Review Article

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Microglial Equilibrium in Brain Function and Dysfunction

Gaurangi Srivastava[1], Rajat Kala[2], Kaushik P Sharma[2], and Kanchan Bisht[2]

[1]Dept of Physical Medicine and Rehabilitation, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Dehradun, Uttarakhand, India

[2]Dept of Neurology, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Dehradun, Uttarakhand, India

Microglia, the neuroimmune cells of the central nervous system (CNS), play a crucial role in brain development, health, and disease. Initially thought to be "resting," they're now known to be highly active, constantly monitoring the brain tissue with their ramified processes to detect small changes in electrical balance, communication between nerve cells, or cell health. Through this constant vigilance, microglia control the removal of excess connections between nerve cells, fine-tune the brain's connections, provide nutrients and energy to cells, and coordinate the body's response to injury or infection. Their interactions with nerve cells, astrocytes, and oligodendrocytes further connect them to the larger network of brain cells that helps keep the brain in balance. However, when microglial regulation goes awry, these same functions can contribute to disease, including nerve cell loss, mental health disorders, brain injury, and autoimmune diseases. This review brings together the latest findings in microglial biology, focusing on their origins, surveillance methods, roles in nerve cell connections, metabolic control, and communication with other brain cells. Together, these insights show that microglia are both protectors of brain function and potential triggers of disease, putting them at the centre of brain health.

Keywords: Microglia; Neuroimmunology; Synaptic pruning; Brain homeostasis; Neurodegeneration

Introduction

Microglia are specialized immune cells that play a vital role in the CNS, making up 5–15% of all glial cells, depending on the brain region. Previously thought to be passive "resting" cells that only activate during injury or disease, microglia are now recognized as highly dynamic and adaptable, constantly monitoring their environment and adjusting their function in response to both physiological and pathological cues.

Microglia originate in the yolk sac from primitive erythromyeloid progenitors (EMPs) during early embryogenesis (Ginhoux et al., 2010; Kierdorf et al., 2013). These progenitors enter the developing brain before the blood–brain barrier forms, colonize the neuroepithelium around embryonic day 8.5 in mice (week 4 in humans), and multiply locally to establish a self-renewing population that lasts throughout life (Ginhoux and Prinz, 2015). Early environmental signals, including growth factors like TGF-β and IL-34, as well as neuronal activity, guide microglial maturation and the acquisition of homeostatic markers such as P2RY12, TMEM119, and CX3CR1, enabling their lifelong adaptation to the CNS niche (Butovsky et al., 2014).

Microglia lie at the center of neuroimmunology, serving as key mediators of communication between the immune and nervous systems. They respond to a wide range of signals, from pathogens and injury to normal neuronal activity, influencing processes such as synaptic plasticity, neurogenesis, and myelination. Dysregulated microglial responses contribute to neurodevelopmental, neuropsychiatric, and neurodegenerative disorders, highlighting their dual role as protectors of brain health and potential drivers of pathology.

This review focuses on the physiological functions of microglia, including their development, surveillance, synaptic refinement, trophic and metabolic support, regional specialization, interactions with other brain cells, and adaptive changes during aging.

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Correspondence Address: Dr. Kaushik P Sharma, Dr. Kanchan Bisht, Dept of Neurology, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Dehradun, Uttarakhand, India.
Email id: kpsharma@srhu.edu.in, kanchanbisht@srhu.edu.in
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Microglial Surveillance, Synaptic Remodelling, and Crosstalk

Microglia are highly dynamic sentinels of the CNS, continuously extending and retracting their fine processes to survey the parenchyma. This vigilance, revealed through two-photon imaging, enables rapid detection of ionic changes, neurotransmitter shifts, or cellular injury. Neuronal "calm down" signals, including CX3CL1–CX3CR1 and CD200–CD200R pathways, restrain excessive microglial reactivity and preserve homeostasis (Diez et al., 2009). When cells become stressed or die, the release of ATP and UDP activates microglial purinergic receptors such as P2RY12, guiding microglial processes to the affected sites (Davalos et al., 2005). Beyond surveillance, microglia provide trophic and metabolic support by releasing factors such as BDNF and IGF-1, regulating adult neurogenesis, and phagocytosing debris and protein aggregates to prevent toxic buildup that contributes to age- and disease-related decline(Parkhurst et al., 2013).

Equally vital is their role in sculpting neural circuits. During development, microglia prune synapses in an activity-dependent manner, with complement proteins (C1q, C3) marking weak synapses for CR3-mediated engulfment (Schafer et al., 2012; Stephan et al., 2012). This refinement ensures efficient wiring of cognitive and sensory networks, while impaired pruning contributes to disorders such as autism and schizophrenia. Even in adulthood, microglia continue to remodel synapses in response to learning, stress, and experience, underscoring their lifelong role in circuit plasticity.

