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Microglia as dynamic cellular mediators of brain function

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Abstract

Originally hypothesized to function solely as immunologic responders within the central nervous system (CNS), emerging evidence has revealed that microglia have more complex roles in normal brain development and in the context of disease. In health, microglia influence neural progenitor fate decisions, astrocyte activation, neuronal homeostasis, and synaptogenesis. In the setting of brain disease, including autism, brain tumors, and neurodegenerative disorders, microglia undergo substantial morphological, molecular, and functional changes, which establish new biological states relevant to disease pathogenesis and progression. In this review, we discuss the function of microglia in health and disease, and outline a conceptual framework for elucidating their specific contributions to nervous system pathobiology.

Keywords

microglia; glioma; precision medicine; macrophage; brain; central nervous system

Microglia: Origins and Function

The brain is composed of numerous distinct cell types, the majority of which derive from neural stem cells within the developing central nervous system. These cellular entities include neurons, glia (oligodendrocytes and astrocytes), and a small population (5–10%) of resident macrophages (microglia). When first described by the Spanish neuroscientist Pío del Río Hortega in 1919 [1], microglia were also thought to derive from the neuroectoderm; however, modern fate mapping studies revealed that microglia actually arise from C-KIT^{+}/CD41^{+} erythromyeloid progenitor cells present before embryonic day 8 (E8) in the developing mouse yolk sac [2]. These precursors migrate into the embryonic mouse brain around E9.5, where they form a population of **SALL1**$^{+}$/**SALL3**$^{+}$/MEIS3^{+} (see **Glossary**) self-renewing cells throughout the neuroaxis [3–5]. In the adult brain, microglia express TMEM119, **CD11B** and P2RY12/P2RY13, but have low expression of CD45, whereas circulating and tissue macrophages have high expression of CD45 and CD11B [6]. These protein markers and others have been extensively used to discriminate resident microglia from infiltrating peripheral monocytes in health and in the setting of CNS disease, largely

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ignoring the fact that the expression of these discriminatory markers can be altered in a context-dependent manner [7–9].

Given their gross similarity to tissue macrophages, microglia were initially hypothesized to be primarily responsible for innate immunity in the brain. While they clearly participate in immune responses within the CNS, they possess many additional capabilities beyond simple immune surveillance. In the healthy brain, both during fetal and postnatal development (Box 1), as well as throughout adulthood (Box 2), microglia serve numerous homeostatic roles. These include instructing progenitor cell fate decisions, communicating with other glial cell populations (astrocytes, oligodendrocytes), enabling synapse formation and regulating neuronal function (Figure 1). Moreover, microglia continuously survey their local environment, and dynamically respond to neuronal activity and local brain perturbations [10–12]. In this regard, microglia promote neurite formation, facilitate synaptogenesis and myelination, regulate synaptic pruning, and augment synchronized synaptic activity [13]. Similarly, in the setting of CNS disease, it is now appreciated that microglia are not passive bystanders that merely react to brain pathology, but instead, have more active roles in the initiation and progression of numerous CNS disorders, ranging from Alzheimer's disease and ALS (amyotrophic lateral sclerosis) to brain tumors and autism (Box 3).

In this review, we highlight new evidence demonstrating that microglia are central integrators of neurologic disease risk, as well as key mediators of nervous system pathology development and progression. Based on these findings, we propose a new conceptual framework with which to consider microglia relevant to defining their precise roles in CNS disease and the design of future treatments for microglia-mediated brain disorders.

Microglia as cellular integrators in the brain

Given that microglia perform a myriad of functions in the healthy developing and adult brain, as well as in the context of CNS disease [13], it is not surprising that they can be reprogrammed at the epigenetic or transcriptional level to adopt new functional and molecular identities in a context-dependent manner (Figure 2) [7, 14, 15]. This could happen through numerous mechanisms relevant to CNS disease risk and pathogenesis. As such, microglia innate functional capabilities, as well as their abilities to react to the local milieu (tissue context), may be determined in part by the influence of germline genetic (*e.g.*, mutations) or genomic changes (*e.g.*, allelic variations), sex, normal aging, systemic disease, and/or environmental exposures.

Germline and somatic genetics

Individuals with neurogenetic disorders start life with a single germline mutation in one (autosomal dominant) or both (autosomal recessive) copies of a specific disease gene, which could change the molecular and functional capacities of microglia in the brain to influence CNS disease. For example, children with Neurofibromatosis type 1 (NF1), an autosomal dominant neurogenetic condition caused by a germline mutation in the *NF1* gene, are prone to learning disabilities, autism spectrum disorder, and attentional deficits [16, 17]. Examination of murine microglia containing a heterozygous *Nf1* mutation revealed increased proliferation and migration relative to wild-type microglia, as well as elevated

expression of numerous growth factors [18]. Analogously, children with Rett syndrome, characterized by severe developmental regression and epilepsy, harbor germline mutations in the methyl-CpG binding protein 2 (*MECP2*) gene, which encodes a protein that broadly regulates gene activity through methylation of chromatin. Microglia bearing *Mecp2* mutations damage neuronal dendrites and synapses, and the addition of wild type bone marrow-derived monocytes ameliorated the pathology in some mouse models of Rett syndrome [19, 20]; however, replication of these findings in other mouse models has been limited [21].

