Published in final edited form as:

Annu Rev Immunol. 2017 April 26; 35: 441–468. doi:10.1146/annurev-immunol-051116-052358.

Microglia Function in the Central Nervous System During Health and Neurodegeneration

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Abstract

Microglia are resident cells of the brain that regulate brain development, maintenance of neuronal networks, and injury repair. Microglia serve as brain macrophages but are distinct from other tissue macrophages owing to their unique homeostatic phenotype and tight regulation by the central nervous system (CNS) microenvironment. They are responsible for the elimination of microbes, dead cells, redundant synapses, protein aggregates, and other particulate and soluble antigens that may endanger the CNS. Furthermore, as the primary source of proinflammatory cytokines, microglia are pivotal mediators of neuroinflammation and can induce or modulate a broad spectrum of cellular responses. Alterations in microglia functionality are implicated in brain development and aging, as well as in neurodegeneration. Recent observations about microglia ontogeny combined with extensive gene expression profiling and novel tools to study microglia biology have allowed us to characterize the spectrum of microglial phenotypes during development, homeostasis, and disease. In this article, we review recent advances in our understanding of the biology of microglia, their contribution to homeostasis, and their involvement in neurodegeneration. Moreover, we highlight the complexity of targeting microglia for therapeutic intervention in neurodegenerative diseases.

Keywords

microglia; phenotypes; receptors; regulation; homeostasis; neurodegeneration

INTRODUCTION: MICROGLIA AS DISEASE MODIFIERS IN NEURODEGENERATION

Microglia account for approximately 10% of cells and are the most abundant mononuclear phagocytes in the central nervous system (CNS). During development, microglia help shape neural circuits by modulating the strength of synaptic transmissions and sculpting neuronal synapses. During CNS injury, microglia are responsible for phagocytosis and elimination of microbes, dead cells, and protein aggregates, as well as other particulate and soluble

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antigens that may endanger the CNS. Moreover, microglia secrete many soluble factors, such as chemoattractants, cytokines, and neurotropic factors that contribute to various aspects of immune responses and tissue repair in the CNS. When microglial functions are impaired, the CNS can become fertile ground for acute or chronic pathologic processes that may have irreparable consequences. Emerging genetic and functional evidence implicates microglia in the pathogenesis of neurodegenerative diseases. However, whether microglia have beneficial or protective functions is a matter of debate; their role may be context dependent. Here, we review the functions of microglia in homeostatic conditions, their involvement in neurodegeneration, and their suitability as therapeutic targets.

BIOLOGY OF MICROGLIA

Development of CNS Mononuclear Phagocytes

The CNS is equipped with a diffuse and efficient network of mononuclear phagocytes. Microglia are the most abundant cells of this network. Fate-mapping studies have demonstrated that microglia originate from early myeloid progenitors in the embryonic yolk sac that migrate into the developing neural tube, where they proliferate, colonize the entire parenchyma, and subsist throughout the life span of the organism by slow division (1, 2). Bone marrow–derived myeloid precursors do not contribute to the microglia pool.

Macrophages of the meninges, choroid plexus, and perivascular space are also mononuclear phagocytes within the CNS. Until recently, these mononuclear cells were thought to derive from the bone marrow and have a quite rapid turnover. However, a recent study showed that perivascular and meningeal macrophages are, in fact, long-lived macrophages that derive from primitive progenitors (3). Only choroid plexus macrophages have a dual origin and turn over more rapidly. During inflammation, the CNS becomes infiltrated with blood-derived monocytes, which are derived from the bone marrow. The disparate origins of microglia and other CNS mononuclear phagocytes have been extensively reviewed elsewhere (4).

Microglia development and maintenance depend on constant engagement of colony stimulating factor 1 receptor (CSF1R), a receptor tyrosine kinase that transmits intracellular signals, such as activation of protein kinase B (also known as AKT) and extracellular signal-regulated kinases (ERK), that promote microglia proliferation and survival (5). Genetic defects in CSF1R and pharmacological blockade of CSF1R drastically reduce microglia numbers (5, 6). CSF1R binds two ligands, CSF1 and IL-34 (7–10). IL-34 is secreted by neurons throughout the brain with the exception of the cerebellum; CSF1 is secreted by neurons, as well as glial cells, including microglia. Despite substantial differences in the primary amino acid sequences, IL-34 and CSF1 have very similar conformations and bind to CSF1R at largely overlapping sites (11). Thus, IL-34 and CSF1 are partially redundant, such that genetic defects in either IL-34 or CSF1 result in a partial reduction of microglial numbers.

Resting and Activated Microglia Are Highly Dynamic

Microglia appear quite dynamic in two-photon imaging studies (12–14). In the steady state, microglia are ramified cells with multiple branches and processes, which extend from the

somata and terminate with bulbous endings. These processes are in continuous motion, protruding and retracting to cover long distances and survey large areas of the brain. Microglia processes contact neurons, astrocytes, and blood vessels and constantly monitor the functional state of synapses. Laser-induced microlesions stimulate microglia in the immediate vicinity, which direct their processes toward the site of injury to form ball-and-chain structures that phagocytose damaged tissue. Larger injuries or inflammatory stimuli induce microglia to morph from a ramified to an amoeboid shape. Cell bodies enlarge while cell processes become shortened and cover more limited areas. Amoeboid morphology reflects a highly activated state associated with phagocytosis and proinflammatory function. Bipolar rod-shaped microglia that form strings of cells aligned end-to-end at the damaged site have also been observed after brain injury (15). Rod-shaped microglia colocalize with neurons and axons but not with other glia after brain injury. Thus, the shape and movement of microglia reflect their responses to a broad variety of stimuli ranging from normal neuronal activity to physical, chemical, and microbial insults and aggravated neuronal hyperactivity.

Microglia Express a Wide Range of Immune Receptors

Microglia express many pattern-recognition receptors (PRRs) that detect pathogen-associated molecular patterns (PAMPs) or tissue damage–associated molecular patterns (DAMPs).Microglial PRRs include Toll-like receptors (TLRs), such as TLR4 and TLR1/2, and their coreceptors, such as CD14 (16, 17); NOD-like receptors (NLRs), such as the NLRP3 inflammasome (17); receptors for nucleic acids (18); and C-type lectin receptors (CLRs), such as CLEC7A (19). Microglia also express several families of receptors that enable phagocytosis or endocytosis of apoptotic cells, protein aggregates, and lipoprotein particles. These receptors include scavenger receptors, such as CD36, SR1, and MARCO (20); LDL receptor family members, such as LDLR, ApoER2, and VLDL (21); and three receptor tyrosine kinases, Tyro3, Axl, and Mertk (TAM) (22). Mertk and Axl are expressed in resting and activated microglia, respectively (23). TAM receptors bind the soluble adapter protein growth arrest–specific 6 (GAS6) and protein-S, which opsonize apoptotic cells exposing phosphatidylserine. Microglia also capture and endocytose immune complexes and complement-opsonized protein complexes through Fc receptors and complement receptors.

Microglia express chemokine receptors, such as CX3CR1 and CXCR4, as well as integrins, such as CD11b and CD11c, that control migration and positioning of microglia within the CNS and enhance their capacity to bind target cells to be phagocytosed and eliminated. CX3CR1 is fairly specific for all microglia (24, 25); CD11b is constitutively expressed while CD11c is upregulated in activated microglia. Additionally, microglia express immune receptors that regulate the amplitude and duration of activation. These receptors include immunoglobulin superfamily (Ig-SF) molecules that deliver either activating or inhibitory signals through protein tyrosine kinase and protein tyrosine phosphatase pathways, respectively. Among the most studied, TREM2 (triggering receptor expressed on myeloid cells 2) is an activating receptor that binds phospholipids (26); CD33 binds sialic acids and delivers inhibitory signals in human microglia (27); CD200R1 and SIRPA bind CD200 and CD47, respectively, and deliver inhibitory signals (28, 29). Regulatory receptors poorly studied in microglia include tumor necrosis factor receptor (TNFR) family members that

bind cognate TNF family members on neurons and glial cells, as well as signaling lymphocytic activation molecule (SLAM) family members that mediate homotypic adhesion. Microglia activity is also regulated by receptors for proinflammatory and anti-inflammatory cytokines that are produced in the CNS by glial cells or reach the CNS from the circulation, such as IFN-α/β (30), IFN-γ, TNF-α, IL-1β, IL-10, and TGF-β.

