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Microglia: active sensor and versatile effector cells in the normal and pathologic brain

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Microglial cells constitute the resident macrophage population of the CNS. Recent *in vivo* studies have shown that microglia carry out active tissue scanning, which challenges the traditional notion of 'resting' microglia in the normal brain. Transformation of microglia to reactive states in response to pathology has been known for decades as microglial activation, but seems to be more diverse and dynamic than ever anticipated—in both transcriptional and nontranscriptional features and functional consequences. This may help to explain why engagement of microglia can be either neuroprotective or neurotoxic, resulting in containment or aggravation of disease progression. Moreover, little is known about the heterogeneity of microglial responses in different pathologic contexts that results from regional adaptations or from the progression of a disease. In this review, we focus on several key observations that illustrate the multi-faceted activities of microglia in the normal and pathologic brain.

A new view of microglial activity in the healthy CNS

Microglial cells are generally considered the immune cells of the CNS[1]. They respond to any kind of pathology with a reaction termed microglial activation. But their crucial roles under normal physiological conditions have been less studied, even neglected. The properties of microglial cells and of their activation have mainly been studied in animal models of disease or in culture. These experimental paradigms, such as stimulation with the bacterial endotoxin lipopolysaccharide (LPS), usually result in severe inflammatory responses. However, one must ask whether these paradigms accurately reflect microglial functions. LPS stimulation has long been considered the gold standard for microglial activation. It mimics infection by Gram-negative bacteria and produces a massive antimicrobial defense reaction—thereby leading to a view of microglia as neurotoxic and proinflammatory cells. However, on the basis of new findings, we should no longer consider microglial activation an all-or-none event or monophasic process, but should realize that responses to pathologic events are context dependent and adapt as the microenvironment changes.

It is difficult to believe that essential cells such as microglia evolved simply as a 'risk factor' in the CNS. Microglia should be seen from a different perspective, so that their unnoticed actions can also be acknowledged. With this new perspective, we can picture microglia as acting mainly to stabilize the CNS. There is no valid proof (yet) of this concept, but we hypothesize as follows. Microdamage may happen very frequently throughout the CNS—for example, it may result from small ischemic events and localized openings of the blood-brain barrier (BBB), causing influx of plasma constituents into the brain. Microglia are well positioned to sense such disturbances[2] and can react rapidly to even tiny ruptures in blood vessels[3]. Another type of microdamage could be the decline of a single neuron that eventually needs to be removed from its circuitry. It is possible that microglia are constantly engaged in repairing such minute insults. The focal and transient engagement of microglia could occur (conceivably many times a day) without ever being noticed. If microglia can efficiently limit damage, such events will never become clinically manifest. By contrast, clinical and neuropathological records may create a bias toward cases in which microglial attempts to prevent further impairment or to restore functionality have failed. In this review, we argue for this hypothesis.

Microglial cells constantly screen CNS tissue

Ramified morphology and the sparse expression of molecules associated with macrophage function in microglia of the healthy adult CNS have been associated with a 'resting' phenotype. However, resting microglia are not dormant. Studies based on *in vivo* two-photon microscopy in transgenic mice expressing enhanced green fluorescent protein in the *Cx3cr1* locus (encoding CX_3CR1, the receptor for the chemokine CX_3CL1, also known as fractalkine) revealed that microglial processes and arborizations are highly mobile[3,4]. Time-lapse imaging showed that processes are continually rebuilt, with *de novo* formation and withdrawal of processes as well as motile filopodium-like protrusions. Such dynamic and careful reorganization may enable the otherwise stationary microglia to thoroughly scan their environment without disturbing fine-wired neuronal structures. Estimates are that the complete brain parenchyma could be monitored every few hours. Neighboring microglial cells take turns scanning shared regions, guaranteeing exhaustive screening while avoiding contact. The random scanning by processes rapidly changes to a targeted movement toward the site of an injury when microlesions are induced (**Fig. 1**). This response and its directional guidance apparently depend on purinoreceptor stimulation and may involve assistance from astrocytes[4,5].

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It has been assumed for some time that microglia carry out homeostatic surveillance, and their role as sensors of pathologic change was explicitly formulated years ago[6]. The new studies, however, challenge the suitability of the term 'resting' microglia. If such surveillance is an activity that involves constant morphological alteration as well as continuous biochemical sensing and interpretation of environmental cues, the term 'resting' would miss an important constitutive function. The 'resting' state may actually reflect a defined mode of an active cell.

