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Microglia at the scene of the crime: what their transcriptomics reveal about brain health

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Abstract

Purpose of review—Microglia, which arise from primitive myeloid precursors that enter the central nervous system (CNS) during early development, are the first responders to any perturbance of homeostasis. Although their activation has become synonymous with neurologic disease, it remains unclear whether microglial responses are the cause of or response to neuropathology. Here, we review new insights in the roles of microglia during CNS health and disease, including preclinical studies that transcriptionally profile microglia to define their functional states.

Recent findings—Converging evidence suggests that innate immune activation of microglia is associated with overlapping alterations in their gene expression profiles regardless of the trigger. Thus, recent studies examining neuroprotective microglial responses during infections and aging mirror those observed during chronic neurologic diseases, including neurodegeneration and stroke. Many of these insights derive from studies of microglial transcriptomes and function in preclinical models, some of which have been validated in human samples. During immune activation, microglia dismantle their homeostatic functions and transition into subsets capable of antigen presentation, phagocytosis of debris, and management of lipid homeostasis. These subsets can be identified during both normal and aberrant microglial responses, the latter of which may persist long-term. The loss of neuroprotective microglia, which maintain a variety of essential CNS functions, may therefore, in part, underlie the development of neurodegenerative diseases.

Summary—Microglia exhibit a high level of plasticity, transforming into numerous subsets as they respond to innate immune triggers. Chronic loss of microglial homeostatic functions may underlie the development of diseases with pathological forgetting.

Keywords

aging; microglia; neurodegeneration; neuroinfectious disease; transcriptome; viral encephalitis

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Conflicts of interest

There are no conflicts of interest.

INTRODUCTION

Transcriptomic analyses of microglial subsets have led to a revolution in our understanding of the multifaceted functions of these innate cells of the central nervous system (CNS). Microglia are born to sculpt neural networks throughout life via synaptic remodeling [reviewed in [1]], and to phagocytose toxic debris [2], including other microglia. They act as immune sentinels, often being the first responders to information requiring immediate neuroprotective actions, including regulation of blood-brain barrier function [reviewed in [3]], the recruitment of pathogen-specific lymphocytes [4] and exhibit autophagy-mediated destruction of phagocytosed pathogens [5]. Microglia, which comprise approximately 0.5–16% of cells in the human brain [6] or 5–12% in the mouse brain [7], depending on the anatomic region, may also act as antigen presenting cells (APCs) within infected brain parenchyma, and induce apoptosis of virally infected neurons [8]. Many of these processes have been highlighted in studies of neurodegenerative diseases, in which it is unclear whether they contribute to or alleviate neuropathology. This may be partially due to the relatively few studies examining neuroprotective and adaptive responses of microglia in the adult brain: understanding normal functions is required to define aberrancy. Most recently, especially with increasing appreciation of the neurological sequelae of severe acute respiratory syndrome coronavirus 2, more research has emerged into the diverse and crucial roles microglia play during infections with neurotropic and neurovirulent viruses, and during aging, both of which independently impact the state of the neuroimmune system. Here we highlight these developments, including studies that demonstrate similar transcriptomic changes that occur in microglia, but function to elicit and maintain neuroprotective processes throughout the lifespan.

MICROGLIA FUNCTIONS IN THE HEALTHY BRAIN

Microglia maintain the blood-brain barrier

During homeostasis in a healthy brain, anatomical barriers protect the CNS from pathogens, peripheral metabolites and pro-inflammatory molecules and restrict the CNS entry of cells derived from non-CNS tissues. The blood-brain barrier (BBB) is the most prominent among these barriers and is comprised of junctional proteins expressed by brain microvascular endothelial cells, with contributions from astrocyte end-feet, pericytes, and neurons. Microglia can differently affect BBB function and integrity depending on context, although few studies have addressed how resting microglia contribute to the maintenance of the BBB in health. The survival, proliferation, and differentiation of microglia in a healthy brain requires Colony Stimulation Factor 1 receptor (CSF1R) signaling, which can be inactivated both genetically [9] and pharmacologically [10–12]. On the venular side, ablation of microglia via pharmacological inhibition of CSF1R promotes BBB instability [13], while loss of microglia from arterioles interferes with their modulation of cerebral blood flow in response to changes in in neuronal activity [14■■]. This latter function involves microglial purinergic receptor P2Y12 (P2RY12)-mediated detection of adenosine triphosphate. If microglia are depleted, or P2RY12 receptor is genetically deleted, neurovascular coupling as measured by an observed change in microvascular blood flow by laser speckle contrast

imaging in response to whisker stimulation is markedly decreased in mice [14■■]. As P2RY12 receptors are down-regulated during microglial activation regardless of the trigger [15], loss of homeostatic functions of microglia as a consequence of their innate immune responses could underlie BBB instability, which occurs in most neurologic diseases.