In addition to germline mutations, patients can acquire somatic mutations in cells that give rise to microglia. In this manner, patients with an immunologic disorder, histiocytosis, caused by somatic mutations in the *BRAF* gene ($BRAF^{V600E}$ activating mutations), can develop late-onset neurodegenerative disease. Since the myeloid cells that cause this tissue macrophage disorder share a similar yolk sac progenitor as microglia, BRAF-mediated ERK hyperactivation in resident brain microglia partly underlie the pathogenesis of this progressive neurodegenerative condition [22]. While additional work is required to define the mechanisms underlying microglia reprogramming in neurogenetic disorders, these studies support the notion that germline and somatic mutations might reprogram microglia to facilitate the development of disease or lower the threshold for CNS disease progression.

Genomic changes

In addition to germline and somatic mutations that abrogate protein expression or function, genomic variations may have more subtle effects. In this regard, allelic variations in the ***APOE*** gene (*APOE3* versus *APOE4* alleles) alter the risk of several neurodegenerative disorders, including late-onset Alzheimer's disease. Induced pluripotent stem cell (iPSC)-derived microglia-like cells with homozygous *APOE4* alleles exhibit morphologic changes, a greater inflammatory transcriptional profile, and reduced clearance of $Aß_{42}$ relative to microglia with homozygous *APOE3* alleles [23]. Interestingly, when cerebral organoids generated from iPSC lines harboring familial Alzheimer's disease mutations (*APP* duplication or *PSEN1* mutation) were exposed to APOE4 iPSC-derived microglia-like cells, there was greater extracellular amyloid-β accumulation [23]. These intriguing results suggest that this risk factor for Alzheimer's disease operates in part at the level of microglia. Similar to other neurodegenerative disorders (Box 3), it is interesting to note that many Alzheimer's disease susceptibility genes (***TREM2***, ***ABCA7***, ***MS4A***, ***CD33***, and ***PU.1***) are exclusively expressed in microglia [24–28].

Sex

While sexually dimorphic brain phenotypes have been recognized in vertebrates for decades, recent studies have conclusively demonstrated that sex is a major determinant underlying the function of microglia in the brain. This can occur through chromosomal effects or gonadal hormone influences [29]. Examples of these sex differences now abound in the literature, ranging from sex-specific behaviors to neuron damage in the setting of neurodegenerative and neoplastic diseases.

A surge in testicular androgens just before birth initiates lasting structural changes in the rodent brain, which can be mediated by **estradiol**, aromatized from testosterone, to produce prostaglandin E2 (**PGE2**) in the rodent preoptic area (POA) [30]. PGE2 generates two-fold more dendritic spines in males relative to females, and results in male breeding behaviors [31]. In this respect, male mice have twice as many amoeboid microglia as females at the time of birth, which was ameliorated by estradiol or PGE2 administration [32]. Similarly, microglia in the hippocampus of female mice phagocytose more neural progenitor cells, which can be reduced to male levels by masculinization with estradiol [33]. Moreover, transient silencing of microglia during the early postnatal period results in a permanent loss of male sexual behaviors [32, 34]. In addition, during perinatal development, androgens cause higher levels of juvenile rough-and-tumble play in males by increasing microglia phagocytosis during a critical period of amygdala development, such that blocking phagocytosis in males increases astrocyte survival and reduces neuronal excitation during play [35]. Finally, other sexually dimorphic social behaviors in rodents can also be established by microglia and complement-mediated phagocytic activity that eliminate dopamine receptor-expressing neurons in the nucleus accumbens of male, but not female, rats during adolescence [36].

Male and female microglia have distinct phenotypes both *in vitro* and following brain transplantation *in vivo* [37], and exhibit distinct transcriptional profiles [37, 38]. In these studies, male microglia had higher antigen-presenting capacities, elevated expression of purinergic receptors, and a greater ability to respond to ATP relative to their female counterparts. Using single cell RNA sequencing, a distinct population of microglia was identified only in female mice at P4–5, with high expression of ***Cd74***, *Ccl24* and *Arg1* [8]. Similarly, in the setting of experimental murine models of Alzheimer's disease, progressive amyloid-β accumulation induces ***Dkk2***, ***Gpnmb***, and ***Spp1*** expression in female microglia faster than in male microglia [39]. Importantly, some of these sexually dimorphic phenotypes are hardwired, such that female microglia transplanted into male brains were protective against ischemic stroke, whereas male microglia transplanted into female brains had no effect on the outcome of stroke [37].

Another example of a clinically relevant sexual dimorphism operating at the level of microglia is observed in children with NF1. While girls and boys with the NF1 cancer predisposition syndrome develop brain tumors (optic pathway gliomas) at similar rates, girls with these tumors develop progressive vision loss and require treatment 3–5 times more often than boys [40]. Using genetically engineered mice, females with *Nf1* optic gliomas had more retinal ganglion cell (RGC) loss, retinal nerve fiber layer (RNFL) thinning, and visual acuity impairment than males [41]. Surprisingly, this sexually dimorphic difference is mediated by estrogen acting on microglia, such that chemical or surgical ovariectomy, or inhibition of the estrogen receptor ß (ERß) expressed on microglia reversed the sex-specific RGC loss and RNFL thinning in female mice with *Nf1* optic glioma [41]. In contrast, male gonadectomy had no effect on optic glioma-induced retinal pathology. Taken together, these observations demonstrate sex-specific differences in microglia biology in the healthy brain and in response to neurological disease.