Microglia shift activity states, rather than 'become activated'

Microglial activation has been understood as a stepwise transformation of 'resting' cells that occurs upon disturbance of tissue homeostasis or upon experimental stimulation. The term implies that, before activation, microglia are inactive. However, considering the findings of the *in vivo* imaging (and assuming that *Cx3cr1*^{GFP} microglia essentially reflect wild type), the transition between resting and activated states should be considered a change in functional phenotype rather than an awakening. Cells depart from the surveillance mode (one state of activity) and acquire a reactive profile to cope with altered homeostasis. Chemotactic reorientations and other nontranscriptional adjustments can occur in minutes to seconds, and even massive induction of complex gene sets is achieved within a few hours. The signaling periods that are required (the time for which a stimulus needs to be present) can be equally short.

We therefore suggest that 'resting' microglia should be renamed 'surveying' microglia, as they actively search for and read signals (as well as changes in such signals) in the brain environment. This term would take into account their activity as sensors, paying tribute to an earlier definition[6]. However, we will refrain from recommending a similar change to the established term 'activated' microglia, even though 'effector' microglia might better describe cells executing a number of adaptive responses to a given challenge.

Microglial responses involve two signaling principles

Many molecules and conditions can trigger a transformation of resting (or surveying) microglia to activated (alerted or reactive) states. These have in common that they indicate a threat to the structural and functional integrity of the CNS. Microglial cells are prepared to recognize a wide range of signs for homeostatic surveillance, independent of their biochemical nature (peptides, lipoproteins, glycolipids, nucleotides) or diverse (patho)physiological implications (**Table 1**).

Two important signaling principles organize microglial responsiveness. The sudden appearance of factors that are not usually seen (for example, microbial structures, serum components) or are not seen at critical concentrations (for example, intracellular constituents), that are presented in specific functional states (for example, immunoglobulin-antigen complexes, opsonizing complement), or that occur in an abnormal format (for example, protein aggregates) are sensed by an array of receptors that have cognate (matching) specificities[7–9]. For example, the families of pattern recognition receptors, such as Toll-like receptors (TLRs), detect and differentiate viral, bacterial and fungal structures[10,11]. Responses are thereby triggered by induced receptor signaling. However, there is also constitutive signaling with a calming influence, as for the ligand-receptor pairs CD200-CD200R, CX_3CL1-CX_3CR1 and SIRPα-CD47 (refs. 12–15). Here, disrupted signaling ('off' signaling) causes alert and activation. In the former case, activation requires a specific ligand (even in the case of pattern recognition receptors). In the latter, any loss of calming inputs—for example, any impairment of neuronal integrity, regardless of the type of insult—can set off the signal. The principle of 'off' signaling is therefore not simply a

