

Review

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Does neuroinflammation fan the flame in neurodegenerative diseases?

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Abstract

While peripheral immune access to the central nervous system (CNS) is restricted and tightly controlled, the CNS is capable of dynamic immune and inflammatory responses to a variety of insults. Infections, trauma, stroke, toxins and other stimuli are capable of producing an immediate and short lived activation of the innate immune system within the CNS. This acute neuroinflammatory response includes activation of the resident immune cells (microglia) resulting in a phagocytic phenotype and the release of inflammatory mediators such as cytokines and chemokines. While an acute insult may trigger oxidative and nitrosative stress, it is typically short-lived and unlikely to be detrimental to long-term neuronal survival. In contrast, chronic neuroinflammation is a long-standing and often self-perpetuating neuroinflammatory response that persists long after an initial injury or insult. Chronic neuroinflammation includes not only long-standing activation of microglia and subsequent sustained release of inflammatory mediators, but also the resulting increased oxidative and nitrosative stress. The sustained release of inflammatory mediators works to perpetuate the inflammatory cycle, activating additional microglia, promoting their proliferation, and resulting in further release of inflammatory factors. Neurodegenerative CNS disorders, including multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), tauopathies, and age-related macular degeneration (ARMD), are associated with chronic neuroinflammation and elevated levels of several cytokines. Here we review the hallmarks of acute and chronic inflammatory responses in the CNS, the reasons why microglial activation represents a convergence point for diverse stimuli that may promote or compromise neuronal survival, and the epidemiologic, pharmacologic and genetic evidence implicating neuroinflammation in the pathophysiology of several neurodegenerative diseases.

Overview

Once considered an immune-privileged site because of the presence of the blood brain barrier (BBB), it is now clear that while peripheral immune access to the central nervous system (CNS) is restricted and tightly controlled, the CNS is capable of dynamic immune and inflammatory responses to a variety of insults [1]. Infections, trauma, stroke, toxins and other stimuli are capable of producing an immediate and short lived activation of the innate immune system within the CNS [2,3]. This acute neuroinflammatory response includes activation of the resident immune cells (microglia) resulting in a phagocytic phenotype and the release of inflammatory mediators such as cytokines and chemokines [4]. While an acute insult may trigger oxidative and nitrosative stress, it is typically short-lived and unlikely to be detrimental to long-term neuronal survival. Therefore, it is believed that an acute neuroinflammatory response is generally beneficial to the CNS, since it tends to minimize further injury and contributes to repair of damaged tissue.

In contrast, chronic neuroinflammation is a long-standing and often self-perpetuating neuroinflammatory response that persists long after an initial injury or insult. Chronic neuroinflammation includes not only long-standing activation of microglia and subsequent sustained release of inflammatory mediators, but also results in increased oxidative and nitrosative stress [4]. The sustained release of inflammatory mediators works to perpetuate the inflammatory cycle, activating additional microglia, promoting their proliferation, and resulting in further release of inflammatory factors. Owing to the chronic and sustained nature of the inflammation, there is often compromise of the BBB which increases infiltration of peripheral macrophages into the brain parenchyma to further perpetuate the inflammation [1]. Rather than serving a protective role as does acute neuroinflammation, chronic neuroinflammation is most often detrimental and damaging to nervous tissue. Thus, whether neuroinflammation has beneficial or harmful outcomes in the brain may depend critically on the duration of the inflammatory response.

Neurodegenerative CNS disorders, including multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), tauopathies, and age-related macular degeneration (ARMD), are associated with chronic neuroinflammation and elevated levels of several cytokines [5-8]. Neuropathological and neuroradiological studies indicate that neuroinflammatory responses may begin prior to significant loss of neuronal populations in the progression of these diseases. While there is no evidence to support a role for any particular cytokine in the direct triggering of any of these neurodegenerative conditions,

cytokine-driven neuroinflammation and neurotoxicity may modify disease progression in a number of these disorders. For example, inflammatory challenges might act as triggers to uncover pre-existing genetic vulnerabilities that contribute to neuronal dysfunction and death. Alternatively, viruses or bacteria might "prime" the immune system to respond aberrantly to subsequent environmental challenges. The purpose of this article is to review the evidence that microglial activation represents a convergence point for diverse external stimuli that promote neuronal dysfunction and hasten neuronal death, and the epidemiologic, pharmacologic and genetic evidence implicating neuroinflammation in the pathophysiology of several neurodegenerative diseases. If the available evidence supports a role for neuroinflammation in any of these diseases, it may be possible to alter the course of disease development in afflicted individuals with timely delivery of anti-inflammatory therapy.