Microglia continually sculpt neuronal networks in the adult brain

It is well established that microglia sculpt neural networks during critical developmental periods, by strengthening active synapses and pruning inactive ones. However, this process continues throughout life, and is important for inactivation of neuronal networks during normal forgetting [16]. Neuronal expression of classical complement proteins (C3 and C1q) tag synapses for elimination via activation of complement receptor CR3 expressed by microglia, leading to their phagocytosis [16]. New data demonstrate that nonclassical major histocompatibility complex -I molecules, such as Qa-1 (a murine homolog of human human leukocyte antigen -e), which is expressed by excitatory pyramidal neurons in an activity-dependent manner, can mediate the interaction of neurons with microglia via microglial expression of the Qa-1 cognate heterodimeric receptor cluster of differentiation 94/natural killer cell lectin (CD94/NKG2). In a mouse model of ocular deprivation, microglia contralateral to the closed eye undergo morphological changes such as process ramification, which do not occur in mice with genetic deletion of Qa-1 [17■■]. A mouse carrying a point mutation in the Qa-1 that prevents it from interacting with CD94/NKG2 exhibited a similar phenotype, suggesting that the interaction of these two molecules is necessary for activity-dependent elimination of synapses by microglia. Microglial depletion was also shown to disrupt the astrocyte network in mice, leading to decreased synaptic transmission between CA3 and CA1 regions in the hippocampus by a yet unknown mechanism [18]. Further studies need to focus on exact mechanisms by which microglia recognize synapses as active, and therefore in need of maintenance, or inactive, leading to their elimination as a part of normal synaptic plasticity.

Neuroprotective roles of microglia during acute central nervous system infections

Microglia perform established and diverse neuro-protective roles in a variety of neuroinfectious diseases, including those caused viruses and parasites [reviewed in [19]]. Microglia recognize pathogen-associated molecular patterns using several pattern recognition receptors including Toll-like receptors, retinoic acid-inducible gene-like receptors (RIG-I), and nucleotide-binding oligomerization domain-like receptors, which all induce expression of antiviral cytokines by activated microglial that contribute to BBB instability and CNS infiltration of immune cells. Activated microglia exhibit changes in cellular morphology, phagocytic capacity, and gene expression, which depend on the activating stimulus. Next-generation sequencing has revealed that microglial activation occurs on a continuum, with microglia being able to shift from one state to another as they respond and control CNS infections [20–22].

Virologic control during encephalitis caused by Rift Valley Fever Virus, an emerging, neuroinvasive Phlebovirus, requires robust microglial activation downstream of mitochondrial antiviral signaling protein activation, which is triggered by RIG-I [23■]. During encephalitis caused by West Nile virus (WNV), a re-emerging mosquito-borne

neurotropic flavivirus, ablation of microglia via pharmacological inhibition of CSF1R also leads to loss of virologic control and increased mortality [12]. Indeed, sub-cutaneous administration of granulocyte-macrophage colony-stimulating factor, a ligand for CSF2R, significantly improves survival in mice peripherally infected with WNV (65% compared to 20% in vehicle-treated controls), with associated microglia activation and expression of C-C Motif chemokine ligand 2 and interleukin 6 (IL-6) [24■■], which have established roles in trafficking of leukocytes to sites of infection. Similarly, microglial depletion using CSF1R inhibition significantly increases mortality from Herpes Simplex Virus-1 (HSV1) encephalitis in mice [25]. As microglial activation significantly reduces viral titers in the brain, they are likely to play a role in local, virus-specific T cell activation. Consistent with this, CSF1R antagonism is associated with reduced B7 co-stimulatory signals on APCs, limiting local reactivation of CNS-infiltrating virus-specific T cells and loss of virologic control [12]. Evaluation of microglia transcriptomes in the setting of severe HSV1-encephalitis in mice showed they develop a neutrophil-like transcriptional signature, upregulating genes such as resistin-like gamma (Retnlg), retroviral-like aspartic protease, IL-36g, and C-X-C chemokine receptor 2, while also expressing classical microglial markers P2RY12, transmembrane protein 119 (TMEM119), CSF1R, and Fc receptor-like S (Fcrls). These microglia arise in highly infected brain regions such as the thalamus and most likely represent a direct antiviral response of infected microglial cells [26■].

