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Inflammation in neurodegenerative diseases

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Summary

Neurodegeneration, the slow and progressive dysfunction and loss of neurons and axons in the central nervous system, is the primary pathological feature of acute and chronic neurodegenerative conditions such as Alzheimer's disease and Parkinson's disease, neurotropic viral infections, stroke, paraneoplastic disorders, traumatic brain injury and multiple sclerosis. Despite different triggering events, a common feature is chronic immune activation, in particular of microglia, the resident macrophages of the central nervous system. Apart from the pathogenic role of immune responses, emerging evidence indicates that immune responses are also critical for neuroregeneration. Here, we review the impact of innate and adaptive immune responses on the central nervous system in autoimmune, viral and other neurodegenerative disorders, and discuss their contribution to either damage or repair. We also discuss potential therapies aimed at the immune responses within the central nervous system. A better understanding of the interaction between the immune and nervous systems will be crucial to either target pathogenic responses, or augment the beneficial effects of immune responses as a strategy to intervene in chronic neurodegenerative diseases.

Keywords: immune response; inflammation; neurodegeneration; neuroprotection; repair

Introduction

The pathological mechanisms operating in neurodegenerative disorders have gained increased attention, not least because of the aging community in which neurodegenerative diseases are a growing cause of disability. Immune activation within the central nervous system (CNS) is a classical feature of ischaemia, neurodegenerative diseases, immune-mediated disorders, infections and trauma. Often, it may contribute to neuronal damage. Yet, not all

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid-beta; AGE, advanced glycation end-products; ALS, amyotrophic lateral sclerosis; AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor; APP, amyloid precursor protein; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; CB, cannabinoid; CNS, central nervous system; COX, cyclooxygenase; CSF, cerebrospinal fluid; DAMPs, danger-associated molecular patterns; EAE, experimental autoimmune encephalomyelitis; EBV, Epstein–Barr virus; HAD, HIV-associated dementia; HHV6, human herpesvirus-6; HIV, human immunodeficiency virus; HMGB-1, high mobility group box chromosomal protein 1; HSV, herpes simplex virus; ICAM, intercellular adhesion molecule; IFN-γ, interferon-γ; IL, interleukin; iNOS, inducible nitric oxide synthase; LCMV, lymphocytic choriomeningitis virus; MAC, membrane attack complex; MCAo, middle cerebral artery occlusion; MHC, major histocompatibility complex; MHV, murine hepatitis virus; MMPs, matrix metalloproteinases; MPTP, 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine; MS, multiple sclerosis; NCAM, neural cell adhesion molecule; NF-L, neurofilament light; NK, natural killer; NLR, nucleotide-binding oligomerization domain-like receptors; NMDA, *N*-methyl-D-aspartate; NO, nitric oxide; PAMPs, pathogen-associated molecular patterns; PD, Parkinson's disease; PGE_2, prostaglandin E_2; PML, progressive multifocal leucoencephalopathy; PNND, paraneoplastic neurological disorders; PrP, prion protein; PRR, pattern-recognition receptors; RAGE, receptor for AGE; ROS, reactive oxygen species; SFV, Semliki Forest virus; SLE, systemic lupus erythematosus; SOD-1, superoxide dismutase-1; TBI, traumatic brain injury; TGF-β, transforming growth factor-β; Th1, T helper 1; Th2, T helper 2; TLR, toll-like receptors; TMEV, Theiler's murine encephalomyelitis virus; TNF-α, tumour necrosis factor-α; TRAIL, TNF-related apoptosis-inducing ligand.

immune responses in the CNS are detrimental, and in many cases, they actually aid repair and regeneration. For example, microglia clear debris after myelin damage and when this is impeded, delayed regeneration occurs.[1] Immune activation is also crucial to limit neurotropic viral infections and removes necrotic cells following ischaemia. Thus, microglia exert dual roles in neurodegeneration, both as instigators of damage and as guardians of brain homeostasis. Not only microglia, but also T cells can aid recovery during neurodegenerative diseases,[2] although the exact mechanisms for this beneficial role of T cells are not clear. Detailed studies of neuroimmune interaction at both cellular and molecular levels have revealed complex interactions, demonstrating that immune cells secrete both neurotoxic and neuroprotective molecules.

Here, we review the involvement of immune responses in neurodegenerative disorders, and discuss the delicate balance between either pathogenic or repair processes, which can be triggered by the immune response. A better understanding of this interaction will be crucial to harness beneficial responses for therapeutic strategies.

Immune privilege in the CNS

The CNS has developed strategies to limit the entry of immune elements as well as to limit the emergence of immune activation with the tissue itself. This so-called phenomenon of 'immune privilege' was recognized in the mid-20th century by Sir Peter Medawar who was awarded the Nobel Prize with Sir Frank Macfarlane Burnet in 1960 for the discovery of acquired immune tolerance. Medawar's idea of 'immune privilege' led to the notion that immune responses are tightly regulated in the brain. Immune privilege in the CNS is partially dependent on the blood–brain barrier (BBB), which is designed to limit the entry of solutes and ions into the CNS.[3] The early studies by Paul Ehrlich elegantly demonstrated that injection of intravital dyes left the brain unstained, unless the dyes were injected intracranially. Exclusion from, and selective entry of compounds into, the CNS takes place in the capillary venules. In contrast, cell migration takes place at the post-capillary venules, where cell migration is controlled by adhesion molecules, cytokines and chemokines, and their receptors.[4] Not only the physical properties of the BBB, but also potentially damaging immune responses as such are regulated by the suppressive environment within the CNS. Both astrocytes and microglia play a major role in this regulation, while neurons are assumed to play a largely passive role – being only the victims of immune responses. Microglia invade the brain early in development and take on a resting 'protective' role as sentinels, scattered uniformly throughout the CNS and forming a network of potential effector cells. In contrast to peripheral macrophages that are highly effective at inciting pro-inflammatory responses, microglia take on an opposing role, limiting inflammation. This role is extended also to astrocytes, the first cells that CNS-infiltrating immune cells encounter. Astrocytes suppress T helper 1 (Th1) and T helper 2 (Th2) cell activation, the proliferation and effector functions of activated T cells, and possess a wide variety of molecular mechanisms to induce apoptosis in activated T cells.

Contrary to the idea that neurons play an only passive role, many of their products (i.e. neuropeptides and transmitters), as well as the neuronal membrane proteins CD22, CD47, CD200, CX3CL1 (fractalkine), intercellular adhesion molecule (ICAM)-5, neural cell adhesion molecule (NCAM), semaphorins and C-type lectins all regulate inflammation.[5] In addition, neurons express low levels of major histocompatibility complex (MHC) molecules and actively promote T-cell apoptosis via the Fas–Fas ligand pathway (CD95–CD95L). Neuronal expression of the cannabinoid (CB_1) receptor is also implicated in suppressing inflammation. CB_1 knockout mice more readily develop experimental autoimmune encephalomyelitis (EAE), the autoimmune model of multiple sclerosis (MS). Neurons also favour the differentiation of T-regulatory cells, by providing a local microenvironment dominated by transforming growth factor–β1 (TGF-β1). Damaged neurons, however, are less able to maintain this protective shield, allowing further insults. In summary, once primed to antigens in the CNS, the immune-privilege status of the brain and spinal cord is lost despite all efforts to suppress such responses.