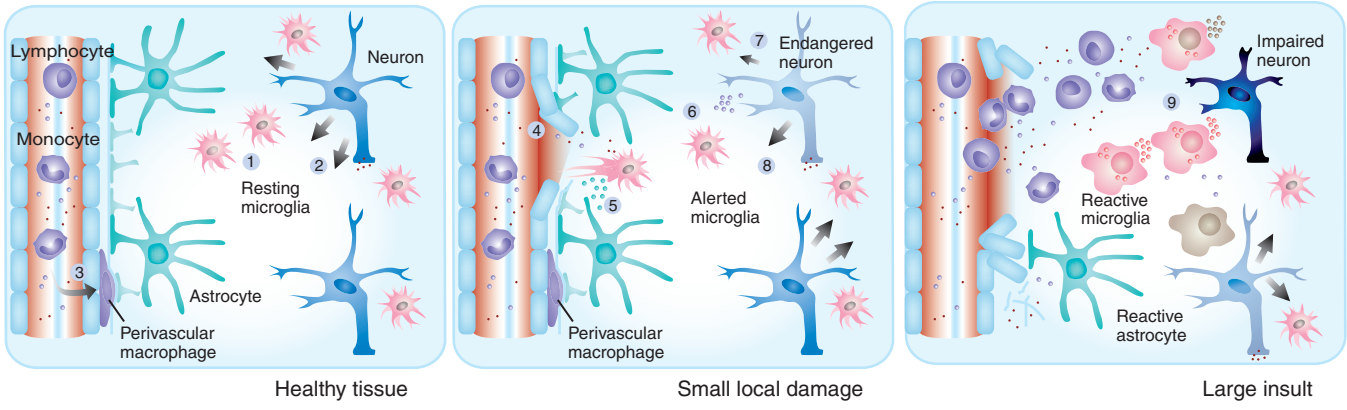

Figure 1 Activity states of microglia. Left, microglial cells in normal tissue constantly screen their environment (1). The term 'resting' does not properly reflect the constitutive surveillance activity of these cells, which would be better termed 'surveying' microglia. Their fine processes undergo continuous rebuilding to allow efficient scanning of their territory. Equipped with receptors for a plethora of molecules, they can immediately sense signs of disturbed structural and functional integrity. Neurons may also deliver signals which keep microglia in this surveillance mode, indicating normal function (2). Besides the parenchymal microglia, there are also perivascular macrophages in closer association with blood vessels (3). Subsets of circulating monocytes may replenish perivascular cells, and to a much lesser extent also replenish the parenchymal microglia. Middle, upon detection of minute homeostatic disturbances, for example tiny vascular or tissue damage, microglia can rapidly respond with a directed reorganization of processes and a change in the activity profile (4). The response is probably supported by neighboring astrocytes releasing, for example, purinoreceptor ligands (5). Microglia can produce neurotrophic factors to support endangered neurons (6). Disruption of ongoing communication through calming signals would allow an endangered neuron to call for microglial assistance (7). Such neurons can also emit signals indicating disturbed functions using molecules that are not usually released (at all or at critical concentrations; 8). Microglial cells may be able to limit further damage and restore normal homeostasis. As a consequence, focal and transient 'activation' never surfaces with overt symptoms and thus remains largely unrecognized. Right, stronger insults to the CNS (infectious challenge or significant tissue injury) may trigger more drastic changes in the functional phenotype of microglia. Depending on the nature of the stimuli and their context, microglial cells need to acquire and adapt reactive behavior. Excessive acute, sustained (chronic) or maladaptive responses of microglia may lead to substantial impairment of neurons and glia (9). Failure of protection and an active contribution to damaging cascades have been attributed to activated microglia in many pathologic scenarios. However, such data probably underestimate the microglial capacity to safeguard and stabilize the CNS.

synonym for inhibition—for example, as brought about by interleukin (IL)-10, transforming growth factor (TGF)-β, glucocorticoids or through the TREM-2 (the receptor expressed on myeloid cells-2)-DAP12 receptor-adaptor pair—although the principles may overlap[8,16]. Notably, based on the two principles, microglia can read and respond to both 'known' and 'unknown' signs of homeostatic disturbance.

Neurotransmitters could also exert calming effects, as they carry information about normal neuronal activity. Indeed, microglial cells express various neurotransmitter receptors[17]. The activation of these receptors can be linked to anti-inflammatory responses, as in the case of adrenergic and $GABA_B$ receptors (reviewed in ref. 18). With their ability to sense synaptic release, microglia seem to be much more integrated into neuronal function than was thought in the past, with exciting discoveries now revealing neuron-microglia communication in pain (addressed in this issue).

Microglial responses show diversity

Activation of microglial cells can result in different response phenotypes (**Fig. 2**). Importantly, phenotypic diversity means functional diversity. Most experimental findings and their conceptual integration concerning the phenotypic diversity of macrophages have been based on studies of extraneural cell populations (see **Supplementary Note** online). Nevertheless, the available information points to a similar versatility of responses in microglia. The release of distinct factors can accompany phagocytosis, depending on the target material, receptors that are involved and context. When microglia are challenged by bacterial invasion, phagocytosis occurs together with the release of inflammatory mediators[19,20]. By contrast, when removing apoptotic cells or myelin debris, microglia release anti-inflammatory factors[21,22].

A series of studies recently addressed the differential induction of microglial properties by the T-cell master cytokines interferon (IFN)-γ and IL-4, which are typically associated with T helper type 1 and 2 (T_H1 and T_H2) adaptive immune responses, respectively (see **Supplementary Note**)[23–25]. Microglia instructed by IL-4 and—surprisingly—by low concentrations of IFN-γ support adult oligodendrogenesis as well as neurogenesis and offer neuroprotection, involving complex regulation of insulin-like growth factor (IGF)-I and tumor necrosis factor (TNF)-α. By contrast, treatment with LPS or amyloid-β (Aβ) aggregates, which represent cytotoxic challenges, or with high levels of IFN-γ, do not support cell renewal; they may even impede it. IL-4 or IL-4-activated microglia can reverse this impediment. These reports support several essential assumptions: first, microglial actions are versatile and stimulus-determined. Second, responses can vary with the stimulus intensity (dose) and context (as discussed below). Third, stimuli compete for dominating influence over microglial actions. Fourth, cells that have been 'instructed' *ex vivo* can carry their functional orientation into tissue *in vivo*. Fifth, microglia communicate intimately with cellular carriers of adaptive immunity by exchanging soluble messengers, such as cytokines, and by physical contact, such as through major histocompatibility complex (MHC)-II structures, which present antigens. Sixth, protective potential and neurogenesis supported by microglia can be assisted by immune-associated mechanisms (that is, local interactions between microglia and T cells; see also ref. 26). Other findings could be cited in support of these assumptions. Notably, microglial cells are embedded in a tissue environment with vulnerable cellular structures and limited restorative capacity—requiring and imposing a tight control over macrophage-like activities. Genomic and proteomic profiling can be expected to deliver more details on distinct microglial responses[27].

