Microglia in neurodegenerative disease

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Abstract | Microglia, the resident macrophages of the CNS, are exquisitely sensitive to brain injury and disease, altering their morphology and phenotype to adopt a so-called activated state in response to pathophysiological brain insults. Morphologically activated microglia, like other tissue macrophages, exist as many different phenotypes, depending on the nature of the tissue injury. Microglial responsiveness to injury suggests that these cells have the potential to act as diagnostic markers of disease onset or progression, and could contribute to the outcome of neurodegenerative diseases. The persistence of activated microglia long after acute injury and in chronic disease suggests that these cells have an innate immune memory of tissue injury and degeneration. Microglial phenotype is also modified by systemic infection or inflammation. Evidence from some preclinical models shows that systemic manipulations can ameliorate disease progression, although data from other models indicates that systemic inflammation exacerbates disease progression. Systemic inflammation is associated with a decline in function in patients with chronic neurodegenerative disease, both acutely and in the long term. The fact that diseases with a chronic systemic inflammatory component are risk factors for Alzheimer disease implies that crosstalk occurs between systemic inflammation and microglia in the CNS.

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Introduction

Resident macrophages are present in all tissues of the body. In peripheral tissues, these cells are the first line of defense against injury and infection, responding rapidly to disturbances of tissue homeostasis. Following activation, macrophages initiate the recruitment of effector molecules and other immune cells to kill pathogens and restore tissue integrity.[1,2] In the CNS, the resident tissue macrophages—microglia and perivascular macrophages (PVMs)—have a similar role to peripheral macrophages. These highly specialized cells are profoundly influenced by their local microenvironment and have a number of distinctive features, such as their 'ramified' morphology and downregulated phenotype.[3,4] As a consequence of brain injury or disease, resident microglia change phenotype from their downregulated state to an 'activated' phenotype, which is characterized by shortened and extensively branched processes and hypertrophy of the cell body. Activated microglia can also be identified by the concomitant upregulation or *de novo* synthesis of a variety of cell-surface and cytoplasmic molecules. The ability to readily identify activated microglia has provoked considerable interest in their value as indicators of pathology and, hence, their diagnostic potential. Furthermore, substantial interest surrounds the possible role of activated microglia in disease pathogenesis, and the question of whether activated microglia activity exacerbates pathology or aids in tissue repair and ameliorates disease is currently a topic of debate.

In this Review, we highlight the highly plastic and diverse phenotypes of microglia, and draw attention to the fact that microglial phenotype and function cannot be extrapolated from morphology. We also discuss evidence indicating that the microglial phenotype is susceptible to modification by systemic events, and that systemic inflammation contributes to the symptoms and progression of chronic neurodegenerative disease.

Competing interests
The authors declare no competing interests.

Origins of microglia

Microglia are the most abundant of the resident macrophage populations in the CNS. These cells are derived from myeloid precursor cells, which enter the developing CNS during embryogenesis.[3] Under the influence of the CNS microenvironment, the microglial precursors mature and develop fine, long processes that form a regular network that 'tiles' the three-dimensional space of the brain parenchyma. Some regional differences in microglial density exist within the brain,[5] and a growing body of data indicates that the expression of tissue macrophage markers on microglia varies from one brain region to another;[6] however, the functional significance of these regional differences is not known. Although often referred to in the literature as 'resting', recent *in vivo* imaging studies clearly demonstrate that microglial processes continually explore and sample the local environment,[7,8] as might be expected of a tissue macrophage with a surveillance function. Local cell division at a very low level maintains the number of resident microglial cells in the brains of rodents,[9] and evidence suggests that microglia are only rarely replaced by bone marrow cells in healthy animals.[10,11] By contrast, PVMs in both rodents and primates show rapid turnover.[12,13] The extremely long-lived nature of microglia—essentially the lifespan of the organism—might have important implications for

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Key points

- The phenotype of microglia is tightly regulated within the normal healthy CNS
- Microglia rapidly change their morphology and expression of diverse molecules in response to changes in homeostasis and pathological insults to the brain
- Morphologically activated microglia display diverse phenotypes that critically depend on the sequence and duration of their exposure to various stimuli in different pathologies
- Microglial morphology and changes in expression of a small number of markers are not simple guides to microglial phenotype and function
- Microglial phenotype is modified by systemic infection and inflammation
- Systemic inflammation influences the symptoms and progression of chronic neurodegenerative disease

the treatment of chronic neurodegenerative diseases, as discussed below.