Brain regional heterogeneity

In addition to germline genetics, genomic changes, and sex, microglia are also highly influenced by brain region, leading to different functional capabilities. As such, microglia isolated from different brain regions have varying responses to ATP stimulation, purinergic receptor expression, and abilities to induce neurotoxicity [42]. There is even variability in microglia density, branching structure, lysosomal content, and membrane polarization properties in microglia from different nuclei within the basal ganglia [43]. These biological differences are also reflected in unique transcriptional profiles [43, 44] supporting the notion that the local environment dictates the innate properties of these highly dynamic cells. Interestingly, acute and chronic stress induce regional alterations in corticolimbic microglia density, cytokine profile, and morphology in a sexually dimorphic manner in rodents [45].

Aging

Normal aging is associated with brain gray matter loss, cortical thinning, reduced hippocampal volume, learning and memory impairments, and reduced remyelination. These changes in brain structure and function may be due to microglial priming or an exaggerated microglial response to stimulation [46–50]. Aging microglia have reduced process speed (necessary for effective surveillance of the local environment), condensed cytoplasm and nucleoplasm, nuclear chromatin remodeling, increased granular content and autofluorescence (suggesting impaired lysosomal function), reduced phagocytic ability, and greater production of reactive oxygen species and proinflammatory cytokines [51–54]. In addition, “dark” microglia, characterized by condensed cytoplasm and nucleoplasm, increased projections to synapses, and increased encircling of axon terminals and dendritic spines, can also be found in the aged, stressed, or diseased brain [52]. Similar to microglia associated with neurodegenerative diseases, aged microglia exhibit elevated expression of transcripts upregulated in DAM, including ***Lgals3*** (galectin 3), ***Axl*** (AXL receptor tyrosine kinase), *Clec7a* (C-type lectin domain family 7, member a), *MHCII* (major histocompatibility class II antigen), and *Cxcr4* (C-X-C motif chemokine receptor 4) [55]. In addition, aging microglia uniquely express proteins, like CD22, which regulate phagocytosis (removal of cellular debris) and, in this manner, influence microglial contributions to normal homeostatic brain functions, such as spatial memory and contextual fear conditioning [56].

Systemic disease

Systemic disease can also affect the function and transcriptional profiles of microglia. While the brain was originally thought to be an immunologically privileged site, accumulating evidence supports the notion that there is a dynamic relationship between brain microglia and the rest of the body. First, in experimental murine models of allergic asthma, microglia in the offspring of mice of females with asthma have gene expression profiles that resemble those found in mice with autism-like symptomatology [57]. Moreover, these pups also exhibit abnormal social, repetitive and perseverative behaviors.

Second, the intestinal microbiota influences microglia function relevant to motor dysfunction in a mouse model of Parkinson’s disease [58], such that germ-free and antibiotic-treated Parkinson’s disease mice have reduced alpha synuclein accumulation, motor symptoms, and Tumor necrosis factor alpha (TNFα) production. When the intestinal

bacteria from patients with Parkinson's disease were fed to previously germ-free mice, the recipient mice developed alpha-synuclein accumulation and motor dysfunction, which was attenuated by pharmacologic inhibition of microglia with minocycline, a tetracycline antibiotic that inhibits microglia activation [59] and reduces T cell contact with microglia [60]. How gut microbes communicate with microglia in the brain involves a combination of immune (*e.g.*, T cells), enteric (*e.g.*, bacteria-derived neuroactive substances), and neural pathways (*e.g.*, vagal transmission) that establish physical and chemical connections [61].

Third, immune system cells, including T lymphocytes, can traffic into the brain [62], where they can interact with microglia. In this regard, low-grade glioma stem cells from *Nf1* mutant mice do not form tumors following transplantation into athymic (*nu/nu*) mice lacking mature T cells [63]. This failure to develop tumors results from an absence of T lymphocytes, which stimulate microglia to produce a critical growth factor (**Ccl5** chemokine) required for glioma growth. Notably, microglia from athymic mice have primary defects in phagocytosis and *Ccl5* gene expression [63], raising the intriguing possibility that systemic disorders involving T cells (*e.g.*, asthma, atopic skin conditions) could influence microglia function in the brain. To this end, patients with asthma have a reduced incidence of brain tumors [64, 65].

Environmental Exposures

Another way in which systemic exposures can alter microglia capabilities is through environmental factors, including medical treatments (radiation and chemotherapy), prenatal toxin exposure, and stress. Cranial radiation causes neurologic decline and cognitive dysfunction by impairing hippocampal neurogenesis. Following cranial radiation, there is a 2.5-fold increase in proliferating microglia within the hippocampus [66], which is in part mediated by **Ccl2** and **Ccr2**-expressing monocytes [67, 68]. In an analogous fashion, chemotherapy with methotrexate, an antifolate agent that suppresses the immune system produces functional changes in microglia that result in dysfunctional myelination and depletion of oligodendrocyte lineage cells [69]. These changes are reversed upon depletion of microglia, suggesting that microglia are critical drivers of chemotherapy-induced neurologic impairment ("chemobrain"). These dynamic changes are important to consider, since treatments alter the function of microglia in the setting of CNS disorders, and establish new homeostatic states relevant to disease progression.