Microglia activation: convergence point for diverse stimuli that compromise neuronal survival

Microglia are the resident tissue macrophages in the central nervous system and are the principle mediators of inflammation. In the resting state, microglia display a small cell soma and numerous branching processes (a ramified morphology). In healthy brain tissue, these processes are dynamic structures that extend and retract sampling and monitoring their microenvironment (Nimmerjahn 2005, Raivich 2005). During the resting state several key surface receptors are expressed at low levels; these include the tyrosine phosphatase (CD) 45 (also known as leukocyte common antigen), CD-14, and CD11b/CD18 (Mac-1) (Kreutzberg 1996). In addition cell surface receptor-ligand pairs such as CD200R/CD200 are present to maintain neuron-glia communication in the CNS (Hock 2000, Cardona 2006).

In the presence of an activating stimulus, microglial cell-surface receptor expression is modified and the cells change from a monitoring role to one of protection and repair (reviewed in [4,9]). In addition to up-regulation of the key surface receptors mentioned above, there is up-regulation of proteins such as CD1, lymphocyte function-associated antigen 1 (LFA-1), intercellular adhesion molecule 1 (ICAM-1 or CD54), and vascular cell adhesion molecule (VCAM-1 or CD106). Activated microglia secrete a variety of inflammatory mediators including cytokines (TNF, and interleukins IL-1 β and IL-6) and chemokines (macrophage inflammatory protein MIP-1 α , monocyte chemoattractant protein MCP-1 and interferon (IFN) inducible protein IP-10) that promote the inflammatory state. The morphology of the cells changes from ramified to amoeboid as they take on a phagocytic role. These moderately active microglia are thought to perform

beneficial functions, such as scavenging neurotoxins, removing dying cells and cellular debris, and secreting trophic factors that promote neuronal survival. Persistent activation of brain-resident microglia may increase the permeability of the BBB and promote increased infiltration of peripheral macrophages, the phenotype of which is critically determined by the CNS environment [10].

Microglia are the critical convergence point for the many diverse triggers that elicit an adaptive immune response (Figure 1). Stroke, hypoxia, and trauma compromise neuronal survival and indirectly trigger neuroinflammation as microglia become activated in response to the insult in an attempt to limit further injury. Infectious agents activate microglia either through damage to infected cells or direct recognition of foreign (viral or bacterial) proteins. Following exposure to neurotoxins such as the mitochondrial complex I inhibitor 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), the dopamine analog 6-hydroxydopamine (6-OHDA), or the pesticide paraquat, microglia become activated and primed. Microglial responses to these toxins may contribute to neuronal dysfunction and eventually hasten neurodegeneration (Czlonkowska et al., 1996; Kohutnicka et al., 1998; Liberatore et al., 1999; Dehmer et al., 2000; Vila et al., 2001). In addition, genetic mutations that give rise to increased production of toxic oligomeric, aggregated/truncated, or oxidized protein species promote sustained activation of microglia and may prime the immune system for aberrant responses to subsequent insults. Regardless of the initiating factor, all of these external or internal stimuli have the potential to trigger a self-perpetuating inflammatory response that, if left unresolved, may contribute to death of vulnerable neuronal populations.

Evidence of neuroinflammation and cytokine involvement in neurodegenerative diseases **Alzheimer's Disease (AD)**

Although the etiology of sporadic AD in humans is unknown, mutations in Amyloid Precursor Protein (APP) or components of its processing machinery (β -secretase and γ -secretase) result in overproduction of A β 1-40 and 1-42 peptides and are sufficient to cause disease [11-17]. Over 20 years ago, microglia were reported to localize to amyloid plaques in AD brain [18] and since then, the association between neuroinflammation and AD has been extensively investigated [7,19-24] and reviewed [19,25]. Human microglia display an activated phenotype when they surround plaques [23] that includes upregulation of Human Leukocyte Antigen-DR (HLA-DR) [18]. In addition to producing cytokines and other pro-inflammatory mediators [19,26], microglia have also been reported to exert toxicity on neurons that have been pre-exposed to low concentrations of A β 42 via a CD14-dependent process [27]. Although it is clear that not all microglia activa-

tion is injurious to neurons, it is becoming widely accepted that a type of neurotoxic microglia phenotype has a central role in the pathophysiology of AD.