The capacity of microglia to exist as distinct phenotypes that are morphologically dissimilar from each other begs the question—what components of the CNS microenvironment are involved in the regulation of microglial morphology and phenotype? Neurons express cell-surface ligands that interact with receptors on the surface of microglia to induce these highly specialized cells to adopt their resting phenotype.[3] For example, CD200 expressed on neurons binds to its receptor CD200R on the microglial surface. CD200R has a cytoplasmic immunomodulatory tyrosine inhibitory motif (ITIM), which antagonizes other receptors expressed by the microglia that have an immunomodulatory tyrosine activating motif within the cytoplasmic tail.[14] The importance of these interactions is illustrated by CD200 null mice. In these knockout mice, microglia take on a morphology typically associated with activation, and a more rapid onset of symptoms in inflammatory disease is evident in these mice when compared with control animals.[15] Data from human studies support the idea that a reduction in CD200 expression is associated with microglial activation.[16] In addition to CD200–CD200R interactions, other ligand–receptor interactions can modulate microglial phenotype, including neuronal CX3CL1 and microglial CX3CR1 receptor interactions,[17] and CD47 and CD172a interactions.[18]

The functions of microglia in the normal healthy brain beyond immune surveillance are unclear, although observational studies indicate that microglia might perform a nutritive or supportive function for neurons.[19] By contrast, PVMs are routinely described as cells with a phagocytic role and might help to keep the perivascular spaces clear and facilitate the normal drainage of proteins from the brain.[20] PVMs are also implicated in the presentation of antigens to T cells that have been activated in the periphery, thereby facilitating the recognition of CNS antigens.[12]

Activated microglia

Microglia are often referred to as sensors of pathology, and almost any manipulation or insult to the brain that disturbs homeostasis leads to microglial activation, which manifests as a change in morphology and the upregulation or *de novo* synthesis of cell-surface receptors.[21] By use of immunocytochemistry, the presence of activated microglia has been documented in a plethora of animal models of brain injury and disease, as well as in equivalent conditions in humans.[3,4] In fact, evidence of brain pathology that is not accompanied by the activation of microglia is hard to find. The demonstration that the peripheral benzodiazepine receptor is upregulated in activated microglia led to the development of a ligand, ^{11}C-*R*-PK11195, which binds to this receptor. ^{11}C-*R*-PK11195 has been shown to label activated microglia and can be used *in vivo* in conjunction with PET to image activated microglia in the living brain.[22,23] The use of ^{11}C-*R*-PK11195 in PET studies has enabled clinicians to investigate whether quantification of activated microglia in the living brain is a useful indicator of disease onset or progression. In patients with Alzheimer disease (AD), initial studies suggest that the ^{11}C-*R*-PK11195 signal correlates inversely with cognitive function.[24] Furthermore, as cognitive function declines over time, the ^{11}C-*R*-PK11195 signal increases without a change in the signal from the PET ligand Pittsburgh compound B (^{11}C-PIB), which binds to amyloid. This observation is consistent with the view that activated microglia contribute to or reflect neuronal dysfunction in neurodegenerative disease.