Innate and adaptive responses in the CNS

Despite the immune-privileged environment, it is clear that both innate and adaptive inflammatory responses do occur in the CNS. Activation of the innate immune system is a crucial first line of defence, to opsonise and clear apoptotic cells. Furthermore, innate immune responses recruit cells of the adaptive immune system by secreting various cytokines and chemokines that induce adhesion molecules on the BBB, and by inducing the expression of costimulatory molecules on microglia.

Through conserved pattern-recognition receptors (PRRs), local CNS cells may be triggered to develop innate responses. Among these receptors are Toll-like receptors (TLRs), which bind highly conserved structural motifs either from pathogens (pathogen-associated molecular patterns, or PAMPs) or from damaged or stressed tissues (danger-associated molecular patterns, or DAMPs). Thus, not only invading micro-organisms, but also endogenous signals can switch on innate responses in the CNS. Some DAMPs, including heat shock proteins, uric acid, chromatin, adenosine and ATP, high mobility group box chromosomal protein 1 (HMGB-1), galectins and

thioredoxin have adjuvant and pro-inflammatory activity. Other DAMPs include surfactant proteins A and D, hyaluronan, fibrinogen and aggregated, modified or misfolded proteins such as amyloid-beta (Aβ), α-synuclein and microtubule associated protein-tau. Only for some of these endogenous stimuli of innate responses are the receptors known.

TLRs can be widely up-regulated during neurological disorders in varying patterns on microglia, astrocytes, oligodendrocytes[6] and neurons (Fig. 1a; Table 1). When activated, TLRs are generally assumed to promote the production of pro-inflammatory cytokines, evoking a damaging environment that may contribute to neuronal damage. For example, a role of TLR2 and TLR4 in neurodegeneration is indicated because mice deficient in these TLRs exhibit reduced levels of pro-inflammatory cytokines and milder clinical disease following traumatic brain injury[7] or middle cerebral artery occlusion, suggesting a pathogenic role of TLRs during stroke in humans. TLR2, TLR3 and TLR4 are increased in Parkinson's disease (PD), stroke and amyotrophic lateral sclerosis (ALS). In Alzheimer's disease (AD), microglia are associated with neurons expressing Aβ (Fig. 1b), and TLR2 and TLR4 expression is present in Aβ plaques. *In vitro*, Aβ activates microglia through TLRs.[8–10] TLRs also aid the uptake of Aβ and other aggregated proteins, thereby promoting their clearance from the CNS. Although in this manner, TLRs may seem to play a beneficial role in AD, it is

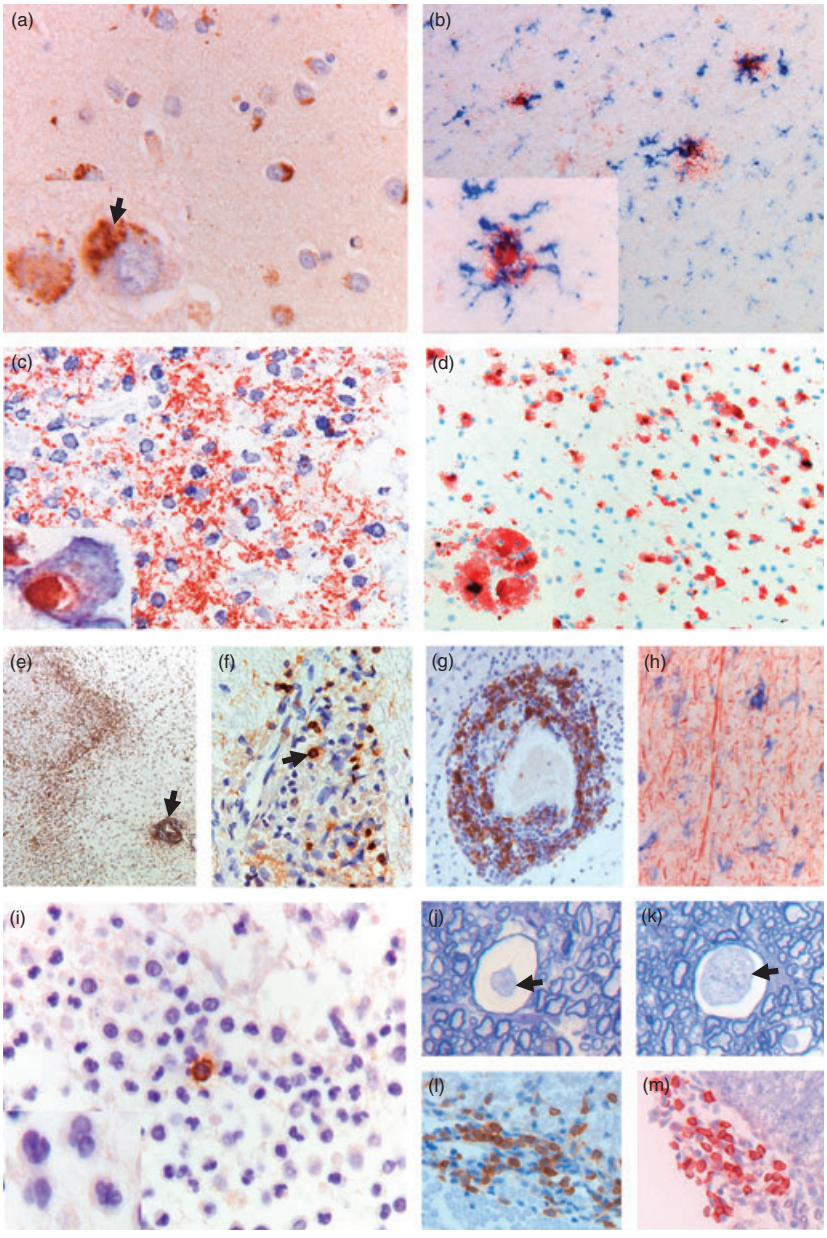

Figure 1. Pathology of human and experimental neurodegenerative disorders showing involvement of the immune response. (a) Toll-like receptor 3 (TLR3) expression in neurons in multiple sclerosis (MS). The insert shows the granular appearance of the receptor in the cytoplasm (arrow). (b) Activated microglia, as depicted by human leucocyte antigen (HLA) class II expression (blue) around amyloid-beta (Aβ)-positive accumulations (red) inside neurons in Alzheimer's disease. (c) HLA class II expression by activated microglia (blue) phagocytosing myelin basic protein (red) in stroke. (d) Lipid-laden (oil red O positive) foamy macrophages (blue) in an active MS lesion. (e) HLA class II-positive microglia (brown) at the edge of a chronic active lesion in MS. Activated microglia/macrophages surrounding a blood vessel in the lesion (arrow). (f) $CD45^+$ lymphocytes (arrow) and (g) $CD20^+$ B cells (brown) in perivascular infiltrates in MS. (h) HLA class II-positive microglia (blue) close to a damage axon red (arrow) stained for neurofilament light (NF-L). (i) Meningeal infiltrate in acute bacterial meningitis containing a single $CD20^+$ cell (brown). The majority of cells are polymorphonuclear cells (inset). (j, k) Shrunken and swollen axons (arrows) in the spinal cord of mice with experimentally induced neuronal damage following immunization with NF-L. In the same mice, $CD3^+$ T cells (l), and (m) B cells in the meninges close to areas of neuronal degeneration, are shown.