Microglial functions are further shaped by their diversity and interactions with surrounding cells. Single-cell transcriptomics reveals region-specific signatures reflecting local demands and vulnerabilities in disorders like Alzheimer's or Parkinson's disease. Crosstalk with other glia and neurons refines their responses while neuronal neurotransmitters and extracellular vesicles actively reprogram microglial states. Together, these surveillance, remodeling, and communication roles establish microglia as central coordinators of homeostasis, immunity, and plasticity in the CNS.

Microglia in Aging

As individuals age, microglial cells undergo significant changes in their physiology, marking a key transition point between their roles in maintaining homeostasis and triggering disease. In older microglia, altered morphology, reduced mobility, impaired surveillance, and decreased ability to clear debris, and synaptic remodelling contribute to age-related cognitive decline and an increased risk of neurodegenerative conditions (Spittau, 2017; Rim et al., 2024). At the molecular level, aging microglia experience shifts in gene expression, with increased activity of genes related to interferon response, oxidative stress, and antigen presentation. Simultaneously, there is a loss of key markers of homeostasis, such as P2RY12, TMEM119, and CX3CR1 (Hickman et al., 2013; Galatro et al., 2017). This results in a functional shift towards chronic, low-grade activation, which makes neurons more vulnerable to damage. However, aged microglia are not uniformly harmful; in some instances, they can still provide support and participate in repair, although with reduced effectiveness.

Researchers are exploring methods to rejuvenate or reset the function of aged microglia. Approaches under investigation include targeting the CSF1R protein to remove and replace aged microglia, reprogramming their metabolism, utilizing senolytic interventions to eliminate senescent cells, and modulating the communication between the immune system and the brain(Elmore et al., 2018). These efforts emphasize the flexibility of microglial cells and the potential to mitigate age-related dysfunctions that increase the risk of disease.

Microglial Heterogeneity and Pathological Roles

One of the most striking findings in recent years is the recognition that microglia are highly heterogeneous, varying across brain regions, developmental stages, and pathological contexts (Masuda et al., 2019, 2020). Early morphological observations hinted at this diversity, but advances in single-cell RNA sequencing and spatial transcriptomics have uncovered distinct transcriptional and functional states. In the healthy brain, homeostatic microglia express markers such as P2RY12, TMEM119, and TREM2, which help distinguish them from infiltrating macrophages (Butovsky et al., 2014). Under stress or disease, however, they transition into specialized subtypes.

A prominent example is disease-associated microglia (DAM), first described in Alzheimer's models, which downregulate homeostatic genes while upregulating phagocytic and lipid metabolism pathways, including Apoe, Trem2, and Tyrobp (Keren-Shaul et al., 2017). At the ultrastructural level, dark microglia emerge in states of chronic stress, aging, and neurodegeneration, exhibiting condensed cytoplasm, fragmented organelles, and enhanced synaptic engulfment, features consistent with hypervigilant or

stressed phenotypes (Bisht et al., 2016). Another recently described population, lipid-droplet–accumulating microglia (LDAM), arises in aging and neurodegeneration, characterized by impaired phagocytosis, elevated oxidative stress, and disrupted lipid metabolism (Marschallinger et al., 2020). Together, these examples underscore the remarkable plasticity of microglia and highlight the need for therapeutic approaches tailored to context- and state-specific functions.

Microglia in Neurological Disorders

Microglia play a key role in many brain diseases. In neurodegenerative disorders, they gather around amyloid-β plaques and tau tangles in Alzheimer's disease (AD), where they might remove aggregates through phagocytosis (Yuan et al., 2016). However, when activated chronically, they release cytokines and reactive oxygen species that cause synaptic loss. Genes linked to AD, such as TREM2, CD33, and CR1, are highly expressed in microglia, highlighting their importance. In Parkinson's disease, extracellular α-synuclein aggregates activate toll-like and inflammasome pathways, maintaining inflammation and oxidative stress; PET scans show increased microglial activity that correlates with disease severity. In amyotrophic lateral sclerosis and frontotemporal dementia, microglia initially support neurons but later turn proinflammatory, with mutations like C9orf72 impairing lysosomal function and increasing toxicity.

In traumatic and acquired CNS injuries, microglia quickly respond by clearing debris and releasing growth factors, but prolonged activation can damage the blood–brain barrier, cause swelling, and lead to long-term problems like post-traumatic epilepsy and dementia risk.

Finally, in psychiatric and neurodevelopmental disorders, microglia are involved in mood and cognitive issues. Chronic stress increases their inflammatory activity in depression, with antidepressants partly working through immune modulation. Excessive synaptic pruning in schizophrenia, influenced by C4 gene variants, leads to synapse loss. Maternal immune activation and changes in cytokine signaling link microglial dysfunction to autism spectrum disorder.