Prenatal exposure to diesel exhaust particles, believed to be the primary toxic component of air pollution, results in behavioral changes and increased toll-like receptor 4 (TLR4) expression in murine microglia [70]. Interestingly, these changes appeared more notable in male mice, resulting in increased microglia-neuron interactions hypothesized to underlie the changes in cortical volume seen during development and in adult male mice [70]. In addition, antenatal exposure to bisphenol A (BPA), a compound commonly found in plastic food packaging, increases the number of microglia in the murine dorsal telencephalon and hypothalamus at E15.5 with a concomitant increase in TNFα expression [71]. Further studies will be required to establish cause-and-effect relationships.

Stress is another factor that impacts on the function of microglia [72]. Early life stress in mice, elicited by brief daily maternal separation, increases the density of hippocampal

microglia at P14 and alters their transcriptional profiles at P14 and P28 [73]. Moreover, hippocampal microglia from these mice exhibit increased phagocytic activity and a transcriptional profile similar to immature microglia [73]. Taken together, microglia function can be dramatically altered by numerous environmental factors, which can establish different cellular capabilities, both at baseline and in the setting of neurological disease.

Re-conceptualizing microglia: A new taxonomy

Microglia have historically been classified based on their function (phagocytic versus surveilling), inflammatory profile (M1 versus M2), and/or shape (amoeboid versus ramified) [74]. However, with the advent of single cell RNA sequencing, it has become increasingly clear that this classification scheme is too simplistic, and does not fully capture the diversity of microglia contributions to CNS development, homeostasis, and disease pathogenesis [7, 75, 76]. In these single cell RNA sequencing studies, numerous populations of microglia have been identified that reflect the developmental age of the mouse (embryonic, postnatal, and old mice), the local biological events occurring during those developmental periods (myelination, synaptogenesis), and the pathologic context (neurodegenerative disease, brain tumor). For example, Proliferative-region-Associated Microglia (PAM) are localized to actively myelinating regions, and operate during a defined developmental window in the first week of life [7], whereas Disease-Associated Microglia (DAM) and Glioma-Associated Microglia (GAM) predominate in the settings of neurodegenerative disease and glioma, respectively [15, 55, 75, 77–80]. However, these subpopulations have never been directly confirmed to be distinct, rather than overlapping, populations, and future studies should aim to elucidate whether these subtypes are unique microglia subpopulations or a single subpopulation that arises in specific developmental or disease states.

Microglia subpopulations may arise regionally as a result of their local microenvironment

Numerous studies have now revealed an ever-expanding number of distinct populations of microglia that exist in the normal brain at different stages of development and aging, as well as in the context of CNS disease (Figure 3). These microglial species could all co-exist in the normal and developing brain as distinct microglia subtypes, where their local density is specified by the biological events occurring in that specific brain region. In this scenario, the spectrum of microglia capabilities for each population would be hardwired during microglia speciation/differentiation, and diversity created only through preferential recruitment and/or expansion. Implicit in this idea is the notion that the different microglia populations have normal functions, which are differentially required during brain development and homeostasis. As such, in areas where myelination is occurring, either during development or in the setting of dysmyelinating disorders, PAM may predominate. Similarly, in areas where neurons or neural progenitors are being culled during brain development, during establishment of new neuronal connections (neuronal plasticity), or in the context of neurodegenerative disease, DAM may emerge as the dominant species, where their continued presence may contribute to further disease progression. While one species may predominate in any disease context, it is possible that there are also essential roles for the minor microglia populations. For example, in gliomas where the dominant microglia (GAM) promote glioma cell growth through the elaboration of paracrine factors [81], PAM might

function to disrupt oligodendrocyte precursor cell dynamics resulting in impaired neuronal function or an increase in the cancer stem cell pool, whereas DAM may mediate neuronal damage or phagocytose cellular debris resulting from tumor growth. In this manner, the diversity of microglia populations is a direct reflection of the developmental and pathological context [8, 82].

The local microenvironment could reprogram microglia to establish new functional states

Alternatively, the distinct microglia subtypes encountered in the normal brain or in the setting of neurological disease could reflect the innate dynamic nature of tissue monocytes, in which the local milieu actively reprograms uncommitted microglia to establish new functional states with distinct gene expression signatures. This model envisions microglia as "transformers", whose function and transcriptomal profiles are dictated by their local environment. In this manner, targeting microglia might become a game of "whack-a-mole", in which selective modulation of one population facilitates the emergence of new populations with different capabilities. Moreover, to complicate matters further, the innate capabilities of microglia in each of these models are highly influenced by genomic, genetic, sexually dimorphic and systemic factors. As such, the phenotype of DAM or PAM could be different, depending on these factors, leading to varying effects on normal brain functions (*e.g.*, learning, myelination) and in the setting of CNS disease risk and progression (*e.g.*, neuronal damage).