The term 'activated microglia', although useful shorthand, has limitations and can be misleading. The term fails to take into account the fact that activated microglia are highly plastic cells, which can exist as numerous functionally distinct phenotypes,[1,2] The phenotypes that activated microglia can adopt—presumably in response to chemical or cell-based cues—are not readily apparent from either their morphology or from a limited number of cell-surface antigens that they are known to express. Several grades of microglial activation have been proposed, suggesting linear progressive activation from varying degrees of partial activation to full activation. In other contexts, the macrophage phenotype has been viewed as a dichotomy, with M1 (classically activated via toll-like receptors or interferon γ) and M2 (alternatively activated by interleukin 4 or interleukin 13) phenotypes being proposed.[25] In reality, however, macrophages seem to exist in a diverse range of forms, each of which synthesizes a different spectrum of cytokines and expresses distinct cell-surface receptors. The diversity of macrophage phenotypes seems to depend on the sequence of exposure to various cues, which might lead to a phenotype that is not readily forced into one or another 'type'. A scheme has been proposed that takes into account the diverse phenotypes that macrophages can adopt. The scheme identifies three broad families of macrophages—classically activated, wound healing and regulatory—but it recognizes that a continuum of different intermediates might exist.[2] An implicit requirement of the model is that the macrophages do not have fixed phenotypes, but can switch from one phenotype to another. Evidence for phenotype switching in response to biochemical cues has been obtained from *in vitro* experiments; however, this phenomenon has been less well studied *in vivo*.[26,27] It seems likely that the contribution of different macrophage and microglial populations, including resident cells and those recruited from the blood, to the outcome of CNS injury or pathology will depend on both the nature of the

stimulus that provokes the initial insult and subsequent secondary events that influence their phenotype.

Inflammation in the brain

The field of neuroimmunology and neuroinflammation has long been dominated by concepts derived from the study of multiple sclerosis (MS) and the animal model that mimics aspects of this disease—experimental allergic encephalomyelitis (EAE). Few people would doubt that the symptoms of MS are caused by an immune assault on the brain by T cells and macrophages, and that damage to the blood–brain barrier, myelin sheath, axons and neurons is mediated by these cells. The immunopathology of MS and EAE has been extensively reviewed elsewhere,[28,29] and we do not dwell on it here, except to note that activated microglia—largely determined by morphology—are not only present in the focal plaques of demyelination, but are also widespread in the white matter beyond the plaque and in the gray matter of the diseased brain. How the microglia both within the focal plaques and distant from the plaques contribute to tissue damage, disease symptoms and disease progression are active areas of research.

Innate inflammation

Acute injury

A key role of tissue macrophages is the rapid response to tissue injury. A diverse array of receptors on the macrophage surface respond to the presence of molecules—so-called damage-associated molecular pattern molecules (DAMPs)—released from injured or degenerating cells, which include high-mobility group box 1 proteins, heat shock proteins, histones, oxidized lipids, DNA, ATP, and potentially many others.[30,31] The receptors that detect DAMPs include scavenger receptors, toll-like receptors, and the receptor for advanced glycation end products (RAGE). In addition, macrophages must be able to detect the presence of pathogens that can invade wound sites. These pathogens activate a further array of macrophage cell-surface and intracellular receptors, including the toll-like receptors, and NOD (nucleotide-binding oligomerization domain) and NALP (NACHT, leucine-rich repeat and pyrin domain) proteins.[32,33] Microglia are known to express several of these receptors, including toll-like receptors, RAGE and a number of purinergic receptors.[34,35] Acute injury to the brain, such as a traumatic brain injury or stroke, will lead to the rapid degeneration of neurons and neuronal processes, and subsequently will lead to the generation of DAMPs, which in turn could activate microglia.

Studies in both animal models of acute injury and humans show that microglia in the core of an acute lesion and in the surrounding penumbra rapidly respond to tissue degeneration. The synthesis of proinflammatory cytokines and other inflammatory mediators is rapidly induced following acute injury, and these molecules contribute to the demise of neurons in the penumbra.[36,37] Well-studied molecules that promote neuronal degeneration include interleukin 1β and tumor necrosis factor (TNF). These cytokines in turn induce the synthesis of chemokines, leading to the recruitment of neutrophils and monocytes from the blood. Although microglia seem to be morphologically activated in the region of the lesion for an extended period of time, the synthesis of some of these inflammatory mediators is restricted in time,[37] and to different subsets of macrophages and microglia.[38] Evidence from animal models of acute injury indicates that the innate inflammatory response exacerbates lesion size and is detrimental to neurological outcome.[36] However, scavenging of cell debris after injury, in which microglia have a role, seems to be a prerequisite for synaptic regeneration.[39]