Microglia Express Receptors for Neurotransmitters

In addition to immune receptors, microglia express multiple receptors for neurotransmitters and neuropeptides released by neurons that promote neural-glia communications (31). These receptors allow microglia to monitor neuronal activity by guiding microglia processes toward neuronal synapses in order to influence synaptic plasticity and sculpt dendritic spine density. Moreover, neurotransmitter receptors enable detection and elimination of damaged neurons and promote secretion of neurotrophic factors for neuronal regeneration. Finally, neurotransmitter receptors can either augment or moderate the release of inflammatory cytokines. Microglia express glutamate ionotropic receptors, such as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) receptors, as well as glutamate metabotropic receptors, such as mGlutR2. The AMPA receptor inhibits TNF-α release, whereas mGlutR2 promotes TNF-α release and neurotoxicity (32, 33). Microglia express various purinergic receptors for ATP, such as P2Y12 and P2X7. P2Y12 is active in resting microglia but downregulated upon activation; it drives migration and phagocytosis. P2X7 promotes microglial release of TNF-α in response to high ATP concentrations. Adenosine receptors, such as A2a, promote secretion of inflammatory mediators and phagocytosis. Receptors for gamma-aminobutyric acid (GABA), adrenergic, dopaminergic, and cholinergic receptors modulate microglial inflammatory responses. Receptors for neuropeptides, such as substance P and bradykinin, facilitate the transition of microglia into an inflammatory state, thereby amplifying inflammation.

Functional States of Microglia: Beyond the M1/M2 Paradigm

Microglia activation is often categorized as either classical (M1) or alternative (M2) (34), following the paradigm used for macrophages (35). M1 activation is a proinflammatory and neurotoxic state typically induced by simultaneous triggering of TLR and IFN-γ signaling pathways. M1 microglia produce proinflammatory cytokines and chemokines, such as TNF-α, IL-6, IL-1β, IL-12, and CCL2. M1 microglia also express the NADPH oxidase, which generates superoxide and reactive oxygen species (ROS), as well as inducible nitric oxidase, which converts arginase into nitric oxide (NO). NO increases the toxic effect of glutamate, thereby potentiating NMDA receptor–mediated neurotoxicity. Another important inflammatory mediator produced by M1 microglia is matrix metallopeptidase 12 (MMP12). M1 microglia also express high amounts of MHC class II, costimulatory molecules, Fc receptors, and integrins. Ultimately, M1 microglia induce inflammation and neurotoxicity.

M2 activation describes the anti-inflammatory and healing activities of microglia. It can be induced by IL-4, IL-13, IL-10, ligation of Fc receptors by immunocomplexes, and detection of apoptotic cells, as well as activation of the transcription factors peroxisome proliferator-activated receptor gamma (PPARγ), liver X receptor (LXR), and retinoic acid receptor (RXR) by fatty acids, oxysterols, and 9-*cis*-retinoic acid, respectively (16). M2 activation

promotes the release of anti-inflammatory cytokines, such as IL-10 and TGF-β, and induces arginase 1, which promotes the conversion of arginine into polyamines. M2 microglia secrete growth factors such as insulin-like growth factor I (IGF-I), fibroblast growth factor (FGF), and CSF1, as well as neurotrophic factors such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophins (NT) 4/5, and glial cell–derived neurotrophic factor (GDNF). Neurotrophic factors engage a family of receptor tyrosine kinases known as Trk receptors, which regulate synaptic strength and plasticity. M2 microglia also release the prosurvival factor progranulin.

Although the M1 and M2 categories have been helpful for conceptualizing microglia activities in vitro, it is increasingly accepted that the M1/M2 paradigm is inadequate to describe microglia and macrophage activation in vivo, as microglia rarely display a significant bias toward either the M1 or M2 phenotype. In fact, transcriptome studies show that microglia activation is varied and context dependent. During normal CNS function, microglia have a “resting,” or homeostatic, transcriptome profile that reflects a surveilling activity (36–41) (Figure 1). In models of neurodegeneration, microglia express both neurotoxic and neuroprotective factors; genes involved in oxidative phosphorylation; and lysosome, ribosome, and spliceosome factors involved in responses to misfolded proteins, stress, and neuronal death or injury (36, 42) (Figure 1). Ongoing studies are likely to define multiple phenotypes of microglia associated with aging, different neuropathological conditions and stages of disease.

Transcriptome and Regulomes Underpinning Programs Unique to Microglia

Since microglia derive from a primitive yolk sac progenitor and develop within the unique CNS environment, it is not surprising that phenotypic and functional features of microglia reflect an idiosyncratic program of gene expression. Analysis of the microglia transcriptome in comparison with that of other tissue macrophages has revealed a strong influence of TGF-β signaling, which culminates in the activation of SMAD proteins that induce transcription of specific target genes, including the purinergic receptor P2Y12 (37, 38, 43).

Recent analysis of microglia enhancers has provided further insight into the molecular mechanisms underpinning distinctive microglia gene expression programs (38, 44). Enhancers active in microglia contained DNA sequences bound to the macrophage lineage-determining factor PU.1. Moreover, these DNA sequences also bound secondary transcription factors, which collaborate with PU.1 in activating transcription of microglia-specific genes. Secondary transcription factors included SMAD proteins that are induced by TGF-β in the CNS microenvironment.

In addition to identifying circuitries that regulate the transcriptional programs of microglia, these studies facilitated the identification of markers selectively expressed on microglia that might be used to distinguish them from bone marrow–derived macrophage and monocytic subsets. These markers include P2Y12, TMEM119, CX3CR1, Siglec-H, and olfactomedin-like 3 (37–40, 42). Though helpful, some of these markers may be modulated by activation and/or expressed in other cell types outside of the CNS; therefore, they may not be suitable for unequivocally identifying or targeting tissue-resident microglia.

Recent transcriptional analysis of microglia from different regions of the healthy adult brain has revealed remarkable regional diversity of microglia beyond a core transcriptome (45). Microglia in mouse cerebellum and hippocampus predominantly expressed immunoregulatory (and bioenergetics)-related transcripts compared to other brain regions, at least in young adult mice. Cerebellar microglia displayed a more immune-vigilant state. Moreover, microglia heterogeneity was differentially sensitive to aging: Old adult mice showed increased distinction of cerebellar microglia, but reduced distinction of hippocampal microglia. Understanding the causes and physiological impact of spatiotemporal diversity of microglia remains an important goal.

The Microbiota Affects Microglia

Emerging evidence indicates that themicrobiota affects brain development, neurochemistry, physiology, and behavior. Studies in germfree mice have shown that themicrobiota affects neurogenesis in certain areas of the brain, myelination, and exploratory behavior (46–48). Studies in humans have shown an association between irritable bowel syndrome and lingering inflammation with depression (49). The microbiota can influence various aspects of CNS biology through multiple mechanisms, including alteration of neurotransmitters levels (50) and the blood-brain barrier (BBB) (51). A recent study showed that commensal bacteria influence microglial function (52). In germfree mice, microglia were immature and had impaired immune responses. Similarly, eradication of microbiota with antibiotics affected microglia function. Partial restoration of the microbiota failed to rescue microglia function, whereas reconstitution of microbiota complexity restored microglial function. The microbiota acted, at least in part, by generating short-chain fatty acids, which are produced through the catabolism of complex carbohydrates (52). Indeed, microglia defects similar to those observed in germfree mice were observed in mice lacking the short-chain fatty acid receptor FFAR2. Thus, the microbiota is essential for microglia maturation and function. Future studies will be important to determine whether probiotics can be exploited to improve microglial function and, ultimately, alleviate CNS disorders.