Table 1. Immune responses in neurodegenerative disorders

Disorder	Innate immune response	Adaptive immune response	References
Alzheimer's disease	TLR2 and TLR4 increased on microglia in AD brains. Aβ induces TLR expression *in vitro*. Increased pro-inflammatory cytokines and complement components are present around Aβ plaques	T-cell recruitment after Aβ injection. TNF-α and IFN-γ production	8–12,17,22,23,26,34
Parkinson's disease	TLR2, TLR5 and CD14 increases in PD CNS. Activated NK cells. Microglial activation. Increased expression of CD14 and TLR4 in the substantia nigra of an MPTP animal model	Increases of $CD4^+$ T cells, $CD4^+$ T cells infiltrate in PD brains, influence of Fas ligands, but not of IFN-γ	8–10,23,26
Amyotrophic lateral sclerosis	TLR3 in Purkinje neurons. TLR1,2,7,9 and CD14 expression in ALS	Increase in complement components. Alterations in peripheral levels of $CD4^+$ and $CD8^+$ T cells	8–10,26,35,37
Traumatic brain injury	Myd88 involvement in inflammation following TBI, independently of TLR2/4	CD4 and CD8 infiltration in the acute and chronic phases of TBI	7,38
Stroke	Up-regulation of TLRs on endothelium, neurons and glia	Bias towards Th2 responses	8–10
Paraneoplastic disorders		Antibodies to neuronal antigens	26
Systemic lupus erythematous	IgG autoantibody, complement C4 on necrotic cells	Antibodies to double-stranded DNA	26,27
Multiple sclerosis	NK cells, microglial activation	CD4 and CD8 T cells close to neurons	6,13–15,18–20,26,32,33

Aβ, amyloid-beta; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; CNS, central nervous system; IFN-γ, interferon-γ; MPTP, 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine; NK, natural killer; PD, Parkinson's disease; TBI, traumatic brain injury; TNF-α, tumour necrosis factor-α; TLR, toll-like receptor.

currently unclear whether cellular activation by TLRs in another way may also contribute to AD progression.[11,12] Likewise, TLR expression is increased during MS[6] and EAE. Intriguingly, TLR4 knockout mice are resistant to EAE, while TLR9-deficient mice develop less severe clinical disease and inflammation.[13,14] Therefore, rather than only playing a pathogenic role, several TLRs also play a role in repair during neurodegenerative disorders, under non-infectious conditions, suggesting that activation of at least some TLRs can also be used as a therapeutic strategy in CNS disorders.[15]

Another family of PRRs include the nucleotide-binding oligomerization domain-like receptors (NLRs). These intracellular soluble proteins expressed in glia cells recognize intracellular invaders. Evidence for their involvement in neurodegenerative diseases is sparse, although it has been suggested that in AD the NLRs activate innate immune responses.[16] They are highly expressed in EAE, although their exact role under these conditions is still unknown.

Accumulation of advanced glycation end-products (AGE) is characteristic of aging, but accelerated accumulation is observed in neurological disorders such as MS and AD. The receptor for AGE (RAGE) is increased following oxidative stress, immune and/or inflammatory responses, and upon altered cell functions, suggesting that AGE accumulation also occurs during these processes. Engagement of RAGE induces the release of pro-inflammatory cytokines and free radicals, thus perpetuating a cycle of damage. RAGE is increased in AD, where it is found to be expressed on neurons and astrocytes. In the case of astrocytes, AGE proteins appear as granules, suggesting that astrocytes are responsible for the uptake of, and the degradation of, glycated proteins.[17] In MS, RAGE is expressed on oligodendrocytes in response to stress,[18] and the levels of soluble RAGE have been implicated as a predictor of disease severity.[19] One known ligand of RAGE, HMGB1, a DNA-binding protein with pro-inflammatory properties, and one that is generally seen as a member of DAMPs, is also increased in MS lesions, and has been suggested to amplify the inflammatory response that causes the disease.[20]

Yet other receptors expressed by microglia are the group of adenosine receptors.[21] These receptors modulate neuronal and synaptic functions, and regulate inflammation by modulating the cytokine release. The expression of adenosine receptors is altered in AD, but little is known about their possible role in other neurodegenerative disorders. As the receptors are assumed to be beneficial in disease by both modulating inflammation and

aiding neuroprotection, attempts are currently focused on generating ligands as potential therapeutic agents.[22] As a consequence of innate immune activation, increased levels of the inflammatory cytokines tumour necrosis factor-α (TNF-α) and interleukin (IL)-6, and of the chemokine CXCL8, are seen in many neurodegenerative disorders (Table 1). Downstream effects, including an increase in caspase activity, of intracellular calcium levels and of the production of reactive oxygen species (ROS) have been implicated in AD, systemic lupus erythematosus (SLE), traumatic brain injury (TBI) and Huntington's chorea. The presence of inflammatory cytokines and matrix metalloproteinases (MMPs) in the cerebrospinal fluid (CSF) of SLE patients with neurological involvement are equally indicative of immune activation in the CNS in this condition.

The complement system is often regarded as a bridge between the innate and adaptive immune responses. Most complement components and receptors are expressed by astrocytes, microglia and neurons. This is particularly prominent in neurodegenerative disorders where they may be useful for the elimination of aggregated proteins.[23,24] Gliosis, axonal death and basal ganglia abnormalities observed in SLE are associated with IgG and complement factor C4 deposition on necrotic cells. During development, C1q and C3 act as markers of synapses destined for elimination by microglia-expressing C3 receptors. That these proteins are increased in the CNS in AD, ALS, SLE, Huntington's chorea, MS, PD and cerebral ischaemic injury indicates a broad role for complement in neuronal degeneration. Much of the evidence for the role of the complement system in disease has been extrapolated from animal models. Crucially, these studies demonstrate not only a pathogenic role of complement, but equally show a role in neuroprotection and neuroregeneration.[25]

In contrast to the fact that innate immune responses frequently emerge within the CNS, it appears more difficult to locally initiate adaptive immune responses. This is in part because of an active anti-inflammatory environment, as discussed above, and it is evidenced by the survival of foreign tissue grafts within the CNS. For many neurodegenerative disorders it is unclear exactly how adaptive immune responses are involved in neuronal damage, and whether such activation is an epiphenomenon or a consequence. Nevertheless, in paraneoplastic neurological disorders (PNND), neuronal degeneration is directly linked with pathogenic antibodies against the neuronal antigens that are expressed on tumours. Removing the tumour, or performing plasmapheresis, is often beneficial, particularly when autoantibodies are pathogenic. Antibodies to neurons are also present in other neurodegenerative diseases,[26,27] where some have been found to be clearly pathogenic,[28] while others exert protective effects and thus may be useful for therapy.[29] In many cases, it is unknown how and why these antibodies to neurons arise, or, indeed, whether they are produced within the CNS. In some movement disorders, antibodies to group A beta-haemolytic streptococcal infections cross-react with human basal ganglia tissue, resulting in motor and psychiatric symptoms.[28] Fortunately in these cases, treatment with antibiotics is very effective. In MS it is apparent that antibodies are produced intrathecally, because oligoclonal immunoglobulins are present in the CSF but not in serum. Despite many efforts to clarify the specificity or functional significance of these antibodies, their origin and role in MS remain elusive. Non-specific activation of the intrathecal B-cell pool as a result of Epstein–Barr virus (EBV) infection could explain the presence of these antibodies. Intriguingly, recent studies suggest that EBV infection in the CNS in MS might be the underlying trigger for the emergence of intrathecal antibodies.[30–32] While this idea currently remains an issue of debate,[33] the involvement of EBV infection in MS deserves further study.

