Innate and adaptive immune responses in the CNS

Ari Waisman, Roland S Liblau, Burkhard Becher

Almost every disorder of the CNS is said to have an inflammatory component, but the precise nature of inflammation in the CNS is often imprecisely defined, and the role of CNS-resident cells is uncertain compared with that of cells that invade the tissue from the systemic immune compartment. To understand inflammation in the CNS, the term must be better defined, and the response of tissue to disturbances in homoeostasis (eg, neurodegenerative processes) should be distinguished from disorders in which aberrant immune responses lead to CNS dysfunction and tissue destruction (eg, autoimmunity). Whether the inflammatory tissue response to injury is reparative or degenerative seems to be dependent on context and timing, as are the windows of opportunity for therapeutic intervention in inflammatory CNS diseases.

Introduction

The role of inflammation in various CNS diseases is debated. Although the role of the immune system in disturbed tissue homoeostasis is becoming better understood, inflammation in the CNS is thought to be different from that in the periphery. The CNS is often described as an immune-privileged site, and evidence supports the notion that the CNS receives limited immune surveillance by peripheral lymphocytes (panel 1) under physiological conditions: the blood–brain barrier limits the movement of cells and macromolecules between the blood and CNS tissue; there was thought to be no professional antigen-presenting cells in the CNS, and little expression of MHC molecules, limiting antigen recognition by invading T lymphocytes; and the immune response to allografts implanted into the CNS is delayed compared with those in the periphery.

The notion that the CNS must be immune privileged, hiding behind a selectively permeable barrier, has now been revised. Although there are no antigen-presenting cells within the CNS parenchyma (panel 1), these cells exist in association with blood vessels in the CNS. Neural-derived antigens are reportedly released from the CNS and are subsequently detected in CNS-draining cervical lymph nodes. Hence, immune responses to CNS antigens or pathogens in the CNS can be mounted in these dedicated secondary lymphoid structures. More importantly, if immune privilege were absolute, why would immunosuppressed patients develop disorders such as primary CNS lymphoma or progressive multifocal leukoencephalopathy, a usually fatal viral disease characterised by progressive damage of white matter, when the virus can multiply in the absence of control by invading T lymphocytes? These occurrences suggest that under physiological conditions, the CNS is under close surveillance by the immune system, and pathogens or aberrant cells in the CNS are well controlled.

In this Review, we show that the CNS is not only an immune competent organ, closely interacting with the systemic immune compartment under physiological conditions, but also that almost all pathological changes within the CNS elicit a prominent inflammatory reaction. We aim to define and classify the most prominent features of inflammation in the context of CNS diseases.

We classify CNS disorders as innate or adaptive immune-mediated disorders, with specific examples of each mechanism. We will also discuss innate inflammatory responses to pathological CNS disorders and compare them with antigen-driven autoimmune disorders, in which T cells and B cells (panel 1) orchestrate an attack against CNS autoantigens.

Inflammation and innate versus adaptive immunity

The term inflammation, from the Latin verb *inflammare* (to burn), is not actually synonymous with infection, although infection is often the cause of inflammation. To understand inflammation, it is important to distinguish innate and adaptive immune responses. There are many definitions of the innate and adaptive aspects of immunity involved in the formation of an immune response, and these components are not separate but are functionally intertwined. Innate immunity is a feature of most life forms, from plants and fungi to invertebrate and vertebrate animals. The innate immune system components, such as tissue-resident macrophages (panel 1), dendritic cells, mast cells, circulating phagocytes, and complement molecules (panel 1), represent the first line of defence against invading pathogens or malignancy. Adaptive immune responses exist only in more complex vertebrates and involve a specialised leucocyte (panel 1) population that uses variable cell-surface antigen receptors generated by somatic recombination or gene-conversion events. In mammals, only B cells and T cells are capable of generating specialised antigen receptors to interact with microbial pathogens or eliminate tumours. This highly evolved immune system is, however, also the cause of several autoimmune diseases.