In any focal lesion of the brain, the degeneration of neural tissue is not localized to the initial lesion but will also initiate retrograde degeneration of neurons connected to the damaged region. Anterograde Wallerian degeneration of axons also occurs following death of the neuronal cell body. Wallerian degeneration in the CNS is accompanied by the activation of microglia along the degenerating fiber tracts and, over time, foam cells, which are responsible for the removal of degenerating axons and myelin, become evident. Wallerian degeneration is much slower in the CNS than in the PNS, and the phagocytic macrophages of the CNS seem relatively ineffective at removing the degenerating axons and myelin; in fact, the macrophages might persist at the site of injury for several years.[40] These microglia, although shown by morphological assessment to be activated, do not express appreciable levels of proinflammatory cytokines in either rodents[41] or humans.[42] Instead, the activated microglia display a phenotype that is dominated by molecules typically associated with an anti-inflammatory or 'alternatively activated' phenotype. The persistence of these innate immune cells for many years is an interesting example of long-term 'innate immune memory' of a tissue injury.

Chronic neurodegenerative disease

Microglia with a morphologically activated phenotype are present in large numbers in CNS tissue from patients with chronic neurodegenerative diseases including AD, Parkinson disease (PD), amyotropic lateral sclerosis (ALS) and prion disease (Figure 1). Interest in activated microglia as contributors to the progression of chronic neurodegeneration, rather than simply being a consequence of the pathology, was first proposed in AD.[43] Data from epidemiological studies demonstrated that people who take NSAIDs for relatively long periods of time seem to have a reduced risk of developing AD.[44,45] Unfortunately, prospective clinical trials that used NSAIDs to treat patients with AD were unable to show that these drugs are effective at halting the progression of AD, although some evidence exists that they might attenuate AD progression.[46] Possible reasons for these negative findings have been discussed in detail elsewhere;[47] however, the fact that inhibition of cyclooxygenase activity by NSAIDs only inhibits the release of a limited number of inflammatory mediators secreted by microglia could be one explanation. The studies focusing on the utility of NSAIDs in the treatment of AD show that we do not fully understand

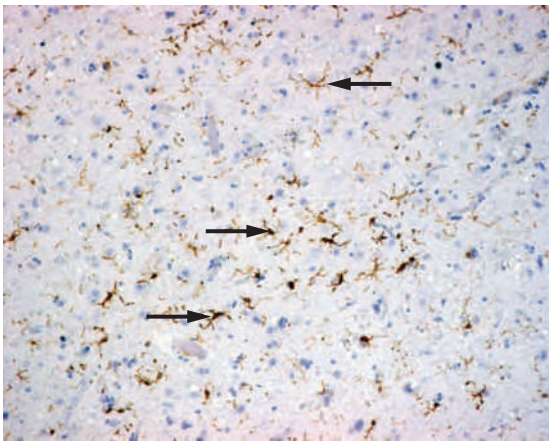

Figure 1 | Diffuse distribution of activated microglia in the cerebral cortex of a patient with Creutzfeldt–Jakob disease. Activated microglia identified by means of immunohistochemical staining for MHC class II molecules are indicated by arrows.

the cellular and molecular components of the innate inflammatory response associated with a slow progressive degenerative disease. Furthermore, the negative results from the clinical trial suggest that different aspects of the innate inflammatory process are important to different stages of the disease. The persistent activation of microglia in chronic neurodegenerative diseases might result either from the presence of misfolded proteins, such as amyloid fibrils in the case of AD, or from the degeneration of neurons. These processes are both slow, progressive events that are likely to activate the microglia in a way that induces a phenotype distinct from that found following acute brain injury.

Misfolded proteins

The scavenger, RAGE and toll-like receptors expressed by microglia can all bind amyloid fibrils.[34] Despite expressing these receptors, which are thought to confer a phagocytic phenotype, microglia do not efficiently remove amyloid unless further stimulated. Parallels might be drawn with systemic amyloidosis, in which tissue macrophages are also inefficient at removing amyloid plaques and, notably, do not mount a proinflammatory response.[48] In this condition, the association of the acute-phase reactant serum amyloid P (SAP) with all forms of amyloid substantially contributes to the lack of recognition of the amyloid plaques by peripheral macrophages.[49] In AD, amyloid in both plaques and blood vessel walls in the brain is associated with SAP[50] and, as in peripheral tissues, SAP might prevent the efficient phagocytosis of the amyloid deposits. Studies on the degradation of amyloid-β (Aβ) peptides—the main constituent of amyloid plaques in AD—have shown that SAP inhibits proteolysis of Aβ *in vitro*.[51] By contrast, complexes of Aβ, SAP and C1q complement protein stimulate increased cytokine synthesis.[52] The presence of SAP, other pentraxins or acute-phase proteins is likely to influence the phenotype of microglia and their capacity to bind to or be activated by amyloid.

