

Microglia in neurodegenerative diseases

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Abstract

A major feature of neurodegeneration is disruption of central nervous system homeostasis, during which microglia play diverse roles. In the central nervous system, microglia serve as the first line of immune defense and function in synapse pruning, injury repair, homeostasis maintenance, and regulation of brain development through scavenging and phagocytosis. Under pathological conditions or various stimulations, microglia proliferate, aggregate, and undergo a variety of changes in cell morphology, immunophenotype, and function. This review presents the features of microglia, especially their diversity and ability to change dynamically, and reinterprets their role as sensors for multiple stimulations and as effectors for brain aging and neurodegeneration. This review also summarizes some therapeutic approaches for neurodegenerative diseases that target microglia.

Key Words: central nervous system; microglia; neurodegeneration; neuroinflammation; plasticity

Introduction

Disruption of central nervous system (CNS) homeostasis leads to the development of neurodegenerative diseases (Kabba et al., 2018). Microglia, often referred to as CNS macrophages, have emerged as an essential component in innate immunity and they play a vital role in CNS development, health, response to injuries, and neurodegenerative diseases. They have immense phenotypic diversity with age and in response to disease (**Figure 1**). During development, microglia scavenge and phagocytose foreign materials that threaten the CNS, prune synapses of neural circuits, and maintain homeostasis. They are producers and targets of neuroprotective factors that are produced under physiological and pathological conditions, thus reinforcing the microglial neuroprotective phenotype (Polazzi and Monti, 2010).

Microglia are sensitive to many stimuli or changes in the microenvironment of the CNS. As an effector, microglia affect the development of neuronal networks and the progress of many diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Huntington's disease, stroke, epilepsy, autism spectrum disorder, schizophrenia, and the affective disorders (**Figure 2**).

All references cited in this review were retrieved by an electronic search of the PubMed database. More than 80% of all references cited were published in the past 10 years and more than 50% of them in the past 5 years. The following key

search terms were used: microglia, central nervous system, neurodegeneration, neuroinflammation, plasticity, aging, hypoxia, ischemia, and therapeutic approaches.

Biology of Microglia

Origin, diversity, and relevant signaling pathways of microglia

Brain-resident microglia originate from yolk sac macrophages during embryogenesis. They then migrate to the brain (Ginhoux et al., 2010) where they account for 10% to 15% of all cells (Nayak et al., 2014) (**Figure 1**). The origin of repopulated microglia remained controversial until recently. It was previously believed that repopulated microglia originated from nestin-positive cells (Elmore et al., 2014). With the use of colony-stimulating factor-1 receptor (CSF1R) inhibitors, Elmore et al. (2014) observed that almost all microglia in the adult CNS were eliminated. Once these inhibitors were withdrawn, microglia rapidly repopulated, the CNS after an increase in nestin-positive cells throughout the CNS, which represent microglial progenitor cells (Elmore et al., 2014). A neuroectodermal lineage was implicated for the repopulating microglia because microglia are myeloid lineage cells and nestin-positive progenitor cells originate from the neuroectodermal lineage (Ajami et al., 2007; Ginhoux et al., 2010; Schulz et al., 2012). In contrast, Varvel et al. (2012) demonstrated that repopulated microglia are derived from myeloid progenitor cells.

However, a recent study, based on an adult mouse model, appears to disprove the above theories. Huang et al. (2018)

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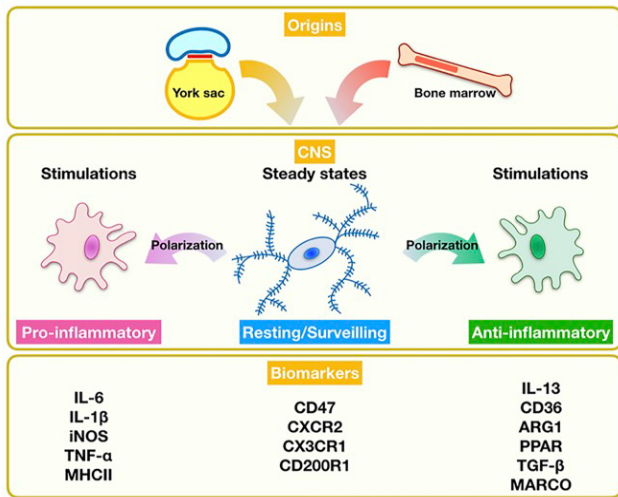


Figure 1 | The origin and biology of microglia.

Microglia originate from the yolk sac during embryogenesis and from bone marrow during repopulation. They act as an immunological surveillant in steady states. ARG1: Arginase 1; CNS: central nervous system; CD200R1: CD200 receptor 1; CX3CR1: CX3C chemokine receptor 1; CXCR2: C-X-C motif chemokine receptor 2; IL: interleukin; iNOS: inducible nitric oxide synthase; MARCO: macrophage receptor with collagenous structure; MHCII: major histocompatibility complex II; PPAR: peroxisome proliferator-activated receptor; TGF- β : transforming growth factor- β ; TNF- α : tumor necrosis factor- α .

demonstrated that repopulated microglia are not derived from blood cells, nestin-positive cells, astrocytes, oligodendrocyte precursor cells, or neurons. After selective elimination of more than 99% of microglia, the repopulated microglia originated from the proliferation of the surviving microglia (< 1%). Thus, the residual microglia are the only source of the repopulated microglia, and these newly formed microglia rapidly repopulate the whole brain (Nayak et al., 2014).

The diversity of microglia relies on genetic, epigenetic, intrinsic, and extrinsic factors (Grubman et al., 2016; Thion et al., 2018). The transcriptional profiles and motility of microglia, the effects of aging, stress, and other microenvironmental stimuli are different in various brain regions. Morphology, biomarkers, phenotypes, functions, and signaling pathways are diverse among microglia (Orihuela et al., 2016; Kierdorf and Prinz, 2017).