The innate and adaptive aspects of inflammation in CNS diseases are easily distinguished. Part of the innate immune defence against pathogens entering the CNS is the blood–brain barrier. This selectively permeable barrier is formed by capillary endothelial cells connected by tight junctions along most CNS capillaries; some regions of the brain, such as the circumventricular organs, have widespread vasculature but no healthy blood–brain barrier.
In the CNS parenchyma, two additional cell types are actively involved in immune defence: astrocytes and microglia, the CNS-resident macrophages (panel 1). Astrocytes are large, ramified cells of neuroectodermal origin that share a developmental pathway with neurons and oligodendrocytes (panel 1) and are thought to have several functions in the CNS, including structural support, metabolism, synaptic plasticity, and immune defence. Astrocytes are also thought to be crucial for the integrity of the blood–brain barrier. However, very few in-vivo studies directly address the function of astrocytes under physiological or pathological conditions, and much of what we know about the biology of astrocytes has been learned from in-vitro studies.

Microglia are haemopoietic cells with self-renewing capacity, which are derived early during embryonic development from yolk-sac myeloid cells (panel 1). Therefore, there is a phenotypically and functionally
homogeneous population of myeloid cells within the CNS parenchyma. Under pathological conditions, monocytes (panel 1) from the blood cross the blood–brain barrier, enter the CNS, and invade the microglial niche. The observation of this process led to the idea that some microglia might be of bone-marrow or monocytic origin, or even constantly replaced by fresh bone-marrow emigrants. However, a series of experiments showed that the previously recorded microglia turnover is the result either of pathological changes, inflammation, or an experimental artifact induced by CNS irradiation. Although we have come a long way in understanding the developmental origin of microglia, we know little about their contribution to immune responses within the CNS. Microglia have a defined role in CNS development, in which they are needed as phagocytic cells, clearing debris of apoptotic cells, and for shaping the synaptic architecture. Furthermore, microglia maintain trophic support and synapse remodelling throughout life. Evidence for the association of microglia in autoimmune diseases is mostly circumstantial, as good models for testing their direct association with autoimmunity have been developed only recently. Microglia are phagocytic, express MHC molecules, and release proinflammatory cytokines, and therefore have the capacity to interact with other immune cells. It is also possible that microglial cells have only a minor role under pathological conditions and that their abundance in the CNS is because of their function in CNS homoeostasis and neuronal development. Under physiological conditions, microglia seem to monitor the CNS constantly. Whichever is true, microglia are among the earliest responders to changes in the CNS and therefore are the first cell types to respond to any pathological insult. Whether the morphological and functional changes of microglia actually contribute to pathogenesis is a matter of some debate. We have illustrated the part that microglia and astrocyte activation might play under physiological and pathological conditions in the figure.

Few patients have true autoimmune diseases driven by adaptive immune responses involving self-reactive B cells, T cells, or both. This does not mean that these innate responses are not compounding or restricting the underlying pathogenesis, but it does mean that this sort

---

**Figure: Involvement of various cell types in CNS inflammation**

In almost every non-physiological disorder, the CNS-resident astroglia and microglia become activated, proliferate, and change to have an inflammatory expression signature. In some inflammatory diseases of the CNS, myeloid cells cross the neurovascular unit and invade the CNS. Lymphocytes with recombined antigen receptors (T cells and B cells) can also penetrate the CNS and target CNS-resident antigens in many inflammatory diseases (panel 2).
of inflammation is rarely the primary driver of tissue damage and neurological deficits. By contrast, there are some chronic inflammatory CNS diseases in which adaptive, rather than innate, immunity dominates the pathogenesis.

**Innate immunity in the CNS**

In diseases such as Alzheimer’s disease, Parkinson’s disease, and amyotrophic lateral sclerosis (ALS), the microglia show many morphological and molecular changes (panel 2). Microglia have the ability to phagocytose and to produce trophic factors, prostaglandins, chemokines, cytokines, complement proteins, proteases, reactive oxygen species, and nitric oxide. Because some of these mediators might have an adverse effect on CNS-resident cells, or attract other cells that can cause damage, reactive microglia are thought to contribute to tissue damage. However, although microglia display a more amoeboid appearance (panel 1) and retract their processes during phagocytosis, this might not signify activated microglia, but rather exhausted or dysfunctional microglial cells.