Concluding Remarks

The importance of developing a classification system for microglia based on context, cell surface marker expression, and function cannot be understated. Given the profound transcriptional and functional changes adopted by microglia in response to genetic and genomic factors, sex, environmental exposures, and systemic disease or medical treatments, a better understanding of how these factors alter microglia population dynamics and biology may emerge (see Outstanding Questions). This is relevant for both researchers and physicians alike. For the scientific community, striking a balance between oversimplified classification schemes (*e.g.*, analogous to M1and M2 in macrophages) and highly complicated taxonomies, in which molecular markers define an ever-increasing number of microglia populations without functionally relevant differences, will be essential. As these populations become fully elucidated, their developmental origins and relationship to brain homeostasis will hopefully emerge. For the clinician, it is crucial to define how modifying factors (*e.g.*, germline genetics, sex, environmental factors) operate at the level of microglia relevant to CNS disease risk assessment. It is conceivable that these modifying effects change the set point for microglia responses, both at baseline, but also in the face of CNS pathology (*e.g.*, brain tumors, stroke). With the advent of human induced pluripotent stem cell (hiPSC) engineering, future risk assessment approaches might entail the generation and analysis of hiPSC-generated microglia [83, 84]. In addition, since microglia are likely to operate as integrators of many cellular signals, treatment strategies that interrupt microglia function in the setting of nervous system disease could evolve into future adjuvant therapies (see Clinician's Corner). These future approaches could involve targeting specific populations or functions of microglia, rather than global microglia inhibition strategies (*e.g.*,

minocycline, **PLX3397**), which have not demonstrated efficacy in human clinical trials to date. Additionally, since T cells can traffic to the brain hematogenously or through direct vascular channels from the skull bone marrow [85] to interact with microglia, it is possible that T cell therapies that interrupt microglia priming could attenuate CNS disease. This type of Trojan horse approach could also be engineered with a suicide signal to eliminate the infiltrating T cells when needed, and thus control treatment duration and minimize off-target effects. Collectively, the recent explosion in our appreciation of microglia as primary effectors of brain health and disease uniquely positions the research and medical communities to identify clever approaches to microglia targeting for the future management of human neurologic diseases.

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Glossary

ABCA7	ATP binding cassette subfamily A member 7. A gene encoding a protein involved in lipid homeostasis that is expressed predominantly in myeloid/lymphatic tissues
APOE	Gene encoding Apolipoprotein E, a protein that binds to lipids and cholesterol
Axl	AXL receptor tyrosine kinase. A protein in the Tyro3-Axl-Mer (TAM) receptor tyrosine kinase subfamily involved in signal transduction from extracellular matrix to regulate growth, migration, aggregation and inflammation
CCL2	C-C motif chemokine ligand 2. A chemokine implicated in the pathogenesis of diseases characterized by monocyte infiltration
CCL5	C-C motif chemokine ligand 5. A chemokine that functions as a chemoattractant for monocytes, memory T helper cells and eosinophils
CCR2	C-C motif chemokine receptor 2. Encodes a protein that acts as a receptor for the monocyte chemoattractant protein-1, a chemokine mediating monocyte chemotaxis
CD11B	Integrin subunit alpha M. A cell surface protein that combines with Integrin beta 2 chain to form a leukocyte-specific integrin, macrophage receptor 1
CD33	Sialic acid-binding Ig-like lectin 3. A transmembrane receptor expressed in myeloid cells

CD47	Gene encoding a membrane protein that increases intracellular calcium after cell adhesion to extracellular matrix proteins
CD74	Encodes a protein that associates with MHC class II molecules to regulate antigen presentation
Dkk2	Dickkopf WNT signaling pathway inhibitor 2. Protein involved in embryonic development and Wnt signaling pathway
Estradiol	Estrogen steroid hormone involved in female secondary sexual characteristics and the female reproductive cycle
Gpnmb	Glycoprotein nmb. A transmembrane glycoprotein homologous to a melanocyte protein, possibly involved in growth regulation
Lgals3	Galectin 3. Carbohydrate binding protein involved in apoptosis, innate immunity, cell adhesion, and T cell regulation
MS4A	Membrane-spanning 4A. Encodes a transmembrane protein that is likely involved in olfactory perception in mice
PGE2:	Prostaglandin E2. An inflammatory mediator generated by COX2
PLX3397	Receptor tyrosine kinase inhibitor of CSF-1R, Kit and Flt3. Reduces the number of tissue macrophages
PU.1	Transcription factor that acts as a lymphoid-specific enhancer
SALL1	Spalt like transcription factor 1. Zinc-finger protein involved in embryonic development, but exact function of this protein is unknown
SALL3	Spalt like transcription factor 3. Zinc-finger protein involved in embryonic development, but exact function of this protein is unknown
SIRPα	Signal-regulatory protein alpha. Membrane glycoprotein that interacts with CD47 to inhibit cellular destruction by immune cells
Spp1	Secreted phosphoprotein 1; osteopontin. Protein involved in the attachment of osteoclasts to bone and the regulation of IL-12 expression