Advances in Microglial Biology and Therapeutic Frontiers

Over the past decade, research has completely changed our understanding of microglia. Initially seen as passive immune defenders, they're now recognized as key players in central nervous system health. Single-cell RNA sequencing, ATAC sequencing, and spatial transcriptomics have revealed that microglia exist along a spectrum of states, rather than fitting into distinct categories like resting or activated. For instance, in Alzheimer's disease, microglia take on disease-related traits marked by the loss of homeostatic molecules, such as P2RY12 and TMEM119. At the same time, they activate programs related to lipid metabolism and phagocytosis, influenced by genes like APOE and TREM2. These shifts are driven by epigenetic regulators, including PU.1, Sall1, and IRF8 for maintaining balance, and NF-kappa B and STATs for inflammatory reprogramming (Gosselin et al., 2017). Environmental stressors and systemic inflammation can also leave lasting imprints, modulating responses throughout the lifespan.

Recent advances in technology have led to unprecedented insights into in vivo processes. Two-photon microscopy has shown that microglia constantly extend and retract their processes to monitor brain tissue and respond quickly to threats. PET imaging using TSPO ligands has allowed researchers to visualize microglial activity in patients, while newer tracers like CSF1R and P2RY12 ligands offer greater precision (Garland et al., 2023). Genetic and chemogenetic approaches, including Cre driver lines and DREADDs, now enable researchers to manipulate microglial signaling in experiments. Additionally, human-induced pluripotent stem cell-derived microglia and brain organoid systems have provided personalized platforms for studying disease mutations and discovering new treatments.

A key focus has been immunometabolism. Depending on activation state, microglia shift between glycolysis and oxidative phosphorylation (Borst et al., 2019; Jung et al., 2025). Glycolysis supports quick inflammatory signaling, while fatty acid oxidation encourages repair and trophic support (Bernier et al., 2020). Disruption of lipid metabolism, such as with TREM2 mutations, can impair protective functions. Metabolites like succinate and NAD act as regulators of microglial activity and aging (Xie et al., 2020). These insights have guided therapeutic efforts with metabolic modulators such as metformin and PPAR gamma agonists, along with CSF1R inhibitors, TREM2 agonists, and inflammasome blockers. Complementary strategies include exercise, dietary changes, neurostimulation, and microbiome interventions.

Nevertheless, major challenges still exist. Microglial diversity across regions and disease stages

complicates therapy design. Current therapies often affect both microglia and peripheral macrophages, raising the need for central nervous system selective delivery. Biomarkers remain limited, with TSPO lacking specificity, although soluble TREM2 and multimodal ligand panels show promise. Looking forward, integration of multiomics, CRISPR functional screens, neuroimmuno engineering, and advanced organoid systems may enable patient-tailored strategies that preserve beneficial roles such as pruning and trophic support while suppressing maladaptive states. Ultimately, microglia must be understood as active regulators of lifelong brain health whose plasticity can be harnessed for resilience and repair.

Discussion

Microglia are now recognized as key players in maintaining the balance between neural health and disease. In normal physiology, they aid in synaptic refinement, trophic signaling, and tissue surveillance while constantly communicating with neurons, astrocytes, oligodendrocytes, endothelial cells, and peripheral immune signals. This ongoing interaction supports circuit stability and plasticity, placing microglia at the core of the neuroimmune network.

In pathology, however, microglia take on roles that can be both protective and harmful depending on timing and context. In neurodegenerative conditions such as Alzheimer's, Parkinson's, and frontotemporal dementia, they initially cluster around deposits and promote clearance, but prolonged activation increases oxidative stress and causes synaptic dysfunction. After trauma or ischemic stroke, their early functions include debris removal and supporting axonal regeneration, yet ongoing inflammatory signals can worsen secondary damage. In psychiatric and neurodevelopmental disorders, abnormal pruning and altered cytokine signaling interfere with circuit maturation, leading to long-term vulnerability. These varied outcomes are affected by genetic factors, age, sex, local cellular interactions, and systemic immune responses.

Therapeutic strategies, therefore, need careful calibration. Interventions that broadly suppress or activate microglia risk removing their essential protective functions. Current approaches aim to redirect microglial states instead of silencing them completely. This includes drugs like CSF1R inhibitors, inflammasome modulators, and TREM2 agonists, as well as complementary strategies such as lifestyle changes, neuromodulation, and microbiome-based therapies. The challenge is ensuring that treatments are specific to the context, controlled over time, and ideally tailored to the individual.

The emerging framework of precision neuroimmunology offers a path forward. Multiomics profiling, CRISPR functional analysis, humanized organoids, and computational models now allow detailed mapping of protective and pathogenic states. Incorporating variables such as aging, sex, and systemic immunity will be essential to determine therapeutic windows. Ultimately, the future of microglial therapy rests on preserving their indispensable functions while selectively mitigating their harmful contributions. Microglia should be viewed not only as contributors to pathology but also as potential allies in maintaining and restoring central nervous system health.

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