Microglia exhibit ‘plasticity’ and they undergo a series of morphological changes, becoming ramified, reactive, active or amoeboid, depending on their location in the brain (Lawson et al., 1990; Karperien et al., 2013; Taylor et al., 2014). Ramified microglia can also be regarded as resting microglia, with small cell bodies and long processes. Resting microglia are not passive in the CNS, rather they monitor the condition of the CNS (Karperien et al., 2013; Taylor et al., 2014; Prinz et al., 2019). Steady state microglia survey the surrounding microenvironment and maintain homeostasis via receptors for CX3C-chemokine ligand 1 (CX3CL1) (also called fractalkine), CD47, CD200, and CD22 (Nimmerjahn et al., 2005; Sierra et al., 2010; Tremblay et al., 2010; Thion et al., 2018). Microglia promote the release of inflammatory mediators, chemokines, proteases, and present antigens (Orihuela et al., 2016). The anti-inflammatory microglia express cytokines, such as interleukin (IL)-4, IL-5, IL-10, IL-13, glucocorticoids, transforming growth factor- β , and wound-healing genes, including arginase-1, CD36, CD163, macrophage receptor with collagenous structure, nerve and insulin growth factors, and peroxisome proliferator-activated receptor (**Figure 2**) (Mantovani et al., 2002; Nimmerjahn et al., 2005; Sierra et al., 2010; Tremblay et al., 2010; Orihuela et al., 2016; Thion et al., 2018). Advances in genome-wide expression profiling and computational biology, together with germline and epigenetic

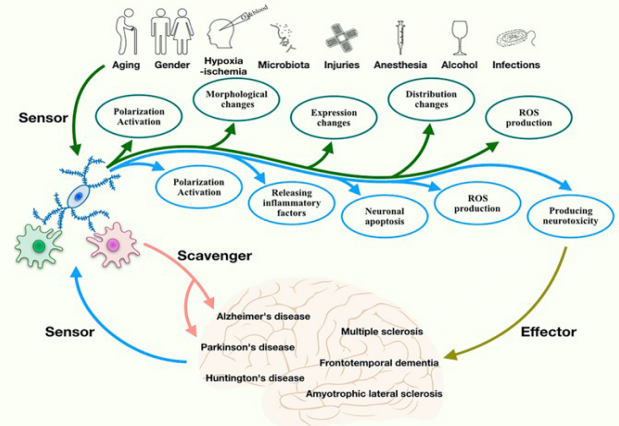


Figure 2 | Microglia act as both sensors and effectors.

Microglia are activated, change morphology and distribution, and produce reactive oxygen species (ROS) in response to various conditions, including aging, sex, stress, injuries, infections, hypoxia-ischemia, ROS, microbiota, anesthesia and alcohol, which suggests that they can act as a sensor. Once activated, microglia can produce ROS and inflammatory factors to induce neurotoxicity and neuronal apoptosis. They can, therefore, act as an effector in neurodegenerative diseases. These diseases can further affect the function and aggregation of microglia.

analyses, will facilitate better understanding of microglia and their crucial functions (Link et al., 2015; Romanoski et al., 2015; Amit et al., 2016; Crotti and Ransohoff, 2016).

Microglia are functionally diverse and are the primary immune defense in the CNS. They promote regrowth and remapping of damaged neural circuitry through synaptic pruning, and provide support for neurons (Gehrmann et al., 1995; Streit, 2006; Perry et al., 2010). They have an impact on the developing cerebral cortex through selective settlement in the main sub-ventricular zone and the phagocytosis of neural precursor cells as neurogenesis nears completion (Cunningham et al., 2013). Microglia continuously monitor the microenvironment by selectively responding to intercellular molecules. Resting microglia regulate their phenotypes to adapt to the microenvironment of the CNS, and are sensitive to any change in the extracellular microenvironment or pathological imbalance (Colonna and Butovsky, 2017).

Microglia are regulated and activated by various signaling pathways, including the nuclear factor kappa B (NF- κ B), Toll-like receptors (TLRs), mitogen-activated protein kinases (MAPKs), Janus protein tyrosine kinase-signal transducers and activators of transcription, peroxisome proliferator-activated receptor, Notch, and the fractalkine–fractalkine receptor (CX3CL1–CX3CR1) signaling pathways (Cardona et al., 2006; Bensinger and Tontonoz, 2008; Thurston and Kitajewski, 2008; Hanamsagar et al., 2012; Frakes et al., 2014; Mathur et al., 2017; Younger et al., 2019). TLRs activate pro-IL-1 β and pro-IL-18, which then develop into their active forms through the inflammasome (Kawai and Akira, 2010).

Microglial homeostasis and dynamics

In a healthy brain, microglia constantly seek signs of damage and debris. To achieve this, they are highly mobile through their dynamic processes (Davalos et al., 2005; Nimmerjahn et al., 2005). Powerful imaging techniques enable a comprehensive understanding of microglial dynamics *in vivo* (Wake et al., 2009; Tremblay et al., 2010).

Time-lapse imaging techniques have been applied to investigate microglial dynamics. These studies have shown the origin of microglia and their differentiation characteristics. For example, microglia may change to a ramified form

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Table 1 | Microglia act as sensors to multiple stimulations

Stimulations	Biomarkers	Functions	References
Aging	IL-1 β , IL-12, IL-23, TNF- α , iNOS, CD40, MHC1, MHCII and TREM2	Lead to telomere shortening, DNA damage, and oxidative stress; Give rise to an increase in inflammatory states in the retina; impede spatial learning; lose inhibitory ligand-receptor correlations; accumulate misfolded proteins	Vijg and Campisi, 2008; Xu et al., 2008; Perry and Holmes, 2014; Rawji et al., 2016; Scheffold et al., 2016; Niraula et al., 2017; Wolf et al., 2017
Stress	IL-1 β , TNF- α , IL-6, CCL2, MHCII, TLR4 and CD14	Aggravate behavioral abnormalities and neuroimmune responses	Frank et al., 2007; Wohleb et al., 2011; Prinz and Priller, 2014; Ramirez et al., 2015; Ramirez et al., 2016
Injuries	TLR, RAGE, IL-1 β and TNF- α ; IL-4, IL-10 and TGF	Scavenge cell debris; long-term “innate immune memory”	Nimmerjahn et al., 2005; Haynes et al., 2006; Kono and Rock, 2008; Salminen et al., 2009; Perry et al., 2010
Infections	MHCII, CD163, IL-1, TNF- α , S100 β , IL-8, IL-6, CCL2/MCP-1 and CCL5/RANTES	Affect the apoptosis and survival pathway of microglia	Valle et al., 2004; Schwarcz et al., 2012; Chen et al., 2017
Hypoxia	IL-1 β , IL-6, TNF- α and TLR4	Promote cell death and inflammation	Pineau and Lacroix, 2009; Tschopp and Schroder, 2010; Lim and Pack, 2014; McDonough et al., 2017; Cengiz et al., 2019
ROS	TNF- α , IL-1 β , iNOS, prostaglandin E2, and MCP-1	Damage cellular molecules; change the structure of membrane	Naik and Dixit, 2011; Yang et al., 2011; D’Amico et al., 2013; Qin et al., 2013; Kierdorf and Prinz, 2017
Microbiota	Slight increasing CSF1R and CD31	Maintain homeostasis	Berer et al., 2011; Kamada et al., 2013; Miron et al., 2013; Braniste et al., 2014; Yano et al., 2015; Matcovitch-Natan et al., 2016

