Innate immune activation in neurodegenerative disease

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Abstract | The triggering of innate immune mechanisms is emerging as a crucial component of major neurodegenerative diseases. Microglia and other cell types in the brain can be activated in response to misfolded proteins or aberrantly localized nucleic acids. This diverts microglia from their physiological and beneficial functions, and leads to their sustained release of pro-inflammatory mediators. In this Review, we discuss how the activation of innate immune signalling pathways — in particular, the NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasome — by aberrant host proteins may be a common step in the development of diverse neurodegenerative disorders. During chronic activation of microglia, the sustained exposure of neurons to pro-inflammatory mediators can cause neuronal dysfunction and contribute to cell death. As chronic neuroinflammation is observed at relatively early stages of neurodegenerative disease, targeting the mechanisms that drive this process may be useful for diagnostic and therapeutic purposes.

For decades, the brain has been viewed as an immune-privileged organ, where inflammation can only occur through direct infection or after the breakdown of the blood–brain barrier and subsequent infiltration of peripheral immune cells. It is now known that different cell types in the brain express specialized pattern recognition receptors (PRRs) that can trigger inflammatory signalling pathways. These PRRs are able to sense microbial molecules — so-called pathogen-associated molecular patterns (PAMPs) — that typically accumulate in infected tissues. Additionally, there is evidence that host-derived PRR ligands — termed danger-associated molecular patterns (DAMPs) — can be found in diseased brains in the form of misfolded proteins, aggregated peptides or mislocalized nucleic acids. As these DAMPs can directly serve as triggers of neuroinflammation in different brain cell types, our perspective of neurodegenerative diseases has fundamentally changed in recent years. Such pro-inflammatory reactions divert immune-competent cells in the brain from their beneficial 'housekeeping' functions. Instead, these cells contribute to the development and progression of neurodegenerative disease through their sustained release of pro-inflammatory mediators.

In this Review, we discuss the evidence suggesting that innate immune activation and neuroinflammation develop in various neurodegenerative diseases and indeed promote pathology. As microglia represent the major immunologically active cell type in the brain, we focus our attention on these cells. It should be noted that other cell types in the brain — including astrocytes, neurons and endothelial cells —also express and can be activated through innate immune receptors. In addition, many cells express receptors for cytokines and other inflammatory mediators, and are thereby involved in the coordination of inflammatory responses in the brain. We first outline the key innate immune pathways that seem to be commonly activated across neurodegenerative diseases, before discussing the pathways that have been observed in specific diseases. Most of the relevant mechanistic studies that pertain to neuroinflammation have been carried out in the context of Alzheimer's disease and we place a particular emphasis on this disorder. However, a role for neuroinflammation in the pathogenesis of other neurodegenerative diseases is also emerging. Hence, we also cover the key data that suggest a role for innate immune activation in the pathogenesis of frontotemporal dementia (FTD), Parkinson's disease, amyotrophic lateral sclerosis (ALS) and Huntington's disease.

Innate immunity in the central nervous system

The innate immune system of the central nervous system. Microglia represent the major cellular component of the innate immune system of the brain. They derive from precursors that express macrophage colony-stimulating

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factor receptor, which are found in the mesodermal yolk sac between embryonic day 8.5 and 9.5, at a time before the blood–brain barrier closes and restricts cell migration into the brain[1–3]. Microglia are distributed throughout the brain, although their densities vary between different brain areas[4]. Depending on their localization, microglia acquire a compact or ramified phenotype[4]. The ramified phenotype is characterized by a high number of processes that are constantly moving and that facilitate the interaction of microglia with neighbouring blood vessels, neurons and astrocytes. These interactions have only recently been described in detail and they were shown to be important for cerebral tissue maintenance and neuronal plasticity[5–8].

The microglial cell surface is equipped with numerous transporters, channels and receptors. These include receptors for neurotransmitters, neurohormones, neuromodulators, cytokines and chemokines, as well as PRRs. During embryonic synaptogenesis, microglia assist synapse formation between neurons by secreting growth hormones and thrombospondins[9]. Microglia use their fine processes to constantly scan for dysfunctional synapses, which they are able to eliminate by phagocytosis[6,10]. Synaptic activity is further influenced by microglia through their secretion of brain-derived neurotrophic factor (BDNF), a molecule that is crucial for learning-dependent synapse formation[5]. It is possible that other microglial cell-secreted products also contribute to synapse remodelling and neuronal network modulation. In addition, microglia are able to influence adult neurogenesis in the brain[11].

In summary, the physiological functions of microglia are important for maintaining tissue homeostasis, neuronal integrity and network functioning in the brain (FIG. 1). The loss, deviation or functional perturbation of microglia may occur in response to neurodegeneration and may contribute to pathogenesis and disease progression. Other cell types in the brain — such as astrocytes, neurons and endothelial cells — are also equipped with innate immune receptors and can directly respond to DAMPs or PAMPs. Therefore, these cells can also contribute to inflammatory responses in the brain.

Triggers and consequences of immune responses in the central nervous system. In several neurodegenerative diseases, microglia are exposed to non-physiological levels of immune activators. The activation of microglia by these substances occurs through the triggering of PRRs, including Toll-like receptor 2 (TLR2), TLR4 and TLR6. In addition to these receptors, some TLR ligands also engage co-receptors such as CD36 (also known as platelet glycoprotein 4), CD14 and CD47 (REFS 12–17). The activation of TLRs and their co-receptors by DAMPs and PAMPs initiates an immune response that is geared towards protecting the brain against invading pathogens. As there is a strong overlap between the signalling pathways that are induced by PAMPs and DAMPs, microglia may not be able to discriminate between invading pathogens and misfolded or aberrant endogenous molecular patterns. Various self molecules that are present in degenerating brains could activate immune receptors — for example, aggregated amyloid-β, α-synuclein, mutant huntingtin (HTT), mutant superoxide dismutase 1 (SOD1), the S100A9–S100A8 complex (also known as MRP14–MRP8) and chromogranin A. In all likelihood, not a single factor but several of these factors will promote microglial cell activation during the course of neurodegenerative disease (FIG. 1).

Although various signalling pathways contribute to the microglial cell response, a common feature of neurodegenerative diseases is the excessive production and release of pro-inflammatory cytokines of the interleukin-1β (IL-1β) family, including IL-1β and IL-18. Both IL-1β and IL-18 are initially expressed as leaderless, biologically inactive pro-forms that are activated following cleavage by caspase 1 or caspase 8. The activation of caspase 1 itself is controlled by large multimolecular signalling platforms termed inflammasomes[16]. Inflammasomes consist of a sensor molecule from the NOD-like receptor (NLR) family or the pyrin and HIN domain-containing protein (PYHIN) family, the adaptor protein ASC and caspase 1 (REF. 17). The NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasome is of particular importance in the development of acute and chronic inflammatory responses, as it can sense a wide range of aggregated molecules. There are other inflammasomes — such as absent in melanoma 2 (AIM2), NLRP1 and NLRP2 — that might have a pathological role in the brain but so far this has only been suggested in the context of brain trauma[18–20].