While microglia can become activated after exposure to fibrillary A β *in vitro* and are capable of phagocytosing it *in vitro* [28-30], it has been reported that in the presence of inflammatory cytokines or certain extracellular matrix proteins, microglia cannot phagocytize A β [31]. This observation has been used to support the idea that the persistence and accumulation of amyloid plaques *in vivo* may be a direct result of this inhibitory behavior exerted by neuroinflammation. Moreover, numbers of IL-1 α positive (i.e., pro-inflammatory) microglia are increased in the cortical layers affected by plaque pathology in AD patients [32]. Since microglia are found in large numbers around neuritic amyloid plaques, but not diffuse in human AD patients, and in mice transgenic for mutant APP [33], it has been postulated that microglia play a role in the conversion of diffuse to neuritic senile plaques but not in the origin of diffuse plaques [34]. Specifically, post-mortem analyses of microglia density in the neocortex of three groups of nondemented individuals at different stages of senile plaque formation versus AD patients revealed that the mean density of microglia was highest in the AD group and that microglia were associated with neuritic plaques much more often than with diffuse plaques. Interestingly, individuals with some neuritic plaques also had microglia within a greater proportion of their diffuse plaques than individuals who only had diffuse plaques. While these findings raise the possibility that microglial activity may promote conversion of diffuse plaques into neuritic plaques, an important caveat of this study is that this conclusion is based on correlative observations postmortem and were not derived from a dynamic *in situ* analysis of microglial activity around diffuse or neuritic plaques.

The pro-inflammatory effect of A β deposition in brain has been recapitulated in aged mice transgenic for a familial AD mutation of APP, in which astrocytes and microglia expressing IL-1 β , IL-6 and TNF have been found surrounding amyloid plaques [35]. The bacterial endotoxin lipopolysaccharide (LPS), a powerful inducer of inflammatory responses [36], exacerbates the appearance and severity of AD pathology in the APPV717F transgenic mouse [37], the APP^{swe} transgenic mouse [38], and the triple-transgenic (3xTgAD) mouse [39]. In addition, the Transforming Growth Factor- β (TGF- β) cytokine family increases A β accumulation in the cerebral blood vessels of mice transgenic for human APP and is upregulated in blood vessels of human patients with Cerebral Amyloid Angiopathy (CAA) [40]. Co-addition of TGF- β 1, 2 and 3 isoforms with A β causes increased A β accumulation in organotypic hippocampal slices [41]. Together, these

