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Invited Review

Inflammation in Alzheimer's disease: Lessons learned from microglia-depletion models

Elizabeth E. Spangenberg, Kim N. Green *

Department of Neurobiology and Behavior, Institute for Memory Impairments and Neurological Disorders, United States

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ABSTRACT

Microglia are the primary immune cell of the brain and function to protect the central nervous system (CNS) from injury and invading pathogens. In the homeostatic brain, microglia serve to support neuronal health through synaptic pruning, promoting normal brain connectivity and development, and through release of neurotrophic factors, providing support for CNS integrity. However, recent evidence indicates that the homeostatic functioning of these cells is lost in neurodegenerative disease, including Alzheimer's disease (AD), ultimately contributing to a chronic neuroinflammatory environment in the brain. Importantly, the development of compounds and genetic models to ablate the microglial compartment has emerged as effective tools to further our understanding of microglial function in AD. Use of these models has identified roles of microglia in several pathological facets of AD, including tau propagation, synaptic stripping, neuronal loss, and cognitive decline. Although culminating evidence utilizing these microglial ablation models reports an absence of CNS-endogenous and peripheral myeloid cell involvement in Aβ phagocytosis, recent data indicates that targeting microglia-evoked neuroinflammation in AD may be essential for potential therapeutics. Therefore, identifying altered signaling pathways in the microglia-devoid brain may assist with the development of effective inflammation-based therapies in AD.

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* Corresponding author at: 3208 Biological Sciences III, University of California, Irvine, Irvine, CA 92697-4545, United States.
E-mail address: kngreen@uci.edu (K.N. Green).

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1. Introduction

Microglia are the brain's resident immune cells, comprising approximately 5–12% of all cells found in the brain. They function as the brain's first line of defense to protect the CNS from injury and invading pathogens. Originally presumed to be "resting", microglia in the healthy adult brain are highly dynamic, surveying the entire brain parenchyma every 24 h (Nimmerjahn et al., 2005). In this "surveying" state, microglia exhibit a ramified morphology and serve to support neuronal function and health via physical and biochemical interactions. Upon detection of an insult, microglia respond by becoming activated. This process may involve the migration to and proliferation of these cells at the site of the insult, as well as dramatic transformation into an amoeboid morphology, depending on the type and extent of the insult. Activated microglia produce and secrete several proinflammatory mediators, including tumor necrosis factor-α (TNFα), interleukin (IL)-6, and nitric oxide (NO), all of which can confer neurotoxicity (Akiyama et al., 2000). Neuroimmune regulatory proteins (NiReg) modulate the microglia-mediated immune response to resolve the inflammatory process (Hoarau et al., 2011), which then promotes tissue repair through the secretion of several neurotrophic factors, including insulin-like growth factor 1 (IGF-1), brain-derived neurotrophoc factor (BDNF), transforming-growth factor-β (TGF-β), and nerve growth factor (NGF) (Polazzi and Monti, 2010). In acute inflammatory events, the pro-inflammatory response resolves and microglia continue their surveillance of the brain parenchyma. However, in neurodegenerative disease, the equilibrium between microglial surveillance and activation is disturbed, creating a feedforward loop that results in a chronic neuroinflammatory state, promoting inflammation and tissue atrophy. Although astrocytes also participate in and propagate the neuroinflammatory environment in AD, for the purposes of this review, the focus will remain on microglia-mediated inflammation in AD pathogenesis. Here, we briefly review the various implications of microglia and other myeloid cells in neurodegeneration and discuss current methods that allow for investigations into the biology of microglia in AD.

2. Homeostatic microglial functions

2.1. Phagocytosis

One of the more extensively studied functions of microglia in the brain is their role in clearance via phagocytosis, by which these cells both protect the brain from invading pathogens as well as remove cellular debris from the neural environment. Aside from the clearance of cellular debris, microglia may also phagocytose viable neurons in a process known as "phagoptosis", which specifically targets senescent or damaged cells (Brown and Neher, 2014). For this reason, proper degradation of internalized components by microglia is essential for normal CNS function. Consequently, dysregulated or abnormal degradation of material can result in the intracellular accumulation of toxic molecules, including reactive oxygen species (Underhill and Goodridge, 2012). Importantly, studies have shown that microglia are involved in the phagocytosis of supranumerous apoptotic neuroblasts in the subgranular zone of young mice, implicating their involvement in neurogenesis (Sierra et al., 2010).