CCL2: CC-chemokine ligand 2; CCL5: CC-chemokine ligand 5; CSF1R: colony-stimulating factor-1 receptor; IL: interleukin; iNOS: inducible nitric oxide synthase; MCP-1: monocyte chemoattractant protein-1; MHC: major histocompatibility complex; RAGE: advanced glycation end products; RANTES: regulated upon activation, normal T cell expressed and secreted; ROS: reactive oxygen species; S100 β : S100 calcium-binding protein β ; TGF: transforming growth factor; TLR: Toll-like receptor; TNF- α : tumor necrosis factor- α ; TREM2: triggering receptor expressed in the myeloid cell 2.

under highly dynamic conditions (Goldmann et al., 2016). Long-range non-invasive imaging of the dynamics of microglial precursors at a high spatio-temporal resolution has been especially informative. The transparent nature of the zebrafish brain makes it a perfect model to explore microglial dynamics during early development using advanced imaging techniques (Peri and Nüsslein-Volhard, 2008; Li et al., 2012). Time-lapse imaging techniques can be used in zebrafish to track the dynamic colonization of the brain by microglia. This colonization involves neuronal cell death, with lysophosphatidylcholine helping to maintain microglial homeostasis, which reduces the damage caused by the entrance of microglia precursor cells into the brain (Xu et al., 2016). The number of microglia can be increased by ultraviolet-irradiation-induced or ectopically-induced apoptosis (Casano et al., 2016). After entry into the brain, microglial proliferation in situ contributes to the expansion of the microglia population (Du and Du, 2016). During embryogenesis, CNS-associated macrophages maintain a steady state through homeostatic proliferation (Tay et al., 2017). CSF1R, binding colony stimulating factor 1, and IL-34 are vital for microglial development because they transmit intracellular signals and activate kinases that regulate extracellular signals, which are beneficial for the proliferation and survival of microglia (Greter et al., 2005; Wang et al., 2012; Guan et al., 2016).

Microglia: Active Sensors Linking the Extrinsic Environment to Central Nervous System Homeostasis

Microglia, as sensors, are sensitive to aging, sex hormones, stress, injury, infection, ROS, hypoxia, microbiota, anesthesia, alcohol, and other stimuli (Figure 2 and Table 1).

Aging

Aging reduces the number and activity of microglia; aged microglia perform their normal functions less effectively (Rawji et al., 2016). There are fewer microglia in the aged mouse cortex compared with the young adult mouse cortex and they are smaller, less symmetrical, and more elongated with fewer ramifications (Tremblay et al., 2012). Microglia are affected by telomere shortening, DNA damage, and oxidative stress during aging. Telomeres, the ends of eukaryotic chromosomes, shorten with age and correlates with the

decline in microglial self-renewal (Ajami et al., 2007; Vijg and Campisi, 2008; Scheffold et al., 2016; Niraula et al., 2017; Wolf et al., 2017). Aged microglia are less restricted from the outer retina, leading to an increase in its inflammatory state (Xu et al., 2008). Aging causes microglia to acquire intracellular auto-fluorescent lipofuscin deposits, which adversely affect vision (Xu et al., 2008). Aged microglia express increased tumor necrosis factor- α (TNF- α) and IL-6 and show dystrophic morphology, which impedes spatial learning (Niraula et al., 2017). Senescent microglia display increased levels of pro-inflammatory cytokines and reduced levels of chemokines, and decreased phagocytosis of amyloid beta (A β) fibrils (Niraula et al., 2017). Microglia exhibit a ‘primed’ phenotype, characterized by an augmented and out-of-control inflammatory response to an immune stimulus (Perry and Holmes, 2014).

The triggering receptor expressed on myeloid cells 2 (TREM2) pathway involves down-regulation of microglia checkpoints, which has significance for therapeutic approaches to AD and other neurodegenerative diseases (Keren-Shaul et al., 2017; Krasemann et al., 2017) that involve microglial responses triggered by energy metabolism (Ulland et al., 2017). Microglia experience distinct senescence, which inhibits the regenerative and repair response in the aging CNS (Shaw et al., 2013). Furthermore, microglial dynamics are modulated by sensory experience and/or neuronal activity (Tremblay et al., 2010; Bohlen et al., 2017). A significant association exists between microglia and late-onset AD, as demonstrated by single-cell RNA sequencing (Calderon et al., 2017; Masuda et al., 2019).

Sex

Sex through sex hormones, especially estradiol, causes differences in microglia (Villa et al., 2016; Thion et al., 2018). There are more microglia within the cortex, hippocampus, and amygdala of male than female mice in early postnatal development, an effect associated with the increased expression of CC-chemokine ligand (CCL) 20 and CCL4 because testosterone, the dominant masculinizing hormone, is aromatized to estradiol in the mouse brain. In adult female mice, microglia are thicker, with longer processes in the hippocampus, cortex, and amygdala than in male mice (Wolf et al., 2017; Thion et al., 2018). In germ-free mice, sexual dimorphism between microglia is decreased (Thion et al., 2018). The results of deep sequencing show that sex

has a greater impact on microglia in adulthood than during development. Immune-related genes in the microglia of adult mice are expressed more highly in females than in males (Thion et al., 2018).