Microglia and Gender

Studies in mice have shown that sex is associated with considerable differences in microglia during and after development (53, 54). Male mice have more microglia within the cortex, hippocampus, and amygdala in early postnatal development than do female mice. Thus, in the event of a neonatal infection, male mice may produce more inflammatory cytokines that can cause long-term deficits in cognition and memory in adulthood. More dense microglia colonization in the developing male cortex and hippocampus may be in part related to increased expression of the chemokines CCL20 and CCL4, which can drive microglia colonization. In adulthood, however, female mice have significantly more microglia with thicker, longer branches in the hippocampus, cortex, and amygdala than do male mice.

Steroid sex hormones, particularly estradiol, affect microglia in various brain areas, including the preoptic area involved in behaviors that reflect differences between males and females (55). Estradiol also reduces microglia inflammatory potential (53). Although some reports have revealed differences in the transcriptome profiles of microglia from male and female mice, it is unclear whether these differences are related to the influence of steroid sex

hormones or differential doses of immune genes encoded on the sex chromosomes. Future studies are also required to investigate whether the differences between male and female microglia in mice are replicated in humans.

Microglia and Aging

Aging affects microglia in several ways. The relative frequency of microglia increases with aging, which reflects the ability of microglia to persist throughout life via constant slow division, while other glial cells and neurons decrease in number (56, 57). However, aging microglia display signs of dystrophy, including reduced ramification and short, tortuous, swollen processes (58). The ability of microglia to survey the brain and respond to insults also declines with aging (59). Increased myelin fragmentation with age leads to the formation of insoluble, lipofuscin-like lysosomal inclusions in microglia, which contribute to microglial senescence and dysfunction (60). Microglia aging is paralleled by reduced expression of M1 markers, while expression of M2 markers and genes involved in neuroprotection are upregulated, suggesting that aging microglia shifts toward neuroprotective phenotype (Figure 1) (40).

MICROGLIA CONTRIBUTE TO THE FUNCTION OF A HEALTHY CNS

Microglia Are Involved in Neurogenesis

Microglia are necessary for the proper assembly of complex neuronal networks. During prenatal development, microglia are the first glial cells to migrate into the CNS. At this stage, microglia are located at the crossroads of vital neuronal migratory routes and axonal tract pathways, where they act as guidepost cells, guiding neurons and axons in forming prenatal circuits (61). In the adult brain, microglia are integral components in the neurogenic niches of the subventricular zone (SVZ) and subgranular zone (SGZ) of the dentate gyrus, producing neurons that integrate into the olfactory bulb and hippocampus, respectively. Signals that attract microglia to neurogenic niches include CXCL12, which activates microglial CXCR4 (62) and, in zebrafish, ATP, which is released by apoptotic neurons and activates purinergic receptors on microglia (63). Microglia phagocytose apoptotic neural stem cells generated during neurogenesis. This process is mediated by TAM receptors that engulf apoptotic cells opsonized by Gas6 and protein S (23) (Figure 2). Microglia also eliminate excess newborn progenitor cells in animal models of temporal lobe epilepsy, in which status epilepticus acutely enhances neurogenesis (64). During aging, progressive activation and proinflammatory cytokine secretion by microglia creates an antineurogenic microenvironment that attenuates neural stem cell proliferation (65).

Microglia Control Synaptic Density and Connectivity

During postnatal development, microglia eliminate redundant neurons that do not establish functional circuits. Importantly, microglia shape neuronal synapses by phagocytosing dendritic spines that are not receiving inputs from synaptic contacts (66, 67). Synaptic stripping is achieved through several mechanisms. Two proteins of the complement cascade, C1q and C3, tag unused synapses for microglia recognition via complement receptor 3 (CR3; a heterodimer of CD11b and CD18), or for direct lysis via the complement cascade (68, 69) (Figure 2). Mice lacking CR3 or C3 cannot effectively prune retinogeniculate

synapses, impairing the segregation of axonal projections of retinal ganglion cells into the lateral geniculate nucleus. Astrocytes contribute to synaptic pruning by secreting TGF-β, which induces the expression of C1q and C3 in retinal ganglion cells (70).

Microglia also mediate synaptic pruning via CX3CR1, which interacts with CX3CL1, a transmembrane glycoprotein expressed on the neuronal surface that is also released as a soluble molecule after proteolytic cleavage (Figure 2). Lack of CX3CR1-CX3CL1 interactions curtails the engulfment of PSD95-immunoreactive postsynaptic densities and ultimately impairs connectivity and afferent synaptic inputs in the mouse hippocampus (71). CX3CR1-CX3CL1 interactions are also required for functional maturation of thalamocortical synapses (72).

Microglia-Derived Cytokines Regulate Synaptic Plasticity

Microglia impact synapse strength and plasticity through release of proinflammatory cytokines, ROS, and NO as well as neurotrophic factors (73). Changes in synapse strength can be antecedent to microglia-mediated synaptic pruning. One type of synaptic plasticity includes long-term potentiation (LTP) and long-term depression (LTD), which promote rapid adjustments in the strength of individual synapses in response to specific temporal patterns of synaptic activity (74). Microglia enhance glutamate-induced LTD (75). When neurons release glutamate and activate microglial NMDA receptors, microglia turn on NADPH oxidase and release ROS, which induces serine/threonine protein phosphatase 2A (PP2A) in neurons. PP2A promotes the internalization of AMPA receptors, thereby weakening AMPA receptor–mediated synaptic transmission (Figure 2). Similarly, hypoxia and inflammatory stimuli, such as LPS, act synergistically via microglial CR3 to induce the ROS-PP2A-AMPA receptor endocytosis cascade that depresses synaptic efficacy (76). A decrease in synapse strength could be antecedent to microglia-mediated synaptic pruning, which has a longer onset than does LTD.

A crucial impact of microglia on learning-related synapse plasticity was recently found in mice engineered to inducibly express diphtheria toxin (DT) receptor in microglia (77). Administration of DT and subsequent depletion of microglia in these mice caused a significant reduction in motor-learning-dependent glutamatergic excitatory synapses and impaired performance in multiple learning tasks. In this model, microglia-induced synaptic plasticity depended on BDNF secretion, which activated neuronal Trk, a key mediator of synaptic plasticity (Figure 2). Genetic targeting of BDNF in microglia or its cognate receptor Trk recapitulated the effects of microglia depletion. Activation of microglia and secretion of IL-1β disrupts the BDNF signaling cascade that promotes the formation of dendritic spines, which is essential for the LTP-type synaptic plasticity (78, 79).

Microglia-secreted BDNF also impacts synapse activity during neuropathic pain transmission. After nerve injury, ATP-stimulated microglia release BDNF, which activates Trk in spinal neurons; this leads to downregulation of the cation-chloride cotransporter KCC2 and disruption of chloride homeostasis (80). As a result, GABA- and glycine receptor–mediated inhibitory signals are converted into excitatory signals, thereby inducing neuron hyperexcitability and neuropathic pain.

Microglia also influence another type of synaptic plasticity known as synaptic scaling, which promotes even adjustments in the strength of all synapses on a neuron in response to prolonged changes in the cell's electrical activity (81). Microglia-derived cytokines regulate synaptic scaling indirectly through astrocytes (82). Specifically, microglia secrete TNF-α, which activates TNFRI on astrocytes; astrocytes then release ATP and glutamate, which activate presynaptic metabotropic receptors on neurons and elevate synaptic current (Figure 2).

Microglia Prevent Excitotoxicity

Excitotoxicity occurs when neurotransmitters are released in excess, leading to sustained depolarization, neurotoxicity, and axonal swelling. CNS damage can instigate excessive release of glutamate, which activates NMDA receptors and causes inappropriate neuronal excitation. Excitotoxicity also triggers the release of ATP (83). Recent studies of organotypic hippocampal slice cultures have shown that microglia are crucial for protection against NMDA-induced toxicity (84). ATP released by damaged neurons activates the microglia receptor P2X7, inducing secretion of TNF-α, which tempers NMDA-induced toxicity. Engagement of purinergic and glutamate receptors on microglia also promotes the outgrowth of microglial processes, which migrate to and wrap around swollen axons, induce membrane repolarization, and prevent excitotoxicity (85).