The activation of microglia also promotes their release of reactive oxygen species (ROS) and nitric oxide (NO) through the induction or activation of NADPH oxidase[21], myeloperoxidase (MPO)[22] and inducible NO synthase (iNOS; also known as NOS2)[23,24]. The consequences of microglial activation for neighbouring cells, in particular for neurons, are multifaceted and they remain incompletely understood. However, the sustained release of pro-inflammatory mediators has been shown to be involved in the suppression of axonal transport and adult neurogenesis[25]. Activated microglia are characterized by the retraction of their processes, which is a phenotypic change that may correlate with an impaired ability to remodel synapses. This effect, along with the suppressive effects of cytokines and NO, may contribute to impaired synaptic plasticity in neurodegenerative disease. Furthermore, neuroinflammation restricts the supply of neurotrophic factors to glial cells[26] and probably affects physiological processes that are important for intraneuronal protein handling[27]. Microglial cell-driven neuroinflammation may not only affect neurons but may also cause detrimental feedback effects on microglia in the diseased tissue. For example, sustained exposure to bacterial lipopolysaccharide (LPS) or to other pro-inflammatory mediators was shown to restrict microglial phagocytosis of misfolded and aggregated proteins[28–30]. The mechanisms that are described in this section seem to be relevant across a number of neurodegenerative diseases (FIG. 1; TABLE 1). In the following sections, we focus on the inflammatory pathways that may be relevant in specific neurodegenerative diseases.

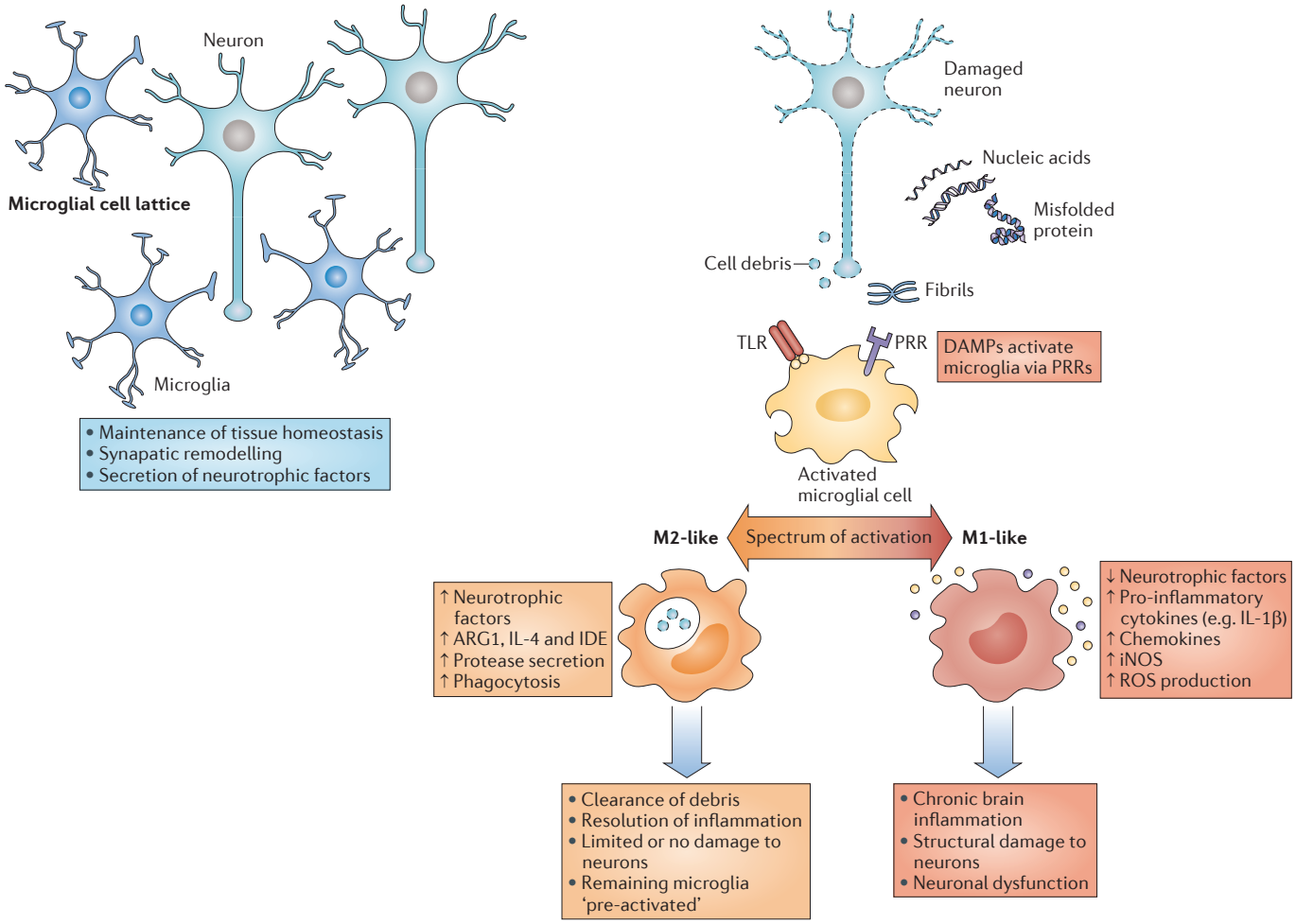

Figure 1 | **Beneficial and detrimental functions of microglia in the brain.** In the healthy brain, microglia form an almost evenly distributed lattice. Microglia are in close contact with the dendrites and synapses of neighbouring neurons. They remodel synapses and secrete neurotrophic factors — such as brain-derived neurotrophic factor (BDNF) — that maintain proper neuronal network function. Microglia also remove accumulating debris from the brain and are thus pivotal for the maintenance of tissue homeostasis. Several endogenous proteins (including amyloid-β, α-synuclein, mutant huntingtin, mutant superoxide dismutase 1 and chromogranin A) can bind to pattern recognition receptors (PRRs) — such as Toll-like receptor 2 (TLR2), TLR4, TLR6, CD33, CD36 and triggering receptor expressed by myeloid cells 2 (TREM2) — which are expressed on the surface of microglia and this promotes their activation. Depending on the signalling strength, tissue site and environmental conditions, microglia may respond by enhancing the removal of the stimulant or by secreting inflammatory mediators. Typically, 'M2-like' activation of microglia is associated with the increased secretion of neurotrophic factors and proteases, the production of interleukin-4 (IL-4), the expression of the enzymes arginase 1 (ARG1) and insulin-degrading enzyme (IDE), and enhanced phagocytic activity. By contrast, 'M1-like' activation of microglia is associated with the expression of inducible nitric oxide synthase (iNOS), the production of reactive oxygen species (ROS) and pro-inflammatory mediators (such as IL-1β) and the decreased secretion of neurotrophic factors. These divergent responses may determine whether microglial cell activity leads to the clearance of tissue debris and the resolution of the inflammatory response or leads to chronic neuroinflammation. Clearance mechanisms are likely to leave the local neuronal network intact, whereas ongoing and chronic neuroinflammation may cause neuronal cell dysfunction and death. DAMPs, damage-associated molecular patterns.

Alzheimer's disease

Alzheimer's disease is characterized by progressive memory decline and cognitive dysfunction. It is the most common dementing illness and currently affects approximately 150 million individuals worldwide. Histologically, Alzheimer's disease is defined by the parenchymal deposition of amyloid-β, the formation of neurofibrillary tangles that are composed of microtubule-associated protein tau (which is encoded by *MAPT*) and neuroinflammation. The deposition of amyloid-β probably commences decades before tau protein levels increase in the cerebrospinal fluid (CSF) and before memory decline becomes clinically apparent[31]. Amyloid-β is constitutively generated from amyloid precursor protein (APP) by sequential cleavage, which is mediated by two aspartyl proteases, γ-secretase and β-secretase 1 (also known as BACE1)[32]. Limiting the concentration of amyloid-β in the brain tissue seems

