Acta Neuropathol (2010) 119:89–105
DOI 10.1007/s00401-009-0622-0

REVIEW

Microglia: biology and pathology

Manuel B. Graeber · Wolfgang J. Streit

Received: 30 November 2009 / Accepted: 2 December 2009 / Published online: 13 December 2009

Abstract The past 20 years have seen a gain in knowledge on microglia biology and microglia functions in disease that exceeds the expectations formulated when the microglia "immune network" was introduced. More than 10,000 articles have been published during this time. Important new research avenues of clinical importance have opened up such as the role of microglia in pain and in brain tumors. New controversies have also emerged such as the question of whether microglia are active or reactive players in neurodegenerative disease conditions, or whether they may be victims themselves. Premature commercial interests may be responsible for some of the confusion that currently surrounds microglia in both the Alzheimer and Parkinson's disease research fields. A critical review of the literature shows that the concept of "(micro)glial inflammation" is still open to interpretation, despite a prevailing slant towards a negative meaning. Perhaps the most exciting foreseeable development concerns research on the role of microglia in synaptic plasticity, which is expected to yield an answer to the question whether microglia are the brain's electricians. This review provides an analysis of the latest developments in the microglia field.

Keywords Astrocytes · Bone marrow-derived microglia · Microglial development · Neuroimmunology · Pain · Synaptic plasticity

M. B. Graeber
Division of Neuropathology, Department of Pathology and Clinical Laboratory Medicine, Faculty of Medicine, Neurosciences Center, King Fahad Medical City, Riyadh, Kingdom of Saudi Arabia

M. B. Graeber (✉)
The Brain and Mind Research Institute, University of Sydney, 94 Mallett Street, Camperdown, Sydney, NSW 2050, Australia
e-mail: manuel@graeber.net

W. J. Streit
Department of Neuroscience, McKnight Brain Institute, University of Florida College of Medicine, Gainesville, FL, USA

Introduction

Microglia are small glial cells found in the brain and spinal cord which unlike classical neuroglia (astroglia and ependymal cells, oligodendrocytes) are mesodermal in origin. It is now accepted that microglial cells can be acutely blood-derived in the adult under certain pathological conditions ("bone-marrow derived microglia", e.g. [198]). Microglial cells have the potential to develop into full-blown macrophages but their morphological and functional spectrum is highly regulated in vivo resulting in various intermediate states of activation. Adapted to their CNS environment, the functions of microglia differ from those of macrophages in other organs.

Twenty years have passed since we proposed the concept of the microglial "immune network" in the CNS [65]. At the time, a leading textbook of neuropathology questioned the very existence of microglial cells and suggested to abandon the term [45]. Obviously, this did not happen and more than 10,000 articles on microglia have been published since then. Microglia are now firmly established as a key cellular element in the CNS and they are recognized to serve as the brain and spinal cord's innate immune system [168]. This article aims to provide a critical review of the most recent developments in the microglia literature dating back no more than 5 years in most cases.

Interactions with other cells

The view that glia merely represent non-excitable support cells has changed radically in recent years. Astrocytes are now seen as local communication elements within the CNS that can generate various signals, e.g. through the regulated release of 'gliotransmitters' including glutamate [187]. "Microgliotransmitters" are not known at present but astrocytes certainly represent a highly communicative partner of microglial cells. Therefore, it is reasonable to assume that astrocytic information-processing [4] can be influenced by microglial activation. This novel concept gives an additional, CNS specific functional meaning to a number of the phenomena discussed below. The reverse is certainly also true: astrocytes have an influence upon microglial behavior. For instance, astrocytes play a critical role in the activation of microglia under infectious conditions [140], and chemokine expression by astrocytes appears to be involved in microglia/macrophage activation in multiple sclerosis with MCP-1/CCL2 and IP-10/CXCL10 directing reactive gliosis [178]. Together, astrocytes and microglia differentially regulate trafficking of lymphocyte subsets across brain endothelial cells [79], and IL-10 production by microglia and astrocytes can be induced through pro-inflammatory cytokines released from leptomeningeal cells [196].

Microglia subtypes and microglia cellular markers

Brain regional specialization of glial cells as determined by anatomical constraints is a well known fact. Microglial cells also vary in terms of numerical density throughout the CNS. However, whether there are true subsets of microglia is a different matter. This was originally suggested in 1998 [12] but no substantial follow-up research has been performed. In contrast, functional subsets of microglial cells do make their appearance under pathological conditions [33]. For instance, in Alzheimer's disease (AD) two microglial subtypes have been suggested to play different neuroimmunomodulating roles [160].

Microglial markers are crucial for the identification of microglial cells in tissue sections and much of the historical controversy surrounding them can be explained by a decades-long lack thereof. Today, we have a number of established markers for microglial cells in different species but a single specific molecular marker that does not also label peripheral macrophages is so far unknown and perhaps does not even exist [158]. Known microglia markers are cell-type specific in the sense that they do not label other glia or neurons. The comprehensive molecular characterization of microglia by means of high-throughput technologies such as microarrays [2, 23, 47, 57, 60, 129, 130, 147, 189] is in its infancy but a cell-type specific systems biological definition of microglia is likely to emerge. However, simple expression signatures of microglia may vary between cells from different brain regions or between individual cells, as functional and phenotypic heterogeneity of microglial cells has long been known to exist.

Perhaps the most versatile immunocytochemical marker for microglial cells is Iba1, which is detectable by an antibody directed against the EF hand protein which was developed in Shinichi Kohsaka's laboratory [82, 84]. Monoclonal and polyclonal versions of this antibody are available which enable most useful double-labeling procedures [69, 171, 194].

More recently identified markers of microglia are GLUT5 [157], CD163 [19, 149], and the C-type lectin CD209b [141]. CCR2 [198] and nestin [176] have also been described in microglia as well as CD34 [5, 98]. Toll-like receptor 2 (TLR2) and Toll-like receptor 4 (TLR4) are suggested to be involved in the determination of microglia phenotype and function [104]. Detection of the neurotransmitter gamma-aminobutyric acid (GABA) and of glutamic acid decarboxylase (GAD-67) in microglia following long exposure (more than 10 days) to low doses (10 ng/ml) of the 'proinflammatory' T-cell derived cytokine, IFN-gamma [22] attests to their great functional plasticity, which is especially pronounced in vitro.

Microglial cell lines

One microglial cell line, BV-2 [14] has become particularly popular with researchers but reservations exist that it does not model primary microglia accurately [42, 78]. For instance, BV-2 cells did not give reliable results in chemotaxis assays, not only with chemokines but also with other well-known attractors of microglial cells such as ATP [42]. Horvath et al. [78] recommended that the use of this microglial cell line should be carefully considered. While there is a reasonable motivation to reduce the number of animal experiments [75], we feel that BV-2 should only be used for screening purposes with validation performed in primary cultures or, preferably, an established experimental in vivo setting. The same applies to other microglial cell lines since immortalization significantly affects a cell's biology.

Recent findings

Developmental aspects

The role of microglia during normal development of the nervous system is not fully understood [25]. Monier et al. [126] studied the topographical distribution of microglia

during development of the human diencephalon and telencephalon. At 5.5 gestational weeks (gw), the first intracerebral microglial cells were seen close to the meninges and choroid plexus near the di-telencephalic fissure [126]. The authors also reported that in the developing diencephalon, microglial clusters were located in junctional regions of the white matter anlagen, most notably at the junctions of the internal capsule with the thalamic projections, the external capsule, and the cerebral peduncle. At 10–12 gw, Iba1+/RCA-1+/CD68+/CD45+ cells accumulated in the cortical anlagen, forming a tangential band at the junction between the cortical plate and the subplate [126]. Subsequently, microglial clusters increased markedly in size and cellular density (10–16 gw). Beginning in the middle of the second trimester, microglial cells colonized the entire cerebral parenchyma, they developed a ramified morphology, and down-regulated their surface antigens, but remained more numerous in the white matter [126]. In another study using human brain tissue, the finding of transient, developmental stage-dependent overabundance of CD68-activated microglia in the cerebral white matter of fetuses was interpreted as potential "priming" of this area for brain insults such as periventricular leukomalacia, where microglial activation occurs in immature cerebral white matter secondary to hypoxia–ischemia and/or infection [13]. Checchin and co-workers [28] investigated whether microglia are implicated in retinal blood vessel formation in humans and rodents. They concluded that the traditional definition of microglia as "merely immunocompetent cells" should be reconsidered to encompass a new function related to blood vessel formation.

In a study in cats, the phenotype of microglial cells was found to depend on the postnatal visual experience, suggesting that microglia may interact with axons of visual neurons [150]. Normal microglia are not believed to play an active role in triggering apoptosis of developing motor neurons. Instead, they are thought to act as phagocytes for the removal of dying cells during the process of programmed cell death [25]. This may be different in fish [142]. It is worth noting that subventricular zone microglia possess a special capacity for massive in vitro expansion [118]. Another recent observation is that MHC class II expressing microglial cells are found in focal cortical dysplasia where they have been suggested to contribute to the epileptogenicity of such foci [16].

Functions of microglia in normal brain

More than a decade ago, Georg Kreutzberg coined the term "microglial sensor of pathology" [97] which captures the essence of microglial cell function and, not surprisingly, has become a widely accepted notion today. Clearly, microglia are involved in most if not all known CNS pathologies. However, strong emphasis on the role of microglia in disease conditions may distract from the fact that "resting microglia" are resident but not functionally silent cells. It seems that they have important roles to play in normal brain. For instance, Wake et al. [188] have shown recently that part of the dynamic motility of resting microglial processes in vivo is directed toward synapses and the authors propose that microglia vigilantly monitor and respond to the functional status of synapses. Their work also shows that microglia sense defunct synapses and suggests that the integrity of the CNS circuitry may be monitored and diagnosed by the "microglial sensor". This work indicates a possible novel function of microglia as the CNS 'electrician' which deserves specific study. Wake et al.'s work further underlines the validity of the hypothesis posited above that microglia can potentially influence information processing in the CNS, either indirectly via their interactions with astrocytes, or directly by interacting with synapses.

Microglial cells possess alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and metabotropic glutamate receptors which mediate their directed chemotaxis [108]. It seems possible that this mechanism plays a role in "synaptic stripping" [15, 66, 182] including in human cortex (cf. Fig. 1). Constant surveillance of CNS tissue by microglial cells is considered to be of special relevance for the defense against viruses [180]. Viral encephalitis is typically accompanied by the formation of microglial rod cells (Fig. 1) which appear to form in cerebral cortex as a result of microglial-dendritic interactions.