In some neurodegenerative diseases, such as AD and prion disease, most misfolded protein accumulates extracellularly and activates the microglia in the local microenvironment. By contrast, the misfolded proteins present in other disorders such as PD, ALS and Huntington disease (HD) accumulate intracellularly, but are nevertheless still associated with microglial activation. In PD, which is characterized by the accumulation of α-synuclein within Lewy bodies in the affected neurons, activated microglia have been shown to be present in the substantia nigra and the striatum. Raised levels of proinflammatory cytokines and inducible nitric oxide synthase have also been detected in these brain regions, providing evidence of a local inflammatory reaction.[53] Epidemiological studies have shown that NSAIDs might have a neuroprotective effect in PD as well as in AD, which suggests that inflammation could contribute to PD progression. Unfortunately, this neuroprotective effect has not been universally replicated. In fact, a recent meta-analysis suggests that NSAIDs offer no neuroprotective effects for patients with PD.[54] A study in which injection of endotoxin—a potent activator of microglia—into the substantia nigra led to microglial activation and death of dopaminergic cells, however, supports the hypothesis that activated microglia and inflammation might be contributory factors to PD pathogenesis.[55]

In ALS, microglia are activated in the vicinity of degenerating motor neurons.[56] Evidence that activated microglia contribute to disease progression in ALS comes from elegant studies in transgenic mice that express mutated superoxide dismutase 1 (SOD1) as a model of familial ALS. Precisely how mutant SOD1 leads to the demise of motor neurons is not clear, but the mutated protein is expressed in all cells including microglia. When the mouse lines are manipulated to reduce the expression of mutant SOD1 in microglia, including those adjacent to the diseased motor neurons, the rate of disease progression is slowed and lifespan extended.[57,58] Microglia expressing the mutated SOD1 protein generate more superoxide and nitric oxide when challenged with endotoxin than do wild-type microglia. These experiments are a powerful demonstration that defects in some protein misfolding diseases are not neuron autonomous.

Neurodegeneration

As mentioned above, the slow degeneration of neurons and their processes might also activate microglia. In fact, a positive feedback loop has been hypothesized in which microglia activated by neuronal degeneration secrete neurotoxic molecules, which in turn promote further neurodegeneration, thereby initiating a self-perpetuating degenerative process.[59] In this scenario, we know little about the signals from the degenerating neurons and their processes that might be involved in this positive feedback loop. Furthermore, the impact of a slow, protracted degenerative process that might lead to adaptation or tolerance in the microglial population has not been investigated. For many years, the focus in chronic neurodegenerative disease was on the mode of cell death of the neuronal cell soma, and we now know that neurons die through apoptosis in many such conditions.[60] The

recognition of apoptotic cells by macrophages is accomplished via a number of different receptors, including the phosphatidylserine receptor and the CD36 and CD14 receptors, the result of which is to promote an anti-inflammatory macrophage phenotype.[61] Clearance of apoptotic cells is an important homeostatic mechanism in the resolution of inflammation; therefore, adopting an anti-inflammatory phenotype is appropriate for microglia involved in this process.

In addition to widespread apoptosis, evidence is accumulating that synaptic loss is also prominent in neurodegenerative diseases such as AD. Synaptic loss correlates positively with dementia progression,[62] and is probably an early component of the neuronal degeneration. If DAMPs are released from degenerating synapses, as in acute brain injury, a proinflammatory microglial phenotype could be envisaged. By contrast, if molecules such as those associated with neuronal apoptosis are released from degenerating synapses, an anti-inflammatory microglial phenotype would be predicted. To date, the phenotype of microglia activated by slow synaptic degeneration *per se* has not been well defined and requires further study.