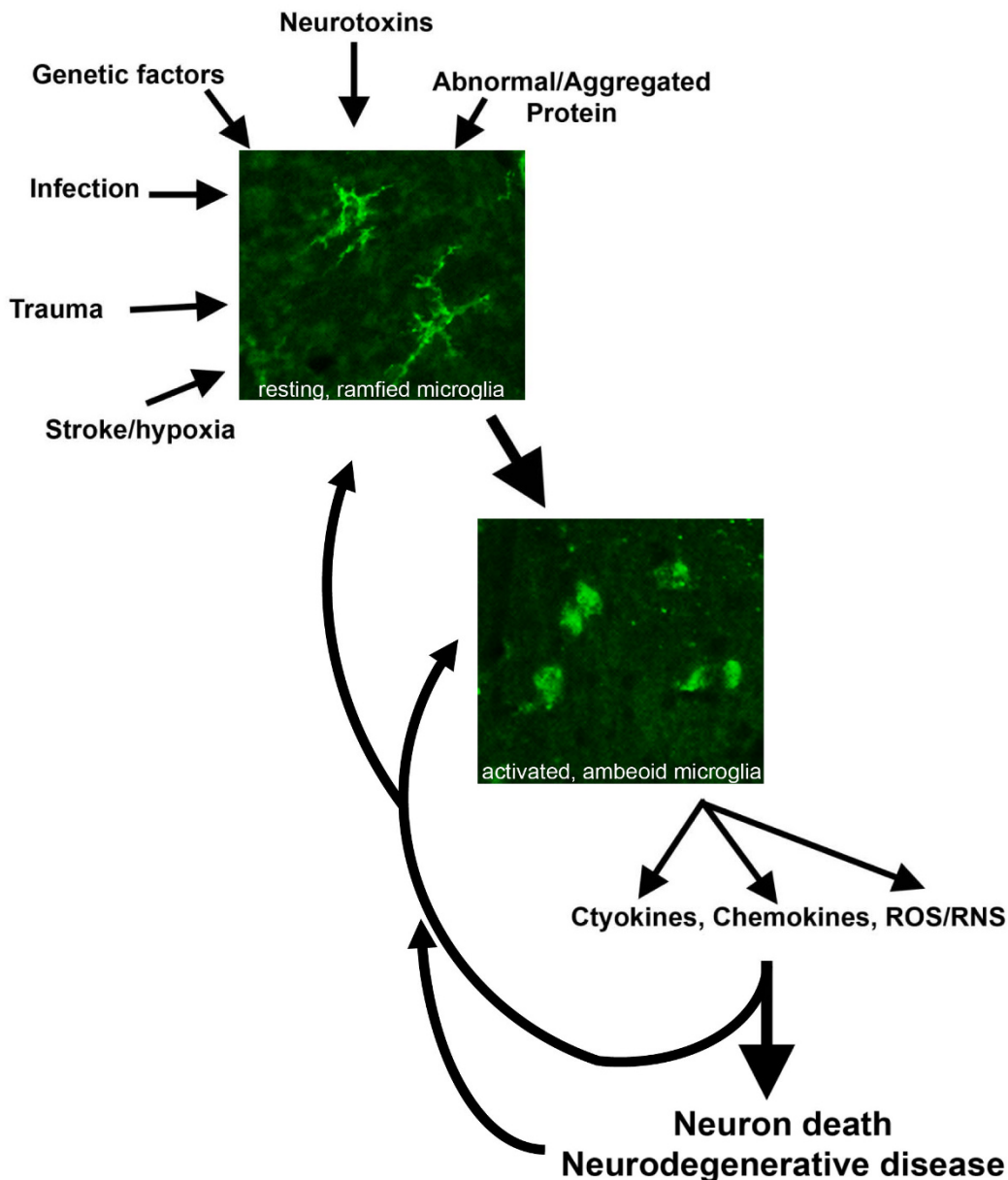


Figure 1
Neuroinflammation can precede and contribute to neuronal dysfunction and degeneration. Divergent initiating triggers directly or indirectly converge to activate microglia (stained here with an antibody against F4/80) from a ramified/resting state to an amoeboid-shape/activated state, initiating a self-propelling cycle of neuroinflammation and chronic over-production of inflammatory mediators. These mediators impact susceptible neuronal populations in the CNS and contribute to their demise within the context of each neurodegenerative disorder. The progressive loss of neurons that characterizes these disorders further contributes to generation of debris and keeps microglia activated indefinitely maintaining microglia in an activated state long-term.

findings demonstrate the close association between microglia and plaque deposition and the ability of certain chronic inflammatory stimuli to exacerbate and accelerate amyloid-associated pathology. The emerging idea is that an inflamed CNS environment may influence the ability of microglia to contribute to plaque deposition rather than plaque removal, strongly suggesting that the micro-environment of the brain can influence whether microglia perform beneficial or deleterious functions in pathophysiological states.

While the role of inflammatory responses in AD are just beginning to be understood, there is little dispute that inflammatory mediators may represent both potentially useful biomarkers and targets for drug development. Cyclooxygenase 2 (COX2), a pro-inflammatory protein that is one of the targets of non-steroidal anti-inflammatory drugs (NSAIDs), and its homolog COX-1 [42], are elevated in AD brains [43]. Serum levels of the acute phase protein α 1-antichymotrypsin, which is upregulated by injury, trauma and infection, are also significantly higher in AD patients than healthy controls [44]. And clinically, a proteomic study of plasma from control subjects, patients with Mild Cognitive Impairment (MCI) and patients with AD suggested that dysregulated systemic immune responses are present in patients who progress from MCI and go on to develop AD, raising the interesting possibility that this inflammation "communicome" may serve as signature for early detection of the disease [45].

Not only is neuroinflammation believed to be one of the earliest consequences of A β deposition, it has been shown to accelerate neurodegeneration and contribute to progression of pathology [46]. Epidemiological studies suggest a link between chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) and reduced risk for AD. In a study of siblings who all eventually developed AD, regular use of NSAIDs delayed the onset of AD and reduced the risk of AD with each year of use [47]. Participants in the Baltimore Longitudinal Aging Study also exhibited a reduced risk for AD with the use of NSAIDs, with those patients who had taken NSAIDs for more than 2 years showing the most reduction in AD risk [48]. Comparison of brains of aged but cognitively normal patients who used NSAIDs chronically with that of cognitively normal patients who did not use NSAIDs revealed no changes in the appearance of senile plaques, but a 3-fold decrease in the number of activated microglia in the brains of chronic NSAID users [49]. Most recently in what is the largest and longest duration epidemiological study to date, long-term (> 5 yrs) NSAID use, in particular ibuprofen, was shown to be protective against development of AD [50]. These findings suggest that the protection afforded by chronic NSAID use in the studies of AD patients may in part be derived by attenuation of microglia activation. Consistent

with the epidemiological findings on ibuprofen, chronic ibuprofen administration in aged transgenic mice reduced the number and area of amyloid plaques, as well as the numbers of activated microglia [51], and administration of R-flurbiprofen rescued deficits in hippocampal and medial temporal lobe-dependent memory and learning [52]. However, thus far, clinical trials using systemic administration of NSAIDs have yielded mixed or inconclusive results [53-55], reflecting the need to identify and target the key inflammatory mediators that promote amyloid-associated neuropathology.