States of microglial activation may also progress throughout a pathologic process (**Fig. 2**). Much as primary stimuli and their context determine diverse initial responses, signals from resident CNS and infiltrating immune cells could modulate and shape reactive profiles[24,28–31]. IFN-γ, as a typical T_H1 cytokine, completely reorganizes the microglial chemokine profile in models of bacterial confrontation[20], resulting in simultaneous reduction of neutrophil- and T_H1-attracting signals. Similarly, under normal conditions, microglial cells have a low conductance with little voltage-gated component. Twelve hours after a facial nerve lesion, microglial cells in the facial nucleus express large inward rectifying conductances, similar to those found in cultured microglia. After 24 h, a further outward rectifying component is present, similar to that recorded from LPS-stimulated cultures[32]. In other words, distinct functional macrophage phenotypes may follow each other, as indicated by proof-of-principle experiments[33–36]. Although continuous adjustments could eventually resolve activation and support repair, the fate of microglia after activation remains largely unclear. The history of

Table 1 Examples of signals and modulators of microglial activation

Class of compound	Examples
Surface structures and DNA/RNA of viral, bacterial or fungal origin	Agonists of members of the pattern recognition receptor families, notably TLR1/2, TLR3, TLR4,TLR6/2 and TLR9, such as bacterial LPS or cell wall proteoglycans and lipoteichoic acid (LTA), gp41, gp120 (the TLR4-agonistic LPS serving as a common model agent)
Abnormal endogenous proteins	β-amyloid (aggregates), Aβ25–35, Aβ40, Aβ42, prion protein (PrP)
Complement	Complement factors C1q, C5a
Antibodies	Immunoglobulin of various classes and isotypes (IgA, IgG, IgM), presented in immune complexes
Cytokines	Colony stimulating factors (M-CSF, GM-CSF), IL-1β, IL-2, IL-4, IL-6, IL-10, IL-12, IL-15, IL-18, IFN-γ, TGF-β, TNF-α
Chemokines	Ligands for chemokine receptors: CCR3, CCR5, CXCR2, CXCR, CXCR4, CX3CR1, IL-8R
Neurotrophic factors	Brain-derived neurotrophic factor (BDNF), glial-derived neurotrophic factor (GDNF), nerve growth factor (NGF), neurotrophin 3 (NT-3), NT-4
Plasma components	Albumin, fibronectin, fibrinogen, thrombin
Other proteins and peptides	Apolipoprotein E (ApoE), heat shock proteins hsp60 and hsp70, CD40L, melanocyte-stimulating hormone (MSH), endothelin, S100 proteins, vasoactive intestinal peptide (VIP)
Neurotransmission-related compounds	ATP (and related purines), β-adrenergic agonists, glutamate, kainate, NMDA
Ions	K^+, Mn^{2+}
Other compounds	Cannabinoids, ceramide, gangliosides, lysophosphatidic acid (LPA), melatonin, opioids (endomorphines), platelet-activating factor (PAF), prostaglandin E_2 (PGE_2), steroid hormones, vitamin D_3

[1]Chemokine receptors can accept several chemokines owing to their promiscuous nature.

Further information is provided by recent reviews[7,8,17,18].