Evidence for the involvement of cellular immune responses in neurodegenerative disorders has emerged from observations of elevated T-cell responses to specific CNS antigens, or shifts in $CD4^+$ and $CD8^+$ cell populations in the periphery as well as in the CNS. Extrapolation of findings in peripheral blood to events in the CNS, however, is difficult. One important issue is that T cells directed to myelin or neuronal antigens can also be found in healthy control subjects.[34,35] Their direct involvement as a causative factor in CNS disorders is therefore difficult to substantiate. Nevertheless, alterations in peripheral levels of $CD4^+$ and $CD8^+$ T cells, as observed in AD,[36] ALS[37] and TBI[38] are potentially relevant and may reflect persistent antigenic challenge.

Within the CNS, microglia, astrocytes and endothelial cells may act as antigen-presenting cells, and neurons themselves may promote immune activation via the secretion of complement factors, chemokines, MMPs and DAMP molecules. Activated microglia/macrophages are observed in neurodegenerative disorders and phagocytose debris (Fig. 1c–e). Despite the otherwise immunosuppressive environment, T cells do enter and can survive in the CNS. For example $CD4^+$ T cells are observed in the substantia nigra in PD patients, TBI[38] and in the CNS in MS (Fig. 1f).[39] In the latter case, CD8 T cells not only outnumber CD4 T cells, but they have been shown to be in close contact with neurons, indicating that neuronal damage in such cases may be mediated by cytotoxic $CD8^+$ T cells.[40] That both B cells (Fig. 1g) and $CD4^+$ T cells, as well as $CD8^+$ T cells, can play a role in neurodegeneration[41] is also evidenced by the close association of T cells expressing TNF-related apoptosis-inducing ligand (TRAIL) with dying spinal motor neurons in MS.[41] While all these findings appear to implicate T cells in the process of neurodegeneration, there is also evidence for their

role in protection and repair.[42] Some T-cell responses are accompanied by production of neuroprotective factors such as brain-derived neurotrophic factor (BDNF).[43] As discussed earlier, microglia and macrophage uptake of myelin during damage enhances regeneration and repair in the CNS.[1] Recently, autoimmune T cells have been shown to augment this process,[44] emphasizing that in several cases, autoimmune responses in the CNS are not always destructive but, instead, are crucial for repair and regeneration.

Infections and neurodegeneration

Neurotropic viruses can induce significant neuronal dysfunction and degeneration of specific neuronal populations, sometimes leading to devastating, life-threatening consequences for the host[45] (Table 2). Viruses injure neurons in a number of ways (Fig. 2), including direct killing as a result of viral replication and cell lysis, as seen in poliomyelitis. Alternatively, viruses can induce apoptosis. Some neuronal cells affected by viruses display a 'dying back' pattern of degeneration.[46] Infected neurons do fight back and rather than undergoing self-destruction use a process of autophagy, an intracellular lysosomal-degradation pathway.[47]

Regardless of the route of entry to the CNS, infection with neurotropic viruses tends to activate both innate and adaptive immune responses. Viral and bacterial antigens, for example, are highly likely to activate TLRs and NLRs, and TLRs 3, 7 and 8 are preferentially activated by viral antigens. Apart from the possibility that innate responses damage neurons, for example by release of free radicals by activated microglia, adaptive immune responses may also lead to neuronal damage (Table 2). In some cases, direct damage and killing occurs of virally infected neurons. In other cases, neurons may be damaged as a side-effect of inflammation.[48–56]

In an immunocompetent host, viruses are often rapidly cleared. However, the immune-privileged status of the CNS, as well as the post-mitotic state of neurons,

Table 2. Neurodegeneration in infectious disorders in humans

Disease	Neurodegeneration	Immune involvement	References
Viral			
Enteroviruses Poliovirus	Apoptosis of motor neurones	Unknown	45
Japanese B Encephalitis	Neuronal death	Increase in pro-inflammatory mediators, iNOS, COX-2, IL-6, IL-1β, TNF-α and CCL2	48
Epstein–Barr virus	Grey-matter atrophy Encephalopathy and acute quadriparesis; anterior horn cell degeneration	EBV antibodies associated with MRI markers of grey-matter damage Cellular infiltration of nerve roots Production of viral IL-10	49,50
Human herpesvirus 6	Meningoencephalitis and leucoencephalitis. Dead and dying neurons undergoing neuronophagia	Lymphocytes and microglia in the meningeal and cortical lesions	51
Cytomegalovirus	Transverse myelitis	CSF pleocytosis indicative of CNS inflammation. Unclear if neuronal damage is immune mediated	52
Rabies virus	Cognitive changes Neuronal destruction	Induces expression of HLA-G to aid latency	53
Herpes simplex virus	Cognitive changes Neuronal destruction	Induces expression of HLA-G to aid latency. Production of viral chemokine receptor analogue	53
Measles	Myelin damage	Possible autoimmunity	54
PML JC virus	Infection of oligodendrocytes, astrocytes and neurons		55
HIV	Dementia (HAD)	Infected macrophages migrate to CNS	56
Bacterial			
Bacterial meningitis	Neuronal loss and damage, apoptosis	TLR-dependent activation of microglia	57
Prion disease			
CJD	Apoptotic neurons	Inflammation and cytokine production in regions of apoptotic neurons	58

CJD, Creutzfeldt-Jakob disease; CNS, central nervous system; COX2, cyclooxygenase 2; CSF, cerebrospinal fluid; EBV, Epstein–Barr virus; HAD, HIV-associated dementia; HIV, human immunodeficiency virus; HLA, human leucocyte antigen; IL, interleukin; iNOS, inducible nitric oxide synthase; MRI, magnetic resonance imaging; PML, progressive multifocal leucoencephalopathy; TNF-α, tumour necrosis factor-α; TLR, toll-like receptor.

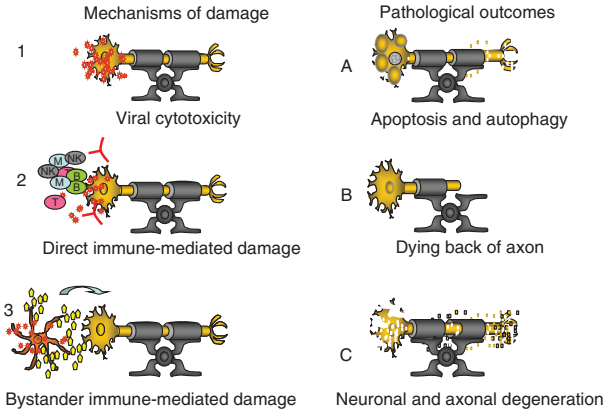

Figure 2. Proposed mechanisms of viral-induced neuronal damage and the outcomes. 1. Infection of neurons with viruses leads to apoptosis, necrosis or autophagy (A). 2. Immune-mediated attack of neurons by viral-specific immunity by, for example, $CD8^+$ T cells, leads to direct cytotoxic death, apoptosis, autophagy (A), dying back of the neurons (B) or neuronal death (C) and myelin damage. 3. Infection of cells (e.g. astrocytes) leads to so-called bystander damage as the result of release of cytokines or reactive oxygen species (ROS) that damage neurons in a variety of ways (A–C).

provided the ideal environment for viral latency. Under normal conditions, neurotropic viruses may aid the immune-suppressive environment within the CNS by actively down-regulating immune responses. One example of this is induction of expression of HLA-G, a molecule thought to promote immune tolerance.[53] Also, herpesviruses such as human herpesvirus-6 (HHV6) and EBV carry a repertoire of genes designed to subvert the host's immune response. They can interfere with MHC processing, and secrete analogues of immune-regulatory molecules such as IL-10. Often, latency of viruses only becomes apparent in an immunocompromised host, for example during immune-suppressive therapies.