In summary, the evidence suggests that neither extracellular amyloid deposits nor chronic neurodegeneration alone will lead to a robust proinflammatory response. In chronic neurodegenerative diseases where misfolded proteins accumulate within neurons, glia and microglia, the phenotype of microglia would be expected to differ from that in diseases characterized by extracellular accumulation of amyloid.

Models of neurodegeneration

Mouse models of neurodegeneration have been developed in which genes associated with familial forms of chronic neurodegenerative disease such as AD, ALS, PD and HD have been inserted into the mouse genome to recapitulate aspects of the diseases.[63,64,65] For example, widespread amyloid deposits are evident within the brain of transgenic mice carrying the human amyloid precursor protein (*hAPP*) gene or *hAPP* plus presenilin 1 (*PS1*) genes with AD-causing mutations. A notable feature of these mice, and of triple transgenic mice that carry tau genes bearing frontotemporal dementia-causing mutations, in addition to the *hAPP* and *PS1* genes, is the lack of widespread and catastrophic neurodegeneration typical of AD.[66] These mice, however, have a valuable role in research into aspects of AD, which is demonstrated by their use in studying the kinetics of amyloid deposition and in testing novel imaging techniques for the detection of amyloid.[67] Nevertheless, the paucity of neurodegeneration in these mice is an important issue if we wish to explore the relationship between amyloid deposition, chronic slowly evolving neurodegeneration and the innate immune response in the brain.

In both the human brain and the brains of *hAPP* transgenic mice, activated microglia accumulate around the amyloid plaques, but they seem to be relatively inefficient in the removal of the amyloid protein. The profile of inflammatory mediators in the brains of *hAPP* mice has been documented, and the levels of proinflammatory molecules are relative low in comparison to the levels of such molecules observed in other inflammatory conditions.[68] The lack of neurodegeneration in these models might account for this low proinflammatory phenotype; however, in other models of neurodegeneration where substantial neurodegeneration is evident, the cytokine profile of the affected brain regions also lacks high levels of proinflammatory mediators. For example, in a mouse model of prion disease, which shows widespread neuronal degeneration, large numbers of activated microglia can be detected, but the cytokine profile is anti-inflammatory and dominated by TGF-β.[69] Furthermore, the anti-inflammatory phenotype first becomes apparent at a stage of the disease when synaptic degeneration occurs in the absence of neuronal loss. One hypothesis suggests that microglia might remove synapses from injured neurons—so-called synaptic stripping[70]—and that this process could induce an anti-inflammatory phenotype. Indeed, *in vivo* imaging studies have shown that microglia make more-prolonged contacts with synapses in the ischemic brain than in the healthy brain,[71] although electron microscopy studies in prion disease have demonstrated that the degenerating synapses are enveloped by dendritic spines rather than the processes of microglia.[72]

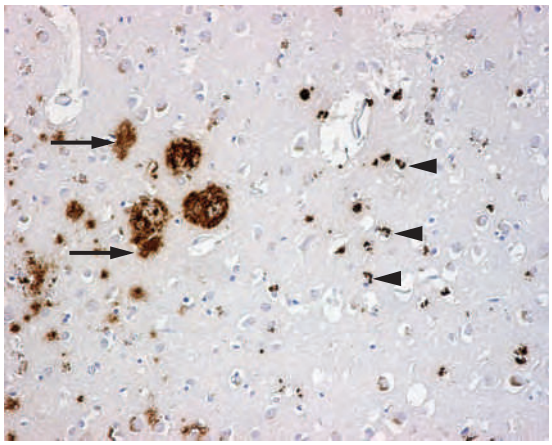

Figure 2 | Aβ immunization in Alzheimer disease induces amyloid plaque phagocytosis by activated microglia. Amyloid plaques identified via immunohistochemical staining for Aβ42 are indicated by arrows on the left-hand side of the image. On the right-hand side of the image, where the plaques have been removed, Aβ42 is present in activated microglia (indicated by arrowheads) and is presumed to represent plaque Aβ that has been phagocytosed by the microglia. Abbreviation: Aβ, amyloid-β.