Mechanisms of microglial activation

Activated microglia in tissue sections are identified based on combined morphological and immunophenotypic changes which distinguish them from their resting phenotype. These changes in microglial appearance provided the foundation for introducing the concept of microglia functional plasticity in the 1980s [170] and they remain relevant today. As mentioned, even after 20 years of intense research, there is still no single molecular marker that allows the unequivocal distinction between resting and activated microglia, although some rat antibodies have been claimed to fulfill that purpose. ED1 and OX-6 antibodies are examples of this, but both have their unique shortcomings: ED1 is a marker for phagocytic activity but does not label activated, non-phagocytic cells, and OX-6, while often upregulated on some activated cells does not get expressed by all of them and is also found on some resting microglia in normal brain. Thus, the distinction between activated/non-phagocytic and activated/phagocytic, which is embedded in the functional plasticity concept, has been confirmed using

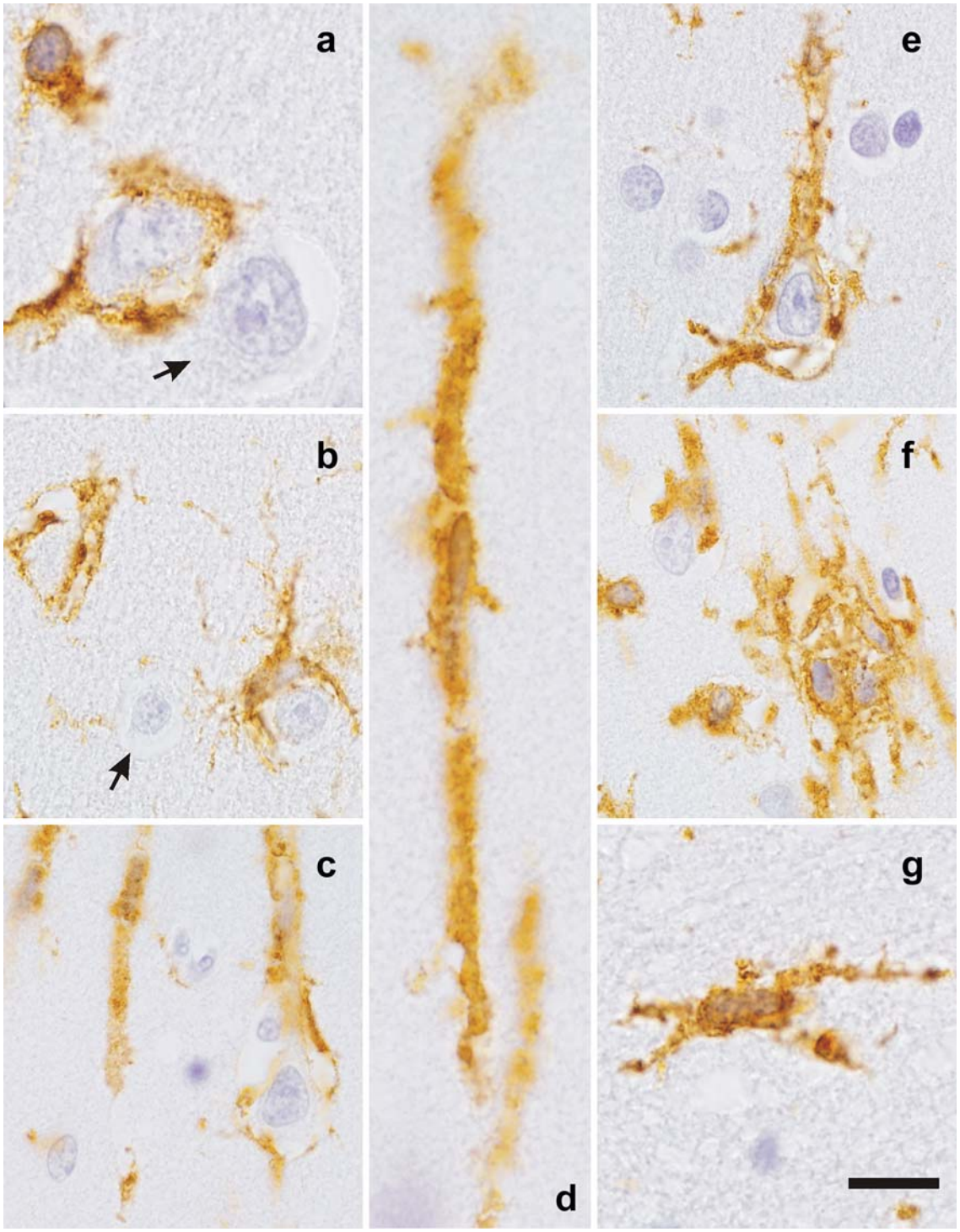

Fig. 1 MHC class II labeled microglia in human cortex (serologically confirmed SSPE). **a** and **b** demonstrate how selective the microglia "attack" on cortical neurons is (*arrows* point to unaffected nerve cells) suggesting that the phenomenon is reactive rather than aggressive. **c**, **e** Some nerve cells become completely "wrapped" by microglia while microglial rod cells form along dendrites (**d**). Occasional neuronophagia (**f**) is also observed whereas white matter shows individual activated microglial cells with stout processes (**g**). *Scale bar* 20 μm in **a**, **d**, **g**, and 40 μm in **b**, **c**, **e**, **f**

multiple markers in combination with morphological assessments. Ideally, such differences are validated in a paired experimental model [127] but trained observers are quite capable of recognizing even subtle states of microglial activation on the basis of their increased expression of marker molecules because the latter is usually combined

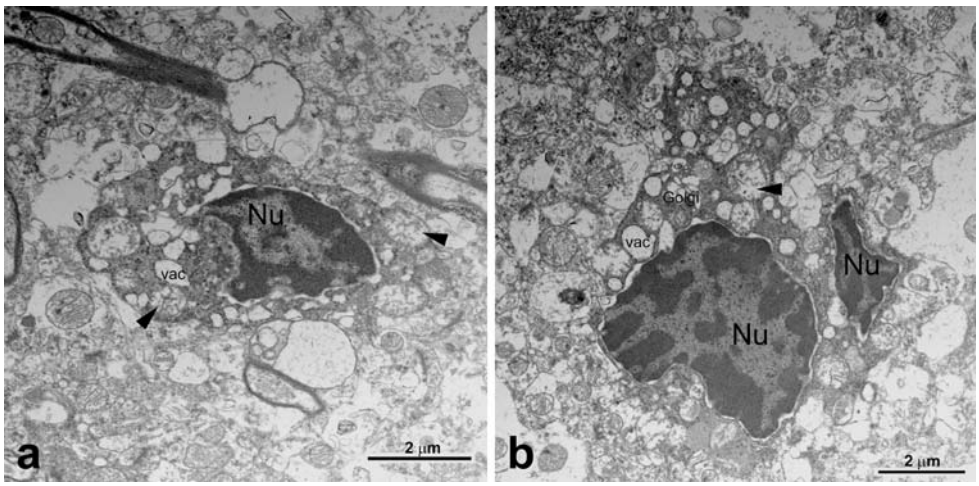

Fig. 2 Shown are two examples (**a**, **b**) of dystrophic microglial cells from a 91-year-old female AD subject, Braak stage IV (tissue provided by Dr. Thomas Beach, Bannerhealth Research Institute, Sun City, AZ, USA). The ultrastructure reveals widespread vacuolation (vac) throughout the cells' cytoplasm likely representing dilated ER and Golgi, as well as swollen mitochondria (*arrowheads*). Nuclei (Nu) are strongly heterochromatic, as is typical for microglia. Nucleus in **b** is cut in two places. Magnification indicated by *scale bars*

with morphological alterations making the cells stand out against resting phenotypes. In recent years, the concept of microglia functional plasticity has been expanded with the recognition of a fourth microglial phenotype, termed dystrophic [173] (Figs. 2, 3). Conceptually, the addition of microglial dystrophy has widened our biological perspective in that microglial degeneration, in addition to activation, now becomes a consideration. As discussed here and elsewhere [169], microglial dystrophy is likely to be relevant especially in the context of aging and aging-related neurodegenerative diseases while primary gliodegeneration also exists [35]. Much needs to be learned about the processes that lead to microglial degeneration, as well as the consequences of microglial cell death for brain function. However, one interesting possibility is that chronic microglial activation if sustained over long periods could lead to microglial over-activation followed by microglial degeneration. Currently, there is in vitro evidence to support the idea that overactivation leads to microglial cell death [106, 143], and degenerating microglia can be found sporadically throughout the aged human brain. The prevalence of degenerating microglia increases dramatically in Alzheimer's disease (AD) and in Down's syndrome where damaged microglia are colocalized with neurofibrillary degeneration, thus raising the possibility that this kind of neurodegeneration could be a consequence of dwindling microglial neuroprotection. This idea could help resolve the long-standing debate over whether microglial activation is neurotoxic in that one might argue that if overactivation was potentially damaging to neurons, as claimed by numerous authors, a solution for defusing this hazardous situation would be for microglia to die thereby removing the source of danger. Biologically speaking, this would make sense because, unlike most other cells in the CNS, microglia can be replaced and are therefore relatively expendable.

According to recent research, microglial activation is considered one mechanism by which early-life seizures contribute to increased vulnerability to neurologic insults in adulthood [164]. Thus, microglial cells may develop a functional "memory" causing increased disease susceptibility. However, in a positive sense microglial malleability is likely to represent a key mechanism underlying beneficial functional plasticity of the CNS.

Recent findings also indicate that microglial activation during stress differs qualitatively from those of infection or inflammation [175]. Zinc has been identified as a novel trigger for microglial activation [94], and CD38 (ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase) has been found to link microglial activation to activation-induced cell death by controlling the amount of NO that microglia cells produce [121]. Activation of P2X7 purinoreceptors induces CCL3 production in microglial cells through transcription factor NFAT [92]. In addition, the P2X7R signaling pathway may negatively regulate autophagic flux through the impairment of lysosomal functions, leading to stimulation of a release of autophagolysosomes/phagolysosomes into the extracellular space [177].

Schwartz et al. [159] have made the suggestion that microglia "comprise a family of cells with diverse phenotypes" in order to explain observations on their seemingly contradictory "beneficial" or "destructive" properties under various experimental conditions [159]. We disagree with the concept of 'bipolar' microglial activation states and suggest that there is instead a prototypical but highly malleable, i.e. functionally plastic microglial cell type that not only has its unique ontogenesis but which

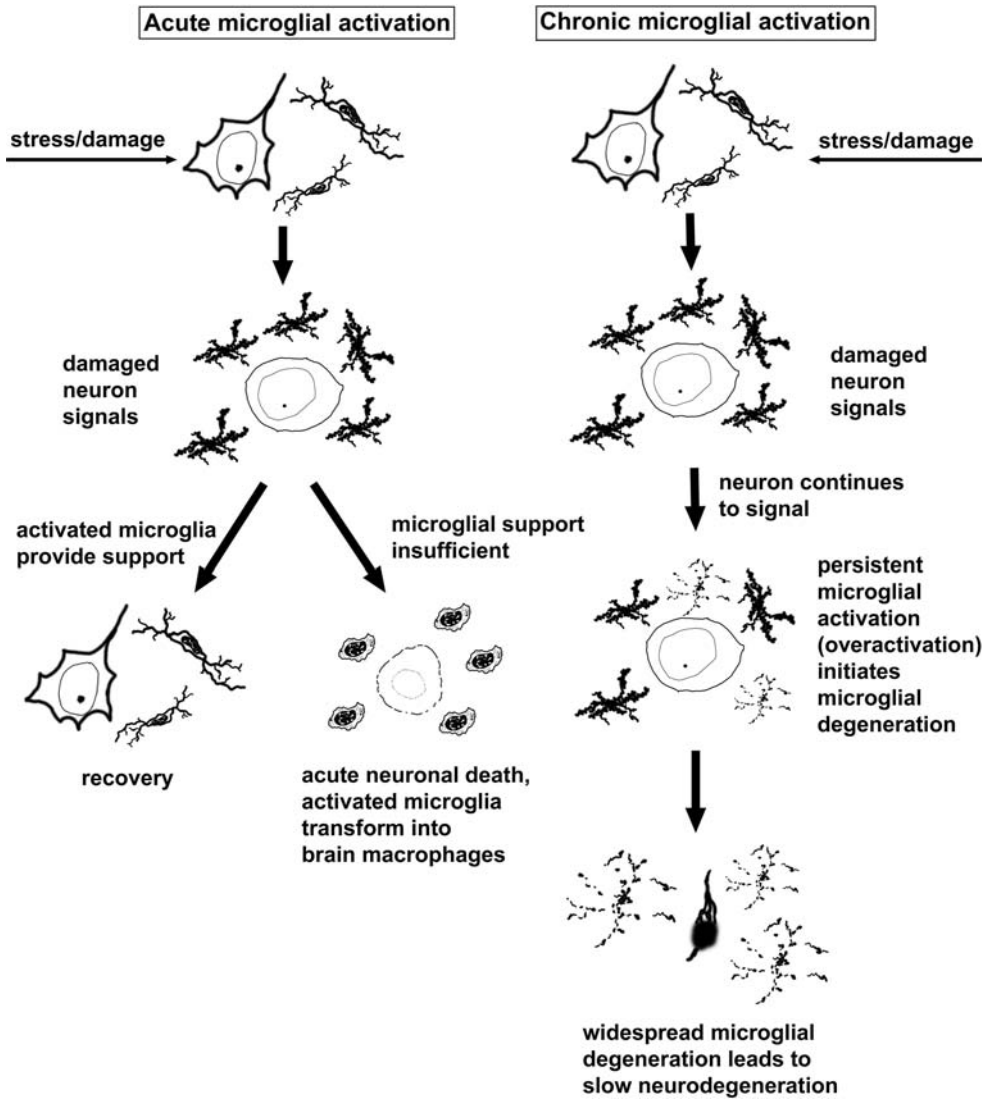

Fig. 3 An updated view on microglia functional plasticity involving neuronal-microglial interactions during acute and chronic activation. The initial trigger for microglial activation are signals emitted by damaged or stressed neurons that tell resting cells to divide, increase production of cytokines and growth factors, and change surface antigen expression. This increase in microglial activities, reflected in cellular hypertrophy, represents an acute neuroinflammatory reaction that is designed to bring about neuronal recovery from stress or injury. If successful, excess numbers of activated microglia are eliminated through programmed cell death [88]. If unsuccessful, acute neuronal death will result in the formation of microglia-derived brain macrophages that clear out debris. A chronic neuroinflammatory reaction occurs if damaged neurons continue to send out activating signals that result in persistent microglial activation. Such prolonged overactivation will cause some microglia to become senescent and undergo degenerative changes and eventually lead to widespread microglial degeneration. Once a critical number of microglia have undergone this type of accidental cell death, neurons will have lost all microglial support and are destined to follow a path of slow neurodegeneration, reflected morphologically by abnormal inclusions (e.g. Lewy bodies) and/or neurofibrillary degeneration

may also become directly affected by disease. Both ontogenetic aspects and its anatomic location could influence a microglial cell's functional repertoire. The view that microglia can contribute to neuronal diseases is expressed by some authors in the increasingly popular but imprecise term, "non-cell autonomous".