Subventricular zone	A region of the brain located in close proximity to the brain ventricles containing neural stem cells and astroglial progenitors
TREM2	Triggering receptor expressed on myeloid cells 2. A cell surface protein expressed by myeloid cells that interacts with TYROBP to regulate cell growth and inflammatory responses to injury or disease

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Box 1. Microglia Function in the Developing Brain

During development, microglia are critical cellular elements that maintain an optimal number of synapses in the brain, such that defects in microglia function delay brain maturation [86, 87]. Microglia also control neuronal content by modulating the survival of neural precursor cells [88–91], and promote neural progenitor cell proliferation and differentiation, as well as stimulate neuron and oligodendrocyte production in the developing forebrain **subventricular zone** [92, 93]. In addition, microglia are involved in synaptic pruning, important for synaptic remodeling in the healthy brain and neurodegenerative disease pathogenesis, a process that involves complement (C3, C1q) expressed on neurons and complement receptors (CR3) expressed on microglia [94, 95], as well as “don’t eat me” signaling through microglial **SIRPα** and neuronal **CD47** interactions [96]. Further support for a critical role for microglia in normal brain function derives from the study of genetically engineered mice. Deletion of the *Cx3cr1* gene, encoding an essential microglia chemotactic receptor, results in delayed colonization of microglia in the barrel cortex, late maturation of glutamatergic synapses, decreased hippocampal microglia, and abnormal maturation of hippocampal structure and synapses [86, 97]. Relevant to these deficits, a population of highly metabolically active microglia (termed PAM, proliferative-region-associated microglia) undergo expansion in the developing murine white matter during the first week of life, which phagocytose newly formed oligodendrocytes to maintain normal neuronal integrity and function [7]. In addition, children with homozygous mutations in a microglia chemotactic receptor, Colony Stimulating Factor 1 Receptor (CSF1R), which leads to congenital absence of microglia, have agenesis of the corpus callosum, ventriculomegaly, periventricular calcifications, mega cisterna magna, and abnormalities of the cerebellar vermis [98].

Box 2. Microglia Function in the Adult Brain

In the adult brain, microglia are necessary for behavior, learning and memory, and regulate which newborn neural progenitor cells mature into adult neurons [90]. Consistent with a crucial role for microglia in adult brain function, adult *Cx3cr1*-deficient mice exhibit impaired social interactions, grooming behaviors, long-term potentiation, and learning-dependent memory [99, 100]. In addition, transient elimination of microglia in adult mice using a microglia specific tamoxifen-inducible diphtheria toxin caused impairments in learning and memory [101]. Similarly, local depletion of hippocampal microglia with clodronate, a drug that promotes apoptosis of phagocytes, impaired performance on learning and social interaction measures, whereas global high dose PLX3397 (microglia colony stimulating factor receptor-1, CSF1R, inhibitor) treatment transiently impaired spatial learning [102]. Interestingly, these behavioral effects are reversed when microglia repopulated the brain [102]. Moreover, microglia are also critical for the maintenance of the adult oligodendrocyte progenitor pool, and dictate CNS remyelination after brain injury [103, 104].

Box 3. Microglia in CNS disease

Microglia play important pathogenic roles in numerous brain disorders. First, in neurodegenerative disorders, like Alzheimer's disease (AD) [105], amyotrophic lateral sclerosis (ALS), and frontotemporal dementia (FTD), a unique population of microglia (disease-associated microglia; DAM microglia) [15, 77] phagocytoses Aß plaques and neurofibrillary tangles in the setting of AD [106], as well as releases inflammatory cytokines to result in neurotoxicity [107]. Relevant to disease pathogenesis, genetic reduction of the microglial triggering receptor expressed on myeloid cells 2 (TREM2) attenuates brain atrophy in a mouse model of tau pathology (FTD), supporting a key role for microglia in this neurodegenerative disorder [77, 108]. In addition, many neurodegenerative disorder susceptibility genes are highly expressed in microglia [109–111], further underscoring the idea that microglia might partly mediate neurodegeneration. Second, microglia are particularly susceptible to and mediate brain entry of neurotropic viruses through Gas6/Axl interactions, as well as Axl kinase-mediated downregulation of interferon signaling (in the case of Zika virus) [112, 113]. In addition, microglia can induce neuropathology through complement-mediated synapse elimination (in the setting of West Nile virus) [114], leading to profound neurologic impairments in children. In addition, microglia can recruit T cells to the brain through the elaboration of cytokines [115, 116]. Third, the absence of microglia significantly worsens brain injury in the setting of cerebral ischemia by de-regulated neuronal signaling, reduced spreading depolarization and increased excitotoxic injury [117]. Fourth, neuropsychiatric disorders, such as catatonia, may also be initiated by microglia, such that pharmacologic microglia depletion alleviated the psychomotor features observed in rodent models [118]. In addition, mice lacking the microglia chemokine receptor (Cx3cr1) exhibit defects in social interaction and increased repetitive behaviors [100], while those with microglia *Trem2* loss have sociability deficits [119], similar to those seen in children with autism. Fifth, microglia/macrophages comprise 30–50% of the cells in astrocytomas (gliomas) of all grades [120, 121], where they increase glioma cell proliferation and spread through the elaboration of numerous paracrine factors [18, 81, 120, 122, 123]. Moreover, genetic reduction or elimination of monocytes in murine models can delay low-grade gliomagenesis [124] and reduce glioma growth in rodents [18, 63, 81, 125, 126]. In summary, microglia play critical roles in the pathogenesis of many neurologic diseases, and are intimately involved in the brain response to injury and infection.

