DOI: 10.1002/alz70855_106751

BASIC SCIENCE AND PATHOGENESIS

POSTER PRESENTATION

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

MOLECULAR AND CELL BIOLOGY

Decoding transcriptional regulation of microglia associated with amyloid plaques

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Abstract

Background: Beyond the progressive accumulation of amyloid-beta and hyperphosphorylated tau, Alzheimer's disease (AD) is accompanied by phenotypic changes in microglia, the innate immune cells of the brain. In particular, microglia in the vicinity of Amyloid-plaques, also known as MGnD or DAM, are defined by distinct changes in their gene expression signature, e.g., upregulation of *Trem2* mRNA. However, the precise transcriptional mechanism that drives microglia phenotype in response to amyloid is not defined.

Method: Here, we isolated microglia from the APP/PS1 transgenic mouse model followed by ATAC-seq.

Result: We provide evidence for a model in which differential activation of a common set of transcriptional regulators that includes members of the MITF/TFE, AP-1 and EGR transcription factor families drives the amyloid-plaque associated microglia phenotype.

Conclusion: Collectively, these findings reveal the framework of the transcriptional circuitry that is used to establish a range of neurodegenerative pathology-associated microglia phenotypes.