**Innate immunity in amyotrophic lateral sclerosis**

ALS is a progressive and fatal neurodegenerative disease that affects motor neurons in the spinal cord, motor cortex, and brainstem. The exact pathophysiological mechanisms underlying neurodegeneration in ALS remain largely unclear, but a common pathological hallmark is the presence of cytoplasmic inclusions in degenerating neurons, followed by a local inflammatory reaction. ALS is not thought to be mainly an inflammatory or immune-mediated disease, but immune mechanisms seem to play a part in its pathogenesis. Typically, inflammation in ALS is characterised by astrocyte activation (gliosis; panel 1) and the accumulation of large numbers of amoeboid (phagocytic) microglia in the brain. This altered activation state of glial cells in ALS is marked by increased production of potentially cytotoxic molecules such as reactive oxygen species, inflammatory mediators such as prostaglandins produced by the enzyme COX-2, and proinflammatory cytokines including interleukin 1β, tumour necrosis factor α (TNFα), and interleukin 6. Whether this local immune response limits or accelerates the pathogenesis of ALS is unclear.

ALS is modelled in mice with different mutations in the Cu–Zn superoxide dismutase (SOD1) gene. Mutations of the SOD1 gene occur in about 20% of patients with ALS, and reactive microglia and some tissue-invading myeloid cells can also be found in the CNS of SOD1 mutant mice. In human brain material, neuropathologists cannot distinguish between invading monocytes and reactive microglia. Using the SOD1 mutant murine model of ALS, it was shown that monocytes are recruited to the CNS during disease development, and the inhibition of this process by neutralising antibodies against the chemokine receptor CCR2—needed for monocyte recruitment into tissues—resulted in slight disease amelioration. Monocytes with a similar transcriptional signature were identified in the blood of patients with progressive ALS, suggesting that these cells contribute to neuronal damage.

Although soluble mediators such as interleukin 1β and TNFα were shown to have neurotoxic properties in vitro, disease progression is not affected by deletion of the genes coding for TNFα or interleukin 1β alone in SOD1 mutant mice, only by deficiency of both together. Motor neuron death in ALS is therefore probably the result of many factors acting in a redundant and complementary manner.

Even though motor neurons are the main cells affected in ALS, evidence points to the involvement of neighbouring astrocytes when these cells are directly affected by mutations. Disease progression is slower when mutant SOD1 is specifically deleted from astrocytes. Similarly, SOD1 mutant mice in which the mutant gene was deleted exclusively in microglia showed slower progression of the disease. However, this could be because mutant SOD1 might also be deleted in other myeloid cells. Similar results were seen in bone-marrow chimeric mice in which only haemopoietic cells were deficient for SOD1, and it was shown that the presence of host, wild-type SOD1 astrocytes substantially delayed onset of motor neuron degeneration. Microglia are hypersensitive to any trigger, including those induced by activated astrocytes. Primary activation of astrocytes would probably result in the activation of microglia, which can propagate the damage within the CNS. Damage caused first in astrocytes, as probably occurs with the SOD1 mutation, leads to local, sterile inflammation in the CNS, which in turn can contribute to neuronal damage.

