“All Roads Lead to Microglia”
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Almost exactly a century ago, microglia were identified by Hortega, distinguished from oligodendrocytes and characterized as mesodermal in origin. About 80 years later, they were shown to derive from primitive yolk sac macrophages, with conclusive confirmation coming from birth-dating studies several years ago. Microglia colonize the murine central nervous system (CNS) at E9.5-10.5, and expand under the influence of CSF1 and IL34, produced by neuronal progenitors. Thereafter, the microglial population is maintained locally without input from the bone marrow. Microglia acquire their distinctive functional and phenotypic attributes from their primitive-hematopoietic ontogeny and from their residence in the unique CNS environment, in intimate relation to neuroepithelial cells.

Microglia participate in neurodevelopment across the time course of CNS organogenesis. In the developing CNS, microglia guide fasciculation of fiber tracts; contribute to the positioning of cortical interneurons; affect the neurotransmitter-receptor maturation of neurons within barrel cortex and other sites; promote apoptosis and remove apoptotic cell corpses; secrete growth factors for neuronal survival; and refine synaptic networks. Accordingly, perturbing microglial function (for example, by exposure to maternal inflammatory responses to systemic infection) may dysregulate network circuitry.

Adult brain function is also substantially contingent on microglial functions, which include: producing neuromodulatory factors that support synaptic plasticity and learning; modulating neuronal firing rates to optimize network properties; and fine-tuning the neuroblast output of the neurogenic niche by removing stressed or apoptotic cells. Learning what microglia do in the healthy brain will profoundly inform how their dysfunction contributes to neurodegenerative and neurodevelopmental disease and enable therapeutic initiatives. We propose that microglia are bristling with drug targets that only await our deciphering.

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