Stress

Microglia can be affected by stress from the time of embryogenesis to an aged state. Prenatal stress can lead to the elevation of IL-1 β , which has an effect on microglial density and development in the embryonic brain (Meyer et al., 2006; Bittle and Stevens, 2018) and can result in an increased risk of psychiatric disorders (Bittle and Stevens, 2018).

Long-term exposure to stress results in microglial hyperactivation and morphological changes, with large amoeboid cell bodies and thicker processes (Frank et al., 2007; Wohleb et al., 2011; Xu et al., 2016). Stress increases the microglial expression of pro-inflammatory factors, including TNF- α , IL-1 β , IL-6, CCL2, antigen presentation molecules including major histocompatibility complex (MHC) II, and cell surface markers including TLR4 and CD14, an effect that persists for at least 24 days after stress (Frank et al., 2007; Wohleb et al., 2011; Ramirez et al., 2015, 2016).

Stress interacts with aging; exposure to psychological stressors enhances the immune response in the aged rat brain (Niraula et al., 2017). It is also proposed that stress-induced morphological activation of microglia is different in males and females. Neither acute nor chronic stress substantially affect microglia activation. In females, stress can change the proportions of microglia showing different states of morphological activation, and can alter the expression of microglia-associated genes, especially CD40 (Bollinger et al., 2016). Psychological stress can induce aging-like sensitization of microglia and increased reactivity to secondary challenges (Niraula et al., 2017). These findings reveal the different effects of stress on microglia, depending on age and sex.

Injury

Resting microglia constantly monitor the brain parenchyma (Nimmerjahn et al., 2005) and can change into their activated state following injury. Microglia quickly respond to damage-associated molecular pattern molecules generated by the rapid degeneration of neurons and neuronal processes (Kono and Rock, 2008; Scheffold et al., 2016) and microglial processes rapidly move to the site of the injury (Davalos et al., 2005; Sieger et al., 2012). Damage-associated molecular pattern molecules are immediately detected by scavenger receptors, TLRs, and the receptor for advanced glycation end products (Haynes et al., 2006; Salminen et al., 2009), which activate microglia to express IL-1 β and TNF for the scavenging of cell debris (Scheffold et al., 2016). Microglial processes can isolate lesion sites, and protect the brain from further injury (Younger et al., 2019), which can occur when microenvironmental homeostasis is disrupted (Nimmerjahn et al., 2005; Orihuela et al., 2016).

Interestingly, these microglia seem to have activated morphology, but they do not express any pro-inflammatory cytokines. Instead, they express IL-4, IL-10, and transforming growth factor for long-term 'innate immune memory' (Scheffold et al., 2016).

Infections

To reveal the relationship between microglia and various infections, human immunodeficiency virus (HIV) can be used as an example. HIV-1 infection leads to disruption of microglia homeostasis through the activity of MAPK and NF- κ B (Chen et al., 2017). Chronic HIV-1 infection may result in severe metabolic disorders, such as increased concentrations of kynurenine pathway metabolites, including quinolinic acid, the major CNS source of which is microglia (Valle et al., 2004;

Schwarcz et al., 2012; Chen et al., 2017; Rawat and Spector, 2017). Microglia are a major reservoir of HIV-1 in the CNS (Rawat and Spector, 2017). During HIV-1 infection, microglia are morphologically activated (Rawat and Spector, 2017) and pro-inflammatory cytokines, including IL-6, IL-8, IL-10, and TNF- α , are increasingly expressed (Chen et al., 2017).

Hypoxia-ischemia

Hypoxia-ischemia can induce inflammation and death of microglia. During hypoxia-ischemia, microglia increase their expression of IL-1 β , IL-6, TNF- α , and TLR4 (Pineau and Lacroix, 2009; Tschopp and Schroder, 2010; Lim and Pack, 2014; McDonough et al., 2017; Cengiz et al., 2019).

TLRs and type-1 interferon (IFN) are expressed in the brain after hypoxia-ischemia (McDonough et al., 2017). According to McDonough et al. (2017), both hypoxia-exposed and ischemia-induced microglia express increased levels of IFN-stimulated genes (ISGs), dependent on IFN- α / β receptor 1. IFN- β induces concentration-dependent secretion of ISG chemokines in cultured microglia and a significant increase in ISG expression in microglia both *in vitro* and *in vivo*. TLR4 and IFN- α / β receptor 1 help microglial ISG chemokines respond to TLR4 agonists and mediate neuroprotection pathways (McDonough et al., 2017). Once CNS homeostasis is perturbed, microglia are over-activated and synthesize pro-inflammatory factors, promoting cell death and inflammation. These mechanisms, including peripheral inflammation, indirectly activate microglia via neural transmission or direct passage of pro-inflammatory molecules across the BBB and via damage-associated molecular pattern molecules being released from adjacent injured cells. Direct microglial activation occurs by chronic intermittent hypoxia, which may be related to ROS production and may regulate and activate microglia (Pineau and Lacroix, 2009; Tschopp and Schroder, 2010; Lim and Pack, 2014).

Reactive oxygen species (oxidative stress)

ROS, including superoxide, peroxides, hydroxyl radicals and singlet oxygen, are oxygen-containing reactive chemical species (Hayyan et al., 2016), whose main sources in microglia are from nicotinamide adenine dinucleotide phosphate oxidase (NOX) and mitochondria. Oxidative stress is one of the negative effects of ROS (D'Amico et al., 2013). Oxidative stress can damage cell molecules and change the structure of the cell membrane, leading to cell death and other changes in metabolism (D'Amico et al., 2013). ROS induced by lipopolysaccharide, A β , and other proteins, can regulate the activation of microglia with increased expression of pro-inflammatory cytokines and chemokines, including TNF- α , IL-1 β , inducible nitric oxide synthase, prostaglandin, and monocyte chemoattractant protein-1 through NF- κ B, which may aggravate neurodegenerative disorders (Naik and Dixit, 2011; Yang et al., 2011; Qin et al., 2013; Kierdorf and Prinz, 2017). A recent study has demonstrated that NOX can produce sustained microglial activation, and dopaminergic neurodegeneration can inhibit the formation of ROS (Qin et al., 2013).