Despite this, neurotropic viruses can initiate adaptive immune responses (Fig. 2b), which may, in turn lead to myelin and neuronal damage. Axonal injury and neurodegeneration may also occur secondarily to myelin damage or as the result of a bystander response to infected cells in the vicinity of neurons (Fig. 2c). In many demyelinating diseases, neuronal loss may occur when the tropic support of myelin is lost. This may occur when viruses induce myelin damage by destruction of oligodendrocytes, as, for example, observed during subacute sclerosing panencephalitis, a fatal disease in children and young adults caused by persistent measles virus,[54] or during progressive multifocal leucoencephalopathy (PML), caused by JC papovirus. Recently, however, JC virus has been shown to also infect neurons directly.[55] Dementia is well known to be associated with human immunodeficiency virus (HIV), which enters the CNS in macrophages. Once inside the CNS, HIV-1 induces activation of chemokine receptors and the production of inflammatory mediators and extracellular matrix-degrading enzymes, and it induces glutamate receptor-mediated excitotoxicity, all of which have detrimental effects on neuronal and glial function.[56]

Just like virus infections, bacterial infections may also lead to neuronal damage. They do so by secreting bacterial toxins, activating innate immune responses via PRRs, or by activating an adaptive immune response that precipitates neuronal damage (Fig. 1i).[57] Space does not allow for details to be discussed here of viral-induced neurodegenerative disorders and we have summarized the main features in Table 2, which also lists the possible role of immune responses against infectious agents in human neurodegenerative disorders, including prion disease.[58]

Experimental models of neurodegeneration

Animal models represent a key tool to study molecular and cellular mechanisms underlying neurodegeneration in human disorders, although only a few are really predictive of the human response (Table 3). This is probably because the underlying cause of many human CNS disorders is still unknown in most cases and inadequately represented in laboratory animals. Often, one can only speculate as to the initiation events and disease-promoting conditions that have to be mimicked in animal models. Here, we will briefly discuss models for the major neurological disorders, taking into account that such disease-specific models may also be useful to study mechanisms operating in other neurodegenerative disorders.

Alzheimer's disease

The major pathological features of AD are the extracellular accumulation of Aβ peptide in the senile plaque and the intracellular accumulation of abnormally phosphorylated tau protein as neurofibrillary tangles. Aggregates of the Aβ peptide cleaved from the amyloid precursor protein (APP) accumulate in the plaques and vessel walls. Some of these features are observed in aged animals, but these do not fully model AD. Soluble oligomers of Aβ disrupt synaptic function, as has been shown in invertebrate models such as *Drosophila* sp. and *Caenorhabditis elegans*. However, it has only been with the development of transgenic animals that overexpress Aβ protein or tau, or indeed, in triple transgenic mice expressing APP, mutated presenilin and tau, that the mechanisms underlying the pathology of AD can be investigated in more detail (Table 3).[59,60] The degree to which pathological changes thus provoked are associated with altered behaviour, loss of inhibition and other cognitive changes, is dependent on the background and gender of the mice. Despite this restriction, these models allow investigation of how such protein accumulation leads to neuronal damage, and how this impacts on immune responses

Table 3. Experimental models of neurodegeneration

Disease	Animal model	Mechanism of neurodegeneration	References
Alzheimer's disease	APP transgenic mice	Increased APP deposition. Behavioural and , cognitive changes, amyloid pathology, increased , plaques and accumulation of Aβ	59,60
	Transgenic mice expressing B secretase and APP, or presenilin-1 and APP		
Parkinson's disease	Mice overexpressing e.g. human alpha-synuclein	Microglial activation. Adaptive immunity directed ,to neurons expressing alpha-synuclein	61–65
	Neurotoxins such as MPTP	$CD4^+$ T-cell-mediated damage	
Stroke	MCAo, photothrombotic model (non-invasive)	Microglial TNF-α-induced neuronal damage	66,67
		Role for T cells and cytokines	
Traumatic brain injury	Injury to brain or spinal cord	Neurons damaged close to activated microglia	68,69
		Pathogenic T and B cells induce neuronal injury	
ALS	SOD-1 mutation	ER stress-related toxicity	70,71
	Immunization with motor neurons	Autoimmune attack	
Multiple sclerosis	Secondary progressive EAE in mice immunized, with spinal cord homogenate or MOG., Outside-in model[1]	Neuronal and axonal loss as a result of chronic inflammation. Heterogeneous mechanisms	27,72–77
		Direct attack on neurons and axons	
	Spasticity in mice immunized with NF-L., Inside-out model[2]	Loss of trophic support by myelin	
		Heterogeneous mechanisms	
	SFV, TMEV, MHV infections		
Infectious			
Viral	Human foamy virus – mice	Ataxia. Damage to cerebellar granule cells	78
	Tick-borne encephalitis virus – mice	Necrosis	79
	TMEV in mice	Virus-induced neuronal death, IFN-γ protects from neuronal death	80
	LP-BM5 murine leukaemia virus	Activation of AMPA receptors	80
	Mouse hepatitis virus	$CD8^+$ T cells and antibodies	81
	LCMV – mice	Virus-induced neuronal death $CD8^+$ T cells	82
	Murine retrovirus	Protein misfolding induces neuronal death	83
	Herpes simplex virus type 1	Neuronal cytoskeletal disruption	84
	Borna disease virus – rodents	Immune-mediated damage, glutamate excitotoxicity	85
Bacterial	Pneumococcal meningitis of mice	Spatial learning deficits in mice	86
Prion	Spongioform neurodegeneration	Prion protein aggregation activation of microglia	87
Parasitic	*Toxoplasma gondii* – mice	Immune-mediated neuronal loss	88

[1]Outside-in model refers to siltation whereby myelin (on the outside) is damaged before axons (on the inside).

[2]Inside-out model refers to axonal/neuronal damage (inside) occurs prior to myelin damage.

Aβ, amyloid-beta; AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor; APP, amyloid precursor protein; EAE, experimental autoimmune encephalomyelitis; ER, endoplasmic reticulum; IFN-γ, interferon-γ; LCMV, lymphocytic choriomeningitis virus; MCAo, middle cerebral artery occlusion; MHV, murine hepatitis virus; MOG, myelin oligodendrocyte glycoprotein; NF-L, neurofilament light; SOD1, superoxide dismutase 1; SFV, Semliki Forest virus; TMEV, Theiler's murine encephalomyelitis virus.

within the CNS that may ultimately contribute to neurodegeneration.