Table 1 | **Comparison of pathology in different neuroinflammatory diseases**

Disease	Characteristics						
	Astrogliosis	Microgliosis	Caspase 1 activation	Intracellular protein aggregation	Extracellular protein deposition	TLR activation	Associated DAMPs
Alzheimer's disease	Yes	Yes	Yes (associated with NLRP3 inflammasome)	No	Yes	Yes	• Amyloid-β • Chromogranin A • S100A9
Dementia with Lewy bodies	Yes	Yes	Not shown	Yes	Yes	Unknown	α-synuclein
Parkinson's disease	Yes	Yes	Yes (associated with NLRP3 inflammasome)	Yes	No	Yes	α-synuclein
Amyotrophic lateral sclerosis	Yes	Yes	Yes	Yes	No	Yes	Mutant SOD1
Frontotemporal dementia	Yes	Yes	Not shown	Yes	No	Unknown	Unknown
Huntington's disease	Yes	Yes	Not shown	Yes	No	Unknown	mHTT

DAMPs, danger-associated molecular patterns; mHTT, mutant huntingtin; NLRP3, NOD-, LRR- and pyrin domain-containing 3; SOD1, superoxide dismutase 1; TLR, Toll-like receptor.

to be crucial for preventing its aggregation. The overproduction of amyloid-β can be caused by mutations in the genes encoding enzymes that contribute to the generation of the APP, such as presenilin 1 (PS1; which is encoded by *PSEN1*) and PS2 (which is encoded by *PSEN2*). *PSEN1* and *PSEN2* encode proteins that form the catalytic core of the γ-secretase complex and mutations in these genes account for most hereditary forms of Alzheimer's disease[33]. By contrast, impaired clearance mechanisms may be responsible for the majority of sporadic, non-hereditary cases[34].

Neuroinflammation as a risk factor for Alzheimer's disease. In the past two decades, epidemiological evidence has emerged that implicates neuroinflammation as an important contributor to Alzheimer's disease pathogenesis[35–37]. In addition, non-steroidal anti-inflammatory drugs have been reported to reduce the risk of developing Alzheimer's disease[38]. Moreover, several lifestyle factors and events that are known to increase the risk of developing Alzheimer's disease have an associated inflammatory component. For example, a history of systemic infection, obesity and reduced physical activity — which are collectively characterized by an increase in the concentrations of inflammatory mediators in the periphery — are known risk factors for Alzheimer's disease[39–46] (FIG. 2). Recent clinical studies suggest that patients who have experienced severe infections show accelerated cognitive decline and this is positively correlated with peripheral levels of tumour necrosis factor (TNF)[40]. Likewise, the US Health and Retirement Study found that septicaemia is followed by a more severe loss of cognitive skills in subsequent years[39], and sepsis survivors demonstrate persistent cognitive alterations, hippocampal atrophy and changes in electroencephalography[41]. Additionally, individuals who suffer from chronic periodontitis due to poor oral health show an increased risk of developing Alzheimer's disease[45–47].

Inflammatory pathways are activated in Alzheimer's disease. Increased levels of pro-inflammatory mediators — including complement components, eicosanoids, chemokines and cytokines — have been found in the brain and CSF of patients with Alzheimer's disease, which indicates that inflammatory processes are pathologically activated. Ongoing neuroinflammation can be visualized in patients using the positron emission tomography (PET) ligand [^{11}C](R)-PK11195 (REF. 48) and this helps to identify patients who are likely to progress from experiencing mild cognitive impairment to the development of clinical Alzheimer's disease[49]. Recently, an unbiased analysis of gene regulatory networks that are involved in late-onset Alzheimer's disease has identified genes that are associated with innate immune pathways and microglial cells[50]. Interestingly, several pathways that are involved in phagocytosis — and therefore, presumably, amyloid-β clearance — were highlighted in this network analysis. These findings are further supported by recent genome-wide association study (GWAS) analyses of sporadic Alzheimer's disease, which revealed a set of genes that point to a pathogenic role for neuroinflammation in Alzheimer's disease. Variants that are associated with an increased risk of developing Alzheimer's disease have been found in the genes that encode complement receptor 1 (CR1)[51], myeloid cell-expressed membrane-spanning 4-domains subfamily A member 6A (MS4A6A), putative membrane-spanning 4-domains subfamily A member 4E (MS4A4E)[52,53] and CD33 (also known as SIGLEC3)[54]. CD33 is a receptor that is expressed at the surface of myeloid cells and is involved in the inhibition of cellular responses[52]. In accordance with this, CD33 activation was shown to suppress the production of pro-inflammatory cytokines by monocytes[55] and to prevent microglial cell-mediated removal of amyloid-β *in vitro* and *in vivo*[54]. Furthermore, microglia from patients with Alzheimer's disease show increased expression of CD33 (REF. 56).

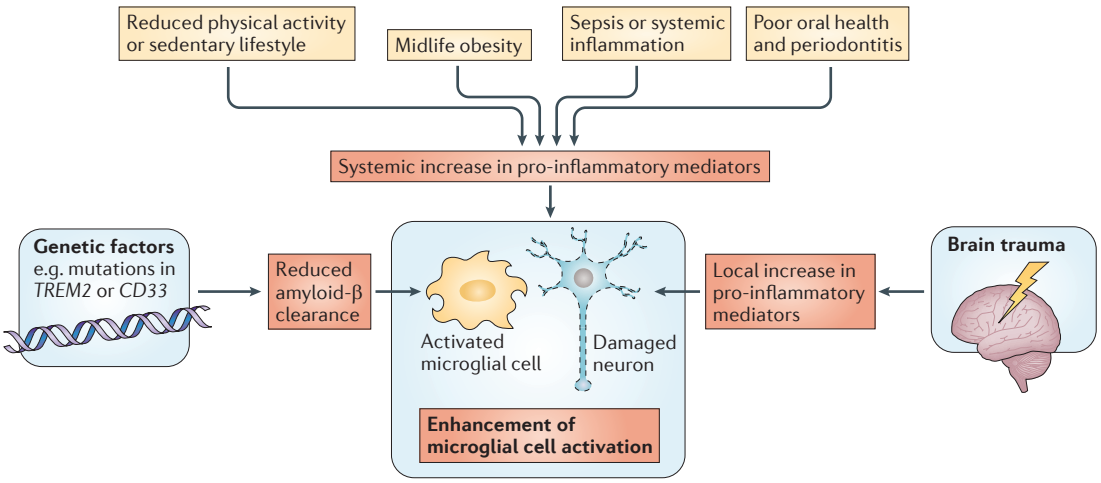

Figure 2 | **Risk factors for Alzheimer's disease increase innate immune activation by inducing local or systemic inflammation.** Several conditions or lifestyles that are associated with an increased risk of developing Alzheimer's disease are characterized by a systemic increase in the levels of pro-inflammatory mediators. For example, reduced physical activity or a sedentary lifestyle lead to increased levels of pro-inflammatory cytokines in the blood circulation. Likewise, white adipose tissue is a constant source of pro-inflammatory cytokines that can affect the function of distant organs, including the brain. Systemic infection and sepsis have been shown to cause brain atrophy and to accelerate the progression from mild cognitive impairment to full-blown Alzheimer's disease. Similarly, poor oral health and, in particular, chronic periodontitis may represent persistent sources of systemic inflammation. Thus, although aggregated forms of amyloid-β may induce the initial activation of microglial cells in the brain, the activation of these cells may be further exacerbated and prolonged by systemic inflammation. Genetic factors may also affect the microglial cell reaction to aggregated forms of amyloid-β. Mild head trauma also leads to a local increase in the levels of neuroinflammatory mediators, which may stimulate amyloid-β generation and restrict phagocytic clearance. *TREM2*, triggering receptor expressed by myeloid cells 2.

In addition, a rare variant of the triggering receptor expressed on myeloid cells 2 (TREM2) has been associated with an increased risk for Alzheimer's disease[57,58]. The TREM2 cell surface receptor initiates immune signalling in macrophages and dendritic cells by forming a receptor complex with TYRO protein tyrosine kinase-binding protein (TYROBP). In the brain, TYROBP is expressed by microglia cells and increased expression of TYROBP has been described at sites of amyloid-β deposition in *APP* transgenic mice[59,60]. TREM2 may also be involved in promoting the phagocytic clearance of cellular debris and in the downregulation of inflammatory signalling in response to TLR ligation[61,62]. Notably, in studies characterizing gene expression networks in late-onset Alzheimer's disease, the expression of *TYROBP* showed the strongest association with disease[50].