**Innate immunity in Parkinson’s disease**

Parkinson’s disease is the second most common progressive neurodegenerative disorder. The motor symptoms of Parkinson’s disease result from the death of dopaminergic neurons in the substantia nigra, located in the midbrain. Like ALS, Parkinson’s disease is associated with neuroinflammation, the hallmarks of which are the presence of reactive microglia and astrocytes in the substantia nigra. Parkinson’s disease is associated with increased production of cytokines, chemokines, reactive oxygen species, and nitric oxide in the substantia nigra. Cumulative oxidative damage in the CNS is deemed an important mechanism because age is the single most important factor contributing to induction of sporadic forms of Parkinson’s disease. Neuronal death itself, including release of protein aggregates, is proposed to induce activation of microglia during Parkinson’s disease. Additional activation of microglia might be caused by the release of aggregated α-synuclein from neurons into the extracellular space. Extracellular α-synuclein can be phagocytosed by
microglia, and oxidised forms of α-synuclein have been seen to induce microglial activation. The internalisation of α-synuclein by microglia is followed by activation of NADPH oxidase, resulting in production of reactive oxygen species. Local immune cells—namely microglia—together with reactive astrocytes, are thought to cause the neuronal damage in a non-antigen-specific manner, although this is under debate. It is possible that interrupting microglia activation in patients with Parkinson’s disease might be beneficial in reducing further neuronal damage.

Adaptive immunity in the CNS

Inflammatory CNS diseases that are very probably caused by pathogenic T cells, B cells, or both, are varied (panel 2), and include infectious meningoencephalitis, in which the damage caused by the immune reaction against the pathogen is sometimes more harmful than the direct damage caused by the infectious agent. In patients with progressive multifocal leukoencephalopathy and immune reconstitution inflammatory syndrome, who are recovering from an immunodeficient state, a T-cell response specific to John Cunningham virus in the brain, largely involving CD8 T cells, probably brings about virus elimination and killing of CNS-resident cells with concomitant inflammation. Multiple sclerosis is another example, but because reviews have discussed the potential contribution of T cells and B cells and have speculated about their antigenic targets in multiple sclerosis, we will concentrate on rarer autoimmune diseases of the CNS in which the immunopathogenesis is better understood and in which the target antigens have been identified, such as anti-Hu-antibody-associated neuronopathy, a paraneoplastic syndrome in which auto-reactive T cells are probably the major immune effectors, and neuromyelitis optica, a disorder in which autoantibodies have proven pathogenic properties.

T-cell-mediated autoimmunity in CNS paraneoplastic syndromes

T-cell-mediated autoimmunity is usually studied with laboratory models of autoimmune encephalomyelitis induced by immunisation of rodents with specific myelin components or adoptive transfer of myelin-reactive T cells. In human beings, T-cell-mediated CNS inflammatory diseases include acute disseminated encephalomyelitis, Rasmussen’s encephalitis, and some paraneoplastic neurological disorders, such as the anti-Hu-antibody-associated syndrome and paraneoplastic cerebellar degeneration (panel 2). Paraneoplastic encephalomyelopathy and paraneoplastic sensory neuronopathy (anti-Hu syndrome) are associated with a partly effective antitumour immune response, in which tumours are reduced but not eliminated, and usually follow a sub-acute course, characterised by autoantibodies targeting intracellular neuronal antigens. These neuronal self-antigens are ectopically expressed in tumour cells.

For example, small cell lung cancers consistently express the HuD protein, and low concentrations of anti-HuD antibody can be detected in 16–22% of patients with small cell lung cancers. However, about 1.4% of patients with small cell lung cancers develop high serum antibody titres, associated with the anti-Hu syndrome. Serum IgG in these patients shows cross-reactivity for HuB, HuC, and HuD, which are physiologically expressed neuron-
specific RNA-binding intracellular proteins. Detection of high anti-Hu IgG serum titres in patients with neurological manifestations represents a highly specific diagnostic test and should lead to a thorough search for the underlying cancer.

