

Review of: "Arg1+ microglia are critical for shaping cognition in female mice"

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The manuscript by Stratoulas et al., investigates a population of Arg1+ Iba-1+ microglia in the brains of wild-type C57BL6 and YARG mice during different developmental stages-- P10, P28, P60 and P100. Whole brain clearing/immunofluorescence staining and transmission electron microscope analyses were used to determine the number and regions in the brain harboring these microglia and study their morphological features and association with axons. The group also crossed *Arg1^{flox/flox}* mice to *Cx3cr1^{CreER}* mice to generate mice with microglia deficient in Arg1 expression.

Arg1+ and Iba-1+ reactivity distinguishes at least two classes of microglial subtypes. The Arg1+ microglia are localized to the basal forebrain and ventral striatal regions. Arg1+ microglia decline with development and are rarely detected at P100.

Bulk gene expression analyses of Arg1+ microglia showed an activated immune profile with some overlap with previously reported "Cluster1" (P4/P5) microglia subtypes. There are caveats and limitations to these types of analyses, but other findings support the overall premise of the study. Figure 6d show many nuclei, one Arg1+ microglia in close association with p75NTR+ cholinergic neuron. What cells are these? They could be phagocytic macrophages and/or phagocytic microglia (that have lost Arg1 expression among other markers), but this was not probed further.

Interestingly, the authors were able to connect Arg1 function in microglia in P60 mice to 1) proper dendritic structure and spine maturation of axons projecting into the hippocampus and 2) through behavioral assays of memory that show female mice lacking Arg1 expression have deficits in cognition and impairment in long-term memory. Interestingly, no cognitive deficits were detected in male mice. The authors cite original studies suggesting regulation of Arg1 by steroid hormones. In total, the robust study and data collected show how an early deficiency of a subpopulation of microglia in the basal forebrain and ventral striatum possessing Arg1 function are critical during development of the brain for the long-term impact on cognition in female mice. Perhaps compensatory sex-determinant mechanisms that occur postnatally in males is able to overcome the impacts of Arg1 deficiency.