2.2. Synaptic sculpting and cognition

In addition to phagocytosis, microglia are also involved in the removal of synapses from neuronal cell bodies via synaptic stripping. This phenomenon was first observed in a model of facial nerve injury in rats (Blinzinger and Kreutzberg, 1968), in which microglial localization to the site of injury and interaction with facial motor neurons resulted in the removal of synaptic contacts. In the developing brain, microglia form brief, repetitive contacts with synapses, eliminating any weak or unnecessary synaptic structures, a process which is modulated by sensory experiences (Tremblay et al., 2010). Recently, it was shown that knockout of the microglial purigenic receptor P2Y12, which mediates process motility during injury response, also disrupts plasticity in the visual system (Sipe et al., 2016). While the exact mechanism behind microglia-mediated synaptic elimination (whether it be by phagocytosis or the secretion of various factors) has yet to be elucidated, it is clear that the interaction between microglia and synapses is crucial for activity-dependent plasticity in the developing brain. Accumulating evidence points to neuron-microglia crosstalk as an essential mechanism for proper synapse and network maintenance. One pathway implicated in this crosstalk involves the fractalkine receptor (CX3CR1) expressed on microglia and its ligand CX3CL1, released by neurons. For example, knockout of CX3CR1 during development produces deficits in synaptic pruning, characterized by an excess of dendritic spines and immature synapses, resulting in weakened synaptic transmission and decreased functional brain connectivity (Paolicelli et al., 2011). Behaviorally, loss of CX3CR1 in juvenile mice manifests in impaired social interactions reminiscent of autism spectrum disorder and other neuropsychiatric disorders (Zhan et al., 2014). Furthermore, disruption of signaling between complement 3 (C3), which is localized to synaptically-enriched regions, and its receptor, complement receptor 3 (CR3), in the mouse retinogeniculate system impairs microglial phagocytosis of synaptic inputs, leading to sustained deficits in brain wiring (Schafer et al., 2012). Collectively, these studies underscore the role of microglia as regulators of the synaptic landscape in the developing brain, implicating neuron-microglia crosstalk as a crucial process for proper brain development. In addition to complement and fractalkine signaling, paired immunoglobulin-like receptor B (PirB) is also involved in the regulation of synaptic plasticity. In the CNS, PirB is expressed by both neurons and glia and binds several ligands, including major histocompatibility complex-I (MHC-I) (Syken et al., 2006), which is believed to direct cellular recognition by immune cells. In adult mice, disruption of PirB signaling in the visual cortex increased dendritic spine density and induced the formation of functional synapses, as evidenced by increases in miniature excitatory postsynaptic currents (Bochner et al., 2014). Whether microglia are mediating the PirB-induced synaptic changes remains unresolved, although this cell type is a likely candidate.

While the role of microglia in synaptic sculpting during development is well-described, it remains unclear whether microglia contribute to the synaptic landscape in adulthood. We recently reported that the absence of microglia in the healthy adult mouse brain increases total dendritic spine density and intensity of immunolabeling for the synaptic surrogates PSD95 and synaptophysin (Rice et al., 2015), indicating that microglia continue to regulate the synaptic landscape in adulthood. Collectively, these studies point to microglia as critical mediators of synaptic sculpting in development and adulthood, providing an important role in shaping and modulating neuronal circuitry to maintain normal brain connectivity.

As microglia are heavily implicated in shaping the synaptic landscape of the brain during the incorporation of new memories and experiences into the neural network, the CNS immune system is also thought to be involved in cognitive function. Genetic ablation of microglia using CX3CR1^{CreER} mice to drive diphtheria toxin receptor expression in these cells found that mice devoid of microglia, following administration of diphtheria toxin, exhibited impaired performance on cue-based fear condition and novel object recognition tasks, as well as impaired dendritic spine