However, it is important to note that the presence inflammatory responses may also be necessary to prevent amyloid-associated neurotoxicity. For example, the activation of complement factor C3, the central component of the complement system and a key inflammatory protein may be necessary for plaque clearance by microglia in the AD-afflicted brain [56,57]. In addition, an important component of any inflammatory response is the activation of anti-inflammatory loops that serve to limit and resolve the initial inflammatory response. The Peroxisome Proliferator-Activated Receptor- γ (PPAR γ), a nuclear receptor which is activated by metabolites of prostaglandins generated by the COX enzymes and by certain NSAIDs, is upregulated in concert with the COX enzymes in AD brain [42]. As such, PPAR γ activation exerts an anti-inflammatory effect, and PPAR γ agonists have been shown to inhibit the production of cytokines and pro-inflammatory mediators in response to A β [58]. In addition, there appears to be a feedback signaling loop between A β and IL-1 β : A β can induce the production of IL-1 β [7], and the presence of IL-1 β greatly increases the secretion of cytokines IL-6 and IL-8 in response to A β by astrocytes; in the other direction, IL-1 α and IL-1 β both upregulate the expression of APP, thus probably upregulating the production of A β [59]. The ratio of the pro-inflammatory cytokine IL-1 β to the anti-inflammatory cytokine IL-10 is drastically elevated in the serum of AD patients, giving these patients a definite pro-inflammatory profile [60]. Increases in levels of IL-1 β have been correlated with decreases in LTP in the hippocampus, showing that the cytokine itself may impair memory [61]. Other evidence, however, suggests that IL-1 β may not be driving AD pathogenic processes. For example, functional inhibition of IL-1 β signaling in mice by genetic ablation of the IL1 receptor [62] or by infusion of IL-1ra did not modulate A β deposition. In addition, IL-1 β was recently shown to upregulate the α -secretase TACE, thus increasing non-amyloidogenic cleavage of APP and decreasing A β production [63]. Therefore, while it may participate in neuroinflammatory responses in AD brain by activating microglia to secrete other inflammatory mediators, IL-1 β is not required to drive A β deposition and may in fact activate non-amyloidogenic pathways.

An interesting approach to treating amyloid pathology in AD has been the active or passive immunization against A β . Immunizing PDAPP mice with A β 42 prevented or reduced the progression of AD pathology in these mice, depending on whether the immunization took place before or after the development of plaque pathology [64]. Vaccination with A β peptides also ameliorated cognitive deficits in mice transgenic for a familial AD (FAD) mutation in APP and an FAD mutation in PS1 [65]. As an alternative delivery route, intranasal administration of A β peptides reduced amyloid deposition in AD mouse models [66,67]. A β vaccinations were also found successful in reducing A β levels in two non-human primates, the rhesus monkey [68] and the Caribbean vervet [69]. A clinical trial of A β 42 vaccinations was undertaken by Elan Pharmaceuticals in AD patients, and the immunizations resulted in significant clearance of A β and plaque removal in some of the patients [70,71], as well as a slowing of the cognitive decline in patients who produced antibodies against the peptide [72]. Unfortunately, the immunization also resulted in dangerous T-lymphocyte meningoencephalitis in some patients, causing the arrest of these trials [70,73]. Passive immunization of PDAPP mice peripherally infused with antibodies that recognize aggregated A β in neuritic plaques rapidly increased microglial clustering around plaques detectable by *in vivo* multiphoton microscopy [74] and reduced plaque burden and AD pathology in PDAPP mice [75]. Administration of antibodies specifically directed against oligomers of A β improved learning and memory in Tg2576 mice [76]. Therefore, passive immunization may be a safer approach in AD patients. In addition, there is strong evidence that using shorter A β peptides is safer than using full-length A β 40 or 42 as the immunogen [77]. In short, A β immunotherapy holds promise but will need to be made safer and more effective in its ability to generate good antibody titers in the elderly [78]. If these novel immunogens can enhance A β antibody generation without the adverse events seen in the earlier clinical trial, neuroimmune modulation by vaccination may become an effective way to prevent AD.