Pathophysiological, the anti-Hu syndrome is interpreted as an autoimmune disease triggered by aberrant expression of neuronal self-antigens by malignant cells. One key question with major therapeutic implications with regard to disease pathogenesis is which components of the immune system mediate nervous tissue damage. Intrathecal synthesis of HuD-specific IgG was strongly suggested by isoelectric focusing followed by immunoblotting on HuD-loaded membranes and calculation of a CSF–serum anti-Hu antibody index. Anti-Hu IgG is also deposited in the nervous tissue, but whether this shows a post-mortem technical artifact or an in-vivo occurrence of potential pathogenic relevance remains uncertain. Because the anti-Hu antibodies are specific for intracellular and predominantly nuclear antigens, they might not access their target antigens in vivo. Their pathogenic potential is therefore questionable. Infusion of mice with purified IgG from patients with high titres of anti-Hu antibody did not result in any CNS lesion despite strong cross-reactivity between the two species, and the effect of anti-Hu antibodies on in-vitro neuronal cell cultures is difficult to interpret. Inflammatory infiltrates are commonly identified in the CNS perivascular space (panel 1) and parenchyma of patients with anti-Hu syndrome. The perivascular cuffs (panel 1) are mainly composed of T cells, macrophages, and occasionally B cells. Inflammatory cells within the parenchyma are mostly T cells and microglial cells. CD8 T cells are the prominent lymphocyte population within the inflamed CNS parenchyma, and usually form clusters around neurons. Immunohistochemical analyses revealed intimate contact between the targeted neurons and cytotoxic granule-containing T cells. HLA class I molecule expression (panel 1) has been described on neurons in inflamed nervous tissue from patients with anti-Hu syndrome; therefore, the close apposition of CD8 T cells with neurons is probably indicative of in-vivo antigen presentation by neurons to CD8 T cells, leading to neuronal cell death. Microglia are located in the clusters of inflammatory cells surrounding neurons, indirectly suggesting their association with neuronophagy, but this finding should be interpreted with caution.

The exact antigen recognised by the CNS-infiltrating T cells remains elusive. However, blood mononuclear cells from patients with high anti-Hu antibody titres secrete more interferon γ in response to HuD protein than blood mononuclear cells from cancer patients without anti-Hu antibodies. These data suggest that autoreactive CD4 T cells could be implicated in the anti-Hu syndrome. It is unclear whether HuD-specific CD8 T cells are present more frequently or with greater functional properties in the blood of patients with anti-Hu syndrome. However, a report suggested that an unconventional non-cytotoxic interleukin-5-producing and interleukin-13-producing anti-HuD CD8 T-cell population could be detected in some patients. By contrast, a classic cytotoxic Yo antigen-specific CD8 T-cell response is detected in paraneoplastic cerebellar degeneration. Further studies on CNS-infiltrating T cells and blood mononuclear cells of patients and controls should better define the antigen-specificity and molecular characteristics of the pathogenic T cells, thereby offering much needed therapeutic targets.

Antibody-mediated autoimmunity in neuromyelitis optica

The pathogenesis of autoantibody-mediated neurological diseases was first studied at the neuromuscular junction in myasthenia gravis and Lambert-Eaton myasthenic syndrome. Newly described neurological or neuro-psychiatric disorders have been associated with autoantibodies targeting neuronal or axonal surface antigens, most notably neurotransmitter receptors or channel proteins (panel 2). The autoantibody-related mechanisms of tissue injury are best defined in neuromyelitis optica. However, these mechanisms might not be applicable to CNS diseases associated with autoantibodies against neuronal synaptic proteins, which have been shown to induce a reversible decreased density of the target protein through internalisation but without neuronal death.

Neuromyelitis optica is typically characterised by inflammatory demyelinating lesions in the optic nerves and spinal cord. Pathologically, neuromyelitis optica lesions are generally more destructive than multiple sclerosis lesions, show loss of astrocytes consistent with demyelination and axonal damage, and contain eosinophils and neutrophils. The implication of humoral immunity in neuromyelitis optica lesions became clear on the basis of the prominent deposition of immunoglobulins and activated complement components, most notably at the outer rim of vessel walls. IgG autoantibodies specific for aquaporin 4 (AQP4), a water channel localised on astrocyte foot processes and pial surface, were identified as a highly specific serum biomarker for neuromyelitis optica. AQP4 is particularly expressed in the spinal cord grey matter and in the optic nerve. AQP4 aggregates into larger structures forming orthogonal arrays of particles on the astrocyte membrane.