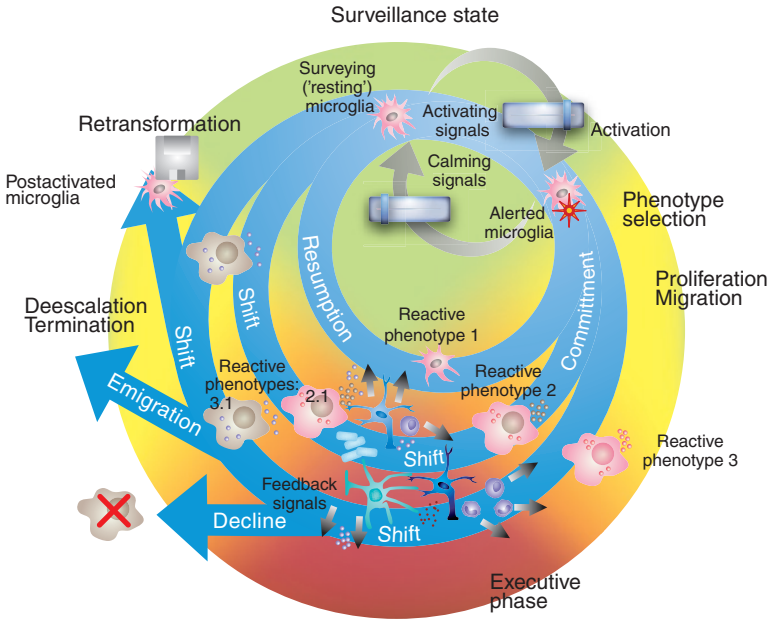

Figure 2 Microglial activity states throughout the activation process. Microglial cells in the surveillance (sentry) state—traditionally termed 'resting' state—constantly scan for signals that would indicate a potential threat to CNS homeostasis. The appearance of such 'activating' signals (in infection, trauma or cell impairment) or the loss of constitutive 'calming' signals triggers a transition to an alerted state. Signals and their context are interpreted and converted to an initial response of 'activation'. Cells hence further commit to distinct reactive phenotypes, constituted by transcriptional profiles and nontranscriptional changes, and enter their executive phase (for example, release of cytokines and chemokines, phagocytotic activity). Three examples are depicted (phenotypes 1, 2, 3), but the diversity could be larger. Throughout the subsequent period, the reactive behavior of microglia may change (reactive phenotypes 2.1, 3.1), largely controlled by a fading (or elimination) of the initial activating signals as well as influences from resident CNS and invading immune cells (illustrated as feedback signals). Reactive phenotypes may thus shift, eventually leading to a more repair-orientated profile. While some cells may emigrate to the blood system or die (indicated by an 'X' over cell, others may revert to a 'resting' (surveying) state. Some cells may not retransform to a completely naive status and may remain as 'postactivated' microglia. These cells could keep subtle changes, for example, in transcriptional activity, that affect their sensitivity to constitutive (calming) signals or alter responses to subsequent stimulation. Postactivated microglia could thus have acquired some experience (indicated as memory in the figure by a floppy disk icon).

previous challenges might determine subsequent activation episodes (**Fig. 2**). Conceivably, it could even determine how CNS tissues will resist or succumb to aging-related processes.

Microglial cells are of myeloid origin and have low turnover

Microglial cells were first described in 1919 by Rio-Hortega, a student of Ramón y Cajal, as a cell population distinct from classical glia (astrocytes) and neurons[37]. The origin of microglial cells has been debated for many years, but current data indicate that they are of mesenchymal origin and invade the brain during development (recently reviewed in ref. 38). The invasion occurs in two waves, the first during fetal development (during the first two trimesters in humans and between embryonic days 10 and 19 in rodents). The second population invades the brain during early postnatal days, as well characterized in rodents. These cells have been termed ameboid microglia and were already recognized by Rio-Hortega. They have properties of monocytes and probably derive from blood-born precursors. Microglial cells eventually differentiate into a phenotype characterized by a small soma and highly branched processes—that is, 'resting' (surveying) microglia. At the end of development, microglial cells have populated all regions of the CNS, including the retina.

Populational renewal of tissue macrophages occurs by intrinsic proliferation and by recruitment from external sources. In mice, a subpopulation of $CCR2^{-}CX_3CR1^{hi}Ly6C^{-}$ circulating monocytes may preferentially provide normal tissue replenishment[39]. The turnover rate of microglia in the healthy brain is still debated, and constitutive proliferation is probably low, but under pathologic conditions, larger numbers of monocytic cells can invade the brain[40–43]. In a mouse model of scrapie, about 50% of brain microglia were replaced by bone marrow–derived cells even before the onset of clinical symptoms[44]. Such massive invasion has also been reported for other disease states, such as ischemia.

To address the turnover of microglia under normal conditions, several groups have transplanted bone marrow cells after depleting the intrinsic monocyte population by irradiation. There is a low but significant turnover of microglial cells. A study on mouse retina reported complete turnover within 6 months[45]. However, a criticism of this general approach (see also above) is that irradiation itself may damage the BBB and augment cell infiltration. Moreover, transfer of bone marrow cells flushed from the femur will also expose the hematopoietic system to nonphysiological circulating progenitor cells. There is also a population of perivascular cells in the space between the endothelial cells and the glial end feet that shares features with immature microglia. These cells turn over more rapidly, within 14 weeks, and probably turn over equally in different brain areas[46,47]. Thus, it is important to distinguish between this population and parenchymal microglia. If microglial turnover in humans is even lower than in mice, and individual cells may persist for decades, the aging of microglia becomes a most relevant topic—in particular with regard to altered protective capacities or loosening of control mechanisms that contain potentially harmful activities[48,49].