A family of CNS macrophages consisting of at least five subtypes exists [67]. We believe that their definition and distinction from microglia is of great practical utility as well as conceptual importance. This holds true even if a certain overlap with "bone marrow-derived microglia" exists.

"Inflamed" microglia?

There is probably no area of microglial research that has attracted more attention in recent years than inflammatory phenomena associated with their activation process. The underlying mechanisms, however, have remained largely

unclear and the interpretation of some findings related to the "activated" microglial phenotype continues to be problematic. Currently, many authors appear to consider any response of microglial cells to tissue pathology, which is regularly associated with increased expression of MHC class II molecules, as evidence of nervous tissue "inflammation". The incorrect term, "inflamed microglia" has also been used. However, 'inflamed' in pathology refers to interactions of cells and a cellular response to injury, which is a beneficial process unless it becomes chronic or directed against self antigens resulting in autoimmune disease.

The equation 'detection of MHC class II antigens in microglial cells' equals 'evidence of inflammation' represents a generalization which does not take into account that expression of MHC class II molecules does not suffice to start an immune response, and to prove this point, cells of the peripheral immune system are typically missing in the allegedly "inflamed" brain tissue of AD cortex or Parkinsonian substantia nigra. The fact is that the term "neuroinflammation" is still in need of a consensus definition, and it is unfortunate that it is almost always used in a negative way (i.e. a chronic, destructive process or autoimmune attack). There is clear experimental evidence which shows that activated microglia can be beneficial [49]. In addition, it is increasingly appreciated that interactions between peripheral immune cells and the nervous system differ with each type of insult [73]. The problem will be discussed in detail in the section on neurodegeneration.

The active participation of microglial cells in established autoimmune diseases such as multiple sclerosis is, however, accepted. Interleukin (IL)-17-producing helper T cells may play a pivotal role in the pathogenesis of multiple sclerosis, and IL-17 has been found to upregulate the microglial production of IL-6, macrophage inflammatory protein-2, nitric oxide, adhesion molecules, and neurotrophic factors [95]. Microglia also are the major cellular source of inducible nitric oxide synthase during experimental herpes encephalitis [117]. In bacterial infections, nucleotide-binding oligomerization domain-2 (NOD2), a member of the novel nucleotide-binding domain leucine-rich repeat region containing a family of proteins (NLR) that functions as an intracellular receptor for a minimal motif present in all bacterial peptidoglycans, is functionally expressed by both microglia and astrocytes [27]. Toll-like receptor 4 (TLR4) has a critical role in ethanol-induced microglial activation which is also considered inflammatory [54]. Another recent finding suggests that microglia are able to cross-present exogenous antigens on major histocompatibility complex (MHC) class I molecules to CD8(+) T cells [9]. Importantly, following IFN-gamma stimulation, production of neuroprotective factors by microglia appears to be down-regulated [130].

Role in neurodegeneration

The suggestion that microglial cells pose a threat to neurons in neurodegenerative conditions although presently popular is not backed by firm evidence. The view that microglia are dangerous to nerve cells in vivo is largely based on extrapolation from cell culture studies, non-physiological models such as LPS injection to simulate Parkinson's disease, or the hypothetical view that any microglial cell that expresses MHC class II molecules and perhaps cytokines is in a state of cytotoxic activation. However, this is not justifiable any longer in view of increasing evidence to the contrary [61, 76, 136, 144]. Furthermore, a large number of distinct brain pathologies exist. The sheer number of different disease states which are considered to be due to unrelated etiologies is incompatible with the simplistic view that for example expression of IL-1 [161] is of the same high pathophysiological importance in each state and across an entire spectrum of very different disorders. It is obvious that a significant number of publications dealing with microglia and inflammation in the field of neurodegeneration, and notably common diseases such as Alzheimer's or Parkinson's, have a high propaganda index [89].

Amyotrophic lateral sclerosis

Microglia have been assigned a "non-cell autonomous" function in ALS pathogenesis [18], which is a cryptic way of saying they contribute to motor neuron death. Based on work employing mSOD1-overexpressing BV-2 microglial cell lines it has been suggested that mSOD1 expression in ALS facilitates microglial neurotoxic inflammatory responses via TLR2, which seems mediated by uncontrolled ROS generation [110]. Furthermore, it has been suggested that macrophage colony-stimulating factor (M-CSF) exacerbates ALS in a mouse model through altered responses of microglia expressing mutant superoxide dismutase [62]. ALS microglia have been implicated as a source of the increased monocyte chemoattractant protein-1 (MCP-1) levels which are detected in ALS patients and in the ALS mouse model [155]. A review of the proposal that ROS mediate ALS pathogens demonstrates that a new twist has been introduced: it is ROS produced by microglia [17]. However, Gowing and co-workers have found that ablation of proliferating microglia does not affect motor neuron degeneration in amyotrophic lateral sclerosis caused by mutant superoxide dismutase, allowing these authors to conclude that "microglia are fundamentally neuroprotective cells but that expression of mutant SOD1 renders them neurotoxic" [61]. In line with this conclusion is an alternative view of microglial involvement in ALS expressed by

Fendrick et al. [53], namely, that motoneuron death is the result of microglial malfunction and, ultimately, degeneration occurring during the course of the disease, thus attributing neurodegeneration to a loss of microglial neuroprotection.

Alzheimer's disease

One of us [171] has demonstrated that microglial dystrophy coincides spatially with presence of and precedes temporally the spread of tau pathology in AD. Deposits of amyloid-beta protein (Abeta) devoid of tau-positive structures were found to be colocalized with non-activated, ramified microglia, suggesting that Abeta does not trigger microglial activation. The findings further indicate that when microglial activation does occur in the absence of an identifiable acute central nervous system insult, it is likely to be the result of systemic infectious disease. These findings argue strongly against the hypothesis that neuroinflammatory changes contribute to AD dementia [171] but do not exclude interactions between microglia and beta-amyloid deposits.

Microglia have indeed been shown to play a role in amyloid removal, particularly compacted amyloid deposits, under certain conditions [131]. Microglia also internalize soluble Abeta from the extracellular milieu through a nonsaturable, fluid phase macropinocytic mechanism that is distinct from phagocytosis and receptor-mediated endocytosis both in vitro and in vivo [115]. Abeta activates a purinergic autocrine/paracrine stimulatory loop in microglia of which the P2X(7) receptor is an obligate component [154]. The TLR2 signaling pathway has been implicated in the mediation of fibrillar Abeta peptide-induced activation of microglial cells [85], and microglia activation has been suggested to mediate fibrillar amyloid-beta toxicity in the aged primate cortex [103].

Alterations in levels of signaling molecules secreted by microglia may in part be responsible for the defective neurogenesis observed with FAD-linked mutant PS1 in vivo, a finding supporting a non-cell-autonomous role for mutant PS1 in hippocampal neurogenesis [32]. Indeed, microglia expressing FAD-linked PS1 variants impair proliferation of neural progenitor cells [32]. This supports our view that 'sick glia' in degenerative CNS diseases may have a direct pathogenic role [35].

It has become common practice in neurobiology to extrapolate from mouse models to human pathology. However, there are great differences even between rodent species as exemplified by the propensity of mouse CNS to become infiltrated by peripheral inflammatory cells. For instance, following peripheral nerve axotomy mice show significant infiltration of CNS tissue by peripheral immune cells whereas rats do not [146]. Therefore, experiments utilizing inflammatory infiltration in the CNS of AD mice [50, 51] have to be interpreted with caution. In fact, recent experimental evidence argues strongly against inflammation as a driving force for amyloid deposition [26]. Furthermore, at least in mice, neither amyloid plaque formation and maintenance nor amyloid-associated neuritic dystrophy depends on the presence of microglia [71].

Parkinson's disease

The involvement of microglia in the pathogenesis of Parkinson's disease (PD) remains controversial. We do not think that the currently available evidence provides sufficient support for the hypothesis that microglial cells, or "microglial inflammation", exert an active, disease-promoting role in PD. This critical view is based on a number of facts. First, a mechanism by which activated microglia might specifically target dopaminergic neurons is missing [151]. Second, T cells are not usually observed in Parkinsonian substantia nigra and a report claiming the presence of small numbers of scattered cells [21] is awaiting independent confirmation. Thus, the title of a recent publication, "T cell-microglial dialogue in Parkinson's disease and amyotrophic lateral sclerosis: are we listening?" [3] is likely to cause confusion. Third, a popular LPS injection model of PD [80] which has been used to provide experimental support for the role of 'microglial inflammation' in PD seems quite artificial. Fourth, an infectious etiology [86] does not appear to be of relevance in the vast majority of PD cases because the underlying concept does not do justice to other, well-established findings in PD, such as deficits in mitochondrial function, the role of oxidative and nitrosative stress, dysfunction of the ubiquitin–proteasome system (UPS) and functional defects caused by disease-causing mutations whose role in PD is well established [64]. Finally, it is worth mentioning that in contrast to a study in mice [100], the human substantia nigra does not contain the highest density of microglial cells [124].

Speculations on an active role of microglial cells in PD were originally based on their expression of MHC class II molecules in the Parkinsonian nigra [122]. However, MHC class II antigen expression by microglia in the substantia nigra cannot be used as an indicator of clinical PD severity or disease progression [36]. We have previously suggested that microglial MHC class II expression that is widespread in neurodegenerative diseases could serve to down-regulate rather than up-regulate antigen presentation capacity and thus serve as a protective "firewall" against unwanted immune attacks when it occurs in the absence of co-stimulators [63]. This hypothesis is in line with the finding of CD163 upregulation by nigral microglia specifically in PD cases with a shorter disease course. Because CD163 has been implicated in anti-inflammatory signaling pathways,

this observation suggests that "microglial inflammation" is modulated, rather than self-propagating, in PD [37]. In addition, from a systems biological point of view, only a smaller part of the emerging common pathway of PD [128] shows links to immunological or inflammatory mechanisms. The latter might include Nurr1 modulation in microglia and astrocytes [52, 153]. Overall, the biological association between PD and "inflammatory" parameters may have to be interpreted in a modified way which takes the specifics of nervous tissue into account.

In keeping with the view that microglia in PD are reactive rather than aggressive, synuclein has been found to stimulate microglia [174]. It has also been observed that the homocysteine-induced endoplasmic reticulum protein (herp) is up-regulated in PD substantia nigra [163]. Relevance of herp for PD is also supported by another study [31]. Homocysteine promotes proliferation and activation of microglia [204], and it has been proposed that it may be promising to regulate microglia activation in PD via targeting CD200–CD200R signaling pathways [192].

Taken together, we find the hypothesis attractive that similar to AD [166] and Huntington's disease [162], glia in PD may be compromised [48]. In other words, microglia themselves may be affected by the disease process, and may therefore not be capable of exerting sufficient neuroprotective functions such as glutathione peroxidase expression [144]. In line with this view, chronic nicotine treatment increases the number of HLA− DR+ microglia in monkey substantia nigra after nigrostriatal damage and results in improved nigral integrity and function [145].