Microglia also have established roles during antiparasitic responses to neuroinvasive toxoplasmosis, a condition caused by chronic infection with *Toxoplasma gondii*. Innate immune signaling via interferon γ (IFNγ)-STAT1 is vital for controlling this parasite within the murine CNS. Microglial-specific deletion of STAT1 leads to a profound increase in mortality and a 300-fold increase in parasite levels in the brain [27■■]. These STAT1-deficient microglia displayed a loss of transcriptional signatures characteristic of microglial activation, failing to downregulate both homeostatic genes including C-X3-C Chemokine receptor 1 (CX3CR1), Fcrls and transforming growth factor beta 1 and upregulation of genes characteristic of a disease-associated microglia (DAM) signature, including integrin subunit alpha X, Axl, cyto-chrome B-245 beta chain and glycoprotein non-metastatic melanoma protein B. This shift in transcriptional profile shows that STAT1 plays a fundamental role in microglial ability to transition to a more activated state focused on pathogen killing and offers an explanation as to why STAT1-deficient mice were highly vulnerable to T. *gondii* challenge. Overall, microglial responses during CNS infections define an important pro-inflammatory role that limits dissemination of pathogens within the brain and promote healing of injured tissue.

AGE-RELATED CHANGES IN MICROGLIA

Microglia display substantial changes with aging, including changes in gene expression, ultrastructure, and the epigenome which affect their morphology, liposomal dysfunction (increased accumulation of lipofuscin and senescence-associated β-galoctosidase expression), and promote dysregulation of cell cycle protein machinery, including proteins p53, p21, and $p14^{Ink4a}$ [reviewed in [28]]. These cells have been described in the literature as dystrophic or senescent and accumulate over time during normal brain aging [29]. Profound changes in transcriptional profiles with aging also result in secretion of various

pro-inflammatory cytokines, a phenomenon referred to as senescence-associated secretory phenotype [28,30], characterized by increased secretion of IL-1, IL-6, and decreased secretion of various growth factors necessary for neuronal support. Aged microglia also display changes in expression of histone deacetylases (HDACs), which are important epigenetic regulators. HDAC levels, especially HDAC1, 3, and 7, are increased in purified murine aged microglia or by inducing aging-like phenotypes by via bleomycin treatment, or via repeated passage of microglia in culture [31▪].

Higher brain levels of another histone deacetylase, Sirtuin 1 were shown to correlate with longevity in rhesus macaques, indicating that different epigenetic modulators can have opposing effects during normal aging [32]. Aged microglia also exhibit decreased capacity for stimulation of T-cells, resulting in lower production of interferon, which contributes to increase viral burden in aged animals subjected to WNV infection compared to younger mice. In this model, aged microglia also show increased levels of activation markers such as MHC-II and CD68 in concordance with transcriptional studies of aged microglia [33]. Transcriptomic and proteomic analyses of microglia isolated from human brain autopsy samples uncovered an array of changes that characterize aged microglia. Specifically, aged microglia downregulated genes associated with TGFβ signaling, which regulates cell proliferation, differentiation, survival and scar formation, while demonstrating enrichment of genes responsible for endoplasmic reticulum-phagosomal pathway. Notably, these aged microglia also demonstrated enrichment of genes attributed to antigen processing and interferon signaling, indicating that age-related changes may resemble changes that occur during neuroinflammation of autoimmune or infectious etiology [33,34▪▪]. While there has been great progress in understanding the changes that microglia undergo during normal aging, many questions remain regarding potential interplay between neuroinflammation, aging and neurodegenerative disease.

MICROGLIA IN DISEASE

Neurodegenerative diseases

There are significant similarities in transcriptomes of microglia from healthy aging brain when compared to microglia occurring in cases of neurodegenerative disease such as Alzheimer's and Parkinson's, and in post-viral memory impairments [33,34▪▪,35,36▪,37▪,38]. Importantly, aging and neurodegenerative diseases also result in microglia that are distinct from homeostatic microglia from younger brains. These DAM, downregulate expression of homeostatic microglial genes such as CX3CR1, P2RY12, and TMEM119, while showing increased expression of genes involved in innate immune signaling, including upregulation of complement and interferon responses. Although these responses are likely adaptive, limiting transsynaptic spread of pathogens or Tau [39], they may become dysregulated in the setting of Alzheimer's disease [40▪] and flavivirus-induced memory impairments [41–43].

Recovery from infections with WNV and ZIKV are associated with new syndromes of memory impairments, especially those in the domains of immediate and visuospatial/ constructional memory [44,45]. During recovery from WNV infection in mice, two distinct populations of activated microglia emerge, each with a distinct gene expression profile.

Similar to DAM in neurodegenerative diseases, both activated microglia populations exhibit reduced expression of homeostatic genes P2RY12, CX3CR1, TMEM119, Fcrls, sialic acid-binding immunoglobulin-like lectin H, G-protein coupled receptor 34, and hexosaminidase subunit beta. One activated microglial cluster exhibited upregulation of genes important for MHC and antigen presentation, such as *Cd74, H2-Ab1*, and *H2-Eb1*, while another expressed a genetic signature more like microglia derived from aged humans or mice, or to those obtained from individuals with neurodegenerative disorders [36▪,46,47]. These data support the notion that viral infections may be a trigger for progressive neurodegenerative diseases.