Role of amyloid-β and host DAMPs in activating innate immune pathways. It is thought that aggregated amyloid-β elicits an initial, acute immune response by activating microglia via the cell surface receptor CD36 (FIG. 3). This subsequently triggers the formation of a TLR2–TLR6 heterodimer and results in augmented nuclear factor-κB (NF-κB) signalling[13]. In addition, a recent report has shown that CD36 contributes to amyloid-β aggregation in endocytic membranes, thus promoting its stimulatory capacity[63]. It is tempting to speculate that aggregated amyloid-β could mimic a conserved molecular pattern against which the innate immune system has evolved PRRs. Indeed, several microorganisms — including bacteria and fungi — express surface amyloid fibrils, which are known as curli fibres[64–66]. We suggest that the recognition of fibrillary amyloids by the immune system in the brain may be a consequence of the evolution of antimicrobial defence mechanisms at this site, although there is no formal proof of this. Sensing of amyloid-β aggregates by TLRs is followed by the activation of intracellular machinery that leads to the assembly of the NLRP3 inflammasome, which is a complex that controls the production of the pro-inflammatory cytokine IL-1β[67] (FIG. 3). The expression of active caspase 1 is increased in brains of patients with Alzheimer's disease compared with those of age-matched controls[68]. In the APP/PS1 transgenic mouse model of Alzheimer's disease, mice that are deficient for NLRP3 or the inflammasome adaptor ASC are mostly protected from amyloid pathology[67,68]. Indeed, NLRP3-deficient APP/PS1 mice showed almost normal cognitive function and they were protected from the amyloid-β-induced suppression of synaptic plasticity[68]. The suppression of synaptic plasticity by amyloid-β is particularly sensitive to IL-1β, as excessive activation of this cytokine is able to disrupt the formation of dendritic spines — which is promoted by BDNF signalling through the TRKB receptor (also known as NTRK2) — and thereby interferes with memory consolidation[69]. In addition, immune stimulation in response to amyloid-β and pro-inflammatory cytokines can impair microglial cell-mediated clearance of amyloid-β and neuronal debris, which could also contribute to disease pathogenesis.

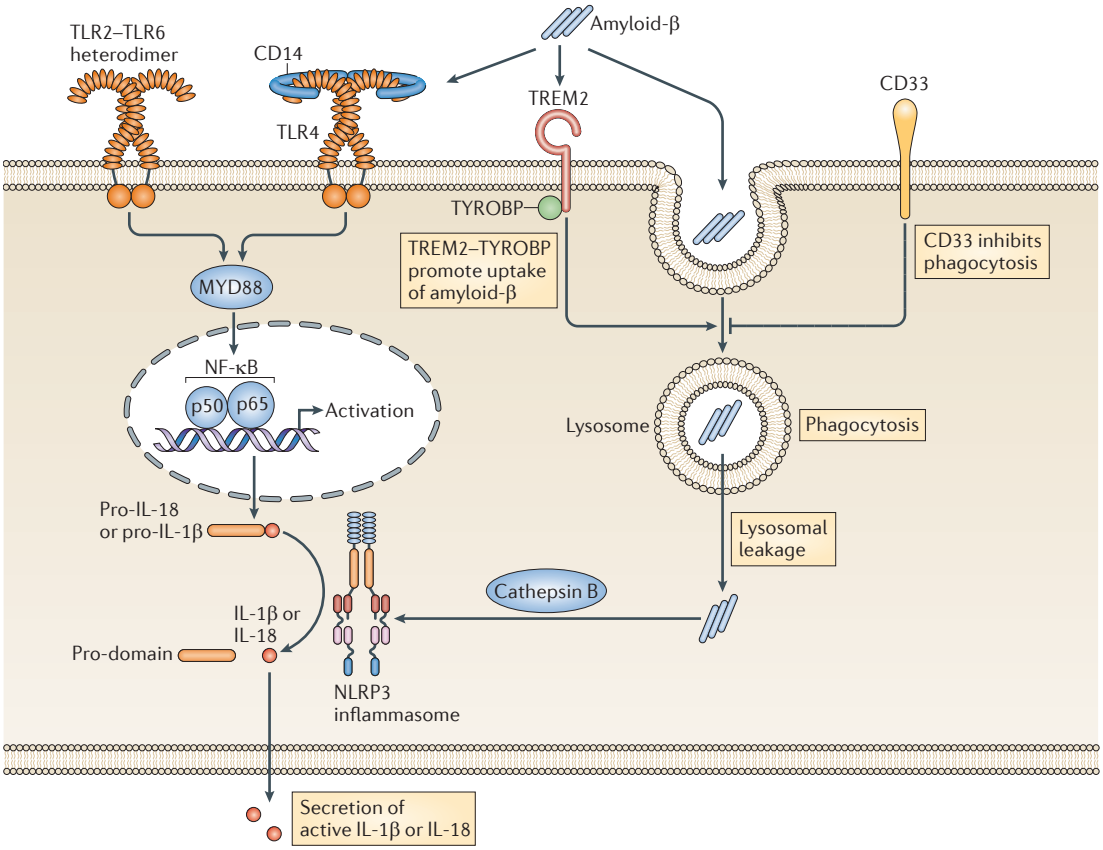

Figure 3 | **Mechanisms of microglial cell activation in response to misfolded or aggregated proteins.** Several neurodegenerative diseases are characterized by the accumulation of misfolded or aggregated proteins in the brain. Such aberrant proteins may accumulate in the extracellular tissue space (for example, amyloid-β) or they may accumulate within the neurons (for example, α-synuclein) and be released into the tissue as a consequence of neuronal cell degeneration and death. Microglial cells express pattern recognition receptors (PRRs) that can sense and respond to damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). Such PRRs include CD36, CD14, Toll-like receptor 2 (TLR2), TLR4, TLR6, triggering receptor expressed by myeloid cells 2 (TREM2) and CD33. Ligation of CD36, TLR2, TLR4 and TLR6 leads to pro-inflammatory signal transduction via the myeloid differentiation primary response protein 88 (MYD88)–nuclear factor-κB (NF-κB) pathway. When NF-κB activation occurs concomitantly with phagocytosis and lysosomal damage, these pathways jointly lead to formation of the NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasome. The NLRP3 inflammasome generates mature cytokines from pro-forms through activation of caspase 1. TREM2 and CD33 are receptors that are involved in phagocytosis. TREM2–TYRO protein tyrosine kinase-binding protein (TYROBP) signalling increases the clearance of amyloid-β aggregates, whereas CD33 antagonizes this action. NLRP3 inflammasome activation has been detected in a number of neurodegenerative diseases, including Alzheimer's disease and amyotrophic lateral sclerosis. IL, interleukin.

In line with the hypothesis that pro-inflammatory molecules impair microglial cell clearance functions, disrupting the function of IL-1 receptor-associated kinase 4 (IRAK4) — which is an essential downstream mediator of TLR and IL-1β receptor signalling — improves amyloid-β clearance and shifts microglial cells from a pro-inflammatory to an anti-inflammatory phenotype[70]. Immune activation may also be induced by host molecules other than amyloid-β — including ATP[71], chromogranin[72] or double-stranded DNA (dsDNA) — that 'leak' from degenerating neurons. Recently, a DAMP that is formed by two members of the S100 protein family, the S100A9–S100A8 complex, has been found to be more abundant in the brain and CSF of patients with Alzheimer's disease[73,74]. Of note, S100A9–S100A8 binds to TLR4 and promotes the upregulation of β-secretase 1, which is the rate-limiting enzyme in amyloid-β generation. Hence, factors that promote neuroinflammation could be involved in a feedforward loop that influences amyloid-β homeostasis.