Although some plasma cells are able to synthesise anti-AQP4 IgG intrathecally, the serum:CSF anti-AQP4 IgG ratio in patients with neuromyelitis optica suggests there is substantial production of IgG outside the CNS. Colonies of blood plasmablasts are expanded during neuromyelitis optica relapse and are a source of anti-AQP4 IgG, which is detected at high concentrations in the serum and CSF of patients with neuromyelitis optica and sustains the survival of these cells, and therefore represents a promising therapeutic target.
Patient IgG has shown pathogenic potential in vivo after injection into laboratory animals.92,93 This pathogenic property is lost when IgG preparations are depleted of anti-AQP4 antibodies, suggesting that anti-AQP4 IgG is the probable cause of the damage.77,78 In primary astrocyte cultures, anti-AQP4 IgG bind the extracellular domains of AQP4 resulting in internalisation of the AQP4–autoantibody complexes with subsequent endolysosomal proteolysis of AQP4 and activation of the complement pathway or of cell-surface-bound Fc receptors by the anti-AQP4 IgG.95

The modulation of AQP4 on the astrocyte surface has consequences beyond water movement. The excitatory aminoacid transporter-2 (EAAT2), which plays a key part in glutamate homoeostasis in the CNS, forms a macromolecular complex with AQP4 on astrocytes. Loss of both AQP4 and EAAT2 has been documented in neuromyelitis optica lesions.95 When primary astrocytes are incubated with anti-AQP4 IgG, AQP4 and EAAT2 are downregulated and glutamate uptake is substantially reduced. Activation of the ionotropic glutamate receptors might result in axonal injury and oligodendrocyte changes and death.96 This could underlie the clinical benefit of plasma exchange in some patients.97

On IgG binding to AQP4, the Fc portion of the IgG can trigger complement activation and antibody-dependent cell-mediated cytoxicity. The large and consistent deposition of immunoglobulin and of activated complement fractions in lesions suggests a crucial role of complement in tissue injury.79,80 Complement activation also generates strongly chemoattractive molecules, notably C5a, which is recorded at high concentrations in the CSF of patients with neuromyelitis optica.97 Eculizumab, a monoclonal antibody against the C5 protein, showed efficacy in neuromyelitis optica optica patients in an open-label trial,98 pointing to the pathological relevance of this pathway in patients.

Tissue-invading myeloid cells such as monocytes, eosinophils, and neutrophils probably have an amplifying role in neuromyelitis optica pathophysiology. Fc receptors are present on the surface of all these cell types, and their interaction with anti-AQP4 IgG bound to tissue can stimulate release of cytokines, chemokines, reactive oxygen species and cytotoxic degranulation, resulting in antibody-dependent cell-mediated cytotoxicity.81,82

**Activation of adaptive immune responses in the periphery**

CNS inflammatory diseases that are attributable to adaptive immune responses probably start within lymphoid structures outside the nervous tissue. Specific antigen receptors of T cells or B cells are either activated by CNS-derived soluble antigens presented by peripheral antigen-presenting cells, by autoantigens also expressed in peripheral tissues,82 by cross-reactive foreign antigens,83 or by neo-autoantigens of tumours.84 The adaptive immune system is associated with active immune surveillance of the CNS, so aberrantly activated T cells and B cells can—in principle—access the CNS and cause antigen-driven inflammatory CNS diseases (panel 2). Tissue damage then allows CNS antigens to access the cervical lymph nodes, thereby potentially sustaining autoimmunity by introducing the antigen to the peripheral immune system.3

**Therapeutic strategies targeting CNS autoimmune mechanisms**

The treatment of CNS autoimmune diseases relies on various approaches depending on the lymphocyte subset(s) implicated. Immune cell-depleting strategies, such as those using anti-CD52 (alemtuzumab) or anti-CD20 (rituximab, ocrelizumab, ofatumumab) monoclonal antibodies, are probably the more radical approaches. These strategies efficiently inhibit CNS inflammation in multiple sclerosis but, with their indiscriminate targeting of both pathogenic and protective immune cells, might have side-effects.94