Cross Talk Between Microglia and Astrocytes

Astrocytes contribute to the maintenance of neuronal functions through multiple mechanisms (86). Astrocytes capture glutamate, which prevents its accumulation in the synapses and thereby protects synaptic activity from glutamate toxicity (87). Moreover, astrocytes act as positive modulators of synaptic inhibition: They facilitate the action of endozepines on GABAergic transmission in the thalamic reticular nucleus by increasing the concentration of diazepam-binding inhibitor family peptides (88).

Astrocytes send multiple signals to microglia. Following laser-induced microinjury, astrocytes direct microglia processes to the site of injury by releasing ATP, which activates microglial P2Y12 (13). Astrocytes attenuate microglial inflammatory responses through the release of GABA, which curtails microglia activation (89), and by triggering the microglial transcription factor Nrf2, which induces the antioxidant molecule heme oxygenase 1 (90). Reciprocally, microglia deliver various signals to astrocytes. Microglial IL-1β induces astrocytes to express tissue inhibitor of matrix metalloproteinases 1 (TIMP-1), a regulator of proteolysis (91). In the mouse mutant model of demyelination twitcher, microglia produce prostaglandin D2, which acts on the DP1 receptor on astrocytes, thereby inducing astrogliosis and demyelination (92). Astrocytes and microglia coordinately regulate neuronal synaptic pruning. Astrocytes produce TGF-β, which induces neurons to express C1q; in turn, C1q tags the synapses for microglia pruning. Astrocytes and microglia also cooperate to eliminate apoptotic cells. Astrocytes release milk fat globule protein epidermal growth factor 8 (MFGE8), which binds phosphatidylserine on apoptotic cells and tags them for elimination by microglial phagocytosis (93).

Do Microglia Function as Antigen-Presenting Cells?

Microglia express phagocytic and endocytic receptors that enable them to capture antigens. Microglia also have the lysosomal machinery required for processing antigens and express MHC class II and costimulatory molecules necessary for presentation of antigenic peptides. Thus, microglia can function as antigen-presenting cells (APCs). Macrophages and dendritic cells (DCs) in the meninges, choroid plexus, and perivascular spaces may also function as APCs. However, given the rarity of naive T cells in the CNS during homeostasis, it is unlikely that microglia or other mononuclear phagocytes prime naive T cells in the brain. Rather, microglia may stimulate memory T cells that reach the CNS during inflammation. The impact of antigen-presenting function of microglia in healthy brain remains unknown.

MICROGLIA IN DEGENERATIVE DISEASES

The Prion Paradigm

Prion diseases include spongiform encephalopathies caused by progressive accumulation of the prion protein PrP^{Sc}, a β sheet–rich higher-order aggregate of the membrane protein PrP^{C} (94). PrP^{Sc} aggregates generate seeds that promote further misfolding and aggregation of prion proteins. Moreover, PrP^{Sc} can transmit disease to new hosts by acting as exogenous seeds that cause protein misfolding, aggregation, and ultimately disease after a long incubation period in the absence of microbial agents, viruses, or inflammation.

The prion paradigm has been expanded to many neurodegenerative diseases, including Alzheimer disease (AD), Parkinson disease (PD), amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and others (94). These diseases develop from seeded aggregation of endogenous proteins rather than exogenous seeds. The nature of the seeds varies from disease to disease, but the pathogenic cascade is similar: Endogenous proteins generated by cells in the brain are misfolded and aggregate into small oligomers that assemble into fibrils, which self-propagate and aggregate into masses that form intracellular inclusions or extracellular masses.

Neurodegenerative diseases hinge not only on misfolding of endogenous proteins, but also on protein clearance. Imbalance between generation and disposal of misfolded proteins leads to irreversible autopropagation. Moreover, progression of neurodegeneration is modified by cellular responses to biochemical alterations (95). Neurons may transmit seeds by transporting them along defined anatomical tracts. Neurons and glial cells may also propagate seeds through the release of extracellular vesicles (96, 97). Although these extracellular vesicles contain proteins, mRNAs, and microRNAs that support neuronal function in the steady state, in neurodegenerative diseases they may contain misfolded proteins, contributing to disease dissemination. Microglia can alter the course of neurodegeneration by clearing misfolded proteins by phagocytosis or, conversely, by releasing inflammatory mediators that promote protein aggregation and neuron damage (Figure 3). In the following paragraphs we highlight beneficial and detrimental effects of microglia in various neurodegenerative diseases.

Microglia in Prion Diseases

Prion diseases are associated with activation of microglia and astrocytes, which contribute to PrP^{Sc} clearance. Accordingly, PrP^{Sc} deposits and infectivity titers are elevated in cerebellar slices from transgenic mice that express the suicide gene HSV-TK in microglia (CD11b-HSV-TK mice) and have been treated with intracranial ganciclovir to delete microglia (98). Additionally, increased PrP^{Sc} deposition and accelerated prion disease progression are evident in IL-34-deficient mice, which have relatively few microglia (98). Microglia clearance of PrP^{Sc} requires the cooperation of astrocytes, which release MFGE8 that tags PrP^{Sc}-containing apoptotic cells for phagocytosis (93). Lack of MFGE8 led to less efficient clearance of cerebellar apoptotic bodies and increased prion titers, which accelerated disease in prion-infected mice. Although microglia and other CNS macrophages phagocytose PrP^{Sc} aggregates, this activity may be insufficient in vivo (99). In the final stages of the disease, the inability of microglia to effectively degrade prions may paradoxically facilitate spreading of the disease through migration of microglia.

Microglia and Alzheimer Disease

AD is the most common form of senile dementia, characterized by lesions consisting of extracellular masses of amyloid β (Aβ) peptides and intracellular bundles of fibrillar Tau protein. Accumulation of Aβ plaques and Tau tangles depends on prion-like seeding of Aβ and hyperphosphorylated Tau as well as defective clearance. Initial genetic studies demonstrated that mutations in amyloid precursor protein (APP) and presenilin components of γ-secretase complex lead to generation of the $A\beta_{1–42}$ peptide that is prone to misfolded aggregation (100) (Figure 4). These mutations explain hereditary AD but not sporadic AD, which accounts for the vast majority of cases.

Subsequent studies in sporadic AD revealed that a polymorphism of apolipoprotein E (ApoE), the ApoE4 allele, is strongly associated with an increased risk of AD, whereas the ApoE2 allele is associated with protection (101). ApoE is produced by astrocytes and, to a minor extent, microglia, under the control of nuclear hormone receptors such as PPARγ and LXR, which form heterodimers with RXR. Although ApoE is likely to influence AD through multiple mechanisms, an important effect is enhancement of phagocytosis of Aβ aggregates by microglia while tempering their inflammatory responses (102) (Figure 4). Accordingly, PPARγ and RXR agonists, such as pioglitazone and bexarotene, shrank the Aβ plaque burden, reversed neuropathological changes, and restored cognitive functions in an ApoE- and microglia-dependent fashion (103, 104).

While microglial phagocytosis of Aβ may be beneficial, chronic stimulation of microglia by Aβ may be deleterious and cause prolonged inflammation (Figure 3) (17). Microglia express multiple receptors that can bind Aβ and trigger inflammation, such as CD36 (105), TLR2, TLR4, TLR6 (17), and NLRP3 (106) (Figure 4). Moreover, microglia can be stimulated by DAMPs, such as ATP and DNA. Engagement of these receptors induces release of TNF-α and IL-1β, which mediate neuroinflammation and neurotoxicity and further contribute to Aβ aggregation. Lack of NLRP3, TLR, and IL-1β signaling in transgenic mouse models of AD that express human APP and presenilin 1 mutations, attenuates Aβ deposition and prevents cognitive defects (17).

Regulatory Immune Receptors in Alzheimer Disease

Recent large-scale genome-wide association studies of sporadic forms of AD have provided further evidence that microglia dysfunction plays a crucial role in AD progression. These studies have demonstrated that an increased risk for developing AD is significantly associated with rare variants of innate immune receptors expressed in microglia, including TREM2 (107, 108), CD33 (109), and complement receptor 1 (CR1) (110) (Figure 4).