Parkinson's disease

The mechanisms leading to PD rely on an interaction between environmental and genetic factors. Neuropathologically, there is profound loss of dopaminergic neurons and of neurons in the substantia nigra, accompanied by accumulation of alpha-synuclein aggregates into Lewy bodies. Experimental models of PD can be induced using dopaminergic neurotoxins such as 6-hydroxydopamine and 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP), allowing examination of at least some of the key features of PD. To model familial forms of PD, transgenic mice have been developed in which genes such as those for α-synuclein, DJ-1, LRRK2, Parkin, UCH-L1 and PINK1 have been targeted.[61,62] The notion that mitochondrial dysfunction may play a role in PD has emerged from studies in which genes of the mitochondrial respiratory pathway were selectively manipulated. As neuroinflammation is also seen in PD, inflammation-based experimental models have been developed, using, for example, lipopolysaccharide as a stimulus to activate TLR-mediated innate responses. Progressive features have been demonstrated in these models, particularly in the MPTP model, which leads to microglial activation as a prominent and persistent feature.[63] That the substantia nigra is most

often affected possibly correlates with the high number of microglia in this area. One factor that could contribute to microglial activation is overexpression of human alpha-synuclein in a transgenic model.[61] In addition, while effector $CD4^+$ T cells can be neurodestructive in the MPTP model,[64] infiltration of $CD4^+$ T-regulatory cells appears to be neuroprotective in this context.[65]

Stroke

Human stroke results from the occlusion of vessels in the CNS. Experimental ischaemia, accompanied by development of a prenumbra and cell death, reflects key features of stroke in humans.[66] In animal models, the pathology and clinical outcome of stroke induction heavily depends on the method used to mimic such occlusion. The models include reperfusion, occlusion of the middle cerebral artery (MCAo), and photothrombotic stroke models (Table 3). While the extent of damage and repair mechanisms varies, the immune response provoked plays a crucial role in mediating neuronal damage. Experimental stroke is biphasic, generally involving the activation of leucocytes and the development of neurodegeneration. Recent studies have suggested that, in particular, the production of IL-23 and IL-17 by T cells entering the brain contributes to the neurological deficits that arise.[67]

Traumatic brain injury

Models of TBI invariably show activation of microglial cells, although it is unclear whether such activation promotes neuronal survival, or exacerbates neuronal damage.[68] Also, adaptive immune responses play a role. In a model of spinal cord injury, T cells isolated from diseased animals induce transient hind limb paralysis and spinal cord inflammation when injected into naïve recipients. B cells in this model are also pathogenic. Although innate responses are considered protective, there is a delicate balance between the innate immune system and the adaptive immune system in mediating either pathogenic or repair processes under these conditions.[69]

Amyotrophic lateral sclerosis

ALS is a group of degenerative disorders in which progressive motor neuron death leads to paralysis and death. Several experimental animal models for ALS exist that are induced by viral and immune-mediated mechanisms. A transgenic mouse model is also available, which is reliant on the overexpression of the mutated superoxide dismutase-1 (SOD-1) gene.[70] Evidence in ALS patients supports a role for autoimmune processes in this disorder. Consequently, experimental models have been designed in which animals are immunized with grey-matter tissues or with spinal motor neuron antigens.[71]

Multiple sclerosis

MS is considered an autoimmune disease in which involvement of viruses are suspected. Thus, both autoimmune models and viral models have been developed to study the pathogenesis. The autoimmune model EAE is induced in susceptible animals upon immunization with CNS antigens. Chronic-relapsing EAE in Biozzi ABH mice demonstrates significant axonal and neuronal cell loss in the spinal cord, and reproduces many clinical characteristics of secondary-progressive MS.[72,73] In mice immunized with myelin antigens, neurological deficits and neurodegeneration occurs subsequent to demyelination. Such a model can be referred to as an 'outside-in' model because the myelin is attacked first (Fig. 3).[74] Conversely, models in which neuronal damage occurs before myelin damage are considered 'inside-out' models (Fig. 3). Examples are models induced by immunization with neuronal antigens such as neurofilament light (NF-L)[27,75] (Fig. 1j–m) or by infection with Theiler's murine encephalomyelitis virus (TMEV), resulting in a chronic demyelinating disease.[76] Viral models of MS also include experimental infection with Semliki Forest virus (SFV) or murine hepatitis virus (MHV).[77]

Infectious models of neurological diseases

Much of what is known about the role of viruses in neurodegeneration has been learnt from animal models (Table 3). These experimental diseases show that neuronal damage is often caused directly by viral infection, or by immune responses that occur in attempts to remove

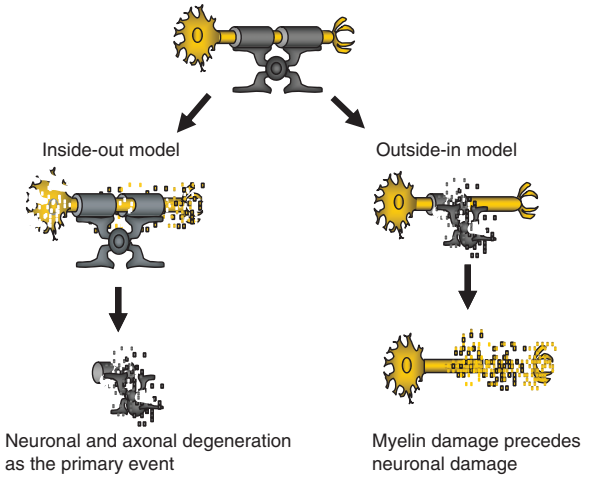

Figure 3. Pathways of immune-mediated neurodegeneration. In the inside-out model, immune-mediated damage leads to direct neuronal damage or axonal loss. As a result, myelin degenerates. In the outside-in model, as a result of direct attack on myelin, axons are vulnerable to damage by, for example, reactive oxygen species (ROS), leading to neuronal damage and degeneration.

virus-infected cells. In the former case, for example, transgenic mice expressing genes of the human foamy virus develop severe neurodegeneration, indicating that such gene products are indeed neurotoxic.[78]

The impact of the immune response in neurodegeneration frequently involves cytotoxic T-cell-mediated lysis of neurons that express viral antigens in the context of MHC class I. An example is tick-borne encephalitis.[79] Recent experimental studies indicate that $CD8^+$ cells may well contribute to an immunopathological process leading to neuronal damage.[80] Also, pathogenic antibodies may lead to neurodegeneration. The neuronal damage observed in the LP-BM5 murine leukaemia virus infection of mice is associated with the development of autoantibodies to the α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor.[81] Another mouse model of viral-induced neuronal death is lymphocytic choriomeningitis virus (LCMV) infection. LCMV is a human pathogen that causes substantial injury to the developing brain, the disease which can be modelled in rats. In many cases, LCMV remains latent and only in the presence of an activated immune response does neuronal damage ensue.[82] The neurovirulence of ecotropic murine retroviruses causes a spongiform neurodegenerative disease. This is a result of protein misfolding in experimental animals, similar to that observed in several human degenerative disorders.[83] Likewise, infection with herpes simplex virus 1 (HSV-1) induces neurite damage and neuronal death. While the exact involvement of the immune response in this context is unclear, it has been suggested that neurodegeneration is caused by cytoskeletal disruption.[84]

Borna disease virus is a neurotropic virus that targets the neurons of the limbic system and is associated with behavioural abnormalities. The virus infects and induces disease in a wide range of animals and thus is a useful model for studying neurological disorders in humans.[85] The disease consists of an acute phase, characterized by CD4 and CD8 T-cell infiltration, and a chronic phase. Neurological damage has been associated with immune damage and more recently has been suggested to result from the activation of microglia by astrocytes.

Among the neurological diseases related to bacterial infection, pneumococcal meningitis is the main cause for lasting neurological disabilities. Bacterial meningitis is a serious infection in the brain and spinal cord membranes, caused by *Streptococcus pneumoniae*. A new pneumococcal meningitis model was established in mice, using a strain of *S. pneumoniae* in which infected mice showed persistent deficits in spatial learning, despite normal motor function.[86] These observations mimic the typical neuropsychological sequelae of human bacterial and viral meningitis.