Microbiota

A complex gut microbiota, affected by age, sex, genes, oxygen, bile concentration, antimicrobial mediators, medicine, mental states, behavioral factors, and diet, helps maintain the homeostasis of microglia, disruption to which may promote microglial maturation, differentiation, and functional disorders (Berer et al., 2011; Kamada et al., 2013; Dorrestein et al., 2014; Erny et al., 2015; Wekerle, 2017; Thion et al., 2018). Microbiota can affect CNS biology through changes in neurotransmitter levels, and integrity of the BBB (Braniste et al., 2014; Yano et al., 2015). The impairment of remyelination in aging mice is related to decreased numbers of regulatory macrophages or microglia (Miron et al., 2013). The density of microglia is higher, with more branching processes during

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embryogenesis, in germ-free male mice compared with germ-free female mice (Matcovitch-Natan et al., 2016; Thion et al., 2018), while disorders normally occur during adulthood in germ-free male mice (Thion et al., 2018).

Disruption of gut microbiota leads to overexpression of α -synuclein (α -Syn), which can induce microglia activation in PD patients (Erny et al., 2015; Sampson et al., 2016; Thion et al., 2018). Moreover, the identification of key regulators that influence the homeostasis and function of microglia will contribute to the discovery of principles that govern their functions in animal models, and how they benefit or harm the brain under various circumstances (Belkaid and Hand, 2014).

Anesthesia-evoked neural responses

Exposure to sevoflurane, one of the most commonly used volatile anesthetics during surgery, may lead to a favorable microenvironment for endogenous neurogenesis through the activity of microglia (Dang et al., 2018; Yu et al., 2019). Treatment with 3% sevoflurane, 2 hours daily for 3 days, can result in an increase in calcium levels in young mice, which can generate TNF- α and IL-6 through NF- κ B signaling, followed by the induction of microglial activation, which can result in the generation of more pro-inflammatory cytokines (Shen et al., 2013).

Despite the beneficial influence of microglial activation, it is also regarded as toxic to nearby neurons because of the generation of cytotoxic mediators (Burm et al., 2015; Qiu et al., 2016). Microglial brain-derived neurotrophic factor increases the phosphorylation of neuronal tropomyosin-related kinase receptor B, which is a key mediator of synaptic plasticity (Parkhurst et al., 2013). Under appropriate conditions, activated microglia secrete neuroprotective factors including brain-derived neurotrophic factor (Prinz et al., 2019).

The neuroprotective effects of propofol after traumatic brain injury appear to be mediated, in part, through the suppression of NOX (Luo et al., 2013). Propofol limits microglial activation after experimental brain trauma through inhibition of NOX, and isoflurane promotes transcription activity of NF- κ B in microglia of mice, while anti-inflammatory treatment with ketorolac ameliorates sevoflurane anesthesia-induced cognitive impairment in mice (Zhang et al., 2013).

Alcohol-induced neurotoxicity

Alcohol misuse and abuse can induce various neuropsychiatric and neurological diseases. It has been reported that microglia are never activated by acute alcohol exposure in the absence of pronounced cell death (Wong et al., 2018). Analysis of the morphology and dynamics of microglia shows that developmental alcohol exposure may lead to residual impairment of neural plasticity, even in a brain region where microglia do not acutely assume or maintain an activated phenotype (Wong et al., 2018). Alcohol-treated traumatic brain injury mice exhibit increased numbers of cortical microglia. A single alcohol injection significantly increased microglial activation in the nucleus accumbens and the expression of the pro-inflammatory cytokine IL-1 β after traumatic brain injury (Karelina et al., 2017, 2018). Minocycline inhibits microglial production of the pro-inflammatory cytokines IL-1 β and TNF- α and increases the production of the anti-inflammatory IL-10 (Crews et al., 2013; Kobayashi et al., 2013). Alcohol-induced release of high mobility group box 1, a danger signal or 'alarmin', activates TLR4 in microglia, neuronal apoptosis inhibitory protein, MHCII, heterokaryon incompatibility and telomerase-associated protein 1 (NACHT), the NLR family pyrin domain containing 3 (NLRP3) inflammasome, neuronal hyperexcitability, and excitotoxicity neuronal death (Wolf et al., 2017). During all stages of life, the physiological phenotype of microglia is affected by alcohol consumption, which may result in the breakdown of synaptic

plasticity (Wong et al., 2018).

In maintaining CNS homeostasis, microglia simultaneously act as both sensors and effectors (**Figure 2**).

Microglia: A Versatile Effector in the Healthy and Pathological Brain

Physiology

Microglia play a vital role during development by promoting neural precursor cell proliferation and survival. Microglia are the major orchestrator of the brain's inflammatory response. Microglia express a wide range of immune receptors, as well as neurotransmitters. Microglia also express pattern-recognition receptors, including TLRs and their coreceptors, nucleotide-binding oligomerization domain-like receptors, and C-type lectin receptors, to detect pathogen-associated molecular patterns (Michell-Robinson et al., 2015; Wolf et al., 2017).

Microglial checkpoint mechanisms from development to old-age ensure that the organism responds to various stimuli and any physical abnormality in the microenvironment of the CNS, but during chronic diseases and aging, microglial checkpoint mechanisms have deleterious effects on the CNS because of limitations in microglia functions (Deczkowska et al., 2018). Single-cell RNA-sequencing with high-dimensional cytometry, bulk RNA-sequencing, fate-mapping, and microscopy indicate the diversity of non-parenchymal brain macrophages, and provide a framework for understanding the interaction between host macrophages in healthy and diseased brains (Masuda et al., 2019; Van Hove et al., 2019).

Microglia also express neurotransmitters, which are very important signaling molecules in the CNS. Importantly, they can regulate the release of inflammatory cytokines (Pocock and Kettenmann, 2007). All of the receptors and neurotransmitters expressed by microglia help maintain homeostasis in the CNS.

Neurodegeneration

Microglia in AD

AD is a progressive neurodegenerative disease characterized by the formation of A β plaques, entangled nerve fibers, and loss of neurons, with higher morbidity compared with other types of dementia (Burns and Iliffe, 2009). An AD-associated microglia subtype is unique to AD (Keren-Shaul et al., 2017).