TREM2 is transmembrane glycoprotein expressed in myeloid cells that transmits intracellular signals through two associated transmembrane adapters, DAP12 (also known as Tyrobp) and DAP10 (Hcst) (26, 111, 112). DAP12 recruits the protein tyrosine kinase Syk, which activates multiple downstream signaling mediators, including PLC-γ, PI-3K, and ERK (111, 112). DAP10 directly recruits PI-3K (113). TREM2 binds polyanions, particularly phospholipids and sulfatides that may be exposed in the brain during Aβ accumulation due to neuronal cell apoptosis and myelin damage (114). TREM2 also binds to phospholipids exposed on apoptotic cells and lipoprotein particles, such as HDL and LDL, which may contain Aβ as a cargo (115, 116). TREM2 binds ApoE, but whether it binds lipidated ApoE (116) or ApoE protein remains unclear (117, 118). TREM2 promotes proliferation (119), survival (119), and phagocytosis of apoptotic cells (120–122). However, it curtails cytokine production in response to TLR ligands (122–124).

A rare arginine 47 histidine (R47H) variant of TREM2 is associated with an increased risk for AD (107, 108). This variant impairs binding of TREM2 to many phospholipid ligands (114, 125). Even more rare loss-of-function mutations of TREM2 or DAP12 cause a form of recessively inherited presenile dementia, called Nasu-Hakola disease (126, 127). These mutations result in complete lack of TREM2 or DAP12 expression. In mouse models of AD, complete TREM2 deficiency or TREM2 haploinsufficiency results in markedly less clustering of microglia around Aβ plaques (114, 128, 129). This weakening of microglial barriers around Aβ facilitates spreading and invasiveness of fibrillar amyloid at early stages of disease (130, 131) followed by later accumulation of Aβ during disease progression (114, 132).

Additional TREM2 variants reported to be associated with an increased risk for AD or other neurodegenerative diseases in various populations either debilitate binding to phospholipid ligands (114, 115) or impair TREM2 cell surface transport and expression (133). However, two TREM2 variants markedly enhance binding to phospholipids (115), suggesting that TREM2 signaling helps protect against AD but can cause harm in excess. Thus, proper TREM2 function is important to counteract disease progression. Recent studies have shown that TREM2 is cleaved from the microglial cell surface by proteases such as ADAM10 and ADAM17, generating a soluble form of TREM2 (133, 134). Whether cleavage regulates TREM2 expression and function and/or soluble TREM2 has its own function remains unclear. Regardless, cerebrospinal fluid levels of soluble TREM2 are a potential biomarker for microglia activity in early-stage AD and correlate with neuronal injury markers (135, 136).

CD33 is a cell surface molecule of the immunoglobulin superfamily that binds to sialic acids. In humans, CD33 transmits intracellular signals through cytoplasmic tyrosine-based

motifs that recruit protein tyrosine phosphatases, such as SHP1 and SHP2 (27). These phosphatases antagonize protein tyrosine kinases, thereby inhibiting multiple downstream signaling pathways. Thus, CD33 and TREM2 have opposite effects. Consistent with this, a CD33 variant associated with an increased risk for AD is expressed at relatively high levels, increasing CD33 inhibitory effects on myeloid functions, such as internalization of the $A\beta_{1–42}$ peptide (137). Conversely, another CD33 variant associated with protection from AD is expressed at relatively low levels, reducing CD33 inhibitory potential (138). Moreover, in mice, CD33 deficiency is associated with reduced levels of insoluble $A\beta_{1–42}$ in the brain as well as fewer amyloid plaques. Overall, these results are consistent with the conclusion that inappropriate inhibition of microglia is deleterious in AD.

Given the role of microglia and complement in synaptic pruning, the identification of CR1 variants associated with an increased risk for AD has suggested that inappropriate synapsis phagocytosis by microglia may also contribute to AD progression. Accordingly, in a mouse model of AD, complement was activated before plaque deposition and microglia were responsible for complement-mediated synaptic loss (139). Lack of C1q, C3, or CR3 curbed microglia activation and synaptic loss during amyloid plaque deposition. Inhibition of the complement pathway may be beneficial not only in Aβ but also in Tau pathology. Transgenic mice expressing a soluble variant of CR1-related gene/protein y (Crry), which inhibits the complement cascade, and P301L mutant Tau had fewer dystrophic neurons than did mice expressing mutant Tau alone. Moreover, intrahippocampal injection of an adeno-associated virus encoding mutant human P301L Tau caused more neurite dystrophy in mice lacking CD59a, an inhibitor of the terminal complement pathway, than in wild-type mice (140). In contrast to these studies, however, it was shown that mice lacking Crry had lower levels of Tau phosphorylation in brain lysates (141). Moreover, expression studies in human brain parenchyma found very modest correlations between CR1 expression and AD-associated CR1 genetic variants (142). Thus, the role of CR1 and complement in AD pathogenesis requires more investigations.

Alzheimer Disease and Macrophages

While much of the genetic and functional evidence indicates an important role for microglia as AD modifiers, several experimental studies have suggested a role for peripheral myeloid cells in Aβ phagocytosis. In mouse models of AD and cerebral amyloid angiopathy, blood monocytes and perivascular macrophages were shown to contribute to Aβ clearance in brain parenchyma and vessels (143–145). Lack of CCR2 reduced monocytes' ability to reach the brain and remove Aβ deposits (144). More recently, TREM2 was also proposed to facilitate brain monocytic infiltration in AD (129). In many of these experiments, the contribution of bone marrow–derived myeloid cells to Aβ clearance has been based on bone marrow transplantations between congenic mouse strains, which enable distinction between microglia of the recipient and bone marrow–derived monocytes of the donor. However, irradiation of the donor prior to transplantation may disturb the BBB, artificially facilitating brain engraftment of peripheral monocytes (146). Indeed, parabiosis studies using nonirradiated congenic marked mouse pairs have failed to detect significant infiltration of monocytes into the brain in AD models (130, 147). Therefore, the impact of peripheral monocytes as AD modifiers remains poorly understood.

Amyotrophic Lateral Sclerosis and Microglia

ALS is a neurodegenerative disease characterized by a progressive loss of motor neurons that in paralysis and death. ALS is one of a spectrum of related brain disorders that also includes FTD. Aggregation-prone proteins implicated in ALS/FTD include mutated superoxide dismutase (SOD1), C9orf72, Tau, TAR-DNA binding protein 43 (TDP-43), fused in sarcoma (FUS), and heterogeneous nuclear ribonucleoproteins (148). Studies in transgenic mice expressing the G93A SOD1 ($SOD1^{G93A}$) mutation indicate that SOD1 aggregation within motor neurons is the major determinant of cell loss at disease onset. In this early phase, microglia are not affected by SOD1 accumulation, and, in fact, they protect motor neurons. However, during disease progression, neuronal injury is aggravated by dysfunctional interactions between motor neurons and microglia. Misfolded SOD1 and other stress signals released by motor neurons activate microglia, which, in turn, release ROS and proinflammatory cytokines, further advancing motor neuron injury. Moreover, accumulation of mutant SOD1 in microglia may further amplify their proinflammatory and neurotoxic activity (149, 150). Corroborating this, restraining microglial activation by ablating NF-κB signaling rescued motor neurons from microglia-mediated death in vitro and extended survival of $SOD1^{G93A}$ mice (151). In addition to microglia, peripheral macrophages that infiltrate motor axons during disease progression may also be neurotoxic (152), although the relative contributions of microglia and bone marrow–derived macrophages to the pathogenesis of disease is a matter of debate (42).

The transcriptional profile of microglia isolated from $SOD1^{G93A}$ transgenic mice revealed expression of both neuroprotective factors, such as progranulin and IGF-I, and neurotoxic factors, like NADPH oxidase (42). Changes in the expression of lysosome, ribosome, spliceosome, and oxidative phosphorylation genes were also noted, as was enrichment for transcripts related to AD, including Tau, presenilin 2, and ApoE. Thus, microglia in ALS have a distinct gene-expression signature that does not fit the M1/M2 paradigm but reflects microglial response to protein aggregates, stress, and neuronal cell death and partially overlaps with that of other neurodegenerative diseases (Figure 1).

