating above a monolayer culture of mixed neonatal glial cells. The size of each microglia harvest generally decreases with successive harvests. This suggests that microglia progenitors in the attached monolayer may become senescent after multiple rounds of the cell cycle, leading to stagnation in the generation of new floating microglia. We evaluated microglia progenitor senescence in neonatal mixed-glia cultures by labeling with BrdU, a thymidine analog taken up by proliferating cells and remaining in their daughters. Microglia harvested from these cultures weekly were assessed for BrdU incorporation using flow cytometry and immunofluorescent microscopy. We co-labeled floating microglia and dissociated monolayer mixed glia cultures with antibodies directed against a progenitor marker (CD133), a microglia marker (Iba1), and BrdU. The attached mixed-glia cell layer was also labeled for SA-ß-Gal, an indicator of cellular senescence. Progenitor senescence will be detected by a decrease in CD133/BrdU-positive cells and an increase in CD133/ SA-ß-Gal positive cells.