Inflammatory cytokines in Alzheimer's disease. In addition to the IL-1β family members and TNF, other pro-inflammatory cytokines that are produced by myeloid cells may affect Alzheimer's disease pathogenesis. For example, increased levels of IL-12p40 (also known as IL-12 subunit-β; a subunit that is shared by IL-12 and IL-23) can be detected in the CSF of patients with Alzheimer's disease, which suggests that there is increased activation of the IL-12 and IL-23 signalling pathways in these individuals[75]. Indeed, genetic ablation of the genes encoding the IL-12p40, IL-12p35 (also known IL-12 subunit-α) or

IL-23p19 (also known as IL-23 subunit-α) components of this pathway led to decreased levels of amyloid-β in the brains of APP/PS1 transgenic mice and these animals had fewer behavioural deficits compared with control APP/PS1 mice[75]. Indeed, intracerebroventricular administration of IL-12p40-specific neutralizing antibodies lowered the levels of soluble amyloid-β peptides in the brain and improved spatial memory in mice[75]. Importantly, resident microglia are the major source of IL-12 and IL-23 in the brain, and genetic ablation of the IL-12 or IL-23 signalling pathways does not alter APP processing[75]. As the IL-23 receptor is strongly expressed on astrocytes[75], microglial cell-derived IL-12p40 may stimulate astroglial cell uptake of amyloid-β. Astrocytes may also indirectly interfere with microglial cell-mediated removal of amyloid-β by releasing lipidated apolipoprotein E (APOE), which is important for microglial cell-mediated phagocytosis of amyloid-β[76].

Reactive nitrogen and oxygen intermediates. Small-molecule mediators, such as NO, peroxynitrite and ROS, have well-described roles in inflammatory processes in various tissues. During Alzheimer's disease, iNOS is expressed by neurons and glial cells[23,24] in response to pro-inflammatory cytokines. Although NO has been suggested to be involved in neurodegenerative processes — including axonal and synaptic damage, the inhibition of mitochondrial respiration and the induction of neuronal apoptosis — the amyloid-β peptide itself also represents a direct target of the NO reaction product peroxynitrite. Nitration of the tyrosine residue at position 10 of the amyloid-β peptide has been demonstrated in patients with Alzheimer's disease and in mouse models[77]. This post-translational modification enhances the propensity of the peptide to aggregate and it is exclusively found to occur in amyloid-β peptides that are found in the core of senile plaques. Importantly, nitrated amyloid-β was found to more potently suppress synaptic plasticity compared with non-nitrated amyloid-β, and both genetic ablation and pharmacological inhibition of iNOS protected against spatial memory dysfunction in mouse models of Alzheimer's disease[77].

Loss and replenishment of microglial cells in Alzheimer's disease. One might speculate that the neuroinflammatory reaction might lead to changes in immune cell numbers in the brain. If so, there could be cell loss, proliferation of cells or the presence of cells that invade from the periphery. Analyses based on MHC class II expression have suggested that there is no overall change in the actual number of microglial cells in the brain in the late stages of Alzheimer's disease[78]. Nevertheless, chronic activation of microglia in Alzheimer's disease may lead to their loss and subsequent replenishment within the brain at early stages of disease through the proliferation of tissue-resident microglia. One may hypothesize that microglia that proliferate within an inflamed microenvironment develop a different gene expression pattern compared with microglia that had previously resided in the affected brain area. Over time, such newly generated, 'divergent' microglia could sustain a chronic type of neuroinflammation in Alzheimer's disease. Another possibility is that peripheral myeloid cells are attracted to sites of neuroinflammation by locally released chemokines. Indeed, there is evidence that myeloid cells from the periphery, in particular from the perivascular space, enter the brain in rodent models of Alzheimer's disease and that they are recruited to sites of plaque formation in a process that is dependent on CC-chemokine receptor 2 (CCR2)[79,80]. Notably, ablation of *Ccr2* results in a gene dose-dependent aggravation of amyloid pathology and premature death in the Tg2576 mouse model of Alzheimer's disease[79] (TABLE 2).

Innate immune mechanisms link amyloid-β deposition and tau pathology. Amyloid-β deposition occurs at an early stage of Alzheimer's disease and is followed by the intraneuronal formation of neurofibrillary tangles (NFTs) after years or even after decades. NFTs represent a further pathological hallmark of the Alzheimer's disease and consist of hyperphosphorylated tau, which is a protein that normally stabilizes microtubules. There is evidence that formation of NFTs is caused by microglial cell-driven neuroinflammation, as bacterial LPS-induced systemic inflammation increased tau pathology through cyclin-dependent kinase 5 activation[81]. These data have been substantiated by similar findings in various murine models of systemic inflammation[82]. However, in Alzheimer's disease, such a peripheral immune challenge may not be required, as local microglial cell-driven immune responses may be sufficient to drive tau pathology. Indeed, microglial cell activation preceded NFT formation in young P301S transgenic mice[83], and early immunosuppression led to reduced tau pathology and increased the lifespan of these mice. In line with this, activation of microglia induced tau phosphorylation in primary mouse neurons[84]. This process required IL-1β receptor activation and p38 mitogen-activated protein kinase (MAPK)-mediated signal transduction[84]. In addition, acute increases in IL-1β expression in aged transgenic mice further increased tau pathology[84]. Interestingly, CX_3C-chemokine receptor 1 (CX_3CR1) expression by microglia seems to restrict this pathological mechanism, as the knockdown of *Cx3cr1* in mice further increased tau phosphorylation and aggregation, which was probably due to increased IL-1β release[84]. These findings suggest that innate immune mechanisms are an important and accessible link between amyloid-β deposition and tau pathology in Alzheimer's disease. Given the fact that NFTs cause neurodegeneration from within, neuroinflammation may link the early deposition of amyloid-β with tau-mediated neuronal demise.

The combined evidence suggests that innate immune mechanisms are strongly involved in the progression of the sporadic form of Alzheimer's disease. Amyloid-β may act as a DAMP to initiate the immune response, which may later be fuelled by additional immune-stimulatory molecules that are released or generated during ongoing neuroinflammation. Several lifestyle factors that are known to promote inflammatory pathways may potentiate the risk for the development of Alzheimer's disease by further stimulating neuroinflammation. This may also explain the link between the two canonical pathologies of Alzheimer's disease; amyloid-β deposition