Macular degeneration

Retinal microglia have also been implicated in disease [30]. For instance, CX3C chemokine receptor 1 (CX3CR1)-dependent subretinal microglia cell accumulation is associated with cardinal features of age-related macular degeneration (AMD) [34], and the cells have been suggested to contribute to the progression of this most common cause of blindness in the elderly [29]. Amyloid-beta which is a major component of retinal drusen (plaques) in AMD has been found to up-regulate complement factor B in retinal pigment epithelial cells through cytokines released from recruited macrophages/microglia [190]. However, whether microglia activated by primary rod cell death actively kill adjacent photoreceptors [72] remains to be established. Finally, it should be noted that normal aging also takes its toll on microglia [167, 172].

Microglia in brain tumors

This is a rapidly developing field. There can be little doubt that the macrophage population in brain tumors is recruited from more than one source, i.e. brain and blood, although the mechanisms of macrophage tumor-attraction and invasion are unclear. The hypoxia-inducible factor (HIF)-1alpha-CXCR4 pathway is of particular interest because it has been implicated in microglia migration [191]. Interestingly, HIF-1alpha also blocks differentiation of malignant gliomas [112]. Tumor cell-derived MCP-3, but not MCP-1 [43], facilitates the infiltration of macrophage/microglia into tumor tissues [139]. In contrast, a role for the chemokine system CX3CL1 and its receptor CX3CR1 has been excluded at least in the GL261 murine model of malignant glioma [107]. Historically, a tumor cytotoxic role of microglial cells has been proposed and apoptosis of glioma cells can be induced by microglia-secreted molecules, such as nitric oxide and cathepsin B [81]. However, under normal conditions microglia support glioma growth. We first made this surprising observation more than a decade ago [70], and the effect has been confirmed by other authors [39, 40]. More recent discoveries in this area include the induction of microglial MT1-MMP by glioma cells [116], and the regulation of glioblastoma invasion by microglia-derived TGF-beta [193]. In contrast, the relevance of some immunological phenomena in high-grade gliomas remains unclear. Compared with human control brains, a significant increase in the percentage of parenchymal IL-16+ macrophages/microglia was observed in grade II astrocytomas, a further increase was observed at the transition from grade II to III astrocytomas, and this increase in IL-16 immunoreactivity correlated with WHO grades of human astrocytic brain tumors [105].

Gemistocytic astrocytomas contain unusually high numbers of microglial cells, and the higher the number of class II immunoreactive gemistocytes, the fewer class II positive microglial cells can be detected. This may be related to the especially poor prognosis of gemistocytic astrocytomas for which induction of T cell anergy could provide one explanation [58].

CNS trauma

An understanding of the molecular mechanisms underlying microglial "activation", and clarification of where and when alternative macrophage activation pathways [119] are involved, will also be of importance for our understanding of the role microglia play in CNS trauma. It has been suggested that microglia mediate secondary tissue damage in traumatic brain injury but this does not represent a well-founded speculation. Early infiltration of lesions of traumatic brain injury in rats by CD8+ macrophages/microglia has been reported, and the cells co-expressed endothelial monocyte-activating polypeptide II and P2X4 receptor indicating a central role for these factors in lesion development [200]. Lünemann and co-workers who

believe that microglia cause secondary damage after brain trauma [113] have characterized a new macrophage/microglia activation factor, MAF and propose that MAF expression plays a functional role in the differentiation of microglia into a phagocytosing phenotype and that MAF may be required for phagocytotic activity, specifically in traumatic tissue lesions. Brain trauma induces expression of diacylglycerol kinase zeta in microglia [134].

Transection of the adult rat facial nerve leads to an increase in the number of microglia in its central nucleus of origin, with a peak of proliferation 3–5 days after axotomy. These proliferating microglia do not produce deleterious factors for neurons but express macrophage-colony stimulating factor (M-CSF) and granulocyte macrophage-CSF (GM-CSF) as well as their specific receptor proteins, c-Fms and GM-CSFRalpha [133]. Microglia also promote astrogliogenesis and maintenance of neural stem cells by activating Stat3 function and via notch and sox9 signaling pathways [203].

Microglia and neuropathic pain

Recent findings challenge the neuron-centric view of neuropathic pain etiology and pathology [198]. There is a rapidly growing body of evidence indicating that microglial cells have a causal role in the pathogenesis of pain hypersensitivity following nerve injury [83]. Neuropathic pain, a debilitating pain condition that commonly occurs after nerve damage, is a reflection of the aberrant excitability of dorsal horn neurons [183]. The chemokine CCL2, produced by both damaged and undamaged primary sensory neurons, is a key mediator of microglia activation in neuropathic pain states [179]. Its receptor, CCR2 appears to be critical in the activation of spinal microglia and is expressed in both resident and bone marrow-derived cells [198]. The receptor for the cytokine IFN-gamma, IFN-gammaR also appears to be a key element in the molecular machinery through which resting spinal microglia transform into an activated state that drives neuropathic pain [183]. Furthermore, ligation of L5-L6 spinal nerves evokes an accumulation of active, phosphorylated STAT3, mediated mainly via IL-6 signaling, in microglial cells of dorsal spinal cord mostly in projection areas of injured nerves [46]. Microglia have been shown to be involved in intestinal pain [20]. Both astrocytes and microglia of the locus coeruleus are involved in cardiac pain processing after acute cardiac injury [199].

Cannabinoid receptor type 2 (CBR2) inhibits microglial reactivity and mitogen-activated protein kinase-phosphatase (MKP)-3 induction is part of the mechanism underlying the reduction of pro-inflammatory factors and microglial migration caused by CBR2 agonists [152]. Interleukin-18-mediated microglia/astrocyte interactions in the spinal cord enhance neuropathic pain processing after nerve injury [125]. In contrast, the anti-inflammatory cytokine interleukin-10 reduces the number of spontaneous flinches in the early and delayed phases of the formalin test of inflammatory pain, and this correlates with a block in phosphorylation of p38 and reduced expression of 26 kDa full-length membrane spanning tumor necrosis factor-alpha in spinal microglia [202]. It has been hypothesized that microglial TNFalpha may enhance the efficacy of synaptic transmission [11].

Extracellular nucleotides, which act through purinoceptors, especially the G-protein-coupled P2Y receptor P2Y(12)R, have been implicated as signaling molecules used by microglia to sense adverse physiological conditions such as neuronal damage [181]. P2Y(12)R is a metabotropic ATP receptor that is thought to be involved in the pathogenesis of neuropathic pain [96, 181]. P2X(4) receptors are expressed de novo by activated microglia in the spinal cord in response to nerve injury and mediate BDNF release as well as neuropathic pain [184]. A hypothesis has been formulated that P2X(7) receptors on the presynaptic terminal and those on the microglia synergistically act to ensure feedback pathways that reset to a high level the efficacy of synaptic transmission, thus ensuring chronic neuropathic/neuroinflammatory pain even when the initial insult has subsided [11].

Loss of glycinergic and GABAergic synaptic inhibition (i.e. dis-inhibition) in the spinal cord dorsal horn has been increasingly recognized as an important process in the development and maintenance of chronic pain of both inflammatory and neuropathic origin [197]. The production of inflammatory mediators and/or the activation of immune cells appear to be critical for both and a model of microglia-induced dis-inhibition in neuropathic pain states has been proposed [197]. Remote activation of microglia and pro-inflammatory cytokines predict the onset and severity of below-level neuropathic pain after spinal cord injury in rats [44].

Future perspectives

Microglia imaging—the future has begun

Microglia research entered a new era when it became possible to study microglia activation in vivo [6, 7, 24]. In the context of microglia imaging, mitochondria have become a subject of special interest [8]. The spectrum of suitable positron emission tomography ligands has been extended in the meantime [114, 185, 186], and it has also become possible to watch microglial cells patrolling and at work in the living brain using two-photon microscopy [137]. In vivo imaging of microglial cells is now also being

performed in fish in order to understand basic neurobiological mechanisms [142]. However, it should be pointed out that there are known species differences even between mice and humans concerning macrophage activation pathways [119]. In addition to ex vivo live imaging [101], biophotonic/bioluminescence molecular imaging has been used recently to visualize transcriptional activation of microglial cells in the brains of live animals [99]. Attempts to target activated microglia in a transgenic mouse model of Alzheimer's pathology by means of intraventricular delivery of a phagocytosable MRI contrast agent have been made [132]. Microglia containing gadolinium-grafted nanoparticles have also been employed for in vivo imaging [148].

Bone marrow-derived microglia

There has been significant confusion in the literature over many years as to whether and if so to what extent microglia and macrophage precursors derived from the bone marrow exchange in the adult brain. Recent studies appear to settle the issue and it has been suggested that certain pathological conditions can trigger the recruitment of new, bone marrow-derived microglia [55]. However, microglia progenitor recruitment from the circulation in denervation or CNS neurodegenerative disease conditions remains a controversial issue [1, 123]. If it occurs at all in non-experimental conditions, it should be extremely limited. However, the ontogenetic link between bone marrow-derived cells and microglia now seems firmly established [41, 59, 165]. Interestingly, the functional phenotype of bone marrow-derived microglia appears to differ from that of resident cells [91]. Microglia recruit monocytes into the brain during peripheral organ inflammation [38]. Conversely, microglia- and bone marrow-derived dendritic cells can leave the CNS via the blood stream [77].

Microglia cell-based therapies

The use of genetically modified microglia precursors to study microglial cells in adult CNS has long been envisioned [65]. The development of microglia-based cell therapies now appears to be within reach [41, 68, 135]. A number of therapeutic uses of microglia have been proposed.

Hematoma resolution may be one potential therapeutic application [201]. Microglia have also been proposed as vehicles for inducible thymidine kinase gene therapy [148]. Nanotubes which are taken up by microglia could be utilized as novel vehicles for targeted therapy in brain cancers [93] although precautions have to be taken because the side-effects of nanotubes have not been sufficiently studied. While depletion of peripheral macrophages and brain microglia increases therapeutically desirable brain tumor titers of oncolytic viruses [56], irradiation-induced loss of microglia occurs in the young brain possibly contributing to the development of cognitive deficits [90].

A number of attempts have been made to control microglial activation through pharmacological intervention ranging from herbal medicine [109] to antibiotics [74] and neurotransmitter analogs [195]. Activation of adenosine 2A receptors after intrathecal administration may be a novel, therapeutic approach for the treatment of neuropathic pain by increasing IL-10 in the immunocompetent cells of the CNS [111]. IL-10 production is reduced by hypothermia but augmented by hyperthermia in rat microglia [120]. Modulation of microglia is of special interest for the potential treatment of inflammatory disease conditions. Moreover, enhanced microglial activation and proinflammatory cytokine upregulation have been linked to increased susceptibility to seizures and neurologic injury [164].

It appears that microglia can be used to both minimize cytotoxicity and maximize neuroprotection in neurodegenerative diseases. Specifically, wild-type microglia extend survival in PU.1 knockout mice with a familial amyotrophic lateral sclerosis mutation [10]. Similarly, activation of bone marrow-derived microglia promotes photoreceptor survival in inherited retinal degeneration [156]. Resident microglia and recently bone marrow-derived cells are assumed to co-operate [87]. Furthermore, bone marrow-derived mesenchymal stem cells reduce brain amyloid-beta deposition and accelerate the activation of microglia in an acutely induced Alzheimer's disease mouse model [102]. Finally, microglia have been recently implicated in volume recovery in non-neurogenic brain regions during abstinence after alcohol dependence preceding neurogenesis [138].

Acknowledgments We would like to thank Dr Hua Yao for the electron micrographs and Dr Qing-Shan Xue for the preparation of the schematic drawing.