A role of mutated proteins in microglia has been observed also in other genetic types of ALS caused by expansions of a hexanucleotide repeat (GGGGCC) in the noncoding region of C9orf72. C9orf72 is required for the normal function of myeloid cells, and altered microglial function may contribute to neurodegeneration in carriers of C9orf72 expansion (153). Accordingly, lack of C9orf72 in mice led to lysosomal accumulation and altered immune responses in microglia and macrophages, along with neuroinflammation similar to that seen in human C9orf72 ALS.

While many studies indicate that excessive microglia activation is detrimental during disease progression, some microglial functions may be beneficial in ALS. It was shown that T cells that enter the spinal cord slow disease progression by directing microglia to express neurotrophic factors (154). Thus, microglia may stimulate the protective role of T cells. Moreover, the AD-associated R47H variant of TREM2, which impairs microglial activation, survival, and proliferation, was also found to be a risk factor for sporadic ALS (155). Finally, genetic studies have provided evidence that defects in autophagy predispose to ALS (156, 157). Rare variants of the kinase TBK1 that affect its capacity to bind and activate the

autophagy protein optineurin cause hereditary ALS. Since TBK1 is highly expressed in myeloid cells, it is likely that TBK1 mutations affect the ability of microglia to degrade misfolded protein aggregates. Thus, impairment of some microglial functions may be detrimental. Most likely, the impact of microglia on ALS pathogenesis depends on whether they act at early or late stages of the disease.

Microglia in Parkinson Disease

PD is a late-onset neurodegenerative disease characterized by both motor and nonmotor symptoms. It is associated with misfolded α-synuclein seeds that assemble into fibrillary inclusions, called Lewy bodies and Lewy neuritis, and by loss of dopamine neurons in the substantia nigra. In addition to directly inducing neuronal toxicity, oligomeric α-synuclein triggers microglial activation and proinflammatory responses, which can accelerate disease progression. α-Synuclein activates microglia through the TLR1/2 heterodimer (158). Moreover, α-synuclein can reach microglia through neuron-derived exosomes, which facilitate α-synuclein spreading and inflammatory responses. A recent study has indicated that the detrimental role of microglia in α-synuclein pathology may be mediated by the phagocytic receptor Axl (23). In transgenic mice overexpressing a mutated form of human α-synuclein (*SNCA*^{A53T}), which leads to a hereditary form of PD, spinal cords expressed high amounts of the microglial receptor Axl. Moreover, lack of Axl together with another TAM receptor, Mertk, partially delayed neurodegeneration and death. These results suggest that microglia may accelerate lethality by TAM-dependent phagocytosis of distressed spinal motor neurons.

In addition to α-synuclein, genetic studies have identified the leucine-rich repeat kinase 2 (*LRRK2*) as one of the most commonly mutated genes in both idiopathic and familial PD (159). LRRK2 protein has multiple functions in neuronal and non-neuronal cells. Among immune cells, the highest expression is observed in monocytes, macrophages, and microglia, raising the possibility that LRRK2 mutations contribute to disease progression through both neuron-intrinsic and neuron-extrinsic mechanisms. A correlation between LRRK2 expression in myeloid cells and dopaminergic neurodegeneration has been observed in rats. Adeno-associated virus-mediated transduction of human α-synuclein induced dopaminergic neurodegeneration in the substantia nigra and elevated expression of LRRK2 in myeloid cells of wild-type rats. LRRK2-deficient rats, in contrast, had no significant loss of neurons and reduced numbers of activated myeloid cells in the substantia nigra (160). Further suggesting a role for microglia dysfunction in the pathogenesis of PD, recent genetic analyses have identified the R47H variant of TREM2 as a risk factor for PD in addition to AD (161). Finally, the detrimental effects of hyperactivated or dysfunctional microglia can be attenuated through CX3CR1 (162). In a model of PD induced by the administration of the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), microglia were neurotoxic in mice lacking CX3CR1, which had more extensive neuronal cell loss than did CX3CR1-sufficient littermate controls.

Microglia in Other Neurodegenerative Diseases

Huntington disease (HD) is an inherited neurodegenerative disease caused by a polyglutamine expansion in the huntingtin protein (HTT). Although HTT is expressed in

many cells, several studies have indicated that mutated HTT has an important impact on microglia and neuroinflammation during HD pathogenesis (163). Positron emission tomography (PET) studies in presymptomatic HD gene carriers showed increased microglial activation, which correlated with striatal neuronal dysfunction (164). Analysis of peripheral blood monocyte transcriptomes from HD patients has revealed a proinflammatory phenotype, perhaps reflecting a priming effect of mutant HTT (165). Analysis of macrophages and cultured microglia from the YAC128 mouse model of HD, which expresses the human HTT protein with 128 glutamine-encoding CAG repeats, has also revealed an enhanced response of myeloid cells to inflammatory stimuli, such as metalloproteases (166, 167). More studies are required to determine the impact of microglia on disease progression and the underlying mechanisms.

Diseases of the Optic Nerve and Retina Associated with Neurodegeneration

Diseases of the optic nerve and retina, such as glaucoma and age-related macular degeneration (AMD), are leading causes of vision loss and blindness in the elderly (168, 169). These diseases are associated not only with chronic and progressive neuronal loss, but also with dysfunction of innate immune cells that may contribute to pathogenesis (170–173). In human, rare gain-of-function mutations of TBK1 are associated with normal tension glaucoma. These mutations may affect autophagy and phagocytic functions of microglia (157). In a mouse model of glaucoma, the complement pathway is upregulated before retinal ganglion cell death, while induction of C1q deficiency protects from glaucoma (69). Modulation of inflammation through the adenosine A2A receptor (A2AR) also prevented neuroinflammation and protected retinal ganglion cells in vitro and in vivo (174). In AMD, retinal microglia and other glial populations are activated and proliferate. Moreover, complement factors are inappropriately activated. Thus, further insight into the mechanisms of chronic neuroinflammation in the retinal disease and optic neuropathies may be of key importance for therapeutic intervention.

Microglia and Psychiatric Diseases

Neurodevelopmental and psychiatric disorders, such as autism spectrum and obsessive-compulsive disorders, are considered to be of neuronal origin. However, given the role of microglia in sculpting and regulating the strength of neuronal synapses, microglia dysfunction may contribute to the pathogenesis of these diseases. Mice lacking the homeobox gene *Hoxb8* in all cells or only in myeloid and endothelial cells spend twice as much time grooming as do their littermates, leading to hair loss and skin lesions reminiscent of a human compulsive disorder known as trichotillomania (175). After lethal irradiation and reconstitution with bone marrow from wild-type mice or RAG-deficient mice (which lack B cells and T cells), *Hoxb8*-deficient mice acquire normal behavior, suggesting that the abnormal behavior is due to *Hoxb8* deletion in myeloid cells. Because the lethal irradiation used in transplantation experiments causes leakage in the BBB, it is unclear whether the myeloid cells responsible are brain-resident microglia, bone marrow–derived monocytes that engraft into the brains of recipient mice, or both.

Rett syndrome is an X-linked autism spectrum disorder. After reaching 6–18 months of age, girls affected by Rett syndrome begin to regress developmentally and have seizures and

other progressive neurological symptoms. Rett syndrome is caused by the loss of function of methyl-CpG binding protein 2 (MeCP2), which binds methylated DNA and controls epigenetics. Lack of MeCP2 in neurons of $MeCP2^{-/y}$ male mice recapitulates the human disease. However, MeCP2 is also essential for the functions of astrocytes and microglia (176, 177). Whether restoration of MeCP2 in microglia or monocytes populating the brain after bone marrow transplantation is sufficient to attenuate Rett syndrome pathology is a matter of debate (178, 179). Regardless of whether microglia express MeCP, they contribute to Rett syndrome by causing excessive synaptic loss (180).

Emerging studies indicate that microglia may also be involved in major depressive disorder (MDD), a mood disorder of multifactorial origin that occurs worldwide. Studies have revealed microglial activation in depressed patients, with a greater magnitude of activation in individuals who completed suicide (181–183); this suggests that neuroinflammation may have a role in the pathogenesis of depression (97, 184). Recent studies using animal models of depression have consistently reported microglial reactivity in different brain regions, although a pathophysiological role for microglial activation has not been clearly delineated (185). Further studies are warranted to validate this link and understand the pathogenic mechanisms involved.