Immune receptors can transmit either excitatory or inhibitory signals. TYROBP, serves as a direct partner/adaptor for TREM2, CD33, and CR3 (Guerreiro et al., 2013; Haure-Mirande et al., 2017). TREM2, a transmembrane glycoprotein, is able to transmit signals through DAP12 and DAP10 proteins, and is regarded as a protective factor in AD. TREM2 is a microglial A β receptor with the ability to transduce physiological and AD-related pathological effects related to A β (Colonna and Wang, 2016; Zhao et al., 2018). This can disturb immune defenses and neurotoxicity produced by the accumulation of inflammatory factors accelerates the patient's deterioration (Lambert et al., 2013; Colonna and Wang, 2016; Hopperton et al., 2018). During A β accumulation, TREM2 binds to polyanions, phospholipids, sulfatides, and apolipoprotein E (APOE) (Wang et al., 2015; Yeh et al., 2016; Colonna and Butovsky, 2017) and participates in the proliferation, survival and phagocytosis of apoptotic cells (Takahashi et al., 2005; Otero et al., 2009; Yeh et al., 2017). Up-regulation of TREM2 can relieve neuropathology and spatial cognitive impairment in AD (Jiang et al., 2014).

Different CD33 variants expressed at different levels play various roles in AD. A CD33 variant, expressed at relatively high levels, increases CD33 inhibitory effects on myeloid functions and the risk of AD, while another CD33 variant, expressed at

relatively low levels, reduces the inhibitory potential of CD33 and the risk of AD (Bradshaw et al., 2013). Inappropriate activation of microglia or the absence of fully differentiated disease-associated microglia are deleterious in AD (Keren-Shaul et al., 2017; Mass et al., 2017). Immunotherapy through APOE can clear A β deposition in the brain of AD patients, but it may damage the CNS (Salloway et al., 2014). Microglia produce APOE, which can moderate the inflammatory response (Xu et al., 2000; Cudaback et al., 2011; Terwel et al., 2011; Mandrekar-Colucci et al., 2012). The concept of homeostatic and reactive microglia suggests that the relevant risk factors for AD are associated with multifunctional and complex microglia responses to amyloid plaques (Sala Frigerio et al., 2019), which affect different branches of the phenotypic spectrum.

Microglia in PD

PD is characterized by the aggregation of α -Syn in Lewy bodies. During the early stage of the disease, microglia are activated and release ROS (Sanchez-Guajardo et al., 2013; Daher et al., 2014; Kumaran and Cookson, 2015). α -Syn can be scavenged by and activate microglia, which can aggravate inflammation to exacerbate PD (Lu et al., 2009; Sanchez-Guajardo et al., 2013). Microglia activation by α -Syn can induce increased expression of pro-inflammatory cytokines, including TNF, IL-1 β , IL-6, and inducible nitric oxide synthase, the release of ROS, which further perturbs the balance of dopamine neuron survival and death, and the production of nitric oxide, which leads to the death of surrounding neurons and cells, via various signaling pathways, including p38 MAPK, NF- κ B, and TLR pathways (Sanchez-Guajardo et al., 2013; Daher et al., 2014; Kumaran and Cookson, 2015). The aggregation of α -Syn leads to motor dysfunction, and is associated with gut microbiota (Sampson et al., 2016). As discussed previously, gut microbiota have a significant impact on the regulation of microglia; dysfunction of microglia is related to PD (Erny et al., 2015; Matcovitch-Natan et al., 2016; Sampson et al., 2016).

In addition to α -Syn, leucine-rich repeat kinase 2, one of the most commonly mutated genes in both idiopathic and familial PD, is highly expressed in microglia (Melrose et al., 2007), and induces microglial activation in response to inflammation through p38 MAPK and NF- κ B signaling pathways. Leucine-rich repeat kinase 2 mutations contribute to PD progression by changing the microenvironment (Kim et al., 2012). TREM2 has been reported to be involved in PD. Down-regulation of TREM2 leads to the expression of pro-inflammatory factors and aggravates PD; while up-regulation of TREM2 ameliorates microglial inflammation, thereby limiting the progression of PD (Zhang et al., 2018).

In a mouse PD model produced by administration of the dopaminergic neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, microglia are neurotoxic owing to the lack of CX3CR1 (Paolicelli et al., 2011). CX3CL1 and CX3CL1–CX3CR1 signaling can inhibit the expression of pro-inflammatory cytokines and microglial activation to protect neurons and limit PD progression (Zujovic et al., 2000; Cardona et al., 2006).

Microglia in ALS

ALS is characterized by selective motor neuron degeneration and progressive paralysis (Kiernan et al., 2011) and is related to MHCI and aggregation-prone proteins, including mutated superoxide dismutase 1 (SOD1), chromosome 9 open reading frame 72, Tau, trans-activation response element DNA binding protein 43 (TDP-43) and heterogeneous nuclear ribonucleoproteins (Beers et al., 2006; Butovsky et al., 2012; Renton et al., 2014; Colonna and Butovsky, 2017; Nardo et al., 2018). Microglia in ALS patients express high levels of MHCI. Depletion of MHCI in microglia can reduce

the neuroinflammation in SOD1G93A mice (Nardo et al., 2018). Aggregation-prone proteins can activate the microglial NLRP3 inflammasome, resulting in caspase-1 activation and IL-1 β secretion, which aggravate the ALS-like phenotype of SOD1G93A mice and TDP-43Q331K mice (Deora et al., 2020). As ALS progresses, microglia, activated by misfolded SOD1 and other stress signals released by motor neurons, attack TNF- α , IL-1 β , nitric oxide, ROS, and major histocompatibility complex II causing neurotoxicity, proinflammation, and the exacerbation of motor neuronal injury (Beers et al., 2006; Butovsky et al., 2012; Renton et al., 2014; Colonna and Butovsky, 2017). rNLS8 mice, an inducible mouse model of ALS used to examine the relationship between TDP-43, disease onset, progression, and neuroinflammation, express hTDP43 Δ NLS in neurons in a doxycycline-regulated manner, such that hTDP43 Δ NLS expression is suppressed in the presence of doxycycline 26, which results in the formation of TDP-43 aggregates (Walker et al., 2015; Spiller et al., 2016). When the proliferation of microglia is inhibited during the early recovery phase using PLX3397, a CSF1R and c-kit inhibitor, rNLS8 mice cannot acquire full motor function, indicating an important neuroprotective role for microglia (Elmore et al., 2014; Spiller et al., 2018). Additionally, an inhibitor targeting the microglial NLRP3 inflammasome and depletion of MHCI in microglia provide new therapeutic approaches to treat ALS as well as neuroinflammation during neurodegeneration (Nardo et al., 2018; Deora et al., 2020).