Clinician's Corner

- There are numerous populations of microglia in the brain and spinal cord that play distinct roles at different stages during brain development, homeostasis, and disease.
- Microglia integrate genetic, genomic, and environmental signals to create new functional states relevant to neurologic disease risk.
- Microglia are critical drivers of numerous CNS diseases, ranging from autism and neurodegenerative disorders to gliomas and multiple sclerosis.
- Changes in microglia function may underlie neurologic disease pathogenesis, progression, and response to therapy. Thus, targeting microglia may provide new strategies for the treatment of CNS disorders.
- Currently there are no clinically approved drugs that target specific microglia populations for CNS disorders.

Highlights

- Microglia integrate genomic and genetic alterations, as well as local microenvironment and systemic signals, to establish new functional states that modify neurologic diseases.
- Transcriptional profiling has revealed several different microglia populations/states with distinct functional properties.
- Understanding the molecular mechanisms that govern microglia adaptation and plasticity may lead to the development of targeted therapies for a broad range of neurologic disorders.

Outstanding Questions

- What microglia populations/states exist during normal brain development, and what are their individual functions?
- How do genetic mutations, sex, and systemic medical conditions change microglia biology relative to neurologic disease risk?
- Which microglia populations/states emerge or disappear in the setting of CNS disease?
- How do these populations contribute to neurologic disease development, progression, and response to therapy?
- Can specific microglia populations be targeted as adjuvant therapies for CNS disorders?

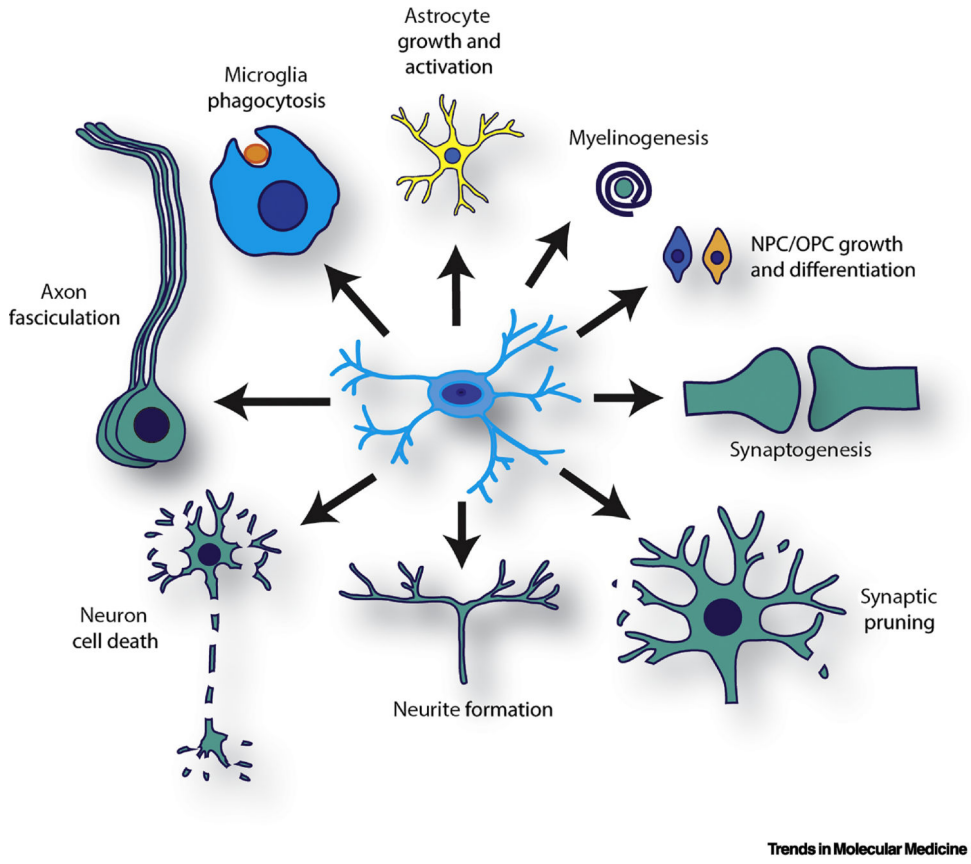

Figure 1. Microglia perform a myriad of functions in the normal brain.

Microglia (center) are critical for proper neuronal function in the brain, including regulating axon fasciculation (left), programmed cell death, neurite formation, synaptic homeostasis ("pruning"), and synaptogenesis. In addition, microglia specify neural progenitor cell (NPC) and oligodendrocyte progenitor cell (OPC) expansion and differentiation, promote myelinogenesis, and increase astrocyte activation and proliferation. Lastly, microglia engulf cellular debris (phagocytosis).