Table 2 | **Mouse models of neuroinflammatory disease**

Mouse model	Human disease	Type of model	Nature of inducing agent	Disease phenotype	Refs
Tg2576	Alzheimer's disease	Genetic	Transgenic mice expressing human *APP* containing the double Swedish mutation (K670N and M671L) under the control of the hamster prion protein promoter	• Abundant amyloid-β plaques by 11–13 months of age and some vascular amyloid-β deposition • Oxidative lipid damage • Astrogliosis and microgliosis • No neurofibrillary tangles	161
APP/PS1	Alzheimer's disease	Genetic	Mice expressing chimeric mouse–human *APP* carrying the Swedish mutation (K670N and M671L) and mutant human *PSEN1* (ΔExon9) both under the control of the mouse prion protein promoter	• Amyloid-β deposits detected from 6 months of age, with abundant plaques in the hippocampus and cortex by 9 months • No neurofibrillary tangles • Astrogliosis and microgliosis • Impaired performance in the Morris water maze by 12 months of age	162
P301S	• Alzheimer's disease • Frontotemporal dementia	Genetic	Transgenic mice expressing the P301S mutant form of the human *MAPT* gene under the control of the mouse prion protein promoter	• Neuronal loss by 8–12 months of age (originating in the hippocampus and later spreading to the neocortex and entorhinal cortex) • Neurofibrillary tangles (in the neocortex, amygdala, hippocampus, brainstem and spinal cord) • Astrogliosis and microgliosis • Impairments in spatial memory and learning ability in the Morris water maze • Paralysis at 7–10 months of age, which is associated with a hunched-back posture • Early mortality (median survival approximately 9 months)	83
MPTP	Parkinson's disease	Drug based	Induced by MPTP administration	• Loss of tyrosine hydroxylase-positive neurons in the substantia nigra pars compacta • Symptoms resembling Parkinson's disease (akinesia, rigidity, tremor, and gait and posture disturbances)	163
6-OHDA	Parkinson's disease	Drug based	Induced by 6-OHDA administration	• Motor disturbances • Loss of dopaminergic neurons	164
AAV–α-synuclein	Parkinson's disease	Viral	AAV-mediated expression of human α-synuclein under the control of the CMV promoter	• Loss of dopaminergic neurons • Microgliosis • Activation of adaptive immune responses	165
$SOD1^{G93A}$	Amyotrophic lateral sclerosis	Genetic	Mice transgenic for the human *SOD1* gene carrying the G93A mutation	• Motor neuron degeneration • Early mortality (death by 5–6 months of age) • Astrogliosis and microgliosis • Decreased grip strength • Early paralysis • Muscle atrophy	166
$SOD1^{G37R}$	Amyotrophic lateral sclerosis	Genetic	Mice transgenic for the human *SOD1* gene carrying the G37R mutation	• Motor neuron degeneration • Early mortality (50% survival at 27 weeks) • Astrogliosis and microgliosis • Decreased grip strength • Muscle atrophy	167
R6/2	Huntington's disease	Genetic	Mice transgenic for exon 1 of human *HTT* containing 142 CAG repeats	• Neurological phenotype mimics the features of human disease: mice show choreiform-like movements, involuntary stereotypic movements, tremor and epileptic seizures, as well as non-movement-related components, such as unusual vocalization patterns • Disease onset occurs at 9–11 weeks of age • Motor impairment starts at 5–6 weeks of age and cognitive impairment at 3 weeks of age • Mice show neuronal intranuclear inclusions containing HTT	168

6-OHDA, 6-hydroxydopamine; AAV, adeno-associated virus; *APP*, amyloid precursor protein; CMV, cytomegalovirus; HTT, huntingtin; *MAPT*, microtubule-associated protein tau; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; *PSEN1*, presenilin 1; SOD1, superoxide dismutase 1.

and NFT formation. These results have stimulated further research into the role of inflammatory mechanisms in other neurodegenerative diseases and these studies are summarized in the following sections.

Frontotemporal dementia

FTD is a form of progressive neuronal atrophy that is characterized by the loss of cells from the frontal and temporal cortices. Dementia is accompanied by changes in personality, behaviour and language skills. FTD is the second most common type of dementia, with Alzheimer's disease being the most common[85]. Histopathologically, most patients show intraneuronal inclusions of the cytosolic phosphorylated TAR DNA binding protein-43 (TDP43; also known as TARDBP)[86].

As is the case in most neurodegenerative diseases, neuroinflammation is a major component of FTD. This is supported by the finding that patients with FTD have increased CSF levels of TNF and transforming growth factor-β (TGFβ)[87]. Studies using the microglial cell-associated marker [^{11}C](R)-PK11195 suggest that there is increased activation of microglial cells in the frontotemporal lobe of patients with FTD[88]. A *TREM2* variant that was initially identified as a risk factor for Alzheimer's disease has also recently been associated with FTD[89]. An indication that neuroinflammation might not only be a bystander effect of this disease arose from the finding that mutations in the *GRN* gene, which encodes the inflammation-related protein progranulin, lead to a tau-negative form of FTD[90]. The exact mechanism involved has not been unravelled yet but all of the identified *GRN* mutations result in truncated mRNAs that most likely lead to *GRN* haploinsufficiency[90]. In the brain, expression of GRN is restricted to microglia and neurons under physiological conditions but is selectively upregulated in microglia after excitotoxic activation[91]. This might also explain the observation that, remarkably, carriers of *GRN* mutations have increased *GRN* mRNA levels in affected brain regions, due to the increased transcription of the unmutated allele in proliferating microglia[92].

There are several findings that suggest that progranulin acts as a mediator of the inflammatory response. Progranulin is thought to be processed by metalloproteinases into distinct granulin peptides[93]. Some granulin peptides are able to attract and activate microglia in the brain and to increase their phagocytic function[94]. Compared with those from wild-type mice, macrophages that are generated from progranulin-deficient mice produce higher levels of pro-inflammatory cytokines and lower levels of anti-inflammatory cytokines when exposed to LPS[95,96]. In addition, conditioned media from progranulin-deficient microglia was shown to promote neuronal cell death[95]. Progranulin-deficient mice displayed greater activation of microglial cells and astrocytes *in vivo*, in addition to neuronal accumulation of TDP43 (REF. 97), which itself has been linked to the development of FTD and synaptic dysfunction[98]. Together, these results suggest that the loss of progranulin may result in a dysregulated inflammatory response in microglia that could have detrimental effects on neuronal cell survival and promote the development of FTD.

Parkinson's disease

Parkinson's disease is characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta within the mid-brain. This is associated with the activation of microglia[99], increased cytokine levels[100], activation of astrocytes[101] and the presence of intraneuronal aggregates (called Lewy bodies) that mainly consist of α-synuclein. There are several polymorphisms in inflammatory genes that have been associated with Parkinson's disease. Examples include polymorphisms in the genes encoding TNF, TNF receptor 1 (TNFR1), IL-1β, IL-1 receptor antagonist and CD14 (all reviewed in REF. 102) and, more recently, TREM2 (REF. 89). In addition, a GWAS has revealed the *HLA-DRB5* locus as another susceptibility gene[103,104]. However, most cases of Parkinson's disease are sporadic and the risk of developing the disease is only mildly increased in carriers of this haplotype. Neuroinflammation has been shown to have an important role in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced mouse models of Parkinson's disease (TABLE 2), as microglial cell-restricted deletion of *Tlr4* resulted in an increased number of surviving dopaminergic neurons and decreased microglial cell activation[105]. In another mouse model of Parkinson's disease that is induced by 6-hydroxydopamine (6-OHDA) (TABLE 2), co-injection of 6-OHDA and a lentivirus expressing a dominate-negative mutant form of *Tnf* attenuated the loss of dopaminergic neurons and improved behavioural deficits that result from striatal dopamine depletion[106], which underlines the importance of this inflammatory cytokine in Parkinson's disease.

Hereditary forms of Parkinson's disease that are related to abnormalities in the presynaptic protein α-synuclein — which is involved in vesicular transport — account for about 5% of all cases. It is thought that molecular changes in the α-synuclein protein increase its propensity to aggregate and that this is central to the development of disease. It is known that α-synuclein can be secreted by exocytosis from neuronal cells but it may also be released from dying cells. In addition to its direct effects on neurons, α-synuclein activates microglia and this enhances α-synuclein-elicited neurotoxicity *in vitro*[107], providing a link between neuronal cell death and microglial cell activation. In Parkinson's disease, a notable component of the inflammatory response is the presence of oxidative damage that is caused by the upregulation of NADPH oxidase[108], iNOS[109] and MPO[110]. As a result, the increased production of superoxide and NO is thought to induce post-translational modifications in proteins, in particular the nitration of α-synuclein that is present in Lewy bodies[111]. In co-cultures of microglia and neurons, the activation of microglia increased the nitration of α-synuclein and resulted in neuronal cell death[110]. On a cellular level, neuronal stem cells from carriers of the A53T α-synuclein mutation showed early nitrosative and endoplasmic reticulum (ER) stress[111]. As the cause of the initial inflammatory stimulus is unknown, one might speculate that either the release of protein aggregates from neurons leads to microglial activation[112] or that it is caused by an external stimulus that induces peripheral inflammation. A role for an external stimulus

is supported by the observation that adeno-associated virus (AAV)-mediated expression of α-synuclein in the substantia nigra results in only a slow degeneration of dopaminergic neurons but a marked increase in the number of $CD68^+$ microglia and the production of IL-6, IL-1β and TNF in mice[113]. This reaction was found to be dependent on MHC class II expression, as MHC class II deficiency prevented α-synuclein-induced microglial cell activation and, most importantly, the loss of dopaminergic neurons[114].