MICROGLIA AS THERAPEUTIC TARGETS IN NEURODEGENERATION

Understanding how microglia affect neurodegenerative disease is critical to identify new therapeutic strategies. Initial studies suggested that M1 activation of microglia, primarily secretion of inflammatory cytokines, is detrimental whereas M2 activation, especially secretion of neurotrophic factors, is beneficial. Thus, research has been focused on therapeutic agents capable of inducing M2 or preventing M1 polarization. However, it is increasingly clear that microglial activity during neurodegeneration does not fit the M1/M2 polarization paradigm. Moreover, M1 activation is not always detrimental nor is M2 activation necessarily beneficial. M1 microglia may be neurotoxic in some cases but promote axonal regeneration in others (186). In models of AD, M1 functions promote removal of amyloid plaques, while M2 functions may facilitate amyloid spreading (187). Microglial phagocytosis can also be a double-edged sword in neurodegeneration. On one hand, it may facilitate the clearance of misfolded proteins at disease onset; on the other hand, it may facilitate the spreading of pathogenic seeds during disease progression if protein digestion is impaired, or contribute to synapse loss if too many synapses are pruned. Thus, therapeutic agents that target microglia may have beneficial effects but also adverse effects.

Humanized antibodies that target misfolded proteins, such as Aβ, have been developed and are currently being tested in clinical trials (188, 189). Microglia are likely to contribute to the therapeutic effects of these antibodies by phagocytosing opsonized plaques through Fc receptors. Accordingly, impairment of microglia activation, as observed in TREM2-deficient mice, reduces the efficacy of the anti-Aβ antibodies (190). Antibodies directly targeting proinflammatory cytokines, such as IL-6 and IL-1, or their receptors, which are currently used in the treatment of autoimmune diseases, may have beneficial effects by blocking inflammatory microglia functions. Antibodies and compounds that ablate microglia by

targeting CSF1R have been extensively used to understand microglial function in AD (6, 191). While these agents may have therapeutic potential in neurodegenerative diseases in which microglia promote inflammation and/or neuronal death (192), caution should be exercised, as CSF1R haploinsufficiency has been implicated in the pathogenesis of adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (193). Moreover, studies in mouse models suggest that CSF1R ligands, such as IL-34 and CSF1, may provide neuroprotective and survival signals in neurodegeneration by activating CSF1R on selected neuron populations rather than microglia (194).

Cholesterol-lowering statins (195) and other metabolic drugs (196) have been reported to subdue inflammatory microglial functions and have beneficial effects on cognitive function in mouse models of AD. Moreover, the results of observational and randomized trials in humans have shown conflicting results (195). RXR agonists are also promising metabolic drugs in neurodegeneration. Oral administration of the RXR agonist bexarotene in a mouse model of AD facilitated rapid clearance of soluble Aβ (103). The therapeutic effect was linked to the induction of increased levels of ApoE. Moreover, a recent study showed that bexarotene induces TREM2 expression in microglia (197). Given that TREM2 can bind ApoE and activate the TREM2 signaling pathway, it is possible that bexarotene acts, at least in part, by enhancing TREM2 signaling in microglia. Anti-ApoE antibodies in carriers of the ApoE4 allele may also be useful in preventing proamyloid deposition effects (198).

While neuronal autophagy has been shown to have a protective effect in neurodegenerative models through degradation of misfolded proteins and reduced release of inflammatory mediators (199), there is little information regarding the impact of this pathway on microglia. Loss-of-function mutations of TBK1 that affect autophagy in myeloid cells are linked to ALS susceptibility (157). Moreover, one study showed that microglial autophagy facilitates clearance of extracellular Aβ fibrils and reduces Aβ-induced NLRP3 activation (200). Another recent study showed that microglial autophagy is involved in synaptic pruning and regulates behavior (201). Further studies of autophagy in microglia will be essential to determine whether drugs that enhance autophagy have beneficial or detrimental effects.

Microglia carrying genetic defects could be replaced with genetically edited autologous stem cells or monocytes, as well as with allogeneic stem cells or monocytes from healthy donors through bone marrow transplantation. Although the bone marrow transplantation approach has been successfully pioneered in X-linked adrenoleukodystrophy, its extension to other neurological diseases warrants caution because of the risks inherent in bone marrow transplantation. Moreover, two recent studies showed that brain-engrafted bone marrow–derived cells either do not acquire microglial functions or do so only after a long time (202, 203).

Finally, the identification of many regulatory immune receptors on microglia, some of which are mutated in AD and other neurodegenerative diseases, provides a new opportunity to modulate microglia functions in diseases using specific antibodies or ligands. Since AD is associated with hypomorphic mutations of TREM2 and hypermorphic mutations of CD33, antibodies activating TREM2 or blocking CD33 might be helpful in correcting microglial

dysfunction. Similarly, activating and inhibitory ligands of purinergic receptors may be valuable tools for modulating microglial function. Finally, given the role of complement in synaptic loss and the association of CR1 mutations in AD, targeting of complement components may be a valuable option for both Aβ and Tau pathologies. The broad variety of immune receptors expressed on microglia provides a plethora of targets for future avenues of therapeutic intervention in neurodegeneration.

ACKNOWLEDGMENTS

We would like to thank Susan Gilfillan, Wilbur Song, and Tyler Ulland for critical comments. M.C. is supported by the NIH (RF1 AG051485) and the Cure Alzheimer Fund. O.B. is supported by the NIH-NINDS (R01NS088137), the NIH-NIA (R01AG051812), the National Multiple Sclerosis Society (5092A1), the Amyotrophic Lateral Sclerosis Association (ALSA2087), a Nancy Davis Foundation Faculty Award, ALS Finding a Cure, and MAPP.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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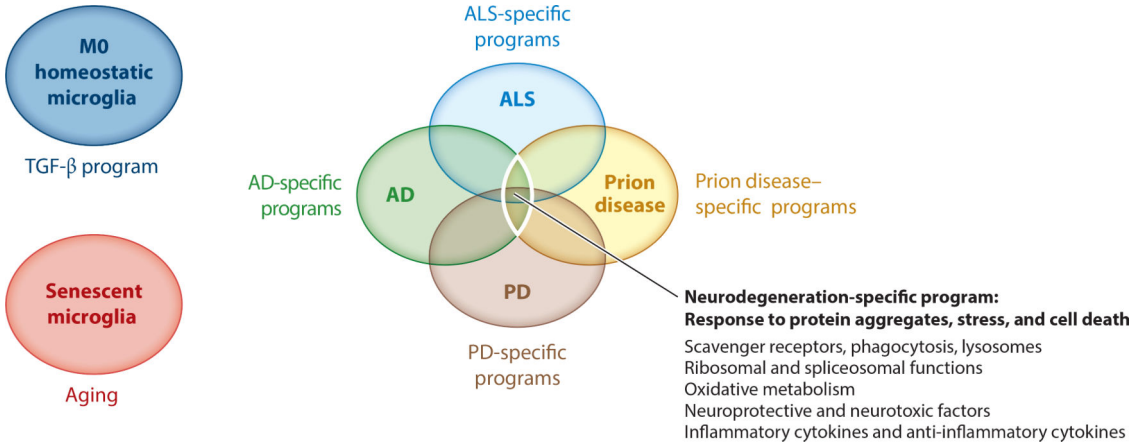

Figure 1.

Schematic representation of the transcriptional and functional programs of microglia in homeostatic conditions (M0), during aging, and in models of neurodegeneration. Abbreviations: AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; PD, Parkinson disease.

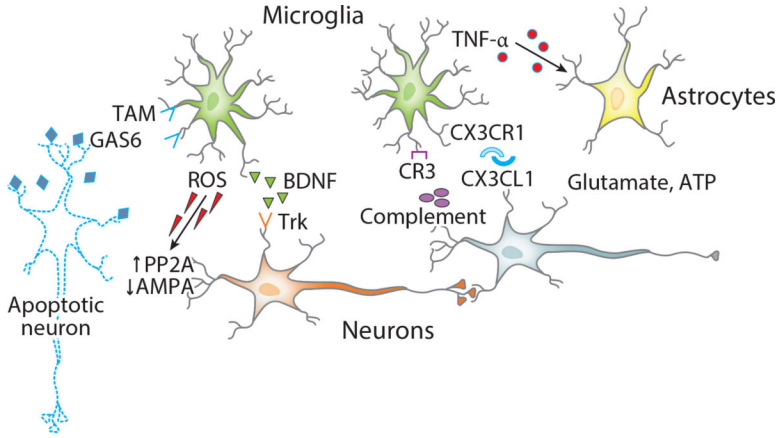

Figure 2.