Little evidence for different microglial populations

Surprisingly little is known about microglial heterogeneity among and within brain regions. Parenchymal microglia are distinct from other macrophage-like populations (such as those found in perivascular or meningeal locations)[50]. Nevertheless, CNS regions may contain 'provincially adapted' microglia. The structural organization (white or gray matter), proximity to the vasculature, BBB features and biochemical micromilieu could impose specific adjustments[51,52]. Substances released from neurons can influence microglial release activity (at least in culture)[53]. Subsets of microglia might exert different activities without being distinguishable by morphology or by a single marker. However, there are only a few reports that indicate constitutive or inducible diversity of microglia in CNS subdivisions. For example, hippocampal microglia express higher levels of messenger RNA for TNF-α, CD4 and FcγRII than do microglia from the diencephalon, tegmentum, cerebellum and cerebral cortex[54]. Neurotrophin-3 expression is selectively found in microglia from the cerebral cortex, globus pallidus and medulla, but

not in those from other CNS tissues[55]. A region-specific role of TNF-α is indicated by the consequences of TNF receptor deficiency in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxicity model of Parkinson's disease, in which reduced microglial activation and neuronal degeneration occur in the striatum, whereas exacerbated damage occurs in the hippocampus[56]. Evidence for intrinsic specialization is similarly rare. In rat mixed glial cultures, two types of microglial cell can be distinguished on the basis of morphology and their ability to respond to LPS[57]. Markers for reactive microgliosis have been used to define subpopulations of microglia that respond to minor CNS injury[58].

Anatomical diversity in constitutive and inducible microglial activities could also be overlaid with developmental adjustments. Proliferative or phagocytotic behavior changes with the transition from embryonic to neonatal or postnatal stages until adulthood[41]. The ability to respond to internal signals or foreign material as an innate immune cell is likely to undergo similar maturation[59].

Microglial activation can exacerbate damage or protect

There is ample evidence that fully activated microglial cells are neurotoxic[1,9] (**Fig. 1**). They release reactive oxygen species, nitric oxide (NO) or TNF-α—a plethora of compounds at quantities and in combinations that potentially can damage neurons, oligodendrocytes or extracellular matrix structures. We could term this the full-blown inflammatory state. But under what pathologic conditions do microglia acquire such a state, and how does it correlate with tissue damage and functional impairment? In this section, we discuss examples illustrating that the inflammatory state can aggravate brain damage and that attenuation of microglial activation has protective value. Conversely, we discuss examples making the case for damage-limiting action[1].

Traditionally, the notion of microglial activation often blended cellular changes without much distinction. It appears, however, that the tilt toward harmful or beneficial outcomes depends on the activating conditions[8]. Experiments that showed the toxic potential of microglia *in vitro* often used stimuli eliciting defense-oriented reactions, such as LPS. They did not offer broad signal variety and signaling context[36].

In demyelinating disorders, such as multiple sclerosis or Guillain-Barré syndrome, and animal models, such as experimental autoimmune encephalomyelitis and experimental autoimmune neuritis, the responses of macrophages and microglia are important for the clinical outcome[60]. Their depletion or blockade can prevent disease progression[61]. In a complex mouse model of a demyelinating disorder in which microglial activation is reduced, disease development is attenuated[62]. The authors concluded that microglial paralysis would be beneficial, reduce inflammatory lesions and limit demyelination. However, suppression of macrophages and microglia can impair remyelination in toxin-induced models of de- and remyelination[63]. Macrophages or microglia may deliver (or indirectly organize) trophic factors and support myelin regeneration[64,65]. In addition, phagocytotic removal of myelin debris is a prerequisite for repair attempts in multiple sclerosis or Guillain-Barré syndrome, as such material obstructs remyelination and axon outgrowth[66–68]. However, the uptake and degradation of potentially autoimmunogenic material may not simply neutralize the threat but rather result in presentation of antigen to T cells—and could thus critically affect further immune attacks.

Patients with Parkinson's disease show increased IFN-γ in the plasma, and so MPTP-induced neuronal death[69] in the substantia nigra pars compacta was studied in IFN-γ-deficient mice[70]. The mice showed reduced microglial activation and reduced loss of dopaminergic cells. These data were supported by an *in vitro* model in which toxin-induced dopaminergic cell loss requires the presence of microglia. Here, too, IFN-γ participates in the death of dopaminergic neurons by regulating microglial activity. Moreover, the application of LPS can induce dopaminergic neuronal degeneration *in vitro*, the effect being attenuated by immunosuppressive IL-10 (ref. 71). Thus, in models of Parkinson's disease, microglial activation seems to be detrimental.