Similarly to aggregated amyloid-β, aggregated α-synuclein can induce the production of IL-1β[113] in a process that has been shown to depend, at least *in vitro*, on cathepsin B and the NLRP3 inflammasome[115]. This effect may be mediated by a member of the TLR family, as α-synuclein was shown to induce the upregulation of TLRs on microglia[116]. In summary, the role of innate immune responses in the onset of Parkinson's disease has not yet been fully established, but internal and external factors that influence inflammation may affect the physiology of innate immune cells in the brain and thus influence disease progression.

Amyotrophic lateral sclerosis

ALS is a fatal neurodegenerative disease that primarily affects the upper and lower motor neurons, causing corticospinal tract signs, and the wasting and atrophy of targeted muscles. These changes ultimately lead to complete paralysis. Several pathological factors — including excitotoxic, apoptotic and metabolic mechanisms — have been implicated in the pathogenesis of ALS and proposed as therapeutic targets[117]. Similarly to the neurodegenerative disorders discussed above, ample evidence now points to a contribution of the innate immune system in ALS. In line with this, microglial cell activation can be found at the sites of neurodegeneration[118]. In addition, the importance of microglia in ALS has recently been highlighted by a study demonstrating that classical NF-κB activation is required to induce motor neuron death in a mutant superoxide dismutase 1 ($SOD1^{G93A}$) mouse model of ALS[119] (TABLE 2). These findings are further substantiated by PET imaging of patients with ALS using the ligand [^{11}C](R)-PK11195 and studies have suggested that microglial cell activation is increased in affected brain areas[120]. In addition, the extent of microglial cell activation positively correlated with the severity of clinical symptoms in these studies[120].

The innate immune system may affect the function and survival of motor neurons in ALS by at least three mechanisms. First, there is evidence to suggest that aggregates of mutant SOD1 — which is derived from microglial and astroglial cells — activate neighbouring microglia by binding to TLR2, TLR4 and CD14, and subsequently promote neuronal cell death[121]. Indeed, knockdown of *SOD1* in microglial or astroglial cells did not affect the onset of disease in $SOD1^{G93A}$ transgenic mice[122–124] but did effectively prolong the survival of the animals. Second, the release of pro-inflammatory cytokines, and of ROS and reactive nitrogen species may drive motor neuron damage. SOD1 can be detected in the CSF of patients with ALS, which suggests that it may be either actively secreted or passively released from dying cells, and it can promote the activation of the NLRP3 inflammasome[125]. Activated caspase 1 has been found in the CSF of patients with ALS[126] and in samples of brain tissue from mutant *SOD1* transgenic mice[127]. Disruption of caspase 1, IL-1β or the IL-1β receptor prolonged the survival of mutant *SOD1* transgenic animals[125,128]. Third, although poorly understood, a mechanism has been suggested on the basis of the functional analysis of microglial cells that express mutant *SOD1* (REF. 129). These cells showed impaired overall motility and a reduced capacity to clear neuronal cell debris. Impairment of microglial cell phagocytosis may therefore contribute to the accumulation of further immunostimulatory proteins, including mutant SOD1, chromogranin A and dsRNA, thereby resulting in disease progression.

Interestingly, neuroinflammation in models of ALS has been shown to be further aggravated by systemic immune activation. Pre-symptomatic $SOD1^{G37R}$ animals (TABLE 2) showed an accelerated course of disease development in response to chronic LPS exposure[130]. Nevertheless, modulation of the involved immune pathways may be more complicated than anticipated. Some of the putative pathological mechanisms may also have neuroprotective effects and, in addition, the time-point of therapeutic intervention may be of pivotal importance. Two anti-inflammatory strategies (namely, the use of the broad-spectrum antibiotic minocycline and the activation of peroxisome proliferator-activated receptor-γ (PPARγ) by pioglitazone) have shown protective effects in preclinical models of ALS[131,132]. However, these effects could not be verified in clinical studies[133–135].

Huntington's disease

Huntington's disease is an autosomal dominant neurodegenerative disease that is caused by the expansion of a trinucleotide CAG (which codes for the amino acid glutamine) in the gene that encodes huntingtin (*HTT*). This results in the production of a mutant form of HTT (mHTT) that possesses a polyglutamine expansion at the amino terminus, which affects the stability of the protein. Neuropathologically, Huntington's disease is characterized by the loss of medium spiny neurons within the striatum. Recently, inflammatory responses have been suggested to have pathological roles in Huntington's disease. Post-mortem studies of the brains of patients who had Huntington's disease have shown increased microgliosis and astrogliosis[136]. Compared with non-affected regions of the brain, affected regions also showed evidence of microglial cell production of complement components (C3 and C9)[136] and increased levels of IL-1β[137]. Interestingly, a proteomic profile of plasma samples from patients with Huntington's disease detected several members of the complement cascade or their respective precursors, including C9 (REF. 138). Similarly, the mRNA levels of *CCL2*, *IL10*, *IL6*, *IL8* and *TNF* were increased in the diseased brains of patients[139,140]. In plasma samples from patients, TNF levels were found to be elevated in the early stages of Huntington's disease and increased levels of TNF correlated with clinical progression[139].

PET analyses have detected microglial cell activation in the early stages of Huntington's disease and have shown that increased microglial cell activation correlates with reduced neuronal cell activity in pre-symptomatic carriers of the mutant *HTT* allele[141]. This suggests that the observed changes in microglial cell activity are causally involved in Huntington's disease pathogenesis[141]. A study analysing R6/2 mice, which are a model of Huntington's disease (TABLE 2), found that microglia that are activated at the early stages of disease contain ferritin, an iron-storage protein[142]. As a known characteristic of Huntington's disease, this pathological iron accumulation in the striatum could reflect the attempt of microglia to dispose of the accumulating iron. Interestingly, similar to data from the mouse model, patients with Huntington's disease showed an accumulation of ferritin in microglial cells at the early stages of disease[142]. In microglia, the expression of mHTT results in the activation of PU.1, which is a transcription factor that is normally expressed during the differentiation and activation of myeloid cells[143]. In addition, the capacity to induce neuronal cell death is increased in microglia that express mHTT under conditions of sterile inflammation[143].