Regulation of neuronal networks and functions by microglia. Microglia engulf apoptotic neurons via TAM receptor–mediated recognition of GAS6-opsonized cells. Microglia control synaptic plasticity through secretion of ROS, which downregulate AMPA receptors, and BDNF, which engages Trk receptors that modulate activities of various synapses. Microglia can strip synapses that are tagged by complement as well as through CX3CR1-CX3CL1 interactions. Finally, microglia can affect neuronal activity indirectly via astrocytes, which release glutamate and ATP in response to TNF-α released by microglia. Abbreviations: BDNF, brain-derived neurotrophic factor; TAM, Tyro3 and Axl and Mertk receptors; GAS6, growth arrest–specific 6; ROS, reactive oxygen species; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; PP2A, protein phosphatase 2A; Trk, neurotrophic receptor tyrosine kinase.

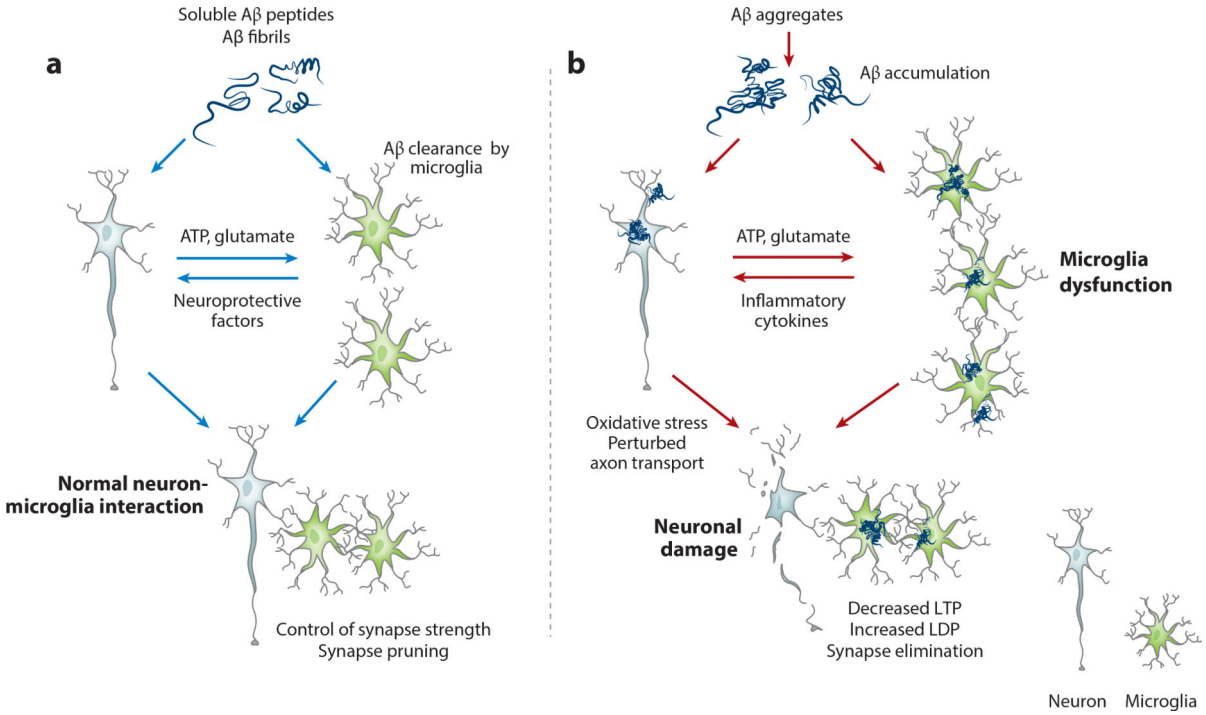

Figure 3.

Neuron-microglia interaction in healthy brain and during Aβ pathology. (*a*) In a healthy brain, soluble Aβ peptides and small amounts of Aβ seed are cleared by microglia. Microglia receive signals from neurons and secrete neuroprotective factors, control synapse strength, and prune inactive synapses. (*b*) During Aβ pathology microglia are incapable of removing excessive Aβ aggregates that chronically activate and damage both neurons and microglia. Neurons release excessive neurotransmitters and DAMPs, such as ATP, that further activate microglia. In turn, microglia release inflammatory cytokines that further damage neurons and facilitate Aβ deposition. Aβ-mediated and microglia-mediated insults contribute to neuronal damage, consisting of oxidative stress, reduced axonal transport, weakening of synaptic strength, and excessive elimination of synapses. Abbreviations: DAMP, damage-associated molecular pattern; LTD, long-term depression; LTP, long-term potentiation.

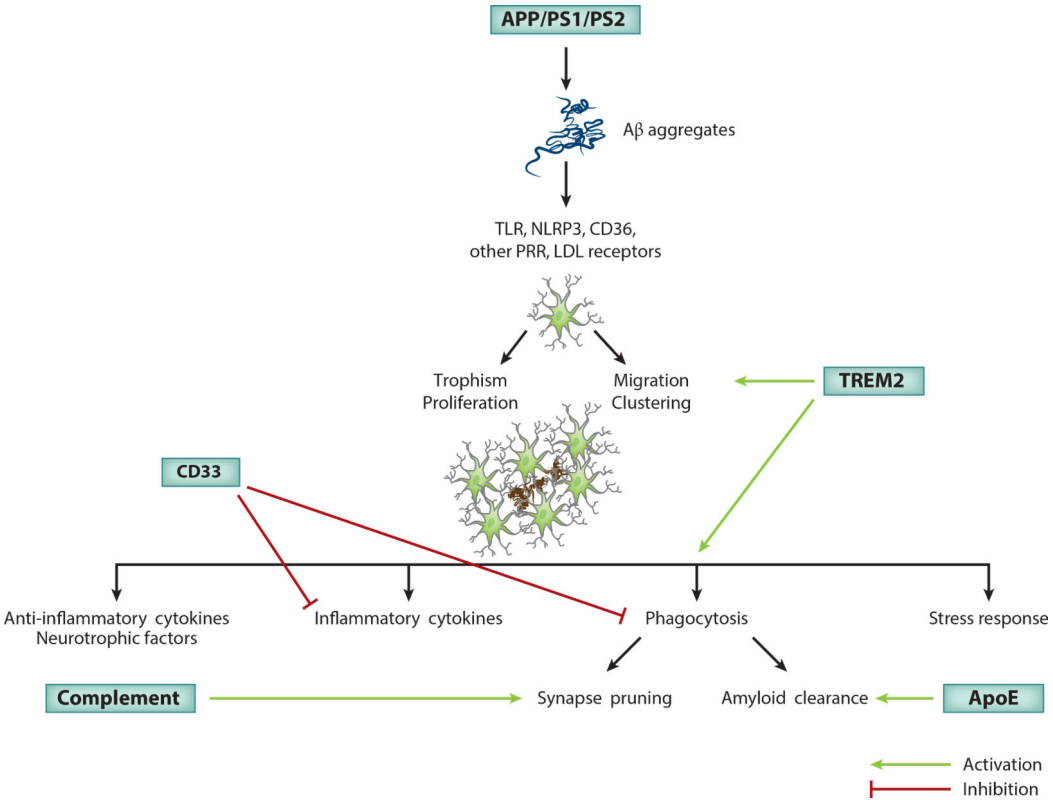

Figure 4.

Function of proteins affected by Alzheimer disease–associated mutations in microglia-mediated response to Aβ. Abbreviations: ApoE, apolipoprotein E; APP, amyloid precursor protein; PS, presenilin; PRR, pattern-recognition receptor; TLR, Toll-like receptor.