References

1. Ajami B, Bennett JL, Krieger C, Tetzlaff W, Rossi FM (2007) Local self-renewal can sustain CNS microglia maintenance and function throughout adult life. Nat Neurosci 10:1538–1543
2. Albright AV, González-Scarano F (2004) Microarray analysis of activated mixed glial (microglia) and monocyte-derived macrophage gene expression. J Neuroimmunol 157:27–38
3. Appel SH, Beers DR, Henkel JS (2009) T cell-microglial dialogue in Parkinson's disease and amyotrophic lateral sclerosis: are we listening? Trends Immunol. doi:10.1016/j.it.2009.09.003
4. Araque A (2008) Astrocytes process synaptic information. Neuron Glia Biol 4:3–10
5. Asheuer M, Pflumio F, Benhamida S, Dubart-Kupperschmitt A, Fouquet F, Imai Y, Aubourg P, Cartier N (2004) Human CD34+

cells differentiate into microglia and express recombinant therapeutic protein. Proc Natl Acad Sci USA 101:3557–3562
6. Banati RB, Myers R, Kreutzberg GW (1997) PK ('peripheral benzodiazepine')-binding sites in the CNS indicate early and discrete brain lesions: microautoradiographic detection of [3H]PK11195 binding to activated microglia. J Neurocytol 26:77–82
7. Banati RB, Newcombe J, Gunn RN, Cagnin A, Turkheimer F, Heppner F, Price G, Wegner F, Giovannoni G, Miller DH, Perkin GD, Smith T, Hewson AK, Bydder G, Kreutzberg GW, Jones T, Cuzner ML, Myers R (2000) The peripheral benzodiazepine binding site in the brain in multiple sclerosis: quantitative in vivo imaging of microglia as a measure of disease activity. Brain 123:2321–2337
8. Banati RB, Egensperger R, Maassen A, Hager G, Kreutzberg GW, Graeber MB (2004) Mitochondria in activated microglia in vitro. J Neurocytol 33:535–541
9. Beauvillain C, Donnou S, Jarry U, Scotet M, Gascan H, Delneste Y, Guermonprez P, Jeannin P, Couez D (2008) Neonatal and adult microglia cross-present exogenous antigens. Glia 56:69–77
10. Beers DR, Henkel JS, Xiao Q, Zhao W, Wang J, Yen AA, Siklos L, McKercher SR, Appel SH (2006) Wild-type microglia extend survival in PU.1 knockout mice with familial amyotrophic lateral sclerosis. Proc Natl Acad Sci USA 103:16021–16026
11. Bennett MR, Farnell L, Gibson WG (2009) P2X(7) regenerative-loop potentiation of glutamate synaptic transmission by microglia and astrocytes. J Theor Biol 261:1–16
12. Bertolotto A, Agresti C, Castello A, Manzardo E, Riccio A (1998) 5D4 keratan sulfate epitope identifies a subset of ramified microglia in normal central nervous system parenchyma. J Neuroimmunol 85:69–77
13. Billiards SS, Haynes RL, Folkerth RD, Trachtenberg FL, Liu LG, Volpe JJ, Kinney HC (2006) Development of microglia in the cerebral white matter of the human fetus and infant. J Comp Neurol 497:199–208
14. Blasi E, Barluzzi R, Bocchini V, Mazzolla R, Bistoni F (1990) Immortalization of murine microglial cells by a v-raf/v-myc carrying retrovirus. J Neuroimmunol 27:229–237
15. Blinzinger K, Kreutzberg G (1968) Displacement of synaptic terminals from regenerating motoneurons by microglial cells. Z Zellforsch Mikroskop Anat 85:145–157
16. Boer K, Spliet WG, van Rijen PC, Redeker S, Troost D, Aronica E (2006) Evidence of activated microglia in focal cortical dysplasia. J Neuroimmunol 173:188–195
17. Boillée S, Cleveland DW (2008) Revisiting oxidative damage in ALS: microglia, Nox, and mutant SOD1. J Clin Invest 118:474–478
18. Boillée S, Yamanaka K, Lobsiger CS, Copeland NG, Jenkins NA, Kassiotis G, Kollias G, Cleveland DW (2006) Onset and progression in inherited ALS determined by motor neurons and microglia. Science 312:1389–1392
19. Borda JT, Alvarez X, Mohan M, Hasegawa A, Bernardino A, Jean S, Aye P, Lackner AA (2008) CD163, a marker of perivascular macrophages, is up-regulated by microglia in simian immunodeficiency virus encephalitis after haptoglobin-hemoglobin complex stimulation and is suggestive of breakdown of the blood-brain barrier. Am J Pathol 172:725–737
20. Bradesi S, Svensson CI, Steinauer J, Pothoulakis C, Yaksh TL, Mayer EA (2008) Role of spinal microglia in visceral hyperalgesia and NK1R up-regulation in a rat model of chronic stress. Gastroenterology. doi:10.1053/j.gastro.2008.12.044
21. Brochard V, Combadière B, Prigent A, Laouar Y, Perrin A, Beray-Berthat V, Bonduelle O, Alvarez-Fischer D, Callebert J, Launay JM, Duyckaerts C, Flavell RA, Hirsch EC, Hunot S (2009) Infiltration of CD4+ lymphocytes into the brain contributes to neurodegeneration in a mouse model of Parkinson disease. J Clin Invest 119:182–192
22. Butovsky O, Bukshpan S, Kunis G, Jung S, Schwartz M (2007) Microglia can be induced by IFN-gamma or IL-4 to express neural or dendritic-like markers. Mol Cell Neurosci 35:490–500
23. Byrnes KR, Garay J, Di Giovanni S, De Biase A, Knoblach SM, Hoffman EP, Movsesyan V, Faden AI (2006) Expression of two temporally distinct microglia-related gene clusters after spinal cord injury. Glia 53:420–433
24. Cagnin A, Brooks DJ, Kennedy AM, Gunn RN, Myers R, Turkheimer FE, Jones T, Banati RB (2001) In vivo measurement of activated microglia in dementia. Lancet 358:461–467
25. Calderó J, Brunet N, Ciutat D, Hereu M, Esquerda JE (2009) Development of microglia in the chick embryo spinal cord: implications in the regulation of motoneuronal survival and death. J Neurosci Res. doi:10.1002/jnr.22084
26. Chakrabarty P, Jansen-West K, Beccard A, Ceballos-Diaz C, Levites Y, Verbeeck C, Zubair AC, Dickson D, Golde TE, Das P (2009) Massive gliosis induced by interleukin-6 suppresses A{beta} deposition in vivo: evidence against inflammation as a driving force for amyloid deposition. FASEB J. doi:10.1096/fj.09-141754
27. Chauhan VS, Sterka DG, Furr SR, Young AB, Marriott I (2009) NOD2 plays an important role in the inflammatory responses of microglia and astrocytes to bacterial CNS pathogens. Glia 57:414–423
28. Checchin D, Sennlaub F, Levavasseur E, Leduc M, Chemtob S (2006) Potential role of microglia in retinal blood vessel formation. Invest Ophthalmol Vis Sci 47:3595–3602
29. Chen J, Connor KM, Smith LE (2007) Overstaying their welcome: defective CX3CR1 microglia eyed in macular degeneration. J Clin Invest 117:2758–2762
30. Chen L, Yang P, Kijlstra A (2002) Distribution, markers, and functions of retinal microglia. Ocul Immunol Inflamm 10:27–39
31. Chigurupati S, Wei Z, Belal C, Vandermey M, Kyriazis GA, Arumugam TV, Chan SL (2009) The homocysteine-inducible endoplasmic reticulum stress protein counteracts calcium store depletion and induction of CCAAT enhancer-binding protein homologous protein in a neurotoxin model of Parkinson disease. J Biol Chem 284:18323–18333
32. Choi SH, Veeraraghavalu K, Lazarov O, Marler S, Ransohoff RM, Ramirez JM, Sisodia SS (2008) Non-cell-autonomous effects of presenilin 1 variants on enrichment-mediated hippocampal progenitor cell proliferation and differentiation. Neuron 59:568–580
33. Clausen BH, Lambertsen KL, Babcock AA, Holm TH, Dagnaes-Hansen F, Finsen B (2008) Interleukin-1beta and tumor necrosis factor-alpha are expressed by different subsets of microglia and macrophages after ischemic stroke in mice. J Neuroinflamm 5:46
34. Combadière C, Feumi C, Raoul W, Keller N, Rodéro M, Pézard A, Lavalette S, Houssier M, Jonet L, Picard E, Debré P, Sirinyan M, Deterre P, Ferroukhi T, Cohen SY, Chauvaud D, Jeanny JC, Chemtob S, Behar-Cohen F, Sennlaub F (2007) CX3CR1-dependent subretinal microglia cell accumulation is associated with cardinal features of age-related macular degeneration. J Clin Invest 117:2920–2928
35. Croisier E, Graeber MB (2006) Glial degeneration and reactive gliosis in alpha-synucleinopathies: the emerging concept of primary gliodegeneration. Acta Neuropathol 112:517–530
36. Croisier E, Moran LB, Dexter DT, Pearce RK, Graeber MB (2005) Microglial inflammation in the parkinsonian substantia nigra: relationship to alpha-synuclein deposition. J Neuroinflammation 2:14. doi:10.1186/1742-2094-2-14
37. Croisier E, Moran LB, Graeber MB (2007) Expression of the scavenger receptor CD163 in Parkinson's disease. Meeting of