Microglia in stroke

In murine models of stroke, microglia can be protective or disruptive for BBB function depending on their activation state. Pro-inflammatory microglia-derived cytokines such as tumor necrosis factor (TNF) and reactive oxygen specifies acting on astrocytes to induce expression of matrix metalloproteases (MMPs), with MMP inhibitors currently being assessed for their therapeutic potential in stroke recovery [48,49]. Microglia also secrete anti-inflammatory cytokines including IL-4, IL-10, arginase 1, and TGFβ, which can promote resolution of inflammation and stroke recovery [reviewed in [50]]. Persistent neuroinflammation that follows stroke can lead to microglial phagocytosis of astrocytic end feet, increasing BBB permeability [reviewed in [51]]. Pharmacological ablation of microglia via CSF1R inactivation during stroke increases BBB permeability, while minocycline restores BBB integrity down-regulation of microglia expression of proinflammatory and phagocytic molecules including CD68, CD86, TNF, IL-1β, and IFNγ expression [52,53]. A genetic model of increased microglial activity due to genetic ablation of Na^+/H^+ exchanger displays increased levels of oxidative phosphorylation, significantly reduced mortality, and improved cognitive ability during poststroke recovery. This was accompanied by increased phagocytic capacity of microglia and improved oligodendrogenesis [54▪▪]. Finally, temporary microglial depletion vis CSFR1 antagonism during intracerebral hemorrhage resulted in reduced leukocyte infiltration and neuronal death, with improved behavior scores and BBB function. After re-establishment of CNS myeloid cell populations, reduced expression of inflammatory cytokines IL-1β, TNF, and IL-6 were observed, although the exact nature and source of these cells remain under investigation [55].

New putative targets and therapeutics are continually revealed by profiling microglia in various preclinical neurologic disease models. However, studies that completely elucidate distinct pathways that are neuroprotective versus neurotoxic are needed to define how to manipulate microglial activation states depending on specific therapeutic needs.

NOVEL STRATEGIES TARGETING MICROGLIAL DYSFUNCTION

Approaches aimed at addressing microglial dysfunction in aging and neurologic disease are being tested in preclinical models. Microglia ablation in aged mice restores CNS levels of IL-6 and IL-10 to those observed in younger mice, and decreases expression of $p16^{Ink4a}$, a ubiquitously expressed protein involved in cell cycle regulation and a marker of cellular senescence [56]. Another novel approach involves immunization against *Mycobacterium*

vaccae, a common bacterium in the environment. Aged microglia from rats immunized against *M. vaccae* displayed lower levels of activation markers such as MHC-II and CD68, most prominently in the amygdala and hippocampus [57].

More recently, based on accumulating evidence linking alterations in gut microbiota to neurologic disease, various approaches that target the gut-brain axis have been explored [58,59]. Nicotinamide N-oxide (NAMO) is generated in the gut by certain commensal bacteria and is capable of crossing the BBB, where it acts on microglia to limit microglial activation by inducing mitophagy, a form of programmed cell death that occurs in response to mitochondrial damage [60]. Disruption of the microbiota via administration of antibiotics ablates these effects. As many viral infections are associated with intestinal dysbiosis, leading to lowered numbers of NAMO-producing bacteria [60,61▪], further research should address whether post-viral CNS effects may be ameliorated via therapeutic targeting of intestinal dysregulation. Indeed, Metformin, a widely used antidiabetic drug, reduces cellular senescence, microglial activation and neuroinflammation following intracerebral hemorrhage [62], sepsis [63▪] and early stages of aging [64]. Mechanisms of this effect are unclear, but evidence from fecal transplants suggests that this effect is also, in part microbiota-dependent [62,63▪].

CONCLUDING COMMENTS

Microglia are essential for brain health, in part, by their ability to quickly differentiate into activated subsets that direct the functions of both immune and neural cell types. However, recent studies indicate the persistence of activated microglia during various neurologic diseases. Depending on their location and CNS region involved, these activated microglia contribute to BBB instability, chronic elimination of synapses, maintenance of resident memory T cells, and elevated baseline expression of cytokines that alter the functions of numerous neural and immune cell types. While these activated microglia are believed to underlie neuropathologic effects observed in many neurologic diseases, new studies of the functions of genes expressed by homeostatic microglia suggest that their downregulation during microglial activation may, in fact, be an important cause of altered CNS function. Thus, the efficacy of microglial ablation and replacement therapies for neurologic diseases may depend on simultaneous targeting of gut microbiota alterations that contribute to their activation.

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KEY POINTS

- Microglia are the resident innate immune cells of the brain and play a variety of roles in brain homeostasis and disease.
- Recent research indicates that microglia undergo profound transcriptomic changes during CNS infection, stroke, traumatic brain injury, and aging.
- Better understanding of molecular mechanisms of microglial functions should serve as a basis for the development of new therapeutics.