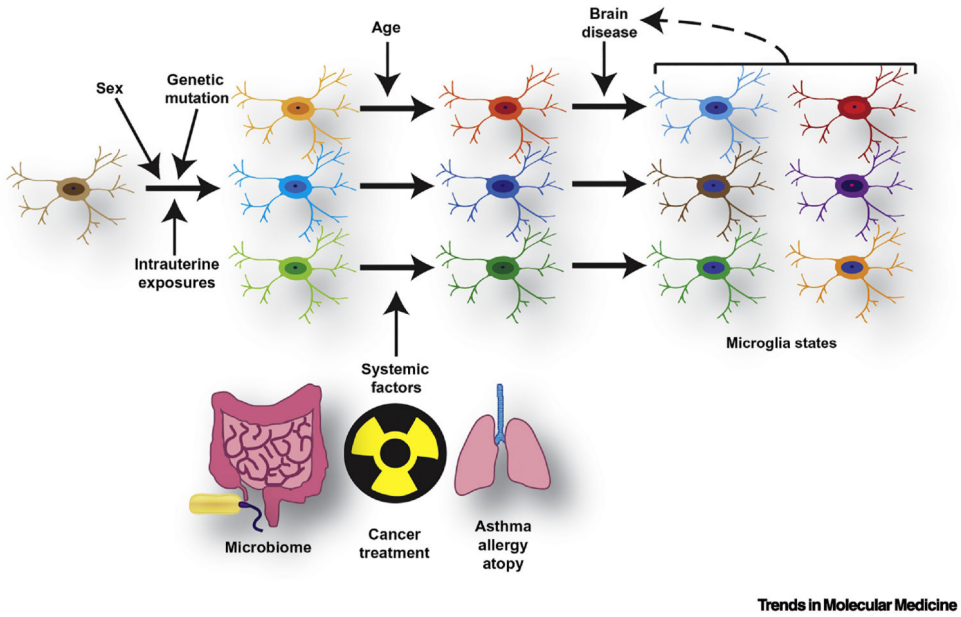

Figure 2. Microglia as central cellular integrators of disease.

Microglia attain early developmental programming (left) imparted by intrauterine exposures, sex and underlying genetic factors (germline mutations, genomic polymorphisms) to create monocytic cells with slightly different baseline capabilities (indicated by different colors). These microglia are subsequently altered by age and systemic factors (microbiome, asthma, eczema, environmental exposures, radiation/chemotherapy), as well as by contextual signals found in the brain in the setting of different brain disorders. Each of these factors operate to establish significant microglia diversity (dynamic microglia states; right), which in turn influences the course of brain disease pathogenesis and response to therapy.

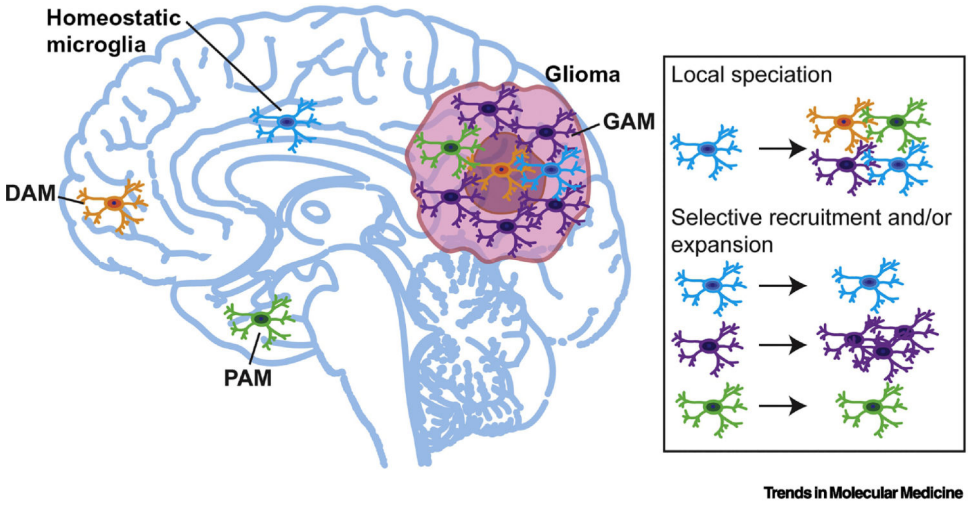

Figure 3. Microglia taxonomy.

A variety of distinct microglial populations with different functions likely exist within the normal brain at different ages and brain regions. For example, disease-associated microglia (DAM, orange), proliferative-region-associated microglia (PAM, green), and glioma-associated microglia (GAM, purple) states have been reported, each with different functional capabilities, molecular dependencies, and gene expression signatures. These subtypes may be further specified by the local brain environment or disease states, through two non-mutually exclusive mechanisms – local speciation (insert, upper panel) versus selective recruitment and/or expansion (insert, lower panel). In this regard, gliomas (red area) contain numerous different microglia populations, but the dominant one that uniquely specifies tumor biology is the GAM. Importantly, the other minor microglia subtypes perform different functions, such as progenitor cell expansion (PAM) or phagocytosis of degenerating neurons (DAM). Similarly, in the context of neurodegenerative diseases, DAM predominate, whereas in dysmyelinating disorders, PAM might play larger instructive roles. In all cases, these microglia populations evolve as the disease progresses or in response to treatment.