Parkinson's Disease (PD)

Classically, the neuropathological hallmark of idiopathic PD includes the presence of α -synuclein-positive inclusions in the cell body (Lewy bodies) and processes (Lewy neurites) of specific neurons of the brainstem and a classic motor phenotype resulting from substantial loss of dopaminergic neurons from the substantia nigra pars compacta (SNpc) (reviewed in [79]). A number of studies have confirmed the presence of inflammatory mediators (including TNF, IL-1 β , IL-6, and IFN γ) in the cerebrospinal fluid (CSF) of patients with PD as well as in the post-mortem SNpc in PD patient brains [80-84]. Significantly elevated levels of TNF mRNA and protein can be detected

in the rodent midbrain substantia nigra within hours of *in vivo* administration of two neurotoxins widely used to model parkinsonism in rodents, 6-hydroxydopamine (6-OHDA) [8] and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [85-87]. Consistent with a role of TNF in contributing to dopaminergic neuron death in chronic parkinsonism, plasma TNF levels were shown to remain elevated in MPTP-treated non-human primates one year after administration of the neurotoxin [88]. In contrast, studies involving mice deficient in TNF or both TNF receptors have yielded conflicting results in that one group reported lack of TNF receptors altered dopamine metabolism and reduced survival of dopaminergic terminals [86] and other groups reported TNF-deficient mice to have reduced sensitivity to MPTP-induced neurotoxicity [85,87]. Loss of TNF receptors versus TNF ligand during development might alter the behavior of microglia or other immune cell populations and contribute to conflicting outcomes in these studies. In addition, the use of different MPTP lesioning regimens in these two studies make it difficult to compare them directly.

Additional evidence that inflammation (and in particular TNF) is involved in nigral DA neuron degeneration comes from two endotoxin rat models. In the first model chronic low dose lipopolysaccharide (LPS) infusion into SNpc of rats results in delayed, selective and progressive loss of nigral DA neurons [89]. In the second model exposure of pregnant rats to LPS and thus, *in utero* exposure of embryos to the endotoxin, caused a loss of DA neurons in postnatal brains [90]. Most importantly, chronic infusion of dominant negative TNF inhibitor proteins into SNpc of adult rats protected nigral DA neurons from LPS and 6-OHDA induced degeneration [91] as did a single nigral injection of a lentivirus encoding DN-TNF in 6-OHDA hemiparkinsonian rats [92]. Given that TNF receptors are expressed in nigrostriatal dopamine neurons [93,94] and these neurons are selectively vulnerable to TNF-induced toxicity [95-99], these early genetic studies and the more recent chronic inflammation models of PD strongly implicate TNF and its downstream targets in neurotoxin- and endotoxin-induced loss of nigral DA neurons. However, because it is clear that the permeability of the BBB increases with age increases the likelihood of peripheral immune cell infiltration into the CNS, TNF produced by brain-resident microglia may not be acting alone in mediating DA neuron cell death but in concert with other circulating neurotoxic factors to increase the inflammatory susceptibility of nigral DA neurons and development of PD.

Another link between inflammation and neurodegeneration comes from studies of single nucleotide polymorphisms that are associated with over-production of cytokines, chemokines and acute phase proteins. These

polymorphisms are over-represented in specific cohorts of individuals affected with PD and may confer increased susceptibility for the disease [100-104]. However, most of these findings have not been replicated in independent studies and a meta-analysis of multiple association studies is needed to assess the overall genetic effect of cytokine gene polymorphisms on neurodegenerative disease. Lastly, the advent of technologies such as positron emission tomography (PET) brain scans has enabled clinicians to image microglial activation in living patients. Recent PET studies confirm that patients with idiopathic PD have markedly elevated microglia activation in the pons, basal ganglia, striatum, and frontal and temporal cortical regions irrespective of the number of years with the disease compared to healthy age-matched controls [81]. Persistent activation of the abundant number of microglia in the midbrain region are likely the direct result of elevated levels of cytokines acting in an autocrine manner to potentiate inflammatory responses (e.g., auto-amplification of reactive oxygen species, nitric oxide, and superoxide radicals to form highly oxidizing peroxynitrite species)[7,105-108]. Given that DA neurons in the mid-brain have an inherently elevated oxidative intracellular environment as a result of oxidation reactions required for the synthesis of the neurotransmitter dopamine, chronic neuroinflammation is likely to further enhance oxidative stress, hasten dysfunction, and eventually lead to death of DA neurons.

Huntington's Disease (HD)

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder that has been linked to mutations in the *huntingtin* gene (*htt*) [109]. CAG repeat expansions in the *htt* gene result in an increased number of glutamine residues in the huntingtin protein (polyglutamine expansion). Mutant *htt* causes degeneration of neurons, predominately in the caudate putamen and cortex, causing HD patients to suffer from uncontrolled movements, emotional disturbances and dementia. While the mechanism by which mutant *htt* causes neurodegeneration remains obscure, evidence supporting inflammation as an important player in HD is accumulating.