the British Neuropathological Society, 108th Meeting, Institute of Child Health, London UK, January 2007. Neuropathol Appl Neurobiol 33:266
38. D'Mello C, Le T, Swain MG (2009) Cerebral microglia recruit monocytes into the brain in response to tumor necrosis factor{alpha} signaling during peripheral organ inflammation. J Neurosci 29:2089–2102
39. Daginakatte GC, Gutmann DH (2007) Neurofibromatosis-1 (Nf1) heterozygous brain microglia elaborate paracrine factors that promote Nf1-deficient astrocyte and glioma growth. Hum Mol Genetics 16:1098–1112
40. Daginakatte GC, Gianino SM, Zhao NW, Parsadanian AS, Gutmann DH (2008) Increased c-Jun-NH2-kinase signaling in neurofibromatosis-1 heterozygous microglia drives microglia activation and promotes optic glioma proliferation. Cancer Res 68:10358–10366
41. Davoust N, Vuaillat C, Androdias G, Nataf S (2008) From bone marrow to microglia: barriers and avenues. Trends Immunol 29:227–234
42. de Jong EK, de Haas AH, Brouwer N, van Weering HR, Hensens M, Bechmann I, Pratley P, Wesseling E, Boddeke HW, Biber K (2008) Expression of CXCL4 in microglia in vitro and in vivo and its possible signaling through CXCR3. J Neurochem 105:1726–1736
43. Deng YY, Lu J, Ling EA, Kaur C (2009) Monocyte chemoattractant protein-1 (MCP-1) produced via NF-kappaB signaling pathway mediates migration of amoeboid microglia in the periventricular white matter in hypoxic neonatal rats. Glia 57:604–621
44. Detloff MR, Fisher LC, McGaughy V, Longbrake EE, Popovich PG, Basso DM (2008) Remote activation of microglia and pro-inflammatory cytokines predict the onset and severity of below-level neuropathic pain after spinal cord injury in rats. Exp Neurol 212:337–347
45. Dolman CL (1991) Microglia. In: Davis RL, Robertson DM (eds) Textbook of neuropathology. Williams and Wilkins, Baltimore, pp 141–163
46. Dominguez E, Rivat C, Pommier B, Mauborgne A, Pohl M (2008) JAK/STAT3 pathway is activated in spinal cord microglia after peripheral nerve injury and contributes to neuropathic pain development in rat. J Neurochem 107:50–60
47. Duke DC, Moran LB, Turkheimer FE, Banati R, Graeber MB (2004) Microglia in culture: what genes do they express? Dev Neurosci 26:30–37
48. Duke DC, Moran LB, Kalaitzakis ME, Deprez M, Dexter DT, Pearce RK, Graeber MB (2006) Transcriptome analysis reveals link between proteasomal and mitochondrial pathways in Parkinson's disease. Neurogenetics 7:139–148
49. Ekdahl CT, Kokaia Z, Lindvall O (2008) Brain inflammation and adult neurogenesis: The dual role of microglia. Neuroscience. doi:10.1016/j.neuroscience.2008.06.052
50. El Khoury J, Luster AD (2008) Mechanisms of microglia accumulation in Alzheimer's disease: therapeutic implications. Trends Pharmacol Sci 29:626–632
51. Ethell DW, Shippy D, Cao C, Cracchiolo JR, Runfeldt M, Blake B, Arendash GW (2006) Abeta-specific T-cells reverse cognitive decline and synaptic loss in Alzheimer's mice. Neurobiol Dis 23:351–361
52. Fan X, Luo G, Ming M, Pu P, Li L, Yang D, Le W (2009) Nurr1 expression and its modulation in microglia. Neuroimmunomodulation 16:162–170
53. Fendrick SE, Xue QS, Streit WJ (2007) Formation of multinucleated giant cells and microglial degeneration in rats expressing a mutant Cu/Zn superoxide dismutase gene. J Neuroinflammation 4:9
54. Fernandez-Lizarbe S, Pascual M, Guerri C (2009) Critical role of TLR4 response in the activation of microglia induced by ethanol. J Immunol. doi:10.4049/jimmunol.0803590
55. Flügel A, Bradl M, Kreutzberg GW, Graeber MB (2001) Transformation of donor-derived bone marrow precursors into host microglia during autoimmune CNS inflammation and during the retrograde response to axotomy. J Neurosci Res 66:74–82
56. Fulci G, Dmitrieva N, Gianni D, Fontana EJ, Pan X, Lu Y, Kaufman CS, Kaur B, Lawler SE, Lee RJ, Marsh CB, Brat DJ, Van Rooijen N, Stemmer-Rachamimov AO, Rachamimov AS, Hochberg FH, Weissleder R, Martuza RL, Chiocca EA (2007) Depletion of peripheral macrophages and brain microglia increases brain tumor titers of oncolytic viruses. Cancer Res 67:9398–9406
57. Gebicke-Haerter PJ (2005) Microarrays and expression profiling in microglia research and in inflammatory brain disorders. J Neurosci Res 81:327–341
58. Geranmayeh F, Scheithauer BW, Spitzer C, Meyer FB, Svensson-Engwall AC, Graeber MB (2007) Microglia in gemistocytic astrocytomas. Neurosurgery 60:159–166
59. Getts DR, Terry RL, Getts MT, Müller M, Rana S, Shrestha B, Radford J, Van Rooijen N, Campbell IL, King NJ (2008) Ly6c+ "inflammatory monocytes" are microglial precursors recruited in a pathogenic manner in West Nile virus encephalitis. J Exp Med 205:2319–2337
60. Glanzer JG, Enose Y, Wang T, Kadiu I, Gong N, Rozek W, Liu J, Schlautman JD, Ciborowski PS, Thomas MP, Gendelman HE (2007) Genomic and proteomic microglial profiling: pathways for neuroprotective inflammatory responses following nerve fragment clearance and activation. J Neurochem 102:627–645
61. Gowing G, Philips T, Van Wijmeersch B, Audet JN, Dewil M, Van Den Bosch L, Billiau AD, Robberecht W, Julien JP (2008) Ablation of proliferating microglia does not affect motor neuron degeneration in amyotrophic lateral sclerosis caused by mutant superoxide dismutase. J Neurosci 28:10234–10244
62. Gowing G, Lalancette-Hébert M, Audet JN, Dequen F, Julien JP (2009) Macrophage colony stimulating factor (M-CSF) exacerbates ALS disease in a mouse model through altered responses of microglia expressing mutant superoxide dismutase. Exp Neurol. doi:10.1016/j.expneurol.2009.08.021
63. Graeber MB (2000) Glial inflammation in neurodegenerative diseases. In: 8th Annual Congress of the British Society for Immunology, Harrogate, 5–8 December 2000, Immunology Issue Supplement. Blackwell, Oxford (Abstract)
64. Graeber MB (2009) Biomarkers for Parkinson's disease. Exp Neurol 216:249–253
65. Graeber MB, Streit WJ (1990) Microglia: immune network in the CNS. Brain Pathol 1:2–5
66. Graeber MB, Bise K, Mehraein P (1993) Synaptic stripping in the human facial nucleus. Acta Neuropathol 86:179–181
67. Graeber MB, Blakemore WF, Kreutzberg GW (2002) Cellular pathology of the central nervous system. In: Graham DI, Lantos PL (eds) Greenfield's neuropathology, chap 3, 7th edn. Edward Arnold, London, pp 123–191
68. Graeber MB, Scheithauer BW, Kreutzberg GW (2002) Microglia in brain tumors. Glia 40:252–259
69. Graeber MB, López-Redondo F, Ikoma E, Ishikawa M, Imai Y, Nakajima K, Kreutzberg GW, Kohsaka S (1998) The microglia/macrophage response in the neonatal rat facial nucleus following axotomy. Brain Res 813:241–253
70. Grasbon-Frodl EM, Flügel A, Wolz P, Klinkert WEF, Kreutzberg GW, Graeber MB (1998) Untersuchungen zur Funktion von Mikroglia in Hirntumoren: Förderung des Wachstums von C6-Gliomzellen in vitro. Jahrestagung der Neuroonkologischen

Arbeitsgemeinschaft der Deutschen Gesellschaft für Neurochirurgie in Dresden, 6–7 November 1998
71. Grathwohl SA, Kälin RE, Bolmont T, Prokop S, Winkelmann G, Kaeser SA, Odenthal J, Radde R, Eldh T, Gandy S, Aguzzi A, Staufenbiel M, Mathews PM, Wolburg H, Heppner FL, Jucker M (2009) Formation and maintenance of Alzheimer's disease beta-amyloid plaques in the absence of microglia. Nat Neurosci. doi:10.1038/nn.2432
72. Gupta N, Brown KE, Milam AH (2003) Activated microglia in human retinitis pigmentosa, late-onset retinal degeneration, and age-related macular degeneration. Exp Eye Res 76:463–471
73. Harry GJ, Kraft AD (2008) Neuroinflammation and microglia: considerations and approaches for neurotoxicity assessment. Expert Opin Drug Metab Toxicol 4:1265–1277
74. Hayakawa K, Mishima K, Nozako M, Hazekawa M, Mishima S, Fujioka M, Orito K, Egashira N, Iwasaki K, Fujiwara M (2008) Delayed treatment with minocycline ameliorates neurologic impairment through activated microglia expressing a high-mobility group box1-inhibiting mechanism. Stroke 39: 951–958
75. Henn A, Lund S, Hedtjärn M, Schrattenholz A, Pörzgen P, Leist M (2009) The suitability of BV2 cells as alternative model system for primary microglia cultures or for animal experiments examining brain inflammation. ALTEX (Alternativen zu Tierexperimenten) 26:83–94
76. Hines DJ, Hines RM, Mulligan SJ, Macvicar BA (2009) Microglia processes block the spread of damage in the brain and require functional chloride channels. Glia. doi:10.1002/glia.20874
77. Hochmeister S, Zeitelhofer M, Bauer J, Nicolussi EM, Fischer MT, Heinke B, Selzer E, Lassmann H, Bradl M (2008) After injection into the striatum, in vitro-differentiated microglia- and bone marrow-derived dendritic cells can leave the central nervous system via the blood stream. Am J Pathol 173:1669–1681
78. Horvath RJ, Nutile-McMenemy N, Alkaitis MS, DeLeo JA (2008) Differential migration, LPS-induced cytokine, chemokine, and NO expression in immortalized BV-2 and HAPI cell lines and primary microglial cultures. J Neurochem 107:557–569
79. Hudson LC, Bragg DC, Tompkins MB, Meeker RB (2005) Astrocytes and microglia differentially regulate trafficking of lymphocyte subsets across brain endothelial cells. Brain Res 1058:148–160
80. Hunter RL, Cheng B, Choi DY, Liu M, Liu S, Cass WA, Bing G (2009) Intrastriatal lipopolysaccharide injection induces parkinsonism in C57/B6 mice. J Neurosci Res 87:1913–1921
81. Hwang SH, Yoo BC, Jung JS, Oh ES, Hwang J, Shin JA, Kim S, Cha S, Han IO (2009) Induction of glioma apoptosis by microglia-secreted molecules: the role of nitric oxide and cathepsin B. Biochim Biophys Acta. doi:10.1016/j.bbamcr.2009.08.011
82. Imai Y, Ibata I, Ito D, Ohsawa K, Kohsaka S (1996) A novel gene iba1 in the major histocompatibility complex class III region encoding an EF hand protein expressed in a monocytic lineage. Biochem Biophys Res Commun 224:855–862
83. Inoue K, Tsuda M (2009) Microglia and neuropathic pain. Glia. doi:10.1002/glia.20871
84. Ito D, Imai Y, Ohsawa K, Nakajima K, Fukuuchi Y, Kohsaka S (1998) Microglia-specific localisation of a novel calcium binding protein, Iba1. Mol Brain Res 57:1–9
85. Jana M, Palencia CA, Pahan K (2008) Fibrillar amyloid-beta peptides activate microglia via TLR2: implications for Alzheimer's disease. J Immunol 181:7254–7262
86. Jang H, Boltz D, Sturm-Ramirez K, Shepherd KR, Jiao Y, Webster R, Smeyne RJ (2009) Highly pathogenic H5N1 influenza virus can enter the central nervous system and induce neuroinflammation and neurodegeneration. Proc Natl Acad Sci USA 106:14063–14068
87. Joly S, Francke M, Ulbricht E, Beck S, Seeliger M, Hirrlinger P, Hirrlinger J, Lang KS, Zinkernagel M, Odermatt B, Samardzija M, Reichenbach A, Grimm C, Remé CE (2009) Cooperative phagocytes: resident microglia and bone marrow immigrants remove dead photoreceptors in retinal lesions. Am J Pathol 174:2310–2323
88. Jones LL, Banati RB, Graeber MB, Bonfanti L, Raivich G, Kreutzberg GW (1997) Population control of microglia: does apoptosis play a role? J Neurocytol 26:755–770
89. Jones N (2009) 'Propaganda index' proposed for medical literature. Nature Med 15:1100–1101
90. Kalm M, Lannering B, Björk-Eriksson T, Blomgren K (2009) Irradiation-induced loss of microglia in the young brain. J Neuroimmunol 206:70–75
91. Kaneko H, Nishiguchi KM, Nakamura M, Kachi S, Terasaki H (2008) Characteristics of bone marrow-derived microglia in the normal and injured retina. Invest Ophthalmol Vis Sci 49:4162–4168
92. Kataoka A, Tozaki-Saitoh H, Koga Y, Tsuda M, Inoue K (2009) Activation of P2X7 receptors induces CCL3 production in microglial cells through transcription factor NFAT. J Neurochem 108:115–125
93. Kateb B, Van Handel M, Zhang L, Bronikowski MJ, Manohara H, Badie B (2007) Internalization of MWCNTs by microglia: possible application in immunotherapy of brain tumors. NeuroImage 37(Suppl 1):S9–S17
94. Kauppinen TM, Higashi Y, Suh SW, Escartin C, Nagasawa K, Swanson RA (2008) Zinc triggers microglial activation. J Neurosci 28:5827–5835
95. Kawanokuchi J, Shimizu K, Nitta A, Yamada K, Mizuno T, Takeuchi H, Suzumura A (2008) Production and functions of IL-17 in microglia. J Neuroimmunol 194:54–61
96. Kobayashi K, Yamanaka H, Fukuoka T, Dai Y, Obata K, Noguchi K (2008) P2Y12 receptor upregulation in activated microglia is a gateway of p38 signaling and neuropathic pain. J Neurosci 28:2892–2902
97. Kreutzberg GW (1996) Microglia: a sensor for pathological events in the CNS. Trends Neurosci 19:312–318
98. Ladeby R, Wirenfeldt M, Dalmau I, Gregersen R, García-Ovejero D, Babcock A, Owens T, Finsen B (2005) Proliferating resident microglia express the stem cell antigen CD34 in response to acute neural injury. Glia 50:121–131
99. Lalancette- Hébert M, Phaneuf D, Soucy G, Weng YC, Kriz J (2009) Live imaging of Toll-like receptor 2 response in cerebral ischaemia reveals a role of olfactory bulb microglia as modulators of inflammation. Brain. doi:10.1093/brain/awn345
100. Lawson LJ, Perry VH, Dri P, Gordon S (1990) Heterogeneity in the distribution and morphology of microglia in the normal adult mouse brain. Neuroscience 39:151–170
101. Lee JE, Liang KJ, Fariss RN, Wong WT (2008) Ex vivo dynamic imaging of retinal microglia using time-lapse confocal microscopy. Invest Ophthalmol Vis Sci 49:4169–4176
102. Lee JK, Jin HK, Bae JS (2009) Bone marrow-derived mesenchymal stem cells reduce brain amyloid-beta deposition and accelerate the activation of microglia in an acutely induced Alzheimer's disease mouse model. Neurosci Lett 450:136–141
103. Leung E, Guo L, Bu J, Maloof M, Khoury JE, Geula C (2009) Microglia activation mediates fibrillar amyloid-beta toxicity in the aged primate cortex. Neurobiol Aging. doi:10.1016/j.neurobiolaging.2009.02.025
104. Li W, Gao G, Guo Q, Jia D, Wang J, Wang X, He S, Liang Q (2009) Function and phenotype of microglia are determined by Toll-like receptor 2/Toll-like receptor 4 activation sequence. DNA Cell Biol. doi:10.1089/dna.2009.0856