Dual role for microglia in Alzheimer's disease

In Alzheimer's disease, features of microglia that relate to phagocytosis are beneficial, whereas those that relate to inflammation are detrimental. Microglia can be neuroprotective by degrading Aβ plaques. Apparently, this task is mainly accomplished by recruiting blood-derived cells into the brain, which then transform into microglia, as recently shown in an animal model of AD, the APP_{swe}/PS1-transgenic mouse. After irradiation (which could have effects on its own) and transplantation of bone marrow cells, most of the microglial cells associated with plaques are newly recruited from the hematopoietic system[72]. Depletion of microglia also results in increased plaque load, indicating that the newly recruited population has different phagocytic properties from intrinsic microglia. Microglia and macrophages also seem to have different abilities to phagocytose Aβ peptide[73]. Microglial lysosomes are less acidic than those of a macrophage cell line, which impairs degradation of fibrillary Aβ. Treatment with macrophage colony stimulating factor (M-CSF) acidifies the lysosomes of microglia, facilitating Aβ degradation. Deficiency in the chemokine receptor CCR2 impairs the accumulation of microglial cells in a mouse model of Alzheimer's disease and results in increased plaque load and shorter mouse survival[74]. Another approach that showed the importance of microglia for plaque removal used intraventricular transplantation of exogenous microglia, which migrate into the parenchyma and increase the clearance of amyloid plaques[75].

The phagocytic activity of microglia is attenuated by proinflammatory cytokines[76], indicating that microglia committed to an inflammatory response may have a lower phagocytotic capacity. In studies with anti-inflammatory drugs, suppression of the inflammatory response by microglia attenuates symptoms in a mouse model of Alzheimer's disease. The anti-inflammatory drug minocycline does not affect Aβ deposition, but reduces the number of activated microglia. The treatment significantly improves the behavioral performance of transgenic mice expressing the mutant human Aβ precursor protein[77]. Activation of microglia results in an increase in inducible NO synthase (iNOS) expression. By breeding mice that overexpress human amyloid precursor protein and presenilin-1 with iNOS-deficient mice, it was possible to study the importance of iNOS for the progression of Alzheimer's disease. The results indicated that iNOS deletion protects the mice from plaque formation and premature mortality[78]. Ramirez *et al.*[79] found an interesting connection between cannabinoid-mediated neuroprotection and microglia. Cannabinoids acting through CB2 receptors attenuate microglial activation due to Aβ peptides. In another mouse model of Alzheimer's disease, transgenic mice carrying a mutant form of human tau, prominent microglial activation occurs before the formation of tangles. Feeding these mice at young age with the anti-inflammatory drug FK 506 attenuates tau pathology and increases their life spans. This indicates that an early inflammatory state of microglia could be an important condition for the disease.

Microglia or macrophages confer neuroprotection in ischemia

After an ischemic lesion, microglial cells accumulate at the lesion site and in the penumbra, the area surrounding the core lesion. As the BBB is impaired after such an insult, these cells represent a mixture of intrinsically activated microglia and infiltrating blood cells[80]. There are several lines of evidence that the accumulation of microglia correlates with the reduction of neuronal damage, rendering microglia

a neuroprotective factor. A transgenic mouse system has proven to be an important tool for determining the role of microglia in a damage cascade. This transgenic mouse expresses a mutant form of the herpes simplex virus thymidine kinase driven by the CD11b promoter, which is specific for myeloid cells (including microglia). Treatment with ganciclovir leads to the ablation of proliferating (microglial) cells. When these animals are challenged by transient middle cerebral artery occlusion, leading to an ischemic injury, the ablation of microglial cells results in a significant increase in the size of the infarct, associated with an increase in apoptotic neurons[81]. The authors also provided evidence that, in the first 72 h after the ischemic injury, resident microglial cells are preferentially affected, indicating that the resident population confers neuroprotection. This convincingly shows that proliferating microglial cells protect neurons from ischemic damage.

In another approach, microglia were isolated from brain cultures and injected into the blood of Mongolian gerbils, where they home to an ischemic hippocampal lesion. This microglial homing results in more neurons surviving, compared to controls[82]. The administration of exogenous microglia leads to an increase in the expression of brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor, which may explain the positive effect of microglia on neuronal survival. The authors even speculated that exogenous microglia could be a candidate for therapy after ischemia. When a similar approach was used in rats, with microglia being injected into the ventricle after middle cerebral artery occlusion, significant neuroprotection was also observed[83].

Microglial glutamate removal could underlie neuroprotection

Mainly on the basis of data from cultured microglia, several mechanisms have been proposed for how these cells mediate neuroprotection (recently reviewed in ref. 84). Damage might be limited by yet another microglial mechanism. Glutamate has been identified as an important neurotoxic substance that acts through NMDA receptors on neurons and leads to an increase in intracellular calcium and cell death. Glutamate-mediated neurotoxicity is involved in many neurodegenerative processes, such as brain injury and ischemia. Under physiological conditions, excess glutamate resulting from synaptic activity is taken up predominantly by astrocytes, the cells that control extracellular glutamate levels under physiological conditions. However, under pathologic conditions, astrocytic glutamate uptake is impaired. Microglia activated by LPS can express the glutamate uptake protein GLT-1; the expression is induced by autocrine TNF-α stimulation[85].