Plasma levels of clusterin (a protein that is associated with the clearance of cellular debris) and IL-6 seem to increase over time in patients with Huntington's disease, and these proteins become more abundant as the disease becomes clinically apparent[138]. This may be indicative of microglial cell activation or could represent an independent immune response in the periphery[138]. By contrast, another study has described increased IL-6 levels in the plasma years before the onset of any clinical symptoms in carriers of Huntington's disease[139]. Further evidence of innate immune activation in Huntington's disease comes from data showing that increased plasma levels of CCL4, CCL11 and CCL26 occur during disease progression[144]. Extending these observations, a gene expression analysis of symptomatic striatal tissue derived from the R6/2 mouse model identified pro-inflammatory genes — including those that encode TNF, interferon-γ (IFNγ) and TGFβ1 — as potential key regulators of disease[145]. Experiments using cell and brain slice cultures have shown that microglia are activated and proliferate in the vicinity of degenerating neurites of mHTT-expressing neurons[146]. Interestingly, the co-culture of mHTT-expressing neurons with wild-type microglia increased their survival[146], which suggests that microglia may be able to provide some neuroprotective support to these neurons. However, microglia may themselves be altered by expression of mHTT and, as a consequence, the microglia of patients with Huntington's disease may not show these neuroprotective functions. In support of this view, mHTT-expressing monocytes derived from pre-symptomatic carriers of Huntington's disease and from various mouse models were found to produce higher levels of IL-6 as compared with control monocytes following stimulation with IFNγ and LPS[139]. This suggests a cell-autonomous role for mHTT in promoting the activation of myeloid cells[139]. Likewise, mHTT expression compromised cell migration and the motility of cellular processes in microglia and monocytes that were derived from mouse models or pre-symptomatic carriers of Huntington's disease[147].

The reason for the increased immune response seen in mHTT-expressing neurons could be the higher activity of NF-κB — a key transcriptional regulator of pro-inflammatory signalling cascades — which may occur as a result of a direct interaction between mHTT and inhibitor of NF-κB kinase (IKK)[148]. Caspase 1 activation, which probably occurs as a result of inflammasome activation, has also been shown to contribute to disease progression and neurodegeneration in R6/2 mice[137]. The activation of caspase 1 may lead to neurodegeneration either through the direct cleavage of HTT (and a subsequent increase in small HTT peptides and neuronal intranuclear inclusions) or by converting pro-IL-1β to active IL-1β and the induction of pyroptosis. In further support for a detrimental function of microglial cell-driven neuroinflammation, microglial cell-restricted deficiency of cannabinoid receptor 2 was found to increase neuroinflammation and disease symptoms in R6/2 mice, and also to reduce their lifespan[149]. By contrast, activation of the cannabinoid receptor 2 on microglia resulted in neuroprotection in R6/2 mice[149]. However, in Huntington's disease, mHTT is also expressed by astrocytes. Mice expressing mutant *HTT* under the control of the human glial fibrillary astrocytic protein (*GFAP*) promoter showed age-dependent neurological deficits and a shorter lifespan compared with wild-type controls[150,151]. Glutamate uptake, which is an important glial function that is involved in the control of excitotoxicity, was reduced in these mice and this probably contributed to neuronal dysfunction and death[150,151].

Although most of the studies discussed above have focused on the mHTT protein itself as a direct trigger for microglial cell activation, a novel and intriguing hypothesis has been suggested to explain how innate immune pathways become activated in Huntington's disease. As mentioned above, the mutant *HTT* gene that causes Huntington's disease is characterized by the addition of CAG repeats. It has been suggested that these trinucleotide repeats can lead to the formation of hybrid double-stranded RNAs (dsRNAs) that are subsequently cleaved by the ribonuclease Dicer into single-stranded RNA CAG-repeat septamers, which can activate intracellular TLRs and cause cell death[152]. In support of this idea, such a mechanism was shown to drive neurotoxicity in a *Drosophila melanogaster* model of Huntington's disease[152,153].

In summary, mHTT — or even pathological single-stranded RNAs that are derived from the mutant *HTT* gene — may induce pathological immune activation in the brain and peripheral tissues of patients with Huntington's disease. The fact that increased inflammation has been clearly linked to a more severe disease phenotype and symptomatic progression in Huntington's disease suggests that inflammatory pathways may serve as future therapeutic targets. Similar to hereditary forms of Alzheimer's disease, patients that will develop Huntington's disease in the future can be identified

by genetic screening. Therefore, it may be possible to develop early interventions that delay or even inhibit the development of Huntington's disease by targeting inflammatory pathways.

Other neurodegenerative diseases

Neuroinflammation is also observed in the brains of patients who are affected by dementia with Lewy bodies (DLB), which is a neuropathology that shares disease characteristics with both Alzheimer's disease and Parkinson's disease. The level of neuroinflammation that is seen in patients with DLB seems to be lower than that observed in patients with Alzheimer's disease[154]. Nevertheless, a higher number of activated microglia has been observed in patients with DLB compared with control patients[155]. In addition, increased expression of IL-1α and TNF has been observed in microglia that are in close proximity to neurons bearing inclusions[156]. It has to be mentioned that this observation might have derived from studying patients with a mixed Alzheimer's disease–DLB phenotype and might, therefore, be unrelated to DLB itself[157].

To date, there has been very little data published concerning neuroinflammation in other neurodegenerative diseases. However, there are a few studies that are worth mentioning. First, brain sections from patients with spinocerebellar ataxia type 3 (also known as Machado–Joseph disease; a neurodegenerative disease that leads to a loss of muscle control) showed evidence of microglial cell activation, particularly in the nucleus raphe interpositus[158]. Second, in patients with multiple system atrophy, PET imaging studies have indicated increased microglial cell activation in the dorsolateral prefrontal cortex, putamen, pallidum, pons and substantia nigra, which reflects the known distribution of the neuropathological changes that occur in this disorder[99]. Finally, in a *Drosophila melanogaster* model of the neurodegenerative disease ataxia-telangiectasia — which is caused by knockdown of the gene encoding ataxia-telangiectasia mutated (ATM; also known as Tefu) — an elevated innate immune response was observed in glial cells and this was shown to be causally involved in neuronal cell death[159,160].

Conclusions and perspective

Inflammation is a natural response of the immune system to stressful stimuli such as infections, tissue damage or metabolic derangements. The inflammatory tissue response aims to kill pathogenic microbes, repair injured tissue and remove harmful deposits of metabolites. Once inflammation has resolved, tissue homeostasis is restored. Chronic effects of immune stressors and the incomplete resolution of inflammatory responses are known to be important triggers of tissue pathology in numerous diseases as diverse as atherosclerosis, rheumatoid arthritis, psoriasis and diabetes, for example. Neuroinflammation accompanies a variety of neurodegenerative diseases and it is becoming increasingly evident that in some (if not all) of these, neuroinflammation is not only a consequence but could be a trigger of pathology. In fact, in many neurodegenerative pathologies, various triggers of inflammation — such as aggregated substances that are known to be triggers of innate immune pathways — are found and can be diagnostic for the particular disease. Therefore, immune activation could be an early cause rather than a late consequence in neurodegenerative diseases and this suggests that anti-inflammatory therapies could be a promising treatment approach.

Several open questions remain. For one, the role of activated microglia in propagating neurodegeneration from one brain region to another has not yet been fully elucidated. Also, regional differences in microglial cell numbers and distribution may modify the nature of the innate immune responses that occur at these sites and could represent a contributing factor in the susceptibility to different types of neurodegeneration. Furthermore, it is possible that receptors of the innate immune system show specificity for different immunostimulatory molecules that are found in the brain, such as dsRNAs and aggregated or post-translationally modified proteins. It is tempting to speculate that triggering these receptors could promote beneficial effects in the healthy brain, such as the removal of cellular debris. An overabundance of the same material, however, could drive pathogenic responses such as the induction of neuronal cell death during neurodegeneration.

Of particular relevance, new tools have recently been generated that will allow researchers in the field to decipher the contribution of microglial cells (or other cell types) to neuroinflammation and to the development of pathology in different murine disease models. There is ample evidence suggesting that not only microglial cells but also other cell types in the brain — such as astrocytes, neurons and endothelial cells — are immunocompetent and express innate immune receptors that are capable of recognizing danger signals. An increased understanding of these processes will be required to safely develop and test new therapeutic interventions that target inflammatory pathways in the context of neurodegenerative disease.

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