105. Liebrich M, Guo LH, Schluesener HJ, Schwab JM, Dietz K, Will BE, Meyermann R (2007) Expression of interleukin-16 by tumor-associated macrophages/activated microglia in high-grade astrocytic brain tumors. Arch Immunol Ther Exp (Warsz) 55:41–47
106. Liu B, Wang K, Gao HM, Mandavilli B, Wang JY, Hong JS (2001) Molecular consequences of activated microglia in the brain: overactivation induces apoptosis. J Neurochem 77:182–189
107. Liu C, Luo D, Streit WJ, Harrison JK (2008) CX3CL1 and CX3CR1 in the GL261 murine model of glioma: CX3CR1 deficiency does not impact tumor growth or infiltration of microglia and lymphocytes. J Neuroimmunol. doi:10.1016/j.jneuroim.2008.04.016
108. Liu GJ, Nagarajah R, Banati RB, Bennett MR (2009) Glutamate induces directed chemotaxis of microglia. Eur J Neurosci 29:1108–1118
109. Liu H, Wang J, Sekiyama A, Tabira T (2008) Juzen-taiho-to, an herbal medicine, activates and enhances phagocytosis in microglia/macrophages. Tohoku J Exp Med 215:43–54
110. Liu Y, Hao W, Dawson A, Liu S, Fassbender K (2009) Expression of amyotrophic lateral sclerosis-linked SOD1 mutant increases the neurotoxic potential of microglia via TLR2. J Biol Chem 284:3691–3699
111. Loram LC, Harrison JA, Sloane EM, Hutchinson MR, Sholar P, Taylor FR, Berkelhammer D, Coats BD, Poole S, Milligan ED, Maier SF, Rieger J, Watkins LR (2009) Enduring reversal of neuropathic pain by a single intrathecal injection of adenosine 2A receptor agonists: a novel therapy for neuropathic pain. J Neurosci 29:14015–14025
112. Lu H, Li Y, Shu M, Tang J, Huang Y, Zhou Y, Liang Y, Yan G (2009) Hypoxia-inducible factor-1alpha blocks differentiation of malignant gliomas. FEBS J. doi:10.1111/j.1742-4658.2009.07441.x
113. Lünemann A, Ullrich O, Diestel A, Jöns T, Ninnemann O, Kovac A, Pohl EE, Hass R, Nitsch R, Hendrix S (2006) Macrophage/microglia activation factor expression is restricted to lesion-associated microglial cells after brain trauma. Glia 53:412–419
114. Maeda J, Higuchi M, Inaji M, Ji B, Haneda E, Okauchi T, Zhang MR, Suzuki K, Suhara T (2007) Phase-dependent roles of reactive microglia and astrocytes in nervous system injury as delineated by imaging of peripheral benzodiazepine receptor. Brain Res 1157:100–111
115. Mandrekar S, Jiang Q, Lee CY, Koenigsknecht-Talboo J, Holtzman DM, Landreth GE (2009) Microglia mediate the clearance of soluble Abeta through fluid phase macropinocytosis. J Neurosci 29:4252–4262
116. Markovic DS, Vinnakota K, Chirasani S, Synowitz M, Raguet H, Stock K, Sliwa M, Lehmann S, Kälin R, Van Rooijen N, Holmbeck K, Heppner F, Kiwit J, Matyash V, Lehnardt S, Kaminska B, Glass R, Kettenmann H (2009) Gliomas induce and exploit microglial MT1-MMP expression for tumor expansion. Proc Natl Acad Sci USA. doi:10.1073/pnas.0804273106
117. Marques CP, Cheeran MC, Palmquist JM, Hu S, Lokensgard JR (2008) Microglia are the major cellular source of inducible nitric oxide synthase during experimental herpes encephalitis. J Neurovirol 14:229–238
118. Marshall GP, Demir M, Steindler DA, Laywell ED (2008) Subventricular zone microglia possess a unique capacity for massive in vitro expansion. Glia 56:1799–1808
119. Martinez FO, Helming L, Gordon S (2009) Alternative activation of macrophages: an immunologic functional perspective. Ann Rev Immunol 27:451–483
120. Matsui T, Kakeda T (2008) IL-10 production is reduced by hypothermia but augmented by hyperthermia in rat microglia. J Neurotrauma 25:709–715
121. Mayo L, Jacob-Hirsch J, Amariglio N, Rechavi G, Moutin MJ, Lund FE, Stein R (2008) Dual role of CD38 in microglial activation and activation-induced cell death. J Immunol 181:92–103
122. McGeer PL, Itagaki S, McGeer EG (1988) Expression of the histocompatibility glycoprotein HLA-DR in neurological disease. Acta Neuropathol 76:550–557
123. Mildner A, Schmidt H, Nitsche M, Merkler D, Hanisch UK, Mack M, Heikenwalder M, Brück W, Priller J, Prinz M (2007) Microglia in the adult brain arise from Ly-6ChiCCR2+ monocytes only under defined host conditions. Nat Neurosci 10:1544–1553
124. Mittelbronn M, Dietz K, Schluesener HJ, Meyermann R (2001) Local distribution of microglia in the normal adult human central nervous system differs by up to one order of magnitude. Acta Neuropathol 101:249–255
125. Miyoshi K, Obata K, Kondo T, Okamura H, Noguchi K (2008) Interleukin-18-mediated microglia/astrocyte interaction in the spinal cord enhances neuropathic pain processing after nerve injury. J Neurosci 28:12775–12787
126. Monier A, Evrard P, Gressens P, Verney C (2006) Distribution and differentiation of microglia in the human encephalon during the first two trimesters of gestation. J Comp Neurol 499:565–582
127. Moran LB, Graeber MB (2004) The facial nerve axotomy model. Brain Res Rev 44:154–178
128. Moran LB, Graeber MB (2008) Towards a pathway definition of Parkinson's disease: a complex disorder with links to cancer, diabetes and inflammation. Neurogenetics 9:1–13
129. Moran LB, Duke DC, Turkheimer FE, Banati RB, Graeber MB (2004) Towards a transcriptome definition of microglial cells. Neurogenetics 5:95–108
130. Moran LB, Duke DC, Graeber MB (2007) The microglial gene regulatory network activated by interferon-gamma. J Neuroimmunol 183:1–6
131. Morgan D (2009) The role of microglia in antibody-mediated clearance of amyloid-Beta from the brain. CNS Neurol Disord Drug Targets 8:7–15
132. Mundt AP, Winter C, Mueller S, Wuerfel J, Tysiak E, Schnorr J, Taupitz M, Heinz A, Juckel G (2009) Targeting activated microglia in Alzheimer's pathology by intraventricular delivery of a phagocytosable MRI contrast agent in APP23 transgenic mice. NeuroImage 46:367–372
133. Nakajima K, Graeber MB, Sonoda M, Tohyama Y, Kohsaka S, Kurihara T (2006) In vitro proliferation of axotomized rat facial nucleus-derived activated microglia in an autocrine fashion. J Neurosci Res 84:348–359
134. Nakano T, Iseki K, Hozumi Y, Kawamae K, Wakabayashi I, Goto K (2009) Brain trauma induces expression of diacylglycerol kinase zeta in microglia. Neurosci Lett. doi:10.1016/j.neulet.2009.06.001
135. Neumann H (2006) Microglia: a cellular vehicle for CNS gene therapy. J Clin Invest 116:2857–2860
136. Neumann J, Gunzer M, Gutzeit HO, Ullrich O, Reymann KG, Dinkel K (2006) Microglia provide neuroprotection after ischemia. FASEB J 20:714–716
137. Nimmerjahn A, Kirchhoff F, Helmchen F (2005) Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. Science 308:1314–1318
138. Nixon K, Kim DH, Potts EN, He J, Crews FT (2008) Distinct cell proliferation events during abstinence after alcohol dependence: microglia proliferation precedes neurogenesis. Neurobiol Dis 31:218–229
139. Okada M, Saio M, Kito Y, Ohe N, Yano H, Yoshimura S, Iwama T, Takami T (2009) Tumor-associated macrophage/microglia infiltration in human gliomas is correlated with MCP-3, but not MCP-1. Int J Oncol 34:1621–1627