As well as viral and bacterial infections, models for neurological diseases include parasitic infections and prion disorders, although the latter are not generally considered to be disorders in which neurons are damaged via 'immune-mediated' mechanisms. Similarly to Aβ, prion protein fibrils co-localized with a broad range of complement factors, acute-phase protein, pro-inflammatory cytokines and clusters of activated microglia,[87] suggesting that activated microglia may play a role in disease. Likewise, mice infected with *Toxoplasma gondii* exhibit neurological and behavioral abnormalities secondary to inflammation and loss of brain parenchyma.[88]

Pathological mechanisms

Neuronal death may occur via several mechanisms, including necrosis, apoptosis and autophagy (Fig. 4). Necrosis is generally observed in acute brain injury as a result of the release of glutamate, nitric oxide (NO), ROS and calcium. L-glutamic acid (glutamate) plays a major role in brain development, affecting neuronal migration, differentiation, axonogenesis and neuronal survival. However, when present in excess quantities, glutamate induces neuronal death. Necrotic death of neurons caused by glutamate excitotoxicity occurs in acute viral encephalomyelitis, AD and PD, leading to increased Ca^{2+} influx and the induction of ROS and NO. Figure 4 depicts the diverse mechanisms by which immune responses could contribute to neurodegeneration. Initial events probably include activation of macrophages and microglia that become activated as a result of infections and trauma caused by the engagement of PRRs, key molecules that drive the innate immune responses. In different ways, innate immune responses in the CNS can become activated to remove infectious agents, dying and apoptosing neurons, or altered proteins that may arise as a result of stress (e.g. heat shock proteins), aging (e.g. AGE), damage or aggregation (e.g. Aβ). As a first response, macrophages and microglia produce ROS, TNF-α, NO, IL-1β and prostaglandin E_2 (PGE_2). While not acutely detrimental to neurons, and even protective, chronic microglia activation may lead to neuronal damage by signalling to the BBB. This leads to the recruitment of cells of the adaptive immune system into the CNS. Consequently, cytotoxic CD8 T cells contribute to neuronal damage or destruction by directly targeting neurons. Once targeted, $CD8^+$ T cells act to attack virus-infected cells or contribute to neurodegenerative disorders, such as Rassmussen's syndrome.[89] Neurons express MHC class I, and MHC class I-restricted $CD8^+$ T lymphocytes are directly involved in the transection of neuritis.[90] In MS lesions, direct contact has been observed between $CD8^+$ T cells and demyelinated axons or dying motor neurons.[41] $CD8^+$ T cells mediate neuronal damage either via the perforin pathway, by delivery granzymes into the neuron, or by Fas-fas ligand interactions, which leads to events culminating in neuronal damage. Under these conditions, direct attack or damage to the axons or neuron occurs, leading to Wallarian

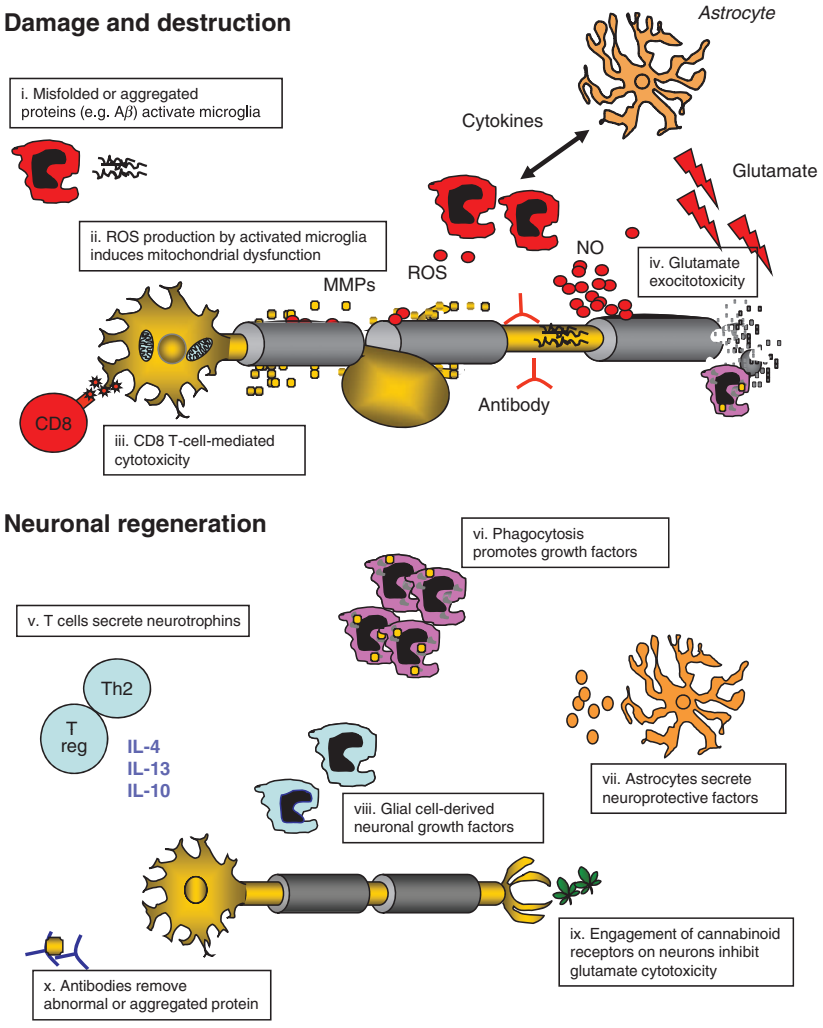

Figure 4. Proposed mechanisms of immune involvement in neurodegeneration and neuronal repair. Damage to neurons or mutations in proteins leads to misfolded or aggregated proteins (i) while macrophage and microglia activation stimulates, for example, reactive oxygen species (ROS) production known to induce mitochondrial dysfunction that could, unchecked, lead to neuronal damage, (ii) CD8 T-cell-mediated cytotoxicity, (iii) induced Fas:-FasL or perform mediated damage, and (iv) excess glutamate leading to exocitotoxicity. Neuroprotection and regeneration is afforded by cells of the immune system. T cells secrete neuroprotective factors and suppress pro-inflammatory responses, while macrophages/microglia carry out phagocytosis and astrocytes stimulate growth and repair via glial cell-derived neuronal growth factors. Endocannabinoids inhibit glutamate cytotoxicity. IL, interleukin; MMPs, matrix metalloproteinases; NO, nitric oxide; Th2, T helper 2; T reg, T regulatory.

degeneration (i.e. dying back of the axon). Neuronal cytotoxicity of neurons by $CD8^+$ T cells may also occur via bystander mechanisms, for example, as the result of $CD8^+$ T-cell-mediated damage to myelin.

In several disorders such as PNND, antibodies directed against neuronal and axonal proteins are indeed pathogenic, as reported for many neurodegenerative disorders.[26] Antibodies to neurons correlate with CNS injury in SLE, and they may well be *N*-methyl-D-aspartate (NMDA) receptors, inducing neuronal excitotoxicity. Autoantibodies to neurofascin and contactin-2 have been isolated from MS patients, and mediate axonal injury in mice.[91,92] Once bound to their target, antibodies to neuronal antigens may activate the complement system, inducing damage as a result of membrane attack complex (MAC) formation. Alternatively, aggregated prion proteins and amyloid bind C1q directly,[93] thus activating complement in the absence of antibodies. In the rat model of ALS the complement factor C5a has been shown to play a role in the pathological process and neuronal degeneration,[94] while deficiency of the complement regulator exacerbates Wallarian degeneration, clearly showing a role for complement in neurodegeneration.[95]

Thus, immune responses clearly contribute to neuronal damage and degeneration. We have summarized some of these pathways in Fig. 4; however, immune responses are also helpful in controlling and limiting the pathogenic responses.