Recent studies have demonstrated that inflammation appears both peripherally and in the central nervous system (CNS) during the progression of HD and HD-like pathology. The R6/2 mouse model of HD displays increased serum levels of IL-6 and in downstream IL-6 effectors, such as alpha-2-macroglobulin (A2 M) and complement components [110]. In the CNS, microarray profiling of several brain regions from HD patients and controls revealed increased gliosis and expression of inflammation-related genes, including GFAP and complement proteins. Increases were most pronounced in the caudate putamen where brain pathology is most severe in

HD patients [111]. Increases in labeling of complement proteins in neurons and astrocytes and a 2-5 fold increase in activators and regulators of the classical complement pathway have also been detected in human HD brains by RT-PCR [112]. Lastly, clinical plasma samples from HD gene carriers contain increased levels of pro-inflammatory cytokines involved in the innate immune response, such as IL-6 [113].

A number of studies indicate that the altered immune profile in HD occurs before onset of clinical HD symptoms, suggesting that striatal and cortical neurodegeneration could be exacerbated by inflammation. For example, plasma samples from HD gene carriers contain increased levels of pro-inflammatory cytokines involved in the innate immune response before the onset of clinical symptoms and investigators have been able to discriminate controls from presymptomatic HD mutation carriers by measuring the levels of 3 cytokines, IL-5, IL-6, and IL-10 in plasma [113]. In brains of mutant *htt* carriers, microglia are activated before onset of symptoms and increased microglial activation correlates with an increased chance of developing HD symptoms in 5 years [114]. Once symptoms have manifested, microglial activation correlates with disease severity [115,116]. In the 3-nitropropionic acid neurotoxin model of HD in rats, treatment with Celastrol, an anti-inflammatory and antioxidant compound derived from plants, reduced striatal lesion volume [117], indicating that controlling an inflammatory response could be therapeutically beneficial as HD progresses. However, treatment with acetylsalicylate or rofecoxib, anti-inflammatory drugs commonly used in the clinic, was not neuroprotective in either the R6/2 or N171-82Q transgenic mouse models of HD [118].

Since mutant *htt* is known to cause a number of deleterious effects in cells, it is possible that increased inflammation in HD brains is simply the CNS response to neuronal death that is a direct result of mutant *htt* toxicity. However, several studies point to the intriguing possibility that mutant *htt* might itself trigger an inflammatory response, the by-products of which could cause degeneration of neurons. For example, inflammation in HD could be a result of overactive immune cells, such as macrophages in the periphery and microglia in the CNS. Monocytes from HD patients secrete abnormally high levels of the pro-inflammatory cytokine IL-6 in response to a combination of interferon-gamma (IFN- γ) and LPS. Microglia from YAC128 and R6/2 mouse models of HD respond in a similar overactive manner [113]. Mutant *htt* is found in glial nuclei where it can act to alter gene expression, probably because of its aberrant interactions with transcription factors that are made possible by glutamine expansion-related conformational changes in the *htt* protein [119].

Interestingly, mutant, but not normal htt activates the IKK complex, the major kinase that leads to phosphorylation-induced degradation of I κ Bs, leading to increased translocation of NF- κ B dimers to the nucleus in mouse striatal cells [120]. Since NF- κ B can promote expression of IL-6 and other inflammatory cytokines in glia, such an interaction provides a candidate mechanism by which mutant htt could alter the activity of immune cells leading to an abnormally robust inflammatory response.

The presence of increased inflammatory mediators in the periphery and in the CNS beg the question of whether CNS inflammation "leaks" into the periphery to alter the peripheral immune profile or whether inflammation is triggered in the periphery and immune modulators are allowed to cross the BBB to trigger or contribute to a central inflammatory response. Another possibility is that an inflammatory response is triggered in the periphery and the CNS by an analogous mechanism. These alternatives are just beginning to be explored.

Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) involves a progressive degeneration of motor neurons in the brain and spinal cord. While most cases are sporadic in origin, approximately 5-10% of the cases are caused by an autosomal dominant mutation. ALS is typically fatal within 5 years of diagnosis due to a progressive, generalized paralysis that eventually affects the muscles of respiration, causing respiratory failure. Areas where degenerating motor neurons are present in both ALS patients and mouse models are marked by the presence of cytokines and immune cells, including T cells, activated microglia, and astrocytes [121,122]. In addition PET imaging of ALS patients showed an increase in activated microglia in the motor cortex that correlates with upper motor neuron symptoms [123]. In some ALS disease models the presence of immune cells precedes the disease phenotype [124], and the chemokine MCP-1, a potent chemotactic stimulus for microglia [125] is elevated in the CSF of ALS patients [126], suggesting that neuroinflammation could contribute to disease progression. In addition, the levels of general markers of inflammation in the serum of ALS patients correlate positively with the severity of their disability [127]. While multiple genetic loci have been identified as causal in familial forms of ALS, 20% of familial cases involve a gain of function mutation in Cu/Zn superoxide dismutase I (SOD1) [128]. In addition to the well-established role of SOD1 as a critical anti-oxidant enzyme, evidence suggests that part of its normal function is to protect against protein aggregation, a phenomenon that is known to hasten neuronal degeneration. Nevertheless, several studies have suggested that SOD1 mutations in neurons alone are insufficient to cause ALS and that dysfunction in support glia may contribute to disease development and

progression [129-132]. For example, ablating microglial expression of mutant SOD 1 (mSOD1) or transplanting bone marrow from wild-type mice into mSOD1 transgenic mice increases the life span of mutant mice [133,134], suggesting that SOD1 mutations may indirectly contribute to neuronal death by affecting glial rather than neuronal function. Consistent with this idea, mSOD1 mice stimulated with LPS secrete more inflammatory mediators, including TNF [135], MCP-1, TGF- β [121] and IFN- γ [136], than control mice. Importantly, levels of TNF correlate with severity of motor neuron loss in mouse models of the disease [137,138] and both TNF receptors are elevated in the serum of ALS patients [139].

In pre-clinical mouse models, certain anti-inflammatory treatments aimed at suppressing microglia activation have been shown to increase the life expectancy of mice expressing human mutant SOD1 by more than 30% [140]. Anti-inflammatory treatments also prevented neurotoxicity when the CSF of ALS patients was applied to rat spinal cord motor neurons [141]. Although a generalized neuroinflammatory response may be driving progressive loss of motor neurons, not all inflammatory mediators have been strongly implicated in ALS. For instance, IL-1 β may not be critical to ALS pathogenesis as genetic deletion of IL-1 β does not change the lifespan or rate of motor neurodegeneration in mSOD-1 mice [142].

Summary and Conclusion

It is becoming increasingly evident that neuroinflammation plays a crucial role in the development and progression of many neurodegenerative diseases. Glia and in particular microglia are central to mediating the effects of neuroinflammation. While neuroinflammation and microglia provide an attractive therapeutic target in the treatment and prevention of neurodegenerative diseases investigators face several challenges ahead (Appendix 2) which must be overcome before one can advocate in favor of large-scale anti-inflammatory trials in the clinic. Some of these include developing approaches to improve the access of drugs to CNS tissue as well as developing therapies that maintain or optimize the beneficial effects of neuroinflammation while eliminating or minimizing its detrimental effects.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MGT: primary manuscript content, primary writing of Parkinson's disease, shared primary writing of overview, and secondary contributions to microglial activation and Alzheimer's disease. TCFC: primary writing of microglia activation, ALS, and conclusions, and shared primary writing of overview. LTA: primary writing of Huntington's

disease, secondary contributions to Parkinson's and Alzheimer's disease sections. FEM: primary writing of Alzheimer's disease and secondary contributions to ALS section. All authors' contributed to editing and revision of manuscript and have read and approved the final manuscript.

Appendix 1: Key Observations

1. Neurodegenerative diseases are associated with signs of chronic neuroinflammation
2. A variety of initiating triggers (some as yet unknown) associated with the different neurodegenerative disorders converge at a common intersection point - activation of microglia.
3. While the initial neuroimmune response may be aimed at limiting the disease process, chronic neuroinflammation driven by persistent microglia activation is likely to aid in the progression of the disease and the hastening of neuronal demise.
4. How the inflammatory response affects specific neuronal and glial populations and contributes to specific neurodegenerative diseases remains a critical and unanswered question.

Appendix 2: Critical challenges involved in developing neuroprotective anti-inflammatory therapeutic strategies

1. Identify internal and external factors that trigger chronic neuroinflammatory responses, with a focus on how acute immune responses become chronic.
2. Identify inflammatory mediators that compromise survival of specific neuronal populations.
3. Develop therapeutic compounds that cross the blood brain barrier (BBB)
4. Selectively target destructive inflammatory mediators without compromising beneficial survival-promoting effects and overall immune function.
5. Develop inclusion and exclusion criteria for human subjects to be enrolled in clinical trials taking into account their immune status.

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