140. Ovanesov MV, Ayhan Y, Wolbert C, Moldovan K, Sauder C, Pletnikov MV (2008) Astrocytes play a key role in activation of microglia by persistent Borna disease virus infection. J Neuroinflammation 5:50
141. Park JY, Choi HJ, Prabagar MG, Choi WS, Kim SJ, Cheong C, Park CG, Chin CY, Kang YS (2009) The C-type lectin CD209b is expressed on microglia and it mediates the uptake of capsular polysaccharides of Streptococcus pneumoniae. Neurosci Lett 450:246–251
142. Peri F, Nüsslein-Volhard C (2008) Live imaging of neuronal degradation by microglia reveals a role for v0-ATPase a1 in phagosomal fusion in vivo. Cell 133:916–927
143. Polazzi E, Contestabile A (2006) Overactivation of LPS-stimulated microglial cells by co-cultured neurons or neuron-conditioned medium. J Neuroimmunol 172:104–111
144. Power JH, Blumbergs PC (2009) Cellular glutathione peroxidase in human brain: cellular distribution, and its potential role in the degradation of Lewy bodies in Parkinson's disease and dementia with Lewy bodies. Acta Neuropathol 117:63–73
145. Quik M, Campos C, Parameswaran N, Langston JW, McIntosh JM, Yeluashvili M (2009) Chronic nicotine treatment Increases nAChRs and microglial expression in monkey substantia nigra after nigrostriatal damage. J Mol Neurosci. doi:10.1007/s12031-009-9265-9
146. Raivich G, Jones LL, Kloss CU, Werner A, Neumann H, Kreutzberg GW (1998) Immune surveillance in the injured nervous system: T-lymphocytes invade the axotomized mouse facial motor nucleus and aggregate around sites of neuronal degeneration. J Neurosci 18:5804–5816
147. Reynolds AD, Glanzer JG, Kadiu I, Ricardo-Dukelow M, Chaudhuri A, Ciborowski P, Cerny R, Gelman B, Thomas MP, Mosley RL, Gendelman HE (2007) Nitrated alpha-synuclein-activated microglial profiling for Parkinson's disease. J Neurochem. doi:10.1111/j.1471-4159.2007.05087.x
148. Ribot E, Bouzier-Sore AK, Bouchaud V, Miraux S, Delville MH, Franconi JM, Voisin P (2007) Microglia used as vehicles for both inducible thymidine kinase gene therapy and MRI contrast agents for glioma therapy. Cancer Gene Ther 14:724–737
149. Roberts ES, Masliah E, Fox HS (2004) CD163 identifies a unique population of ramified microglia in HIV encephalitis (HIVE). J Neuropathol Exp Neurol 63:1255–1264
150. Rochefort N, Quenech'du N, Watroba L, Mallat M, Giaume C, Milleret C (2002) Microglia and astrocytes may participate in the shaping of visual callosal projections during postnatal development. J Physiol Paris 96:183–192
151. Rogers J, Mastroeni D, Leonard B, Joyce J, Grover A (2007) Neuroinflammation in Alzheimer's disease and Parkinson's disease: are microglia pathogenic in either disorder? Int Rev Neurobiol 82:235–246
152. Romero-Sandoval EA, Horvath R, Landry RP, Deleo JA (2009) Cannabinoid receptor type 2 activation induces a microglial anti-inflammatory phenotype and reduces migration via MKP induction and ERK dephosphorylation. Mol Pain 5:25
153. Saijo K, Winner B, Carson CT, Collier JG, Boyer L, Rosenfeld MG, Gage FH, Glass CK (2009) A Nurr1/CoREST pathway in microglia and astrocytes protects dopaminergic neurons from inflammation-induced death. Cell 137:47–59
154. Sanz JM, Chiozzi P, Ferrari D, Colaianna M, Idzko M, Falzoni S, Fellin R, Trabace L, Di Virgilio F (2009) Activation of microglia by amyloid beta requires P2X7 receptor expression. J Immunol 182:4378–4385
155. Sargsyan SA, Blackburn DJ, Barber SC, Monk PN, Shaw PJ (2009) Mutant SOD1 G93A microglia have an inflammatory phenotype and elevated production of MCP-1. Neuroreport. doi:10.1097/WNR.0b013e328331e8fa
156. Sasahara M, Otani A, Oishi A, Kojima H, Yodoi Y, Kameda T, Nakamura H, Yoshimura N (2008) Activation of bone marrow-derived microglia promotes photoreceptor survival in inherited retinal degeneration. Am J Pathol 172:1693–1703
157. Sasaki A, Yamaguchi H, Horikoshi Y, Tanaka G, Nakazato Y (2004) Expression of glucose transporter 5 by microglia in human gliomas. Neuropathol Appl Neurobiol 30:447–455
158. Schmid CD, Melchior B, Masek K, Puntambekar SS, Danielson PE, Lo DD, Sutcliffe JG, Carson MJ (2009) Differential gene expression in LPS/IFNgamma activated microglia and macrophages: in vitro versus in vivo. J Neurochem 109(Suppl 1):117–125
159. Schwartz M, Butovsky O, Brück W, Hanisch U (2006) Microglial phenotype: is the commitment reversible? Trends Neurosci 29:68–74
160. Shimizu E, Kawahara K, Kajizono M, Sawada M, Nakayama H (2008) IL-4-induced selective clearance of oligomeric beta-amyloid peptide(1–42) by rat primary type 2 microglia. J Immunol 181:6503–6513
161. Simi A, Tsakiri N, Wang P, Rothwell NJ (2007) Interleukin-1 and inflammatory neurodegeneration. Biochem Soc Trans 35:1122–1126
162. Simmons DA, Casale M, Alcon B, Pham N, Narayan N, Lynch G (2007) Ferritin accumulation in dystrophic microglia is an early event in the development of Huntington's disease. Glia 55:1074–1084
163. Slodzinski H, Moran LB, Michael GJ, Wang B, Novoselov S, Cheetham ME, Pearce RK, Graeber MB (2009) Homocysteine-induced endoplasmic reticulum protein (herp) is up-regulated in parkinsonian substantia nigra and present in the core of Lewy bodies. Clin Neuropathol 28:333–343
164. Somera-Molina KC, Nair S, Van Eldik LJ, Watterson DM, Wainwright MS (2009) Enhanced microglial activation and proinflammatory cytokine upregulation are linked to increased susceptibility to seizures and neurologic injury in a 'two-hit' seizure model. Brain Res 1282:162–172
165. Soulet D, Rivest S (2008) Bone-marrow-derived microglia: myth or reality? Curr Opin Pharmacol 8:508–518
166. Streit W (2005) Microglia and neuroprotection: implications for Alzheimer's disease. Brain Res Rev 48:234–239
167. Streit WJ (2006) Microglial senescence: does the brain's immune system have an expiration date? Trends Neurosci 29:506–510
168. Streit WJ, Kincaid-Colton CA (1995) The brain's immune system. Sci Am 273(5):54–55, 58–61
169. Streit WJ, Xue QS (2009) Life and death of microglia. J NeuroImmune Pharmacol. doi:10.1007/s11481-009-9163-5
170. Streit WJ, Graeber MB, Kreutzberg GW (1988) Functional plasticity of microglia: a review. Glia 1:301–307
171. Streit WJ, Braak H, Xue QS, Bechmann I (2009) Dystrophic (senescent) rather than activated microglial cells are associated with tau pathology and likely precede neurodegeneration in Alzheimer's disease. Acta Neuropathol 118:475–485
172. Streit WJ, Miller KR, Lopes KO, Njie E (2008) Microglial degeneration in the aging brain—bad news for neurons? Front Biosci 13:3423–3438
173. Streit WJ, Sammons NW, Kuhns AJ, Sparks DL (2004) Dystrophic microglia in the aging human brain. Glia 45:208–212
174. Su X, Maguire-Zeiss KA, Giuliano R, Prifti L, Venkatesh K, Federoff HJ (2007) Synuclein activates microglia in a model of Parkinson's disease. Neurobiol Aging 29:1690–1701
175. Sugama S, Takenouchi T, Fujita M, Conti B, Hashimoto M (2009) Differential microglial activation between acute stress and lipopolysaccharide treatment. J Neuroimmunol 207:24–31
176. Takamori Y, Mori T, Wakabayashi T, Nagasaka Y, Matsuzaki T, Yamada H (2009) Nestin-positive microglia in adult rat cerebral cortex. Brain Res. doi:10.1016/j.brainres.2009.03.014

177. Takenouchi T, Nakai M, Iwamaru Y, Sugama S, Tsukimoto M, Fujita M, Wei J, Sekigawa A, Sato M, Kojima S, Kitani H, Hashimoto M (2009) The activation of P2X7 receptor impairs lysosomal functions and stimulates the release of autophagolysosomes in microglial cells. J Immunol 182:2051–2062
178. Tanuma N, Sakuma H, Sasaki A, Matsumoto Y (2006) Chemokine expression by astrocytes plays a role in microglia/macrophage activation and subsequent neurodegeneration in secondary progressive multiple sclerosis. Acta Neuropathol 112:195–204
179. Thacker MA, Clark AK, Bishop T, Grist J, Yip PK, Moon LD, Thompson SW, Marchand F, McMahon SB (2009) CCL2 is a key mediator of microglia activation in neuropathic pain states. Eur J Pain 13:263–272
180. Town T, Jeng D, Alexopoulou L, Tan J, Flavell RA (2006) Microglia recognize double-stranded RNA via TLR3. J Immunol 176:3804–3812
181. Tozaki-Saitoh H, Tsuda M, Miyata H, Ueda K, Kohsaka S, Inoue K (2008) P2Y12 receptors in spinal microglia are required for neuropathic pain after peripheral nerve injury. J Neurosci 28:4949–4956
182. Trapp BD, Wujek JR, Criste GA, Jalabi W, Yin X, Kidd GJ, Stohlman S, Ransohoff R (2007) Evidence for synaptic stripping by cortical microglia. Glia 55:360–368
183. Tsuda M, Masuda T, Kitano J, Shimoyama H, Tozaki-Saitoh H, Inoue K (2009) IFN-{gamma} receptor signaling mediates spinal microglia activation driving neuropathic pain. Proc Natl Acad Sci USA. doi:10.1073/pnas.0810420106
184. Ulmann L, Hatcher JP, Hughes JP, Chaumont S, Green PJ, Conquet F, Buell GN, Reeve AJ, Chessell IP, Rassendren F (2008) Up-regulation of P2X4 receptors in spinal microglia after peripheral nerve injury mediates BDNF release and neuropathic pain. J Neurosci 28:11263–11268
185. Venneti S, Wagner AK, Wang G, Slagel SL, Chen X, Lopresti BJ, Mathis CA, Wiley CA (2007) The high affinity peripheral benzodiazepine receptor ligand DAA1106 binds specifically to microglia in a rat model of traumatic brain injury: implications for PET imaging. Exp Neurol 207:118–127
186. Venneti S, Wang G, Nguyen J, Wiley CA (2008) The positron emission tomography ligand DAA1106 binds with high affinity to activated microglia in human neurological disorders. J Neuropathol Exp Neurol 67:1001–1010
187. Volterra A, Meldolesi J (2005) Astrocytes, from brain glue to communication elements: the revolution continues. Nat Rev Neurosci 6:626–640
188. Wake H, Moorhouse AJ, Jinno S, Kohsaka S, Nabekura J (2009) Resting microglia directly monitor the functional state of synapses in vivo and determine the fate of ischemic terminals. J Neurosci 29:3974–3980
189. Walker DG, Link J, Lue LF, Dalsing-Hernandez JE, Boyes BE (2006) Gene expression changes by amyloid beta peptide-stimulated human postmortem brain microglia identify activation of multiple inflammatory processes. J Leukocyte Biol 79:596–610
190. Wang J, Ohno-Matsui K, Yoshida T, Shimada N, Ichinose S, Sato T, Mochizuki M, Morita I (2009) Amyloid-beta up-regulates complement factor B in retinal pigment epithelial cells through cytokines released from recruited macrophages/microglia: another mechanism of complement activation in age-related macular degeneration. J Cell Physiol. doi:10.1002/jcp.21742
191. Wang X, Li C, Chen Y, Hao Y, Zhou W, Chen C, Yu Z (2008) Hypoxia enhances CXCR4 expression favoring microglia migration via HIF-1alpha activation. Biochem Biophys Res Commun 371:283–288
192. Wang XJ, Ye M, Zhang YH, Chen SD (2007) CD200-CD200R regulation of microglia activation in the pathogenesis of Parkinson's disease. J NeuroImmune Pharmacol 2:259–264
193. Wesolowska A, Kwiatkowska A, Slomnicki L, Dembinski M, Master A, Sliwa M, Franciszkiewicz K, Chouaib S, Kaminska B (2008) Microglia-derived TGF-beta as an important regulator of glioblastoma invasion—an inhibition of TGF-beta-dependent effects by shRNA against human TGF-beta type II receptor. Oncogene 27:918–930
194. Wirenfeldt M, Clare R, Tung S, Bottini A, Mathern GW, Vinters HV (2009) Increased activation of Iba1(+) microglia in pediatric epilepsy patients with Rasmussen's encephalitis compared with cortical dysplasia and tuberous sclerosis complex. Neurobiol Dis. doi:10.1016/j.nbd.2009.02.015
195. Wodarski R, Clark AK, Grist J, Marchand F, Malcangio M (2008) Gabapentin reverses microglial activation in the spinal cord of streptozotocin-induced diabetic rats. Eur J Pain. doi:10.1016/j.ejpain.2008.09.010
196. Wu Z, Zhang J, Nakanishi H (2005) Leptomeningeal cells activate microglia and astrocytes to induce IL-10 production by releasing pro-inflammatory cytokines during systemic inflammation. J Neuroimmunol 167:90–98
197. Zeilhofer HU (2008) Loss of glycinergic and GABAergic inhibition in chronic pain—contributions of inflammation and microglia. Int Immunopharmacol 8:182–187
198. Zhang J, Shi XQ, Echeverry S, Mogil JS, De Koninck Y, Rivest S (2007) Expression of CCR2 in both resident and bone marrow-derived microglia plays a critical role in neuropathic pain. J Neurosci 27:12396–12406
199. Zhang J, Cheng H, Chen J, Yi F, Li W, Luan R, Guo W, Lv A, Rao Z, Wang H (2009) Involvement of activated astrocyte and microglia of locus coeruleus in cardiac pain processing after acute cardiac injury. Neurol Res. doi:10.1179/174313208X355486
200. Zhang Z, Artelt M, Burnet M, Trautmann K, Schluesener HJ (2006) Early infiltration of CD8+ macrophages/microglia to lesions of rat traumatic brain injury. Neuroscience 141:637–644
201. Zhao X, Grotta J, Gonzales N, Aronowski J (2008) Hematoma resolution as a therapeutic target. The role of microglia/macrophages. Stroke. doi:10.1161/STROKEAHA.108.533158
202. Zhou Z, Peng X, Hao S, Fink DJ, Mata M (2008) HSV-mediated transfer of interleukin-10 reduces inflammatory pain through modulation of membrane tumor necrosis factor alpha in spinal cord microglia. Gene Ther 15:183–190
203. Zhu P, Hata R, Cao F, Gu F, Hanakawa Y, Hashimoto K, Sakanaka M (2008) Ramified microglial cells promote astrogliogenesis and maintenance of neural stem cells through activation of Stat3 function. FASEB J 22:3866–3877
204. Zou CG, Zhao YS, Gao SY, Li SD, Cao XZ, Zhang M, Zhang KQ (2009) Homocysteine promotes proliferation and activation of microglia. Neurobiol Aging. doi:10.1016/j.neurobiolaging.2008.11.007