Immunotherapy in neurodegenerative disorders

Evidence for the involvement of immunity in the development and progression of neurodegenerative disorders has provoked a plethora of therapeutic immune-modulatory approaches. Some of these are proving to be partially effective, while others that make use of antibodies to the misfolded or aggregated protein have been surprising in their pathogenicity.

A well-documented immune-modulatory strategy in AD is the administration of antibodies directed against Aβ, or Aβ itself, in an attempt to reduce the accumulation of

such peptides. Studies in transgenic animal models have shown a reduction in protein aggregation and improvement in clinical signs of disease upon such treatments.[96] While initial clinical trials were promising, a phase 2 clinical trial was stopped because of a sudden case of lethal encephalopathy in a patient actively vaccinated with Aβ. In this case the T-cell response, rather than antibodies, caused the side effect. Conversely, long-term administration of Aβ in DRB1*1501 transgenic mice effectively cleared antibody accumulation [97] and injection of Th2 cells specific for Aβ improved cognitive impairment in another model of AD,[98] suggesting a delicate balance between pathogenic and protective roles of T cells in AD. Similar approaches, administering misfolded proteins, have also been adopted in managing prion diseases. In this case, the target antigen is the scrapie prion protein (PrP^{Sc}), a misfolded conformation of the cellular protein PrP^{C}. Studies *in vitro* demonstrated that antibodies directed to PrP^{C} can inhibit the formation of PrP^{Sc} aggregates, although *in vivo*, these antibodies turned out to be less effective. To overcome the apparent challenge, several other strategies are in development, including the use of Fab fragments of the antibody against PrP, Fc-region ablated antibodies, or anti-idiotypic antibodies.[99] Likewise, antibody-based therapies have been used in the treatment of PD, targeting α-synuclein that accumulates as Lewy bodies in dopaminergic neurons.[100]

Immunotherapies are a first-line approach when the adaptive immune responses are known to be involved. In PNND, plasmapheresis reduces the autoantibody titre in the sera of these patients, although in many cases this is only partially successful and combined therapies targeting the tumour are necessary.[101]

As the emergence of activated microglia is a common feature of neurodegenerative disorders, several approaches have explored ways to inhibit or modulate microglial activation. Certain treatments, such as the use of minocycline or nicergoline, target the otherwise unwanted production of TNF-α, IL-1β and inducible nitric oxide synthase (iNOS), thought to contribute to neuronal damage.[102]

The strong involvement of the immune system in MS has led to a plethora of immune-modulatory therapeutic approaches for this condition, including, for example, blocking the entry of immune cells into the CNS, or selective antibody-mediated inactivation or depletion of T or B cells.[103] Such approaches, however, are not without side effects, as interference with routine immune surveillance may provoke the emergence of PML and other viral infections. Nevertheless, anti-inflammatory approaches have also been applied to AD.[104,105] Several

Table 4. Immunotherapeutic approaches in neurodegenerative disorders

Treatment	Disease	Efficacy, expectations	References
Aβ antibody and T cells	AD	Clearance of Aβ aggregates	96,98
PrP^{Sc} antibody	Prion diseases	Inhibition of PrP^{Sc} aggregates	99
Alpha synuclein antibody	PD	Inhibition of Lewy Body formation	100
Modulation of microglial activation			
Combination therapy, Plasmapheresis, Removal of tumour.	Paraneoplastic neurological disorders	Removal of anti-neuronal antibodies	101
Antibiotics Minocyclin	Neurodegeneration	Inhibition of inflammation and anti-apoptoic activity	102
Immunotherapy, Copaxone, IFN-β, Natalizumab, Cladribine, Ritixumab, Alemtuzumab, FTY 720	MS	Inhibition of specific T-cell and/or B-cell responses Inhibition of immune-cell entry into the CNS	103
Non-steroidal anti-inflammatory	AD	Inhibition of COX1 and COX-2	104,105
RAGE antagonists	AD	Reduction of formation or activation of innate immune responses by inhibiting/blocking AGEs	106
Glutamate antagonists	PD	Blocking glutamate	107
Anti-oxidants	Neurodegeneration	Reduction of oxidative stress	108,109
Complement inhibition	Stroke, TBI	Blocking complement-mediated neuronal damage	110,111
Cannabinoids	Huntington's disease, MS	Attenuates excitotoxic glutamatergic neurotransmission	112,113
Diet, Calorific restriction	AD, PD	Antioxidant functions, Inhibits COX-2 and iNOS (Curcumin) Reduction in free radicals and oxidative stress	114–116

Aβ, amyloid-beta; AD, Alzheimer's disease; AGE, advanced glycation end-products; CNS, central nervous system; COX, cyclooxygenase; IFN-β, interferon-β; iNOS, inducible nitric oxide synthase; MS, multiple sclerosis; PD, Parkinson's disease; RAGE, receptor for AGE; TBI, traumatic brain injury.

other approaches are effective in inhibiting neurodegenerative disorders in experimental systems, although they have not yet been applied clinically. We have summarized these in Table 4, along with those mentioned in this section. For example, blocking RAGE,[106] glutamate antagonists,[107] targeting oxidative stress,[108,109] or the complement pathway are beneficial in some disorders.[110,111]

CB-derived drugs are promising neuroprotective strategies and have been shown to have, in addition to neurprotection, some immunosuppressive activity. Neuronal CB_1 receptors when activated have been shown to attenuate excitotoxic glutamatergic neurotransmission. This is suggested to trigger signalling pathways that, in animal models of neurodegenerative disorders, are effective in inhibiting signs of degeneration.[112,113]

Finally, certain risk factors, such as diet, obesity and lifestyle, may predispose to the development of dementia. Several recent studies indicate that diets rich in antioxidants and anti-inflammatory components are beneficial in neurodegenerative disorders or in preventing such disorders, probably because of their anti-inflammatory and antioxidant activities.[114,115] Moreover, studies in animal models indicate that reduced calorific intake may also lower age-related cognitive declines and the risk of developing neurodegenerative diseases.[116] Whether this can be translated to the aging population in humans remains to be seen.

Conclusions

Despite the notion that the CNS is an immune-privileged site, innate and adaptive immune responses regularly take place in the CNS and are crucial for elimination of infectious agents and for clearing debris. Also, they stimulate tissue repair. In this sense, immune responses in the CNS should therefore be considered as primarily beneficial. Yet, chronic activation of immune responses can lead to problems. Although probably triggered by many different initiating events in the early stages, many neurodegenerative diseases share chronic immune activation as a common feature. What drives chronic inflammation in these cases is not yet fully clear in most cases. Possibly, it is the alignment of both innate and adaptive responses against certain stimuli, such as misfolded and/or aggregated proteins, heat shock proteins and other local DAMPs that may contribute to a final pathogenic pathway. Conceivably, a vicious cycle may be initiated if immune responses stimulate the reappearance of the original trigger, either directly or indirectly. Adaptive immunity to local triggers includes T-cell responses and antibodies. Relevant adaptive responses may be generated by cross-reactivity between local factors that act as targets, and tumour antigens or infectious agents that act as triggers.

Despite the undeniable potential of immune responses to become pathogenic, it should be kept in mind that especially innate immune responses in the CNS have profound immune-modulatory and reparative qualities. Identification of such protective pathways of immune activation, and harnessing them, may well contribute to the control of chronic CNS disorders.

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Disclosures

The authors state that they have no conflicts of interest.

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