Microglia in MS and EAE

MS is characterized by multifocal white matter lesions and experimental autoimmune encephalomyelitis (EAE) is an animal model of inflammatory demyelinating diseases (Milo and Kahana, 2010). Microglia serve as antigen-presenting cells to invading T cells by proliferating and up-regulating MHCI (Wolf et al., 2017).

Activity of the E3 ubiquitin ligase, Peli1, which is normally important in the inactivation of microglia mediated by TLR and IL-1 signaling, leads to MS progression (Lereim et al., 2016). However, microglia also have beneficial effects in MS, one of which is the removal of apoptotic cells and myelin debris, which supports tissue regeneration and affects the maturation of oligodendrocyte progenitor cells. Microglia are very early elements involved in the onset of MS (Bogie et al., 2014; Wolf et al., 2017).

In the acute stages of MS, T cells are the first to initiate contact with resting resident microglia in the parenchyma (Heppner et al., 2005; Hirasawa et al., 2005), while activated microglia and repopulated microglia may emerge as antigen presenting cells in the chronic phase of EAE (Greter et al., 2005; McMahon et al., 2005). Although the short stimulatory impulse in the auto-aggressive effector T cells during the early stage of CNS invasion cannot cause the proliferation of T cells, it is enough to affect the overall process involved in the acute autoimmune reaction (Lodygin et al., 2013). 3H-1,2-dithiole-3-thione and its substituted derivative, 5-amino-3-thioxo-3H-(1,2) dithiole-4-carboxylic acid ethyl ester, have anti-inflammatory effects in EAE (Kuo et al., 2018). 5-Amino-3-thioxo-3H-(1,2) dithiole-4-carboxylic acid ethyl ester holds promise as a new therapeutic strategy for MS and EAE.

Therapeutic Approaches Targeting Microglia

Therapeutic approaches to the diseases discussed above include pharmacology, lifestyle changes, laboratory interventions, and gene therapy (Table 2).

Glucose metabolism influences inflammation by altering histone deacetylase 4 protein levels, NLRP3 inflammasome formation, and receptor for advanced glycation end product receptor activation (Manigrasso et al., 2014). Calorie restriction and a ketogenic diet can inhibit glucose utilization

Table 2 | Microglia-targeted gene therapy in neurodegeneration diseases

Intervention	Diseases	Signaling pathways	Effects	References
P2RY12 and TMEM119	MS	Lipid processing and PPAR γ signaling	Therapeutic target for MS	Shemer et al., 2018
IFN- β therapy	EAE	MSC immunomodulatory function	Reducing disease progression and frequency of acute exacerbations	Vigo et al., 2019
Inhibition of TREM2-APOE	ALS AD	TREM2-APOE	Restore homeostatic microglia	Krasemann et al., 2017; Pimenova et al., 2017
Deletion of C1qa gene	FTD	C1qa	Decrease synaptic shearing by progranulin GRN ^{-/-} microglia; Alleviate behavioral phenotypes and premature mortality; Prevent neurodegeneration in GRN ^{-/-} mice	Lui et al., 2016
miR-124	EAE	miR-124	Contribute to systematically inactive macrophages reduce the activation of myelin-specific T cells	Ponomarev et al., 2011
PLX3397	AD	CSF1R and c-kit	Beneficial improves the spatial and emotional memory deficits	Elmore et al., 2014; Spiller et al., 2018

AD: Alzheimer's disease; ALS: amyotrophic lateral sclerosis; APOE: apolipoprotein E; CSF1R: colony-stimulating factor-1 receptor; EAE: experimental autoimmune encephalomyelitis; FTD: frontotemporal dementia; GRN: progranulin; IFN- β : interferon- β ; MS: multiple sclerosis; MSC: mesenchymal stem cell; TMEM119: transmembrane protein 119; TREM2: transmembrane protein 2.

to reduce brain inflammation, tissue loss, and functional impairment after brain injury (Camberos-Luna and Massieu, 2020). Additionally, calorie restriction can hinder cortical-injury-induced and aging-related activation of microglia and mitigate fever and microglial activation induced by lipopolysaccharide (Radler et al., 2014). Physical exercise is associated with up-regulation of neurotrophic factors and anti-inflammatory cytokines, down-regulation of pro-inflammatory cytokines, and inhibition of microglial activation (Svensson et al., 2015). In a rat model of cerebral ischemia, exercise decreased the induction of TLR2, TLR4, myeloid differentiation primary response 88, and NF- κ B (Vetreno et al., 2017). Chronic sleep insufficiency leads to microglial up-regulation of pro-inflammatory factors and further aggravates disease (Imeri and Opp, 2009). Therefore, calorie restriction, sufficient physical exercise, and sleep are beneficial for neurodegenerative diseases.

Minocycline belongs to the tetracycline class of antibiotics. It has high lipid solubility and can easily penetrate the BBB (Kriz et al., 2002; Kobayashi et al., 2013). Increased microglial TNF- α and IL-1 β levels in the hippocampus were accompanied by a decrease in tumor necrosis factor receptor 2 receptor expression, which was reduced by minocycline (Mattei et al., 2014). Ginsenosides, extracted from natural ginseng, have anti-aging, anti-oxidative, and anti-apoptotic effects, and may promote neuronal regeneration by inhibiting the secretion of TNF- α and nitric oxide (Ong et al., 2015; Wolf et al., 2017).

IFN- β is widely used to treat patients with relapse-remission MS to reduce disease progression and frequency of deterioration, and IFN- β treatment can improve EAE in mice (Vigo et al., 2019). Importantly, it regulates key dopaminergic signaling genes, and its expression is decreased in both aged and PD post-mortem brains and in PD patients (Jakaria et al., 2019). Cytokine production and oxidative stress can be induced in microglia and astrocytes (Al-Haddad et al., 2019).

