A single-cell atlas of mouse brain macrophages reveals unique transcriptional identities shaped by ontogeny and tissue environment

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While the roles of parenchymal microglia in brain homeostasis and disease are fairly clear, other brain-resident myeloid cells remain less well understood. By dissecting border regions and combining single-cell RNA-sequencing with high-dimensional cytometry, bulk RNA-sequencing, fate-mapping and microscopy, we reveal the diversity of non-parenchymal brain macro- phages. Border-associated macrophages (BAMs) residing in the dura mater, subdural meninges and choroid plexus consisted of distinct subsets with tissue-specific transcriptional signatures, and their cellular composition changed during postnatal development. BAMs exhibited a mixed ontogeny, and subsets displayed distinct self-renewal capacity following depletion and repopulation. Single-cell and fate-mapping analysis both suggested that there is a unique microglial subset residing on the api- cal surface of the choroid plexus epithelium. Finally, gene network analysis and conditional deletion revealed IRF8 as a master regulator that drives the maturation and diversity of brain macrophages. Our results provide a framework for understanding host–macrophage interactions in both the healthy and diseased brain.

Keywords : macrophage, microglia, brain, neuroimmunology, single-cell
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