Therapeutic implications

Modulating microglial phenotype

Several studies have investigated whether microglia in mouse models of AD can be encouraged to phagocytose the amyloid plaques. Delivery of a large dose of a potent proinflammatory agent such as lipopolysaccharide directly into the brain, for example, will enhance phagocytosis of amyloid by microglia.[73] Other manipulations of the innate immune system that lead to enhanced phagocytosis include whole-body irradiation followed by bone marrow transplantation (BMT),[74] in which the bone

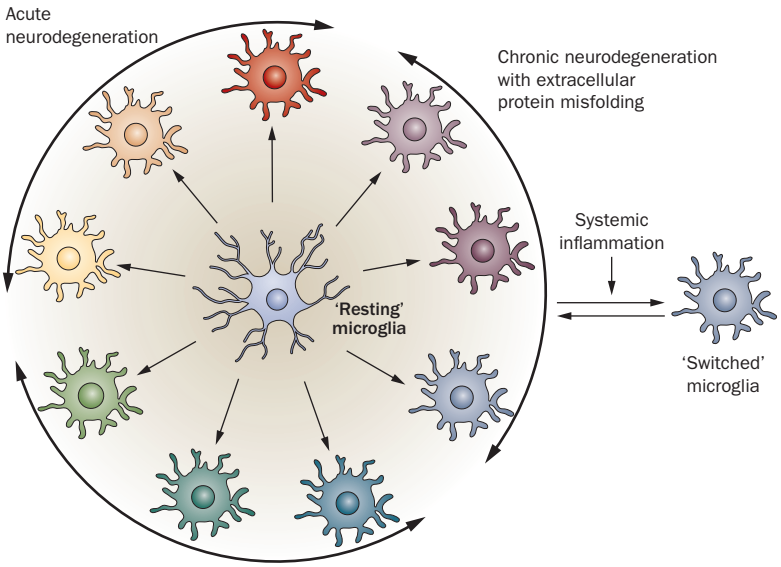

Figure 3 | Microglial phenotypes. Resident microglia can become activated to adopt one of many diverse phenotypes depending on the disease type, stage of disease, age of the patient and many other variables. Microglia activated in acute neurodegeneration, for example, will have different phenotypes depending on the extent of the injury, time of examination after injury and age of the patient; these diverse phenotypes are represented by activated microglia of differing colors. Similarly, in chronic neurodegenerative disease the microglial phenotype will vary depending on whether the cause of the neurodegeneration is an intracellular or extracellular misfolded protein, and will also be affected by the stage of disease and age of the individual. The microglial phenotype could be further influenced by systemic inflammatory events that lead to a switch in phenotype that might or might not be reversible, and that either ameliorates or accelerates disease progression. Neither the morphology of the activated microglia nor the cell-surface markers that are known to be expressed by these cells seem adequate to specifically identify all the diverse phenotypes and functions that microglia can adopt in different diseases.

marrow-derived cells have been observed to phagocytose the amyloid, and systemic injection of macrophage colony stimulating factor 1 (CSF-1).[75] These approaches would, however, be of little clinical relevance in an elderly, frail population with AD, since BMT carries substantial risks, and CSF-1 is a proinflammatory factor that exacerbates inflammatory disease.[76] Nevertheless, these manipulations do raise important questions as to the roles of resident and recruited macrophage populations in the removal of amyloid from the brain, and indicate that the whole-body irradiation used for BMT has complex pathological effects on microglial kinetics, perhaps by influencing both peripheral and brain macrophage populations.[77] The fact that small numbers of recruited monocytes can have a profound effect on amyloid deposits suggests that we need to look beyond the microglia–amyloid interactions to establish what factors regulate amyloid turnover.[74,78] One study in *hAPP* transgenic mice, for example, showed that neither amyloid formation and maintenance nor amyloid-associated neuritic dystrophy is dependent on microglia, suggesting a benign role for microglia in this component of the pathology.[79]

A further ambitious approach that has been suggested to encourage amyloid plaque phagocytosis involves modification of the adaptive immune response to aid the removal of amyloid. Immunization of *hAPP* transgenic mice with Aβ peptide led either to prevention of amyloid formation or clearance of the amyloid, depending on the time of immunization.[80] Subsequently, other approaches, such as delivery of specific anti-Aβ antibodies (passive immunization), have demonstrated similar effects. These interventions both increased the removal of amyloid, and also led to improvements in the cognitive and functional abilities of the mice,[81] indicating that systemic modifiers of inflammation might be clinically beneficial for patients with AD.