In another study, antigen-specific autoimmune T cells triggered microglial glutamate uptake, although LPS could not mimic this effect[86]. Regardless of this discrepancy, microglia could be important for control over glutamate levels under pathologic conditions, and thereby could improve neuronal survival.

Glioma cells trigger a distinct microglia phenotype

In the context of a glioma, microglial cells acquire an interesting phenotype, which is induced by the tumor cells. Glioma tissue consists of tumor cells and up to 30% microglia or macrophages. Microglial cells are attracted to the glioma site and accumulate at its margins in particular. Glioma-conditioned medium changes the microglial phenotype into an activated form that is distinct from the inflammatory phenotype. Glioma-associated activation does not trigger the release of proinflammatory cytokines, such as TNF-α or IL-6, but leads to other transcriptional changes, such as the upregulation of metalloprotease-II[87,88]. Microglial cells can even promote glioma growth and invasion.

The purinergic system seems to be involved in this cellular interaction, as A1 adenosine receptors are upregulated in microglia in contact with glioblastomas, and A1 receptor deficiency results in more vigorous glioma growth. As a result, adenosine attenuates glioblastoma growth, acting through microglial A1 receptors[89]. Thus, gliomas instruct microglia not to attack, but instead to help them spread within the brain.

Microglial cells influence neurogenesis

Not only do microglial cells assist in CNS maturation during development—for example, by mediating the developmental death of neurons[90]—but they can also release factors that influence adult neurogenesis and glial development[24,91–93]. Microglial cells can thus exert dual effects. Inflammation-associated microglia can attenuate neurogenesis, whereas microglia activated by certain T helper cell cytokines promote neurogenesis. The impact on oligodendrocyte development is of particular interest, as microglial cells migrate along white matter tracts during their postnatal invasion, at a time when oligodendrocytes are differentiating. Cytokine-mediated effects on astroglial development have also been considered.

Recent evidence indicates that microglial cells could even be a source of other brain cells. Isolated microglial cells in culture have the potential to generate neurons, astrocytes and oligodendrocytes[94–96]. If this is true, cells of mesodermal origin could undergo neuroectodermal differentiation—a challenging perspective. There is, however, need for convincing evidence that this occurs *in vivo*. Similarly surprisingly, it has been claimed that both microglia and astrocytes develop from a bone marrow precursor[97]. Genetically marked cells (by viral tag or using male donors) transferred to female adult mice were subsequently identified not only as microglia, but also as cells expressing glial fibrillary acidic protein, indicating astrocytic nature. However, it remains possible that the tag was transferred to resident glial cells through phagocytosis. These intriguing observations will thus require thorough confirmation.

Microglial influences on regeneration

By what further mechanisms could microglia improve neuronal function and survival? Besides releasing a number of neurotrophic factors, microglia also structurally remove synapses from damaged neurons[98,99]. This process was termed synaptic stripping by Georg Kreutzberg in the 1960s. Moreover, microglial cells can remove entire dendritic structures after depletion of appropriate inputs. Microglial cells accumulate, through signaling mediated by the chemokine receptor CXCR3, at the lesion site in the molecular layer of the dentate gyrus after entorhinal cortex lesion. When microglial cells are present, the dendritic structures disappear within a few days, probably through microglial phagocytosis. In CXCR3-deficient animals, in which microglia does not accumulate at the lesion site, removal of the dendrites does not occur[100].

In the late, postinflammatory period of meningitis, circulating monocytes invade the brain parenchyma and differentiate into microglia. These cells are found in close apposition to apoptotic cells and contribute to the clearance of damaged tissue[43]. We assume that removal of structures (cells, dendrites or synapses) that have lost their function is beneficial for the system. It makes space for new connections, thereby helping the system to regenerate.

Conclusions

Recent findings on microglial activities under normal and pathologic conditions will change our view on the role of this cell type in health and disease. In particular, the concept of 'resting' versus 'activated' microglia needs substantial modification. In the past, microglia in CNS diseases was associated with detrimental net actions and failure of protection. By contrast, beneficial functions of microglia in successful transient activation episodes might have been easily overlooked. Microglia that are challenged may adapt to different stimuli and stimulatory contexts

and pass through a sequence of reactive profiles. Moreover, microglia may prove more heterogeneous by and within anatomical regions, as required for constitutive functions and underlying differential response options. Finally, the term 'microglial activation' may no longer sufficiently reflect the complexity, dynamics and outcomes of this response. These changes in terminology are not concerned merely with definitions, but with the biology behind them. Microglia should be seen as generally very active and versatile cells. New evidence- and hypothesis-based concepts of microglial function especially deserve attention and conversion into basic and clinical research efforts, particularly with regard to a disease-relevant tilt from beneficial to detrimental contributions.

Note: Supplementary information is available on the Nature Neuroscience website.

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