A more selective option is the pharmacological interference of immune cell migration to the CNS. Inhibition of immune cell trafficking through blockade of the α4 integrin with natalizumab or small molecule antagonist against S1P and S1P-receptor functional antagonists (fingolimod, siponimod) has proven effective in multiple sclerosis. Such approaches could be applicable in other CNS inflammatory or autoimmune diseases. Diseases in which CD8 T cells or autoreactive helper T cells are the main immune effectors might also be controlled by strategies acting on adhesion molecules other than α4 integrin95 or on specific chemokine receptors such as CCR5.96,97 The major drawback of this approach is low selectivity, thereby resulting in reduced overall immune surveillance of the CNS.

Neutralising of the harmful immune effectors without affecting the rest of the immune response could include selective neutralisation of effector molecules implicated in the disease process (either in the initiation or the effector phase). For some antibody-mediated diseases, such as neuromyelitis optica, plasmapheresis and neutralisation of complement factors can be efficient strategies. However, in patients with other antibody-mediated diseases, such as encephalitis associated with anti-NMDA receptor antibodies, B-cell clonal expansion and affinity maturation can take place within CNS niches, blunting the efficiency of strategies targeting humoral immune components in the periphery, because these cannot cross the blood–brain barrier. It seems that inflamed tissues have the capacity to host B cell maturation, albeit not as effectively as dedicated secondary lymphoid organs such as lymph nodes. Studies of multiple sclerosis reveal that disease-associated B-cell clones can mature either in the periphery or within the CNS, with an active connection between the two compartments.97
Neutralisation of proinflammatory cytokines such as interleukin 23, interleukin 17A, granulocyte-macrophage colony-stimulating factor, interleukin 6, or their receptors is under investigation in multiple sclerosis and neuromyelitis optica. This approach has been successful in chronic inflammatory diseases outside the CNS but whether it will also be useful to treat CNS autoimmunity remains unclear. Surprisingly, blocking the interleukin 2RA chain with daclizumab seems to have indirect mechanisms of action involving inhibition of T-cell activation by dendritic cells and expansion of regulatory CD56 bright natural killer cells (panel 1). Inhibition of T-cell or B-cell activation, proliferation signals, or promotion of regulatory pathways—including boosting the numbers or functions of CD4 regulatory T cells—are plausible future avenues for immune intervention in neuroimmunological diseases.

Local activation of innate immune cells, namely microglia and astrocytes, can be the result but also the cause of CNS tissue damage. Therefore, strategies that target innate immune cells or their mediators for the treatment of inflammatory diseases of the CNS are likely to gain momentum in the coming years. These could include inhibition of tyrosine kinases, inhibition of NF-κB, and scavengers for reactive oxygen species and nitric oxide, or pharmacological interference with their production.

Inflammasomes are key multiprotein platforms associated with the inflammatory cascade, notably production of active interleukin 1 and interleukin 18 as a result of recognition of foreign or endogenous danger signals. Accumulating evidence supports the rationale of targeting inflammasome activation in the CNS in future trials. Interfering with cytokine networks can also dampen adverse microglial activation.

These methods are selected examples of strategies to control the destructive activation of local immune cells in the CNS. We need to keep in mind that in some groups of diseases, such as ALS and Parkinson’s disease, it is probably not sufficient to block the influx of immune cells from the peripheral immune system, as described above, but the use of new tactics to restrain microglia and astrocyte activation should be considered. Repurposing existing therapies to this end is also an actively investigated avenue. The use of statins in multiple sclerosis and the use of monoclonal antibodies or antagonists blocking cytokines binding to their receptors (interleukin 1, interleukin 6, interleukin 12) might prove successful.