These studies should be contrasted with other studies in which systemic inflammation following brain injury and disease seem to exacerbate brain injury and disease progression. In a mouse model of prion disease, a systemic challenge with a single dose of endotoxin has been shown to instigate a switch in the microglial phenotype from anti-inflammatory to proinflammatory.[69] This switch in microglial phenotype was associated with exaggerated symptoms of sickness behavior such as fever and reduced mobility, increased neuronal loss, and an increase in disease progression.[69,82] Importantly, however, the switch in phenotype was not accompanied by a change in microglial morphology. Inflammation induced by either single or repeated systemic challenge also exaggerated neuronal loss in models of motor neuron disease[83] and PD.[84] The loss of neurons and their ligands that bind ITIM receptors on microglia, as well as the presence of DAMPs, leads to microglial 'priming' as neurodegeneration progresses. Thus, microglia retain an innate immune memory of the ongoing neuropathology, which is in turn associated with a heightened responsiveness to the presence of systemic inflammation. Systemic inflammation, therefore, communicates with the brain via both neural and humoral routes as part of our host defense against injury and infection.[85]

Systemic inflammation in clinical disease

The data from animal models of chronic neurodegeneration provide two contrasting views of the role of inflammation in a disease such as AD. On the one hand, provoking inflammation in the brain seems to increase the removal of amyloid deposits and ameliorate disease progression. On the other hand, by increasing the production of neurotoxic molecules and promoting neuronal loss, inflammation can exacerbate neurodegenerative disease progression. We now ask: how does manipulation of the adaptive immune response in patients affect the progression of neurodegenerative disease?

Immunization of AD patients with Aβ peptides or anti-Aβ antibodies, in the hope of removing or reducing the amyloid load in the brain, is perceived to be an area of considerable therapeutic promise. In keeping with the studies in animal models, the immunization of patients who have AD has indeed led to clearance of amyloid plaques, which was associated with amyloid phagocytosis by macrophages and microglia (Figure 2).[86,87] However, despite the reduction in amyloid burden, this immunization trial did not arrest cognitive decline or increase the time to death in the cohort.[87] This immunization strategy is also not without risk, as a small percentage of the patients

developed adverse effects that were probably a consequence of an autoimmune assault on the brain.[88,89]

As reviewed in this journal, a wealth of clinical experience indicates that systemic events, including infection, medication and surgery, can all lead to acute changes in cognition and attention, which can result in the syndrome of delirium.[90] According to epidemiological evidence, a single bout of delirium can accelerate cognitive decline in patients with AD.[91,92] Furthermore, a study published in 2009 demonstrated that both acute and chronic systemic inflammation are associated with raised levels of serum TNF, which in turn is associated with accelerated, delirium-independent cognitive decline in patients with AD.[93] Also of note is the fact that many of the risk factors for AD, such as obesity,[94] smoking,[95] diabetes,[96] atherosclerosis[97] and periodontitis,[98] are associated with chronic systemic inflammation.

Conclusions

Clearly, we have much to learn about the role of inflammation in the development and progression of neurodegenerative disease. A body of evidence indicates that activated microglia can adopt many different phenotypes depending on the disease in question, the stage of the disease, and also systemic influences (Figure 3). Microglia have the potential to be relatively benign, contribute to disease progression, or perhaps even be protective. However, as highlighted by two genome-wide association studies of late-onset AD,[99,100] which demonstrated associations between components of the innate immune response and AD, a better comprehension of inflammatory pathways will be vital to our understanding of the pathogenesis of neurodegenerative disease and, hence, the development of effective therapies.

Review criteria

PubMed, ISI Web of Science and the reference lists of papers were searched for articles published in English, with the following search terms: "microglia", "macrophage", "amyloid", "protein misfolding", "Alzheimer's", "Parkinson's", "prion", "ALS", "inflammation", and "neuroinflammation". Inclusion of particular references was based on the authors' judgment and available space.

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