Nerve growth factor has a strong anti-inflammatory effect on microglia and guides them to neuroprotective phenotypes (Cattaneo and Capsoni, 2019). Microglia depletion and relevant reproduction are promising cell replacement therapies (Han et al., 2019). Thus, exosomes can be a powerful diagnostic tool, a promising therapeutic tool for natural nanoparticles, and also a means of disease transmission and transmission of neurodegenerative factors (Zagrean et al., 2018).

Depletion of CSF1R-mediated microglia may resolve tissue destructive inflammation. Treatment with low doses of the selective CSF1R inhibitor, PLX5562, (leading to 30% depletion) strongly reduced microglia accumulation at amyloid plaques in the 3xTg-AD mouse model (Dagher et al., 2015). Other studies with CSF1R inhibitors tested in combination with

nursing or immunotherapy include the application of BLZ 945 and PRD001 (an anti-programmed cell death-1 antibody) in solid tumors, and PLX3397 combined with ozolamide and radiotherapy (Sevenich, 2018).

In the steady state, A20 has a key role in controlling the activation of microglia, including preventing the activation of NLRP3 inflammatory bodies. Targeted expression of A20 in microglia to inhibit their activation might be an important approach in against diseases (Voet et al., 2018). The molecular and functional heterogeneity of parenchymal brain macrophages highlight potential clinical implications for hematopoietic stem cell transplantation aimed to ameliorate lysosomal storage disorders, microgliopathies, or general monogenic immune deficiencies (Shemer et al., 2018). The transcription factor PU.1 plays a key role in regulating several microglial functions. PU.1 and other microglia-specific transcriptional factors should be further studied to determine possible therapeutic possibilities for neurological disorders (Yeh and Ikezu, 2019).

The receptor-mediated serine/threonine-protein kinase 1 is involved in the conversion of microglia to a disease-associated phenotype. A non-cell-death pathogenesis activates a disease-associated microglia phenotype, including the induction of an inflammatory response, a reduction in phagocytosis, and receptor-mediated serine/threonine-protein kinase 1-evoked transcription, which contributes to the etiology of AD (Ofengeim et al., 2017; Mullard, 2018).

The genetic deletion of chemokine receptor CX3CR1 and passive anti-A β immunization in mice to increase microglial encapsulation of plaques has been reported (Condello et al., 2015). Constitutive BRAFVE expression in microglia promotes neurodegeneration. A BRAF inhibitor prevents the phosphorylation of extracellularly regulated protein kinases and reduces microglia accumulation and astrogliosis, phagocytosis, demyelination, neuronal loss, and APP deposits (Mass et al., 2017).

The activation of APOE is dependent on TREM2, and the TREM2-APOE pathway regulates microglia phenotypes in neurodegeneration to restore homeostatic microglia (Krasemann et al., 2017; Pimenova et al., 2017). Microglia play an important role in stimulating synapse formation and circuit maturation. Knockout mice lacking complement factors display cortical excitatory hyperconnectivity, revealing a key role for microglia in the removal of excess synapses in the neocortex (Chu et al., 2010; Parkhurst et al., 2013; Weinhard et al., 2018).

Deletion of the C1qa gene dramatically decreases synaptic shearing by progranulin knockout (GRN^{-/-}) microglia, alleviates behavioral phenotypes, and prevents neurodegeneration and

premature mortality of GRN^{-/-} mice. GRN has been shown to suppress aberrant microglia activation during aging (Lui et al., 2016).

The microRNA, miR-124, contributes to inactive macrophages and reduces the activation of myelin-specific T cells, resulting in marked inhibition of EAE. These results show that miR-124 acts both as a vital regulator of microglia quiescence and as a potential modulator of monocyte and macrophage activation (Ponomarev et al., 2011). Clearly, modification of the glial inflammatory response also has a primary role in estrogen-mediated neuroprotection (Suzuki et al., 2007).

Microglial activation and dysfunction are involved in most diseases and injuries of the CNS, so it is necessary to find therapeutic approaches targeting microglia (Prinz and Priller, 2014; Crotti and Ransohoff, 2016; Colonna and Butovsky, 2017; Wolf et al., 2017).

Conclusions and Outlook

The vital role of microglia in many neurodegenerative diseases is becoming increasingly evident. Microglia are affected by environmental stimuli as well as neurodegeneration. Microglia originate from the yolk sac and differentiate from myeloid cells during embryogenesis. However, there is some disagreement regarding postpartum repopulation of microglia. Myeloid lineage cells and nestin-positive progenitor cells used to be considered the source of repopulated microglia (Ajami et al., 2007; Ginhoux et al., 2010; Schulz et al., 2012; Elmore et al., 2014; Colonna and Butovsky, 2017). The origin, characteristics, and mechanisms involved in microglia repopulation may be clarified in the future through transcriptome, lineage, and single-cell analysis, as well as genome-editing and other techniques.

Additionally, it is uncertain whether the results of experiments in mice can be applied to humans. Many proteins are expressed to different degrees in mouse and human microglia and whether human microglia and microglia respond in the same way to drugs remains to be unequivocally established (Smith and Dragunow, 2014). In the future, we expect that more precisely targeted therapeutic approaches will be developed to eliminate the adverse effects and to potentiate the beneficial effects of microglia.

Finally, organoid techniques may be a good approach to solve the problems listed above. Organoids are three-dimensional *in vitro* tissue cultures derived from self-organizing stem cells that have become very popular in tumor research and have been proposed for use in new models of aging (Hu et al., 2018; Jin et al., 2018). They can be used for disease modeling and can contribute to the development of precision medicine (Jin et al., 2018). Thus, we believe that these techniques may serve as new models to investigate microglia functions.

Microglia have diverse effects on CNS homeostasis. Appropriately activated microglia can help patients recover from illness or slow down the progression of a neurodegenerative disease. They also have protective effects on the brain through their immune defense functions including the maintenance of homeostasis, phagocytosis, and synaptic pruning. However, over-activated microglia may hasten the disease process and appropriate inhibition of microglial activation can be helpful. Several studies have shown that the activation of microglia is controllable, which provides patients with diseases of the CNS with hope for better treatment, although therapeutic strategies targeting microglia for CNS disorders have yet to be developed. In addition, microglia act as effectors for many neurodegenerative disorders, but whether they can be used for screening and diagnosis remains to be determined.

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