In autoimmune diseases of the CNS, rather than using broad strategies that target useful immune components indiscriminately to neutralise a few harmful immune cells, the ultimate goal is to selectively modulate the autoreactive lymphocytes associated with pathogenesis. Antigen-specific immunotherapy shows effects in preclinical animal models, but has not yet met clinical expectations. Recent efforts aim either to use myeloid-derived peptides or proteins to inactivate autoreactive T and B cells in multiple sclerosis, or selectively block the interaction between the pathogenic anti-AQP4 antibodies and their target.

Conclusions and future directions
In this Review, we have attempted to explain inflammation in the context of CNS diseases. There is ample evidence that inflammation occurs in almost all CNS disorders, irrespective of whether immunity is the primary driver of disease (as in autoimmune encephalitides) or represents the tissue response to degenerative processes (eg, Parkinson’s disease, ALS, Alzheimer’s disease). CNS tissue destruction can be initiated by neural antigen-specific T or B cells, as seen in neuromyelitis optica and in paraneoplastic neurological diseases. Conversely, CNS inflammation and ultimately damage can also be initiated by malfunction or aberrant activation of the CNS-resident cells. We have an incomplete understanding of the molecular pathways associated with the pathogenic, and potentially protective, contribution of both CNS-resident and CNS-infiltrating immune cells to CNS diseases. Several issues remain unsettled, including understanding the roles of blood-borne myeloid cells and microglia in the diseased CNS. Additionally, there is evidence that immune responses favour repair after CNS damage. If CNS inflammation can actually be either damaging or disease limiting, we need to understand the mechanisms of each aspect to develop new therapeutic strategies that exploit the protective elements of inflammation.

Most neurological diseases show clear involvement of the immune system; therefore, therapies aimed at blocking immune cells is an obvious strategy. Such strategies are already successful in the treatment of people with multiple sclerosis, and could prove beneficial for other inflammatory diseases of the CNS. Beyond these proven therapies, the question of whether we can harness the innate and adaptive immune system to eliminate toxic components such as aggregated or misfolded proteins within the CNS remains unanswered. One strategy would be to engineer CNS-infiltrating immune cells to express factors important in neuroprotection or neuroregeneration, and in such a way to not only reduce inflammation, but also protect the tissue and promote the repair process.
CNS diseases involving the influx of systemic leucocytes, including B and T cells, are amenable to treatment with modern biological drugs. Diseases such as ALS, Parkinson’s disease, and Alzheimer’s disease, in which lymphocytes probably have at most a minor role, all share a clear inflammatory tissue response to the degenerative processes. This tissue inflammation is only now recognised as having detrimental effects and to possibly accelerate disease progression. In view of the speed at which fundamental discoveries are now being translated to treat patients, we predict that controlling innate inflammation will hold great promise for the treatment of neurodegenerative diseases. Moreover, knowledge about the genetic bases and the immune mechanisms underlying CNS inflammatory diseases should offer unique opportunities for more targeted therapies.

Contributors
All authors contributed equally.

Declaration of interests
AW declares a grant and consultancy fees from Novartis. RSL declares grants from Pierre Fabre and consultancy fees from Genzyme, Servier, and GSK. BB holds a patent application by the University of Zurich and the Charité–Universitätsmedizin Berlin entitled “Modulators of IL-12 and/or IL-23 for the Prevention or Treatment of Alzheimer’s Disease” (PCT/EP2012/050066).

Acknowledgments
We thank Khalad Karram for the preparation of the figure. The authors’ work is supported by Inserm, CNRS, Toulouse III University, and ANR (RSL); the Swiss National Science Foundation, the European Union, FP7 TargetBrain (279007), and the Swiss Multiple Sclerosis Society (BB); the German Research Foundation SFB/TR 128, the Research Centre for Immunotherapy, and the Focus Program in Neuroscience (A W), and a grant from the European Union, FP7-PEOPLE-2012-ITN NeuroKine (AW, RSL, and BB). Funding sources had no roles in the writing of the manuscript or the decision to submit it for publication.

References


